I would like to thank all those who have believed in my dreams, supported my aspirations, and tolerated my pursuit of them. To my parents, whose spirit of discovery, determination, and resilience in the face of challenge instilled in me a desire to always do my best and make the world a better place; and to my sister Elisabeth, her husband Michael, and their children Justin, Benjamin, and Nathan who are the future; and most of all to my wife Doris for always being there for me.

J. E. Szalados, M.D.

I wish this work to honor the many teachers, students, residents, and fellows who over the years have made me think and grow in the subject of critical care. I especially wish to honor the contributions of two great teachers: the late Dr. Thomas Iberti M.D. who taught me to ask the key question of clinical medicine, “why?”; and Prof. Dr. Lachmann who made me into a scientist. To truly balance one’s life we need love and support, and without the great love of my wife Susan and son Yanni I would not be able to find my inner strength. And to my father who taught and guided me that with hard work you always win, a special thanks. Also to my friends Allan Ross and Anne Snyder at Elsevier who supported me in this and many other projects, we did it again.

P. J. Papadakos, M.D.
Contributors

Michael J. Apostolakos, MD
Associate Professor of Medicine
Director, Adult Critical Care
University of Rochester Medical Center
Rochester, New York

Timothy J. Barreiro, DO
Assistant Clinical Professor
Department of Medicine
Northeast Ohio College of Medicine
Youngstown, Ohio

Rinaldo Bellomo, MD, FRACP, FCCP
Professorial Fellow
University of Melbourne Medical School
Melbourne
Victoria, Australia
Director of Intensive Care Research
Austin Hospital
Melbourne
Victoria, Australia

Ali Borhan, MD
Urology Resident
University of Rochester Medical Center
Rochester, New York

Sanjeev V. Chhangani, MD, MBA
Associate Professor of Anesthesiology
University of Rochester School of Medicine and Dentistry
Rochester, New York
Medical Director
Surgical Intensive Care Unit,
Rochester General Hospital
Rochester, New York

Ashwani Chhibber, MD
Associate Professor
Anesthesiology and Pediatrics
Vice Chair Anesthesiology
University of Rochester
Rochester, New York

Guglielmo Consales, MD
Senior Specialist
Department of Anesthesia and Intensive Care
University of Florence
Azienda Ospedaliero-Universitaria Careggi
Florence
Italy

Susan E. Dantoni, MD, FACOG
Clinical Assistant Professor of Obstetrics and Gynecology
University of Rochester
Rochester, New York
Clinical Adjunct Professor Health Professions
Rochester Institute of Technology
Rochester, New York
Attending Physician
Highland Hospital, Strong Memorial Hospital,
Park Ridge Hospital
Rochester, New York
A. Raffaele De Gaudio, MD  
Professor of Anesthesiology and Intensive Care  
Director, Section of Anesthesiology and Intensive Care  
Azienda Ospedaliero-Universitaria Careggi  
University of Florence  
Florence  
Italy

Joseph Dooley, MD  
Associate Professor of Anesthesiology and Neurosurgery  
University of Rochester  
Rochester, New York  
Attending Physician, Anesthesiology and Critical Care Medicine  
University of Rochester Medical Center  
Rochester, New York

D. Jay Duong, MD  
Resident in Anesthesiology  
University of Rochester  
Rochester, New York

Jason Dziak, MD  
Assistant Professor  
Department of Anesthesiology  
University of Rochester  
Rochester, New York

Dina M. Elaraj, MD  
Senior Resident  
Department of Surgery  
University of Rochester  
Rochester, New York

Erdal Erturk, MD  
Professor of Urology  
Director of Kidney Stone Treatment Center  
University of Rochester Medical Center  
Rochester, New York

Curtis E. Haas, PharmD  
Assistant Professor  
Department of Pharmacy Practice  
University of Pharmacy and Pharmaceutical Sciences  
University of Buffalo  
Buffalo, New York  
Clinical Assistant Professor  
Department of Surgery  
School of Medicine and Dentistry  
University of Rochester  
Rochester, New York

Jack J. Haitsma, MD, PhD  
Visiting Research Fellow  
Division Critical Care Medicine  
University of Rochester  
Rochester, New York  
Member Department of Anesthesiology  
Erasmus MC-Faculty  
Rotterdam  
The Netherlands

David Kaufman, MD, FCCM  
Associate Professor of Surgery, Anesthesia, Medicine and Medical Humanities  
University of Rochester  
Medical Director, Surgical Intensive Care Unit  
Strong Memorial Hospital  
Rochester, New York

John A. Kellum, MD, FACP, FCCP  
Associate Professor of Critical Care Medicine, Anesthesiology and Medicine  
University of Pittsburgh  
Department of Critical Care Medicine  
CRISMA (Clinical Research Investigation and Systems Modeling of Acute Illness)  
Pittsburgh, Pennsylvania  
Intensitist, Cardiothoracic and Liver Transplant Intensive Care Units  
University of Pittsburgh Medical Center  
Pittsburgh, Pennsylvania

Heidi B. Kummer, MD, MPH  
Assistant Clinical Professor of Anesthesiology  
Tufts Medical School  
Boston, Massachusetts  
Senior Physician  
Lahey Clinic  
Burlington, Massachusetts

Burkhard Lachmann, MD, PhD  
Director of Anesthesia Research  
Professor of Anesthesiology  
Erasmus MC-Faculty  
Rotterdam  
The Netherlands

Jaclyn M. LeBlanc, PharmD  
Critical Care Pharmacy Research Fellow  
College of Pharmacy  
The Ohio State University  
Columbus Ohio
Christopher W. Lentz, MD, FACS
Director, Strong Regional Burn Center
Associate Professor, Department of Surgery and Pediatrics
University of Rochester
Rochester, New York

