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Sepsis Management 2010

Editor's Note

Sepsis is a disease process that exists on a spectrum increasing in severity from sepsis to severe sepsis to septic shock. The common thread between these elements is a disseminated inflammatory response to infection characterized by clinical and laboratory findings. Severe sepsis is sepsis complicated by organ dysfunction. Septic shock is sepsis with refractory hypotension. It is estimated that a patient with severe sepsis or septic shock presents to an emergency department every minute.[1] Over the last 10 years, several strategies to manage septic patients have emerged and have been summarized in international guidelines supported by international medical specialty organizations.[2] Despite publications explaining the importance of specific therapies, use of these therapies and public awareness of sepsis remain suboptimal.[3,4]

A previous *EM Reports* discussed the pathophysiology and treatment strategies of sepsis in 2005. This issue will highlight changes over the last 5 years, particularly the importance of early detection of high-risk patients, appropriate antimicrobials, source control, hemodynamic optimization (clarity in fluid therapy and vasopressor selection), and the results of large-scale efforts to implement bundles of care.

Introduction

The optimal treatment of sepsis has concerned physicians for millennia. In its original Greek language, "sepsis" means the "decomposition of animal or vegetable organic matter in the presence of bacteria."[5] Today, we use the term sepsis to refer to the syndrome occurring in a patient who has an infection and whose body is mounting a response to get rid of that infection in an attempt to rid the body of the offending organism. From this definition, it is easily inferred that sepsis can include self-limited viral syndromes or life-threatening bacterial infections. Thus, sepsis refers to a disease spectrum whose categories all feature a disseminated inflammatory response to infection characterized by specific clinical and laboratory findings.

In the 1980s several large clinical trials were performed on patients with severe sepsis and septic shock, all revolving around the same central hypothesis: A drug targeted at minimizing this disseminated inflammatory response to infection will lower mortality. These studies included the administration of non-steroidal anti-inflammatory medications, delivery of high-dose steroids, and novel agents targeting bacterial components including antibodies to lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria, and immunotherapy against inflammatory mediators such as anti-tumor necrosis factor antibodies and interleukin-1 receptor antagonists. All of these studies showed either no efficacy or worse outcomes in the intervention arm of the trial. For example, Bone et al, in a randomized, double-blind, placebo-controlled trial, investigated the infusion of high-dose methylprednisolone for patients with severe sepsis or septic shock and demonstrated no significant differences in the prevention of shock, reversal of shock, or overall mortality.

Executive Summary

- Sepsis is the most expensive, common, lethal diagnosis in the ED that requires hospitalization.
- Early goal-directed therapy delivers aggressive fluid resuscitation as well as inotropes and blood transfusion in the first 6 hours.
- Antimicrobials should be broad spectrum and given as early as feasible.
- Steroids remain controversial but may be reasonable in very severe cases.

For the a priori defined subgroup of patients with elevated serum creatinine level (> 2 mg/dL), those treated with methylprednisolone had significantly higher mortality than those treated with placebo (59% vs. 29%; $p < 0.01$).[6]

Researchers were confused by the failure of these seemingly promising agents and decided to hold a consensus conference on sepsis to further investigate the clinical entity and codify definitions. One of the concerns was that patients enrolled in sepsis trials were very heterogeneous. Uniform inclusion criteria were not employed between trials or sites within an individual trial. The initial ACCP/SCCM consensus conference, held in Chicago in 1991, had the goals of agreeing on definitions of sepsis and its sequelae; improving early bedside detection and therapeutic intervention; and standardization of research protocols. The consensus conference defined sepsis as the systemic inflammatory response to infection, which can be further characterized as the presence of a suspected or confirmed infection accompanied by two or more systemic inflammatory response syndrome (SIRS) criteria.[7] (*See Table 1.*) Despite this seemingly concrete definition, the concept of sepsis came under fire for having arbitrary parameters and being nonspecific.[8]

Soon after the 1991 consensus definitions were published, researchers started investigating whether the definitions had clinical utility. For example, Rangel-Frausto and colleagues examined the epidemiology of the newly defined categories in three ICUs and three hospital wards at the University of Iowa Hospitals. They found "stepwise increases in mortality rates in the hierarchy from SIRS, sepsis, severe sepsis, and septic shock: 7%, 16%, 20%, and 46%, respectively."[9] Many physicians, however, continued to believe that no common definition of sepsis existed.[10]

In 2001, representatives from SCCM/ESICM/ACCP/ATS/SIS convened to revisit the definitions of sepsis and related conditions. While increasing the laboratory and clinical findings that define sepsis, this second consensus conference found no evidence to change the definitions of sepsis. This ratification of the existing definitions of sepsis did little to bring clarity to the clinical management of sepsis. In fact, the term sepsis continues to be misused and controversial.

Historically, management of patients with the sepsis syndrome has involved antimicrobials, intravenous fluids, vasopressors as needed to support perfusion, and possibly steroids. Although always supported by biologic plausibility, we now have data to support the importance of correcting hemodynamic endpoints and administering antimicrobials within one hour of identifying septic shock.

In 2001, a landmark paper, "Early goal-directed therapy in the treatment of severe sepsis and septic shock," altered the clinical landscape of sepsis management.[11] Two hundred sixty-three patients with severe sepsis, defined as two SIRS criteria, a source of infection, and a serum lactate > 4 mmol/L, or septic shock, defined as two SIRS criteria, a source of infection, and systolic blood pressure (SBP) < 90 mmHg after adequate fluid challenge, were randomized to receive either standard therapy or early goal-directed therapy (EGDT). During the first six hours of care, patients in the EGDT arm received statistically significantly more intravenous fluids, inotropes, and blood transfusions. By moving an aggressive, algorithmic resuscitation strategy to the proximal phase of critical infection and inflammation, Rivers and colleagues demonstrated a 16% absolute reduction in in-hospital mortality. This reduction in mortality was accompanied by a decreased use of vasopressors and mechanical ventilation over the first 72 hours of hospitalization. These results spurred a renewed interest in improving sepsis management in the ED and led to numerous implementation studies and quality improvement initiatives, showing improved in-hospital, 28-day, and up-to-one-year mortality with implementing EGDT[3,11,12-43] and a decrease in health-care resource consumption.[44-46]

Relevancy of the Problem to the Adult Population/ Epidemiology

Sepsis (including pneumonia) is the most expensive, common, and lethal diagnosis necessitating hospital admission.[47,48] It is estimated that a patient with severe sepsis or septic shock presents to an emergency department (ED) every minute.[1] Put another way, in 2001, using 1995 hospital discharge data from seven states, Angus and colleagues extracted hospital discharge ICD-9 codes for infection and acute organ dysfunction to estimate that approximately 751,000 cases of severe sepsis or septic shock occurred annually in the United States, with an in-hospital mortality of 28.6%.[49] Wang and his colleagues used the National Hospital Ambulatory Medical Care

