SEPSIS WITH ACUTE ORGAN DYSFUNCTION

By

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KEY POINTS

- Sepsis is the combination of a known or suspected infection and an accompanying systemic inflammatory response syndrome.
- Severe sepsis is sepsis with acute dysfunction of one or more organ systems; septic shock is a subset of severe sepsis.
- Severe sepsis is common, frequently fatal and expensive. More than 750,000 cases occur annually in the United States.
- Effective management of patients with severe sepsis requires early identification, cardiopulmonary support, antibiotics, source control, and general supportive care.
- The prognosis of the patient with severe sepsis is related to the number of dysfunctional organs.
- Cardiopulmonary support consists of early and aggressive fluid resuscitation, maintenance of mean arterial pressure ≥ 60 mm Hg, and measures to maximize and maintain tissue oxygenation.
- Patients should receive early intravenous empirical antibiotics directed at all possible sources of infection. Appropriate antibiotics reduce mortality by 10% to 15% in patients with severe sepsis.
- Source control can be surgical or nonsurgical and is intended to remove or lessen the burden from the primary focus of infection.
- Despite appropriate antibiotics, source control and organ support, mortality in patients with severe sepsis remains at 28% to 50%.
- Specific antisepsis interventions have recently been introduced that target multiple pathophysiological aspects of the sepsis cascade and can improve outcomes.
- To maximize outcomes, supportive measures must be introduced to ensure proper nutrition, maintain fluid and electrolyte homeostasis, promote tissue oxygenation and prevent complications.

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INTRODUCTION

Sepsis with acute organ dysfunction (severe sepsis) is common, frequently fatal and represents a significant healthcare burden. The incidence and associated mortality and morbidity of severe sepsis are commonly under-estimated. This is a function of a number of factors. Severe sepsis is not generally reported as a primary diagnosis. For example, while steps are underway to address this issue, the most recent edition of the ICD-9 CM lacks a diagnostic code for severe sepsis. Instead, severe sepsis is often coded as a complication of another disorder (eg, cancer, pneumonia). Several recent publications have evaluated the epidemiology of severe sepsis in the United States (US). (Angus DC et al, 2001) (Martin GS ET AL, 2003, 2003) They estimate that the annual incidence of severe sepsis in the US is in the 240.4 to 300 cases per 100,000 population range. Consequently, in 2003 there were approximately three-quarters of a million cases of sepsis in the US. In Europe, the incidence of severe sepsis exceeds 200,000 annually. (Davies A et al, 2001) Reported mortality rates in patients with severe sepsis range from 28% to 50% or greater. (Angus DC et al, 2001) (Zeni F et al, 1997) Thus, in the United States and Europe, at least 700 to 1300 patients die daily from severe sepsis. Patients with severe sepsis account for annual healthcare expenditures in excess of $16 billion in the United States and £5.2 billion in Europe. (Angus DC et al, 2001) (Davies A et al, ESICM, 2001)

The incidence of severe sepsis peaks in children younger than 12 months of age, remains low until midlife and then progressively increases. (Angus DC et al, 2001) In the study by Angus et al, of the patients who developed severe sepsis nearly two-thirds were older than 65 years of age. This population also accounts for more than three-fourths of the overall healthcare costs of the disease. The incidence of severe sepsis is anticipated to increase approximately 1.5% per year until at least 2050. (Angus DC et al, 2001) This increase is due to a number of factors including age shifts in the population, prevalence of more critically ill patients (eg, transplant recipients), and increases in the numbers of invasive diagnostic procedures and monitoring techniques. This predicted increase has significant implications for the critical care community since it has been estimated that by 2020 there will be a 22% shortfall of available intensivists’ hours to meet this demand. (Angus DC et al, 2000.)

DEFINITIONS

In 1992, members of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) developed a set of consensus definitions for sepsis and related disorders (Table 1). (Bone RC, Balk RA ET AL, 1992, 1992) (Table 1. ACCP/SCCM Criteria for Sepsis and Related Disorders) The Consensus Committee believed that standardized terminology would improve the ability of clinicians to make an early diagnosis of sepsis, provide for more reliable reporting of the incidence and severity of sepsis and facilitate early therapeutic interventions. In addition, they hoped that acceptance of the definitions would help to standardize research protocols and improve the dissemination and application of clinical information from subsequent studies. The Consensus Committee acknowledged that the clinical presentation of sepsis spanned a continuum of severity; however, they recognized certain common phases and provided specific definitions for them (Figure 1) (Figure 1. Sepsis Venn Diagram). Sepsis was defined as the presence of at least 2 of the 4 systemic inflammatory response (SIRS) criteria developing in response to a documented or suspected infection. Severe sepsis was sepsis plus acute organ dysfunction (Table 2). (Table 2. Clinical Manifestations of Acute Organ Dysfunction) Although these definitions have provided an important framework, they have been criticized as being too sensitive and not providing enough information for clinicians attempting to make a diagnosis. (Vincent JL, 1997) In addition, the definitions lack a clear pathologic basis and fail to incorporate the hemostatic component of severe sepsis. (Bone RC, 1992)

However, the ACCP/SCCM definitions have held up to the test of time. In December 2001, representatives from the SCCM, the ACCP, the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society met to revisit the definitions of sepsis and related disorders. (Levy MM et al, 2003) Following an intensive review, the group concluded that there was no evidence that would justify altering the definitions first proposed by the ACCP/SCCM. A part of the discussion, however, they expanded the lists of signs and
symptoms of sepsis that are reflected from experience gained at the bedside that prompts a clinician to say that the patient “looks septic.” Among these criteria, they included additional general (eg, altered mental status, significant edema or positive fluid balance, hyperglycemia), inflammatory (increased C-reactive protein or procalcitonin), hemodynamic (SV_{\text{O}2} \geq 70\%, cardiac index \geq 3.5 \text{ L/min}^1\text{m}^2), organ dysfunction (coagulation abnormalities, ileus, hyperbilirubinemia), and tissue perfusion (decreased capillary refill or mottling) abnormalities. They also emphasized the need for a precise method to characterize and stage patients with sepsis. Creation and validation of such a system would bring an increased degree of precision to clinical trials, and facilitate the abilities of clinicians to more fully characterize the disease and to select appropriate therapies. As a subject for debate, they proposed the PIRO (PreDisposition, Insult/Infection, Response, Organ dysfunction) model: a staging process that utilizes concepts from the tumor nodes metastases (TNM) system of clinical oncology.

PATHOGENESIS

The pathogenesis of the septic response involves interaction of the host with a microbial invader. The outcome of the process is then dependent upon the capability of the immune system, endothelium and hemostatic mechanisms to contain and then eliminate the process and the ability of the patient’s physiology to restore homeostasis.

MICROBIAL FACTORS

Microbes possess a number of factors that facilitate their growth in a normally sterile environment (Figure 2). (Figure 2. Pathogenic Microbial Factors) These include properties of their capsule or envelope, cell wall, and metabolic factors such as the production of exotoxins. Pili of strains of Escherichia coli can enable the coliform bacillus to adhere to Tamm-Horsfall protein coating the urothelium of the lower urinary tract or P-blood group antigens expressed on the epithelium of the renal pelvis. Capsular polysaccharides of certain strains of Streptococcus pneumoniae render the organism resistant to phagocytosis. The cell wall of gram-negative bacteria consists of an inner phospholipid bilayer with embedded transport proteins and an outer layer composed of lipoproteins, lipopolysaccharide, outer membrane proteins, and capsular polysaccharides. Bacterial lipopolysaccharide is generally considered to be the principle element in the initiation of the septic response in patients with severe gram-negative infections. While components of the cell wall of gram-positive bacteria may be able to elicit some of the effects of endotoxin, much of the pathogenicity of gram-positive organisms is the result of exotoxins. Some of these exotoxins can function as superantigens: chemical substances that simultaneously bind to common sequences on both the major histocompatibility complex (MHC) and the T cell receptor (TCR). Superantigen-binding and T cell activation can produce a flood of cytokines and is independent of the antigenic specificity normally required for activation of various T cell clones and the need for costimulatory. Streptococcal and Staphylococcal pyrogenic exotoxins acting as superantigens are believed to play a critical role in the pathogenesis of toxic shock syndrome. Hyaluronidase secreted by some bacteria can facilitate their spread along tissue planes.

HOST FACTORS

The host has a spectrum of mechanisms that support its ability to resist the invasive properties of some microorganisms (Table 3). (Table 3. Host Factors that Have Been Established to Contribute to an Increased Risk for Sepsis) The epithelium is the first line of defense against infection. It not only provides a mechanical barrier but also contributes other protective functions in a site-specific fashion (eg, mucociliary flow in the respiratory tract, gastric pH). The immune status of the host is a function of both inherited and acquired components. Genetic polymorphisms can be responsible for dissimilar responses to infection. For example, polymorphisms in toll like receptors may govern an individual’s response to endotoxin while variants in the promoter region of the tumor necrosis factor gene can help determine the risk for sepsis following trauma. (O’Keefe GE et al, 2002.) Age, disease, exposures and interventions are all acquired risk factors for sepsis. Young children and the elderly have an increased incidence of sepsis. Various morbidities can increase the risk of sepsis. Patients with diabetes mellitus are at increased risk of infection for a variety of reasons. Hyperglycemia appears to facilitate colonization and growth of organisms such as Staphylococcus aureus and Candida species. In addition, they have a variety of defects in cell-mediated immunity and phagocytosis. Genetic and acquired factors often
interact to determine susceptibility to disease. For example, HIV-positive patients who are heterozygous for a deletion in the gene for the macrophage CCR5 receptor or in the promoter region of the gene have slow progression of HIV disease compared to patients with the wild-type genotype.

