Severe Sepsis and Septic Shock: Review of the Literature and Emergency Department Management Guidelines

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Severe sepsis and septic shock are as common and lethal as other acute life-threatening conditions that emergency physicians routinely confront such as acute myocardial infarction, stroke, and trauma. Recent studies have led to a better understanding of the pathogenic mechanisms and the development of new or newly applied therapies. These therapies place early and aggressive management of severe sepsis and septic shock as integral to improving outcome. This independent review of the literature examines the recent pathogenic, diagnostic, and therapeutic advances in severe sepsis and septic shock for adults, with particular relevance to emergency practice. Recommendations are provided for therapies that have been shown to improve outcomes, including early goal-directed therapy, early and appropriate antimicrobials, source control, recombinant human activated protein C, corticosteroids, and low tidal volume mechanical ventilation. [Ann Emerg Med. 2006;48:28-54.]

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INTRODUCTION

Severe sepsis and septic shock are conditions with a mortality rate approaching 50%.[1-3] Aside from early initiation of antimicrobials,[4] until recently, there has not been a scientific basis for identification of high-risk patients, or a practice standard for hemodynamic optimization and adjunctive pharmacologic therapies in the emergency department (ED). During the past few years, several randomized, controlled trials in patients with severe sepsis and septic shock have demonstrated significant reductions in mortality rates with the institution of new or newly applied therapies.[5-7] Concurrently, antimicrobial resistance to several agents has emerged and changed considerations about empirical therapy.[8,9] Advances in imaging and noninvasive interventional techniques have also led to new diagnostic and therapeutic strategies for early source control.

Many patients with severe sepsis and septic shock present to the ED where there are often long delays in transfer to an ICU bed.[10,11] Some of the new approaches to management of severe sepsis and septic shock appear to be time dependent, suggesting a "golden hour" and "silver day"[12] perspective to the management of this disorder, giving the ED a more important role in the care of these patients.

This article is an independent clinical review of contemporary management strategies for ED patients with severe sepsis and septic shock. The need for an emergency

Grading of recommendations

A. Supported by at least 2 level-I investigations
B. Supported by 1 level-I investigation
C. Supported by level II investigations only
D. Supported by at least 1 level-III investigation
E. Supported by level IV or V evidence

Grading of evidence

I. Large, randomized trials with clear-cut results; low risk of false-positive (α) error or false-negative (β) error
II. Small, randomized trials with uncertain results; moderate to high risk of false-positive (α) or false-negative (β) error
III. Nonrandomized, contemporaneous controls
IV. Nonrandomized, historical controls and expert opinion
V. Case series, uncontrolled studies, and expert opinion

Figure 1. System used to grade recommendations.[13]

medicine–based review and recommendations was conceived (D.A.T.) and developed by the Emergency Department Sepsis Education Program and Strategies to Improve Survival executive committee (E.P.R., H.B.N., G.J.M., and D.A.T.), which met in July 2003, when the outline for and scope of the manuscript were established. The executive committee identified a working group of experts in emergency medicine, critical care, and infectious diseases (F.M.A., E.A., S.T., D.T.H., T.O. and D.S., with the executive committee members) to write individual sections of the manuscript (specific author contributions are listed in Appendix E1, available online at http://www.annemergmed.com). The primary authors of each section (listed first in Appendix E1) initially drafted the proposed recommendations and associated grading of evidence. After meeting in March 2004, the executive committee developed an initial consensus on the final content, recommendations, and grading of evidence. Individual section authors then completed their review, which was edited by the executive committee for consistency and then distributed to the working group at large. The executive committee coordinated regular distribution of manuscript drafts through the development and revision process by e-mail until final consensus was achieved. The literature was reviewed and referenced through the time of the last revision, January 2006, and a final consensus was reached with all authors.

Because of the breadth of this topic, the authors have attempted to summarize and reference the literature and comment on the strength of the scientific evidence in each area according to previously published criteria (Figure 1).[13] Specific and practical recommendations for ED management of severe

Infection,* documented or suspected, and some of the following:

General variables
- Fever (core temperature >38.3°C [101.0°F])
- Hypothermia (core temperature <36°C [96.8°F])
- Pulse rate >90 beats/min or >2 SD above the normal value for age
- Tachypnea (respiratory rate >20 breaths/min)
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg during 24 h)
- Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables
- Leukocytosis (WBC count >12,000/mm^3)
- Leukopenia (WBC count <4,000/mm^3)
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic variables
- Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or >2 SD below normal for age)
- SvO_2 >70%†
- Cardiac index >3.5 L/min/m^2

Organ dysfunction variables
- Arterial hypoxemia (PaO_2/FIO_2 <300)
- Acute oliguria (urine output <0.5 mL/kg/h for at least 2 h)
- Creatinine increase >0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or aPTT >60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000/μL)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)

Tissue perfusion variables
- Hyperlactatemia (>2 mmol/L)
- Decreased capillary refill or mottling

SBP, Systolic blood pressure; *MAP,* mean arterial blood pressure; *SvO_2,* mixed venous oxygen saturation; *INR,* international normalized ratio; *aPTT,* activated partial thromboplastin time.

*Infection defined as a pathologic process induced by a microorganism.

†SvO_2 can be low (<70%) in early sepsis, signifying inadequate oxygen delivery and global hypoperfusion. $ScvO_2$ has been used as a surrogate of SvO_2.[5,43]

Figure 2. Diagnostic criteria for sepsis, adapted from Levy et al.[16] Copyright ©2001 Springer. With kind permission of Springer Science and Business Media.

sepsis and septic shock based on the best available evidence and authors' expert opinion are provided.

DEFINITIONS

Sepsis is defined as the presence or presumed presence of an infection accompanied by evidence of a systemic response called the systemic inflammatory response syndrome. Systemic inflammatory response syndrome is defined as the presence of 2 or more of the following: (1) temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F); (2) pulse rate greater than 90 beats/min; (3) respiratory rate greater than 20 breaths/min (or $PaCO_2$ less than 32 torr); and (4) WBC count greater than 12,000/mm^3 or less than 4,000/mm^3, or greater than 10% immature band forms.[14] To address the nonspecificity and limited number of parameters of systemic inflammatory response syndrome[15] that do not well model the broader considerations by physicians, the North American and European Intensive Care Societies proposed a revised sepsis definition.[16] The new definition, although more comprehensive than systemic inflammatory response syndrome, is vague in its requirement of *some* of the many clinical and laboratory findings in addition to suspicion of infection (Figure 2). By definition, sepsis describes only the presumed existence of an infection and at least a minimal systemic response and therefore would not necessarily imply the existence of hemodynamic compromise or a bacterial cause, as is often suggested by the still-common usage of this term.

Severe sepsis is defined as the presence of sepsis and 1 or more organ dysfunctions. Organ dysfunction can be defined as acute lung injury; coagulation abnormalities; thrombocytopenia; altered mental status; renal, liver, or cardiac failure; or hypoperfusion with lactic acidosis.[16,17] Septic shock is defined as the presence of sepsis and refractory hypotension, ie, systolic blood pressure less than 90 mm Hg, mean arterial pressure less than 65 mm Hg, or a decrease of 40 mm Hg in systolic blood pressure compared to baseline unresponsive to a crystalloid fluid challenge of 20 to 40 mL/kg.

Bacteremia is the presence of viable bacteria in the blood and is found only in about 50% of cases of severe sepsis and septic shock, whereas 20% to 30% of patients will have no microbial cause identified from any source.[1,14]

Frequently, the presentation and clinical course of infected ED patients is not as distinct as the definitions of severe sepsis and septic shock would suggest. Also, according to the current understanding of pathophysiology of sepsis and the types of patients enrolled in pivotal clinical trials, severe sepsis and septic shock are closely related. Septic shock can be viewed as severe sepsis with cardiovascular failure. Therefore, for the purposes of this review, the term severe sepsis/septic shock will be used.

EPIDEMIOLOGY OF SEPSIS

Until October 2003, only 1 *International Classification of Diseases, Ninth Revision (ICD-9)* code was used for sepsis, severe sepsis, and septic shock (038.x septicemia). Since then, *ICD-9* codes have been revised to include septic shock (785.52), and also proposed for severe sepsis (995.92), to distinguish these high-risk patients from patients with sepsis. The previous available *ICD-9* codes for "severe sepsis" and "septic shock" resulted in limitations to epidemiology studies of these conditions. A recent study defined severe sepsis as "infection" and "new-onset organ dysfunction,"[3] using consensus definitions,[14] and validated the coding scheme with prospective clinical data. The study estimated that there are 751,000 cases of severe sepsis per year in the United States. The incidence increased exponentially with age, suggesting that the number of cases will increase in coming years as baby boomers grow older. National hospital costs were $16.7 billion annually. Overall hospital mortality rate was 28.6%, or 215,000 deaths per year.[3] By comparison, 180,000 persons die of acute myocardial infarction and 200,000 die of lung or breast cancer annually.[18]

Although it is difficult to accurately quantify the incidence of sepsis in the ED, existing data suggest that approximately 458,200 cases (or 61% of severe sepsis/septic shock presentations) are first encountered in the ED annually.[3,19] Pneumonia is the most common cause of sepsis in the United States.[1,3,20]

PATHOGENESIS

A series of pathogenic events are responsible for the transition from sepsis to severe sepsis/septic shock. The initial reaction to infection is a neurohumoral, generalized pro- and antiinflammatory response. This begins with a cellular activation of monocytes, macrophages, and neutrophils that interact with endothelial cells through numerous pathogen recognition receptors.[21] A further host response includes the mobilization of plasma substances as a result of this cellular activation and endothelial disruption. These plasma substances include cytokines such as tumor necrosis factor, interleukins, caspase, proteases, leukotrienes, kinins, reactive oxygen species, nitric oxide, arachidonic acid, platelet activating factor, and eicosanoids. Activation of the complement [22] and coagulation cascades further amplifies this elaborate chain of events.[23-27]

The vascular endothelium is the predominant site of these interactions, and, as a result, there is microvascular injury, thrombosis, and a loss of endothelial integrity (capillary leak), resulting in tissue ischemia.[23] This diffuse endothelial disruption is responsible for the various organ dysfunctions and global tissue hypoxia that accompany severe sepsis/septic shock (Figure 3). Key therapies that have led to mortality benefits in severe sepsis/septic shock are directed at reversing these pathogenic mechanisms.