Xavier M. Leverve, MD, PhD
Laboratoire de Bioénergétique Fondamentale et Appliquée
Université Joseph Fourier
Also: Service de Réanimation Médicale
Hospital A. Michallon
Centre Hospitalier Universitaire
Grenoble
France

Carlos J. Lopez III, MD
Associate Professor of Anesthesiology and Critical Care
Section Chief, Anesthesia Critical Care
Upstate Medical University
Syracuse, New York
Attending Intensivist, Attending Anesthesiologist
Co-Director, Surgical Intensive Care Unit
University Hospital at Upstate Medical University
Syracuse, New York

Stephen M. Luczycki, MD, MBA
Assistant Professor
Department of Anesthesiology
Yale University School of Medicine
New Haven, Connecticut

Stewart J. Lustik, MD
Associate Professor of Anesthesiology
University of Rochester School of Medicine and Dentistry
Rochester, New York
Strong Memorial Hospital
Rochester, New York

Ralph Madeb, MD
Urology Resident
University of Rochester Medical Center
Rochester, New York

Edward M. Messing, MD, FACS
W.W. Scott Professor
Professor of Oncology and Pathology
Chairman, Department of Urology
Deputy Director, James P. Wilmot Cancer Center
University of Rochester Medical Center
Rochester, New York

Iqbal Mustafa, MD, PhD
Professor of Anesthesiology
Intensive Care Unit
Harapan Kita Cardiovascular Center
Jakarta
Indonesia

Roger R. Ng, MD
Resident
Department of Anesthesiology
University of Rochester
Rochester, New York

Craig Nicholson, MD
Urology Resident
University of Rochester Medical Center
Rochester, New York

Peter J. Papadakos, MD, FCCP, FCCM
Director, Division of Critical Care Medicine
Professor of Anesthesiology, Surgery, and Neurosurgery
University of Rochester School of Medicine and Dentistry
Rochester, New York

Charles R. Phillips, MD
Assistant Professor of Medicine
Department of Pulmonary and Critical Care Medicine
Oregon Health and Science University
Portland, Oregon

Simone Rinaldi, MD
Research Fellow in Anesthesiology and Intensive Care
University of Florence
Florence
Italy

Claudio Ronco, MD, PhD
Lecturer
University of Padua Medical School
Padua
Italy

Contributors ix

†Deceased
Marc J. Shapiro, MD, FACS, FCCM
Professor of Surgery and Anesthesiology
State University of New York
Stony Brook, New York
Chief, General Surgery Trauma, Critical Care and Burns
University Hospital
Stony Brook, New York

Jeffrey Spike, PhD
Associate Professor of Medical Humanities
Florida State University College of Medicine
Tallahassee, Florida

David Story, MD, FANZCA
Department of Anaesthesia
Austin & Repatriation Medical Centre
Melbourne
Victoria, Australia

James E. Szalados, MD, JD, MBA, MHA, FCCP, FCCM
Partner, Westside Anesthesiology Associates of Rochester, LLP
Attending in Anesthesiology, Critical Care and Medicine
Medical Director of Respiratory Care
Unity Health System at Park Ridge Hospital
Adjunct Clinical Professor, Rochester Institute of Technology
Rochester, New York

Judit Szolnoki, MD
Assistant Professor of Anesthesiology and Critical Care
Department of Anesthesiology
Upstate Medical University
Syracuse, New York
Attending Anesthesiologist
VA Hospital of Syracuse and University Hospital
in Syracuse
Syracuse, New York

Per A. J. Thorborg, MD, PhD
Associate Professor
Department of Anesthesiology and Perioperative Medicine
Oregon Health and Science University
Portland, Oregon

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

Jacek A. Wojtczak, MD, PhD
Associate Professor of Anesthesiology
University of Rochester School of Medicine and Dentistry
Rochester, New York


It is an incontrovertible fact that anesthesiology is the practice of medicine. Therefore, anesthesiologists must be fluent in the theories and techniques of preoperative medical assessment, intraoperative cardiopulmonary life support, and postoperative critical care intervention. Anesthesiology is the synthesis of the basic medical sciences, including anatomy, physiology, biochemistry, pharmacology, and epidemiology; and is a bridge that spans the disciplines of medicine and all its subspecialties, surgery, and obstetrics. The making of an anesthesiologist is therefore the culmination of premedical and medical schooling, a four-year intense postgraduate clinical residency program, and possibly thereafter a subspecialized fellowship. Most importantly, there then follows a lifetime commitment to learning and further honing of technical skills.

It is likely that no person will ever trust anyone else to the extent that they trust their anesthesiologist. The patient undergoing surgery will depend on the anesthesiologist for safety and comfort during a time when their body is subjected to extreme stress. It is a remarkable fact that most patients accept the risks of anesthesia without questions, are incognizant of the fact that they will fully be on “life support” for the duration of their operation, and most do not remember the experience or even the name of their anesthesiologist. That the public at large can have such trust and high expectations from medical professionals who will only be transiently involved in their care is a testament to the training, professionalism, and skill of anesthesiologists as well as a reflection of the many technological advances in medical science which have made modern anesthesiology a safer experience.