INNATE IMMUNE SYSTEM
The human immune system is composed of adaptive and innate components. The adaptive elements are specialized B- and T-cells. Each of these cells has a structurally-unique B- or T-cell antigen receptor that is generated randomly (ie, not genomically encoded). When a lymphocyte bearing a useful receptor encounters a pathogen, it is selected for clonal expansion. While adaptive immunity contributes significantly to the overall immune response, as well as providing protection against future encounters with the organism, generation of a significant primary humoral or cellular immune response takes days to weeks, time unavailable to a patient with severe sepsis. Unlike the adaptive immune system, elements of the innate immune system can respond instantly to a challenge. This property helps explain the overwhelming systemic inflammatory response generated in patients with severe sepsis. We will therefore focus the remainder of this section on innate immunity.

Cellular Components of Innate Immunity
In humans, cellular effectors of innate immunity are monocytes/macrophages, neutrophils, natural killer (NK) cells and platelets. The monocyte/macrophage is the human component of the amebocyte: an innate immune cell present in invertebrates. Monocytes originate in the bone marrow and then transit the peripheral blood to lodge in tissues as macrophages, Kupffer cells and other reticuloendothelial elements. Pathogen-associated molecular pattern receptors are a key component of the innate immune system. (Medzhitov R et al, 2000.) Unlike the antigen receptors of B- and T-cells, these receptors are encoded in the germline, are functionally divided into three classes (secreted, endocytic, signaling), and trigger an immediate effector function. Secreted pathogen-associated molecular pattern identification is discussed in the section on fluid-phase elements of innate immunity. Endocytic pattern recognition receptors such as the macrophage mannose- or scavenger-receptor recognize highly-conserved molecular components of microbial cell walls and mediate their phagocytosis by monocytes/macrophages. Signaling receptors on monocytes/macrophages identify microbial molecular patterns and activate signal transduction pathways that upregulate a spectrum of immune response genes responsible for a variety of cellular functions including cytokine release.

The toll gene, a transmembrane signaling protein present in organisms as primitive as the fruit, is believed to be very important to humans in the septic state. Humans possess at least 10 toll gene homologues known as toll like receptors (TLRs). The TLR genes code for cell membrane molecular pattern receptors that play an integral role in the generation of local and systemic inflammatory responses. Natural ligands of the various TLRs include lipopolysaccharide (TLR4), peptidoglycan (TLR2), and flagellin (TLR5). The role of TLR proteins can be illustrated by the response of the innate immune system to lipopolysaccharide (LPS). Lipopolysaccharide is an outer leaflet compound molecule that is unique to gram-negative bacteria; following infusion into humans, LPS reproduces many of the features of sepsis including activation of the coagulation and complement systems. (Suffredini AF et al, 1989.) (Tapper H et al, 2000.) Upon entering the plasma, LPS is recognized, bound, and transported to innate immune effector cells by LPS-binding protein (LBP). The cell membrane CD14 receptor on monocytes and neutrophils accepts the LPS from LBP and forms a trimeric complex with TLR4 and MD-2, another membrane protein. Once formed, the complex activates a signal transduction pathway that phosphorylates IκB. As a result, IκB undergoes degradation and releases bound NF-κB. The latter then migrates into the nucleus where it induces transcription of a wide variety of immune- and inflammatory-response genes. (Medzhitov R et al, 2000.) Transcription of these genes is responsible for the upregulation of tissue factor (TF) on monocytes/macrophages and endothelium, and for the cytokine cascade that creates many of the elements of SIRS in patients exposed to LPS. These key elements of the inflammatory response are therefore linked to the coagulation cascade, with these two responses combining to form the major facets of the pathophysiologic derangements in septic humans.
Tissue factor is responsible for initiating coagulation through the previously named extrinsic pathway, now called the tissue factor pathway. Tissue factor is expressed constitutively on a limited number of cells and can be induced in a wide variety of cells following exposure to endotoxin or cytokines. Cells normally expressing TF include extravascular monocytes/macrophages and fibroblasts. (Doshi SN et al, 2002.) Sequestered from circulating factor VIIa, these cells are poised to activate coagulation immediately following disruption of a blood vessel wall. Tissue factor expression can be upregulated in a variety of other cells that don’t express the cell membrane protein constitutively. As a result, following exposure to tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), CD40 ligand, or other substances, TF expression can be identified on subsets of cells including circulating monocytes, vascular smooth muscle cells, a subset of endothelial cells, and possibly alveolar epithelial cells. (Marshall BC et al, 1991.) During acute inflammation, activation of the cytokine cascade is followed by rapid upregulation of TF on monocytes and a shift of components of the hemostatic system from an antithrombotic to a prothrombotic state. Circulating TF antigen and microparticles shed from inflammatory cells and platelets contribute to the process.

**Fluid-Phase Elements: Cytokines and Complement**

Once monocytes/macrophages have been activated, there is a response by fluid phase elements. These include cytokines and activated components of the complement system. Tumor necrosis factor-α is a central cytokine in this process. Once released, it functions in an autocrine, paracrine and endocrine fashion in a positive feedback loop to stimulate additional TNF-α production as well as production of other cytokines. A variety of other proinflammatory cytokines are released including IL-1, IL-2, IL-6, IL-8, IL-10, platelet activating factor (PAF), and interferon-γ. The cytokine cascade produces a vast array of biological effects recognized as the systemic inflammatory reaction.

As sepsis persists, however, there may be a shift in the cytokine profile from an inflammatory to a predominantly antiinflammatory one. (Hotchkiss RS et al, 2003.) Loss of T cells, B cells, and follicular dendritic cells through apoptosis may also contribute to the immunosuppression through two processes: (1) loss of immunocytes, and; (2) the direct immunosuppressive effect of apoptotic cells. (Hotchkiss RS et al, 2001.) (Hotchkiss RS et al, 2002a) As the antiinflammatory reaction progresses, the septic patient may become anergic. While it can be helpful to think that the response of the immune system to a septic insult progresses in discrete and identifiable stages, this may not be true. In fact, some have proposed that distant from the original source or inflammatory focus, the body’s reaction is predominantly antiinflammatory from the onset. (Mumford RS et al, 2001.) The complex nature of this process may partially explain why clinical trials of various biologic response modifiers (BRMs) such as TNF-α antagonists have not improved overall survival and have even been detrimental in some cases.

Plasma components of the complement system circulate in an inactive state and develop enzymatic activity only after proteolysis or a conformational change. The system works by depositing components of complement on foreign substances/organisms requiring opsonization and by promoting inflammation. Complement can be activated through three pathways: (1) classical pathway; (2) alternate pathway; and, (3) mannann-binding lectin pathway. The classical pathway is activated by IgM or IgG antibodies bound to a particular pathogen or by C-reactive protein (CRP) released during the acute phase reaction. The classical pathway serves as a link between the complement and hemostatic systems. Components generated during activity of the classical pathway increase the exposure of phosphatidylserine on endothelial cell surfaces. (Vervloet MG et al, 1998.) This provides the phospholipid that is essential for various phases of clot formation. Activation of the alternate pathway results when complement binds directly to pathogen associated molecular patterns on the surfaces of bacteria or fungi. Mannann-binding lectin is an example of a secreted pathogen-associated molecular pattern receptor. It is synthesized in the liver and secreted into the plasma during the acute phase reaction. It binds to carbohydrate structures common to gram-positive and gram-negative bacteria, yeasts, and some viruses and parasites. Once binding occurs, mannann-binding lectin-associated proteases are activated and help to destroy the organism. Following complement activation, some of the molecular elements of the system are cleaved
producing fragments with biological activity. For example, N-terminal proteolysis of C3, C4, and C5 release small peptides (eg, C5α) which bind to G-protein-coupled receptors on a variety of cells to produce chemotaxis, increased vascular permeability, etc. It has been proposed that C5a in excess can paralyze neutrophil function. In an experimental model, antibody-mediated neutralization of excess C5a protected animals against septic death. (Riedemann NC et al, 2002.)

ENDOTHELIAL CELL DYSFUNCTION
With approximately 10\(^{11}\) endothelial cells and a surface area estimated to exceed 1000 m\(^2\), the endothelium surpasses the skin as the largest organ in the body. (Sporn LA et al, 2001.) (Hack CE et al, 2001.) The great majority of the endothelium is located in the microvasculature: in that region, the endothelial surface area per unit of blood volume is two to three thousand times greater than in the larger blood vessels. (Esmon CT, 2001.) The endothelium serves as the interface between inflammation and coagulation. (Levi M et al, 2002.) Situated at the junction of the flowing blood and extracellular space, the endothelium influences a variety of inflammatory and hemostatic processes (eg, cell-trafficking, vasoregulation, thrombosis/antithrombosis) and plays a key role in the inflammatory, prothrombotic and impaired fibrinolytic components of sepsis. (Gross PL et al, 2000)

Endothelial dysfunction is a key element in the pathogenesis of severe sepsis. This may be secondary to the effects of endotoxin or proinflammatory cytokines on endothelial cells. For example, a single injection of endotoxin in rabbits produces desquamation of approximately 25% of the aortic endothelial surface area within five days. (Leclerc J et al, 2000.) Alternately, organisms such as Rickettsiae can directly infect endothelial cells. Severe endothelial injury can produce a microvascular coagulopathy and acute organ dysfunction. (Vincent J-L, 2001.) Importantly, however, endothelial cells are differentially regulated in space and time. That is, the endothelium of the lung may respond differently to a septic insult than similar cells in the spleen. (Aird WC, 2003.) The phenotype of endothelial cells also varies over time. For example, an endothelial cell population with an antithrombotic phenotype may transiently switch to prothrombotic for a period of time following exposure to TNF-α.

