

REVIEW ARTICLE

DRUG THERAPY

Management of Sepsis

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A BETTER UNDERSTANDING OF THE INFLAMMATORY, PROCOAGULANT, AND immunosuppressive aspects of sepsis has contributed to rational therapeutic plans from which several important themes emerge.¹ First, rapid diagnosis (within the first 6 hours) and expeditious treatment are critical, since early, goal-directed therapy can be very effective.² Second, multiple approaches are necessary in the treatment of sepsis.¹ Third, it is important to select patients for each given therapy with great care, because the efficacy of treatment — as well as the likelihood and type of adverse results — will vary, depending on the patient.

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THE SPECTRUM OF SEPSIS

Nomenclature is important when it helps us understand the pathophysiology of a disease. This is true for sepsis, since nomenclature has informed the design of randomized, controlled trials and, ultimately, the prognosis of sepsis. Sepsis is defined as suspected or proven infection plus a systemic inflammatory response syndrome (e.g., fever, tachycardia, tachypnea, and leukocytosis).³ Severe sepsis is defined as sepsis with organ dysfunction (hypotension, hypoxemia, oliguria, metabolic acidosis, thrombocytopenia, or obtundation). Septic shock is defined as severe sepsis with hypotension, despite adequate fluid resuscitation. Septic shock and multiorgan dysfunction are the most common causes of death in patients with sepsis.⁴ The mortality rates associated with severe sepsis and septic shock are 25 to 30%⁵ and 40 to 70%,⁶ respectively.

There are approximately 750,000 cases of sepsis a year in the United States,⁷ and the frequency is increasing, given an aging population with increasing numbers of patients infected with treatment-resistant organisms, patients with compromised immune systems, and patients who undergo prolonged, high-risk surgery.⁷

PATHOPHYSIOLOGY

Sepsis is the culmination of complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses.⁸ The rationale for the use of therapeutic targets in sepsis has arisen from concepts of pathogenesis (Table 1).

Both the host responses and the characteristics of the infecting organism influence the outcome of sepsis. Sepsis with organ dysfunction occurs primarily when host responses to infection are inadequate. In addition, sepsis often progresses when the host cannot contain the primary infection, a problem most often related to characteristics of the microorganism, such as a high burden of infection and the presence of superantigens and other virulence factors, resistance to opsonization and phagocytosis, and antibiotic resistance.

Table 1. Pathways and Mediators of Sepsis, Potential Treatments, and Results of Randomized, Controlled Trials (RCTs).*

Pathway	Mediators	Treatment	Results of RCTs
Innate immunity	Superantigens: TSST-1	Anti-TSST-1	Not evaluated
	Streptococcal exotoxins (e.g., streptococcal pyrogenic exotoxin A)	Antistreptococcal exotoxins	Not evaluated
	Lipopolysaccharide (endotoxin)	Antilipopolysaccharide ⁹	Negative
	TLR-2, TLR-4	TLR agonists ¹⁰ and antagonists	Not evaluated
	Monocytes, macrophages	GM-CSF, interferon gamma ¹¹	Not evaluated
Adaptive immunity	Neutrophils	G-CSF†	Not evaluated
	B cells (plasma cells and immunoglobulins)	IgG	Not evaluated
Proinflammatory pathway	CD4+ T cells (Th1, Th2)		
	TNF- α	Anti-TNF- α ^{13,14}	Negative
	Interleukin-1 β	Interleukin-1-receptor antagonist ¹⁵	Negative
	Interleukin-6	Interleukin-6 antagonist	Not evaluated
	Prostaglandins, leukotrienes	Ibuprofen, ¹⁶ high-dose corticosteroids ¹⁷	Negative
	Bradykinin	Bradykinin antagonist ¹⁸	Negative
	Platelet-activating factor	Platelet-activating factor acetyl hydrolase ¹⁹	Negative
	Proteases (e.g., elastase)	Elastase inhibitor‡	Negative
	Oxidants	Antioxidants (e.g., N-acetylcysteine) ²⁰	Not evaluated
	Nitric oxide	Nitric oxide synthase inhibitor ²¹	Negative

INNATE IMMUNITY AND INFLAMMATION IN EARLY SEPSIS

Host defenses can be categorized according to innate and adaptive immune system responses. The innate immune system responds rapidly by means of pattern-recognition receptors (e.g., toll-like receptors [TLRs]) that interact with highly conserved molecules present in microorganisms¹⁰ (Fig. 1). For example, TLR-2 recognizes a peptidoglycan of gram-positive bacteria, whereas TLR-4 recognizes a lipopolysaccharide of gram-negative bacteria (Fig. 1). Binding of TLRs to epitopes on microorganisms stimulates intracellular signaling, increasing transcription of proinflammatory molecules such as tumor necrosis factor α (TNF- α) and interleukin-1 β , as well as antiinflammatory cytokines such as interleukin-10.³² Proinflammatory cytokines up-regulate adhesion molecules in neutrophils and endothelial cells. Although activated neutrophils kill microorganisms, they also injure endothelium by releasing mediators that increase vascular permeability, leading to the flow of protein-rich edema fluid into lung and other tissues. In addition, activated endothelial cells release nitric oxide, a potent vasodilator that acts as a key mediator of septic shock.

SPECIFICITY AND AMPLIFICATION OF THE IMMUNE RESPONSE BY ADAPTIVE IMMUNITY

Microorganisms stimulate specific humoral and cell-mediated adaptive immune responses that amplify innate immunity. B cells release immunoglobulins that bind to microorganisms, facilitating their delivery by antigen-presenting cells to natural killer cells and neutrophils that can kill the microorganisms.

T-cell subgroups are modified in sepsis. Helper (CD4+) T cells can be categorized as type 1 helper (Th1) or type 2 helper (Th2) cells. Th1 cells generally secrete proinflammatory cytokines such as TNF- α and interleukin-1 β , and Th2 cells secrete antiinflammatory cytokines such as interleukin-4 and interleukin-10, depending on the infecting organism, the burden of infection, and other factors.³³

DISTURBANCE OF PROCOAGULANT–ANTICOAGULANT BALANCE

Another important aspect of sepsis is the alteration of the procoagulant–anticoagulant balance, with an increase in procoagulant factors and a decrease in anticoagulant factors (Fig. 2). Lipopolysaccharide stimulates endothelial cells to up-regulate tis-

Table 1. (Continued.)

Pathway	Mediators	Treatment	Results of RCTs
Procoagulant pathway	Decreased protein C	Activated protein C ⁵	Positive
	Decreased protein S	Protein S ²²	Not evaluated
	Decreased antithrombin III	Antithrombin III ²³	Negative
	Decreased tissue factor–pathway inhibitor	Tissue factor–pathway inhibitor ²⁴	Negative
	Increased tissue factor	Tissue factor antagonist ²⁵	Not evaluated
	Increased plasminogen-activator inhibitor 1	Tissue plasminogen activator	Not evaluated
Antiinflammatory	Interleukin-10	Interleukin-10§	Not evaluated
	TNF- α receptors	TNF- α receptors ¹³	Negative
Hypoxia	Hypoxia-inducing factor 1 α , vascular endothelial growth factor	Early, goal-directed therapy ²	Positive
		Supernormal oxygen delivery	Negative
		Erythropoietin ²⁶	Not evaluated
Immunosuppression or apoptosis	Lymphocyte apoptosis	Anticaspases ²⁷	Not evaluated
	Apoptosis of intestinal epithelial cells	Anticaspases ²⁷	Not evaluated
Endocrine	Adrenal insufficiency	Corticosteroids ²⁸	Mixed results¶
	Vasopressin deficiency	Vasopressin ²⁹	Not evaluated
	Hyperglycemia	Intensive insulin therapy ^{30,31}	Not evaluated

* TSST denotes staphylococcal toxic shock syndrome toxin 1, GM-CSF granulocyte–macrophage colony-stimulating factor, G-CSF granulocyte colony-stimulating factor, Th1 type 1 helper T cells, and Th2 type 2 helper T cells. Organism features means components of bacteria that are toxic to the host and that are potential therapeutic targets in sepsis.

