

STEVEN M. OPAL, M.D.  
CHRISTIAN E. HUBER, M.D.

Sepsis, along with the multiorgan failure that often accompanies the systemic inflammatory response syndrome (SIRS), is a leading cause of mortality in the intensive care unit.<sup>1,2</sup> As many as 700,000 patients develop sepsis annually in the United States.<sup>3</sup> Nearly half of these patients manifest severe sepsis and septic shock. The mortality for septic shock remains approximately 35% to 45%, despite a concerted effort to improve the treatment options and outcome.<sup>1,3</sup>

Septic shock has become a major focus of critical care research. Although modest improvements in the prognosis have been made over the past 2 decades and promising new therapies have appeared in the past few years, innovations in the management of septic shock are still required.<sup>4</sup> This chapter reviews some of the remarkable advances achieved in the understanding of the molecular pathophysiology of sepsis, the diagnostic and therapeutic strategies emerging from this research, and the current management of septic shock.

## Definitions of Sepsis

Sepsis, septic shock, SIRS, and multiple organ dysfunction syndrome (MODS) were defined at the American College of Chest Physicians/Society for Critical Care Medicine (ACCP/SCCM) Consensus Conference on Definition [see Table 1].<sup>5</sup> The definitions take into account the finding that sepsis may result from a multitude of infectious agents and microbial mediators and may or may not be associated with actual bloodstream infection. Despite the clinical logic, intrinsic simplicity, and widespread acceptance

of these consensus definitions, their clinical applicability has been justifiably criticized.<sup>6,7</sup> The SIRS definition is so broad and non-specific that it lacks discriminatory power; many patients admitted to general medical services and most ICU patients have conditions that meet the definition of SIRS. The current definition of sepsis fits virtually every person within the first 24 hours of an episode of influenza because the SIRS criteria are met and an infectious agent (an orthomyxovirus) causes the syndrome; however, clinicians do not generally regard the flu as sepsis. Nevertheless, a consensus conference held in 2001 to address some of these concerns concluded that, apart from a need to expand the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence existed to support a change in the definitions.<sup>8</sup>

One of the tenets on which these definitions are based is that the inflammatory response itself, not the infectious organism, drives the septic process. This hypothesis may be largely correct, but the nature of the microbial pathogen responsible for sepsis clearly contributes to the ultimate fate of the patient. Microbial pathogens differ in their susceptibility to host defenses, their potential for developing antimicrobial resistance, and their ability to generate toxins—all of which affect their pathogenicity.<sup>9</sup> Failure to account for these intrinsic differences in microbial virulence limits the utility of current sepsis definitions.

Although the definition of septic shock includes hypotension that is unresponsive to fluid challenge, there is disagreement regarding the level of fluid resuscitation necessary to distinguish between sepsis and hypovolemia. In addition, the amount of vasopressor agent necessary to allow one to confidently conclude that the patient has true septic shock continues to be debated. Controversy also surrounds the difficulty in distinguishing pre-existing morbidities and organ dysfunction from morbidity and

Table 1 The Terminology of Sepsis

Term	Definition	Comments
ARDS* (acute respiratory distress syndrome) <sup>106</sup>	Acute onset Bilateral infiltrates on chest radiograph Hypoxemia ( $P_aO_2/F_iO_2$ ratio $\leq 200$ mm Hg) No evidence of left atrial hypertension (pulmonary arterial wedge pressure $\leq 18$ mm Hg)	Severity can be scored by use of clinical parameters such as presence of hypoxemia, radiologic evidence of lung consolidation and compliance, and PEEP data from mechanical ventilation (Murray lung injury score) <sup>107</sup>
Bacteremia	Detection of viable bacteria in the bloodstream	Transient bacteremia without clinical symptoms is common; may or may not be found in sepsis
SIRS (systemic inflammatory response syndrome)	Fever ( $> 38.5^\circ\text{C}$ [ $101.3^\circ\text{F}$ ]) Tachypnea ( $> 20$ breaths/minute) Tachycardia ( $> 90$ beats/minute) Leukocytosis ( $> 12,000$ cells/ $\text{mm}^3$ or $> 10\%$ immature forms)	Two or more criteria needed; may be caused by infectious and noninfectious etiologies; clinical features may be caused by release of inflammatory mediators into circulation
Sepsis	SIRS caused by an invasive infection	May be caused by viral, bacterial, fungal, or parasitic pathogens; bloodstream infection need not be present
MODS (multiple organ dysfunction syndrome)	Major organ dysfunction from sepsis	A primary determinant of outcome in sepsis
Severe sepsis	Sepsis accompanied by major organ dysfunction (CNS, renal, pulmonary, hepatobiliary, hematologic, or metabolic)	Sometimes referred to as sepsis syndrome
Septic shock	Severe sepsis with hypotension not responsive to fluid challenge	Systolic blood pressure $< 90$ mm Hg despite adequate fluid resuscitation

\*European-American Consensus Committee on ARDS definition.

$F_iO_2$ —fraction of inspired oxygen  $P_aO_2$ —arterial oxygen tension PEEP—positive end-expiratory pressure

organ dysfunction induced by the septic process itself. Many patients with sepsis have major underlying organ dysfunction from a variety of disease entities. The degree to which sepsis contributes to further disordered organ function may be difficult to determine with accuracy. The same can be said for the degree to which sepsis contributes to the mortality in patients who suffer from other serious underlying diseases. All these factors limit the discriminatory value of the consensus definitions of sepsis and jeopardize valid comparisons between different study populations, compromising the ability to pool data and generalize the findings.

Further refinements in sepsis terminology may be possible when rapid diagnostic techniques become available to assess the immune status of septic patients. Functional genomics and proteomics (the study of human gene sequences and protein sequences, respectively) may assist in characterizing septic patients in the future. In the meantime, the current consensus definitions will be used despite their limitations.

## Epidemiology

Between 1979 and 2000, the incidence of sepsis increased by 8.7% annually, from 82.7 to 240.4 per 100,000 population.<sup>3,10</sup> This trend will probably continue in the foreseeable future because sepsis has largely become a disease of medical progress. Successful management of a variety of severe medical and surgical diseases has produced a large patient population with critical illness and impaired host defenses; these patients have a greatly increased risk of developing sepsis. Innovations in organ transplantation, implanted prosthetic devices, and long-term vascular access devices continue to expand this patient population. The gradual aging of the population in many developed countries and the increasing prevalence of antibiotic-resistant microbial pathogens also contribute to the rising incidence of septic shock.

## Pathogenesis: Microbial Factors

### CAUSATIVE MICROORGANISMS

The microbiology of sepsis has undergone a remarkable transition in the past 25 years. The predominant microbial pathogens responsible for sepsis in the 1960s and 1970s were gram-negative bacilli and *Pseudomonas aeruginosa*, but there has been a progressive increase in the incidence of sepsis caused by gram-positive bacteria<sup>4,11,12</sup> and opportunistic fungi. The rapid evolution of antibiotic-resistance genes in gram-positive bacterial pathogens and the frequent occurrence of vascular catheter-related bacterial sepsis may account for the increasing prevalence of gram-positive pathogens as a cause of sepsis.

### THE ROLE OF BACTERIAL ENDOTOXIN

Bacterial endotoxin, which is composed of lipopolysaccharide (LPS), is an intrinsic component of the outer membrane of gram-negative bacteria and is essential for the viability of enteric bacteria.<sup>13</sup> The unique potency of endotoxin is illustrated by the recent isolation of an endotoxin-deficient strain of *Neisseria meningitidis* that is at least 100-fold less potent an inducer of cytokine production than wild-type bacteria.<sup>14</sup> Endotoxin may enter the human circulatory system in its free form (released from dead organisms or shed from the membrane of viable organisms) or bound to the cell wall of intact bacteria. Whether free or bound, endotoxin appears to function essentially as an alarm molecule that

alerts the host to the presence of invading gram-negative bacteria,<sup>14,15</sup> and its presence provokes a rigorous systemic inflammatory response. The host response to the endotoxin, rather than the endotoxin itself, accounts for the endotoxin's potentially lethal properties. As a species, humans are especially susceptible to the profound immunostimulant properties of endotoxin; even minute doses may be lethal.