Thrombomodulin (TM), ICAM-1, E-selectin and von Willebrand factor are normal membrane-bound and intracellular endothelial cell components. Therefore, elevated circulating levels of the soluble (s) forms of these proteins are markers of endothelial dysfunction and injury. (Reinhart K et al, 2002a) In children with septic shock, soluble TM levels are increased and the levels correlate with survival status and the extent of organ dysfunction. (Krafte-Jacobs B et al, 1998.) Immunohistochemical studies of skin biopsy samples from patients with meningococcal septicemia demonstrate decreased stainable TM and endothelial cell protein C receptor (EPCR). (Faust SN et al, 2001.) This appears to result from a combination of shedding of cell surface TM and EPCR plus downregulation of endothelial cell synthesis and/or expression of these essential molecules. These changes suggest that many patients with sepsis may have insufficient TM and EPCR to convert Protein C to Activated Protein C, though this is not universally true. (de Kleijn ED et al, 2003.). In a population of patients with sepsis, plasma levels of von Willebrand factor, ICAM-1 and sE-selectin were significantly increased within 8 hours of the development of the acute respiratory distress syndrome (ARDS). (Moss M et al, 1996) Damaged endothelium and activated leukocytes and platelets also release microparticles with procoagulant properties (eg, MP-associated TF). (Combes V et al, 1999.)

Apoptosis differs from necrosis in that it is a highly-regulated physiologic process that plays an important role in cell physiology. Apoptosis can be identified through both morphological and molecular techniques. Cytokines and inflammatory cells can damage the endothelium and induce apoptosis. (Hack CE et al, 2001.) In patients with severe sepsis, the apoptotic process also varies in space and time. That is, the apoptotic process may not occur uniformly, in all organs, at the same time, or with all types of infections. (Hotchkiss RS et al, 2002.) This may help to explain the commonality of the ARDS in patients with severe sepsis. Endothelial cell apoptosis may produce abnormalities in cell trafficking, vasoregulation, and antithrombosis/thrombosis that may contribute to the pathogenesis of septic manifestations such as multiple organ dysfunction, impaired microvascular blood flow, and inability of the body to restore homeostasis.
PATHOPHYSIOLOGY

CARDIOVASCULAR SYSTEM

Severe sepsis is accompanied by significant alterations in cardiovascular physiology. Sepsis-induced hypotension is multifactorial in origin. Contributory factors include redistribution of blood flow, impaired metabolic autoregulation, release of vasoactive mediators, third-spacing of fluids, dehydration, increased insensible fluid losses, vomiting, diarrhea, etc. Early in the process, systemic vascular resistance (SVR) may be high and cardiac output (CO) decreased. However, the systemic vascular resistance typically falls and cardiac output increases—producing a hyperdynamic circulatory state.

Myocardium

Reversible myocardial dysfunction of variable severity may occur in as many as 40% of patients with severe sepsis. (Fernandez CJ Jr et al, 1999) Myocardial depression often occurs in survivors very early in the septic process, progresses over the first three days, and then resolves after 7 to 10 days in survivors. (Kumar A et al, 2000.) Dysfunction may be systolic, diastolic, left- or biventricular. Potential explanations include myocardial injury mediated by cytokines such as tumor necrosis factor, release of non-cytokine mediators such as prostanoids and nitric oxide (NO), catecholamine-induced myofibrillar damage, and myocardial ischemia with reperfusion injury (Ruiz Bailén MR, 2002.) An aggregate of clinical studies suggest that a circulating myocardial depressant factor, not global myocardial ischemia, is a major contributor to myocardial dysfunction in patients with severe sepsis. In a study of coronary hemodynamics in patients with severe sepsis and septic shock, Dhainaut et al reported that coronary blood flow and net myocardial lactate consumption are increased in this disorder. (Dhainaut JF et al, 1987.)

Cardiovascular dysfunction may also be manifest by ventricular dilation, abnormalities of wall motion, increased levels of cardiac troponin and electrocardiographic changes. The explanation for the paradoxical association of a hyperdynamic circulation and myocardial dysfunction involves an interaction of compensatory mechanisms that may maintain cardiac output in the face of impaired myocardial contractility. In an uncompensated state, with the fall in cardiac contractility, the left ventricular ejection fraction often falls. With adequate fluid resuscitation, acting through the Frank Starling mechanism, an increase in pre-load will help to maintain the ejection fraction and cardiac output. The decrease in SVR that often accompanies sepsis reduces afterload, a mechanism that can improve SV and maintain the EF.

The introduction of pulmonary artery catheters with thermodilution cardiac output capacity and portable radionuclide cineangiographic techniques has allowed a greater understanding of cardiovascular physiology and outcomes in patients with severe sepsis. Parker et al reported that patients who survived severe sepsis experienced an acute decrease in left ventricular ejection fraction (LVEF) that was accompanied by left ventricular dilatation: pathophysiologic abnormalities that resolved over a 7- to 10-day period. (Parker MM et al, 1984) This is associated with a negative correlation between the ejection fraction and the left ventricular end-diastolic volume index. (Parker MM et al, 1989.) Nonsurvivors, on the other hand, did not undergo left ventricular dilation, had preserved ejection fraction, exhibited a lower systemic vascular resistance compared to survivors, and had a positive relationship between their ejection fraction and their left ventricular end-diastolic volume index. There are several potential explanations for this apparently paradoxical phenomenon. The lower systemic vascular resistance in nonsurvivors may allow them to maintain their cardiac output without the need for ventricular dilation. Alternately, the endothelial damage and microvascular dysfunction may be more severe in nonsurvivors; this could lead to a significant microcapillary leak, severe interstitial edema of the myocardium, and impaired cardiac compliance. Lastly, the inability of the heart to dilate may be a surrogate for significant multiorgan dysfunction and inability of the host to respond to the multiple alterations associated with severe sepsis.

Vascular System

Vasoconstriction is the physiologic response to low blood pressure in patients with hemorrhagic or cardiogenic shock. In contrast, shock in patients with severe sepsis is vasodilatory in nature. That is, their peripheral blood vessels not only dilate but all too often fail to show an adequate physiologic or pharmacologic contractile response to vasopressors. Severe
sepsis is the most common cause of vasodilatory shock. (Landry DW et al, 2001) However, vasodilatory shock is also a component of disorders with impaired tissue oxygenation such as carbon monoxide intoxication and can serve as a final common pathway of any form of profound and long-lasting shock. At the vascular level, the pathophysiology of shock in patients with severe sepsis involves three major mechanisms: (1) activation of the ATP-sensitive potassium (K\textsubscript{ATP}) channels in vascular smooth muscle cells; (2) synthesis of increased amounts of NO through induction of the inducible form of NO synthase (iNOS); and, (3) vasopressin deficiency. (Landry DW et al, 2001)

**Vascular Smooth Muscle Cell Membrane Hyperpolarization in Vasodilatory Shock**

When the membrane potential of vascular smooth muscle cells is within the physiologic range of -30 to -60 mV, vasopressors such as norepinephrine and angiotensin II open voltage-gated calcium channels and allow calcium to enter cells; through a complex process involving calmodulin, myosin phosphorylation and myosin ATPase, cytosolic hypercalcemia produces muscle contraction. Under conditions of tissue hypoxia or increased tissue metabolic activity, lactic acidosis activates the K\textsubscript{ATP} channels. The resultant entry of potassium into the cell hyperpolarizes the vascular cell membrane, closes the calcium channels, decreases intracellular calcium concentrations, relaxes smooth muscle, and dilates the blood vessels. In patients with severe sepsis, elevated circulating levels of atrial natriuretic peptide, calcitonin gene-related peptide, nitric oxide, and adenosine can also open K\textsubscript{ATP} channels and contribute to membrane hyperpolarization. (Schneider F et al, 1993) (Arnalich F et al, 1996) (Martin C et al, 2000a)

**The Role of Nitric Oxide in Vasodilatory Shock**

Nitric oxide is a potent endogenous vasodilator. In patients with severe sepsis and shock, cytokines upregulate iNOS in a number of cells including vascular smooth muscle and endothelium. (Taylor BS et al, 2000) Nitric oxide then presumably exerts its vasodilatory activity through activation of myosin light-chain phosphatase and perhaps by activating vascular smooth muscle cell potassium channels such as the calcium-sensitive channel (K\textsubscript{Ca}). The latter would then augment the K\textsubscript{ATP}-induced hyperpolarization of the membrane of vascular smooth muscle cells.

**The Role of Vasopressin Deficiency in Vasodilatory Shock**

In addition to its role in water conservation, vasopressin secreted under baroreceptor control constricts vascular smooth muscle. During the initial phases of shock in patients with severe sepsis, vasopressin helps to maintain arterial blood pressure. However, over time neurohypophyseal stores of the hormone become depleted and plasma vasopressin concentrations decline. (Landry DW et al, 2001) Administration of vasopressin in doses large enough to produce plasma concentrations comparable to those seen in acute hypotension will raise arterial blood pressure by 25 to 50 mm Hg. (Zerbe R et al, 1983.) This marked hypersensitivity to exogenous vasopressin in patients with vasodilatory shock appears to results from a number of factors including: (1) availability of receptors for occupancy by the exogenous hormone; (2) autonomic dysfunction; (3) ability of vasopressin to potentiate the activity of high levels of circulating endogenous catecholamines; (4) direct and indirect blunting of the contributions of NO to vasodilation; and, (5) inactivation of K\textsubscript{ATP} channels with restoration of vascular smooth muscle cell membrane potential towards normal. The role of vasopressin in inhibiting the effects of NO and blocking vascular K\textsubscript{ATP} channels has been employed clinically in patients with severe sepsis and shock who are refractory to other maneuvers to raise mean arterial blood pressure (MAP). The efficacy of vasopressin in septic shock is currently being evaluated within the context of a multicenter, randomized controlled trial in Canada.