Physiology of Systemic Oxygen Transport and Utilization

Because microvascular injury leads to decreased oxygen delivery and consumption at the cell and tissue level, the principles of oxygen transport physiology become requisite to an understanding of the pathogenic, diagnostic, and therapeutic implications of global tissue hypoxia. Oxygen is delivered to the

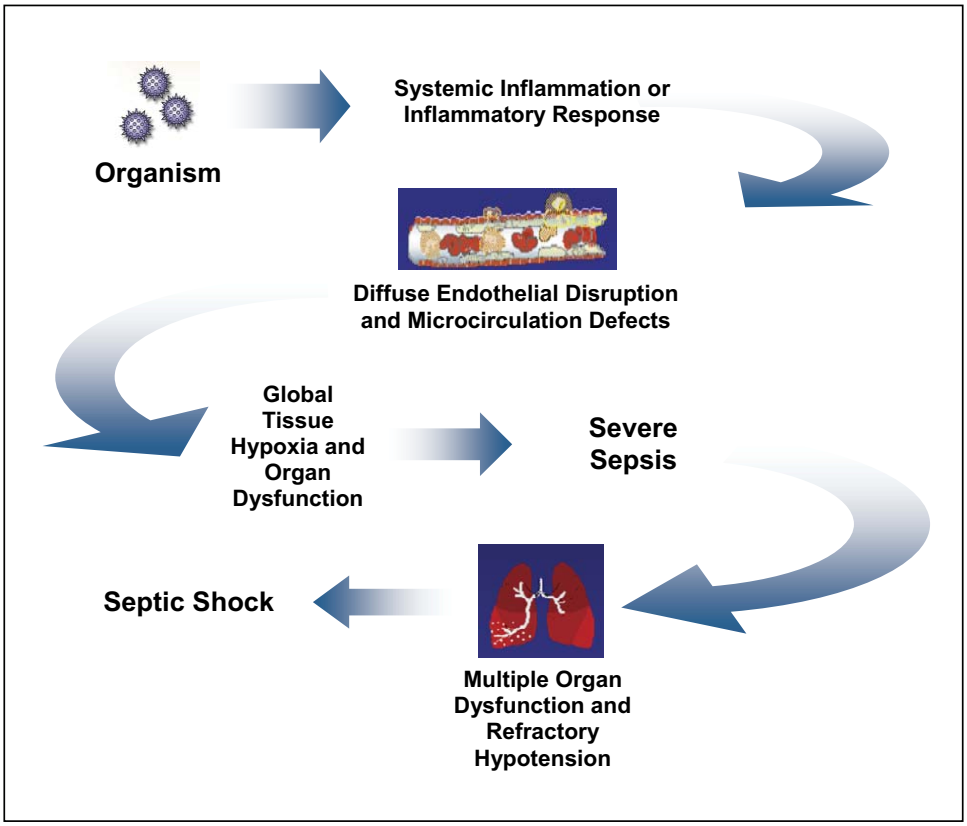


Figure 3. Pathogenic mechanisms from infection to septic shock. The initial response to an infecting organism is a systemic response, with release of inflammatory mediators and activation of the coagulation cascade. Microvascular injury, thrombosis, and diffuse endothelial disruption follow, resulting in imbalance between oxygen delivery and oxygen consumption. Global tissue hypoxia and cytopathic (cellular) hypoxia develop, leading to multiple organ dysfunction and irreversible shock.

tissues as a product of cardiac output and oxygen content (which is a product of hemoglobin oxygen saturation and hemoglobin). After oxygen is extracted at the tissue level, the remainder returns to the venous circulation. The product of systemic oxygen delivery and the percentage of oxygen extracted (normally 25%) by the tissues is the systemic oxygen consumption. The balance between systemic oxygen delivery and consumption is reflected by the mixed venous hemoglobin oxygen saturation (SvO_2). Global tissue hypoxia results when there is an inability of systemic oxygen delivery to meet the oxygen requirements (ie, consumption) of the tissues and results in lactic acidosis.

Cardiovascular Insufficiency and Global Tissue Hypoxia

One of the most important events leading to morbidity and mortality in patients with sepsis is the development of cardiovascular insufficiency and resulting global tissue hypoxia.[1,28,29] Global tissue hypoxia (or oxygen deprivation), which can occur before the development of hypotension,[30] results in further endothelial activation and generalized inflammation.[25,31-34]

Global tissue hypoxia develops from multiple mechanisms of cardiovascular insufficiency. These mechanisms include decreased preload, vasoregulatory dysfunction, myocardial depression, increased metabolic demands, and impaired tissue oxygen use resulting from microcirculatory dysfunction and cytopathic hypoxia.[25,35,36] First, although sepsis is commonly characterized as hyperdynamic, some patients may present in the early stages with a decreased preload because of concomitant left ventricular dysfunction and hypovolemia.[37] After fluid resuscitation to normalize filling pressures, compensatory mechanisms of ventricular dilatation and tachycardia permit a transition to a hyperdynamic state or high cardiac output. Second, even in the presence of a normal or high cardiac output in severe sepsis/septic shock, hypoperfusion abnormalities can still exist. This "distributive shock" refers to a state of either systemic or regional hypoperfusion as a result of derangements in blood flow distribution and loss of vasoregulatory control to the vascular beds. Third, myocardial depression reflecting a hypodynamic state with low cardiac output, thought to occur as a result of effects of inflammatory mediators, can be the predominant hemodynamic feature in up to 15% of patients presenting with severe sepsis/septic shock and may be especially profound in patients with preexisting cardiac disease.[38,39] Fourth, the inflammatory response accompanying sepsis is also associated with increased metabolic demands, reflected by an

increase in splanchnic and total body oxygen consumption.[40-42] The combination of measuring central venous oxygen saturation ($ScvO_2$),[43] which is usually 5% to 7% higher than SvO_2 with very good correlation coefficients,[44-52] and lactate[53,54] during initial patient assessment allows for the early recognition of these contributors to cardiovascular insufficiency and global tissue hypoxia that can occur despite the presence of stable vital signs.[55] Last, in addition to sepsis causing an impairment in oxygen delivery, the bioenergetics of cellular oxygen extraction and use or respiration may also be impaired.[36,56] This cytopathic hypoxia can manifest with a normal or high SvO_2 and lactic acidosis. These derangements further contribute to the cardiovascular insufficiency and may occur independent of hemodynamic parameters, such as arterial blood pressure.

DIAGNOSIS

To diagnose severe sepsis/septic shock as early as possible, it is necessary to recognize historical, clinical, and laboratory findings that are indicative of infection, organ dysfunction, and global tissue hypoxia. Studies of the diagnostic utility of various laboratory tests, either alone or in combination, in addition to clinical findings among a broad-based ED population do not exist. The recommended findings and laboratory studies to detect severe sepsis/septic shock derive mainly from enrollment criteria of the pivotal clinical trials that will be discussed below (Grade E).

Both epidemiologic (eg, contact risk for meningococcemia) and patient risk for infection must first be considered. The presence of immunocompromising conditions and prosthetic devices such as intravenous lines, heart valves, and urinary catheters increases infection risk. Focal findings of infection should be sought on medical history and physical examination. The hallmark finding of infection is fever. General thresholds for abnormally high or low temperatures are based on studies of various populations and can vary among individuals and time of day (ie, temperatures tend to be lower in the early morning). The elderly and patients with myocardial dysfunction and shock tend to have lower temperatures than younger adults.[57,58] Oral temperature above 37.2°C or 99.0°F (or rectal temperatures above 37.5°C or 99.5°F) should be considered a fever in the elderly. Temperature less than 36°C or 96.8°F is associated with the presence of severe infection.[28,59] Also, some patients may present without fever, and develop fever during their evaluation or after resuscitation. Other systemic inflammatory response syndrome criteria (ie, tachycardia and tachypnea) were entry criteria in pivotal trials and when accompanied by a source of infection, ill appearance, or hypotension should trigger an expedited ED evaluation for the presence of severe sepsis/septic shock.

Certain laboratory value abnormalities are among the criteria for sepsis (Figure 2), and therefore, various tests are recommended when a severe infection is suspected. These include a CBC count with the differential, standard chemistry panel including bicarbonate, creatinine, liver enzymes, lactate, and coagulation studies. Leukocytosis, neutrophilia, and bandemia (ie, premature granulocytes) are typically associated with the presence of bacterial infection but have poor sensitivity and specificity and, thus, cannot be used alone to either exclude or confirm the diagnosis of bacterial infection.[60-65] Presence of Döhle's bodies, toxic granulation, and vacuoles heightens the likelihood of bacterial infection.[60] Overwhelming severe sepsis/septic shock can also be associated with leukopenia and neutropenia. Initial measurement of hemoglobin and hematocrit levels will commonly reveal hemoconcentration because of significant hypovolemia, and fluid resuscitation is expected to decrease RBC concentrations. Because a hematocrit level less than 30% is a specific criterion for transfusion in resuscitation protocols to be discussed below, repeated evaluations are recommended.

Thrombocytopenia, which frequently heralds the onset of disseminated intravascular coagulation, is an independent predictor of multiple organ failure and poor outcome.[66-68] In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of 1,690 patients with severe sepsis, a baseline elevated D-dimer and prolonged prothrombin time were observed in 99.7% and 93.4% of patients, respectively.[6,69] Although nonspecific, an elevated D-dimer level has been shown to be associated with the development of severe sepsis/septic shock and death, and declining levels are associated with positive response to therapy.[6,69-71] If severe sepsis/septic shock is suspected, platelet count and prothrombin time should be measured, with activated partial thromboplastin time, D-dimer, fibrin degradation products, and fibrinogen tested if there is evidence of disseminated intravascular coagulation.

A standard chemistry panel that reveals acidosis may represent the presence of lactic acidosis. Of note, hyperlactatemia, along with systemic inflammatory response syndrome criteria and suspected infection, was an enrollment criterion in one pivotal trial to be discussed below.[5] Hyperlactatemia is not always accompanied by a low bicarbonate level or increased anion gap, and, thus, the lactate level must also be measured if severe sepsis is suspected.[72,73] Increased lactate levels among ED patients admitted to the hospital with infection and upward trends in lactate levels are associated with poor prognosis and may be used to guide response to therapy.[74-77] Arterial lactate correlates well with mixed venous (pulmonary artery) and central venous lactate levels.[78,79] However, peripheral venous lactate should be interpreted cautiously because of its inadequate agreement with arterial lactate measurements. The likelihood of arterial hyperlactatemia is reduced considerably by a normal peripheral venous lactate but is only slightly increased if the peripheral venous lactate is increased.[80] Therefore, although a normal peripheral venous lactate level lowers the likelihood of the presence of severe sepsis/septic shock, an arterial or central venous sample should be sent if a peripheral venous lactate level is increased.

More than 80 biological markers of sepsis (eg, C-reactive protein, interleukin 6, procalcitonin, protein C) have been

investigated both for their diagnostic and prognostic capabilities.[81] In general, presence of these markers has been associated with increasing morbidity and mortality. However, lack of availability, long result turnaround times, and nonstandardized assays and cutoff values limit their practical use.

Establishing a definitive microbial cause of severe sepsis/septic shock is difficult during ED evaluation. Nonetheless, identification of the organism(s) and antimicrobial susceptibilities can be important in subsequent management. Obtaining appropriate cultures before antimicrobial treatment (ie, when not associated with an unreasonable delay in therapy) optimizes pathogen identification. Blood cultures will be positive in about 50% of patients with severe sepsis/septic shock.[28] The recommended practice is to culture more than 20 mL of blood divided evenly into aerobic and anaerobic bottles.[82] Blood culture yield increases with greater blood volume obtained.[83] The total volume appears to be more important than timing or use of multiple sites.[84,85] However, there is some incremental yield with multiple specimens, and it may also be useful in distinguishing true pathogens from contaminants.[86,87] Therefore, patients being evaluated for severe sepsis/septic shock should have at least a pair (2 full volume sets) of blood cultures obtained. For suspected indwelling line infection, the catheter should be removed as soon as possible and the tip cultured.