Table 1: Sepsis Definitions

Systemic Inflammatory Response Syndrome (SIRS)
Two or more of the following criteria: • Temperature < 36 or > 38° C • Heart rate > 90 beats/minute • Respiratory rate > 20 or $PaCO_2$ < 32 • WBC < 4000 or > 12,000; or band > 10%
Sepsis
Two or more SIRS criteria plus suspected or confirmed infection
Severe Sepsis
Sepsis + organ dysfunction (examples below) • Altered mental status • Hypotension responsive to 20 cc/kg fluid bolus • Arterial hypoxemia (PaO_2/FiO_2 < 300) • Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs) • Creatinine increase > 0.5 mg/dL from baseline • Coagulation abnormalities (INR > 1.5 or aPTT> 60 sec) • Ileus (absent bowel sounds) • Thrombocytopenia (platelet count < 100,000/uL) • Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL)
Septic Shock
Severe sepsis + hypotension unresponsive to 20 cc/kg fluid bolus

Key:
WBC = white blood cell count; INR = international normalized ratio; aPTT = activated partial thromboplastin time; PaO_2 = partial pressure of oxygen in arterial blood; FiO_2 = fraction of inspired oxygen

Adapted from: Engineer R, Blicker J, Patel A. Sepsis management. *Emerg Med Rep* 2005;11:133.

Survey to generate estimates of the number of patients presenting to the ED each year who are suspected of having severe sepsis. These estimates were generated from ED-ICD-9 codes for infection, vital sign abnormalities, and evidence of organ dysfunction and suggested 571,000 cases of severe sepsis present to U.S. EDs each year. Mean length of ED stay for these patients was 4.7 hours.[1] Taking a different approach, Dombrovskiy and colleagues used the Nationwide Inpatient Sample, a stratified 20% sample of U.S. hospitals, to examine changes in incidence of severe sepsis from 1993-2003. They found that the percentage of severe sepsis cases among all sepsis cases increased from 25.6% to 43.8% during the study period, while in-hospital mortality fell from 45.8% to 37.8%.[50]

Etiology and Pathophysiology

The evolution of sepsis and the progression from sepsis to severe sepsis to septic shock is a complex process centered around the interaction between a pathogen and its human host. Infection begins when a pathogen — a bacterium, virus, fungus, or parasite — comes into contact with a human host and begins to multiply. The location of the organism becomes the initial source of infection. The person mounts an immune response in an attempt to eliminate the organism. This immune response is triggered by toxins and other components of the causative micro-organism. The prototypical toxin triggering an inflammatory response is endotoxin, or lipopolysaccharide (LPS), a highly conserved component of the cell wall of most gram-negative organisms. The majority of the body of LPS is inert carbohydrate, which terminates in the active, well-conserved terminal lipid A unit. White blood cells are mobilized to the source of infection and an elevated white blood cell count, the one laboratory finding that is part of the SIRS criteria, often occurs. An inflammatory response ensues, and this inflammatory response triggers common physiological responses including fever, tachycardia, and tachypnea — the three clinical signs that are part of the SIRS criteria. (*See Table 1.*) Inflammatory markers produced during this phase of sepsis include TNF-α, IL-1, IL-2, IL-4, IL-6, IL-8, and other endogenous mediators of inflammation. These include endothelin-1, platelet activating factor, heat shock proteins, and various adhesion molecules, among others.[51] These inflammatory mediators trigger endothelial and mitochondrial dysfunction, and reversible organ dysfunction follows. The body also mounts a subsequent compensatory anti-inflammatory response (CARS) as an endogenous attempt to modulate inflammation. Components of CARS include IL-10. Without intervention, reversible organ dysfunction becomes irreversible multi-organ dysfunction syndrome, microcirculatory abnormalities produce shock, and death follows.

Clinical Features

Clinical features of sepsis include the SIRS criteria — an elevated or low temperature (> 100.4°F or < 96.8°F); tachycardia (> 90 beats per minute); and tachypnea (> 20 breaths per minute). Clinical features of severe sepsis reflect bedside findings suggestive of acute organ dysfunction. These include acute brain dysfunction, manifested as confusion, delirium, or agitation and measured by changes in Glasgow Coma Score; acute lung injury (ALI) or

acute respiratory distress syndrome (ARDS), manifested as increased oxygen requirements and increased work of breathing; myocardial dysfunction manifested as relative or overt hypotension; hepatic dysfunction manifested as acute jaundice; gastrointestinal dysfunction, manifested as ileus; mottled skin; renal dysfunction, manifested as oliguria or increased creatinine; hematologic dysfunction; and tissue-level hypoperfusion, reflected in an elevated serum lactate level. (*See Table 1.*)

Identification of Patients and Initial Diagnostic Studies

Screening for patients with a potential diagnosis of sepsis should begin in triage. An initial triage exam offers a tremendous amount of information: a chief complaint (many of which are suggestive of infection), a brief history of the present illness, three of the four SIRS criteria, pulse oximetry, and blood pressure. These components identify a significant percentage of patients with sepsis and begin to identify whether patients have sepsis, severe sepsis, or septic shock. Fever is an important clinical indicator of infection and inflammation but is easily missed in patients presenting to the ED. Tachypnea, mouth breathing, and oxygen administration can lower oral temperature. If clinical suspicion is moderate or high, or if the patient has unexplained tachypnea or mouth breathing, consider obtaining a rectal temperature.[52] Some patients are hypothermic.

The SIRS criteria, originally considered very sensitive but not specific for sepsis, may, in fact, be neither sensitive nor specific. Elderly patients have altered hypothalamic responses to typical pyrogens; some elderly patients cannot breathe fast enough to become tachypneic; and many drugs block a patient's ability to mount a tachycardia. In a large database study of ED patients with suspected sepsis (antibiotics given; blood cultures sent), Shapiro and colleagues found that 34% of patients with severe sepsis and 24% of patients with septic shock did not meet SIRS criteria during their ED stay. Thus, it is important that emergency physicians develop a strategy for early identification and treatment of patients with severe sepsis in their EDs.[53]

Risk Stratification of Patients. Several methods of risk stratifying ED sepsis patients have been studied. These include early lactate measurement, quantification of number of organ dysfunctions present, and application of ICU-based or ED-derived scoring systems.