**RESPIRATORY SYSTEM**

Approximately 40% of cases of acute lung injury (ALI) are ascribed to sepsis. (Martin GS et al, 2001) Presumably, this is a consequence of the organ’s large microvascular surface area. In patients with severe sepsis of extrapulmonary origin, acute lung injury initially occurs through an indirect process; however, as the disease progresses, secondary pneumonia, mechanical ventilation and its associated complications may contribute to ALI and, through both direct and indirect mechanisms, produce ARDS.

**Systemic Components of Acute Lung Injury**

The alveoli and pulmonary capillary bed are separated by two layers of cells: pneumocytes (type I and type II) and endothelial cells. In
patients with severe sepsis, acute lung injury appears to begin with endothelial injury from circulating bacterial products plus cytokines released into the circulation during the initial stages of SIRS. Endotoxin has been shown to be a potent proinflammatory molecule that can induce a variety of endothelial cell inflammatory responses and produce endothelial cell dysfunction or apoptosis. (Bannerman DD et al, 2003.) Under the influence of IL-1, TNF-α, components of complement and other endogenous mediators, the endothelial phenotype is altered. Activated endothelial cells become prothrombotic, upregulate adhesion molecules and secrete a variety of inflammatory mediators including chemotactic cytokines. (Hack CE et al, 2001.) Neutrophilic leukocytes attracted to the pulmonary microvasculature become adherent, activated and migrate from the capillary lumen into the alveolar space: a process accompanied by the release of a variety of oxidants, proteases, leukotrienes, and inflammatory mediators such as platelet activating factor (PAF). In response to alveolar wall damage, pulmonary macrophages also secrete a number of cytokines which amplify the process. Damage to endothelium and the easily injured type I pneumocytes allows flooding of alveoli by proteinaceous edema fluid. Injury to type II pneumocytes reduces the production and turnover of surfactant while the protein-rich alveolar fluid inactivates it. (Banna P et al, 1985) (Whitsett JA et al, 2002) All of these factors contribute to the dyspnea, tachypnea, pulmonary infiltrates and decreased PaO\textsubscript{2}:FiO\textsubscript{2} ratio of acute lung injury.

The coagulopathy of sepsis is also seen at the organ level and can also contribute to the development and progression of acute lung injury. Compared to controls, the bronchoalveolar lavage fluid of patients with ARDS shows significant increases in the concentrations of both TF and activated coagulation factor VII (P<0.001). (Idell S et al, 1989.) Activation of the TF pathway of coagulation in the presence of large amounts of fibrinogen-rich intra-alveolar exudate can lead to extravascular fibrin deposition, hyaline membrane formation, inflammation, and pulmonary dysfunction. (Tomashefski JF Jr, 1990) With the passage of time, this exudative stage can be replaced by proliferative and fibrotic changes that can lead to pulmonary fibrosis. Deposition and persistence of alveolar fibrin is potentiated by depression of pulmonary fibrinolytic activity. (Idell S, 2003.) The fibrinolytic defect is largely the consequence of local amplification of plasminogen activator inhibitor-1 (PAI-1) coupled with inhibition of urokinase plasminogen activator (uPA) and downregulation of its receptor (uPAR). (Idell S, 2002.) Failure of uPA to bind to uPAR on pneumocytes and alveolar macrophages can impair the remodeling that is an essential element of recovery from acute lung injury and ARDS. At autopsy, patients with ARDS also show a predictable gamut of vascular changes that mirror those within the pulmonary parenchyma. (Tomashefski JF Jr, 1990.) For example, post-mortem angiograms of patients with ARDS demonstrate the presence of serial vascular alterations that include thrombotic, fibroproliferative and obliterative changes. The clinical significance of these lesions is signified by the development of pulmonary hypertension in patients with severe ARDS.

**Mechanical Ventilation and Acute Lung Injury**

Mechanical ventilation is a common supportive measure in patients with severe sepsis who develop respiratory failure. In addition to its many life-saving benefits, mechanical ventilation is also potentially harmful to patients with severe sepsis and other types of critical illness. The presence of an endotracheal tube bypasses normal airway defenses. When combined with impaired host defenses and malnutrition, patients with severe sepsis from an extrapulmonary source are at risk for a ventilator-associated pneumonia (VAP). In the absence of preexisting disease, pneumonia can be the primary cause of ALI and ARDS. Furthermore, high concentrations of inspired oxygen can damage alveolar membranes and worsen acute lung injury. Lastly, barotrauma can mechanically stress alveolar and capillary walls while shear forces generated during intratidal opening and closing of pulmonary units can also damage lung tissue. (Gattinoni L et al, 2003.) In addition to regional effects, barotrauma can induce release of cytokines into the pulmonary parenchyma and systemic circulation. These cytokines can contribute to the development of the multiple organ dysfunction syndrome in mechanically ventilated patients with severe sepsis. (Gattanoni L et al, 1998.) As an example of how dysfunctional organs may interact in the septic patient, it is thought that ALI (and mechanical ventilation) may contribute to dysfunction of other organs. Through its effects
on splanchnic blood flow, neurohumoral systems and proinflammatory cytokines, mechanical ventilation has the potential to adversely affect the gastrointestinal (GI) tract and predispose the patient to GI complications. (Mutlu GM et al, 2001.) Interestingly, in the Acute Respiratory Distress Syndrome Network (ARDSNet) tidal-volume study, patients ventilated with the lower tidal volumes (6 mL/kg ideal body weight) had lower levels of IL-6, increased numbers of organ failure-free days, and improved survival. (The Acute Respiratory Distress Syndrome Network, 2000.) The complicated therapeutic considerations regarding mechanical ventilatory support in ALI will be discussed later in the chapter.

GASTROINTESTINAL SYSTEM

With the decrease in the effective arterial blood volume (EABV), hypoperfusion of the gut becomes an important pathophysiologic component of severe sepsis. Early in the process, experimental evidence indicates that autoregulation of the microcirculatory blood flow is largely intact. (Hiltebrand LB et al, 2003.) Prior to adequate fluid resuscitation, this regulatory process diverts blood from the muscularis mucosa to the more metabolically active mucosa. Redistribution of blood flow within the gut may preserve the mucosal barrier protection and prevent bacterial translocation. However, this redistribution of blood flow may not always be sufficient to meet mucosal oxygen demand. During this time, the pH of the gut decreases and lactate levels in the portal venous blood rise. Experiments indicate that mesenteric lymph, rather than portal blood, may be the avenue that disseminates cytokines, endotoxin and other bacterial products, and microorganisms from the compromised gut to other parts of the body. In separate experiments, Magnotti, Sambol and their associates have shown that gut-derived mesenteric lymph, not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock and that ligation of the mesenteric lymphatic duct provides long-term organ protection. (Magnotti LJ et al, 1998) (Sambol JT et al, 2000.)

Alverdy et al have cautioned, however, that experimental demonstrations of alterations in the permeability of the gut mucosa to substances such as labeled dextran do not indicate a cause and effect relationship between the “leaky mucosa” and gut-derived sepsis or multiorgan failure. (Alverdy JC et al, 2003.) Instead, the two processes may be unrelated and gut-derived sepsis is a manifestation of nosocomial pathogens that express “potent virulence traits while competing for scarce resources in the hostile environment of the intestinal tract of a critically ill patient.” Whatever the mechanism of gut derived sepsis, experimental evidence has shown that early enteral feeding protects against bacterial translocation. (Giannotti L et al, 1994.) Whether or not such effects of enteral feeding are beneficial to overall patient outcomes is the point of ongoing study.

HEPATOBILIARY TRACT

The liver plays multiple key roles in patients with severe sepsis. (Dhainaut J-F et al, 2001.) As we discussed with regard to the lungs, the liver is both a source and a target of inflammatory mediators. Its central role in the pathophysiology of severe sepsis is a function of the organ’s blood flow and its cellular composition. In the postabsorptive state, the liver receives approximately 25% of the cardiac output. Decreased perfusion is the most important event initiating hepatic dysfunction in the first hours following a septic insult. (Szabo G et al, 2002.)

The three most important cellular elements participating in the liver’s response to severe sepsis are Kupffer cells, hepatocytes, and endothelial cells. Although described separately, the liver’s reaction to severe sepsis represents a collective and interactive response of all three cellular elements. The central role of the endothelium in sepsis pathogenesis has been discussed in detail above.

Kupffer Cells

Kupffer cells are the fixed macrophages of the liver. They represent approximately 70% of the organ’s total macrophage pool. They clear the portal blood of endotoxin, bacteria, cytokines, toxins, and activated coagulation factors. Once primed, Kupffer cells secrete a variety of cytokines including TNF-α, IL-1, IL-6, IL-8, IL-12, IL-18, G-CSF, and GM-CSF. In a paracrine fashion, Kupffer cells modulate the response of adjacent hepatocytes to inflammatory signals through synthesis and release of acute phase proteins and other mediators.

Hepatocytes

Hepatocytes play an integral role in the body’s response to severe sepsis. (Dhainaut J-F et al, 2001.) They bear receptors for endotoxin,
vasoactive substances, various inflammatory mediators and a number of cytokines. As a result of metabolic alterations during sepsis, hepatocytes reprioritize their metabolism toward gluconeogenesis, amino acid uptake, and protein synthesis. Alterations in protein synthesis, however, are nonuniform with levels of albumin, protein C (PC) and antithrombin (AT) declining while the concentrations of a variety of acute phase proteins rise. The latter include $\alpha_1$-antitrypsin ($\alpha_1$AT), ceruloplasmin (CP), $\alpha_2$-macroglobulin ($\alpha_2$MG), CRP, fibrinogen, C4-binding protein (C4BP), and thrombin-activatable fibrinolysis inhibitor (TAFI). Antiproteinases such as $\alpha_1$AT neutralize elastase and other proteases released by leukocytes. Both CP and $\alpha_2$MG serve a scavenger function by inactivating superoxides, hydroxyl radicals and cytokines such as IL-6. Since many of the aforementioned proteins are involved in the hemostatic response to sepsis, they will be discussed in the following section. As the septic process evolves, patients may develop a secondary hepatocellular dysfunction. This is a consequence of hepatocellular inflammation that results from the local release of inflammatory mediators and damage to the hepatic parenchyma by activated neutrophils within the hepatic sinusoids.

