Severe Sepsis and Septic Shock
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This chapter reviews the remarkable recent advances in the understanding of the molecular basis that underlies the pathophysiology of sepsis. This knowledge has improved diagnostic techniques and introduced new therapeutic agents into the standard management of patients with severe sepsis/septic shock. The current treatment regimens for sepsis are discussed, and the evidence to support each major treatment strategy is outlined in detail. Research priorities to further the optimal management of septic shock in the future are highlighted.

Sepsis: Definitions and Epidemiology

Definitions

The terminology used to describe the septic process is, by necessity, imprecise and lacking in analytical clarity since there is no single, universally accepted, diagnostic or confirmatory test for sepsis. This has plagued the field of sepsis research as the majority of intensive care specialists in a recent survey felt that the current definitions are inadequate and frequently miss the correct diagnosis. The loosely applied term *sepsis* is used to connote a syndrome when a patient develops a deleterious systemic host response to an infectious process. In its early stages, sepsis can be difficult to distinguish from an appropriate and localized inflammatory reaction to an uncomplicated infection. The innate immune response and coagulation networks evolved to defend the host from blood loss and generalized infection following minor injury. These same inflammatory and clotting systems can be detrimental when they become excessive or dysfunctional, as they often become following major injury or systemic infection.

The clinical syndrome of sepsis becomes more readily recognizable and distinguishable for controlled inflammation when overt signs of systemic inflammatory responses, tissue hypoperfusion, and organ dysfunction develop. According to current consensus definitions, sepsis accompanied by objective signs of organ dysfunction is classified as *severe sepsis*. It is often apparent only in retrospect that the patient was "becoming septic," and that subtle, telltale signs were progressing to a potentially devastating pathologic state such as severe sepsis. *Septic shock* is defined as sepsis complicated by organ dysfunction and systemic hypotension refractory to an adequate fluid challenge. These definitions are independent of the nature of the infecting microorganism, and they correctly acknowledge the central role of the host inflammatory and coagulation response rather than microbial factors in the pathogenesis of sepsis. A brief summary of the recommended terminology of sepsis definitions is listed in Table 15.1. While these consensus definitions are imperfect and have limitations, they have stood the test of time, and the sepsis definitions in common parlance today are still useful as working definitions for clinical use and for comparative clinical trials.

Epidemiology and Secular Trends

Sepsis, and the associated multiorgan failure that often accompanies this systemic inflammatory process, remains a leading cause of mortality in the intensive care units (ICUs) worldwide. It is currently estimated that as many as 700,000 patients develop severe sepsis each year in the United States, with similar incidence rates in several European countries. The incidence of severe sepsis/septic shock has continuously increased over the past three decades, and the occurrence of sepsis likely will further increase over the next several decades as the population of elderly and vulnerable patients continues to expand. The mortality rate for fully developed septic shock remains between 35% and 45% despite recent improvements in treatment options and outcome. The outcome in sepsis is highly variable and dependent on a large number of preexisting and physiological elements; nonetheless, it is clear that this process alone accounts for hundreds of thousands of deaths per year.

The incidence of sepsis is increasing for several reasons, but primary among them is the fact that sepsis largely has become a disease of medical progress. While sepsis certainly...
TABLE 15.1. Classification and Working Definitions of Sepsis.

| Term                  | Definition                                                                 | Comments                                                                                                                                 |
|-----------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Bacteremia (or fungemia) | Presence of viable bacteria (or fungi) in the bloodstream                | Bacteremia or fungemia is not necessary or sufficient for the diagnosis of sepsis. Microorganisms may transit the bloodstream briefly and without clinical consequences; fatal septic shock may occur in the absence of documented bacteremia or fungemia. |
| Sepsis                | A clinical syndrome manifested as a deleterious host response to an infectious process | Infection (local or systemic) accompanied by a systemic inflammatory response (e.g., fever, leukocytosis, tachycardia, tachypnea). It may be difficult to distinguish a physiologic host response to infection from a deleterious (septic) response. |
| Severe sepsis         | Sepsis complicated by one or more major organ dysfunction(s)              | Sepsis-induced organ dysfunction (central nervous system dysfunction, acute lung injury, renal failure, hepatic dysfunction, coagulopathy, metabolic acidosis, cardiovascular dysfunction) remote from the site of active infection; this should be distinguished from preexisting organ dysfunction. |
| Septic shock          | Severe sepsis with systemic hypotension refractory to early fluid therapy | This is clinically defined as failure to maintain a systolic blood pressure above 90mmHg (or mean arterial pressure >65mmHg) following an adequate fluid challenge (>40ml/kg over 6h). |

Source: From Levy et al., by permission of Critical Care Medicine.

The human resource losses attributable to sepsis for affected patients, family members, and society in terms of years of life lost, long-term disability, and diminished quality-of-life indices are enormous and incalculable. Recent evidence indicates that the long-term disability suffered by survivors of sepsis and other critical illnesses is considerable. The financial implications in health care expenditures for the management of sepsis are daunting as well. Each episode of severe sepsis extends the average hospital length of stay by 11 additional days and costs approximately $40,000/episode. The added costs accrued from sepsis that develops in patients while hospitalized for other medical or surgical indications may be even higher. Angus and colleagues estimated that expenditures in the United States for sepsis alone account for an incremental annual cost of nearly $17 billion.

Sepsis Pathogenesis

Predisposing Factors

Severe sepsis and septic shock usually arise in an unexpected fashion in patients who have another primary illness, and the severity of the underlying illness is a principal determinant of the mortality rate attributable to sepsis. This relationship was first noted by Jackson and McCabe several decades ago, and it remains true today despite numerous advances and innovations in supportive care and in medical and surgical management. The source of the septic focus has repeatedly been shown to have a major impact on the risk of adverse outcome from sepsis. Catheter-related sepsis and urinary tract infections have the most favorable prognosis, while intraabdominal sites of sepsis and pulmonary sources of sepsis are associated with the worst outcome. The risk of disseminated infection and sepsis following the onset of tissue invasion by pathogens from an initial site of injury varies markedly depending on the type of infection, location and degree of tissue invasion, and the intrinsic viru-
lence of the causative pathogen. The likelihood of developing multiorgan dysfunction, hemodynamic compromise, and lethal septic shock after infection begins is heavily dependent on the antimicrobial defense capacity and fundamental nature of the individual host response to the microbial challenge. Many hereditary and acquired factors contribute to the risk of severe sepsis following similar types of microbial challenge. While it is widely appreciated that the elderly patient, the neutropenic patient, and the asplenic patient all have readily measurable differences in outcome when compared with the same type of systemic infection in an otherwise healthy young adult, it is increasingly apparent that much of the mortality risk from sepsis is actually determined by our genomic background.

An expanding array of polymorphisms in immune response and regulatory genes are known to potentially affect the risk of sepsis and its outcome. A major research priority in clinical research at present is the development of an information system that can rapidly and correctly identify and balance the influence of all the relevant genes and gene products that ultimately determine the fate of patients with systemic inflammatory states. The magnitude, dynamics, and complexity of interacting networks that contribute to acute inflammatory states such as sepsis indicate that deciphering this process in real-time patient care settings will be a challenge indeed. An entirely different conceptual framework on which to formulate a greater understanding of sepsis pathophysiology may be required to adequately integrate this information.

