Current Concepts

Treating Patients with Severe Sepsis

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SEPSIS is an infection-induced syndrome defined as the presence of two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation.[1] When an organ system begins to fail because of sepsis, the sepsis is considered severe. Each year, sepsis develops in more than 500,000 patients in the United States, and only 55 to 65 percent survive.[2,3] Fortunately, the death rates in some subgroups of patients with sepsis-induced organ failure have decreased, even though there is no specific therapy for sepsis.[3,4] The reduced mortality may be due to changes in the definition of sepsis, better detection and treatment of the underlying infection, or improved supportive care. Agents tested in large, well-designed trials have not reduced overall mortality, though there have been benefits in some subgroups of patients. These studies, however, have dramatically expanded our knowledge of sepsis, especially considering that only a decade ago, there was no consistent definition of the syndrome.[1,5]

THE INFLAMMATORY CASCADE

Normally, a potent, complex immunologic cascade ensures a prompt protective response to microbial invasion in humans. A deficient immunologic defense may allow infection to become established; however, an excessive or poorly regulated response may harm the host through a maladaptive release of endogenously generated inflammatory compounds. The complexity of immunologic defenses makes the development of pharmacologic interventions difficult.[6] Conceptually, one approach is to prevent infection in patients at high risk with the timely use of immune stimulants and then provide brief, targeted immunosuppressive therapy if sepsis ensues (Fig. 1).[7]

Despite some uncertainty, a reasonable diagram of the early biochemical events in sepsis can be constructed (Fig. 2). A key element is cytokines, which are host-produced, pleomorphic immunoregulatory peptides. The most widely investigated cytokines are tumor necrosis factor, interleukin-1, and interleukin-8, which are generally proinflammatory, and interleukin-6 and interleukin-10, which tend to be antiinflammatory.[8] A trigger, such as a microbial toxin, stimulates the production of tumor necrosis factor and interleukin-1, which in turn promote endothelial cell–leukocyte adhesion,[9-12] release of proteases and arachidonate metabolites,[13] and activation of clotting.[14] Interleukin-1 and tumor necrosis factor are synergistic and share many biologic effects, and their inhibition improves organ function and survival in animal models of sepsis.[15-18] Interleukin-8, a neutrophil chemotaxin, may have an especially important role in perpetuating tissue inflammation.[19,20] Interleukin-6 and interleukin-10, which are perhaps counterregulatory, inhibit the generation of tumor necrosis factor, augment the action of acute-phase reactants and immunoglobulins, and inhibit T-lymphocyte and macrophage function.[21,22] Despite intensive investigation, only one study of the Jarisch–Herxheimer reaction in patients with *Borrelia recurrentis* infection suggests that altering tumor necrosis factor concentrations has physiologic effects and changes cytokine levels further downstream in the cascade.[23] However, the efficacy of cytokine antagonists in lowering the mortality rate among critically ill patients with sepsis remains unproved.[24]

The arachidonic acid metabolites thromboxane A_2 (a vasoconstrictor), prostacyclin (a vasodilator), and prostaglandin E_2 participate in the generation of fever, tachycardia, tachypnea, ventilation–perfusion abnormalities, and lactic acidosis.[25] Use of the cyclooxygenase inhibitor ibuprofen to suppress production of these metabolites reduces temperature, heart rate, minute ventilation, and lactic acidosis but does not appear to result in a lower mortality rate.[26] Investigational treatments designed to augment the host defense, treat the underlying infection, block triggering events, prevent leukocyte–vessel interaction, or inhibit vasoactive substances, cytokines, or lipid mediators continue to be tested (Table 1).