In order for the anesthesiologist to provide the level of medical care that will result in the best outcome for the patient, the anesthesiologist must be comfortable in the role of a “perioperative physician.” That physician who cares for patients as they undergo the stress of surgery is best positioned to understand the preoperative and postoperative issues. Every preoperative patient requires that the anesthesiologist perform a careful and detailed assessment of their medical condition including coexisting illnesses, physical limitations, and their general fitness for anesthesia and surgery. It is a seldom-voiced tacit understanding among anesthesiologists that each and every patient who undergoes elective surgery becomes critically ill, albeit perhaps only for a limited time period. Of course, those patients who come to the operating room in the setting of severe trauma, overwhelming organ dysfunction due to illness, or patients who present with severe comorbidities for emergency surgery are de facto critically ill and are likely to remain so for some time postoperatively. There was once a time when patients could be deemed “too sick for surgery.” However, this adage is seldom employed today and anesthesiologists, surgeons, as well as patients and their families in weighing the risks against the potential benefits often determine that the short and intense stress of surgery compares favorably to the alternative. Patients come to the operating room in septic shock for the control of their septic source, following an acute myocardial infarction for emergency coronary revascularization, in multiple organ failure and end-stage liver disease for liver transplantation, and after massive trauma; each patient’s condition can be further complicated by systemic diseases such as chronic lung disease, severe atherosclerotic coronary and vascular disease, renal failure, diabetes mellitus, malnutrition, and others. Therefore, anesthesiology is unique in that there is no other specialty of medicine where every single patient encounter requires both knowledge and application of advanced life-support skills. All these patient groups will require elements of mechanical ventilation, sedation and analgesia, neuromuscular blockade, intravascular volume replacement, management of electrolytes, hemodynamic support and monitoring, monitoring of and
replacement of blood and coagulation factors, as well as
related monitoring and interventions directed at mini-
mizing secondary injuries.

It is because anesthesiology is also the practice of
critical care medicine that this textbook summarizes for
anesthesiologists the state-of-the-art and the standard of
care for the management of critically ill patients.
It is incumbent on anesthesiologists to understand and
apply the principles of critical care medicine that are
relevant to the management of intraoperative patients as
well as their continued postoperative care. We recog-
nize that not all anesthesiologists will participate in the
care of patients in the intensive care unit. However, all
anesthesiologists will use critical care principles in the
operating room. Therefore, new advances in modes of
mechanical ventilation, new understanding regarding
optimization of oxygen delivery to tissues, new perspec-
tives on the evaluation and management of severe
comorbidities, as well as preparedness for emerging
threats such as biological and chemical terrorism are
matters of interest to all anesthesiologists. Finally, for
those physicians who also practice in the intensive care
unit, this book is intended to highlight established
principles, evolving standards of care, and new
opportunities to provide excellence in patient care.

Peter J. Papadakos, M.D.
James E. Szalados, M.D.
Sepsis: The Systemic Inflammatory Response
JEAN-LOUIS VINCENT, M.D., Ph.D

Definition and Diagnosis
Pathophysiology
Inflammatory Mediators
  Pro-inflammatory Cytokines
  Anti-inflammatory Cytokines
  Other Mediators
Coagulation and Inflammation
Management of Sepsis
  Hemodynamic Stabilization
  Immunomodulating Therapy
Conclusion

Sepsis, the inflammatory response to infection, is perhaps the most common disease encountered by the critical care physician, complicating some 30 to 40% of intensive care unit (ICU) admissions and accounting for considerable morbidity and mortality. The exact incidence of sepsis is difficult to determine because of differences in definitions and populations. An international study across eight countries involving 14,364 ICU patients reported that there were 3034 infectious episodes giving a crude incidence of infections of 21.1%. Interestingly, one-fifth of these infections did not fit into any of the definition categories proposed by the ACCP/SCCM classification, which has been widely used in studies of sepsis. The mortality rate in patients with repeated infectious episodes was 53.6% compared to 16.9% in non-infected patients. A recent study, the Sepsis Occurrence in Acutely Ill Patients (SOAP), involving 3147 patients in 24 European countries, reported that 37.4% of patients were infected at some point during their ICU stay. Interestingly, the occurrence of sepsis ranged from 17.5 to 72.5% between countries. Importantly, the incidence of sepsis seems to be increasing with one study reporting an annual increase of 8.7% in the USA, from 82.7 cases per 100,000 population in 1979 to 240.4 per 100,000 population in 2000. Thus, although the risk of death per individual case may be falling, overall mortality rates are increasing as the size of the problem increases. This chapter briefly considers some of the basic features and the latest developments in this critically important field of sepsis in terms of diagnosis, pathophysiology, and management.

DEFINITION AND DIAGNOSIS

For many years definitions of sepsis have relied on those proposed by the ACCP/SCCM consensus conference published back in 1992. This conference introduced the systemic inflammatory response syndrome (SIRS) concept, whereby a patient was said to have SIRS if they met two or more of the following conditions: temperature greater than 38°C or less than 36°C, tachycardia, tachypnea, white blood cell count greater than 12,000 cells/mm³ or less than 4000 cells/mm³. Sepsis was then defined as infection plus SIRS, severe sepsis as sepsis plus organ dysfunction, and septic shock as severe sepsis with hypotension despite adequate fluid resuscitation and evidence of perfusion abnormalities. However, the SIRS criteria are very sensitive, and are met by most ICU patients and many general ward patients, making them of little practical value in identifying the patient with sepsis.

Recently, a sepsis definitions conference involving 29 physicians from Europe and North America was held in Washington, DC, to improve and standardize definitions in the field of sepsis. The conference participants agreed with the 1992 definitions in that sepsis should be defined as infection plus signs of systemic inflammation, but felt that the SIRS criteria were too non-specific and proposed rather a much longer list of possible signs of sepsis (Table 1-1). Unfortunately, as yet, no individual sign is specific for sepsis and clinical diagnosis relies on the combined presence of several signs and symptoms that together confirm the likelihood of sepsis as the diagnosis.
Definitions of severe sepsis and septic shock remained unchanged from the 1992 publication.