Selection of other culture sites should be based on the clinical scenario. The most common sites of infection causing severe sepsis/septic shock are pulmonary, genitourinary, intraabdominal, skin, and indwelling lines. Urine cultures are easily obtained and are appropriate in most patients unless there is an obvious alternate source. Culture and Gram's stain of sputum has low overall yield but are recommended for patients hospitalized with pneumonia.[88] Any purulent material from skin and soft tissue infections and normally sterile fluids (eg, joint, cerebrospinal, pleural fluid) should be obtained for culture and Gram's stain if there is evidence of localized infection. At the present time, nonculture microbiologic testing (eg, antigen testing, polymerase chain reaction) is not useful in the routine evaluation of these patients.[88,89]

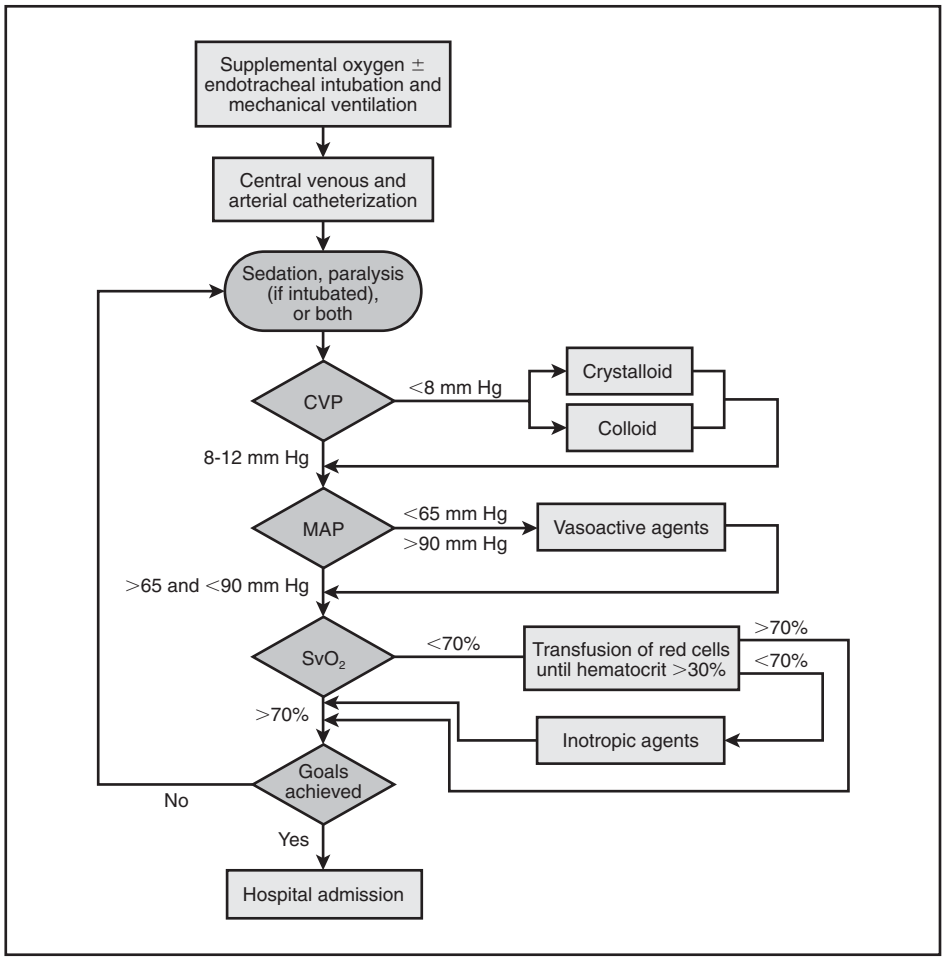
EARLY HEMODYNAMIC OPTIMIZATION

A goal-directed hemodynamic resuscitation of severe sepsis/septic shock includes a systematic approach to restoration of systemic oxygen delivery through a manipulation of preload (volume), afterload (blood pressure), and contractility (stroke volume) to preserve effective tissue perfusion while avoiding excessive increases in myocardial oxygen consumption (ie, tachycardia) and maintaining coronary perfusion pressure.

Hemodynamic optimization strategies have been widely studied with inconclusive results. Several studies did not find any outcome advantage to increasing oxygen delivery among patients with severe sepsis/septic shock enrolled while in the ICU.[90,91] Such trials included patients with unspecified ICU stays and times from disease onset and recognition before study interventions. Thus, these studies are potentially confounded by inclusion of patients who either recovered from their initial insult or had advanced refractory shock. Furthermore, these studies had strategies aimed at supranormal hemodynamic goals [92] that may have resulted in adverse effects from the therapeutic interventions.

Recently, a trial of early hemodynamic resuscitation to normal physiologic parameters, or early goal-directed therapy, was conducted in ED patients with severe sepsis/septic shock and revealed a significant mortality reduction.[5] Early goal-directed therapy is an algorithmic approach to hemodynamic optimization and resolution of global tissue hypoxia within the first 6 hours of disease presentation (Figure 4). The strategy targets normal oxygen delivery by optimizing preload, afterload, oxygen content, and contractility to achieve a balance between tissue oxygen delivery and consumption (guided by central venous pressure, mean arterial pressure, and $ScvO_2$ monitoring).[43,45,47,48,51] Specifically, patients are treated by (1) fluid resuscitation with either crystalloid or colloid to achieve a central venous pressure goal of 8 to 12 mm Hg, (2) vasoactive agents to achieve a mean arterial pressure goal of 65 to 90 mm Hg, (3) blood transfusion to a hematocrit level greater than 30%, (4) inotrope therapy, and (5) intubation, sedation, and paralysis as necessary to achieve a $ScvO_2$ of greater than 70% as measured by continuous central venous oxygen saturation monitoring (Figure 4).[5]

Rivers et al [5] examined efficacy of early goal-directed therapy in 263 patients with infection associated with hypotension after a fluid bolus or serum lactate level greater than or equal to 4 mmol/L who were randomly assigned to receive standard resuscitation or early goal-directed therapy (133 control versus 130 early goal-directed therapy) in the ED before ICU transfer. ICU physicians were blinded to patient study assignment. During the first 6 hours in the ED, the early goal-directed therapy group had significantly greater amount of fluid therapy than the control group (5.0 versus 3.5 L, respectively), RBC transfusion (64.1% versus 18.5%, respectively), and inotrope (ie, dobutamine) administration (13.7% versus 0.8%, respectively). The primary outcome variable, inhospital mortality rate, was 46.5% in the control group versus 30.5% in the early goal-directed therapy group (relative reduction in mortality rate of 34.4%; RR 0.58; 95% confidence interval [CI] 0.38 to 0.87; $P=.009$). During 6 to 72 hours in the ICU after receiving early goal-directed therapy, the treated patients had significantly higher $ScvO_2$ and pH, with a lower lactate level and base deficit than the control group. The early goal-directed therapy group had significantly less fluid therapy (8.6 versus 10.6 L), RBC transfusion (11.1% versus 32.8%), vasopressor therapy (29.1% versus 42.9%), and mechanical ventilation (2.6% versus 16.8%) between 6 and 72 hours in the ICU compared with the control group ($P<.05$). Organ dysfunction scores were significantly better in the early goal-directed therapy group during the first 72 hours. Of the patients who survived to



The Institute for Healthcare Improvement recommends that a resuscitation bundle incorporating early goal-directed therapy be started immediately and completed within 6 hours of recognition of severe sepsis/septic shock.[286]

1. Serum lactate measured.
2. Blood cultures obtained before antibiotic administration.
3. From the time of presentation, broad-spectrum antibiotics administered within 3 hours for ED admission.
4. In the event of hypotension:
    a. Crystalloid (or colloid equivalent) delivered at a minimum of 20 mL/kg.
    b. For hypotension not responding to volume resuscitation, vasopressors used to maintain mean arterial pressure >65 mm Hg.
5. In the event of persistent arterial hypotension refractory to volume resuscitation (septic shock) or initial lactate >4 mmol/L (36 mg/dL):
    a. Central venous pressure >8 mm Hg achieved.
    b. Central venous oxygen saturation 70% achieved.

Figure 4. Early goal-directed therapy protocol.[5]

hospital discharge, early goal-directed therapy was associated with significantly shorter hospital length of stay (3.8 days) (P=.04). Early goal-directed therapy was also associated with a significant 2-fold decrease in the incidence of sudden cardiopulmonary complications, such as cardiac arrest, hypotension, or acute respiratory failure (P=.02).

The study was performed in the ED with the research team present at the patient bedside in the early goal-directed therapy

Table 1. Vasoactive agents.

Drug	Dose/Mixture	Action	Hemodynamic Effects				Adverse Effects and Comments
			Cardiac Stimulation	Vasoconstriction	Vasodilation	Cardiac Output	
Norepinephrine	2-20 μg/min 4 mg/250 mL	Primarily α-1, some β-1	++	++++	0	Slight increase or no change	Dose-related, reflex bradycardia; useful when loss of venous tone predominates, spares the coronary circulation
Dopamine	0.5-20 μg/kg/min 400 mg/250 mL	α, β, and dopaminergic	++ at 5–10 μg/kg/min	++ at 7 μg/kg/min	+ at 0.5–5.0 μg/kg/min	Usually increases	Tachydysrhythmias, increases myocardial oxygen consumption; a cerebral, mesenteric, coronary and renal vasodilator
Phenylephrine	40-200 μg/min 10 mg/250 mL	Pure α	0	++++	0	Decrease	Reflex bradycardia, headache, restlessness, excitability, rarely arrhythmias; ideal for patients in shock with tachycardia or supraventricular arrhythmias
Vasopressin	0.01–0.04 U/min 20 U/100 mL	α and V1	0	++++	+	Decrease	Outcome data on its use are lacking; infusions of >0.04 U/min may lead to adverse, likely vasoconstriction-mediated events; reserved for refractory hypotension.
Epinephrine	1–10 μg/min 1 mg/250 mL	α and β	++++ at 0.03–0.15 μg/kg/min	++++ at 0.15–0.30 μg/kg/min	+++	Increases	Causes tachydysrhythmias, leukocytosis; increases myocardial oxygen consumption and lactate production
Dobutamine	2.5–20 μg/kg/min 250 mg/250 mL	β-1, Some β-2 and α-1 in large dosages	++++	+	++	Increase	Causes tachydysrhythmias, occasional gastrointestinal distress, increases myocardial oxygen consumption, hypotension in volume-depleted patient; has less peripheral vasoconstriction than dopamine.
Nitroglycerin	5-60 μg/min 100 mg/250 mL	Smooth muscle relaxation of coronary and systemic vessels	0	0	+++	Slight decrease	Causes headache, dizziness, tachycardia, orthostatic hypotension, hypersensitivity reaction

0, No effect; +, mild effect; ++, moderate effect; +++, marked effect; ++++, very marked effect.

group. Thus, it is possible that subsequent treating physicians were aware of the initial interventions; however, these physicians treating control and treatment patients during the remainder of the hospital stay were blinded to the study randomization. This period represented only 6 to 8 hours of a 13-day average hospital stay. Concerns about the appropriateness and an inability to discern the individual effects of specific interventions or strategies that were bundled in early goal-directed therapy have been raised, such as the use of blood products, monitoring of central venous oxygen saturation, and inotrope use.[93] The components of early goal-directed therapy are all recommended approaches and treatments by the Society of Critical Care Medicine, as described in their guidelines for the management of severe sepsis/septic shock.[94,95] Because this was a research study conducted at 1 institution, it is unclear whether outcomes can be generalized to every ED practice, with varying expertise and resources for implementation.[96]

In patients with severe sepsis/septic shock, early goal-directed therapy should be used as the first means of resuscitation, with simultaneous prioritization of appropriate empirical antimicrobials and source control (Grade B). The specific procedures to institute early goal-directed therapy are discussed below.

