Guillermo Ortiz-Ruiz
Marco A. Perafán
Eugen Faist
Carmelo Dueñas Castell *Editors*

Sepsis

Second Edition

Springer

AMAREY NOVA-MEDICAL S.A.

Sepsis

Second Edition

Sepsis

Second Edition

Guillermo Ortiz-Ruiz, MD
Professor of Pulmonary and Critical Care Medicine
Universidad del Bosque
Bogotá, Colombia

Marco A. Perafán, MD
Professor of Cardiology and Critical Care Medicine
Fundacion Clinica Shaio
Bogotá, Colombia

Eugen Faist, MD
Professor, Department of Surgery
Klinikum Grosshadern, University of Munich
Munich, Germany

Carmelo Dueñas Castell, MD
Professor of Pulmonary and Critical Care Medicine
Hospital Bocagrande
Cartagena, Colombia

Editors

Springer

Guillermo Ortiz-Ruiz, MD
Pulmonary and Critical Care Medicine
Universidad del Bosque
Bogotá, Colombia

Eugen Faist, MD
Department of Surgery
Klinikum Grosshadern
University of Munich
Munich, Germany

Marco A. Perafán, MD
Intensive Care Unit
Fundacion Clinica Shaio
Bogotá, Colombia

Carmelo Dueñas Castell, MD
Pulmonary and Critical Care Medicine
Hospital Bocagrande
Cartagena, Colombia

Library of Congress Control Number: 2005935333

ISBN-10: 0-387-29816-9
ISBN-13: 978-0387-29816-0

Printed on acid-free paper.

Printed in the United States of America. (BS/MVY)

9 8 7 6 5 4 3 2 1

springer.com

Preface

The mortality of severe sepsis (infection-induced organ dysfunction or hypoperfusion abnormalities) and septic shock (hypotension not reversed with fluid resuscitation and associated with organ dysfunction or hypoperfusion abnormalities) remains unacceptably high. Similar to an acute myocardial ischemic attack and an acute brain attack, the speed and appropriateness of therapy administered in the initial hours after the syndrome develops likely influence the outcome.

The care of critically ill patients in a modern intensive care unit (ICU) results in a large societal burden in terms of both manpower and monetary cost. The high cost of critical care can largely be attributed to high overhead costs (e.g., need for experienced staff and expensive equipment), and high demand for ICU services. With the continued increase in healthcare costs, there is an increasing need to establish whether new therapies are not only effective, but also cost-effective. Although this is true throughout medicine, the issue of cost-effectiveness is especially important in critical care medicine. ICU costs in the United States exceed $150 billion, representing up to one third of all hospital costs. Furthermore, attempts to reduce ICU costs by other mechanisms, such as reduction in lengths of stay, have proven to be difficult.

The concern over the financial effect of new therapies in the ICU is so intense that scrutiny begins even before therapies are approved by the Food and Drug Administration (FDA). Before ever gaining approval, the antiendotoxin monoclonal antibody HA-1A stimulated considerable furor and debate not only in the medical literature, but also in the national media over its anticipated cost. Currently, the FDA does not explicitly consider cost when evaluating new therapies. However, infections have placed pressure on the agency. It is perhaps as a consequence of this pressure that many recent antisepsis biologic therapies have been burdened with proving their ability to decrease mortality to gain FDA approval. This burden is greater than that faced by many less expensive therapies (e.g., antibiotics).

This book provides both a summary of this expanding field and a practical approach for clinicians to treat patients with sepsis syndrome and its complications in the critical care unit. The focus of this effort is to provide a clinical approach to specific at-risk populations who present with sepsis. This approach,

rather than an organism-directed organization, has been used because of our firm belief that one must consider the clinical and epidemiological picture of the patient before one can consider a specific microbial cause for a sepsis syndrome. This clinical approach must have a firm scientific foundation.

This book begins with a scientific review of the Latin American epidemiological approach to sepsis syndrome. It provides the principles for clinical assessment of different kinds of clinical complications as well as therapeutic strategies in this clinical field. This book is edited by four physicians with experience and interest in different aspects of the critical care point of view: three experts in the field from Colombia, as well as the international perspective of Dr. E. Faist from Germany. In this way, we believed that we could identify and recruit authoritative authors for each chapter. We are grateful to our contributing authors for all of their efforts toward this project.

Guillermo Ortiz-Ruiz — Bogotá, Colombia
Marco A. Perafán
Carmelo Dueñas Castell
Eugen Faist — Munich, Germany

Contents

List of Contributors

Carlos Arturo Alvarez, MD
Chief, Infectology Unit, Hospital Universitario San Ignacio; Department of Internal Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia

Alejandro Bruhn, MD
Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium

Carmelo Dueñas Castell, MD
Professor of Medicine, Universidad de Cartagena; Intensive Care Unit Director, Hospital Bocagrande; Intensive Care Director, Clinica Madre Bernarda, Cartagena, Colombia

Michael Cheatham, MD, FACS, FCCM
Director, Surgical Intensive Care Units, Orlando Regional Medical Center, Orlando, FL, USA

Carla Marie Clausi, MD
Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium

Jorge Alberto Cortés, MD
Infectology Unit, Hospital Universitario San Ignacio; Department of Internal Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia

Daniel De Backer, MD, PhD
Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Belgium

Rodolfo J. Dennis, MD, MSc
Professor of Medicine, Pontificia Universidad Javeriana; Department of Internal Medicine, Fundacion Cardioinfinatil, Bogotá, Colombia

E. Wesley Ely, MD, MPH
Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine; Veterans Affairs Tennessee Valley Geriatric Research, Education, and Clinical Center, Nashville, TN, USA

Eugen Faist, MD
Professor, Department of Surgery, Klinikum Grossharern, University of Munich, Munich, Germany

Timothy D. Girard, MD
Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

Marco A. González, A., MD
Department of Critical Care Medicine, Medellín Clinic and Universidad Pontificia Bolivariana, Medellín, Colombia

Marcela Granados, MD, FCCM
Director, Fellowship Program in Critical Care, Section of Critica Care Medicine, Universidad Del Valle, Cali, Colombia

Rao Ivatury, MD
Professor, Department of Surgery, Director, Trauma, Critical Care and Emergency Surgery, Virginia Commonwealth University Medical Center, Richmond, VA, USA

Fabián Jaimes, MD, MSc, PhDc
Assistant Professor of Medicine and Clinical Epidemiology, Universidad de Antioquia, Medellín, Colombia

Anand Kumar, MD, FRCPC
Associate Professor of Medicine, Section of Critical Care Medicine, Health Sciences Center, University of Manitoba, Winnipeg, Canada; Associate Professor of Medicine, Division of Cardiovascular Diseases and CCM, Cooper Hospital/University Medical Center, University of Medicine and Dentistry, New Jersey, Camden, New Jersey, USA

Manu LNG Malbrain, MD
Director, Intensive Care Unit, ZiekenhuisNetwerk Antwerpen, Antwerp, Belgium

Cristhiaan D. Ochoa, MD
Research Fellow, Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Guillermo Ortiz-Ruiz, MD
Professor, Pulmonary and Critical Care Medicine, Universidad del Bosque; Chief, Intensive Care Unit, Hospital Santa Clara, Bogotá, Colombia

Fernando Pálizas, MD
Intensive Care Unit Director, Clinica Bazterrica, Buenos Aires, Argentina

Marco Antonio Perafán C., MD
Professor of Cardiology and Critical Medicine, Chief, Intensive Care Unit, Fundacion Clinica Shaio, Bogotá, Colombia

Michael Sugrue, MD
Director of Trauma, Liverpool Hospital, University of New South Wales, Sydney, Australia

Jean-Louis Vincent, MD, PhD, FCCP
Professor, Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium

Justin Wong, MD, FRCPC
Fellow, Section of Critical Care Medicine, Health Sciences Center, University of Manitoba, Winnipeg, Canada

1
When to Transfuse Septic Patients

Carmelo dueñas Castell

Patients who enter the intensive care unit (ICU) frequently have anemia and 70% to 95% of patients in ICU have a hemoglobin count lower than normal.[1–4]

Why Critical Patients Have Anemia

The cause of anemia is multifactorial:

1. Hemodilution. Generally due to crystalloid infusions to keep the hemodynamics parameters.
2. Increased blood loss: There are many reasons for critical patients' blood loss:
   a. Bleeding: Digestive, trauma, loss because of procedures, etc.[2–4]
   b. Phlebotomies.[3–4] Pioneer studies reported a blood loss from phlebotomies from 60 to 70 cc/day.[5] Recent publications have established some minor losses that are the result of technological advances and a more rational use of the blood.[6]
   c. Reduction of half-life of the red cells: Not much is known about the half-life of the red cells in critical patients. However, the red cell destruction can be mediated by the systemic inflammation, activation of the complement, and the macrophages.[7] Anemia of chronic disorders or anemia by inflammation reduces the half-life of the red cells to less than 90 days.[8,9]
3. Decrease or alteration in blood production: Chronic inflammatory disorders lead to a reduction in the production of red cells.[10] More than 90% of critical patients have low levels of serum iron and capacity to bind the iron[2,11] with high levels of ferritin,[5,12] although the levels of erythropoietin are only slightly increased with little evidence of response from the reticulocytes to the endogen erythropoietin.[2] There are at least four contributing factors to the erythropoietin levels[2,13–15]:
   a. Direct inhibition to the erythropoiesis by circulating inflammatory mediators, among them interleukins 1, 6, and tumor necrosis factor.
   b. Reduction of available iron.

c. Unsuitably low levels of erythropoietin.
d. Poor response of the precursor cells of the red cell to erythropoietin.[2]
Others: Deficiency of folic acid has been found in 25% of critical patients.[2]

How Much Blood Is Transfused in ICU?

More than half of the patients in ICU receive red blood cell transfusion during their stay in intensive care[3,4,16] and it can be up to 85% of patients who stay more than 1 week in ICU.[17]

Paradoxically, many patients tolerate hemoglobin levels near 7 without complications.[1–4] A liberal transfusion strategy of red blood cells, in which a transfusion is made to keep the hemoglobin above 10 g/dL, has been associated with deplorable clinic outcomes.[2–4,16]

The transfusion in clinical practice has been subjected to multiple careful examinations in the past 20 years.[2–4,18,19] But transfusion methods have not changed in the past century.[20,21]

Sepsis and Transfusion

The frequency of sepsis has increased 139% from 1979 to 1987.[22] It is estimated that 18 million people per year suffer from sepsis.[22] With a mortality of approximately 30%, sepsis is considered the leading cause of death worldwide.[23] In Table 1.1 the epidemiologic studies that evaluate sepsis are shown. From them, the importance of this pathology in critical patients can be seen.

The recommendations and present practices to use blood components to treat sepsis are based on the extrapolation of results of heterogeneous groups of critical patients, from studies in noncritical patients and from consensus guides.[29] In an

Table 1.1. Sepsis Epidemiologic Studies Worldwide

Author, year (reference)	Countries	Number of ICU entries evaluated	Incidence	Mortality
Alberti, 2002[24]	6 European countries, Canada, Israel	14,364	21.1%	22.1% vs. 43.6%
Padkin, 2003[25]	England, Wales and, Northern Ireland	56,673	27.1%	35% vs. 47%
Annane, 2003[26]	France	100,554	8.2%	60.1%
EPISEPSIS, 2004[27]	France	3,738	14.6%	35% vs. 41.9%
Finfer, 2004[28]	Australia and New Zealand	5,878	11.8%	26.5% vs. 32.4%

observation study in the United States, 11% of the patients with a diagnosis of sepsis entry had hemoglobin <8.[21] The optimum hemoglobin for patients with sepsis is uncertain. This is an essential aspect, as the hemoglobin in patients with sepsis varies between 8 to 10 g/dL.[29] The hemoglobin reduction in septic patients is related to different factors, as discussed above, and frequently presents in this type of patient[29]: (1) ineffective erythropoiesis, and (2) hemodilution, a reduction of 1–3 g in hemoglobin is expected during the reanimation from septic shock with crystalloids and colloids.[29]

In the majority of patients, this grade of anemia is tolerated well as the reduction in the viscosity decreases the afterload, increases the venous return, and increases the beating volume and the cardiac output.[29] The reduction in the blood viscosity can compensate for other rheological changes of the septic patients, making the microvascular flow easy. However, different factors can affect the capacity of the patient to tolerate the reduction in the hematocrit and these should be taken into account:

1. The cardiac disorder, when presented in the septic patient, because it can limit the compensation of the cardiac output as a result of reduced viscosity.[29]
2. In hypermetabolic stages, the increase in the cardiac output may not be enough to compensate the reduction in the oxygen-carrying capacity caused by the anemia.
3. The incapacity to extract oxygen related to anatomic anomalies, such as coronary illness or physiological changes due to sepsis, which can cause major oxygen dependence.[30,31]

The transfusion risks are well described and should be similar in septic patients. However, secondary immunosuppression to transfusion can be particularly important in septic patients. Thus, an increase of nosocomial infection with poor prognosis in transfused patients has been reported.[30–36]

It is not easy to establish a causal association between transfusion and clinical outcomes due to the factors of confusion and because of the design of the studies.[37,38] However, the literature suggests an increase in mortality in transfused patients.[29–38] Later we will review the complications caused by red blood cell transfusion.

What Is the Appropriate Hemoglobin Level at Which to Transfuse Red Blood Cells in Patients with Sepsis?

The optimal level of hemoglobin in severe sepsis has not been investigated specifically. For this reason the final decision must be based on wise and reasonable analysis of the risks and benefits of the anemia compared to the risks and benefits of the transfusion.

It is believed that red blood cell transfusion increases the oxygen-carrying capacity, benefits the tissues, and minimizes or prevents ischemia. The transfusion effects in septic patients have been evaluated in different studies (see Table

1.2).[39–48] From these studies it can be surmised that red blood cell transfusion obviously improves the hemoglobin level and increases the oxygen-carrying capacity for the tissues, but the changes in the consumption of oxygen are very erratic, the improvement of the tissue oxygenation is not demonstrated, and it has not generated favorable clinical outcomes.[39–48]

At the same time, transfusion increases the pulmonary vascular resistance and the intrapulmonary shunt, consequences that can be catastrophic in the septic patient.[29]

The Spanish group also did not find benefit with the use of supranormal oxygen values in 63 patients with severe sepsis and septic shock.[49] On the contrary, there was an increase of 13% in mortality in this transfused group.

A possible explanation for the poor results in cellular oxygenation derived from red blood cell transfusion is that the cells have been stored in blood banks. The European and American studies on transfusions demonstrate that the time of storage of the transfused blood was 16 days for the European study and 21 days for the American study.[3,21,29,50]

A study of septic patients showed that the stored red cells do not improve the oxygen-carrying capacity, have reduced levels of 2,3-disphosphoglycerate, and

TABLE 1.2. Studies that Evaluate the Effect of the Transfusion on the Oxygen-Carrying Capacity and Its Consumption

Study	Number of patients	Transfusion	Hemoglobin change	Results
Gilbert, 1986[39]	17	To get Hb 10–12	8.6 to 10–12	Increase of DO2 and VO2 only in those with high lactate
Mink, 1990[40]	8	8–10 cc/kg in 1–2 h	10.2 to 13.2	Increase in DO2 but not increase in VO2
Lucking, 1990[41]	7	10–15 cc/kg in 1–3 h	9.3 to 12.4	Increase in DO2, VO2
Conrad, 1990[42]	19	591 cc in 4.2 h	8.3 to 10.7	Increase in DO2 but not in VO2
Steffes, 1991[43]	21	1–2 U in 2 h	9.3 to 10.7	Increase in DO2 and VO2 in normal lactate
Silverman, 1992[44]	19	2 U	8.4 to 10.6	Increase in DO2 but not in VO2
Marik, 1993[45]	23	3 U 90–120 min	9.0 to 11.9	Increase in DO2 but not in VO2. Increase in SVR and PVR
Lorente, 1993[46]	16	800 cc in 90 min	9.6 to 11.6	Increase in DO2 but not in VO2. Increase in SVR and PVR
Gramm, 1996[47]	19	1–2 U	9.4 to 11.5	Increase in DO2 but not in VO2
Fernandez, 2001[48]	10	1 U in 1 h	9.4 to 10.1	No improvement of lactate, DO2, VO2, increase in PVR

cannot transport oxygen.[45,50–55] Additionally, they have a reduced deformity and can produce splanchnic ischemia.[21,29,45,50,55–58] Reaffirming the infrequent use of transfused red blood cells in tissue oxygenation, a recent study of 51 patients with anemia who had cardiovascular surgery demonstrated that red blood cell transfusion only improved the systemic oxygen-carrying capacity, without generating benefits at the cellular oxygenation level. On the contrary, oxygen ventilation at 100% improved not only the systemic oxygen but also the tissue oxygen.[59] On the other hand, improving the cardiac output, with inotropics, for example, can have a better risk/cost/benefit relationship than red blood cell transfusion when looking at tissue oxygenation factors.[60]

In the United States more than 10 million units of red blood cells are transfused each year.[54] Despite great technological and scientific advances, there are still complications derived from red blood cell transfusion[54,55]:

1. Infectious complications
   a. Infections by the virus that causes acquired immune deficiency syndrome (HIV): The risk for HIV infection per unit of transfused blood has been estimated as 1 : 676,000 (from 1 : 200,000–1 : 2,000,000).
   b. Viral hepatitis: The risk of infection per unit of transfused blood is 1 : 63,000 for hepatitis B and 1 : 103,000 for hepatitis C.
   c. Other viruses: Such as parvovirus.
   d. Creutzfeldt-Jakob illness.
   e. Bacterial contamination: This is more frequent for blood platelet transfusion, but it has been described that this can occur in 1 per each million units of red blood cells transfused.[54,55]
2. Noninfectious complications[54,55]
   a. Hemolytic and alloimmunization reactions: These are less frequent each time. However, they are present in 0.5 to 1.4% of the transfusions. These reactions can cause death in 1 : 250,000 to 1 : 1,000,000 transfusions.
   b. Transfusion-related acute lung injury: It is not an usual reported complication despite being the third most frequent cause of death associated with transfusion.[56] It is a disease that generally presents within 4 h after the transfusion.[54–57] It occurs in one out of 5,000 transfusions. If all the blood components have been implicated in this pathology, it is associated more frequently with total blood transfusion, red blood cells, blood platelets, and frozen fresh plasma.[56] For its diagnosis it is necessary to exclude volume overload, sepsis, and cardiogenic pulmonary edema.[56]
   c. Immunomodulation: This refers to the phenomenon in which the allogenic blood transfusion generates an immune response in the host that makes the patient vulnerable to infections, recurrence of malignancy, or reactivation of latent viral infections.[54,55]
   d. Hypotensive transfused reactions: These are more frequent in patients who receive angiotensin-converting enzyme inhibitors or patients exposed to extracorporeal circulation.[54,55]

A recent publication states that the frequency of complications associated with transfusion depends on the development index of the country.[60] Thus, in countries with a low index of economic development, the risk of these complications is higher than in countries with a high index of development.[61] Given that increase in risk, it is suggested that in developing countries the level of hemoglobin transfused should be less than the level in developed countries.[61]

The evidence of transfusion effects from several important clinical studies can be summarized from some Canadian studies and from the CCCTG (controlled clinical trial of transfusion in critical care—Canadian Critical Care Trials Group) study, which suggests that a hemoglobin count of 7 to 9 g/dL is adequate for the majority of critical patients and this level is not associated with increased mortality.[21,29,51–53]

However, in favor of transfusion for septic patients the Rivers study proposes a hemoglobin level of 10 g/dL in patients with low oxygen venous saturation during the first 6 h of reanimation of the septic shock and severe sepsis.[62] These studies demonstrated that achieving the previously proposed goals reduced mortality rates. For every six patients who received treatment as proposed by the Rivers study, one life could be saved.[62] Patients who were transfused in those first 6 h and in whom the proposed goals were met received fewer liquids and fewer transfusions. Thus, during the first 6 h of reanimation of a septic patient, specific levels of central venous pressure (CVP), mean arterial pressure (MAP), diuresis, and mixed venous saturation should be achieved. When the mixed venous saturation is low, despite obtaining the goals of CVP (8–12 mmHg) and MAP (65–90 mmHg), the administration of red blood cells and dobutamine should be considered. This has been verified in a recent review from the Society of Critical Care Medicine (SCCM).[63]

From the Rivers study, a metaanalysis from a study in cardiovascular surgery, the literature establishes that only when goals are achieved or are normalized to the maximum early in treatment are clinical outcomes obtained.[59,64,65] This would suggest that in the studies where therapy was started too late, the usefulness of treatment has not been demonstrated. Another possible explanation for the studies that have not reported the usefulness of transfusion is that it would require 540 patients in each study group to detect clinically important differences in mortality.[52] Thus, the mortality in sepsis is not reduced by normalizing the maximum oxygen-carrying capacity because:

1. Treatment is given too late.
2. The majority of patients are not able to obtain supranormal values.
3. A cause/effect relationship between normalizing the maximum oxygen delivery and reducing mortality has not been demonstrated.
   a. If a causal effect exists, the association between the two will always be there, but it might not be found.
   b. If a causal effect does not exist, aggressively increasing the contribution of supranormal values could be dangerous.

Short-term physiological studies suggest that flow, tissue, or cellular factors can be more important than the oxygen arterial content in improving tissue oxygenation.[21,29,39,45,50] Clinical studies to evaluate the long-term physiological effects or the impact on outcomes from transfusions have not been conducted for septic patients. However, Neilipovitz and Hébert[66] suggest that the results of CCCTG are applicable in septic patients.

More than pursuing a magical number of hemoglobin, the reasonable use of laboratory tests to reduce the frequency and amount of phlebotomy, control the hemorrhage quickly, optimize the oxygenation, and guarantee an adequate intravascular volume must be performed before considering red blood cell transfusion.

Some septic patients need a high level of hemoglobin. Thus, the level of transfusion used in septic patients requires individualization and consideration of altered physiological function. Specific group of patients, such as those with myocardial ischemia or severe hypoxemia, require higher levels of hemoglobin, but the effectiveness of transfusion in these patients is inadequately characterized.[31,32] More studies are required to characterize the course of anemia in sepsis and evaluate the impact of transfusion to define a clear course of action. But while studies continue, experience and clinical judgment define the treatment.

In summary, within the first 6 hours for septic patients, using Rivers's proposed goals, obtain hemoglobin of 10 g/dL to guarantee mixed venous saturation above 70%. Once the hypoperfusion has been obtained and in the absence of special circumstances such as acute coronary illness or acute hemorrhage, a red blood cell transfusion should be made only when the hemoglobin is under 7 g/dL to keep the hemoglobin between 7 and 9 g/dL.[29]

References

1. Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. J Crit Care 2001;16:36–41.
2. von Ahsen N, Muller C, Serke S, et al. Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. Crit Care Med 1999;27:2630–9.
3. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499–507.
4. Corwin HL, Parsonnet KC, Gettinger A. RBC transfusion in the ICU. Is there a reason? Chest 1995;108:767–71.
5. Smoller BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults. Pattern of use and effect on transfusion requirements. N Engl J Med 1986;314: 1233–5.
6. Foulke GE, Harlow DJ. Effective measures for reducing blood loss from diagnostic laboratory tests in intensive care unit patients. Crit Care Med 1989;17:1143–5.
7. Jurado RL. Iron, infections, and anemia by inflammation. Clin Infect Dis 1997;25: 888–95.
8. Moldawer LL, Marano MA, Wei H, et al. Cachectin/tumor necrosis factor-alpha alters red blood cell kinetics and induces anemia in vivo. FASEB J 1989;3:1637–43.

9. Salvarani C, Casali B, Salvo D, et al. The role of interleukin 1, erythropoietin and red cell bound immunoglobulins in the anaemia of rheumatoid arthritis. Clin Exp Rheumatol 1991;9:241–6.
10. Corwin HL, Krantz SB. Anemia of the critically ill: "Acute" anemia of chronic disease. Crit Care Med 2000;28:3098–9.
11. Van Iperen CE, Gaillard CAJM, Kraaijenhagen RJ, et al. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. Crit Care Med 2000;28:2773–8.
12. Mickler TA, Longnecker DE. The immunosuppressive aspects of blood transfusion. J Intensive Care Med 1992;7:176–88.
13. Johnson CS, Cook CA, Furmanski P. In vivo suppression of erythropoiesis by tumor necrosis factor-alpha (TNF-alpha): reversal with exogenous erythropoietin (EPO). Exp Hematol 1990;18:109–13.
14. Jelkmann W, Pagel H, Wolff M, et al. Monokines inhibiting erythropoietin production in human hepatoma cultures and in isolated perfused rat kidneys. Life Sci 1992;50: 301–8.
15. Hellwig-Burgel T, Rutkowski K, Metzen E, et al. Interleukin-1beta and tumor necrosis factor-alpha stimulate DNA binding of hypoxia-inducible factor-1. Blood 1999; 94:1561–7.
16. Littenberg B, Corwin H, Gettinger A, et al. A practice guideline and decision aide for blood transfusion. Immunohematology 1995;11:88–92.
17. Groeger JS, Guntupalli KK, Strosberg M, et al. Descriptive analysis of critical care units in the United States: patient characteristics and intensive care unit utilization. Crit Care Med 1993;21:279–91.
18. Consensus Conference: Perioperative red blood cell transfusion. JAMA 1988;260: 2700–3.
19. American College of Physicians: Practice strategies for elective red blood cell transfusion. Ann Intern Med 1992;116:403–6.
20. Spence RK, Cernaianu AC, Carson J, et al. Transfusion and surgery. Curr Probl Surg 1993;30:1101–80.
21. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. Crit Care Med 2004;32:39–52.
22. Centers for Disease Control and Prevention. Current trends increase in National Hospital Discharge Survey rates for septicemia—United States, 1979–1987. MMWR 1990;39(2):31–4.
23. Slade E, Tamber PS, Vincent JL. The surviving sepsis campaign: raising awareness to reduce mortality. Crit Care 2003;7(1):1–2.
24. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 2002;28(2):108–21.
25. Padkin A, Goldfrad C, Brady AR, et al. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med 2003;31(9):2332–8.
26. Annane D, Aegerter P, Jars-Guincestre MC, et al. Current epidemiology of septic shock: The CUB-Rea network. Am J Respir Crit Care Med 2003;168(2):165–72.
27. The EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 2004; 30(4):580–8.

28. Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 2004;30(4): 589–96.
29. Zimmerman JL. Use of blood products in sepsis: An evidence-based review. Crit Care Med 2004;32:S542–7.
30. Claridge JA, Sawyer RG, Schulman AM, et al: Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg 2002;68: 566–72.
31. Chelemer SB, Prato S, Cox PM, et al. Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. Ann Thorac Surg 2002;73: 138–42.
32. Hill GE, Frawley WH, Griffith KE, et al. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a metaanalysis. J Trauma 2003;54:908–14.
33. Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma 2003;54:898–907.
34. Leal-Noval SR, Rincón-Ferrari MD, García-Curiel A, et al. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 2001;119:1461–8.
35. Taylor RW, Manganaro L, O'Brien J, et al. Impact of allogenic packed red cell transfusion on nosocomial infection rates in the critically ill patient. Crit Care Med 2002; 30:2249–54.
36. Shorr AF, Mei-Sheng D, Kelly KM, et al. Red blood cell transfusion and ventilator-associated pneumonia: A potential link? Crit Care Med 2004;32:666–74.
37. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? Blood 2001;97:1180–95.
38. Vamvaka EC, Carven JH. RBC transfusion and postoperative length of stay in the hospital or the intensive care unit among patients undergoing coronary artery bypass graft surgery: the effects of confounding factors. Transfusion 2000;40:832–9.
39. Gilbert EM, Haupt MT, Mandanas RY, et al. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Resp Dis 1986;134:873–8.
40. Mink RB, Pollack MM. Effect of blood transfusion on oxygen consumption in pediatric septic shock. Crit Care Med 1990;18:1087–91.
41. Lucking SE, Williams TM, Chaten FC, et al. Dependence of oxygen consumption on oxygen delivery in children with hyperdynamic septic shock and low oxygen extraction. Crit Care Med 1990;18:1316–19.
42. Conrad SA, Dietrich KA, Hebert CA, et al. Effect of red cell transfusion on oxygen consumption following fluid resuscitation in septic shock. Circ Shock 1990;31: 419–29.
43. Steffes CP, Bender JS, Levinson MA. Blood transfusion and oxygen consumption in surgical sepsis. Crit Care Med 1991;19:512–17.
44. Silverman HJ, Tuna P. Gastric tonometry in patients with sepsis, effects of dobutamine infusions and packed red blood cell transfusions. Chest 1992;102:184–8.
45. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993;269:3024–9.
46. Lorente JA, Landín L, dePablo R, et al. Effects of blood transfusion on oxygen transport variables in severe sepsis. Crit Care Med 1993;21:1312–18.
47. Gramm J, Smith S, Gamelli RL, et al. Effect of transfusion on oxygen transport in critically ill patients. Shock 1996;5:190–3.

48. Fernandes CJ, Akamine N, DeMarco FVC, et al. Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. Crit Care 2001;5: 362–7.
49. Alia I, Esteban A, Gordo F, et al. A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. Chest 1999;115:453–61.
50. Ward NS, Levy MM. Blood transfusion practice today. Crit Care Clin 2004;20: 179–86.
51. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion in critical care. N Engl J Med 1999;340:409–17.
52. Hébert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med 2001;29:227–34.
53. Hébert PC, Blajchman MA, Cook DJ, et al. Do blood transfusions improve outcomes related to mechanical ventilation? Chest 2001;119:1850–7.
54. Goodenough LT, Brecher ME, Kanter MH, et al. Transfusion medicine: blood transfusion. N Engl J Med 1999;340:438–47.
55. Park KW, Chandhok D. Transfusion-associated complications. Int Anesthesiol Clin 2004;42(3):11–26.
56. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury. Chest 2004;126:249–58.
57. Napolitano LM, Corwin HL. Efficacy of red blood cell transfusion in the critically ill. Crit Care Clin 2004;20:255–68.
58. Hebert PC, Van der Linden P, Biro G, et al. Physiologic aspects of anemia. Crit Care Clin 2004;20:187–212.
59. Suttner S, Piper SN, Kumle B, et al. The influence of allogeneic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension alter cardiac surgery. Anesth Analg 2004;99:2–11.
60. Linden PA, De Hert S, BS, De Groote F, et al. Comparative effects of red blood cell transfusion and increasing blood flow on tissue oxygenation in oxygen supply-dependent conditions. Am J Respir Crit Care Med 2001;163:1605–8.
61. Marcucci C, Madjdpour C, Spahn DR. Allogeneic blood transfusions: benefit, risks and clinical indications in countries with a low or high human development index. Brit Med Bull 2004;70:15–28.
62. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
63. Rhodes A, Bennett ED. Early goal-directed therapy: an evidence-based review. Crit Care Med 2004;32:S448–50.
64. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002;30:1686–92.
65. Pölönen P. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000;90:1052–9.
66. Neilipovitz D, Hébert PC. Blood transfusion and sepsis. In: Vincent JL, Carlet J, Opal SM, eds. The Sepsis Text. New York: Kluwer, 2002;23:401–10.

2
Sepsis Occurrence and Its Prognosis in Latin America

Fabián Jaimes and Rodolfo J. Dennis

At the annual congress of the European Society of Intensive Care Medicine (ESICM, October 2002), the *Surviving Sepsis Campaign* issued their "Barcelona Declaration," a call for global action against sepsis. The campaign, a collaborative effort of the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the International Sepsis Forum (ISF), estimates that the number of sepsis cases has now reached 18 million annually. With a mortality rate of close to 30%, sepsis is still considered a leading cause of death worldwide.[1] As such, any effort made toward improving prevention, diagnosis, and treatment represents a potentially valuable response to an urgent need.

This chapter provides an overview of sepsis global epidemiology, as well as an outline regarding the description and characterization of the problem in Latin America. It should be noted that there are specific characteristics between developed and developing countries that may impact the occurrence of sepsis and its consequences. Specifically, Latin America exhibits substantial differences in ethnic background, cultural heritage, health services, and clinical research. These features support the importance of exploring, from an epidemiologic and clinical point of view, the sepsis panorama in our setting.

In the Latin American context, the approach to the problem has been limited and in many instances susceptible to bias, in the estimates obtained. Unfortunately, it is unlikely that this situation represents a benign scenario of perhaps lower incidence or better prognosis. More studies are needed in the Latin American context if an accurate description of the epidemiology of sepsis, including its risk factors and clinical course, is to be obtained in the different populations at risk. These studies should build on the studies already conducted, and should address the limitations observed.

Sepsis Definition

Any description of the occurrence, determinants, and consequences of sepsis needs to start with the caveats surrounding its definition, which we attempt to provide next. Over the past three decades, the syndrome now commonly referred to as "sepsis" has alternately been called septicemia,[2] sepsis syndrome,[3] and,

simply, sepsis, the last definition described jointly with the closely related concept of systemic inflammatory response syndrome (SIRS).[4] A 1992 statement from the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference[4] hypothesized that sepsis is a systemic response to infection, the latter defined as a process whereby pathogenic or potentially pathogenic microorganisms invade normally sterile tissue, fluids, or body cavities. According to this definition, a diagnosis of sepsis requires the presence of both infection, usually caused by bacteria, and SIRS. Following the same model, sepsis with evidence of organic dysfunction would be characterized as severe sepsis; and sepsis with acute circulatory failure characterized by persistent hypotension unexplained by other causes, would be defined as septic shock.[4] SIRS is generally considered to be present when subjects are shown to have more than one of the following four clinical findings:

1. Body temperature >38°C or <36°C;
2. Heart rate >90 beats min^{-1};
3. Hyperventilation, evidenced by a respiratory rate >20 breaths min^{-1} or $PaCO_2$ <32 mm Hg;
4. White blood cell (WBC) count >12,000 cells μL^{-1} or <4,000 μL^{-1} or with >10% immature forms.

However, as Jaimes et al. showed in a recent work[5] and has been pointed out by other authors,[6,7] despite the fact that the SIRS definition is inclusive to the extent that a systemic inflammatory response can be triggered by a variety of conditions (infectious and noninfectious), this particular combination of criteria is neither specific nor sensitive enough to be useful for medical decision making, or to establish an accurate operative definition for the syndrome.

Today, it seems clear that even though no epidemiological evidence exists to support a change in the syndrome's definition, the list of signs and symptoms of sepsis could be more inclusive to reflect clinical bedside experience. According to the last International Sepsis Definition Conference,[8] a diagnosis of sepsis should be considered in the presence of a documented or suspected infection, concurrent with some markers of general illness, inflammation, hemodynamic disturbance, organ dysfunction, and tissue perfusion abnormalities (Table 2.1).

Notwithstanding the lack of conclusive criteria to define *sepsis*, the definitions of *severe sepsis* (sepsis complicated by organ dysfunction) and *septic shock* (systolic blood pressure below 90 mm Hg or a reduction of >40 mm Hg from baseline despite adequate volume resuscitation, in the absence of other causes for hypotension) remain without controversy. In fact, most studies about sepsis epidemiology, and virtually all recent clinical trials testing new therapies, have focused on these two study populations. Unfortunately, this simple classification and range of definitions have strong limitations for an accurate characterization of sepsis, mainly for the early staging of patients. Therefore, the International Sepsis Definitions Conference,[8] on the basis of contributions previously arising in the Fifth Toronto Sepsis Roundtable,[9] has proposed a classification scheme called PIRO. This staging system is intended for use in patient stratification based on their *P*redisposition, the type and extent of the *I*nfection, the nature and magnitude of the host *R*esponse,

TABLE 2.1. Potential Variables Associated with Sepsis (modified from reference 8)

General variables
Temperature >38.3°C or <36°C
Heart rate >90 beats min^{-1}
Tachypnea (respiratory rate >20 breaths min^{-1} in adults)
Altered mental status
Inflammatory variables
WBC >12,000 μL^{-1}, <4,000 μL^{-1} or with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
Systolic blood pressure <90 mm Hg or mean arterial blood pressure <70 mm Hg
Mixed venous oxygen saturation >70%
Cardiac index >3.5 L*min^{-1}
Organ dysfunction variables
PaO_2/FIO_2 <300
Urine output <0.5 mL*kg^{-1}*hr^{-1} or creatinine increase >0.5 mg/dL
International normalized ratio (INR) >1.5 or aPTT >60 sec
Platelet count <100,000 μL^{-1}
Plasma total bilirubin >4 mg/dL
Tissue perfusion variables
Hyperlactatemia >1 mmol/L
Decreased capillary refill or mottling

and the degree of associated *O*rgan dysfunction. A comprehensive empirical evaluation and further validation of the PIRO approach, however, is needed.

Global Perspective

The first relevant study that raised public awareness regarding the burden of sepsis, came from the U.S. Centers for Disease Control and Prevention (CDC) in 1990.[10] The data were obtained from the National Hospital Discharge Survey (NHDS) of CDC's National Center for Health Statistics (NCHS). The report used the discharge diagnosis of *septicemia* (a systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood; International Classification of Diseases, Ninth Revision, Clinical Modification codes 038.0–038.9).

The report included all records from 1979 through 1987, of subjects 1 year of age or older in which a discharge diagnosis of septicemia was recorded. In the 9-year period, septicemia rates increased 139%, from 73.6 per 100,000 (164,000 discharges) to 175.9 per 100,000 (425,000 discharges). Although the septicemia rate increased for all age groups, the increase was greatest (162%) for persons 65 years of age or older (from 326.3 per 100,000 in 1979 to 854.7 per 100,000 by 1987). The fatality rate for patients with a discharge diagnosis of septicemia declined during the study period for all age groups, from 31.0% to 25.3%. However, even by 1987, patients were at significantly greater risk for death if septicemia was one of the discharge diagnoses (relative risk: 8.6; 95% confidence interval: 8.14–9.09).[10]

The most comprehensive study on the clinical significance of the early stages of the septic syndrome, however, came in 1995 from Rangel-Fausto et al. at the University of Iowa Hospital and Clinics.[11] The authors assessed the incidence of SIRS, sepsis, severe sepsis, and septic shock among 3,708 patients admitted during a 9-month period in 3 intensive care units (ICUs) and 3 wards of a 900-bed teaching hospital. They found that 68% of patients studied met at least two criteria for SIRS at some point during their hospital stay. Of those patients with SIRS, 26% developed microbiologically confirmed sepsis, 18% developed severe sepsis, and 4% developed septic shock. Positive blood cultures were found in 16.5% of samples drawn from patients with sepsis, in 25.4% of those with severe sepsis, and in 69% of those with septic shock. A noticeable finding was that less than 50% of all episodes were documented microbiologically, although this proportion increased from 42% when patients only met criteria for SIRS, to 57% in patients with septic shock. Since clinical suspicion of infection is deemed as enough evidence to start antibiotics, the precise cause of the systemic inflammatory response in these culture-negative populations is generally unknown. However, they had similar morbidity and mortality rates when compared with the respective culture-positive populations.[11]

Clearly, these definitions are self-contained, as severe sepsis includes sepsis and in turn, sepsis includes SIRS. Therefore, only in a tautological sense may we consider a truthful continuum through different stages of an inflammatory response from SIRS to septic shock. Indeed, in the study by Rangel-Fausto et al., among patients with sepsis ($n = 649$) just 44% ($n = 285$) had earlier met at least two criteria for SIRS, and of those who met the criteria for severe sepsis (culture-proven; $n = 467$), 271 (58%) had been classified previously as sepsis or SIRS. On the other hand, however, 32% and 36% of patients having 2 or 3 SIRS criteria, respectively, developed culture-proven sepsis by day 14, and 45% of those with 4 criteria developed sepsis between day 14 and 21 thereafter. Conversely, microbiologically confirmed sepsis appears at high risk of evolving rapidly to severe sepsis, as shown by the 64% proportion of cases subsequently developing severe sepsis within a median of 1 day after sepsis. Thus, even without a categorical progression, it is clear there is a close relationship among clinical stages reflecting some degree of systemic inflammation and the presence of infection. Independent of whether infection is finally confirmed, the outcome seems similar, in terms of mortality and most of the organ dysfunctions, within each corresponding stage.

In another similar study published in 1997, Sands et al. evaluated the incidence of the "sepsis syndrome" in both the ICU and ward population at 8 academic tertiary care medical centers.[12] Each center monitored a weighted random sample of ICU patients and non-ICU patients who had blood cultures drawn during a 15-month period. Sepsis syndrome was defined as the presence of either a positive blood culture or the combination of fever, tachypnea, tachycardia, clinically suspected infection, and any one of seven confirmatory criteria, all of them related to organ dysfunction. In total, 12,759 patients were monitored and 1,342 episodes of sepsis syndrome were documented. The extrapolated, weighted estimate of hospital-wide incidence of sepsis syndrome was 2.0 ± 0.16 cases per 100 admissions.

The unadjusted attack rate for sepsis syndrome between individual centers ranged from 1.1 to 3.3 cases per 100 admissions. Patients in ICUs accounted for 59% of total extrapolated cases, non-ICU patients with positive blood cultures for 11%, and non-ICU patients with negative blood cultures for 30%. Septic shock was present at onset of the sepsis syndrome in 25% of patients. Bloodstream infection was documented in 28% of patients, and the total mortality at day 28 was 34%.

It is generally agreed that the most compelling evidence of systemic infection is bacteremia. For this reason, some studies on the incidence of sepsis have focused on bacteremia. Requesting blood cultures, as in the study of Sands et al. mentioned above, is considered a proxy for risk of infection or clinical sepsis. Although clinically appealing and intuitively sound, this last "surrogate marker" is not reproducible enough and should only be considered with caution. There are patients with potential infection who may not have a blood culture performed, and other patients without infection who have cultures requested inappropriately. Furthermore, since patients with comorbidities are often suspected of being at increased risk for infection, clinicians may have a lower threshold for sending blood cultures in these patients. Therefore, any analysis about these cases should take into account the real denominator of population at risk. Nevertheless, positive blood cultures clearly identify infected individuals at higher risk of mortality, and appropriate inferences may be derived from this study population.

Despite the widely ranging definition, two recent reports have added important information regarding the epidemiology of sepsis in the United States in the past 20 years.[13,14] Angus et al., based on a patient register from seven state hospitals' discharge databases during 1995, gave a national estimate for severe sepsis of 3 cases per 1,000 population and 2.26 cases per 100 hospital discharges.[13] Almost 70% (510,000 patients) of severe sepsis cases received intensive care. The estimated mortality rate was 28.6%, or 215,000 deaths nationally, and the average cost per case was $22,100, with an annual total cost of U.S.$16.7 billion. Martin et al., with a more restrictive definition including only a few codes from the ICD-9-CM and working on data from the NHDS, demonstrated an increase in the incidence of sepsis from 82.7 cases per 100,000 population in 1979 to 240.4 per 100,000 population in 2000.[14] This represents an annualized increase of 8.7%. The authors also described a decline in overall in-hospital mortality, from 27.8% during the period from 1979 through 1984, to 17.9% during the period from 1995 through 2000, yet the absolute number of deaths continued to increase.

These results, as well as those from the first CDC report,[10] may be limited by the quality of the database and the inability to audit those data. Moreover, the accuracy of ICD-9-CM coding for the identification of specific medical conditions, and sepsis in particular, remains controversial.[15] Although administrative datasets have become essential resources for epidemiological investigations in which the prospective identification of patients is difficult or not feasible, strict reliance on them for sepsis surveillance or research planning may be prone to substantial random and systematic error.

The first European hospital-wide epidemiologic study in bacteremia and sepsis of which we are aware was a French multicenter study conducted in 1993 in 24

public or public-affiliated hospitals.[16,17] The authors performed a 2-month prospective survey of 85,750 admissions to adult wards and ICUs and recorded an overall incidence rate of bacteremia of 9.8 per 1,000 admissions, more than eightfold higher in ICUs (69/1,000) than in wards (8.2/1,000). Of the 842 bacteremic episodes detected, 63% occurred in medical wards, 19% in ICUs, and 18% in surgical wards. The authors considered that extrapolating these results to the whole country would give a figure of approximately 67,500 bacteremic episodes per year.[18] Of note, nearly half of bacteremic episodes were of nosocomial origin, and although ICU patients were at much higher risk of severe sepsis than ward patients, bacteremic severe sepsis was proportionally less often encountered in ICU than in non-ICU patients. This suggests, as a remarkable concern vis-à-vis previous studies, an important subset of patients besides those in intensive care unit, which traditionally has been considered the natural setting for sepsis occurrence.[19]

Despite the broad distribution of sepsis and severe bacterial infections among hospitalized patients, all of the recent studies outside the United States have considered exclusively patients admitted to ICUs.[20–24] Whether on prospective cohorts[20,23,24] or with administrative databases,[21,22] all but one[20] have focused on severe sepsis or septic shock (Table 2.2).

The wide range of incidence and mortality rates may reflect different definitions of outcome measures, as well as differences in data collection procedures or methodological approaches. Three of these studies additionally provide some

Table 2.2. Worldwide Studies on the Epidemiology of Sepsis

Author, year (reference)	Country	Research design	Number of ICU admissions screened	Outcome	Incidence	Mortality
Alberti, 2002 (20)	Six European countries, Canada, and Israel	Prospective cohort study	14,364	Infectious episodes	21.1%	22.1% vs. 43.6%[a]
Padkin, 2003 (21)	England, Wales, and Northern Ireland	Administrative database	56,673	Severe sepsis	27.1%	35% vs. 47%[b]
Annane, 2003 (22)	France[c]	Administrative database	100,554	Septic shock	8.2%	60.1%
EPISEPSIS, 2004 (23)	France	Prospective cohort study	3,738	Severe sepsis or Shock	14.6%	35% vs. 41.9%[d]
Finfer, 2004 (24)	Australian and New Zealand	Prospective cohort study	5,878	Severe sepsis	11.8%	26.5% vs. 32.4%[e]

[a] Community vs. hospital acquired infection.
[b] ICU vs. hospital mortality.
[c] Paris and its suburbs.
[d] 30 days vs. 2 months mortality.
[e] ICU vs. 28-day mortality.

understanding about time trends.[21–23] Padkin et al. collected data from the British Intensive Care National Audit and Research Centre from 1996 to 1999.[21] They described an increase in the incidence of severe sepsis from 25.9% in 1996 to 29.7% in 1999. In the same period, there was a slight decrease in hospital mortality rates, from 50.2% to 47%. The CUB-Réa Network[22] is a database with information from 35 ICUs in Paris and its suburbs. It found that the overall frequency of septic shock increased from 7 to 9.7 per 100 admissions, from 1993 to 2000, respectively. The crude mortality rate in the same population declined from 62.1% in 1993 to 55.9% in 2000. Similarly, the EPISEPSIS Study Group[23] compared the current findings with their previous studies performed in 1993.[16,17] The data suggest an increase in the attack rate of severe sepsis in ICU patients over the past decade, from 8.4% and 6.3% to 14.6% and 9%, for clinically and microbiologically documented severe sepsis, respectively. The 42% hospital mortality rate recorded in the current study is substantially lower than the 59% corresponding rate recorded in the previous period.

In short, a scan of the global panorama clearly shows that sepsis is a common and frequently fatal condition in developed countries. It consumes considerable resources, and although the overall mortality rate among patients with sepsis seems to be declining, the incidence and the number of sepsis-related deaths have increased significantly over the past two decades.