**BLOOD AND BONE MARROW**

Although dispersed in space, the blood and bone marrow comprise an organ system equal in importance to any other. During severe sepsis, the hematologic system attempts to restore homeostasis by eliminating the pathogen and walling-off the infected focus. In patients with a localized infection, this process functions to the complete benefit of the host. However, in patients with severe sepsis an exuberant response of the hematologic system can have detrimental effects. Elements of the hematologic system can be divided into cellular and fluid components.

Although the cellular elements originate in the marrow, the bone marrow’s response to sepsis is reflected in the peripheral blood. Fluid-phase elements of the hematologic system consist of various coagulation proteins. Changes in the hematologic system in patients with severe sepsis are the result of the influences of cytokines and hematopoietic growth factors such as GM-CSF.

**Cellular Response to Sepsis**

Cellular elements of the peripheral blood involved in patients with severe sepsis include red blood cells, leukocytes, and platelets. *(Goyette RE, 1997)* During the initial stages of severe sepsis, the hematocrit reflects the opposing effects of third-spacing of fluids and results of aggressive fluid resuscitation. Over time, the hematocrit falls due to changes in the erythron, the red blood cell component of the hematologic system. Although an infection by a hemolytic organism such as *Clostridium perfringens* can acutely lower the hematocrit, the principle change in the mass of the erythron is due to a block in the reticuloendothelial transfer of iron to erythroid progenitors, erythroid hypoplasia, and a shortened red blood cell survival. Changes in iron metabolism sequester this essential element from species of microorganisms that require iron as a growth factor.

The white blood cell count may be high, normal or low in patients with severe sepsis. The initial leukocytosis results from recruitment of neutrophils from the marginating pool and release of the more mature granulocytic elements from the bone marrow. As the process continues, the white cells show a “left-shift” as less mature granulocytic elements enter the blood. This is associated with morphologic changes including toxic granulation, Döhle bodies, and toxic vacuolation. Leukopenia may result from migration of large numbers of granulocytes into the infected focus or failure of the bone marrow to meet the demand. Severe sepsis is usually accompanied by a variable degree of thrombocytopenia. Thrombocytopenia is a sign of dysfunction of the hematologic system and is due to platelet adhesion and aggregation throughout the microvasculature.

**Fluid-Phase Response to Sepsis**

Severe sepsis is a prothrombotic state. This is the result of ongoing coagulation and impaired fibrinolysis. In response to acute inflammation, hepatic synthesis of the natural anticoagulants, protein C (PC) and antithrombin (AT), decreases. At the same time, other elements of the PC system are also compromised. Increased synthesis and release of $\alpha_1$AT and $\alpha_2$MG inhibit PC while elevated levels of C4BP bind protein S and prevent it from serving as a cofactor for activation of PC. In combination with the effects of microbial elements and cytokines, release of CRP by the liver upregulates the expression of
TF on various cells. Increased production and release of fibrinogen and TAFI also contribute to the ongoing coagulopathy: the former by providing extra substrate for clotting while the latter inhibits clot dissolution. The ongoing coagulopathy of sepsis is marked in the laboratory by a variable degree of thrombocytopenia, increased levels of D-dimer, a fibrin split product, and by an elevation in the thrombin-antithrombin (TAT) to plasmin-antiplasmin (PAP) ratio. The TAT/PAP ratios are higher in patients with severe sepsis than in those who have sepsis without acute organ dysfunction. (Vervloet MG et al, 1998.) This rise in TAT/PAP may precede the development of organ dysfunction, suggesting that enhanced coagulation and depressed fibrinolysis bears a cause-and-effect relationship with the development of the multiple organ dysfunction syndrome.

KIDNEY
A number of different factors present during an episode of severe sepsis have the potential to damage the kidneys. These include systemic hypotension or redistribution of blood flow, renal vasoconstriction, the effects of endotoxin and cytokines on the endothelium of the renal vasculature, and activation of inflammatory cells by lipopolysaccharide and inflammatory mediators. (Abernathy VE et al, 2002.) In patients with severe sepsis, systemic vasodilation decreases the EABV. As the EABV falls, intrarenal vasoconstriction helps to maintain glomerular blood flow. Substances are released locally that promote intrarenal vasoconstriction in patients with severe sepsis and decreased EABV. They include endothelin, thromboxane A₂, and leukotrienes. (Khan RZ et al, 1999.) Eventually, however, compensatory mechanisms fail, the glomerular filtration rate decreases, prerenal azotemia develops and acute necrosis can develop. Endothelial injury from proinflammatory mediators, contents of neutrophilic granules, and components of complement can impair autoregulation of renal blood flow and may lead to microvascular thrombosis. Since the hypoperfused kidney is sensitive to nephrotoxic agents that are commonly administered in severe sepsis, these patients may be predisposed to the development of acute renal failure. For example, nonsteroidal antiinflammatory drugs (NSAIDs) used to treat fever can inhibit the production of prostaglandins by the afferent arterioles and impair the ability of the kidney to regulate its blood flow. In the patient with severe sepsis and decreased EABV, this may be enough to precipitate acute tubular necrosis.

NERVOUS SYSTEM
Patients with severe sepsis have abnormalities of their central, autonomic and peripheral nervous systems.

Abnormalities of the Central Nervous System
Septic encephalopathy is common in patients with severe sepsis. In a prospective study of 69 patients with sepsis, Young et al reported that 71% exhibited mild to marked abnormalities of cerebral function. (Young GB et al, 1990.) The diagnosis of septic encephalopathy in a patient with severe sepsis requires evidence of extracranial infection plus impaired cerebral function. In patients without previous neurologic disease, septic encephalopathy is characterized by symmetrical neurologic findings without the asterixis, tremor, and multifocal myoclonus observed in subjects with metabolic encephalopathies of hepatic, renal or endocrine origin. (Papadopoulos MC et al, 2000.) Delirium is perhaps the most costly and prevalent form of septic encephalopathy. It has been shown that this form of organ dysfunction occurs in more than 80% of all mechanically ventilated patients and is an independent predictor of poor outcomes. (Ely EW et al, 2001.) Delirium can now be diagnosed by bedside techniques in 1-2 minutes with a high degree of accuracy and reliability, using the Confusion Assessment Method for the ICU (CAM-ICU).

The etiology of the disordered central nervous system function in patients with severe sepsis is multifactorial. It includes abnormalities in the blood-brain barrier, alterations in cerebral blood flow, abnormal cellular physiology, and changes in the composition of neurotransmitters in the reticular activating system. In contrast to hemorrhagic shock in which there is no change, the blood-brain barrier is disrupted in patients with septic shock. (Corday E et al, 1960) (Ely EW et al, 2001) This appears to be secondary to effects of circulating cytokines on cerebral endothelial cells. Accumulated perivascular edema fluid may impede the diffusion of oxygen and metabolic substrates with a resultant decrease in cerebral oxygen consumption. The latter can occur despite an increase in cerebral blood flow and may also reflect the presence of
Role of the Autonomic Nervous System

In an experimental model of sepsis, the parasympathetic nervous system plays a significant role in the body’s response to sepsis. Stimulation of afferent vagal nerve fibers produces the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. (Gaykema RP et al, 1995.) Subdiaphragmatic vagotomy blocks cortisol release in this situation. Stimulation of the vagus nerve also prevents the onset of shock in a mouse model of endotoxemia. (Borovikova LV et al, 2000.) Lastly, the febrile response to IL-1 can be attenuated by experimental vagotomy. (Fleshner M et al, 1998.)

Role of the Peripheral Nervous System and Skeletal Muscles

Abnormalities of the peripheral nervous system and neuromuscular units are a major cause of morbidity in patients with severe sepsis. Two major types of defects can be identified. The primary manifestation in this arena in survivors of severe sepsis and other types of prolonged serious disorders is electromyographic (EMG) abnormalities. In a study by Fletcher et al, 95% of patients with prolonged critical illness had EMG changes indicative of chronic partial denervation: changes that can be found for up to 5 years after discharge from an intensive care unit in more than 90% of patients who were in the unit for 28-days or longer. (Fletcher SN et al, 2003.) Secondly, a critical illness myoneuropathy is present in almost two-thirds of patients. Clinical manifestations can be sensory or motor. The exact etiology of this process is unknown; however, it appears to result from a combination of factors including cytokines, impaired blood flow in the vasa nervosum, extended neuromuscular blockade, immobility, compression, disuse, etc. (Marinelli WA et al, 2002.)

**DIAGNOSIS OF SEPSIS**

Following immediate stabilization, efforts should be directed toward determining the nature of the infection and identifying the presence of organ dysfunction. Special attention should be directed toward any predisposing condition such as trauma, surgery, organ transplantation, or immunosuppression (eg, HIV infection, chemotherapy, and malignancy). Steps that define the nature of the infection and assess the degree of organ dysfunction include a complete history and physical examination, laboratory testing including selected microbiology procedures, and medical imaging studies.

**Clinical Evaluation**

Vital signs are routinely recorded and monitored, though the frequency and method of monitoring depend upon the severity of the process. As a general rule, patients can be considered febrile when they have a temperature of ≥38.0°C (≥100.4°F), or hypothermic with a temperature of ≤35°C (95°F). While the presence of fever is most accurately evaluated by assessing core temperature with a bladder or intravascular thermistor, electronic probes in body orifices are acceptable in appropriate patients. Notably, temperature must be assessed in a fashion that does not facilitate the transfer of nosocomial pathogens. Importantly, less than half of febrile episodes are infectious in origin and almost one-half of septic patients are normothermic or hypothermic. (Rizoli SB et al, 2002.) Variables related to fever may help in the differential diagnosis. Temperatures >41.1°C are most probably non-infectious (ie, drug fever, thyroid storm). Fever with a relative bradycardia and a rash may be drug-induced or indicate S. typhi or S. paratyphi infection. Vital signs can also provide a wealth of information about the patient’s prognosis. In a study of community acquired pneumonia (CAP), a temperature <35°C or ≥40°C, a pulse ≥125 beats/min, a respiratory rate ≥30 breaths/min, and a systolic blood pressure <90 mm Hg were each independently associated with increased mortality. (Fine MJ et al, 1997.)
Altered mental status of the patient is an important clue to the presence of organ dysfunction. Delirium is an acute disorder of attention and cognition. It develops in 60% of hospitalized older patients and in more than 80% of mechanically ventilated patients. (Ely EW, Gautam S et al, 2001)(Ely EW, Margolin R et al, 2001.) Delirium may be hyperactive (agitated) or hypoactive. While healthcare workers commonly recognize the former, hypoactive delirium is commonly missed. The presence of delirium is extremely hazardous in the elderly and is associated with prolonged hospital stays, institutionalization, and death. Changes in mental status are an indication that the septic process is severe, and may also be a clue to the presence of meningitis. Attention to mental status is also important in assessing the necessity to urgently protect the patient’s airway. Photophobia, nuchal rigidity, papilledema, or cranial nerve palsies should direct attention to a focus of infection within the CNS. Orbital pain, periorbital erythema, proptosis, or unilateral rhinorrhea may be seen in a patient with bacterial or fungal sinusitis. While this may be the presenting illness in an immunocompromised patient, it can also be a secondary infection resulting from the obstruction of sinus ostia by nasotracheal or nasogastric tubes. Fetid breath may be detected in some patients with anaerobic oropharyngeal or pulmonary infections. Oral candidiasis may be a clue to fungal septicemia, though it is more commonly a local phenomenon. Immunosuppressed and neutropenic patients may be unable to produce purulent sputum or other exudates and may be unable to vigorously cough. Tachypnea may be the only sign of pneumonia. Careful auscultation of the chest may detect localized rales (crackles). Patients with lower lobe pneumonia may sometimes complain of upper abdominal pain. Associated hypoactive bowel sounds in these patients may be mistakenly ascribed to an intraabdominal focus of infection. Tenderness over the right upper quadrant may indicate the presence of a hepatic or subphrenic abscess or acaulcous cholecystitis. Abdominal tenderness and hypoactive bowel sounds may be the only evidence of a localized intraabdominal infection or peritonitis. Pain, tenderness (direct and/or rebound) localized to the right or left lower quadrant may be evidence of appendicitis or a ruptured sigmoid diverticulum, respectively. Right lower quadrant pain in a neutropenic patient may indicate the presence of typhilitis—a necrotizing mixed bacterial infection of the cecum.

The skin should be carefully examined. Livedo reticularis and poor capillary refill are a signs of impaired cutaneous perfusion and are associated with a poor prognosis in patients with severe sepsis. In neutropenic patients, the nail folds, axillae, perianal region, and groin provide ready entry for systemic pathogens. In this subset of patients, pain and erythema may be more reliable clues to infection than the leukocyte count. The dressings around any implanted device should be removed and the area carefully inspected for purulent discharge, erythema, increased warmth, pain, and crepitus. Patients with vascular catheters should also be carefully checked for evidence of vascular compromise or embolic events originating from an infected device. Sudden hypotension following access of a vascular access device or line is a clue to the presence of an infected line. Operative wound infections are the second most common type of hospital-acquired infection. All surgical dressings should be removed to allow adequate inspection of operative sites. Patients with recent gastrointestinal or gynecologic surgery, diabetes mellitus, or peripheral vascular disease are at risk for invasive polymicrobial infections such as necrotizing fascitis or synergistic gangrene. Clues to the diagnosis include swelling around the wound, rapidly advancing border, crepitus, blisters, necrosis, or the radiographic appearance of gas within the soft tissues.

Medical Imaging Studies

Due to technical limitations, plain radiographs from portable machines are of limited value in characterizing the nature of the infection in patients with severe sepsis. For example, in the critically ill population with pneumonia, portable chest radiographs have a diagnostic accuracy of 0.5, sensitivity of 0.6, and specificity of only 0.28. (Lefcoe MS et al, 1994.) Therefore, imaging studies should be selected based upon the presumed nature of the infection and advantages and disadvantages of various approaches.

Plain films and/or ultrasound have limited utility in establishing the diagnosis of sinusitis. Therefore, a clinical diagnosis of septic sinusitis should be evaluated by computed tomographic (CT) scans of the paranasal sinuses. While the presence of air or fluid levels is abnormal, the diagnosis is not established without recovery of
infected material by sinus puncture, aspirate and culture. The chest x-ray can be used to detect pulmonary edema of cardiogenic and noncardiogenic origin. A chest imaging study should be ordered in patients with suspected pneumonia. In critically ill patients, a portable PA chest film is often considered to be the most feasible procedure. However, in selected patients, an erect PA chest with a lateral view or CT scan will provide more information. Notably, chest radiographs may be essentially normal if the films are taken within the first 24 hours after the onset of symptoms or if the patient is neutropenic. The presence of pleural fluid adjacent to an infiltrate may provide a target for microbiology studies. A flat plate of the abdomen may demonstrate the presence of an ileus, a potential explanation for bacteremia in a patient without localizing findings. Abdominal radiographs may also reveal evidence of a perforated viscus or an intraabdominal abscess. Ultrasonography of the gallbladder may demonstrate evidence of calculous or acalculous cholecystitis, or biliary tract obstruction in a patient with biliary sepsis. Ultrasound or CT studies of the abdomen may demonstrate localized fluid collections, abscesses, ureteral dilatation, or the presence of a perinephric abscess.

Microbiology
All potential infected foci should be cultured in patients with severe sepsis. However, in 20% to 30% of patients, a definite site of infection cannot be identified. (Wheeler AP et al, 1999.) The search for the responsible pathogen should include all measures necessary to establish the site and nature of infection including direct examination and culture of material from the lower respiratory tract, fine needle aspirates, cultures of infected lines, etc. The blood is also an appropriate material to culture. However, 70% of patients with sepsis will not have organisms recovered from the blood. (Wheeler AP et al, 1999.) Material obtained for culture should be immediately gram-stained. Cultures should also be supplemented with appropriate immunologic procedures such as detection of microbial antigens in body fluids, immunostaining, etc. In patients with intraabdominal infections, wound infections, and lung abscesses, the material should also be cultured anaerobically.

Laboratory Markers of Sepsis
A number of biochemical markers have been used to identify the patient with systemic activation of the cytokine cascade. None of the markers are currently widely used to diagnose sepsis, though some clinicians have argued that they should be incorporated into the entry criteria for patients in clinical trials of severe sepsis. Elevated levels of IL-6, IL-1, IL-8, TNF-α, and monocyte chemotactic proteins-1 and -2 are present in septic patients and often correlate with the severity of the disease. Levels of IL-6 are increased in most patients with sepsis and have been shown to correlate with prognosis, but IL-6 is not used in clinical practice for diagnosis or prognostication. (Selberg O et al, 2003) While the level of IL-6 may be able to differentiate cases of infectious from noninfectious SIRS, no correlation has been established between the concentration of IL-6 and outcomes.

C-reactive protein is an acute phase reactant synthesized in the liver. Following exposure to IL-1, IL-6 or TNF-α, CRP levels increase. Levels of CRP have been used for years as a diagnostic marker of systemic inflammation. While levels are normally low, they rise rapidly in patients with sepsis, paralleling the course of infection. (Luzzani A et al, 2003.) As described above, the complement system is activated in patients with sepsis; this may be in part mediated through CRP. Interactions of the complement system with microorganisms generate increased amounts of C3a and terminal components of the cascade. Elevated levels of C3a have been found to be one of the single and most sensitive and specific laboratory markers that can differentiate between sepsis and noninfectious causes of SIRS. (Selberg O et al, 2003.)

Procalcitonin (PCT) is derived from the preprohormone, preprocalcitonin. Although PCT levels are elevated in patients with sepsis, little is known about its source and function. Interestingly, calcitonin levels are normal in this population. In a porcine model of polymicrobial sepsis, immunoneutralization of calcitonin precursors was found to attenuate the adverse physiologic response to the infection. (Wagner KE et al, 2002.) For diagnostic purposes in critically ill patients, PCT levels have a better predictive value for sepsis than either IL-6 or CRP. When PCT concentration was combined with the levels of C3a in a “sepsis score,” the combination had a sensitivity of 91% and a specificity of 80% for sepsis vs noninflammatory
SIRS. (Selberg O et al, 2003) As a prognostic marker, procalcitonin levels have been shown to correlate with mortality, though not to a degree that warrants clinical utilization at this point. (Pettila V et al, 2002.) (Wanner GA et al, 2000.) (Van der Kaay DC et al, 2002.)

MANAGEMENT

Severe sepsis is a medical emergency. The first priority should be to assess and address abnormalities in the “A, B, Cs:” airway, breathing, and circulation. In many instances, the clinical assessment of tissue perfusion and response to therapy can be aided by monitoring devices and laboratory measurements (Table 4. Goals of Therapy). (Table 4. Clinical, Hemodynamic, and Ventilatory Goals) Once immediate stabilization has been accomplished, the source of the infection should be established, controlled, and specific antimicrobial agents administered. After stabilization, source control, initiation of appropriate antimicrobial agents, and further support for dysfunctional organs, disease-specific interventions should be considered.