### Toll-like Receptors

On human immune cells, the Toll-like receptor (TLR) family is the transmembrane receptor for endotoxin and many other microbial mediators, such as peptidoglycan, lipopeptides, and lipoteichoic acid.<sup>16</sup> Ten TLRs have been identified to date. TLR4 is the principal endotoxin receptor,<sup>17</sup> whereas TLR2 and perhaps other TLRs recognize and signal the presence of a variety of microbial mediators, including endotoxin.<sup>18,19</sup> Comparative genomics in mice and fruit flies allowed for the identification of these critical receptors for microbial mediators on human cells.<sup>20</sup> Another TLR, TLR9, has been identified as the cellular receptor for unmethylated CpG motifs found in bacterial DNA but not in eukaryotic DNA. Upon recognition of bacterial DNA, TLR9 mediates an intense inflammatory response.<sup>21,22</sup>

TLRs belong to a family of pattern-recognition molecules that alert the innate immune response system to the presence of a microbial invader. Other pattern-recognition molecules include alternative complement components, mannose-binding lectin,<sup>23</sup> and CD14.<sup>24,25</sup> The innate immune system is by nature a rather nonspecific antimicrobial defense system. It lacks the precision of the acquired immune system (B cells and T cells), but its immediate action—phagocytosis and clearance of pathogens—in the initial stages of infection makes the innate immune response a critical survival mechanism. Activation of the innate immune system and its cellular components (neutrophils, monocytes, macrophages, and natural killer [NK] cells) are primarily responsible for the pathogenesis of septic shock.<sup>26</sup>

### LPS Signaling

LPS is a phosphorylated, polar macromolecule that contains hydrophobic elements in the fatty acids of its lipid A core structure and hydrophilic elements in its repeating polysaccharide surface components. LPS forms microaggregates in biologic fluids and then rapidly interacts with a variety of serum or membrane-bound lipophilic proteins. Three receptors for LPS have been recognized in human cells: (1) soluble or membrane-bound CD14 molecules, (2) CD11/CD18 molecules ( $\beta 2$  integrins), and (3) scavenger receptors for lipid molecules. Soluble and membrane-bound CD14 greatly potentiate the host response to small quantities of LPS and other microbial mediators.<sup>27</sup>

In human blood and body fluids, LPS signaling is mediated by interactions with a hepatically derived, acute-phase plasma protein known as LPS-binding protein (LBP).<sup>27</sup> LBP functions primarily as a shuttle molecule that binds to polymeric LPS aggregates and transfers LPS monomers to CD14, which is a glycosyl phosphatidylinositol-linked protein found on the cell surfaces of such immune effector cells as the monocyte-macrophage and the neutrophil. After docking to membrane-bound CD14, LPS is delivered to an adjacent cell surface LPS receptor TLR4, along with an extracellular accessory protein known as MD2. This complex then triggers a signal to the intracellular space, subsequently activating LPS-responsive genes. CD14 also binds to bacterial peptidoglycan and lipopeptides and delivers these microbial ligands to TLR2 for intracellular signaling.

Through a well-characterized sequence of tyrosine and threonine/serine kinases, intracellular signaling leads to phosphorylation of inhibitory  $\kappa$ B (I $\kappa$ B). This releases nuclear factor  $\kappa$ B (NF $\kappa$ B) from the cytoplasm, allowing it to translocate into the nucleus. Clotting elements and acute phase proteins, cytokines, and nitric oxide synthase genes have NF $\kappa$ B binding sites in their regulatory elements. The outpouring of inflammatory cytokines and other inflammatory mediators after LPS exposure contributes to SIRS and is central to the pathogenesis of septic shock induced by gram-negative bacteria.<sup>28,29</sup>

#### *Bactericidal/Permeability-Increasing Protein*

Another important endotoxin-binding protein found in human plasma is bactericidal/permeability-increasing protein (BPI). This protein is 456 amino acids long, is produced by human neutrophils, and is found in greatest quantities in the azurophilic (primary) granules.<sup>30</sup> Its amino acid sequence is 45% homologous with LBP but has a distinctly antagonistic function with respect to LPS handling: unlike LBP, which facilitates LPS delivery to CD14 and thereby activates cells, BPI inhibits LPS delivery to CD14. BPI competes with LBP for LPS binding in biologic fluids.<sup>30</sup> The relative concentrations of these two endotoxin-binding proteins primarily determine the net effect of LPS release.

In human plasma, the concentration of LBP is two to three orders of magnitude higher than that of BPI. The opposite appears to be the case in abscess cavities, where BPI is present in much greater quantities than LBP.<sup>19</sup> This favors LPS-activating activity in the plasma and LPS-inhibitory activity in abscess cavities. Thus, BPI functions as an endogenous anti-endotoxin molecule; it may become a component of treatment for endotoxin-induced injury.<sup>27,30</sup>

#### *Endotoxin Tolerance*

The phenomenon of endotoxin tolerance (or reprogramming) has been well characterized in experimental models of sepsis and probably also occurs in human sepsis.<sup>31</sup> Endotoxin tolerance is the desensitization to endotoxin-induced lethality after a priming (small) dose of endotoxin before an otherwise lethal challenge dose of endotoxin. This phenomenon appears to be primarily mediated at the transcription level, with down-regulation of inflammatory cytokine genes. The precise molecular explanation for endotoxin tolerance is not fully characterized. The desensitizing dose of endotoxin may induce endogenous corticosteroids or anti-inflammatory cytokines such as interleukin-10 (IL-10), decrease cell surface expression of TLRs, alter nuclear translocation of signal transduction molecules, or decrease the stability of messenger RNA (mRNA) for cytokine genes.

The significance of endotoxin tolerance in humans is unclear, but some degree of endotoxin tolerance has been observed in patients treated with monophosphoryl lipid A.<sup>31</sup> Unquestionably, endotoxin is an important mediator in the pathogenesis of septic shock. Thus, efforts to limit LPS synthesis, prevent activation of host immune response elements, and enhance the clearance of LPS are important therapeutic strategies for the future treatment of septic shock.

#### BACTERIAL SUPERANTIGENS

Another important microbial mediator in the pathogenesis of septic shock is bacterial superantigen. Although they comprise a diverse group of protein-based exotoxins from streptococci, staphylococci, and other pathogens, superantigens share an unusual immunologic property: the capacity to activate large num-

bers of CD4<sup>+</sup> T cells in a short period by bypassing the usual mechanism of antigen processing and presentation.<sup>32</sup>

Conventional bacterial antigens are internalized by antigen-presenting cells (APCs) and undergo limited proteolysis and processing within the endosomal component of the macrophage. Appropriate peptide sequences of the microbial antigens (epitopes) are inserted into the central groove of major histocompatibility (MHC) class II molecules and are then expressed on the cell surface of APCs. Specific CD4<sup>+</sup> T cells that recognize the unique epitope are then activated. Clonal expansion of this small subset of T cells results in a physiologic immune response to the newly introduced antigen. Superantigens, in contrast, do not require intracellular processing by APCs. Superantigens bind directly to class II antigens adjacent to the epitope-specific peptide groove on APCs. Superantigens also bind to a limited number of V $\beta$  regions of the T cell receptor on CD4<sup>+</sup> T cells. This binding brings CD4<sup>+</sup> T cells and macrophages into close proximity, which activates both the monocyte-macrophage and T cell populations.

Whereas a conventional peptide antigen stimulates only about one in 105 circulating lymphocytes that can recognize its unique structural epitope, a superantigen (e.g., toxic shock syndrome toxin-1 from *Staphylococcus aureus*, which binds to the V $\beta$ <sub>2</sub> region of T cells) stimulates 10% to 20% of circulating human lymphocytes. Thus, a single bacterial superantigen can activate as much as 10% of the entire lymphocyte population.<sup>33</sup> This results in excessive activation of both lymphocytes and macrophages, which, in turn, leads to the uncontrolled synthesis and release of inflammatory cytokines.