In addition to discussing problems of definition, the participants at the Washington conference also developed a new system to characterize and stage patients with sepsis, to enable patients to be stratified according to their baseline risk of an adverse outcome and their potential to respond to therapy. Such systems are used widely in other areas of medicine, the prototypical system perhaps being the tumor/nodes/metastases (TNM) staging system for malignant tumors developed by Pierre Denoix in the 1940s. The PIRO system stratifies patients according to their Predisposing conditions, the nature and extent of the Insult, the nature and magnitude of the host Response, and the degree of concomitant Organ dysfunction (Table 1-2).

<table>
<thead>
<tr>
<th>Table 1-1 Diagnostic Criteria for Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection, documented or suspected, and some of the following:</td>
</tr>
<tr>
<td>General variables</td>
</tr>
<tr>
<td>Fever or hypothermia</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Significant edema or unexplained positive fluid balance</td>
</tr>
<tr>
<td>Inflammatory variables</td>
</tr>
<tr>
<td>Leukocytosis or leukopenia</td>
</tr>
<tr>
<td>Increased plasma C-reactive protein (CPR), procalcitonin (PCT) or interleukin-6 (IL-6) levels</td>
</tr>
<tr>
<td>Hemodynamic alterations</td>
</tr>
<tr>
<td>Arterial hypotension</td>
</tr>
<tr>
<td>Hyperkinetic state (high cardiac index – high SvO₂)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
<tr>
<td>Hyerpacticemia</td>
</tr>
<tr>
<td>Organ dysfunction variables</td>
</tr>
<tr>
<td>Arterial hypoxemia</td>
</tr>
<tr>
<td>Creatinine increase or acute oliguria</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Thrombocytopenia – coagulation abnormalities</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Ileus</td>
</tr>
<tr>
<td>Hyperglycemia in the absence of diabetes</td>
</tr>
</tbody>
</table>

Predisposing conditions – As with any disease process, there are certain conditions that predispose a patient to developing sepsis. These include individual characteristics, such as age, presence of chronic disease processes (e.g., cancer), chronic administration of certain medications (e.g., immunodepressant drugs), history of alcohol abuse, etc., which may influence a patient’s response to infection and/or suggest which therapies may be most appropriate in that patient. Recent attention has focused on genetic polymorphisms that may influence a patient’s susceptibility to develop sepsis or affect their outcome if they do develop it. Various potential genetic factors have already been elucidated. A polymorphism of the tumor necrosis factor alpha (TNF-α) gene, the TNF-2 allele, is associated with increased serum levels of TNF and a greater risk of mortality from septic shock. A polymorphism within the intron 2 of the interleukin-1 receptor antagonist (IL-1ra) gene (IL-1RN*2) has been associated with reduced IL-1ra production and increased mortality rates. Similarly polymorphisms of the Toll-like receptor 4 (TLR4) and mannose-binding lectin (MBL) genes that seem to increase susceptibility to sepsis have also been identified. Gender may also influence susceptibility to and outcome from sepsis. Clearly, this is an area of ongoing research and the complex interaction of these predisposing factors requires more research to determine which carry most weight and how knowledge of increased risks can be translated into improved clinical outcomes.

Insult – The insult in sepsis is infection and specific characteristics of the infection that will influence the patient’s immune response to that infection and likely outcome and response to treatment include the site of infection (e.g., urinary tract versus respiratory versus intrabdominal), the specific organism (e.g., Gram-positive versus Gram-negative), the size of the inoculum, the susceptibility of the organism to antimicrobial agents, and the severity of the infection.

Response – The host response to sepsis can be assessed according to the presence or absence of various

<table>
<thead>
<tr>
<th>Table 1-2 The PIRO System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>P: predisposition</td>
</tr>
<tr>
<td>Age, alcoholism, chronic diseases, steroid or immunosuppressive therapy, gender, etc.</td>
</tr>
<tr>
<td>I: insult</td>
</tr>
<tr>
<td>Site (urinary tract, lungs, abdomen, etc.)</td>
</tr>
<tr>
<td>R: response</td>
</tr>
<tr>
<td>Temperature, heart rate, respiratory rate, arterial pressure, etc.</td>
</tr>
<tr>
<td>O: organ dysfunction</td>
</tr>
<tr>
<td>Arterial pressure, urine output, Glasgow coma scale, etc.</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td>Genetic factors</td>
</tr>
<tr>
<td>Bacteriology, assay of microbial products (lipopolysaccharide, mannan, bacterial DNA, etc.)</td>
</tr>
<tr>
<td>White blood cell count, blood lactate, C-reactive protein, procalcitonin, etc.</td>
</tr>
<tr>
<td>PaO₂/FIO₂, creatinine, bilirubin, platelet count, etc.</td>
</tr>
</tbody>
</table>
signs and symptoms and to the degree of elevation of, for example, white cell count, C-reactive protein, procalcitonin, etc. Importantly, initial suggestions that sepsis was simply an uncontrolled inflammatory response and could be treated by blocking or removing any or several of the inflammatory cytokines have been supplanted by the realization that the inflammatory response is a normal and necessary response to infection, and interrupting that response at any point may do more harm than good. Indeed, the early hyperinflammatory phase of sepsis is soon replaced by a hypoinflammatory state. Each individual will mount a different response pattern depending on various factors including those outlined in the predisposing factors and insult sections above, and patients who die from sepsis often have a prolonged hypoimmune stage (Figure 1-1). This differentiation is important in therapeutic terms, as anti-inflammatory therapies may be harmful if given to a patient who is already in the hypoinflammatory phase; such a patient may benefit rather from a pro-inflammatory therapy to boost their immune system.