Lactate is perhaps the best-studied marker of illness severity that is readily available to the majority of emergency physicians and helps to guide initial management of potentially critically ill patients. In 1964, in the journal *Science*, Max Harry Weil published his initial investigations of measurements of excess lactate production in critically ill patients.[54] He made the observations that during times of health, lactate and pyruvate exist in a stable ratio, but at times of stress and limited oxygen delivery, as occurs in critical illness, lactate is produced in excess of pyruvate. He hypothesized that increasing amounts of excess lactate would correlate with worsened outcomes in the critically ill. He found that patients with an excess lactate of 1-2 mmol/L had a mortality of 14%; when their excess lactate exceeded 4 mmol/L, mortality increased to 87% and prompt resuscitation couldn't reverse this outcome. More recently, in an article published in 1994, Aduen and colleagues observed that regardless of chief complaint or clinical presentation, patients with a serum lactate > 4 mmol/L had an in-hospital mortality of 50%.[54] He suggested that these patients needed aggressive management in an attempt to reverse shock.[55] Recognizing the high mortality of patients with significant hyperlactatemia, Rivers and colleagues used a serum lactate > 4 mmol/L as an inclusion criterion in the EGDT trial.

Since the 2001 publication of the EGDT trial, several database studies have further investigated the predictive value of various lactate strata in patients with severe sepsis. In 2005, Shapiro and colleagues published a study examining three different venous lactate strata in 1,278 consecutive adults admitted from the ED with an infection-related diagnosis.[56] The primary outcome was in-hospital mortality. Patients with a lactate < 2.5 mmol/L had an in-hospital mortality of 2.9%; for those with a lactate between 2.5 and 3.9 mmol/L, the rate was 8.7%. When the initial lactate level was ≥ 4 mmol/L, mortality increased to 28.9%. Mikkelsen et al provided further insight into the relationship between lactate and mortality by stratifying 830 adults with severe sepsis by lactate levels (normal, ≤ 2.0 mmol/L; moderately elevated, 2.1-3.9 mmol/L; elevated, ≥ 4 mmol/L) independent of the presence of organ dysfunction or shock.[57] They found that 28-day all-cause mortality increased in a step-wise fashion in both normotensive and hypotensive patients as they moved from normal to moderately elevated to significantly elevated lactate levels. In normotensive patients, mortality was 8.7%, 16.4%, and 31.6%, respectively; in hypotensive patients, mortality was 15.4%, 37.3%, and 46.9%, respectively. These results suggest that initial venous lactate can be used to screen for severity of illness in severe sepsis patients independent of organ dysfunction and shock and should be incorporated into early management strategies.

Hypoperfusion and inflammation cause organ dysfunction, which is initially reversible but becomes irreversible if perfusion isn't restored and the immune response isn't modulated. As the number of dysfunctional organ systems increases, sepsis becomes more severe. In a 2006 publication, Shapiro et al demonstrated that in a database of 3,102 patients with suspected infection, patients with severe sepsis had an in-hospital odds ratio (OR) of death of 4.0 (95% CI, 2.6 to 6.3) when compared to patients with infection without SIRS. Each additional organ dysfunction increased the one-year

adjusted mortality hazard ratio by 80%.[53] This suggests that organ dysfunction may be used to prognosticate in real-time and tailor intensity of therapy.

Several attempts have been made to adapt ICU scoring systems for ED use, seeking to validate them during the time course of ED management of critically ill sepsis patients. In addition, attempts have been made to create new ED-based scoring systems. For example, Jones et al studied the operational performance of various severity scoring systems when applied to non-trauma ED patients with signs of shock. They examined three scoring systems: the New Simplified Acute Physiology Score (SAPS) II; the Morbidity Probability Model at admission (MPMa II); and the Logistic Organ Dysfunction System (LODS). Using values available during the ED stay, they calculated these scoring systems for 91 patients and found that they provided moderate accuracy for predicting in-hospital mortality (area under the curve [AUC]): SAPS II, 0.72; MPMa II, 0.69; and LODS, 0.60).[58] Shapiro and colleagues attempted to derive a unique ED-based scoring system. They utilized a 3,000-patient data set to derive and validate a nine-part scoring system they called the Mortality in Emergency Department Sepsis (MEDS) score, which yielded five categories ranging from very low risk to very high risk. The ROC area for the scoring system was 0.82 in the derivation set and 0.79 in the validation set.[59] This scoring system has been criticized for excessive reliance on the presence of a terminal illness and transfer to the ED from a nursing home. A validation study by Jones et al demonstrated poor performance for the MEDS score when applied to a cohort of critically ill sepsis patients (area under ROC curve, 0.61 [95% CI, 0.50-0.72]).[60] However, it has been used in subsequent ED trials of sepsis treatment strategies.[61]

Many scoring systems have been moderately useful in predicting mortality,[58-61] but the best seems to be the SOFA score.[62] Jones and colleagues previously conducted a prospective, observational study of 248 severe sepsis patients qualifying for a standardized quantitative resuscitation protocol and calculated SOFA scores upon ED recognition (T0) and 72 hours later (T72). In this cohort of patients who had an in-hospital mortality of 21%, the area under the ROC curve for T0 was 0.75 (95% CI, 0.68-0.83) and for T72 was 0.84 (95% CI, 0.77-0.90). This suggests that a SOFA score calculated at the time of recognition of severe sepsis in the ED can provide accurate prognostic information about in-hospital mortality — at least in the sickest severe sepsis patients who are treated with a protocolized resuscitation strategy.[63]

Application of the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system in the ED is complicated by the fact that the scoring system is calculated based on the worst values during the first 24 hours after admission to the ICU.[64] However, in the EGDT trial, Rivers and colleagues reported an ED, time-zero, APACHE II score in all of the subjects. Lee and colleagues conducted a small pilot study applying APACHE II to patients evaluated in the resuscitation rooms of a Hong Kong hospital and found good correlation of a modified ED APACHE II score with outcomes.[65] They conducted a larger, prospective multicenter study in an attempt to validate these findings. The acute physiological status component of APACHE II, typically calculated from worst values over the first 24 hours, was modified so that it was calculated from the first available values and the variable of oxygenation was eliminated completely. This resulted in 11 physiological variables being included in the scoring system along with the patient's age and chronic medical conditions. Mortality for the 867 patients included in the study was 12.2%; the modified APACHE II score for survivors was 14.4 vs. 21.2 for non-survivors, $p < 0.001$; the area under the ROC for predicting mortality was 0.743 (95% CI, 0.696-0.790). The authors concluded that a modified APACHE II score had moderate predictive accuracy in a group of mixed, critically ill ED patients.[66]

Differential Diagnosis

The initial presentation of patients with severe sepsis can be straightforward with a narrow differential diagnosis or can be complicated, with sepsis being only one of many possible explanations for the patient's presentation. For example, patients with bacterial meningitis initially can appear to have a primary seizure disorder or to be suffering from a cerebral vascular accident. Similarly, a patient with multifocal pneumonia and sepsis-induced myocardial dysfunction can appear to be having an episode of congestive heart failure or an acute coronary syndrome.

Physicians managing critically ill patients in the ED need to avoid making premature closure on the differential diagnosis and incorporate new data as they emerge. This process can include distinguishing sepsis from other causes of SIRS, including pancreatitis, trauma, rhabdomyolysis, and withdrawal syndromes including alcohol withdrawal. Also, remember that the host inflammatory response associated with sepsis can be stimulated by many types of organisms. An example of nonbacterial sepsis seen frequently, but with seasonal variation, is influenza-associated sepsis.

Management

The initial management of critically ill sepsis patients is focused on the ABCs of resuscitation — making sure the airway is patent; ensuring that the patient has adequate ventilation and oxygenation, which should be corrected with early mechanical ventilation if they are inadequate; and ensuring that circulation is sufficient to maintain organ and tissue perfusion. In general, this includes placement of two large-bore intravenous catheters, infusion of an adequate bolus of crystalloid to restore intravascular volume, sending screening labs and cultures, and obtaining targeted imaging studies. Also, priority should be given to early

administration of broad-spectrum antimicrobials.

Source Control. Like controlling a burning fire, the initial management of infection is obtaining source control. In the ED, this may mean removing a foreign body, draining a cutaneous abscess, or obtaining urgent consultation for surgical debridement of necrotic tissue. In 2004, Marshall and colleagues reviewed the role of source control in treating severe infections. They divided source control into four categories: draining infected fluid; removing infected devices or foreign bodies; debriding infected tissues; and correcting anatomic abnormalities causing ongoing infection. Despite the obvious logic of source control in sepsis as the best way to reduce the bacterial inoculum, they acknowledged that no randomized studies exist to support prioritizing source control to the early phases of severe sepsis management.[67]

Endpoints of Resuscitation. In 1999 the American College of Critical Care Medicine (ACCM) published guidelines for the management of patients with severe sepsis and septic shock, offering several hemodynamic goals to pursue when resuscitating this patient population. These goals included a pulmonary artery occlusion pressure of 12-15 mmHg, and adequate MAP, preload, and contractility. These guidelines were the result of expert consensus, as no positive clinical trials of hemodynamic optimization in critically ill sepsis patients had been performed. As mentioned above, in 2001, Rivers and colleagues published their landmark study on EGDT, which revolutionized the approach to treating patients with severe sepsis and septic shock. This study acknowledged several realities of this patient population: severe sepsis and septic shock are time-dependent diseases; a window of opportunity exists to reverse pathophysiologic changes developing at the organ and tissue levels before damage becomes irreversible; during the supply-dependent phase of oxygen consumption, severe sepsis and septic shock patients will consume more oxygen if it is delivered to the tissues.

The standard therapy arm of the trial was resuscitated with the following goals: CVP of 8-12 mmHg; MAP of > 65 mmHg; and urine output > 0.5 mL/kg/hr. In the EGDT arm, a systematic, algorithmic resuscitation strategy was employed with the following goals: CVP of 8-12 mmHg; MAP of 65 to 90 mmHg; and $ScvO_2$ > 70%. One of the main differences in the two groups was the early aggressive use of fluids in the EGDT arm. Using this approach, a 16% absolute reduction in in-hospital mortality in EGDT patients vs. standard therapy patients was realized (46.5 vs 30.5%). There are a few reasons suggested by the authors for this mortality reduction: decrease in sudden cardiovascular collapse, decreased vasopressor use, and reductions in inflammatory markers.

The potential for a significant reduction in severe sepsis mortality if the results of the EGDT trial could be replicated at a large percentage of hospitals worldwide led to a groundswell of enthusiasm for EGDT and the development of algorithmic resuscitation programs at diverse institutions in the United States and abroad. In 2006, Otero and colleagues summarized these implementation studies in an article published in *Chest* on the fifth anniversary of the EGDT article. The implementation studies included more than 3,000 patients, approximately half constituting historic controls and half EGDT patients. Mortality was reduced from 45.6 ± 7.9% pre-implementation to 25.8 ± 5.7% post-implementation.[68] To date, more than 34 publications representing more than 6,000 patients of equal illness severity have shown the same mortality reduction as the original EGDT study.[3,11,12-43] Despite this strong evidence supporting the EGDT algorithm, clinicians continue to search for alternative endpoints of resuscitation. The reasons for this include concern about the validity of specific endpoints (e.g., CVP), the desire for less invasive endpoints, and a belief that CVP, MAP, and $ScvO_2$ alone don't completely describe adequacy of resuscitation or when to scale back the aggressiveness of therapy.

An understanding of how various physiological variables become abnormal during the development of sepsis and possible ways of monitoring them gives insight into their potential role in assessing the adequacy of resuscitation.

Heart Rate (HR). When molecular components unique to pathogens trigger an immune response, cytokines such as TNF-α, IL-1, and IL-6 cause vasodilatation. This vasodilatation, in turn, is recognized by volume-dependent receptors in the vascular system, which increase the heart rate in an attempt to maintain cardiac output. Healthy individuals have a significant amount of heart rate variability (HRV) over time. It has been demonstrated that infusion of LPS, which triggers release of TNF-α and other cytokines, reduces this HRV in an animal model of endotoxin challenge.[69] There is interest in examining changes in HRV in humans as a marker of severity of sepsis.

Respiratory Rate (RR). Respiratory rate increases as metabolic acidosis, related to inadequate tissue-level oxygen delivery, ensues. Recent studies have suggested that tachypnea is a marker for ED severity of illness in critically ill patients, including those with severe sepsis. For example, Farley et al demonstrated that ED tachypnea predicts transfer from admission to floor beds to ICU. In a retrospective study of 74 patients transferred from floor beds to ICUs compared to control patients, each 10-breath increase in respiratory rate had an OR of 2.79 (95% CI, 1.41 to 5.51) of ICU transfer.[70]

Blood Pressure (BP). Blood pressure initially increases in conditions of intravascular volume depletion as the same factors that produce vasodilatation trigger an increase in endogenous catecholemines, which raise blood pressure. If the inflammatory response goes unchecked, persistent vasodilatation, intravascular

volume depletion, and myocardial suppression may result in hypotension. Patients with cryptic shock (global tissue hypoxia with preserved blood pressure) have similar mortality as those with clearly recognized shock. The lack of early recognition of illness severity leads to inadequate therapeutic intervention and resolution of global tissue hypoxia.[71]

Urine Output (UO). Based on expert opinion, a urine output less than 0.5 mL/kg/hr suggests that a patient is in septic shock without adequate tissue-level perfusion. Early hemodynamic optimization should deliver sufficient intravascular fluid resuscitation to restore adequate urine output during the golden hours of sepsis resuscitation.[72]

Central Venous Pressure (CVP). Central venous pressure is one of the physiological goals pursued in EGDT to correct hemodynamic derangements in critically ill sepsis patients. Preload, or the amount of fluid in the vascular system returning to the right side of the heart, is measured by CVP. In healthy adults, CVP ranges from 0 to 8 mmHg; when patients are intubated, CVP typically increases by several mmHg and the normal range is 8-12 mmHg. Central venous pressure is a controversial physiological variable for a couple of reasons. Disorders affecting the right side of the heart, including pulmonary hypertension, tricuspid regurgitation, and pulmonary stenosis, affect CVP. Vasopressor use increases afterload and raises CVP. Even without these complicating factors, it is unclear whether CVP is a good measure of intravascular volume and fluid responsiveness. For example, in a systematic review published in *Chest* in 2008, Marik and colleagues reviewed 24 articles on CVP and reached the conclusion that CVP is a very poor measure of blood volume or whether a patient will respond to a fluid bolus.[73] However, it is difficult to extrapolate from the 24 studies used in this review, all performed either in the operating room or ICU, to the management of severely ill sepsis patients at the proximal phase of critical infection. These patients on ED presentation are most often vasoconstricted and volume-depleted. In the original EGDT trial, the mean baseline CVP (hour 0) in the standard therapy group was 6.1 ± 7.7 mmHg and in the EGDT group was 5.3 ± 9.5 mmHg. During the first six hours of resuscitation, the standard therapy group received a total fluid volume of 3499 ± 2438 mL, while the EGDT group received 4981 ± 2984 mL. At hour 6, these values had increased to 11.8 ± 6.8 mmHg and 13.8 ± 4.4 mmHg, respectively. These results suggest that CVP can be used to assess volume responsiveness at the proximal phase of critical infection.

Central Venous and Mixed Venous Oxygen Saturation ($ScvO_2$/SvO_2). These values represent the amount of oxygen that remains in venous blood after it has passed through the capillary beds and oxygen to fuel cellular metabolism has been extracted. While $ScvO_2$ is measured from the tip of a catheter placed at the atriocaval junction, SvO_2 is measured more distally, from the tip of a pulmonary artery catheter (PAC). Because of the relative ease of and increased safety related to placing a central venous catheter rather than a PAC, clinicians have used $ScvO_2$ as a surrogate for SvO_2. Blood from the coronary sinus, which typically has a low venous oxygen saturation, is included in SvO_2 measurements, and SvO_2 is typically 5-7 percent lower than $ScvO_2$. Reinhart conducted an experiment in anaesthetized dogs and demonstrated that $ScvO_2$ correlated well with SvO_2 over a broad range of changes in the cardiovascular system, including experimentally induced hypoxia, hemorrhagic shock, and volume resuscitation.[74] The EGDT resuscitation strategy is centered on correcting low $ScvO_2$ — increasing oxygen delivery or decreasing oxygen consumption to raise abnormal $ScvO_2$ into a normal range. This correction represents a restoration of adequate oxygen delivery to meet oxygen consumption needs. Of note, there remains some controversy over the routine use of these catheters despite the excellent results from EGDT. A current NIH trial should bring clarity to this issue in the near future. An interesting observation emerged as clinicians translated EGDT to diverse clinical settings — what about patients whose initial $ScvO_2$ levels are supranormal? What is the meaning of a supranormal central venous oxygen level, and does this level have implications for severity of illness and survival? An $ScvO_2$ level > 90% is considered to represent venous hyperoxia — possibly reflecting microcirculatory abnormalities or oxygen extraction deficits at the mitochondrial level. Pope et al investigated this idea by pooling together 619 EGDT patients from four databases and examining $ScvO_2$ levels divided into low (< 70%), normal (70-90%), and high (>90%). Mortality was highest when the maximum $ScvO_2$ achieved during ED resuscitation fell into the low or high groups (mortality was 40% vs 21% vs. 34% for the low, normal, and high $ScvO_2$ groups, respectively).[75] $ScvO_2$ is a trigger for transfusion,[76] allows for early detection of myocardial dysfunction (inotropes),[77] and the need for decreasing systemic oxygen consumption (mechanical ventilation).[78] Outcome studies have demonstrated that reaching this endpoint is associated with improved survival and reduction in organ dysfunction, including acute lung injury.[34,78-81] This suggests that therapies targeting mitochondrial dysfunction and venous hyperoxia need to be developed and tested clinically.

Thenar Oxygen Saturation (StO_2). The search for a non-invasive substitute for $ScvO_2$ or SvO_2 has included investigation of the utility of StO_2, measured through a device applied to the thenar eminence of the hand. For example, Mesquida and colleagues studied the relationship between StO_2 and $ScvO_2$ in ICU patients with severe sepsis or septic shock after normalization of intravascular volume and blood pressure. They found that an StO_2 < 75% correlated with an $ScvO_2$ < 70% with poor sensitivity (0.44) but good

specificity (0.93).[82] In 40 patients being treated with EGDT, Napoli and colleagues examined the relationship between StO_2 and $ScvO_2$. They found that StO_2 overestimates $ScvO_2$ when it is in a low range and underestimates $ScvO_2$ when it is in a higher range and concluded that tissue oxygenation doesn't reflect central venous oxygenation in this patient population.[83]

Microcirculation. Flow in the microcirculation (arterioles, capillaries, venules) can be measured using orthogonal polarizing spectral (OPS) imaging, and patients in shock typically demonstrate slower flow and more heterogenous flow than hemodynamically normal subjects. Images are collected and then require extensive post-hoc analysis of flow rates and patterns of flow. Trzeciak and colleagues used this technique to gather images in 26 severe sepsis and septic shock patients being treated with EGDT. They found that nonsurvivors and patients with increased hemodynamic compromise had lower flow velocity and more microcirculatory heterogeneity.[84] However, OPS technology does not currently have real-time capability for use in sepsis resuscitations. These results highlight the importance of microcirculation in severe sepsis and suggest that further technological developments are needed to allow for real-time assessment of the microcirculation.

Lactate Clearance. There has been a lot of interest in whether changes in serum lactate levels reflect adequacy of resuscitation. As oxygen delivery is restored, aerobic metabolism recommences and excess lactate production is halted while increased perfusion improves lactate clearance. Nguyen and colleagues studied a convenience cohort of patients with severe sepsis and septic shock, examining whether a high lactate clearance at six hours (prior to ICU transfer) was associated with a decreased mortality rate. They found that survivors had a significantly greater lactate clearance than non-survivors (38.1 ± 34.6 vs 12.0 ± 51.6%), respectively. For each 10% increase in lactate clearance, the likelihood of mortality was reduced 11%.[85] These findings helped form the rationale for the randomized clinical trial conducted by Jones and colleagues where severe sepsis and septic shock patients were randomized to resuscitation by an EGDT strategy or one where lactate clearance was substituted for $ScvO_2$ as the third resuscitation goal.[61] They found no difference in these two management strategies in regard to in-hospital mortality. However, only 29/300 (10%) of patients required either a blood transfusion or dobutamine administration to correct abnormalities in either lactate clearance or $ScvO_2$ during the first 6 hours of resuscitation. Furthermore, the patients in this trial had a significantly lower mean lactate level, higher $ScvO_2$ values, and lower illness severity than those in the EGDT trial, suggesting they may not have had as much hypoperfusion; thus, they may be less likely to need manipulation of their oxygen delivery. This limits the conclusions that can be drawn about the use of lactate clearance as a surrogate for $ScvO_2$.

Change in Mental Status. Inflammatory cytokines and inadequate cerebral perfusion are believed to contribute to the altered mental status that can accompany severe sepsis and septic shock. This change in mental status is a marker for increased mortality. Sprung and colleagues performed a retrospective analysis of patients enrolled in the Veterans Administration Systemic Sepsis Cooperative Study of glucocorticoid therapy, a large randomized, double-blind trial demonstrating no efficacy to high-dose corticosteroids. In the retrospective analysis, they examined the relationship between acute change in mental status and mortality. They found that 307/1333 (23%) of patients enrolled in the trial had an acute mental status change and these patients had a mortality of 49% vs. 26% in patients with a normal mental status ($p < .000001$).[86] More recently, Shapiro and colleagues investigating SIRS, sepsis, and organ dysfunctions showed that altered mental status (called neurological organ dysfunction) had a significant effect on increased likelihood of in-hospital death (OR 1.8, 95% CI, 1.2-2.7).[53]

Antimicrobials

Appropriate, timely antimicrobial administration is central to treating the infectious component of the sepsis syndrome and gaining definitive source control. Although we do not have prospective, randomized controlled trial data (nor will we ever), it makes biological sense that the sooner appropriate antimicrobials are given, the better for the patient. The magnitude of the impact of timeliness of antimicrobials is likely directly associated with the patient's severity of illness. Kumar and colleagues published a study of time to antibiotics in a murine model of gram negative, intra-abdominal contamination. Survival duration, hemodynamic responses, circulating inflammatory markers, and lactate levels were assessed in relation to time to antibiotic treatment. The investigators discovered a pattern of inflammation and organ dysfunction, characterized by increasing inflammatory markers, elevation in lactate, and sustained hypotension with a tipping point around 12 hours after the intra-abdominal contamination. When antibiotics were initiated at or before 12 hours, mortality was < 20%. However, when initiated at or after 15 hours, mortality jumped to > 85%. Earlier administration of antibiotics was associated with attenuation of inflammatory markers, decrease in lactate elevation, and less hypotension.[87]

Kumar and colleagues continued to add to this discussion with a retrospective cohort study of 2,731 adults patients with septic shock. Survival to hospital discharge was assessed in relation to duration of hypotension prior to initiation of effective antimicrobial therapy. They discovered a strong relationship between delays to effective antimicrobials and in-hospital mortality. When effective antimicrobials were initiated within the first hour of documented hypotension,

Table 2: Septic Shock Antibiotic Algorithm

* Draw blood cultures from 2 separate sites and obtain other cultures as indicated. * Choose antibiotics based on presence of neutropenia (ANC < 1000) first, then source, if known.		
Source	**No Penicillin Allergy**	**Penicillin Allergy**
Neutropenic * If dialysis dependent give Vanco 1st	1. Pip/Tazobactam 4.5 gm over 30 min 2. Vancomycin 1 gm IV over 60 min	1. Aztreonam 2 gm IV over 30 min 2. Vancomycin 1 gm IV over 60 min
CAP	1. Ceftriaxone 1 gm over 30 min 2. Azithromycin IV over 60 min	1. Moxifloxacin 400 mg IV over 60 min
HCAP	1. Pip/Tazobactam 4.5 gm over 30 min 2. Vancomycin 1 gm IV over 60 min 3. Amikacin 7.5 mg/kg over 30 min	1. Aztreonam 2 gm IV over 30 min 2. Vancomycin 1 gm IV over 60 min 3. Amikacin 7.5 mg/kg over 30 min
Urine	1. Ceftriaxone 1 gm over 30 min	1. Ciprofloxacin 400 mg IV over 60 min
Abdomen	1. Pip/Tazobactam 4.5 gm over 30 min	1. Ciprofloxacin 400 mg IV over 60 min 2. Metronidazole 500 mg IV over 60 min
Skin/Soft Tissue	1. Vancomycin 1 gm IV over 60 min 2. Pip/Tazobactam 4.5 gm over 30 min	1. Vancomycin 1 gm IV over 60 min 2. Ciprofloxacin 400 mg IV over 60 min 3. Metronidazole 500 mg IV over 60 min
Unknown * If dialysis dependent give Vanco 1st	1. Pip/Tazobactam 4.5 gm over 30 min 2. Vancomycin 1 gm IV over 60 min	1. Ciprofloxacin 400 mg IV over 60 min 2. Vancomycin 1 gm IV over 60 min 3. Metronidazole 500 mg IV over 60 min
From: Washington Hospital Center, Department of Emergency Medicine		

mortality was 20%. Each hour of delay in antimicrobial administration over the next six hours was associated with an average increase in mortality of 7.6%.[88] While these results are robust, the retrospective nature of this investigation of a heterogeneous group of ICU patients limited the investigators' ability to gauge adequacy of resuscitation, which, as previously discussed, has been demonstrated to have a significant impact on mortality. When patients present to the ED with hemodynamic instability, they require multiple time-consuming initial interventions, including obtaining vascular access and initial fluid resuscitation, which often take precedence over antimicrobial administration.

Gaieski and colleagues attempted to determine the impact of time to antibiotic administration on survival in patients with severe sepsis or septic shock treated with goal-directed resuscitation initiated in the ED. In a cohort of 261 patients, when examining time from triage to appropriate antibiotic administration, mortality was decreased by 13.7% when appropriate antibiotics were administered in < 1 hr vs. > 1 hr (19.5% vs 33.2%; OR, 0.3; 95% confidence interval, 0.11–0.83; p = .02). When examining time from qualification for EGDT to appropriate antibiotics, mortality was reduced by 13.5% when antibiotics were administered in < 1 hr vs. > 1 hr (25.0% vs 38.5%; OR, 0.5; 95% confidence interval, 0.27–0.92; p = .03).[89] These results isolate time to appropriate antimicrobial administration in patients managed with a uniform resuscitation strategy and speak to the importance of making appropriate antimicrobial administration one of the key components of ED resuscitation.

Equally important to antimicrobial timeliness is antimicrobial choice. Select antimicrobials based on patient-specific factors including immunocompetence, allergies, and severity of illness; local antibiotic resistance patterns, ideally regularly updated within the hospital; suspected source; exposure to hospital-acquired organisms; and cost/availability. Creating an antibiogram (*see Table 2*) that takes all of these factors into consideration will help overcome systematic barriers to antibiotic timeliness. After choosing antimicrobials for the antibiogram, consider storing them in the ED medication system to eliminate

delays associated with obtaining medications from the central pharmacy.

When a patient presents in septic shock, the exact source of the infection is often unclear during the proximal phase of management. Without a clear source of infection, it is important to consider all of the possible infectious locations and to administer appropriately broad antimicrobials. This may result in administering a primary, or "anchor," drug that is broad and likely to be effective, and secondary drugs that are focused on specific organisms, including methicillin-resistant *Staphylococcus aureus* and atypical causes of community-acquired pneumonia including Legionella species. It is important to administer the "anchor" drug first, unless organisms only susceptible to the secondary antimicrobials are highly suspected.

Vasopressors

A defining component of septic shock is hypotension, a systolic blood pressure of less than 90 mmHg or a decrease in 40 mmHg from baseline unresponsive to a fluid bolus of 20 cc/kg. After adequate volume resuscitation, or in profound hypotension, vasopressors should be started to ensure organ perfusion. Until recently, surprisingly little data existed to guide selection and use of vasopressors.[90] Dopamine and norepinephrine, both adrenergic agonists, historically have been considered first-line vasopressors.[91] Several small studies have suggested that dopamine is less efficacious and potentially has more associated complications.[92] In a multicenter observational cohort study of 1058 adult ICU patients, Sakr and colleagues demonstrated that dopamine administration was an independent risk factor for ICU mortality in patients with shock.[93] The results of the study prompted a multicenter, randomized trial published in 2010, by De Backer and colleagues. They prospectively compared norepinephrine to dopamine in 1679 patients with shock, 1044 of whom had septic shock, with a primary outcome of rate of death at 28 days; secondary endpoints included the occurrence of adverse events. They found a trend toward an increased rate of death (52.5% vs 48.5%; P=0.10) and significantly more arrhythmic events (24.1% vs 12.4%; p < 0.001) among those treated with dopamine.[94]

Several investigators have described low endogenous vasopressin levels in various forms of shock, including septic shock, and have postulated using vasopressin as a form of hormone replacement therapy. The largest such trial is the Vasopressin and Septic Shock Trial (VASST), a randomized, double-blind trial comparing low-dose vasopressin to norepinephrine in patients with septic shock who already are being treated with norepinephrine. The investigators found no difference between vasopressin and norepinephrine in 28-day mortality rate or rates of serious adverse events. They did, however, note that in the prospectively defined stratum of less severe septic shock (as defined by norepinephrine dosing), the mortality rate was lower in the vasopressin group than in the norepinephrine group (26.5% vs. 35.7%, P=0.05%).[95] While these data are interesting, they do not justify the routine use of vasopressin.

Given the results of these recently published trials, clinicians should consider norepinephrine as the first-line vasopressor in septic shock. Consider starting patients at 2-4 mcg/min and titrating the dose every 10-15 minutes for a goal MAP of 65 mmHg.

Activated Protein C

Because of its antithrombotic, anti-inflammatory, and profibrinolytic properties, clinicians and researchers have been interested in the application of recombinant activated protein C in patients with severe sepsis and septic shock. Bernard and colleagues published results of a large, randomized, double-blind trial (known as the PROWESS trial) using recombinant activated protein C to treat patients with severe sepsis, which demonstrated a reduction in 28-day mortality from 30.8% in the placebo group to 24.7% in the treatment group (p = 0.005).[96] Post-hoc subgroup analysis suggested this mortality benefit was a result of improvements in mortality in the sickest patients (APACHE II > 25). The Food and Drug Administration approved activated protein C for that subgroup of severe sepsis patients. A follow-up study showed no efficacy when activated protein C was used to treat severe sepsis patients with APACHE II scores < 25. The trial was stopped early at interim analysis due to low likelihood of demonstrating a treatment effect.[97] The main question for emergency physicians is whether there is any role for activated protein C in the ED setting. An implementation study, conducted by Nguyen and colleagues, used activated protein C as part of a bundle of ED-based severe sepsis care if patients had an APACHE II score > 25 during their ED stay. Of the 24 patients included in the analysis, eight were treated with activated protein C at the emergency physician's discretion, demonstrating that it is feasible to identify candidates for and administer starting doses of activated protein C in the ED.[98] The role of activated protein C in the management of critically ill sepsis patients during their ED stay remains unclear.

Ventilator Management

More than 40% of oxygen delivery can be utilized by the respiratory muscles in early severe sepsis and septic shock. Under these conditions, the vital organs such as the brain, heart, kidneys, and mesentary are deprived of critical oxygen delivery. Thus, the introduction of mechanical ventilation not only makes physiologic sense but enhances the attainment of the endpoints of EGDT.[78] Many patients with severe sepsis or septic shock develop some form of ALI or its more severe form, ARDS. In a landmark trial published in 2000, investigators studied whether employing a low tidal volume ventilator strategy using 6 cc/kg predicted body weight and plateau pressure of < 30 cm H_2O

is superior to traditional ventilator strategy using 12 cc/kg predicted body weight and plateau pressure of < 50 cm H_2O in patients with ALI or ARDS. The trial was stopped early because mortality was significantly lower in the group treated with lower tidal volumes and plateau pressure (31% vs 39.8%, P=0.007).[99]

In the proximal phase of care, ALI or ARDS may not have developed or may go unrecognized. In high-risk patients with ventilator-dependent severe sepsis, it is reasonable to use low-tidal volume ventilator settings regardless of the presence of established ALI/ARDS. Gajic and colleagues demonstrated a robust association between initial tidal volume and the development of ALI. In their retrospective cohort study of intubated patients without ALI at the onset of ventilation, they noted that one of the main risk factors for development of ALI was the use of large tidal volumes, with an odds ratio of 1.3 for each mL above 6 mL/kg predicted body weight ($p < 0.001$).[100] Strongly consider using low tidal volume ventilation using predicted body weight in septic patients who require mechanical ventilation.

Insulin

There has been a lot of interest in the optimal way to manage blood glucose levels in critically ill patients, including those with sepsis. Initial results from Van den Berghe and colleagues suggested that, in a population of surgical ICU patients, tight glucose control, targeting glucose levels between 80 and 110 mg/dL, reduced ICU mortality from 8.0 to 4.6% ($p = 0.005$), when compared to a normal glucose regimen where insulin was only infused if glucose levels were > 215 mg/dL. These improvements in outcome were the result of decreased mortality in patients whose ICU stays were > 5 days and who had multi-organ dysfunction from a sepsis etiology.[101] Brunkhorst and colleagues further investigated the role of tight glucose control in patients with severe sepsis and demonstrated no mortality benefit and excess episodes of symptomatic hypoglycemia.[102] Taken together, these studies suggest that there is no role for tight glucose management in the care of critically ill sepsis patients; EPs should treat serum glucose levels only when they exceed 215 mg/dL and a reasonable target is a serum glucose of approximately 150 mg/dL.

Steroids

The role of steroids in the management of critically ill sepsis patients is another area with conflicting results and uncertainty. Studies conducted in the 1980s examining the administration of high-dose steroids (up to 3 grams/day of methylprednisolone) to septic shock patients showed no efficacy to the therapy.[103,104] As more knowledge accrued about the physiologic replacement dose (200-300 mg of hydrocortisone per day) in the presence of relative adrenal insufficiency in critical illness, there was renewed interest in examining a role of steroids in treating septic shock. In a randomized, double-blind, placebo-controlled trial, Annane and colleagues gave a seven-day course of low-dose hydrocortisone (50 mg every 6 hours or 200 mg/day) and fludrocortisone to patients with septic shock. In patients with relative adrenal insufficiency (non-responders to cosyntropin stimulation test), the steroid group had lower mortality (63% vs 53%; $p = 0.02$) and more vasopressor-free patients by hospital day 28 (57% vs 40%; $p = 0.01$) than the placebo group.[105] Based upon these results, clinicians started to monitor for adrenal insufficiency and give low-dose steroids to vasopressor-dependent septic shock patients. However, lingering doubts about the applicability of the results of the Annane trial to all patients with septic shock remained. The CORTICUS trial published in 2008 is the latest study that tries to answer the question of steroid effectiveness in septic shock. The results demonstrated no efficacy to corticosteroids in reducing mortality or reversing shock in septic shock patients, regardless of whether they were responders or non-responders to the cosyntropin stimulation test.[106] Do the results of these two studies conflict with one another? The answer is likely no. Annane and colleagues enrolled a sicker group of patients as evidenced by their more rigid inclusion criteria and much higher overall mortality. More importantly for EPs, Annane enrolled patients within three hours of the onset of shock vs. within 72 hours in the CORTICUS trial. While there is no conclusive data to support the use of steroids in all patients with septic shock, the judicious use of hydrocortisone 50 mg intravenous bolus (given once in the ED, then every six hours for 7 days, along with daily fludrocortisone) for patients with ventilator-dependent septic shock and multi-organ dysfunction syndrome is reasonable.

The Outcome Evidence for the Use of Sepsis Bundles

In 2003, leaders from 11 international organizations, including the American College of Emergency Physicians, organized a consensus group called the Surviving Sepsis Campaign (SSC). Their objectives were to increase awareness and improve outcomes in severe sepsis. Their first guidelines were published in 2004 and subsequently revised in 2008.[2,107] Although not universally accepted, they represent a comprehensive summary of sepsis management options bundled into two sets of targets, or "resuscitation" and "management" treatment bundles, to be completed within six and 24 hours, respectively. From the beginning, the SSC planned to formally examine the impact of the guidelines, which they recently completed and published. During the course of a two-year period, the investigators saw a linear increase in bundle compliance and a reduction in hospital mortality (37% to 30.8%, $p = 0.001$).[108] The major limitation of this study is the substantial decrease in database enrollment in the last quarter of this study. In an examination of the literature of more than 3000 patients pre-implementation

and more than 3000 post-implementation, a mortality reduction of 16-18% has been realized in more than 25 publications.[13-46,81] Overall, the decrease in mortality was associated with a decrease in hospital resource consumption and cost (5-day decrease in hospital length of stay).

Summary

Sepsis remains a highly lethal spectrum of disease. Tenets of care for EPs are early recognition, antimicrobial therapy using a hospital-specific antibiogram, source control, risk stratification using organ dysfunction and lactate, and implementing endpoints of resuscitation to guide aggressive volume repletion and vasoactive use, namely norepinephrine. Further refining care by considering judicious use of steroids and activated protein C, moderate glucose control, and low-tidal volume/plateau pressure ventilation may increase the probability of a good outcome for patients. As the father of resuscitation science, Peter Safar, once said, "Critical care is a concept, not a location." It is our responsibility as EPs to understand and deliver critical care to critically ill patients with severe sepsis and septic shock while they are in our EDs.

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Physician CME Questions

121. Sepsis is defined as:
    A. 2 or more SIRS criteria, hypotension, and a confirmed infection
    B. 2 or more SIRS criteria, hypotension, and a suspected infection
    C. 2 or more SIRS criteria, and a suspected or confirmed infection
    D. infection, hypotension, and organ dysfunction

122. Severe sepsis or septic shock is estimated to occur approximately how frequently in the United States?
    A. 5,000 annual cases
    B. 25,000 annual cases
    C. 100,000 annual cases
    D. 750,000 annual cases

123. Patients treated with early goal-directed therapy received:
    A. more intravenous fluids than the control group
    B. quicker antibiotics than the control group
    C. less blood than the control group
    D. less vasopressors than the control group

124. Which of the following is a systemic inflammatory response syndrome (SIRS) criterion?
    A. heart rate < 90 beats per minute
    B. respiratory rate < 20 breaths per minute
    C. systolic blood pressure < 90 mmHg
    D. temperature < 96.8° F (36.0° C)

125. Mikkelsen and colleagues demonstrated that an initial venous lactate > 4 mmol/L in a patient with severe sepsis:
   A. only predicted mortality in the absence of shock
   B. only predicted mortality in the presence of shock
   C. did not predict mortality
   D. predicted mortality independent of the presence of shock

126. Relative to norepinephrine, dopamine use in shock is associated with:
   A. increased in-hospital survival
   B. increased number of arrhythmic events
   C. increased vasopressor free days
   D. increased 28 day survival

127. Low tidal volume ventilation refers to tidal volumes of:
   A. 6 cc/kg predicted body weight
   B. 6 cc/kg actual body weight
   C. 10 cc/kg predicted body weight
   D. 10 cc/kg actual body weight

128. The use of steroids:
   A. is indicated in most patients with sepsis
   B. is not indicated in septic shock
   C. is reasonable in patients with ventilator-dependent septic shock and multiorgan dysfunction syndrome
   D. is reasonable in patients being admitted to the hospital with sepsis or severe sepsis

129. In patients with septic shock, antimicrobials should be:
   A. administered based on recommendations from an infectious disease consultant
   B. given after adequate volume resuscitation
   C. given after a bacterium is isolated and sensitivities confirmed
   D. broad spectrum and given as soon as possible

130. In septic shock, vasopressin:
   A. is considered standard of care
   B. is associated with similar mortality as norepinephrine
   C. has been shown to be superior to dopamine
   D. is associated with a lower mortality vs norepinephrine in the sickest patients

In Future Issues

STEMI and NSTEMI Therapeutic Updates

CME Answer Key

121. C; 122. D; 123. A; 124. D; 125. D; 126. B; 127. A; 128. C; 129. D; 130. B

Correction

The authors and editor wish to correct a statement in the November 8, 2010, issue on ENT Emergencies. On page 283, the statement regarding inflating the nasal balloon to control epistaxis should be corrected to inflate the balloon with saline, and not air. Subscribers can access a corrected pdf of the issue at www.emreports.com.

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