INITIAL RESUSCITATION

The initial therapeutic intervention in patients with severe sepsis is to reverse organ hypoperfusion. Patients with severe sepsis often have a relative intravascular hypovolemia. Consequently, initial therapy often consists of the rapid administration of large amounts of fluids.

Fluid Resuscitation

Large amounts of fluids may be required to restore tissue perfusion and oxygen delivery. In some instances, correction of large fluid deficits may require 6 to 10 liters of crystalloid. Rackow et al conducted a study of fluid resuscitation in patients with circulatory shock. (Rackow EC et al, 1983.) Patients were administered fluid challenges of 250 mL of test fluid every 15 minutes until the pulmonary artery occlusive (wedge) pressure (PAOP) reached 15 mm Hg. During the first 24 hours, patients required more than 8 liters of normal saline to produce the desired hemodynamic effect; the same effect was achieved by 25% to 50% of the volume when the test fluid was a colloid solution. The difference between the two is related to osmotic properties of colloids that produce a greater expansion of plasma volume for an equivalent amount of fluid.

Fluid resuscitation is often titrated by the responses of clinical endpoints of heart rate, BP and urine output. (Society of Critical Care Medicine, 1999.) Appropriate amounts of fluid will improve the cardiac index by 25% to 40%. In approximately 50% of patients with severe sepsis who present with hypotension, fluid resuscitation alone will normalize BP and restore hemodynamic stability. Hemodynamic monitoring should be considered for patients who do not respond rapidly to the initial fluid challenge and those with a history of coronary heart disease. In most patients with severe sepsis, filling pressures between 12 mm Hg and 15 mm Hg will optimize cardiac output. Fluid in amounts that increase the PAOP to 18 mm Hg or above do not improve cardiac indices and increase the patient’s risk for congestive heart failure.

Choice of Fluids

There has been an ongoing debate as to whether fluid resuscitation is best accomplished with crystalloids or colloids. Choi et al conducted an evaluation of randomized clinical trials of crystalloids vs colloids in adult patients requiring fluid resuscitation. (Choi PTL et al, 1999.) They reported that there were no apparent differences in the incidences of pulmonary edema, mortality or length of stay in patients who received crystalloid or colloid fluid resuscitation. On the other hand, Schierhout et al compared crystalloid vs colloid resuscitation in 26 unconfounded clinical trials. (Schierhout G et al, 1998.) They reported that resuscitation with colloids was accompanied by an increased absolute risk of mortality of 4% (95% confidence interval: 0% to 8%). They concluded that since colloids were not associated with improved survival and are significantly more expensive than crystalloids, the evidence does not support the continued use of colloids for volume replacement in the critically ill. Currently, the crystalloid vs colloid controversy continues. (Wilkes, Ann Intern Med 2001). However, in the presence of normal oncotic pressure, most patients are managed with crystalloid; patients requiring osmotic support can also be treated with colloid such as 25% albumin. (Wilkes MM et al, 2001.)

Pyruvate is a potent antioxidant and free radical scavenger. (Fink MP, 2003) Although it is unstable in aqueous solution, its ethyl derivative
has greater stability. Ringer’s ethyl pyruvate has been evaluated in a number of preclinical models and has been shown to improve survival and decrease inflammatory markers in acute endotoxemia, acute bacterial peritonitis, hemorrhagic shock, and mesenteric ischemia/reperfusion injury. (Fink MP, 2003.)

There is some basic science and clinical evidence that suggest that infusions of small amounts of hypertonic saline may have some future role in the resuscitation of patients with severe sepsis. In 1980, Velasco et al reported that administration of a hypertonic solution of 7.5% saline has beneficial effects in a canine model of hemorrhagic shock. (Velasco IT et al, 1980.) Experimental studies in models of severe sepsis confirmed beneficial effects similar to those originally reported. Small clinical studies have also reported beneficial effects on cardiac indices, systemic vascular resistance, and oxygen transport. (Hannemann L et al, 1996) (Oliveira E et al, 1996) While it was initially proposed that the beneficial effect of this intervention was on cardiac preload, increasing evidence suggests that its effects extend far beyond hypertonic saline’s osmotic properties. Hypertonic saline also appears to improve myocardial contractility, reduces endothelial and interstitial edema, improves microcirculatory blood flow, and exerts immunomodulatory activity. (Oliveira RP et al, 2002.) Its effects on endothelial cell function and microvascular blood flow are particularly interesting in light of the growing evidence of endothelial cell dysfunction in patients with severe sepsis. Endothelial cell edema can serve as a surrogate for endothelial injury and potential dysfunction. Edema of the endothelial cells occurs in the initial phases of hypovolemia. Small infusions of hypertonic saline can reduce endothelial volume by approximately 20%, increase tissue perfusion, and improve cellular function. (Corso CO et al, 1998) Microcirculatory blood flow is also improved as the hypertonic fluid produces hemodilution and decreased blood viscosity.

Patients with severe sepsis very often have dramatic reductions in hemoglobin (Hb) levels. This is secondary to a number of factors including hemodilution and impaired erythropoiesis. Furthermore, fluid resuscitation may lower the Hb by up to 1-3 g/dL. (Society of Critical Care Medicine, 1999) This degree of anemia is tolerated by most patients since the resultant decrease in blood viscosity reduces afterload and improves venous return. Potential benefits of transfusion in this population include an increase in arterial oxygen content and an improvement in systemic oxygen availability. However, transfusions of packed red blood cells have a number of potentially detrimental effects. These include rheologic changes which reduce red blood cell deformability and increase blood viscosity, immunosuppression, disease transmission, risk of nonhemolytic transfusion reactions, and the fact that oxygen delivery is not immediately restored after transfusion since the infused red blood cells must restore their depleted 2,3-DPG levels to improve oxygen release.

Hébert et al conducted a multicenter, controlled trial of restrictive vs liberal transfusion strategies in a population of critically-ill patients. (Hébert PC et al, 1999.) They enrolled 838 euvoicmic, critically ill patients who had Hb concentrations less than 9.0 g/dL within 72 hours of admission to the intensive care unit. Patients were then randomized to either a restrictive transfusion strategy in which Hb concentrations were maintained in the 7.0 to 9.0 g/dL range and transfusions only administered if the Hb dropped below 7.0 g/dL or to a strategy in which Hb levels were maintained in the 10.0 to 12.0 g/dL range and transfusions given if the Hb dropped below 10.0 g/dL. While the overall 30-day mortality was similar in both groups, patients who were less severely ill as stratified by an APACHE II score of ≤20, and patients, who were younger than 55 years of age, had a significantly lower in-hospital mortality rate (22.2% vs 28.1%; P=0.05). This benefit did not extend to patients with acute coronary syndromes. However, Rivers et al recently released the results of a clinical trial of early goal-directed therapy (EGDT) that suggest that there may be some benefit of Hb concentrations of 10 g/dL or greater. (Rivers E et al, 2001.) Although these results are discussed below, they emphasize the importance of proper tissue oxygenation.

At this time, the optimal Hb level for patients with severe sepsis is unclear. The default transfusion threshold used by many ICUs is now a conservative one of 7.0 g/dL, unless patients are elderly and have a history of myocardial infarction, in which case a more liberal threshold of 10 g/dL is supported by an 80,000 patient observational study by Wu et al (Wu WC et al, 2001.)
CARDIORESPIRATORY SUPPORT

Vasopressors

Patients who remain hypotensive despite aggressive fluid resuscitation are candidates for pressor support; however, vasopressors should not be considered in lieu of adequate fluid resuscitation. Blood pressures determined by a cuff are often inaccurate and an arterial cannula are usually inserted to monitor intra-arterial BP in patients receiving vasopressor therapy. A variety of agents with different pharmacodynamic properties are available to treat the hypotensive patient with severe sepsis (Table 5). (Table 5. Vasoactive and Inotropic Drugs) Patients receiving pressor support should be monitored to ensure that treatment restores perfusion to vital organs without compromising stroke volume. Surrogates of improved peripheral perfusion and splanchnic blood flow include increase in mean arterial pressure (MAP) (65 mm Hg or greater is often used), warming of the extremities, and resolution of cutaneous mottling and impaired capillary refill. Increased urinary output and improved mentation are other good surrogates of adequate systemic perfusion. Goals should be a urine output of >0.5 mL/kg/hr and an alert and oriented cognitive status.

The principles of vasopressor support require knowledge of the effects of the drug on the various adrenergic receptors, the presence of a dose-responsive relationship with some agents in which one type of receptor is stimulated at low levels while higher concentrations activate a different receptor, and the fact that various pressor agents can also affect hemodynamics through reflex actions. One of the obstacles to determine the “best” pressor in patients with severe sepsis is the lack of large-scale, randomized controlled trials. The majority of studies of various pressor agents have been observational in nature. Norepinephrine appears to be the preferred agent for initial blood pressure support in patients with severe sepsis who remain hypotensive despite an adequate fluid challenge. Because of its pure α-adrenergic activity, phenylephrine may be useful in patients with coronary heart disease who may be at risk for tachycardia or arrhythmias from agents with β-agonist properties. Meadows et al evaluated the effects of norepinephrine on reversal of shock in ten patients with severe sepsis. (Meadows D et al, 1988.) Patients with severe sepsis who remained hypotensive and oliguric despite expansion of their plasma volume to a target pulmonary artery occlusion pressure (PAOP) and infusions of increasing doses of dopamine and dobutamine were then treated with norepinephrine monotherapy. After discontinuation of dopamine and dobutamine, an infusion of norepinephrine significantly elevated the MAP, reversed the hypotension, and increased the systemic vascular resistance, left ventricular stroke work index and the urinary output without significantly affecting the heart rate. In a separate study, Martin et al evaluated the effect of norepinephrine on the outcome of patients with septic shock. (Martin C et al, 2000b.) These investigators evaluated the effects of various independent variables that might affect outcome in an observational cohort of 97 adult patients with severe sepsis. Patients who received norepinephrine as a component of their hemodynamic support had a significantly lower hospital mortality rate compared with those treated with high-dose dopamine and/or epinephrine (62% vs 82%; 95% confidence interval: 0.68, range 0.54 to 0.87; P<0.001). Further support for the use of norepinephrine as the pressor of choice was provided by Di Giantomasso et al. (Di Giantomasso D et al, 2002.) They evaluated the effects of norepinephrine on vital organ blood flow in a sheep model. They concluded that norepinephrine infusion does not induce ischemia in vital organs in normal mammalian circulation. In addition, infusion of norepinephrine significantly increases coronary and renal blood flow with associated improvements in urine output and serum creatinine.