Organ dysfunction - Organ dysfunction can be measured using scores such as the sequential organ failure assessment (SOFA; Table 1-3). This system uses parameters that are routinely available in all ICUs to assess the degree of dysfunction for six organ systems, respiratory, cardiovascular, renal, coagulation, neurologic, and hepatic, with a scale of 0 (no dysfunction) to 4 for each organ. Importantly, organ dysfunction can be recorded for each organ separately or a composite score can be calculated. Thus with repeated scores, a dynamic picture of the effects of sepsis on individual or global organ dysfunction can be developed and followed. Sequential assessment of SOFA during the first few days of ICU admission has been shown to be a good indicator of prognosis, with an increase in SOFA score during the first 48 hours in the ICU predicting a mortality rate of at least 50%.

The PIRO system is newly developed and each item requires weighting and validation in septic patients. However, one could envisage patients receiving a PIRO stage, e.g., P4R3O2, which would help determine prognosis and direct treatment. This is an important advance in this field and, in addition to characterizing individual patients, will facilitate comparison of patient populations for clinical trial purposes, and help focus clinical research. Importantly, as new developments are made in gene mapping, or new markers of disease presence and severity are identified, the relevant component of the PIRO system would need to be modified accordingly.

**PATHOPHYSIOLOGY**

**Inflammatory Mediators**

The pathophysiology of sepsis is complex and although huge advances have been made, many facets remain unclear; indeed, while each new discovery provides new understanding, it also reveals new intricacies requiring further clarification. Essentially, the sepsis response is initiated directly by an invading organism, or by particular products or features of the organism, such as endotoxin (Gram-negative), peptidoglycan, and lipoteichoic acid (Gram-positive). These microbial products stimulate endothelial damage, the release of cytokines, the generation of complement, the activation of coagulation, and a range of other effects, both directly and via so-called mediators of sepsis. The activities and identities of many of the mediators of sepsis have been widely studied, but many features of the response remain unclear. Initiation occurs as microbial components are recognized by soluble or cell-bound pattern recognition molecules or receptors, such as CD14 and TLRs. For Gram-negative organisms, endotoxin (lipopolysaccharide, LPS) binds to a specific LPS-binding protein (LPB) in the plasma, which carries the LPS to a macrophage membrane receptor, CD14. The LPS/LBP complex then interacts with a signal-transducing receptor in the membrane, TLR4, and MD-2. Activation of TLR4 induces the transcription of inflammatory and immune response genes via a nuclear factor-κB (NF-κB)-mediated mechanism, resulting in the release of cytokines. Pro-inflammatory cytokine release then attracts further macrophages and monocytes and the cycle repeats. The LPS/LBP complex can also bind to a soluble CD14 receptor present in the serum that promotes LPS binding to endothelial cells, again via TLRs. For Gram-positive and fungal organisms, the sequence is probably similar with cell-wall components such as lipoteichoic acid or peptidoglycan binding to CD14, which then binds to TLR2, again stimulating cytokine release. Bacterial components can also act directly to stimulate the coagulation (see below) and complement
### Table 1.3 The Sequential Organ Failure Assessment (SOFA) Score

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>Respiration</th>
<th>Coagulation</th>
<th>Liver</th>
<th>Cardiovascular</th>
<th>Central nervous system</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PaO₂/FIO₂, mmHg</td>
<td>Platelets × 10⁹/mm³</td>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>Hypotension</td>
<td>Glasgow coma score</td>
<td>Creatinine, mg/dL (µmol/L) or urine output</td>
</tr>
<tr>
<td>0</td>
<td>&gt;400</td>
<td>&gt;150</td>
<td>&lt;1.2 (&lt;20)</td>
<td>No hypotension</td>
<td>15</td>
<td>&lt;1.2 (&lt;110)</td>
</tr>
<tr>
<td>1</td>
<td>≤400</td>
<td>≤150</td>
<td>1.2–1.9 (20–32)</td>
<td>MAP &lt;70 mmHg</td>
<td>13–14</td>
<td>1.2–1.9 (110–170)</td>
</tr>
<tr>
<td>2</td>
<td>≤300</td>
<td>≤100</td>
<td>2.0–5.9 (33–101)</td>
<td>Dopamine ≤5 or dobutamine (any dose)*</td>
<td>10–12</td>
<td>2.0–3.4 (171–299)</td>
</tr>
<tr>
<td>3</td>
<td>≤200 (with respiratory support)</td>
<td>≤50</td>
<td>6.0–11.9 (102–204)</td>
<td>Dopamine &gt;5 or epinephrine ≤0.1 or norepinephrine ≤0.1*</td>
<td>6–9</td>
<td>3.5–4.9 (300–440) or &lt;500 ml/d</td>
</tr>
<tr>
<td>4</td>
<td>≤100 (with respiratory support)</td>
<td>≤20</td>
<td>&gt;12.0 (&gt;204)</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1*</td>
<td>&lt;6</td>
<td>&gt;5.0 (&gt;440) or &lt;200 ml/d</td>
</tr>
</tbody>
</table>

* Adrenergic agents administered for at least one hour (doses given are in µg/kg/min).
systems; the overall host response is thus a complex interaction between multiple factors.

**Pro-inflammatory Cytokines**

Cytokines are produced by a variety of cell types under normal and pathological conditions, and have systemic and local effects. They are commonly divided into pro- or anti-inflammatory cytokines although some may have both effects at different times or on different cells or tissues. Some of the key pro-inflammatory cytokines are TNF and IL-1, -6, and -8.