An initial attempt at accomplishing the goal of reanalyzing sepsis in the genomic era has been proposed as the PIRO system, which stands for predisposing factors, infection, response, and organ dysfunction. This classification system is depicted in Table 15.2 and is fashioned after the TNM (tumor, nodes, metastases) system in codifying malignant diseases. It is predicated on the hypothesis that breaking down sepsis into its component parts (the reductionist approach to complexity) will lead to an improved understanding of the mechanisms that underlie sepsis itself. Intuitively, a classification scheme that adequately separates a number of important and easily recognizable subgroups of patients with very different risk factors for the development of sepsis, and risk of death from sepsis, is an appealing strategy in better understanding sepsis in general.

### Microbial Factors

#### Microbial Mediators

The microbiology of sepsis (or the I in the PIRO system) has changed over the past 50 years from what was once a primarily gram-negative bacterial infection in the 1950s through the 1980s (previously termed _gram-negative sepsis or endotoxemic shock_) to what is now principally a gram-positive bacterial process. The ubiquitous use of vascular catheters, other implantable devices, progressive antibiotic resistance among gram-positive bacteria, and improved antimicrobial agents against gram-negative bacterial pathogens have all contributed to the progressive emergence of gram-positive bacterial pathogens as the major causative microorganisms of sepsis by the beginning of the 21st century.

Fungal organisms are increasingly recognized as important pathogens as a cause of sepsis in ICU patients, and these infections are associated with a markedly increased mortality rate compared to bacterial sepsis. Polymicrobial infections account for up to 30% of severe sepsis and are primarily related to complex infections such as a contaminated wound, perforated viscus, or intraabdominal abscess. No clear microbial agent is recognized in approximately 15% of septic patients, and this is most often attributable to the widespread use of empiric antibiotic therapy that obscures culture documentation of infection. Translocation and circulation of microbial mediators in the absence of viable and cultivable

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**TABLE 15.2. The PIRO Conceptual Framework for the Study of Sepsis.**

| Category          | Specific element                                                                 | Comments                                                                                     |
|-------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| P: Predisposing   | Recognition of preexisting conditions in sepsis pathogenesis (immunodeficiency, | The use of genomics and proteomics may define genetic polymorphisms of the immune response to  |
| factors           | diabetes, cancer, chronic disease states, medications), genetic factors, nutritional,| systemic infection; need to recognize important patient subgroups based on baseline predisposing |
|                   | age, and gender differences                                                      | factors.                                                                                     |
| I: Infection      | Accounts for differences in the site of infection, quantity, and intrinsic virulence | Outcomes differ in sepsis depending on the site of infection and number and type of pathogen. Rapid |
|                   | of each type of infecting microorganism; different causative organisms induce    | microbial detection systems (LPS, lipopeptides, fungal elements, bacterial DNA or RNA) may direct |
|                   | different signaling networks within the innate immune and coagulation systems    | sepsis therapies according to the nature of the pathogen.                                    |
| R: Response       | Mortality risk primarily determined by the patient's response to sepsis, optimal  | Markers of inflammation (PCT or IL-6); status of host responsiveness (e.g., HLA-DR, TNF receptor, or TLR |
|                   | host mediator-targeted therapy predicated on ability to rapidly assess individual | density); or gene transcript profiles by genomics and proteomics may guide individualized therapy in the |
|                   | host responses                                                                   | future.                                                                                     |
| O: Organ dysfunction | Preexisting organ damage and variations in the pattern of organ dysfunction affect | Dynamic measures of organ-specific cellular and microcirculatory responses to infection or insult |
|                   | outcome in sepsis; organ damage caused by microbial pathogen or its toxins requires | (apoptosis, cytotoxic hypoxia, cell stress, and energy depletion) may provide a system to guide therapy for |
|                   | different approach than remote organ injury from host immune response            | individual patient needs.                                                                       |

*Source: Adapted from Levy et al., by permission of Critical Care Medicine.*

*HLA, human leukocyte antigen; IL, interleukin; LPS, lipopolysaccharide; PCT, procalcitonin; TLR, Toll-like receptor; TNF, tumor necrosis factor.*
Role of 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. An endotoxin-deficient strain of Neisseria meningitidis has been isolated that is viable and is 10- to 100-fold less potent an inducer of cytokine production than wild-type bacteria. Lipopolysaccharide 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.

Humans are one of the most susceptible species to the profound immunostimulant properties of endotoxin, which may be lethal following intravenous challenge in minute doses. Whether endotoxin is shed from the membrane of viable organisms as microparticles or bound to the cell wall of intact bacteria, an intense systemic inflammatory response results. Endotoxin in the prototypic pathogen-associated molecular pattern (PAMP) that functions to alert the host's innate immune defenses to the presence of invading gram-negative bacteria. It is the host response to the systemic release of endotoxin (or other PAMPs), rather than the endotoxin itself, that accounts for its potentially lethal consequences.

In human plasma, endotoxin immediately comes in contact with endotoxin-binding proteins, the most important of which is LPS-binding protein (LBP). This protein facilitates the transfer of LPS to the surface of immune effector cells expressing the anchoring receptor molecule CD14. Another endogenous LBP in plasma is bactericidal permeability-increasing protein (BPI), which is principally expressed on neutrophil membranes and primary granules. Bacterial permeability-increasing protein binds with high affinity to LPS and is a potent inhibitor of endotoxin activity. The concentration of LBP in the plasma is two to three orders of magnitude higher than that of BPI, and therefore, most of the LPS released in the plasma binds to LBP and is efficiently carried to myeloid cells in its active form. The BPI functions as an endogenous antiendotoxin molecule, and systemic infusions of high levels of BPI may become a treatment strategy for endotoxin-induced injury.

The long-sought-after primary cellular receptor for endotoxin on immune cells has been identified. The Toll-like receptors (TLRs) are type 1 transmembrane receptors and are now known to be the receptors for multiple microbial structures such as endotoxin, peptidoglycan, bacterial lipopeptides, viral and bacterial nucleic acids, flagella, and lipoteichoic acid. The TLRs belong to a network of pattern recognition receptors of the innate immune system that alert effectors cells to the presence of a microbial pathogen. This system includes up to 11 TLRs, CD14, and components of the alternate complement system and mannose-binding lectin system (Table 15.3).

Table 15.3. Human Toll-like Receptors, Their Ligands, and Other Pattern Recognition Receptors.

| Receptor | Major cell type | Known actions and recognized ligands |
|----------|-----------------|-------------------------------------|
| TLR1     | Myeloid cells, T and B lymphocytes, NK cells | Forms heterodimers with TLR2 for bacterial lipopeptide, outer surface proteins of Borrelia spp., and possibly other microbial ligands |
| TLR2     | Myeloid cells, T cells | Bacterial and Mycoplasma lipopeptide, peptidoglycan, lipoarabinomannan from Mycobacteria, lipoteichoic acid, fungal cell wall components, LPS of spirochetes |
| TLR3     | Dendritic cells, epithelial cells | Double-stranded viral RNA probably signals from inside endosomal vacuoles |
| TLR4     | Myeloid cells | LPS, respiratory syncytial virus proteins, HSP60, fibrinogen, heparan sulfate |
| TLR5     | Myeloid cells, epithelial cells | Flagellin from gram-positive or gram-negative bacteria |
| TLR6     | Myeloid cells, dendritic cells | Forms heterodimers with TLR2 in recognition of Mycoplasma lipopeptides and fungal elements [zymosan] |
| TLR7     | B cells, plasmacytoid dendritic cells | Binds to single-strand ss RNA in mice (? humans); binds to antiviral compounds, imidazooquinolines |
| TLR8     | Myeloid cells, dendritic cells | Recognizes ssRNA in humans inside intracellular endosomes; binds imidazooquinolines |
| TLR9     | B cells, plasmacytoid dendritic cells, epithelial cells | Unmethylated CpG motifs in microbial DNA; signaling occurs inside endosomal vacuoles |
| TLR10    | B cells, myeloid cells | Unknown, may interact with TLR2 to form heterodimers |
| TLR11    | Macrophages, uroepithelial cells | Recognizes uropathogenic bacteria in the urogenital tract in mice (? humans) |
| CD14     | Myeloid cells | Recognizes LPS, peptidoglycan, lipoarabinomannan, fungal antigens, binds with TLRs for cell signaling |
| Alternate C pathway | Plasma proteins | Pathogen-associated molecular patterns that are exposed to the C3 thiolester bond |
| MBL      | Plasma protein | Recognizes mannosides expressed on bacterial, fungal, viral surfaces and activates C4 and C2 |

C, complement; HSP, heat-shock protein; LPS, lipopolysaccharide; MBL, mannose-binding lectin; TLR, Toll-like receptor.