The Latin American View

For this view of the panorama of sepsis in Latin America, three databases were systematically searched during 2004 by one of the authors (FJ): PUBMED (National Library of Medicine), EMBASE (EMBASE.com[SM]), and LILACS (Literatura Latino Americana e do Caribe em Ciências da Saúde). The latter is produced by Biblioteca Regional de Medicina (BIREME) and the Pan-American Health Organization (PAHO), at the Latin American and Caribbean Health Sciences Information Center in São Paulo, Brazil, since 1982 (www.bireme.org/ accessed May 2004).

Different combinations of the terms "sepsis," "septicemia," "bacteremia," "sepsis syndrome," "epidemiology," "incidence," and "prevalence" were used for the search strategy. For PUBMED and EMBASE, the search strategy also included additional terms for "Latin America," "South America," "Central America," or restriction to Spanish language. The first step was the screening of more than 1,000 potentially related titles, most of them from LILACS, and the second stage was a detailed review of selected abstracts. This process yielded 20 references from studies published from 1990 to 2004.[5,25–43] A relevant finding was the significant number of high-quality papers regarding neonatal sepsis and severe infections in pediatric populations. For adult patients, however, the number and scope of the investigations appeared to be more limited. Additionally, there was available only the abstract for one study,[25] and 7 out of the remaining 18[26,28,29,34,38,40,41] analyzed sepsis as a secondary outcome among a wide definition of nosocomial infections (Table 2.3).

TABLE 2.3. Latin American Research on Sepsis

Author, year (reference)	Country	Design	Study population (*n*)	Main clinical outcome	Frequency of sepsis or bacteremia (denominator)	Mortality
Zanon, 1990 (25)[a]	Brazil	Administrative registers	Discharges at 10 hospitals (*n* = 23,079)	Septicemia	3/1,000 vs. 7/1,000[b] (discharges)	45.8% vs. 58.2%[b]
Del Rio, 1993 (26)	Cuba	Surveillance	Surgical patients—community hospital (*n* = 324)	Nosocomial infection	184/324[c] (nosocomial infections)	Not reported
Pazmiño, 1993 (27)	Ecuador	Prospective case series	Sepsis patients at ICU (*n* = 435)	Characterization of sepsis patients	Not reported[c]	50.6%
Ponce de León, 1994 (28)	Mexico	Case control	Patients with nosocomial bacteremia (*n* = 245)	Risk factors for primary nosocomial bacteremia	25/1,000 (hospital discharges)	40%
Bembibre, 1997 (29)	Cuba	Surveillance	Patients with nosocomial infection (*n* = 299)	Nosocomial infection	91/299[c] (nosocomial infections)	Not reported
Arcienega, 1998 (30)	Bolivia	Retrospective case series	Sepsis patients at ICU (*n* = 222)	Characterization of sepsis patients	Not reported	30%
Jaimes, 1998 (31, 32)[d]	Colombia	Retrospective case series	Patients with bacteremia (*n* = 432)	Characterization of bacteremic patients	1.7/100 vs. 7/100[e] (hospital discharges)	38%
Hernandez, 1999 (33)	Chile	Cross-sectional	SIRS[f] plus organ dysfunction at 5 ICUs (*n* = 102)	Clinical course of severe SIRS vs. severe sepsis	79/518 (ICU admissions)	43% vs. 51%[g]
Ponce de León, 2000 (34)	Mexico	Cross-sectional	Admissions at 254 ICUs (*n* = 895)	1-day prevalence of infections	294/895 (ICU admissions)	33.6%
Zapata, 2001 (35, 36)[d]	Colombia	Prospective cohort study	Patients with non traumatic SIRS[f] at 2 hospitals (*n* = 533)	Sepsis	Not reported	23.5%

Sifuentes, 2001 (37)	Mexico	Cross-sectional	Patients with bacteremia ($n = 600$)	Characterization of bacteremic patients	3,428/19,530[h] (blood cultures)	28%
Morales, 2001 (38)	Cuba	Cross-sectional	Hospitalized patients[9]	Nosocomial infections	4/100[c,i] (discharges)	Not reported
Bilevicius, 2001 (39)	Brazil	Retrospective case series	Admissions at ICU ($n = 249$)	Sepsis	54/249 (ICU admissions)	56%
Lujan, 2002 (40)	Cuba	Surveillance	Patients with nosocomial infections at 3 hospitals[i]	Nosocomial infections	5.3/100[c,i] (discharges)	Not reported
Cordero, 2002 (41)	Cuba	Retrospective case series	Patients with nosocomial infection ($n = 1,241$)	Nosocomial infections	219/1,241[c] (nosocomial infections)	Not reported
Notario, 2003 (42)	Argentina	Retrospective case series	Patients with bacteremia ($n = 596$)	Characterization of bacteremic patients	596/6605[h] (blood cultures)	Not reported
Jaimes, 2003 (5)	Colombia	Prospective cohort study	Patients admitted at two emergency rooms ($n = 734$)	Sepsis	657/734 (infection as cause for admission)	30.7%
Jaimes, 2004 (43)	Colombia	Cross-sectional	Patients with request of blood cultures ($n = 500$)	Nosocomial bacteremia	89/500[h] (blood cultures)	22.6% vs. 36%[j]
Silva, 2004 (47)	Brazil	Prospective cohort study	Patients admitted to ICUs ($n = 1383$)	Sepsis, severe sepsis, septic shock	Sepsis incidence: 61.4 per 100 patient-days	Sepsis, severe sepsis, septic shock: 34, 47 & 52%.

[a] Only abstract available.
[b] Community vs. nosocomial acquired.
[c] The definition of sepsis was not clearly established.
[d] Two different studies with the same population.
[e] Positive blood cultures vs. requested blood cultures.
[f] Systemic inflammatory response syndrome.
[g] ICU vs. hospital mortality.
[h] Positive blood cultures among total requested.
[i] Only rates reported.
[j] Negative vs. positive blood cultures.

The studies reviewed were extremely heterogeneous in design, population, sample size, end-points, and subject follow-up. Furthermore, the fundamental challenge of lack of consensus on the clinical definition of sepsis seems more critical in the Latin American literature. Thus, it is impossible to infer any overall estimator about the magnitude of the problem in Latin America. On the other hand, some data suggest that in terms of frequency and mortality, the picture of sepsis and severe systemic infections may be even worse than in developed countries. What follows is a brief analytical description of the most relevant studies encountered.

Zanon et al., in 10 hospitals during 1990,[25] using ICD-9-CM codes for septicemia, estimated a mortality of 46% and 58% for community and nosocomial acquired sepsis, respectively. In spite of potential underreporting, the incidence of bacteremia in these hospitals were roughly similar to European estimates.[16] Studies performed at ICUs[27,30,33,34,39] between 1993 and 2001 demonstrated a mortality ranging from 33.6% in a cross-sectional study by Ponce de Leon et al. in Mexico[34] to 56% in a retrospective case-series by Bilevicius et al. in Brazil.[39]

All studies, except one,[33] recruited a general population of sepsis patients, without restrictions to organ dysfunction (i.e., severe sepsis) or septic shock. Thus, a higher mortality rate on this latter subset is to be expected, which has comprised the usual study population for European and North American studies.[13,22–24] Two prospective cohort studies from Colombia[5,35] in infected patients admitted to the emergency room with SIRS found a mortality rate between 24% and 31%, which increased to 40% for patients in the ICU or with positive blood cultures.[36] Ponce de León et al., at a tertiary center in Mexico,[28] described a rate of nosocomial bacteremia without an identifiable source—called "primary bacteremia"—of 25/1,000 discharges in 1994, with a mortality rate of 40%. This subset of primary bacteremia may represent less than 20% of the total affected population with bacteremia or sepsis.[44,45] Jaimes et al.[31,32] estimated that severe infections and bacteremia were the main causes for emergency admission in 7 out of 100 patients at a university hospital, and blood cultures were requested in 2 out of 10 inpatients at some time during their hospitalization.[32,43] Silva et al.,[47] in a good study recently conducted in 5 mixed ICUs in Brazil, prospectively followed 1,383 consecutive adult admissions for the development of sepsis. Sepsis and related conditions were diagnosed following the ACCP/SCCM criteria. In this highly selected population of critically ill patients, the incidence density for sepsis, for the total cohort, was 57.9 per 1,000 patient-days, and for those surviving longer than 24 hours, 61.4 per 1,000 patient-days. They found a trend for increased mortality from sepsis, severe sepsis, and septic shock: 34%, 47%, and 52%, respectively.

Sifuentes et al.,[37] at a referral center in Mexico, conducted the only study that allows for some approach regarding time trends. They described an overall frequency of bacteremia of 18% among patients with blood cultures. The overall mortality rates were 70% and 30% for nosocomial and community acquired bacteremia, respectively. They randomly analyzed samples of positive blood

cultures in three different periods: from 1981 to 1984, from 1985 to 1988, and from 1989 to 1992. Interestingly, the overall mortality rate remained practically without change through the three study periods: 29.5%, 27.5%, and 27%, respectively. The authors pointed out that the mortality rate remained constant, even after adjusting for source of bacteremia (community or nosocomially acquired, figures not shown in the original report).

As an additional concern, only the studies by Hernandez et al.[33] and Silva et al.[47] showed a mean age higher than 50 years in patients with sepsis (mean = 61; range = 18–87, and mean = 66 years, IQR: 48–78 years, respectively). All of the remaining study populations, whether in ICUs, general wards, or emergency rooms, exhibited mean ages at or below 50 years. These results strongly contrast with North American and European studies, in which the mean age has been at or above 60 years.[13,14,20,22,24] Whatever demographic or epidemiologic explanation we have, it seems that we are facing sepsis in a younger and probably "healthier" population, but with morbidity and mortality rates that are at least as high as those from developed countries.

Finally, Ponce de Leon et al.,[34] in a cross-sectional study in 254 multidisciplinary ICUs through Mexico in 1995, demonstrated a 1-day point prevalence of 16% and 17% for sepsis and severe sepsis or septic shock, respectively. For diseases with short duration and early mortality, such as sepsis, prevalence studies may underestimate their frequency, and they do not provide a true estimate of risk. Even so, these figures are higher than those corresponding in prospective cohort studies performed at European and Australian ICUs.[23,24,46]

Conclusion

Sepsis is an increasing problem everywhere. It bears a high burden of mortality, morbidity, and resource consumption. In the Latin American context, unfortunately, the approach to the problem has been marginal and in many instances prone to bias in the estimates obtained. Unfortunately, it is unlikely that this situation represents a benign scenario of perhaps lower incidence or better prognosis. Instead, it seems that the first two points of the action plan stated by the "Barcelona Declaration"[1] are particularly necessary in our setting:

- "Increase awareness of health care professionals, governments, health and funding agencies, and the public of the high frequency and mortality associated with sepsis."
- "Improve the early and accurate diagnosis of sepsis by developing a clear and clinically relevant definition of sepsis and disseminating it to our peers."

More studies are needed in the Latin American context, if an accurate description of the occurrence of sepsis, including its risk factors and clinical course, is to be obtained in different populations at risk, not only in patients admitted to ICUs. These studies should build on the studies conducted, but addressing the limitations observed.

References

1. Slade E, Tamber PS, Vincent JL. The Surviving Sepsis Campaign: raising awareness to reduce mortality. Crit Care 2003;7(1):1–2.
2. Pierce G, Murray PR. Current controversies in the detection of septicemia. Eur J Clin Microbiol 1986;5:487–91.
3. Bone RC, Fisher CJ Jr, Clemmer TP, et al. Sepsis syndrome: a valid clinical entity. Methylprednisolone Severe Sepsis Study Group. Crit Care Med 1989;5:389–93.
4. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
5. Jaimes F, Garces J, Cuervo J, et al. The systemic inflammatory response syndrome (SIRS) to identify infected patients in the emergency room. Intensive Care Med 2003;29:1368–71.
6. Vincent J-L. Dear SIRS, I'm sorry to say that I don't like you. Crit Care Med 1997;25:372–4.
7. Marshall JC. SIRS and MODS: What is their relevance to the science and practice of intensive care? Shock 2000;14:586–9.
8. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.
9. Marshall JC, Vincent J-L, Fink MP, et al. Measures, markers, and mediators: Toward a staging system for clinical sepsis. A report of the Fifth Toronto Sepsis Roundtable, Toronto, Ontario, Canada, October 25–26, 2000. Crit Care Med 2003;31: 1560–7.
10. Centers for Disease Control and Prevention. Current Trends Increase in National Hospital Discharge Survey Rates for Septicemia—United States, 1979–1987. MMWR 1990;39(2):31–4.
11. Rangel-Frausto S, Pittet D, Costignan M, et al. The natural history of the systemic inflammatory response syndrome. JAMA 1995;273:117–23.
12. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. Academic Medical Center Consortium Sepsis Project Working Group. JAMA 1997;278(3):234–40.
13. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303–10.
14. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United Sates from 1979 through 2000. N Engl J Med 2003;348:1546–54.
15. Ollendorf DA, Fendrick AM, Massey K, et al. Is sepsis accurately coded on hospital bills? Value Health 2002;5(2):79–81.
16. Brun-Buisson C, Doyon F, Carlet J. Bacteremia and severe sepsis in adults: a multicenter prospective survey in ICUs and wards of 24 hospitals. French Bacteremia-Sepsis Study Group. Am J Respir Crit Care Med 1996;154(3):617–24.
17. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995;274(12):968–74.
18. Brun-Buisson C. The epidemiology of the systemic inflammatory response. Intensive Care Med 2000;26 Suppl 1:S64–74.
19. Moss M, Martin GS. A global perspective on the epidemiology of sepsis. Intensive Care Med 2004;30(4):527–9.

20. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 2002;28(2):108–21.
21. Padkin A, Goldfrad C, Brady AR, et al. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med 2003;31(9):2332–8.
22. Annane D, Aegerter P, Jars-Guincestre MC, et al. Current Epidemiology of Septic Shock: The CUB-Rea Network. Am J Respir Crit Care Med 2003;168(2):165–72.
23. The EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 2004; 30(4):580–8.
24. Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 2004;30(4): 589–96.
25. Zanon U, Pereira Lde O, Kelm LS, et al. Septicemia: incidencia, mortalidade, letalidade e condicioes predisponentes em 10 hospitais brasileiros e 23,079 pacientes. Rev Med St Casa 1990;2(3):213–8.
26. Del Rio J, Hernandez JM, Peon A, et al. Infeccion nosocomial. Estudio de 2 años. Revista Cubana de Cirugia 1993;32(1):14–23.
27. Pazmiño L, Cifuentes A. Estudio epidemiologico de 435 pacientes septicos en una unidad de cuidados intensivos general. Revista Hospital Eugenio Espejo 1993;3(1): 1–13.
28. Ponce de Leon S, Rivera I, Romero C, et al. [The risk factors in primary bacteremias: a case-control study]. Gac Med Mex 1994;130(5):368–72; discussion 373.
29. Bembibre R, Gonzales E, Quintero C. Sepsis nosocomial. Revista Cubana de Medicina 1997;36(2):95–9.
30. Arcienega TL, Barron M. Caracteristicas de infecciones en Unidad de Terapia Intensiva. Experiencia durante periodo de diez años. Archivos Bolivianos de Medicina 1998;5(58):25–30.
31. Jaimes F, Valencia M, Vélez L. Significado Clínico de los Hemocultivos. Una Cohorte Retrospectiva en el Hospital San Vicente de Paul. Infectio 1998;2(2):69–76.
32. Jaimes F, Martinez CE, Valencia M, et al. Prediccion de mortalidad en pacientes con bacteremia y sepsis. Acta Medica Colombiana 1999;24(3):96–101.
33. Hernandez G, Dougnac A, Castro J, et al. [Systemic inflammatory response syndrome: is it comparable with severe sepsis?]. Rev Med Chil 1999;127(11):1339–44.
34. Ponce de Leon-Rosales SP, Molinar-Ramos F, Dominguez-Cherit G, et al. Prevalence of infections in intensive care units in Mexico: a multicenter study. Crit Care Med 2000;28(5):1316–21.
35. Jaimes F, Garcés J, Cuervo J, et al. Factores pronósticos en el síndrome de respuesta inflamatoria sistémica (SRIS). Desarrollo de un índice de severidad. Acta Medica Colombiana 2001;26(4):149–57.
36. Zapata L, Jaimes F, Garces J, et al. Descripción de una cohorte de pacientes con criterios de síndrome de respuesta inflamatoria sistémica en dos hospitales de tercer nivel. Iatreia 2001;14(1):26–34.
37. Sifuentes-Osornio J, Guerrero-Almeida MC, Ponce de Leon-Garduno LA, et al. [Trends for bacteremia and risk factors for death in a tertiary hospital in Mexico City. 1981–1992]. Gac Med Mex 2001;137(3):191–202.
38. Morales C, Fresneda G, Guanche H. Prevalencia puntual de infeccion nosocomial. Revista Cubana de Enfermeria 2001;17(2):84–9.

39. Bilevicius E, Dragosavac D, Dragosavac S, et al. Multiple organ failure in septic patients. Braz J Infect Dis 2001;5(3):103–10.
40. Lujan M. Tendencias y pronosticos de las infecciones nosocomiales en la provincia de cienfuegos. Revista Cubana de Higiene y Epidemiologia 2002;40(1):20–5.
41. Cordero DM, Garcia AL, Barreal RT, et al. Comportamiento de la infeccion nosocomial en las unidades de terapia en un periodo de 5 años. Revista Cubana de Higiene y Epidemiologia 2002;40(2):79–88.
42. Notario R, Borda N, Gambande T, et al. [Bacteremia in 2 hospitals in Rosario, Argentina]. Rev Argent Microbiol 2003;35(3):167–70.
43. Jaimes F, Arango C, Ruiz G, et al. Predicting bacteremia at the bedside. Clin Infect Dis 2004;38(3):357–62.
44. Wenzel RP. Perspective: treating sepsis. N Engl J Med 2002;347:966–7.
45. Angus DC, Wax RS. Epidemiology of sepsis: an update. Crit Care Med 2001;29: S109–16.
46. Alberti C, Brun-Buisson C, Goodman SV, et al. Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. Am J Respir Crit Care Med 2003;168(1):77–84.
47. Silva E, Almeida P, Beltrami A, et al. Brazilian sepsis epidemiological study (BASES study). Crit Care Med 2004;8:R251–60.

3
Novel Therapies in Critically Ill Septic Patients

Jean-Louis Vincent, Carla Marie Clausi, and Alejandro Bruhn

Introduction

Sepsis, the inflammatory response to infection, is perhaps the most common disease encountered by the critical care physician, complicating some 30% to 40% of ICU admissions and accounting for considerable morbidity and mortality. Septic shock affects some 10% to 15% of intensive care unit patients and carries mortality rates of 50% to 60%. Recent years have seen major advances in the understanding of the pathophysiology of sepsis and, as a result, new treatments and approaches to management have become available.

The search to find effective therapies for sepsis, one of the most common disease processes on the intensive care unit, has been rewarded in recent years with the development and licensing of drotrecogin alfa (activated), the first of the so-called immunomodulatory drugs to be shown to improve outcomes in patients with severe sepsis. This milestone in the history of sepsis research has added new impetus to the ongoing quest for strategies to help decrease the still high mortality rates associated with this condition. This chapter presents some of the recent advances in sepsis management, including corticosteroids and drotrecogin alfa (activated), before reflecting on some of the possible interventions and drugs of the future.

Immunomodulatory Therapies: Present

Corticosteroids

Corticosteroids have been considered as being of potential benefit in sepsis for years, but when high doses were found to be of no benefit,[1,2] they were discontinued. However, recent studies have suggested that more physiological doses can be beneficial.[3–5] Annane et al.[5] demonstrated improved survival in patients with septic shock and relative adrenal insufficiency treated with a 50 mg intravenous bolus of hydrocortisone every 6 h and fludrocortisone (50 µg tablet once daily) for 7 days. So far, this strategy has only been tested in patients with septic shock, and further study is needed to define its effectiveness in patients with less severe

forms of sepsis. In addition, definitions of relative adrenal insufficiency are not clear, and if corticosteroid administration is to be guided by ACTH stimulation tests, which test should be used?

Drotrecogin Alfa (Activated)

A landmark year in the history of sepsis was 2001—after many years of apparently fruitless research into immunomodulatory therapies for sepsis, drotrecogin alpha (activated) was licensed by the FDA for the treatment of adult patients with severe sepsis or septic shock. U.S. licensing was followed by acceptance in Europe and other countries worldwide, and this drug now forms part of standard-of-care management for patients with severe sepsis at high risk of death.[6] The development of drotrecogin alfa (activated), a recombinant version of a natural anticoagulant protein, activated protein C, was the result of insight into the important links between the coagulation system and the inflammatory response to sepsis.[7] In a multicenter randomized controlled trial involving 1,690 patients, the drug, at a dose of 24 μg/kg/h, was shown to improve survival from 30.8% in the placebo group to 24.7% in the drotrecogin alfa (activated) group, giving a 19.4% relative reduction in mortality rate (i.e., only 16 patients needed to be treated to save one life).[8] Drotrecogin alfa (activated) was also shown to improve organ function, causing significantly faster resolution of cardiovascular and respiratory dysfunction and significantly slower onset of hematologic organ dysfunction compared with placebo patients.[9] Importantly, too, its effects on outcome are sustained beyond the traditional 28-day endpoint. There is an increased risk of bleeding with drotrecogin alfa, with serious bleeding events occurring during the infusion period in 2.8% of patients and during the 28-day study period in 5.3% of patients.[10] Of the bleeding events during the infusion period, 43% were procedure related. The instructions for the use of drotrecogin alfa (activated), therefore, clearly state that patients at high risk of bleeding should not be given the drug, and it is contraindicated in patients with active internal bleeding, recent hemorrhagic stroke, intracranial or intraspinal surgery, severe head trauma, presence of an epidural catheter, intracranial neoplasm, or evidence of cerebral herniation. In addition, infusion should be interrupted for surgery or invasive interventions. Importantly, treatment with drotrecogin alfa (activated) seems to be most effective when started early,[11] and it should not be reserved as a last-resort option. Although expensive, its cost-effectiveness profile seems to be in keeping with other commonly used interventions in intensive care.[12,13]

Immunomodulatory Therapies: Future

The complexities of the immune response to sepsis are far from being clearly defined and the interactions of one mediator on another make it difficult to determine the effects of interfering with the activity of any individual player. This is a field of intensive experimental research activity, as results repeatedly demonstrate

the intricacies of this amazing network of mediators and cells. It is not possible to discuss here all the potential agents of the future, many of which have yet to be discovered (!), but I will discuss some of the leading areas of current research.

Hemoperfusion Strategies

By removing inflammatory mediators, blood purification systems could potentially improve outcomes, and several strategies have been suggested, although this remains a controversial field. Continuous hemofiltration was not shown to reduce mediator levels or the extent of subsequent multiple organ dysfunction[14] and is not recommended for the treatment of sepsis independent of renal replacement needs.[6] However, research is continuing in an attempt to find the combination of membrane and ultrafiltration rate that may benefit septic patients. Coupled plasma filtration adsorption (CPFA) nonselectively reduces the circulating levels of pro- and antiinflammatory mediators, and early studies have suggested that CPFA improves blood pressure and restores immune function in patients with septic shock.[15,16] Further studies are clearly needed to confirm these results.

New Antiendotoxin Strategies

Endotoxin is a key initiator of sepsis. Once in the circulation, endotoxin binds to lipopolysaccharide binding protein (LBP), which can transfer endotoxin to cell bound or soluble CD14 (resulting in cellular activation), or to lipoproteins (resulting in endotoxin inactivation). Normal plasma lipoprotein concentrations provide an excess of endotoxin-binding sites, but in acute illness, lipoprotein levels are reduced.[17,18] Experimental studies in human volunteers and animal models have shown that high-density lipoprotein (HDL) can block the effects of endotoxin.[19,20] Experimental studies with an emulsion of phospholipid, the predominant lipid in HDL, also reported significantly lowered serum endotoxin and tumor necrosis factor (TNF)-alpha, preserved cardiac output and ejection fraction, and attenuated increases in systemic and pulmonary vascular resistances.[21] Phase II clinical trials with this phospholipid emulsion are ongoing.

Apoptosis Inhibition

Apoptosis is the programmed death of cells and is essential for homeostatic cell turnover. However, sepsis is associated with disordered apoptosis with increased lymphocyte and epithelial cell apoptosis. Caspase-inhibitors,[22] which prevent apoptosis, and other strategies to limit apoptosis[23–25] have improved survival in animal models of sepsis, and antiapoptotic strategies may have a place in the future treatment of sepsis.

High-Mobility Group B-1 Protein

High-mobility group B-1 protein (HMGB1) is a late mediator of systemic inflammation, released from endotoxin-stimulated macrophages some 8–12 h after the

release of the early cytokines. Activities of HMGB1 include activation of macrophages to release TNF and IL-1, stimulation of neutrophil and smooth muscle cell chemotaxis, and induction of epithelial cell permeability.[26] In animal models, ethyl pyruvate inhibits systemic HMGB1 release and prevents the lethal sequelae of endotoxemia or peritonitis even when the first dose is given 24 h after the induction of sepsis.[26,27] The potential broader therapeutic time frame for treatments targeted against HMGB1 makes this an interesting goal for future clinical research.

Poly (ADP) Ribose Polymerase/Synthetase (PARP/PARS)

PARP is involved in modulating nuclear-factor kappa B (NF-κB)-mediated transcription of various inflammatory mediators including inducible nitric oxide synthase (iNOS) and intercellular adhesion molecule (ICAM). Pharmacological inhibition of PARP improved survival in a porcine model of severe hypodynamic sepsis induced by *E. coli* clot implantation and has been shown to improve hemodynamics and outcome in various animal models of endotoxemia.[28] However, a randomized controlled clinical study of the NOS inhibitor in septic shock, 546C88, showed increased mortality rates in the treated patients,[29] and we need to have a clearer understanding of the interactions between PARP/PARS and NO before this area of immunomodulation undergoes clinical testing.

General Management

Although the development of specific sepsis-directed immunomodulatory therapies is exciting, these agents are of little benefit if used alone, and must be used in conjunction with other general management strategies, including optimal hemodynamic resuscitation and metabolic support.

Optimal Hemodynamic Support

Optimal hemodynamic support depends on adequate fluid resuscitation and the use of vasoactive agents when fluids alone fail to achieve the desired endpoints. Comprehensive guidelines on hemodynamic management of the patient with septic shock have been published recently.[6] Importantly, *early* hemodynamic optimization is most effective at reducing mortality.[30] The "best" choice of fluid has generated some debate, although there are no data indicating that any one fluid is superior to another and in making a selection, the clinician needs to take into account the different properties and side effects of the available solutions and specific characteristics of the patient in question, including hemodynamic stability, coagulation profile, and renal function. Some fluids (e.g., some hydroxyethyl starch solutions or hemoglobin solutions) may have specific effects on the microcirculation that may make them of greater use in the septic patient, but this requires further study. Patients with shock may also have a relative vasopressin

deficiency, and the administration of low doses of vasopressin may be a valuable strategy. Some studies have indicated that patients with septic shock may benefit from the administration of a continuous infusion of low doses of vasopressin in terms of reduced catecholamine requirements and improved renal function,[31,32] but prospective randomized clinical trials need to confirm these findings.

Glucose Control

In an important study, Van den Berghe et al.[33] randomized more than 1,500 ICU patients to intensive management aimed at keeping blood sugar levels within tight limits of 80 to 110 mg/dL versus conventional management of hyperglycemia; mortality rates were reduced from from 8.0 to 4.6% ($p < .04$) in the intensive treatment group. In addition, intensive treatment was associated with shorter ICU stays, less requirement for renal replacement therapy, less hyperbilirubinemia, fewer blood stream infections, fewer ICU neuropathies, and a reduced need for transfusion. Further study has suggested that these results were indeed due to the control of glucose levels rather than to the insulin administered.[34,35] Although this study did not focus on septic patients, septic complications were reduced, and it would seem reasonable that glucose levels should also be carefully monitored and adjusted in patients already presenting with sepsis. In addition, while the strategy appears to be a simple way to improve outcomes, it poses several logistic problems including increased nursing time, additional blood sampling, and risk of hypoglycemia. Specially designed insulin protocols may help limit these difficulties.[36,37]

Nutrition

Nutritional support is important in the management of the septic patient. Early nutrition seems to be beneficial in all acutely ill patients, except maybe those who have a risk of gut hypoperfusion associated with hemodynamic instability. The enteral route is preferred because it helps to maintain the integrity of the gut mucosa or because it avoids the possibly harmful effects of parenteral nutrition. Immunonutrition (using enteral solutions enhanced with various amino acids and fatty acids) may have beneficial effects by improving the host response to the acute disease,[38] but further study is needed to better define which constituents should be included.

Conclusion

The past few years have seen exciting developments in the treatment of severe sepsis and septic shock. The standard, and still vitally important, management of severe sepsis relies on adequate resuscitation with fluids and vasoactive agents, eradication of the causative infection using antibiotics and surgical removal where necessary, and individual organ support including renal dialysis and

Table 3.1. The PIRO Concept to Characterize Sepsis[39]

P: Predisposing factors: age, sex, genetic factors, immunodepression,
I: Infection: local or systemic, causative microorganism(s), source,
R: Response: fever, white blood cell count, increase in CRP, tachycardia,
O: Organ dysfunction: renal dysfunction, alterations in gas exchange, coagulation abnormalities.

mechanical ventilation. Importantly, early resuscitation is associated with improved outcomes.[30] Corticosteroids, drotrecogin alfa (activated), and careful glucose control must now also form part of management protocols.

The future will see many more agents being tested, and some will also be shown to improve outcomes. The challenge then will be to determine which drug(s) to give to which patient. Genetic typing and improved markers of sepsis and of the inflammatory response may help define an individual ICU sepsis package for each patient. The recently suggested PIRO (predisposition, infection, immune response, organ dysfunction) system of "staging" sepsis (see Table 3.1)[39] will also help to characterize patients, to target treatments, and to monitor response to therapy.

References

1. Bone RC, Fisher CJJ, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317:653–8.
2. The Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 1987;317:659–65.
3. Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 1998;26:645–50.
4. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999;27:723–32.
5. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862–71.
6. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858–73.
7. Amaral A, Opal SM, Vincent JL. Coagulation in sepsis. Intensive Care Med 2004; 30:1032–40.
8. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.
9. Vincent JL, Angus DC, Artigas A, et al. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. Crit Care Med 2003;31:834–40.
10. Bernard GR, Macias WL, Joyce DE, et al. Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis. Crit Care 2003;7: 155–63.
11. Vincent JL, Levy MM, Macias WL, et al. Early intervention with drotrecogin alfa (activated) improves survival benefit. Crit Care Med 2003;3:834–40.

12. Manns BJ, Lee H, Doig CJ, et al. An economic evaluation of activated protein C treatment for severe sepsis. N Engl J Med 2002;347:993–1000.
13. Angus DC, Linde-Zwirble WT, Clermont G, et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. Crit Care Med 2003;31:1–11.
14. Cole L, Bellomo R, Hart G, et al. A phase II randomized, controlled trial of continuous hemofiltration in sepsis. Crit Care Med 2002;30:100–6.
15. Ronco C, Brendolan A, Lonnemann G, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. Crit Care Med 2002;30:1250–5.
16. Formica M, Olivieri C, Livigni S, et al. Hemodynamic response to coupled plasma-filtration-adsorption in human septic shock. Intensive Care Med 2003;29:703–8.
17. Gordon BR, Parker TS, Levine DM, et al. Low lipid concentrations in critical illness: implications for preventing and treating endotoxemia. Crit Care Med 1996; 24:584–9.
18. van Leeuwen HJ, Heezius EC, Dallinga GM, et al. Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 2003;31:1359–66.
19. Pajkrt D, Doran JE, Koster F, et al. Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. J Exp Med 1996;184:1601–8.
20. Cue JI, DiPiro JT, Brunner LJ, et al. Reconstituted high density lipoprotein inhibits physiologic and tumor necrosis factor alpha responses to lipopolysaccharide in rabbits. Arch Surg 1994;129:193–7.
21. Goldfarb RD, Parker TS, Levine DM, et al. Protein-free phospholipid emulsion treatment improved cardiopulmonary function and survival in porcine sepsis. Am J Physiol Regul Integr Comp Physiol 2003;284:R550–7.
22. Hotchkiss RS, Chang KC, Swanson PE, et al. Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. Nat Immunol 2000;1:496–501.
23. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Prevention of lymphocyte cell death in sepsis improves survival in mice. Proc Natl Acad Sci USA 1999;96:14541–6.
24. Chung CS, Song GY, Lomas J, et al. Inhibition of Fas/Fas ligand signaling improves septic survival: differential effects on macrophage apoptotic and functional capacity. J Leukoc Biol 2003;74:344–51.
25. Weaver JG, Rouse MS, Steckelberg JM, et al. Improved survival in experimental sepsis with an orally administered inhibitor of apoptosis. FASEB J 2004;18:1185–91.
26. Yang H, Ochani M, Li J, Qiang X, et al. Reversing established sepsis with antagonists of endogenous high-mobility group box 1. Proc Natl Acad Sci USA 2004;101:296–301.
27. Ulloa L, Ochani M, Yang H, et al. Ethyl pyruvate prevents lethality in mice with established lethal sepsis and systemic inflammation. Proc Natl Acad Sci USA 2002; 99:12351–6.
28. Pacher P, Cziraki A, Mabley JG, et al. Role of poly(ADP-ribose) polymerase activation in endotoxin-induced cardiac collapse in rodents. Biochem Pharmacol 2002;64:1785–91.
29. Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 2004;32:21–30.
30. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
31. Malay MB, Ashton RC, Jr., Landry DW, et al. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999;47:699–703.
32. Patel BM, Chittock DR, Russell JA, et al. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002;96:576–82.

33. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patient. N Engl J Med 2001;345:1359–67.
34. Van den BG, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med 2003;31:359–66.
35. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. JAMA 2003;290:2041–7.
36. Laver S, Preston S, Turner D, et al. Implementing intensive insulin therapy: development and audit of the bath insulin protocol. Anaesth Intensive Care 2004;32:311–6.
37. Kanji S, Singh A, Tierney M, et al. Standardization of intravenous insulin therapy improves the efficiency and safety of blood glucose control in critically ill adults. Intensive Care Med 2004;30:804–10.
38. Galban C, Montejo JC, Mesejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med 2000;28:643–8.
39. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.

4
Dissemination Control of the Antimicrobial Resistance in the Intensive Care Unit

Carlos Arturo Alvarez and Jorge Alberto Cortés

Introduction

The impact of antimicrobial resistance (AMR) in the ICU is serious and it is more frequent each time with the consequent effect over morbimortality.[1–3] According to an AMR surveillance study, in more than 100 intensive care units (ICU) in the United States the following percentages of resistant bacterias were found: methicillin-resistant *Staphylococcus aureus* (MRSA), 57.1%; methicillin-resistant coagulase-negative *Staphylococcus* (MR CNS), 89.1%; vancomycin-resistant *Enterococcus faecium* (VRE), 27.5%; imipenem-resistant *Pseudomonas aeruginosa*, 22.3%; third-generation cephalosporin-resistant *Enterobacter spp.*, 32.2%.[3] The presence of AMR additionally contributes to a considerable increase in care costs[4–7] and a major morbimortality.[8–10]

Cause of Antimicrobial Resistance in ICU

The causes of AMR appearance or increase are multiple and can be summarized in factors that depend on the bacteria—the host and the environment. AMR incidence in the ICU is generally the reflection of the institution resistance situation, since in it, not only the critical patients but also AMR from other services or institutions are concentrated here. In addition, ICUs play a critical role in an AMR emergency because they facilitate a high percentage of patients who are taking extended-spectrum antibiotics, patient germ dissemination, patients with severe diseases, invasive procedures, and the transference of colonized or infected patients between services. In Figure 4.1, the possible reasons in which AMR is selected and disseminated in the ICU are schematized (it has been modified since the concepts proposed by Lipsitch and Samore).[11] Because these are not the only factors, antimicrobial and nonfulfillment measures to prevent and control the infection constitute, without any doubt, the main reasons for resistance in the ICU.

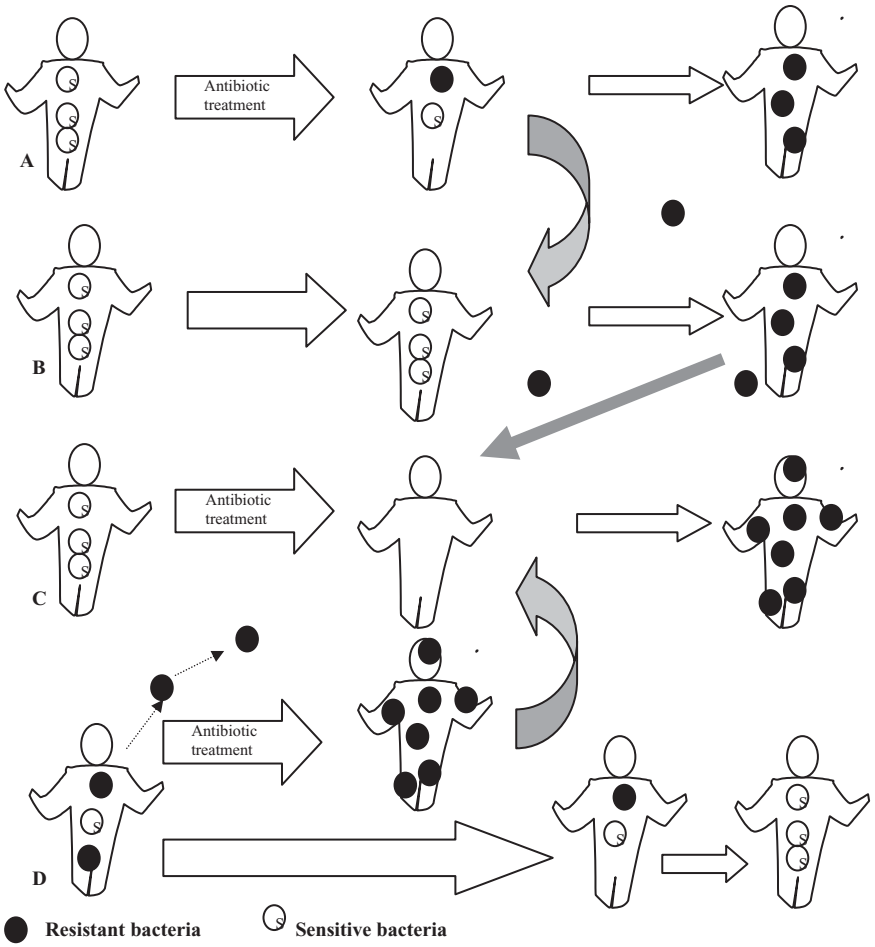


FIGURE 4.1. Mechanisms of transmission of the bacterial resistance.

The Use of Antimicrobial Agents

The appearance and use of antibiotics go hand in hand with the appearance of resistance. However, resistance is not found in the same percentage for all antibiotics and for all germs. The differences depend on the intrinsic features of the germs and molecules and the manner in which we use them.

Certain bacterias, such as *P. aeruginosa* and *Acinetobacter baumanii*, can generate a resistance of 20% to antibiotics during their administration mainly because of a high possibility of using different resistance mechanisms.[12–16] In the *P. aeruginosa* case, the studies made during treatment showed an adjusted risk to developing resistance that varies according to the antibiotic used: imipenem, 2.8; piperacillin, 1.7; ciprofloxacin, 0.8, and ceftazidime, 0.716.

Other germs such as *Stenotrophomonas maltophilia* already have natural resistance mechanisms to carbapenems, so use of antimicrobials is needed only to favor dissemination when the bacterial flora that competes with them (Figure 4.1d) is eliminated.

The appearance of new mutations or the phenotopic expression from resistance genes has a low spontaneous incident. When it appears, it mainly induces antibiotic pressure. Such is the case of the extended-spectrum beta-lactamases (EESBL), in which the change of one amino acid in a resistant gene assists the appearance of new enzymes within that major spectrum.[17] However, when the pharmacokinetic and pharmacodynamic features allow it, this process can be accelerated; such is the case in the relationship between MRSA and some quinolones.[18] In the case of the EESBL, certain cephalosporins have a major capacity of resistance induction.[19] Therefore, the patterns of use of the different cephalosporins have determined the appearance of the different types of EESBL.[20]

Another appearance mode of AMR is the selection of resistant flora. This feature occurs with all antibiotics, and the difference among the molecules depends on the spectrum of each one: the more extensive spectrum the antimicrobial has, the more extensive the change generated in the normal flora will be.[21] The bacterial populations are not homogeneous and many times the patients are colonized by resistant strains. In Table 4.1 examples of bacterial resistance inductive antibiotics are illustrated.

TABLE 4.1. Examples of Resistance Induction Produced by Antibiotics

Antibiotic used	Induced resistance	Observation	Reference
Gentamicin	To aminoglycosides		42
Second- and third-generation cephalosporin	EEBL	Depending on the geographic area	43–45
Cefoxitin, third-generation cephalosporin, aminopenicillins	AmpC		46–48
Ceftazidime and ticarcillin	Overexpression of the flow pump MexAMexBoprM; resistance to quinolones, carbapenems, tetracyclines, chloramphenicol		12
Quinolones: ciprofloxacin	Flow pumps induction, quinolone resistance	Related to pharmacokinetics of the medicine	12, 49, 50
Imipenem	oprD-: carbapenem resistance	Related to the appearance of *Acinetobacter spp.* and *S. maltophilia*	51
Vancomycin	Appearance of vancomycin-resistant *Enterococcus spp.* (VRE)		30, 52
Metronidazole, cephalosporins	VRE appearance	Associated to the effect over the anaerobic flora	52

Nonfulfillment of Control Measures

The lack of adequate adherence to handwashing and the violation of isolation protocols are responsible for the colonization, infection, and AMR persistence in the majority of ICUs (Figure 4.1).

AMR can be transmitted in a clone or polyclone mode. The former occurs due to failure to follow hygienic rules. An AMR from a patient can be disseminated among other patients and inclusively colonize the environment. In this case, the resistance profile of the isolated germ is the same (i.e., MRSA persistence). The latter mode of dissemination occurs through the use of antimicrobials in the ICU, which can generate the appearance of AMR and the resistance profile can be different. Even more so, the bacterias can be different among patients depending on the type of antibiotic used in each case. Finally, in many ICUs the problem is mixed: an AMR is selected by antibiotic pressure, and then it is disseminated due to the lack of hygiene measures.

Control of the Resistance Dissemination

The following strategies are used to control bacterial resistance[22]:

1. Implementation of an antimicrobial resistance periodic monitoring system in community and nosocomial isolations.
2. Implementation of a periodic monitoring system of antibiotic use according to the location in the hospital or prescription service.
3. Monitor of the relationship between the use of antibiotics and antimicrobial resistance: assignment of responsibilities through practical guides or other institutional policies.
4. Preventive applications of isolation contact in known patients or those with suspicious colonization or infection by germs that are epidemiologically important.

Measures for Settlement of Control Infection

Containment measures to control infection, such as the isolation of patients, handwashing, wearing gloves, and an adequate use of face shield, plus a wise evaluation of the antibiotic use in the services are some of the strategies recommended to prevent the appearance and selection of resistant germs.[23,24] These strategies are detailed below.

Control Program Implementation

Implementation of the adopted measures by the personnel is a determinant of the efficacy of the AMR control program. The control program must have adequate resources as well as provide training and motivation for the entire health team. Also it is best to audit the practices periodically (isolation techniques and the

antibiotic use) in order to verify the concordance between the reality of use and the strategy adopted in the guidelines.

Identification of the Infected Carrier or Colonized Patients

Infected patients must be identified quickly. At the moment that an AMR is detected, the appropriate measures must be taken without delay. In certain cases, the isolation of carrier patients should be recommended. This isolation should be selective and done quickly in cases of possible epidemic or if the patients show, at the moment of admission, risk factors of carrying AMR (for instance, hospitalization in another third-level institution). This would consist of an active search for AMR as well as for MRSA or VRE, in nasal fossae, the rectum, and so forth. In a study in an ICU, with high rates of colonization, strategies of microbiological isolation in all patients when they enter the unit and the wearing of gloves in all patients or those selected as high risk[25] were proposed. The lesson is that once the germs are identified, the patients should be suitably isolated.

Technical Isolation

Technical isolation measures will establish barriers around the colonized or infected patient. These contact precautions include wearing sterile gloves, a reinforcement of washing and antisepsis of hands (especially when leaving the room or cubicle), the use of other protections (face shields and gowns when there is close contact and risk of splashes), and the individualization of care materials (e.g., stethoscope, pulsoximeter). The cleaning and disinfection of the environment, in particular the surfaces located near the carrier patient, must be done regularly.

Geographic Isolation

Geographic isolation utilizes an individual room or a place of handwashing or an alcohol dispenser near the patient's bed. Entry into the isolation rooms must be limited as well as the circulation of carrier patients. One must not forget that the hands are the main reservoir and provider of transmission.

Isolation Measures

Isolation measures are all those strategies used to establish barriers to microorganisms transmission. There are some general hygienic precautions that are applied to all patients independent of their infectious status. These measures have been called by the U.S. Centers for Disease Control (CDC) and the French recommendations[24,26] the "Standard Measures" and are listed here and summarized in Table 4.2.

Hygienic Handwashing

Handwashing is the most effective general measure to control infection dissemination in the ICU.

TABLE 4.2. Standard Precautions to Respect During the Treatment of Every Patient

Strategy	Recommendation
Hygienic handwashing	Before contact with the patient and after discarding the gloves Between two activities in the same patient Between two patients
Wearing gloves Gloves must be changed between two patients and between two activities in the same patient	If there is risk of contact with blood or another human fluid, mucus, or nonintact skin of the patient, especially at the moment of interventions with a puncture risk (hemocultures, inserting or removing poisonous accesses, catheter, taking blood samples, etc.) and with the manipulation of tubes with biological samples, clothes, and dirty material **AND** During all procedures in which hands are in contact with the patient's injuries
Use of gown, eye protection, and face shield	If in the care or treatment of the patient there is a risk of splashing or spraying of blood or another human fluid (aspiration, endoscopy, operative functions, autopsy, manipulation of material, dirty clothes, etc.)
Contaminated material	Sharp or stabbing items: Do not recap or remove cap from disposable syringes or used needles by hand, discard them after use, and place them in appropriate puncture-resistant containers
Contaminated surfaces	Clean and disinfect with the appropriate disinfectants all surfaces contaminated by splashes and sprays of blood or other human fluids
Transport of biological samples, clothes, and contaminated material	Biological samples, clothes, and instruments contaminated by blood or other human fluids must be transported with an impermeable packing, hermetically sealed

Wearing Gloves

It must always be taken into consideration that the main objective of gloves is to protect the patient. As a consequence, avoid frequent practices such as bathing the patient, and then, with the same gloves, doing other activities. Always take off the gloves, wash hands, and put another pair of gloves on when different procedures are done for the same patient.

Isolation Measures

In addition to the standard measures, it is necessary to take particular precautions of geographic or technical isolation in order to prevent the transmission or diffusion of microorganisms. These particular precautions are defined according to the infectious agent (reservoirs, ways of transmission, resistance in the external environment) and the infection (location and seriousness). In Table 4.3 the isolation measures are summarized according to the transmission type and the related microorganisms.