Hemodynamic Monitoring

Optimal titration of fluids and vasoactive therapy is performed more objectively with invasive monitoring. Central venous access allows measurement of central pressure and $ScvO_2$. $ScvO_2$ can be measured continuously by use of a fiberoptic, central venous catheter (Edwards Lifesciences, Irvine, CA), as was used in the Rivers et al study.[5] $ScvO_2$ can also be measured by intermittent central venous blood gas sampling, and depending on the frequency of sampling, stability of the patient, and rapidity with which therapies can be modified, it may be a reasonable alternative to continuous monitoring. With use of vasopressor agents, intraarterial pressure monitoring is preferred, with the femoral site being recommended over the radial artery because of a more accurate reflection of central aortic pressure.[97]

Volume Therapy

The first parameter to target in hemodynamic optimization is intravascular volume with the use of fluid therapy targeting a central venous pressure of 8 to 12 mm Hg. No outcome benefit has been demonstrated in using colloids compared to crystalloids with respect to mortality or hospital length of stay.[98-100] However, in one investigation a trend to improved survival with the use of colloid (albumin) in sepsis was observed.[100] The volume of crystalloids required may be 2 to 3 times that required of colloids to restore the optimal volume. One liter of normal saline solution adds 275 mL to the plasma volume, whereas 1 L of 5% albumin will increase plasma volume by 500 mL.[101] In patients with low central venous pressure and concurrent pulmonary edema, a colloid may be combined with a crystalloid to avoid a large volume of crystalloid and to rapidly achieve the central venous pressure goal.[102]

Vasoactive Agents

Vasopressors should be administered when hypotension is persistent or mean arterial blood pressure less than 65 mm Hg after a crystalloid volume challenge of 20 to 40 mL/kg regardless of the central venous pressure. In the presence of hypotension, organ perfusion cannot be maintained with fluids alone. Existing evidence does not clearly support the superiority of one vasopressor over another.[103] Vasopressor agents, their dosages, actions, and adverse effects are summarized in Table 1. Norepinephrine, at a dosage of 2 to 20 μg/minute, or dopamine, at a dosage of 5 to 20 μg/kg/minute, have been advocated as first-line agents in septic shock patients.[95] Norepinephrine may be more effective in correcting hypotension in septic shock while avoiding the potential tachycardia induced by dopamine.[104] A potential survival benefit has been suggested with the use of norepinephrine compared with dopamine.[105] Dopamine is both an α- and β-adrenergic agonist up to 10 μg/kg/minute and is an alternative in a patient who is in need of a combination vasopressor and inotrope. Phenylephrine, a pure α-adrenergic agonist, at a dosage of 40 to 200 μg/minute is an alternative vasopressor for patients with significant tachycardia because of its ability to induce reflex bradycardia.[106,107] Its use, however, may reduce splanchnic blood flow and decrease cardiac output.[108]

In the patient with refractory hypotension, vasopressin deficiency should be considered.[109,110] Vasopressin, which is deficient in many septic shock patients, is an endogenously produced hormone. When administered in a relatively small, physiologic dosage, 0.01 to 0.04 U/minute, vasopressin corrects the deficiency through a hypersensitive physiologic response.[111] Additionally, a synergistic effect is seen with other vasopressors that increases mean arterial pressure and frequently allows for catecholamine withdrawal.[111,112] However, vasopressin is not considered a first-line agent, and its administration may be associated with a decrease in cardiac output, so it is commonly used in combination with other vasoactive drugs. Dosages greater than 0.04 U/minute are not of greater benefit and may be harmful. Epinephrine at a dosage of 1 to 10 μg/minute is often considered as last-resort therapy. In patients unresponsive to other vasopressors, epinephrine increases mean arterial pressure by increasing cardiac output and stroke volume. Its use can be deleterious, however, because it may impair splanchnic circulation and increase lactate production.[113]

Patients may have normal or increased blood pressure in the presence of tissue hypoperfusion or severe sepsis without traditional hypotensive shock.[114] Afterload reduction can be considered if mean arterial pressure is elevated. Although it is primarily a venodilator, nitroglycerin at a dosage of 5 to 60 μg/minute can be used to lower the mean arterial pressure, especially in the presence of elevated central venous pressure.

Preliminary data suggest that nitroglycerin improves microcirculatory blood flow in patients with septic shock.[115]

Increasing Oxygen Carrying Capacity

A low $ScvO_2$, coupled with an elevated lactate level, suggests a mismatch between systemic oxygen delivery and oxygen consumption of the tissues. When a low $ScvO_2$ is identified, therapies to augment 1 or more of the 3 components of oxygen delivery are recommended to restore the balance between systemic oxygen delivery and consumption: (1) oxygen carrying capacity; (2) cardiac output; or (3) arterial oxygen saturation. This is the rationale for using packed RBC transfusion, inotropic agents, and supplemental oxygen or mechanical ventilation to increase $ScvO_2$.

After mean arterial pressure has been optimized, patients with inadequate oxygen delivery reflected by $ScvO_2$ less than 70%, elevated lactate, and hematocrit less than 30% should receive a transfusion of packed RBCs to achieve a hematocrit level greater than 30%. Some studies have suggested that a restrictive strategy of transfusion, in which packed RBCs are transfused when hematocrit level is less than 21%, may be appropriate.[116,117] However, these are studies of outcomes among heterogeneous populations of stable hospitalized patients as opposed to randomized trials of ED patients with severe sepsis/septic shock, making generalization to these patients problematic.

Inotropic Therapy

After adequate volume, mean arterial pressure, and hematocrit goals are met and $ScvO_2$ is persistently less than 70%, dobutamine to improve contractility, in a dosage of 2.5 to 20 μg/kg/minute, titrated to achieve $ScvO_2$ greater than 70%, is recommended. Patients with poor cardiac contractility may have increased central venous pressure and appear to be volume overloaded, requiring diuresis. However, unresuscitated severe sepsis/septic shock patients will often have underlying hypovolemia. Inotropic support with dobutamine in these patients may treat the myocardial depression and unmask hypovolemia.[118,119] Volume resuscitation, instead of diuresis, in these situations will prevent subsequent cardiovascular collapse and vasopressor use. Because the vasodilatory effect of dobutamine could worsen hypotension, it should be used in combination with vasopressors for patients with persistent hypotension. In addition, dobutamine may also exacerbate tachycardia.

Decreasing Oxygen Consumption

When the goals of central venous pressure, mean arterial pressure, and hematocrit are met but $ScvO_2$ remains less than 70% after a trial of dobutamine, or dobutamine causes an exaggerated response such as significant tachycardia and hypotension, one should consider reducing systemic oxygen demand and consumption. One of the greatest contributors to increased systemic oxygen demand is increased respiratory muscle use in breathing. In this situation, intubation and mechanical ventilation, sedation, and paralysis decrease the work of breathing and redistribute blood flow from the respiratory muscles to splanchnic and other vital vascular beds.[120,121]

Resuscitation Endpoints

Trends of vital signs are not sufficient endpoints to determine an adequate response to therapy. Rady et al[114] showed that 31 of 36 patients presenting with shock and resuscitated to normal vital signs continued to have global tissue hypoxia, as evidenced by decreased $ScvO_2$ and increased lactate levels. A post hoc analysis of the early goal-directed therapy study[5] in patients with mean arterial pressure greater than 100 mm Hg showed that control patients with persistently abnormal $ScvO_2$ and lactate levels at 6 hours had a significantly higher mortality rate compared with the early goal-directed therapy patients whose values had reached therapeutic goals (60.9% versus 20.0%, $P<.05$).[122] Other studies have also showed that a persistently high lactate is associated with increased mortality.[74,77,123,124] Therefore, continuous $ScvO_2$ and serial lactate measurements during resuscitation may help identify patients requiring continued intensive therapy.

ANTIMICROBIAL THERAPY

Timeliness and In Vitro Antimicrobial Activity

In light of the dramatic reduction in mortality observed with the advent of modern antimicrobial therapy, it would be unethical to randomize patients with severe sepsis/septic shock either to receive antimicrobials immediately or after some period of delay or to receive antimicrobials expected to have or not have in vitro activity against anticipated pathogens.

Several retrospective cohort studies of bacteremic patients with community-acquired infections have examined the institution of "appropriate" empirical antimicrobials with respect to mortality, ie, those given with in vitro activity against the blood culture isolate within 48 hours of specimen collection versus inappropriate antimicrobials.[125-141] These studies had variable proportions of patients with community-acquired infections and shock. Most studies found a lower mortality rate associated with the institution of appropriate antimicrobials, a result also found in 2 studies that evaluated patients with septic shock,[127,135] 1 study that evaluated patients with community-acquired bacteremia,[135] and an analysis of patients with severe sepsis caused by community-acquired pneumonia who were enrolled in the PROWESS trial.[6,142] These results support the importance of accurately predicting the bacterial cause of sepsis and the associated antimicrobial susceptibility when choosing empirical antimicrobials (Grade D).

Although these studies examined antimicrobial administration within 48 hours of blood culture collection, there are only limited data on the effect of more rapid administration of antibiotics for various types of serious infections within the typical time of ED care, ie, several hours. Among patients with meningococcemia, studies by Cartwright

et al[143] found a lower mortality rate associated with administration of antibiotics by general practitioners before transfer to the hospital compared with administration at the hospital, but these differences were not statistically significant. Among a risk-adjusted group of 14,069 Medicare patients (older than 65 years) admitted with community-acquired pneumonia, Meehan et al[144] found a significantly lower mortality rate associated with antimicrobial administration within 8 hours of arrival at the ED compared with later administration. Silber et al[145] found no difference in time to clinical stability between adults hospitalized with moderate to severe community-acquired pneumonia who were given antibiotics within 4 hours compared with later administration. More recently, Houck et al[4] found that antibiotic treatment within 4 hours was associated with lower mortality rate among 13,771 risk-adjusted hospitalized Medicare patients with community-acquired pneumonia, and this timing goal has been recommended by the Infectious Diseases Association of America and the Centers for Medicare Quality Improvement Project.[88,146]

Although there are insufficient data to conclude that delays on the order of hours are deleterious, administration of antibiotics within the time of ED care and as soon as possible once there is a reasonable suspicion of severe sepsis/septic shock will likely increase the chance of favorable outcome compared with later administration (Grade E).

Infection Site and Bacterial Cause

Most studies describing the bacteriology and site of infection in severe sepsis/septic shock include a combination of community- and hospital-acquired infections (defined as infections detected within or after 48 hours of hospitalization, respectively). The situation is further complicated by the fact that some infections may not be clearly classified as community or hospital acquired (eg, recent outpatient surgery).[147,148]

Among studies of both community- and hospital-acquired infections, the sites of infection for patients with severe sepsis/septic shock are as follows: lung (35%), abdomen (21%), urinary tract (13%), skin and soft tissue (7%), other site (8%), and unknown primary site (16%) (compiled from 16 studies between 1963 and 1998 that included 8,667 patients).[20,28,149-163] Among patients older than 65 years, a urinary tract source is the most common infection site.[134,164] Since the late 1980s, Gram-positive bacteria have replaced Gram-negative bacteria as the predominant pathogens in severe sepsis/septic shock.[165] Although several studies describe community-acquired bacteremia, in most studies only a fraction had severe sepsis/septic shock. In one multicenter study of 339 patients admitted to the ICU with community-acquired bacteremia, with sepsis in 86 cases (25%), severe sepsis in 69 cases (20%), and septic shock in 184 cases (55%), the sites of infection were lung (21%), abdomen (20%), urinary tract (20%), endocarditis (4%), other (10%), and bloodstream infection without known primary source (25%). The most common pathogens were *Escherichia coli* (25%), *Streptococcus pneumoniae* (16%), and *Staphylococcus aureus* (14%).[166] In another study of 169 bacteremic patients admitted from nursing homes (only 20% had hypotension), the most common pathogens were *E coli* (27%), *S aureus* (18%), and *Proteus* spp (13%).[164] Generally, anaerobes are not a cause of severe sepsis/septic shock, except rarely in the case of intraabdominal, pelvic, and necrotizing skin and muscle foci, in which they are often part of mixed aerobic/anaerobic infections.