Source: Adapted from Cristofaro and Opal, by permission of Expert Opinion on Therapeutic Targets.
The principal endotoxin transmembrane receptor is TLR4.\(^4^3\) It functions along with an extracellular adaptor protein known as MD2 and a critically important pattern recognition receptor CD14 that anchors microbial antigens to the surface of myeloid cells.\(^3^9,^5^1\) These surface receptor molecules aggregate on membrane regions known as lipid rafts where the intracellular signaling process begins. The precise mechanisms by which TLR4 activates gene transcription of cytokines, acute-phase proteins, coagulation, and nitric oxide synthase [NOS] are known in considerable detail (Fig. 15.1),\(^4^6\) although other regulatory and accessory pathways of gene induction and control have not yet been fully characterized.\(^5^3\) A well-characterized series of tyrosine and threonine/serine kinases is activated by TLR4 engagement with LPS, and this intracellular signaling leads to phosphorylation of IκB (inhibitor of nuclear factor kappa B [NF-κB]). This releases the transcriptional activator NFκB from the cytoplasm and allows it to translocate into the nucleus. The NFκB and a number of other of transcriptional activators are transferred to the nucleus, where hundreds of genes are activated or suppressed in response to the presence of endotoxin.\(^5^2,^5^3\) Details of these events and interactions are important as they form the molecular basis for novel therapeutic agents to treat sepsis.

The receptor TLR2 recognizes a large number of bacterial, fungal, mycobacterial, and mycoplasma surface structures in heterodimeric combination with either TLR1 or TLR6.\(^5^4\) Toll-like receptor 9 is the cellular receptor for unmethylated CpG motifs found in bacterial DNA,\(^5^5\) while TLR3 recognizes double-strain viral RNA,\(^5^6\) and TLR8 detects single-strand RNA.\(^4^7\) Also, TLR5 recognizes bacterial flagellin found on motile gram-positive and gram-negative bacteria.\(^5^7\)

The TLRs belong to the pattern recognition molecules’ innate immune system and initiate this rather nonspecific, antimicrobial defense system. It lacks the precision of the highly specific and clonal acquired immune system (B cells and T cells), yet its rapid reaction time in phagocytosis and clearance of pathogens in the early phases of microbial invasion makes the innate immune response a critical host defense mechanism. Excessive activation and disordered regulation of the innate immune system and its cellular components (neutrophils, monocytes, macrophages, natural killer [NK] cells) are primarily responsible for the pathogenesis of early septic shock.\(^2^3,^3^8\) Elements of the acquired immune system and defects in adaptive immunity may play a pivotal role in toxic shock syndromes\(^4^8\) and in the later stages of sepsis (the late immune-suppressive phase of sepsis).\(^5^9\)

**Bacterial Superantigens**

Another important microbial mediator in some forms of septic shock from gram-positive bacterial pathogens is bacterial superantigen. Superantigens are a unique group of microially derived protein antigens found in some streptococci,
Staphylococci, and perhaps other pathogens; each possesses an unusual immunologic property. These superantigens have the capacity to rapidly activate large numbers of CD4+ T cells by circumventing the conventional antigen-processing and presentation system of adaptive immunity. Conventional antigen-presenting cells (APCs) and undergo limited proteolysis. They are then processed within the endosomal component of macrophages or dendritic cells. Appropriate size peptide sequences of these antigens [epitopes] are then processed and inserted into the central groove of major histocompatibility (MHC) class II molecules on the membrane surface of APCs. Specific, clonotypic CD4+ T cells that recognize each unique epitope are then activated. Clonal expansion of this small subset of T cells results in a physiologic immune response to the neoantigen. Superantigens, by contrast, do not undergo processing by APCs and bind directly to class II molecules outside the epitope-specific peptide groove on APCs. Superantigens then bind to the VB region of the T-cell receptor [TCR] on CD4+ T cells. This binding brings CD4+ T cells, and APC forms a bridge that then activates both the APC and T-cell populations expressing the appropriate VB region of the TCR. Conventional peptide antigens specifically stimulate about 1 in 10^5 circulating lymphocytes that can recognize its unique epitope. Superantigens such as the toxic shock syndrome toxin-1 from Staphylococcus aureus binds to the VB2 region of T cells that is found in up to 10%-20% of human lymphocyte populations. This activates large numbers of both lymphocytes and macrophages, and the synthesis and release of proinflammatory cytokines proceeds in an uncontrolled fashion. Staphylococcal and streptococcal strains can produce a variety of different superantigenic exotoxins capable of widespread immune activation if introduced into the circulation.

Superantigen-induced immune activation may terminate in a form of septic shock known as toxic shock syndrome if the source of the superantigen is not expeditiously removed. Polymicrobial infections that release both bacterial superantigens and endotoxin may be particularly injurious to the host. The systemic toxicity of bacterial endotoxin is magnified by immune activation by superantigens that prime the immune system to overreact to endotoxin signaling (Fig. 15.2). Peptidoglycan from the cell wall of bacteria, capsular antigens, lipoteichoic acid, lipopeptides, microbial DNA, viral RNA, fungal elements, microbial toxins, and procoagulant substances produced by microbial pathogens may all contribute to the pathogenesis of sepsis. Peptidoglycan and lipopeptides from gram-positive bacteria interact with CD14 molecules and activate inflammatory cells via TLR2 in a manner comparable to that observed by bacterial endotoxin. Moreover, gram-positive bacterial and fungal pathogens may induce hypotension with redistribution of blood flow and splanchnic vasoconstriction. The ischemia and reperfusion of blood vessels that supply the mucosal surfaces of the gastrointestinal [GI] tract may disrupt the permeability barrier to bacterial products. Translocation of microbial antigens, including bacterial endotoxin, may occur during periods of hypoperfusion of the GI mucosa. This injurious process has prompted interest in efforts to boost the GI mucosal barrier through immunonutrition, epithelial growth factors, and selective decontamination of the GI tract in critical illness.
Host Response

Cytokine Networks

Proinflammatory cytokines play a pivotal role in the pathogenesis of sepsis. In animal studies, the administration of human tumor necrosis factor-α [TNF-α], an endogenous monocyte-macrophage-derived protein, is potentially lethal, and pronounced hemodynamic, metabolic, and hematologic changes occurred when TNF-α was administered to human volunteers. Hypotension induced by even minute amounts of interleukin-1α (IL-1α) when given as an infusion to humans is a graphic demonstration of the pathologic potential of proinflammatory cytokines.