TABLE 4.3. Particular Precautions to Take into Consideration as a Complement to the Standard Precautions According to the Infection

Transmitted by air	Transmitted by drops	Transmitted by contact
⇨ Measles	⇨ Infections by *H. Influenzae type B*	⇨ Infections or colonizations of skin, injuries, gastrointestinal tract, respiratory tract by multiresistant germs
⇨ Varicella	⇨ *N. meningitidis*	⇨ Enteric infections
⇨ Tuberculosis	⇨ Multiresistant *S. pneumoniae*	⇨ *C. difficile*
	⇨ *Mycoplasma*	⇨ *Shigella*
	⇨ Influenza	⇨ Hepatitis A
	⇨ Parvovirus B19	⇨ *E. coli 0157:H7*
	⇨ German measles	⇨ VSR and parainfluenza
	⇨ Diphtheria	⇨ Enterovirus
	⇨ Adenovirus	⇨ Zoster varicella
		⇨ Herpes simplex
		⇨ Forunculosis
		⇨ Scabiosis
		⇨ Pediculosis
		⇨ Impetigo

Protective isolation must be provided for patients who have decreased immune defenses in order to protect them against external contamination as well as to avoid contact with microorganisms. The measures include the regulation of people circulation, the use of individual rooms, the use of sterile protectors (gowns, gloves, masks), and nutrition without raw products. Some recomendations related to the risk are:

- If there is transmission risk by interhuman contact (take contact precautions),
- If it is by airborne transmission (air precautions), and
- If there is orotracheobronchial secretions transmission (drops precautions) (Tables 4.3 and 4.4).

TABLE 4.4. Particular Precautions to Take into Consideration as a Complement to the Standard Precautions in the Function of the Transmission Route of the Infection

	Air precautions	Drop precautions	Contact precautions
Handwashing	Standard	Standard	Hygienic (before and after)
Individual room	+	+	+
Eye protection, face shield	+	+	Standard
Gloves	Standard	Standard	At the entrance of the room
Gown	Standard	Standard	At the contact with the patient or the environment*
Material and clothes	Standard	Standard	Standard
Patient transport	To limit	To limit	To limit

* In the case of isolation due to suspicion of colonization or infection by multiresistant germs, wearing gowns will depend on the possibility of close contact with the skin or contaminated injuries of the patient. + = use the precautions.

All colonized and infected patients with AMR must be isolated. The decontamination of colonized patients is not recommended. The efficiency of the chemical decontamination in AMR has been demonstrated only in MRSA nasal carrier patients in which the use of mupirocin temporarily eradicates its presence.[27,28]

Searching for and decontaminating personnel is not necessary because they are rarely carriers in a lasting manner (only temporarily), after contact with the patients. In cases of outbreaks, where the reservoirs are in the environment (*P. aeruginosa*, *Acinetobacter spp.*), complementary measures should be taken in order to clean and disinfect the environment.

It is recommended to start a relative information system of an AMR carrier with the objective to identify the AMR carrier patients quickly in the moment of their transfer. The system should include information related to the agencies that received the patient temporarily, ensured her or his transfer. This is especially a concern to those providing diagnostic images, as well as in the surgery rooms and the departments or centers where the patients were hospitalized.

Antibiotic Control

Good Use of Antibiotics

This section emphasizes the importance of an antibiotic policy inside the hospital and the ICU. The recommendations for clinical practice and the efficiency or resistance to their use have been demonstrated in studies for more than 20 years.[22,29–31]

The patient must be treated with the most effective and the least toxic antibiotic for the required period of time and with the adequate doses to cure and prevent an infection, producing the least possible amount of resistance. Enacting this rule is difficult, as most often the initiation of an antibiotic is empirical. The following are some of the strategies that have demonstrated to be efficient to fulfill this objective.

Antibiotic Restriction

Restricting antibiotics is one of the most commonly used measures and consists of the prescription limitation of one of the molecules or antibiotic families. The strategies to control the limitation are diverse:

- Prescription authorization granted to only a limited number of physicians.
- Authorization in the pharmacy to dispatch antibiotics for only certain pathologies and for a brief period of time.
- Authorization granted only with previous justification.
- No purchase and no prescription authorizations as a policy from the managing department of the institution or unit.
- Implementation of additional forms for the antibiotics, their doses, and the appropriate intervals.[32]

The implementation of multidisciplinary strategies is more appropriate than individual strategies. The more useful ones are academic input; feedback from the infirmary, physicians, and pharmacologist; the local adoption of handling guides; and the assisted computerized prescription.[31,33] Bisson et al. found that restricting the use of third-generation cephalosporins decreases the incidence of fecal colonization of *E. coli* and *Klebsiella spp*., which are EEBL producers.[34]

Antibiotic Rotation

Rotating antibiotics is another measure in which the use of antibiotic A or a family is restricted for a predetermined period of time and it is replaced by B; then a new one, C, is used, or A is used again.[35] This strategy tries to anticipate a resistance occurring by predetermined rotation guidelines.[36,37] There are certain limitations to this strategy in the available studies[38]:

- The studies have small sample size and are not comparable.
- In some studies, other control measures were done in parallel, and it is difficult to evaluate the impact in each intervention separately.
- The intervention time varies from months to 10 years. Consideration should also be given to the fact that the adequate time to avoid the resistance occurring between microorganisms is different, and this can make it difficult to determine the time of each cycle.
- Almost all of the studies were done to control an outbreak or to decrease high resistance, but not to avoid the resistance occurring, which should be the initial objective here.

One must be careful that the clinical abuse of an antibiotic does not become habitual. If a strategy is decided upon, it should be taken into account not to include an inductor molecule of resistance in the antibiotic's cyclical replacement. It is possible that the cyclical use of antibiotics amounts to a restriction of them for certain periods of time.

Antibiotic Combinations

Remember that the use of two or more antibiotics in order to decrease the resistance is a theoretic approximation, validated in infections such as tuberculosis, leprosy, and malaria, but its clinical usage to control AMR in the ICU has been demonstrated in an anecdotal way, and if the dynamic of the occurrence of the resistance is taken into consideration (Figure 4.1), an even higher pressure produces higher resistance. In ICUs there is discussion about whether use of the combination of β-lactams and aminoglycosides is not only effective but if the occurrence of the resistance decreases. Recently, two metaanalyses, one in neutropenic patients[39] and another in patients with gram-negative bacteremias,[40] did not find a difference in the mortality in patients with monotherapy versus combined therapy. Additionally, in the first study the same rate of superinfections with

AMR in the two groups was found but with a decrease in the adverse effects in the monotherapy group.

A Strategy in Real Life

The control resistance policy has been considered a problem for *everybody* and for this reason the first recommendation is to count on support from *everybody*. Thus, teamwork is essential among the clinical laboratory, pharmacy, ICU personnel, the infectious diseases unit, and the administrative component of the institution.

A second recommendation is establishing clear guidelines as to when to start an antibiotic treatment, and once it is decided to do so, to keep in mind the features of the microbial flora of each unit and the pharmacokinetic/pharmacodynamic parameters of antimicrobials. To improve the use of antibiotics, it is recommended for physicians to know the profile of the antimicrobial susceptibility and, based on this, to design guides and protocols for their own unit. Treat infections, not colonizations. The unnecessary treatment in colonization cases increases the resistance to the antibiotics used.

A third recommendation is to restrict the use of antibiotics in order to protect the environment and restrain the resistance from occurring. The selection is done with two criteria:

- The demonstration of being a main inductor of resistance, such as ceftazidime, cefotaxime, ceftriaxone, cefoxitin, imipenem, and gentamicin. These are not the only inductors, but they are the most important ones to stimulate the appearance of β-lactams.
- Selection of multiresistant flora to selective antibiotic pressure. This is the case with ciprofloxacin and vancomycin.

This does not mean that these medications can never be prescribed, but they must be prescribed only in strict situations according to the policies established in the protocols. The way to determine restriction depends on the features of the hospital: human resources, technical and administrative support, and so forth.

Resistance Surveillance to Antibiotics

The resistance surveillance to antibiotics is complementary to the nosocomial infections. This is essential, as it not only helps in the selection of antibiotics, but also provides valuable information on the epidemiology and the prevention of nosocomial infections. This surveillance has the following objectives:

- To guide the selection of individual therapeutics.
- To define the protocols of the first-intention antibiotic therapy against well-defined medical situations, especially in presumptive treatments.
- To guide and reinforce the measures taken to control the infections caused by AMR.

- To help distinguish the bacterial strains responsible for the nosocomial infections from the ones responsible for acquired infections in the community. Certain types of resistance, can, in effect, be considered as real markers of hospital acquisition: MRSA, production of EEBL, or resistance to certain aminoglycosides in *E. coli*, *P. mirabilis*, or *Klebsiella spp.* strains.
- To identify the multiresistant bacteria (MRB) defined by a phenotype of resistance associated with various antibiotics that can compromise the therapeutic possibilities (MRSA, VRE, production of EEBL in enterobacteria, resistance to the carbapenems of *P. aeuruginosa*, *Acinetobacter spp.*, *S. maltophilia*, etc.). The identification of a cross-transmission of multiresistant strains must initiate measures to prevent the epidemic diffusion inside the unit and the hospital. The frequency of AMR acquisitions in a clinical service or hospital must be considered as a quality marker of the organization of the services.[41]

References

1. Howard D, Cordell R, McGowan JE, Jr., et al. Measuring the economic costs of antimicrobial resistance in hospital settings: summary of the Centers for Disease Control and Prevention-Emory Workshop. Clin Infect Dis 2001;33:1573–8.
2. McGowan JE, Jr. Economic impact of antimicrobial resistance. Emerg Infect Dis 2001;7:286–92.
3. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control 2003;31:481–98.
4. Chaix C, Durand-Zaleski I, Alberti C, et al. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. JAMA 1999;282:1745–51.
5. Saulnier FF, Hubert H, Onimus TM, et al. Assessing excess nurse work load generated by multiresistant nosocomial bacteria in intensive care. Infect Control Hosp Epidemiol 2001;22:273–8.
6. The cost of antibiotic resistance: effect of resistance among *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* on length of hospital stay. Infect Control Hosp Epidemiol 2002;23:106–8.
7. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000;118:146–55.
8. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115: 462–74.
9. Montravers P, Gauzit R, Muller C, et al. Emergence of antibiotic-resistant bacteria in cases of peritonitis after intraabdominal surgery affects the efficacy of empirical antimicrobial therapy. Clin Infect Dis 1996;23:486–94.
10. Nguyen MH, Yu VL, Morris AJ, et al. Antimicrobial resistance and clinical outcome of *Bacteroides bacteremia*: findings of a multicenter prospective observational trial. Clin Infect Dis 2000;30:870–6.
11. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. Emerg Infect Dis 2002;8:347–54.

12. Livermore DM. Of Pseudomonas, porins, pumps and carbapenems. J Antimicrob Chemother 2001;47:247–50.
13. Danes C, Navia MM, Ruiz J, et al. Distribution of beta-lactamases in *Acinetobacter baumannii* clinical isolates and the effect of Syn 2190 (AmpC inhibitor) on the MICs of different beta-lactam antibiotics. J Antimicrob Chemother 2002;50:261–4.
14. Giamarellou H. Prescribing guidelines for severe Pseudomonas infections. J Antimicrob Chemother 2002;49:229–33.
15. Quinn JP. Clinical problems posed by multiresistant nonfermenting gram-negative pathogens. Clin Infect Dis 1998;27 Suppl 1:S117–24.
16. Carmeli Y, Troillet N, Eliopoulos GM, et al. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. Antimicrob Agents Chemother 1999;43:1379–82.
17. Rasmussen BA, Bradford PA, Quinn JP, et al. Genetically diverse ceftazidime-resistant isolates from a single center: biochemical and genetic characterization of TEM-10 beta-lactamases encoded by different nucleotide sequences. Antimicrob Agents Chemother 1993;37:1989–92.
18. Weber SG, Gold HS, Hooper DC, et al. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. Emerg Infect Dis 2003;9:1415–22.
19. Muller A, Lopez-Lozano JM, Bertrand X, et al. Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of *Enterobacter cloacae*. J Antimicrob Chemother 2004;54:173–7. Epub 2004 May 18.
20. Wang H, Kelkar S, Wu W, et al. Clinical isolates of Enterobacteriaceae producing extended-spectrum beta-lactamases: prevalence of CTX-M-3 at a hospital in China. Antimicrob Agents Chemother 2003;47:790–3.
21. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect Dis 2001;1:101–14.
22. Shlaes DM, Gerding DN, John JF, Jr., et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis 1997;25:584–99.
23. Fridkin SK. Increasing prevalence of antimicrobial resistance in intensive care units. Crit Care Med 2001;29:N64–8.
24. Ministere de la solidarite. 100 Recommandations pour la surveillance at la prevention des infections nosocomiales. Paris, 1999.
25. Trick WE, Weinstein RA, DeMarais PL, et al. Colonization of skilled-care facility residents with antimicrobial-resistant pathogens. J Am Geriatr Soc 2001; 49:270–6.
26. Pirwitz S. HICPAC guidelines for isolation precautions: Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1997;25:287–8.
27. Scully BE, Briones F, Gu JW, et al. Mupirocin treatment of nasal staphylococcal colonization. Arch Intern Med 1992;152:353–6.
28. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. N Engl J Med 2002;346:1871–7.
29. Farr BM, Salgado CD, Karchmer TB, et al. Can antibiotic-resistant nosocomial infections be controlled? Lancet Infect Dis 2001;1:38–45.
30. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 1995;44:1–13.

31. Gross PA, Pujat D. Implementing practice guidelines for appropriate antimicrobial usage: a systematic review. Med Care 2001;39:II55–69.
32. Perez A, Dennis RJ, Rodriguez B, et al. An interrupted time series analysis of parenteral antibiotic use in Colombia. J Clin Epidemiol 2003;56:1013–20.
33. Geissler A, Gerbeaux P, Granier I, et al. Rational use of antibiotics in the intensive care unit: impact on microbial resistance and costs. Intensive Care Med 2003;29: 49–54.
34. Bisson G, Fishman NO, Patel JB, et al. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species: risk factors for colonization and impact of antimicrobial formulary interventions on colonization prevalence. Infect Control Hosp Epidemiol 2002;23:254–60.
35. Pujol M, Gudiol F. Evidence for antibiotic cycling in control of resistance. Curr Opin Infect Dis 2001;14:711–5.
36. Sanders WE, Sanders CC. Cycling of antibiotics: an approach to circumvent resistance in specialized units of the hospital. Clin Microbiol Infect 1996;1:223–5.
37. John JF, Jr. Antibiotic cycling: is it ready for prime time? Infect Control Hosp Epidemiol 2000;21:9–11.
38. Sandiumenge A, Rello J. [Cyclic rotation of antibiotics. Is all that glitters gold?]. Enferm Infecc Microbiol Clin 2003;21:93–100.
39. Paul M, Soares-Weiser K, Grozinsky S, et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. Cochrane Database Syst Rev 2002:CD003038.
40. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis 2004; 4:519–27.
41. Lewis D. Antimicrobial resistance surveillance: methods will depend on objectives. J Antimicrob Chemother 2002;49:3–5.
42. Gerding DN, Larson TA, Hughes RA, et al. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. Antimicrob Agents Chemother 1991;35:1284–90.
43. Patterson JE. Extended-spectrum beta-lactamases. Semin Respir Infect 2000;15: 299–307.
44. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001;14:933–51, table of contents.
45. Lin MF, Huang ML, Lai SH. Risk factors in the acquisition of extended-spectrum beta-lactamase *Klebsiella pneumoniae*: a case-control study in a district teaching hospital in Taiwan. J Hosp Infect 2003;53:39–45.
46. Lynch JP, 3rd. Antimicrobial resistance: it's time to reverse the trend. Chest 2001;119: 371S–2S.
47. Phillips I, Shannon K. Importance of beta-lactamase induction. Eur J Clin Microbiol Infect Dis 1993;12 Suppl 1:S19–26.
48. Mulgrave L. The changing ecology of hospital bacteria and the selective role of cephalosporins. Epidemiol Infect 1991;106:121–32.
49. Lautenbach E, Fishman NO, Bilker WB, et al. Risk factors for fluoroquinolone resistance in nosocomial Escherichia coli and Klebsiella pneumoniae infections. Arch Intern Med 2002;162:2469–77.
50. Guyot A, Barrett SP, Threlfall EJ, et al. Molecular epidemiology of multi-resistant *Escherichia coli*. J Hosp Infect 1999;43:39–48.

51. Lee SO, Kim NJ, Choi SH, et al. Risk factors for acquisition of imipenem-resistant Acinetobacter baumannii: a case-control study. Antimicrob Agents Chemother 2004;48:224–8.
52. Fridkin SK, Edwards JR, Courval JM, et al. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. Ann Intern Med 2001;135:175–83.

5
Diaphragmatic Dysfunction in Intensive Care

Guillermo Ortiz-Ruiz

Mechanical ventilation is a method of vital support that is considered useful in a great number of patients who are treated in the intensive care unit (ICU). The benefits of using mechanical ventilation are not only found in the gas exchange but also in preventing respiratory muscle fatigue and muscle fiber damage in the septic patient and perfusion of vital organs, as it decreases the consumption of oxygen from the respiratory muscles.[1,2]

As with all therapeutic interventions, mechanical ventilation, although it has great benefits such as those mentioned above, can produce undesirable effects in patients to whom it is applied, such as infection, barotraumas, cardiovascular compromises, tracheal injuries, oxygen toxicity, and pulmonary injury induced by the ventilation.[3]

Therapeutic intervention, in this case mechanical ventilation, should be used within the context in which it works, that is, for critical patients with local or general hypoperfusion, organic dysfunction, and in a large percentage of patients with a sepsis diagnosis. This chapter discusses the structural and functional changes that occur in the diaphragm of a critical patient during hospitalization in the ICU.[4]

An increase in studies related to diaphragm function is seen in the international medical literature, in which the patient is treated with mechanical ventilation for conditions in which the muscle is inactive. This phenomenon is known as diaphragmatic dysfunction induced by a ventilator (DDIV).

In general, critical care providers spend a great amount of time removing mechanical ventilation. It has been estimated that 20% to 25% of the patients who have been given mechanical ventilation have difficulties suspending it, with 40% of the mechanical ventilation time invested in this process.[5] The respiratory muscles and especially the diaphragm play an important role in determining the success in removing mechanical ventilation,[1] and it is probable that the DDIV has a great impact in daily clinical practice despite some recent observations made in patients who have had trouble being weaned from mechanical ventilation where no clear association between the presence of diaphragmatic fatigue and failure in the process could be found.[6]

From the clinical point of view, DDIV is considered a diagnosis of exclusion, based on an appropriate clinical history, preferably using the mechanical ventilation in a controlled mode and excluding other causes of diaphragm weakness.[2]

The typical scenario is of a patient who has difficulty being weaned from mechanical ventilation after using it in a controlled mode. In this case the failure to wean is related to the dysfunction of the inspiratory muscles. Other causes of muscle weakness such as shock, sepsis, malnutrition, hydroelectrolytic disorders,[7] and neuromuscular disorders acquired in the intensive care unit[8] must be excluded before proposing the diagnosis of DDIV.

There is evidence found in clinical studies in relation to the existence of DDIV. Studies conducted with animals have shown consistently that the use of mechanical ventilation in a controlled mode is associated with a decrease in the capacity to generate strength from the diaphragm.[9–14] In healthy diaphragms from live species of animals studied, a marked diminution in the generation of transdiaphragmatic pressure is observed during phrenic nerve stimulation through the maximum and submaximum frequencies.[9–11] This happens in a time-dependent manner, meaning that the decrease of strength is detected as early as one day in rabbits[11] and three days in pigs,[10] and it worsens as time extends.

It is also observed that diaphragm resistance is severely altered, as indicated in the reduction of the capacity to keep inspiratory strength against a load.[9] Diminution in the diaphragmatic capacity to generate forces should not be attributed to changes in the lung volume or in abdominal distension.[9,10] It has been shown that transmission of the nerve impulse by the phrenic nerve and in the neuromuscular joint remains intact.[10] However, it has also been documented that there is a decrease of the potential of muscle action after the controlled use of mechanical ventilation, suggesting an incapacity in the excitement of the fiber or disengagement in the mechanism of excitation-contraction.[10]

It is important to recognize from the structural point of view that these changes in the diaphragmatic function are not related directly or exclusively to muscular atrophy, which suggests that besides the macroscopic changes, many of the pathophysiologic changes in DDIV are located at a cell or subcell level inside the same diaphragmatic muscle fibers.[14]

Although the evidence of DDIV in animals models is convincing, the evidence obtained in relation to the existence of DDIV in humans is less conclusive. This, in part, can be explained by the considerable confusion regarding contributing factors (comorbidity, medications, ventilator modes, previous illnesses) as well as the inability of measuring the diaphragmatic function directly in critical care. In a recent publication of a study of 33 patients clinically stable in mechanical ventilation with a variety of previous illnesses, a decrease of around 50% in the transdiaphragmatic pressure was found after magnetic stimulation.[15] Although the study is not explicitly in relation to ventilator strategy, it can be speculated that at least some of the patients were handled in a controlled mode.

Structural Diaphragmatic Changes Associated with DDIV

Even though the reduction in strength generated by the diaphragm after the use of the mechanical ventilation cannot be exclusively attributed to muscular atrophy, the proteolysis that occurs in these patients in a systemic manner and contributes

to the diaphragmatic thinness can also contribute to the incapacity to generate maximum inspiratory pressures. Furthermore, due to diaphragmatic atrophy, and an inverse relationship with the possibility of generating maximum strength, this atrophy will increase the risk of developing fatigue once spontaneous ventilation is resumed.[16]

In experimental studies it has been observed in animals that the use of mechanical ventilation in a controlled manner is associated with a diminution of the diaphragm mass and the atrophy of the muscular fibers.[9,12] The diaphragmatic atrophy is developed very quickly, as early as within 18 h, compared with the time for development of atrophy in other muscular groups.[17]

In general terms, atrophy due to disuse can be the result of a reduction of protein synthesis[18] or an increase of proteolysis.[19] The increase of proteolysis has been documented in rat diaphragms within 18 h of mechanical ventilation in a controlled mode.[17] In these studies an association between oxidative stress and activation of the route of proteasome has been found, in which it modulates in a preponderant manner the muscular proteolysis in critical patients who frequently reach the catabolic stage.

Oxidative Stress

Use of controlled mechanical ventilation is associated with an increase in the oxidative stress in the diaphragm, which is demonstrated through an increase in the protein oxidation and products derived from the lipid peroxidation.[17] These changes occur as quickly as within 6 h from initiation of mechanical ventilation, a scenario in which the enzymes are produced in antioxidant activity as the superoxide dismutase are also increased, suggesting that the antioxidant defenses try simultaneously to limit the unchained cell damage.[20]

The changes related to an increase in oxidative stress have been associated in a direct manner with diaphragmatic dysfunction and weakness,[21] probably due to the contractile protein elements involved in the excitative process, where contraction and generation of strength can modify its structure for its oxidation. One study[20] showed the diaphragmatic protein oxidation associated with the use of mechanical ventilation, through the dosage of insoluble proteins in a stage of oxidation with molecular weights of 200, 128, 85, and 40 kd. This increases the possibility that the actin and myosin would also be victims of oxidative modification during controlled mechanical ventilation. This hypothesis awaits confirmation through the demonstration of a structural modification of these proteins.

Structural abnormalities have been found in diaphragmatic muscular fibers after 2 or 3 days of mechanical ventilation.[11–14] The predominant findings are myofibril disruptions and the presence of very small abnormal mitochondria with solutions of focal continuity in its cellular membrane.[14] Some studies show similar changes in the external intercostal muscles of animals exposed to mechanical ventilation.[14]

The injury mechanisms have not been identified clearly but at least three plausible explanations have been proposed: first, the activation of calpains, proteases with the ability to degrade sarcomeric proteins[17]; second, direct cellular damage

derived from an increase of oxidative stress[17]; and finally, the injury generated by the diaphragmatic muscle activity during mechanical ventilation. This last explanation makes reference especially to the moment in which the muscle resumes a workload after an inactivity period, or "atrophy for use."[22] These findings suggest that part of the clinical manifestation of DDIV can be the increase in the susceptibility of the diaphragm for the induced injury due to the muscle contraction when it resumes its ventilation function as well as during the attempt to end mechanical ventilation.

Searching deeper into the more molecular level, it is known that myosin heavy chains create the most important structural component of this protein and they are the key to classifying traditionally the muscular fibers into those of slow contraction (type I) and fast contraction (type II). The muscle can modify the profile of myosin heavy chains because of atrophy or preferential hypertrophy of the fibers that have a specific type of myosin heavy chains[2] or transform from one type to another.

Mechanical ventilation for the short term (48 hours) rather than long term results in the least meaningful modifications of the diaphragm myosin chains. It has been shown in rats exposed to mechanical ventilation, after 18 hours, that not only type I fibers but also type II fibers decreased their size, but there is a greater grade of atrophy in type II fibers.[17] In rabbits, after two days of mechanical ventilation in a controlled manner, atrophy of the respiratory muscles is observed and there is a diminution of the transversal area of type II fibers.[14] It is probable that this transition from fast fibers to slow fibers that are resistant to fatigue is associated with a decrease in the capacity to generate strength.[23]

However, evaluation of the diaphragmatic structure during more prolonged episodes of mechanical ventilation seems to have different results[11–13] after two to four days of mechanical ventilation. The rats' diaphragms show an increase in the percentage of the muscular fibers called hybrids, with coexpression of the fast and slow isoforms of the myosin heavy chain. This is found only at the expense of type II[13] fibers and would indicate a late transformation of type I fibers to type II fibers.

In the extremity muscles, inactivity during short periods of time can result in a transformation of type II fibers to type I, but long periods of inactivity generate an increase in type II fibers.[4] The time required to observe these changes in the extremity muscles is higher than in the diaphragm, which suggests that the diaphragm is particularly a muscle vulnerable to fatigue.

It is not clear if enzymatic metabolic changes associated with DDIV can happen, although a study shows an increase in the activity of the citrate synthetase after 18 h of mechanical ventilation.[24] Longer periods of mechanical ventilation have not been associated with significant changes in the involved enzymes in the Krebs cycle or in diaphragmatic anaerobic glycolysis.[11,12] On the other hand, a decrease in the efficiency of the mitochondrial oxidative phosphorylation has been suggested in rabbits that used mechanical ventilation for two days.[14]

Recent publications[25] show that with rats exposed to hard respiratory exercises, an increase of the plasmatic cytokine levels not produced by the circulating

monocytes is observed. Being well documented as to diaphragmatic local cytokine production pro- and antiinflammatory in a time-dependent way, it can be speculated that these cytokines are taken into circulation and could be responsible for the systemic effects associated with changes in the respiratory pattern[26] or fatigue sensation.[27]

Clinical Implications

The most relevant clinical implications for the information provided in this chapter is that during short periods of mechanical ventilation, weakness and diaphragmatic structural changes can occur with the expected sequences that follow in the process of mechanical ventilation weaning. The experimental data also support the idea that the intercostals muscles can be compromised in a similar way.[14]

In clinical practice, there are more questions than answers in relation to muscular performance and especially in the diaphragmatic muscle. One of the main points of controversy is if there is a minimum level of muscular effort that allows physicians to prevent or revert the DDIV once it has been established. Logically, this would be related to the partial support modes during mechanical ventilation. Probably an absolute answer to this question does not exist. One can think that an alternative to resolving muscular inactivity during the controlled ventilation is partial support, but the course of recovery as well as the specific type of support and time for its application are unknown. Moreover, some studies in peripheral skeletal muscles make reference to a period of muscular "vulnerability" when they try to resume their functions, engendering a structural fiber injury.[22] Studies with tetraplegic patients have shown that the use of a phrenic pacemaker can diminish the diaphragmatic atrophy through a gradual instauration.[28]

Another question related to DDIV is whether the programmed parameters in the mechanical ventilation influence the development of DDIV frequency, PEEP (positive end expiratory pressure), tidal volume, and so forth. During mechanical ventilation the diaphragm is exposed to a repetitive and intermittent shortening. This creates a change in the tidal volume, and the respiratory frequencies used will necessarily affect the frequency and the extension of the shortening. The use of PEEP favors this shortening as it keeps the functional residual capacity stable.

Some studies have shown that the shortening in the skeletal muscle can be harmful and avoiding this can diminish the loss of sarcomeres.[4] Two studies that included the use of PEEP associated with a controlled mode of mechanical ventilation showed a major shortening of the sarcomeres with significant decrease in its optimum length, a finding that suggests a mechanism of sarcomere loss.[17–19] A clinical trial that had as its objective to demonstrate the influence of albuterol in the diaphragmatic contractility in patients with chronic obstructive pulmonary disease (COPD) exposed to mechanical ventilation concluded that the positive changes observed after the intervention are exclusively due to a diminishing of the lung hyperinflation and the improvement of diaphragmatic strength.[30] This

makes one think that the diaphragmatic position, especially its shortening level associated with the programmed parameters in the ventilator, must be taken into consideration in the generation and the evaluation of the interventions for DDIV.

A recent publication[31] of a study made with rabbits compared the effect of mechanical ventilation in a controlled mode with the assist control ventilation mode in the generation of strength and expression of muscular atrophy factor in the diaphragm. It was observed that there was a preservation of contractility conditions with the partial use of the diaphragm during the mechanical ventilation and a decrease in the expression of the atrophy factor. For patients who will be exposed to mechanical ventilation for a prolonged period of time it is better to use ventilation in which the diaphragm participates during each breath, and the use of sedatives drugs and muscle relaxants in high doses in which the diaphragmatic movement is inhibited should be avoided.

Another question that might have a relevant clinical application is related to the previous stage of diaphragmatic dysfunction in the appearance of DDIV. It highlights that the majority of the studies made with animals showed a previously healthy diaphragm, which makes it difficult to deduct how mechanical ventitation influences a diaphragm that has been previously altered. This is the case, for instance, where an increase of oxidative stress is demonstrated not only in a sepsis condition but also in patients exposed to mechanical ventilation, which can diminish the capacity to generate strength in the diaphragm in a transitory manner.[17–29] What we do not know is if the same happens in previously altered diaphragms that have been exposed to a major load and with probable major basal oxidative stress. The literature does not give us answers to this question.

The literature supports a relation to the loss or diminution of the diaphragm in generating the load during mechanical ventilation, and many times with septic patients it is multifactorial in that phenomena such as atrophy, oxidative stress, myofibrilar disruption, and remodeling processes are involved, making it difficult to establish the specific influence of each of them as well as the role of other mechanisms such as in the case of apoptosis. The studies in animals suggest that all these changes develop quickly, often within hours, a phenomenon that has been evident when the diaphragm of vegetative state postmortem patients is examined.

At a time when there is great uncertainty related to this pathology, the question would be whether to avoid DDIV. Based on what we know, the first conclusion would be to avoid the use of mechanical ventilation in a controlled mode, especially in elderly patients who have a greater chance of developing muscle atrophy from inactivity.[4]

Some studies have tried to prove that the strategy of partial support could counteract DDIV.[4] Moreover, some medical indications, in which classically ventilation was considered with a controlled strategy, as in the case of the syndrome of acute respiratory distress, consider the best strategy to be partial support.[29] Furthermore, some years ago it was considered that patients who had previously shown a failure after the removal of the mechanical ventilation should thereafter have a controlled strategy applied to revert the muscular fatigue.

However, the present evidence suggests that there is no clear support for leaving these muscles in complete rest after a failure in weaning from the mechanical ventilation.[31]

As for not using ventilation measures, it is recommended to provide adequate nutrition and to avoid the use of systemic corticoids as these therapeutic measures are also associated in a synergic manner with muscular atrophy. The present evidence solidly suggests that mechanical ventilation is associated with lung injury. Also evidence is growing as to the structural and functional injuries this intervention can cause in the respiratory muscles. There is no doubt that at the present time there are large gaps in knowledge about the mechanisms that conduct DDIV and one hopes that they can be resolved. Overall it is most important to remember that the diaphragm is a malleable and vulnerable structure, not an inert organ that can be replaced easily by a mechanical ventilator.

References

1. Vassilakopoulos T, Zakynthinos S, Roussos C. The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med 1998;158:378–85.
2. Ebiara S, Hussain SNA, Danialou G, et al. Mechanical ventilation protects against diaphragm injury in sepsis: interaction of oxidative and mechanical stresses. Am J Respir Crit Care Med 2002;165:221–8.
3. American Thoracic Society, European Society of Intensive Care Medicine, Societé de Reanimation de Langue Francaise. International consensus conferences in intensive care medicine; ventilator-associated lung injury in ARDS. Am J Respir Crit Care Med 1999;160:2118–4.
4. Vassilakopoulus T, Petrof B. Ventilate induced diaphragmatic dysfunction. Am J Respir Crit Care Med 2004;169:336–41.
5. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 1995;332:345–50.
6. Laghi F, Cattapan S, Jubran A, et al. Is weaning failure caused by low frequency fatigue of the diaphragm? Am J Respir Crit Care Med 2003;167:120–7.
7. Vassilakopoulos T, Zakynthinos S, Roussos C. Respiratory muscles and weaning failure. Eur Respir J 1996;9:2383–400.
8. Deem S, Lee CM, Curtis JR. Acquired neuromuscular disorders in the intensive care unit. Am J Respir Crit Care Med 2003;168:735–9.
9. Anzueto A, Peters JT, Tobin MJ, et al. Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. Crit Are Med 1997;25:1187–90.
10. Radell PJ, Remabl S, Nichols DG, et al. Effects of prolonged mechanical ventilation and inactivity on piglet diaphragm function. Intensive Care Med 2002;28:358–65.
11. Sassoon CS, Caiozzo VJ, Manka A, et al. Altered diaphragm contractile properties with controlled mechanical ventilation. J Appl Physial 2002;92:2585–95.
12. Le Bourdelles G, Viires N, Boczkowski J, et al. Effects of mechanical ventilation on diaphragmatic contractile properties in rats. Am J Respir Crit Care Med 1994;149: 1539–44.
13. Yang L, Luo J, Bourdon J, et al. Controlled mechanical ventilation leads to the remodeling of the rat diaphragm. Am J Respir Crit Care Med 2002;166:1135–40.

14. Bernard N, Matecki S, Py G, et al. Effects of prolonged mechanical ventilation on respiratory muscle ultrastructure and mitochondrial respiration in rabbits. Intensive Care Med 2003;29:111–8.
15. Watson AC, Hughes PD, Louise HM, et al. Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit Care Med 2001;29:1325–31
16. Bellemare F, Grassino A. Force reserve of the diaphragm in patients with chronic obstructive pulmonary disease. J Appl Physiol 1983;55:8–15.
17. Shanely RA, Zergeroglu MA, Lennon SL, et al. Mechanical ventilation-induced diaphragmatic atrophy is associated with oxidative injury and increased proteolytic activity. Am J Respir Crit Care Med 2002;166:1369–74.
18. Ku Z, Yang J, Menon V, Thomason DB. Decreased polysomal HSP-70 may slow polypeptide elongation during skeletal muscle atrophy. Am J Physiol 1995;268: C1369–74.
19. Bodine SC, Latres E, Baumhueter S, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Setence 2001;294:1704–8.
20. Zergeroglu MA, McKenzie MJ, Shanely RA, et al. Mechanical ventilation-induced oxidative stress in the diaphragm. J Appl Physiol 2003;95:1116–24.
21. Reid MB. Redox modulation of skeletal muscle contraction: what we know and what we do not. Invited review. J Appl Physiol 2001;90:724–31.
22. Vijayan K, Thompson JL, Norenberg KM, et al. Fibertype susceptibility to eccentric contraction-induced damage of hindlimb-unloaded rat AL, muscle. J Appl Physiol 2001;90:770–6.
23. Geiger PC, Cady MJ, Macken RL, et al. Maximum specific force depends on myosin heavy chain content in rat diaphragm muscle fibers. J Appl Physiol 200;89: 695–703.
24. Shanely RA, Coombes JS, Zergeroglu AM, et al. Short-duration mechanical ventilation enhances diaphragmatic fatigue resistance but impairs force production. Chest 2003;123:195–201.
25. Vassilakopoulos T, Divangahi M, Rallis G. Differential cytokine gene expression in the diaphragm in response to strenuous resistive breathing. Am J Respir Crit Care Med 2004;170:154–61.
26. Vassilakopoulos T, Zakynthinos S, Roussos C. Strenuous resistive breathing induces pro-inflammatory cytokines and stimulates the HPA axis in humans. Am J Physiol 1997;277:R1013–9.
27. Cileeson M. Interleukins and exercise. J Physiol 2000;529:1.
28. Talmadge RJ. Myosin heavy chain isoform expression following reduced neuromuscular activity: potential regulatory mechanisms. Muscle Nerve 2003;23:661–79.
29. Supinski G, Nethery D, DiMarco A. Effect of free radical scavengers on endotoxin-induced respiratory muscle function. Am Rev Respir Dis 1993;148:1318–24.
30. Hatipoglu V, Laghi F, Tobin M. Does inhaled albuterol improve diaphragmatic contractility in patients with chronic obstructive pulmonary disease? Am J Respir Crit Care Med 1994;160:1916–21.
31. Sassoon C, Zhu E, Caiozzo V. Assist-control mechanical ventilation attenuates ventilator induced diaphragmatic dysfunction. Am J Respir Crit Care Med 2004;170: 626–32.

6
Myocardial Depression in Sepsis and Septic Shock

Justin Wong and Anand Kumar

Introduction

In the setting of severe sepsis and septic shock, myocardial depression is common despite an apparently normal or increased cardiac output. Myocardial depression represents a spectrum of cardiac dysfunction present in varying degrees in virtually all cases of sepsis and septic shock. This myocardial depression persists throughout the course of the disorder and either improves with patients' recovery or accompanies them to their death. If a patient does survive, myocardial function usually returns to baseline within 7 to 10 days. The pathogenesis of the myocardial dysfunction derives from a cascade of events triggered by the initial inciting infection. This cascade results in the production of a variety of endogenous inflammatory cytokines (e.g., TNF-α, IL-1β) and other factors (e.g., lysozyme, platelet activating factor, leukotrienes, prostaglandins), which cause severe cardiovascular derangement including myocardial depression. The exact sequence of events leading to myocardial depression have not been fully elucidated but likely involve, in part, nitric oxide dependent and independent pathways and early events of programmed myocardial cell death (apoptosis).

Despite advances in modern medical knowledge and treatment of sepsis and septic shock, its incidence and mortality continue to rise. Over the past 40 years, age-adjusted mortality has increased from 0.5 to 0.7 per 100,000 episodes of sepsis and septic shock.[1] The incidence of severe sepsis in the United States is 750,000 cases per year, with 215,000 deaths annually.[2] The majority of these patients die of refractory hypotension and cardiovascular collapse.

Sepsis has been defined as the systemic inflammatory response to infection.[3] The inciting focus of sepsis, either an organism, component of an organism, or product of the organism, causes local and systemic release of a wide variety of inflammatory mediators like tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β),[4] platelet activating factor (PAF),[5,6] oxygen free radicals,[7] interferon gamma (IFN-γ),[8] and arachidonic acid metabolites[9] from monocytes/macrophages and other cells.[4] In order to maintain a homeostasis (and likely as part of a feedback mechanism), several antiinflammatory mediators are also released as part of the cascade including interleukin-10 (IL-10), transforming growth

factor-β (TGF-β), and interleukin-1 receptor antagonist (IL-1ra). If the balance is sufficiently shifted in favor of the inflammatory component, cardiovascular stress may result. An inability to respond adequately to this challenge, on the basis of either excessive cardiovascular dysfunction or limited cardiovascular reserve, results in septic shock. One of the components of septic cardiovascular stress (whether overt shock is present or not) is myocardial depression.

This chapter reviews the following aspects of septic myocardial dysfunction: right and left ventricular failure, systolic and diastolic dysfunction, and cardiovascular prognosticating factors. Potential pathophysiologic mechanisms of myocardial depression from organ to molecular/cellular level are also examined.

Clinical Manifestations of Cardiovascular Dysfunction

Historical Perspectives

Prior to the introduction of new techniques such as the balloon-tipped pulmonary artery catheter (PAC) and echocardiography to assess cardiovascular performance, much of our understanding of septic hemodynamics was based on clinical findings. There were two distinct clinical presentations of septic shock: warm shock characterized by high cardiac output (CO), warm dry skin, bounding pulses, and hypotension; and cold shock characterized by low CO, cold clammy skin, and diminished pulses.[10] Clowes et al.[11] went on to describe a relationship between warm and cold shock as a continuum in which either recovery or progression to death occurred. This notion was supported by other studies showing a correlation between survival and a high cardiac index (CI).[10,12] However, all these studies used central venous pressure (CVP) as a reflection of left ventricular end-diastolic volume (LVEDV) and adequacy of resuscitation. The importance of adequate volume status and its relation to survival and CI was suggested in only a handful of studies.[13,14] Based on evidence collected over the past four decades, we now know that CVP is a poor measure of preload in critically ill patients, particularly septic patients.[15] In addition to allowing the routine measurement of cardiac output, the introduction of the PAC enabled the routine measurement of preload as pulmonary capillary wedge pressure (PCWP). Using the PAC, several studies have now shown that adequately resuscitated septic shock patients have a persistent hyperdynamic state, high CO, and low SVR (systemic vascular resistance).[16,17] In nonsurvivors this hyperdynamic state usually persists until death (Figure 6.1).[18,19]

Since cardiac output is the product of heart rate (HR) and stroke volume (SV), septic patients can have a hyperdynamic circulation (high CO, low SV) even in the setting of significant myocardial depression as manifested by decreased left ventricular stroke work index (LVSWI).[20] Myocardial dysfunction could be explained by a change in contractility or compliance. Radionuclide cineangiography (RNCA) and its application to critically ill patients have offered insight into the relative contribution of decreased contractility and compliance in myocardial depression.

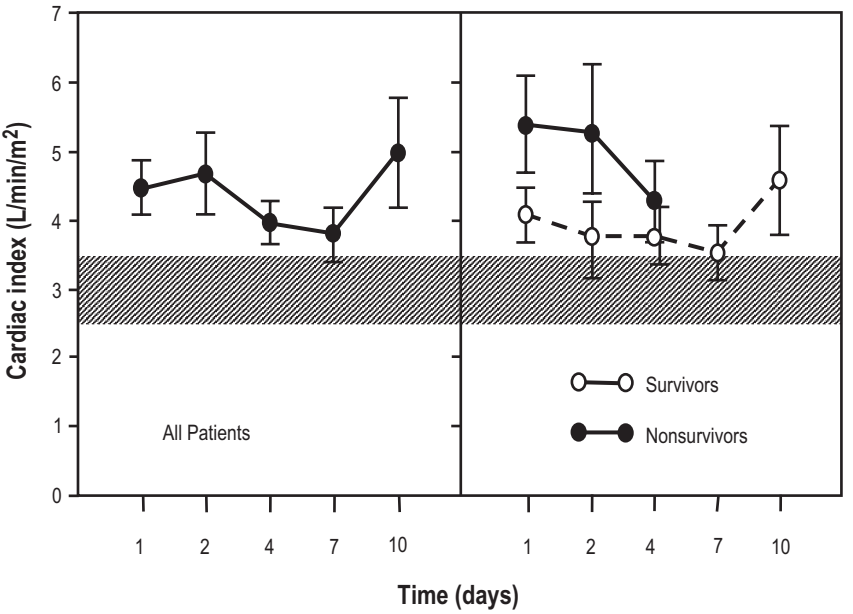


FIGURE 6.1. The mean (±SEM) cardiac index plotted against time for all patients, survivors, and nonsurvivors. The hatched areas show the normal range. All groups maintained an elevated cardiac index throughout the study period. The difference between the survivors and nonsurvivors was not statistically significant.

Ventricular Function

Elements of both right and left ventricular dysfunction exist in sepsis and septic shock; the relative contribution and importance of each to clinical manifestations are not clearly delineated. Similarly, there are elements of systolic and diastolic dysfunction in patients with septic myocardial depression, and a controversy regarding their relative roles in generating clinical manifestations has been argued. It is broadly accepted that in patients who survive their episode of septic shock, cardiac function returns to baseline within 7 to 10 days.

Left Ventricular Function

Systolic dysfunction has been shown to be impaired in septic patients in a number of studies. Parker et al.[21] demonstrated that survivors had decreased left ventricular ejection fraction (LVEF) and acute left ventricular (LV) dilatation evidenced by increased LVEDV index (LVEDVI) (Figure 6.2) using RNCA. These changes in survivors corrected to baseline in 7 to 10 days. Nonsurvivors sustained normal LVEF and LVEDVI until death. Despite systolic dysfunction, these patients

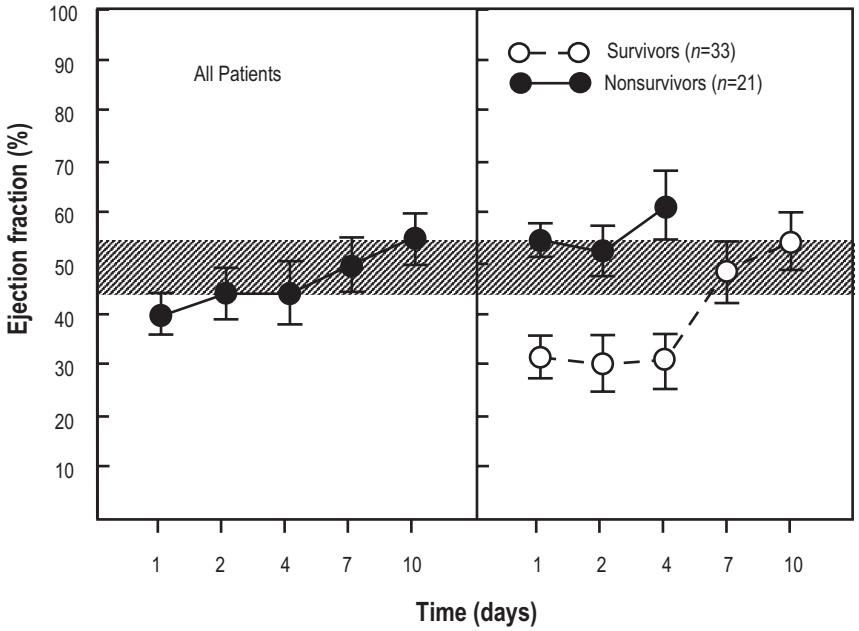


FIGURE 6.2. The mean (±SEM) left ventricular ejection fraction (LVEF) plotted versus time for all patients, survivors and nonsurvivors. Overall, septic shock patients showed a decreased LVEF at the time of initial assessment. This effect was due to marked early depression of LVEF among survivors that persisted for up to 4 days and returned to normal within 7 to 10 days. Nonsurvivors maintained LVEF in the normal range. The hatched area represents the normal range.

maintained a high CO and low SVR as shown by the PAC. In a later study, Ognibene et al.[22] compared left ventricular performance curves (plotting LVSWI vs. LVEDVI) of septic and nonseptic critically ill patients (Figure 6.3). They showed a flattening of the curve in septic shock patients, with significantly smaller LVSWI increments in response to similar LVEDVI increments when compared to nonseptic critically ill controls. In the years since these observations, other studies have confirmed the presence of significant left ventricular systolic dysfunction in septic patients.[23–26]

Diastolic dysfunction in septic patients is less clearly defined. The acute LV dilatation shown by Parker et al.[21] and a concordant relation between PAWP and LVEDV do not support the presence of significant diastolic dysfunction. However, more recent studies using echocardiography have shown impaired compliance as evidenced by slower left ventricular filling,[27] aberrant left ventricular relaxation,[28,29] and failure of ventricular dilatation[25,26] in septic patients. The clinical impact and relative contribution of diastolic dysfunction to myocardial depression is yet to be elucidated.