Superantigen-induced immune activation may terminate in septic shock if the process is left unchecked. Polymicrobial infections with pathogens that release both bacterial superantigens and endotoxin may be particularly injurious to the host; the toxicity of bacterial endotoxin may be greatly enhanced by superantigens that prime the immune system to react to endotoxin in an overly sensitized manner [see Figure 1].

#### OTHER MICROBIAL MEDIATORS

Peptidoglycan from the cell wall of bacteria, capsular antigens, lipoteichoic acid, lipopeptides, microbial DNA, microbial toxins, and procoagulant substances produced by microbial pathogens may all contribute to the pathogenesis of sepsis. It has been observed that peptidoglycan from gram-positive bacteria interacts with CD14 molecules and activates inflammatory cells via TLR2 in a manner comparable to that observed with bacterial endotoxin.<sup>18,19,33,34</sup> CD14-dependent activation of mononuclear cells may occur from both gram-positive and gram-negative bacteria, although the level of activation is quantitatively less with gram-positive components.<sup>35,36</sup> TLR9-dependent, CD14-independent recognition of the unmethylated CpG motifs found in bacterial DNA also results in a vigorous inflammatory response.<sup>22</sup>

Moreover, gram-positive bacterial and fungal pathogens may induce systemic hypotension, resulting in redistribution of blood flow and in splanchnic vasoconstriction. The ischemia and subsequent reperfusion of the gastrointestinal tract may disrupt the intestinal mucosal barrier to bacterial products. Translocation of intact microbial pathogens as well as bacterial endotoxin from the GI tract to the circulation may occur during periods of severe stress and during periods of hypoperfusion of the GI mucosa.<sup>37</sup> Bacterial endotoxin and perhaps other gut-derived microbial mediators may play a pathogenic role in the ongoing inflammatory process after systemic hypotension produced by infectious and noninfectious insults. This finding has initiated interest in at-

tempts to strengthen the GI mucosal barrier through immunonutrition, epithelial growth factors, and selective decontamination of the GI tract in critical illness. These treatments remain potentially viable options and are areas of active research in the management of sepsis.

## Pathogenesis: Host-Derived Mediators

### CYTOKINE NETWORKS

Inflammatory cytokines play a pivotal role in the pathogenesis of sepsis. In animal studies, the administration of human tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), an endogenous monocyte-macrophage-derived protein, was shown to have lethal consequences; in human volunteers, dramatic hemodynamic, metabolic, and hematologic changes were observed after administration of TNF- $\alpha$ .<sup>38,39</sup> The injurious effects of systemic levels of IL-1 $\beta$  have also been demonstrated.<sup>40</sup>

The major inflammatory cytokines, TNF- $\alpha$  and IL-1 $\beta$ , induce their hemodynamic and metabolic effects in concert with an expanding group of host-derived inflammatory mediators that work in a coordinated fashion to produce the systemic inflammatory response [see Figure 1 and Table 2].<sup>40,41</sup> The cytokine system functions as a network of communication signals between neutrophils, monocytes, macrophages, and endothelial cells. Autocrine and paracrine activation results in synergistic potentiation of the inflammatory response once it is activated by a systemic microbial challenge (e.g., endotoxemia). Much of the inflammatory response is localized and compartmentalized in the primary region of initial inflammation (e.g., lung tissue or the GI tract). If left unchecked, the inflammatory response spills over into the systemic circulation, resulting in a generalized reaction and culminating in diffuse endothelial injury, coagulation activation, and septic shock. The endocrinelike effect of the systemic

release of cytokines and chemokines drives the inflammatory process and causes coagulopathies throughout the body.<sup>12</sup>

The multitude of inflammatory cytokines and chemokines found in excess quantities in the bloodstream in patients with septic shock is impressive and is matched by an equally daunting group of anti-inflammatory mediators [see Table 2]. The inflammatory mediators tend to predominate in the early phases of sepsis (the first 12 to 24 hours), whereas the endogenous anti-inflammatory components often prevail in the later phases of sepsis.<sup>41</sup> It has been observed that mice deficient in T cells and B cells respond to endotoxin challenge in the same way as normal mice.<sup>42</sup> Thus, monocyte-macrophage-generated cytokines are sufficient to drive the early septic process. However, lymphocyte-derived cytokines and interferons become important in the regulation of later phases of sepsis and may ultimately determine the outcome in septic shock.

### CD4<sup>+</sup> T Cells

Important functional differences exist within CD4<sup>+</sup> T cells. Activated, yet uncommitted, CD4<sup>+</sup> T cells (T<sub>H0</sub> cells) have two major pathways of functional differentiation. T<sub>H0</sub> cells exposed to IL-2 in the presence of IL-12 are driven toward a T<sub>H1</sub>-type functional development. These cells produce large quantities of interferon gamma (IFN- $\gamma$ ), TNF- $\alpha$ , and IL-2 and promote an inflammatory, cell-mediated immune response. In contrast, T<sub>H0</sub> cells exposed to IL-4 will preferentially develop into a T<sub>H2</sub>-type phenotype; T<sub>H2</sub> cells secrete IL-4, IL-10, and IL-13. These cytokines promote humoral immune responses and attenuate macrophage and neutrophil activity.

Of interest is that T<sub>H1</sub>-type cytokines suppress the expression of T<sub>H2</sub>-type cytokines; IFN- $\gamma$  inhibits the synthesis of IL-10. Conversely, IL-10 from T<sub>H2</sub> cells is a potent inhibitor of TNF- $\alpha$  and IFN- $\gamma$  synthesis by T<sub>H1</sub> cells. The nature of the initial lymphocyte response is critical because the system tends to polarize over time into either a T<sub>H2</sub>-type or T<sub>H1</sub>-type response.<sup>43</sup> Evidence now

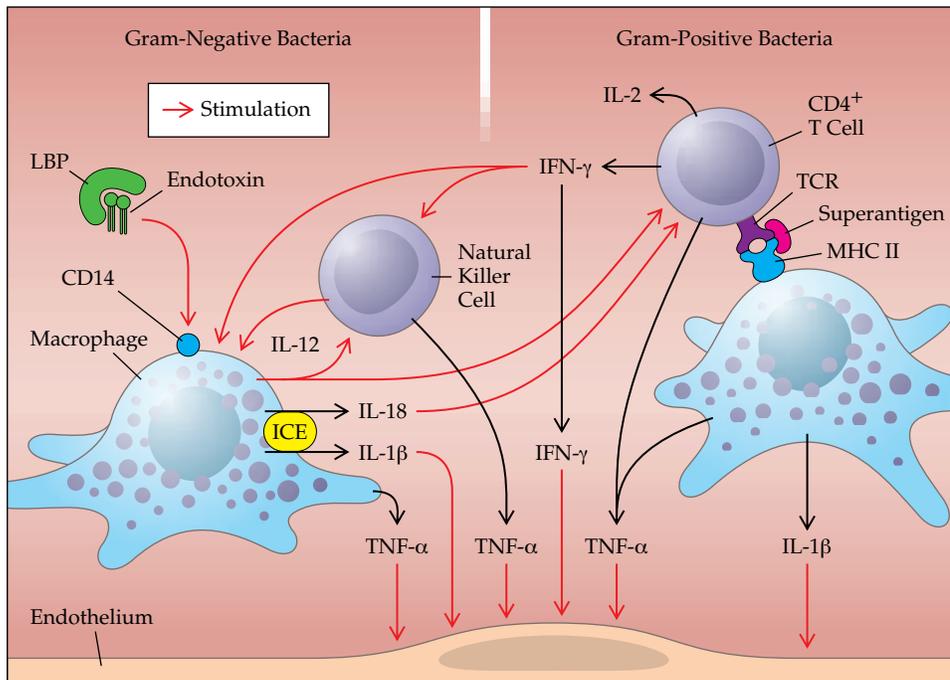


Figure 1 Interactions between bacterial endotoxin and bacterial superantigens are shown. (ICE—interleukin-1 $\beta$ -converting enzyme; IFN- $\gamma$ —interferon-gamma; IL—interleukin; LBP—LPS-binding protein; TNF- $\alpha$ —tumor necrosis factor- $\alpha$ )