Over a short period of time, tachyphylaxis may appear as vascular smooth muscle becomes resistant to the effects of norepinephrine and other catecholamines. Vasopressin is involved in cardiovascular homeostasis. Normally, it plays only a minor role in BP control. However, in hypotensive patients vasopressin released under baroreflex receptor control stimulates vascular smooth muscle and helps restore BP. In fact, during the initial phases of severe sepsis-induced hypotension high levels of vasopressin contribute to the effects of endogenous catecholamines in attempting to restore BP. As shock worsens, however, plasma concentrations of vasopressin decline significantly and become inappropriately low for the patient’s mean arterial blood pressure. This is presumably because neurohypophyseal stores of the hormone

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are depleted in the face of constant baroreceptor stimulation. In support of this hypothesis, Landry et al have demonstrated by immunohistochemistry in a canine model that after 1 hour of hemorrhagic shock, the stainable hormone is essentially absent in tissue from the animal’s neurohypophysis. (Landry DW et al, 2001.) In patients with severe sepsis and other forms of vasodilatory shock, administration of vasopressin to produce concentrations similar to those identified during acute episodes of hypotension increases arterial blood pressure by 25 to 50 mm Hg. It has been postulated that the marked sensitivity of blood pressure to vasopressin in this situation is multifactorial in origin: (1) in patients with severe sepsis and established hypotension, plasma levels of vasopressin are low and its receptors on vascular smooth muscle are unoccupied; (2) patients with severe sepsis may have dysfunction of the sympathetic nervous system and be more responsive to noncatecholamine pressor agents; (3) plasma concentrations of norepinephrine are markedly elevated in patients with vasodilatory shock and vasopressin potentiates the effects of the catecholamine; (4) vasopressin directly activates $K_{\text{ATP}}$ channels in vascular smooth muscle, and; (5) vasopressin directly and indirectly inhibits the vasodilatory activity of nitric oxide. (Landry DW et al, 2001)

Studies support the role of vasopressin in this situation. Landry et al report that an infusion of 0.04 U/min of vasopressin in 10 hypotensive patients with severe sepsis increased arterial blood pressure from a mean of 92/52 mm Hg to 146/66 mm Hg. (Landry DW et al, 1997.) Importantly, however, withdrawal of vasopressin resulted in hypotension in 6 patients in whom it was the only pressor. In a blinded study of 24 patients with septic shock, Patel et al compared the effects of norepinephrine and vasopressin. (Patel BM et al, 2002.) Doses of vasopressin and norepinephrine, starting at 0.01 U/min and 2 µg/min, respectively, were titrated to maintain a clinically acceptable mean arterial blood pressure. Treatment with vasopressin produced a significant catecholamine-sparing activity (P<0.001) and its use was accompanied by a higher urine output volume and an improved creatinine clearance (P<0.05). Although these preliminary observations require a large scale randomized trial to confirm the beneficial effects of vasopressin in patients with vasodilatory shock, critical care specialists are commonly treating patients with severe sepsis who are refractory to catecholamines with vasopressin.

**Inotropic Agents**

Patients with severe sepsis have a normal to low blood pressure, elevated cardiac index, and decreased systemic vascular resistance. However, myocardial depression is common. (Society of Critical Care Medicine, 1999) It is characterized by a decreased ejection fraction, ventricular dilation, impaired contractile response to volume loading, and a low ratio of peak systolic pressure to end-systolic volume. In patients who are unable to maintain an adequate cardiac index, mean arterial pressure, mixed venous oxygen content, and/or urine output, an inotropic agent such as dobutamine may be useful. (Rivers E et al, 2001). However, since inotropic agents can produce significant tachycardia in patients who have not been adequately fluid-resuscitated, it is important to ensure that the dobutamine candidate has adequate or increased PAOP. In addition, the increased myocardial oxygen consumption in patients treated with an inotrope can produce angina or an acute coronary syndrome. While dobutamine was a significant part of the successful protocol employed by Rivers et al, the role of inotropes remains infrequent in the management of severe sepsis patients.

**Oxygen and Mechanical Ventilation**

Sepsis places significant stress on the respiratory system. At presentation, most patients are tachypneic and hypoxemic. These clinical manifestations result from a combination of factors including increased oxygen requirements, decreased pulmonary compliance, increased airway resistance, and impaired efficiency of the respiratory and other muscles. (Wheeler AP et al, 1999) Approximately 85% of patients with severe sepsis will require ventilatory support, generally for 5 to 10 days. Therefore, the patient’s arterial oxygen saturation ($\text{SaO}_2$) and/or the $\text{PaO}_2$ should be evaluated and steps taken to maintain $\text{SaO}_2$ at ≥90% by either increasing the amount of inspired $\text{O}_2$ ($\text{FiO}_2$) or improving respiratory physiology with institution and adjustments of mechanical ventilation.

Prone positioning has the potential to improve oxygenation in critically ill patients with severe sepsis. Position-related changes in respiratory physiology are a function of changes in end-expiratory lung volume, ventilation-perfusion matching and chest wall mechanics. However,
During intubation and immediately thereafter, encephalopathy or a potentially fatal arrhythmia. Before they aspirate, develop hypoxemic respiratory failure so that the patient can be intubated early and receive respiratory support. Importantly, the clinician should be proactive and recognize the signs of impending respiratory failure so that the patient can be intubated early and receive respiratory support before they aspirate, develop hypoxemic encephalopathy or a potentially fatal arrhythmia. During intubation and immediately thereafter, the patient should receive an FIO2 in the .95 to 1.0 range in order to maximize the SaO2. However, through the formation of oxygen free radicals and other mechanisms, FIO2s > .50 can damage the lung within hours. Therefore, the FIO2 should be tapered to the minimum level that maintains adequate oxygenation to avoid oxygen toxicity.

Oxygen delivery is a function of the CO, the Hb, and the SaO2 (DO2 = 10 x CO x (1.34 Hb x SaO2 + 0.003 x PaO2)). If filling pressures are low, the CO can be raised by fluids; alternately, patients who do not respond to fluids and have normal or elevated filling pressures may benefit from an inotrope. While it is important that oxygen delivery is maximized, the therapy required to achieve supranormal DO2 may be injurious in some patients. (Gattinoni L et al, 1995.) In a prospective randomized study of 109 critically-ill patients, Hayes et al attempted to maximize DO2 by volume expansion. (Hayes MA et al, 1994.) Patients failing volume expansion alone were randomized to either a control or a treatment group. The intervention group was treated with intravenous dobutamine (5 to 200 µg/kg/min). All nine patients who responded to volume replacement alone survived to leave the hospital.

The predicted risk of death for the remaining 100 patients was 34%. However, the in-hospital mortality was lower in the control group (34%) than in the supranormal DO2 (54%) group, suggesting that the aggressive efforts to increase tissue oxygen delivery were detrimental.

One reasonable ventilatory strategy in patients requiring mechanical ventilation is to employ assist-control or intermittent mandatory ventilation to provide 75% to 100% of the minute ventilation. Lower rates of intermittent mandatory ventilation with pressure support to deliver adequate tidal volumes are appropriate in patients with intact ventilatory drive and respiratory muscle strength. Positive end-expiratory pressure (PEEP) can be employed to reduce the risk of ventilator-induced injury and reduce the FIO2 required to maintain the SaO2 ≥90%. The advantages of PEEP must be balanced against the potential risks of barotrauma, decreased cardiac output, and lowered BP. Although the VT is normally 6 to 8 mL/kg ideal body weight, historically, mechanical ventilators had been adjusted to deliver a VT in the 12 to 15 mL/kg range. Such large and non-physiological VT may produce additional damage to the lungs and lead to excess deaths. The results of the ARDSNet Tidal Volume Study indicated that a lung protective strategy employing tidal volumes of 6 mL/kg (as compared to 12 mL/kg) can significantly improve outcomes in patients with acute lung injury or ARDS. (The Acute Respiratory Distress Syndrome Network, 2000.) Patients who were randomized to the lower tidal volume had significantly lower mortality (31.0% vs 39.8%; P=0.007), increased ventilator-free days (12 vs 10; P=0.007), increased organ failure-free days (15 vs 12; P =0.006), and lower levels of the proinflammatory cytokine, IL-6. It is important that every effort be made to reduce mechanical ventilation settings to detect readiness for extubation from the ventilator.

The spontaneous breathing trial (SBT) is the best indicator of the patient’s ability to breathe without mechanical support. (MacIntyre NR et al, 2001.) Ely et al reported that an SBT protocol using respiratory therapists and nurses significantly reduced the number of days that patients spent on a ventilator (1 vs 3 days; P<0.001), decreased the complication rate by half, and cut the costs of ICU care by over $5,000 per patient. (Ely EW et al, 1996.) (Ely EW, Meade MO et al, 2001)