Right Ventricular Function

The peripheral vasodilatation seen in sepsis leads to decreased left ventricular afterload and eventually preload. The increase in cardiac output can be limited by decreased preload if the patient is not adequately volume resuscitated. However, the right ventricular (RV) afterload is frequently elevated due to increased pulmonary vascular resistance (PVR) from acute lung injury.[30] Because of the variability in RV afterload, it may not behave like the LV in septic patients. This is the reason for a number of studies looking into RV function in sepsis.

Systolic RV dysfunction has been shown by decreased right ventricular ejection fraction (RVEF) and RV dilatation in volume resuscitated patients.[31–34] Kimchi et al.[31] and Parker et al.[33] showed that RV dysfunction can occur even in the absence of increased pulmonary artery pressures and pulmonary vascular resistance, suggesting that increased RV afterload may not be the sole explanation for RV dysfunction in septic shock. Parker et al.[33] also showed that RV and LV function

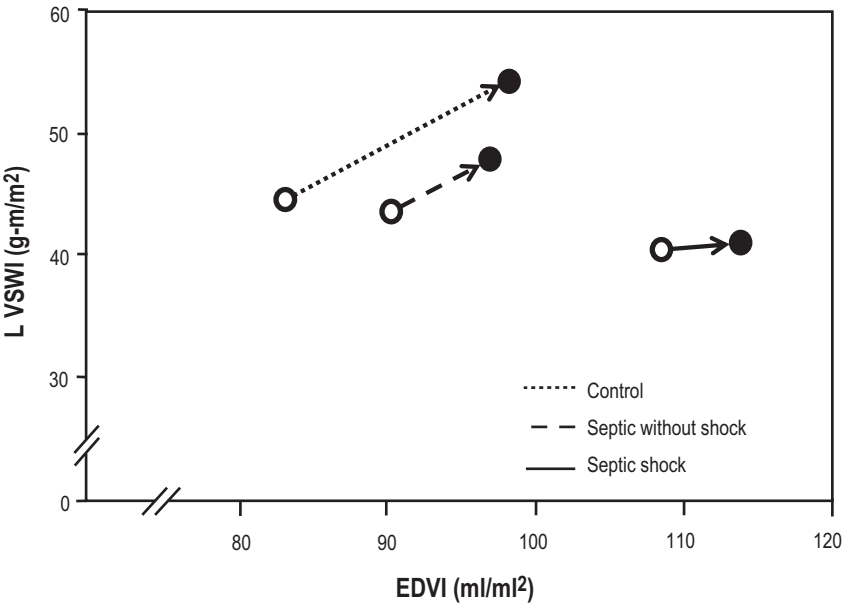


FIGURE 6.3. Frank-Starling ventricular performance relationship for each of the three patient groups. Data points plotted represent the mean prevolume and postvolume infusion values of end-diastolic volume index (EDVI) and left ventricular stroke work index (LVSWI) for each patient group. Control patients showed a normal increase of EDVI and LVSWI in response to volume infusion. The absolute increases of EDVI and LVSWI in patients with sepsis without shock were less than those of control subjects, but the slope of the curve is similar to control patients. Patients with septic shock had a greatly diminished response and showed a marked rightward and downward shift of the Frank-Starling relationship.

paralleled each other in dysfunction and recovery (Figure 6.4). In this study survivors showed RV dilatation and decreased RVEF and right ventricular stroke work index (RVSWI), which normalized in 7 to 14 days. As with the LV, the RV was only moderately dilated and RVEF marginally decreased; both persisted through their course of sepsis.

Diastolic dysfunction of the RV has also been demonstrated in a number of studies. Kimchi et al.[31] noticed a lack of correlation between right atrial pressure and right ventricular end-diastolic volume (RVEDV), suggesting altered RV compliance. In another study, a subgroup of patients who were volume loaded demonstrated increase in CVP but not right ventricular end-diastolic volume index (RVEDVI).[32] As in the LV, the relative contribution of systolic and diastolic dysfunction in the RV is unknown.

Cardiovascular Prognostic Factors in Septic Shock

The cardiac index (CI) appears not to be a reliable predictor of mortality in septic shock. Despite early evidence suggesting low CI as a poor prognostic factor,[10–13] introduction of the PAC has shown that septic shock patients, when adequately fluid-resuscitated, have a high CI and low SVR among both survivors and non-

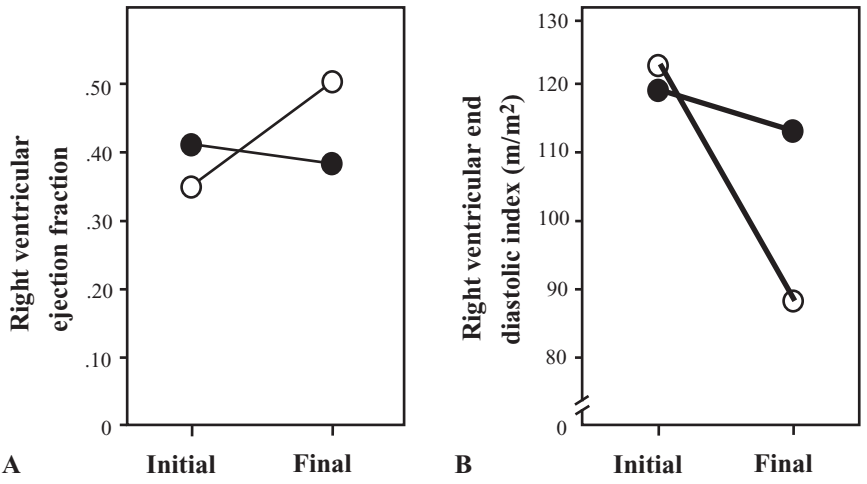


FIGURE 6.4. Serial changes in right ventricular ejection fraction and end-diastolic volume index during septic shock in humans. (A) Mean initial and final right ventricular ejection fractions for survivors (closed circles, $p < 0.001$) and nonsurvivors (open circles, $p < 0.001$). (B) Mean initial and final right ventricular end-diastolic volume index for survivors (closed circles, $p < 0.05$) and nonsurvivors (open circles, p = not significant). The right ventricle, similar to the left, undergoes dilation with a drop in ejection fraction with the acute onset of septic shock. In 7 to 10 days, right ventricular dilation and decreased ejection fraction revert to normal in survivors.

survivors.[16,17] Armed with the PAC, other hemodynamic parameters were investigated as prognostic indicators.

Baumgartner et al.[35] recognized that patients with extremely high CI (>7.0 L/min/m^2) and accordingly low SVR had poor outcomes. Groenveld et al.[36] also found nonsurvivors had lower SVRs than survivors after matching other characteristics, concluding that there may be a link between outcome in septic shock and the degree of peripheral vasodilation.

Parker et al.[18] reviewed hemodynamic data from septic shock patients on presentation and at 24 hours to identify prognostic value. On presentation, only heart rate <106 beats/min suggested a favorable outcome. At 24 hours, heart rate < 95 beats/min, systemic vascular resistance index (SVRI) > 1529 dynes·sec·cm^5/m^2, a decrease in heart rate > 18 beats/min, and a decrease in CI > 0.5 L/min/m^2 all predicted survival. In a subsequent study,[19] the same authors confirmed previous findings of decreased LVEF and increased LVEDVI in survivors of septic shock but not in nonsurvivors, a finding that has been confirmed by other groups.[25,26] Although myocardial depression has been historically linked to increased mortality, these data may imply that depression, at least as manifested by decreased ejection fraction with ventricular dilatation, may actually represent an adaption to stress rather than a maladaptive manifestation of injury.

From the studies of Parker et al.[18,19] it is apparent that, despite not developing significant LV dilatation overall, nonsurvivors could be divided into two patterns: those with progressively declining LVEDVI and CI, and the others with incremental increases in LVEDVI while maintaining CI. Based on this, Parker et al. described different hemodynamic collapse profiles leading to death in septic shock.[18,19] First, some patients die from refractory hypotension secondary to distributive shock with preserved or elevated CI. The other pattern consists of cardiogenic form of septic shock with decreased CI and a mixture of cardiogenic and distributive shock patterns. The explanation of the two patterns came from a study by Parker et al.[19] It appears that patients who cannot dilate their LV (decreasing CI and LVEDVI) die from a cardiogenic form of septic shock. The other fatal pattern consists of those patients who can dilate their LV and preserve CI (increase LVEDVI while maintaining CI) but eventually die of distributive shock.

The prognostic value of RV hemodynamic parameters has been debated. A number of studies[31–34] have shown that RV dilatation and decreased RVEF, if persistent, is associated with poor prognosis.[33,34] However, Vincent et al.[34] suggested that high initial RVEF portends a good prognosis. On the other hand, Parker et al.[33] found that the survivors had a lower RVEF. The answer to this question requires additional investigation.

The other prognostic parameter is response of hemodynamic parameters to dynamic challenges, namely dobutamine. Nonsurvivors of septic shock have a blunted response to dobutamine,[37–39] whereas survivors demonstrated increased SVI (stroke work index), increased mixed venous oxygen saturation, ventricular dilatation, and a decrease in diastolic blood pressure after a dobutamine challenge. The above response to dobutamine predicts survival in patients with septic shock.

Etiology of Myocardial Depression in Sepsis and Septic Shock

The exact sequence of events in the pathophysiology of septic myocardial depression has only begun to be elucidated in recent years. There are likely a multitude of mechanisms and factors that play a role. A number of potential pathogenic mechanisms have been proposed. The two major theories have been myocardial hypoperfusion and a circulating myocardial depressant substance.

Organ Level

Myocardial Hypoperfusion

The potential of myocardial hypoperfusion leading to myocardial depression via global ischemia has been largely dismissed by a number of studies. Cunnion et al.[40] inserted thermodilution catheters into the coronary sinus of septic patients and measured serial coronary flow and metabolism (Figure 6.5). Normal or elevated coronary flow was present in septic patients in comparison to normal controls with comparable heart rates. There was also no difference in myocardial

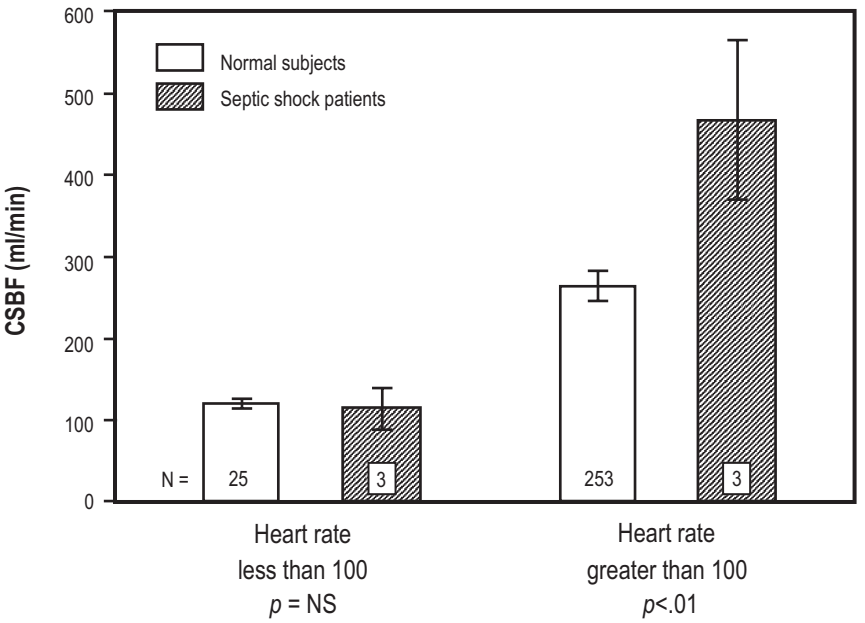


FIGURE 6.5. Mean coronary sinus blood flow (CSBF) in seven patients with septic shock compared with normal subjects. Flow measurements were stratified into heart rates above and below 100 beats/min. Coronary blood flow in septic shock patients equaled (heart rate < 100/min) or exceeded (heart rate > 100/min) coronary blood flow in control patients.

blood flow between septic patients who did and did not developed myocardial dysfunction. There also was no net lactate production.

Dhainaut et al.[41] also confirmed these findings while employing similar methods. In addition to human studies, a canine model of sepsis study[42] showed that myocardial high energy phosphates and oxygen utilization were preserved in septic shock. Both of these observations argue against neither global myocardial ischemia nor hypoperfusion.

Perfusion aside, there is evidence for myocardial cell injury evidenced by increased troponin I levels in septic shock.[43] A study by Elst et al.[44] examined levels of troponin I and T in patients with septic shock. A correlation between LV dysfunction and TnI (troponin I) positivity (78% vs. 9% in cTnI negative patients $p < .001$) existed. They also found that older patients with underlying cardiovascular disease more often had both troponin positivity and LV dysfunction. However, whether the clinically inapparent myocardial cell injury contributes to or is a consequence of septic shock is yet to be determined.[44] Although troponin is used as a marker of myocardial injury (particularly in the context of myocardial ischemia), it does not specifically suggest myocardial hypoperfusion in other contexts.

Myocardial Depressant Substances

The theory of a circulating myocardial depressant factor was put forth by Wiggers et al.[45] in 1947 in the context of hemorrhagic shock. The presence of such a factor was confirmed by Brand and Lefer[46] in 1966. Lefer's work prompted further research into septic myocardial depressant substances.[46–54]

A number of endogenous substances have been implicated as potential causes of septic myocardial depression. These have included estrogenic compounds, histamine, eicosanoids/prostaglandins, and several novel substances that could never be effectively isolated[46–54] (for review[55]). In the past decade, the dominant focus has been on inflammatory cytokines.

In one of the seminal studies in the field, Parillo et al. in 1985[56] showed a link between myocyte depression and septic serum from a patient with sepsis-associated myocardial depression. The serum from patients demonstrated concentration-dependent depression of in vitro myocyte contractility (Figure 6.6). Parillo et al. were also able to correlate a temporal and qualitative relationship between in vivo myocardial depression (decrease LVEF) and in vitro cardiac myocyte depression induced by serum from corresponding patients. In another study[57] investigators noted that higher levels of myocardial depressant activity correlated with higher peak serum lactate, increased ventricular filling pressures, increased LVEDVI, and higher mortality (36% vs. 10%) when compared with patients with lower or absent activity levels.

Potential circulating myocardial depressant substances include arachidonic acid metabolites, platelet activating factor, histamine, and endorphins. Filtration studies[57] found that the substance was water soluble, heat labile, and greater than

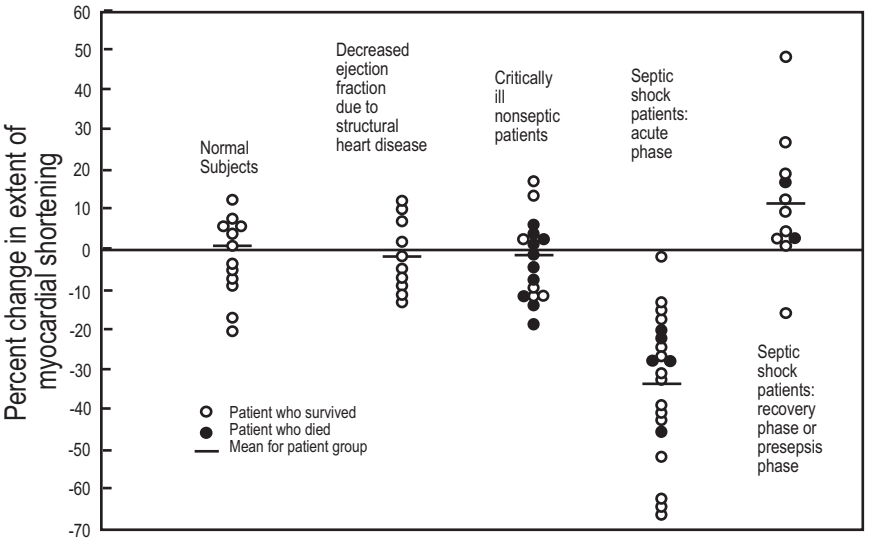


FIGURE 6.6. The effect of serum from septic shock patients and control groups on the extent of myocardial cell shortening of spontaneously beating rat heart cells in vitro. Septic shock patients during the acute phase demonstrated a statistically significant lower extent of shortening ($p < .001$) compared with any other group.

10 kd. These characteristics pointed toward a protein or polypeptide consistent with cytokines such as TNF-α and IL-1β.

TNF-α likely has a role as a myocardial depressant substance for a number of reasons. TNF-α shares the same biochemical profile as myocardial depressant substances.[56,58] Clinically, TNF-α is associated with fever, increased lactic acid, disseminated intravascular coagulation, acute lung injury, and death. The hemodynamic effects of TNF-α are similar to sepsis, in particular hypotension, increased cardiac output, and low systemic vascular resistance.[59,60]

Healthy human volunteers given TNF-α infusions have similar responses.[61,62] Experimentally, TNF-α given to in vitro and ex vivo animal and human myocardial tissue demonstrated a concentration dependent depression of contractility.[49,63] Kumar et al.[64] showed that removal of TNF-α from patients serum with septic shock decreased the myocardial depression. Also, Vincent et al.[65] in a pilot study showed improved LVSWI with administration of anti-TNF-α monoclonal antibody, even though there was no survival benefit.

IL-1β produces similar hemodynamic responses to TNF-α. IL-1β levels are also elevated in sepsis and septic shock.[66] In vitro and ex vivo myocardial contractility is depressed when cardiac tissue is exposed to IL-1β.[63,67,68] Removal of IL-1β via immunoabsorption from septic human serum attenuates the depression of cardiac myocytes.[64] The effects of IL-1β antagonist on cardiac function and survival are unimpressive[69–71] even though metabolic derangements are attenuated by IL-1β antagonist.[70,71]

It is likely that cytokines such as TNF-α and IL-β, rather than working in isolation, synergize to exert their depressant effects. In isolation, TNF-α and IL-1β require very high concentration to induce in vitro rat myocyte depression.[64] However, when combined, they act synergistically and require concentrations 50 to 100 times lower than those required individually.[64,72] These concentrations are within the range of those found in septic shock patients.

Another recent series of studies by Pathan et al. have strongly implicated circulating IL-6 as an important myocardial depressant substance in human septic shock.[73–75] These investigators have demonstrated that meningococcal sepsis is associated with induction of IL-6 expression in blood mononuclear cells and that the level of serum IL-6 corresponds with the degree of cardiac function in such patients. Further, they have recently shown that IL-6 depresses contractility of myocardial tissue in vitro and that neutralization of IL-6 in serum from patients with meningococcal septic shock neutralizes this effect.[73]

Evidence for other potential myocardial depressant substances continue to be developed. Recently, Mink et al. have implicated lysozyme c (consistent with that found in the spleen, leukocytes in the spleen or other organs) as a potential myocardial depressant substance (MDS).[47] In the canine model of *E. coli* sepsis lysozyme c caused myocardial depression and attenuated response to beta-agonists.[47] The potential mechanism proposed was lysozyme binding or hydrolyzing the membrane glycoprotein of cardiac myocytes, thereby affecting signal transduction (linking physiologic excitation with physiologic contraction). The levels of lysozyme c were found to be elevated in the heart and spleen, but not in lymphocytes when compared to preseptic levels.[47] Mink et al. went on further to show that pretreatment with an inhibitor of lysozyme (N,N′,N″-triacetylglucosamine) prevented myocardial depression in canine sepsis.[76] However, the effect of this lysozyme inhibitor (TAC) was only seen in pretreatment and early treatment groups (1.5 hours after onset of septic shock) and not in late treatment groups (greater than 3.5 hours).[76]

An important microbial factor that has recently been shown to potentially exert hemodynamic and myocardial depressant activity in sepsis and septic shock is bacterial nucleic acid. Several investigators have demonstrated that unique aspects of bacterial nucleic acid structure may allow bacterial DNA to generate a shock state similar to that produced by endotoxin when administered to animals.[77] Extending these observations, we have recently demonstrated depression of rat myocyte contraction with bacterial DNA and RNA.[78] This effect was more marked when DNA and RNA came from pathogenic strains of *S. aureus* and *E. coli*. These effects were not seen when the rat myocyte was pretreated with DNase and RNase.

Cellular Level

The sequence of mechanisms leading from an MDS to cellular dysfunction remains substantially opaque. There are several potential mechanisms that may

play a role at the cellular level. Overproduction of nitric oxide (NO) and derangements of calcium physiology in the myocardial cell are two potential cellular mechanisms.

In vitro, myocyte depression in response to inflammatory cytokines can be divided into early and late phases. Early depression of cardiac myocyte depression occurs within minutes of exposure to either TNF-α or IL-1β, or TNF-α and IL-1β given together or as septic serum.[64,79] TNF-α also demonstrates the ability to cause rapid myocardial depression in dogs.[60,80] Besides the early effects of TNF-α, IL-1β and supernatants of activated macrophages also have a later, prolonged effect on in vitro myocardial tissue.[67,68,80,81] This late phase establishes within hours and lasts for days. This suggests a different mechanism from early myocardial depression.

Production of NO may be a potential explanation for both early and late myocardial depression. NO is produced from conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). NOS has two forms: one is constitutive (cNOS) and the other is inducible (iNOS). NO produced by cNOS appears to have a regulatory role in cardiac contractility.[82–84] However, when cardiac myocytes are exposed to supraphysiologic levels of NO or NO donors (nitroprusside and SIN-1), there is a reduction in myocardial contractility.[85] Paulus et al.[86] infused nitroprusside into coronary arteries, which decreased intraventricular pressures and improved diastolic function.

Current evidence suggests that early myocyte dysfunction may occur through generation of NO and resultant cyclic guanosine monophosphate (cGMP) via cNOS activation in cardiac myocytes and adjacent endothelium.[72,79,87] Late myocardial depression may be secondary to induction of synthesis of iNOS NO.[68,79,88,89] In addition, the generation of peroxynitrite via interaction of the free radical NO group and oxygen may also play a role in more prolonged effects.[90] We have demonstrated that the early phase may involve both a NO dependent but β-adrenergic-independent mechanism and a NO-independent defect of β-adrenoreceptor signal transduction.[55,87,91,92] Others have shown that IL-6 can cause both early and late NO-mediated myocardial depression in an avian myocardial cell model via sequential activation of cNOS followed by induction of iNOS, a finding that could explain recent human data implicating IL-6 in meningococcal septic myocardial dysfunction.[73,74,93–95] This study suggests the role for sequential production of NO from cNOS and iNOS in the pathogenesis of myocardial depression from cytokines.

Potential Therapies

In the minority of cases where septic myocardial depression may be sufficiently expressed clinically to require treatment, options are available. Epinephrine, dobutamine, milrinone, and digoxin have all been shown to improve cardiac function in low-output septic shock.[96–98] However, these modalities are supportive in nature and do not specifically attempt to neutralize myocardial depressant pathways.

Research into the pathophysiology of sepsis-induced myocardial depression naturally leads to potential specific therapies to reverse septic myocardial dysfunction. Several investigators have examined the use of various hemofiltration modalities in septic shock.[53,99–102] However, results have been highly inconsistent. Mink et al.[99] utilized continuous arteriovenous hemofiltration combined with systemic vasopressor therapy to reverse cardiac depression and hypotension in an endotoxicosis-equivalent canine *E. coli* sepsis model. Freeman and colleagues, however, were unable to demonstrate such a benefit.[100]

Inflammatory cytokine antagonists are another area of research. As previously mentioned TNF-α monoclonal antibodies have improved LV function when given to patients in septic shock[65] despite failing to show a survival benefit. IL-1β antagonists have shown mixed results. Despite the absence of a survival benefit, attenuation of metabolic derangements in septic shock was noted,[70,71] although no hemodynamic benefit was apparent.[69]

Further down the sequence of pathogenesis in septic myocardial depression are the therapeutic potential of NO scavengers or NO inhibitors. Methylene blue (NO scavenger) has been shown to attenuate the hemodynamic alterations in a randomized open label pilot of 20 patients with sepsis.[103] Suzuki et al.[104] used an inhibitor of iNOS (L-canavanine) in septic rats which showed prevention of myocardial contractility depression. However, L-canavanine itself depressed myocardial contractility via decreased coronary blood flow, an effect that was thought to be potentially responsible for the increased mortality in the only randomized double-blinded clinical study of a NOS inhibitor in clinical septic shock.[105,106]

Conclusion

Myocardial dysfunction is an important component in the hemodynamic collapse induced by sepsis and septic shock. A series of inflammatory cascades triggered by the inciting infection generate circulatory myocardial depressant substances, including TNF-α, IL-1β, PAF, and lysozyme. Their effects are partly mediated through NO generation. How NO depresses cardiac contractility is largely unknown. The research into the pathophysiology of septic myocardial depression will hopefully yield potential therapies. Until then, volume resuscitation, with inotropic and vasopressor support, is the current standard of care to restore tissue perfusion.

References

1. Centers for Disease Control and Prevention. National Center for Health Statistics. Mortality patterns—United States, 1990. Monthly Vital Statistics Report 1993; 41:5.
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29(7):1303–10.

3. Bone RC, Balk R, Cerra FB, et al. ACCP/SCCM Consensus Conference: Definitions for sepsis and organ failure and guidelines for use of innovative therapies in sepsis. Chest 1992;101:1644–55.
4. van der Poll T, van Deventer SJ. Cytokines and anticytokines in the pathogenesis of sepsis. Infect Dis Clin North Am 1999;13(2):413–26.
5. Alloatti G, Penna C, De Martino A, et al. Role of nitric oxide and platelet-activating factor in cardiac alterations induced by tumor necrosis factor-alpha in the guinea-pig papillary muscle. Cardiovasc Res 1999;41(3):611–9.
6. Chang S, Feddersen CO, Henson PM, et al. Platelet activating factor mediates hemodynamic changes and lung injury in endotoxin treated rats. J Clin Invest 1987;79: 1498–509.
7. Cheng ZQ, Bose D, Jacobs H, et al. Sepsis causes presynaptic histamine H3 and alpha2-adrenergic dysfunction in canine myocardium. Cardiovasc Res 2002;56(2): 225–34.
8. Silva AT, Cohen J. Role of interferon-gamma in experimental gram-negative sepsis. J Infect Dis 1992;166:331–5.
9. Fujioka K, Sugi K, Isago T, et al. Thromboxane synthase inhibition and cardiopulmonary function during endotoxemia in sheep. J Appl Physiol 1991;71(4): 1376–81.
10. MacLean LD, Mulligan WG, McLean APH, et al. Patterns of septic shock in man: A detailed study of 56 patients. Ann Surg 1967;166:543–62.
11. Clowes GHA, Vucinic M, Weidner MG. Circulatory and metabolic alterations associated with survival or death in peritonitis. Ann Surg 1966;163:866–44.
12. Nishijima H, Weil MH, Shubin H, et al. Hemodynamic and metabolic studies on shock associated with gram-negative bacteremia. Medicine (Baltimore) 1973;52: 287–94.
13. Weil MH, Nishijima H. Cardiac output in bacterial shock. Am J Med 1978;64: 920–2.
14. Blain CM, Anderson TO, Pietras RJ, et al. Immediate hemodynamic effects of gram-negative vs gram-positive bacteremia in man. Arch Intern Med 1970;126: 260–5.
15. Packman MI, Rackow EC. Optimum left heart filling pressure during fluid resuscitation of patients with hypovolemic and septic shock. Crit Care Med 1983;11:165–9.
16. Winslow EJ, Loeb HS, Rahimtoola SH, et al. Hemodynamic studies and results of therapy in 50 patients with bacteremic shock. Am J Med 1973;54:421–32.
17. Krausz MM, Perel A, Eimerl D, et al. Cardiopulmonary effects of volume loading in patients with septic shock. Ann Surg 1977;185:429–34.
18. Parker MM, Shelhamer JH, Natanson C, et al. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. Crit Care Med 1987;15:923–9.
19. Parker MM, Suffredini AF, Natanson C, et al. Responses of left ventricular function in surviviors and non-survivors of septic shock. J Crit Care 1989;4:19–25.
20. Weisul RD, Vito L, Dennis RC, et al. Myocardial depression during sepsis. Am J Surg 1977;133:512–21.
21. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;100:483–90.
22. Ognibene FP, Parker MM, Natanson C, et al. Depressed left ventricular performance: response to volume infusion in patients with sepsis and septic shock. Chest 1988;93:903–10.

23. Ellrodt AG, Riedinger MS, Kimchi A, et al. Left ventricular performance in septic shock: reversible segmental and global abnormalities. Am Heart J 1985;110: 402–9.
24. Raper R, Sibbald WJ. Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. Chest 1986;89(3):427–34.
25. Vieillard BA, Schmitt JM, Beauchet A, et al. Early preload adaptation in septic shock? A transesophageal echocardiographic study. [comment]. Anesthesiology 2001;94(3):400–6.
26. Jardin F, Fourme T, Page B, et al. Persistent preload defect in severe sepsis despite fluid loading: a longitudinal echocardiographic study in patients with septic shock. Chest 1999;116(5):1354–9.
27. Jafri SM, Lavine S, Field BE, et al. Left ventricular diastolic function in sepsis. Crit Care Med 1991;18:709–4.
28. Munt B, Jue J, Gin K, et al. Diastolic filling in human severe sepsis: An echocardiographic study. Crit Care Med 1998;26:1829–33.
29. Poelaert J, Declerck C, Vogelaers D, et al. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997;23:553–60.
30. Sibbald WJ, Paterson NAM, Holliday RL, et al. Pulmonary hypertension in sepsis: measurement by the pulmonary artery diastolic-pulmonary wedge pressure gradient and the influence of passive and active factors. Chest 1978;73:583–91.
31. Kimchi A, Ellrodt GA, Berman DS, et al. Right ventricular performance in septic shock: a combined radionuclide and hemodynamic study. JACC 1984;4:945–51.
32. Schneider AJ, Teule GJJ, Groenveld ABJ, et al. Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study. Am Heart J 1988;116: 103–12.
33. Parker MM, McCarthy KE, Ognibene FP, et al. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. Chest 1990;97:126–31.
34. Vincent JL, Reuse C, Frank N, et al. Right ventricular dysfunction in septic shock: assessment by measurements of right ventricular ejection fraction using the thermodilution technique. Acta Anaesthesiol Scand 1989;33:34–8.
35. Baumgartner J, Vaney C, Perret C. An extreme form of hyperdynamic syndrome in septic shock. Intensive Care Med 1984;10:245–9.
36. Groenveld ABJ, Nauta JJ, Thijs L. Peripheral vascular resistance in septic shock: its relation to outcome. Intensive Care Med 1988;14:141–7.
37. Rhodes A, Lamb FJ, Malagon R, et al. A prospective study of the use of a dobutamine stress test to identify outcome in patients with sepsis, severe sepsis or septic shock. Crit Care Med 1999;27.
38. Vallet B, Chopin C, Curtis SE. Prognostic value of the dobutamine test in patients with sepsis syndrome and normal lactate values: a prospective, multicenter study. Crit Care Med 1993;21:1868–75.
39. Kumar A, Schupp E, Bunnell E, et al. The cardiovascular response to dobutamine in septic shock. Clin Invest Med 1994;17:B18#107.
40. Cunnion RE, Schaer GL, Parker MM, et al. The coronary circulation in human septic shock. Circulation 1986;73:637–44.
41. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. Circulation 1987;75:533–41.

42. Solomon MA, Correa R, Alexander HR, et al. Myocardial energy metabolism and morphology in a canine model of sepsis. Am J Physiol 1994;266:H757–68.
43. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. Crit Care Med 1999;27(9):1775–80.
44. ver Elst KM, Spapen HD, Nguyen DN, et al. Cardiac troponins I and T are biological markers of left ventricular dysfunction in septic shock. Clin Chem 2000;46(5):650–7.
45. Wiggers CJ. Myocardial depression in shock. A survey of cardiodynamic studies. Am Heart J 1947;33:633–50.
46. Lefer AM. Mechanisms of cardiodepression in endotoxin shock. Circ Shock suppl. 1979;1:1–8.
47. Mink SN, Jacobs H, Bose D, et al. Lysozyme: a mediator of myocardial depression and adrenergic dysfunction in septic shock in dogs. J Mol Cell Cardiol 2003;35: 265–75.
48. Li X, Eschun G, Bose D, et al. Histamine H3 activation depresses cardiac function in experimental sepsis. J App Physiol 1998;85(5):1693–701.
49. Gu M, Bose R, Bose D, et al. Tumor necrosis factor-α but not septic plasma depresses cardiac myofilament contraction. Can J Anaesth 1998;45:352–9.
50. Maksad KA, Chung-Ja C, Clowes GHA, et al. Myocardial depression in septic shock: physiologic and metabolic effects of a plasma factor on an isolated heart. Circ Shock 1979;1:35–42.
51. Lovett WL, Wangensteen SL, Glenn TM, et al. Presence of a myocardial depressant factor in patients with circulatory shock. Surgery 1971;70:223–31.
52. Benassayag C, Christeff MC, Auclair MC, et al. Early released lipid-soluble cardiodepressant factor and elevated oestrogenic substances in human septic shock. Eur J Clin Invest 1984;14:288–94.
53. Gomez A, Wang R, Unruh H, et al. Hemofiltration reverses left ventricular dysfunction during sepsis in dogs. Anesthesiology 1990;73:671–85.
54. Jha P, Jacobs H, Bose D, et al. Effects of *E. coli* sepsis and myocardial depressant factor on interval-force relations in dog ventricle. Am J Physiol 1993;264: H1402–10.
55. Kumar A, Krieger A, Symeoneides S, et al. Myocardial dysfunction in septic shock, Part II: Role of cytokines and nitric oxide. J Cardiovasc Thorac Anesth 2001;15(4): 485–511.
56. Parrillo JE, Burch C, Shelhamer JH, et al. A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest 1985;76:1539–53.
57. Reilly JM, Cunnion RE, Burch-Whitman C, et al. A circulating myocardial depressant substance is associated with cardiac dysfunction and peripheral hypoperfusion (lactic acidemia) in patients with septic shock. Chest 1989;95:1072–80.
58. Seckinger P, Vey E, Turcatti G, et al. Tumor necrosis factor inhibitor: purification, NH2-terminal amino acid sequence and evidence for anti-inflammatory and immunomodulatory activities. Eur J Immunol 1990;20:1167–74.
59. Eichacker PQ, Hoffman WD, Farese A, et al. TNF but not IL-1 in dogs causes lethal lung injury and multiple organ dysfunction similar to human sepsis. J Appl Physiol 1991;71:1979–89.
60. Eichenholz PW, Eichacker PQ, Hoffman WD, et al. Tumor necrosis factor challenges in canines: patterns of cardiovascular dysfunction. Am J Physiol 1992;263: H668–75.

61. van der Poll T, van Deventer SJ, Hack CE, et al. Effects on leukocytes following injection of tumor necrosis factor into healthy humans. Blood 1992;79:693–8.
62. van der Poll T, Romjin JA, Endert E, et al. Tumor necrosis factor mimics the metabolic response to acute infection in healthy humans. Am J Physiol 1991;261: E457–65.
63. Weisensee D, Bereiter-Hahn J, Low-Friedrich I. Effects of cytokines on the contractility of cultured cardiac myocytes. Int J Immunopharmacol 1993;15:581–7.
64. Kumar A, Thota V, Dee L, et al. Tumor necrosis factor-alpha and interleukin-1 beta are responsible for depression of in vitro myocardial cell contractility induced by serum from humans with septic shock. J Exp Med 1996;183:949–58.
65. Vincent JL, Bakker J, Marecaux G, et al. Administration of anti-TNF antibody improves left ventricular function in septic shock patients: results of a pilot study. Chest 1992;101:810–15.
66. Hesse DG, Tracey KJ, Fong Y, et al. Cytokine appearance in human endotoxemia and primate bacteremia. Surg Gynecol Obstet 1988;166:147–53.
67. Gulick T, Chung MK, Pieper SJ, et al. Interleukin-1 and tumor necrosis factor inhibit cardiac myocyte adrenergic responsiveness. Proc Natl Acad Sci 1989;86:6753–7.
68. Hosenpud JD, Campbell SM, Mendelson DJ. Interleukin-1-induced myocardial depression in an isolated beating heart preparation. J Heart Transplant 1989;8: 460–4.
69. Vincent JL, Slotman G, van Leeuwen PAM, et al. IL-1ra administration does not improve cardiac function in patients with severe sepsis. Intensive Care Med 2004;21: S11.
70. Fisher CJ Jr, Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. JAMA 1994;271(23):1836–43.
71. Fisher CJ Jr, Slotner GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. Crit Care Med 1994;22:12–21.
72. Cain BS, Meldrum DR, Dinarello CA, et al. Tumor necrosis factor-α and interleukin-1β synergistically depress human myocardial function. Crit Care Med 1999;27: 1309–18.
73. Pathan N, Hemingway CA, Alizadeh AA, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet 2004;363(9404):203–9.
74. Pathan N, Sandiford C, Harding SE, et al. Characterization of a myocardial depressant factor in meningococcal septicemia. Crit Care Med 2002;30(10):2191–8.
75. Thiru Y, Pathan N, Bignall S, et al. A myocardial cytotoxic process is involved in the cardiac dysfunction of meningococcal septic shock [see comment]. Crit Care Med 2000;28(8):2979–83.
76. Mink SN, Jacob HS, Duke K, et al. N,N′,N″-triacetylglucosamine, an inhibitor of lysozyme, prevents myocardial depression in *E. coli* sepsis in dogs. Crit Care Med In press.
77. Sparwasser T, Miethke T, Lipford G, et al. Bacterial DNA causes septic shock. Nature 1997;386(6623):336–7.
78. Paladugu B, Kumar A, Parrillo JE, et al. Bacterial DNA and RNA induce rat cardiac myocyte contraction depression in-vitro. Shock 2004;21(364):369.
79. Finkel MS, Oddis CV, Jacobs TD, et al. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 1992;257:387–9.

80. Walley KR, Hebert PC, Wakai Y, et al. Decrease in left ventricular contractility after tumor necrosis factor-α infusion in dogs. J Appl Physiol 1994;76:1060–7.
81. DeMeules JE, Pigula FA, Mueller M, et al. Tumor necrosis factor and cardiac function. J Trauma 1992;32:686–92.
82. Hare JM, Keaney JF, Balligand JL, et al. Role of nitric oxide in parasympathetic modulation of beta-adrenergic myocardial contractility in normal dogs. J Clin Invest 1995;95:360–6.
83. Sawyer DB, Colucci WS. Nitric oxide in the failing myocardium. Cardiol Clin North America. 1998;16:657–64.
84. Balligand JL, Kobzik L, Han X, et al. Nitric oxide-dependent parasympathetic signalling is due to activation of constitutive endothelial (type III) nitric oxide synthase in cardiac myocytes. J Biol Chem 1995;270:14582–6.
85. Brady AJ, Poole-Wilson PA, Harding SE, et al. Nitric oxide production within cardiac myocytes reduces their contractility in endotoxemia. Am J Physiol 1992;263: H1963–6.
86. Paulus WJ, Vantrimpont PJ, Shah AM. Acute effects of nitric oxide on left ventricular relaxation and diastolic distensability in humans. Assessment by bicoronary sodium nitroprusside infusion. Circulation 1994;89:2070–8.
87. Kumar A, Brar R, Wang P, et al. The role of nitric oxide and cyclic GMP in human septic serum-induced depression of cardiac myocyte contractility. Am J Physiol 1999;276:R265–76.
88. Rozanski GJ, Witt RC. IL-1 inhibits β-adrenergic control of cardiac calcium current: role of L-arginine/nitric oxide pathway. Am J Physiol 1994;267:H1753–8.
89. Smith JA, Radomski MW, Schulz R, et al. Porcine ventricular endocardial cells in culture express the inducible form of nitric oxide synthase. Br J Pharmacol 1993;108:1107–10.
90. Szabo C. The pathophysiological role of peroxynitrite in shock, inflammation, and ischemia-reperfusion injury. Shock 1996;6:79–88.
91. Anel R, Paladugu B, Makkena R, et al. TNFα induces a proximal defect of β-adrenoreceptor signal transduction in cardiac myocytes. Crit Care Med 1999; 27:A95.
92. Kumar A, Brar R, Sun E, et al. Tumor necrosis factor (TNF) impairs isoproterenol-stimulated cardiac myocyte contractility and cyclic AMP production via a nitric oxide-independent mechanism. Crit Care Med 1996;24:A95.
93. Kinugawa K, Takahashi T, Kohmoto O, et al. Nitric oxide-mediated effects of interleukin-6 on [Ca2+]i and cell contraction in cultured chick ventricular myocytes. Circ Res 1994;75:285–95.
94. Kinugawa KI, Kohmoto O, Yao A, et al. Cardiac inducible nitric oxide synthase negatively modulates myocardial function in cultured rat myocytes. Am J Physiol 1997;272(1 Pt 2):H35–47.
95. Ishibashi Y, Urabe Y, Tsutsui H, et al. Negative inotropic effect of basic fibroblast growth factor on adult rat cardiac myocyte. Circulation 1997;96(8):2501–4.
96. Barton P, Garcia J, Kouatli A, et al. Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, interventional study. Chest 1996;109:1302–12.
97. Le Tulzo Y, Seguin P, Gacouin A, et al. Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. Intensive Care Med 1997;23(6):664–70.
98. Nasraway SA, Rackow EC, Astiz ME, et al. Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure, and systemic hypoperfusion. Chest 1989;95:612–5.

99. Mink SN, Jha P, Wang R, et al. Effect of continuous arteriovenous hemofiltration combined with systemic vasopressor therapy on depressed left ventricular contractility and tissue oxygen delivery in canine Escherichia coli sepsis. Anesthesiology 1995;83(1):178–90.
100. Freeman BD, Yatsiv I, Natanson C, et al. Continuous arteriovenous hemofiltration does not improve survival in a canine model of septic shock. J Am Coll Surg 1995;180(3):286–92.
101. Mink SN, Li X, Bose D, et al. Early but not delayed continuous arteriovenous hemofiltration improves cardiovascular function in sepsis in dogs. Intensive Care Med 1999;25(7):733–43.
102. Lee PA, Matson JR, Pryor RW, et al. Continuous arteriovenous hemofiltration therapy for Staphylococcus aureus-induced septicemia in immature swine. Crit Care Med 1993;21(6):914–24.
103. Kirov MY, Evgenov OV, Evgenov NV, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med 2001;29(10): 1860–7.
104. Suzuki N, Sakamoto A, Ogawa R. Effect of L-canavanine, an inhibitor of inducible nitric oxide synthase, on myocardial dysfunction during septic shock. J Nippon Med Sch 2002;69:1–13.
105. Davis JO, Freeman RH. Mechanisms regulating renin release. Physiol Rev 1976; 56:1–56.
106. Grover R, Zaccardelli D, Colice G, et al. An open-label dose escalation study of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88), in patients with septic shock. Crit Care Med 1999;27:913–22.

7
Toward a Consensus on Intraabdominal Hypertension

Manu LNG Malbrain, Michael Sugrue, Michael Cheatham, and Rao Ivatury

Introduction

There has been an exponentially increasing interest in intraabdominal hypertension (IAH) and the abdominal compartment syndrome (ACS) over the past decade; however, until now no uniform definitions have been suggested. Definitions of IAH or ACS stand or fall with the accuracy and reproducibility of the IAP measurement method.[1] Not only the absolute numbers but also the use of mean, median, or maximal IAP values will influence the incidence of IAH.[2] Different threshold values have been suggested for IAH and ACS and some have interchanged the terms IAH and ACS. Others suggested terms as surgical or medical ACS, but with ever changing definitions. To date it is therefore very difficult to interpret the literature data, and a consensus on definitions of issues related to IAH is needed in order to approach scientific accuracy in comparing different clinical reports and to plan for future clinical trials. These definitions should be comprehensive, detailed, simple, practical, and acceptable to the majority of the scientific community working in this particular field. Until such a consensus is achieved, this chapter will provide some definitions to be used as a basis for it, so that the data and results from future studies can be more easily compared.[3]

Definitions

Intraabdominal Pressure (IAP)

The IAP is the steady state of pressure concealed within the abdominal cavity. The IAP shifts with respiration as evidenced by an inspiratory increase (diaphragmatic contraction) and an expiratory decrease (relaxation). A normal IAP value is around 5 mmHg, but can be substantially higher in the morbidly obese or the postoperative period. For example, it has been demonstrated that increased sagittal abdominal diameter in morbidly obese patients is associated with elevated IAP in the absence of other significant pathophysiology.[4] Previous studies have

documented that recent abdominal operations are associated with elevations of IAP.[5,6] Before the diagnosis of pathological IAP or intraabdominal hypertension, which may potentially require therapeutic intervention, can be made, a sustained increase in the IAP reflecting a new pathological phenomenon or entity in the abdominal cavity needs to be demonstrated.[7]

IAP Measurement

Clinical examination of the abdomen or the use of an abdominal perimeter are inaccurate for the prediction of the hidden IAP.[8–12] Therefore, the correct IAP value needs to be measured. Since the abdomen and its contents can be considered as relatively noncompressive and primarily fluid in character, behaving in accordance to Pascal's law, the IAP can be measured in nearly every part of it.[13] Different direct and indirect measurement methods have been suggested in the literature. Most of the currently used indirect methods were summarized in a recent review on this topic.[1] The IAP should be expressed in mmHg and measured at end-expiration in the complete supine position, ensuring that abdominal muscle contractions are absent and the transducer zeroed at the level of midaxillary line (conversion factor from mmHg to cmH_2O is 1.36). Until other methods are available, the bladder is considered as the indirect gold standard for intermittent IAP measurement. Figure 7.1 shows a diagram for intermittent bladder pressure measurement. Recently, new measurement kits, either via a Foley Manometer (Holtech Medical, Kopenhagen, Denmark), AbViser-valve (Wolfe Tory Medical, Salt Lake City, Utah, USA), or continuous IAP measurement via a balloon-tipped stomach catheter (Spiegelberg, Hamburg, Germany) have become commercially available.[1]

A continuous IAP tracing can also be obtained via a standard 18 Fr three-way Foley bladder catheter. The continuous IAP measurement is performed via the irrigation port of the three-way catheter, in which continuous sterile normal saline irrigation is maintained and connected through a two-way stopcock and normal saline filled tubing to a pressure transducer placed in line with the iliac crest at the midaxillary line.[14] The transducer is zeroed and the continuous IAP measurement is recorded on the bedside monitor.