† G-CSF is effective in patients with sepsis who have profound neutropenia.¹²

‡ Elastase inhibitor was ineffective in a phase 2 trial involving patients with acute lung injury.

§ Interleukin-10 was ineffective in a phase 2 trial involving patients with acute lung injury.

¶ Corticosteroids had no effect on overall 28-day mortality but decreased mortality in a subgroup of patients with no response to corticotropin (see text for details). Additional trials of corticosteroids in patients with septic shock are in progress.

|| Intensive insulin therapy decreased the mortality rate among critically ill surgical patients but has not yet been evaluated in patients with sepsis.

sue factor, activating coagulation. Fibrinogen is then converted to fibrin, leading to the formation of microvascular thrombi and further amplifying injury.

Anticoagulant factors (e.g., protein C, protein S, antithrombin III, and tissue factor–pathway inhibitor) modulate coagulation. Thrombin- α binds to thrombomodulin to activate protein C by binding to endothelial protein C receptor.³⁴ Activated protein C inactivates factors Va³⁵ and VIIIa³⁶ and inhibits the synthesis of plasminogen-activator inhibitor 1.³⁷ Activated protein C decreases apoptosis,³⁸ adhesion of leukocytes,³⁹ and cytokine production.⁴⁰

Sepsis lowers levels of protein C, protein S, antithrombin III, and tissue factor–pathway inhibitor.⁴¹ Lipopolysaccharide and TNF- α decrease the synthesis of thrombomodulin and endothelial protein C receptor, impairing the activation of protein C,⁴² and increase the synthesis of plas-

minogen-activator inhibitor 1, thus impairing fibrinolysis.

Key to an understanding of sepsis is the recognition that the proinflammatory and procoagulant responses can be amplified by secondary ischemia (shock) and hypoxia (lung injury) through the release of tissue factor and plasminogen-activator inhibitor 1.⁴³

IMMUNOSUPPRESSION AND APOPTOSIS IN LATE SEPSIS

Host immunosuppression has long been considered a factor in late death in patients with sepsis,⁴⁴ since the sequelae of anergy, lymphopenia,⁴⁵ hypothermia, and nosocomial infection all appear to be involved.⁴⁶ When stimulated with lipopolysaccharide *ex vivo*, monocytes from patients with sepsis express lower amounts of proinflammatory cytokines than do monocytes from healthy subjects, possibly indicating relative immunosuppression.⁴⁷

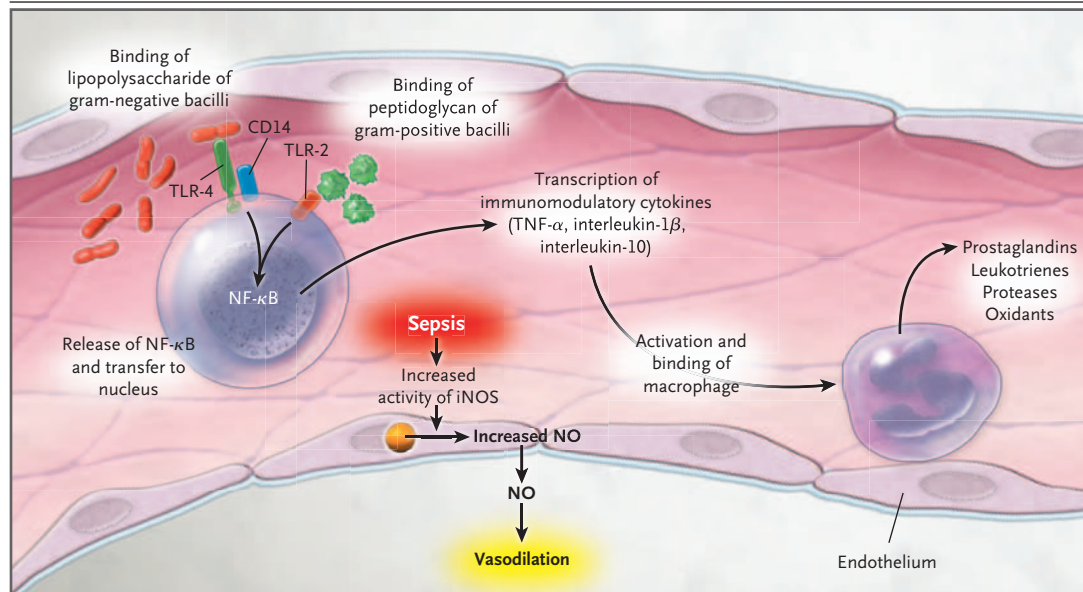


Figure 1. Inflammatory Responses to Sepsis.

Sepsis initiates a brisk inflammatory response that directly and indirectly causes widespread tissue injury. Shown here are key components of this process and their interactions at the level of the microvasculature of a representative vital organ. Gram-positive and gram-negative bacteria, viruses, and fungi have unique cell-wall molecules called pathogen-associated molecular patterns that bind to pattern-recognition receptors (toll-like receptors [TLRs]) on the surface of immune cells. The lipopolysaccharide of gram-negative bacilli binds to lipopolysaccharide-binding protein, CD14 complex. The peptidoglycan of gram-positive bacteria and the lipopolysaccharide of gram-negative bacteria bind to TLR-2 and TLR-4, respectively. Binding of TLR-2 and TLR-4 activates intracellular signal-transduction pathways that lead to the activation of cytosolic nuclear factor κ B (NF- κ B). Activated NF- κ B moves from the cytoplasm to the nucleus, binds to transcription initiation sites, and increases the transcription of cytokines such as tumor necrosis factor α (TNF- α), interleukin-1 β , and interleukin-10. TNF- α and interleukin-1 β are proinflammatory cytokines that activate the adaptive immune response but also cause both direct and indirect host injury. Interleukin-10 is an antiinflammatory cytokine that inactivates macrophages and has other antiinflammatory effects. Sepsis increases the activity of inducible nitric oxide synthase (iNOS), which increases the synthesis of nitric oxide (NO), a potent vasodilator. Cytokines activate endothelial cells by up-regulating adhesion receptors and injure endothelial cells by inducing neutrophils, monocytes, macrophages, and platelets to bind to endothelial cells. These effector cells release mediators such as proteases, oxidants, prostaglandins, and leukotrienes. Key functions of the endothelium are selective permeability, vasoregulation, and provision of an anticoagulant surface. Proteases, oxidants, prostaglandins, and leukotrienes injure endothelial cells, leading to increased permeability, further vasodilation, and alteration of the procoagulant–anticoagulant balance. Cytokines also activate the coagulation cascade.