Antimicrobial Susceptibility

Because of the association of survival with an initial antimicrobial regimen that possesses in vitro activity against the offending bacterial pathogen, it is important to have an understanding of current antimicrobial resistance patterns and trends that may help anticipate future resistance. To the best of our knowledge, no series exist for bacterial pathogens and their associated antimicrobial susceptibility patterns among ED patients with severe sepsis/septic shock. However, general antimicrobial susceptibility surveys of the 3 major pathogens, *E coli*, *S aureus*, and *S pneumoniae*, have been conducted, and some report on community-acquired strains. These studies are often limited by lack of specific knowledge about outpatient setting/exposure, previous antimicrobial use, and site of infection. Populations are limited to patients with cultures, and their results describe susceptibility patterns of several years before publication. It is important to understand antimicrobial resistance rates locally, and national and international resistance trends may also be helpful. Antimicrobial use by patients within the previous several months is a recognized risk factor for being colonized or infected with a strain resistant to a previously administered antimicrobial or other antimicrobials.

More than 90% of community-acquired *E coli* isolates (and other Enterobacteriaceae) in the United States are susceptible to aminoglycosides, fluoroquinolones, and advanced-generation cephalosporins.[167-170] Garau et al[171] reported, however, that 9% to 17% of community-acquired *E coli* isolates in Barcelona collected between 1992 and 1996 were resistant to ciprofloxacin (typically, there is cross-resistance with other fluoroquinolones). Of these strains, the resistance rates to aminoglycosides and cephalosporins were about 10%.[171]

The prevalence of community-acquired strains of *S pneumoniae* with penicillin, macrolide, or trimethoprim-sulfamethoxazole resistance has significantly increased in the last decade.[172-177] Rates of high-level penicillin resistance (ie, >2 μg/mL) range from 8% to 26%.[172-177] Resistance rates to third-generation cephalosporins such as ceftriaxone and cefotaxime are still low, ranging from 3% to 5%, especially because recently the cutoff above which a minimal inhibitory concentration would be defined as "resistant" was revised upward (ie, from >2 μg/mL to >4 μg/mL).[172-178] Resistance rates to respiratory fluoroquinolones such as levofloxacin are low (generally less than 1%) but are increasing in North America.[172-178] A Canadian study reported that, among adults, the prevalence of pneumococci with reduced susceptibility to fluoroquinolones increased from 1.5% in 1993 and 1994 to 2.9% in 1997 and 1998.[177] In Hong Kong, 13% of *S pneumoniae* isolates were

Table 2. Empirical antimicrobial recommendations for adult ED patients with severe sepsis and septic shock.

Sepsis Source	Recommended Antimicrobial Regimen (Standard Adult Dosing)	Comments
Unknown source	Vancomycin* 1 g Q 12 h and levofloxacin† 750 mg Q 24 h and gentamicin‡ 7 mg/kg Q 24 h	Consider abdominal/pelvic imaging if physical examination, chest radiograph, and urinalysis do not reveal an infection source.
Community-acquired pneumonia	Vancomycin* 1 g Q 12 h and levofloxacin†§ 750 mg Q 24 h (and gentamicin‡ 7 mg/kg Q 24 h if recent hospitalization/nursing home residence, recent antibiotic use, or bronchiectasis)	Consider *Pneumocystis carinii* pneumonia treatment in AIDS patients and obtain an echocardiogram to evaluate endocarditis with septic emboli in intravenous drug users.
Meningitis	Vancomycin* 1 g Q 12 h and ceftriaxone 2 g Q 12 h (and ampicillin 2 g Q 4 h if immunocompromised or elderly) *after* dexamethasone 10 mg intravenously Q 6 h (no data exist on the use of high- or low-dose steroids for patients with bacterial meningitis and severe sepsis/septic shock)	If altered mental status or focal neurologic abnormalities, consider adding acyclovir (10 mg/kg Q 8 h) to treat herpes encephalitis.
Urinary tract infection	Piperacillin/tazobactam‖ 3.375 g Q 6 h and gentamicin‡ 7 mg/kg Q 24 h	Complicated urinary tract infections may be caused by *Enterococcus* species, *Pseudomonas aeruginosa*, or *Staphylococcus aureus* (nonnitrite producers), for which gentamicin and piperacillin/tazobactam are preferred. If nitrite production or Gram's stain suggests Enterobacteriaceae, levofloxacin or ceftriaxone can be substituted for gentamicin. Obtain imaging to rule out obstruction as soon as possible.
Intraabdominal/pelvic infection	Piperacillin/tazobactam‖ 3.375 g Q 6 h and gentamicin‡ 7 mg/kg Q 24 h	Obtain imaging to identify infection focus and potential for percutaneous or open drainage, and/or surgical consultation.
Skin and soft tissue infection/necrotizing infection	Vancomycin* 1 g Q 12 h and piperacillin/tazobactam‖3.375 g Q 6 h and clindamycin 900 mg Q 8 h	For suspected necrotizing infections, obtain surgical consultation for tissue debridement as soon as possible.

Dosages are for ~70-kg non-pregnant adults with normal renal function.
*May substitute linezolid.
†May substitute gatifloxacin.
‡May substitute ceftazidime, cefepime, aztreonam, imipenem, or meropenem.
§May substitute moxifloxacin.
‖May substitute ampicillin/sulbactam, imipenem, or meropenem.

shown to have decreased susceptibility to fluoroquinolones.[179] There are no reports of vancomycin-resistant *S pneumoniae*.

Community-associated methicillin-resistant *S aureus* (CA-MRSA) infection appears to be rapidly increasing in many areas in the United States.[180-184] Several studies have demonstrated that the proportion of CA-MRSA infections has increased compared with hospital-associated methicillin-resistant *S aureus*.[182] Recent reports suggest that in some areas, CA-MRSA is the most common pathogen isolated in community-acquired skin and soft tissue infections among patients presenting to the ED.[185,186] Most of these patients have no identified risk factors for methicillin-resistant *S aureus*. CA-MRSA has also been associated with severe sepsis and pneumonia, primarily in pediatric patients.[180] Antimicrobials with consistent activity against CA-MRSA isolates include vancomycin, trimethoprim-sulfamethoxazole, rifampin, daptomycin, and linezolid.[183] Most are resistant to macrolides and quinolones, and many are resistant to tetracycline, including doxycycline. Inducible clindamycin resistance exists among some CA-MRSA strains and has been associated with clinical failures.[187]

Clinical Antimicrobial Studies and Combination Therapy

Combination antimicrobial therapy is commonly used in severe sepsis/septic shock for several reasons: one agent may not be adequate to cover the spectrum of all possible pathogens, polymicrobial infections may not be treatable with a single drug, combinations may prevent selection of antimicrobial resistance,[184] and combinations may have synergy against a single pathogen. Although data exist about in vitro synergy between various combinations of antimicrobial agents, less research is available about the clinical significance of combination therapy and antimicrobial synergy.[188]

Few situations exist in which combination therapy has been shown to be clinically superior to monotherapy. Combination therapy with a β-lactam and aminoglycoside has been associated with more rapid clearance of bacteremia with staphylococcal endocarditis and more reliable cure with enterococcal endocarditis than therapy with a β-lactam alone.[189] For severe group A β-hemolytic streptococcal infections (eg, necrotizing fasciitis), high-dose clindamycin is considered more effective than cell-wall-active antibiotics such as β-lactams, likely because of the ability to suppress production of bacterial toxins and kill

bacteria that are in stationary growth phase and thus, may be additionally effective when combined with a β-lactam agent.[190,191]

Serious infections that may be due to *Pseudomonas aeruginosa* are commonly treated with combination antimicrobials. None of the drugs with recognized activity against *P aeruginosa* have universal activity. Most of the studies demonstrating clinical antimicrobial synergy with a combination β-lactam plus aminoglycoside had few patients and were analyzed together with infections caused by other microorganisms.[192] A prospective study of 200 patients with *P aeruginosa* bacteremia found a lower mortality rate among patients treated with combination therapy compared with patients treated with monotherapy (27% versus 47%, $P<.02$).[193] Combination therapy has theoretical advantages for some other difficult-to-treat Gram-negative organisms such as *Klebsiella*, *Enterobacter*, *Acinetobacter*, and *Serratia*, although studies demonstrating the association of combination therapy with improved outcomes are not definitive.[194-197] These organisms are also uncommon in community-acquired infections. In a large prospective study of Gram-negative bacteremia, combination therapy showed no advantage over treatment with a single β-lactam agent, except in neutropenic patients.[198] Because neutropenic patients can have rapidly developing fatal infections, those patients with signs of severe sepsis/septic shock should receive combination antimicrobial therapy with activity against a broad spectrum of organisms, including *P aeruginosa.*[199]

Combination antimicrobial therapy is recommended for severe sepsis/septic shock to decrease the likelihood that the infecting organism is not treated with a drug with in vitro activity (Grade E).

Empirical Antimicrobial Recommendations

Antimicrobial recommendations for patients with severe sepsis/septic shock based on pathogen prevalence, susceptibility patterns, and results of clinical trials are summarized in Table 2. The recommendations are also based on the principle that because this subgroup of patients has a predicted mortality of 20% to 50% and in vitro activity of the treatment regimen against the causative bacteria is associated with lower mortality, the empirical regimens should be sufficiently broad, so there is little chance (ie, less than 5%) that the offending pathogen will not be effectively covered (Grade E). Compared with the potential benefit of this approach, promotion of antimicrobial resistance is a minor risk, and the antimicrobial regimens can be tailored once pathogen identification and susceptibilities are available in a few days. Specific empiric drug regimens are listed as examples to facilitate implementation and in part were chosen according to availability in EDs. The inclusion of specific drugs is not meant to imply that these are the exclusive drugs of choice. Some reasonable alternative therapies are footnoted (Table 2).