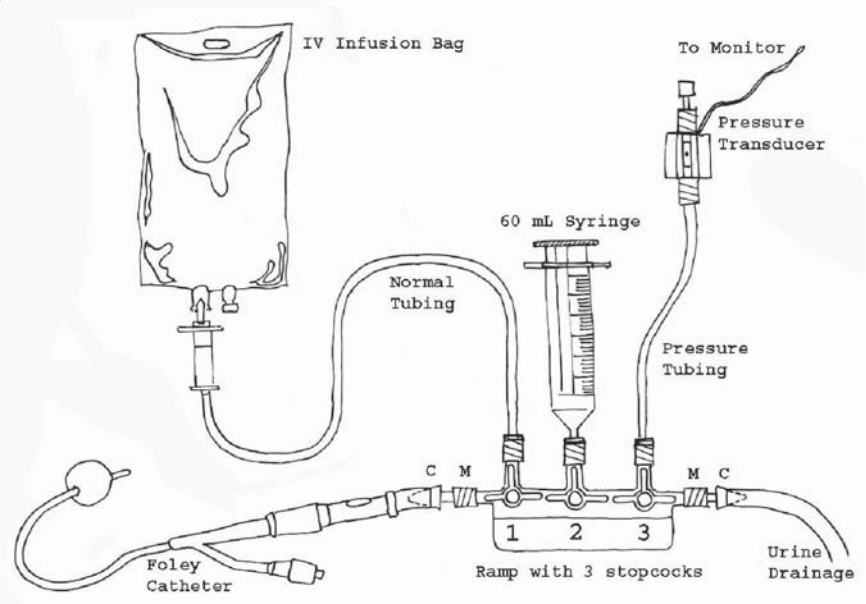
Abdominal Perfusion Pressure

Analogous to the widely accepted and utilized concept of cerebral perfusion pressure (CPP), calculated as mean arterial pressure (MAP) minus intracranial pressure (ICP) (CPP = MAP − ICP), the abdominal perfusion pressure (APP), calculated as MAP minus IAP (APP = MAP − IAP), has been suggested as a useful endpoint for resuscitation.[15,16]

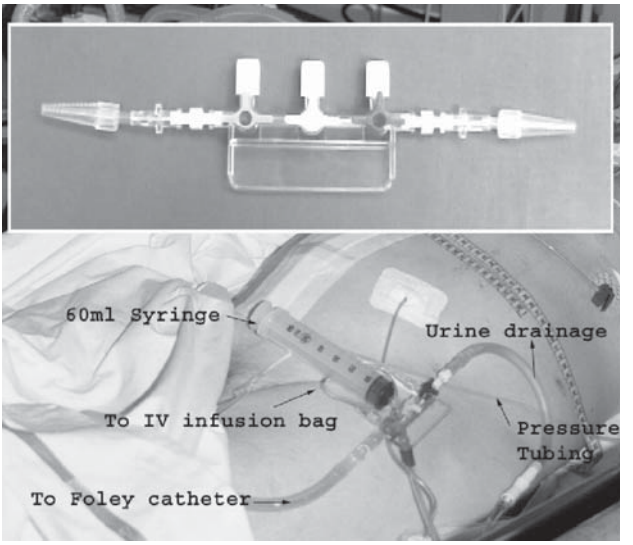
Intraabdominal Hypertension (IAH)

The exact level of IAP that defines IAH still remains a subject of debate. In the early surgical literature the level of 15 to 18 mmHg (20 to 25 cmH_2O) came

A


IV Infusion Bag
To Monitor
Pressure Transducer
60 mL Syringe
Normal Tubing
Pressure Tubing
C M
M C
1 2 3
Foley Catheter
Ramp with 3 stopcocks
Urine Drainage

B


60ml Syringe
Urine drainage
To IV infusion bag
Pressure Tubing
To Foley catheter

forward. Burch et al. defined a grading system of IAH/ACS to guide therapy: grade I corresponds to a bladder pressure of 7.5 to 11 mmHg, grade II to > 11 to 18 mmHg, grade III to > 18 to 25 mmHg, and grade IV > 25 mmHg.[17] Obviously, pathological IAP is a continuum ranging from mild increases without clinical adverse effects to a substantial elevation with grave consequences to all organ systems. Although the use of a single IAP parameter to define IAH could be questioned, it is important that a consensus on this point is reached in the future.

Currently, the definition of IAH in the literature varies most commonly between 12 and 25 mmHg.[2,9,18–27] Some studies have shown deleterious effects on organ function after increases in IAP as low as 10 or 15 mmHg, respectively.[3,16,28–31] A recent, and so far the only, multicenter study aimed at establishing the prevalence, etiology, and predisposing factors associated with IAH in a mixed population of

FIGURE 7.1. (A) A closed needle-free revised method for measurement of intraabdominal pressure. A sterile Foley catheter is used and the urinary drainage system connected. Using a sterile field and gloves, the drainage tubing is cut (with sterile scissors) 40 cm after the culture aspiration port after disinfection. A ramp with three stopcocks (Manifold set, Pvb Medizintechnik Gmbh, a SIMS Trademark, 85614 Kirchseeon, Germany, REF: 888-103-MA-11;or any other manifold set or even three stopcocks connected together will do the job) is connected to a conical connection piece (Conical Connector with female or male lock fitting, B Braun, Melsungen, Germany, REF: 4896629 or 4438450) at each side with a male/male adaptor (Male to Male connector piece, Vygon, Ecouen, France, REF: 893.00 or 874.10). The ramp is then inserted in the drainage tubing. A standard intravenous (IV) infusion set is connected to a bag of 1,000 mL of normal saline and attached to the first stopcock. A 60 mL syringe is connected to the second stopcock and the third stopcock is connected to a pressure transducer via rigid pressure tubing. The system is flushed with normal saline and the pressure transducer is zeroed at the symphysis pubis (or the midaxillary line when the patient is in the completely supine position). The pressure transducer is fixed at the symphysis or the thigh. At rest the three stopcocks are turned "off" to the IV bag, the syringe and transducer giving an open path for urine to flow into the urometer or drainage bag; said otherwise, the three stopcocks are turned "on" to the patient. To measure IAP, the urinary drainage tubing is clamped distal to the ramp device and the third stopcock is turned "on" to the transducer and the patient and "off" to the drainage system. The third stopcock also acts as a clamp. The first stopcock is turned "off" to the patient and "on" to the IV infusion bag, the second stopcock is turned "on" to the IV bag and the 60 mL syringe. Hence, 50 mL of normal saline can be aspirated from the IV bag into the syringe. The first stopcock is turned "on" to the patient and "off" to the IV bag and the 50 mL of normal saline is instilled in the bladder through the urinary catheter. The first and second stopcock are then turned "on" to the patient, and thus turned "off" to IV tubing and the syringe. The third stopcock already being turned "on" to the transducer and patient allows the immediate IAP reading on the monitor. (B) Mounted patient view of the device and close-up of manifold and conical connection pieces. (Both reprinted with permission from *Malbrain ML. Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal. Intensive Care Med 2004;30(3):357–371, © Springer.*)

intensive care patients defined IAH as a maximal IAP value of 12 mmHg or more in at least one measurement.[2] With the lack of a consensus, and in order to exclude brief, temporary elevations of IAP that are not clinically significant, we suggest that IAH be defined as *a consistent increased IAP value of ≥12 mmHg that is recorded by a minimum of three standardized pressure measurements that are conducted 4 to 6 hours apart*. After establishing this minimum threshold for defining IAH, stratification or gradation of the pathological IAP values, as Burch et al. suggested, is probably needed to calibrate and quantify the "threat" of the insult to produce clinically significant manifestations.

Abdominal Compartment Syndrome (ACS)

Most syndromes are preceded by a prodromal phase during which a number of nonspecific symptoms and signs appear. ACS is no exception to this general rule, and IAH represents the prodromal phase of ACS. Within the last statement rests the theoretical distinction between IAH and ACS, namely that IAH in combination with overt organ dysfunction represents ACS (Figure 7.2). In practice that

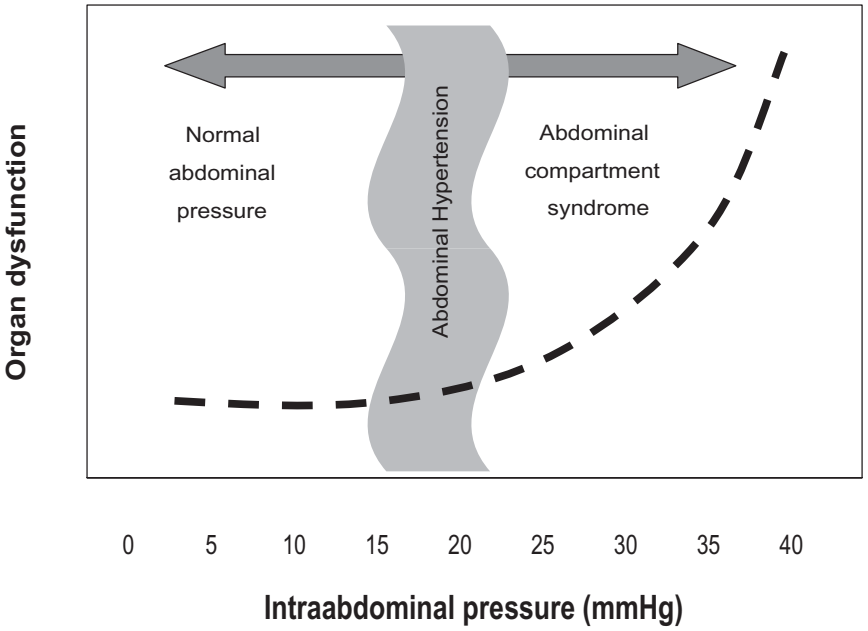


FIGURE 7.2. Distinctions between normal intraabdominal pressure (IAP), intraabdominal hypertension (IAH), and abdominal compartment syndrome (ACS). The shaded area illustrating IAH may undergo shifts to the right or left depending on the clinical scenario.

pathological point is harder to elucidate, hence the indistinct margins defining IAH and the modest change in organ dysfunction. As with prediction of outcome in the critically ill, the extremes are obvious, but with those in the middle range prediction of survival or death is difficult. Patients with an IAP of less than 15 mmHg and organ dysfunction explicable by their underlying pathology are unlikely to benefit from abdominal decompression.

A more accurate definition of ACS will require a combination of numerical value identified with increased IAP with the significant clinical consequences of the prolonged IAH (i.e., the development of disturbances in the different organ systems). In a recent study by Malbrain et al.,[2] ACS was defined as IAP ≥ 20 mmHg with failure of one or more organ systems. They defined organ failure as a sequential organ failure assessment (SOFA) organ subscore ≥3.[32]

The SOFA score includes the sum of six organ system scores (respiratory, cardiovascular, renal, coagulation, liver, and neurologic) ranging from 0 (normal) to 4 (severe derangement) for each organ system. The SOFA score is calculated using the worst values of the day and does not account for organ systems that are not included in the score, of which the most important is the gastrointestinal system. Until a consensus agreement on a definition of ACS is reached, we submit the following to be used in future clinical studies: *ACS is defined as IAH with a gradual and consistent increased IAP value of ≥20 mmHg recorded during a minimum of three standardized measurements that are performed 1 to 6 hours apart and that is directly associated with single or multiple organ system failure which was not previously present (as assessed by the daily SOFA or equivalent scoring system; organ failure is defined as a SOFA organ system score of ≥3).*

In contrast to IAH, the ACS should not be graded, since ACS is an all or nothing phenomenon. Further assessment of organ function can be done by examining the direct clinical effects of ACS on different variables (see Organ Function Assessment, below).

Classification of IAH/ACS

With the increasing recognition of ACS as a significant contributor to the development of multiple organ failure in critically ill patients and the multitude of conditions associated with ACS, it is useful to categorize ACS according to the underlying pathology. In trauma patients, primary ACS has been defined as a recognized complication of damage control laparotomy, and secondary ACS as a condition reported in patients without abdominal injury who require aggressive fluid resuscitation.[26,33] In the intensive care environment, primary ACS has been considered as surgical (e.g., ruptured abdominal aortic aneurysm, abdominal trauma) and secondary ACS as medical (e.g., pneumonia with septic shock, toxin release, capillary leak, and massive fluid overload).[3] Occasionally a combination of the two may occur, for example when a patient develops sepsis and capillary leak with fluid overload after initial surgical stabilization for trauma.[34] This overlap of clinical conditions and potential etiologies has added to the confusion

regarding the definitions. Additional difficulty arises when patients develop ACS after previous surgical treatment for the prevention of IAH.[22,35–37] *For further fine-tuning and classification of IAH/ACS four essential questions need to be answered with regard to the duration (chronic, acute, subacute, hyperacute), the initial underlying problem (intra- or extraabdominal), the etiology (medical, surgical, trauma, or burn), and the localized or generalized character.*

The following examples and suggestions for definitions were recently suggested[3,31]:

Hyperacute IAH lasts only seconds or minutes: laughing, straining, coughing, sneezing, defecation, or physical activity.

Acute IAH occurs within hours: trauma or intraabdominal hemorrhage of any cause (e.g., ruptured abdominal aortic aneurysm).

Subacute IAH occurs within days: most medical causes (e.g., fluid resuscitation and capillary leak).

Chronic IAH occurs within months or years: morbid obesity, intraabdominal tumor (large ovarian cyst, fibroma), chronic ascites (liver cirrhosis or CAPD), or pregnancy.

Primary ACS: defined as a condition associated with injury or disease in the abdomino-pelvic region (e.g., severe acute pancreatitis, spleen rupture).

Secondary ACS: refers to conditions that do not originate from the abdominal cavity (such as pneumonia with sepsis and capillary leak, major burns, and other conditions requiring massive fluid resuscitation).

Tertiary ACS: refers solely to the condition where ACS develops following prophylactic or therapeutic surgical or medical treatment of primary or secondary ACS (e.g., persistence of ACS after decompressive laparotomy, formerly termed the open abdomen compartment syndrome).[35]

Some examples of classification are:

1. A patient with chronic liver failure complicated with variceal bleeding and cardiorespiratory collapse and an IAP of 18 mmHg: chronic, primary, medical, grade II IAH.
2. A patient with penetrating thoracic injury, presenting with cardiorespiratory collapse requiring massive resuscitation develops an increased IAP above 21 mmHg on the third day of hospitalization: subacute, secondary, trauma, grade III IAH.
3. A patient with a septic shock due to localized intestinal perforation and an IAP of 25 mmHg: acute, primary, medical, grade IV IAH.

Organ Function Assessment

After identification of the at-risk patient by means of IAP thresholds and SOFA score, the impact of IAH on the different organ-specific parameters should be assessed.

Abdominal Assessment

Ongoing assessment of IAP should be done by either intermittent or continuous IAP monitoring, together with APP. However, the bladder pressure alone can never be considered as a surrogate tool for bedside clinical examination of the patient. IAH should be seen as an "organ failure" for which specific interventions may be considered, depending on the actual IAP level, such as diagnostic (CT scan,[38] echocardiography,[39] correct interpretation of intrathoracic blood and filling pressures[3,40]), therapeutic (the use of higher PEEP levels,[3,41] the application of externally continuous negative abdominal pressure[42]), and surgical (damage control surgery, decompressive laparotomy). Abdominal wall complications (infections, necrosis, hernias) can occur during peritoneal dialysis due to diminished abdominal wall compliance and rectus sheath blood flow.[43]

Cardiovascular Assessment

Cardiovascular failure is defined by the SOFA score as the need for vasopressors (either dopamine >5μgr or (nor)epinephrine <0.1μgr). Cardiovascular dysfunction is defined by the SOFA score as the need for vasopressors (either dopamine <5μgr or dobutamine at any dose).

As originally described over 80 years ago by Emerson, rising IAP increases intrathoracic pressure through cephalad deviation of the diaphragm.[44] Increased intrathoracic pressure significantly reduces venous return and cardiac output and compresses both the aorta and pulmonary parenchyma, raising systemic vascular resistance.[45–50] Such alterations have been demonstrated to occur at an IAP of only 10 mmHg.[46,50] Hypovolemic patients, those with marginal cardiac contractility, those requiring positive pressure ventilation (with high PEEP), and those with chronic obstructive lung disease (and auto-PEEP) appear to sustain reductions in cardiac output at lower levels of IAP than do normovolemic patients.[47,48]

In summary, IAH decreases venous return and cardiac output, while systemic and pulmonary vascular resistances increase, heart rate remains stable or may increase, the mean arterial pressure initially increases but afterward decreases, and pulmonary arterial pressure increases. The left ventricular compliance and regional wall motion decreases. As a result IAH makes preload assessment difficult since pulmonary artery wedge pressure and central venous pressure rise despite the reduced venous return and cardiac output, while transmural filling pressures usually remain stable or may even decrease. Volumetric and functional hemodynamic parameters on the other hand will better reflect the true volemic status and the volume responsiveness of the patient: global and right ventricular end-diastolic and intrathoracic blood volumes remain stable or may decrease, extravascular lung water increases (in the presence of capillary leak), and stroke volume and pulse pressure variations remain stable or may increase. Finally, there is an increased risk for peripheral edema and venous thrombosis due to the increased femoral vein pressures and the reduced venous blood flow and the

resulting rise in venous hydrostatic pressure. This may lead to fatal pulmonary embolism on decompression.[3]

Pulmonary Assessment

Respiratory failure is defined by the SOFA score as a paO_2/FiO_2 ratio <200 with the need for respiratory support in the form of mechanical ventilation. Respiratory dysfunction is defined by the SOFA score as a paO_2/FiO_2 ratio <300 regardless of the need for respiratory support.

Increases in intrathoracic pressure, through cephalad elevation of the diaphragm, also result in extrinsic compression of the pulmonary parenchyma with development of alveolar atelectasis, decreased diffusion of oxygen and carbon dioxide across the pulmonary capillary membrane, and increased intrapulmonary shunt fraction and alveolar dead space.[46,47,49,50] This dysfunction begins at an IAP of 15 mmHg and is accentuated by the presence of hypovolemia.[50] In combination, these effects lead to the arterial hypoxemia and hypercarbia that characterize ACS.[28,46,50]

In summary, IAH increases intrathoracic and pleural pressure leading to edema and atelectasis, causing a decrease in functional residual capacity and all other lung volumes (mimicking restrictive lung disease). In mechanically ventilated patients auto-PEEP, peak, plateau, and mean airway pressures increase (possibly leading to alveolar barotrauma), while dynamic and static total respiratory system compliance drop (due to a diminished chest wall compliance, with reduced spontaneous tidal volumes, while lung compliance remains unchanged, thus the lower inflection point increases while the upper inflection point shifts to the left). IAH hence results in hypercarbia, hypoxia with a drop in paO_2/FiO_2 ratio, increased dead-space ventilation, and intrapulmonary shunt. Lung neutrophils are activated with increased pulmonary inflammatory infiltration and alveolar edema (extravascular lung water increases), increased risk for pulmonary infection, and compression atelectasis, all resulting in difficult and prolonged ventilation and weaning.[3]

Renal Assessment

Renal failure is defined by the SOFA score as a serum creatinine level ≥3.5 mg/dL (≥300 µmol/L) or oliguria <500 mL/day. Renal dysfunction is defined by the SOFA score as a serum creatinine level ≥2 mg/dL (≥170 µmol/L).

Elevated IAP significantly decreases renal artery blood flow and compresses the renal vein, leading to impaired venous drainage and renal dysfunction and failure.[51,52] There seems also to be an indirect effect by arterial vasoconstriction mediated by the stimulation of the sympathetic nervous and renin-angiotensin-aldosterone systems. Oliguria develops at an IAP of 15 mmHg and anuria at 30 mmHg in the presence of normovolemia and at lower levels of IAP in the patient with hypovolemia.[52] Renal perfusion pressure (RPP) and renal filtration gradient (FG) have been proposed as key factors in the development of IAP-induced renal failure.[53] The FG is the mechanical force across the glomerulus and

equals the difference between the glomerular filtration pressure (GFP) and the proximal tubular pressure (PTP): FG = GFP – PTP. In the presence of IAH, PTP may be assumed to equal IAP, and GFP can be estimated as MAP – IAP. The FG can then be calculated by the formula: FG = MAP – 2*IAP. Thus, changes in IAP have a greater impact upon renal function and urine production than will changes in MAP. It should not be surprising, therefore, that decreased renal function, as evidenced by development of oliguria, is one of the first visible signs of IAH.

In summary, IAH decreases RPP, the FG, and renal blood flow. Oliguria develops, tubular dysfunction increases, glomerular filtration rate drops, renal vascular resistance increases, renal vein and ureter compression increases, renin, aldosterone, and antidiuretic hormone levels increase, while adrenal blood flow usually remains preserved.[3]

Gastrointestinal Assessment

Gastrointestinal failure is not defined by a SOFA subscore. The gut appears to be particularly sensitive to IAH with virtually all intraabdominal and retroperitoneal organs demonstrating decreased blood flow in the presence of elevated IAP.[54] Reductions in mesenteric blood flow may appear with an IAP of only 10 mmHg.[55] Celiac artery blood flow is reduced by up to 43%, and superior mesenteric artery blood flow by as much as 69% in the presence of an IAP of 40 mmHg.[55,56] The negative effects of IAP on mesenteric perfusion are augmented by the presence of hypovolemia or hemorrhage.[20,49,55] Bowel ischemia and inadequate perfusion initiate a vicious cycle of worsening perfusion, increased capillary leak, decreased intramucosal pH, and systemic metabolic acidosis.[20,48,57] An IAP of 20 mmHg diminishes intestinal mucosal perfusion and has been speculated as a possible mechanism for subsequent development of bacterial translocation, sepsis, and multiple system organ failure.[20,48,56–58] Bacterial translocation to mesenteric lymph nodes has been demonstrated to occur in the presence of hemorrhage with a sustained IAP of only 10 mmHg during a period of only 30 minutes.[58]

In summary, IAH decreases abdominal perfusion pressure, as well as celiac blood flow, superior mesenteric artery blood flow, the blood flow to all intraabdominal organs, and in particular mucosal blood flow. Intramucosal gastric pH drops, while regional CO_2 and the CO_2-gap increase. IAH also leads to mesenteric vein compression, promoting venous hypertension and intestinal edema and visceral swelling, which triggers a vicious cycle. Enteral feeding becomes difficult, intestinal permeability increases, and bacterial translocation may occur, finally leading to multiple system organ failure. IAH increases the risk for gastrointestinal ulcer (re)bleeding, and the increased variceal wall stress may lead to varciceal (re)bleeding. Finally, there is an increased risk for peritoneal adhesions.[3]

Hepatic Assessment

Hepatic failure is defined by the SOFA score as a serum bilirubin level ≥6 mg/dL (≥102 µmol/L). Hepatic dysfunction is defined by the SOFA score as a serum bilirubin level ≥2 mg/dL (≥33 µmol/L).

Hepatic artery blood flow is directly affected by IAP-induced decreases in cardiac output, while hepatic vein and portal vein blood flow are reduced by extrinsic compression.[48] These changes have been documented with IAP elevations of only 10 mmHg and in the presence of both normal cardiac output and mean arterial blood pressure.[48]

In summary, IAH decreases hepatic artery flow and portal venous blood flow, while portocollateral flow increases, lactate clearance drops, glucose metabolism diminishes, mitochondrial and cytochrome P450 function decreases, as well as the plasma disappearance rate for indocyanine green.[3]

Neurologic Assessment

Neurologic failure is defined by the SOFA score as a Glasgow Coma Scale <10. Neurologic dysfunction is defined by the SOFA score as a Glasgow Coma Scale <13.

In summary, IAH increases intracranial pressure (ICP) by transdiaphragmatic IAP transmission, leading to an elevation of pleural and central venous pressure; these elevations are sustained as long as the IAH is present.[59,60] The combination of elevated central venous pressure and increased ICP can lead to a substantial decrease in cerebral perfusion pressure, especially in hypotensive, hypovolemic patients where it can lead to progressive cerebral ischemia. The IAP has also been suggested as the cause of idiopathic intracranial hypertension in the morbidly obese[4,61–63] or the neurologic deterioration in patients with multiple trauma but without overt neurotrauma.[64] This hypothesis makes laparoscopy less indicated and less safe in patients with intracranial pathology.[3]

Treatment

Patients with organ dysfunction and an IAP above 20 mmHg should undergo decompressive surgery.[65] But what of those between 15 to 20 mmHg with mild organ dysfunctions? This defines the group with IAH but potential ACS. A judgment call between risk and benefit is required. On balance, from the available accumulating evidence, such patients should probably be decompressed and the diagnosis confirmed or refuted retrospectively. It is within this narrow no-man's-land of IAH between normal IAP and ACS that our efforts should be concentrated in an attempt to clarify definitions and thereby treatment options. Reliance on standard hemodynamic parameters is too crude, but measurement of splanchnic perfusion is too difficult in the clinical scenario to be currently applicable. The exact causative role of bacterial and vasoactive mediator translocation in the genesis and evolution of multisystem organ failure is a further controversial area of critical care medicine.[56,66] It is indisputable, though, that the gut is sensitive to low-flow states and is rendered ischemic at pressures below those expected to induce the ACS; therefore, any attempt should be made to prevent the development of overt ACS.

Different medical treatment procedures have been suggested to decrease IAP.[16] These include the use of paracentesis, gastric suctioning, rectal enemas, gastroprokinetics (cisapride, metoclopramide, domperidone, erythromycin), colonoprokinetics (prostygmine), furosemide either alone or in combination with human albumin 20%, continuous venovenous hemofiltration with aggressive ultrafiltration, continuous negative abdominal pressure, and finally sedation and curarization. Curarization has been shown to decrease IAP, a phenomenon known for a long time in the operating theater.[67,68] Fentanyl, on the contrary, may acutely increase IAP by stimulation of active phasic expiratory activity.[69]

Since no low-morbidity procedure is available to decompress ACS, Voss et al. developed a percutaneous procedure to increase abdominal capacity and to decrease IAP, based on the principles of abdominal wall components separation.[70] This minimally invasive procedure was feasible and effective in a porcine model of ACS. In burn patients a similar procedure had the same beneficial effects.[71]

In an interesting and original study it was recently demonstrated that the application of external negative abdominal pressure (NEXAP) was able to decrease IAP in 30 ICU patients; however, baseline IAP values were quite low.[42] This study hence confirms previous animal results.[72,73]

Implications for Future Research?

Studies examining the prevalence and incidence of IAH/ACS should be based on the above cited definitions and classifications. The results should be given for mean, median, and maximal IAP values on admission and during the study stay. The ideal frequency for IAP measurement also needs to be elucidated as well as the diurnal and nocturnal variations during continuous IAP monitoring, since this may affect the mean and maximal daily IAP levels as well as the incidence and prevalence of IAH when different thresholds are used.

Studies examining IAP thresholds should be based on the analysis of receiver operating characteristics (ROC) and the area under the ROC curve.[74] As an example, in a recent retrospective study ROC curves were generated for IAP and APP in order to identify the threshold values of each endpoint that were most predictive of patient outcome.[15] ROC curves graph the sensitivity of a diagnostic test (true positive proportion) versus one minus specificity (false positive proportion) and provide an improved measure of the overall discriminatory power of a test as they assess all possible threshold values. A test that always predicts survival has an area under the ROC curve of 1.0, and a test that predicts survival no more often than would be done by chance has an area under the ROC curve of 0.5. The point on the ROC curve closest to the upper left corner is generally considered to optimize the sensitivity and specificity of the test. In this study, the area under the ROC curve was 0.726 for APP and 0.748 for IAP (Figure 7.3). Although the areas under the ROC curves for APP and IAP are not statistically different, the curves demonstrate that the sensitivity and specificity of APP are

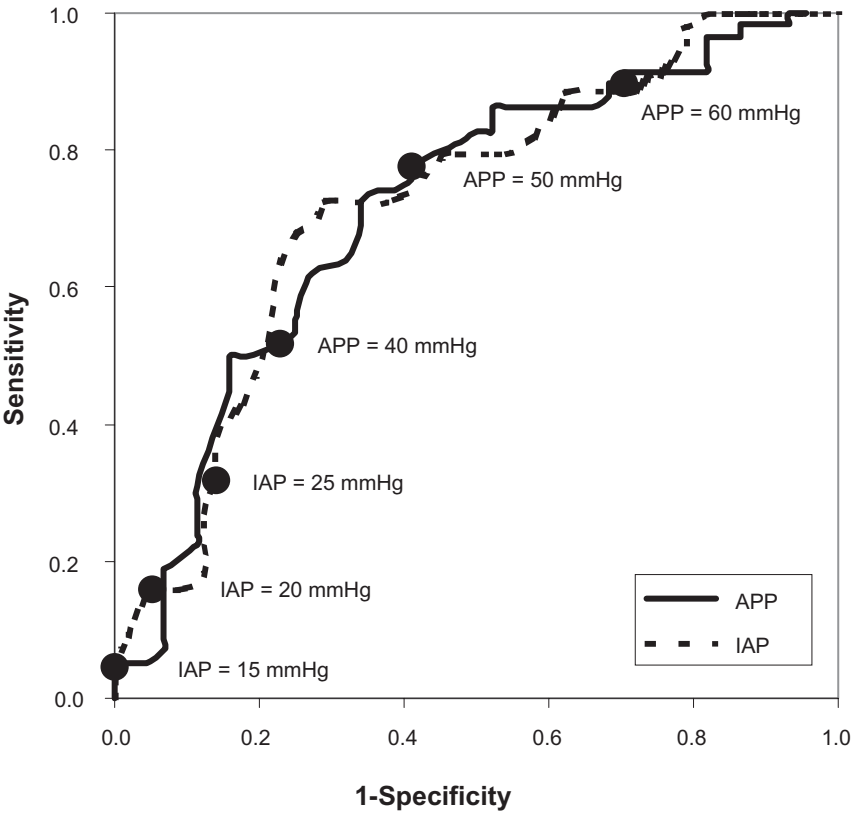


FIGURE 7.3. Receiver operator characteristic (ROC) curves for IAP and APP with clinically useful decision points (IAP has been plotted against mortality instead of survival as in the original study while APP is plotted against survival). IAP—intraabdominal pressure, APP—abdominal perfusion pressure.

both superior to that of IAP for the clinically useful decision thresholds. Maintenance of an APP of at least 50 mmHg appears to maximize both the sensitivity (76%) and specificity (57%) of APP as a predictor of patient survival. The commonly utilized MAP resuscitation endpoint of 70 mmHg achieved a sensitivity of only 57% and specificity of 61%. Although an IAP threshold of 30 mmHg achieved a sensitivity of 70% and specificity of 72%, this endpoint exceeds what is now recognized as being clinically acceptable, and its application would place the patient at risk for significant end-organ malperfusion. Within the currently advocated ranges of 10 to 25 mmHg, IAP was specific but not sensitive for predicting patient outcome. APP appears to be a clinically superior resuscitation endpoint and predictor of patient survival during treatment of IAH and ACS as it addresses not only the severity of IAH, but also the adequacy of end-organ perfusion.

Studies examining new devices to measure IAP should always compare the new IAP measurement method with some form of gold standard. The validation of the new technique should not be limited to the analysis of (significant) correlation coefficients with R^2 (since a good correlation coefficient is not enough to compare two different methods) but should go further into detail with an analysis according to Bland and Altman, who proposed to test for a systematic bias, precision, and agreement between two methods by plotting the mean difference against the mean of two measurements.[75]

Future research should not only focus on epidemiology. The crucial question before widespread acceptance, practice, and clinical use of IAP still remains unanswered to date: Is IAP a phenomenon or an epiphenomenon? The impact that IAP has on therapeutic decision making and outcome when an intervention is undertaken to influence IAP have still to be studied. Before IAP is accepted as a valid tool in practice, it has to be demonstrated that interventions to treat ACS alter patient outcome (if not mortality, then at least morbidity). Maybe it is now time for such multicenter, multinational interventional studies.

Conclusion

All definitions of a clinical situation or syndrome fail to include all possible conditions and variations of an inherently complex phenomenon. Nevertheless, in order to approach scientific accuracy in comparing different clinical reports and to plan for future clinical trials, definitions are required that are comprehensive, detailed, simple, practical, and acceptable to the majority of the scientific community working in the particular field. This review does not, and cannot, provide bullet-proof definitions for all issues associated with increased IAP, but puts forward arguments and suggestions that may serve as a springboard for further consensus-building endeavors. These definitions also allow better comparisons of data between groups of researchers and may lead to refined and better definitions themselves.

References

1. Malbrain ML. Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal. Intensive Care Med 2004;30(3):357–71.
2. Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. Intensive Care Med 2004;(30):822–9.
3. Malbrain ML. Is it wise not to think about intraabdominal hypertension in the ICU? Curr Opin Crit Care 2004;10(2):132–45.
4. Sugerman H, Windsor A, Bessos M, et al. Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. J Intern Med 1997;241(1):71–9.
5. Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. Ann Surg 1984;199(1):28–30.
6. Sanchez NC, Tenofsky PL, Dort JM, et al. What is normal intra-abdominal pressure? Am Surg 2001;67(3):243–8.

7. Yang EY, Marder SR, Hastings G, et al. The abdominal compartment syndrome complicating nonoperative management of major blunt liver injuries: recognition and treatment using multimodality therapy. J Trauma 2002;52(5):982–6.
8. Kirkpatrick AW, Brenneman FD, McLean RF, et al. Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? Can J Surg 2000;43(3):207–11.
9. Sugrue M, Bauman A, Jones F, et al. Clinical examination is an inaccurate predictor of intraabdominal pressure. World J Surg 2002;26(12):1428–31.
10. Platell CF, Hall J, Clarke G, et al. Intra-abdominal pressure and renal function after surgery to the abdominal aorta. Aust N Z J Surg 1990;60(3):213–6.
11. Castillo M, Lis RJ, Ulrich H, et al. Clinical estimate compared to intra-abdominal pressure measurement. Crit Care Med 1998;26[Suppl 1]:78A.
12. Van Mieghem N, Verbrugghe W, Daelemans R, et al. Can abdominal perimeter be used as an accurate estimation of intra-abdominal pressure? Crit Care 2003;7[Suppl 2]: P183.
13. Malbrain ML. Abdominal pressure in the critically ill. Curr Opin Crit Care 2000; 6:17–29.
14. Balogh Z, Jones F, D'Amours S, et al. Continuous intra-abdominal pressure measurement technique—a new gold standard. Am J Surg. In press.
15. Cheatham ML, White MW, Sagraves SG, et al. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma 2000; 49(4):621–6.
16. Malbrain ML. Abdominal perfusion pressure as a prognostic marker in intra-abdominal hypertension. In: Vincent JL, ed. Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer-Verlag, 2002:792–814.
17. Burch JM, Moore EE, Moore FA, et al. The abdominal compartment syndrome. Surg Clin North Am 1996;76(4):833–42.
18. Sugrue M, Jones F, Lee A, et al. Intraabdominal pressure and gastric intramucosal pH: is there an association? World J Surg 1996;20(8):988–91.
19. Meldrum DR, Moore FA, Moore EE, et al. Prospective characterization and selective management of the abdominal compartment syndrome. Am J Surg 1997;174(6): 667–72.
20. Ivatury RR, Porter JM, Simon RJ, et al. Intra-abdominal hypertension after life-threatening penetrating abdominal trauma: prophylaxis, incidence, and clinical relevance to gastric mucosal pH and abdominal compartment syndrome. J Trauma 1998; 44(6):1016–21.
21. Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. J Trauma 2000;49(3):387–91.
22. Raeburn CD, Moore EE, Biffl WL, et al. The abdominal compartment syndrome is a morbid complication of postinjury damage control surgery. Am J Surg 2001;182(6): 542–6.
23. McNelis J, Marini CP, Jurkiewicz A, et al. Predictive factors associated with the development of abdominal compartment syndrome in the surgical intensive care unit. Arch Surg 2002;137(2):133–6.
24. Loftus IM, Thompson MM. The abdominal compartment syndrome following aortic surgery. Eur J Vasc Endovasc Surg 2003;25(2):97–109.
25. Hong JJ, Cohn SM, Perez JM, et al. Prospective study of the incidence and outcome of intra-abdominal hypertension and the abdominal compartment syndrome. Br J Surg 2002;89(5):591–6.

26. Balogh Z, McKinley BA, Holcomb JB, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. J Trauma 2003;54(5):848–59.
27. Offner PJ, de Souza AL, Moore EE, et al. Avoidance of abdominal compartment syndrome in damage-control laparotomy after trauma. Arch Surg 2001;136(6): 676–81.
28. Cheatham M. Intra-abdominal hypertension and abdominal compartment syndrome. New Horiz 1999;7:96–115.
29. Papavassiliou V, Anderton M, Loftus IM, et al. The physiological effects of elevated intra-abdominal pressure following aneurysm repair. Eur J Vasc Endovasc Surg 2003;26(3):293–8.
30. Malbrain ML. Abdominal pressure in the critically ill: measurement and clinical relevance. Intensive Care Med 1999;25(12):1453–8.
31. Malbrain ML. Intra-abdominal pressure in the intensive care unit: Clinical tool or toy? In: Vincent JL, ed. Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer-Verlag, 2001:547–85.
32. Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22: 707–10.
33. Balogh Z, McKinley BA, Cocanour CS, et al. Secondary abdominal compartment syndrome is an elusive early complication of traumatic shock resuscitation. Am J Surg 2002;184(6):538–43.
34. Biffl WL, Moore EE, Burch JM, et al. Secondary abdominal compartment syndrome is a highly lethal event. Am J Surg 2001;182(6):645–8.
35. Gracias VH, Braslow B, Johnson J, et al. Abdominal compartment syndrome in the open abdomen. Arch Surg 2002;137(11):1298–300.
36. Ertel W, Oberholzer A, Platz A, et al. Incidence and clinical pattern of the abdominal compartment syndrome after "damage-control" laparotomy in 311 patients with severe abdominal and/or pelvic trauma. Crit Care Med 2000;28(6):1747–53.
37. Maxwell RA, Fabian TC, Croce MA, et al. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. J Trauma 1999;47(6):995–9.
38. Quintel M, Pelosi P, Caironi P, et al. An increase of abdominal pressure increases pulmonary edema in oleic acid induced lung injury. Am J Respir Crit Care Med 2004;169(4):534–41.
39. Sakka SG, Huettemann E, Petrat G, et al. Transoesophageal echocardiographic assessment of haemodynamic changes during laparoscopic herniorrhaphy in small children. Br J Anaesth 2000;84(3):330–4.
40. Malbrain ML, Cheatham ML. Cardiovascular effects and optimal preload markers in intra-abdominal hypertension. In: Vincent JL, ed. Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer-Verlag, 2004:71–9.
41. Malbrain ML, Deeren D, Nieuwendijk R, et al. Partitioning of respiratory mechanics in intra-abdominal hypertension. Intensive Care Med 2003;29[Suppl 1]: S85.
42. Valenza F, Bottino N, Canavesi K, et al. Intra-abdominal pressure may be decreased non-invasively by continuous negative extra-abdominal pressure (NEXAP). Intensive Care Med 2003;29(11):2063–7.
43. Diebel L, Saxe J, Dulchavsky S. Effect of intra-abdominal pressure on abdominal wall blood flow. Am Surg 1992;58(9):573–5.

44. Coombs HC. The mechanism of the regulation of intra-abdominal pressure. Am J Physiol 1922;61:159–70.
45. Cullen DJ, Coyle JP, Teplick R, et al. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. Crit Care Med 1989;17(2):118–21.
46. Richardson JD, Trinkle JK. Hemodynamic and respiratory alterations with increased intra-abdominal pressure. J Surg Res 1976;20(5):401–4.
47. Kashtan J, Green JF, Parsons EQ, et al. Hemodynamic effect of increased abdominal pressure. J Surg Res 1981;30(3):249–55.
48. Diebel LN, Wilson RF, Dulchavsky SA, et al. Effect of increased intra-abdominal pressure on hepatic arterial, portal venous, and hepatic microcirculatory blood flow. J Trauma 1992;33(2):279–82.
49. Ridings PC, Bloomfield GL, Blocher CR, et al. Cardiopulmonary effects of raised intra-abdominal pressure before and after intravascular volume expansion. J Trauma 1995;39(6):1071–5.
50. Simon RJ, Friedlander MH, Ivatury RR, et al. Hemorrhage lowers the threshold for intra-abdominal hypertension-induced pulmonary dysfunction. J Trauma 1997;42(3): 398–403.
51. Bradley SE, Bradley GP. The effect of increased intra-abdominal pressure on renal function in man. J Clin Invest 1947;26:1010–5.
52. Harman PK, Kron IL, McLachlan HD, et al. Elevated intra-abdominal pressure and renal function. Ann Surg 1982;196(5):594–7.
53. Ulyatt DB. Elevated intra-abdominal pressure. Aust Anaes 1992;108–14.
54. Caldwell CB, Ricotta JJ. Changes in visceral blood flow with elevated intraabdominal pressure. J Surg Res 1987;43(1):14–20.
55. Friedlander MH, Simon RJ, Ivatury R, et al. Effect of hemorrhage on superior mesenteric artery flow during increased intra-abdominal pressures. J Trauma 1998; 45(3):433–89.
56. Diebel LN, Dulchavsky SA, Brown WJ. Splanchnic ischemia and bacterial translocation in the abdominal compartment syndrome. J Trauma 1997;43(5):852–5.
57. Sugrue M, Jones F, Janjua KJ, et al. Temporary abdominal closure: a prospective evaluation of its effects on renal and respiratory physiology. J Trauma 1998;45(5): 914–21.
58. Gargiulo NJ III, Simon RJ, Leon W, et al. Hemorrhage exacerbates bacterial translocation at low levels of intra-abdominal pressure. Arch Surg 1998;133(12):1351–5.
59. Bloomfield GL, Ridings PC, Blocher CR, et al. A proposed relationship between increased intra-abdominal, intrathoracic, and intracranial pressure. Crit Care Med 1997;25(3):496–503.
60. Bloomfield GL, Ridings PC, Blocher CR, et al. Effects of increased intra-abdominal pressure upon intracranial and cerebral perfusion pressure before and after volume expansion. J Trauma 1996;40(6):936–41.
61. Sugerman HJ. Effects of increased intra-abdominal pressure in severe obesity. Surg Clin North Am 2001;81(5):1063–75, vi.
62. Sugerman HJ. Increased intra-abdominal pressure in obesity. Int J Obes Relat Metab Disord 1998;22(11):1138.
63. Sugerman HJ, DeMaria EJ, Felton WL, III, et al. Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. Neurology 1997;49(2):507–11.

64. Bloomfield GL, Dalton JM, Sugerman HJ, et al. Treatment of increasing intracranial pressure secondary to the acute abdominal compartment syndrome in a patient with combined abdominal and head trauma. J Trauma 1995;39(6):1168–70.
65. Ghimenton F, Thomson SR, Muckart DJ, et al. Abdominal content containment: practicalities and outcome. Br J Surg 2000;87(1):106–9.
66. Doty JM, Oda J, Ivatury RR, et al. The effects of hemodynamic shock and increased intra-abdominal pressure on bacterial translocation. J Trauma 2002;52(1):13–7.
67. De Waele JJ, Benoit D, Hoste E, et al. A role for muscle relaxation in patients with abdominal compartment syndrome? Intensive Care Med 2003;29:332.
68. Macalino JU, Goldman RK, Mayberry JC. Medical management of abdominal compartment syndrome: case report and a caution. Asian J Surg 2002;25(3):244–6.
69. Drummond GB, Duncan MK. Abdominal pressure during laparoscopy: effects of fentanyl. Br J Anaesth 2002;88(3):384–8.
70. Voss M, Pinheiro J, Reynolds J, et al. Endoscopic components separation for abdominal compartment syndrome. Am J Surg 2003;186(2):158–63.
71. Latenser BA, Kowal-Vern A, Kimball D, et al. A pilot study comparing percutaneous decompression with decompressive laparotomy for acute abdominal compartment syndrome in thermal injury. J Burn Care Rehabil 2002;23:190–5.
72. Bloomfield G, Saggi B, Blocher C, et al. Physiologic effects of externally applied continuous negative abdominal pressure for intra-abdominal hypertension. J Trauma 1999;46(6):1009–14.
73. Saggi BH, Bloomfield GL, Sugerman HJ, et al. Treatment of intracranial hypertension using nonsurgical abdominal decompression. J Trauma 1999;46(4):646–51.
74. Pepe MS, Janes H, Longton G, et al. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol 2004;159(9):882–90.
75. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307–10.

8
Resuscitation Goals in Severe Sepsis and Septic Shock

Fernando Pálizas

Introduction

One of the main consequences of systemic inflammatory response syndrome (SIRS)[1] is the generalized arterial and venous vasodilatation produced by the increase in the production of large amounts of nitric oxide (NO).[2] The intensity of the arterial vasodilatation is correlated with the severity of the hemodynamic derangement that occurs in severe sepsis and with the outcome of these patients.[3]

Overt hypotension occurs when the increase in cardiac output is not able to compensate arterial vasodilatation. One hindrance to increasing cardiac output to the proper levels is the presence of myocardial depression.[4]

Plasma volume expanders, vasoconstrictors, and inotropes are the main basic tools available for treatment of hypotension and shock in sepsis. The proper use of these therapeutic tools in hemodynamic resuscitation maneuvers can make the difference between a good outcome or the evolution to multiorgan dysfunction syndrome (MODS)[1] and death.

The basic principles for use of plasma volume expanders and vasoactive drugs in initial resuscitation of severe sepsis and septic shock are:

- Plasma volume expanders are the main therapeutic tool to resuscitate severe sepsis and septic shock patients (they must be used cautiously in cardiac failure).
- Due to the intensity of vasodilatation, the volume of plasma expanders to be used is very important (3,000 to 6,000 mL of crystalloids). It is recommended to infuse this volume in a short period of time (30 to 120 minutes).
- Generalized edema is unavoidable after proper volume expansion due to the presence of "leaking" capillaries.[5,6]
- Vasoconstrictors will be used only if normal pressure is not achieved with adequate volume expansion.
- The dosage of vasoconstrictors used in sepsis to achieve normal arterial pressure is much higher than in nonseptic patients. This is due to the important decrease in the number and sensitivity of adrenergic receptors.[3]

- Dopamine and noradrenaline are the vasoconstrictors recommended to treat hypotension in sepsis. There is no evidence to recommend one drug over the other. Some authors recommend using dopamine up to a maximum dose of 25 to 30 µg/kg/min. If at that point normal pressure has not been achieved, infusion should be switched to a noradrenaline infusion.
- The goal to achieve in terms of mean arterial pressure (MAP) will be 65 to 70 mmHg. There is no difference in outcome or progression of organ dysfunctions when pressure is raised up to 75 or 85 mmHg.[7]
- When arterial pressure has been normalized and a raise in cardiac output is needed, the use of dobutamine is recommended. If a drop in arterial pressure is seen with dobutamine infusion, adrenaline infusion can be tried.

Central Venous Pressure in Hypotensive Septic Patients

The level of jugular distention and, when available, central venous pressure (CVP), will be useful to evaluate right ventricle preload. This is essential to guide the amount of volume expansion needed in the initial resuscitation of hypotensive septic patients. When plasma volume is expanded, the value of CVP accepted as a goal by most experts is between 8 and 12 mmHg (approximately 10 to 15 cmH_2O).[8] If initial values are higher, resuscitation should start directly with vasoconstrictors like dopamine or noradrenaline. If values are lower than 10 cmH_2O, a challenge with aggressive volume expansion has to be implemented. In some patients with intermediate values a moderate volume expansion test can also be tried to evaluate the response.

It is necessary to recall here that CVP values are "permissive" and not "mandatory." This means that if the goal value of CVP has not been achieved when arterial pressure has already risen to normal, expansion maneuvers must be stopped. When a septic patient is normotensive, the volume will not be expanded, although the CVP is zero.

Vasoconstrictors Infusion

If restoration of normal MAP values is not achieved after adequate volume expansion, it is recommended to start with an infusion of a vasoconstrictor, such as dopamine or noradrenaline. If the MAP value is between 50 and 60 mmHg, infusion of vasoconstrictors should start with a dopamine infusion with an initial dose of 5 to 10 µg/kg/min or noradrenaline with an initial dose of 0.05 to 0.1 µg/kg/min. The dose will be raised to reach a MAP of 65 to 70 mmHg.

In patients with severe hypotension (<50 mmHg), infusion must be started with a high-dose regimen and, when normotension is achieved, the infusion will be changed to a "reasonable" dose regimen, dopamine at approximately 20 µg/kg/min or noradrenaline 0.15 to 0.20 µg/kg/min. Adjustments will be done to maintain a MAP of 65 to 70 mmHg.

Initial Hemodynamic Management

Hernandez et al.[9] developed a noradrenaline-based strategy of initial resuscitation of septic shock. It has been validated through years of experience, and the mortality of septic shock patients managed with this approach is approximately 30%.

The strategies of this approach include:

1. Plasma volume expansion: Start a rapid infusion of saline (30 to 60 min) to achieve a CVP of 10 to 12 mmHg. If a Swan-Ganz catheter has already been inserted, saline infusion will be stopped when wedge pressure reaches 14 to 16 mmHg.
2. If MAP remains <65 mmHg, a noradrenaline infusion is started using an initial dose of 0.05 µg/kg/min. If hypotension persists, infusion dose is incremented in steps of 0.05 µg/kg/min up to a normotensive level (70 mmHg). When a dose of noradrenaline higher than 0.1 to 0.2 µg/kg/min is needed, a pulmonary artery catheter is inserted to guide ulterior hemodynamic maneuvers.
3. Nurses will adjust noradrenaline infusion hourly to the minimum dose required to maintain a MAP of 70 mmHg. CVP or wedge pressure will also be measured hourly to maintain appropriate preload values (see step 1).
4. When a stable value of MAP is achieved, different signs and symptoms are used to evaluate tissue perfusion:
   - Skin perfusion
   - Oliguria (<0.5 mL/kg/h)
   - Lactate levels
   - Cardiac index (CI) <2.5 L/min/m^2

If one of these signs indicates abnormal tissue perfusion, dobutamine infusion is started using an initial dose of 2 µg/kg/min. This dose will be increased using steps of 2 µg/kg/min until signs of tissue hypoperfusion are improved or a cardiac rate >140 x' or hypotension appears.

5. If it is not possible to achieve a MAP ≥ 70 mmHg using noradrenaline, adrenaline infusion is started at a dose of 0.05 µg/kg/min. The dose will be increased in steps of 0.05 µg/kg/min up to a value of MAP of 70 mmHg. In this moment of the resuscitation protocol the patient should be connected to mechanical ventilation (if the patient has not been ventilated previously).
6. Once the patient becomes stable and if the CI is lower than 2.5 L/min/m^2, dobutamine is started following the recommendations of point 4.

Septic Shock: Hemodynamic, and "Metabolic" Disease

Oxygen "Debt" Concept

When different strategies of treatment for septic shock are analyzed, most physicians tend to believe that septic shock is mainly a hemodynamic problem. Therapeutic maneuvers usually end when clinical or instrumental hemodynamic goals are achieved.

It is well established that hypotension is the main goal of initial resuscitation in septic shock, but we must consider the "metabolic" aspects of shock in the therapeutic strategies if we want to improve morbidity and mortality.

Crowell and Smith,[10] in a remarkable experiment published in 1964, have set the basis for our modern view of therapy for different forms of shock. The model used by these authors consisted of a severe model of hemorrhagic shock provoked by bleeding dogs through a catheter placed in the aorta. Blood extracted from dogs was stored in a reservoir to be reinfused later in the experiment. MAP was maintained at a constant level of 30 mmHg during different periods of time in different groups of animals. Besides the MAP, oxygen consumption (VO_2) was also measured during the experiment.

After hemorrhagic shock was started, blood extracted and stored was reinfused at different established periods of time in different groups of dogs. MAP and VO_2 oxygen consumption were measured during the shock period and after blood reinfusion up to compensation or death of the animals (Figure 8.1).

As it is shown in Figure 8.1, the difference between basal VO_2 and the level of VO_2 reached during the shock period was called "oxygen debt." It was measured and registered minute to minute. When the oxygen debt was projected to the duration of the shock period, the total amount of oxygen debt was established. The longer the period of shock, the higher the magnitude of oxygen debt.

When blood was reinfused in a short period of time (20 to 30 min) after the beginning of hemorrhage, all the animals recovered their basal values of MAP. VO_2 also recovered very quickly, but VO_2 values achieved were much higher than basal values. These high values were sustained during a period of time long enough to balance the magnitude of oxygen debt acquired during the shock

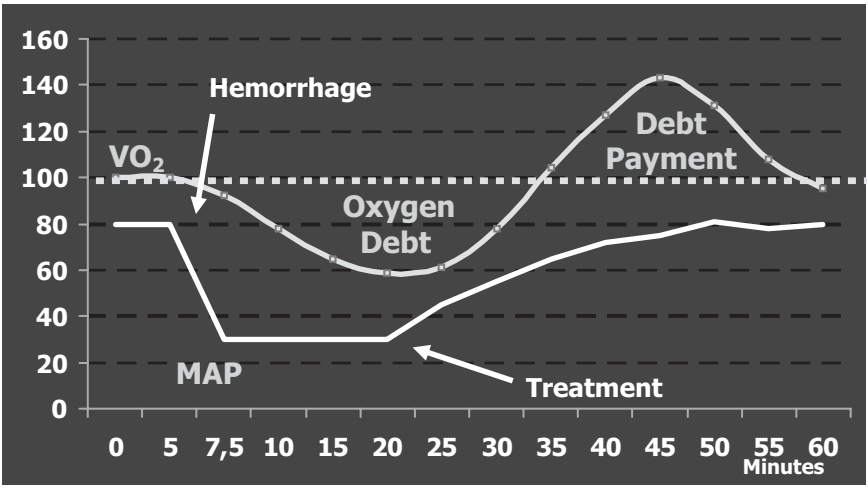


FIGURE 8.1. Shock, oxygen debt, and early resuscitation.
Source: Adapted from Crowell and Smith.[10]

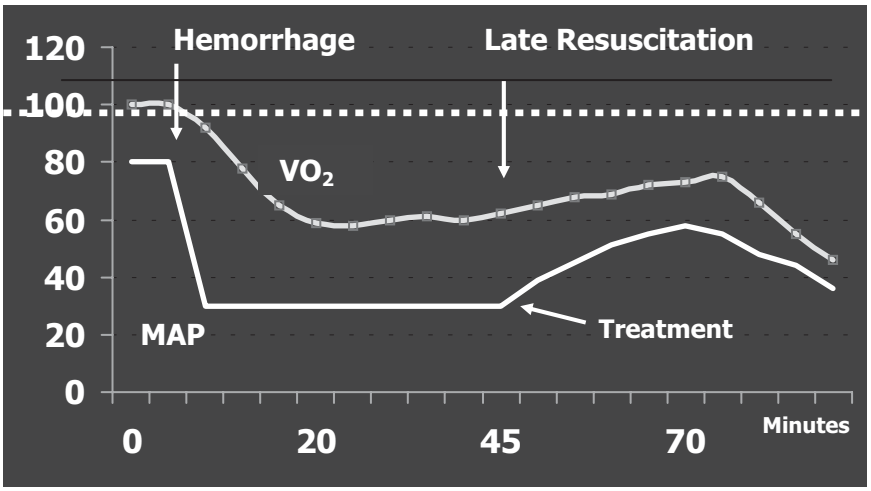


FIGURE 8.2. Shock, oxygen debt, and late resuscitation.
Source: Adapted from Crowell and Smith.[10]

period. This period of "overconsumption" of oxygen is known as the period of "debt payment."

When blood was reinfused late (more than 45 min) after the beginning of hemorrhagic shock, MAP was partially restored but after several minutes it tended to fall again and all the animals eventually died. Looking at the behavior of VO_2, it was clear that it never reached values of "overconsumption"; therefore, oxygen debt was never paid (Figure 8.2).

If shock severity and treatment were equivalent, why was there a difference in outcome between these experiments? The answer appears to be easy: the difference was secondary to the treatment delay in late resuscitation. Forty years ago the authors tried to explain the findings described. They argued that after a long period of time without treatment, the cumulative oxygen debt reached a level high enough to produce an irreversible status in tissue metabolism. The amount of the oxygen debt necessary to produce this metabolic picture in this experimental model was 120 mL/kg. When this level of oxygen debt was surpassed the animals reached a status of "irreversible shock." After this period, the treatment failed to restore normal physiology in all the animals. These arguments seem to be valid after 40 years of evolution in the knowledge of shock physiopathology. As a matter of fact, this concept constitutes the main basis of modern research aimed to improve outcome in the treatment of septic shock.[11]

Comparing the Crowell and Smith experiment and real patients with shock, several differences are easily found. First, in real life the exact moment of shock beginning is frequently unknown, and second, we can hardly define the amount of oxygen debt the patient has accumulated. Is the patient just starting to accumulate oxygen debt or is the patient very close to the point of no return (irrevers-

ible shock)? These questions teach us that two patients with an identical clinical picture of septic shock may have very different outcomes after the resuscitation maneuvers depending on the magnitude of the cumulated oxygen debt.

After all the arguments discussed it can be concluded that:

- All septic shock patients must be aggressively managed as if they were reaching the irreversible shock point.
- The goals of resuscitation will be accomplished *only* when the hemodynamic alterations *and* the oxygen debt have been restored to normal.

Evaluation of Oxygen Debt

One of the main problems intensivists have to deal with is how to take the concept of oxygen debt and irreversible shock into clinical practice. A clear method to assess the exact amount of oxygen debt has not been described, but different approaches have been proposed to solve this issue:

1. *Hyperresuscitation*: This strategy was described several years ago by Shoemaker et al.[12,13] The purpose of this strategy is to ensure the tissues a huge oxygen supply, irrespective of the magnitude of oxygen debt. The original description of this approach was based upon the introduction of a pulmonary artery catheter. After hemodynamic measurements were made, plasma volume expanders or vasoactive drugs were used to reach "high" levels of oxygenation parameters. The goals defined were:

   a. Cardiac index >4.5 L/min/m^2
   b. Oxygen transport >600 mL/min/m^2
   c. VO_2 >170 mL/min/m^2

Although this approach seems reasonable, the success of its implementation has been argued by different investigators and its use is still controversial.

2. *Arterial lactate levels*: As one main product of anaerobic metabolism, arterial lactate has been proposed as a marker of severity in shock of different etiologies. The higher the lactate values, the higher the mortality in all types of shock. Most authors agree that in low-flow states, as in hypovolemic and cardiogenic shock, a good correlation exists between lactate levels and the magnitude of anaerobic metabolism. When a high level of lactate is observed in low-flow states, maneuvers aimed to raise cardiac output are recommended by most experts. The problem is different in sepsis due to the important amount of lactate that can be produced by metabolic disturbances not related to tissue hypoxia.[14] Some authors have proposed that only 30% of arterial lactate measured in sepsis is secondary to anaerobic metabolism. Probably, high lactate levels are more closely related to tissue hypoxia in the beginning of septic shock than late in sepsis evolution.[15]

3. *Mixed or central venous oxygen*: Venous oxygen is the result of the balance between oxygen supply to the tissues and the amount of oxygen consumed.[16,17] When hemoglobin saturation in mixed or central venous blood is higher than 65 to 70%, a good supply of oxygen to tissues can be assumed.[18] The use of this

parameter to guide maneuvers in "late" resuscitation in critically ill patients did not improve outcome.[19] More recently, a central venous oxygen saturation guided protocol improved the evolution and reduce mortality in a group of patients with septic shock.[11] The main difference in this protocol was that resuscitation maneuvers started immediately after admission of the septic shock patients in the emergency department. This approach was called the "early goal-directed resuscitation protocol."

4. *Indirect parameters of tissue perfusion. Gut PCO_2*: It has been shown recently that digestive mucosa production of CO_2 is closely related to the magnitude of mucosal perfusion.[20] Because the digestive tract is one of the first regions to suffer a dramatic decrease in blood flow in shock states, tonometric pCO_2 values have been used as an early warning of general circulatory derangements.[21] Some publications have shown that gastric tonometry is a good therapeutic guide to use in resuscitation maneuvers in critically ill patients. A decrease in the number of organ dysfunctions and also a decrease in mortality have been shown when gastric tonometry was used as a guide in early resuscitation strategies.[22]

Oxygen Debt to Guide Resuscitation Timing

Previously in this chapter the importance of rapid correction of hemodynamic and oxygenation parameters has been established. However, the therapeutic attitude of emergency department physicians and intensivists may vary depending on the evolution period of shock when the patients are admitted. Three different situation can be described:

1. The ideal scenario would be to predict the appearance of shock. In this theoretical situation, therapeutic maneuvers could be directed to "prevent" the generation of hypotension and oxygen debt. It has been called "preventive resuscitation." In the clinical field, high-risk preoperative patients can be assimilated into this group.
2. The second clinical scenario is the initial treatment of septic shock, immediately after the hospital admission. In this situation all the therapeutic efforts have to be directed to a rapid resuscitation of hypotension and of oxygenation parameters. The first 6 h of this resuscitation strategy have been called "early resuscitation."
3. When patients are seen more than 6 h after the beginning of septic shock, the efficacy of resuscitation procedures decreases and the strategy may vary in comparison with previous situations. This strategy is called "late resuscitation" and it probably includes most of the treatments implemented in the ICU.

A scheme of the timing of resuscitation strategies is described here and summarized in Figure 8.3.

Preventive Resuscitation

Different authors have shown that the use of the already mentioned "hyperresuscitation" parameters result in a significant decrease in mortality when they are

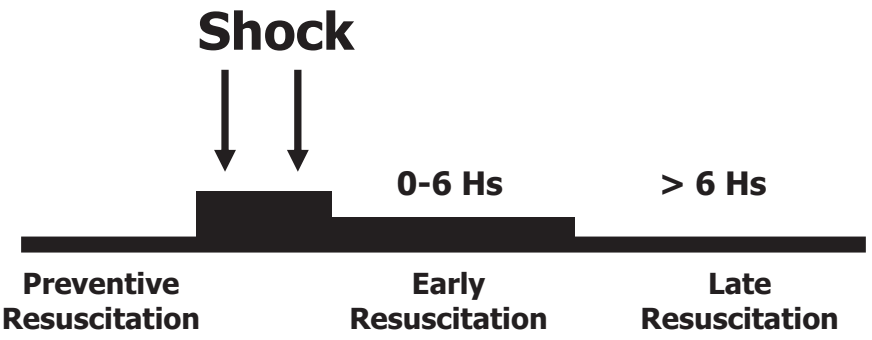


FIGURE 8.3. Timing of resuscitation strategies in shock.

used as a preventive resuscitation strategy in high-risk surgical patients. Due to the severity of previous chronic diseases or the severity of acute situations, these patients have a perioperative mortality higher than 20%.

In these protocols,[12,13,23,24] a pulmonary artery catheter is inserted prior to or immediately after surgery and maneuvers are oriented to reach the hyperresuscitation values. Patients with severe sepsis and septic shock are considered high-risk patients when they have to go to the operating room. In this type of situation a preventive strategy may be implemented. Three randomized trials have shown an important decrease in mortality using this strategy. A recent multicenter trial[25] showed no difference when this strategy was implemented. However, some experts think that this group of patients does not qualify as high risk because the mortality observed in the control group was "only" 7%.

Early Resuscitation

As previously mentioned, initial resuscitation goals in septic shock are mainly directed to normalize hemodynamic parameters. The importance of the "adequate" payment of oxygen debt to improve outcome was also widely discussed. Recently, Rivers et al.[11] published a new strategy based upon these principles that have changed the way patients are managed during this special period. The strategy was called "early goal-directed therapy" and it stated what to do in the first 6 h of resuscitation. This first 6 h could be christened as the "golden" hours of hemodynamic resuscitation in septic shock.

Rivers et al. studied septic shock patients immediately after their admission to the emergency department. The main aim of the study was to compare the outcome of septic shock patients resuscitated with a special goal-directed protocol with the outcome of "normal" resuscitation strategy during the first 6 h after admission.

Patients were randomized to enter the "normal" or the "goal-directed" groups. The parameter used to guide resuscitation in the goal-directed group was the

"central" venous O_2 saturation, measured with a special catheter inserted into the jugular vein. (See "Evaluation of Oxygen Debt.") The first part of the study in both groups was similar, and the first objective was to raise up MAP to 65 mmHg using crystalloids to expand plasma volume. If a CVP of 8 to 12 mmHg was achieved without normalization of MAP, dopamine infusion was started.

If central venous O_2 saturation was lower than 70% after hemodynamic compensation, additional maneuvers aimed to increase cardiac output were implemented in the goal-directed group. The authors use red cells transfusion to increase the O_2 carrying capacity and dobutamine (5 to 20 µg/kg/min) to increase cardiac output. If venous saturation were still below the target, sedation and mechanical ventilation were implemented to decrease VO_2.

To reach the resuscitation target in the "goal-directed" group during the first 6 h, a higher volume of crystalloids (5,000 vs. 3,500 mL), a higher number of red cells in the transfusion (64.1 vs. 18.5%) and more prescriptions of dobutamine infusion were needed.

After this study period, patients were moved to the ICU to follow normal therapeutic protocols implemented by physicians unaware of the study. The most important finding of the study was the important decrease in mortality observed in the goal-directed group compared with the normal group (30.5% vs. 46.5% mortality). The incidence of organ dysfunction was also lower in the goal-directed group.

As a conclusion it can be stated:

a. Shock septic patients must be resuscitated as soon as possible after hospital admission.
b. An aggressive initial resuscitation protocol aimed to correct hemodynamic parameters should be implemented.
c. A parameter capable of evaluating tissue oxygenation should be used as a guide to resuscitation after hypotension is normalized during the first 6 h of treatment.

Late Resuscitation

With the initial therapeutic maneuvers already described, most of the patients become normotensive and tissue oxygenation and perfusion were restored.

However, a portion of these patients become hemodynamically "unstable." Hemodynamic instability means that these patients may present, after initial compensation, one of the following:

- Requirement of new maneuvers of volume expansion
- Increase in vasoconstrictor doses previously sufficient
- Use of two or more vasoactive drugs
- Persistent oliguria
- Severe metabolic acidosis
- Need to use PEEP levels >10 cmH_2O

When one of these situations is present in septic patients the adequate hemodynamic management calls for insertion of a pulmonary artery catheter (PAC). PAC is needed because clinical assessment of preload, systemic vascular resistance, and cardiac output is absolutely inaccurate in this kind of patient.[26]

The main objective of PAC insertion is to evaluate hemodynamic variables to use plasma expanders or vasoactive drugs properly. Besides that, several authors tried to use the measurements derived from the use of PAC to implement protocols aimed to pay oxygen debt.[8] Hyperresuscitation goals, mixed venous O_2 saturation, and gastric tonometry failed to improve outcome when they were used as a therapeutic guide in late resuscitation protocols.[19,22,27]

Most experts recommend that therapeutic hemodynamic goals when PAC is inserted are just normal hemodynamic and oxygenation parameters. Cardiac index 2.8 to 3.0 L/min/m^2, oxygen transport index 450 to 600 mL/min/m^2, and VO_2 130 to 150 mL/min/m^2 could be established as "reasonable" targets to achieve in late resuscitation.[8]

References

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
2. Yuji Kadoi, Fumio Goto. Selective inducible nitric oxide inhibition can restore hemodynamics, but does not improve neurological dysfunction in experimentally-induced septic shock in rats. Anesth Analg. 2004;99(1):212–20.
3. Pickkers P, Jansen Van Rosendaal AJ, Van Der Hoeven JG, et al. Activation of the ATP-dependent potassium channel attenuates norepinephrine-induced vasoconstriction in the human forearm. Shock. 2004;22(4):320–5.
4. Court O, Kumar A, Parrillo JE, et al. Clinical review: Myocardial depression in sepsis and septic shock. Crit Care 2002;6(6):500–8.
5. Marx G. Fluid therapy in sepsis with capillary leakage. Eur J Anaesthesiol 2003; 20(6):429–42.
6. Hasibeder WR. Fluid resuscitation during capillary leakage: does the type of fluid make a difference. Intensive Care Med 2002;28(5):532–4.
7. LeDoux D, Astiz ME, Carpati CM, et al. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 2000;28(8):2729–32.
8. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Crit Care Med 1999;27:639–60.
9. Hernandez G. Management of septic shock with a norepinephrine-based haemodynamic algorithm. Resuscitation 2005;66(1):63–9.
10. Crowell JW, Smith EE. Oxygen deficit and irreversible hemorrhagic shock. Am J Physiol 1964;206(2):313–6.
11. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–77.
12. Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94(6): 1176–86.

13. Shoemaker WC. Goal-oriented hemodynamic therapy. N Engl J Med 1996;334: 799–800.
14. Douzinas EE, Tsidemiadou PD, Pitaridis MT, et al. The regional production of cytokines and lactate in sepsis-related multiple organ failure. Am J Respir Crit Care Med 1997;155(1):53–9.
15. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32(8): 1637–42.
16. Krafft P, Steltzer H, Hiesmayr M, et al. Mixed venous oxygen saturation in critically ill septic shock patients: the role of defined events. Chest 1993;103:900–6.
17. Lee J, Wright F, Barber R, et al. Central venous oxygen saturation in shock: a study in man. Anesthesiology 1972;36:472–8.
18. Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. Circulation 1969;40:165–72.
19. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025–32.
20. Dubin A, Murias G, Estenssoro E, et al. Intramucosal-arterial PCO_2 gap fails to reflect intestinal dysoxia in hypoxic hypoxia. Crit Care 2002;6(6):514–20.
21. Clark CH, Gutierrez G. Gastric intramucosal pH: a noninvasive method for the indirect measurement of tissue oxygenation. Am J Crit Care 1992;1(2):53–60.
22. Gutierrez G, Palizas F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 1992;339(8787):195–9.
23. Boyd O, Ground RM, Bennet ED. A randomised clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high risk surgical patients. JAMA 1993;270:2699.
24. Lobo SMA, Salgado PF, Castillo V, et al. Effects of maximizing oxygen delivery on morbidity and mortality in high risk surgical patients. CCM 2000;28:3396.
25. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348(1): 5–14.
26. Connors AFJ, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996;276:889–97.
27. Hayes MA, Timmins AC, Yau EHS, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717–22.

9
Coagulation Disorders in Critically Ill Septic Patients

Marcela Granados

Sepsis still causes the majority of morbidity and mortality in intensive care units, even though we try to understand and control it. Intervention with antibodies and antiinflammatories has not given the hoped-for results. In recent years, there has been enthusiasm for modifying directly the clotting system of critically ill patients, especially those with sepsis.[1]

The Normal Clotting System

The traditional view of the clotting system has changed radically in recent years: the traditional view of the platelet plug, coagulation cascade, and fibrinolytic system has shifted to the current view of a complex system where different cell surfaces besides the vascular endothelium[2] and receptors share multiple interactions with other systems, like the complement and kinin system. These are not completely understood, and complex transformations are affected by inflammatory mediators.

The objective of these reactions is to maintain a normal state of homeostasis. That is to say that all of these mechanisms must avoid hematic loss by extravasation *and* must keep blood fluidity, which is necessary to carry nutrients to the tissues and remove waste products. This can be viewed as a perfectly designed self-conservation system in human beings.[3,4]

The coagulation system can be activated by *different* factors, not only the endothelium damage as we previously thought. Once this process is started, three phases that were recently described occur:

1. Initiation phase
2. Amplification phase
3. Propagation phase

Initiation Phase

The initiation phase begins with the activation of the tissue factor on the cellular surface. Then it binds with factor VII (Figure 9.1). Tissue factor is expressed by

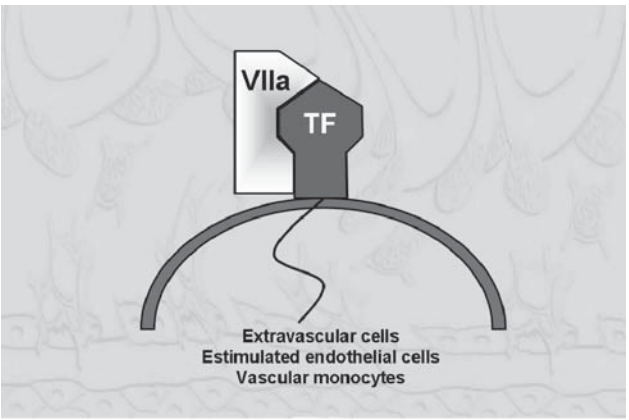


FIGURE 9.1. Initation phase.

epithelial cells, macrophages, and other cell types that are normally separated from blood and circulating coagulation factors. Classically, thrombin generation is triggered when disruption of vascular integrity allows plasma coagulation factors to contact extravascular tissue. Thus the coagulation cascade provides a mechanism for converting mechanical information in the form of tissue damage or vascular leak into biochemical information in the form of the active protease thrombin.

Tissue factor is expressed at low levels on circulating monocytes and leukocyte-derived microparticles. These sources of intravascular tissue factor can be tethered to activated platelets and endothelial cells and concentrated in this way at sites of injury or inflammation.[5,6] This alters the local balance between activation and inhibition of the coagulation cascade and triggers thrombin production. Tissue factor is also expressed at low levels by cytokine-stimulated endothelial cells, perhaps to promote thrombin generation at sites of inflammation.[7]

Amplification Phase

The amplification phase occurs when the activation of the tissue factor and factor VII starts the "thrombin explosion." Thrombin is the main effector protease of the coagulation cascade, a series of zymogen conversions that is triggered when circulating coagulation factors contact tissue factor. Tissue factor is a type 1 integral membrane protein that functions as an obligate cofactor for activation of zymogen factor X by factor VIIa. Factor Xa (with the assistance of cofactor factor Va) then converts prothrombin to active thrombin. Other zymogen conversions provide both amplification and negative feedback loops that regulate thrombin production. Thrombin is short lived in the circulation and, in the context of a normal endothelium, its actions tend to terminate its production. Thus thrombin is thought to act near the site at which it is produced.[8] Thrombin also has a host of direct actions on cells.[9] It triggers shape change in platelets and the release of the platelet activators ADP, serotonin, and thromboxane A2, as well as

chemokines and growth factors. It also mobilizes the adhesion molecule P-selectin and the CD40 ligand to the platelet surface[10,11] and activates the integrin αIIb/β3.[12] The latter binds fibrinogen and von Willebrand factor (vWF) to mediate platelet aggregation. Thrombin also triggers expression of procoagulant activity on the platelet surface, which supports the generation of additional thrombin.[13] In cultured endothelial cells, thrombin causes release of vWF,[14] the appearance of P-selectin at the plasma membrane, and production of chemokines—actions thought to trigger binding of platelets and leukocytes to the endothelial surface in vivo.[15,16] Endothelial cells also change shape and the endothelial monolayer shows increased permeability in response to thrombin[17]—actions predicted to promote local transudation of plasma proteins and edema.[18] Thrombin can also regulate blood vessel diameter by endothelium-dependent vasodilatation; in the absence of endothelium, thrombin acting on smooth muscle cells evokes vasoconstriction. In cultures of fibroblast or vascular smooth muscle cells, thrombin regulates cytokine production and is mitogenic, and in T lymphocytes it triggers calcium signaling and other responses. These cellular actions suggest that thrombin connects tissue damage to both hemostatic and inflammatory responses and perhaps even to the decision to mount an immune response. They also raise the possibility that regulation of endothelial and other cell types by thrombin might have a role in leukocyte extravasations, vascular remodeling, or angiogenesis in contexts other than tissue injury. The recent characterization of receptors that mediate thrombin signaling provides an opportunity to test these ideas.

In summary, thrombin generation not only stimulates the formation of blood clot but it also has antiinflammatory, anticoagulant, and antithrombolitic properties and it stimulates the cellular proliferation (Figure 9.2).

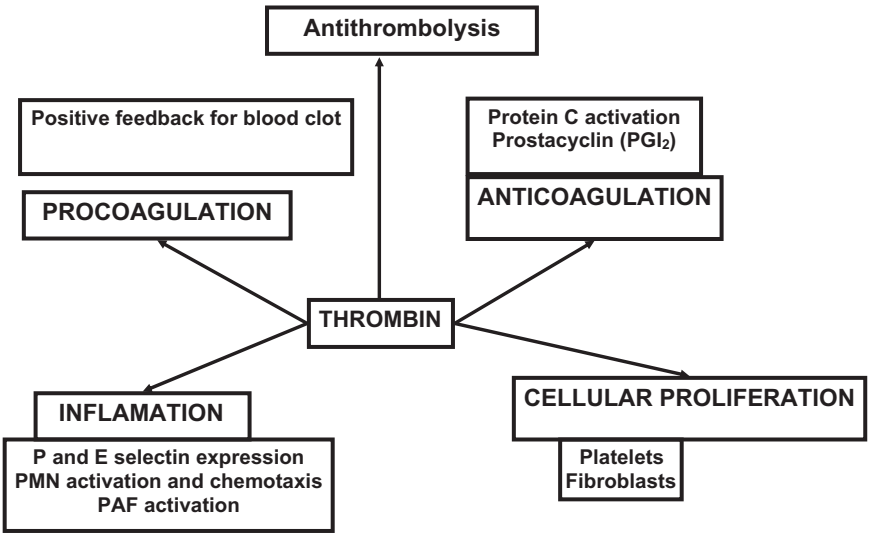


FIGURE 9.2. Propagation Phase: Thrombin actions.

Propagation Phase

The propagation phase continues with thrombin converting circulating fibrinogen to fibrin monomer, which polymerizes to form fibrin polymer, the fibrous matrix of blood clots. This is observed after damage or inflammation, a procoagulant reaction starts with the binding of small amounts of factor VII to tissue factor. The complex then activates factor X and factor IX. Factor Xa generation later is accelerated by formation of intrinsic factor Xasa, that is composed by IXa and VIIIa binding to cell surface. Finally, factor Xa, formed by both enzymatic complexes binding factor Va to the cell surface, produces prothrombinase complex which converts prothrombin to thrombin. We can say that the procoagulant system can synthesize in three dependent vitamin K enzymatic complexes, each composed of one protease with serine residues and a proteic cofactor (Figure 9.3):[19]

1. Factor VII—tissue factor complex
2. Factor VIII—factor IX complex
3. Factor V—factor X complex

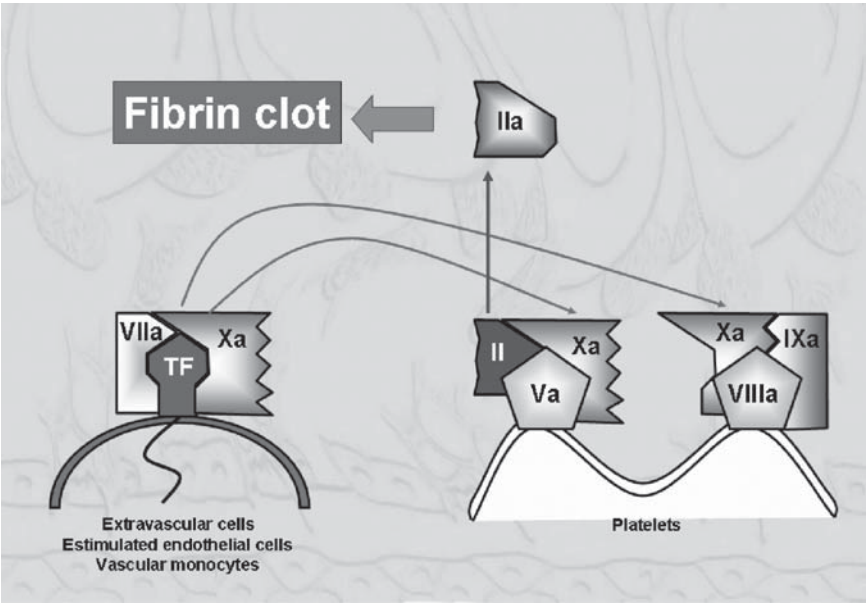


FIGURE 9.3. After mechanical or inflammatory damage, the procoagulant reaction begins with the binding of the small quantities of preexistent factor Xa with tissue factor. This complex activates factor X and factor IX. Generation of factor Xa later accelerates the formation of the intrinsic factor Xasa complex, composed of factor IXa and factor VIIIa binding to the membrane composed of factor IXa and factor VIIIa. Finally, factor Xa formed by both enzymatic complexes binding with factor Va and the cell surface produces the prothrombin compound which converts prothrombin to thrombin.

Antithrombotic Mechanism

Anticoagulant compounds and mechanisms are found in the blood in a higher than procoagulant amount. They comprise a dynamic system that includes the thrombin-thrombomodulin complex, which is localized in the endothelium of the blood vessels, active protein C, and antithrombin III, which are stoichiometric inhibitors for proteases with serine residues. Another system, tissue factor pathway inhibitor (FTPI), blocks the reaction of factor VII–factor Xa–tissue factor. Paradoxically thrombin is not only a procoagulant and antifibrinolytic factor but also an anticoagulant.[20–22]

This system is activated when the thrombin produced from the prothombinase binding with thrombomodulin (Tm) is linked to the membrane surface, activates protein C, and blocks thrombin-fibrinogen and factor V reaction. Activated protein C acts with factors V and VIII are bound to the cell membrane. Then this natural anticoagulant determines the half-life of these procoagulant factors. Protein C can also bind factor Xa and IXa, inhibiting them in the same way. Antithrombin III forms a complex with factor Xa, thrombin, and IXa residues, neutralizing the residual procoagulant enzymes.

Of all the antithrombotic compounds, protein C–thrombomodulin and the protein C receptor deserve special attention. Evidence for the existence of a circulating thrombin-activated protein, autoprothrombin II-A, now referred to as APC, was first presented in the early 1960s[23] and was followed by the discovery and isolation of its precursor, protein C (PC) in 1976.[24–26] PC is a vitamin K–dependent plasma glycoprotein that is synthesized by the liver and circulates as a two-chain biologically inactive species.[27] It is transformed to its active form, APC, by thrombin-mediated cleavage of PC at the N-terminus. Effective activation of PC by thrombin requires the transmembrane glycoprotein, thrombomodulin (TM), as a cofactor for thrombin,[28] amplifying this event >1,000-fold. When complexed with TM, thrombin has reduced procoagulant activity as exhibited by its reduced ability to cleave fibrinogen, activate factor V, and trigger platelet activation. Thus, thrombin's substrate specificity is entirely switched by TM.

PC activation by the thrombin–TM complex is further enhanced (almost equal to) 20-fold in vivo when PC is bound to the endothelial cell protein C receptor (EPCR).[29] Platelet factor 4 (PF4) may additionally accelerate PC activation by inducing a conformational change in PC that increases its affinity for thrombin–TM.[30]

Why is the efficient but controlled generation of APC so important? First and foremost, APC is a natural anticoagulant in that it suppresses further thrombin formation by proteolytically destroying coagulation factors Va and VIIIa, facilitated by the cofactor for APC, protein S (PS). APC also may increase fibrinolytic activity by neutralizing plasminogen activator inhibitor 1 (PAI-1). Overall, the clinical relevance of PC activation by the thrombin–TM/thrombin–EPCR complexes is evident from the hypercoagulable states in humans often associated with functional deficiencies of PC or PS[31,32] and in individuals with factor V Leiden polymorphism, in which a mutation in factor Va renders it resistant to inactivation by APC.

The role of APC extends beyond hemostasis. APC has potent antiinflammatory properties. Much effort has been expended to define the mechanisms by which APC exerts its antiinflammatory properties. By downregulating thrombin generation through its actions on factors Va and VIIIa, APC interferes with thrombin-induced proinflammatory activities that include platelet activation, cytokine-induced chemotaxis for monocytes and neutrophils,[33,34] and upregulation of leukocyte adhesion molecules. However, APC also directly dampens inflammation by inhibiting monocyte/macrophage expression of tissue factor and tumor necrosis factor (TNF)-α,[35] nuclear factor (NF)-κB translocation, cytokine signaling, TNF-α–induced upregulation of cell surface leukocyte adhesion molecules,[36] and leukocyte–endothelial cell interactions.[37,38,39] Many of these protective effects of APC are mediated by proteolytic cleavage of protease activated receptor 1 (PAR1).[40,41,42] APC may also protect the vasculature by blocking p53-mediated apoptosis in ischemic cerebral vasculature.[43] In some models, the antiapoptotic function of APC[43] is independent of its anticoagulant function, requires EPCR as a cofactor, and is mediated via PAR1.

TM is also a cofactor for thrombin-mediated activation of the thrombin-activatable fibrinolysis inhibitor (TAFI).[44] TAFI is a plasma procarboxypeptidase B that, when activated to TAFIa, catalyzes the removal of the C-terminal basic amino acid residues Lys and Arg. Inhibition of fibrinolysis is accomplished by removal of Lys residues from modified fibrinogen, which impedes the conversion of plasminogen to plasmin. Although the in vivo significance of TAFIa as a regulator of fibrinolysis has not been clearly established,[45] its potential role as a natural antiinflammatory molecule is currently being explored, with recognition of its ability to inactivate the potent anaphylatoxins C3a and C5a[46] and the proinflammatory mediators bradykinin and osteopontin.[47]

It is less than 20 years ago that Esmon and Owen identified and isolated TM.[48,49] Since that time, steady progress has been made in elucidating the molecular mechanisms by which this single molecule regulates coagulation, inflammation, fibrinolysis, and cellular proliferation. Although originally described as a vascular endothelial cell receptor, TM has since been detected in a variety of cells and tissues in adults and during development, including astrocytes, keratinocytes, mesothelial cells, neutrophils, monocytes, and platelets.[50–55] Consequently, it is no surprise that it has functions beyond coagulation.

Encoded by an intronless gene, the mature single-chain glycoprotein in the human is 557 amino acids long, structurally organized into five distinct domains. From the intracellular C-terminus, TM has a short cytoplasmic tail, deletion of which in mice has no effect on development, survival, coagulation, or inflammation.[56] After a well-conserved membrane-spanning region, there is a serine/threonine-rich domain with potential sites for O-linked glycosylation, which support the attachment of a chondroitin sulfate (CS). Biochemical studies, yet to be confirmed in vivo, indicate that the CS of TM enhances the PC cofactor activity of TM,[57] accelerates the neutralization of thrombin by heparin–antithrombin and by the protein C inhibitor, and facilitates binding of PF4 to PC to increase its activation.

Adjacent to the serine/threonine-rich region is the best-characterized domain, which comprises six epidermal growth factor (EGF)-like repeats. This domain has mitogenic effects on cultured fibroblasts and vascular smooth muscle cells, mediated via activation of protein kinase C and mitogen-activated protein kinases (MAPK). The clinical significance of these findings has not been established, but they suggest a possible role in cellular proliferation and atherogenesis.[58,59] EGF-like repeats 3, 4, 5, and 6 (EGF3 to 6) have been studied in detail by several groups and are essential for activation of PC and TAFI by thrombin.[60–62] Via its anion-binding exosite I, thrombin binds to EGF5 through EGF6, whereas EGF4 through EGF6 are required for activation of PC.[63] In contrast, activation of TAFI by thrombin–TM requires EGF3 through EGF6.[64] Additional antifibrinolytic activity is supported by the EGF-like repeats of TM, because they also accelerate thrombin-mediated conversion of single-chain urokinase-type plasminogen activator (scu-PA) to thrombin-cleaved two-chain urokinase-type plasminogen activator (tcu-PA/T),[65] thereby interfering with the generation of plasmin.[66,67]

At the N-terminus of the molecule and joined to the first EGF-like repeat by a 72-amino acid residue hydrophobic stretch, there is a 154-amino acid residue module with homology to other C-type lectins.[68,69] Electron microscopy and computer models indicate that the lectin-like domain of TM is globular and situated farthest from the plasma membrane, such that it might effectively and easily interact with other molecules.[70,71] Although lacking in anticoagulant function, this domain plays a major role in inflammation and cell survival.

EPCR, constitutively expressed by endothelial cells, is structurally similar to the major histocompatibility complex class 1/CDI family of proteins, which are commonly involved in immunity/inflammation.[72] EPCR accelerates thrombin-mediated activation of PC while concentrating it near the surface of the vessel wall. In contrast to TM, EPCR is more prominently expressed in large vessel endothelial cells[72,73] but is also detected in neutrophils. When APC is generated, it remains bound to EPCR for a short time before associating with protein S on the surface of platelets or endothelium, whereupon it cleaves its substrates, factors Va/VIIIa, after which it is inactivated by α_1-antitrypsin, the protein C inhibitor[74] or α_2-macroglobulin.[75] In addition to its role in amplifying activation of PC, EPCR switches the substrate specificity of APC, analogous to TM and thrombin. When APC is released from EPCR, it has anticoagulant properties, yet when transiently complexed with EPCR, APC cleaves PAR1, initiating intracellular signaling that provides antiapoptotic protection.

TM functions as an antiinflammatory molecule at several levels. First, as a critical cofactor in the activation of PC, TM has an obligate role in regulating the antiinflammatory properties of APC. Thus, high levels of antiinflammatory/anticoagulant/vasculoprotective APC would be generated locally in the presence of adequate or excess functional TM and thrombin. Indeed, in a vascular restenosis model in rabbits, administration of TM via adenovirus prevented restenosis and dampened the inflammatory response.[76] Conversely, downregulation of TM would be expected to yield low APC levels and a proinflammatory procoagulant diathesis. In this respect, Weiler et al. demonstrated that mice with low APC levels

($TM^{pro/pro}$ mice) display a heightened inflammatory response to systemic endotoxemia.[77] However, the story is more complicated, because the $TM^{pro/pro}$ mice, when exposed to respiratory bacterial pathogens, did not generate a proinflammatory response, despite enhanced fibrin/fibrinogen deposition.[78]

There are additional indirect mechanisms by which TM may provide antiinflammatory protection. For example, the putative role that TAFIa plays in suppressing complement activation also requires an intact thrombin–TM complex. Recombinant soluble TM prevented leukocyte infiltration into the kidney in a rat model of glomerulonephritis, an effect that was at least partly mediated through an increase in TAFIa and subsequent complement inactivation.[79] Furthermore, when associated with TM, the proinflammatory properties of thrombin are abrogated, and indeed reversed; thus TM, a "sink" for thrombin, once again behaves effectively, albeit indirectly, as an antiinflammatory molecule. When TM expression is downregulated by, for example, cytokines such as TNF-α or IL-1β, thrombin would then be available to promote coagulation and inflammation.

It has long been recognized that C-type lectins, through interactions between their carbohydrate recognition domains and carbohydrates attached to proteins, often participate in innate immune functions, including complement activation, leukocyte trafficking, and regulation of apoptosis.[80,81] This observation prompted us to explore the possibility that the C-type lectin-like domain of TM might play a direct role in modulating inflammation. For this reason, transgenic mice that lack the N-terminal lectin-like domain of TM ($TM^{LeD/LeD}$) were generated.[82] Although appearing normal under baseline conditions, further phenotypic analysis revealed that they have reduced survival after endotoxin exposure, accumulate more neutrophils in their lungs, respond with larger infarcts after myocardial ischemia/reperfusion, and develop worse arthrogen-induced arthritis than their wild-type counterparts.[83] Notably, deletion of the lectin-like domain of TM did not interfere with in vivo activation of PC, indicating that the apparent proinflammatory effect seen in the $TM^{LeD/LeD}$ mice was not caused by suppression of APC. Rather, the lectin-like domain of TM was demonstrated to have direct antiinflammatory properties, conferring protection by interfering with neutrophil adhesion to endothelial cells. Increased leukocyte adhesion to $TM^{LeD/LeD}$ endothelium was at least partially explained by enhanced expression of leukocyte adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1), mediated by increased phosphorylation of MAPK (extracellular signal-regulated kinase [ERK], ERK1/2), and activation of NF-κB. Recent studies further suggest that the lectin-like domain of TM may be important to maintain the integrity of cell–cell interactions, and thus might also prevent leukocyte transmigration.[84] Overall, the lectin-like domain of TM dampens the response of the vascular endothelium to proinflammatory stimuli by suppressing activation of well-conserved intracellular signaling pathways. Notably, the mechanisms by which APC and the lectin-like domain of TM exert their antiinflammatory effects are similar, indicating the close coordination and importance of these apparently redundant protective biologic systems.

From this discussion, it is apparent that TM, APC, and EPCR have diverse yet distinct regulatory, structural, and functional motifs regulating multiple biological

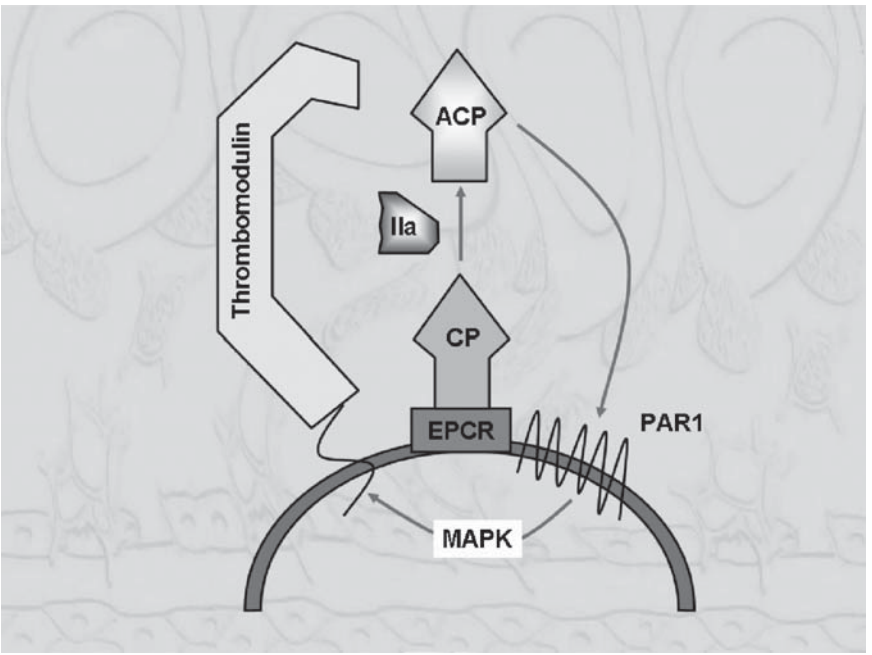


FIGURE 9.4. Protein C–thrombomodulin complex–protein C endothelial receptor.

functions, including coagulation, fibrinolysis, inflammation, and apoptosis. In health and disease, these appear to be well integrated to maintain homeostasis. Under normal conditions or in response to minor injury, the vascular endothelium remains protected, as TM sequesters thrombin, generating adequate local levels of APC to protect the vasculature from inflammatory, procoagulant, and proapoptotic forces. Signals mediated directly by APC, the APC-EPCR complex via PAR1, and the lectin-like domain of TM help to suppress cytokine release and tissue factor expression by circulating leukocytes, interfere with endothelial cell apoptosis, dampen endothelial cell activation of MAPKs, and prevent expression of leukocyte adhesion molecules, impeding local accumulation of neutrophils and monocytes (see Figure 9.4).

Fibrinolytic System

Once the blood clot is formed a process of vessel repair begins. There are three principal activating substances of the fibrinolytic system: Hageman factor fragments, urinary plasminogen activator or urokinase (uPA), and tissue plasminogen activator (tPA). The main physiological regulators tPA and uPA spread to endothelial cell and convert plasminogen into plasmin.