The major proinflammatory cytokines, TNF-α and IL-1β, function in concert with an expanding group of host-derived proinflammatory mediators and an equally impressive array of antiinflammatory mediators that work in a coordinated fashion to produce the systemic inflammatory response [see Table 15.4]. Cytokines and chemokines function as a network of communication signals among neutrophils, monocytes, macrophages, lymphocytes, and endothelial cells. Autocrine and paracrine activation amplifies cytokine signaling of the inflammatory response within the microenvironment once it is activated by a systemic microbial challenge (e.g., endotoxemia). Much of the proinflammatory response is compartmentalized within the proximal region of initial injury (e.g., lung tissue or peritoneum). If local control is not achieved, then the inflammatory response spills over into the systemic circulation, resulting in a generalized reaction with endothelial injury, coagulation activation, and remote organ injury. The endocrine-like effects of the circulating cytokines and chemokines maintain the generalized inflammatory process that typifies the septic state.

The proinflammatory mediators are activated in the early phases of sepsis [the first 12 to 24 h] and are rapidly countered by the endogenous antiinflammatory components of the systemic immune response. Cytokine antagonists, decoy receptors, soluble receptors, antiinflammatory cytokines, and downregulation of tissue receptors prevail in the later phases of sepsis.

Mice deficient in T cells and B cells respond to endotoxin challenge in the same manner as normal mice, indicating that neutrophils and monocyte-macrophage generated cytokines are sufficient to induce the early septic process. Lymphocyte activity and their cytokines and interferons become important in the regulation of later phases of sepsis and may ultimately determine the outcome in septic shock.

Immune-Refractory State of Sepsis

Important functional differences exist within CD4+ T cells. Activated, yet uncommitted, CD4+ T cells [TH0 cells] have two major pathways of functional differentiation. The T cells exposed to IL-12 in the presence of IL-2 are driven toward a TH1-type functional development. These cells produce large quantities of interferon-γ (IFN-γ), TNF-α, and IL-2 and promote a proinflammatory, cell-mediated immune response. Uncommitted CD4+ T cells exposed to IL-4 will preferentially develop into a TH2-type phenotype; TH2 cells secrete IL-4, IL-10, and IL-13. These cytokines promote humoral immune responses and attenuate macrophage and neutrophil activity.

The TH1-type cytokines suppress the expression of TH2-type cytokines. Interferon-γ inhibits the synthesis of IL-10; conversely, the TH2-cell-derived cytokine IL-10 is a potent inhibitor of TNF-α and IFN-γ synthesis by TH1 cells. The nature of the initial lymphocyte response is critical because the system tends to polarize over time into either a TH1- or

TABLE 15.4. Host-Derived Inflammatory Mediators in Septic Shock.

| Proinflammatory mediators                            | Antiinflammatory mediators                      |
|------------------------------------------------------|-------------------------------------------------|
| Proinflammatory cytokines:                           | Antiinflammatory cytokines:                     |
| TNF-α, interleukins-1, -2, -12, -18, lymphotoxin-α   | Interleukins-4, -6, -10, -11, -13                |
| Fas ligand                                            | Interleukin-1 receptor antagonist                |
| Proinflammatory chemokines:                          | Soluble cytokine receptors:                     |
| IL-8, MCP-1                                           | sTNF receptor, sIL-1 receptor, sIL-6R            |
| Interferon-γ                                          | Type 1 interferons (IFN-αβ)                      |
| Complement activators and components:                | Complement inhibitors:                          |
| C3a, C5a, MBL, C reactive protein                    | Cl inhibitor, factor H                           |
| Lipid mediators:                                     | Stress hormones:                                |
| Leukotriene B4, platelet-activating factor, oxidized  | Glucocorticoids, epinephrine, norepinephrine    |
| phospholipids, phospholipase A2                      | Prostaglandin E2, prostacyclin                   |
| Bradykinin, histamine                                | Antioxidants:                                   |
| Prooxidants                                          | Glutathione, selenium, uric acid                |
| Reactive oxygen and nitrogen species                 | Granulocyte colony-stimulating factor           |
| Granulocyte-macrophage colony-stimulating factor     | Macrophage colony-stimulating factor            |
| Macrophage migration inhibitory factor               | Decoy cytokine receptors (IL-1 type 2 R)        |
| Upregulation of receptors:                           | Downregulation of receptors:                    |
| TLR4, TLR2, CD14                                      | TLR4, MHC II, TNF R, glucocorticoid receptors   |
| Coagulation factors:                                 | Anticoagulants:                                 |
| Thrombin, factor Xa, tissue factor: FVIIa, fibrinogen,| Antithrombin, tissue factor pathway inhibitor,   |
| heparan sulfate, uPAR                                | activated protein C                            |
| High-mobility group box-1                            | Transforming growth factor-β                     |
|                                                      | Vagal cholinergic antiinflammatory reflex       |

MLB, mannos-binding lectin; MCP, monocyte chemoattractant protein; R, receptor; TLR, Toll-like receptor; uPAR, urokinase plasminogen activator receptor.
TH\textsubscript{1}-type response.\textsuperscript{73} Functional differentiation of CD8 cells has also been detected (CD8\textsuperscript{+} type 1 and type 2 cells).\textsuperscript{70} Cytotoxic T cells can induce apoptosis by surface expression of Fas ligand, which fixes to cell membrane Fas on target cells and via the release of perforins and granzymes. Regulation of T-cell activity in sepsis is clinically relevant. A generalized TH\textsubscript{2}-type response characteristically occurs after an initial septic insult. The stress hormone response in septic shock, with expression of adrenocorticotropic hormone, corticosteroids, prostaglandins, and catecholamines, promotes a TH\textsubscript{2} response after systemic injury.

Hotchkiss et al.\textsuperscript{59,72} have provided another potential explanation for the relative immune suppression (or immune paralysis) that often accompanies sepsis. Selective apoptosis of CD4\textsuperscript{+} T cells and B cells along with follicular dendritic cells is highly characteristic of severe sepsis. This selective loss of immune effector cells may contribute to the increased risk for secondary bacterial or fungal infection in the later phases of sepsis. Neutrophils are naturally apoptotic cells, and inflammatory cytokines and growth factors actually cause delayed apoptosis of neutrophils in sepsis.\textsuperscript{73} Accelerated caspase function and excess apoptosis also occur in intestinal epithelial cells, compromising mucosal permeability barrier function of the gut.\textsuperscript{59} This pathophysiologic state is further aggravated by sepsis-induced endotoxin tolerance (or reprogramming)\textsuperscript{74} and deactivation of monocytes, macrophages, and neutrophils by cytokine inhibitors such as IL-1 receptor antagonist and antiinflammatory cytokines such as IL-10.\textsuperscript{75} Depressed expression of MHC class II antigens (HLA-DR), TNF receptors, TLRs, and perhaps other cell surface activation signals may contribute to this functionally immunosuppressed state.\textsuperscript{59}

Role of Nitric Oxide

Nitric oxide (NO) is a freely diffusible gas and highly reactive free radical with a short half-life (1-3 s).\textsuperscript{76} It has an essential role in the pathophysiology of septic shock. Nitric oxide is generated by one of three isoforms of NOS (endothelial, neuronal, and inducible NOS).\textsuperscript{77} Regulation of the human NOSs is complex. Full expression of the inducible form of NOS requires TNF-α, IL-1, LPS, and probably other regulatory elements. Nitric oxide is the major endothelial-derived relaxing factor that initiates the systemic hypotension observed in septic shock. Nitric oxide activates guanylate cyclase, which increases cyclic guanosine monophosphate levels inside vascular smooth muscle cells. The resultant smooth muscle relaxation in precapillary arterioles lowers peripherial vascular resistance.\textsuperscript{76}

The other major physiologic effects of NO in septic shock are increased intracellular killing and regulation of platelet and neutrophil adherence. In the presence of reactive oxygen intermediates such as superoxide anion, NO leads to the formation of peroxynitrite. Peroxynitrite decays intracellularly into highly cytotoxic molecules, including hydroxyl radicals and nitrosyl chloride. These reactive nitrogen intermediates (RNI) activate an intracellular enzyme known as PARP (poly ADP-ribose polymerase). This enzyme rapidly depletes the cellular contents of adenosine triphosphate (ATP), resulting in cellular energy starvation.\textsuperscript{78} These RNIs also induce lipid peroxidation and cause loss of cell viability.\textsuperscript{76} Nitric oxide also inhibits a variety of metalloenzymes and essential enzymes in the tricarboxylic acid cycle, the glycolytic pathway, DNA repair systems, and electron transport pathways.

As with many other elements of the host inflammatory response, NO may have both advantageous and disadvantageous properties in sepsis. Nitric oxide regulates microcirculation to vital organs and contributes to intracellular killing of microbial pathogens. Excess and prolonged release of NO, however, results in systemic hypotension and contributes to septic shock. Regulation of NO synthesis remains an experimental target in the treatment of sepsis, but preservation of the favorable attributes of NO in the microcirculation while limiting its toxic effects remains a major therapeutic challenge.\textsuperscript{77}

Role of the Coagulation System

Activation of the coagulation system, generation of a consumptive coagulopathy, systemic fibrinolysis, and diffuse microthrombi are potentially life-threatening complications of severe sepsis.\textsuperscript{79} The innate immune system and the coagulation system coevolved as early defense systems against microbial invasion and tissue injury and remain highly integrated and coregulated. The tissue factor pathway (formerly known as the extrinsic pathway) is the principal mechanism by which the coagulation system is activated in human sepsis.\textsuperscript{80} The contact factors (also known as the intrinsic pathway) play an accessory role as amplifiers of clotting once thrombin is generated (Fig. 15.3). Intravascular fibrin deposition impairs blood flow, promotes neutrophil and platelet adherence, and may contribute to at least some forms of multiorgan failure in sepsis.\textsuperscript{81} Depletion of coagulation factors and activation of plasmin, antithrombin, and activated protein C may result in a hemorrhagic diathesis in some septic patients. Depletion of endogenous anticoagulants and impaired fibrinolysis may generate a procoagulant state and portend a poor prognosis.\textsuperscript{82}

Inflammatory signals generated by intravascular thrombin generation and fibrin deposition contribute to microvascular injury as neutrophils and monocytes are drawn into areas of clot formation. Specialized receptors known as the protease-activated receptors (PAR 1-4) recognize thrombin, tissue factor-factor VII complex, factor X, and activated protein C.\textsuperscript{83} These receptors are present on endothelial surfaces, neutrophils, and platelets and initiate the release of inflammatory cytokines, chemokines, platelet-activating factor, and P-selectin, among other mediators. The clotting system works in concert with the inflammatory networks in an attempt to localize the site of injury or infection from the rest of the host tissues. Extensive injury or failure of the early local control mechanism leads to generalized coagulation activation, inflammation, and the pathologic process of severe sepsis and septic shock.\textsuperscript{84}

Clinical trials with recombinant tissue factor pathway inhibitor,\textsuperscript{85} activated protein C,\textsuperscript{86} and plasma-derived antithrombin\textsuperscript{87} for treatment of sepsis resulted in disappointing results except for recombinant human activated protein C (drotrecogin alfa activated). This treatment strategy yielded a statistically significant survival benefit in a multicenter clinical trial with 1690 patients. The 28-day all-cause mortality in the recombinant human activated protein C group was 24.7%, while the mortality rate in the placebo group was
1. Neutrophil Activation (Cytokines, Complement)

2. Neutrophil Rolling (Selectins)

3. Neutrophil Adherence (β2 Integrins (CD11/CD18))

4. Transmigration

FIGURE 15.3. The interactions between coagulation and inflammation in sepsis. Solid bold arrows, major coagulation pathways; thin solid arrows, accessory and amplification clotting pathways; open arrows, inflammation and clotting interactions; dashed open arrows, inhibitory pathways; TFP, tissue factor; tPA, urokinase plasminogen activator; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; Fbg, fibrinogen; PAR, protease-activated receptor; IL, interleukin; TNF, tumor necrosis factor; MIF, macrophage migration inhibitory factor; MCP-1, monocyte chemotactic protein-1.

30.9% [P < .005, with a 6.1% absolute reduction in mortality]. This drug received regulatory approval in 2002 for the use of drotrecogin alfa activated in severe sepsis/septic shock at high risk of mortality (e.g., multisystem failure or an APACHE [Acute Physiology and Chronic Health Evaluation] II score of 25 or greater). The precise mechanism of action of recombinant human activated protein C that accounts for its beneficial effects is not entirely clear, but it is not likely to be its direct anticoagulant activity. Heparin alone and other anticoagulants such as hirudin have not been shown to improve outcome in clinical settings or experimental models of sepsis, and all of these endogenous anticoagulants have antiinflammatory properties. Activated protein C also has profibrinolytic activity and antiapoptotic activities on endothelial cells in experimental systems, which may spare the endothelial surface for the injurious effects of systemic inflammation and disordered coagulation. Clinical investigations with antithrombin, tissue factor pathway inhibitor, and other coagulation inhibitors continue as possible treatment regimens for specific subgroups of septic patients.

MONOCYTE, PLATELET, NEUTROPHIL, AND ENDOTHELIAL CELL INTERACTIONS IN SEPSIS

The recruitment of neutrophils, platelets, and other inflammatory cells to an area of localized infection or clot formation is an essential component of the host innate immune response. Localization and eradication of invasive microorganisms at the initial site of injury is the primary defense strategy against microbial pathogens. This physiologic process may become deleterious if diffuse neutrophil–endothelial cell interactions occur throughout the circulation in response to systemic inflammation. The mechanisms responsible for the migration of neutrophils from the intravascular space into the interstitium, where invasive microorganisms are found, are depicted in Figure 15.4. Activated neutrophils degranulate and expose endothelial surfaces and surrounding structures to reactive oxygen and nitrogen intermediates, and a number of lytic proteases, including elastase. This process involves ongoing communication between endothelial surfaces and inflammatory cells. The process is initiated by the selectins and culminated by engagement of neutrophil β2 integrins (CD11/CD18) and adhesion molecules on endothelial cells such as...
intercellular adhesion molecule-1 and -2. Neutrophil egress commences and chemotactic factors direct phagocytic cells to the site of microbial infection. Platelet and monocyte infiltration follow and provide additional inflammatory signals, adherence molecules, and procoagulant surfaces for clot formation and cell migration. This process may lead to diffuse endothelial injury in the face of generalized systemic inflammatory responses. Regulation of events at the neutrophil-endothelial interface is an important area for therapeutic intervention in the management of sepsis.79,81,84,88,91