**Table 2** Host-Derived Inflammatory Mediators in Septic Shock

<i>Proinflammatory Mediators</i>	<i>Anti-inflammatory Mediators</i>
Tumor necrosis factor- $\alpha$	Interleukin-1 receptor antagonist
Interleukin-1 $\beta$	Soluble tumor necrosis factor receptor
Interferon gamma	Soluble interleukin-1 receptor
Lymphotoxin- $\alpha$	Transforming growth factor- $\beta$
Interleukin-2	Interleukin-4
Interleukin-8	Interleukin-6
Interleukin-12	Interleukin-10
Interleukin-18	Interleukin-11
Complement	Interleukin-13
Leukotriene B <sub>4</sub>	Prostaglandin E <sub>2</sub>
Platelet-activating factor	Granulocyte colony-stimulating factor
Bradykinin	Antioxidants
Nitric oxide	Interferon alfa
Granulocyte-macrophage colony-stimulating factor	Interferon beta
Chemokines	
Macrophage inhibitory factor	

suggests that similar forms of functional differentiation exist for CD8 cells as well (CD8<sup>+</sup> type 1 and type 2 cells).<sup>44</sup>

This process of functional differentiation is clinically relevant because sepsis is often accompanied by a late T<sub>H2</sub>-type response after an initial septic insult. The stress hormone response in septic shock—expression of adrenocorticotropic hormone, corticosteroids, and catecholamines—promotes a T<sub>H2</sub> response after systemic injury. This may lead to a phase of relative immune refractoriness (immune paralysis) in which the patient may be at increased risk for secondary bacterial or fungal infection.<sup>41</sup> This pathophysiologic state is associated with endotoxin tolerance; anti-inflammatory cytokine synthesis; and deactivation of monocytes, macrophages, and neutrophils. Methods to detect this immunosuppressed state and restore immune competence are under investigation. Patients with depressed expression of MHC class II antigens (e.g., HLA-DR) on the cell surface of macrophages may be in a functionally immunosuppressed state and may benefit from IFN- $\gamma$  treatment.<sup>45</sup>

#### THE COAGULATION SYSTEM

Activation of the coagulation cascade and generation of a consumptive coagulopathy and diffuse microthrombi are well-recognized complications of severe sepsis. Studies of endotoxin challenge and TNF challenge in normal human volunteers indicate that the extrinsic pathway (tissue factor pathway) is the predominant mechanism by which the coagulation system is activated in human sepsis.<sup>46,47</sup> The contact factors in the intrinsic pathway are also activated, which secondarily initiates vasodilation through the generation of bradykinin.<sup>47</sup> Activation of intravascular coagulation results in microthrombi and may contribute to the multiorgan failure that occurs in septic patients. Depletion of coagulation factors and activation of plasmin, antithrombin III, and protein C may subsequently lead to a hemorrhagic diathesis. Depletion of these endogenous anticoagulants may secondarily lead to a procoagulant state and portend a poor prognosis.<sup>48</sup>

Current interest in the administration of tissue factor pathway inhibitor, activated protein C, and antithrombin III<sup>49</sup> for treatment of sepsis attest to the potential therapeutic value of regulation of the coagulation system in sepsis.<sup>50</sup> A phase 3 clinical trial in which 1,690 patients were treated with recombinant human

activated protein C (drotrecogin alfa activated) was stopped when an interim analysis revealed a survival benefit for patients receiving activated protein C; mortality was 24.7% in treated patients versus 30.8% in placebo recipients ( $P < 0.005$ ).<sup>51</sup> In contrast, a 2,300-patient multicenter trial with antithrombin III did not show any benefit.<sup>49</sup> Results of a phase 3 trial with tissue factor pathway inhibitor are pending at the time of this writing.

#### NEUTROPHIL-ENDOTHELIAL CELL INTERACTIONS

The recruitment of neutrophils to an area of localized infection is an essential component of the host inflammatory response. Localization and eradication of invading microbial pathogens at the site of initial infection is the principal objective of the immune response to microbial pathogens. This physiologic process may become deleterious if diffuse neutrophil-endothelial cell interactions occur throughout the circulation in response to systemic inflammation.

Complex mechanisms govern the migration of neutrophils from the intravascular space into the interstitium, where invasive microorganisms may reside [see Figure 2]. Activated neutrophils degranulate, exposing endothelial surfaces and surrounding structures to reactive oxygen intermediates, nitric oxide, and a variety of proteases. This process contributes not only to microbial clearance but also to diffuse endothelial injury in the setting of generalized systemic inflammatory responses. Regulation of neutrophil activity may represent a new area for therapeutic intervention in the management of sepsis.<sup>52</sup>

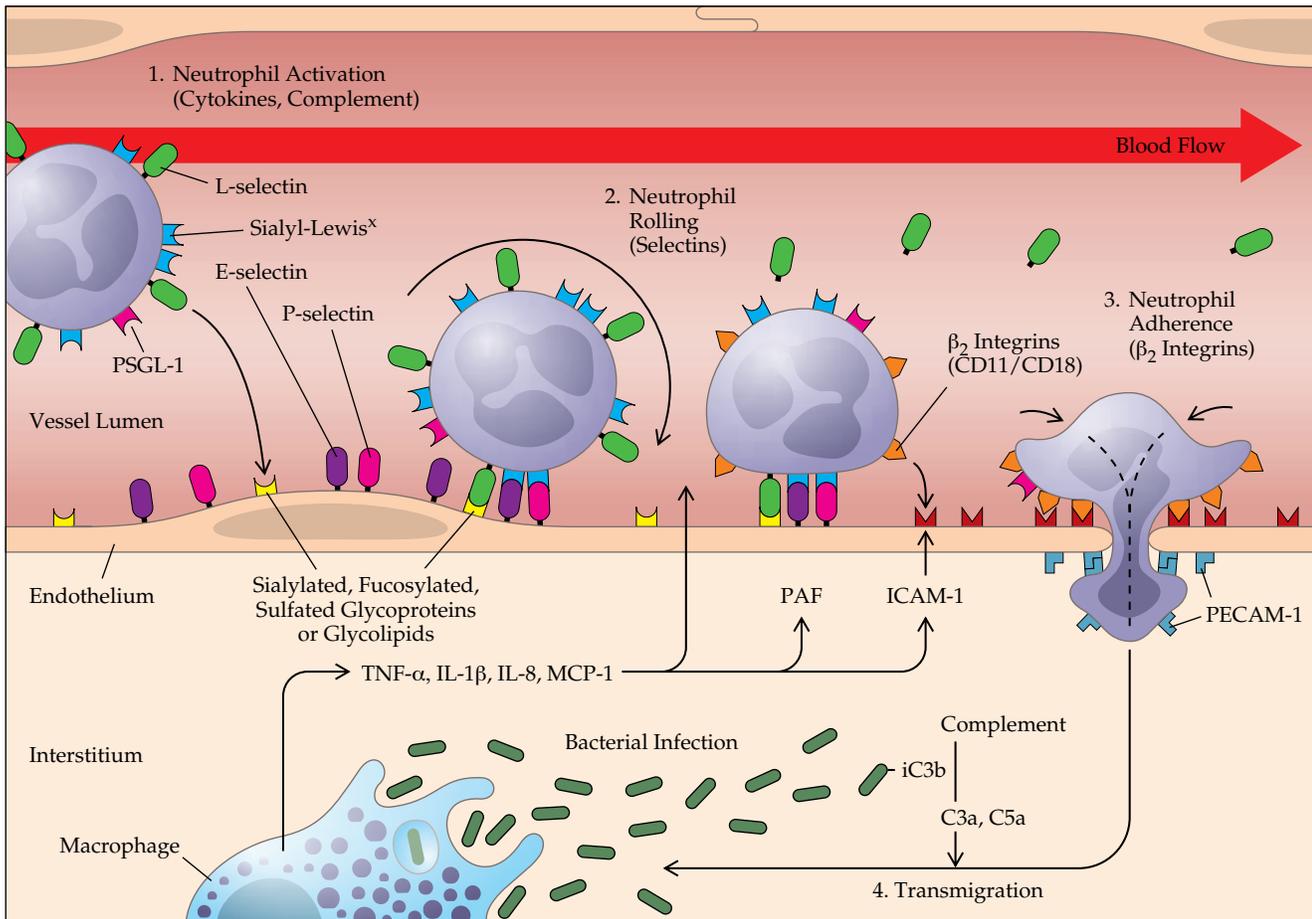
#### NITRIC OXIDE

Nitric oxide is a highly reactive free radical that plays an essential role in the pathophysiology of septic shock. It has a very short half-life (1 to 3 seconds), which tends to limit its activity to local tissues, where it is first generated by one of three isoforms of nitric oxide synthase. Regulation of the nitric oxide synthases is complex. Full expression of inducible nitric oxide synthase requires TNF- $\alpha$ , IL-1, LPS, and probably other regulatory elements.