For infections likely to be caused by *S aureus* (ie, sepsis source unclear, skin and soft tissue infections, and community-acquired pneumonia), vancomycin is recommended because of the significant prevalence of CA-MRSA. In subset analyses of randomized clinical trials, linezolid has been found to have greater efficacy than vancomycin in the treatment of patients with nosocomial and ventilator-associated methicillin-resistant *S aureus* pneumonias.[200]

For infections likely to be caused by *S pneumoniae* (ie, sepsis source unclear and community-acquired pneumonia), any of the respiratory fluoroquinolones is recommended because of excellent in vitro activity and favorable reported bacteriologic and clinical experience in patients with bacteremic pneumococcal pneumonia, which has been specifically reported with levofloxacin.[201] Further, for community-acquired pneumonia, fluoroquinolones have activity against other pathogens such as *Legionella* and *Mycoplasma*. The addition of vancomycin is recommended because of the recognition of fluoroquinolone-resistant *S pneumoniae* strains and CA-MRSA. Use of a fluoroquinolone is consistent with pneumonia treatment guidelines[88] and may be preferable, along with vancomycin, to the alternative β-lactam and macrolide because of better in vitro activity and higher serum levels (than macrolides). For bacterial meningitis, ceftriaxone or cefotaxime provides good cerebrospinal fluid penetration and has activity against *Neisseria meningitidis* and most *S pneumoniae* strains; the addition of vancomycin is recommended for coverage of *S pneumoniae* infections caused by cephalosporin-nonsusceptible strains.[202]

For infections likely to be caused by aerobic Gram-negative bacilli such as *E coli* (ie, urinary tract and intraabdominal infections), because of inconsistent in vitro activity of any one class of antimicrobials, combination therapy with any of a third-generation cephalosporin, aminoglycoside, β-lactam/β-lactamase inhibitor antibiotic, or fluoroquinolone is recommended. Patients with complicated urinary tract infections are infected with a wider range of pathogens than those with uncomplicated infections (typically caused by *E coli*), including *P aeruginosa* and *Enterococcus* spp, and, therefore, the combination of a β-lactam/β-lactamase inhibitor antibiotic with antipseudomonal activity (eg, piperacillin/tazobactam) and an aminoglycoside is recommended. Intraabdominal infections may be caused by Gram-negative bacteria, anaerobes, or *Enterococcus* spp, and, therefore, a β-lactam/β-lactamase inhibitor antibiotic or carbepenem with an aminoglycoside is recommended.

For skin and soft tissue infections, including necrotizing fasciitis, in which *Streptococcus pyogenes* or *Clostridia* spp may be involved, the addition of clindamycin to a broad-spectrum regimen such as piperacillin/tazobactam and vancomycin is recommended because of experimental and clinical observations associating its use with improved outcomes and its activity against CA-MRSA and anaerobes.[190,191] Because clindamycin or macrolide resistant CA-MRSA have been recognized, the addition of vancomycin or linezolid is recommended to be included for empirical treatment.[203]

Aminoglycosides have excellent in vitro activity against aerobic Gram-negative bacilli and have traditionally been included in empirical septic shock regimens. Aminoglycosides, however, are associated with increased rates of toxicities compared with alternative therapies, in particular, nephrotoxicity. Although the complication of renal dysfunction is generally associated with prolonged treatment, septic shock patients often have renal impairment and may require imaging studies with potentially nephrotoxic radiographic dye. Therefore, although aminoglycosides are recommended because of the long experience with their use for this condition, based on these concerns and the lack of comparative studies demonstrating a clear outcome advantage, alternative Gram-negative therapies (eg, fluoroquinolones, advanced-generation cephalosporins, carbepenems) should also be considered.

SOURCE CONTROL

Early detection of the site of infection determines the presumptive microbiologic cause and facilitates eradication by source control measures. Such measures include abscess drainage, debridement, and removal of devitalized infected tissue or infected prostheses. The following section identifies common eradicable foci of infection. In patients with severe sepsis/septic shock, source control is an integral component of therapy, and due to difficulty in performing randomized clinical trials in this subject, the rationale for recommended therapies is mostly based on case series or expert opinion (Grade E).[204,205]

Drainage of complicated parapneumonic effusions (eg, empyema) reduces the risk of sepsis-related mortality.[206] Tube thoracostomy is indicated for parapneumonic effusions when 1 or more of the following findings are present: pus, positive Gram's stain or culture, pH less than 7.20 and greater than or equal to 0.15 U lower than the arterial pH, and glucose less than 40 mg/dL.[207-209] Drainage is also recommended for parapneumonic effusions that are large, free flowing (at least half of the hemithorax), or loculated or demonstrate thickened parietal pleura on contrast-enhanced computed tomography (CT) scan.[208]

Advances in diagnostic or interventional radiology and surgical procedures have revolutionized the management of many intraabdominal infections. Specifically, the diagnostic impact of abdominal CT scan has been significant in patients with multiple potential causes of their acute abdominal pain or sepsis of unknown origin.[210-212] Ultrasonography has an overall lower diagnostic accuracy than CT scan for the evaluation of appendicitis or intraabdominal abscesses.[213-215] In the ED, abdominal ultrasonography is typically used to evaluate gallbladder and biliary tree pathology. Depending on the pathology, surgical interventions such as resection, closure, drainage, and debridement may be needed. Sonographically guided or CT-guided surgical procedures (eg, percutaneous drainage of an abscess) provide an alternative means of source control, eliminating the need for more invasive and involved surgical interventions.[213,216,217]

Severe sepsis/septic shock caused by a urinary source may be associated with renal/perirenal abscess, an obstructive process (eg, kidney stone with pyonephrosis), or emphysematous pyelonephritis. Clinical diagnosis of such complications is difficult, and therefore, urgent radiographic evaluation should be strongly considered. Helical CT scan is considered the imaging modality of choice for most renal pathologies.[218] Ultrasonography, which can be performed in the ED, is also a valuable screening tool and demonstrates hydronephrosis and distal hydroureter with high sensitivity.[219] Interventions to decompress an obstructed urinary tract can include retrograde ureteral stenting or percutaneous nephrostomy.[220-222] Guided aspiration/drainage of abscesses and placement of percutaneous nephrostomy tubes can be performed with a high degree of accuracy under ultrasonographic or CT guidance.[223-225] Drainage or nephrectomy should also be undertaken early for emphysematous pyelonephritis.[226,227] Severe sepsis/septic shock caused by urinary tract infection associated with ureteral stent and indwelling urethral catheters necessitates removal of the device.[228,229] Patients with septic abortion should undergo prompt dilatation and curettage. Infected intrauterine devices need to be removed. Tubo-ovarian abscesses in patients with severe sepsis/septic shock mandate immediate surgical intervention.

A significant decrease in mortality has been observed when surgical interventions (eg, debridement, fasciotomy, amputation) are undertaken early for necrotizing skin and soft tissue infections.[230-232] Plain radiographs are the appropriate initial study for the evaluation of subcutaneous air; however, deeper fascial gas may not be evident on plain radiographs.[233,234] Although both contrast-enhanced CT and magnetic resonance imaging have been purported to be more sensitive than plain radiographs, their use can delay surgical exploration.[233-235] Decubitus ulcers can also be the cause of severe sepsis/septic shock. Patients with these infections benefit from early surgical debridement.[236,237]

Intravascular catheters should be removed and cultured if there are signs of infection at the insertion site (eg, drainage of pus, erythema) or there is evidence of severe sepsis/septic shock with no other source of infection.[238,239] Prompt removal of the catheter is also warranted when intravascular catheterization is complicated by septic thrombophlebitis.[239]

RECOMBINANT HUMAN ACTIVATED PROTEIN C

Cleavage of protein C by thrombin associated with thrombomodulin generates activated protein C, which has potent anticoagulant, profibrinolytic, antiinflammatory, and antiapoptotic effects.[6,240] Preclinical and clinical studies demonstrate that administration of recombinant human activated protein C (drotrecogin alfa [activated]) reduces mortality from severe sepsis/septic shock.[6,241-243] PROWESS, a multicenter, international, placebo-controlled study investigating the ability of drotrecogin alfa (activated) to reduce 28-day mortality, was terminated after a second interim analysis

by an independent data and safety monitoring board when predetermined statistical thresholds for efficacy were crossed.[6] Entry into the PROWESS study required clinical evidence of infection, presence of a systemic inflammatory response syndrome, and at least 1 sepsis-induced organ dysfunction present for fewer than 48 hours. Evidence of organ dysfunction included fluid-unresponsive hypotension (systolic blood pressure <90 mm Hg or mean arterial blood pressure <70 mm Hg >1 hour), decreased urine output, hypoxemia, lactic acidosis, or thrombocytopenia. A total of 1,690 patients were enrolled, and 28-day mortality rates were reduced from 30.8% in the placebo group to 24.7% in the treatment group (relative reduction in mortality rate of 19.8%; RR 0.80; 95% CI 0.69% to 0.94%; P=.005). Benefit from drotrecogin alfa (activated) was present in patients with various causes of bacterial infection and in those for whom culture results were negative. This suggests that common mechanisms leading to organ dysfunction and death are involved in patients with severe sepsis/septic shock and are amenable to therapy with drotrecogin alfa (activated), independent of the infecting microorganism as identified by cultures.

Survival benefit with drotrecogin alfa (activated) was associated with higher severity of illness, described by either the number of sepsis-induced organ failures or the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, which incorporates laboratory, clinical, age, and chronic illness components.[244] In analyses prespecified in the protocol, drotrecogin alfa (activated) was found to reduce absolute mortality by 13% in septic patients with APACHE II scores of greater than or equal to 25 or greater than or equal to 2 sepsis-induced organ dysfunctions.[245] Recent data from the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis trial in patients with single organ dysfunction or an APACHE II score less than 25 showed that these patients may not be at high risk and do not benefit from drotrecogin alfa (activated).[246] In the same study, patients with surgery within 30 days and single organ dysfunction who received drotrecogin alfa (activated) had higher 28-day mortality rate compared to patients receiving placebo. Multiple patient populations, such as those with end-stage liver disease (ie, Pugh-Child's class C) or requiring hemodialysis for end-stage renal disease, in which severe sepsis/septic shock is common, were excluded from the PROWESS study. The efficacy of drotrecogin alfa (activated) in such groups is unknown. Most important, patients at high risk for bleeding were excluded because of concerns about the anticoagulant properties of drotrecogin alfa (activated). A recent, randomized, double-blind, placebo-controlled trial examining the efficacy of drotrecogin alfa (activated) in pediatric patients was discontinued because of lack of efficacy. In this study, drotrecogin alfa (activated) did not show a benefit compared to placebo in the resolution of organ dysfunction over 14 days.[247]

As expected, given the anticoagulant properties of drotrecogin alfa (activated), the major risk with its use is bleeding.[6,243,245,248] Severe bleeding episodes considered to be life threatening or requiring the transfusion of more than 3 units of packed RBCs per day for 2 consecutive days were present in 3.5% of patients receiving drotrecogin alfa (activated) in the PROWESS study compared with 2.0% in the placebo group (P=.06).[6] Intracranial hemorrhage occurred during the infusion period in 0.2% of the drotrecogin alfa (activated)–treated group in the PROWESS study and has been reported to occur in 0.5% of patients during drotrecogin alfa (activated) infusion in subsequent controlled and open-label trials.[249] If all bleeding events are considered, administration of drotrecogin alfa (activated) approximately doubles the risk.[245] Additional analyses have also demonstrated that platelet counts below 30,000/mm^3 are associated with higher frequency of severe bleeding with drotrecogin alfa (activated).[249] The absolute contraindications to administration of drotrecogin alfa (activated) are active internal bleeding; hemorrhagic stroke within 3 months; intracranial or intraspinal surgery or severe head trauma within 2 months; trauma with an increased risk of life-threatening bleeding; presence of an epidural catheter; intracranial neoplasm, mass lesion, or evidence of cerebral herniation; or known hypersensitivity to drotrecogin alfa (activated).