OTHER MEDIATORS OF SEPSIS

It has been discovered that several host-derived mediators may contribute to the pathogenesis of septic shock. Macrophage migration inhibitory factor (MIF) is a late mediator induced by glucocorticoid excess; it has many proinflammatory actions on effector cells, including the capacity to upregulate TLR4 expression,93 impair myocardial function,94 delay neutrophil apoptosis,95 and contribute to lethal septic shock.96 Inhibitors of MIF may have a potential therapeutic role in human sepsis.94,96

High-mobility group box-1 [HMGB-1] protein is a late-acting cytokine-like DNA-binding protein that appears to contribute to late-onset inflammatory activities in septic shock.97,98 Inhibitors of HMGB-1 demonstrate some therapeutic benefit in experimental sepsis.99 Complement components, particularly the chemoattractant factor C5a,100 and loss of the regulatory element C1 esterase inhibitor91 can produce vasodilatation and may participate in the pathogenesis of septic shock. The triggering receptor expressed on myeloid cells TREM-1100 and NOD1/NOD2 [nucleotide-binding oligomerization domain protein]102 are additional, recently identified, signaling systems that mediate inflammatory signals independent of the TLRs and may play a pathogenic role in the initiation of the septic process. The cholinergic antiinflammatory system is a well-characterized vagally transmitted mechanism by which the nervous system is able to directly modulate host macrophage inflammatory signals via a nicotinic receptor-mediated process.103 This neuronal–immune communication system may also prove to be amenable to therapeutic modulation in the care of septic patients.

Diagnostic Methods for Severe Sepsis/Septic Shock

Fully developed septic shock is obvious to the clinician, yet the early phases of severe sepsis and even septic shock may be quite subtle even to experienced clinicians. Early symptoms include confusion, apprehension, or decreased sensorium. Sudden and unexplained dyspnea [respiratory alkalosis] is a frequent early event, and it is often missed or attributed to other causes [congestive heart failure, anemia, pulmonary embolus, bronchial plugging, etc.]. Fever is usually, but not invariably, present. Hypothermia in fact is a more specific and reliable finding; its presence portends an unfavorable prognosis. An unexplained decrease in urinary output, sudden onset of cholestatic jaundice, unexplained metabolic acidosis, excessive bleeding at venipuncture sites, or even sudden unexplained hypotension may be the presenting finding in septic shock. Clinicians need to recognize these early signs and symptoms since successful outcomes from severe sepsis/septic shock depend on early recognition and rapid intervention.2

Myriad clinical, laboratory, and hemodynamic abnormalities are recognized in septic shock (Table 15.5). There is no single clinical or laboratory test that is pathognomonic of septic shock; therefore, the clinical diagnosis of sepsis remains a challenging problem.1 Blood cultures need not be positive [and reveal no pathogen in about two-thirds of septic patients], leukocytosis or neutropenia may occur, hyperglycemia, eu- glycemia, or hypoglycemia may be observed; and a variety of acid-base abnormalities may occur. It is the progressive evolution of a constellation of signs and symptoms that leads to a clinical 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. Vasodilatation within the peripheral vascular system is principally related to increased NO synthesis; however, downregulation of adrenergic receptors with progressive loss of catecholamine sensitivity, excess production of the vasoactive mediators histamine, adrenomedullin, platelet-activating factor, and bradykinin, and deficiency of vasopressin all contribute to reduced vascular tone in sepsis.84,100,104-106 The heart attempts to compensate for the loss of systemic vascular tone despite diminished myocardial performance even in the early phases of septic shock.100 Without adequate intervention, circulating blood volume is continually lost into the interstitial spaces and intracellular locations. The heart cannot compensate indefinitely as myocardial depressant factors [NO, MIF, IL-6, TNF, other factors] are released, and cardiac performance deteriorates. Late septic shock is marked by systolic hypotension despite intense peripheral vasoconstriction and reduced cardiac index.93,94,100

Septic shock may be associated with a loss of normal autoregulation within the microcirculation, with an imbalance between oxygen delivery and oxygen consumption.107 A supply-dependent dysoxia may occur, and cytopathic hypoxia108 from diminished oxygen utilization may develop as well. Attempts to enhance oxygen delivery in sepsis to supranormal levels have not improved outcomes,5,109 but a controlled clinical trial of early goal-directed resuscitation found rapid restoration of tissue perfusion and oxygen delivery remains a critically important target in sepsis therapy.110

Experimental Diagnostic Methods and Biomarkers for Sepsis

Since timely intervention is essential for successful outcomes in severe sepsis/septic shock, a concerted effort has been undertaken to improve the early diagnostic tools available to detect sepsis. Improved blood culture methods or measurement of plasma endotoxin levels may have diagnostic utility.111 Circulating levels of bacterial superantigens can be detected in selected patients with toxic shock syndrome.112 Interleukin-6 has been considered an indicator of cytokine activation as its synthesis is induced by TNF-α and IL-1β. Patients with elevated IL-6 levels appear to respond favorably to anticytokine therapies.113 In several studies,113-115 elevations of IL-6 or failure of IL-6 levels to decline over time have been associated with poor outcome. Unfortunately, the variability and lack of specificity or IL-6 measurement limits its reliability as a diagnostic method for septic shock.
TABLE 15.5. Characteristic Hemodynamic and Laboratory Findings in Severe Sepsis.

| Parameter                        | Common findings       | Clinical interpretation and implications                                      |
|----------------------------------|-----------------------|--------------------------------------------------------------------------------|
| Mixed venous O₂ saturation       | <70%                  | Low mixed venous O₂ indicates inadequate O₂ delivery to tissues in sepsis     |
| Cardiac index [cardiac output/m² [surface area]] | >4 l/min/m²            | Cardiac index elevated in early septic shock may be depressed in late septic shock |
| Pulmonary arterial wedge pressure [PAWP] | 4-10 mmHg            | Volume resuscitation should continue until return of normal MAP or PAWP reaches 12-15 mmHg |
| Systemic vascular resistance [SVR] | <800 dyne/s/cm⁻⁵      | SVR characteristically low in early septic shock secondary to peripheral vasodilation |
| Oxygen delivery [D₉]             | ≤100 ml/min/m²        | Goal of treatment is to provide sufficient D₀ to maintain adequate mixed venous O₂ saturation |
| Cl x Arterial O₂ content         | <550 ml/min/m²        | Poor prognostic factor in sepsis, increased bleeding risk; thrombocytopenia may be accompanied by DIC |
| Platelet count                   | <100.000/μl           | Acute stress response (hyperglycemia), inhibition of hepatic gluconeogenesis [hypoglycemia] |
| Glucose                          |                       | Coagulopathy often seen with systemic endotoxin release; coagulation activation is almost uniform in sepsis but clinically overt DIC is uncommon |
| Clotting measurements            | Elevated PT, aPPT, d-dimer, FDPs, low fibrinogen, AT, PC | Hypermetabolism, hyperperfusion of tissues, inhibition of pyruvate dehydrogenase |
| Plasma lactate                   | (>2.2 mmol/l)         | Acute-phase proteins and products of immune cells, variable levels, sensitive but not specific indicators |
| C-reactive protein, procalcitonin, IL-6 | Elevated          | Measurements of O₂ content and mixed venous O₂ saturation useful in management to ensure adequate tissue oxygenation and fluid resuscitation |
| Arterial blood gases             | Respiratory alkalosis (early), metabolic acidosis (late) |                                                                             |

aPPT, activated partial thromboplastin time; AT, antithrombin; DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; IL, interleukin; PC, protein C; PT, prothrombin time.

Procalcitonin (PCT) is the propeptide of calcitonin, and under pathological conditions of systemic inflammation PCT is produced in abundant amounts by a variety of tissues. A specific protease cleaves procalcitonin into calcitonin, katanalcin, and an amino-terminal peptide. Procalcitonin has many favorable attributes as a potential marker for sepsis. It has a long half-life (approximately 24 h) and will increase from undetectable levels to greater than 100 ng/ml in severe sepsis/septic shock. Higher levels are associated with more severe systemic infection. The diagnostic and therapeutic value of PCT measurement needs to be tested in large clinical trials to determine its ultimate clinical applicability. The usefulness of plasma C-reactive protein, clotting factors, platelet counts, and plasma lactate levels are listed in Table 15.5. It is anticipated that progress in real-time functional genomics and proteomics in the near future will greatly aid the early recognition of incipient sepsis in patients, although the level of complexity and heterogeneity in host responses remain major, unsolved challenges in this field of medical informatics.

Organ Dysfunction in Sepsis

One of the most remarkable and characteristic findings in sepsis is the development of organ injury remote from the initial site of infection. The development of one or more organ dysfunctions at the onset of severe sepsis, or over the course of sepsis, is a poor prognostic factor and major determinant of outcome (Table 15.6). The diffuse endothelial injury, proapoptotic signals, immune dysregulation, and coagulopathy induced from septic shock conspire in concert to produce organ dysfunction distant from the original site of infection. It is generally assumed that the activation signals in the pathogenesis of multiorgan injury derive from plasma factors (e.g., proinflammatory cytokines, complement, phospholipid mediators), but cellular signals from circulating blood components or neuroendocrine signals may also contribute to remote organ injury.

Inadequate blood supply to vital tissues likely contributes to organ dysfunction. The failure of the microcirculation to maintain tissue viability is related to hypoperfusion, 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 NO, reactive oxygen and nitrogen intermediates, proinflammatory cytokines, activated cytotoxic T cells and NK cells, and inducers of apoptosis may directly damage endothelial surfaces.

Acute lung injury occurs as a result of damage to the pulmonary vascular circulation and the alveolar-capillary membranes. The acute respiratory distress syndrome (ARDS) remains a major cause of morbidity and mortality in septic shock. Avoidance of barotrauma and volutrauma, avoidance of oxidant injury, maintenance of functional alveolar capillary units through position change (prone position), judicious
TABLE 15.6. Organ Dysfunction Syndromes that May Accompany Severe Sepsis.

| Organ system         | Clinical-metabolic abnormalities                                                                 | Histopathologic findings                                                                 |
|----------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Immune system        | Initial activation of innate immunity and late depression of innate and adaptive responses       | Adherence and extravasation and delayed apoptosis of neutrophils, selective loss of B cells, CD4+ T cells, and follicular dendritic cells |
| Musculoskeletal system | Muscle tenderness, loss of muscle mass and power                                                  | Increased muscle catabolism, progressive loss of somatic muscle tissue                    |
| Central nervous system | Encephalopathy, decreased sensorium                                                                 | Cerebral edema, microthrombi                                                              |
| Cardiovascular       | Decreased myocardial performance; myocardial depressant factors (TNF, IL-1, IL-6, nitric oxide) | Altered calcium influx, interstitial edema, myocardial hibernation                        |
| 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                                              |
| Endocrine            | Relative adrenal insufficiency, adrenal hemorrhage, decreased vasopressin output, thyroid abnormalities | Focal or diffuse hemorrhage, ischemic necrosis of adrenals, increased vascular sensitivity to vasopressin |
| Hepatobiliary system | Cholestatic jaundice, acute phase protein response, decreased clotting factors, hepatic metabolism of drugs | Zonal necrosis, acalculous cholecystitis                                                  |
| Gut                  | Translocation of endotoxin and microorganisms, decreased motility, increased permeability         | Diffuse interstitial edema, breaks in the epithelial membrane integrity, mucosal necrosis |

Initial Resuscitation

Fluid resuscitation is an essential first step in the management of septic shock. The loss of vasomotor tone and increased vascular permeability necessitate immediate correction to maintain tissue perfusion and provide adequate circulating blood volume. Debate has raged for decades over the relative merits of colloids 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 favored the use of saline solutions for volume expansion.121,122 A large, controlled clinical trial was undertaken recently in Australia and New Zealand in an effort to finally settle this debate.123 In a comparative study of nearly 7000 critically ill patients randomized to saline versus 4% albumin, the 28 day all-cause mortality was virtually identical (relative risk 0.99, \( P = n.s. \)). This would seem to have settled the debate except that a subgroup analysis of over 1200 septic patients suggested an improved outcome in the albumin group (30.7% vs. 35.3% saline group, \( P = .06 \)). Current consensus opinion still favors crystalloid solutions.3

The optimal amount of fluid therapy for patients in septic shock remains unclear, but a study by Rivers and colleagues110 supported the notion that early, aggressive, and goal-directed resuscitation fluids should be widely adopted as the standard approach to early fluid administration. They recommended a treatment regimen aimed at resolving lactic acidemia, recovery of mean arterial blood pressure over 65 mmHg, and return of central venous pressure above 8 mmHg and mixed venous oxygen saturation above 70% within 6h of initial presentation (grade B evidence).

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 mmHg is considered a reasonable starting point for those patients with a hemodynamic monitor in place (grade B).3

Use of Vasopressors for Blood Pressure Support

When patients fail to recover hemodynamic stability with fluid resuscitation alone, vasopressor agents are indicated to reestablish systemic arterial blood pressure. Dopamine has been the vasopressor agent of choice for several decades based on its presumed salutary effects on renal vasodilatation and its modest inotropic effects.12 The actual clinical value of dopamine compared with other vasopressor agents has been brought into question. Dopamine has complex effects as this catecholamine has its own receptors (D1 and D2 dopaminergic receptors) and variable affinities for α- and β-adrenergic receptors. The net effect of dopamine depends on many variables, including the receptor density in specific vascular beds, blood volume, and the rate of administration of drug dose used. Higher doses of dopamine increase the systemic vascular resistance by its effects on α-adrenergic receptors in the peripheral circulation. Dopamine may have adverse effects on splanchic blood flow,3,124 and there is no evidence in controlled trials that dopamine has any meaningful renal perfusion benefits.3 The use of dopamine as a “renal-sparing” agent is no longer justified (grade B).3,125

Norepinephrine is a potent vasoconstrictor that is 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 suggested that norepinephrine may actually increase urine output and creatinine clearance in septic patients.125 Norepinephrine may rapidly restore perfusion pressure within the glomerulus and result in improved glomerular filtration in patients with adequate fluid resuscitation. Current consensus opinion recommends either dopamine or norepinephrine as the initial vasopressor to correct hypotension in septic shock (grade D).3

Vasopressin is a potent vasopressor in refractory sepsis. Endogenous vasopressin levels rapidly fall in sepsis, and vasopressin has its own vascular receptors that are distinct from adrenergic receptors and often upregulated in sepsis.127 There is concern about diminished splanchic blood flow with higher doses of vasopressin, and myocardial ischemia may occur at infusion rates above 0.04 unit/min. Vasopressin may be considered in refractory shock, but it has not replaced dopamine or norepinephrine as the initial vasopressor in septic shock (grade E).3

Dobutamine, a β-agonist, may improve cardiac output and oxygen delivery in some patients in septic shock with persistently low cardiac output. Dobutamine may cause peripheral vasodilatation in septic patients, and it increases myocardial oxygen consumption by its inotropic effects.3

Another approach to improved tissue oxygen delivery is by use of vasodilators to open up poorly perfused capillary beds in patients with septic shock. Spronk et al.128 reported the use of nitroglycerin therapy in patients following intravascular volume resuscitation. Using an optical device to measure microcirculatory flow (orthogonal polarization spec-
Van den Berghe et al. demonstrated improved survival, shorter ICU stays, and less bacteremia in some surgical patients (grade D). Hyperglycemia can increase procoagulant activity on endothelial surfaces and may induce excess apoptosis.