Nitric oxide is the major endothelial-derived relaxing factor that initiates the vasodilatation and systemic hypotension observed in septic shock. Nitric oxide activates guanylate cyclase, which increases cyclic guanosine monophosphate levels inside vascular smooth muscle cells. This results in systemic vasodilatation and decreased vascular resistance. Within minutes of administration of an inhibitor of nitric oxide synthesis, blood pressure in hypotensive patients in septic shock moves toward normal levels.<sup>53</sup>

The other major physiologic effects of nitric oxide in septic shock are increased intracellular killing of microbial pathogens and regulation of platelet and neutrophil adherence. Nitric oxide is a highly diffusible gas that does not require specific receptors to enter eukaryotic or prokaryotic cells. In the presence of superoxide anion, nitric oxide leads to the formation of peroxynitrite. The peroxynitrite subsequently decays into highly cytotoxic molecules such as hydroxyl radicals and nitrosyl chloride, which, in turn, initiate lipid peroxidation and cause irreversible cellular damage. Nitric oxide inhibits a variety of key enzymes in the tricarboxylic acid pathway, the glycolytic pathway, DNA repair systems, electron transport pathways, and energy-exchange pathways. Because of its potent reactivity, nitric oxide alters the function of many metalloenzymes, carrier proteins, and structural elements.

Like many other components of the host inflammatory response, nitric oxide may have both advantageous and disadvantageous properties in sepsis. Nitric oxide regulates microcirculation to vital organs and contributes to intracellular killing of mi-



**Figure 2** Neutrophil–endothelial cell interactions in sepsis. (C—complement; ICAM-1—intercellular adhesion molecule-1; IL-1β—interleukin-1β; MCP-1—monocyte chemoattractant protein-1; PAF—platelet-activating factor; PECAM-1—platelet endothelial cell adhesion molecule-1; PSGL-1—P-selectin glycoprotein ligand-1; TNF-α—tumor necrosis factor-α)

icrobial pathogens. However, excessive and prolonged release of nitric oxide results in generalized vasodilatation and the systemic hypotension of septic shock. For those reasons, nitric oxide has become a target for therapeutic strategies in the management of sepsis.<sup>54</sup> Nonselective inhibitors of nitric oxide synthase, for example, have been shown to improve the hemodynamics of septic patients.<sup>55</sup> Unfortunately, this finding was not confirmed in a phase 3 trial.<sup>55</sup>

#### OTHER HOST-DERIVED MEDIATORS

At least two additional host-derived mediators contribute to the pathogenesis of septic shock. Macrophage migration inhibitory factor (MIF) is a late mediator that activates immune cells, upregulates TLR4 expression, and contributes to lethal septic shock.<sup>56</sup> This corticosteroid-regulated mediator promotes inflammation and has become a target for therapeutic agents in sepsis. High-mobility group-1 (HMG-1) protein also appears to contribute to late-onset inflammatory activities in septic shock. Inhibitors of HMG-1 may prove to have a therapeutic role in sepsis as well.<sup>57</sup>

#### Pathogenesis: Organ Dysfunction

The diffuse endothelial injury accompanying septic shock results in organ dysfunction distant from the original site of the

septic insult. The signal that results in diffuse endovascular injury is thought to be relayed by plasma factors (e.g., inflammatory cytokines, complement, kinins, and other host-derived inflammatory mediators) or by a cellular element found in one or more of the immune effector cells.

Inadequate blood supply to vital tissues produces MODS. The failure of the microcirculation to support tissue maintenance may be the result of hypoperfusion of capillary beds, redistribution of blood flow within vascular beds, functional arteriovenous shunting, obstruction of blood flow from microthrombi, platelet or white blood cell aggregates, or abnormal deformability of red blood cells. Direct endothelial injury from nitric oxide, reactive oxygen intermediates, inflammatory cytokines, and inducers of apoptosis may directly damage endothelial surfaces. Endothelial swelling from the movement of intravascular fluid into the extravascular and intracellular spaces may mechanically obstruct the lumens of the capillary beds as well.

Although the origin of multiorgan failure in sepsis is principally related to microvascular effects, myocardial performance and pulmonary function also diminish over the course of septic shock and may contribute significantly to the development of MODS. Myocardial contractility decreases in response to a variety of myocardial depressant factors found in the plasma of septic patients. TNF-α is a prominent cause of myocardial dysfunction; IL-1, nitric oxide, and other host-derived inflammatory me-

Table 3 Standard Laboratory Values in Sepsis

Laboratory Study	Typical Findings	Comments
White blood cell count	Leukocytosis or leukopenia	Stress response, increased margination of neutrophils in sepsis; toxic granulation may be seen; occasionally, bacteria may be found in the peripheral blood smear
Platelet count	Thrombocytopenia	Look for evidence of fragmentation hemolysis in the peripheral blood smear; thrombocytopenia may or may not be accompanied by disseminated intravascular coagulation
Glucose	Hyperglycemia or hypoglycemia	Acute stress response, inhibition of gluconeogenesis
Clotting measurements	Elevated prothrombin time, activated partial thromboplastin time, low fibrinogen levels, and evidence of fibrinolysis	Coagulopathy often seen with systemic endotoxin release
Liver enzymes	Elevated alkaline phosphatase, bilirubin, and transaminases; low albumin	—
Blood cultures	Bacteremia or fungemia	The presence of positive blood culture does not make the diagnosis, and its absence does not exclude the diagnosis
Plasma lactate	Mild elevations (> 2.2 mmol/L)	Hypermetabolism, anaerobic metabolism, inhibition of pyruvate dehydrogenase
C-reactive protein	Elevated	Acute-phase reactant, sensitive but not specific for sepsis
Arterial blood gases	Respiratory alkalosis (early); metabolic acidosis (late)	Measurements of O <sub>2</sub> content and mixed venous O <sub>2</sub> saturation useful in management

diators may be contributing factors.<sup>58</sup> Acute lung injury occurs in septic shock as a result of damage to the pulmonary vascular circulation and the alveolocapillary membranes. A supply-dependent dysoxia (cytopathic hypoxia) may contribute to tissue injury in multiorgan failure in sepsis.<sup>59</sup>

### Diagnostic Approach to Septic Shock

#### GENERAL FEATURES

In his classic treatise on human nature (*The Prince*, circa 1505), Machiavelli states, "Hectic fever [i.e., sepsis by current consensus definitions] at its inception is difficult to recognize but easy to treat; left untended, it becomes easy to recognize but difficult to treat." This statement is as true today as it was 500 years ago. Fully developed septic shock is a readily apparent clinical syndrome

that is seldom confused with other pathologic states. However, the early phases of septic shock may be quite subtle even in carefully monitored patients. Early signs and symptoms may include confusion, apprehension, or decreased sensorium. Although fever is characteristic, hypothermia may occur and connotes a poor prognosis. An unexplained decrease in urinary output, sudden onset of cholestatic jaundice, unexplained metabolic alkalosis, excess bleeding at venipuncture sites, or even sudden unexplained hypotension may be the presenting finding in septic shock. It is essential that clinicians recognize these early signs and symptoms because successful management of septic shock depends on early recognition and appropriate intervention.