Multiorgan dysfunction in sepsis may be caused, in part, by a shift to an antiinflammatory phenotype and by apoptosis of key immune, epithelial, and endothelial cells. In sepsis, activated helper T cells evolve from a Th1 phenotype, producing proinflammatory cytokines, to a Th2 phenotype, producing antiinflammatory cytokines.⁴⁸ In addition, apoptosis of circulating and tissue lymphocytes (B cells and CD4+ T cells) contributes to immunosuppression.⁴⁹ Apoptosis is initiated by proinflammatory cytokines, activated B and T cells, and circulating glucocorticoid levels, all of which are increased in sepsis.⁵⁰ Increased levels of TNF- α

and lipopolysaccharide during sepsis may also induce apoptosis of lung and intestinal epithelial cells.⁵¹

SEPSIS AND WIDESPREAD ORGAN DYSFUNCTION

The altered signaling pathways in sepsis ultimately lead to tissue injury and multiorgan dysfunction. For example, cardiovascular dysfunction is characterized by circulatory shock and the redistribution of blood flow, with decreased vascular resistance, hypovolemia, and decreased myocardial contractility associated with increased levels of nitric oxide,⁵² TNF- α ,⁵³ interleukin-6,⁵⁴ and other media-

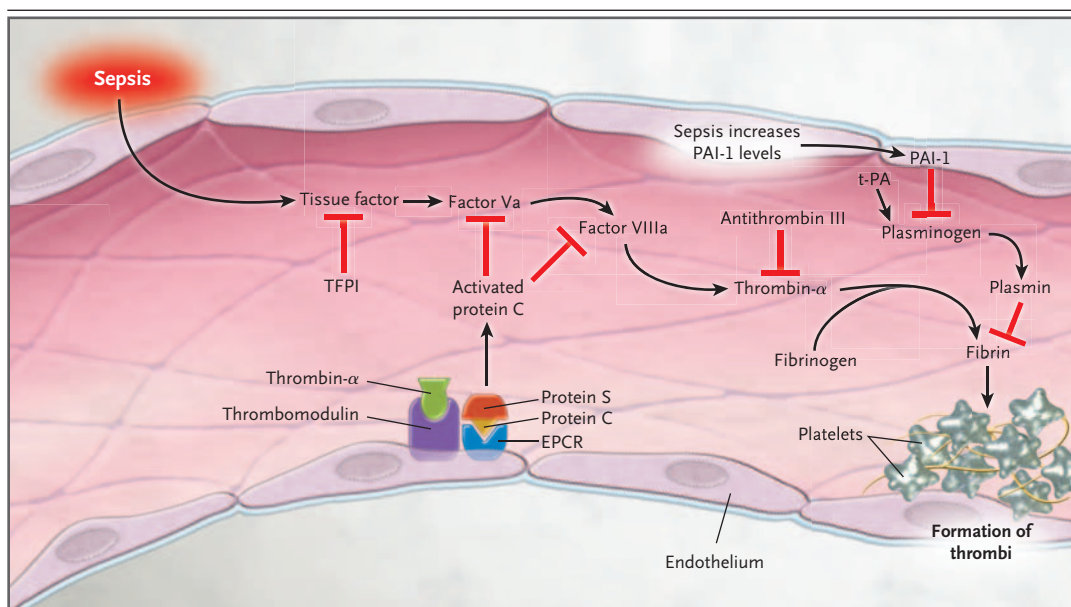


Figure 2. Procoagulant Response in Sepsis.

Sepsis initiates coagulation by activating endothelium to increase the expression of tissue factor. Activation of the coagulation cascade, and especially factors Va and VIIIa, leads to the formation of thrombin- α , which converts fibrinogen to fibrin. Fibrin binds to platelets, which in turn adhere to endothelial cells, forming microvascular thrombi. Microvascular thrombi amplify injury through the release of mediators and by microvascular obstruction, which causes distal ischemia and tissue hypoxia. Normally, natural anticoagulants (protein C and protein S), antithrombin III, and tissue factor–pathway inhibitor (TFPI) dampen coagulation, enhance fibrinolysis, and remove microthrombi. Thrombin- α binds to thrombomodulin on endothelial cells, which dramatically increases activation of protein C to activated protein C. Protein C forms a complex with its cofactor protein S. Activated protein C proteolytically inactivates factors Va and VIIIa and decreases the synthesis of plasminogen-activator inhibitor 1 (PAI-1). In contrast, sepsis increases the synthesis of PAI-1. Sepsis also decreases the levels of protein C, protein S, antithrombin III, and TFPI. Lipopolysaccharide and tumor necrosis factor α (TNF- α) decrease the synthesis of thrombomodulin and endothelial protein C receptor (EPCR), thus decreasing the activation of protein C. Sepsis further disrupts the protein C pathway because sepsis also decreases the expression of EPCR, which amplifies the deleterious effects of the sepsis-induced decrease in levels of protein C. Lipopolysaccharide and TNF- α also increase PAI-1 levels so that fibrinolysis is inhibited. The clinical consequences of the changes in coagulation caused by sepsis are increased levels of markers of disseminated intravascular coagulation and widespread organ dysfunction. t-PA denotes tissue plasminogen activator.

tors. Respiratory dysfunction is characterized by increased microvascular permeability, leading to acute lung injury. Renal dysfunction in sepsis, as discussed recently by Schrier and Wang,⁵⁵ may be profound, contributing to morbidity and mortality.

TREATMENT ACCORDING TO THE EARLY AND LATER STAGES OF SEPSIS

Consensus guidelines for the management of sepsis have recently been published.⁵⁶ The following therapeutic plan, informed by such guidelines, considers emergency care for the early stage of sepsis (0 to 6 hours) and treatment for patients in later stages who require critical care.

EARLY, GOAL-DIRECTED THERAPY

The cornerstone of emergency management of sepsis is early, goal-directed therapy,² plus lung-protective ventilation,¹ broad-spectrum antibiotics,^{57,58} and possibly activated protein C⁵ (Fig. 3 and Table 2). Rivers and colleagues² conducted a randomized, controlled trial in which patients with severe sepsis and septic shock received early, goal-directed, protocol-guided therapy during the first 6 hours after enrollment or the usual therapy. In the group receiving early, goal-directed therapy, central venous oxygen saturation was monitored continuously with the use of a central venous catheter. The level of central venous oxygen saturation served to trigger further interventions recommended in the

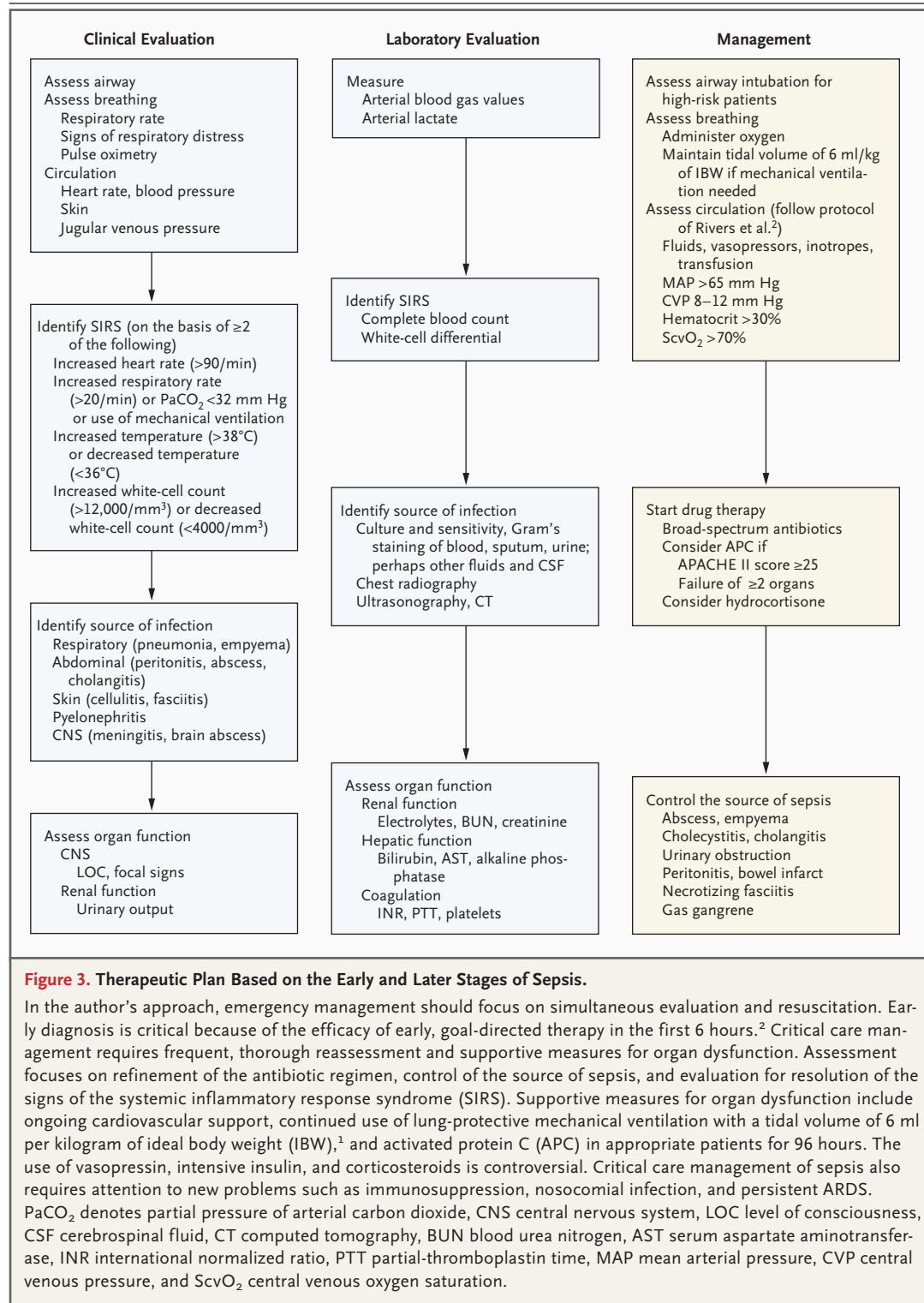


Table 2. Results of Positive Randomized, Controlled Trials.*

Group	Study	No. of Patients	Intervention Group	Control Group	Mortality Rate† Intervention Group Control Group %	NNT‡	Level of Evidence
Patients with acute lung injury and ARDS§	ARDS Clinical Trials Network¹	861	Low tidal volume (6 ml/kg of ideal body weight)	High tidal volume (12 ml/kg of ideal body weight)	31 40	11	I
Patients with severe sepsis and septic shock	Rivers et al.²	263	Early, goal-directed therapy	Usual therapy	33 49	6	I
Patients with severe sepsis and septic shock	Bernard et al.⁵	1690	Activated protein C	Placebo	25 31	16	I
Patients with severe sepsis and septic shock, at increased risk for death¶	Bernard et al.⁵	817	Activated protein C	Placebo	31 44	7.7	I
Patients in septic shock	Annane et al.²⁸	299	Hydrocortisone + fludrocortisone	Placebo	55 61	NA	I–II
Patients in septic shock**	Annane et al.²⁸	229	Hydrocortisone + fludrocortisone	Placebo	53 63	10	I–II
Critically ill surgical patients	Van den Berghe et al.³¹	1548	Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)	Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)	4.6 8	29	I
Patients in medical ICU††	Van den Berghe et al.³⁰	1200	Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)	Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)	37 40	NA	I

* The inclusion criteria were as follows: for the ARDS Clinical Trials Network,¹ a ratio of the partial pressure of arterial oxygen to the forced inspiratory volume in 1 second of less than 300, pulmonary infiltrates, mechanical ventilation, no congestive heart failure; for Rivers et al.,² sepsis plus either increased lactate levels (severe sepsis) or hypotension (septic shock); for Bernard et al.,⁵ severe sepsis; for Annane et al.,²⁸ vasopressor-dependent septic shock, mechanical ventilation, oliguria, and increased lactate levels. One study by Van den Berghe et al.³¹ involved patients in the surgical intensive care unit (ICU), 62% of whom had undergone cardiac surgery. The other study by Van den Berghe et al.³⁰ involved patients in the medical ICU. The 28-day mortality rate is shown for all groups except those studied by Van den Berghe, for which the intensive care unit (ICU)³¹ or in-hospital³⁰ mortality rate is shown.

† Values are the number needed to treat (NNT) to save one life.

‡ Many of the patients had sepsis.

§ An increased risk of death was defined by an Acute Physiology and Chronic Health Evaluation (APACHE) II score of at least 25.

¶ The level of evidence is I for the overall trial, but only II for the subgroup of patients with no response to the corticotropin stimulation test.

** The patients had no response to a corticotropin stimulation test with 250 µg of corticotropin.

†† This trial is included in the table because its results contrast with those of a similar positive trial involving patients in the surgical ICU.³¹

protocol. Crystalloids were administered to maintain central venous pressure at 8 to 12 mm Hg. Vasopressors were added if the mean arterial pressure was less than 65 mm Hg; if central venous oxygen saturation was less than 70%, erythrocytes were transfused to maintain a hematocrit of more than 30%. Dobutamine was added if the central venous pressure, mean arterial pressure, and hematocrit were optimized yet venous oxygen saturation remained below 70%. Early, goal-directed therapy in that study decreased mortality at 28 and 60 days as well as the duration of hospitalization. Patients in the early, goal-directed therapy group received more fluids, transfusions, and dobutamine in the first 6 hours, whereas control subjects received more fluids and more control subjects received vasopressors, transfusion, and mechanical ventilation for a period of 7 to 72 hours. The mechanisms of the benefit of early, goal-directed therapy are unknown but may include reversal of tissue hypoxia and a decrease in inflammation and coagulation defects.⁵⁹

VENTILATION

Once early, goal-directed therapy has been initiated, lung-protective ventilation should be considered. Acute lung injury often complicates sepsis, and lung-protective ventilation — meaning the use of relatively low tidal volumes — is thus another important aspect of management. Furthermore, lung-protective ventilation decreases mortality¹ and is beneficial in septic acute lung injury.⁶⁰ Excessive tidal volume and repeated opening and closing of alveoli during mechanical ventilation cause lung injury. Lung-protective mechanical ventilation, with the use of a tidal volume of 6 ml per kilogram of ideal body weight (or as low as 4 ml per kilogram if the plateau pressure exceeds 30 cm H₂O) as compared with 12 ml per kilogram of ideal body weight (calculated in men as $50 + 0.91$ [height in centimeters – 152.4] and in women as $45.5 + 0.91$ [height in centimeters – 152.4]) has been shown to decrease the mortality rate (from 40 to 31%), to lessen organ dysfunction, and to lower levels of cytokines.⁶¹ Positive end-expiratory pressure (PEEP) decreases oxygen requirements; however, there is no significant difference in mortality between patients treated with the usual PEEP regimen of the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network¹ and those treated with higher PEEP levels.⁶²

Patients receiving ventilation require appropriate but not excessive sedation, given the risks of prolonged ventilation and nosocomial pneumonia.⁶³ Titrating sedation⁶⁴ and interrupting sedation daily until patients are awake⁶³ decrease the risks associated with sedation. Neuromuscular blocking agents should be avoided to reduce the risk of prolonged neuromuscular dysfunction.⁶⁵

BROAD-SPECTRUM ANTIBIOTICS

Because the site of infection and responsible microorganisms are usually not known initially in a patient with sepsis, cultures should be obtained and intravenous broad-spectrum antibiotics administered expeditiously while the host immune status is ascertained. The rising prevalence of fungi, gram-positive bacteria, highly resistant gram-negative bacilli, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, and penicillin-resistant pneumococcus,⁶⁶ as well as local patterns of antibiotic susceptibility, should be considered in the choice of antibiotics. Observational studies indicate that outcomes of sepsis⁶⁷ and septic shock⁵⁷ are worse if the causative microorganisms are not sensitive to the initial antibiotic regimen.

ACTIVATED PROTEIN C

Once goal-directed therapy, lung-protective ventilation, and antibiotic therapy have been initiated, the use of activated protein C should be considered. Therapy with activated protein C (24 µg per kilogram per minute for 96 hours) has been reported to decrease mortality⁵ and to ameliorate organ dysfunction⁶⁸ in patients with severe sepsis. Activated protein C is approved for administration to patients with severe sepsis and an increased risk of death (as indicated by an Acute Physiology and Chronic Health Evaluation [APACHE] II score greater than or equal to 25 or dysfunction of two or more organs); such patients have had the greatest benefit — an absolute decrease in the mortality rate of 13% — from this therapy.⁶⁹ However, a subsequent trial of activated protein C in patients with a low risk of death (the Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis [ADDRESS] trial) was halted after an interim analysis for lack of effectiveness.⁷⁰ This outcome suggests that activated protein C is not beneficial in low-risk patients. The effectiveness of activated protein C does not appear to depend on the site

of infection or the infecting microorganism, possibly because all bacteria and fungi decrease protein C levels.⁷¹

Recent trauma or surgery (within 12 hours), active hemorrhage, concurrent therapeutic anticoagulation, thrombocytopenia (defined as a platelet count of less than 30,000 per cubic millimeter), and recent stroke were exclusion criteria for safety reasons in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of activated protein C.⁵ In that trial, there was a trend toward a higher rate of serious bleeding (defined as bleeding requiring the transfusion of 3 U of packed red cells over a period of 2 days or intracranial hemorrhage) among patients receiving activated protein C than among patients in the placebo group (3.5% vs. 2%, $P=0.06$), especially during infusion of the activated protein C (2.4% vs. 1%).⁵ Intracranial hemorrhage occurred in two patients who received activated protein C and in one who received placebo.⁵ In the Extended Evaluation of Recombinant Human Activated Protein C United States (ENHANCE U.S.) trial, intracranial hemorrhage occurred in 0.6% of patients given activated protein C.⁷² Meningitis and severe thrombocytopenia may be risk factors for intracranial hemorrhage.⁶⁹

When the data are examined together, activated protein C would appear to be cost-effective for patients with severe sepsis and a high risk of death, with the cost per quality-adjusted year of life gained ranging from \$24,484⁷³ to \$27,400,⁷⁴ which is similar to the costs of therapies such as organ transplantation⁷⁵ and drug-eluting stents.⁷⁶

The mechanism of action by which activated protein C improves the clinical outcome is unknown. Activated protein C was shown to increase protein C and decrease markers of thrombin generation (e.g., D-dimer, a marker of disseminated intravascular coagulation) in one study.⁷⁷ Although activated protein C prevents hypotension, it has little effect on coagulation in a human intravenous endotoxin model of sepsis,⁷⁸ suggesting that modulation of coagulation may not be the primary mechanism underlying the cardiovascular benefit. Other anticoagulant therapies have included antithrombin III²³ and tissue factor–pathway inhibitor,²⁴ yet only activated protein C was effective, perhaps because of its complex antiinflammatory,⁷⁹ antiapoptotic, and anticoagulant³⁷ actions.

TREATMENT OF ANEMIA IN SEPSIS

Anemia is common in sepsis⁸⁰ in part because mediators of sepsis (TNF- α and interleukin-1 β) decrease the expression of the erythropoietin gene and protein.⁸¹ Although treatment with recombinant human erythropoietin decreases transfusion requirements,²⁶ its use in randomized, controlled trials failed to increase survival. Erythropoietin takes days to weeks to induce red-cell production and thus may not be effective.

Two trials used different transfusion strategies in different stages of sepsis.^{2,80} Rivers et al.² used a hematocrit of 30% as a threshold for transfusion in early sepsis as part of a 6-hour protocol. Transfusion was associated with an improved outcome. Hebert et al. compared hemoglobin values of 70 and 100 g per liter as a threshold for transfusion later in the course of critical care.⁸⁰ Patients were expected to stay in the intensive care unit (ICU) for more than 3 days, and two transfusion strategies were compared during their entire ICU stay. There was no significant difference in mortality between patients who received transfusion on the basis of higher hemoglobin levels (100 to 120 g per liter) and those who did so on the basis of lower levels (70 to 90 g per liter).⁸⁰

Transfusion is worthwhile if needed during the emergency stage of sepsis; Rivers et al. observed a marked decrease in mortality when transfusion was provided early.² Hebert et al. suggest maintaining hemoglobin levels at 70 to 90 g per liter after the first 6 hours to decrease transfusion requirements.⁸⁰ (Because the protocol of Rivers et al. did not extend beyond 6 hours, it is not known whether a higher transfusion threshold would be useful after 6 hours.)

CORTICOSTEROIDS IN PATIENTS WHO REQUIRE CRITICAL CARE

Although corticosteroids have been considered for the management of sepsis for decades, randomized, controlled trials suggest that an early, short course (48 hours) of high-dose corticosteroids does not improve survival in severe sepsis.^{82,83} Because adrenal insufficiency is being reconsidered as part of septic shock, there has been renewed interest in therapy with corticosteroids, with a focus on timing, dose, and duration. Several controversies over their use persist, however. First, the concept of adrenal insufficiency in sepsis is controversial.

Second, only two (of five)⁸³ small randomized, controlled trials⁸⁴ have shown that corticosteroid therapy (low-dose hydrocortisone) decreases the need for vasopressor support in patients with sepsis. Third, only one adequately powered trial reported a survival benefit of such treatment in patients who had no response to a corticotropin-stimulation test.²⁸

Annane and colleagues²⁸ evaluated oliguric patients with vasopressor-dependent septic shock who required ventilation. Patients underwent a 250- μ g corticotrophin-stimulation test²⁸ and were classified as having adrenal insufficiency (no response) when the serum total cortisol level rose by less than 10 μ g per deciliter.⁸⁵ Patients were then randomly assigned to receive placebo or hydrocortisone plus fludrocortisone for 7 days. Corticosteroids significantly improved survival both in the overall cohort and in the prospectively defined subgroup of patients who had no response to corticotropin; however, over a 28-day period, the difference in mortality was not significant ($P=0.09$). Patients without a response to corticotropin who received corticosteroids had significantly lower mortality than patients who received placebo. Subgroup analyses provide inadequate evidence for a change in therapy, however, given the many examples of therapies that were purportedly successful according to subgroup analysis but were subsequently shown not to be useful in adequately powered, randomized, controlled trials.⁸⁶

Observational studies⁸⁷ offer no data that indicate how patients respond to corticosteroids and thus provide limited guidance as compared with randomized, controlled trials. Marik and Zaloga⁸⁷ reported that 95% of patients in septic shock had serum cortisol levels under 25 μ g per deciliter; another group⁸⁵ have stated that during septic shock, cortisol levels of less than 15 μ g per deciliter should be used as an indicator of relative adrenal insufficiency.

A recent study of serum free cortisol has added further complexity to the diagnosis of adrenal insufficiency in the critically ill.⁸⁸ Serum total cortisol reflects both cortisol bound to protein (cortisol-binding globulin and albumin) and free cortisol (the physiologically active form). Patients with sepsis who have low serum albumin levels may have low serum total cortisol levels (falsely suggesting adrenal insufficiency), despite normal or even increased serum free cortisol levels (indicating truly normal cortisol levels) — a relevant point because

hypoalbuminemia is common in sepsis. Indeed, Hamrahian and colleagues⁸⁸ reported that critically ill patients with hypoalbuminemia had corticotropin-stimulated serum total cortisol levels that were subnormal but corticotropin-stimulated serum free cortisol levels that were higher than normal. When survivors were reassessed 6 to 10 weeks after hospital discharge, their corticotropin-stimulated serum free cortisol levels had declined to the normal range. Therefore, random and corticotropin-stimulated serum total cortisol levels must be interpreted cautiously in patients with sepsis and hypoalbuminemia. Annane and colleagues²⁸ measured serum total cortisol to identify patients who would have a response to corticotropin. Further studies of corticotropin-induced changes in serum free cortisol levels during septic shock are needed.

Corticosteroids have also been considered for the treatment of persistent ARDS.⁸⁹ Although mortality was lower among patients treated with methylprednisolone than among those given placebo in one small trial,⁸⁹ patients in the placebo group crossed over to the methylprednisolone group. A randomized, placebo-controlled trial of methylprednisolone for persistent ARDS, conducted by the ARDS Network, showed no difference between groups in 60-day mortality.⁹⁰

Corticosteroids can have important adverse effects in patients with sepsis, including neuro-miopathy and hyperglycemia, as well as decreased numbers of lymphocytes, immunosuppression, and loss of intestinal epithelial cells through apoptosis. The immunosuppression that accompanies corticosteroid use in sepsis may lead to nosocomial infection and impaired wound healing.

Thus, the use of corticosteroids, as well as the diagnosis of adrenal insufficiency, in patients with sepsis is complex. Randomized, controlled trials indicate that early use of short-course, high-dose corticosteroids does not improve survival in severe sepsis.

EVALUATION AND CONTROL OF THE SOURCE OF SEPSIS

Successful management of the critical care stage of sepsis requires support of affected organs (Fig. 3). If a causative organism is identified (20% of patients with sepsis have negative cultures⁹¹), then the antibiotic regimen should be narrowed to decrease the likelihood of the emergence of resis-

tant organisms. A thorough search for the source of sepsis may require imaging (e.g., ultrasonography or computed tomography) and drainage (e.g., thoracentesis).

VASOPRESSIN

Vasopressin deficiency²⁹ and down-regulation of vasopressin receptors⁹² are common in septic shock. Vasopressin dilates renal,⁹³ pulmonary, cerebral, and coronary⁹⁴ arteries. Intravenous infusion of low-dose vasopressin (0.03 to 0.04 U per minute) has been reported to increase blood pressure, urinary output, and creatinine clearance, permitting a dramatic decrease in vasopressor therapy.^{29,95} However, vasopressin therapy may cause intestinal ischemia,⁹⁶ decreased cardiac output,⁹⁵ skin necrosis, and even cardiac arrest, especially at doses greater than 0.04 U per minute.⁹⁵ Virtually all studies of vasopressin in patients with sepsis have been small and have involved acute infusion (an infusion provided in 1 to a few hours as compared with 1 or more days). Inhibition of nitric oxide synthase with NG-methyl-L-arginine hydrochloride also decreased vasopressor use but significantly increased mortality from septic shock,²¹ suggesting that apparent short-term improvement in surrogate markers such as hemodynamics can be associated with an increased risk of death.

HYPERGLYCEMIA AND INTENSIVE INSULIN THERAPY

Hyperglycemia and insulin resistance are virtually universal in sepsis. Hyperglycemia is potentially harmful because it acts as a procoagulant,⁹⁷ induces apoptosis,⁹⁸ impairs neutrophil function, increases the risk of infection, impairs wound healing, and is associated with an increased risk of death. Conversely, insulin can control hyperglycemia and improve lipid levels⁹⁹; insulin has antiinflammatory,¹⁰⁰ anticoagulant, and antiapoptotic¹⁰¹ actions.

The appropriate target glucose range and insulin dose in patients with sepsis are unknown, because no randomized, controlled trial has been conducted to specifically study patients with sepsis. The results of a randomized, controlled trial of insulin in surgical patients suggested that intensive insulin therapy might be of benefit in sepsis. Van den Berghe and colleagues³¹ randomly assigned critically ill surgical patients to receive insulin infusion to maintain blood glucose levels at 4.4 to 6.1 mmol per liter (intensive insulin dose) or 10.0 to 11.1 mmol per liter (conventional in-

sulin dose). The study involved intubated surgical patients (primarily those undergoing cardiac surgery), not patients with sepsis. Intensive insulin therapy decreased the rate of death in the ICU, especially among patients who remained in the ICU for at least 5 days. Intensive insulin therapy also significantly decreased the prevalence of prolonged ventilatory support, renal-replacement therapy, peripheral neuromuscular dysfunction, and bacteremia. A recent trial by the same group in medical ICU patients showed no significant difference in mortality with the use of intensive or conventional insulin therapy; intensive insulin therapy decreased the rate of death among patients who remained in the ICU for 3 or more days³⁰ but increased the rate of death among patients whose stay lasted fewer than 3 days.

The mechanisms by which intensive insulin therapy benefits surgical patients are not known, but they could include the induction of euglycemia, the benefits related to increased insulin levels, or both.^{101,102} Intensive insulin therapy is antiinflammatory¹⁰⁰ and protects endothelial¹⁰¹ and mitochondrial¹⁰³ function.

Although intensive insulin therapy appears to be beneficial in surgical patients, the lack of efficacy in medical patients, combined with the risks involved for patients who have a short stay in the ICU, indicates clinical equipoise and the need for a randomized, controlled trial in patients with sepsis.^{30,31}

RENAL DYSFUNCTION AND DIALYSIS

Acute renal failure is associated with increased morbidity, mortality, and resource use in patients with sepsis.⁵⁵ Continuous renal-replacement therapy decreases the incidence of adverse biomarkers, but there is little evidence that it changes outcomes.¹⁰⁴ Low-dose dopamine (2 to 4 μ g per kilogram per minute) neither decreases the need for renal support nor improves survival and, consequently, is not recommended.¹⁰⁵ Lactic acidosis is a common complication of septic shock; however, sodium bicarbonate improves neither hemodynamics nor the response to vasopressor medications.¹⁰⁶

SUPPORT AND GENERAL CARE

The goal of cardiovascular support should be adequate perfusion, though whether it is beneficial to try to maintain central venous oxygen saturation

above 70%² after the first 6 hours is unknown. Respiratory support requires continued application of a tidal volume of 6 ml per kilogram and a well-defined weaning protocol (e.g., that of the ARDS Clinical Trials Network^{1,62,90}). Because sepsis increases the risk of deep venous thrombosis, prophylactic heparin — which can be added to activated protein C — is recommended for patients who do not have active bleeding or coagulopathy.¹⁰⁷

Enteral nutrition is important because it is generally safer and more effective than total parenteral nutrition.¹⁰⁸ However, total parenteral nutrition may be required in patients who have had abdominal sepsis, surgery, or trauma. For patients with sepsis who are receiving mechanical ventilation, stress ulcer prophylaxis with the use of histamine H₂-receptor antagonists may decrease the risk of gastrointestinal hemorrhage.¹⁰⁹ Proton-pump inhibitors may be effective but have not been fully evaluated for stress ulcer prophylaxis.

