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Sepsis, Severe Sepsis, And Septic Shock: Current Evidence For Emergency Department Management

In the middle of a busy shift, a patient arrives by ambulance from a local long-term care facility with a report of altered mental status. You enter the room to find a chronically ill-appearing 85-year-old man with fever, tachycardia, and hypotension, and it is instantly apparent that this patient is septic. What is not clear is what the source is, what modifications in treatment might be necessary based on preexisting microbial resistance, and which of the array of invasive resuscitation techniques are appropriate when meaningful recovery is questionable and efforts may not be desired by the patient and family. You order IV fluids and broad-spectrum antibiotics; send lab tests, including lactate and cultures of blood, urine, and sputum; and begin to review his extensive history to discuss goals of care with his family and primary doctor.

While reviewing these issues, a 54-year-old woman with a history of asthma is brought straight back from triage with respiratory distress. You listen to her lungs, expecting wheezes, but hear decreased lung sounds at the right base, preserved air movement elsewhere, and her skin radiates heat. Now, on the monitor, she has a heart rate of 135 beats per minute, blood pressure of 90/60 mm Hg, O_2 saturation of 86%, and a temperature of 39.4° C (103°F). You again identify sepsis and instruct your team that you will be using your department's severe sepsis protocol. Equipment for monitoring and procedures is assembled, your staff provides preprinted order and moni-

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CME Objectives

Upon completion of this article, you should be able to:

1. Recognize and differentiate uncomplicated sepsis, severe sepsis, and septic shock.
2. Formulate plans for timely delivery of broad-spectrum empiric antibiotics when presented with a patient with severe sepsis or septic shock.
3. Cite the relevant measurements and be familiar with the techniques required to meet the goals of early goal-directed therapy in sepsis.
4. Develop and implement institutional guidelines and management tools to apply the best practice management of sepsis.

Prior to beginning this activity, see "Physician CME" information on page 24.

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toring flow sheets, and the ICU is alerted. Within an hour, the patient is intubated, has a central line placed, and has received IV fluids, broad-spectrum antibiotics and norepinephrine, and you are pleased to see a MAP of 67 mm Hg, a lactate decreasing from an initial value of 7.0, CVP of 10, and $ScvO_2$ of 78%.

With as many as 700,000 cases of severe sepsis per year in the United States with 500,000 emergency department (ED) presentations, and a mortality of approximately 40%, sepsis presents a significant challenge in healthcare.[1,2] Because of the absence of a single gold standard marker of this disease, attempting to identify evidence to support decision-making is extremely difficult.[3] However, an organized, evidence-based approach can have an immediate impact in reducing morbidity, mortality, and even cost in sepsis care.[4,5] Of sepsis patients initially presenting to the ED, 1 in 5 will remain more than 6 hours, meaning that a majority of the early interventions that have demonstrated short- and long-term improvements are dependent on the emergency clinician's competence.[6] This issue of *Emergency Medicine Practice* will seek to provide an update on the current understanding of sepsis pathophysiology, to place sepsis in the context of clinical decision-making, and to promote early and comprehensive critical care to improve patient outcomes.

Table Of Contents

Available Online At No Charge To Subscribers

EM Practice Guidelines Update: "Current Guidelines For ED Management Of Patients With Acetaminophen Overdose," www.ebmedicine.net/APAPOD