A variety of clinical, laboratory, and hemodynamic abnormalities are recognized in septic shock [see Tables 3 and 4]. Unfortunately, no single clinical or laboratory test is sufficiently specific and sensitive to reliably confirm the diagnosis of septic shock.

Table 4 Hemodynamic Findings in Sepsis

Parameter	Typical Findings	Comments
Heart rate	> 100 beats/min	Major compensatory mechanism for low systemic vascular resistance
Mean arterial blood pressure	< 65 mm Hg	Hallmark of septic shock
Cardiac index (cardiac output/m <sup>2</sup> [surface area])	> 4 L/min/m <sup>2</sup>	Cardiac index elevated in early septic shock; may be depressed in late septic shock
Pulmonary arterial wedge pressure	4–10 mm Hg	Must be sure that hypovolemia is not the cause of hypotension; perform fluid resuscitation until pulmonary arterial wedge pressure returns to normal
Systemic vascular resistance (SVR)	< 800 dyne/sec/cm <sup>-5</sup>	SVR often low in early septic shock; may become elevated in later phases of septic shock
Oxygen delivery (DO <sub>2</sub> ) Cardiac index (CI) × arterial O <sub>2</sub> content (A)	< 550 ml/min/m <sup>2</sup>	Try to provide sufficient DO <sub>2</sub> to maintain adequate mixed venous O <sub>2</sub> saturation
Mixed venous O <sub>2</sub> saturation	< 70%	Low mixed venous O <sub>2</sub> indicates inadequate O <sub>2</sub> delivery to tissues in sepsis
Oxygen consumption (VO <sub>2</sub> ) (CI) × (A-VO <sub>2</sub> ) × 10	> 180 L/min/m <sup>2</sup>	Typically increased in early septic shock

**Table 5 Multiple Organ Dysfunction Syndrome in Severe Sepsis**

<i>Organ System</i>	<i>Clinical-Metabolic Abnormalities</i>	<i>Histopathologic Findings</i>
CNS	Encephalopathy, decreased sensorium	Cerebral edema, microthrombi
Cardiac	Decreased myocardial performance	Altered calcium influx, interstitial edema
Lung	Acute respiratory distress syndrome	Exudation of fluid into the alveolar spaces, neutrophil plugging, hyaline membrane formation
Kidney	Acute tubular necrosis	Hypoperfusion, focal ischemia, microthrombi
Adrenal	Relative adrenal insufficiency, adrenal hemorrhage	Focal or diffuse hemorrhage, ischemic necrosis
Hepatobiliary system	Cholestatic jaundice, decreased hepatic synthesis of albumin, presence of clotting factors	Zonal necrosis, acalculous cholecystitis
Gut	Translocation of bacterial endotoxin and microorganisms, increased permeability	Diffuse interstitial edema, breaks in the epithelial membrane integrity, mucosal necrosis

Patients may have positive or negative blood cultures, leukocytosis or neutropenia, hyperglycemia or hypoglycemia, and respiratory alkalosis or metabolic acidosis. It is the constellation of signs and symptoms that leads to a diagnosis of septic shock.

The most common hemodynamic findings in early septic shock are a high cardiac output and a low systemic vascular resistance state, with initial maintenance of the systolic blood pressure as the heart attempts to compensate for the loss of systemic vascular tone. Myocardial performance is diminished even in the early phases of septic shock.<sup>60</sup> Without adequate intervention, circulating blood volume is continually lost into the interstitial space and intracellular locations. The heart can no longer compensate sufficiently, and systolic hypotension results. Deterioration of myocardial performance, accompanied by diffuse vasoconstriction, marks the late refractory state of septic shock.

**MULTIPLE ORGAN DYSFUNCTION SYNDROME**

One of the hallmarks of septic shock is the development of MODS. A constellation of clinical and metabolic abnormalities characterizes this syndrome [see Table 5]. The development of organ failure at the onset of sepsis or during its course is a poor prognostic factor and is a primary determinant of outcome.<sup>61</sup>

*Acute Respiratory Distress Syndrome*

The acute respiratory distress syndrome (ARDS) remains a major cause of morbidity and mortality in septic shock.<sup>62</sup> Increased capillary permeability in these patients results in pulmonary edema, which manifests clinically as dyspnea and cough; a standard anteroposterior chest x-ray will typically show bilateral, symmetrical alveolar opacities in all four quadrants [see 14:X Pulmonary Edema].

**EXPERIMENTAL DIAGNOSTIC TECHNIQUES**

The current assays used to diagnose septic shock are cumbersome and slow. Research to develop better assays is ongoing.

*Plasma Endotoxin Levels*

The measurement of plasma endotoxin levels may prove useful in helping to predict the development of shock.<sup>63</sup> Unfortunately, endotoxin levels are not uniformly elevated in patients with septic shock and may be spuriously elevated in patients with gram-positive infections or other hypotensive disorders. Also, the host responsiveness to endotoxin is variable and does not correlate with circulating endotoxin levels.

*Bacterial Superantigen Levels*

Circulating levels of bacterial superantigens have been successfully measured in selected patients with toxic shock syndrome.<sup>64</sup> Such measurements may prove useful in specific clinical situations.

*IL-6 Levels*

IL-6 is a cytokine that has myriad biologic activities, some of which are inflammatory and others of which are anti-inflammatory. IL-6 has been considered an indicator of cytokine activation because it is reliably present after activation of TNF- $\alpha$  and IL-1 $\beta$ . Patients with elevated IL-6 levels may respond favorably to anti-cytokine therapies.<sup>65</sup> In several studies, elevations of IL-6, as well as failure of IL-6 levels to fall after initiation of treatment for sepsis, was associated with a poor outcome.<sup>65-68</sup> Unfortunately, IL-6 levels are not specific for sepsis and may be elevated in a variety of inflammatory and infectious states. This lack of specificity limits the reliability of IL-6 measurement as a diagnostic method for septic shock.

*Procalcitonin Levels*

Procalcitonin, the propeptide of calcitonin, is normally produced by C cells in the thyroid.<sup>69</sup> In septic patients, procalcitonin is generated by numerous extrathyroidal tissues; its precise origin in this situation is unclear.<sup>70,71</sup> Procalcitonin has attributes that make it a potential marker for sepsis. It has a long half-life (approximately 24 hours), and measured levels will increase from undetectable to over 100 ng/ml during the course of septic shock. Procalcitonin levels do not become elevated as rapidly as IL-6 or IL-8 levels; elevated levels of procalcitonin are seen 4 to 6 hours after a systemic challenge with endotoxin or other septic stimuli.<sup>72</sup>

Of interest is that procalcitonin levels are elevated in severe sepsis but not in localized infections,<sup>71</sup> severe viral infections, or inflammatory conditions of noninfectious origin. In organ transplant recipients, procalcitonin levels may allow differentiation between the fever associated with rejection and that associated with sepsis.<sup>71</sup> Although the precise physiologic role of procalcitonin in sepsis has yet to be defined, procalcitonin elevation appears to be the most sensitive and reasonably specific indicator of severe sepsis currently available.<sup>70,72</sup>

*Other Potential Markers*

C-reactive protein and plasma lactate have been used as potential markers for sepsis, but their lack of specificity and sensi-

tivity limits their diagnostic value. IL-8 may prove useful, with or without IL-6, as an indicator of sepsis.<sup>73</sup>

Phospholipase A<sub>2</sub> is essential for the generation of platelet-activating factor and arachidonic acid derivatives, including thromboxane, prostacyclin, prostaglandins, and leukotrienes. Phospholipase A<sub>2</sub> or its precursor, type I phospholipase A<sub>2</sub> propeptide, may prove to be a marker for sepsis, but the diagnostic value of measurements of this enzyme needs to be confirmed in clinical studies.<sup>74</sup>

### Management of Septic Shock

There are four goals in the management of septic shock: (1) early recognition and resuscitation; (2) reestablishment of tissue perfusion and arterial blood pressure; (3) provision of optimal supportive care; and (4) timely initiation of treatment to eradicate the causative septic focus. After 2 decades in which the means for achieving these goals remained largely the same, the treatment approach has now changed, with the use of drotrecogin alfa activated,<sup>51</sup> low-dose corticosteroids,<sup>75</sup> and other supportive strategies for the management of septic shock.<sup>76,77</sup> In addition, modest improvements in outcome have accrued as the result of improved nutrition and supportive care and the skillful use of vasopressor agents.