The TNF family is primarily involved in the regulation of cell proliferation and apoptosis, but TNF-α also recruits and activates neutrophils, macrophages, and lymphocytes, and stimulates the release of other pro-inflammatory cytokines and acute-phase proteins. TNF-α exerts its actions by binding to two distinct TNF receptors (TNFR1 and TNFR2). TNFR1 stimulation leads to classic TNF effects, while TNFR2 stimulation facilitates binding of TNF-α to the TNFR1 receptor.

IL-1 includes two related proteins, IL-1α and IL-1β, which activate the same receptors and thus have similar biological actions. The spectrum of activity of IL-1 is similar to that of TNF-α, although it generally produces less severe effects; these two cytokines work synergistically to give a greater effect than stimulation of either alone.

IL-6 is released largely under the influence of TNF-α and IL-1, and is involved in stimulating the release of acute-phase proteins, such as C-reactive protein (CRP), by the liver. It also induces B-cell growth and T-cell differentiation, and has been implicated in the myocardial depression seen in septic shock. IL-6 levels correlate more closely than other cytokines with the severity and outcome of septic shock.

IL-8 is released predominantly on stimulation by TNF-α and IL-1. Its major role is as a chemokine, i.e., it recruits inflammatory cells to the site of injury. It promotes recruitment and activation of leukocytes, upregulates expression of adhesion molecules, and enhances degranulation.

**Anti-inflammatory Cytokines**

Anti-inflammatory cytokines are released alongside the pro-inflammatory cytokines to modulate the inflammatory response. IL-10 is synthesized by monocytes, macrophages, T cells and B cells. IL-10 inhibits the release of TNF, IL-1, and IL-6, and suppresses monocyte procoagulant activity. Soluble TNF receptors are present in septic patients and bind to TNF, thus acting to limit TNF activity. IL-1 receptor antagonist (IL-1ra) is a competitive inhibitor of the IL-1 receptor and is produced by sepsis-activated monocytes and polymorphonuclear cells.

**Other Mediators**

Many other sepsis mediators are involved in the propagation or control of the septic response; some of the key agents are platelet activating factor (PAF), interferon (IFN)-γ, IL-4, macrophage inhibitory factor, high mobility group (HMG) proteins, transforming growth factor (TGF)-β, arachidonic acid metabolites, reactive oxygen species, nitric oxide, and cell adhesion molecules.

**Coagulation and Inflammation**

One of the key concepts that has changed our view, and indeed management, of sepsis is new understanding of the interaction of inflammation, coagulation, and fibrinolysis. The imbalance in hemostatic mechanisms may manifest as disseminated intravascular coagulopathy (DIC) and microvascular thrombosis and could be a key factor in the development of organ dysfunction, ultimately leading to multiple organ failure and death.

Essentially, the cycle starts with early endothelial damage initiated both directly by endotoxins and other infectious products, and indirectly by the initial components of the inflammatory response to the invading microorganism, including TNF-α and IL-1. Subendothelial structures are exposed and collagenases are released. Exposed tissue factor triggers the extrinsic coagulation cascade and accelerates the production of thrombin. At the same time, the endothelial damage further exacerbates inflammation, with neutrophil activation, neutrophil-endothelial cell adhesion, and continued elaboration of inflammatory cytokines, which in turn produce more endothelial damage, compromising microvascular function. Endogenous modulators of homeostasis, such as protein C and antithrombin, are consumed as the body attempts to return to a normal functional state. Under normal conditions, the endothelial surface proteins, thrombomodulin and endothelial protein C receptor (EPCR), activate protein C and its modulating effects; however, in sepsis the endothelial damage impairs this function of thrombomodulin and EPCR, thereby contributing to the loss of control. In addition to activated coagulation, fibrinolysis is suppressed, with increased levels of two of the key inhibitors of fibrinolysis: plasminogen activator inhibitor 1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI). There is thus a cascade of inflammation and coagulopathy that drives the sepsis response, leading to multiple organ failure and death for many patients.

**MANAGEMENT OF SEPSIS**

**Hemodynamic Stabilization**

The basic management of sepsis involves appropriate and rapid antimicrobial therapy, surgical removal of any infectious nidus, and hemodynamic stabilization following the VIP (ventilate, infuse, pump) principles. The optimal hemodynamic management of septic shock has been
the subject of some debate, in particular regarding the choice of fluid and vasoactive agents. Patients with septic shock can be successfully resuscitated with crystalloid or colloid, and when crystalloids and colloids are titrated to the same level of filling pressure they restore tissue perfusion to the same degree. However, because of their propensity for leakage into the extravascular space, to achieve the same effect approximately three times greater volume of crystalloid is required than colloid, and slightly longer infusion periods may be necessary to achieve comparable hemodynamic endpoints. The choice of fluid is probably less important than the quantity given, with cardiac output and systemic oxygen delivery increasing in proportion to the degree of intravascular volume expansion achieved. Repeated fluid challenges, in which a predefined amount of fluid is infused over a set time and the chosen clinical endpoints and pressure safety limits monitored, can be conducted to assess the adequacy of fluid resuscitation (Table 1-4).

Colloid solutions are much more expensive than crystalloid solutions, even when taking into account the reduced volumes required. Crystalloids are often regarded as first-line fluids for the hemodynamically stable patient and colloids are administered in addition to rather than in lieu of crystalloids. However, when the patient is hemodynamically compromised many clinicians prefer colloids. With several recent studies suggesting that new generation hydroxyethyl starches may reduce the inflammatory response and directly improve tissue oxygenation, the precise choice of fluid may become more important; however, further study is needed to confirm these observations.

The choice of vasoactive agent similarly has been the subject of some debate, with a keen search to determine which agent, if any, has direct beneficial effects on the microcirculation. However, there remains no evidence in favor of one agent or another, with dopamine and norepinephrine both valid choices as first-line agents.