Table 15.7. Suggested Initial Empirical Antibiotic Choices for Severe Sepsis.

| Suspected source of infection | Primary pathogens | Antimicrobial choice |
|-------------------------------|-------------------|---------------------|
| Intraabdominal infections     | Enteric aerobic gram-negative bacilli, enterococci, bowel anaerobes | Third- or fourth-generation cephalosporins or extended-spectrum penicillins or β-lactam-β-lactamase inhibitor with metronidazole or clindamycin; or carbapenem ± an aminoglycoside (alternative: fluoroquinolone) |
| Soft tissue infections        | Staphylococci, streptococci, mixed aerobes/anaerobes | Extended-spectrum penicillin or third- or fourth-generation cephalosporin or carbapenem or β-lactam-β-lactamase inhibitor; add clindamycin if streptococcal or staphylococcal toxic shock suspected |
| Community-acquired pneumonia | Streptococcus pneumoniae, S. aureus, Legionella, oral anaerobes | Third-generation cephalosporin with a macrolide (alternative: fluoroquinolones) |
| Hospital-acquired pneumonia  | S. aureus, Pseudomonas aeruginosa, gram-negative bacilli | Third-/fourth-generation cephalosporins, extended-spectrum penicillins ± an aminoglycoside (alternatives: fluoroquinolones, carbapenems, β-lactam-β-lactamase inhibitor) |
| Urinary tract infections      | Gram-negative aerobic bacilli, enterococci | Extended-spectrum β-lactam agent (third-generation cephalosporin or extended-spectrum penicillin); or a fluoroquinolone (add ampicillin or vancomycin if enterococci are present, linezolid if vancomycin-resistant enterococci) |
| Biliary tract infections      | Klebsiella spp., Escherichia coli, Clostridium | Extended-spectrum penicillin ± an aminoglycoside or fluoroquinolone (add metronidazole if hepatic abscess present) |
| Neutropenic patients          | P. aeruginosa, aerobic gram-negative bacilli | Extended-spectrum β-lactam agent ± an aminoglycoside or quinolone (add vancomycin if evidence of gram-positive infection) |

*Assuming no drug allergies an empiric choice should be based on local antibiotic resistance patterns.

offending focus of infection when possible (grade E recommendation). Suggested empiric choices of antimicrobial agents are listed in Table 15.7. In septic shock, combinations of bactericidal antimicrobial agents are generally given on an empirical basis, yet monotherapy with an effective broad-spectrum β-lactam or fluoroquinolone is usually sufficient (grade D). Ineffective empiric antibiotic choices for initial therapy for sepsis have adverse consequences, and therefore it is preferable to ensure adequate initial therapy and then deescalate to single narrow-spectrum agents after the causative organism is identified.

**Euglycemia, Steroids, and Recombinant Human Activated Protein C**

Other important supportive management techniques in sepsis are tight regulation of blood glucose levels and use of stress dose glucocorticoids in the presence of relative adrenal insufficiency. Hyperglycemia can increase procoagulant activity on endothelial surfaces and may induce excess apoptosis. Van den Berghe et al. demonstrated improved survival, shorter ICU stays, and less bacteremia in some surgical population with strict control over blood sugar (target was continuous euglycemia) versus conventional care in a cardiovascular ICU setting. It is recommended that blood sugar levels be kept under 150 mg/dl if at all feasible in septic patients (grade D).

Annanne and coworkers reported significant survival benefits in a study of 299 patients with vasopressor-dependent septic shock; the study used hydrocortisone (50 mg every 6 h for 7 days) and fludrocortisone (50 μg/day for 7 days). This treatment strategy is based on the frequent occurrence of relative adrenal insufficiency in patients with septic shock. The low-dose corticosteroid therapy was only effective in those patients with evidence of inadequate adrenal responses to a short corticotropin test. Stress dose steroids should be discontinued if normal cortisol levels and corticotropin responses are found (grade C).

The results of the recombinant human activated protein C trial (drotrecogin alfa activated) represent the first successful phase III international trial in severe sepsis. It is given as a continuous infusion at 24 μg/kg/h for 4 days. Since the molecule is an endogenous anticoagulant, the major side effect of treatment is bleeding. Carefully selected patients benefit from this treatment regardless of the type of infecting microorganism that caused sepsis (grade B recommendation).

**Experimental Therapies for Sepsis**

The wealth of new discoveries into the central molecular events that underlie sepsis and the unmet medical need for improved therapies for sepsis have created an ongoing impetus to develop innovative treatments for sepsis. Some of those experimental strategies that are in clinical trials or nearing clinical investigation are listed in Table 15.8 along with their presumed mechanism of action. Translational research has already brought novel treatments such as stress dose steroids, low stretch mechanical ventilation, enteral nutrition, and activated protein C into clinical use. It is anticipated that the genomic era will speed the development of innovations into clinical practice. Much-needed research continues on preventive strategies, improved diagnostics, and more effective treatment interventions to improve the outlook for this ever-growing population of septic patients.
### TABLE 15.8. Experimental Therapies in the Treatment of Septic Shock.

| Treatment target | Experimental agents | Possible mechanisms |
|------------------|---------------------|---------------------|
| Endotoxin        | Bactericidal/permeability-increasing protein | Endotoxin-neutralizing human protein |
| Endotoxin        | Phospholipid emulsions | Complexes and clears LPS |
| Endotoxin        | E5564                | Toll-like receptor 4 antagonist |
| Endotoxin        | Polymyxin B-binding columns | Endotoxin-binding antibiotic |
| Poly ADP ribosyl polymerase-1 (PARP-1) | Small molecule PARP inhibitor | Inhibits cellular depletion of ATP and limits cellular necrosis |
| High-mobility group box-1 [HMGB-1] | Antibody or small molecule inhibitors of HMGB-1 or its receptor | Blocks the lethal effects of this late-acting cytokine-like molecule |
| Macrophage migration inhibitory factor (MIF) | Antibody to MIF | Blocks the lethal effects of this late-acting cytokine |
| Adrenal function | Low-dose corticosteroids* | Treat adrenal hypofunction of sepsis |
| Coagulation system | Tissue factor pathway inhibitor, recombinant human antithrombin, tissue factor or factor X inhibitors | Inhibitors of DIC, microthrombi; decreases thrombin-induced inflammatory actions |
| Cytokines and endotoxin | Hemoperfusion systems, small molecule signal transduction inhibitors | Removes inflammatory mediators and endotoxin during hemoperfusion, inhibition of cytokine gene induction |
| Disordered microcirculation | Nitroglycerin infusion | Opens up poorly perfused capillary beds along with intravascular fluids |
| Immunonutrition | Arginine, glutamine, nucleic acids, micronutrients | Improves immune function and provides antioxidants |
| Cellular apoptosis | Caspase inhibitors | Block excess apoptosis of immune cells and endothelial cells |

*One clinical trial demonstrated benefit* to other studies are ongoing (recent unpublished report of no benefit for one trial).

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