Plasmin breaks a fibrin polymer into small fragments that are eliminated by the monocyte-macrophage system.[85] The main stimulant for releasing tPA by

endothelial cells is alpha-thrombin. Alpha-thrombin also stimulates the plasminogen inhibitor, making a fine adjustment to that level. Plasmin degrades the fibrinogen. However, this reaction remains localized due to activation of the tPA and uPA made preferably over the plasminogen bound to the blood clot. That occurs because the circulating plasmin is quickly bound and neutralized by alpha-2 antiplasmin. In addition plasminogen activation inhibitor (PAI-1) release from endothelial cell directly blocks the action of tPA.

Fibrinogen degradation products (FDPs) and fibrin have antithrombotic properties and they can destroy factors V and VIII:C. Due to this special effect the FDPs have been termed antithrombin IV. Alpha-2 macroglobulin has the capacity to inhibit the plasmin from forming a compound with it but more slowly than alpha-2 antiplasmin.

Inflammatory Cascade, Coagulation, and Sepsis

There is evidence from many years ago that the inflammatory system and coagulation are related not only in vertebrates but also in invertebrate animals. Both are defense systems against infection or vascular damage. However, an alteration in the balance of this system can produce disseminated intravascular coagulation and multiple organic dysfunctions.

Implications of tissue factor, a glycoprotein 47 kd, are very relevant to sepsis. This molecule is expressed in monocyte and endothelial cells, normally in small amounts for its huge thrombogenic capacity. The relationship between sepsis and tissue factor has been demonstrated in basic and clinical research. Inoculation of endotoxin in healthy volunteers produces activation of the tissue factor–factor VII complex, followed by the generation of fibrin without intrinsic activation.[86] The same activation can be produced with inoculation of tumor necrosis factor-α (TNF-α) interleukin-1(IL-1), and live bacteria (*E. coli*).[87] On the other hand, a decrease in the anticoagulant system has been demonstrated in sepsis which worsens the panorama. One trial suggests that endothelial damage could inhibit the expression of protein C–thrombomodulin, protein S, and factor Va.[88] It also has been demonstrated that endotoxin increases plasminogen activator inhibitor (PAI-1)[89] production and that it could affect lysis clot and bacterial depuration.

Why the coagulation system is changed to a hypercoagulated state in sepsis is unknown, but it is clear that this condition produces thrombosis in small vessels far from the original site of damage. This thrombosis can produce injury in other tissues and organs (multiple organic dysfunctions). The explanation of this paradox "systemic condition–local effect" is based in the endothelium. The vision of the endothelium in a passive role to separate the blood around the tissue has changed. We now know that endothelium is a system with many metabolic activities and multiple regulations.

Under normal conditions, liver, bone marrow, and the other organs continually produce procoagulant and anticoagulant proteins and factors. This continual pro-

duction is integrated in each of the vessels maintaining the homeostasis. In sepsis there is an alteration in the production of these proteins and factors, likewise monocytes can increase or induce the expression of tissue factor, producing an imbalance in the system. Later in sepsis, when endothelium is involved further, the situation is complicated with vasculitis, cytokine activation, and alteration of the endothelium function, as already mentioned a condition of hypercoagulation. These produce fibrin deposit in different organs and stimulation of fibrinolytic mechanisms and disseminated intravascular coagulation (DIC).

Treatments and Therapies

Several trials have shown that anticoagulant proteins and factors could be sepsis markers for its severity. These trials in septic patients have demonstrated how protein C and antithrombin III are decreased and dimer D is increased, being a blood marker of fibrin formation.[90] Likewise, trials in animal models have shown how infusion of activated protein C can prevent the appearance of septic shock and death after an injection of lethal doses of *E. Coli*.[91]

Antithrombin III

It is well documented that the level of antithrombin III decreases in septic patients. Fourrier et al.[92] conducted a double-blind trial with 35 patients in septic shock and documented DIC. Patients received either placebo or antithrombin III (90–120 U/kg bolus and later 90–120 U/kg per day for 4 days). Although a reduction in mortality was found in favor of antithrombin group, the difference was not statistically significant. Levels of antithrombin definitely were improved in the antithrombin group, affecting levels of protein C and S. The authors suggested that further studies should be done, probably with a greater number of patients. Other double-blind trials with 34, 45, and 42 patients, respectively, found no benefit either.[93,94] In a later trial with 120 patients, Baudo et al.[95] found a decrease in mortality in patients treated with antithrombin in septic shock with a significant statistical difference with respect to the placebo group. Finally, the trial of Warren et al.,[96] a prospective, randomized, double-blind trial with more than 2,000 patients, showed no improvement in survival after using antithrombin over 96 h in patients, with severe sepsis and septic shock.

In conclusion, the use of antithrombin in sepsis is still debated, and despite a decrease in DIC, has not consistently demonstrated a decrease in mortality.

Tissue Factor Pathway Inhibitor (TFPI)

Animal models have demonstrated that infusion of recombinant TFPI improved the prognosis of sepsis induced by *E. coli.* Trials in human have not demonstrated benefits to decrease mortality as was demonstrated by Abraham et al.[97] They

conducted a prospective, randomized, double-blind placebo controlled trial of 1,955 patients with severe sepsis with TFPI without improvement in mortality.

Protein C

Depletion of protein C is associated with a variety of critical illnesses including sepsis. Lower levels are related to a worse prognosis. However, the question is: Will the prognosis of the patients change by replenishing the level of protein C? Lorente et al.[98] researched the course of clotting abnormalities and the fibrinolytic system in relation to patients with septic shock. The study included 48 patients, of which 25 died. On days 1, 4, and 7 after admission, levels of protein C, S, antithrombin, thrombin-antithrombin complex (TAT), dimer D, von Willebrand related antigen, tPA-like activator antigen, uPA-like activator antigen, tPA inhibitor antigen, plasminogen, alpha-2 antiplasmin, and fibrinogen were tested. They proved alterations in both pathways of coagulation. All patients had low levels of protein C, antithrombin, and TAT, especially those who did not survive. Recently, Mesters et al.[99] did a trial researching the prognostic value of activated protein C and dimer D in 26 high-risk patients developing sepsis by neutropenia induced by chemotherapy. They concluded that low levels of protein C could be identified sooner in these patients and they speculate that replenishing protein C could be beneficial. Ohishi et al.[100] demonstrated that adding protein C to depleted plasma slowed down the formation of fibrin, which would decrease intravascular clotting. The latest double-blind trial named "Prowess Trial" conducted by Bernard et al.[101] included 1,690 septic patients who were randomized to receive 24 μg/kg/h of activated protein C (drotrecogin alpha) or placebo for 96 hours. This showed a significant reduction of mortality (24.7% vs. 30.8%). Evidence up to now indicates that the use of protein C in septic patients decreases mortality but increases the risk of bleeding.

References

1. Dhainaut J. Introduction to the Margaux Conference on Critical Illness: activation of the coagulation system in critical illnesses. Crit Care Med 2000;28:9.
2. Hoffman M, Monroe DM 3rd. A cell-based model of haemostasis. Thromb Hemost 2001;85(6):958–65.
3. Falabella F. Coagulación. *In*: Restrepo A, Campusano G, Layrisse M, Falabella F, eds. Fundamentos de Medicina—Hematología. 4ª ed. Medellín: C.I.B, 1994:280.
4. Fenton WJ, Ofosu AF, Brezniak VD. Understanding thrombin and hemostasis. Haematol Oncol Clin North Am 1993;7(6):1107.
5. Osterud B. Tissue factor expression by monocytes: regulation and pathophysiological roles. Blood Coag Fibrin Suppl 1998;9:S9–14.
6. Giesen PL. Blood-borne tissue factor: another view of thrombosis. Proc Natl Acad Sci USA 1999;96:2311–15.
7. Bevilacqua MP, Gimbrone MA Jr. Inducible endothelial functions in inflammation and coagulation. Semin Thromb Hemost 1987;13:425–33.

8. Coughlin SR. Thrombin signalling and protease activated receptors. Nature 2000;407:258–64.
9. Coughlin SR. Sol Sherry lecture in thrombosis: how thrombin "talks" to cells: molecular mechanisms and roles in vivo. Arterioscl Thromb Vasc Biol 1998; 18:514–8.
10. Stenberg PE, McEver RP, Shuman MA, et al. A platelet alpha-granule membrane protein (GMP-140) is expressed on the plasma membrane after activation. J Cell Biol 1985;101:880–6.
11. Henn V, Slupsky JR, Grafe M, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature 1998;391:591–4.
12. Hughes PE, Pfaff M. Integrin affinity modulation. Trends Cell Biol 1998; 8:359–64.
13. Sims PJ, Wiedmer T, Esmon CT, et al. Assembly of the platelet prothrombinase complex is linked to vesiculation of the platelet plasma membrane. J Biol Chem 1989;264:17049–57.
14. Hattori R, Hamilton KK, Fugate RD, et al. Stimulated secretion of endothelial vWF is accompanied by rapid redistribution to the cell surface of the intracellular granule membrane protein GMP-140. J Biol Chem 1989;264:7768–71.
15. Subramaniam M, Frennete PS, Suffaripour S, et al. Defects in hemostasis in P-selectin-deficient mice. Blood 1996;87:1238–42.
16. Frenette PS, Mayadas TN, Rayburn H, et al. Susceptibility to infection and altered hematopoiesis in mice deficient in both P- and E-selectins. Cell 1996;84:563–74.
17. Lum H, Malik AB. Regulation of vascular endothelial barrier function. Am J Physiol 1994;267:L223–41.
18. Cirino G, Cicala C, Bucci MR, et al. Thrombin functions as an inflammatory mediator through activation of its receptor. J Exp Med 1996;183:821–7.
19. Mann KQ, Gaffney D, Bovill EG. Molecular biology, biochemistry and life-span of plasma coagulation factors. *In*: Beutler E et al., eds. Williams' Hematology, 5th ed. New York: McGraw-Hill, 1995.
20. van't Veer C, Mann KG. Regulation of tissue factor initiated thrombin generation by the stoichiometric inhibitors tissue factor pathway inhibitor, antithrombin-III, and heparin cofactor-II. J Biol Chem 1997;272:4367.
21. Rosenberg RD. The heparin-antithrombin system: a natural anticoagulant. *In*: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia, PA: Lippincott, 1987:1373.
22. van't Veer C, Golden NJ, Kalafatis M, et al. Inhibitory mechanism of the protein C pathway on tissue factor-induced thrombin generation. J Biol Chem 1997;272: 7983.
23. Ulutin ON, Seegers WH. Autoprothrombin II and autoprothrombin II anticoagulant. Thromb Diath Haemorrh 1962;7:256–63.
24. Esmon CT, Stenflo J, Suttie JW. A new vitamin K-dependent protein. A phospholipid-binding zymogen of a serine esterase. J Biol Chem 1976;251:3052–6.
25. Stenflo J. A new vitamin K-dependent protein. Purification from bovine plasma and preliminary characterization. J Biol Chem 1976;251:355–63.
26. Kisiel W, Canfield WM, Ericsson EH, et al. Anticoagulant properties of bovine plasma protein C following activation of thrombin. Biochem 1977;16:5824–31.
27. Stenflo J, Fernlund P. Amino acid sequence of the heavy chain of bovine protein C. J Biol Chem 1982;257:12180–90.

28. Esmon CT, Esmon NL, Harris KW. Isolation of a membrane-bound cofactor for thrombin-catalyzed activation of protein C. J Biol Chem 1982;257:7944–7.
29. Stearns-Kurosawa DJ, Kurosawa S, Mollica JS, et al. The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. Proc Natl Acad Sci USA 1996;93:10212–6.
30. Slungaard A, Fernandez JA, Griffin JH, et al. Platelet factor 4 enhances generation of activated protein C in vitro and in vivo. Blood 2003;102:146–51.
31. Bovill EG, Bauer KA, Dickerman JD, et al. The clinical spectrum of heterozygous protein C deficiency in a large New England kindred. Blood 1989;73:712–7.
32. Seligsohn U, Berger A, Abend M, et al. Homozygous protein C deficiency manifested by massive venous thrombosis in the newborn. N Engl J Med 1984;310:559–61.
33. Bizios R, Lai L, Fenton JW, 2nd, et al. Thrombin-induced chemotaxis and aggregation of neutrophils. J Cell Physiol 1986;128:485–90.
34. Drake WT, Lopes NN, Fenton JW, 2nd, et al. Thrombin enhancement of interleukin-1 and tumor necrosis factor-α induced polymorphonuclear leukocyte migration. Lab Invest 1992;67:617–27.
35. Grey ST, Tsuchida A, Hau H, et al. Selective inhibitory effects of the anticoagulant activated protein C on the responses of human mononuclear phagocytes to LPS, IFN-γ, or phorbol ester. J Immunol 1994;153:3664–72.
36. Joyce DE, Gelbert L, Ciaccia A, et al. Gene expression profile of antithrombotic protein c defines new mechanisms modulating inflammation and apoptosis. J Biol Chem 2001;276:11199–203.
37. Grinnell BW, Hermann RB, Yan SB. Human protein C inhibits selectin-mediated cell adhesion: role of unique fucosylated oligosaccharide. Glycobiology 1994;4: 221–5.
38. Murakami K, Okajima K, Uchiba M, et al. Activated protein C attenuates endotoxin-induced pulmonary vascular injury by inhibiting activated leukocytes in rats. Blood 1996;87:642–7.
39. Murakami K, Okajima K, Uchiba M, et al. Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production. Am J Physiol 1997;272: L197–202.
40. Riewald M, Petrovan RJ, Donner A, et al. Activation of endothelial cell protease activated receptor 1 by the protein C pathway. Science 2002;296:1880–2.
41. Sturn DH, Kaneider NC, Feistritzer C, et al. Expression and function of the endothelial protein C receptor in human neutrophils. Blood 2003;102:1499–505.
42. Riewald M, Petrovan RJ, Donner A, et al. Activated protein C signals through the thrombin receptor PAR1 in endothelial cells. J Endotoxin Res 2003;9:317–21.
43. Mosnier LO, Griffin JH. Inhibition of staurosporine-induced apoptosis of endothelial cells by activated protein C requires protease-activated receptor-1 and endothelial cell protein C receptor. Biochem J 2003;373:65–70.
44. Bajzar L, Manuel R, Nesheim M. Purification and characterization of TAFI, a thrombin-activatable fibrinolysis inhibitor. J Biol Chem 1995;270:14477–84.
45. Nagashima M, Yin ZF, Broze GJ, Jr. et al. Thrombin-activatable fibrinolysis inhibitor (TAFI) deficient mice. Front Biosci 2002;7:556–68.
46. Campbell WD, Lazoura E, Okada N, et al. Inactivation of C3a and C5a octapeptides by carboxypeptidase R and carboxypeptidase N. Microbiol Immunol 2002;46:131–4.

47. Myles T, Nishimura T, Yun TH, et al. Thrombin activatable fibrinolysis inhibitor: a potential regulator of vascular inflammation. J Biol Chem 2003;278(51):51059–67.
48. Owen WG, Esmon CT. Functional properties of an endothelial cell cofactor for thrombin-catalyzed activation of protein C. J Biol Chem 1981;256:5532–5.
49. Esmon CT, Owen WG. The discovery of thrombomodulin. J Thromb Haemost 2004;2:209–13.
50. Boffa M, Jackman R, Peyri N, et al. Thrombomodulin in the central nervous system. Nouv Rev Fr Hematol 1991;33:423–9.
51. Suzuki K, Nishioka J, Hayashi T, et al. Functionally active thrombomodulin is present in human platelets. J Biochem 1988;104:628–32.
52. McCachren SS, Diggs J, Weinberg JB, et al. Thrombomodulin expression by human blood monocytes and by human synovial tissue lining macrophages. Blood 1991;78:3128–32.
53. Wong V, Hofman FM, Ishii H, et al. Regional distribution of thrombomodulin in human brain. Brain Res 1991;556:1–5.
54. Conway E, Nowakowski B, Steiner-Mosonyi M. Biologically active thrombomodulin is present in synovial fluid and elevated in effusions of patients with rheumatoid arthritis. Clin Res 1992;40:241a.
55. Raife TJ, Lager DJ, Madison KC, et al. Thrombomodulin expression by human keratinocytes. Induction of cofactor activity during epidermal differentiation. J Clin Invest 1994;93:1846–51.
56. Conway EM, Pollefeyt S, Cornelissen J, et al. Structure-function analyses of thrombomodulin by gene-targeting in mice: the cytoplasmic domain is not required for normal fetal development. Blood 1999;93:3442–50.
57. Koyama T, Parkinson JF, Sié P, et al. Different glycoforms of human thrombomodulin—their glycosamino-glycan-dependent modulatory effects on thrombin inactivation by heparin cofactor II and antithrombin III. Eur J Biochem 1991;198:563–70.
58. Hamada H, Ishii H, Sakyo K, et al. The epidermal growth factor-like domain of recombinant human thrombomodulin exhibits mitogenic activity for Swiss 3T3 cells. Blood 1995;86:225–33.
59. Tohda G, Oida K, Okada Y, et al. Expression of thrombomodulin in atherosclerotic lesions and mitogenic activity of recombinant thrombomodulin in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 1998;18:1861–9.
60. Kurosawa S, Stearns DJ, Jackson KW, et al. A 10-kDa cyanogen bromide fragment from the epidermal growth factor homology domain of rabbit thrombomodulin contains the primary thrombin binding site. J Biol Chem 1988;263:5993–6.
61. Suzuki K, Hayashi T, Nishioka J, et al. A domain composed of epidermal growth factor-like structures of human thrombomodulin is essential for thrombin binding and for protein C activation. J Biol Chem 1989;264:4872–6.
62. Wang W, Nagashima M, Schneider M, et al. Elements of the primary structure of thrombomodulin required for efficient thrombin-activable fibrinolysis inhibitor activation. J Biol Chem 2000;275:22942–7.
63. Tsiang M, Lentz SR, Sadler JE. Functional domains of membrane-bound human thrombomodulin. EGF-like domains four to six and the serine/threonine-rich domain are required for cofactor activity. J Biol Chem 1992;267:6164–70.
64. Kokame K, Zheng X, Sadler J. Activation of thrombin-activatable fibrinolysis inhibitor requires epidermal growth factor-like domain 3 of thrombomodulin and is inhibited competitively by protein C. J Biol Chem 1998;273:12135–9.

65. Schenk-Braat EA, Morser J, Rijken DC. Identification of the epidermal growth factor-like domains of thrombomodulin essential for the acceleration of thrombin-mediated inactivation of single-chain urokinase-type plasminogen activator. Eur J Biochem 2001;268:5562–9.
66. DeMunk G, Groeneveld E, Rijken DC. Acceleration of the thrombin inactivation of single chain urokinase-type plasminogen activator (pro-urokinase) by thrombomodulin. J Clin Invest 1991;88:1680–4.
67. Molinari A, Giorgetti C, Lansen J, et al. Thrombomodulin is a cofactor for thrombin degradation of recombinant single-chain urokinase plasminogen activator "in vitro" and in a perfused rabbit heart model. Thromb Haemost 1992;67:226–32.
68. Suzuki K, Kusomoto H, Deyashiki Y, et al. Structure and expression of human thrombomodulin, a thrombin receptor on endothelium acting as a cofactor for protein C activation. EMBO J 1987;6:1891–7.
69. Lu R, Esmon NL, Esmon CT, et al. The active site of the thrombin-thrombomodulin complex. J Biol Chem 1989;264:12956–62.
70. Weisel JW, Nagaswami C, Young TA, et al. The shape of thrombomodulin and interactions with thrombin as determined by electron microscopy. J Biol Chem 1996;271:31485–90.
71. Villoutreix B, Dahlback B. Molecular model for the C-type lectin domain of human thrombomodulin. J Mol Model (On Line) 1998;4:310–22.
72. Fukudome K, Ye X, Tsuneyoshi N, et al. Activation mechanism of anticoagulant protein C in large blood vessels involving the endothelial cell protein C receptor. J Exp Med 1998;187:1029–35.
73. Laszik Z, Mitro A, Taylor FB, Jr., et al. Human protein C receptor is present primarily on endothelium of large blood vessels: implications for the control of the protein C pathway. Circulation 1997;96:3633–40.
74. Suzuki K, Deyashiki Y, Nishioka J, et al. Characterization of a cDNA for human protein C inhibitor. A new member of the plasma serine protease inhibitor superfamily. J Biol Chem 1987;262:611–6.
75. Espana F, Gilabert J, Estelles A, et al. Functionally active protein C inhibitor/plasminogen activator inhibitor-3 (PCI/PAI-3) is secreted in seminal vesicles, occurs at high concentrations in human seminal plasma and complexes with prostate-specific antigen. Thromb Res 1991;64:309–20.
76. Waugh JM, Yuksel E, Li J, et al. Local overexpression of thrombomodulin for in vivo prevention of arterial thrombosis in a rabbit model. Circ Res 1999;84: 84–92.
77. Weiler H, Lindner V, Kerlin B, et al. Characterization of a mouse model for thrombomodulin deficiency. Arterioscler Thromb Vasc Biol 2001;21:1531–7.
78. Rijneveld AW, Weijer S, Florquin S, et al. Thrombomodulin mutant mice with a strongly reduced capacity to generate activated protein C have an unaltered pulmonary immune response to respiratory pathogens and lipopolysaccharide. Blood 2004;103:1702–9.
79. Ikeguchi H, Maruyama S, Morita Y, et al. Effects of human soluble thrombomodulin on experimental glomerulonephritis. Kidney Int 2002;61:490–501.
80. Vasta GR, Quesenberry M, Ahmed H, et al. C-type lectins and galactins mediate innate and adaptive immune functions: their roles in the complement activation pathway. Dev Comp Immunol 1999;23:401–20.
81. Dodd RB, Drickamer K. Lectin-like proteins in model organisms: implications for evolution of carbohydrate-binding activity. Glycobiology 2001;11:71R–9R.

82. Conway EM, Van de Wouwer M, Pollefeyt S, et al. The lectin-like domain of thrombomodulin confers protection from neutrophil-mediated tissue damage by suppressing adhesion molecule expression via nuclear factor kappaB and mitogen-activated protein kinase pathways. J Exp Med 2002;196:565–77.
83. Van de Wouwer M, Clijsters K, Plaisance S, et al. Establishing links between coagulation and inflammation: the lectin-like domain of thrombomodulin confers protection in a murine model of rheumatoid arthritis. J Thromb Haemost 2003;1: 266.
84. Huang HC, Shi GY, Jiang SJ, et al. Thrombomodulin-mediated cell adhesion: involvement of its lectin-like domain. J Biol Chem 2003;278:46750–9.
85. Handin RI. Bleeding and thrombosis. *In*: Fauci A, Braunwald E, Isselbacher K, et al. eds. Harrison's Principles of Internal Medicine, 15th ed. New York: McGraw-Hill, 2001:354–60.
86. van't Veer C, Golden NJ, Kalafatis M, et al. Inhibitory mechanism of the protein C pathway on tissue factor-induced thrombin generation. J Biol Chem 1997;272: 7983.
87. Gando S, Nanzaki S, Sasaki S, et al. Activation of the extrinsic coagulation pathway in patients with severe sepsis and septic shock. Crit Care Med 1998;26: 2005–9.
88. Esmon NL, Esmon CT. Protein C and the endothelium. Semin Thromb Hemost 1988;14:210–5.
89. Cate H. Pathophysiology of disseminated intravascular coagulation in sepsis. Crit Care Med Suppl 2000;28:S9–S11.
90. Mesters RM, Mannucci PM, Coppola R, et al. Factor VIIA and anti-thrombin III activity during severe sepsis and septic shock in neutropenic patients. Blood 1996;88:881–6.
91. Taylor FB Jr, Chang A, Eamon CT, et al. Protein C prevents the coagulopathic and lethal effects of *Escherichia coli* infusion in the baboons. J Clin Invest 1987; 79:918–25.
92. Fourrier F, Chopin C, Huart JJ, et al. Double-blind, placebo-controlled trial of anti-thrombin III concentrates in septic shock with disseminated intravascular coagulation. Chest 1993;104:882–8.
93. Balk RA, Bedrossian C, McCormick L, et al. Prospective double blind placebo-controlled trial of ATIII substitution in sepsis. Abstr Intensive Care Med Suppl 1995;21:S17.
94. Eisele B, Lamy M, Thijs LG, et al. Antithrombin III in patients with severe sepsis: a randomized placebo-controlled double blind multicenter trial plus a meta-analysis on all randomized placebo-controlled multicenter trials with antithrombin III in severe sepsis. Intensive Care Med 1998;24:663–72.
95. Baudo F, Caimi TM, de Cataldo E, et al. Antithrombin III replacement therapy in patients with sepsis and/or surgical complications: a controlled double-blind randomized multicenter study. Intensive Care Med 1998;24:336–42.
96. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869–78.
97. Abraham E, Reinhart K, Opal O, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial JAMA 2003;290:238–47.
98. Lorente JA, Garcia-Frade LJ, Landin L, et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. Chest 1993;103:1536–42.

99. Mesters RM, Helterbrand J, Utterback BG, et al. Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications. Crit Care Med 2000;28:2209–16.
100. Ohishi R, Watanabe N, Aritomi M, et al. Evidence that the protein C activation pathway amplifies the inhibition of thrombin generation by recombinant human thrombomodulin in plasma. Thromb Haemost 1993;70:423–6.
101. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.

10
Vasopressors in Sepsis: Do They Change the Outcome?

Marco A. González and Cristhiaan D. Ochoa

Sepsis is the second most common disease in the intensive care unit (ICU), with a mortality rate between 32% and 60%. The major cause of death among these patients is multiorgan failure syndrome (MOFS), which takes place after a period of systemic and regional hypoperfusion that keeps active the systemic inflammatory and antiinflammatory systems.[1,2]

This hypoperfusion is caused by either an endothelial inflammatory process or by a systemic vasodilatation in response to (1) nitric oxide (NO) production by the inducible form of NO synthase (iNOS); (2) the ATP-dependent activation of a potassium (K^+) channel; or (3) insufficiency of vasopressin, as a consequence of depletion of its stores.[3] If this inflammatory process continues, it could lead to a refractory vasodilatation, which is manifested by systemic hypotension, a decrease in mixed venous oxygen saturation, lactic acidosis, bases deficit, and clinical manifestations of organ hypoperfusion.

Besides targeting the underlying pathogen disease, the main goal should be centered on aggressive resuscitation, an immunological intervention with current therapies (i.e., activated protein C), optimal control of glycemia, and the diagnosis and treatment of adrenal gland failure.[4]

Every treatment that has had a positive impact on the mortality of septic patients used vasopressors; the most frequently used are noradrenaline, followed by dobutamine, dopamine, and adrenaline.[5–7] These medications are coadjuvants in the treatment to maintain vascular tone, preventing vasodilatation and hypotension, which would contribute to multiorgan hypoperfusion.

The fluid status must be aggressively corrected in a shock patient while implementing the antibiotic therapy and treating the infection. This adjustment should be directed by a pulmonary artery catheter. After the volume status is corrected the vasopressor that will be used should be selected. Options available are dobutamine, dopamine, noradrenaline, adrenaline, and vasopressin.

The surviving sepsis guidelines for management of severe sepsis and septic shock recommend inotropes and vasopressors with little scientific evidence; however, in their daily practice intensivists use them to improve blood pressure measurements of patients in septic shock.[8] The question then is: Which vasoactive should be used in order to have a positive impact on patient survival and to prevent deleterious effects?

The answer is still open to discussion since the experience that an intensivist has with these types of patients is still the prevailing factor for selecting vasopressors. The authors' group, in particular, has decided that after achieving an adequate volume status, noradrenaline is the first-line vasopressor to use. The justification for this choice is explained below.

Noradrenaline

Noradrenaline (NE) constitutes 10% to 20% of suprarenal gland medulla catecholamines; the difference with adrenaline centers in the lack of a methyl substitute in the amine group. It has less adverse effects than adrenaline and it activates α-adrenergic postsynaptic receptors 1 and 2 (α-1 and α-2), leading to vasoconstriction. Additionally, it has a beta 1 (β-1) inotropic action. The pulmonary artery vasoconstrictor effect is not important (an average of 5 to 10 torr increase), which is why it could be used if heart failure is present in septic patients.[9] Furthermore, its vasoconstrictory effects do not affect the splanchnic bed flow as it is shown in a large animal experiment by Bellomo and Giantomasso in which they documented that noradrenaline infusion increased blood flow in the splanchnic, hepatic, and renal beds.[10]

NE dosage varies; it could be started as low as 0.05 μg/kg/min and may be increased until reaching the goal preferred by the physician. Doses as high as 3.3 μg/kg/min have been described, but this is extremely rare in everyday practice and could lead to a vasoconstrictor effect in peripheral beds, resulting in distal necrosis.[2]

There is increasing evidence in the literature showing the benefits of NE in comparison to other vasopressors. Martin et al. compared two groups of patients: one received dopamine plus NE and the other received adrenaline and dopamine. He clearly showed that the group receiving NE had a higher survival rate.[11]

Bellomo and Giantomasso[10] demonstrated that the mortality rate, based on the Simplified Acute Physiology Scale (SAPS) II score, of patients receiving NE was lower than patients on adrenaline. The average dose received by the former group was 0.86 μg/kg/min. The average infusion time was 88 hours. These studies support the authors' recommendation for using NE as the first-line vasopressor in patients with refractory septic shock.[12]

Dobutamine

Dobutamine is a synthetic catecholamine with beta-1 and beta-2 (β-1; β-2) activity. Dobutamine has less adverse effects that dopamine. The author's group uses it in combination with NE either when the resuscitation endpoints are not reached or when the attending physician desires a higher cardiac index. The dose utilized is 5 to 15 μg/kg/min. The pharmacological effect starts a few minutes after the IV infusion and ends when the delivery is stopped.[8]

Dobutamine has a coadjuvant role with the vasopressors in septic shock treatment. The final goal of this mixture is to improve the cardiac index and mixed venous oxygen saturation. Dobutamine has a chronotropic effect in addition to its inotropic one, both of which could improve the systolic performance of a septic heart. However, when the heart rate is disproportionately high, it increases the systemic vasodilation, worsening the hypotension.[8] Dobutamine improves cardiac index and reduces pulmonary vascular resistance in patients with sepsis. These effects restore the right heart contractility and increase splanchnic blood flow.

There are no studies showing improvement in mortality rates when dobutamine was used in septic patients, but it was used by Rivers et al. in their classic paper to achieve a higher mixed venous oxygen saturation endpoint after utilizing intravenous fluids and vasopressors.[5]

Dopamine

Dopamine is the most popular catecholamine used in septic shock after adrenaline. Its activity spectrum encompasses, depending upon the dosage, alpha, beta, and dopa receptors. Vincent recommended dopamine as the first-line vasopressor for septic shock in 2001.[13] Dopaminergic effects that favor renal blood flow, with low doses of 5 μg/kg/min and below, have been described. Unfortunately, an Australian randomized, double-blind clinical trial showed that this catecholamine did not prevent renal failure in septic shock patients.[14] Subsequently, a metaanalysis published in 2001 reported that there is no evidence to support its use in septic shock.[15] The surviving sepsis guidelines do not support dopamine as a renal protective agent. Dopamine has a grade-B evidence-based recommendation.[8]

The beta-1 stimulatory effect is reached with doses within the 5- to 10-μg/mL/min range. At this point inotropic and chronotropic effects are both favored. This, however, has deleterious consequences such as the increase in myocardium oxygen consumption.[16]

In addition to its chronotropic effects, dopamine has immunologic and metabolic effects. It diminishes cyclic adenosine monophosphate (cAMP) and inhibits proliferation in lymphocytes, as well as immunoglobulins, cytokines, growth hormone, and thyroid-stimulating hormone (TSH) production. It has been reported that dopamine allows lymphocyte apoptosis. A number of studies have reported intestinal ischemia as a consequence of dopamine infusions at different dosages.[17]

Vasopressin

Vasopressin (VP) levels are usually low in the late phase of septic shock. This contributes to the refractory status of some vasodilatory shock. VP has antidiuretic effects when it binds V2 receptors in renal tubules; it also results in vasoconstriction when it acts on V1 receptors present in vascular smooth muscle cells.[18]

VP blocks directly ATP-dependent K^+ channels in vascular smooth muscle cells, preventing the vasodilatory status from continuing in septic shock. It also blunts the cyclic guanosine monophosphate (cGMP) receptors' response to nitric oxide and atrial natriuretic peptide. The dosage for refractory hypotension due to septic shock is 0.01 to 0.04 U/min. Larger doses show no benefit and may lead to adverse effects.[18–20]

Laudry's studies[3] demonstrated that at this dosage, VP increases arterial pressure, renal blood flow, and diuresis, but it did not increase the cardiac index. There are no studies to report an increase in survival in septic patie nts treated with VP.

Conclusion

The final event in septic shock is multiorgan failure syndrome as a consequence of hypoperfusion resulting from a late, refractory vasodilatory shock. Before starting vasoactive agents, the underlying infectious disease must be under treatment, the volume status aggressively corrected, the immunomodulatory therapy started, and adrenal gland failure ruled out. NE is the vasoactive agent with the best results in refractory shock, and it is probably the vasoconstrictor that most improves mortality in septic patients. VP levels are depleted in the late phase of septic shock. If the patient is hypotensive, even though vasoactive agents and inotropes are used, VP should be started at low doses.

References

1. Annane D, Aegerter P, Jars-Guincestre MC, et al. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 2003;168(2):165–72.
2. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348(16):1546–54.
3. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345(8):588–95.
4. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348(2):138–50.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368–77.
6. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288(7):862–71.
7. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344(10):699–709.
8. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32(3):858–73.
9. Sharma VK, Dellinger RP, SCCM. International Sepsis Forum. The International Sepsis Forum's controversies in sepsis: my initial vasopressor agent in septic shock is norepinephrine rather than dopamine. Crit Care 2003;7(1):3–5.

10. Bellomo R, Giantomasso DD. Noradrenaline and the kidney: friends or foes? Crit Care 2001;5(6):294–8.
11. Martin C, Viviand X, Leone M, et al. Effect of norepinephrine on the outcome of septic shock. Crit Care Med 2000;28(8):2758–65.
12. Morimatsu H, Singh K, Uchino S, et al. Early and exclusive use of norepinephrine in septic shock. Resuscitation 2004;62(2):249–54.
13. Vincent JL, International Sepsis Forum. Hemodynamic support in septic shock. Intensive Care Med 2001;27 Suppl 1:S80–92.
14. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356(9248): 2139–43.
15. Kellum JA, M Decker J. Use of dopamine in acute renal failure: a meta-analysis. Crit Care Med 2001;29(8):1526–31.
16. De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 2003;31(6):1659–67.
17. Asfar P, De Backer D, Meier-Hellmann A, et al. Clinical review: influence of vasoactive and other therapies on intestinal and hepatic circulations in patients with septic shock. Crit Care 2004;8(3):170–9.
18. Holmes CL, Patel BM, Russell JA, et al. Physiology of vasopressin relevant to management of septic shock. Chest 2001;120(3):989–1002.
19. Holmes CL, Walley KR, Chittock DR, et al. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. Intensive Care Med 2001;27(8):1416–21.
20. Patel BM, Chittock DR, Russell JA, et al. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002;96(3):576–82.

11
Lactic Acidosis in Critically Ill Septic Patients

Daniel De Backer

Introduction

Lactic acidosis is often observed in patients with septic shock and is undoubtedly a sign of severity. Several animal studies have reported that lactic acidosis is associated with tissue hypoxia that can be global but also sometimes more focal. The hypoxic origin of lactic acidosis is more difficult to demonstrate in humans. Although some studies have reported that lactate to pyruvate ratio may be elevated, this is not always the case. In septic patients, and especially after hemodynamic stabilization, lactic acidosis may be related to other factors including an increased glycolysis (maybe under the influence of the activation of the Na/K ATPase transporter), the inhibition of pyruvate dehydrogenase, and a decrease in lactate clearance. Some organs produce lactate in larger amounts than others; in particular, the gut and the lungs can markedly contribute to the sepsis-induced hyperlactatemia. However, the net splanchnic lactate release is uncommon, as the liver is usually able to consume large amounts of lactate unless it also becomes hypoxic. Whatever its cause (hypoxic or not), lactic acidosis is associated with a poor outcome. There is no specific therapy for lactic acidosis, but early recognition of lactic acidosis is mandatory as it allows the provision of early interventions that can be lifesaving.

Patients with sepsis often present severe hemodynamic alterations, which include myocardial depression, severe vasoplegia, regional blood flow redistribution, and microcirculatory alterations. These may be associated with a decrease in oxygen availability to the tissues and ongoing tissue hypoxia, which can lead to the development of multiple organ failure. Hence, the detection of tissue hypoxia is essential to avoid the evolution to organ failure. Unfortunately, the detection of tissue hypoxia is difficult at the bedside. In sepsis, the oxygen demand can be elevated above the oxygen supply. Furthermore, an alteration in oxygen extraction capabilities by the tissues can limit their oxygen consumption. On the other hand, some tissues can decrease their metabolic needs to adapt to the decreased oxygen availability (oxygen conformance). Thus the interpretation of the classical hemodynamic parameters including cardiac output, oxygen delivery, oxygen consumption, and mixed-venous oxygen saturation can have serious

limitations in this context. Measurements of blood lactate levels may be useful to detect occult tissue hypoxia and also to monitor the effects of therapy. Lactic acidosis is commonly observed in patients with severe sepsis and septic shock. Although hyperlactatemia is often considered as a hallmark of ongoing tissue hypoxia, this is not always the case, so erroneous conclusions may sometimes be drawn leading to unjustified therapeutic interventions.

Lactate Metabolism

Glycolysis produces adenosine triphosphate (ATP), which is the source of energy for cellular metabolism. First, one molecule of glucose is transformed into two molecules of pyruvate, generating two molecules of ATP. This reaction occurs in the cytoplasm of the cells and does not require the presence of oxygen. In the second phase, which takes place in the mitochondria and requires oxygen, pyruvate enters the Krebs cycle generating CO_2, H_2O, and 18 ATP molecules (per molecule of pyruvate). In normal conditions, a small amount of pyruvate is transformed into lactate, generating two molecules of ATP for one molecule of pyruvate. Lactate can be retransformed in pyruvate in the liver and in the muscle (and brain) using four molecules of ATP. Pyruvate is preferentially incorporated in the Krebs cycle resulting in a 10 : 1 lactate to pyruvate ratio in normal conditions. In the absence of oxygen, pyruvate cannot enter the Krebs cycle and is preferentially transformed into lactate in order to maintain ATP production, even though this metabolic pathway is less efficient. In some cells that do not have mitochondria, such as red blood cells, large amounts will be produced even if oxygen is abundant; however, lactate is rapidly cleared by the other organs. In anaerobic conditions, lactate is produced in large amounts and pyruvate is rapidly consumed so the lactate to pyruvate ratio increases. Ideally pyruvate measurements should be obtained to separate hypoxic from nonhypoxic causes of lactate production; unfortunately, pyruvate measurements are difficult to obtain and frequently unreliable in clinical practice.

Lactic Acidosis versus Hyperlactatemia?

The transformation of pyruvate into lactate produces equimolar amounts of H+. In addition, H+ is also produced by the hydrolysis of ATP, and H+ molecules accumulate as they are no longer used by cytochromes in hypoxic conditions. This usually results in metabolic acidosis. However, arterial pH can be affected in septic patients by many factors such as hyperventilation, administration of bicarbonate (i.e., in continuous hemofiltration), concomitant renal failure, preexisting acid base disorders (such as metabolic alkalosis in a chronic obstructure pulmonary disease (COPD) patient or due to abundant gastric losses), and decreased albumin levels. Accordingly, hyperlactatemia and lactic acidosis may be dissociated, especially in the less severe cases. On the other hand, septic

patients can also present metabolic acidosis unrelated to tissue hypoxia (such as in renal failure or hyperchloremia) and a concomitant hyperlactatemia. Hence, metabolic acidosis may clearly be dissociated from hyperlactatemia.

Evidence for Hypoxic Origin of Lactate in Sepsis

Proof of the anaerobic generation of lactate is difficult to obtain in clinical conditions. In experimental models of endotoxic shock, blood lactate concentrations rise when oxygen consumption becomes dependent on oxygen delivery (VO_2/DO_2 dependency), suggesting an anaerobic origin.[1,2] In septic animals, the increase in blood lactate levels was associated with a decrease in muscle[3–5] and liver[6] bioenergetic status.

In septic patients, hyperlactatemia can also be observed, even when flow is maintained. The hypoxic origin of the sepsis-induced hyperlactatemia is less clear. In patients with acute circulatory failure who are treated with high doses of vasoactive agents, there is a strong suspicion that hyperlactatemia is related to tissue hypoxia.[7–9] Levy et al.[9] observed that hyperlactatemia was associated with signs of anaerobic metabolism, as an increased lactate to pyruvate ratio and decreased arterial ketone body ratio. In these patients, hyperlactatemia is often, but not always, associated with metabolic acidosis. However, tissue hypoxia and anaerobic metabolism cannot be sustained for long periods of time, as the energy produced by anaerobic metabolism is quite low compared to aerobic metabolism. Hence, it is unlikely that a mild hyperlactatemia (2 to 4 mEq/L) in hemodynamically stable septic patients is related to tissue hypoxia.

Alternative Causes of Hyperlactatemia in Sepsis

Lactate can also be produced in increased amounts even in the presence of oxygen. This may be due either to inhibition of several enzymes of the Krebs cycle or to a massive production of pyruvate. Several experimental studies, mainly in rodents, have reported that pyruvate dehydrogenase, an enzyme essential for the incorporation of pyruvate into the Krebs cycle, is inhibited after endotoxin administration or cecal ligation.[10,11] However, the impact of pyruvate dehydrogenase inhibition in septic patients remains to be determined. In a randomized study including 252 critically ill patients with lactic acidosis, Stacpoole et al.[12] observed that the administration of dichloroacetate, which stimulates the oxidation of lactate to acetyl-coenzyme A, bypassing the pyruvate dehydrogenase, resulted in small and clinically insignificant changes in blood lactate levels and arterial pH, while the hemodynamic state and outcome were unaffected. As pyruvate dehydrogenase is an essential enzyme of the Krebs cycle, its inhibition is a form of tissue hypoxia (cytopathic hypoxia), which, of course, cannot be sustained for a long period of time without generating serious tissue damage.

Another, and probably more important, effect is related to the mass effect of increased pyruvate availability due to the acceleration of aerobic glycolysis in sepsis. In hemodynamically stable septic patients with hyperlactatemia, Gore et al.[13] reported that lactate and pyruvate were both markedly increased. They related this increase in lactate and pyruvate to an accelerated glucose turnover, as glucose production was fourfold higher in septic patients compared to healthy volunteers. Tissue hypoxia was not involved in these patients as pyruvate oxidation was also fourfold higher than in healthy volunteers. It is likely that glycolysis is increased in order to provide ATP to the Na/K ATPase ion exchanger[14,15] that is highly stimulated by endotoxin,[16] catecholamines,[17] and insulin.[18] The implication of this exchanger is further highlighted by the fact that ouabain inhibits Na/K ATPase and decreases muscle lactate production.[15] Nevertheless, other experimental models found that Na/K ATPase was reduced[19] rather than increased; hence its contribution is still hypothetical.

What are the clinical implications of glycolysis-induced hyperlactatemia? This may be considered on one hand as a futile reaction, leading to the dissipation of energy stores,[20] but on the other hand some investigators consider that this may be an adaptative phenomenon leading to increased energy production.[21] This is highlighted by the finding that white blood cells produce large amounts in lactate in response to endotoxin exposure.[22] In these cells, a very limited part of the ATP production is of mitochondrial origin, and anaerobic glycolysis provides most of the extra energy requirements for the activated white blood cells, which is associate with the release of large amounts of lactate. Although generated by anaerobic metabolism, this increase in lactate production is not due to O_2 deprivation. Another possibility is that the increased glycolysis, which may affect both aerobic and anaerobic glycolysis, may compensate for the impaired mithochondrial function.[21] However, these observations do not imply a causal link, as coenzyme Q10, which restored cytochrome function, was unable to restore glycolytic function.[23] Hence, it is difficult to differentiate between these various possibilities.

On the other hand, lactate clearance may also be altered in sepsis. Blood lactate concentrations are the result of the balance between lactate production, whatever its cause and source, and lactate clearance. In normal conditions, at rest, the liver accounts for more than half of lactate clearance, and kidneys and muscles account for the remaining part. In sepsis, various factors may influence hepatic lactate clearance, especially liver function and liver blood flow. Extreme conditions of pH can also decrease lactate clearance. Renal lactate clearance is also decreased as it occurs in the renal cortex, and this area is very sensitive to a reduction in blood flow. In addition, striated muscle often fails to metabolize lactate.

Using an external lactate load in hemodynamically stable septic patients, Levraut et al.[24] reported that lactate clearance was markedly altered in patients with mildly elevated blood lactate levels (2 to 4 mEq/L) but not in patients with normal blood lactate concentrations. Levraut et al. recently extended these findings and reported that a low lactate clearance was associated with an impaired outcome.[25]

However, the role of the decreased lactate clearance needs to be somewhat challenged. First, blood lactate concentrations are within normal values in patients with very severely impaired liver function such as in ambulatory cirrhotic patients. Hence, an increased blood lactate concentration suggests that lactate is actively, or has been recently, produced in increased amounts; the impairment in liver function can only be responsible for a delayed clearance, resulting in a more severe and especially more prolonged hyperlactatemia. Second, all the above causes of hyperlactatemia (hypoxia, increased glycolysis, inflammatory processes) are associated with increased lactate production. Third, the methodology of determination of lactate production is complicated and requires a steady state, which may not be easily achieved in critically ill septic patients. Accordingly, it is quite clear that lactate clearance is delayed in patients with septic shock, but this alone cannot explain blood lactate levels. Rapidly increasing blood lactate levels always represent increased lactate production, which may or may not be of hypoxic origin.

Regional Lactate Production

The production of lactate may be selectively increased in some organs, either as a result of regional blood flow alterations leading to local hypoxia or as a result of focal inflammation. Animal studies have reported that the lungs are major lactate producers in sepsis. In endotoxic dogs, Bellomo et al.[26] reported that the lungs released lactate while other organs still consumed lactate. In patients with acute lung injury, several groups have reported that lung lactate production is markedly increased. The lungs can produce tremendous amounts of lactate in acute lung injury. De Backer et al.[27] measured lung lactate production in critically ill patients with acute respiratory failure of various origins and reported that lactate production by the lungs necessitates the presence of an inflammatory process (infection is not a prerequisite) that has to be severe (direct relationship with the severity of the lung disease) and diffuse (absence of lactate production in localized forms of lung disease).

Other organs can also produce lactate. Experimental studies suggest that the gut can produce lactate, which is likely to be of hypoxic origin as indicated by the increased portal lactate to pyruvate ratio.[28] However, the liver is usually able to clear this small amount of lactate produced by the gut, so there is no net lactate release by the splanchnic area. Creteur et al.[29] recently demonstrated that splanchnic lactate release occurred only when the liver is hypoxic, as indicated by a decrease in oxygen delivery below liver critical oxygen delivery. In 90 patients with severe sepsis, De Backer et al.[30] reported that splanchnic lactate release was uncommon (it occurred in only six patients) and was not related to arterial lactate concentrations, abdominal infection, or indirect signs of gut or liver dysoxia (estimated by gastric mucosal to arterial PCO_2 gradient and mixed venous to hepatic venous O_2 saturation gradient). However, we cannot rule out that the gut still produced lactate in some of these patients.

