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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[1] 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,[2] 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,[1] 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.[2]

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.[3] It is currently estimated that as many as 700,000 patients develop severe sepsis each year in the United States,[4,5] with similar incidence rates in several European countries.[6,7] 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.[2,7-9] 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.[4,5]

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 90 mmHg (or mean arterial pressure >65 mmHg) following an adequate fluid challenge (>40 ml/kg over 6 h).

Source: From Levy et al.,[2] by permission of *Critical Care Medicine.*

occurs in previously healthy persons (e.g., meningococcal sepsis, toxic shock syndrome, and severe community-acquired pneumonia), the majority of septic patients have significant underlying diseases that place them at risk for sepsis.[10] Successful management of a variety of severe trauma situations and medical illnesses and advances in surgical interventions are salvaging patients who only a few generations ago would have rapidly succumbed. This has produced a large susceptible population of patients with prolonged critical illness and impaired host defenses.[11] 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 in this patient population. The gradual aging of the population in many developed countries and the increasing prevalence of antibiotic-resistant microbial pathogens also conspire to increase the incidence of severe sepsis/septic shock.

In a study by Martin et al., over 10 million cases of sepsis from the National Hospital Discharge Survey were reviewed over a 21-year time period throughout the United States.[5] They found that the incidence of sepsis increased by an average of 8.7% per year from 1979 to 2000, from 82.7 to 240/100,000 population. Sepsis was consistently and significantly more common in men than women and more common in nonwhite populations compared to white populations. The mean age of patients with severe sepsis was 60 years,[5] but the incidence of sepsis by age was heavily splayed to the extremes of age, with a small peak in the neonatal period and a marked and progressive rise in sepsis in the elderly after age 65.[4]

Gram-positive bacterial pathogens now outnumber gram-negative pathogens as a cause of sepsis, and the incidence of fungal sepsis has increased by over 200% in the past two decades. While the incidence has progressively increased, the overall crude mortality rate has steadily decreased to less than 18% from 27.9% average 20 years earlier.[5] Similar findings have been reported in a large French study, with significant improvements in management outcomes from sepsis noted over the past decade.[10]

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.[12] 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.[13] Angus and colleagues estimated that expenditures in the United States for sepsis alone account for an incremental annual cost of nearly $17 billion.[4]

Sepsis Pathogenesis

Predisposing Factors

Severe sepsis and septic shock usually arise in an unexpected fashion in patients who have another primary illness,[10] 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,[14] and it remains true today despite numerous advances and innovations in supportive care and in medical and surgical management.[15] 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.[16,17]

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,[18] the neutropenic patient,[19] and the asplenic patient[20] 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.[21]

An expanding array of polymorphisms in immune response and regulatory genes are known to potentially affect the risk of sepsis and its outcome.[22–33] 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,[2] 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 *endotoxic shock*) to what is now principally a gram-positive bacterial process.[5] 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.[34]

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.[4,16] 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.[16] 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 cultivatable

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

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

HLA, human leukocyte antigen; IL, interleukin; LPS, lipopolysaccharide; PCT, procalcitonin; TLR, Toll-like receptor; TNF, tumor necrosis factor.

Source: Adapted from Levy et al.,[2] by permission of *Critical Care Medicine*.

microorganisms may also account for some cases of "culture-negative" sepsis.[35]

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.[36] 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.[37] 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 released into the human circulatory system in its free form (released from dead organisms or 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.[38] 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.[2]

In human plasma, endotoxin immediately comes in contact with endotoxin-binding proteins, the most important of which is LPS-binding protein (LBP).[39] This protein facilitates the transfer of LPS to the surface of immune effector cells expressing the anchoring receptor molecule CD14.[40] Another endogenous LBP in plasma is bactericidal permeability-increasing protein (BPI),[41] which is principally expressed on neutrophil membranes and primary granules. Bactericidal 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.[42]

The long-sought-after primary cellular receptor for endotoxin on immune cells has been identified.[43–45] 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.[38] This system includes up to 11 TLRs, CD14, and components of the alternate complement system and mannose-binding lectin system (Table 15.3).[46–50]

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, imidazoquinolines[47]
TLR8	Myeloid cells, dendritic cells	Recognizes ssRNA in humans inside intracellular endosomes; binds imidazoquinolines[47]
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)[48]
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 thioester bond[49]
MBL	Plasma protein	Recognizes mannosides expressed on bacterial, fungal, viral surfaces and activates C4 and C2[50]

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

Source: Adapted from Cristofaro and Opal,[46] by permission of *Expert Opinion on Therapeutic Targets*.

The principal endotoxin transmembrane receptor is TLR4.[43] 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.[39,51] 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),[46] although other regulatory and accessory pathways of gene induction and control have not yet been fully characterized.[23] A well-characterized series of tyrosine and theonine/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.[52,53] 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.[54] Toll-like receptor 9 is the cellular receptor for unmethylated CpG motifs found in bacterial DNA,[55] while TLR3 recognizes double-strain viral RNA,[56] and TLR8 detects single-strand RNA.[47] Also, TLR5 recognizes bacterial flagellin found on motile gram-positive and gram-negative bacteria.[57]

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.[23,38] Elements of the acquired immune system and defects in adaptive immunity may play a pivotal role in toxic shock syndromes[58] and in the later stages of sepsis (the late immune-suppressive phase of sepsis).[59]

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 microbially derived protein antigens found in some streptococci,