The key determinant in survival is early recognition of sepsis and initiation of treatment while the process is readily reversible. This requires constant vigilance by the clinician caring for patients with a variety of medical and surgical illnesses.

#### FLUID RESUSCITATION

Fluid resuscitation is a mandatory first step in the treatment of septic shock. The diffuse vascular leak that occurs in septic shock necessitates provision of adequate circulating blood volume to maintain tissue perfusion.

Debate continues regarding the appropriateness of colloid versus crystalloid fluids. The lack of clear evidence of benefit of colloid agents (e.g., albumin, dextran, and plasma expanders) and their high cost have generally resulted in the use of saline solutions for volume expansion. A 1998 meta-analysis of studies comparing colloid versus crystalloid in sepsis found a slight worsening of outcome with colloid solutions.<sup>78</sup> Further review of these data indicate that differences in outcome are equivocal at best, and debate continues on the relative merits of colloids in sepsis.

The optimal amount of fluid for resuscitation of patients in septic shock remains a source of controversy. A delicate balance is required between maintenance of tissue perfusion and prevention of fluid overload, with its attendant risk of lung injury. Decreased myocardial performance in sepsis may necessitate a higher filling pressure for adequate cardiac output; however, exudation of fluids into the alveolar space in lung tissue and into the interstitium in other vital organs continues to be a major problem. Maintenance of a pulmonary arterial occlusion pressure of approximately 12 mm Hg is considered a reasonable starting point in patients who have hemodynamic monitors in place.<sup>79</sup> Rapid resuscitation with the goal of establishing normal mean central venous pressure and oxygen delivery to tissues has been shown to be of clinical value.<sup>76</sup> Diligent care and maintenance of central lines will reduce the frequency of catheter-related sepsis.<sup>80</sup>

#### VASOPRESSOR THERAPY

When patients fail to improve hemodynamically with fluids alone, vasopressor agents are often employed to reestablish sys-

temic arterial blood pressure. Clinicians may choose among several vasopressor agents; however, the use of any vasopressor agent in septic shock carries with it certain risks and should be reserved for patients with significant hemodynamic instability that is unresponsive to fluid therapy.

#### *Dopamine*

Dopamine has been the vasopressor agent of choice for the past 2 decades because of its presumed favorable effects on renal perfusion (through promotion of renal vasodilation) and its modest inotropic effects. However, the validity of the privileged status of this choice has been questioned.<sup>81</sup> Dopamine effects are complicated by the fact that this catecholamine has its own receptors (D<sub>1</sub> and D<sub>2</sub> dopamine receptors) as well as variable affinities for alpha- and beta-adrenergic receptors. The effects of dopamine depend on the receptor density in specific vascular beds, the blood volume, and the dose used. Higher doses of dopamine increase the systemic vascular resistance by the drug's effects on alpha-adrenergic receptors in the peripheral circulation. Dopamine may have adverse effects on splanchnic blood flow,<sup>82</sup> and it has never been shown to be clearly beneficial to septic patients in an adequately controlled clinical trial.

#### *Norepinephrine*

Norepinephrine is a potent vasoconstrictor that is being used more frequently to treat the hemodynamic effects of septic shock. Earlier concerns regarding adverse consequences of norepinephrine on renal blood flow may have been overstated; studies suggest that norepinephrine may actually increase urine output and creatinine clearance in septic patients.<sup>83</sup> Norepinephrine may rapidly restore perfusion pressure within the glomerulus and result in improved glomerular filtration in patients with adequate fluid resuscitation.

#### *Vasopressin*

Vasopressin, which has its own vascular receptors distinct from adrenergic receptors, has gained favor as a vasopressor in sepsis. The clinical utility of vasopressin and related molecules (e.g., terlipressin) will ultimately be determined through large clinical comparative trials with other vasopressor agents.

#### *Dobutamine*

Dobutamine, a beta agonist, may improve cardiac output and oxygen delivery in some patients in septic shock who have low cardiac output. However, dobutamine may result in peripheral vasodilatation, which may be harmful in septic patients. Moreover, dobutamine increases myocardial oxygen consumption by its positive inotropic effects, which also may be detrimental. In one randomized trial in a heterogeneous group of critically ill patients, the use of dobutamine to boost the cardiac index and systemic oxygen delivery failed to improve outcome.<sup>84</sup>

#### VASODILATOR THERAPY

Another approach to improving the delivery of oxygen to the tissues of patients with septic shock is the use of vasodilators to open up poorly perfused capillary beds. Spronk and colleagues<sup>85</sup> recently presented a study of nitroglycerin therapy after intravascular volume resuscitation. Using an optical device to measure microcirculatory flow (orthogonal polarization spectral imaging), improved microvascular flow rates were achieved in septic patients who received adequate fluid repletion. This is an

**Table 6 Suggested Empirical Antibiotic Choices in Severe Sepsis**

Source of Infection	Antimicrobial Choice
Community-acquired pneumonia	Third-generation cephalosporin with a macrolide (alternative: fluoroquinolones)
Hospital-acquired pneumonia	Third- or fourth-generation cephalosporins, extended-spectrum penicillins with or without an aminoglycoside (alternatives: fluoroquinolones, carbapenems, $\beta$ -lactam- $\beta$ -lactamase inhibitor)
Urinary tract infections	Extended-spectrum $\beta$ -lactam agent with or without an aminoglycoside (add ampicillin or vancomycin when enterococci are present)
Intra-abdominal infections	Third- or fourth-generation cephalosporins with or without metronidazole or clindamycin or extended-spectrum penicillins or $\beta$ -lactam- $\beta$ -lactamase inhibitor with or without an aminoglycoside (alternatives: carbapenem, trovafloxacin)
Biliary tract infections	Extended-spectrum penicillin with or without an aminoglycoside
Neutropenic patients	Extended-spectrum $\beta$ -lactam agent with an aminoglycoside (add vancomycin when there is evidence of gram-positive infection)

appealing strategy to improve tissue oxygenation in septic shock, and it deserves further clinical trials.

The most reliable indicator to assess the adequacy of tissue perfusion in septic shock is not known. Numerous methods of measurement of tissue oxygenation (e.g., gastric tonometry, hepatic venous oxygen measurements, direct tissue oxygen measurements, and microcirculatory probes) have been developed to better measure and understand the critical requirements for oxygen delivery to tissues of septic patients. However, the practical value of these measurements in the clinical management of sepsis remains unclear. Moreover, there remains evidence that even with adequate oxygen delivery, dysoxia may develop in patients with sepsis because intracellular oxygen utilization is impaired by dysfunction of respiratory enzymes.

#### PREVENTING AND TREATING ARDS

Efforts to prevent lung injury include innovations in respiratory support, avoidance of trauma to the alveolocapillary units from excessive tidal and fluid volume, avoidance of oxidant-induced lung injury, salvage of functional alveolocapillary units through position change (prone position), and judicious fluid management.<sup>86</sup> Measurable improvements in the outcome of patients with ARDS have occurred, but considerable room for improvement remains in regard to the sparing of pulmonary function in patients with septic shock.

A major finding in regard to ARDS management was recognition of the hazard of providing excessive tidal volume through overly high ventilator settings. The resulting overdistention of airways can promote the progression of lung injury and the release of inflammatory mediators into the systemic circulation.<sup>87</sup> The ARDS clinical trials network study demonstrated conclusively that low stretch tidal volume settings (6 ml/kg) are clearly superior to the previous conventional high tidal volume setting (12 ml/kg).<sup>88</sup> Consequently, low tidal volume ventilation is now the standard of practice in the management of most forms of acute lung injury.