INFECTION SITE AND MICROBIOLOGIC CONSIDERATIONS

The host response is perhaps as important as the site of infection or type of microorganism in the cause of sepsis. The lung is the most common site of infection, followed by the abdomen and urinary tract (Fig. 3).[26] In 20 to 30 percent of patients, a definite site of infection is not determined,[27-29] and even among patients in whom a site is strongly suspected, a similar proportion have sterile cultures or questionable microbiologic isolates.[30,31] Pleural, peritoneal, and paranasal-sinus infections can easily be overlooked, even with the use of computed tomography. No imaging study can definitively rule out infection. When

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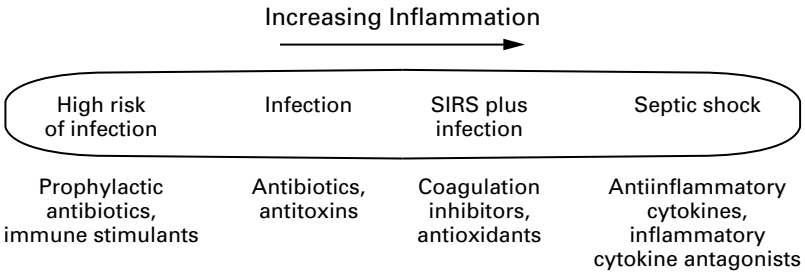

Figure 1. Scheme for Preventing and Treating Sepsis.

Before sepsis develops, augmentation of immunologic defense mechanisms offers the best opportunity for protection. However, if host defense mechanisms are impaired, brief administration of agents that inhibit proximal mediators of inflammation may help block multiple-organ failure. SIRS denotes systemic inflammatory response syndrome. Adapted from Bernard.[7]

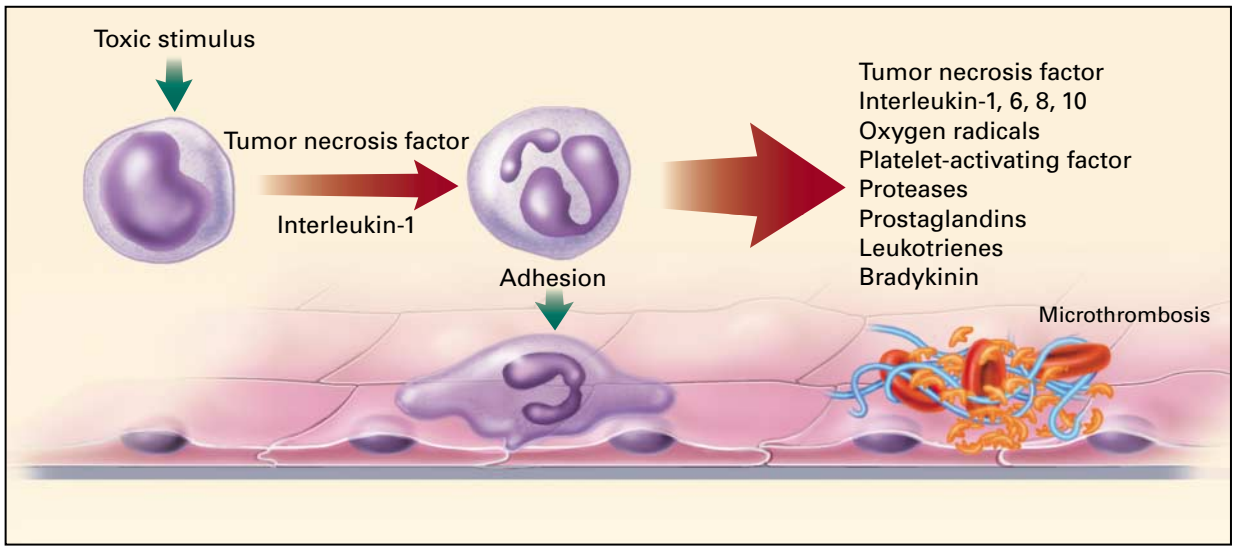

Figure 2. Early Biochemical Events in Sepsis.

An initial toxic stimulus (e.g., endotoxin) triggers the production of proinflammatory monokines (e.g., tumor necrosis factor and interleukin-1). These cytokines, in turn, result in neutrophil–endothelial-cell adhesion, activation of clotting, and generation of numerous secondary inflammatory mediators, including other cytokines, prostaglandins, leukotrienes, and proteases. Antiinflammatory compounds, such as interleukin-6 and interleukin-10, that may serve as negative feedback to the inflammatory process, are also released.

fluid collections are visualized, diagnostic aspiration and culture are required, and most true positive results of culture are obtained before antibiotic therapy is started.[31,32] Positive blood cultures are the accepted proof of serious infection, but blood cultures are positive in only approximately 30 percent of patients.[26,27,33] Patients with negative blood cultures but presumed infection and patients with serious inflammatory conditions not caused by infection (e.g., pancreatitis) have biochemical and physiologic changes, rates of organ failure, and survival rates similar to those of patients with confirmed infection.[3] Limitations of culture techniques or the ability of local infections to trigger a systemic response may explain the inability to confirm the presence of infection, or infection may not be required to activate the inflammatory cascade. In cases of confirmed infection, no single pathogen predominates, and the spectrum of organisms varies over time in response to the selective pressure exerted by antibiotic therapy. These findings also support the argument that the host response is a major determinant of the outcome of sepsis.[34,35]

ANTIMICROBIAL THERAPY

Antimicrobial drugs are necessary but not sufficient for the treatment of sepsis and paradoxically may precipitate septic changes by liberating microbial products.[36-38] Approximately 10 percent of patients

TABLE 1. INVESTIGATIONAL TREATMENTS OF SEPSIS.

COMPOUND	THERAPEUTIC RATIONALE
Antiendotoxin antibodies	Neutralize endotoxin, a compound that triggers sepsis
Antioxidant compounds	Neutralize effects of oxidant-mediated tissue injury
Anticoagulants	Inhibit formation of microthrombi and injury due to tissue ischemia and reperfusion
Bactericidal permeability-increasing protein	Kill bacteria and neutralize endotoxin
Tumor necrosis factor antibodies	Block action of tumor necrosis factor at the tissue level
Constructs of tumor necrosis factor soluble receptor	Block action of tumor necrosis factor at the tissue level
Interleukin-1–receptor antagonists	Inhibit action of interleukin-1 on cellular receptors
Interleukin-1 antibodies	Prevent interleukin-1–receptor interactions
Bradykinin-receptor antagonists	Prevent vasoactive effects of bradykinin
Cyclooxygenase inhibitors	Block inappropriate pyrogen, thromboxane, and prostacyclin production
Thromboxane antagonists	Inhibit inappropriate vasoconstriction and platelet aggregation
Platelet activating factor antagonists	Block platelet activation and inflammatory lipid release
Inhibitors of leukocyte-adhesion molecules	Prevent endothelium–leukocyte interaction
Nitric oxide antagonists	Restore appropriate vasoregulation

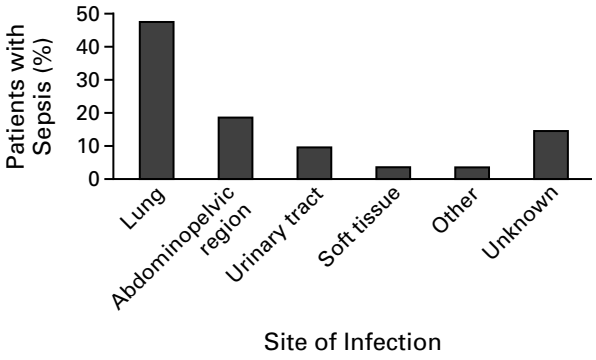

Figure 3. Frequency of Sites of Infection Giving Rise to Severe Sepsis in 455 Patients Enrolled in a Trial of Intravenous Ibuprofen for Sepsis.

More than 15 percent of the patients had an unknown or uncertain site of primary infection. Data are from Bernard et al.[26]

do not receive prompt antibiotic therapy for the causative pathogen, and the mortality rate is 10 to 15 percent higher for such patients than for those who receive prompt, appropriate antibiotic therapy.[29,33] Sites of occult infection, rare or antibiotic-resistant organisms, and polymicrobial infections make it impossible to ensure prompt, complete empirical coverage in all cases. A common approach is to initiate broad antibiotic coverage when the pathogen is uncertain, then narrow the therapy as microbiologic data become available. Unfortunately, indiscriminate use of broad-spectrum antibiotics has led to the development of resistant strains. Enterococci and pneumococci, organisms once susceptible to many commonly used antibiotics, have developed widespread resistance.[39]

ORGAN FAILURE

Effective treatment of organ failure is essential because it is the cumulative burden of organ failure that leads to death.[40] The average risk of death increases by 15 to 20 percentage points with failure of each additional organ. A median of two organs fail during severe sepsis, with an associated mortality rate of 30 to 40 percent.[29,40] The incidence of organ failure varies according to the definition of failure and the patient population; however, when consensus definitions of "clinically significant" failure are used, a common pattern of occurrence is observed.[26,41,42] Lung dysfunction occurs often and early and persists, whereas shock, which also occurs early, resolves rapidly or is fatal (Fig. 4). Serious abnormalities of liver function, coagulation, and central nervous system function tend to occur hours to days after the onset of sepsis and persist for intermediate periods. In addition to the number of organ failures, the severity of each failure affects the prognosis. The lower the partial pressure of oxygen, in the case of respiratory failure, and the higher the serum creatinine, in the case of renal failure, the worse the prognosis.[43,44] Fortunately, the majority of organ failures resolve within one month in survivors of sepsis.

PULMONARY DYSFUNCTION

Sepsis places extreme demands on the lungs, requiring a high minute ventilation precisely when the compliance of the respiratory system is diminished, airway resistance is increased, and muscle efficiency is impaired.[45] Detection of sepsis is facilitated by the nearly universal presence of tachypnea and hypoxemia. Respiratory failure often progresses rapidly; a sustained respiratory rate that exceeds 30 breaths per minute is usually a sign of impending ventilatory collapse, even if arterial oxygen levels are normal. Timely intubation and mechanical ventilation reduce respiratory-muscle oxygen demand and the risk of aspiration and cerebral anoxia from catastrophic respiratory arrest. Nearly 85 percent of patients require ventilatory support, typically for 7 to 14 days, and almost half meet the criteria for the diagnosis of the acute respiratory distress syndrome.[26,46] The increased airflow resistance can be reduced by administering inhaled beta-adrenergic–receptor agonists.[47] Radiographic evidence of the evolution of pulmo-

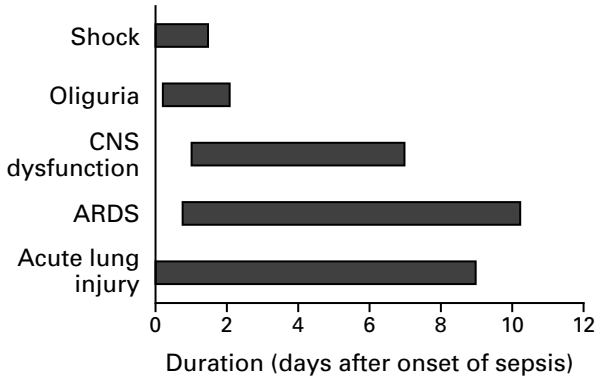

Figure 4. Onset and Resolution of Organ Failure in Patients with Severe Sepsis.

The bars show the duration of organ failure, with the timing of the onset and resolution of organ failure shown at the left and right ends of the bars, respectively. Acute lung injury — or its more severe form, the acute respiratory distress syndrome (ARDS) — develops early and is long-lived, with a mean duration of nine days. Shock and oliguria are similar in the timing of their onset, and the duration of both is brief, averaging less than two days. In contrast, central nervous system (CNS) dysfunction has a delayed onset and an intermediate duration.

nary edema is often mistakenly attributed to worsening pneumonia or heart failure.[48] Although functional impairment can take months to resolve and subclinical spirometric changes are sometimes permanent, unremitting lung failure is uncommon.[49]

There is no strong evidence that one ventilatory strategy is superior to others.[50] One reasonable approach is to use assist–control or intermittent mandatory ventilation adjusted to supply 75 to 100 percent of the minute ventilation required. Alternatively, a lower rate of intermittent mandatory ventilation with enough pressure support to deliver adequate tidal volumes can be used if the respiratory drive and muscle power are sufficient. Tidal volumes of 6 to 12 ml per kilogram of ideal (not actual) body weight are reasonable initially.

Because alveolar involvement in the acute respiratory distress syndrome is heterogeneous, with noncompliant and distensible alveoli juxtaposed, use of airway pressures higher than those required to inflate the normal alveoli may cause detrimental overstretching. Limiting transalveolar pressure, clinically reflected as plateau pressure, to 35 cm of water by reducing the tidal volume may reduce the risk of overstretching.[51,52] However, the resulting lower alveolar ventilation often increases the arterial carbon dioxide tension. Application of sufficient positive end-expiratory pressure (PEEP) to prevent repetitive alveolar collapse and reopening may further reduce the risk of ventilator-induced injury. The results of a lung-protection strategy to prevent overstretching while optimizing alveolar recruitment are encouraging but require confirmation.[53] By boosting the arterial partial pressure of oxygen, PEEP also reduces the required fraction of inspired oxygen, but the risk–benefit ratios for PEEP and supplemental oxygen are poorly delineated.[54] With the balanced use of PEEP and supplemental oxygen, an arterial saturation of 88 to 92 percent is appropriate. Higher saturations add little to oxygen delivery and may require excessive pressures or oxygen concentrations; lower saturations may cause tissue ischemia. A common practice is to use lower PEEP levels (5 to 10 cm of water) until oxygen requirements exceed 40 to 60 percent, whereupon PEEP is preferentially increased.[54] Levels above 20 cm of water are rarely required to achieve acceptable oxygenation with a fraction of inspired oxygen of 60 percent or less. Although the highest safe level of supplemental oxygen is uncertain, the potential risk of oxygen toxicity should not supersede the immediate risk of hypoxia. Despite the encouraging results of some pilot studies, use of corticosteroids, nitric oxide, alprostadil, epoprostenol, surfactant, acetylcysteine, or ketoconazole is not indicated.[24,55-61]

CARDIOVASCULAR FAILURE

Shock is caused by an inadequate supply or inappropriate use of metabolic substrate (especially oxygen), resulting in lactic acidosis and tissue damage. Circulatory adequacy is best gauged with the use of several indexes, including mentation, urinary output, skin perfusion, and blood pressure, supplemented by measurements of oxygen delivery, oxygen consumption, and serum lactate dehydrogenase. Use of blood pressure alone is problematic, because the administration of vasoactive drugs and fluids can normalize blood pressure without correcting the fundamental defect. Despite this limitation, shock is typically defined as a systolic pressure of less than 90 mm Hg that is unresponsive to fluids or that requires vasoactive drugs.[1]

When perfusion is subnormal, treatment is targeted to the pathophysiologic cause (i.e., inadequate filling pressure, cardiac performance, or vascular resistance). Nonetheless, the value of monitoring the central circulation with the use of a pulmonary-artery catheter is unclear.[62,63] Such monitoring appears to be justified in patients with shock, especially in those with serious myocardial, pulmonary, or renal dysfunction. Septic shock is initially characterized by a low capillary wedge pressure, a low cardiac index, and normal or elevated systemic vascular resistance, especially before volume depletion is corrected.[64] Volume depletion results from reduced oral intake, increased losses (e.g., due to bleeding, vomiting, sweating, tachypnea, and increased vascular permeability), and increased venous capacitance. The initial pulmonary-capillary wedge pressure is usually less than 8 mm Hg, and most patients require 4 to 6 liters of crystalloid-containing fluid.[64-66] A high cardiac index and low systemic vascular resistance typically follow volume re-

pletion performed rapidly (over a period of minutes to hours). Fluid administration is guided by the response to therapy (blood pressure, urinary output, and skin characteristics), and colloid has no proven advantage over crystalloid. Clinical assessment may be supplemented by invasive hemodynamic monitoring to ensure a rising cardiac index and mixed venous oxygen saturation.

Hypotension that persists after volume repletion is frequently the result of low systemic vascular resistance, occasionally combined with a reduced cardiac index. Reductions in myocardial contractility stem from myocardial depressant factors, and although there is no way to prevent reduced contractility, beta-adrenergic stimulation often corrects it.[67] Alpha-adrenergic agonists (Table 2) are vasoconstrictive drugs that can boost systemic vascular resistance. All these drugs, except phenylephrine, have marked beta-adrenergic properties as well, increasing the heart rate and myocardial contractility. Dopamine is often used first because it also stimulates dopaminergic receptors, potentially increasing renal blood flow. Apart from the vasoconstrictive effect of dopamine, however, its role in "protecting" the kidneys or augmenting urinary output in patients with sepsis remains unproved.[68] Treatment with norepinephrine often rectifies refractory oliguria and hypotension.[69]

Lactic acidosis may stem from global ischemia (i.e., inadequate oxygen delivery) or regional (organ-specific) ischemia. Since regional ischemia usually results from disordered local autoregulation or cellular dysfunction, it is unlikely to respond to an increase in oxygen delivery. Treatment of hypotension with vasopressors does not always correct lactic acidosis, perhaps because normally responsive vascular beds are constricted with such therapy. Conversely, impaired microcirculation due to ischemia may not benefit from increased flow, because of faulty vasoregulation. Some insight can be gained from distinguishing between acidemia and acidosis. Although correction of the derangement causing anaerobic metabolism (acidosis) is likely to be beneficial, merely normalizing blood pH (acidemia) may not be beneficial, because the underlying anaerobic process continues. Although it is difficult to demonstrate that administration of bicarbonate improves cardiovascular performance,[70] it is commonly used to treat a pH below 7.2.

The benefit of manipulating oxygen delivery or consumption is controversial, even in the case of lactic acidosis.[71] Achieving supraphysiologic oxygen delivery with transfusion and the administration of fluids and vasopressors may improve the outcome in selected patients who have undergone surgery; however, there is no demonstrated benefit of this approach as a treatment for sepsis, and such practices may actually be associated with a reduced survival rate.[72,73] Likewise, the value of augmenting oxygen delivery sufficiently to increase gut perfusion, as estimated by gastric mucosal pH, is uncertain.[74]

RENAL DYSFUNCTION

Although transient oliguria is common and is temporally related to hypotension, anuria is rare. If urinary flow ceases abruptly, obstructive uropathy must be ruled out. Correcting volume deficits and hypotension usually reverses oliguria, but reestablishing urinary flow does not always prevent moderate increases in the serum creatinine level. The benefit of dopamine, diuretics, or fluid loading to prevent renal dysfunction in patients with volume repletion and normal blood pressure has not been proved. Renal failure requiring dialysis occurs in fewer than 5 percent of patients,[26,43] and eventual recovery is common.

GASTROINTESTINAL DYSFUNCTION AND NUTRITION

The liver is a mechanical and immunologic filter for portal blood and may be a major source of cytokines that cause lung injury.[75] For patients with normal base-line hepatic function, abnormalities in serum

TABLE 2. DRUGS COMMONLY USED FOR CIRCULATORY SUPPORT.

DRUG	PHARMACOLOGIC ROLE	CLINICAL EFFECT	USUAL DOSE RANGE
Epinephrine	Alpha- and beta-adrenergic agonist	Chronotropism, inotropism, vasoconstriction	5 to 20 μg/min
Norepinephrine	Alpha- and beta-adrenergic agonist*	Chronotropism, inotropism, vasoconstriction	5 to 20 μg/min
Dopamine	Dopamine and beta-adrenergic agonist, progressive alpha-adrenergic effect with increasing doses	Chronotropism, inotropism, vasoconstriction	2 to 20 μg/kg of body weight/min
Dobutamine	Beta-adrenergic agonist	Chronotropism, inotropism, vasodilation	5 to 15 μg/kg/min
Phenylephrine	Alpha-adrenergic agonist	Vasoconstriction	2 to 20 μg/min

*The alpha-adrenergic effect is greater than the beta-adrenergic effect.

aminotransferase and bilirubin levels are common, but like renal failure, frank hepatic failure is uncommon. Septic shock usually causes ileus, which typically persists for one to two days, well after hypoperfusion has been corrected. The use of high-dose narcotics or sedatives and delays in instituting enteral feeding after the resolution of shock can further delay the return of motility.

Protein and calorie requirements are high and underlying malnutrition is prevalent in patients with sepsis, yet the value of providing nutritional support is disputed.[76] Although it is axiomatic that nutritional support is desirable, the optimal level, route of delivery, timing, composition, and monitoring method are debated.[77] Even though gut mucosal cells derive much of their nutrition directly from luminal content, the importance of enteral feeding in mucosal preservation remains controversial.[78] The superiority of parenteral nutrition over enteral feeding is unproved, as is the importance of specific nutritional components (e.g., nucleic acids, glutamine, and n−3 fatty acids).[79]

Despite these uncertainties, several principles should guide the use of nutritional support. Prolonged starvation (for weeks) is likely to be harmful; however, a brief period (several days) without nutrition is unlikely to have a serious adverse effect; hence, feeding can safely be withheld until hemodynamic stability has been achieved (i.e., for one to two days). Hemodynamically stable patients who have not recently undergone abdominal surgery can usually be fed enterally, even if bowel sounds are diminished or some abdominal distention is present.[80] The advantages of enteral as compared with parenteral feeding include gastric pH buffering, avoidance of the use of parenteral-nutrition catheters, preservation of gut mucosa, avoidance of the introduction of bacteria and toxins from the gastrointestinal tract into the circulation, a more physiologic pattern of enteric hormone secretion, the ability to administer a complete nutritional mixture including fiber, and lower cost.

OTHER ORGAN SYSTEMS

Subclinical coagulopathy, signified by a mild elevation of the prothrombin or partial-thromboplastin time or a moderate reduction in the platelet count or plasma fibrinogen level, is extremely common, but overt disseminated intravascular coagulation is rare.[81] Coagulopathy is caused by deficiencies of the coagulation-system proteins, including protein C, antithrombin III, tissue-factor pathway inhibitor, and the kinin system.[14,82-84] Replacement of these factors is currently under study (Table 1).

Consciousness is frequently altered in patients with sepsis; however, overt central nervous system injury and focal deficits are rare. Although there are data suggesting that some inflammatory mediators directly suppress central nervous system function, the cumulative effects of hypotension, hypoxemia, and treatment with sedatives and analgesics are responsible for most changes in mentation. Substantial reductions in scores on objective scales of neurologic function (e.g., the Glasgow coma scale) that are not due to medication portend a dismal prognosis and are usually the result of anoxia or intracranial hemorrhage.[85,86]

GENERAL SUPPORTIVE CARE

The apparent decline in the mortality rate in some subgroups of patients with severe sepsis, despite growing microbial resistance and in the absence of specific therapy, suggests that improved basic supportive measures are beneficial.[5] Timely provision of enteral nutrition; prevention of nosocomial infections, stress ulcers, skin breakdown, and deep venous thrombosis; and judicious use of sedation[87,88] perhaps play a more important part in the outcome than was once appreciated. Thus, prophylaxis against stress ulcers with the use of histamine antagonists, proton-pump inhibitors, or sucralfate is indicated in high-risk patients who are undergoing mechanical ventilation and cannot be fed enterally.[89] Similarly, unless contraindicated, fixed-dose unfractionated heparin, low-molecular-weight heparin, or venous-compression devices should be used to prevent deep venous thrombosis.[90]

SUMMARY

Between a quarter and half of all patients with sepsis who die have other ultimately fatal illnesses or injuries. Thus, perhaps only 50 percent of all deaths attributed to sepsis are caused exclusively by sepsis, but it is often difficult to determine a single cause of death in patients with multiple-organ-system failure. Aside from the use of antibiotics, treatment approaches continue to focus on eradicating infection and supporting failing organs so that the patient can heal. Mortality due to sepsis may be declining because of improvements in organ-system support and prevention of complications, even in the absence of any single therapeutic advance in the treatment of sepsis. Our enhanced understanding of the biochemistry of sepsis should soon result in the development of effective specific therapies.

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