Use of sedation, neuromuscular-blocking agents, and corticosteroids should be minimized because they can exacerbate the septic encephalopathy, polyneuropathy, and myopathy of sepsis. The use of immune support benefits specific subgroups of patients with sepsis (e.g., patients with neutropenia benefit from treatment with granulocyte colony-stimulating factor).¹² The risk of nosocomial infection in patients with sepsis may be decreased by using narrow-spectrum antibiotics, weaning patients from ventilation, avoiding immunosuppression, and removing catheters.

INEFFECTIVE THERAPIES

Several types of therapy have proven ineffective. Antilipopolysaccharide therapy was ineffective,⁹ perhaps because it was applied late (after the lipopolysaccharide peak in sepsis) or because the antibodies used lacked the ability to neutralize lipopolysaccharide. Numerous therapies that block proinflammatory cytokines have failed, perhaps because the approach was narrowly focused, pathways are redundant, or cytokines are critical to

host defense and their blockade is excessively immunosuppressive.¹⁵ Ibuprofen,¹⁶ platelet-activating factor acetylhydrolase,¹⁹ bradykinin antagonists,¹⁸ and other therapies¹¹⁰ have not improved survival among patients with sepsis.

POTENTIAL NEW THERAPIES

Superantigens and mannose are bacterial products that may be potential therapeutic targets (Table 1). Inhibition of tissue factor, a proximal target, might mitigate excessive procoagulant activity. Strategies to boost immunity could improve the outcome of sepsis when applied early in sepsis if measures of immune competence indicate impaired immunity or when applied late in sepsis. Interferon gamma improved macrophage function and increased survival in one study of sepsis.¹¹ Inhibition of apoptosis (e.g., with anticaspases) improved survival in an animal model of sepsis.²⁷ Lipid emulsion (which binds and neutralizes lipopolysaccharide) is being evaluated in a phase 3 trial; lipids may modulate innate immunity by inhibiting lipopolysaccharide.

SUMMARY

Optimal management of sepsis requires early, goal-directed therapy; lung-protective ventilation; antibiotics; and possibly activated protein C.⁵⁶ The use of corticosteroids, vasopressin, and intensive insulin therapy requires further study. Later in the course of sepsis, appropriate management necessitates organ support and prevention of nosocomial infection. Studies focused on novel targets, mechanisms of action, and combination therapy may improve current treatment.

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REFERENCES

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
2. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
3. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644-55.
4. Russell JA, Singer J, Bernard GR, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. *Crit Care Med* 2000;28:3405-11.
5. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
6. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of

- septic shock: the CUB-Rea Network. *Am J Respir Crit Care Med* 2003;168:165-72.
7. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546-54.
8. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003;348:138-50.
9. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial. *N Engl J Med* 1991;324:429-36.
10. Modlin RL, Brightbill HD, Godowski PJ. The toll of innate immunity on microbial pathogens. *N Engl J Med* 1999;340:1834-5.
11. Docke WD, Randow F, Syrbe U, et al. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nat Med* 1997;3:678-81.
12. Lyman GH. Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: a review of the evidence. *J Natl Compr Canc Netw* 2005;3:557-71.
13. Abraham E, Laterre PF, Garbino J, et al. Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: a randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients. *Crit Care Med* 2001;29:503-10.
14. Abraham E, Wunderink R, Silverman H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome: a randomized, controlled, double-blind, multicenter clinical trial. *JAMA* 1995;273:934-41.
15. Fisher CJ Jr, Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome: results from a randomized, double-blind, placebo-controlled trial. *JAMA* 1994;271:1836-43.
16. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med* 1997;336:912-8.
17. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987;317:653-8.
18. Fein AM, Bernard GR, Criner GJ, et al. Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltidant (CP-0127): results of a randomized, double-blind, placebo-controlled trial. *JAMA* 1997;277:482-7.
19. Opal S, Laterre PF, Abraham E, et al. Recombinant human platelet-activating factor acetylhydrolase for treatment of severe sepsis: results of a phase III, multicenter, randomized, double-blind, placebo-controlled, clinical trial. *Crit Care Med* 2004;32:332-41.
20. Bernard GR, Wheeler AP, Arons MM, et al. A trial of antioxidants N-acetylcysteine and procysteine in ARDS. *Chest* 1997;112:164-72.
21. Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004;32:21-30.
22. Fourrier F, Chopin C, Goudemand J, et al. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. *Chest* 1992;101:816-23.
23. Warren BL, Eid A, Singer P, et al. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;286:1869-78. [Erratum, *JAMA* 2002;287:192.]
24. Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003;290:238-47.
25. Carraway MS, Welty-Wolf KE, Miller DL, et al. Blockade of tissue factor: treatment for organ injury in established sepsis. *Am J Respir Crit Care Med* 2003;167:1200-9.
26. Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999;27:2346-50.
27. Hotchkiss RS, Chang KC, Swanson PE, et al. Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. *Nat Immunol* 2000;1:496-501.
28. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
29. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002;96:576-82.
30. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449-61.
31. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67.
32. Brown MA, Jones WK. NF-kappaB action in sepsis: the innate immune system and the heart. *Front Biosci* 2004;9:1201-17.
33. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383:787-93.
34. Esmon CT. Structure and functions of the endothelial cell protein C receptor. *Crit Care Med* 2004;32:Suppl 5:S298-S301.
35. Walker FJ, Sexton PW, Esmon CT. The inhibition of blood coagulation by activated protein C through the selective inactivation of activated factor V. *Biochim Biophys Acta* 1979;571:333-42.
36. Fulcher CA, Gardiner JE, Griffin JH, Zimmerman TS. Proteolytic inactivation of human factor VIII procoagulant protein by activated human protein C and its analogy with factor V. *Blood* 1984;63:486-9.
37. van Hinsbergh VW, Bertina RM, van Wijngaarden A, van Tilburg NH, Emeis JJ, Haverkate F. Activated protein C decreases plasminogen activator-inhibitor activity in endothelial cell-conditioned medium. *Blood* 1985;65:444-51.
38. Joyce DE, Gelbert L, Ciaccia A, DeHoff B, Grinnell BW. Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis. *J Biol Chem* 2001;276:11199-203.
39. Grinnell BW, Hermann RB, Yan SB. Human protein C inhibits selectin-mediated cell adhesion: role of unique fucosylated oligosaccharide. *Glycobiology* 1994;4:221-5.
40. Murakami K, Okajima K, Uchiba M, et al. Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production. *Am J Physiol* 1997;272:L197-L202.
41. Creasey AA, Reinhart K. Tissue factor pathway inhibitor activity in severe sepsis. *Crit Care Med* 2001;29:Suppl 7:S126-S129.
42. Liaw PC, Esmon CT, Kahnoumou K, et al. Patients with severe sepsis vary markedly in their ability to generate activated protein C. *Blood* 2004;104:3958-64.
43. Lawson CA, Yan SD, Yan SF, et al. Monocytes and tissue factor promote thrombosis in a murine model of oxygen deprivation. *J Clin Invest* 1997;99:1729-38.
44. Meakins JL, Pietsch JB, Bubenick O, et al. Delayed hypersensitivity: indicator of acquired failure of host defenses in sepsis and trauma. *Ann Surg* 1977;186:241-50.
45. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. *J Immunol* 2001;166:6952-63.
46. Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. *Shock* 2001;16:83-96.
47. Ertel W, Kremer JP, Kenney J, et al. Downregulation of proinflammatory cytokine release in whole blood from septic patients. *Blood* 1995;85:1341-7.
48. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflamma-

- tory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. *J Infect Dis* 2000;181:176-80.
49. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med* 1999;27:1230-51.
 50. Ayala A, Herdon CD, Lehman DL, DeMaso CM, Ayala CA, Chaudry IH. The induction of accelerated thymic programmed cell death during polymicrobial sepsis: control by corticosteroids but not tumor necrosis factor. *Shock* 1995;3:259-67.
 51. Crouser ED, Julian MW, Weinstein DM, Fahy RJ, Bauer JA. Endotoxin-induced ileal mucosal injury and nitric oxide dysregulation are temporally dissociated. *Am J Respir Crit Care Med* 2000;161:1705-12.
 52. Herbertson MJ, Werner HA, Walley KR. Nitric oxide synthase inhibition partially prevents decreased LV contractility during endotoxemia. *Am J Physiol* 1996;270:H1979-H1984.
 53. Herbertson MJ, Werner HA, Goddard CM, et al. Anti-tumor necrosis factor-alpha prevents decreased ventricular contractility in endotoxemic pigs. *Am J Respir Crit Care Med* 1995;152:480-8.
 54. Cain BS, Meldrum DR, Dinarello CA, et al. Tumor necrosis factor-alpha and interleukin-1beta synergistically depress human myocardial function. *Crit Care Med* 1999;27:1309-18.
 55. Schrier RW, Wang W. Acute renal failure and sepsis. *N Engl J Med* 2004;351:159-69.
 56. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858-73. [Errata, *Crit Care Med* 2004;32:1448, 2169-70.]
 57. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;118:146-55.
 58. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998;244:379-86.
 59. Kietzmann T, Roth U, Jungermann K. Induction of the plasminogen activator inhibitor-1 gene expression by mild hypoxia via a hypoxia response element binding the hypoxia-inducible factor-1 in rat hepatocytes. *Blood* 1999;94:4177-85.
 60. Eisner MD, Thompson T, Hudson LD, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;164:231-6.
 61. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;282:54-61.
 62. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-36.
 63. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342:1471-7.
 64. Ely EW, Trueman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003;289:2983-91.
 65. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med* 1992;327:524-8.
 66. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992–April 2000, issued June 2000. *Am J Infect Control* 2000;28:429-48.
 67. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003;115:529-35.
 68. Vincent JL, Angus DC, Artigas A, et al. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med* 2003;31:834-40.
 69. Ely EW, Laterre PF, Angus DC, et al. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003;31:12-9.
 70. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005;353:1332-41.
 71. Opal SM, Garber GE, LaRosa SP, et al. Systemic host responses in severe sepsis analyzed by causative microorganism and treatment effects of drotrecogin alfa (activated). *Clin Infect Dis* 2003;37:50-8.
 72. Bernard GR, Margolis BD, Shanies HM, et al. Extended Evaluation of Recombinant Human Activated Protein C United States Trial (ENHANCE US): a single-arm, phase 3B, multicenter study of drotrecogin alfa (activated) in severe sepsis. *Chest* 2004;125:2206-16.
 73. Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med* 2002;347:993-1000.
 74. Angus DC, Linde-Zwirble WT, Clermont G, et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med* 2003;31:1-11.
 75. Whiting JF, Kiberd B, Kalo Z, Keown P, Roels L, Kjerulf M. Cost-effectiveness of organ donation: evaluating investment into donor action and other donor initiatives. *Am J Transplant* 2004;4:569-73.
 76. Weintraub WS. Economics of sirolimus-eluting stents: drug-eluting stents have really arrived. *Circulation* 2004;110:472-4.
 77. Dhainaut JF, Yan SB, Margolis BD, et al. Drotrecogin alfa (activated) (recombinant human activated protein C) reduces host coagulopathy response in patients with severe sepsis. *Thromb Haemostasis* 2003;90:642-53.
 78. Derhaschnig U, Reiter R, Knobl P, Baumgartner M, Keen P, Jilma B. Recombinant human activated protein C (rhAPC; drotrecogin alfa [activated]) has minimal effect on markers of coagulation, fibrinolysis, and inflammation in acute human endotoxemia. *Blood* 2003;102:2093-8.
 79. Riewald M, Petrovan RJ, Donner A, Ruf W. Activated protein C signals through the thrombin receptor PAR1 in endothelial cells. *J Endotoxin Res* 2003;9:317-21.
 80. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409-17. [Erratum, *N Engl J Med* 1999;340:1056.]
 81. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interferon Cytokine Res* 1998;18:555-9.
 82. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. *N Engl J Med* 1984;311:1137-43.
 83. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ* 2004;329:480.
 84. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999;27:723-32.
 85. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003;348:727-34.
 86. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;355:1064-9.
 87. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med* 2003;31:141-5.
 88. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med* 2004;350:1629-38.
 89. Meduri GU, Headley AS, Golden E, et

- al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1998;280:159-65.
90. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006;354:1671-84.
91. Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. *N Engl J Med* 1996;334:1697-702.
92. Grinevich V, Knepper MA, Verbalis J, Reyes I, Aguilera G. Acute endotoxemia in rats induces down-regulation of V2 vasopressin receptors and aquaporin-2 content in the kidney medulla. *Kidney Int* 2004;65:54-62.
93. Tamaki T, Kiyomoto K, He H, et al. Vasodilation induced by vasopressin V2 receptor stimulation in afferent arterioles. *Kidney Int* 1996;49:722-9.
94. Okamura T, Ayajiki K, Fujioka H, Toda N. Mechanisms underlying arginine vasopressin-induced relaxation in monkey isolated coronary arteries. *J Hypertens* 1999;17:673-8.
95. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 2001;27:1416-21.
96. van Haren FM, Rozendaal FW, van der Hoeven JG. The effect of vasopressin on gastric perfusion in catecholamine-dependent patients in septic shock. *Chest* 2003;124:2256-60.
97. Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications* 2001;15:44-54.
98. Ortiz A, Ziyadeh FN, Neilson EG. Expression of apoptosis-regulatory genes in renal proximal tubular epithelial cells exposed to high ambient glucose and in diabetic kidneys. *J Investig Med* 1997;45:50-6.
99. Mesotten D, Swinnen JV, Vanderhoydonc F, Wouters PJ, Van den Berghe G. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab* 2004;89:219-26.
100. Dandona P, Aljada A, Mohanty P, et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 2001;86:3257-65.
101. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005;115:2277-86.
102. Vanhorebeek I, Langouche L, Van den Berghe G. Glycemic and nonglycemic effects of insulin: how do they contribute to a better outcome of critical illness? *Curr Opin Crit Care* 2005;11:304-11.
103. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005;365:53-9.
104. Cole L, Bellomo R, Hart G, et al. A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med* 2002;30:100-6.
105. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000;356:2139-43.
106. Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis: a prospective, controlled clinical study. *Ann Intern Med* 1990;112:492-8.
107. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999;341:793-800.
108. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001;29:2264-70. [Erratum, *Crit Care Med* 2001;29:2387-8.]
109. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998;338:791-7.
110. Eichacker PQ, Parent C, Kalil A, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med* 2002;166:1197-205.

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