#### BLOOD TRANSFUSIONS

The role of blood transfusions in improving the oxygen-carrying capacity of blood has been the subject of considerable debate.<sup>89</sup> Humans have been shown to be remarkably resistant to adverse effects from isovolumetric reduction in hemoglobin values.<sup>90</sup> Banked, stored RBCs are less deformable, are less efficient at releasing oxygen from their 2,3-biphosphoglycerate-depleted hemoglobin stores, and may have immunosuppressive effects.<sup>91</sup> Promotion of endogenous erythrocyte production with erythropoietin may prove to be superior to blood transfusions<sup>92</sup>; further clinical trials with this treatment approach are warranted.

The hemoglobin level at which transfusion is indicated in septic shock has not been defined, but it appears to be considerably lower than the traditional threshold of less than 10 g/dl. Recent studies in ICU patients indicate that a conservative threshold, set as low as 7 g/dl, may in fact be preferable.

#### MANAGEMENT OF MULTIORGAN FAILURE

Expert management of acute renal failure [see 10:VI *Acute Renal Failure*], ARDS [see 14:X *Pulmonary Edema*], hepatic decompensation, coagulopathy, acid-base disturbances, and disordered hemodynamics is of paramount importance in the management of sepsis. Multiorgan failure is potentially reversible if rapid interventions correct the hemodynamic and inflammatory abnormalities.

#### NUTRITIONAL SUPPORT

Nutritional support in septic shock has changed considerably over the past 2 decades. Reliance on total parenteral nutrition has given way to early and extensive use of enteral hyperalimentation. Enteral feeding of septic patients has been shown to benefit enterocyte function, help maintain the intestinal permeability barrier, and help prevent gut-derived endotoxin and cytokine generation.<sup>93</sup> Nutritional supplementation with glutamine, arginine, and omega-3 fatty acids has experimental support and is increasingly being used in septic patients<sup>94</sup> [see 4:XIII *Enteral and Parenteral Nutrition*]. The incremental value of such enriched enteral formulations over standard enteral alimentation has not yet been confirmed in large clinical trials.

#### MANAGEMENT OF FEVER

Fever is a common concomitant of severe sepsis and appears to be an advantageous response.<sup>95</sup> In experimental animals with *Klebsiella pneumoniae* peritonitis, infection resolved and subjects recovered more rapidly when they were allowed to develop fever, compared with control animals in which normothermia was maintained externally.<sup>96</sup> Heat-shock proteins function as intracellular chaperones to stabilize and prevent denaturation of host proteins. Heat-shock protein induction may actually decrease the mortality associated with experimental endotoxin challenge.<sup>97</sup> Efforts to lower body temperature with cooling blankets are largely ineffective and may not benefit the patient in septic shock. This strategy should generally be avoided unless true hyperthermia is present.<sup>98</sup>

#### ANTIMICROBIAL THERAPY

The most appropriate antimicrobial therapy in sepsis depends on the source of infection, susceptibility patterns of microbial pathogens within a given institution, prior antimicrobial exposure, presence or absence of pregnancy, hepatic and renal function, and history of drug allergy. In septic shock, combinations of bactericidal antimicrobial agents are generally given on an empirical basis [see Table 6]. Antibiotic combinations decrease the

**Table 7** Current Adjuvant and Experimental Therapies in the Treatment of Septic Shock

<i>Experimental Agent</i>	<i>Treatment Target</i>	<i>Comment</i>
Bactericidal/permeability-increasing protein	Endotoxin	Endotoxin-neutralizing human protein
Anti-CD14 antibody	Endotoxin/peptidoglycan	Endotoxin and peptidoglycan blocker
E5564	Endotoxin	Lipid A antagonist
Polymyxin B-binding columns	Endotoxin	Endotoxin-binding antibiotic
Platelet-activating factor (PAF)-acetylhydrolase	PAF	Rapid metabolism of PAF
FAB 2' anti-tumor necrosis factor (TNF) monoclonal antibody	TNF	Neutralizes TNF in the circulation
Low-dose corticosteroids*	Adrenal function	Treat adrenal hypofunction of sepsis
Activated protein C <sup>†</sup>	Coagulation system	Inhibits disseminated intravascular coagulation, microthrombi
Hemoperfusion systems	Cytokines and endotoxin	Remove inflammatory mediators and endotoxin during hemoperfusion
Nitroglycerin infusion	Disordered microcirculation	Opens up poorly perfused capillary beds along with I.V. fluids
Arginine, glutamine, nucleic acids, micronutrients	Immunonutrition	Improve immune function and provide antioxidants
Caspase inhibitors	Cellular apoptosis	Block excess apoptosis of immune cells and endothelial cells

\*One recent clinical trial demonstrated benefit; another study is ongoing.

<sup>†</sup>Approved for use in severe sepsis in patients at high risk of mortality (such as an APACHE II [Acute Physiology and Chronic Health Evaluation-II] score > 24 or multiorgan failure); its use in early, less severe sepsis is currently under investigation.

risk that a multidrug-resistant microbial pathogen will be missed and increase the probability that all of the important pathogenic microorganisms will be inhibited by at least one of the antimicrobial agents. Concern continues regarding antibiotic-induced endotoxin release in sepsis, but the clinical relevance of this effect has not been demonstrated and should not affect antibiotic choices for septic shock patients.<sup>99</sup>

#### MANAGEMENT OF BLOOD GLUCOSE LEVELS

Tight regulation of blood glucose levels is an important supportive management technique in sepsis. Van den Berghe and colleagues<sup>77</sup> reported improved survival, shorter ICU stays, and less bacteremia in patients with strict glycemic control (target was continuous euglycemia) versus conventional care in a cardiovascular ICU setting.

#### New Therapies for Sepsis

Over the past 15 years, more than 30 double-blind, placebo-controlled, multicenter, phase 2 or phase 3 trials have been conducted to study the efficacy of new experimental agents in the treatment of septic shock.<sup>1,26,100-102</sup> After a long list of disappointments, two recent studies have now shown convincing positive results. The study of recombinant human activated protein C (drotrecogin alfa activated; see above) represents the first successful phase 3 international trial in severe sepsis.<sup>51</sup> This clinical trial resulted in Food and Drug Administration approval of drotrecogin alfa activated (Xigris) for the treatment of adult patients with severe sepsis who have an especially high risk of dying from sepsis. Carefully selected patients benefit from this treatment regardless of the type of infecting microorganism that caused their sepsis. The drug is given as a continuous infusion at

24 µg/kg/hr for 4 days. Because protein C is an endogenous anticoagulant, the major side effect of treatment is bleeding.<sup>50</sup>

The second successful trial was a multicenter clinical study of low-dose corticosteroids. Annane and coworkers reported a significant improvement in survival in patients with vasopressor-dependent septic shock through the use of hydrocortisone (50 mg every 6 hours for 7 days) and fludrocortisone (50 µg/day for 7 days).<sup>75</sup> This treatment strategy is based on the frequent occurrence of relative adrenal insufficiency in patients with septic shock. In fact, low-dose corticosteroid therapy was effective only in those patients who showed evidence of inadequate adrenal response when given a short corticotropin test.<sup>100</sup> A large clinical trial is under way in Europe and Israel to confirm and extend these exciting results; meanwhile, a German study in 40 patients with septic shock has provided supporting evidence.<sup>103</sup> A follow-up study with a larger number of patients would be worthwhile (the Annane study involved 299 patients), but to date, low-dose corticosteroids appear to be a cost-effective, readily available, and relatively safe treatment option for patients with refractory septic shock.

These improvements in treatment strategies for septic patients reflect the newly heightened understanding of molecular events that underlie sepsis pathophysiology. It is anticipated that forthcoming innovations in therapy [see Table 7] will lead to further improvements in outcome in severe sepsis/septic shock. The genomics era has already provided insights into variations in the risk of developing sepsis<sup>104</sup> and differential responses to therapeutic agents.<sup>105</sup> Much work remains to be done to provide optimal care of the ever-growing septic patient population.

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Figures 1 and 2 Seward Hung.