Although PROWESS was the first successful clinical trial showing outcome benefit with a novel pharmacologic therapy for severe sepsis/septic shock,[250] physicians have not widely adopted its use. Reasons may include the cost of therapy,[251,252] a US Food and Drug Administration–approved indication for only a limited subgroup of patients with APACHE II score greater than or equal to 25, and concern for bleeding.[248] APACHE II was designed to prognosticate mortality according to physiologic variables during the first 24 hours after ICU admission.[244] It was not intended as a practical tool to indicate any therapy in individual patients. The interrater variability in computing APACHE II is also high,[253] leading to further criticism in its use as an indication for drotrecogin alfa (activated). However, patients with APACHE II scores greater than or equal to 25 appear to benefit from drotrecogin alfa (activated) with respect to mortality, long-term survival, and cost-effectiveness.[251,252,254,255] Another concern about the efficacy of drotrecogin alfa (activated) is that the protocol used in PROWESS was modified approximately halfway through the study.[248] After a revised entry criterion to exclude certain high-risk patients, a new placebo composition, and a new cell line to produce drotrecogin alfa (activated) were introduced, there was improved benefit shown in the treatment group. A recent retrospective analysis of patients with severe sepsis caused by community-acquired pneumonia who were enrolled in the PROWESS trial found that the 90-day survival benefit was largely due to an 18.1% absolute reduction in mortality (65.2% to 47.1%) in patients with inadequate antibiotic therapy, and was limited to only 4.0% (37.0% to 33.0%) in patients with adequate antimicrobial treatment.[142] Finally, evaluations of drotrecogin alfa (activated) in clinical use have found adverse

effect and mortality rates higher than in the original PROWESS trial.[256]

With respect to the ED setting, and especially in patients with prolonged ED length of stay, the timing of drotrecogin alfa (activated) administration may be crucial for optimal outcome. In the PROWESS study, the time from organ dysfunction to start of drug infusion was 17.5±12.8 hours.[6] In a global, open-label, single-arm study (Extended Evaluation of Recombinant Human Activated Protein C) enrolling 2,378 patients, those who received drotrecogin alfa (activated) within 24 hours of organ dysfunction had a 28-day mortality of 22.9% compared with 27.4% for patients who received it after 24 hours (P=.01).[257] Other preliminary data also suggest that drotrecogin alfa (activated) given within 24 hours of severe sepsis/septic shock may be associated with better outcome compared with administration after 24 hours of diagnosis.[258-261] A single-center observational study showed that drotrecogin alfa (activated) administration is feasible in the ED setting.[262] However, there are no definitive data demonstrating a decrease in mortality rate with early compared with late administration.

In patients with severe sepsis/septic shock, drotrecogin alfa (activated) should be considered when the APACHE II score is 25 or greater, despite initial hemodynamic optimization (using the principles of early goal-directed therapy) and appropriate and timely initiation of antimicrobial therapy, and contraindications do not exist (Grade B).

CORTICOSTEROIDS

The physiologic response to sepsis is an increased level of stress hormones such as cortisol. Some patients with septic shock will have inadequate adrenal reserve manifested by an inadequate response when challenged with adrenocorticotropic hormone or corticotrophin-releasing hormone.[263-265] Relative adrenal insufficiency, defined as an increase in serum cortisol level of less than or equal to 9 μg/dL 1 hour after administration of 250 μg of adrenocorticotropic hormone, is present in 56% to 77% of mechanically ventilated patients who have fluid-refractory septic shock.[266,267] In the ED setting, one study showed that 19% of hemodynamically unstable, vasopressor-dependent patients had adrenal insufficiency.[268] The presence of inadequate adrenal reserve, as determined by response to adrenocorticotropic hormone, is associated with worse outcomes, including higher mortality rates and prolonged requirements for vasopressors compared to an adequate cortisol response to adrenocorticotropic hormone.[263-265]

Although findings from small, single-center studies of septic shock suggested that prolonged administration of low doses of hydrocortisone could decrease requirements for vasopressors and improve survival,[269,270] this therapeutic approach has only recently been validated in an adequately powered, multicenter, placebo-controlled study in France. Annane et al[7] studied severely ill patients as defined by more than 1 hour of fluid-unresponsive hypotension and a greater than 5 μg/kg per minute requirement for dopamine or other vasopressors, such as norepinephrine or epinephrine. Additional entry criteria included a requirement for mechanical ventilation and evidence of at least 1 additional sepsis-induced organ dysfunction such as urine output less than 0.5 mL/kg per hour, serum lactate level greater than 2 mmol/L, or hypoxemia (PaO_2/FiO_2 less than 280). After an adrenocorticotropic hormone stimulation test at study entry, subjects were randomized to placebo or corticosteroids (hydrocortisone 50 mg intravenously every 6 hours and the mineralocorticoid, 9α-fludrocortisone 50 μg, once daily by mouth) for 7 days. Administration of corticosteroids resulted in a 28-day mortality rate of 63% in the placebo group compared with 53% in the treatment group among patients who did not respond appropriately to adrenocorticotropic hormone (relative reduction in mortality rate of 16%; RR 0.83; 95% CI 0.66% to 1.04%; P=.04). In contrast, there was no improvement in survival when patients with an appropriate cortisol response to adrenocorticotropic hormone were treated with steroids. Time receiving vasopressors was also significantly shortened when low-dose corticosteroids were administered to septic shock patients with inadequate adrenal reserve. Corticosteroid administration was not associated with increases in infectious complications, gastrointestinal bleeding, or mental status changes.[7]

The utility of routine corticosteroid supplementation for sepsis remains limited by the inability to reliably determine adrenal insufficiency within the time of ED management. Additionally, the optimal criteria for defining adrenal insufficiency in the setting of sepsis are unclear.[271] Proposed criteria other than the traditional cosyntropin stimulation test include a lower-dose cosyntropin test,[272] a random cortisol level,[273] and measuring serum free cortisol instead of total cortisol.[274] The Annane et al [7] trial has been criticized for a number of reasons, including the enrollment of a limited subset of severely ill patients,[275] lack of survival advantage in the treated group as a whole without adjustment for covariates,[276] and the criteria for defining adrenal insufficiency. An ongoing large, multicenter trial of corticosteroid therapy in septic shock called CORTICUS may clarify some of these issues.[271]

In patients with severe sepsis/septic shock, low-dose corticosteroids, specifically, hydrocortisone 50 mg intravenously every 6 hours and 9α-fludrocortisone 50 μg orally once a day for 7 days, should be given to mechanically ventilated septic shock patients with organ dysfunction requiring vasopressors, despite initial hemodynamic optimization (using the principles of early goal-directed therapy) and appropriate and timely initiation of antimicrobials.[277] Before corticosteroid treatment is started, an adrenocorticotropic hormone stimulation test or baseline cortisol level should be performed and corticosteroids continued only in patients who demonstrate inadequate adrenal response, as defined by an increase in serum cortisol less than 9 μg/dL (Grade C).

LOW TIDAL VOLUME MECHANICAL VENTILATION

Many patients with severe sepsis/septic shock require mechanical ventilatory support for acute lung injury, defined

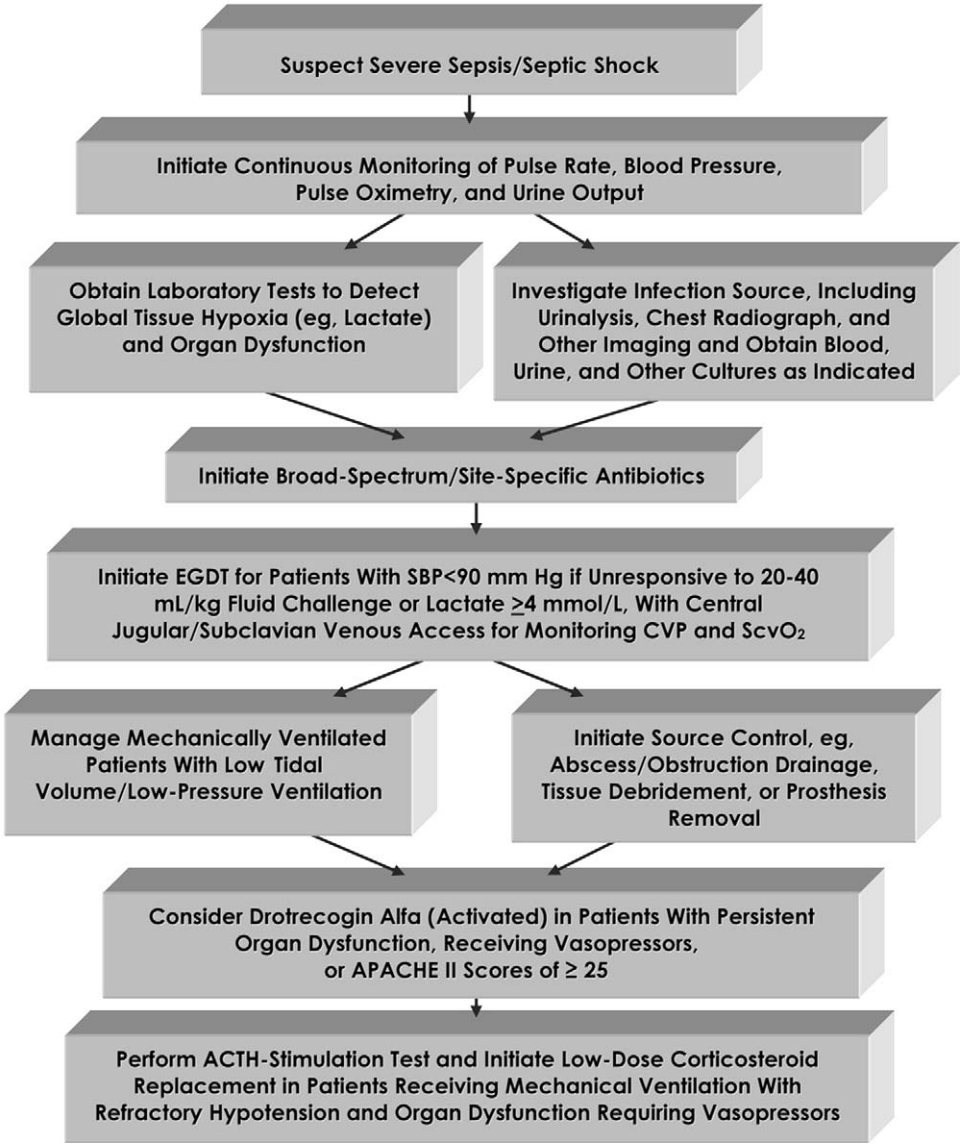


Figure 5. Summary algorithm of management guidelines for ED care of patients with septic shock/severe sepsis. *ACTH,* Adrenocorticotropic hormone; *APACHE,* Acute Physiology and Chronic Health Evaluation; *CVP,* central venous pressure; *EGDT,* early goal-directed therapy; *SBP,* systolic blood pressure.

as bilateral infiltrates consistent with pulmonary edema on chest radiograph, PaO_2/FiO_2 ratio less than 300, and no clinical evidence of left atrial hypertension (as shown by physical examination or a pulmonary capillary wedge pressure <18 mm Hg). It is thought that excessively high tidal volume may cause injurious lung stretch and release of inflammatory mediators. Although low tidal volume mechanical ventilation is not specifically a therapy for severe sepsis/septic shock, a large multicenter trial from the Acute Respiratory Distress Syndrome Network showed that its use when acute lung injury is present reduced mortality rates from 39.8% in the conventionally ventilated patients to 31% in those who received low tidal volume ventilation (relative reduction in mortality rate of 22.1%; 95% CI for the absolute difference between groups 2.4% to 15.3%).[278] In this study, patients with acute lung injury were randomized to either low (6 mL/kg, based on ideal body weight) or conventional (12 mL/kg, based on ideal body weight) tidal volumes. In the low tidal volume group, airway plateau pressures were kept less than or equal to 30 cm H_2O by decreasing the tidal volume to as low as 4 mL/kg if necessary, and in the conventional tidal volume group, airway plateau pressures were not allowed to be greater than 50 cm H_2O.[278]

Patients with severe sepsis/septic shock with acute lung injury requiring mechanical ventilation should be treated with low tidal volumes to maintain airway plateau pressure less than 30 mm Hg (Grade B; Grade E for sepsis without acute lung injury).

Table 3. Summary of rationale and recommendations for the ED treatment of adult patients with severe sepsis or septic shock.

Therapy	Rationale	Evidence of Benefit	Grade of Evidence
Early goal-directed therapy	To optimize oxygen delivery, within 6 h of presentation, patients are treated by (1) fluid resuscitation to achieve a CVP goal of 8-12 mm Hg; (2) vasoactive agents to achieve a MAP of 65–90 mm Hg; (3) blood transfusion to a hematocrit ≥30%; and (4) inotrope therapy and then sedation, paralysis, and intubation as necessary to achieve a $ScvO_2$ of ≥70%.	16.0% decreased absolute mortality rate in a single institution randomized, controlled trial	B
Appropriate antimicrobial therapy	The institution of "appropriate" empirical antimicrobials, ie, those given with in vitro activity against the infecting bacteria, will optimize pathogen killing.	Mortality benefit demonstrated in retrospective cohort studies of bacteremic patients	D
Timely antimicrobial therapy	Administration of antimicrobials as soon as possible once there is a reasonable suspicion of severe sepsis/septic shock will increase the chance of a favorable outcome.	Benefit demonstrated compared to historical controls (no antibiotic) and in retrospective cohort studies of hospitalized elderly with community-acquired pneumonia given antibiotics within 4 to 8 hours	E
Source control	Early detection of the site of infection will allow eradication by source control measures (ie, drainage debridement, or removal of devitalized infected tissue or infected prostheses).	Uncontrolled observations and expert opinion suggest improved outcomes with early source control	E
Recombinant human activated protein C/drotrecogin alfa (activated)	Recombinant human activated protein C has potent anticoagulant, profibrinolytic, antiinflammatory, and antiapoptotic effect in patients with severe sepsis and clinical evidence of infection, presence of a systemic inflammatory response syndrome, and at least 1 sepsis-induced organ dysfunction.	6.1% decreased absolute mortality rate (13.0% decreased mortality for severe sepsis with APACHE II ≥25) in one multicenter, randomized controlled trial, no mortality benefit in patients with single organ dysfunction or APACHE II <25	B
Corticosteroids	Low doses of hydrocortisone and fludrocortisone have potent antiinflammatory and vasoconstrictor effects in vasopressor-requiring septic shock patients with relative adrenal insufficiency.	10% decreased absolute mortality rate for patients not responding to ACTH stimulation	C
Low tidal volume mechanical ventilation	In patients requiring mechanical ventilation for acute lung injury, airway plateau pressure is maintained ≤30 cm H_2O by decreasing the tidal volume to as low as 4 mL/kg if necessary in order to reduce injurious lung stretch and release of inflammatory mediators.	8.8% decreased absolute mortality rate in one multicenter randomized trial	B (E if no evidence of acute lung injury)

PATIENT IDENTIFICATION AND IMPLEMENTING A SEPSIS TEAM

The components of developing a sepsis treatment protocol include early recognition of the high-risk patient, mobilization of resources for the required interventions, performing the interventions, quality improvement program, and a continuing education program and feedback. The early recognition of the high-risk patient uses illness severity markers for appropriate triage and disposition. Current studies suggest that when a patient has a suspected infection, 2 or more systemic inflammatory response syndrome criteria, and lactate level greater than or equal to 4 mmol/L, high mortality risk has been defined.[76,279,280] The additional finding of a systolic blood pressure of 90 mm Hg or lower after administration of a fluid bolus (20 to 40 mL/kg) can further identify the patient in classic septic shock.[14,16] These patients should then be treated expeditiously according to the recommendations in these guidelines.

Effective early intervention teams are based on a reliable mobilization of resources to perform the required critical tasks.

An appropriate number of qualified individuals to perform the level of care is key to successful implementation. This group includes a team leader and appropriate personnel to perform both procedural and nursing interventions. The implementation models include a mobile shock team, ED-centralized model, and ICU-centralized model. A mobile critical care team activated by preset criteria has been advocated for several decades[281] and has shown outcome benefit.[282,283] With previous evidence showing outcome benefits for early treatment of acute myocardial ischemia and stroke, adding sepsis to the list of diseases requiring urgent recognition and intervention would be justified. Setting a goal of "door to resolution of global tissue hypoxia" time of 6 hours from recognition of severe sepsis/septic shock may facilitate the prioritization of these interventions.

The ED-centralized model incorporates existing ED personnel to perform all required interventions until ICU admission. The patient may be treated as routine ED patients, with procedures performed by the ED physician, with a standardized protocol being implemented by a team interaction between the physician and nurses. This model is already common practice for patients in cardiac arrest with the delivery of advanced cardiac life support. The ICU-centralized model involves the initiation of therapy in the ED, with the bulk of care delivered in the ICU. In this model, the patient is identified, the intensive care begins immediately, such as initiation of hemodynamic monitoring, and patient transfer to the ICU is expedited, where the remainder of care is provided.

QUALITY-IMPROVEMENT INITIATIVES

There are international (Surviving Sepsis Campaign)[284] and national (Institute for Healthcare Improvement, http://www.ihi.org; and the Volunteer Hospitals of America Health Foundation, http://www.vha.com;) initiatives that are being developed to create the standards of care for the severe sepsis/septic shock patient. Eleven medical professional societies, including the American College of Emergency Physicians,[285] have endorsed the executive committee recommendations of the Surviving Sepsis Campaign, and many of the therapies endorsed by the Surviving Sepsis Campaign have been included in this ED-centered guideline for practicing emergency physicians. A recommendation from these international organizations is to implement change bundles for the care of severe sepsis/septic shock.[286] These efforts will potentially result in a set of sepsis core measures by the Joint Commission on Accreditation of Healthcare Organizations.

A bundle is a group of interventions related to a disease that, when completed together, improve outcome. A sepsis bundle must meet the following criteria: (1) the interventions are generally accepted clinical practice and supported by evidence; (2) the interventions need to be completed in the same time and space; (3) the completion of each intervention can be determined by a yes or no; and (4) the completion of the whole bundle can be determined by a yes or no. A preliminary resuscitation bundle for severe sepsis/septic shock that is applicable in the first 6 hours of care in the ED is available (Figure 4).[286]

In implementing a sepsis treatment program, in-service education to care providers such as nurses, residents, technicians, physician assistants, and physicians is important to provide peer uniformity and system-wide compliance. Nurses are educated to recognize high-risk septic patients and for competencies in central venous pressure, continuous $ScvO_2$ monitoring, and principles of oxygen transport. Physicians attend regular conferences on the hemodynamic support and advances in sepsis therapy.

When a system of accountability is in place, a quality-improvement program will help monitor compliance and identify solutions to barriers in providing this level of care. This program should be multidisciplinary and will help ensure that effective therapies are delivered. Recognition of illness severity, timing of antibiotic administration and hemodynamic optimization, and pursuit of source control (radiographic diagnosis and surgical consultation) should be reviewed.

SUMMARY OF RECOMMENDATIONS

The following guidelines for the management of severe sepsis/septic shock in the ED are summarized in Figure 5. Therapy and grading of evidence are summarized in Table 3. Although the literature was reviewed and assessed independently by the authors, grading assignments to the recommendations are consistent with those provided by the Surviving Sepsis Campaign[284] and the Society of Critical Care Medicine.[287]

1. Early recognition and management of severe sepsis/septic shock optimizes outcome. Therefore, when patients suspected of having this diagnosis present to the ED, they should be prioritized and receive timely care.
2. Continuous monitoring of vital signs, pulse oximetry, and urine output and initial laboratory testing to assess the severity of global tissue hypoxia and organ dysfunction, including assessment for lactic acidosis, renal and hepatic dysfunction, acute lung injury, and coagulation abnormalities, should be instituted as soon as possible in patients suspected of having severe sepsis/septic shock to facilitate the earliest recognition of this condition.
3. Simultaneously, a source of infection should be sought through clinical evaluation, urinalysis, chest radiography, and other imaging as indicated. Appropriate cultures (including blood, urine, and site specific) should be obtained before the institution of antibiotics.
4. Empiric antibiotics should be initiated as soon as possible. Ideally, site-specific regimens should be given, provided that identification of the site of infection does not significantly prolong the time to institution of antibiotic therapy.
5. Once severe sepsis/septic shock is recognized, early goal-directed therapy should be instituted as soon as possible, with placement of a subclavian or internal jugular central venous catheter for monitoring central venous pressure and $ScvO_2$. After initiation of early goal-directed therapy and achievement of the target hemodynamic goals (central

venous pressure 8-12 mm Hg; mean arterial pressure 65-90 mm Hg; ScvO2 >70%), serial lactate levels should be obtained to evaluate response to therapy.
6. According to the site of infection, source control should be pursued aggressively.
7. Patients requiring mechanical ventilation should be treated with low tidal volume to maintain end-inspiratory plateau pressure less than 30 cm H_2O.
8. Patients who do not respond to institution of early goal-directed therapy, antibiotics, and source control (ie, persistent hypotension, lactic acidosis, low $ScvO_2$, or sepsis-related organ dysfunction) and with high risk of death, reflected by APACHE II score of greater than or equal to 25, should be considered for drotrecogin alfa (activated) administration.
9. Patients who have refractory shock (ie, require vasopressors after adequate volume resuscitation) or organ dysfunction and are receiving mechanical ventilation should have an adrenocorticotropic hormone-stimulation test and be given low-dose replacement corticosteroid therapy.

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APPENDIX E1.

Authors of individual sections are listed, with the first author having primary responsibility for the respective section.

Introduction: DAT, EPR, HBN
Definitions: HBN, DAT
Epidemiology of Sepsis: HBN, DTH
Pathogenesis: EPR, HBN
Diagnosis: DAT, FMA, GJM
Treatment
Early Hemodynamic Optimization: HBN, EPR, TO
Hemodynamic Monitoring: HBN, EPR, TO
Volume Therapy: HBN, EPR, TO
Vasoactive Agents: HBN, EPR, ST, TO
Increased Oxygen Carrying Capacity: HBN, EPR
Inotropic Therapy: HBN, EPR, ST
Decreased Oxygen Consumption: HBN, EPR
Resuscitation Endpoints: HBN, EPR, TO
Antimicrobial Therapy
Timeliness and in Vitro Antimicrobial Activity: DAT
Infection Site and Bacterial Cause: GJM
Antimicrobial Susceptibility: DAT, DS
Clinical Antimicrobial Studies and Combination Therapy: GJM
Empirical Antimicrobial Recommendations: DAT, DS, FMA, GJM
Source Control: FMA
Recombinant Human Activated Protein C: EA, HBN
Corticosteroids: EA, GJM
Low Tidal Volume Mechanical Ventilation: EA
Patient Identification and Implementing a Sepsis Team: HBN, EPR
Quality-Improvement Initiatives: HBN, EPR
Summary of Recommendations: DAT, HBN, EPR, GJM
General editing: DAT, HBN, EPR, GJM, FMA