Chapter 6
New Concepts and Emerging Issues in Sepsis

6.1 Introduction

Severe sepsis and septic shock are manifestations of the host’s immune uncontrolled response to infection. The term sepsis is a poorly defined, but commonly used term in the medical literature, and it is derived from the Greek word “Sépsis” meaning decay. Sepsis is best defined as a life-threatening condition or complex caused by overwhelming inflammatory response to infection associated with dysregulation of the body’s immune mechanism. Sepsis is the leading cause of death in critically ill patients in most intensive care units (ICUs). It has been estimated that in the United States sepsis develops in 750,000 people annually, and more then 210,000 of those die1,2! Infants and children in >42,000 cases of severe sepsis occur annually in the United States and millions worldwide.2 The incidence of septicemia and sepsis have been increasing in the past 3 decades in many countries because of several factors, including longer lifespan with a greater population of the elderly; treatment with immunosuppressives with a greater number of subjects with organ transplantations and cancers; use of invasive and novel treatment with prosthesis, long-term or permanent catheters; and the expanding acquired immunodeficiency syndrome (AIDS) epidemic. In national hospital discharge surveys in the United States, the incidence of septicemia had increased from 73.6 per 100,000 patients in 1979 to 175.9 per 100,000 patients in 1987.3 Surveys in the United States and Europe have estimated that severe sepsis accounts for 2–11% of all admission to hospital or ICUs.1 Observational studies indicate that 30–50% of the cases are admitted through the emergency department, rather than developing in hospitals.4,5 The incidence of sepsis appears to continue to increase by 8.7% annually (with an adjusted rate of increase of nearly 300% from 1979 to 2000),6 but may be greater in the United States (US) with an incidence of 240–300 per 100,000 populations, compared to some European countries (Austria, Germany) with rates of 54–116 per 100,000 population.7

Despite progress in our understanding of the pathophysiology of sepsis, the mortality rate is still high (in those with severe sepsis and septic shock). Although the mortality rate overall has fallen in the United States from 27.8% to 17.9% in septic patients over 2 decades, the mortality rate was 30% in those with any organ
failure and 70% in those with multiple organ failure. Patients with infections and severe sepsis require prolonged stay in ICU and hospital, resulting in increase health care costs. Estimates of direct costs per sepsis patient in the United States are about $50,000 whereas European costs are lower, $26,450–33,350. Thus a crude estimate of the direct annual cost of severe sepsis in the United States is about $17.0 billion.

6.2 Definitions

Sepsis, severe sepsis, and septic shock represent progressive stages of the same disease. The transition from sepsis to septic shock can occur in a few hours, but most occurs during the first 24 h of hospitalization. Since 1992 an expert panel from the American College of Chest Physicians and the Society of Critical Care Medicine produced a consensus statement on definition of sepsis and the stages (see table). A systemic inflammatory response syndrome (SIRS) was defined as a systemic inflammatory reaction, regardless of their etiology (infectious or noninfectious). Sepsis was, therefore, defined as SIRS resulting from a documented infection; severe sepsis as sepsis with organ dysfunction or hypoperfusion; and septic shock as presence of sepsis with refractory hypotension. The above criteria have recently been updated, dismissing the SIRS criteria and proposing prediction/insult/response/organ dysfunction (PIRO) criteria. The application of the definitions for epidemiological and clinical reporting can be problematic but does provide a framework for classification of patients. However, it is likely that the official health statistics will still underestimate the true incidence.

6.3 Immune Response

Sepsis or septic shock syndrome need not be associated with documented bacteremia, but should be accompanied by the pathophysiological changes of SIRS with a site or source of infection. Gram-negative bacteria were the predominant causes of sepsis in the 1960s up until the 1980s but gram-positive bacterial infections have now accounted for more than half the cases in the past 2 decades. Fungal infections such as systemic candidiasis are an increasing cause of sepsis in the ICU and immunosuppressed patients. Among the organisms causing sepsis in 2000 in the United States, gram-positive bacteria accounted for 52.1% of cases, gram-negative bacteria for 37.6%, polymicrobial infections for 4.7%, anaerobes for 1%, and fungi 4.6%.

The first line of defense against invading microorganisms is the innate immune system, which then triggers the adaptive component organized around specialized cells, T-cells and B-cells. There are a limited number of receptors involved in innate immune recognition (in the hundreds) which would not be able to recognize every possible foreign antigen. Thus, the innate immune system by evolution has adapted
to focus on highly conserved structures present in large groups of microorganisms. These structures are named pathogens-associated molecular patterns: i.e., bacterial lipopolysaccharide (LPS), peptoglycan, lipoteichoic acid (plasma membrane of gram-positive bacteria), mannan (cell wall of fungi), bacterial DNA, double-stranded RNA (viral), and glucans. The pathogens-associated molecular patterns are produced only by the microorganisms and not by the hosts, and are invariant structures shared by the entire classes of pathogens. The innate immune system evolve to recognize them by pattern-recognition receptors, which are expressed on many effector cells, such as the macrophages, dendritic cells, and B-cells professional antigen-presenting cells. For example, the LPS present on all gram-negative bacteria can be detected by the pattern-recognition receptor of the host to virtually any gram-negative bacterial infections. Once the pathogen-recognition receptor binds to the pathogen-associated molecular pattern, it activates the effector cells immediately without delaying after proliferation, thus initiating a rapid host defense.

The pattern recognition receptors can be divided into three classes: secreted, endocytic, and signalling. The secreted pattern-recognition molecules (e.g., mannos-binding lectin) functions as opsonins by binding to microbial cell wall and triggers the complement system and phagocytosis. The mannose-binding lectin (MBL) is an acute phase reactant synthesized by the liver that binds carbohydrates on gram-positive and gram-negative bacteria and yeast, as well as some viruses and parasites. MBL-associated serine proteases are activated by microbial ligands binding to MBL with direct activation of the complement pathway, independent of adaptive immune response.

Endocytic pattern-recognition receptors occur on the surface of phagocytes, and mediate the uptake and delivery of the invaders into lysosomes for destruction. Pathogen-derived peptides are present and form a complex with the major histocompatibility – complex (MHC) molecules on the surface of macrophages. The macrophage mannose receptor, (member of the mannose-lectin family) is an endocytic pattern-recognition receptor that recognizes carbohydrates in a large number of microorganisms and mediates their phagocytosis by macrophages. The macrophage scavenger receptor is another endocytic pattern-recognition receptor that binds to bacterial cell wall and enhances phagocytosis and clearance from the circulation. Other recently identified pattern-recognition receptors with relevance to innate immunity include nucleotide-binding and oligomerization-domain proteins, and caspase-recruitment domain helicase.

Signaling receptors include the family of toll receptors that have a major role in the induction of immune and inflammatory responses by mediating the intracellular signaling of microbial products. These toll-like receptors (TLRs) recognize pathogen-associated molecule patterns and activate signal-transduction pathways that induce inflammatory cytokines and costimulatory molecules, essential to the adaptive immune response. TLR4 and TLR2 function as receptors of the innate immune system and activate the transcription nuclear factor (NF-κB) signaling pathway. TLR4 is essential for the recognition of LPS and interacts with LPS-binding protein and another protein, MD-2, to interact with CD14, a receptor on
macrophages and B-cells to form a complex. Thus, for any one microbe, there are a variety of molecules that can activate many different pattern-recognition receptors. The binding of pathogen-associated molecules with pattern-recognition receptor activate several signaling intracellular pathways, resulting in activation of transcription factors (NF-κB, AP-1, FOS, JUN) that control immune response genes (including interferon regulatory factor families) for the release of numerous effector molecules and proinflammatory cytokines. Cytokines are essential for orchestrating the innate and adaptive immune defenses to invading pathogens. The adaptive immune system responds to a pathogen only after recognition by the innate immune system. T-cells antigen receptors recognize ligand (peptide) bound to MHC class II molecules on the surface of antigen-presenting cells. T-cells require signals from the peptide-MHC molecule complex plus a costimulatory signal (CD80 and CD86 molecules) on the surface of antigen-presenting cells to be activated. After activation helper T-cells control activation of cytotoxic T-cells, B-cells, and macrophages (adaptive immune responses).

6.4 Pathogenesis

Although bacterial infections are by far the most common causes of sepsis and septic-like syndrome, this clinical complex can be seen with severe disseminated fungal infections (about 5%) and even rarely with viral illnesses, such as severe acute respiratory syndrome (SARS), avian influenza and hemorrhagic viral infections (dengue, Lassa fever, etc.). Whereas gram-negative bacteria initiate the sepsis syndrome mainly by LPS interacting with LPS-binding protein and CD14 via TLR4 (coreceptor for LPS), gram-positive bacteria (Staphylococci and Streptococci) can initiate the mechanism of SIRS by the components of their cell wall (peptoglycin, lipoprotein, lipoteichoic acid, and phenol soluble modulin) by binding to TLR2. There is also recent evidence that although pneumococcal lipoteichoic acid induces profound inflammatory response and activation of the coagulation pathway through TLR2-dependent route, it is likely amplified by endogenous TLR4 ligands. Gram-positive bacteria can also cause severe sepsis or septic shock by producing exotoxins that act as superantigens, as in staphylococcal or streptococcal toxic shock syndrome and streptococcal necrotizing fasciitis. Superantigens are not processed for clonotypic presentation by antigen presenting cells. Superantigens are a group of powerful antigens that bind directly to MHC class II molecules of antigen-presenting cells and to Vβ chain of T-cell receptors, outside of the normal T-cell receptor site, and are able to react with multiple T-cell receptor molecules. Thus, activating a large number of T-cells nonspecifically (>fivefold than conventional antigens) to produce massive amounts of proinflammatory cytokines.

Macrophages and neutrophils contain the inflammasome, a complex of proteins involved in the innate defense mechanism. At least two types of inflammasome exist, composed mainly of the “NALP” family of proteins, NALP1 inflammasome and NALP3 (the central component of the cryopyrin inflammasome). Stimulation of the cryopyrin inflammasome by pathogenic bacteria results in activation of
caspase I, which in turn activates interleukin-1β (IL-1β) through cleavage of pro-IL-1β. This proinflammatory cytokine (secreted by macrophages) triggers another cascade of molecular events (including -TNFα) that result in inflammation. Cryopyrin-deficient macrophages do not respond efficiently to gram-positive bacteria (i.e., *S. aureus* or *Listeria monocytogenes*) but can recognize gram-negative bacteria (which require other inflammasome components).

Nuclear factor (NF)-κB is involved in regulating the transcription of many of the immunomodulatory mediators involved in sepsis and associated organs dysfunction or failure. Signaling pathways stimulated by bacterial products (LPS, lipoteichoic acid, etc.) or cytokine receptors, including those for TNF-α, IL-1 via TLRs, enhance nuclear activation of NF-κB and transcription of genes encoding expression of cytokines, chemokines, adhesion molecules, apoptotic factors, and other mediators of inflammation and coagulation (Table 6.2). Since NF-κB plays a central role in sepsis modulation of this factor may have therapeutic implications, and suppression in animal models of sepsis decrease acute inflammation and organ dysfunction. Activation of caspase-8 (a cysteine protease required for monocyte differentiation into macrophages) may have therapeutic implications, as it prevents sustained NF-κB activation by down-regulation through cleavage of a kinase receptor-interacting protein1 (RIP1).

Interferon – γ (IFN-γ) plays a major role in immune-modulation after immune stimulation of T-lymphocytes by infectious agents. IFN-γ is essential for killing intracellular organisms by enhancing the synthesis of inducible nitric oxide (NO). However, the role of IFN-γ in immune defense against gram-negative bacterial infection is inconsistent. Interleukin – 18 (IL-18), an IFN-γ inducing factor, essential for IFN-γ production appears to play an important role in sepsis. In mice neutralization of IL-18 protects against endotoxin and ischemia-induced liver damage. Thus, IL-18 blockade may be a therapeutic target to neutralize the pathologic consequences of sepsis via IFN-γ mechanisms.

Monocytes and macrophages are effector cells of the innate immunity which are central in the recognition and elimination of invading pathogens. Molecules and cytokines secreted by macrophages orchestrate the innate and adaptive host immune response. An important cytokine released in large amounts by monocytes and macrophages on exposure to bacterial products is macrophage inhibitory factor (MIF). MIF acts by regulating the expression of TLR4-LPS complex, which are important in the innate immune responses to endotoxin and gram-negative bacterial sepsis. Immuneutralization of MIF protects mice against lethal endotoxemia, gram-positive toxic syndrome and experimental bacterial peritonitis. High blood levels of MIF in children and adults with gram-negative sepsis is associated with parameters of disease severity (shock, disseminated intravascular coagulopathy [DIC], lactic acidosis, etc.), dysregulated pituitary-adrenal function, and early mortality. Excessive production of this potent proinflammatory cytokine appears to play an important role on the sepsis syndrome and associated mortality, and inhibitory agents may help to treat severe sepsis.

High mobility group proteins superfamily, particularly high mobility group box-1 (HMGB1), a DNA-binding protein regulating gene transcription and stabilizing
nucleosome formation has been shown to be a late mediator of inflammation and sepsis.\textsuperscript{25} HMGB1 is released by activated macrophages, induces the delayed release of other proinflammatory mediators (TNF-\(\alpha\), IL-1\(\alpha\), IL-1\(\beta\), IL-1 receptor agonist, IL-6, IL-8, and macrophage inflammatory protein [MIP]), and thus mediates lethality when overexpressed. Administration of anti-HMGB1 antibodies protects against lethal endotoxemia, even after peak activity of circulating TNF.\textsuperscript{26} Delayed treatment with anti-HMGB1 prevents lung pathology independent of pulmonary levels of TNF, IL-1\(\beta\), and MIP-2,\textsuperscript{27} indicating that HMGB1 is an independent mediator of endotoxin-induced inflammation.

A recently discovered receptor of the immunoglobulin superfamily, TREM-1 (triggering receptor expressed on myeloid cells), activates neutrophils and monocytes/macrophages by signaling through the adaptor protein DAP12.\textsuperscript{28} TREM-1 amplifies TLR-initiated responses after microbial invasion and enhances secretion of proinflammatory chemokines and cytokines to bacterial and fungal infections. In animal models of acute sepsis blockade of TREM-1 signaling with TREM-1-IgG fusion protein reduces hyperinflammatory responses and death.\textsuperscript{29}

Neutrophils play a pivotal role in the defense against bacterial and some fungal infections (i.e., invasive candidiasis). However, overwhelming activation of neutrophils can result in tissue damage. Elimination or neutralization of pathogenic bacteria by neutrophils is accomplished by their large stockpile of proteolytic enzymes and rapid production of reactive oxygen radicals to degrade internalized invaders.\textsuperscript{30} Local accumulation of neutrophils in the microvasculature, and release of lytic factors and proinflammatory cytokines extracellularly from tissue-infiltrating neutrophils can result in local damage. During sepsis the homeostatic environment in the microcirculation is compromised partly by formation of leukocytic aggregates, endothelial hyperactivity, fibrin deposition, and tissue exudates that predispose to microvascular occlusion and impairment of tissue oxygenation.\textsuperscript{31} Large numbers of neutrophils accumulate in organs developing failure in sepsis, and widespread recruitment and sequestration probably contribute to subsequent organ dysfunction.\textsuperscript{30} Experimental interventions that deplete or antagonize the activity of neutrophils ameliorate organ dysfunction.\textsuperscript{32} The fact that neutrophil-mediated lung injury (acute respiratory distress syndrome [ARDS]) occurs in patients with neutropenia, indicate that organ dysfunction can be initiated by a few neutrophils sequestered in the microvasculature. A distinct subpopulation of neutrophils with characteristic secretory profiles may account for the organ dysfunction. In animal models of sepsis, immature neutrophils preferentially accumulate in the pulmonary microvasculature, and activation with release of proteolytic enzymes (defensins) induces tissue damage.\textsuperscript{33,34}

6.4.1 Hemodynamics

Sepsis classically produces a vasodilatory shock with low systemic vascular resistance, normal or increased cardiac output, hypovolemia due to arterial and venous vasodilatations, and leakage of plasma into the extravascular space, tachycardia (a
hyper-dynamic shock syndrome), and ultimately hypotension and hypoperfusion (if uncorrected) in 90% of patients.\textsuperscript{35} Although sepsis is the most frequent cause of vasodilatory shock, other causes include carbon monoxide intoxication, nitrogen intoxication, prolonged and severe hypotension of any cause (hemorrhage and cardiogenic shock, severe heart failure with mechanical assist devise, prolonged cardiopulmonary bypass), and other conditions such as lactic acidosis due to drug intoxication, certain mitochondrial disease, cyanide poisoning, and cardiac arrest with pulseless electrical activity (anaphylaxis, liver failure and glucocorticoid deficiency are sometimes listed as causes of vasodilatory shock, but the data is inconclusive\textsuperscript{36}). The basic mechanism responsible for vasodilatory shock is failure of the vascular smooth muscle to contract. This is in contrast to the usual cases of acute hemorrhage or acute cardiogenic shock, or severe dehydration where profound vasoconstriction in the venous and arteriolar circulation is a compensatory mechanism via the neuroendocrine response. In the late stages of septic shock profound vasoconstriction and increased peripheral vascular resistance can occur.

### 6.4.2 Mechanisms

In all form of vasodilatory shock the plasma vasodilators such as atrial natriuretic peptide and nitric oxide concentrations are markedly elevated and the potassium ($K_{\text{ATP}}$) channels or neurohormonal system is activated.\textsuperscript{36} Atrial natriuretic peptide and nitric oxide activate a kinase that interact with myosin phosphatase, dephosphorylate myosin and prevents muscle contraction. Moreover, nitric oxide, atrial natriuretic peptide, calcitonin gene-related peptide, and adenosine (all greatly increased in septic shock) activate the $K_{\text{ATP}}$ channels, allowing efflux of potassium and thus hyperpolarization of the plasma membrane and preventing entry of calcium into the cells, thus, inhibiting catecholamine or angiotensin II-induced vasoconstriction. Activation of the $K_{\text{ATP}}$ channels in arterioles is a critical mechanism in the hypotension and vasodilation characteristic of septic shock. $K_{\text{ATP}}$ channels are further activated by increased intracellular concentration of hydrogen ion and lactate,\textsuperscript{36} consequences of hypoperfusion and tissue anoxia accompanying shock.

Activation of the sympathetic nervous system and the rennin-angiotensin-aldosterone axis, the nonosmotic release of vasopressin, and an increase in cardiac output (secondary to decreased cardiac afterload) are compensatory mechanisms of the body to maintain arterial circulation in patients with severe sepsis and septic shock, but may lead to acute renal failure.\textsuperscript{37} Arginine vasopressin initially increases in septic shock (200–300 pg/ml) and after an hour the plasma levels fall ($\wedge_{30}$ pg/ml), as the neurohypophysial stores are depleted.\textsuperscript{38} This may play a role in septic shock as arginine vasopressin decreases the synthesis of nitric oxide and inactivate the $K_{\text{ATP}}$ channels, thus attenuating the arterial vasodilatation and pressor resistance during sepsis.\textsuperscript{37}

Thus, vasodilatation and hypotension is due to the failure of the smooth muscle to constrict. However, the pathophysiology of sepsis leading to vasodilatation is very complex. Molecules expressed by microbial pathogens interact with plasma...
mediators, monocytes or macrophages, endothelial cells, neutrophils, and platelets to activate the inflammatory cytokine cascade, the complement system, arachidonic acid and the prostaglandin pathway, the coagulation and kinin cascade, the endorphin system, and finally the nitric oxide pathway (see Fig. 6.1). These mediators stimulate widespread vasodilatation, increase vascular permeability, with microvascular dysfunction, acute renal failure, acute respiratory distress syndrome, hepatic failure, and disseminated intravascular coagulation (DIC).

Although the general paradigm is that sepsis is a manifestation of an uncontrolled inflammatory response, the failure of anti-inflammatory agents in randomized clinical trials have raised doubts about this concept. A clear picture of the pathogenesis of sepsis has been evolving over the past decade, and a new paradigm appears to focus on a dysregulated immune response, with an imbalance between proinflammatory and anti-inflammatory cytokines. Moreover the initial stages of sepsis is characterized by hyper-inflammation with excessive proinflammatory cytokines (SIRS) followed by a phase of – compensatory anti-inflammatory response (CARS), with anergy and immunodepression (Fig. 6.1).40

Activated CD4 T-cells are programmed to secrete cytokines of two distinct and antagonistic profiles (proinflammatory and anti-inflammatory).40 The proinflammatory (TH1) response include secretion and induction of tumor-necrosis factor (TNF)-α, interferon-γ, and interleukin (1L)-1 and 2. The anti-inflammatory (TH-2) response results in secretion of 1L-4, 1L-10, and 1L-12. Some studies have shown that 1L-10 is increased in sepsis and that the level predicts mortality41,42 and

Fig. 6.1 Mechanisms of sepsis
that reversal of TH2 response improves survival among septic patients. The anti-inflammatory cytokines can inhibit the synthesis of proinflammatory cytokines and exert several direct opposing effects on different cell types. Thus, IL-10 represents an important autoregulatory mechanism that controls the inflammatory response and toxicity of these mediators.

### 6.4.3 Apoptosis of Immune Cells

Sepsis results in the dysregulation of normal apoptosis which may account for immunosuppression associated with severe sepsis, and in part the excessive inflammatory response. Recent studies of patients dying of sepsis have found profound, progressive apoptosis-induced loss of cells of the adaptive immune system. There are markedly decreased levels of B cells, CD4 T-cells, and follicular dendritic cells, but no significant loss of CD8 T-cells, natural killer cells, or macrophages in severe sepsis. Depletion or loss of these lymphocytes can cause decreased antibody production, macrophage activation, and impaired antigen presentation. In one study of 19 patients with sepsis 15 (78.9%) had severe lymphopenia with absolute lymphocyte count of 500 ± 270/mm³ (normal being above 1,200/mm³). Bacterial lipoproteins also can initiate apoptosis of monocyte cells and epithelial cells through TLR-2, providing a molecular link between microbial products, apoptosis and the host defense mechanism. The type of cell death may determine
the immune response. Apoptotic cells increase anergy or anti-inflammatory cytokines that impair the response to pathogens, whereas necrotic cells cause immune stimulation and enhance antimicrobial defence.\textsuperscript{46,47} The mechanism of lymphocyte apoptosis in sepsis is not completely understood but may be related to stress-induced endogenous release of glucocorticoids\textsuperscript{48} and bacteria have evolved molecules that deregulate caspases to induce apoptosis.\textsuperscript{46}

Neutrophils play a major role in the host’s response to invading pathogens and are essential for their eradication. However, neutrophils through release of oxidants and proteases are believed to be responsible for injury to organs with inflammatory conditions, including sepsis. Excessive neutrophil activation and sequestration in the lungs may play a role in the acute respiratory distress syndrome (ARDS), commonly present with severe sepsis. Neutrophils are recruited to the site of infections and normally die within 6–8 h after their release into the circulation. Inflammation is terminated and controlled in part, by the apoptosis of neutrophils. There is recent evidence that apoptosis is delayed in neutrophils from patients with sepsis.\textsuperscript{49} This may result in failure to down-regulate proinflammatory cells, leading to prolongation of inflammation.\textsuperscript{50} Failure of the regulatory pathway of apoptosis can prolong survival of neutrophils, resulting in death by necrosis with up-regulation of inflammation. The mechanism of delayed apoptosis involves activation of NF-κB, via caspase-1 and generation of IL-1.\textsuperscript{51} Pre-B cells colony enhancing factor (PBEF) a growth factor for B cells (produced by activated lymphocytes), and up-regulated by LPS stimulation, appears to inhibit apoptosis of neutrophils.\textsuperscript{52}

Thus it is clear that there is deregulation of apoptosis in sepsis which appears to play a role in the pathogenesis. Enhanced apoptosis of organ tissues may contribute to increased intestinal permeability (gastrointestinal epithelial cells exhibit external apoptotic cell death) and organ failure. Large numbers of lymphocytes and gastrointestinal epithelial cells die by apoptosis during sepsis.\textsuperscript{53} While failure to initiate apoptosis process in neutrophils may prolong and enhance the inflammatory reaction, enhanced lymphocytic apoptosis may result in immunosuppression.

### 6.4.4 Immunoparalysis

It has become evident over the past decade that the early mortality of fulminant sepsis is associated with excessive systemic inflammation mediated by various proinflammatory cytokines. After this initial phase (few days), counter-regulatory pathways activation with excessive anti-inflammatory cytokines and increased apoptosis of lymphocytes is associated with immunodepression or “immunoparalysis,” which probably contribute to late mortality from secondary nosocomial infections.\textsuperscript{54} Sepsis is thus associated with reduced responsiveness of immune cells to release proinflammatory cytokines at a later stage. There is diminished responsiveness of circulating monocytes, granulocytes, and lymphocytes. It has been proposed that the hyporesponsiveness of immune cells is confined to circulating blood cells, and not to local-tissue immune cells which remain responsive to bacterial antigen.\textsuperscript{55}
The mechanism of secondary immune paralysis in sepsis is not fully understood, but may involve the anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGFβ). In an animal model of sepsis depression of splenocyte immune responses was mediated by IL-6 and TGFβ and plasma from septic patients greatly depress normal monocyte secretion of TNF-γ through functional deactivation by IL-10. Since immunoparalysis could contribute to the late mortality of the septic syndrome, strategies to restore immune function in septic patients are being investigated. Biologics that may reverse monocyte deactivation in vitro and animals, thus of potential therapeutic benefit in sepsis, include interferon-γ (INF-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF). In a small pilot study of nine patients with sepsis and immunoparalysis (defined as <30% HLA-DR-positive monocytes), daily subcutaneous injection of INF-γ for 3 days restored TNF-production capacity of monocytes and eight patients survived. Thus, further clinical trials with IFN-γ in late sepsis is warranted.

The type of cell death also determines the immunologic function of surviving immune cells. Apoptotic cells induce anergy or anti-inflammatory cytokines that impair host response to pathogens, and necrotic cells cause immune stimulation and increase host immune defence. Thus, in late sepsis immunodepression is a result of quantitative depletion of circulating lymphocytes and monocytes, as well as functional impairment of the remaining mononuclear cells.

Although clinical and animal experiments support the concept of early deaths in sepsis being related to hyper-inflammation and late mortality being associated with excessive anti-inflammatory cytokines, this is likely an oversimplification of a complex process. Thus, a simple plasma measurement of cytokines may not be adequate to define the status of immune response during sepsis as suggested. Two recent studies in a murine model of sepsis with monitoring of plasma cytokines during the evolution of the syndrome have been reported from the same laboratory. In the early phase there was simultaneous increase in proinflammatory (IL-6, TNF, IL-1β, MIP-1 and -2, exotoxin) and anti-inflammatory (TNF-soluble receptors, IL-10, IL-1 receptor antagonist) cytokines in early deaths (day 1–5). Both pro- or anti-inflammatory cytokines were reliable in predicting mortality up to 48 h. During the later phase of sepsis, some mice die with evidence of immunosuppression (increased bacterial growth and low IL-6), while others die with immunostimulation (high IL-6 and bacterial growth) none of the surviving mice after day 4 exhibited increased IL-6. This complex response does not support the use of proinflammatory cytokine measurement for classifying the inflammatory status during sepsis.

### 6.4.5 Tissue Oxygenation

While microvascular blood flow redistribution undoubtedly occurs in sepsis, investigators have shown increased tissue oxygen tension in the organs of animals and patients with sepsis. Thus, suggesting that the predominant defect might be in cellular oxygen use (tissue dysoxia) rather than in oxygen delivery. Studies on
skeletal muscles biopsies of critically ill patients with sepsis have found that ATP concentration was significantly lower in patients who subsequently died than survivors and controls.\textsuperscript{65} There was an association of nitric oxide overproduction, antioxidant depletion, mitochondrial dysfunction, and decreased ATP concentrations that relate to organ failure and eventual outcome. Therefore, bioenergetics failure appears to be a pathophysiological mechanism underlying multiorgan dysfunction in sepsis.\textsuperscript{62}

### 6.4.6 Coagulation

Dysfunction of the blood coagulation cascade and fibrinolysis are common in patients with sepsis but clinically overt DIC is uncommon. However, septic shock is nearly always associated with some degree of DIC, with microvascular thrombosis, consumption of platelets and coagulation of proteins, and stimulation of the fibrinolytic system, with increased risk of hemorrhage.\textsuperscript{66} Hemostatic abnormalities and endothelial changes are some of the earliest manifestations of a wide spectrum of infections. Changes in the fibrinolytic system are seen soon after a single infusion of endotoxin with many of the abnormalities seen in early clinical sepsis.\textsuperscript{67} Rapid release of tissue plasminogen activator (\(\tau\)-PA) was followed by an early increase in plasminogen activation, reaching a maximum by 2–3 h and decreased by 3–5 h. The decrease in fibrinolytic activity was due partly to appearance of plasminogen-activator inhibitor (PAI)-1 activity at 3–5 h. Sepsis can activate the coagulation pathway at multiple sites, via activation of chemical mediators on the endothelium and monocytes, and through activation of the proinflammatory cascade. Endotoxin and other toxins can directly activate the extrinsic pathway by up-regulation of tissue factor (TF) and factor VII leading to thrombin and clot formation. TF activation is considered the primary initiator of coagulation in sepsis.\textsuperscript{68} In addition, sepsis activates the contact system (intrinsic pathway) through induction of TNF-\(\alpha\) and interleukins via activation of Hageman factor (XII), to factor XIa, which acts as trigger of the intrinsic coagulation pathway. Activated factor XII (a) also hydrolyses pre-kallikrein to the proteolytic kallikrein which cleaves kininogen to release bradykinin (a potent vasodepressor), which is thought to contribute to hypotension in early sepsis.\textsuperscript{69}

General activation of the coagulation depletes the natural antithrombotic factors, protein C, antithrombin, and TF pathway inhibitor. Protein C is converted to activated protein C (APC) by thrombin binding to thrombomodulin on endothelium surface, and counter prothrombotic state, and exhibit anti-inflammatory properties by decreasing proinflammatory cytokines and neutrophil rolling on endothelium. Protein C and protein S inhibit endotoxin-induced production of TNF, 1L-1\(\beta\), and 1L-6 by monocytes in vitro and in vivo, activated protein C reduce TNF secretion in endotoxemic rats.\textsuperscript{55} Activated protein C controls coagulation by proteolytically inactivating factors Va and VIIa. In sepsis conversion of protein C to the activated form is impaired by increased consumption of its cofactor protein S. Several processes during sepsis and inflammation have been associated with the reductions
in endothelial-cell thrombomodulin and endothelial protein C receptor. These include down-regulation of transcription genes encoding these factors in response to cytokines and sepsis, and enzymatic cleavage of protein C activation complex. Thus, disruption of the activated protein C complex in sepsis is an early event that leads to widespread thrombosis and DIC, and may play a role in perpetuation of an uncontrolled inflammatory response. In severe sepsis the activities, besides activated protein C, of TF pathway inhibitor, antithrombin, and fibrinolysis are impaired, resulting in a procoagulant state.

Plasminogen activator inhibitor type I (PAI-1), a major inhibitor of the fibrinolytic system, has been implicated in the pathogenesis of sepsis. High circulating levels of PAI-1 are predictive of poor outcome in septic patients, and polymorphism in the gene encoding PAI-1 influences the development of septic shock in patients with meningococcal sepsis. However, experiments in gene knockout mice found that PAI-1 is essential for host defense against severe gram-negative pneumonia. Mice with deletion of PAI-1 had increased bacterial overgrowth and lethality, whereas, mice with transgenic overexpression of PAI-1 protected the animals against Klebsiella pneumonia, by promoting neutrophil recruitment to the pulmonary compartment.

6.4.7 Complement System

The complement-activation pathways play integral roles in the immune defense against invading pathogens, and are therefore important in the pathogenesis of the sepsis syndrome. All the three major pathways and other neutrophil/macrophage-associated pathway can be activated in sepsis. Activation of the classical pathway occurs after contact with IgG- and IgM-immune complexes and C-reactive protein, with interaction of the subunits of C 1 (q,r and s). The lectin pathway involves interaction of MBL and mannose residue on bacterial surfaces, resulting in activations of MBL-associated serine protease complex. Both the classical and lectin pathways converge resulting in cleavage of C4 and C2, and generation of C3 convertase (C4b–C2a). The alternative pathway is stimulated by bacterial LPS, interacting with C3b, factors B and D to subsequently generate C3 convertase. At this stage the three main pathways converge, resulting in generation of C3a fragment which is an anaphylatoxin that causes vasodilation and increased vascular permeability. The C3b fragment is an opsonic factor which combines with C3 convertase to form C5 convertase, which cleaves C5 into C5a and C5b. C5a is also an anaphylotoxin, whereas C5b interacts with C6, C7, C8, and C9 to form the membrane attack complex (C5b–C9). Another associated pathway involves cleavage of C5 by proteases from neutrophils and macrophages to generate C5a and other fragments.

C5a enhances the innate immune response by interacting with a receptor (C5aR) on neutrophils, macrophages, and endothelial cells that leads to induction of localized, contained inflammation. Phagocytic cells (neutrophils and macrophages) ability
to engulf and kill bacteria by release of granule enzyme and generation of superoxide anion is enhanced by contact with C5a.\textsuperscript{76,77} C5a also induces chemotactic response of neutrophils and confer resistance to apoptosis.\textsuperscript{78}

Although low and locally regulated concentrations of C5a have positive priming effects on neutrophils and macrophages, excessive generation of C5a, as occurs during sepsis, can have deleterious systemic effects.\textsuperscript{75} Generation of large amounts of C3a and C5a in animals can cause circulatory failure, hypotension, and diffuse capillary leakage.\textsuperscript{79} Relatively high levels (10–100 nM) of C5a in plasma can impair neutrophil function, stimulate macrophages and endothelial cells to produce excessive amounts of proinflammatory mediators, and generate prothrombotic activity that can lead to DIC.\textsuperscript{75} Furthermore, increased levels of C5a can also induce activation of caspase 3 leading to apoptosis of thymocytes and probably lymphocytes.\textsuperscript{80} In experimental animal models of sepsis blockade of C5a or C5aR (by specific antibody against C5a or C5aR antagonist) greatly improve survival in rodents from 20% to 70%.\textsuperscript{81}

### 6.4.8 ARDS in Sepsis

Pulmonary dysfunction is very common in severe sepsis and almost 85% of these patients will require ventilatory support, typically for 7–14 days. Overall, sepsis is associated with the highest risk of progression to acute lung injury or ARDS (\(\wedge 40\%\)).\textsuperscript{82} Although some of the deaths are attributable to ARDS the majority are due to sepsis itself and multiorgan failure. This illness has an early acute phase in all patients with ARDS, and a smaller variable fraction have a late (chronic) phase secondary to pulmonary fibrosis (rare in sepsis-induced ARDS). The acute early phase is characterized by the influx of protein-rich edema fluid into the airspace, due to increased permeability of the alveolar-capillary barrier.\textsuperscript{82}

Although histologic studies and animal models implicate the sequestration and activation of neutrophils (releasing protease and oxygen radicals) as the main pathogenic mechanism in the acute lung injury, there is still some controversy. Patients with profound neutropenia and sepsis can also develop ARDS and some animal models of ARDS are neutrophils independent.\textsuperscript{82} Furthermore, in clinical trials of severe infection patients receiving granulocyte colony-stimulating factor (G-CSF) did not have increased risk of ARDS, despite very high peripheral circulating neutrophils (40,000–70,000/mm\(^3\)).\textsuperscript{83,84}

ARDS is an inflammatory disease with endothelial and epithelial injury, loss of epithelial integrity, increases alveolar-capillary permeability and development of hyaline membranes. It is very likely that there are multiple factors and pathways involved in the pathogenesis. Undoubtedly local and systemic hyperproduction of proinflammatory cytokines (or the imbalance of proinflammatory and anti-inflammatory cytokines) and disturbances of coagulation are important, leading to platelet-fibrin thrombi in small pulmonary vessels. Other factors that may contribute to ARDS include overdistension of alveoli from mechanical ventilation and
disturbance in the production and function of surfactant.\textsuperscript{82} Despite the undisputed role of inflammation in the development of ARDS, anti-inflammatory agents such as corticosteroids have not been beneficial in the early acute or later stage of the disease.\textsuperscript{85,86}

The three main pathogenic processes of ARDS: unchecked inflammation, interstitial/alveolar protein accumulation, and destruction of pulmonary epithelial cells can be controlled by the up-regulation of the host’s heat shock protein (HSP)-70.\textsuperscript{86} Thus, the consequences of ARDS from severe sepsis may be due to a dysregulation or impaired expression in lungs of HSP-70.\textsuperscript{87} The surprising aspect of this study is the improvement in mortality from amelioration of the ARDS, as patients with sepsis rarely die from ARDS but succumb to multiple organ dysfunction syndrome,\textsuperscript{88} or recurrent sepsis. This suggests that the lung itself represents a motor of systemic inflammation that contributes significantly to the overall SIRS.\textsuperscript{88} Another possibility is that generation of HSP-70 in the lungs produces a systemic protective effect on extra-pulmonary organ failure.

### 6.5 Management in Sepsis

Improvement in survival of patients with sepsis has been realized in recent years by a combination of factors: rapid institution of resuscitative measures and broad-spectrum antibiotics in the Emergency Department, and a multidisciplinary approach, are largely responsible for evident improved outcome. Consensus guidelines have been published by an international, multiorganization, multidisciplinary body – the “Surviving Sepsis Campaign” in 2004,\textsuperscript{89} in an attempt to reduce the dismal morbidity and mortality from severe sepsis. The guidelines cover more than 50 aspects of care in the septic patient. The approach to antibiotic therapy was based on expert opinion and common sense rather than on controlled randomized trials.\textsuperscript{90} The main body of these guidelines has focused on resuscitation and management “bundles” (core issues).

### 6.6 Early Goal-Directed Therapy

Early resuscitative measures before admission to the ICU in the Emergency Department or on the clinical units, is a key component of management of severe sepsis (to correct hypotension and lactic acidosis). An elevated serum lactate concentration can provide clues of tissue hypoperfusion even before overt hypotension. Management during the first 6 h of sepsis is the cornerstone of “early goal-directed therapy.”

Previously, two large randomized controlled trials had shown that supranormal hemodynamic goals (maintaining high cardiac output and high oxygen delivery) at various stages of sepsis had no survival benefit.\textsuperscript{91,92} A criticism of these earlier studies
is that goal-directed hemodynamic optimization was started too late, usually when patients arrive in the ICUs. Moreover, besides initiating earlier goal-directed therapy within the “golden period” of opportunity the aims should be to attain more normal hemodynamic optimization, rather than supranormal parameters. Furthermore, reliance on early hemodynamic assessment on physical findings, vital signs, central venous pressure, and urinary output may fail to detect persistent tissue hypoxia. A more definitive early resuscitation strategy to achieve a balance between systemic oxygen delivery and oxygen demand, using a goal-orientated manipulation of cardiac preload, afterload, and contractility has been proposed and tested. Resuscitation end points used in a previous trial of early-goal-directed therapy by Rivers et al., include normalization of mixed venous oxygen saturation (central venous oxygen saturation ≥70% by continuous monitoring), arterial lactate concentration, base deficit, and pH. Crystalloids in 500 ml bolus was given every 30 min to achieve a central venous pressure of 8–12 mmHg; and vasopressors given to maintain a mean arterial pressure of 65–90 mmHg; and urine output maintained ≥0.5 ml/kg/h (similar parameters as standard are). Transfusion of blood was used to maintain a hematocrit of ≥30% (equivalent to hemoglobin 10 g/dl).

In the randomized trial by Rivers et al., 263 patients with severe sepsis and septic shock were enrolled, with 130 assigned early-goal-directed therapy and 133 to standard therapy. During the first 72 h, the patients assigned to early-goal directed therapy had significantly higher mean central venous oxygen saturation (70.4% vs 65.3%), a lower lactate concentration (3.0 vs 3.9 mmol/l), a lower base deficit (2.0 vs 5.1 mmol/l), and a higher pH (7.4 vs 7.36). In-hospital mortality was lower in the early goal-directed therapy (46.5% vs 30.5%, p = 0.009); 28-day mortality (49.2% vs 33.3%, p = 0.01); and 60-day mortality (56.9% vs 44.3%, p = 0.03) were also significantly lower. However, multiorgan failure between the groups was not significantly different (21.8% vs 16.2%, p = 0.27). Although early-goal-directed therapy is considered standard for severe sepsis and septic shock at present, this approach is based on a relatively small number of patients from a single randomized, control trial. Moreover, in a national survey of 100 emergency departments in the US, multiple barriers to time-sensitive resuscitation of septic patients existed in more than half the respondents (due to shortage of nursing staff and central venous pressure monitoring availability). In another survey in England, of the 78 emergency departments responding as of March 2006, only 18.5% initiated early goal-directed-therapy and a further 10% were about to initiate the protocol.

6.7 Antimicrobial Therapy in Severe Sepsis

There is no specific antibiotic regimen of choice for sepsis or septic shock, nor randomized comparative trials to address this issue. Choice of antibiotics should be chosen according to likely microorganisms responsible for each individual setting. For instance, community-acquired versus hospital-acquired; site or source of
infection – i.e. pneumonia, urinary tract, intraabdominal, or intravascular catheter. In general, community-acquired infections are usually more susceptible to standard antibiotics except in those on previous antibiotics, prolonged urethral, or intravascular catheters with multiple healthcare unit exposure. It is important to take into consideration the local epidemiology of the types of microorganisms causing sepsis, and the resistance pattern in each individual hospital, ICU, city, or region before selecting appropriate empiric therapy.

Although international and multicenter studies provide useful insight on the microbial patterns and level of antimicrobial resistance there is tremendous variation at the national and local level. This is exemplified by the wide geographic variation in the incidence of community-acquired MRSA infection between cities and countries. Even in hospitals that are geographically close different spectra of microorganisms and different patterns of antibiotic resistance may exist in ICUs, due to differences in case loads and antibiotic practices.

Current guidelines recommend rapid institution of broad-spectrum antibiotics to cover the most likely pathogen in the given clinical scenario. There is reasonably good data to indicate that prompt administration of appropriate antibiotics is important in modifying the outcome in severe sepsis (based largely on review of observational literature reports). The effect of initial antimicrobial choice and results of microbial cultures in 904 patients with conformed severe sepsis or early septic shock was analyzed from a prospective multicenter trial of an immunomodulating agent. The 28-day mortality was 24% (168/693) for patients adequately treated, versus 39% (82/211) for those receiving inappropriate antimicrobial therapy ($p < 0.001$). A more recent prospective (nonrandomized) study assessed the benefit of appropriate empiric antibiotic therapy in 920 patients with documented sepsis from three medical centers in Israel, Italy, and Germany. In this study the mortality rate were 20.1% (64/319) and 11.8% (68/576) for patients receiving inappropriate empiric therapy and appropriate therapy, respectively ($p = 0.001$). Presumably, patients receiving initial inappropriate therapy would be switched to susceptibility-directed therapy, results of which are usually available after 2–4 days. Similar results were reported from a randomized, controlled sepsis (MON-ARS) trial subgroup analysis of 2,634 patients (as part of the monoclonal anti-TNF trial). Mortality rate among adequately treated patient was 33% versus 43% in those initially inadequately treated ($p < 0.001$). These three prospective studies indicate that rapid institution of appropriate antibiotics results in improved outcome (38–41% improvement), but delaying appropriate therapy for 2–3 days (pending culture and susceptibility) still result in a 60–80% survival in patients with sepsis. Recent reports, however suggests that, outcome with delayed appropriate antibiotic treatment for bacteremias may be organism dependent. In a cohort of 215 patients with \textit{S. aureus} bacteremia from Taiwan (30 with community-acquired MRSA) there was no significant difference in 30-day mortality between methicillin-sensitive \textit{S. aureus} or MRSA infection, even though most patients (83%) with MRSA bacteremia did not receive initial appropriate therapy within the first 48 h. On the other extreme, outcomes of \textit{Pseudomonas aeruginosa} bacteremia with relatively reduced susceptibility to piperacillin-tazbactam is markedly reduced compared to
those infected with highly susceptible strains treated with the same agent. In this retrospective cohort the 30-day mortality rate was 85.7% (6/7) in patients treated with piperacillin-tazobactam with MIC 32–64 mg/l (considered susceptible by the Clinical Laboratory Standards Institute, ≤64 mg/l), but only 30% in those whose organisms were more susceptible (≤16 mg/l) treated with the same antibiotic (N = 10). This small study suggest that the resistance breakpoint for piperacillin-tazobactam should be reduced to >16 mg/l, more in line with the British Society of Antimicrobial Chemotherapy guidelines. Perhaps the most convincing data on relationship between delay in the initiation of effective antimicrobial therapy and mortality was recently reported from a large retrospective cohort of septic shock in adults. In a multicenter study 2,731 patients with septic shock were evaluated, 77.9% of whom had documented infection, and the mortality rate of the entire cohort was 56.2% (higher than recent reports). The median time for initiation of effective antibiotic after identification of recurrent/persistent hypotension was 6 h. In multivariate analysis (including APACHE II score), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Administration of an effective antibiotic within the 1st hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival of 7.6%. In this large cohort collected between 1989 and 2004, only 50% of septic shock patients received effective antibiotic therapy within 6 h of documented hypotension. Although the major limitation of this important study is the retrospective design and, thus, the accuracy of the timing of therapy in relationship to documented shock, current guidelines is to initiate antibiotic therapy immediately after onset of shock or before in suspected severe sepsis. The implications of this study would be more compelling and robust if the data were collected prospectively.

It has been generally recommended to reassess and modify antimicrobial therapy after 2–3 days according to microbiological results and susceptibility, and to step down to a narrow spectrum, less toxic and less expensive agent to reduce resistance, toxicity, and cost. There is no evidence that this strategy is detrimental to the patients’ well being. Empirical antifungal therapy should not be used on a routine basis for severe sepsis or septic shock, but may be considered for selected patients with high risk for invasive candidiasis and for high clinical suspicion. Besides specific treatment directed at likely pathogens, source control or eradication is important to control the infection by drainage of abscesses or infected fluid collections and debridement of necrotic tissue. Although this approach is highly logical the evidence to support these recommendations are based on observational data and thus lower tier.

6.8 Activated Protein C

Recombinant human activated protein C (drotrecogin alpha) is an anti-inflammatory, antithrombotic, profibrinolytic treatment for specific pathophysiologic derangements in severe sepsis. Experimented studies in sepsis models indicate that
activated protein C (APC) has direct anti-inflammatory effect at a cellular level. In a sepsis microcirculation model APC effectively reduced leucocyte rolling and leucocyte firm adhesion in systemic endotoxemia, but the action was unlikely to be related or caused by thrombin inhibition-associated anticoagulatory mechanism. Recombinant APC was approved by the US Food and Drug Administration (FDA) for treatment of patients with severe sepsis, based on the 19.4% reduction in the relative risk of death (absolute risk reduction of 6.1%) found in the PROWESS study. In a post hoc analysis performed by the FDA, the benefit of APC was restricted to the more severely ill patients (APACHE II score of 25 or more or with ≥2 organ dysfunction). A subsequent randomized trial (ADDRESS) showed no significant benefit of APC in patients with severe sepsis and low risk of death. The cost of APC per therapeutic course was $6800 (US) in 2002, and an economic evaluation estimated that it was cost-effective to treat severely septic patients with an APACHE II score of ≥25 ($24,484 per life-year gained). Although APC can result in excessive bleeding sepsis results in a procoagulant state which may predispose to thromboembolic and ischemic conditions. Hence heparin thromboprophylaxis is still required. In a recent multicenter randomized, blinded, control trial with all patients receiving APC, 493 were given subcutaneous enoxaparin prophylaxis and 990 were given placebo. Patients receiving heparin prophylaxis had no greater risk of bleeding but had lower risk of ischemic stroke (71% relative risk reduction) lower venous thromboembolism (1.2% absolute risk reduction) and lower mortality (3.6% absolute risk reduction), not statistically significant.

6.9 Corticosteroids in Severe Sepsis

Controversy on the value of corticosteroids for the management of severe sepsis (septic shock) has existed for several decades. The pendulum of consensus for using corticosteroids in severe sepsis has swing back and forth over this time. Previous trials have shown that early, short course (48 h) of high-dose corticosteroids did not improve the outcome in severe sepsis. Renewed interest in lower-dose corticosteroids for stress-induced relative adrenal insufficiency (secondary to severe sepsis) has been in vogue for the past 5 years. This was based on initially two (of five) small randomized, controlled trials showing that relatively low-dose hydrocortisone decreased the need for vasopressor support for septic patients. An adequately powered study by Annare et al. (N = 300) subsequently showed that hydrocortisone plus fludrocortisone for 7 days significantly improved survival in septic shock syndrome in patients with inadequate response to 250 μg corticotrophin-stimulation test. However, the concept of relative adrenal insufficiency in sepsis and the criteria for this diagnosis has been controversial. Furthermore, total serum corticosal does not reflect the unbound free cortisol (the physiologically active form), and
critically ill patients with hypoalbuminemia commonly have high free serum cortisol but low total cortisol levels after corticotrophin-stimulation.117

In a more recent larger multicenter, randomized, double-blind trial of 499 patients with septic shock, hydrocortisone (50 mg every 6 h for 5 days) did not improve survival or reversal of shock.118 Of the total cohort 233 (46.7%) did not respond to corticotrophin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no difference in survival between the two study groups with “relative adrenal insufficiency” (mortality rate 39.2% vs 36.1%).118 Thus this somewhat larger study did not support use of low-dose corticosteroids or routine corticotrophin testing in severe sepsis. However, the sample size is too small to even show a relative reduction of 15–20% in mortality from a baseline of 35%, which would require a trial of at least 2,600 patients.119 Whether such a large daunting trial should be undertaken is open for debate. At present corticosteroids and corticotrophin test should not be routinely used in the management of severe sepsis or septic shock.

6.10 Intensive Insulin Therapy

Intensive insulin therapy to maintain strict glycemic control (even in non-diabetics) have been advocated for the management of severe sepsis.89 This was based on a study by Van den Berghe et al.120 involving critically ill surgical patients, which showed that strict euglycemia (4.4–6.1 mmol/l or 80–10 mg/dl) resulted in lower in-hospital mortality from 10.9% to 7.2%, mainly by reducing deaths from multiple organ failure in septic patients. In this study of 1,548 patients over 12 months intensive insulin therapy reduced mortality exclusively in the long-stay cohort (10.6% mortality vs 20.2%, \( p = 0.005 \)). The strict glycemic control in this trial not only reduced overall in-hospital mortality by 34%, but also bloodstream infections by 46%, severe acute renal failure requiring dialysis by 41%, reduction in median number of blood transfusions by 50%, and critical illness polyneuropathy by 44%.120 The mechanisms by which intensive insulin therapy could achieve such remarkable results were not clear, unless hyperglycemia or insulin resistance play a major role in the pathophysiology of these complications.

A recent trial confined to patients with severe sepsis \( (N = 537) \) did not confirm the extraordinary benefit with intensive insulin therapy.121 At 28 days there was no significant difference between conventional and intensive insulin therapy in mortality or organ failure, but significantly higher rate of severe hypoglycemia (17.0% vs 4.1%, \( p < 0.001 \)). This study also assessed the value of colloid (10% pentastarch, a low molecular-weight hydroxyethyl starch) compared to crystalloid (modified Ringer’s lactate) for fluid resuscitation. The colloid used in this study appeared to be harmful, with greater risk of renal impairment at recommended doses, and impairment of long-term survival at high doses.121 Thus, neither intensive insulin therapy nor colloid should be used in the management of severe sepsis and septic shock.
6.11 Vasopressin and Vasopressors

Persistent hypotension after infusion of crystalloids in septic shock is generally treated with vasopressors such as dopamine, dobutamine, adrenaline, noradrenaline, and vasopressin (as recommended by guidelines). It is unclear if there is a vasopressor of choice for the treatment of septic shock or for the treatment of shock in general. In a systematic review of eight randomized controlled trials (RCT) comparing various vasopressors, there was inadequate evidence to determine superiority of any one vasopressor to other agents in the treatment of states of shock. In contradiction a recent recommendation, supposedly on the basis of an evidence-based review, maintain that norepinephrine or dopamine is the vasopressor of choice in the treatment of septic shock. Norepinephrine may be combined with dobutamine when cardiac output is being measured. Epinephrine, phenylephrine, and vasopressin were not recommended as first-line agents in the treatment of septic shock. Vasopressin may be considered for salvage therapy, and low-dose dopamine was not recommended for the purpose of renal protection. Dobutamine was recommended as the agent of choice to increase cardiac output to physiological levels.

Vasopressin is an endogenously released stress hormone that is important in shock, and there is a deficiency of vasopressin in patients with septic shock. Low-dose vasopressin is widely used in septic shock based largely on observational studies, and on the postulate that vasopressin administration can restore vascular tone and blood pressure, thus reducing the need for the use of catecholamines. In a recent multicenter, randomized, double-blind trial of 778 patients with septic shock low-dose vasopressin (0.01–0.03 u/minute) or norepinephrine (5–15 μg/minute) in addition to open-label vasopressors were compared. There was no significant difference in the 28-day mortality rate (35.4% and 39.3%, \( p = 0.26 \)) or 90-day mortality (43.9% and 49.6%, respectively; \( p = 0.11 \)). In patients with less severe shock the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs 35.7%, \( p = 0.05 \)), but no difference was noted in those with severe septic shock. The statistical difference in the subgroup with less severe shock should be considered as hypothesis-generating concept to be confirmed by larger trials in subjects with less severe septic shock.

6.12 Blood Products in Sepsis

Anemia is common in critically ill patients, especially in those with severe sepsis. This may be due to a combination of factors including hemolysis from DIC, poor utilization of iron in the reticuloendothelial system secondary to inflammatory mediators, bleeding tendency from stress ulceration of the stomach and thrombocytopenia, as well as decreased generation of erythropoietin from decreased expression of the erythropoietin gene and protein mediated by TNF-\( \alpha \) and IL-1\( \beta \). The indications for blood transfusion in the critically ill patients are somewhat controversial, as there is
evidence that blood transfusion can be immunosuppressive. Furthermore some studies suggest that liberal blood transfusion in these critically ill patients may worsen the outcome. Rivers et al.\textsuperscript{95} as part of the 6 h early goal-directed-therapy recommended a hemacrit of 30\% (corresponding to hemoglobin value of about 10 g/dl), as threshold for blood transfusion. However, a previously randomized controlled, multicenter study on transfusion requirements in critically ill patients with hemoglobin <9 g/dl, compared liberal transfusion with hemoglobin <10 g/dl to restrictive transfusion below hemoglobin 7.0 g/dl to maintain up to 9 g/dl.\textsuperscript{128} The overall 30-day mortality was similar between the two groups. The mortality rate during hospitalization was significantly lower in the restrictive-strategy groups (5.7\% vs 13.0\%, \( p = 0.02 \)), as well as in subgroups with less acute illness, and under 55 years of age.\textsuperscript{128} Restrictive use of blood transfusion was thus least as effective and possible better to liberal red-cell transfusion, except for patients with acute myocardial infarction and unstable angina. This latter study however, was not specially addressing anemia in severe sepsis. Although Rivers et al.\textsuperscript{95} noted marked decrease in mortality when transfusion was provided early (within 6 h) of severe sepsis, this was not the primary intervention of the study.

More recently a large multicenter, observational study was conducted in 198 European ICUs to assess the effect of blood transfusion and mortality in a cohort of 3,147 critically ill patients, 1,040 (33.0\%) received a blood transfusion.\textsuperscript{129} Although there was a direct relationship between number of blood transfusions and the mortality rate, after multivariate analysis and adjustment for confounding variables, blood transfusion itself was not significantly associated with a worse outcome.\textsuperscript{129}

A systemic review of use of blood products in sepsis in 2004\textsuperscript{130} concluded that blood transfusion should be targeted to maintain hemoglobin at 7.0–9.0 g/dl; that erythropoietin is not recommended for sepsis associated anemia; fresh-frozen plasma should be given for documented deficiency of coagulation factors in the presence of active bleeding or before surgical procedures. Although erythropoietin decreases transfusion requirements there is no evidence of improved survival in a RCT in patients with severe sepsis or critical illness.\textsuperscript{130} High-dose antithrombin-III is also not recommended based on a large RCT which failed to show improved survival in patients with severe sepsis.\textsuperscript{131} However, reanalysis of the data in patients with high risk of death (30–60\%, showed lower mortality in the antithrombin-III group versus placebo at day-90 (\( p = 0.04 \)).\textsuperscript{132} Thus more studies are needed to confirm this effect in sicker patients, similar to the observation with activated protein C.

### 6.13 Ventilation and Other Adjunctive Therapy

Mechanical ventilation is a critical component of the management strategy in severe sepsis and acute lung injury or ARDS is a common complication. Lung protection strategy (use of relatively low tidal volumes) is an important component of the overall ventilation management. There is evidence from RCTs that small
tidal volume ventilation decreases mortality in patients with ARDS, and is beneficial in acute lung injury in septic patients. In a review on mechanical ventilation in sepsis-induced lung injury it was also recommended that a minimum amount of positive end-expiratory pressure should be maintained to prevent lung collapse. Prone positioning should be considered in those with severe ARDS, but the role of high-frequency oscillatory ventilation and airway pressure release ventilation in ARDS was uncertain. Unfortunately the ideal fluid management strategy in ARDS is unknown.

Acute renal failure occurs in approximately 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock. The combination of acute renal failure and sepsis is associated with a higher mortality (up to 70%) than sepsis without renal failure (35–45% mortality). The mechanism for renal failure in sepsis is probably multifactorial. Early in sepsis as arterial vasodilatation occurs, it results in renal sympathetic and angiotensin activities leading to renal vasoconstriction with sodium and water retention. Renal perfusion is then further compromised by systemic hypotension, intravascular hypovolemia, diffuse coagulopathy (DIC) with subsequent acute tubular necrosis. Patients with sepsis and acute renal failure are hypercatabolic and studies suggest that increased duration and frequency of dialysis can improve survival. A recent study showed that daily hemodialysis as compared to alternate-day hemodialysis was associated with less systemic inflammatory response of sepsis (22% vs 46%, p < 0.01), lower mortality (28% vs 46%, p < 0.01) and a shorter duration of acute renal failure/mean ± SD, 9 ± 2 vs 16 ± 6 days, p = 0.001).

Continuous renal replacement therapy by veno-venous hemofiltration is becoming more popular for the management of acute renal failure in sepsis. However, there is no definite proof of its superiority over hemodialysis. There is evidence, however, that in patients with sepsis-related acute renal failure, better survival was achieved with aggressive ultrafiltration rate of 45 ml/kg/h than with a rate of 35 ml/kg/h.

### 6.14 Immunotherapies for Sepsis

Polyvalent intravenous immunoglobulins (IVIG) modulate the expression and function of FC receptors, activation of complement and cytokine networks, production of idiotype antibodies, and activation, differentiation, and effector functions of T and B cells; thus, could be beneficial in severe sepsis. However, small RCT of an adjunctive IVIG in bacterial sepsis has shown conflicting results. Two recent systematic reviews and meta-analysis of the value of IVIG in sepsis have arrived at different conclusions. In a review by Paldal and Gotzsche, the meta-analysis of all trials showed a relative risk of death with IVIG of 0.77 (95% CF, 0.68–0.88). High-quality trials, however, showed no significant survival benefit, whereas other less stringent trials showed a relative risk of death of 0.61 (95% CI, 0.5–0.73). Since high-quality trials failed to demonstrate a reduction in mortality, IVIG was not recommended for treatment of sepsis. A more recent review and meta-analysis
analyzed 20 RCT \((n = 2,621)\) and found an overall survived benefit with IVIG (risk ratio 0.74 (95% CI, 0.62–0.89)). The benefit was greatest for those with severe sepsis or septic shock (risk ratio 0.64, CI 0.52–0.79), receiving a total dose of \(\geq 1\ g/kg\) for \(>2\) days.\(^{142}\) A large randomized trial of IVIG was recommended by the authors. However, a sensitivity analysis on high-quality trials found no evidence that IVIG was beneficial in severe sepsis,\(^{143}\) similar to Rildal and Gotzsche\(^{141}\) results.

In a recent multicenter, relatively large RCT \((n = 653)\) of (score defined severity) septic patients there was no significant reduction of mortality with IVIG vs placebo at 7 or 28 days (39.3% vs 37.3%, respectively).\(^{144}\) Although exploratory finding revealed a 3-day shortening of mechanical ventilation in the surviving patients, IVIG did not improve the 4-day pulmonary function, and had no effect on plasma levels of IL-6 and TNF-receptors I and II.\(^{144}\) Thus, IVIG at the dose used 10.9 g/kg total dose) does not appear beneficial in severe sepsis.

Granulocyte-colony-stimulating factor (G-CSF) besides its role on granulopoiesis enhances many functions of mature granulocytes such as chemotaxis, phagocytosis, and microbicidal and oxidative activity. G-CSF seems to combine its proinflammatory effects on several granulocyte function but with anti-inflammatory effects on mononuclear cells.\(^{54}\) G-CSF exerts its anti-inflammatory effects on monocytes by lowering the release of proinflammatory cytokines and increasing the release of anti-inflammatory mediators. There have a few small RCTs of G-CSF in non-neutropenic patients with sepsis. In one of the larger RCT of hospitalized patients with multilobar pneumonia \((n = 480)\), there was no survival benefit with G-CSF but a trend to reduced mortality was noted in patients with pneumococcal bacteremia.\(^{83}\) In a small RCT of 44 preterm neonates with clinical diagnosis of early-onset sepsis, G-CSF did not affect mortality but reduced the incidence of secondary nosocomial infections.\(^{84}\) The clinical benefit of future immunotherapy should be defined by large multicenter RCT utilizing INF-\(\gamma\) and GM-CSF as these drugs might correct the immunoparalysis seen in late severe sepsis.

### 6.15 Genetics and Sepsis

Wide variability exists in the susceptibility to and outcome from sepsis even within similar cohorts matched for age and comorbid illnesses. Some of this variability may be due to genetic variation (polymorphisms) in genes encoding components of the innate immune response. Although experimental models have provided insight on the effects of these genetic polymorphisms in sepsis, there are disparate results observed in many studies of polymorphisms and sepsis outcome in humans.\(^{145}\) Polymorphisms in genes encoding proteins involved in the recognition of bacterial pathogens (TLR-4, CD14, MBL, Fc(gamma) RIIIa) and the response to bacterial pathogens (TNF-\(\alpha\), IL-1\(\alpha\) and \(\beta\), IL-1R agonist, IL-6, IL-10, HSPs, ACE-1, and PAI-1) could all potentially influence the manifestation and outcome of sepsis. In a review of clinical studies on two candidate genes, TNF-\(\alpha\) and TLR4, studies
examining the relationships between single nucleotide polymorphisms (SNPs) and sepsis risk and outcome have found, inconsistencies in the literature. The main limitations relate to the translation of experimental observations into reproducible genotype–phenotype associations. The reasons for these deficiencies are mainly due to insufficient sample size because of the complexities and multifactorial nature of the predisposing and prognostic variables as well as the background genetic heterogeneity.

The complexity of genetic predisposition to sepsis is compounded by the many interacting pathways involved in the sepsis syndrome. Not only genetic variations in genes encoding the innate immune response and the inflammatory cascade that need to be considered, but also polymorphisms of genes regulating the coagulation and fibrinolytic systems, and ARDS need to be included. For instance, deletion polymorphism, within the promoter region of the plasminogen-activator inhibitor-1 gene leads to impaired fibrinolysis and influences the severity and outcome of meningococcal disease and susceptibility to severe sepsis. Also factor V Leiden mutation (associated with thrombotic events) can exacerbate purpura fulminans in meningococcal sepsis, but can provide survival advantage in severe sepsis.

Another genetic factor that could be useful as a predictor of clinical outcome for patients with sepsis is the HLA-DR antigen expression on monocytes which reflects the individual’s immune status. Reports suggest that long-term sharp declines in HLA-DR antigen expression on monocytes corresponds to the level of immunoparalysis and reflects a poor outcome.

In the future it is predicted that therapeutic trials and actual treatment regimens for patients with sepsis are likely to be designed to target specific genotypes and associated cellular responses, to maximize clinical response and patient safety. However, we are many years away from achieving this goal of individualized targeted treatment. To confirm the predictive value of multiple allelic variants and risk for severe sepsis will require large population based studies of thousands of subjects; and to assess prognostic outcome will need several hundreds of septic patients in trials.

6.16 Future Directions

Although our understanding of the pathogenesis of the sepsis syndrome has increased remarkably in the past 2 years, the advances in new therapeutics have been disappointing. In the past 2 decades numerous promising immunomodulatory agents have been tested in clinical trials (see Table 6.1) but only one has proven but limited value (activated proteins C). There are several biological agents which appears very promising in experimental models that need to be tested in large clinical trials (see Table 6.2). However, it is unclear and somewhat dubious that any of these agents will be of proven clinical value to be used in the future for the management of severe sepsis. Even if one or more of these biologics prove to be effective in RCT, it would take several years for approval for marketing and they would likely be very expensive with limited indications for specific subgroups.
Drugs currently approved for other medical conditions have been proposed as novel therapies for the sepsis syndrome and are inexpensive. These include the statins (HMG-CoA reductase inhibitors), which alter the lipid metabolism and also have anti-inflammatory activity, and have proven benefits in many diseases involving vascular inflammation and injury. Recent animal experiments suggest that the statins may reduce morbidity and mortality in sepsis, when administered before the insult. The pleiotropic effects of statins as anti-inflammatory and immunomodulatory agents lend support to the potential for these agents as new therapy for prevention or treatment of severe sepsis. However, many therapeutic interventions, shown effective in animal experiments when administered before the insult, are not effective in the clinical settings of sepsis syndrome. Although large well-designed randomized, blinded trials should be undertaken with statins for sepsis, it would best be tested in critically ill (high risk) patients even before the onset of sepsis (similar to trials of prophylactic heparin).

Table 6.1 Immunomodulatory agents tested in sepsis in clinical trials (Data compiled from [55, 118, 144, 152, 153, 154])

| Anti-inflammatory agents                                      | Comments                                      |
|--------------------------------------------------------------|-----------------------------------------------|
| • Glucocorticoid (high and low dose)                         | No proven benefit                             |
| • TNFα antibodies                                            | Mixed results                                 |
| • Recombinant Type I & II soluble (TNFα) receptors           | No survival benefit                           |
| • Recombinant 1L-1Ra                                        | No survival benefit                           |
| • Platelet activity factor antagonist                        | No survival benefit                           |
| • Bradykinin inhibitor                                       | No survival benefit                           |
| • Ibuprofen                                                  | No survival benefit                           |

Anti-Endotoxin compounds

- Endotoxin antiserum                                        | No survival benefit                           |
- Endotoxin monoclonal antibody                               | No survival benefit                           |
- Recombinant bactericidal/permeability-increasing protein    | Improved morbidity but not survival; further studies needed |

Immunostimulatory agents

- Granulocyte colony-stimulating factor (G-CSF)                | No benefit in larger trials                   |
- Macrophage-granulocyte-CSF                                  | Needs larger trials                           |
- Intravenous immunoglobulin                                  | No proven benefit                             |

Anticoagulation agents

- Activated Protein C                                         | Some improved survival in poor risk           |
- Antithrombin III                                             | Overall no survival benefit, potential benefit in poor risk |
- Tissue factor pathway inhibitor                              | No improvement                                |
Another group of agents, thiazolidinediones, now in use for diabetes mellitus may also have therapeutic benefit in the septic patients. Peroxisome proliferator-activator receptor-gamma (PPAR\(\gamma\)) is a member of the nuclear receptor superfamily and a ligand-activated transcription factor with pleiotropic effects on lipid metabolism, inflammation, and cell proliferation. The thiazolidinediones (pioglitazone, rosiglitazone, troglitazone, and ciglitazone) are synthetic PPAR\(\gamma\) agonists used mainly as insulin-sensitizing drugs. There are several in vitro and in vivo studies that have demonstrated that these agents may be useful in sepsis and inflammation. Thus large clinical trials are warranted in critically ill patients with high risk of sepsis, early or before the event, with these agents.

It should not be surprising that any one biologic agent acting on a single pathway in the complex multisystem pathway process of sepsis should fail (i.e., anti-TNF antibodies). Although excessive production of a molecule (proinflammatory cytokine) may be harmful, blockage will often be harmful as well as these substances serve a useful purpose. Hence we should consider the sepsis syndrome in a different perspective, liken to a polyendocrine acute disorder (without the luxury of time), where we need to achieve a “normal balance” of inflammatory and anti-inflammatory and immune mediators. The distance in the future seems to be far (many years from now), when we can simply do a blood test to determine which mediator(s) need suppression and which needs replacement.

A promising approach for treatment of severe sepsis is a combination of immunomodulatory agents, thymosin \(\alpha_1\) (a naturally occurring thymic peptide to augment T cell function) combined with ulinastatin (a Kunitz-type protease inhibitor found in urine) that can control a series of proinflammatory mediators and cytokines. In a preliminary prospective randomized trial of 120 patients with sepsis caused by carbapenem resistant intra-abdominal infection, 60 patients received the combination study agents and the others placebo. Although there was only a trend

**Table 6.2** Potential new therapies for sepsis (Compiled from data obtained from [23, 24, 26, 58, 81, 155–159])

| Agent | Comments |
|-------|----------|
| Interferon-gamma | Restore monocyte function, counter late immune paralysis |
| 1C14 (CD\(14\) monoclonal antibody) | Suppresses inflammatory response to endotoxin |
| C5a antibodies | Restores neutrophils function |
| CD40-receptor monoclonal antibodies | Decreases lymphocyte apoptosis |
| Anti-HMGB1 antibodies | Inhibit systemic inflammation |
| Anti-macrophage migration inhibitory factor (M1F) antibodies | Suppresses inflammatory reaction |
| Ethyl pyruvate | Anti-inflammatory effect |
| ClinHibitor (CIINH) | Interacts with endotoxin to modify inflammation |
| Antioxidants | Counter-free radicals (i.e., reactive oxygen and nitrogen species) |

HMGB1 = high mobility group box-1
in improved survival (due to small sample size) on day 28, there was significantly greater survival in the immunomodulatory group vs control at 60 and 90 days \((p = 0.033)\). Moreover, the treated study group had significantly shorter duration of mechanical ventilation and ICI stay \((p < 0.001)\), and a lower incidence of shock compared to control group \((p = 0.026)\). Another intriguing approach would be to combine immunomodulators with anticholinergic agents to block \(\alpha 7\) cholinergic receptors, as there is evidence in a murine model of intra-abdominal sepsis that deficiency of \(\alpha 7\) receptor is associated strongly with increased clearance of coliform bacteria and reduced dissemination. The \(\alpha 7\) cholinergic receptors are key to anti-inflammatory cell signaling induced by acetylcholine and the cholinergic anti-inflammatory pathway.

6.17 Conclusion

Sepsis syndrome still carries a high mortality in high-risk patients with organ(s) dysfunction. The pathogenic mechanism is extremely complex and involves several interacting pathways and networks. The end result is dysregulation of the inflammatory and immunomodulatory systems. A new sepsis classification known as “PIRO” has been proposed. PIRO stands for predisposition, infection, response, and organ dysfunction. It is hoped that this system will facilitate better understanding and improved therapeutic interventions for sepsis, but this is doubtful. The evidence suggests that early recognition and early intervention (immediate appropriate antibiotics and early-goal-directed therapy) are most important in affecting outcome. A recent national educational effort to promote bundles of care (a resuscitator tasks to begin immediately and be accomplished within 6 h; and a management bundle – four tasks completed within 24 h), for severe sepsis and septic shock in Spain was associated with improved guideline compliance and lower hospital mortality. However, compliance rates were still low and the improvement in the resuscitation bundle lapsed by 1 year.

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