Finally, any infected or inflamed organ can probably release lactate. We mentioned above the role of white blood cells, which, when activated, can produce large amounts of lactate.[22] Although generated by anaerobic metabolism, this increase in lactate production is not due to O_2 deprivation. Hence, large amounts of lactate can be produced in inflammatory processes even in the absence of tissue hypoxia.

Interpretation of Blood Lactate Concentrations

Increased blood lactate can only be caused by increased anaerobic or aerobic lactate production, eventually combined with decreased lactate clearance (Figure 11.1). Tissue hypoxia should always be excluded first, as persistent tissue hypoxia can lead to multiple organ failure and death. Tissue hypoxia can be global but can also be localized, and special attention should be posted on regional circulations. Sometimes tissue hypoxia can be due to mitochondrial impairment, such as in cytopathic hypoxia.[31,32] Aerobic lactate production, either global or focal (especially in the lungs), is the result of activation of the inflammation cascade. In this context, hyperlactatemia should be considered as a warning indicator of

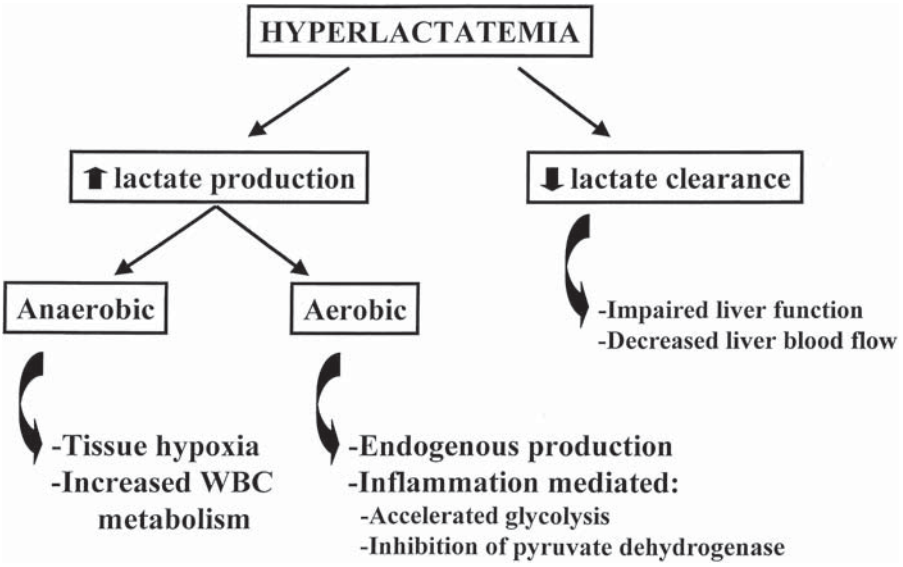


FIGURE 11.1. Interpretation of hyperlactatemia. Blood lactate concentrations reflect the balance between lactate production, either anaerobic, mainly in tissue hypoxia, or aerobic, as a consequence of the sum of the endogenous basal lactate production and the additional lactate production under the influence of overwhelming inflammation, and lactate clearance, mainly by the liver. WBC, white blood cells. Source: De Backer.[41]

a very severe inflammatory state, and one should always review the patient in order to ensure that no focus of infection remains uncovered.

When an altered lactate clearance is involved, it can of course be due to an altered liver metabolism, usually insensitive to hemodynamic manipulations, but also to a decreased perfusion of the liver, which can be improved by hemodynamic interventions.[33]

Prognostic Value

Lactic acidosis is associated with impaired survival, whatever its source. Several studies have reported that admission blood lactate levels are strongly associated with outcome.[34,35] This relationship is not linear but rather sigmoidal, with values below 2 mEq/L associated with nearly 100% survival, values between 4 and 5 mEq/L with 50% survival, and values above 10 mEq/L with lower than 50% survival rates.[36] Interestingly, the prognostic value was better for lactate than for pyruvate or the lactate to pyruvate ratio, suggesting that the prognostic value is not related to tissue hypoxia alone. The prognostic value can be even more accurate when the evolution of blood lactate concentrations under the influence of therapeutic interventions is taken into account. A decrease in blood lactate levels and a smaller area under the curve during the first 24 h are associated with a better outcome.[37] In addition, persistent hyperlactatemia and increasing lactate levels are associated with a worse outcome.

Treatment of Lactic Acidosis

There is no specific therapy for lactic acidosis; the only treatment will be treatment of the underlying cause. Nevertheless, early recognition of hyperlactatemia is essential, as early interventions targeted on hemodynamic endpoints can decrease mortality in patients with severe sepsis and elevated blood lactate levels.[38] However, it has not been proven that specific interventions targeted to normalize blood lactate concentrations can improve outcome.

Apart from the hemodynamic optimization in case of global or focal tissue hypoxia, treatment of lactic acidosis is quite disappointing. In particular the treatment of glycolitic disorders may not be beneficial. Treatment of pyruvate dehydrogenase inhibition with dichloroacetate failed to improve the outcome of septic patients.[12] Some authors have suggest that beta-blocking agents could be used to counteract the stimulation of the Na/K ATPase by catecholamines.[17] Although this therapy might be considered in hemodynamically stable septic patients, this treatment is clearly contraindicated in patients with septic shock.

Finally, the correction of acidosis with bicarbonate is clearly not indicated: bicarbonate administration can be either ineffective[39] or even deleterious.[40]

Conclusion

Lactic acidosis is frequent in patients with septic shock and is associated with an impaired outcome. Measurements of blood lactate concentrations are useful to detect occult tissue hypoxia and to monitor the effects of therapy. Even though hyperlactatemia can be due to other causes than tissue hypoxia, and in particular to inflammatory processes so that hemodynamic interventions may not always be warranted, the rapid recognition of lactic acidosis is essential as it allows the provision of early interventions that can be lifesaving.

References

1. Zhang H, Rogiers P, De Backer D, et al. Regional arteriovenous differences in PCO_2 and pH can reflect critical organ oxygen delivery during endotoxemia. Shock 1996; 5:349–56.
2. Barefield ES, Oh W, Stonestreet BS. Group B streptococcus-induced acidosis in newborn swine: regional oxygen transport and lactate flux. J Appl Physiol 1992; 72:272–7.
3. Lundsgaard-Hansen P, Pappova E, Urbaschek B, et al. Circulatory deterioration as the determinant of energy metabolism in endotoxin shock. J Surg Res 1972;13:282–8.
4. Townsend MC, Hampton WW, Haybron DM, et al. Effective organ blood flow and bioenergy status in murine peritonitis. Surgery 1986;100:205–13.
5. Levy B, Valtier M, de Chillou C, et al. Beneficial effects of L-canavanine, a selective inhibitor of inducible nitric oxide synthase, on lactate metabolism and muscle high energy phosphates during endotoxic shock in rats. Shock 1999;11:98–103.
6. Hart DW, Gore DC, Rinehart AJ, et al. Sepsis-induced failure of hepatic energy metabolism. J Surg Res 2003;115:139–47.
7. Liaw KY. Effect of injury, sepsis, and parenteral nutrition on high-energy phosphates in human liver and muscle. JPEN 1985;9:28–33.
8. Dugas MA, Proulx F, de Jaeger A, et al. Markers of tissue hypoperfusion in pediatric septic shock. Intensive Care Med 2000;26:75–83.
9. Levy B, Sadoune LO, Gelot AM, et al. Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. Crit Care Med 2000;28:114–9.
10. Vary TC, Siegel JH, Nakatani T, et al. Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. Am J Physiol 1986;250: E634-40.
11. Vary TC. Sepsis-induced alterations in pyruvate dehydrogenase complex activity in rat skeletal muscle: effects on plasma lactate. Shock 1996;6:89–94.
12. Stacpoole PW, Wright EC, Baumgartner TG, et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. N Engl J Med 1992;327:1564–9.
13. Gore DC, Jahoor F, Hibbert JM, et al. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg 1996;224:97–102.
14. James JH, Fang CH, Schrantz SJ, et al. Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle: implications for increased muscle lactate production in sepsis. J Clin Invest 1996;98:2388–97.

15. James JH, Luchette FA, McCarter FD, et al. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet 1999;354:505–8.
16. Bundgaard H, Kjeldsen K, Suarez KK, et al. Endotoxemia stimulates skeletal muscle Na+-K+-ATPase and raises blood lactate under aerobic conditions in humans. Am J Physiol Heart Circ Physiol 2003;284:H1028–34.
17. Luchette FA, Robinson BR, Friend LA, et al. Adrenergic antagonists reduce lactic acidosis in response to hemorrhagic shock. J Trauma 1999;46:873–80.
18. Novel-Chate V, Rey V, Chiolero R, et al. Role of Na+-K+-ATPase in insulin-induced lactate release by skeletal muscle. Am J Physiol Endocrinol Metab 2001;280: E296–300.
19. Abad B, Mesonero JE, Salvador MT, et al. Effect of lipopolysaccharide on small intestinal L-leucine transport in rabbit. Dig Dis Sci 2001;46:1113–9.
20. Wolfe R, Herndon D, Jahoor F, et al. Effect of severe burn injury on substrate cycling by glucose and fatty acids. N Engl J Med 1987;317:403–8.
21. L'Her E, Sebert P. A global approach to energy metabolism in an experimental model of sepsis. Am J Respir Crit Care Med 2001;164:1444–7.
22. Haji-Michael PG, Ladriere L, Sener A, et al. Leukocyte glycolysis and lactate output in animal sepsis and ex vivo human blood. Metabolism 1999;48:779–85.
23. L'Her E, Sebert P. Effects of dichloroacetate and ubiquinone infusions on glycolysis activity and thermal sensitivity during sepsis. J Lab Clin Med 2004;143:352–7.
24. Levraut J, Ciebiera JP, Chave S, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 1998;157:1021–6.
25. Levraut J, Ichai C, Petit I, et al. Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. Crit Care Med 2003;31:705–10.
26. Bellomo R, Kellum JA, Pinsky MR. Transvisceral lactate fluxes during early endotoxemia. Chest 1996;110:198–204.
27. De Backer D, Creteur J, Zhang H, et al. Lactate production by the lungs in acute lung injury. Am J Respir Crit Care Med 1997;156:1099–104.
28. Tugtekin I, Radermacher P, Theisen M, et al. Increased ileal-mucosal-arterial PCO_2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med 2001;27:757–66.
29. Creteur J, De Backer D, Sun Q, et al. The hepatosplanchnic contribution to hyperlactatemia in endotoxic shock: effects of tissue ischemia. Shock 2004;21:438–43.
30. De Backer D, Creteur J, Silva E, et al. The hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. Crit Care Med 2001;29:256–61.
31. Adrie C, Bachelet M, Vayssier-Taussat M, et al. Mitochondrial membrane potential and apoptosis peripheral blood monocytes in severe human sepsis. Am J Respir Crit Care Med 2001;164:389–95.
32. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet 2002;360:219–23.
33. De Backer D, Creteur J, Noordally O, et al. Does hepato-splanchnic VO_2/DO_2 dependency exist in critically ill septic patients? Am J Respir Crit Care Med 1998;157:1219–25.
34. Stacpoole PW, Wright EC, Baumgartner TG, et al. Natural history and course of acquired lactic acidosis in adults. Am J Med 1994;97:47–54.
35. Bakker J, Coffernils M, Leon M, et al. Blood lactate levels are superior to oxygen derived variables in predicting outcome in human septic shock. Chest 1991;99:956–62.

36. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 1970;41: 989–1001.
37. Bakker J, Gris P, Coffernils M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 1996;171: 221–6.
38. Rivers E, Nguyen B, Havstadt S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
39. Arieff AI, Park A, Leach W, et al. Systemic effects of NaHCO3 in experimental lactic acidosis in dogs. Am J Physiol 1982;242:F586-91.
40. Graf H, Leach W, Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 1985;227:754–6.
41. De Backer D. Lactic acidosis. Intensive Care Med 2003;29:699–702.

12
Delirium in Septic Patients: An Unrecognized Vital Organ Dysfunction

Timothy D. Girard and E. Wesley Ely

Introduction

Acute organ dysfunction is a defining feature of severe sepsis,[1] with respiratory, cardiovascular, and renal failure recognized in 46%, 24%, and 22% of patients with severe sepsis, respectively.[2] Acute brain dysfunction is much less frequently diagnosed.[3] Using ICD-9 codes for encephalopathy, transient organic psychosis, and anoxic brain damage, Angus et al. found that acute central nervous system (CNS) dysfunction was only reported in 9.3% of severe sepsis cases.[2] Despite these low documentation rates, it has long been recognized that delirium occurs frequently in patients with severe sepsis. The previously common labels for delirium in intensive care unit (ICU) patients—"ICU psychosis" and "ICU syndrome"—are misnomers, implying that this syndrome is an expected, inconsequential outcome of intensive care.[4] In fact, recent studies have revealed that delirium in septic patients is both common *and* deleterious, and it can no longer be regarded as simply a bothersome facet of an ICU stay. Instead, delirium represents the clinical manifestation of acute CNS dysfunction, independently conferring increased risk for morbidity and mortality in patients with severe sepsis even after considering coma.

Historical Perspectives on Delirium in Septic Patients

The association between infection and altered mental status was noted as early as Hippocrates, who described patients with fever, abscesses, and "phrenitis."[5,6] Other notable physicians who recorded this observation included Galen[6] and, much later, Sir William Osler.[7] In the past 25 years, several investigators have worked to understand the mechanisms leading to CNS dysfunction in sepsis (see Table 12.1).[8–14] However, the clinical and pathological features of this syndrome were not systematically studied until Jackson et al. published observations from an autopsy series of 12 patients with "the encephalopathy of sepsis."[15] They noted that the level of consciousness in these patients varied and coma was frequent, computed tomographic head scans and cerebrospinal fluid examinations

TABLE 12.1. Early Clinical Investigations of Delirium in Patients with Severe Sepsis

Source/Ref.	Year	Pts.	Findings
Freund et al.[8]	1978	5	Reversal of CNS dysfunction occurred with BCAA treatment
Jackson et al.[15]	1985	12	Described clinical and pathologic features of delirium in septic pts.
Bowton et al.[12]	1989	9	Cerebral blood flow was reduced in septic pts.
Young et al.[17]	1990	69	Brain dysfunction occurred in 49 (71%) septic pts.
Sprung et al.[16]	1990	1333	Acutely altered mental status occurred in 307 (23%) of septic pts.
Wijdicks et al.[13]	1992	84	Hypotension was a significant predictor of delirium in septic pts.
Young et al.[14]	1992	62	Described the EEG findings that occur in septic pts. with delirium
Bleck et al.[18]	1993	1758	Neurologic complications occurred in 217 (12%) medical ICU pts.
Eidelman et al.[19]	1996	50	CNS dysfunction can be characterized by GCS

Note: Pts., patients; CNS, central nervous system; BCAA, branched chain amino acids; EEG, electroencephalogram; ICU, intensive care unit; GCS, Glasgow Coma Scale.

were usually normal, and electroencephalograms (EEGs) revealed diffuse abnormalities.

Several early studies evaluated the prevalence of delirium in septic patients. Pine et al. evaluated 106 surgical patients with abdominal sepsis and found that 10 (9%) had CNS dysfunction, defined as inability to follow simple commands.[3] Sprung et al. later published data from the large Veterans Administration Systemic Sepsis Cooperative Study showing that 307 (23%) of the 1,333 septic patients studied exhibited an acutely altered mental status.[16] The same year Young et al. reported that 49 (71%) of 69 patients with sepsis developed mild (17 patients) or marked (32 patients) brain dysfunction.[17] Bleck et al. evaluated 1,758 medical ICU patients and reported that 217 (12%) patients developed neurologic complications.[18] Of these complications, metabolic encephalopathy was the most common, and sepsis was the most frequent cause of encephalopathy. Lastly, Eidelman et al. classified CNS dysfunction in septic patients by three different methods and found that the prevalence ranged from 50% to 62% depending upon the method of diagnosis.[19]

These and more recent studies have firmly established delirium as a common clinical syndrome resulting from one or more etiologic processes.[15] It is a rare patient with severe sepsis who demonstrates no risk factor for delirium other than infection and its associated inflammatory state. Instead, these critically ill patients are subjected to multiple host, iatrogenic, and environmental factors, making it difficult to attribute their delirium simply to sepsis alone. Therefore, the term "septic encephalopathy" is now discouraged[20]; "delirium" more appropriately describes the acute confusional state seen in patients with severe sepsis.

Pathogenesis of Delirium in Septic Patients

The pathogenesis of delirium in septic patients remains unclear and is likely multifactorial.[6] Multiple hypotheses exist and animal models have been developed that lend support to each. Early work documented the presence of disseminated microabscesses in the brains of some patients who had died of sepsis,

suggesting that infectious organisms may directly cause CNS dysfunction.[11,15] However, other studies have failed to confirm these findings.[18] More likely to be of pathophysiologic importance are the profound inflammatory and coagulopathic disturbances that are nearly universal in patients with sepsis. We will now outline these briefly, acknowledging that a detailed review is beyond the scope of this chapter.

The inflammatory mediators produced in sepsis—tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and other cytokines and chemokines—initiate a cascade that leads to endothelial damage, thrombin formation, and microvascular compromise.[21] Animal models reveal that these inflammatory mediators cross the blood-brain barrier,[22] increase vascular permeability in the brain,[23] and result in EEG changes consistent with those seen in septic patients with delirium.[6,24] This may occur due to decreased cerebral blood flow, a result of the formation of microaggregates of fibrin, platelets, neutrophils, and erythrocytes in the cerebral microvasculature; as well as cerebral vasoconstriction occurring in response to α_1-adrenoceptor activity[25]; or due to interference with neurotransmitter synthesis and neurotransmission.[26]

Additional potentially important etiologies of delirium in septic patients are abnormalities in neurotransmitter levels. For example, acetylcholine depletion is thought to be central to the pathophysiology of delirium. Inflammatory cytokines as well as tissue hypoxia and hypoglycemia lead to reduced acetylcholine synthesis resulting in delirium and cognitive impairment.[26] Thus, there is a clear association between anticholinergic drugs and the development of delirium. In addition, the monoaminergic neurotransmitters are disturbed in delirium, with increased dopaminergic release (i.e., dopamine excess) and neurotransmission leading to psychotic symptoms. The deliriogenic effects of narcotics may be mediated by their anticholinergic or dopaminergic properties while antipsychotics such as haloperidol likely exert their treatment effects by increasing acetylcholine and blocking dopamine.

Defining Delirium and Its Motoric Subtypes

The word "delirium" finds it root in the Latin word *deliro*, meaning "to be crazy, deranged, or silly." (The Latin word *liro* is an agricultural term meaning to "plough correctly, in a straight line," while *deliro* means to "plough out of your furrow" like a madman.) Although the medical community has historically reserved "delirium" to describe agitated, confused patients and has used "encephalopathy" to describe lethargic, confused patients, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[27] does not make this distinction. It defines delirium as a confusional state characterized by acute onset, fluctuating level of consciousness, inattention, and disorganized thinking. Additionally, disruption of the sleep-wake cycle and psychomotor disturbances (e.g., hallucinations) are associated features of delirium, yet they are not required for its diagnosis.

Multiple schema exist for subtyping delirium, including hyperactive versus hypoactive, cortical versus subcortical, anterior versus posterior cortical, right versus left hemispheric, psychotic versus nonpsychotic, and acute versus chronic.[28] While each of these frameworks has utility when attempting to understand the pathophysiology of delirium, the most clinically relevant and therefore most commonly accepted schema is that of hyperactive versus hypoactive, with the distinguishing feature being the level of motor activity observed. Patients with hyperactive delirium demonstrate psychomotor agitation, semipurposeful activity, and emotional lability, while those with hypoactive delirium demonstrate decreased responsiveness and lethargy.[29,30] Although certain etiologies are commonly associated with a particular subtype of delirium (e.g., alcohol withdrawal and anticholinergic toxicity tend to cause hyperactive delirium, whereas hepatic insufficiency and traumatic brain injury tend to cause hypoactive delirium),[28] patients with severe sepsis frequently develop mixed delirium, exhibiting features of both hyperactive and hypoactive subtypes during the course of their illness.

In a study of 325 noncritically ill inpatients, Liptzin et al. diagnosed 125 with delirium and identified 15% with hyperactive, 19% with hypoactive, 52% with mixed, and 14% with neither subtype of delirium.[31] More recently, Peterson et al. reported on delirium subtypes evaluated among 307 medical ICU patients.[32] Persistently hyperactive delirium was uncommon in both mechanically ventilated and nonventilated patients, hypoactive delirium was less common in ventilated patients (51 vs. 67%, $p = .02$), and mixed delirium was more common in ventilated patients than in nonventilated patients (47% vs. 29%, $p = .008$). These differences are notable in patients with severe sepsis, a population frequently requiring mechanical ventilation, and they may have prognostic and therapeutic implications, a subject of ongoing investigations.

Risk Factors for Delirium in the Septic Patient

Multiple risk factors for the development of delirium in septic patients have been identified. Infection itself was the most common etiology associated with the development of delirium noted by Francis et al. in a study of 229 hospitalized elderly patients.[33] Other independent risk factors noted by Francis et al. included severity of illness, dementia, hypo- or hypernatremia, fever or hypothermia, azotemia, and use of psychoactive drugs. It is important to note that the majority of patients with severe sepsis are exposed to multiple risk factors for delirium, and these factors act in a dose-dependent fashion with rates of delirium increasing as the number of risk factors rises.[33] In a study of 48 medical ICU patients, the majority of patients experienced over 10 risk factors for delirium.[34]

Risk factors for delirium in hospitalized elderly patients have been extensively studied[35–40] and are frequently of significance in patients with severe sepsis (Table 12.2). These risk factors can be divided into three categories: (1) baseline characteristics, (2) features of acute illness, and (3) environmental or iatrogenic

TABLE 12.2. Risk Factors for Delirium in Patients with Severe Sepsis

Baseline Characteristics/Ref.	Features of Acute Illness/Ref.	Iatrogenic Factors/Ref.
Increasing age[35,37]	Infection[33,35]	Medications[33] (e.g., narcotics,[35,38] benozodiazepines[38])
Cognitive impairment[33,35,37,40]	Severity of illness[33,36,40]	Immobilization[39] (e.g., catheters, restraints)
Hearing or vision impairment[36]	Metabolic disturbances[33,36,37] (e.g., Na, K, BUN, glucose)	
Alcohol abuse[37,40]	Fever or hypothermia[33]	
Depression[40]	Hypotension[13]	

Note: Na, sodium; K, potassium; BUN, blood urea nitrogen.

factors. Such a schema allows for easy identification of those risk factors most appropriate for prevention or intervention.

Of particular importance in ICU patients, exposure to psychoactive medications (e.g., narcotic analgesics, benzodiazepines or other sedative/hypnotics, and anticholinergics) has been shown to be an independent risk factor for delirium in multiple studies.[33,35,38] In septic patients, it is likely that drugs, used to improve patients' tolerance of interventions and mechanical ventilation, both induce delirium and serve as a marker for underlying organic brain dysfunction present in these patients. Ongoing research is under way to answer important questions regarding the relationship between psychoactive medications and delirium, long-term cognitive impairment, and health-related quality of life.

Prognostic Significance of Delirium in the ICU

Despite previous misconceptions that confusion in ICU patients was usually a harmless component of the ICU course, it is well documented that delirium is an independent risk factor for multiple adverse outcomes including death. CNS dysfunction may lead to complications of mechanical ventilation, including aspiration, nosocomial pneumonia, self-extubation, and reintubation. Abnormal neurologic status was a significant predictor of failed extubation in studies of neurosurgical[41] and medical ICU patients.[42] Moreover, delirium is associated with increased length of hospital stay and a higher likelihood of discharge to a long-term care facility.[33,43]

Delirium is also believed to be associated with the development of long-term cognitive impairment. Nine prospective studies evaluating a total of 1,885 hospitalized medical and surgical patients found that delirium was associated with the development of dementia over 1 to 3 years from the time of hospital discharge.[44] A pilot study conducted 6 months after discharge in 34 patients who received mechanical ventilation in a medical ICU documented neuropsychological impairment in 11 (32%) patients.[45] Additionally, learning and memory impairment have recently been demonstrated in survivors of an animal model of sepsis induced by cecal ligation and perforation.[46] Ongoing research is being conducted to confirm that ICU delirium is an independent risk factor for the development of long-term neurocognitive dysfunction.

Finally, delirium in septic patients is an independent predictor of higher mortality. Sprung et al. noted that septic patients with delirium had a significantly higher mortality than those who maintained a normal mental status (49 vs. 26%, $p < .001$).[16] Wijdicks et al. made the same observation in a study of 84 septic patients, 14 of whom developed altered mental status and focal neurologic abnormalities.[13] Despite these studies, investigators in the past were uncertain whether delirium was an independent risk factor for increased mortality or simply a marker of higher severity of illness.[19,33] To further address this question, Ely et al. prospectively evaluated 275 mechanically ventilated medical ICU patients for the development of delirium.[47] Nearly half of these patients were admitted with severe sepsis or acute respiratory distress syndrome (ARDS). After adjusting for age, severity of illness, comorbid conditions, coma, and the use of sedatives and analgesics, delirium was independently associated with a threefold increase in the risk of death at 6 months ($p = .008$). Interestingly, delirium occurred just as often among patients who never developed coma as it did among those who did develop coma. The increased mortality rate associated with delirium was not explained by the occurrence or duration of coma; in fact, the strength of the association between delirium and mortality was actually greater after adjusting for coma.[47] Recently, these findings were confirmed in another prospective study that evaluated 102 mechanically ventilated patients and showed that delirium was independently associated with mortality after multivariate analysis (odds ratio, 13.0; 95% confidence interval, 2.69 to 62.91).[48]

Cost of Delirium in the ICU

The costs attributable to the care of patients with severe sepsis are massive and growing. Angus et al. reported that in the United States alone the annual hospital costs associated with the care of patients who developed severe sepsis is over $16 billion, averaging $21,000 to $25,000 per patient.[2] The highest costs are incurred by those patients who require ICU care, which account for up to 50% of all patients with severe sepsis. A significant portion of these costs may be attributable to the development of delirium. In the only study to date to examine the costs associated with delirium in ICU patients, Milbrandt et al. found that patients who developed delirium at some time during their ICU stay incurred significantly higher ICU and hospital costs than those who never developed delirium.[49] The increase in median ICU costs in patients with delirium was greater than $9,000 per patient. Almost half of the patients evaluated in this study had severe sepsis.

Although studies from developing nations are still lacking,[50] it is estimated that over 18 million cases of severe sepsis occur worldwide each year.[51] With delirium occurring in up to 80% of patients admitted to the ICU with severe sepsis,[47] the increase in costs each year in the United States attributable to this often-unrecognized organ dysfunction may be as high as $3 billion. Accurate estimates are currently unavailable to allow for a reasonable projection of the increase in

ICU and hospital costs due to delirium worldwide, but the possibility that the incidence of severe sepsis and associated delirium are higher in developing countries than in the United States[52] further emphasizes the fact that the occurrence of delirium in patients with severe sepsis is a major worldwide public health problem.

Diagnosis and Assessment of Delirium in the ICU

It is important to note that health professionals commonly fail to recognize delirium.[33,53] This omission has been associated with unexpectedly high mortality rates following emergency visits.[54] In a survey of 912 healthcare professionals,[55] Ely et al. found that delirium was considered a significant or very serious problem in the ICU by 92%, yet underdiagnosis was acknowledged by 8 of 10 respondents.

As patients with severe sepsis frequently require mechanical ventilation and its attendant need for sedation, the Surviving Sepsis Campaign clinical practice guidelines recommend the use of a protocol that includes a sedation goal and the use of a standardized sedation scale.[56] Additionally, the Society of Critical Care Medicine (SCCM) guidelines for the use of sedatives and analgesics in critically ill patients recommend routine assessment for delirium in all ICU patients.[57] The routine use of well-validated, reliable, brief assessment tools easily equips critical care nurses and doctors to monitor both level of arousal and content of consciousness, allowing for goal-directed titration of sedatives as well as rapid recognition of delirium.

Several sedation scales have been developed that provide standardized methods for the assessment of a patient's level of arousal or consciousness. Use of a validated sedation assessment scale allows the multidisciplinary ICU team to use a succinct, common language when discussing goals and treatments for patients. A sedation goal should be established by the interdisciplinary medical team and regularly refined according to changes in a patient's course of illness.[57] The Ramsay Scale was one of the first sedation scales developed and has been widely used for 30 years.[58] However, several recently developed instruments, including the Sedation-Agitation Scale (SAS)[59] and the Richmond Agitation-Sedation Scale (RASS),[60] have been better validated and are being widely implemented. The RASS has been validated in multiple studies and was the first sedation scale validated for its ability to follow level of arousal over consecutive days of ICU care.[61]

The gold standard criteria for the diagnosis of delirium are outlined in the DSM-IV as detailed previously (see "Defining Delirium and Its Motoric Subtypes"). Several instruments have been developed to allow nonpsychiatrists to make a formal diagnosis of delirium,[62] including the Confusion Assessment Method (CAM), a sensitive (94% to 100%), specific (90% to 100%), and reliable instrument intended for use in the clinical evaluation of hospitalized, elderly, medical and surgical patients.[63] However, the usefulness of the CAM and most

other delirium assessment instruments is limited in nonverbal patients, because a significant portion of septic patients require mechanical ventilation. Therefore, the Confusion Assessment Method for the ICU (CAM-ICU) was developed and validated in two cohorts of mechanically ventilated critically ill patients (Figure 12.1 and Table 12.3).[64,65] This easy-to-use, quickly administered instrument requires minimal training and was shown to have high sensitivity (93% to 100%), specificity (98% to 100%), and interrater reliability ($\kappa = 0.96$).[65] The CAM-ICU has been translated into numerous languages (e.g., Spanish, Portuguese, French, Dutch, Swedish, Greek, Italian, and Chinese) and is available for download via an educational website (www.icudelirium.org). Its high reliability and validity has also been confirmed in another language and region of the world.[48]

It is important to note that the disruptive, agitated behavior traditionally associated with delirium is typically present in less than half of the cases identified when sensitive screening measures are utilized.[33] The use of sensitive assessment tools, such as the CAM-ICU, allows clinicians to avoid the mistake of failing to recognize this vital organ dysfunction in patients with severe sepsis. Prior to the development of the CAM-ICU, it was frequently thought that the mechanically ventilated patient could not be properly evaluated for delirium due to the high severity of illness and the use of endotracheal tubes and sedatives.[20] ICU practitioners are no longer limited in their assessment of the nonverbal septic patient, and delirium assessment should be part of the daily neurologic assessment of every mechanically ventilated patient in the ICU.

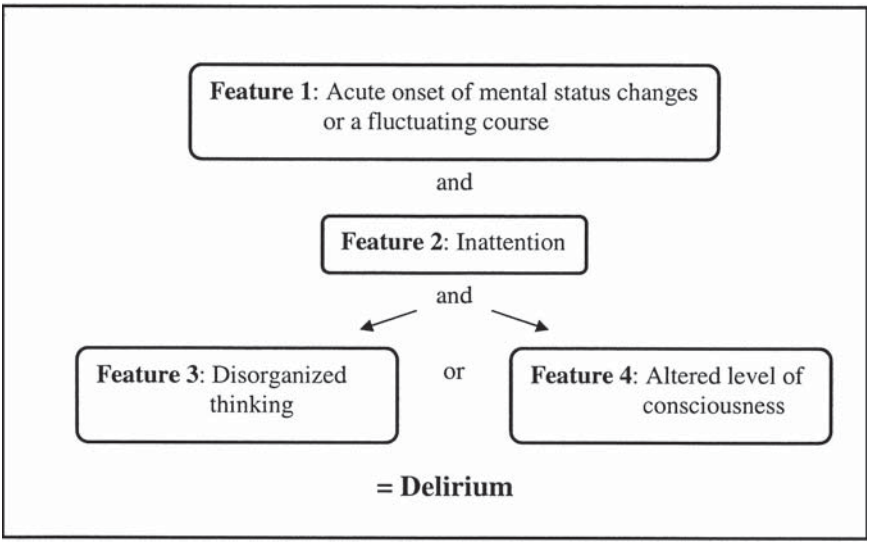


FIGURE 12.1. Diagnosis of delirium with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Used with permission, copyright © 2002, E. Wesley Ely, MD, MPH and Vanderbilt University, all rights reserved.

TABLE 12.3. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Worksheet

CAM-ICU Features and Descriptions		
1. Acute Onset or Fluctuating Course	Absent	Present

A. Is there evidence of an acute change in mental status from the baseline?

OR

B. Did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go, or increase and decrease in severity as evidenced by fluctuation on a sedation scale (e.g., RASS), GCS, or previous delirium assessment?

2. Inattention	Absent	Present

Did the patient have difficulty focusing attention as evidenced by **scores *less than 8*** on either the auditory or visual component of the **Attention Screening Examination (ASE)**?*

3. Disorganized Thinking	Absent	Present

Is there evidence of disorganized or incoherent thinking as evidenced by **incorrect answers to 2 or more of the 4 questions and/or inability to follow the commands**?

Questions (Alternate Set A and Set B):

Set A	**Set B**
1. Will a stone float on water?	1. Will a leaf float on water?
2. Are there fish in the sea?	2. Are there elephants in the sea?
3. Does one pound weigh more than two pounds?	3. Do two pounds weigh more than one pound?
4. Can you use a hammer to pound a nail?	4. Can you use a hammer to cut wood?

Other:

1. Are you having any unclear thinking?
2. Hold up this many fingers. (Examiner holds two fingers in front of patient.)
3. Now do the same thing with the other hand. (Examiner does not demonstrate for the patient with this request.)

4. Altered Level of Consciousness	Absent	Present

Is the patient's level of consciousness anything *other than alert*, such as vigilant, lethargic, or stuporous (e.g., RASS other than "0" at time of assessment)?

Alert	spontaneously fully aware of environment and interacts appropriately
Vigilant	hyperalert
Lethargic	drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
Stuporous	becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli, and as soon as the stimulus ceases, stuporous subject lapse back into the unresponsive state

Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	Yes	No

Note: RASS, Richmond Agitation-Sedation Scale; GCS, Glasgow Coma Scale.

*In performing the auditory ASE, the examiner says to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter "A," indicate by squeezing my hand,*" then reads the letters—S, A, V, E, A, H, A, A, R, T—counting correct responses when the patient squeezes on the letter "A" and does not squeeze on any other letter. The visual ASE is used when the patient is unable to perform the auditory ASE and utilizes a series of pictures provided in the CAM-ICU training manual available at www.icudelirium.org.

Approaches to Prevention and Treatment of Delirium in Septic Patients

Severe sepsis is a multiorgan syndrome that is managed by a comprehensive approach involving both prevention and treatment. Similarly, the clinician's response to delirium in patients with severe sepsis consists of a multidisciplinary plan of prevention and treatment that includes eliminating modifiable risk factors, performing frequent delirium assessments, and using pharmacologic therapies thought to treat delirium when it is identified.

Prevention and Nonpharmacologic Strategies

Although they were not limited to patients with sepsis, several clinical trials have evaluated multicomponent interventions designed to prevent delirium in hospitalized patients.[66–69] Inouye et al. studied 852 older patients hospitalized with a variety of medical illnesses. Standardized intervention protocols included repeated reorientation with information boards and healthcare worker communication, cognitively stimulating activities multiple times daily, a nonpharmacologic sleep protocol enhanced by a sleep-friendly environment, frequent ambulation and exercise, visual and hearing aids, and vigilant volume repletion to prevent dehydration. This strategy resulted in a significant reduction in the incidence of delirium (9.9% in the intervention group versus 15% in the control group, $p = .02$) as well as in the duration of delirium.[66] Unfortunately, there was no sustained benefit noted in clinical outcomes at 6 months following hospital discharge.[70] However, this study and others should form the basis of future work in the arena of delirium prevention. Despite the lack of clinical trials evaluating primary prevention of delirium in critically ill patients, the approach to care utilized by Inouye et al. should form the basis of nonpharmacologic attempts to prevent delirium in patients with severe sepsis: frequent reorientation,[66] daily interruption of sedatives,[71] restoration of the sleep/wake cycle, minimization of unnecessary stimuli, physical therapy,[66] and early mobilization. Additionally, these interventions may continue to be beneficial in the care of septic patients with established delirium, and they should be combined with measures aimed at treating sepsis and correcting associated metabolic derangements.

Pharmacologic Treatment

Pharmacologic management of delirium is frequently attempted in the ICU. Of 912 critical care practitioners surveyed, 717 (79%) reported that delirium requires active intervention.[55] Two-thirds considered haloperidol as the treatment of choice. Although there remain no drugs with an FDA approval for the treatment of delirium and we have no placebo-controlled trials to confirm the best treatment, the SCCM and the American Psychiatric Association guidelines currently recommend haloperidol as the treatment of choice.[57,62] This and other neuroleptic agents

are felt to stabilize cerebral function by dopamine blockade and disinhibition of acetylcholine. Of particular import in patients with severe sepsis, haloperidol is known to have antiinflammatory properties, inhibiting the secretion of proinflammatory cytokines.[72,73] This, along with its procognitive effects, may have resulted in the 15.6% absolute reduction in the risk of hospital mortality noted in a recently published retrospective cohort analysis of 989 mechanically ventilated, critically ill patients.[74] Several randomized, placebo-controlled clinical trials are currently under way that are designed to evaluate the efficacy and safety of haloperidol in the treatment of critically ill patients with delirium.

Perhaps as important as using appropriate pharmacologic agents to treat delirium is withholding those agents known to incite or exacerbate delirium. Although benzodiazepines are the drugs of choice for the treatment of alcohol withdrawal (as well as other drug withdrawal syndromes), this class of drugs is not recommended for the routine treatment of delirium due to the likelihood of promoting confusion, oversedation, and respiratory depression. As stated previously (see "Risk Factors for Delirium in the Septic Patient"), exposure to benzodiazepines and narcotics is a significant independent risk factor for the development of delirium, and use of these drugs should be guided by goal-directed sedation protocols that primarily employ intermittent bolus sedation.[71,75,76]

In the care of patients at risk for severe sepsis, it is imperative that clinicians are focused on the diagnosis and treatment of delirium as well as to the significance of the development of this syndrome. As delirium is often a manifestation of an acute change in the patient's clinical course, abrupt changes in mental status should alert the healthcare team to evaluate the patient for shock, hypoxia, hypercarbia, hypoglycemia, or other metabolic derangements. After rapid evaluation and treatment of these life-threatening problems, attention can be turned toward the treatment of delirium.

Conclusion

Patients with severe sepsis are at high risk for morbidity and mortality. These risks only increase with the failure of multiple organ systems. Although delirium was previously often overlooked, practitioners are becoming increasingly aware of the crucial role that acute CNS dysfunction plays in the course of severe sepsis. Appropriate strategies for the prevention, diagnosis, and treatment of delirium in critically ill patients as outlined in this chapter are the subject of ongoing investigations and should be part of every ICU clinician's armamentarium in the care of patients with severe sepsis.

Acknowledgments. Dr. Girard is supported by grant HL 07123 from the National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Ely is a recipient of the Paul Beeson Faculty Scholar Award from the Alliance for Aging Research and of a K23 from the National Institutes of Health (AG01023-01A1). He has received research funding from Eli Lilly and Co. and Pfizer Inc.

References

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303–10.
3. Pine RW, Wertz MJ, Lennard ES, et al. Determinants of organ malfunction or death in patients with intra-abdominal sepsis. A discriminant analysis. Arch Surg 1983;118:242–9.
4. McGuire BE, Basten CJ, Ryan CJ, et al. Intensive care unit syndrome: a dangerous misnomer. Arch Intern Med 2000;160:906–9.
5. Chadwick J, Mann MN, eds. The Medical Works of Hippocrates. Oxford: Blackwell, 1950.
6. Papadopoulos MC, Davies DC, Moss RF, et al. Pathophysiology of septic encephalopathy: a review. Crit Care Med 2000;28:3019–24.
7. Osler W. The Principles and Practice of Medicine. New York: Appleton, 1892.
8. Freund HR, Ryan JA Jr, Fischer JE. Amino acid derangements in patients with sepsis: treatment with branched chain amino acid rich infusions. Ann Surg 1978;188: 423–30.
9. Jeppsson B, Freund HR, Gimmon Z, et al. Blood-brain barrier derangement in sepsis: cause of septic encephalopathy? Am J Surg 1981;141:136–42.
10. Freund HR, Muggia-Sullam M, Peiser J, et al. Brain neurotransmitter profile is deranged during sepsis and septic encephalopathy in the rat. J Surg Res 1985;38: 267–71.
11. Pendlebury WW, Perl DP, Munoz DG. Multiple microabscesses in the central nervous system: a clinicopathologic study. J Neuropathol Exp Neurol 1989;48:290–300.
12. Bowton DL, Bertels NH, Prough DS, et al. Cerebral blood flow is reduced in patients with sepsis syndrome. Crit Care Med 1989;17:399–403.
13. Wijdicks EF, Stevens M. The role of hypotension in septic encephalopathy following surgical procedures. Arch Neurol 1992;49:653–6.
14. Young GB, Bolton CF, Archibald YM, et al. The electroencephalogram in sepsis-associated encephalopathy. J Clin Neurophysiol 1992;9:145–52.
15. Jackson AC, Gilbert JJ, Young GB, et al. The encephalopathy of sepsis. Can J Neurol Sci 1985;12:303–7.
16. Sprung CL, Peduzzi PN, Shatney CH, et al. Impact of encephalopathy on mortality in the sepsis syndrome. Crit Care Med 1990;18:801–6.
17. Young GB, Bolton CF, Austin TW, et al. The encephalopathy associated with septic illness. Clin Invest Med 1990;13:297–304.
18. Bleck TP, Smith MC, Pierre-Louis SJ, et al. Neurologic complications of critical medical illnesses. Crit Care Med 1993;21:98–103.
19. Eidelman LA, Putterman D, Putterman C, et al. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA 1996;275:470–3.
20. Wijdicks EFM. Neurologic Complications of Critical Illness, second edition. New York: Oxford University Press, 2002.
21. Wheeler AP, Bernard GR. Treating patients with severe sepsis. N Engl J Med 1999;340:207–14.

22. Papadopoulos MC, Lamb FJ, Moss RF, et al. Faecal peritonitis causes oedema and neuronal injury in pig cerebral cortex. Clin Sci (Lond) 1999;96:461–6.
23. Huynh HK, Dorovini-Zis K. Effects of interferon-gamma on primary cultures of human brain microvessel endothelial cells. Am J Pathol 1993;142:1265–78.
24. Krueger JM, Walter J, Dinarello CA, et al. Sleep-promoting effects of endogenous pyrogen (interleukin-1). Am J Physiol 1984;246:R994–9.
25. Breslow MJ, Miller CF, Parker SD, et al. Effect of vasopressors on organ blood flow during endotoxin shock in pigs. Am J Physiol 1987;252:H291–300.
26. Van Der Mast RC. Pathophysiology of delirium. J Geriatr Psychiatry Neurol 1998;11: 138–45.
27. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Washington, DC: American Psychiatric Association, 1994.
28. Trzepacz PT. The neuropathogenesis of delirium. A need to focus our research. Psychosomatics 1994;35:374–91.
29. Lipowski ZJ. Delirium (acute confusional states). JAMA 1987;258:1789–92.
30. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. Semin Clin Neuropsychiatry 2000;5:75–85.
31. Liptzin B, Levkoff SE. An empirical study of delirium subtypes. Br J Psychiatry 1992;161:843–5.
32. Peterson JF, Truman BL, Shintani A, et al. The prevalence of hypoactive, hyperactive, and mixed type delirium in medical ICU patients. J Am Geriatr Soc 2003;51:S174.
33. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990;263:1097–101.
34. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892–900.
35. Schor JD, Levkoff SE, Lipsitz LA, et al. Risk factors for delirium in hospitalized elderly. JAMA 1992;267:827–31.
36. Inouye SK, Viscoli CM, Horwitz RI, et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119:474–81.
37. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994;271:134–9.
38. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. JAMA 1994;272:1518–22.
39. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852–7.
40. Elie M, Cole MG, Primeau FJ, et al. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 1998;13:204–12.
41. Namen AM, Ely EW, Tatter SB, et al. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med 2001;163:658–64.
42. Salam A, Tilluckdharry L, Amoateng-Adjepong Y, et al. Neurologic status, cough, secretions and extubation outcomes. Intensive Care Med 2004;30:1334–9.
43. Thomas RI, Cameron DJ, Fahs MC. A prospective study of delirium and prolonged hospital stay. Exploratory study. Arch Gen Psychiatry 1988;45:937–40.
44. Jackson JC, Gordon SM, Hart RP, et al. The association between delirium and cognitive decline: a review of the empirical literature. Neuropsychol Rev 2004;14: 87–98.

45. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med 2003;31:1226–34.
46. Barichello T, Martins MR, Reinke A, et al. Cognitive impairment in sepsis survivors from cecal ligation and perforation. Crit Care Med 2005;33:221–3.
47. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753–62.
48. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med 2004;32:2254–9.
49. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32:955–62.
50. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. Crit Care 2004;8:222–6.
51. Surviving Sepsis Campaign: Healthcare professional site. Background materials. Surviving Sepsis Campaign. (Accessed January 17, 2005 at http://www.survivingsepsis.org/hcp_backgrounder.html)
52. Silva E, Pedro MA, Sogayar AC, et al. Brazilian Sepsis Epidemiological Study (BASES study). Crit Care 2004;8:R251–60.
53. Inouye SK, Foreman MD, Mion LC, et al. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Arch Intern Med 2001;161:2467–73.
54. Kakuma R, du Fort GG, Arsenault L, et al. Delirium in older emergency department patients discharged home: effect on survival. J Am Geriatr Soc 2003;51:443–50.
55. Ely EW, Stephens RK, Jackson JC, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. Crit Care Med 2004;32:106–12.
56. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858–73.
57. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119–41.
58. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656–9.
59. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999;27:1325–9.
60. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338–44.
61. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983–91.
62. Practice guideline for the treatment of patients with delirium. American Psychiatric Association. Am J Psychiatry 1999;156:1–20.
63. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941–8.
64. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370–9.

65. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703–10.
66. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–76.
67. Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001;49:516–22.
68. Cole MG, McCusker J, Bellavance F, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. CMAJ 2002;167: 753–9.
69. Naughton BJ, Saltzman S, Ramadan F, et al. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. J Am Geriatr Soc 2005;53:18–23.
70. Bogardus ST Jr, Desai MM, Williams CS, et al. The effects of a targeted multicomponent delirium intervention on postdischarge outcomes for hospitalized older adults. Am J Med 2003;114:383–90.
71. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342: 1471–7.
72. Moots RJ, Al Saffar Z, Hutchinson D, et al. Old drug, new tricks: haloperidol inhibits secretion of proinflammatory cytokines. Ann Rheum Dis 1999;58:585–7.
73. Song C, Lin A, Kenis G, et al. Immunosuppressive effects of clozapine and haloperidol: enhanced production of the interleukin-1 receptor antagonist. Schizophr Res 2000;42:157–64.
74. Milbrandt EB, Kersten A, Kong L, et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med 2005;33: 226–9.
75. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999;27: 2609–15.
76. Kollef MH, Levy NT, Ahrens TS, et al. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. Chest 1998;114:541–8.

Index