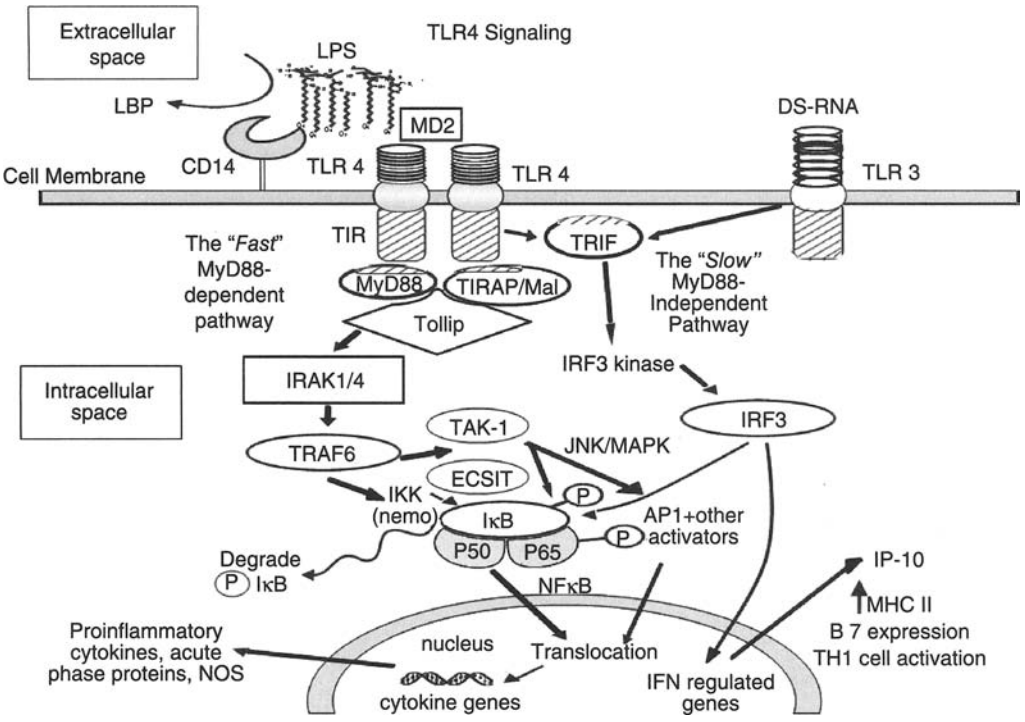

FIGURE 15.1. The signaling pathways of the TLR4 complex. LPS, lipopolysaccharide; DS-RNA, double-stranded ribonucleic acid; LBP, LPS-binding protein; TLR, Toll-like receptor; TIR, Toll interleukin receptor; MyD88, myeloid differentiation factor; TIRAP, Toll interleukin receptor adapter protein; Mal, MyD88 adapter like; Tollip, Toll interactive protein; TRIF, TIR domain adapter inducing interferon-γ; IRAK, interleukin 1 receptor-associated kinase; TRAF6, tumor necrosis factor receptor associated factor 6; ECSIT, evolutionarily conserved signaling intermediate of Toll; TAK-1, transforming growth factor-associated kinase-1; JNK, Janus N-terminal-linked kinase; MAPK, mitogen-activated protein kinase; IRF3, interferon regulatory factor; IFN, interferon; IP-10, interferon-inducible protein-10; IKK, IκB kinase; NEMO (another name for IKK-NFκB essential modulator); IκB, inhibitory subunit κB; NFκB, nuclear factor κB; MHC, major histocompatibility complex; NOS, nitric oxide synthase; TH_1, type 1 thymic-derived $CD4^+$ lymphocyte helper cells. (*Source:* Modified from Cristofaro and Opal,[46] by permission of Expert Opinion on Therapeutic Targets.)

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.[58]

Conventional protein antigens are internalized by 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.[60]

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 Vβ 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 Vβ 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 Vβ2 region of T cells that is found in up to 10%–20% of human lymphocyte populations.[58] 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.[58,60,61]

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).[62]

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.[54] 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.[63] 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.

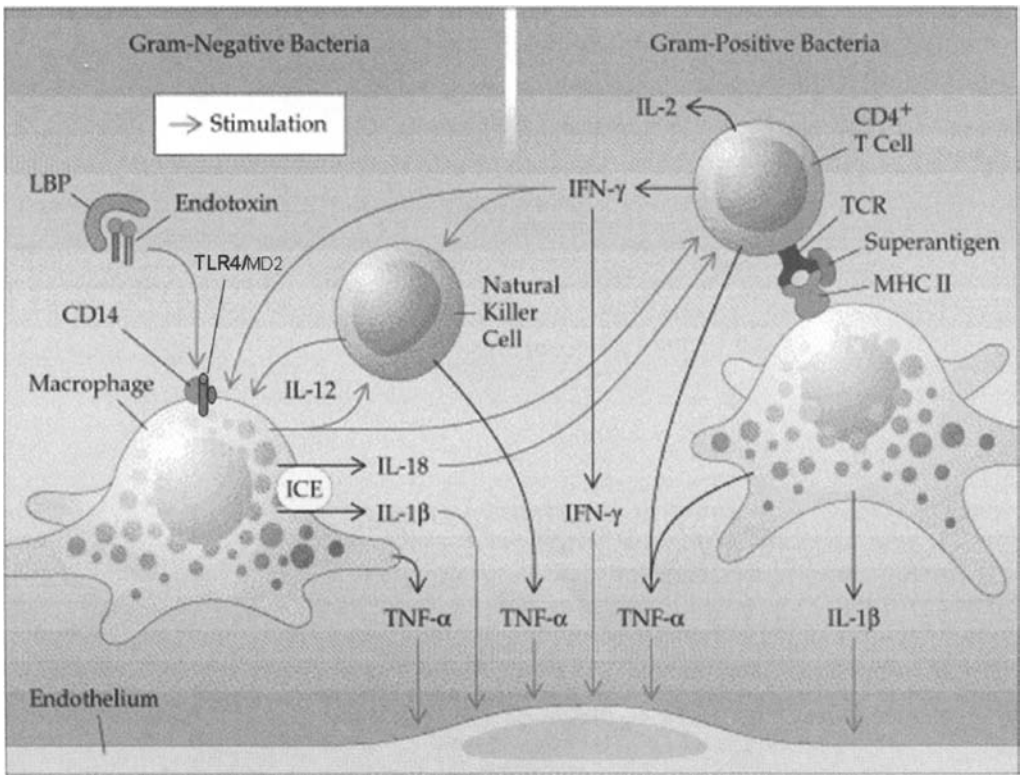

FIGURE 15.2. Interactions between bacterial endotoxin and bacterial superantigen. Interactions between bacterial endotoxin and bacterial superantigens. CD4, $CD4^+$ T cell; TLR2/4, Toll-like receptor 2/4; ICE, interleukin-1β converting enzyme (also known as caspase 1); IFN-γ, interferon-γ; IL, interleukin; LBP, LPS-binding protein; TNF-α, tumor necrosis factor-α. (*Source:* Modified from Opal and Huber,[62] with permission from *Scientific American Medicine.*)

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,[64] and pronounced hemodynamic, metabolic, and hematologic changes occurred when TNF-α was administered to human volunteers.[65] 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.[66]

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.[67,68]

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.[59] Mice deficient in T cells and B cells respond to endotoxin challenge in the same manner as normal mice,[69] 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 (TH_0 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 TH_1-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 TH_2-type phenotype; TH_2 cells secrete IL-4, IL-10, and IL-13. These cytokines promote humoral immune responses and attenuate macrophage and neutrophil activity.[70]

The TH_1-type cytokines suppress the expression of TH_2-type cytokines. Interferon-γ inhibits the synthesis of IL-10; conversely, the TH_2-cell-derived cytokine IL-10 is a potent inhibitor of TNF-α and IFN-γ synthesis by TH_1 cells. The nature of the initial lymphocyte response is critical because the system tends to polarize over time into either a TH_2- or

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

Proinflammatory mediators	*Antiinflammatory mediators*
Proinflammatory cytokines: TNF-α, interleukins-1, -2, -12, -18, lymphotoxin-α Fas ligand	Antiinflammatory cytokines: Interleukins-4, -6, -10, -11, -13 Interleukin-1 receptor antagonist
Proinflammatory chemokines: IL-8, MCP-1	Soluble cytokine receptors: sTNF receptor, sIL-1 receptor, sIL-6R
Interferon-γ	Type 1 interferons (IFN-αβ)
Complement activators and components: C3a, C5a, MBL, C reactive protein	Complement inhibitors: C1 inhibitor, factor H
Lipid mediators: Leukotriene B_4, platelet-activating factor, oxidized phospholipids, phospholipase A_2	Stress hormones: Glucocorticoids, epinephrine, norepinephrine
Bradykinin, histamine	Prostaglandin E_2, prostacyclin
Prooxidants Reactive oxygen and nitrogen species	Antioxidants Glutathione, selenium, uric acid
Granulocyte-macrophage colony-stimulating factor	Granulocyte colony-stimulating factor
Macrophage migration inhibitory factor	Decoy cytokine receptors (IL-1 type 2 R)
Upregulation of receptors: TLR4, TLR2, CD14	Downregulation of receptors: TLR4, MHC II, TNF R, glucocorticoid receptors
Coagulation factors: Thrombin, factor Xa, tissue factor: FVIIa, fibrinogen, heparan sulfate, uPAR	Anticoagulants: Antithrombin, tissue factor pathway inhibitor, activated protein C
High-mobility group box-1	Transforming growth factor-β Vagal cholinergic antiinflammatory reflex

MBL, mannose-binding lectin; MCP, monocyte chemoattractant protein; R, receptor; TLR, Toll-like receptor; uPAR, urokinase plasminogen activator receptor.

TH_1-type response.[71] Functional differentiation of CD8 cells has also been detected ($CD8^+$ type 1 and type 2 cells).[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_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_2 response after systemic injury.

Hotchkiss et al.[59,72] have provided another potential explanation for the relative immune suppression (or immune paralysis) that often accompanies sepsis. Selective apoptosis of $CD4^+$ 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.[73] Accelerated caspase function and excess apoptosis also occur in intestinal epithelial cells, compromising mucosal permeability barrier function of the gut.[59] This pathophysiologic state is further aggravated by sepsis-induced endotoxin tolerance (or reprogramming)[74] and deactivation of monocytes, macrophages, and neutrophils by cytokine inhibitors such as IL-1 receptor antagonist and antiinflammatory cytokines such as IL-10.[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.[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).[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).[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 peripheral vascular resistance.[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.[78] These RNIs also induce lipid peroxidation and cause loss of cell viability.[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.[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.[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.[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.[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.[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.[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.[84]

Clinical trials with recombinant tissue factor pathway inhibitor,[85] activated protein C,[86] and plasma-derived antithrombin[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

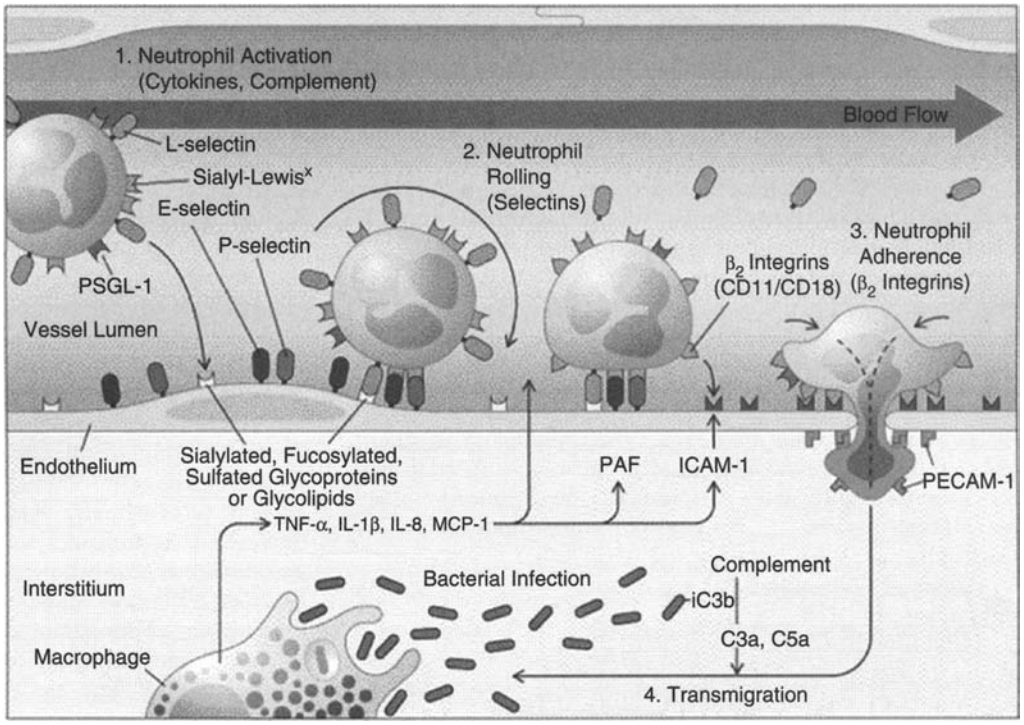

FIGURE 15.3. The interactions between coagulation and inflammation in sepsis. Solid bold arrows, major coagulation pathways; thin solid arrows, accessory and amplification clotting pathways; open arrows, inflammation and clotting interactions; dashed open arrows, inhibitory pathways; TF, tissue factor; uPA, 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 chemoattractant protein-1.

30.9% ($P < .005$, with a 6.1% absolute reduction in mortality).[86] 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.[88] Heparin alone and other anticoagulants such as hirudin have not been shown to improve outcome in clinical settings or experimental models of sepsis,[89,90] and all of these endogenous anticoagulants have antiinflammatory properties.[91] Activated protein C also has profibrinolytic activity and antiapoptotic activities on endothelial cells in experimental systems,[88] which may spare the endothelial surface for the injurious effects of systemic inflammation and disordered coagulation.[81,91] 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.[84,91,92]

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.[62] 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 β-2 integrins (CD11/CD18) and adhesion molecules on endothelial cells such as

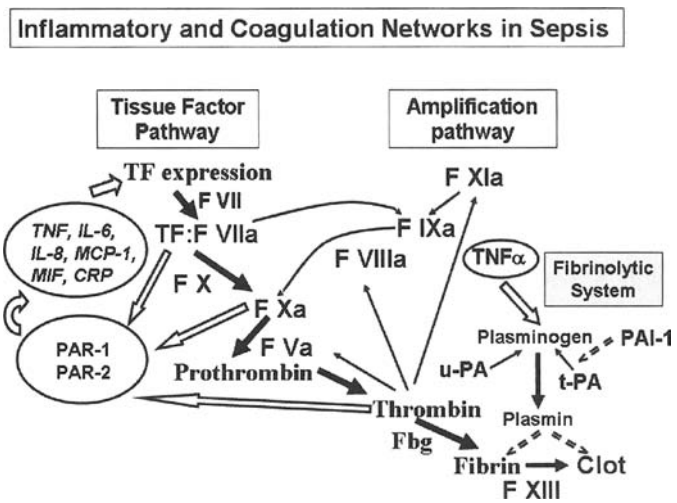

FIGURE 15.4. Neutrophil–endothelial cell interactions in sepsis. Ls, L-selectin; PSGL-1, P-selectin glycoprotein ligand-1; Ps, P-selectin; Es, E-selectin; sLe^x, sialylated-Lewis^x; ICAM-1, intercellular adhesion molecule-1; PAF, platelet-activating factor; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; C, complement; PECAM, platelet endothelial cell adhesion molecule. (*Source:* From Opal and Huber,[62] with permission from *Scientific American Medicine.*)

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.[93,96]

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 inhibitor[91] can produce vasodilatation and may participate in the pathogenesis of septic shock. The triggering receptor expressed on myeloid cells TREM-1[101] 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, euglycemia, 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.[91,94,100]

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 hypoxia[108] from diminished oxygen utilization may develop as well. Attempts to enhance oxygen delivery in sepsis to supranormal levels have not improved outcomes,[3,109] 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 O_2 saturation	<70%	Low mixed venous O_2 indicates inadequate O_2 delivery to tissues in sepsis
Cardiac index (cardiac output/m_2 [surface area])	>4 l/min/m^2	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 (DO_2)		
CI × Arterial O_2 content	<550 ml/min/m^2	Goal of treatment is to provide sufficient DO_2 to maintain adequate mixed venous O_2 saturation
Platelet count	<100,000/μl	Poor prognostic factor in sepsis; increased bleeding risk; thrombocytopenia may be accompanied by DIC
Glucose	Hyperglycemia or hypoglycemia	Acute stress response (hyperglycemia), inhibition of hepatic gluconeogenesis (hypoglycemia)
Clotting measurements	Elevated PT, aPPT, d-dimer, FDPs, low fibrinogen, AT, PC	Coagulopathy often seen with systemic endotoxin release; coagulation activation is almost uniform in sepsis but clinically overt DIC is uncommon
Plasma lactate	(>2.2 mmol/l)	Hypermetabolism, hypoperfusion of tissues, inhibition of pyruvate dehydrogenase
C-reactive protein, procalcitonin, IL-6	Elevated	Acute-phase proteins and products of immune cells, variable levels, sensitive but not specific indicators
Arterial blood gases	Respiratory alkalosis (early); metabolic acidosis (late)	Measurements of O_2 content and mixed venous O_2 saturation useful in management to ensure adequate tissue oxygenation and fluid resuscitation

aPTT, 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, katacalcin, and an amino-terminal peptide.[116] 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.[117] The diagnostic and therapeutic value of PCT measurement needs to be tested in large clinical trials to determine its ultimate clinical applicability.[118] The usefulness of plasma C-reactive protein, clotting factors, platelet counts, and plasma lactate levels are listed in Table 15.5.[62] 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.[52,53]

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).[3,15] 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),[67] but cellular signals from circulating blood components[72] or neuroendocrine signals may also contribute to remote organ injury.[103]

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.[59,72,105]

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.[3] 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

fluid management, and semirecumbent body positioning all reduce progressive lung damage in ventilated patients.[119] The ARDS clinical trials network study confirmed the value of low stretch tidal volume settings (6 ml/kg) over more conventional high tidal volume settings (12 ml/kg).[120] Low tidal volume ventilation should be utilized whenever feasible to minimize further acute lung injury in a ventilated patient. Epidemiologic studies have conclusively demonstrated that even multiple organ dysfunction from sepsis is potentially amenable to treatment if instituted rapidly and skillfully in ICUs.[3,5]

Management of Septic Shock

Priorities in the Management of Sepsis

There are four immediate objectives in the initial management of septic shock: (1) early recognition; (2) reestablishment of tissue perfusion and arterial blood pressure by early resuscitation; (3) optimal supportive care of organ dysfunction; and (4) appropriate intervention to eradicate the causative septic focus. The 2004 surviving sepsis campaign treatment guidelines provide a useful, up-to-date, and evidence-based review of the standard treatment of sepsis.[3] They rank the level of evidence to support treatment decisions as follows: grade A, supported by at least two large, randomized trials; grade B, one large randomized trial; grade C, supported by smaller randomized or nonrandomized trials; grade D, supported by nonrandomized trials; or grade E, nonrandomized clinical data and expert opinion. There is considerable agreement regarding basic resuscitation strategies and organ support maneuvers. There is general consensus about the need to remove the septic focus as soon as possible and initiate appropriate antimicrobial agents against the causative pathogens. Treatment options vary considerably with respect to the timing of interventions, amount and type of fluid administration, value of specific vasopressor therapies, and advisability of treatment interventions of unclear or experimental clinical utility. Areas of general agreement and options lacking uniform consensus are addressed in this section.

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 cystalloid solutions.[3]

The optimal amount of fluid therapy for patients in septic shock remains unclear, but a study by Rivers and colleagues[110] 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 6 h 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.[124] 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 splanchnic 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.[126] 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 splanchnic 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 for first-line vasopressors 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 spectral imaging), they were able to show improved microvascular flow rates in septic patients who received adequate fluid repletion. This is an appealing strategy but must be considered experimental at present until further clinical trials are completed using this approach.

Numerous techniques are under study to clinically measure tissue oxygenation by gastric tonometry, hepatic venous oxygen measurements, direct tissue oxygen probes, and microcirculatory units for visualized capillary blood flow.[3] The practical value of these measurements in the clinical management of sepsis has yet to be demonstrated.

Blood Product Support and Nutritional Support

The relative merits of blood transfusion or erythropoietin necessity to improve the oxygen-carrying capacity of blood remains a subject of considerable debate.[129,130] It has been demonstrated that humans are remarkably resistant to adverse effects from isovolumetric anemia.[131] Banked, stored red blood cells are less deformable, less efficient at releasing their oxygen from 2,3-biphosphoglycerate-depleted hemoglobin stores, and may have immunosuppressive effects.[129] Efforts to promote endogenous erythrocyte production with erythropoietin treatments have yet to be proven superior to blood transfusions.[130] Further clinical trials are warranted with this treatment approach. The lower limit of transfusion threshold in septic shock has not been defined, but it appears to be considerably lower than the traditional transfusion threshold of less than 10 g/dl. Studies of patients in the ICU setting indicated that a conservative transfusion policy at 7–9 g/dl may be preferable[132] (grade B recommendation).

Expert management of acute renal failure, renal replacement therapy, ARDS treatment, hepatic decompensation, acid–base disturbances, and disordered hemodynamics are of critical importance in the management of sepsis. These topics have been addressed in recent treatment guidelines[3] and are dealt with extensively in other chapters in this book. Nutritional support in the critically ill patient has changed radically over the past two 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 prevent gut-derived endotoxin and cytokine generation.[133] Nutritional supplementation with glutamine, arginine, and omega-3 fatty acids has experimental support and remains an active area of research, yet convincing clinical efficacy studies are not yet available.[134]

Fever is frequently concomitant to severe infection and is generally considered advantageous to the host.[135] Experimental animals with peritonitis clear infection and recover more rapidly when allowed to develop fever compared to a control group with externally controlled normothermia.[136] Heat-shock proteins function as molecular chaperones and prevent protein denaturation during cellular stress. Heat-shock protein induction may actually improve outcomes in experimental endotoxin challenge.[137] Cooling blankets to lower body temperature should be avoided as they are uncomfortable for patients and generally ineffective unless true hyperthermia is present.[138]

Antibiotics are considered an adjuvant therapy to source control with drainage, relief of obstruction, or removal of the

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

Suspected source of infection	*Primary pathogens*	*Antimicrobial choice*[a]
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*, *Clostridia*	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)

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

offending focus of infection when possible (grade E recommendation[3]). 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[3]). Ineffective empiric antibiotic choices for initial therapy for sepsis have adverse consequences,[139,140] and therefore it is preferable to ensure adequate initial therapy and then deescalate to single narrow-spectrum agents after the causative organism is identified.[140]

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.[141] Van den Berghe et al.[142] 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[3]).

Annane and coworkers[143] 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.[144,145] The low-dose corticosteroid therapy was only effective in those patients with evidence of inadequate adrenal responses to a short corticotropin test.[143] 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.[86] 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[16] (grade B recommendation[3]).

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[a]	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 intravenous 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

[a]One clinical trial demonstrated benefit[143]; other studies are ongoing (recent unpublished report of no benefit for one trial).

References

1. Poeze M, Ramsay G, Gerlach H, et al. International sepsis survey: A study of doctor's knowledge and perception about sepsis. Crit Care 2004;8:409–413.
2. Levy M, Ramsey G, Fink M, et al. The 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–1256.
3. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for the management of severe sepsis and septic shock. Crit Care Med 2004;32:858–871.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303–1310.
5. Martin GS, Mannino DM, Eaton S, et al. Epidemiology of sepsis in the United States from 1979–2000. N Engl J Med 2003;348:1546–1554.
6. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from international multicenter cohort study. Intensive Care Med 2002;28:108–121.
7. Valles J, Leon C, Alvarez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of the Sociedad Espanola de Medicina Intensiva Unidades Coronarias (SEMIUC). Clin Infect Dis 1997; 24:387–395.
8. Friedman G, Silva E, Vincent J-L. Has the mortality of septic shock changed with time? Crit Care Med 1998;26:2078–2086.
9. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in eight academic medical centers. JAMA 1997; 278:234–240.
10. Brun-Buisson C, Meshaka P, Pinton P, et al. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 2004;30:580–588.
11. Opal SM, Esmon C. Functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis. Crit Care 2003;7:23–38.
12. Hund E. Neurological complications of sepsis: critical illness polyneuropathy and myopathy. J Neurol 2001;248:929–934.
13. Brun-Buisson C, Roudot-Thoraval F, Girou E, et al. The costs of septic syndromes in the intensive care unit and the influence of hospital-acquired sepsis. Intensive Care Med 2003;29:1464–1471.
14. Kreger BE, Craven DE, Carling PC, McCabe WR. Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. Am J Med 1980;68:332–343.
15. Pittet D, Thiívent B, Wenzel RP, et al. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med 1993;19:265–272.
16. Opal SM, Maki D, Larosa S, et al. Systemic host response to sepsis based upon the infectious microorganism and effects of drotrecogin alfa activated. Clin Infect Dis 2003;37:50–58.
17. Cohen J, Brun-Buisson C, Torres A, et al. Diagnosis of infection in sepsis: an evidence-based review. Crit Care Med 2004;32: S466–S494.
18. Ely EW, Wheeler AP, Thompson BT, et al. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. Ann Intern Med 2002; 136:25–29.
19. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34;730–751.
20. Styrt B. Infection associated with asplenia: risks, mechanisms and prevention. Am J Med 1990;88:33N–42N.
21. Sorensen TIA, Nielsen GG, Andersen PK, Teasdale TW. Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 1988;318:727–732.
22. Newport MJ, Huxley CM, Huston S, et al. A mutation in the interferon-γ receptor gene and susceptibility to mycobacterial infection. N Engl J Med 1996;335:1941–1949.

23. Beutler B. Science review: key inflammatory and stress pathways in critical illness. Crit Care 2003;7:39–46.
24. Lorenz E, Mira J-P, Frees KG, Schwartz DA. Relevance of mutations in the TLR4-receptor in patients with gram-negative septic shock. Arch Intern Med 2002;162:1028–1031.
25. Gibot S, Cariou A, Drouet L, Rossignol M, Ripoll L. Association between a genomic polymorphism with the CD14 locus and septic shock susceptibility and mortality rate. Crit Care Med 2002;30:969–973.
26. Agnese DM, Calvano JE, Hahm SJ, et al. Human toll-like receptor 4 mutations but not CD 14 polymorphisms are associated with increased risk of gram-negative infections J Infect Dis 2002;185:1522–1525.
27. Mira JP, Cariou A, Grall F et al. Association of *TNF2*, a TNFα promoter polymorphism, with septic shock susceptibility and mortality. JAMA 1999;282:561–568.
28. Read RC, Camp NJ, Di Giovine FS, et al. An interleukin-1 genotype is associated with fatal outcome of meningococcal disease. J Infect Dis 2000;182:1557–1560.
29. Nadel S, Newport MJ, Booy R, et al. Variation in the tumor necrosis factor-α gene promoter region may be associated with death from meningococcal disease. J Infect Dis 1996;174:878–880.
30. Smirnova I, Mann N, Dols A, et al. Assay of locus-specific genetic load implicates rare Toll-like receptor 4 mutations in meningococcal susceptibility. Proc Natl Acad Sci U S A 2003;100:6075–6080.
31. O'Keefe G, Hybki DL, Munford RS. The G→ a single nucleotide polymorphism at the –308 position in the tumor necrosis factor-alpha promoter increases the risk for severe sepsis. J Trauma 2002;52:817–826.
32. Stuber F, Petersen M, Bokelmann F, et al. A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome patients with severe sepsis. Crit Care Med 1996;24:381–384.
33. Schlüter B, Raufhake C, Erren M, et al. Effect of the interleukin-6 promoter polymorphism (–174G/C) on the incidence and outcome of sepsis. Crit Care Med 1002;30:32–37.
34. Bone RC: Gram-positive organisms in sepsis. Arch Intern Med 1994;154:26–31.
35. Danner RL, Elin RJ, Hosseini JM, et al. Endotoxemia in human septic shock. Chest 1991;99:169–175.
36. Rietschel ET, Kirikae T, Schade FU, et al. Bacterial endotoxin: molecular mechanisms of structure to activity and function. FASEB J 1994;218: 217–225.
37. Pridmore AC, Wyllie DH, Abdillahi F, et al. A lipopolysaccharide-deficient mutant of *Neisseria meningitidis* elicits attenuated cytokine release by human macrophages and signals via toll-like receptor (TLR)2 but not via TLR4/MD2. J Infect Dis 2001;183:89–96.
38. Medzhitov R, Janeway, C. Innate immunity. N Engl J Med 2000;343:338–344.
39. Fenton MJ, Golenbock DT.LPS-binding proteins and receptors. J Leukoc Biol 1998;64:25–32.
40. Pugin J, Heumann ID, Tomasz A, et al. CD14 is a pattern recognition receptor. Immunity 1994;1:509–516.
41. Lin Y, Leach WJ, Ammons WS. Synergistic effect of a recombinant N-terminal fragment of bactericidal/permeability increasing protein and cefamandole in treatment of rabbit gram-negative sepsis. Antimicrobial Agents Chemother 1996;40:65–69.
42. Levin M, Qunit PA, Goldstein B, et al. Recombinant bactericidal/permeability-increasing protein (rBPI$_{21}$) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. Lancet 200;356:961–967.
43. Poltorak A, He X, Smirnova I, et al. Defective signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in *Tlr4* gene. Science 1998;282:2085–2088.
44. Takeuchi O, Hoshino K, Kawai T, et al. Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. Immunity 1999; 11:443.
45. Brightbill HD, Libraty DH, Krutzik SR, et al. Host defense mechanisms triggered by microbial lipoproteins through toll-like receptors. Science 1999;285:732–735.
46. Cristofaro P, Opal S. The human toll-like receptors as a therapeutic target. Expert Opin Therapeutic Targets. 2003;7:603–612.
47. Heil F, Hemmi H, Hochrein H, et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science 2004;303:1526–1529.
48. Zhang D, Zhang G, Hayden MS, et al. A toll-like receptor that prevents infection by uropathogenic bacteria. Science 2004;303:1522–1526.
49. Wolbink GJ, Bossink AW, Groeneveld AB, et al. Complement activation in patients with sepsis is in part mediated by C-reactive protein. J Infect Dis 1998;177:81–87.
50. Roy S, Knox K, Griffiths D, et al. MBL genotype and risk of invasive pneumococcal disease: a case-control study. Lancet 2002;359:1569–1573.
51. Landmann R, Müller B, Zimmerli W. CD14, new aspects of ligand and signal diversity. Microb Infect 2000;2:295–304.
52. Nau GJ, Richmond JF, Schlesinger A, et al. Human macrophage activation programs induced by bacterial pathogens. Proc Natl Acad Sci U S A 2002;99:1503–1508.
53. Boldrick JC, Alizadeh AA, Diehn M, et al. Stereotyped and specific gene expression programs in human innate immune responses to bacteria. Proc Natl Acad Sci U S A 2002;99:972–977.
54. Means TK, Golenbock DT, Fenton MJ. The biology of toll-like receptors. Cytokine Growth Factor Rev 2000;11:219–232.
55. Hemmi H, Osamu T, Kawai T, et al. A toll-like receptor recognizes bacterial DNA. Nature 2000;408:740–744.
56. Alexopoulou L, Holt AC, Medzhitov R, et al. Recognition of double stranded RNA and activation of NFκB by Toll-like receptor 3. Nature 2001;413:732–738.
57. Hayayashi F, Smith KD, Ozinski A, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature 2001;420:1099–1103.
58. Choi Y, Lafferty JA, Clements JRL. Selective expansion of T cells expressing Vb2 in toxic shock syndrome. J Exp Med 1990;172:981.
59. Hotchkiss RS, Karl IE. The pathology and treatment of sepsis. N Engl J Med 2003;348:138–150.
60. Florquine S, Goldman M: Immunoregulatory mechanisms of T-cell-dependent shock induced by bacterial superantigen in mice. Infect Immun 1996;64:3443.
61. Kusunoki T, Hailman E, Juan TS-C, et al. Molecules from *Staphylococcus aureus* that bind CD14 and stimulate innate immune responses. J Exp Med 995;182:1673.
62. Opal SM, Huber CE. Sepsis. Sci Am Med. 2001;30:1–17.
63. Opal SM, Scannon PJ, Vincent JL, et al. Relationship between plasma levels of lipopolysaccharide (LPS) and LPS-binding protein in patients with severe sepsis and septic shock. J Infect Dis 1999;180:1584–1589.
64. Tracey KJ, Beutler B, Lowry SF, et al. Shock and tissue injury induced by recombinant human cachectin. Science 1998;234:470–474.
65. Bauer KA, ten Cate H, Barzegar S, et al. Tumor necrosis factor infusions have a procoagulant effect on the hemostatic mechanism of humans. Blood 1989;74:165.
66. Fisher CJ, Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. Crit Care Med 1994;22:12–21.

67. Dinarello CA, Gelfand JA, Wolff SM. Anticytokine strategies in the treatment of the systemic inflammatory response syndrome. JAMA 1993;269:1825–1832.
68. Luster AD. Chemokines: chemotactic cytokines that mediate inflammation. N Engl J Med 1998;338:436–442.
69. Falk LA, McNally R, Perera PY, et al. LPS-inducible responses in severe combined immunodeficiency (SCID) mice. J Endotoxin Res 1995;2:273.
70. Szabo SJ, Dinghe AS, Gubler U, et al. Regulation of the interleukin (IL)-12Rb2 subunit expression in developing T helper 1 (Th1) and Th2 cells. J Exp Med 1997;185:817.
71. Schneider C, von Aulock S, Siegfried Z, et al. Perioperative recombinant human granulocyte colony-stimulating factor (filgrastim) treatment prevents immunoinflammatory dysfunction associated with major surgery. Ann Surg 2004;239:75–81.
72. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apototic cell death in patients with sepsis, shock and multiple organ dysfunction. Crit Care Med 1999;27:1230–1251.
73. Kell M, Ungethüm U, Steckholzer U, et al. Interleukin-10 counterregulates proinflammatory cytokine-induced inhibition of neutrophil apoptosis during severe sepsis. Blood 1997;90:3356–3363.
74. van Deventer SJH, Buller HR, ten Cate JW, et al. Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic and complement pathways. Blood 1990;76:2520–2526.
75. Greenberger MJ, Strieter RM, Kunkel SL, et al. Neutralization of IL-10 increases survival in a murine model of *Klebsiella pneumonia*. J Immunol 1995;155:722–729.
76. MacMicking J, Xie QM, Nathan C. Nitric oxide and macrophage function. Annu Rev Microbiol 1997;15:323–350.
77. Shenep JL, Toumanen E. Prospective: targeting nitric oxide in the adjuvant therapy of sepsis in meningitis. J Infect Dis 1998;177:766–771.
78. Liaudet L Poly (adenosine 5'phosphate) ribose polymerase activation as a cause of metabolic dysfunction in critical illness. Curr Opin Clin Nutr Metab Care 2002;5:175–184.
79. Vervloet MG, Thijs LG, Hack CE. Derangements of coagulation and fibrinolysis in critically ill patients with sepsis and septic shock. Semin Thromb Hemost 1998;24:33–44.
80. McGilvray ID, Rotstein OD. Role of the coagulation system in the local and systemic inflammatory response. World J Surg 1998;22:179–86.
81. Aird W. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 2003;101:3765–3777.
82. Lorente JA, Garcia-Frade LJ, Landin L, et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. Chest 1993;103:1536–1542.
83. Coughlin SR. Thrombin receptor function and cardiovascular disease. Trends Cardiovasc Med 1994;4:77–83.
84. Levi M, ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341:586–592.
85. Abraham E, Reinhart K, Opal SM, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA 2003;290:238–251.
86. Bernard GR, Vincent JL, Laterre PF, et al. Safety and efficacy of activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.
87. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis. A randomized controlled trial. JAMA 2001;286:1869–1878.
88. Joyce DE, Gelbert L, Ciaccia A, et al. Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis. J Biol Chem 2001;276:11199–11203.
89. Corrigan JJ Jr. Heparin therapy in bacterial septicemia. J Pediatr 1977;91:695–700.
90. Hoffmann JN, Vollmar B, Inthorn D et al. The thrombin antagonist hirudin fails to inhibit endotoxin-induced leukocyte/endothelial cell interaction and microvascular perfusion failure. Shock 2000;14:528–534.
91. Wheeler AP, Bernard GR. Treating patients with severe sepsis. N Engl J Med 1999;340:207–214.
92. Esmon CT. Why do animal models (sometimes) fail to mimic human sepsis? Crit Care Med 2004;32:S219–S22.
93. Roger T, Froidevaux C, Martin C, et al. Macrophage migration inhibitory factor (MIF) regulates host responses to endotoxin through modulation of Toll-like receptor 4 (TLR4). J Endotoxin Res 2003;9:119–123.
94. Garner LB, Willis MS, Carlson DL, et al. Macrophage migration inhibitory factor is a cardiac-derived myocardial depressant factor. Am J Physiol Heart Circ Physiol 2003;285:H2500–H2509.
95. Baumann R, Casaulta C, Simon D, et al. Macrophage migration inhibitory factor delays apoptosis in neutrophils by inhibiting the mitochondria-dependent death pathway. FASEB J 2003;17:2221–2230.
96. Bozza FA, Gomes RN, Japiassu AM, et al. Macrophage migration inhibitory factor levels correlate with fatal outcome in sepsis. Shock 2004;22:309–313.
97. Eriandsson Harris H, Andersson U. Mini-review: the nuclear protein HMGB1 as a proinflammatory mediator. Eur J Immunol 2004;34:1503–1512.
98. Wang H, Yang H. Tracey KJ. Extracellular role of HMGB1 in inflammation and sepsis. J Intern Med 2004;255:320–331.
99. Yang H, Ochani M, Li J, et al. Reversing established sepsis with antagonists of endogenous high-mobility group box 1. Proc Natl Acad Sci U S A 2004;101:296–301.
100. Riedermann NC, Guo RF, Ward PA. Novel strategies for the treatment of septic shock. Nat Med 2003;9:517–524.
101. Bouchon A, Facchetti F, Weigand MA, et al. TREM-1 amplifies inflammation and is crucial mediator of septic shock. Nature 2001;410:1103–1107.
102. Chamaillard M, Hashimoto M, Horie Y, et al. An essential role for NOD-1 in host recognition of peptidoglycan containing diaminopimelic acid. Nat Immunol 2003;4:702–707.
103. Borovikova LV, Ivanov S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000;405:458–462.
104. Nishio K, Akai Y, Murao Y, et al. Increased plasma concentrations of adrenomedullin correlate with relaxation of vascular tone in patients with septic shock. Crit Care Med 1997;25:953–957.
105. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588–595.
106. Zimmermann GA, McIntyre TM, Prescott SM, et al. The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis. Crit Care Med 2002;30(suppl):S294–S301.
107. Shoemaker WC, Montgomery ES, Kaplan E, et al. Physiologic patterns in surviving and non-surviving shock patients. Arch Surg 1973;106:630.
108. Fink M. Cytotoxic hypoxia in sepsis. Acta Anaesthesiol Scand 1997;110:87–95.
109. Hayes MA, Timmins AC, Yau EHS, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717.
110. Rivers E, Nguyen B, Havstadt S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–1377.
111. Marshall JC, Foster D, Vincent JL, et al. Diagnostic and prognostic implications of endotoxemia in critical illness: results of the Medic trial. J Infect Dis 2004;190:527–534.
112. Sriskandan S, Moyes D, Cohen J. Detection of circulating bacterial superantigen and lymphotoxin alpha in patients with streptococcal toxic-shock syndrome. Lancet 1986;348:1315.

113. Reinhart K, Wiegand-Lohnert C, Grimminger F, et al. Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK 195F, in patients with sepsis and septic shock: a multicenter, randomized, placebo-controlled, dose-ranging study. Crit Care Med 1996;24:733–740.
114. Damas P, Ledoux D, Nys M, et al. Cytokine serum levels during severe sepsis in humans: IL-6 as a marker of severity. Ann Surg 1992;215:356.
115. Fisher CJ, Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double blind, placebo-controlled trial. JAMA 1994;271:1836–1843.
116. Karzai W, Oberhoffer M, Meier-Helmann A, et al. Procalcitonin: a new indicator of systemic response to severe infections. Infection 1997;6:629–634.
117. Gendrel D, Assicot M, Raymond J, et al. Procalcitonin as a marker for the early diagnosis of neonatal infection. J Pediatr 1996;128:570–573.
118. deWerra I, Jacchard C, Corradin SB, et al. Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentration: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. Crit Care Med 1997;25:607–615.
119. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocominal pneumonia in mechanically ventilated patients: a randomised trial. Lancet 1999;354:1851–1858.
120. ARDS-Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301.
121. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. BMJ 1998;317:235–240.
122. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. Ann Intern Med 2001;135:149–164.
123. Finfers, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247–2256.
124. Martin C, Papazian L, Perrin G, et al. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest 1993;103:1826.
125. Kellum J, Decker J. Use of dopamine in acute renal failure: a meta-analysis. Crit Care Med 2001;29:1752–1758.
126. Marin C, Eon B, Saux P, et al. Renal effects of norepinephrine used to treat septic shock patients. Crit Care Med 1990;18:282.
127. Holmes CL, Patel BM, Russell JA, et al. Physiology of vasopressin relevant to management of septic shock. Chest 2001;120:989–1002.
128. Spronk PF, Ince C, Gardien MJ et al. Nitroglycerin in septic shock after intravascular fluid resuscitation. Lancet 2002;360:1395–1396.
129. Wu W, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;345:1230–1236.
130. Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. Crit Care Med 1999;27:2346–2350.
131. Weiskopf RB, Viely MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998;279:217–221.
132. Hebert PC, Wells G, Blajchman M, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–417.
133. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992;15:503–508.
134. Bower RH, Cerra FB, Bershadshy B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter prospective, randomized, clinical trial. Crit Care Med 1995;23:436–442.
135. Kluger MJ, Kozak W, Conn C, et al. The adaptive value of fever. Infect Dis Clin North Am 1996;10:1–22.
136. Jiang Q, Cross AS, Singh IS, et al. Febrile core temperature is essential for optimal host defense in bacterial peritonitis. Infect Immun 2000;68:1265–1270.
137. Ribeiro SP, Chu E, Slutsky AS. Heat stress after injection of LPS in rats decreases mortality. Am J Respir Crit Care Med 1996;153:A252.
138. O'Donnell J, Axelrod R, Fisher C, et al. Use and effectiveness of hypothermia blankets for febrile patients in the intensive care unit. Clin Infect Dis 1997;24:1208–1211.
139. Kollef MH. Optimizing antibiotic therapy in the intensive care unit setting. Critical Care 2001;5:189–195.
140. Ibrahim EM, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of blood stream infection on patient outcomes in the ICU setting. Chest 2000;118:146–155.
141. Rao AK, Chouhan V, Chen X, et al. Activation of the tissue factor pathway of blood coagulation during prolonged hyperglycemia in young healthy men. Diabetes 2002;48:1156–1161.
142. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1349–1346.
143. Annane D, Sebille V, Charpentier C, et al. Effects of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862–871.
144. Schroeder S, Wichers M, Klingmüller D, et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. Crit Care Med 2001;29:310–316.
145. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low dose" hydrocortisone in septic shock. A double-blind, randomized, placebo-controlled crossover study. Am J Respir Crit Care Med 2003;167:512–520.