Abbreviations And Acronyms

ARDS: Acute respiratory distress syndrome
APACHE: Acute Physiology and Chronic Health Evaluation
BNP: B-type natriuretic peptide
CORTICUS: Corticosteroid Therapy of Septic Shock study
CRRT: Continuous renal replacement therapy
CVP: Central venous pressure
DIC: Disseminated intravascular coagulation
DVT: Deep venous thrombosis
EGDT: Early goal-directed therapy
FiO_2: Fractional inspired oxygen
LMWH: Low-molecular-weight heparin
LVEF: Left ventricular ejection fraction
MAP: Mean arterial pressure
MEDS: Mortality in Emergency Department Sepsis
MRSA: Methicillin-resistant *Staphylococcus aureus*
NIPPV: Noninvasive positive pressure ventilation
PEEP: Positive end-expiratory pressure
PT: Prothrombin time
PTT: Partial thromboplastin time
rhAPC: Recombinant human activated protein c
SaO_2: Arterial oxygen saturation
$ScvO_2$: Central venous oxygen saturation
SIRS: Systemic inflammatory response syndrome
SOFA: Sequential Organ Failure Assessment score
SvO_2: Mixed venous oxygen saturation
TNF-alpha: tumor necrosis factor-alpha

Critical Appraisal Of The Literature

There is abundant basic science as well as clinical research, reviews, consensus statements, and related guidelines pertaining to sepsis. Among the most prominent of the consensus statements is the Surviving Sepsis Campaign®, a collaborative effort of the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the International Sepsis Forum.[7] This consensus document was most recently updated in 2008, provides one model for an organized, collaborative approach, and has demonstrated improvements in mortality.[4] Varying levels of evidence inform the statements of the Surviving Sepsis Campaign® guidelines; however, the guidelines clearly state that consensus was one of the primary missions. Levels of evidence used for the recommendations fall into the following classes:

Class I: Large, randomized controlled trials, meta-analysis, repeated results
Class II: Controlled trials and large observational studies
Class III: Consensus statements, small trials

The Society for Critical Care Medicine and the American College of Chest Physicians defined sepsis 20 years ago as the presence of infection and the

systemic inflammatory response syndrome (SIRS).[8] More recently, the European and North American Intensive Care Societies proposed a new definition of sepsis, including identification of severe sepsis and septic shock.[3] These definitions are generally straightforward to apply in clinical settings and do have prognostic value, but they are the result of consensus statements and may not necessarily represent discrete pathophysiologic states. For the purposes of this article, clinical guidelines and consensus statements were reviewed, and their supporting literature was reviewed for its relevance and validity. A search of the Cochrane Database of Systematic Reviews and a separate search of the Cochrane Database of Trials for reviews and trials related to sepsis was also completed. An Ovid MEDLINE® search for sepsis, severe sepsis, and septic shock was also completed, with filters for evidence-based medicine reviews and most recent updates. Discrete searches for clarification of pathophysiology and management were also required.

Pathophysiology

A current sepsis definition, outlined in **Table 1**, requires documented or clinical suspicion of infection and the presence of "some" of the listed hemodynamic, laboratory, or physical findings.[3] While a gold standard of diagnosis is currently lacking, basic science research has identified patterns of inflammatory response that appear unique to sepsis and could potentially lead to a refined set of diagnostic criteria.

The inflammatory, immune, coagulation, and complement cascades that fan a localized infection into a conflagration of multiorgan, systemic disease is a critical area of basic science research.[9-13] In the first stages of infection, either Gram-negative bacteria lipopolysaccharide or the Gram-positive cell wall component lipoteichoic acid prompt monocytes to differentiate into macrophages that release proinflammatory cytokines.[14] Increases in monocyte expression of tumor necrosis factor alpha (TNF-alpha) and of high-mobility group box 1 (HMGB1) in response to both invading pathogens and endogenous toxins seems to be one of the important early and late mechanisms in sepsis.[15] Dysfunctional macrophages produce an abundant early release of proinflammatory cytokines with a quick taper to inappropriately low levels.[13,14] The presence of microbes, injured tissue, and cytokines elicited in the initial immune response signal neutrophils to accumulate. Clearance of microbes and injured tissue normally signals neutrophils to initiate the apoptotic pathway and thereby terminate the inflammatory/immune response.[16] Dysfunction of this programmed cell death leads to abnormally long-lived, persistently proinflammatory neutrophils, releasing injurious oxygen metabolites and other toxic substances.[16] At the same time, and potentially even within the same cell, there are additional complement-induced impairments of neutrophil function.[17] The combination of excessive and prolonged activation and impaired function leads to abundant tissue injury, yet an inability to effectively clear pathogens. Microbes, flourishing in the absence of appropriate immune function, provide signals for continued response from the immune and inflammatory system. In contrast to abnormally long-lived neutrophils, there is inappropriately rapid lymphocyte apoptosis, limiting adaptive immunity and failing to produce cytokines that could balance an immune response.[18] The signaling cytokines in the inflammatory and immune response are among the nearly 100 serum biomarkers proposed as possible diagnostic tools in sepsis.[19]

Plasma cytokines, immune cells, and nitric oxide exert their effects in sepsis primarily via interaction

Table 1. Diagnostic Criteria For Sepsis

Documented or suspected infection and some of the following:

- Hyperthermia (temperature > 38.3°C [100.4°F])
- Hypothermia (temperature < 36°C [96.8°F])
- Tachycardia (heart rate > 90/ minute)
- Tachypnea (respiratory rate > 20/ minute)
- Acutely altered mental status
- Hyperglycemia (glucose > 120 mg/dL) in the absence of diabetes
- Significant edema (> 20 mL/ kg positive fluid balance in 24 hours)

Signs of Inflammation

- Leukocytosis (WBC > 12,000/mm^3) or > 10% immature forms
- Leukopenia (WBC < 4000/mm^3)
- C-reactive protein > 2 SD above normal
- Plasma procalcitonin > 2 SD above normal

Hemodynamics

- Hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg)
- SvO_2 > 70%
- Cardiac index > 3.5 L/ min/ m^2

Organ Dysfunction

- Arterial hypoxemia (PaO_2/ FiO_2 < 300)
- Acute oliguria (urine output < 0.5 mL/kg/h for at least 2 hours
- Creatinine increase > 0.5 mg/dL
- Coagulopathy (INR > 1.5 or PTT > 60 sec)
- Ileus
- Thrombocytopenia (platelet count < 100,000 mm^3)
- Hyperbilirubinemia (bilirubin > 4 mg/dL)

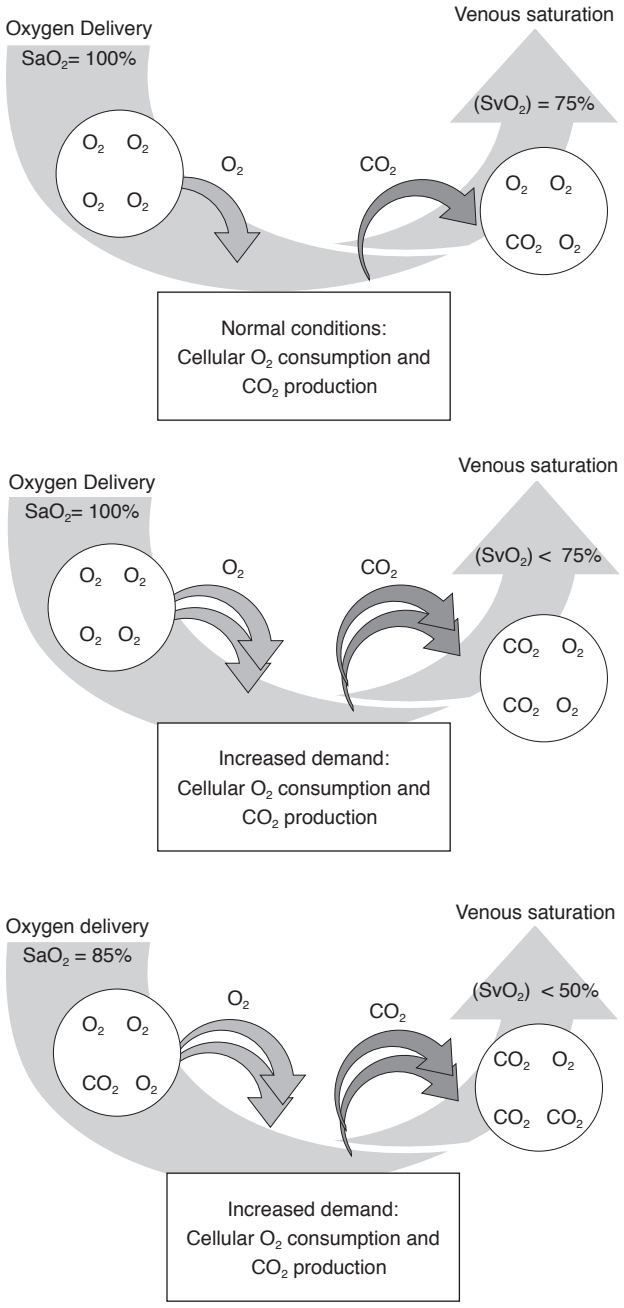
Tissue Perfusion Variables

- Lactate > 2 mmol/L
- Decreased capillary refill or mottling

Abbreviations: FiO_2, fractional inspired oxygen; h, hour; INR, international normalized ratio; MAP, mean arterial pressure; PTT, partial thromboplastin time; SBP, systolic blood pressure; SD, standard deviation; sec, seconds; SvO_2, mixed venous oxygen saturation; WBC, white blood cells.

with the vascular endothelium leading to increased vascular permeability.[20] The endothelium is also metabolically active, producing chemical signals that further affect inflammation and coagulation in the presence of the pro-inflammatory cytokines Il-1, IL-6 and TNF-alpha.[21] The natural anticoagulants, activated protein C (APC) and antithrombin III, while initially activated in sepsis, are quickly depleted.[22] The observation that the depletion of APC is associated with increased mortality in sepsis led to development of a therapy aimed at boosting this anticoagulant. Similar therapeutics were attempted for antithrombin III.[23,24] All of the above inflammatory and coagulation pathways eventually lead to vascular dilation, thrombosis, and capillary leak, which lead to tissue ischemia.[13]

Figure 1. The Effect Of Oxygen Delivery And Tissue Utilization On Venous Oxygen Saturation



Abbreviations: SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.

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Tissue ischemia and impaired oxygen delivery and utilization at the cellular level are some of the key concepts in understanding the evolution and management of sepsis.[12] **(See Figure 1.)** Hypoxia at the cellular level leads to further activation of the proinflammatory pathway and further derangement of endothelium.[25] Oxygen consumption in excess of the oxygen available for metabolic demands leads the cells to anaerobic metabolism and begins to generate lactic acid. In the ED, therapy to maintain hemodynamics is intended to optimize oxygen delivery and, when possible, minimize metabolic demand.[26]

In addition to the peripheral and microvascular derangements, hemodynamics can be compromised by direct myocardial dysfunction via circulating myocardial depressants (TNF-alpha and IL-1 beta are likely involved), leading to a decline in cardiac index.[27,28] Within the myocardium, various cytokines and nitric oxide lead to impaired electromechanical coupling at the myofibrillar level, impaired calcium transport, depressed postreceptor signaling pathways, and down-regulated beta-adrenergic receptors.[29] The eventual outcome is a transient, nonstructural, biventricular impairment of contractility that depresses ventricular stroke work index and ejection fraction.[27] Myocardial dysfunction and recovery are amongst the most important prognostic factors in patients with sepsis.[30] Elevated cardiac troponin in sepsis is likely related to loss in membrane integrity or microvascular thrombotic injury in patients without flow-limiting epicardial coronary vessel disease.[31] Pro-brain natriuretic peptide (BNP) can also be elevated in sepsis similar to increases seen in congestive heart failure.[32]

The pathophysiology of shock is complex and variable. The essential common elements include exposure to invasive pathogens, inappropriate initial immune response, and ongoing destruction via interactions of endothelium, nitric oxide, inflammatory cytokines, and the coagulation and complement cascades all leading to vascular derangement and impaired oxygen delivery. An understanding of this pathophysiology informs management of oxygen delivery and hemodynamics early in serious infection, which may prevent development of further tissue hypoxia, excessive inflammation, cardiovascular compromise, and remote organ dysfunction.

Epidemiology

Large reviews identifying cases based on International Classification of Diseases, Ninth Revision (ICD-9) codes show an ongoing increase in the incidence of sepsis in general as well as severe sepsis.[1] A longitudinal study demonstrated nearly 900,000 cases of sepsis in 2003, with nearly 400,000 cases of severe sepsis (135 cases of severe sepsis per 100,000 population).[33] Overall mortality for severe sepsis has decreased over the last 20 years from approximately 28% to 18%, but the increase in incidence has resulted in an increase in the total number of deaths.[34] Pneumonia is the most commonly identified infection leading to sepsis.[35] Men, diabetics, and nonwhites more commonly develop sepsis, and sepsis-related mortality is highest amongst black men.[36] Age is an independent predictor of decreased survival, with patients over 65 years more likely to die earlier in hospital stays and more likely to be discharged to a skilled nursing facility if they survive.[37]

The development of worsening sepsis leads to increases in mortality with in-hospital mortality of 16% in uncomplicated sepsis, 20% for patients with severe sepsis, and 46% for patients in septic shock.[33] One study of 3762 ED patients in whom blood cultures were drawn showed isolated infection in 45%, sepsis in 29%, severe sepsis in 24%, and septic shock in 1.3%.[38] A decade ago, the majority of care for sepsis occurred in tertiary referral hospitals, and the care of severe sepsis and septic shock outside of these centers was uncommon. It continues to be true that urban, teaching centers receive the highest volumes of sepsis patients and patients with the most comorbidities.[39] As survival has improved and length of hospital stays have shortened, more patients are cared for postrecovery in skilled nursing facilities.[33]

Differential Diagnosis

Table 2 displays a differential diagnosis for sepsis, severe sepsis, and septic shock, including several serious cardiopulmonary, neurologic, and metabolic diseases. In milder disease, one needs to differentiate simple bacterial infection from infection with systemic response. With more severe disease, the emergency clinician must initiate a careful investigation to differentiate causes of shock or noninfectious tissue injury such as trauma, pancreatitis, or acute respiratory distress syndrome (ARDS). A common difficult scenario can occur when distinguishing sepsis from cardiogenic shock in a patient presenting with dyspnea, peripheral edema, and mental status change. The septic patient may not generate a fever or hyperdynamic response due to age, poor cardiac output, or volume depletion.[36] Further confusion could come from an elevated troponin and BNP.[32] Often it is the worsening clinical condition in spite of interventions directed at other possible causes that point to the diagnosis of sepsis.[40]

Prehospital Care

The first few hours of a hospital stay are critical to eventual outcomes, so extending that care to the prehospital setting might be advantageous but has not been well-studied. Initial responders should give supplemental oxygen, consider intravenous (IV) crystalloid, and apply a cardiac monitor. For severely ill patients, intubation for airway control and volume resuscitation to maintain blood pressure in the field may be necessary.

Table 2. Differential Diagnosis For Sepsis, Severe Sepsis, And Septic Shock

Infectious
- Pneumonia
- Urinary tract infection
- Meningitis
- Epidural abscess

Cardiovascular
- Congestive heart failure
- Cardiogenic shock
- Myocardial infarction

Neurological
- Subarachnoid hemorrhage
- Encephalopathy

Pulmonary
- Acute respiratory distress syndrome
- Pulmonary embolism

Tissue Injury
- Pancreatitis
- Trauma
- Transplant rejection

Metabolic
- Thyroid storm
- Acute adrenal collapse
- Tumor lysis syndrome
- Anaphylaxis
- Overdose
- Diabetic ketoacidosis

Iatrogenic
- Blood product reaction
- Anesthesia related
- Neuroleptic malignant syndrome

Emergency Department Evaluation

Initial Assessment

In unstable patients, evaluation and management should begin immediately with IV access, supplemental oxygen, cardiac monitoring, and pulse oximetry. Depressed mental status, respiratory distress, or evidence of respiratory fatigue should prompt immediate airway management. For severely ill patients, central venous access should be established for central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) to guide resuscitation and management.[7] Most patients, however, do not present in extremis. Triage personnel should pay careful attention to the presence of fever, tachycardia, tachypnea, comorbid illness, and advanced age.[38]

History

Fever, dyspnea, and general weakness are the most common triad of complaints but occur in only a quarter of patients.[38] The presence of dyspnea should be a concerning feature, as hypoxia and tachypnea are independent risk factors for increased mortality.[38] Nursing home residents and patients with altered mental status are more likely to progress to sepsis after initial infection.[37] Prevailing seasonal infectious patterns in the surrounding community also impact the etiology of infections.[41] Other relevant history includes malignancy, alcohol dependence, chemotherapy, and immunosuppression (ie, transplant, HIV).[1,33,42] The current or recent presence of urinary catheters and indwelling vascular devices should be elicited.[43] Patients, caregivers, or emergency medical services should be questioned regarding trauma or toxic exposures.[40]

Physical Examination

The patient's general appearance, including rapid assessment of airway, breathing, and circulation, may reveal much to an experienced clinician. Fever, tachycardia, hypotension, and tachypnea may be present; however, vital signs can be normal early in the illness,[40] and up to 30% of elderly patients will have absent or blunted febrile response.[44]

Further examination should focus on the cardiopulmonary system, volume status, mental status, and sources of infection.[40] In addition to respiratory rate and oxygen saturation, the pulmonary examination should assess for the presence of rales, symmetry of air movement, and work of breathing.[35] The cardiovascular examination should include skin temperature, color, and capillary refill as well as pulses and auscultation. The hypotensive, flushed, warm, ill-appearing patient with a bounding pulse from widened pulse pressure is very likely to be septic. An assessment of volume status should include skin turgor, mucus membranes, jugular venous distension, and the presence of edema. The abdominal examination should assess for masses, tenderness, or rigidity. The neurologic examination should focus on potential evidence of central nervous system (CNS) infection such as mental status change and nuchal rigidity. Other than finding intravascular devices, urinary catheters, and necrotic tissue, the presence of audible rales, abdominal tenderness, or signs of CNS infection are the most useful physical findings in predicting sources for infection.[43,45,46]

Diagnostic Studies

Complete Blood Count

The presence of an elevated (> 12,000/mm^3 or > 10% immature forms) or depressed (< 4000/mm^3) white blood cell count is a SIRS criterion and is routinely found in sepsis; however, it offers little prognostic information unless there is profound neutropenia.[8] Sepsis management requires optimizing oxygen delivery, including maintaining carrying capacity, so hemoglobin should be included in initial laboratory evaluation (Class II).[7,26] Peripheral blood smear may show evidence of microangiopathic hemolytic anemia in the setting of disseminated intravascular coagulation (DIC).[47] Thrombocytopenia (platelets < 100,000/mL) is a sign of organ dysfunction and may indicate severe sepsis (Class II).[48]

Chemistries And Creatinine (Comprehensive Metabolic Panel)

Absolute elevation or relative increase (> 0.5 mg/dL) from known baseline creatinine level may signal acute kidney injury and may confirm or support the diagnosis of sepsis as evidence of organ dysfunction. Serum electrolytes should be assessed, because they may be deranged even in the setting of normal pH and because they are used in some calculated illness severity scores.[49] