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Evidence-Based Guidelines for Sepsis Management in the Emergency Department: A Systematic Approach to Patient Risk-Stratification, Stabilization, and Multi-Modal Therapy—Focus on Early, Goal-Directed Therapy, Activated Protein C, Antibiotics, and Corticosteroids

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Sepsis, the systemic inflammatory response to infection,[1] has afflicted human beings throughout the ages. The term originated from the ancient Greeks and Hippocrates, who used "sepsis" to describe putrefaction and a bad smell.[2] Later, the Romans worshipped the goddess Febris (fever), to whom they offered sacrifices as a means of appeasing infection's whimsy.[2] However, centuries passed before the true impact of septic disease was observed. The arrival of firearms and bullets in the 1600s led to experience with deep, poorly draining wounds that were remarkably more infection prone than the open slashes of swords and spears.[2,3] Indeed, foul-smelling infections became so rampant in 18th-century France during the Napoleonic Wars that a new category of disease, the "putrid diseases," was created.[2,3]

Sepsis disorders continue to frustrate the medical community today. The overall incidence of sepsis in the United States steadily is increasing.[4-6] In 1990, the Centers for Disease Control and Prevention (CDC) estimated that there are 450,000 cases of sepsis yearly in the United States, based on hospital discharge data.[4,5] Sepsis was cited as the 13th leading cause of death in hospitalized patients and the leading cause of death in noncoronary intensive care units (ICUs).[4,5] A more recent review estimated that there were 751,000 cases of severe sepsis in 1995.[6] The number of deaths from sepsis in 1995 was extrapolated to equal the number of deaths following myocardial infarction.[6] This pattern was predicted by the CDC in 1990, citing as causes the aging U.S. population and the increased prevalence of HIV.[4,5] Other contributing factors include

the increased use of intra-corporeal devices and prosthetic material, chemotherapy, organ transplantation, growing antibiotic resistance, and improved survival rates in patients prone to sepsis.[7,8] Assuming U.S. Census-projected changes in the population, the annual incidence of sepsis can be expected to increase 1.5% per annum, leading to more than 1 million cases by the year 2020.[6]

The past 30 years have seen significant advances in our understanding of the pathophysiology, microbiology, and morbidity associated with septic disease. Unfortunately, many attempts to translate these observations into improved treatment outcomes have proved futile. Nonetheless, three major trials in the past two years have demonstrated that it is possible—using early, goal-directed therapy, activated protein C (Xigris), and corticosteroids in appropriately selected and risk-stratified patients—to improve outcomes in sepsis.[9] Interestingly, each of these trials addressed a different aspect of the disease process. The following article will explore recent advances in the understanding of the nature of septic disease. After a brief discussion of the pathophysiology of sepsis, it will focus on recent therapeutic advances and their impact on the disease. Finally, the article provides a practical, algorithmic treatment approach for the emergency physician (EP) caring for patients with sepsis.

—The Editor

Definitions

In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine established the current definitions of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. (*See Table 1.*)[1,10] These criteria eliminated much of the confusing terminology surrounding septic disease and since have been accepted globally in both clinical and research settings. For the EP, these definitions provide a helpful framework for the early detection and risk stratification of patients with infection.

The consensus conference coined the term SIRS to characterize the clinical response that results from systemic activation of the immune response, regardless of cause. Implicit in the concept of SIRS is its variable etiology. It may stem from localized or generalized infection, multitrauma, hemorrhage, thermal injury, or sterile inflammatory processes, such as acute pancreatitis.[1] Of these, however, infection is by far the most common.[11]

The term sepsis is used when SIRS results from a confirmed or suspected infection.[1] A positive culture is not required—SIRS with an infiltrate on chest x-ray or pyuria is enough to qualify for a diagnosis of sepsis. Severe sepsis is defined as sepsis associated with hypotension, hypoperfusion, or organ dysfunction. Hypotension, according to the conference, is defined as a systolic blood pressure less than 90 mmHg or a reduction of greater than 40 mmHg from the patient's baseline. Examples of hypoperfusion abnormalities include lactic acidosis, oliguria, or acute alteration of mental status.[1] Since its conception, the term "organ dysfunction" has generated some controversy.[12] As stated in the 1992 consensus statement, the term was intended to recognize the progressive continuum of physiologic derangement and organ failure.[1,12] Dysfunction was described as a phenomenon in which organ function was no longer capable of maintaining homeostasis.[1] Subsequently, several scoring systems and descriptive tools have been developed; the Multiple Organ Dysfunction score and the Sequential Organ Failure Assessment score are the most commonly used.[6,13-15] Table 2 lists some clinical and laboratory methods used to identify organ dysfunction; these variables help alert the EP to the presence of severe sepsis and its associated higher morbidity.[12] Finally, septic shock is defined as severe sepsis accompanied by hypotension that persists even after adequate fluid resuscitation, which is typically defined as fluid bolus of 500-1000 cc of saline.[1,10] Of note, patients who no longer are hypotensive because of inotropic or vasopressor support still are considered to have septic shock.[1]

SIRS, sepsis, severe sepsis, and septic shock now are recog-

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Table 1. Definitions of SIRS and Sepsis

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS):

The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr
- WBC > 12,0000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms

SEPSIS:

The systemic response to infection. This systemic response is manifested by two or more of the following conditions and is a result of infection:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr
- WBC > 12,0000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms

SEVERE SEPSIS:

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

SEPTIC SHOCK:

Sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration of mental status. Patients who are on inotropic or vasopressor agents still may be classified under septic shock even though they are not hypotensive at the time that perfusion abnormalities are measured.

MULTIPLE ORGAN DYSFUNCTION SYNDROME:

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Adapted from: Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:866.

nized to represent a continuum of increasing inflammatory response to infection.[11,16] Current evidence suggests that the morbidity of sepsis is as much a result of the host's inflammatory response as of the infection itself;[17] it follows, then, that the SIRS to septic shock stages should correlate roughly with morbidity and mortality. Indeed, a study of 2527 patients with SIRS demonstrated that their average mortality rate was 6%, twice as high as the mortality among patients who did not meet any of the SIRS criteria.[18] Mortality increased to 16% in patients with sepsis, 20% in severe sepsis, and an impressive 46% in septic shock.[18] The incidence of end-organ dysfunction paralleled that of mortality.[18]

The Inflammatory Cascade

Several decades of research have resulted in a detailed understanding of the pathophysiologic mechanisms underlying sepsis. This understanding has, in turn, provided the rationale for the multitude of clinical trials testing anti-inflammatory agents and anticoagulants in the treatment of sepsis.[17,19]

The current model of sepsis revolves around the concept of a host's pro-inflammatory and pro-coagulant response to invading pathogens.[8,17,19-21] According to this theory, the normal response to most infections is an immunologic cascade that leads to prompt resolution of infection; however, in certain settings and patients, an excessive and unregulated response occurs. The patient's own unchecked inflammation and coagulation may lead to organ injury and morbidity associated with sepsis.[8,17,19,20] In the words of Lewis Thomas, "the micro-organisms that seem to have it in for us ... turn out ... to be rather more like bystanders … It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful … that we are more in danger from them than the invaders."[20,22] The level of derangement that occurs may range in severity from the mild SIRS to multiple organ failure and death.[8,17,19]

In patients who survive this initial hyperinflammatory phase, an anti-inflammatory immunosuppressive state gradually develops.[9,20,23] The "cytokine storm" seen in the initial phase results in depletion of B and CD4 lymphocytes, and the patient enters a state of anergy, becoming susceptible particularly to nosocomial infections.[9,20,23] Meanwhile, apoptosis, or programmed cell death, occurs in large numbers of lymphocytes and gastrointestinal cells.[20] Cells effectively commit suicide through the release of self-degrading proteases. The cumulative effects of infection and apoptosis contribute to the development of late organ failure.[9,20,23]

A basic schematic of the sepsis timeline is shown in Table 3. In the early hours of microbial infection, the host generates a pro-inflammatory and pro-coagulant response.[23-26] In gram-negative infection, the host response is triggered by lipopolysaccharide (LPS) or endotoxin.[24,26] LPS is a peptidoglycan embedded within the bacterial cell wall that is remarkably well conserved among various species and accounts for the clinical similarity seen in infections caused by different gram-negative organisms (i.e., *Escherichia coli* and Klebsiella species).[19] The pathogenesis of gram-positive sepsis is not as well understood but appears to be mediated via the production of exotoxins. What is clear is that both gram-positive and gram-negative infections are equally capable of producing sepsis.[9] The best characterized examples of exotoxins include toxic shock syndrome toxin-1 (produced by *Staphylococcus aureus*) and streptococcal pyrogenic exotoxins (produced by *Streptococcus pyogenes*).[9,19,27]

On the cellular and sub-cellular levels, the inflammatory cascade is initiated when LPS or exotoxins bind and activate monocytes, neutrophils, and endothelial cells, resulting in the release of an abundance of pro-inflammatory cytokines.[17,24,26] The best characterized of these are tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6).[9,17,24,26] Within 90 minutes of exposure to LPS, TNF and IL-1 activate a second level of inflammatory mediators, including cytokines, nitric oxide, and

reactive oxygen species.[9] This army of pro-inflammatory cytokines orchestrates a complex network of responses. Initially, the secondary release of proteases and arachidonic metabolites generates fever and lactic acidosis, and stimulates changes in heart rate, respiratory rate, and white blood cell (WBC) count, i.e., the manifestations of SIRS.[17,23] It is at this stage that most patients seek medical help.[23]

As inflammation continues, TNF and IL-1 promote adhesion of neutrophils to endothelial cells, inciting diffuse capillary injury.[8,17] Hypotension often ensues, leading to tissue ischemia and organ dysfunction.[8] One of the earliest manifestations of capillary leak occurs in the lung in the form of the acute respiratory distress syndrome (ARDS), which is characterized by increased shunt and ventilation-perfusion imbalance.

While inflammation is ongoing, a state of generalized hypercoagulation also occurs. Pro-inflammatory cytokines induce the expression of tissue factor on monocytes and endothelial cells. Tissue factor, in turn, interacts with Factors VIIa and IXa to activate both the extrinsic and intrinsic pathways of the coagulation cascade.[8,9,25,27,28] (*See Figure 1.*) In the final stage, large amounts of thrombin are generated, and fibrinogen is converted to fibrin. Fibrin aggregates with platelets to form clot, which is deposited in blood vessels throughout the body,[8,9,27] causing diffuse microvascular tissue ischemia. Simultaneously, fibrinolysis is impaired.[8,9,27,28] (*See Figure 1.*) LPS induces an increase in levels of plasminogen activator inhibitor 1, which prevents the activation of plasminogen into plasmin and the subsequent breakdown of fibrin clots.[27,28]

Finally, there are three major physiologic anticoagulants—antithrombin III, protein C, and tissue factor-pathway inhibitor (TFPI)—which regulate the coagulation cascade. (*See Figure 2.*) All of these appear to be affected to some degree in patients with sepsis.[8,17,25,27,29,30] Antithrombin III exerts its effects through inactivation of Factor Xa and thrombin.[30] Activated protein C degrades cofactors Va and VIIIa.[30] TFPI directly inhibits the binding of tissue factor to factor VIIa.[30] In septic patients, these anticoagulants are rendered ineffective via several mechanisms. First, ongoing thrombin formation rapidly consumes them.[27,30] Second, activated neutrophils release proteases that hasten anticoagulant degradation.[27,30] Finally, impaired liver function results in decreased synthesis.[27,30]

The result is coagulation that proceeds unchecked. At its most extreme, the imbalance between coagulation and fibrinolysis results in widespread coagulopathy and microvascular thrombosis, or disseminated intravascular coagulation (DIC).[8,27] The development of DIC occurs in 30-50% of patients with severe sepsis and indicates a particularly poor prognosis for the patient[9,27] with a mortality rate that is approximately doubled.[27]

Therapeutic Advances

During the past three decades, it has become disturbingly clear that modern medicine is very good at identifying patients with sepsis, but is poor at translating this knowledge into improved patient outcomes. In several recent reviews, the overall mortality of sepsis was noted to be 30%, rising to 40% in the elderly, and an impressive 50% in patients with septic shock,[6,7] statistics that represent minimal improvement since the early 1980s.[7] In short, the various advances of modern medicine (i.e., aggressive ICU care, broad-spectrum antibiotics, invasive monitoring, vasopressor support, etc.) have had minimal impact on the mortality of the disease for decades.

In the past two years, however, three landmark studies have demonstrated that it is possible to decrease the mortality of critically ill, septic patients. These studies are a noteworthy contrast to the multitude of other trials that have failed to impact the disease. Interestingly, each study targeted a different step in the pathophysiologic cascade described above. The three trials are discussed in detail in the following section.

Early Goal-Directed Therapy

Early and aggressive resuscitation in the septic patient is of critical importance and can be life-saving. In this regard, the EP plays a pivotal role in patient care. This point was highlighted in a recent study in which therapy in the emergency department (ED) that optimized cardiac preload, afterload, and contractility resulted in lower patient mortality.[31]

In this prospective, randomized study, 236 patients with septic shock received either standard therapy or a strategy called early goal-directed therapy (EGT).[31] Patients were enrolled in the

Table 2. Common Clinical and Laboratory Methods to Evaluate Specific Organ System Dysfunction

ORGAN SYSTEM	INDICES OF DYSFUNCTION
Respiratory	• Decreased PaO_2/FiO_2 ratio • Need for supplemental oxygen
Renal	• Elevated serum creatinine, • Decreased urine output, dialysis-dependent
Hepatic	• Jaundice • Hyperbilirubinemia, elevated transaminases
Cardiovascular	• Hypotension, arrhythmias • Vasopressor support • Elevated pulmonary capillary wedge pressure
Hematologic	• Thrombocytopenia, leukocytosis • Elevated PT, PTT
Neurologic	• Confusion, obtundation, coma, psychosis

Key:
PT = prothrombin time; PTT = partial thromboplastin time

Adapted from: Balk R. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. *Crit Care Clin* 2000;16:344-345.

Table 3. Sepsis Timeline

INFECTION			
PATHOPHYSIOLOGY	**TIME COURSE**	**CLINICAL SIGNS**	
• LPS/endotoxin binding to receptors • Activation of monocytes, neutrophils, endothelial cells	0-12 hours	• Fatigue • Somnolence	
• Ongoing phagocyte activation • Cytokine production: **TNF, IL-1, IL-6	12-24 hours	• Body temp > 38°C or < 36°C • Heart rate > 90 beats/min • Resp rate > 20 breaths/min or $PaCO_2$ < 32 mmHg	**S** **I** **R** **S**
• Activation of the coagulation system		• WBC > 12 or < 4 (x 10^9) or > 10% band forms	
• Endothelial cell damage • Ongoing inflammation and hypercoagulation • Fibrin deposition and tissue ischemia	24-72 hours	• Cardiovascular shock • Early organ dysfunction	
• Lymphocyte depletion • Apoptosis	> 72 hours	• Late organ dysfunction	

Adapted from: Takala A, et al. Markers of inflammation in sepsis. *Ann Med* 2002;34:615.

study, on average, within an hour and a half following their arrival to the ED. All patients received arterial and venous cannulation; patients in the standard therapy group then were treated according to the clinicians' discretion and moved to an ICU as quickly as possible (on average, 6.3 hours). In contrast, patients in the EGT group received a central venous catheter capable of measuring central venous oxygen saturation ($SCVO_2$); these patients were treated in the ED for at least six hours and then moved to an inpatient setting. According to the EGT protocol, patients received a 500 cc bolus of crystalloid every 30 minutes until a central venous pressure (CVP) of 8-12 mmHg was achieved.[31] If the mean arterial pressure (MAP) at that time still was less than 65 mmHg, the patient was started on vasopressor support until a MAP of 65 was achieved.[31] If $SCVO_2$ remained less than 70% after the patient reached the target blood pressure, red blood cells were transfused up to a hematocrit of 30%.[31] If the $SCVO_2$ still was less than 70%, a dobutamine infusion was begun to boost cardiac output and oxygen delivery. Finally, patients who did not achieve hemodynamic optimization on dobutamine were paralyzed and intubated to decrease oxygen consumption. The primary endpoint was in-hospital mortality. Other indices of resuscitation, including serum lactate and base deficit, also were followed.

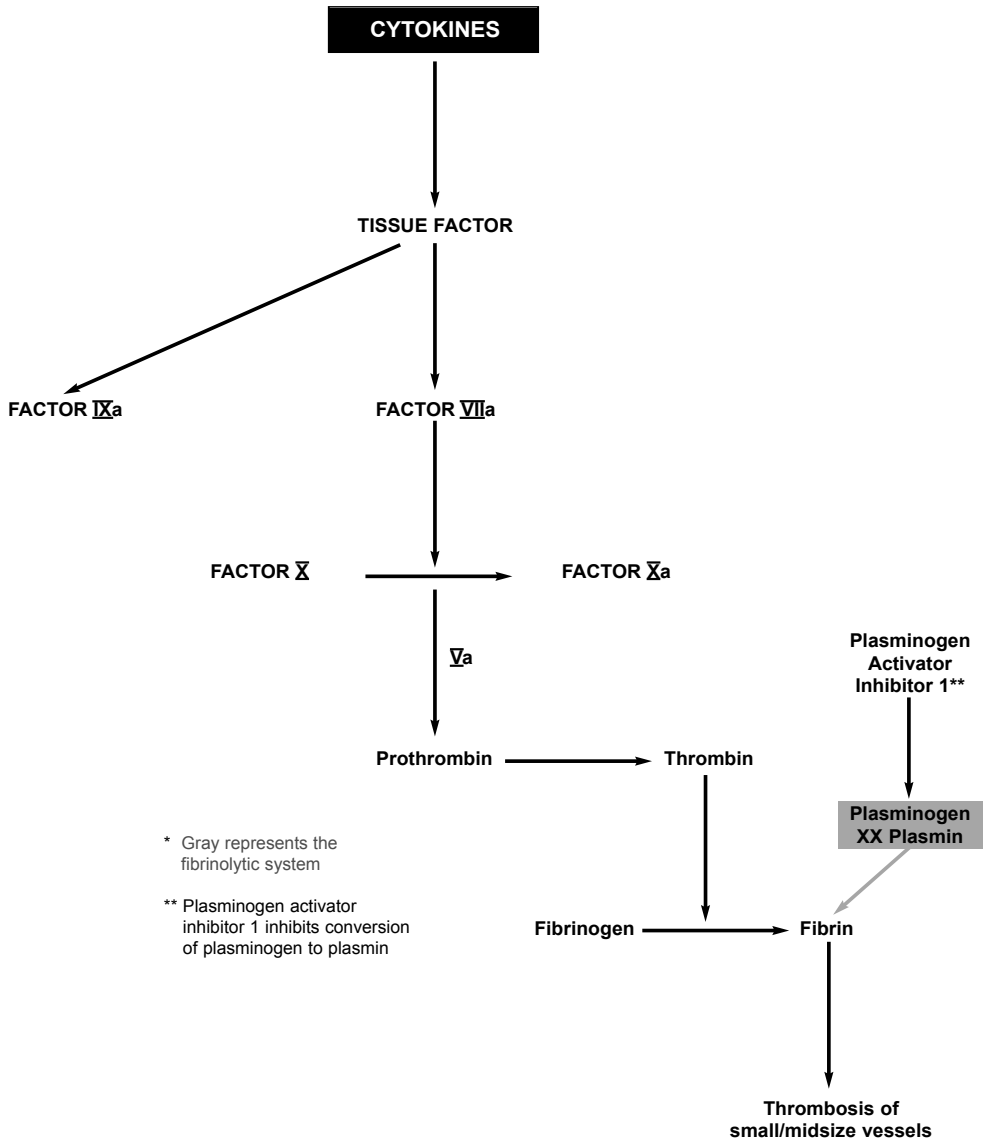
In their results, the researchers noted that in-hospital mortality was significantly higher in the standard therapy group (46%) than in the EGT group (30%, p = 0.009, 95% CI 0.38-0.87).[31] Mortality remained significantly higher at 28 days (49% vs 33%, p = 0.01, 95% CI 0.39-0.87) and at 60 days (57% vs. 44%, p = 0.03, 95% CI 0.46-0.96).[31] The difference in mortality was attributable primarily to lower rates of cardiovascular collapse in the EGT group (10% vs 21%, p = 0.02); levels of multi-organ failure were not significantly different. During the interval from 7 to 72 hours, patients in the EGT group had improved lactate concentrations, pH values, base deficit, and $SCVO_2$.

During the first six hours, patients in the EGT group received on average 1500 cc more fluid (p < 0.001), with a mean amount of 5 liters of fluid administered in the first six hours.[31] Patients in the standard therapy group ultimately received an equal amount of fluid resuscitation as the EGT group, but it occurred primarily in the ICU after the first seven hours of treatment. In contrast, rates of vasopressor support were not different between the two groups. The EGT group also received significantly more blood transfusions than the standard therapy group (64% vs 18%, p < 0.001).[31] Rates of mechanical ventilation were not different.

The results of this landmark study are somewhat surprising in light of several previous ICU trials in which optimization strategies did not improve patient outcomes. In particular, two controlled studies aimed at achieving a normal mixed venous oxygen saturation or a supranormal cardiac index with a combination of fluids and inotropes failed to show any change in mortality; in one study, mortality actually was increased in the treatment group.[32,33] The explanation for these contradictory results may lie in the different time points at which patients were studied. As noted, the group started aggressive resuscitation at an early point of septic shock, presumably before hypoperfusion-induced damage had set in; previous studies involved patients already in the ICU with established critical illness.

For the EP, several important points emerge. Much like the "golden hour" in trauma, the study suggests that there exists an early window of opportunity in the treatment of septic patients; it appears that appropriate resuscitation during the early hours of septic shock may decrease mortality, particularly from cardiovascular collapse. Although $SCVO_2$ catheters may not be available at most hospitals, the underlying concepts still can be applied. This study highlights the critical importance of volume resuscitation. The difference in early fluid administration between the two study groups suggests that physicians may be under-resuscitating critically ill patients. In some patients, placement of a central venous catheter to obtain CVP measurements may be useful. Vasopressor support is most appropriate after adequate volume resuscitation. It is worth noting that the control group in the study spent an average 6.3 hours in the ED before moving to an ICU setting.[54] As ED crowding continues to increase and patients spend more time waiting for inpatient beds, EPs may be expected

Figure 1. Cytokine Activation of the Coagulation Cascade



to manage septic patients for prolonged periods of time. A more detailed review of fluid and pressor management follows in the treatment section.

Activated Protein C

During the past decade, new understanding of the inflammatory nature of sepsis has inspired the search for a "magic bullet," a drug to counteract this hyperinflammation and coagulation. More than 30 trials now have been published; some of the agents studied include corticosteroids, NSAIDS, antiendotoxin antibodies, TNF antagonists, IL-1 antagonists, plasmapharesis, and IV immunoglobulin.[26,34-41] With the exception of steroids, these agents have been overwhelmingly unsuccessful in terms of improving mortality and morbidity. These early failures confirmed that the biochemical derangement associated with sepsis was more complicated than initially envisioned. Furthermore, it suggested that therapies targeting a single pathway of sepsis were overly simplistic and, therefore, ineffective.[20,26]

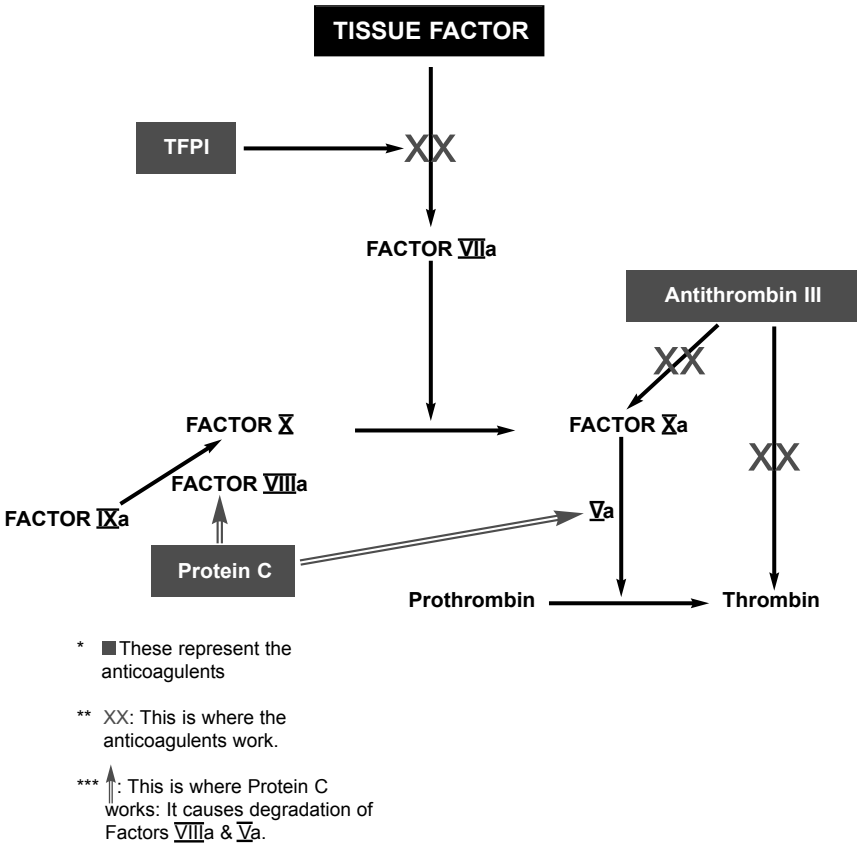
The failure of anti-inflammatory agents, in conjunction with expanding knowledge about the role of coagulation in sepsis, led to experimentation with anticoagulants in septic patients. A large trial of antithrombin III was disappointing.[42] Similarly, tissue factor-pathway inhibitor failed as a treatment for sepsis.[43] However, in 2001, a landmark study examined the effects of activated protein C in patients with severe sepsis.[44] For the first time in any of the anti-inflammatory or anticoagulant trials, a significant survival benefit was found.

The study was a randomized, controlled, double-blind, multicenter trial of 1690 patients with severe sepsis who received either activated protein C infusion (dotrecogin alfa activated) or placebo for 96 hours.[44] Patients were included in the study if they demonstrated sepsis-induced dysfunction of at least one organ system lasting for fewer than 24 hours. The primary endpoint was 28-day mortality,[44] and patients also were monitored for protein C levels and adverse events.[44]

In the final analysis, the group that received activated protein C had a significantly lower mortality rate (24.7%) than the placebo group (30.8%, $p = 0.005$).[44] This mortality difference constituted a 20% relative reduction in the risk of death (95% CI, 0.69-0.94) and a 6% absolute reduction (95% CI, 1.9-10.4).[44] The number needed to treat (NNT) was calculated as one life saved for every 16 patients treated. The incidence of hemorrhage was higher in the protein C group, although this difference did not meet statistical significance (3.5% vs 2.0%, $p = 0.06$). Most of the bleeding episodes consisted of GI and intra-abdominal hemorrhage; two intracranial bleeds were noted in the treatment group, with one in the placebo group. It is worth noting that the patients in both groups were very ill, with an average APACHE II score of 25. Approximately 75% were mechanically ventilated, and 70% were on vasopressor support for septic shock.[44] It also is worth noting that the improvement in mortality among patients treated with activated protein C was consistent even in patients who did not demonstrate protein C deficiency as measured by serum levels (13% of the patient population).[44]

The reason protein C was effective when so many anticoagulants and anti-inflammatory drugs had failed is not entirely clear. It has been suggested that activated protein C has immunosup-

Figure 2. Mechanisms of the Three Anticoagulants



pressive effects in addition to its anticoagulant properties.[9,28,45-48]

Following publication of the study, the Food and Drug Administration (FDA) evaluated activated protein C as a therapeutic modality in patients with severe sepsis.[21,34,49,50] In the extensive post-hoc analysis that followed, multiple questions were raised regarding interpretation of the study results and appropriate use of the drug.[50] The FDA found, on subgroup analysis, that all mortality benefit occurred in the most seriously ill patients—those with APACHE II scores of 25 or more.[21,34,49,50] These individuals consistently demonstrated a 13% reduction in absolute mortality.[34,49-51] However, patients with APACHE II scores less than 25 did not show any mortality benefit, and those individuals in the least ill group (score: 3-19) had a slightly higher mortality when treated with protein C.[34,49,50] *(For a review of the APACHE II score please refer to Knaus W. APACHE II: A severity of disease classification system.* Crit Care Med *1985;13:818-829. For an online site that will calculate a patient's APACHE II score, refer to www.sfar.org/scores2/apache22.html.*)

The issue of bleeding also was raised. Although the risk of intracranial hemorrhage was only 0.2% in Bernard et al's study, subsequent uncontrolled studies noted an incidence that was closer to 1.5%.[49,50] This raised concern that the risk of serious hemorrhage may be substantially greater outside of the highly controlled research setting, emphasizing the importance of careful patient selection when using the drug.[49,50]

In November 2001, the FDA approved recombinant activated protein C for the treatment of patients with severe sepsis who have a high risk of death as determined, for example, by their APACHE II score.[21,50,51] Activated protein C is now the only biologic agent approved in the United States for the treatment of severe sepsis.

The FDA analysis yielded several important points about the drug. Protein C does appear to be effective in some groups of patients with sepsis, particularly those with severe sepsis. However, it is an expensive drug ($6800 per therapeutic dose),[21,50] and the small risk of hemorrhage must be weighed against the benefits of improving outcomes in a very serious disease, a decision that requires prudent clinical judgment and, in most cases, a multidisciplinary evaluation. Future studies are needed to further clarify which patients are good candidates for the drug. Following approval of protein C in septic patients, the FDA requested an additional placebo-controlled study; the manufacturer has committed to conducting such a trial with at least 11,000 patients.[50] At present many hospitals have adopted the drug for use in their most seriously ill septic patients. As a general guideline, activated protein C should be reserved for patients who have more than one dysfunctional organ system, septic shock, or an APACHE II score of at least 25. Patients should not have bleeding diatheses, especially thrombocytopenia (platelet count < 30,000), prolonged prothrombin times, or meningitis.[34,52] Patients with organ failure of greater than 24 hours duration have not been studied.[49]

The Resurrection of Steroids

The use of corticosteroids in patients with sepsis has come full circle during the span of three decades. In the late 1970s, as the role of inflammation in sepsis was being elucidated, a wave of enthusiasm for the use of high-dose steroids in patients with severe sepsis occurred. Support for this approach was rooted in several animal models, in which steroid administration to animals with clinical symptoms of sepsis resulted in improved hemodynamics and survival.[53-56] These studies, along with several case reports, resulted in widespread use of steroids for the treatment of septic shock in the 1970s.[57,58] The 1980s brought two multiple-center, prospective, double-blind clinical trials, each giving high-dose steroids on day 1 of septic shock. In the Veterans Administration trial, septic patients were randomized to receive 30 mg/kg of methylprednisolone within three hours of diagnosis; no difference in 14-day mortality was noted.[59] In a separate trial, administration of 30 mg/kg of methylprednisolone resulted in a higher mortality rate in the treatment group than in the placebo group.[60] These two well-designed studies effectively ended that era of high-dose corticosteroid use in patients with

septic shock, except in the small subset of patients with true adrenal insufficiency.

However, the past three years have brought several well-designed trials that suggest that there may yet be a role for steroid administration in the septic patient, this time in the context of "relative adrenal insufficiency." It has been proposed that a certain subset of septic patients demonstrate glucocorticoid resistance, or a decreased binding affinity of glucocorticoid for its receptor.[58,62] Hence, while the adrenal gland still produces cortisol, peripheral tissues are unable to utilize it. This situation was termed "starvation in plenty" by one set of investigators.[63] These patients would be expected to show high baseline cortisol levels but a decreased ability to raise their cortisol in response to the corticotropin stimulation test.[58,62] In 2000, researchers observed that mortality in patients with septic shock could be predicted according to their baseline cortisol level and response to the corticotropin stimulation test.[55,62,64]

In 2002, a multi-center, prospective, randomized, and double-blind trial examined the effects of physiologic doses of corticosteroids in septic patients. Researchers randomized 300 septic patients with persistent hypotension after fluid replacement and at least one hour of vasopressor support to receive either 100 mg of hydrocortisone and 50 mcg of fludrocortisone, or placebo.[67] All patients underwent the corticotropin stimulation test. The primary endpoint was 28-day survival. In the final analysis, there were 114 non-responders (poor response to the corticotropin stimulation test) and 36 responders (good response) in the treatment group. Use of corticosteroids was associated with a significant decrease in mortality and vasopressor use in the non-responders, with a mortality of 63% in the placebo group and 53% in the treatment group (95% CI, 0.47-0.95; $p = 0.02$).[67] The NNT to save one life in the non-responders was seven. In the group of responders there was a slight (not statistically significant) increase in mortality. Typical corticosteroid-related adverse effects, such as infection and GI bleeding, were not different between the two groups.[67]

Like the APC study, this study has generated much discussion in the medical community. One concern is that the non-responder group actually may have included some individuals with true adrenal insufficiency, rather than relative adrenal insufficiency.[62] Patients with true adrenal insufficiency and acute adrenal crisis easily could be mistaken for septic shock; hence, their inadvertent inclusion in the study would lead to biased results in favor of steroid administration.[61] Furthermore, patients who did not have relative adrenal insufficiency showed a slight, although not significant, trend toward increased mortality.[20,62]

Clearly, more studies are needed to clarify the issue, and validation of the study currently is under way with the European CORTICUS trial. Until then, administration of physiologic dose steroids to certain subsets of septic patients appears to be a viable option. It should be stressed that only critically ill patients have been included in studies to date; physiologic steroids are recommended only for patients with ongoing hypotension despite fluid replacement and vasopressor support. One option in the ED is administration of dexamethasone 3-6 mg IV because this does not interfere with the corticotropin stimulation test. Patients then could be continued on hydrocortisone and fludrocortisone if they later proved to be non-responders. Alternately, the corticotropin stimulation test can be undertaken in the ED. A baseline cortisol level is drawn, followed by administration of 250 mcg of corticotropin IV. A repeat cortisol level is drawn 30 minutes later. Appropriate patients should receive hydrocortisone 50 mg IV every six hours until results of the corticotropin stimulation test are available; in the responders, steroids should be discontinued. Both of these approaches should be enacted in collaboration with the hospital intensivist, given the data suggesting that responders actually may have adverse reactions to steroid administration.

Treatment of the Septic Patient

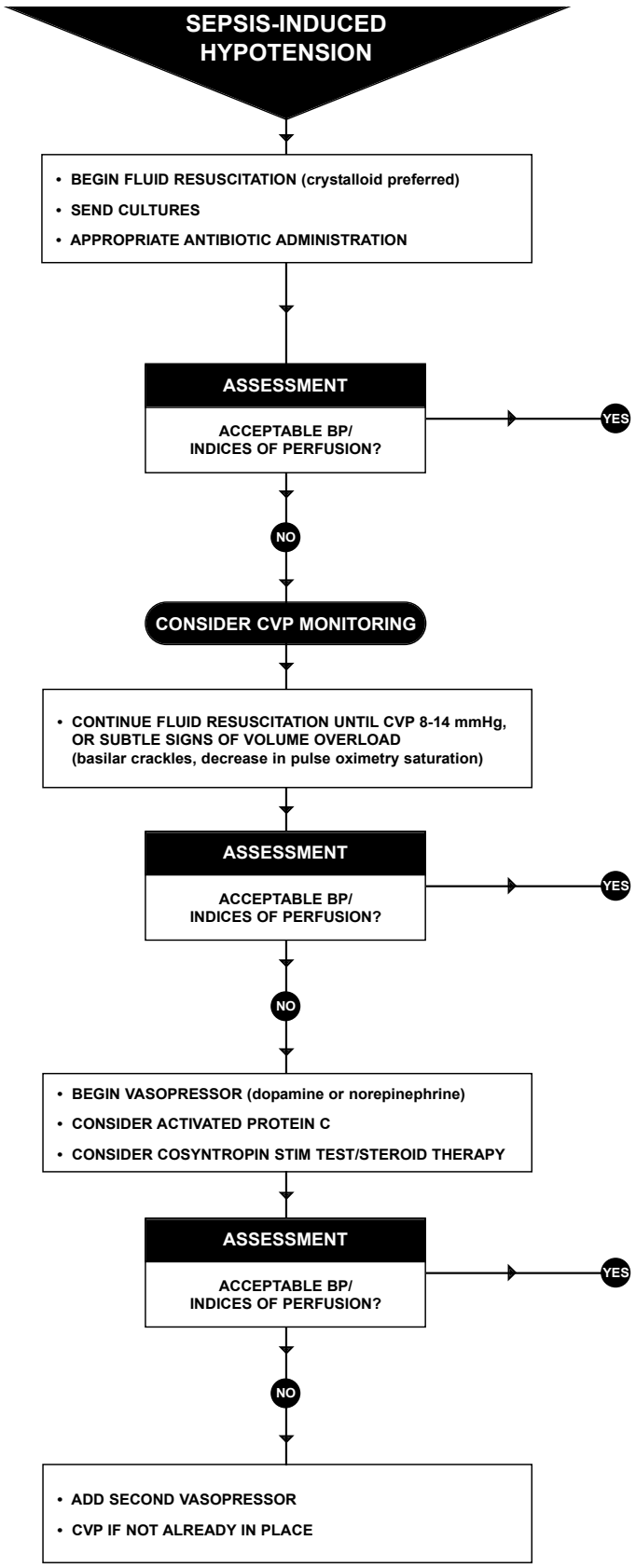
Once airway and ventilation issues have been addressed, the clinician should concentrate on three priorities in the treatment of the septic patient. First, the patient must be hemodynamically resuscitated, focusing on indices of perfusion. Next, the focus of infection rapidly should be identified and treated, either with antibiotic therapy, surgery, or both. Approximately 10% of patients with sepsis do not receive prompt or appropriate antibiotic therapy. There is good evidence that the risk of septic shock and, ultimately, mortality is substantially higher in this subset of patients.[16,68-70] Third, the clinician should consider treatments to quell the pathologic cycle of inflammation. In some patients, efforts toward this goal will include administration of activated protein C. Figure 3 provides an outline for treatment of the critically ill, septic patient.

Intravenous Access and Invasive Monitoring

Close attention to hemodynamic parameters is essential in the septic patient. Intravenous access usually is initiated through peripheral sites, ideally with two large-bore catheters. The patient should have continuous monitoring of heart rate, blood pressure, and pulse oximetry. In patients who do not respond quickly to fluid resuscitation, central venous cannulation is recommended.[71-73] A catheter in the right internal jugular vein allows for rapid infusion of both crystalloid and vasopressors; it also can be used to determine central venous pressure (CVP), which is helpful in guiding fluid management.[71,73] The EP should realize that patients with pneumonia may have a spuriously high CVP secondary to high pulmonary vascular resistance.

The role of the pulmonary artery catheter (PAC) in septic patients is less clear. The PAC may provide helpful data, such as cardiac output, systemic vascular resistance, pulmonary artery wedge pressure, and mixed venous oxygen saturation; however, PACs largely fell into question in 1996 after a retrospective analysis suggested increased harm in patients who underwent pulmonary artery catheterization.[74] Randomized, prospective trials of the PAC in septic patients are lacking. A thorough understanding of hemodynamic physiology is necessary for their optimal use, and even physicians who use the PAC often have gaps in their knowledge of the device.[76] Nonetheless, a PAC may help improve medical decision-making in select groups of patients.[75] Good candidates for a PAC include patients with refractory sep-

Figure 3. ED Treatment Algorithm for the Septic Patient



Key:
CVP = central venous pressur; BP = blood pressure
Adapted from: Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med* 2003;31:951.

tic shock and concomitant heart disease or renal insufficiency.[73]

Arterial cannulation may be helpful in the hypotensive, septic patient.[71] Arterial lines allow for accurate, continuous monitoring of blood pressure and serve as a source for blood gases and other laboratory tests. Common sites for arterial cannulation include radial, brachial, and femoral arteries.[73]

Finally, the serum lactate level is a helpful adjunct to the EP as the test is easy to perform and has a short turn-around time. In septic shock, elevated lactate reflects anaerobic metabolism due to tissue hypoperfusion.[72] Although lactate levels do not universally correlate with tissue hypoxia, increased levels are well correlated with a higher mortality.[72] Hence, the serum lactate can be used to reflect adequacy of resuscitation. As a rule, the trend of lactate concentrations is a better indicator of resuscitation than a single value.[72]

Hemodynamic Resuscitation

Fluid Resuscitation. Early septic shock typically is regarded as the prototypical form of distributive shock. Inflammation at the level of the endothelium results in hypotension (from decreased vascular tone) and maldistribution of blood flow to organs. At the cellular level, mediators of sepsis poison adenosine triphosphate (ATP) production pathways and other cellular metabolism, causing an impaired ability to utilize oxygen supply.[71,72] The typical patient who presents to the ED in septic shock will be very dehydrated. The combined effects of fever, reduced oral intake, vascular vasodilatation, and increased losses (due to bleeding, vomiting, sweating, and tachypnea) all result in a substantial level of hypovolemia.[17,71,72] Initial hemodynamic parameters usually include low blood pressure, low systemic vascular resistance, and variable cardiac index.[77] As demonstrated by Rivers' study, the degree of underlying hypovolemia may be underestimated, resulting in an inadequate preload and, ultimately, higher mortality for the patient. Hence, aggressive fluid resuscitation almost always is the best initial therapy for a septic patient with hypotension.[71,72]

Fluid resuscitation is best initiated with boluses of crystalloid, titrated to clinical indices of heart rate, blood pressure, urine output, and mental status. Bolus therapy offers the advantage of prompt evaluation of successful treatment over slower infusions. While a systolic blood pressure of 90 mmHg or a MAP of 60 mmHg generally are accepted as reasonable initial target parameters,[17,71,72] the clinician over time should focus more on true gauges of perfusion, such as urine output and lactate levels. The level of fluid resuscitation necessary may be surprising: Patients often require 4-6 liters of crystalloid.[31,78-80] In previous years, there has been some debate regarding the appropriateness of crystalloid vs. colloid for volume resuscitation. The theoretical advantage of colloid is less volume administration and, potentially, less edema. However, evidence suggests that there is no significant clinical outcome difference between the two. When crystalloids and colloids are titrated to the same level of filling pressure, they appear to be equally effective and the rate of complications is the same.[71,72,77] Given the much higher cost of colloids, their use seems unjustified outside of cases of spontaneous bacterial peritonitis.[71]

The optimal amount of IV bolus therapy necessary to improve perfusion is variable; what is consistent, however, is the fact that early septic shock patients require large volume resuscitation—often more than 6 liters in the first 12 hours. The aforementioned vasodilatation produces a high compliance vascular tank that further loses fluid through capillary leak. The upper limit of fluid administration can be difficult to ascertain. Fluid administration can be continued until signs of high left-sided filling pressure occur—elevated jugular venous pressure, crackles on lung auscultation, or a drop in oxygen saturation. Alternately, invasive monitoring may be a helpful supplement to clinical assessment. Central venous pressure monitoring and bedside echocardiography further may assist in determining the right amount of fluid admininistration. Although increased pulmonary vascular resistance arising from pneumonia or ARDS artificially may raise the measured CVP pressure, preload usually is considered maximally achieved with pressures in the range of 8-14 mmHg.[71,72]

Bicarbonate Therapy. In the treatment of sepsis-associated lactic acidosis, there is no proven benefit of bicarbonate therapy. In fact, bicarbonate administration paradoxically may worsen intracellular acidosis and impede oxygen unloading at tissues. While at one time it routinely was administered, the use of sodium bicarbonate to reverse sepsis-induced metabolic acidosis now has fallen out of favor. The administration of bicarbonate was predicated on two concepts—first, that acidemia is inherently harmful, and, second, that raising the serum pH can improve cardiovascular outcome in the severely acidemic patients.[71,81] The fear that acidemia, in and of itself, leads to negative consequences largely has been disproven by data on patients undergoing permissive hypercapnia for ARDS or status asthmaticus. In these studies, a pH well below 7.2 was tolerated well.[81]

There have been two studies that compared the impact of bicarbonate administration vs. normal saline on cardiovascular function in acidemic, septic patients.[82,83] Both of these found no difference between bicarbonate and normal saline with regard to heart rate, central venous pressure, pulmonary artery pressure, mixed venous oxyhemoglobin saturation, systemic oxygen delivery, oxygen consumption, arterial BP, or cardiac output.[82,83] The results suggest that any clinical improvement following bicarbonate administration is related primarily to the increase in preload and stroke volume rather than to the change in pH.[81-83] Furthermore, bicarbonate actually may have some negative effects by decreasing ionized calcium levels and raising the $PaCO_2$.[82,83]

In summary, the use of bicarbonate in septic patients does raise serum pH, but this effect is cosmetic and does not result in any hemodynamic benefit. The preferred approach is ongoing resuscitation with isotonic fluids and correction of the underlying problem that is causing the acidosis.

Vasopressor Support. Timing of institution of vasopressors is critical. Although vasopressors may be required transiently before fluid resuscitation is complete to maintain a life-sustaining blood pressure, they generally are withheld until after adequate fluid administration. Hypotension and malperfusion that persist after adequate fluid resuscitation mandate the use of vasopressor support. Again, an MAP of 60 is a reasonable goal, but individual patients vary. Baseline blood pressures should be considered; an MAP of 60 may not be adequate for the chronically hypertensive patient. More important is the fact that vasopressors, especially vasoconstrictors such as phenylephrine, can raise MAP without truly improving perfusion. Therefore, the physician should not merely target a specific MAP number, but rather should seek to improve more important clinical indices of perfusion (i.e., mental status, urine output, skin signs, and lactate levels). Finally, the institution and titration of pressors should be considered therapeutic trials; the clinician should gauge perfusion before and after vasopressor changes.

Commonly used vasopressor agents include dopamine, norepinephrine, phenylephrine, and epinephrine, all of which have been shown to be capable of raising blood pressure in septic patients.[77,84-86] Although dopamine traditionally has been considered the first-line agent for pressor support, recent evidence suggests that norepinephrine is an equally viable alternative in the septic patient. In fact, several experts now recommend norepinephrine as the initial pressor of choice in patients with sepsis-induced hypotension.[71,90]

Dopamine produces different pharmacologic effects at different doses. Doses of 1-3 mcg/kg/min stimulate dopamine receptors and produce dilation of renal, mesenteric, and coronary vasculature. At doses of 3-8 mcg/kg/min, beta-1 receptors are stimulated, causing increased heart rate and contractility. When the dose is increased above 8 mcg/kg/min, dopamine produces vasoconstriction through stimulation of alpha-1 receptors. The clinician should recognize, however, the substantial variability of individual patient response; patients may exhibit beta effects at 2 mcg/kg/min or alpha effects at 6 mcg/kg/min. In the septic patient, blood pressure increases primarily because of increased cardiac index (via augmented stroke volume and tachycardia) and, to a lesser degree, increased systemic vascular resistance.[86,88,89] Dopamine traditionally has been considered the vasopressor of choice because of its renoprotective and splanchnic effects.[72,90] However, studies evaluating splanchnic perfusion in the setting of dopamine administration have produced mixed results. One study demonstrated decreased splanchnic perfusion in patients on dopamine; the authors suggested increased oxygen consumption as a contributing factor.[91] At this point it generally is accepted that dopamine offers no significant renal protective effects.

Norepinephrine is a potent mixed pressor agent exhibiting both alpha and beta effects at low doses, but increasing alpha predominance at higher doses. Dosages range from 0.01 mcg/kg/min to 3.3 mcg/kg/min[72], and the mean dose required by most septic patients is 0.2-1.3 mcg/kg/min.[72] At high doses blood pressure increases primarily as a result of peripheral vasoconstrictive effects, with little change in heart rate or cardiac output. Norepinephrine has been viewed by many as a last resort medication in the moribund patient due to concerns about the effects of intense vasoconstriction and subsequent ischemia in peripheral vascular beds. Indeed, norepinephrine does appear to be more potent than dopamine at reversing hypotension in critically ill, septic patients.[71] Researchers randomized 32 volume-resuscitated

Table 4. Antibiotic Regimens in Septic Shock

SUSPECTED SOURCE	RECOMMENDED ANTIBIOTIC
Pneumonia	Ceftriaxone (Rocephin) *plus* azithromycin (Zithromax)
Hospital-acquired pneumonia	Antipseudomonal beta-lactam (cefepime [Maxipime]) *plus* aminoglycoside *plus* macrolide (if atypical infection suspected)
Urinary tract	Ceftriaxone *or* ciprofloxacin (Cipro) *or* ampicillin *plus* gentamicin (if enterococcus is suspected)
Skin or soft tissue	Nafcillin (add metronidazole *or* clindamycin if anaerobic infection possible)
Meningitis	Third-generation cephalosporin
Intra-abdominal	Third-generation cephalosporin *plus* metronidazole *or* clindamycin
Primary bacteremia	Ticarcillin and clavulanate potassium (Timentin) *or* piperacillin sodium and tazobactam sodium (Zosyn)

Adapted from: Fitch S, Gossage J. Optimal management of septic shock. *Postgrad Med* 2002;111:60. Bosker G. Community-acquired pneumonia (CAP) antibiotic selection and management update. *Emerg Med Rep* 2002;23:109-144. Bosker G, ed. Complicated urinary tract infection: Risk stratification, clinical evaluation, and evidence-based antibiotic therapy—year 2003 update. *Hospital Medicine Consensus Reports* Sept.1, 2003:1-27.

patients to receive either dopamine or norepinephrine infusions. Ninety-three percent of the norepinephrine group achieved normal hemodynamic parameters as compared with 31% in the dopamine group ($p < 0.001$).[89] Of the 11 patients who failed dopamine therapy, 10 achieved normal hemodynamic parameters with the addition of norepinephrine.[89] However, recent evidence suggests that concerns about end-organ damage may be exaggerated. Several studies have demonstrated that the addition of norepinephrine does not exacerbate renal ischemia in septic patients, and may in fact increase urine output and creatinine clearance.[93-95] Five studies found that norepinephrine administration did not increase serum lactate levels, suggesting that tissue oxygenation is not necessarily worsened with the drug.[72,89,93,96,97] A study of patients receiving either norepinephrine or dopamine noted that the effect of norepinephrine on splanchnic blood flow was unpredictable, while dopamine caused a consistently increased flow.[97] In summary, recent data suggest that norepinephrine is a good first-line agent for sepsis-induced hypotension, particularly in patients who cannot tolerate (i.e., those with tachycardia or dysrhythmias) or are unresponsive to dopamine in terms of persistent hypotension—it should not be viewed as an agent of last resort.

Antibiotic Therapy. Antibiotics remain one of the few therapies proven to reduce morbidity and mortality in septic shock.[73] Blood cultures should be drawn and antibiotic therapy begun as quickly as possible. Current practice is to begin broad-spectrum antibiotics, which can be narrowed once the focus of infection is clear.[17,25] Important factors to consider include local resistance patterns, the suspected source of infection, and the immune status of the patient.[25,73] In general, sicker patients will require broader coverage. Table 4 lists some recommendations, but for any given pathogen there are multiple effective regimens.

Blood Transfusions. Although red blood cell (RBC) transfusions may be useful in the acute resuscitation phase of septic shock, they by no means should be undertaken lightly.[98] Beyond the well-known viral transmission and transfusion reaction risks, RBC transfusions additionally can cause acute lung injury, deleterious shifts in oxyhemoglobin dissociation, and immunosuppression.[99] Several well-performed ICU studies have demonstrated that transfusion to keep hemoglobin levels above 9 g/dL leads to worse morbidity and mortality, and, therefore, a higher transfusion threshold generally has been adopted.[98] Thus, anemic, septic patients in the ED should not be transfused when their hemoglobin falls below an arbitrary value, but rather when they show physiologic evidence that anemia is causing or contributing to inadequate perfusion and oxygen debt.

Conclusions

Septic disease remains a major cause of morbidity and mortality in the ED patient population. Current statistics indicate that its prevalence is on the rise, and EPs should expect to see ever-increasing numbers of septic patients. Furthermore, all of the factors that lead to more septic patients (i.e., the aging of the U.S. population and improved survival in patients with chronic medical conditions) also result in increased crowding and utilization of the ED. Patients will wait longer and longer for ICU beds, and the EP may be responsible not only for the patient's first hour of care, but perhaps for the first six hours.

This article has reviewed recent advances in the treatment of septic patients, as well as basic resuscitation issues. The patient with severe sepsis or septic shock presents a challenge to any clinician. By keeping abreast of new treatment modalities, EPs can be sure they are well-equipped to deal with the myriad complications of the disease.

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Physician CME Questions

241. Evidence suggests that patients with SIRS exhibit twice the mortality rate of patients who do not meet any of the SIRS criteria.
    A. True
    B. False

242. The host response to sepsis may include which of the following?
    A. Hyperinflammation
    B. Activation of the coagulation system
    C. Immunosuppression
    D. All of the above

243. Which of the following cause SIRS?
    A. Multitrauma
    B. Hemorrhage
    C. Pancreatitis
    D. A and C only
    E. A, B, and C

244. In the study on early goal-directed therapy, the mean amount of fluid administered in the first six hours to septic patients in the experimental group was:
    A. 2 liters.
    B. 3 liters.
    C. 4 liters.
    D. 5 liters.

245. A concerning side effect associated with activated protein C administration is:
    A. hypoglycemia.
    B. hemorrhage.
    C. sepsis.
    D. anaphylaxis.
    E. acidosis.

246. Reasonable candidates for activated protein C administration include all of the following *except*:
    A. patients with thrombocytopenia.
    B. patients with septic shock.
    C. patients with an APACHE II score > 25.
    D. patients with more than one dysfunctional organ system.

Sourcebook Guides You Through Final EMTALA Rule

You and your facility waited more than a year for the final revisions to the Emergency Medical Treatment and Labor Act (EMTALA), but are they really good news?

Emergency department managers and practitioners, hospital administrators, risk managers and others must quickly digest this complex regulation and determine how the changes will affect patient care. The revised regulation took effect Nov. 10.

EMTALA: The Essential Guide to Compliance from Thomson American Health Consultants, publisher of *Emergency Medicine Reports*, *ED Management*, *ED Legal Letter*, and *Hospital Risk Management*, explains how the changes to EMTALA will affect emergency departments and off-campus clinics. In-depth articles, at-a-glance tables, and Q-and-As on real-life situations are presented, and key differences between the "old" EMTALA and the new changes are succinctly explained.

Here are some of the vital questions you must be able to answer to avoid violations and hefty fines:

• Do the revisions mean hospitals are less likely to be sued under EMTALA?

• How does EMTALA apply during a disaster?

• What are the new requirements for maintaining on-call lists?

• How does EMTALA apply to inpatients admitted through the ED?

• What are the rules concerning off-campus clinics?

Edited by **James R. Hubler, MD, JD, FACEP, FAAEM, FCLM**, attending physician and clinical assistant professor of surgery, Department of Emergency Medicine, OSF Saint Francis Hospital and University of Illinois College of Medicine, Peoria, and reviewed by **Kay Ball, RN, MSA, CNOR, FAAN**, Perioperative Consultant/Educator, K&D Medical, Lewis Center, OH, *EMTALA: The Essential Guide to Compliance* draws on the knowledge and experience of physicians, nurses, ED managers, medicolegal experts, and risk managers to cover the EMTALA topics and questions that are most important to you, your staff, and your facility.

EMTALA: The Essential Guide to Compliance also provides 18 AMA Category I CME credits and 18 nursing contact hours.

Order your copy today for the special price of $249! Call 1-800-688-2421 to receive this valuable guide to the new EMTALA.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

247. Which steroid does *not* interfere with the corticotropin stimulation test?
   A. Hydrocortisone
   B. Dexamethasone
   C. Methylprednisolone

248. The best initial therapy for septic patients with hypotension is:
   A. dopamine.
   B. norepinephrine.
   C. crystalloid.
   D. colloid.

249. Recent evidence suggests that norepinephrine is an equally viable alterntive to dopamine for pressor support in the septic patient.
   A. True
   B. False

250. Giving blood transfusions to keep the hemoglobin level above 9 g/dL has been shown to reduce mortality in septic patients.
   A. True
   B. False

In Future Issues: **Shock**

CME Answer Key

241. A	246. A
242. D	247. B
243. E	248. C
244. D	249. A
245. B	250. B

Emergency Medicine Reports
CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

SARS Audio Program Updates Guidelines

Leading epidemiologists say a global return of severe acute respiratory syndrome (SARS)—which wreaked havoc on the health care systems that had to deal with it—is almost inevitable. The current overriding concern is that SARS will resurface as a seasonal illness along with influenza and other respiratory infections. Indeed, it would be a surprising development if the emerging coronavirus did not return, said Julie Gerberding, MD, MPH, director of the Centers for Disease Control and Prevention in Atlanta.

"As an infectious disease expert, I can say in my experience, I've never seen a pathogen emerge and go away on its own," Gerberding said. "I think we have to expect that somewhere, some time, this coronavirus is going to rear its ugly head again; and that's the whole purpose of all this preparedness effort."

What would happen today if a patient with suspect or probable SARS were admitted to your hospital? To help you prepare for the threat, Thomson American Health Consultants offers the upcoming audio conference: The Resurgence of SARS: Why your hospital may not be as prepared as you think, on Dec. 9, from 2:30-3:30 EST. Let our experts help you answer that and many other critical questions with practical tips and solutions to detect first cases and protect other patients and health care workers.

Our speakers are **Allison McGeer, MD**, director of infection control at Mount Sinai and Princess Margaret Hospitals in Toronto. A veteran epidemiologist, McGeer dealt first hand with SARS patients and occupationally infected workers during the prolonged outbreak in Toronto. Hear the lessons learned by somebody who has dealt with this novel emerging pathogen on the frontlines.

If SARS returns, hospital emergency rooms will certainly be on those frontlines. To provide valuable guidance and critical insight in that setting, **Susan E. Shapiro, PhD, RN, MSN, CEN**, will outline valuable tips and procedures, in addition to addressing and clarifying recently updated CDC recommendations for SARS. Shapiro is a Post Doctoral Fellow in Risk Assessment and Intervention Research with Individuals and Families at Oregon Health & Science University School of Nursing in Portland. A career ED nurse and nurse manager before recently completing a doctoral program, Shapiro is the Emergency Nurses Association's representative to the CDC's SARS task force.

Educate your entire staff for one low fee including 1 hour of CE, CME, or Critical Care credits for all attendees. You may invite as many participants as you wish to listen for the low fee of $249. Information on obtaining audio conference instructions and continuing education forms will be in the confirmation notice, which will be mailed upon receipt of registration. Your fee also includes access to a 48-hour replay following the conference and a CD recording of the program. For information or to register, call customer service at (800) 688-2421 or contact us via e-mail at customerservice@ahcpub.com. When ordering, please refer to effort code 35281.

Emergency Medicine Reports
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Sepsis

Definitions of SIRS and Sepsis

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS):

The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr
- WBC > 12,0000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms

SEPSIS:

The systemic response to infection. This systemic response is manifested by two or more of the following conditions and is a result of infection:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 torr
- WBC > 12,0000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms

SEVERE SEPSIS:

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

SEPTIC SHOCK:

Sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration of mental status. Patients who are on inotropic or vasopressor agents still may be classified under septic shock even though they are not hypotensive at the time that perfusion abnormalities are measured.

MULTIPLE ORGAN DYSFUNCTION SYNDROME:

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Adapted from: Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:866.

Common Clinical and Laboratory Methods to Evaluate Specific Organ System Dysfunction

ORGAN SYSTEM	INDICES OF DYSFUNCTION
Respiratory	• Decreased PaO_2/FiO_2 ratio • Need for supplemental oxygen
Renal	• Elevated serum creatinine, • Decreased urine output, dialysis-dependent
Hepatic	• Jaundice • Hyperbilirubinemia, elevated transaminases
Cardiovascular	• Hypotension, arrhythmias • Vasopressor support • Elevated pulmonary capillary wedge pressure
Hematologic	• Thrombocytopenia, leukocytosis • Elevated PT, PTT
Neurologic	• Confusion, obtundation, coma, psychosis

Key:
PT = prothrombin time; PTT = partial thromboplastin time

Adapted from: Balk R. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. *Crit Care Clin* 2000;16:344-345.

Sepsis Timeline

INFECTION

PATHOPHYSIOLOGY	TIME COURSE	CLINICAL SIGNS
• LPS/endotoxin binding to receptors • Activation of monocytes, neutrophils, endothelial cells	0-12 hours	• Fatigue • Somnolence
• Ongoing phagocyte activation • Cytokine production: **TNF, IL-1, IL-6 • Activation of the coagulation system	12-24 hours	• Body temp > 38°C or < 36°C **S** • Heart rate > 90 beats/min **I** • Resp rate > 20 breaths/min or $PaCO_2$ < 32 mmHg **R** • WBC > 12 or < 4 (x 10^9) or > 10% band forms **S**
• Endothelial cell damage • Ongoing inflammation and hypercoagulation • Fibrin deposition and tissue ischemia	24-72 hours	• Cardiovascular shock • Early organ dysfunction
• Lymphocyte depletion • Apoptosis	> 72 hours	• Late organ dysfunction

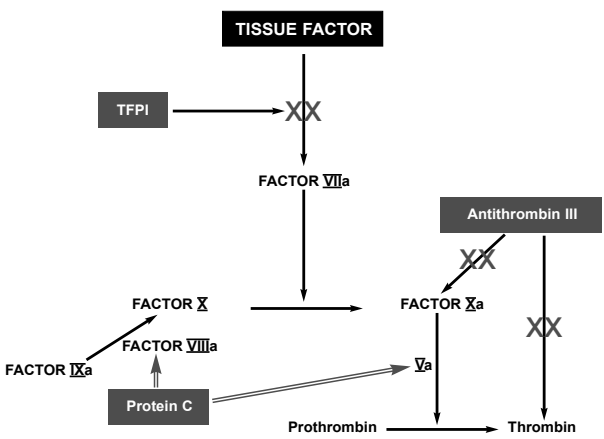
Adapted from: Takala A, et al. Markers of inflammation in sepsis. *Ann Med* 2002;34:615.

Antibiotic Regimens for Septic Shock

SUSPECTED SOURCE	RECOMMENDED ANTIBIOTIC
Pneumonia	Ceftriaxone (Rocephin) *plus* azithromycin (Zithromax)
Hospital-acquired pneumonia	Antipseudomonal beta-lactam (cefepime [Maxipime]) *plus* aminoglycoside *plus* macrolide (if atypical infection suspected)
Urinary tract	Ceftriaxone *or* ciprofloxacin (Cipro) *or* ampicillin *plus* gentamicin (if enterococcus is suspected)
Skin or soft tissue	Nafcillin (add metronidazole *or* clindamycin if anaerobic infection possible)
Meningitis	Third-generation cephalosporin
Intra-abdominal	Third-generation cephalosporin *plus* metronidazole *or* clindamycin
Primary bacteremia	Ticarcillin and clavulanate potassium (Timentin) *or* piperacillin sodium and tazobactam sodium (Zosyn)

Adapted from: Fitch S, Gossage J. Optimal management of septic shock. *Postgrad Med* 2002;111:60. Bosker G. Community-acquired pneumonia (CAP) antibiotic selection and management update. *Emerg Med Rep* 2002;23:109-144. Bosker G, ed. Complicated urinary tract infection: Risk stratification, clinical evaluation, and evidence-based antibiotic therapy—year 2003 update. *Hospital Medicine Consensus Reports* Sept.1, 2003:1-27.

Mechanisms of the Three Anticoagulants

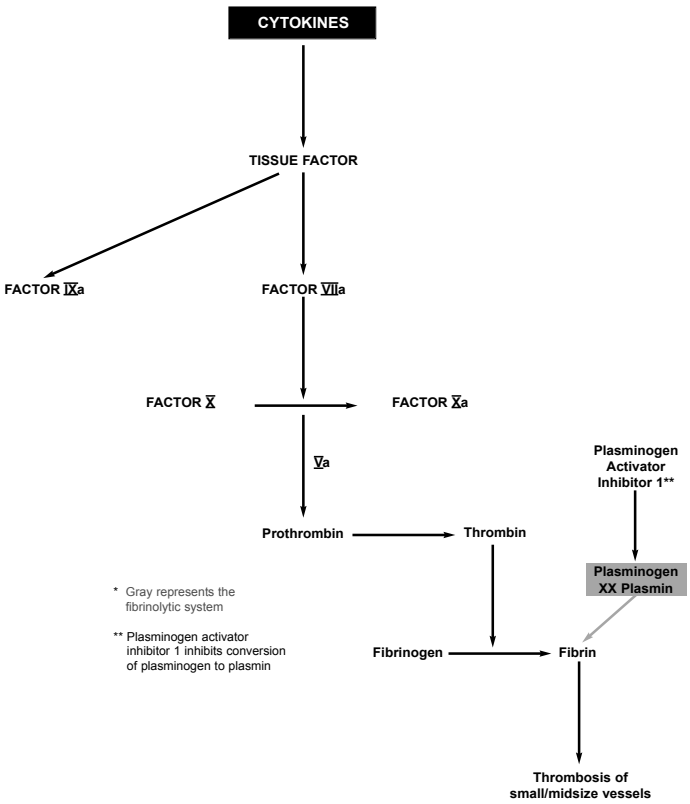


* ■ These represent the anticoagulents

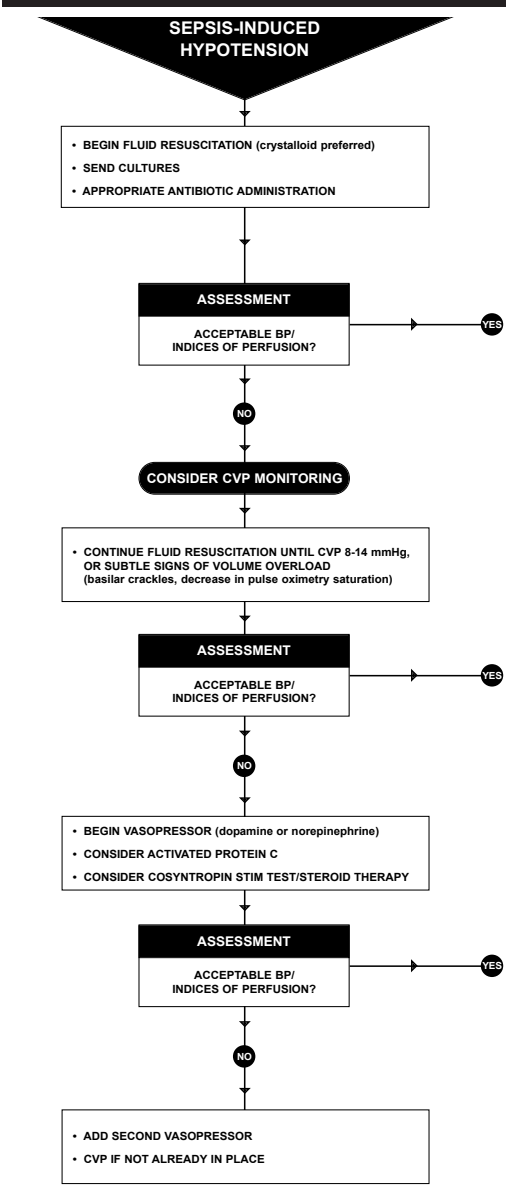
** XX: This is where the anticoagulents work.

*** ↑: This is where Protein C works: It causes degradation of Factors VIIIa & Va.

Cytokine Activation of the Coagulation Cascade



ED Treatment Algorithm for the Septic Patient



Key:
CVP = central venous pressur; BP = blood pressure
Adapted from: Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med* 2003;31:951.

Supplement to *Emergency Medicine Reports*, December 1, 2003: "Evidence-Based Guidelines for Sepsis Management in the Emergency Department: A Systematic Approach to Patient Risk-Stratification, Stabilization, and Multi-Modal Therapy—Focus on Early, Goal-Directed Therapy, Activated Protein C, Antibiotics, and Corticosteroids." *Authors:* **Mary Meyer, MD,** Attending Physician, Kaiser Walnut Creek and Kaiser Richmond, CA; **Robert Rodriguez, MD,** Clinical Associate Professor of Medicine, University of California—San Francisco, Department of Emergency Medicine, Alameda County Medical Center, Oakland, CA.