One of the key features of hemodynamic stabilization in septic patients is that it should be done early. Early goal-directed therapy in patients with severe sepsis and septic shock improves mortality rates compared to standard therapy.

### Immunomodulating Therapy

The recognition of the important interaction between the coagulation system and the inflammatory response outlined above led to the development of the first immunomodulating therapy to be shown to reduce mortality in patients with severe sepsis. A recombinant form of activated protein C, known as drotrecogin-alfa (activated), given at a dose of 24 μg/kg/hour for 96 hours improves organ dysfunction and decreases mortality in patients with severe sepsis and septic shock. The mechanisms of action of this drug are still uncertain, but combine anticoagulant properties and direct effects on the inflammatory response. Activated protein C can reduce LPS-induced TNF release, inhibit leukocyte adhesion, decrease leukocyte activation, inhibit NF-κB formation, and inhibit induction of inducible nitric oxide synthase (iNOS), all key factors in the systemic inflammatory response to sepsis. Activated protein C also has anti-apoptotic effects. As expected, drotrecogin alfa (activated) administration is associated with an increase in the risk of bleeding, although this is mostly associated with use of invasive procedures. It is therefore 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 (Table 1-5). Care should be taken in other

<table>
<thead>
<tr>
<th>Table 1-4</th>
<th>Clinical Example of Fluid Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td>Patient with Arterial Hypotension (MAP 65 mmHg, CVP 12 mmHg)</td>
</tr>
<tr>
<td>Select type of fluid</td>
<td>Ringer's lactate</td>
</tr>
<tr>
<td>Select rate of infusion</td>
<td>1000 ml/30 min</td>
</tr>
<tr>
<td>Select clinical end-points</td>
<td>MAP 75 mmHg</td>
</tr>
<tr>
<td>Select pressure safety limits</td>
<td>CVP 15 mmHg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>Baseline</th>
<th>Fluid Challenge</th>
<th>Fluid Challenge</th>
<th>Fluid Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>65</td>
<td>70</td>
<td>75</td>
<td>OR 65</td>
</tr>
<tr>
<td>CVP</td>
<td>12</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Urine output</td>
<td>0</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>Mottled</td>
<td>OK</td>
<td>OK</td>
<td>Mottled</td>
</tr>
<tr>
<td>Action</td>
<td>Continue</td>
<td>Stop</td>
<td>Stop</td>
<td></td>
</tr>
</tbody>
</table>
CONTRAINDICATIONS
Active internal bleeding
Trauma with risk of life-threatening bleeding (spleen, liver, retroperitoneal, etc.)
Central nervous system (CNS)
  Recent hemorrhagic stroke (3 months)
  Recent CNS surgery or head trauma (2 months)
Intracranial mass
Epidural catheter

CAUTIONS
Abnormal coagulation
  Bleeding diathesis
  Platelet count < 30,000/mm³
  Very prolonged INR
  Recent thrombolytic therapy
Significant risk of bleeding
Polytrauma
Active ulcer
Esophageal varices
Recent ischemic stroke (3 months)

Severe sepsis and septic shock are common causes of morbidity and mortality, and their incidence is increasing. Improved understanding of the pathophysiology of the sepsis response, in particular regarding the interaction between inflammation and coagulation, has seen a major advance in the treatment options with the development of drotrecogin alfa (activated). Importantly, as other effective immunomodulatory strategies become available, strategies to characterize the patient with sepsis, such as the PIRO system, will become increasingly important to help determine which therapy or therapies should be given to which patient and when.

SELECTED READING
Respiratory failure is a condition in which the respiratory system fails in one or both of its gas-exchanging functions (oxygenation of or carbon dioxide removal from mixed venous blood). Thus, respiratory failure is a syndrome rather than a specific disease.

Respiratory failure may be acute or chronic. Acute respiratory failure is associated with life-threatening alterations in arterial blood gases and acid–base status whereas chronic respiratory failure is a more indolent process. This chapter focuses on acute respiratory failure.

Respiratory failure may be divided into two broad categories: hypoxemic (type 1) and hypercapnic (type 2). Hypoxemic respiratory failure is defined as an arterial PO2 less than 55 mmHg when the fraction of inspired air (FIO2) is 0.60 or greater. Hypercapnic respiratory failure is defined as an arterial PCO2 greater than 45 mmHg.

Disorders that initially cause hypoxemia may be complicated by respiratory pump failure and hypercapnia (Table 2-1). Conversely, diseases that produce respiratory pump failure are frequently complicated by hypoxemia due to secondary pulmonary parenchymal processes (e.g., pneumonia) or vascular disorders (e.g., pulmonary embolism).

### HYPOXEMIA

Hypoxemia may be broadly divided into four major categories:

1. Ventilation/perfusion (V/Q) mismatch
2. Shunt
3. Diffusion limitation
4. Hypoventilation and low FIO2

These will now be addressed individually in reverse order.

Hypoventilation and low FIO2 are rare causes of hypoxemia in the intensive care unit (ICU). One should suspect hypoventilation as the cause of hypoxemia in patients with elevated PaCO2. Oversedation or hypercarbic respiratory failure are common causes of this condition. Low FIO2 should not be a cause of this condition in the ICU unless there is an inadvertent oxygen disconnection. Hypoventilation and low FIO2 may be separated from the other causes of hypoxemia in that they are the only ones associated with a normal alveolar-arterial (A-a) PO2 gradient (Table 2-2).

The A-a PO2 gradient represents the difference between alveolar and arterial PO2. The A-a PO2 gradient may be calculated from the following equation: A-a PO2 gradient = FIO2*(Pb*PH2O) – (PaCO2/R) – PaO2, where FIO2 is the fraction of inspired O2, Pb is the barometric pressure, PH2O is the partial pressure of water, and R is the respiratory quotient. The A-a PO2 gradient is normally less than 10 mmHg on room air. In adults over the age of 65, normal values may extend up to 25 mmHg.

<table>
<thead>
<tr>
<th>Table 2-1 Common Causes of Hypoxemia and Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypoxemia</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>
it may lead to CO2 retention. 

and by itself does not lead to hypoxemia. If severe, Ventilation without perfusion is simply deadspace ventilation. Reduced or absent ventilation leads to hypoxemia. With reference to hypoxemia, only perfusion with cardiac output and hence decreases available time for gas exchange) and/or to overcome diseases which cause diffusion limitation. Except for severe end-stage lung disease (e.g., fibrosis, emphysema), this is a very rare occurrence and, hence, a very rare cause of acute hypoxemia. Diffusion limitation, in general, is something that is handled by the pulmonary specialist over a long period of time. 

Diffusion limitation is a very rare cause of hypoxemia and no other cause of hypoxemia, such as pneumonia, needs to be implicated. The normal A-a PO2 gradient separates this category of hypoxemia from the other three categories. 

Diffusion limitation is a very rare cause of hypoxemia in the ICU. The alveolar capillary unit has about 1 second in which to exchange carbon dioxide for oxygen. This normally occurs within the first 0.3 seconds. This leaves approximately 0.7 seconds as a buffer. This protects against hypoxemia during exercise (which increases cardiac output and hence decreases available time for gas exchange) and/or to overcome diseases which cause diffusion limitation. Except for severe end-stage lung disease (e.g., fibrosis, emphysema), this is a very rare occurrence and, hence, a very rare cause of acute hypoxemia. Diffusion limitation, in general, is something that is handled by the pulmonary specialist over a long period of time. 

V/Q mismatch is the most common cause of hypoxemia. With reference to hypoxemia, only perfusion with reduced or absent ventilation leads to hypoxemia. Ventilation without perfusion is simply deadspace ventilation and by itself does not lead to hypoxemia. If severe, it may lead to CO2 retention. 

To understand this completely, one needs to call to mind the following equations: 

\[ V_k = \dot{V}_0 + \dot{V}_a \] 
\[ PaCO_2 = k \times VCO_2 / V_a \] 

where \( V_k \) equals total minute ventilation, \( \dot{V}_0 \) equals deadspace minute ventilation, \( \dot{V}_a \) equals alveolar minute ventilation, and \( VCO_2 \) equals CO2 production. Normally \( \dot{V}_0 \) and \( \dot{V}_a \) represent 30% and 70% respectively of total ventilation. Also, as \( k \) is a constant and \( VCO_2 \) can generally be considered constant, \( PaCO_2 \) is inversely proportional to \( \dot{V}_a \) (i.e., \( PaCO_2 \approx 1 / \dot{V}_a \)). This will become important to understand when adjusting ventilator settings. 

When assessing hypoxemia it is important to understand the normal physiology of the lung (Figure 2-1A). The pulmonary artery is the only artery in the body that delivers unoxygenated blood. A normal blood gas obtained from the pulmonary artery is \( pH = 7.35 / PCO_2 = 45 \text{ mmHg} / PO_2 = 40 \text{ mmHg} / O_2 \text{ sat} = 75\% \). The alveolar \( PO_2 \) is approximately 110 mmHg (obtained from the alveolararterial gas equation), and alveolar \( PCO_2 \) is 40 mmHg. A perfectly matched alveolar capillary unit will produce pulmonary venous blood with a \( pH = 7.4 / PCO_2 = 40 \text{ mmHg} / PO_2 = 110 \text{ mmHg} \) and \( O_2 \text{ sat} = 100\% \). However, a “normal” arterial blood gas obtained peripherally will yield something like: \( pH = 7.4 / PaCO_2 = 40 \text{ mmHg} / PaO_2 = 95 \text{ mmHg} / O_2 \text{ sat} = 98\% \). The difference between the pulmonary venous blood and the arterial blood gas is due to anatomic shunt. Approximately 2% of venous return from the systemic circulation is returned to the left side of the circulation without going through the pulmonary circulation. Two major contributors to this shunt are the bronchial circulation and the thebesian veins of the heart. A combination of 98% of pulmonary venous blood and 2% anatomic shunt (systemic venous) blood yields the “normal” peripheral ABG. 

V/Q mismatch leads to hypoxemia when perfused alveolar units have reduced oxygen levels in the alveolar space due to reduced ventilation. This reduced ventilation is generally due to some obstruction (bronchiolar edema or mucus related to infection, bronchospasm secondary to asthma, etc.). V/Q mismatch, however, may be overcome with additional FIO2 (Figure 2-1B). Shunt is simply the extreme of V/Q mismatch where there is no ventilation but perfusion persists. (Remember ventilation without perfusion is deadspace ventilation.) Shunt will not be overcome by additional FIO2 (Figure 2-1C).

**HYPOXEMIA: MANAGEMENT**

Quite simply there are two major ways to improve oxygenation: (i) increase FIO2 and (ii) increase mean airway pressure. 

Increasing FIO2 is simple and can only be done one way. Increasing mean airway pressure can be done by a multitude of ways. Increasing mean airway pressure improves oxygenation by recruiting partially or fully collapsed alveoli, thus better matching ventilation to perfusion and reducing shunt. Mean airway pressure may be

### Table 2-2 Type 1 Respiratory Failure Mechanisms, Responsiveness to Supplemental O2, and Presence of A-a Gradient

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Responds to Added O2</th>
<th>Increased A-a PO2 Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased FIO2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shunt</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>V/Q Mismatch</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diffusion Limitation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>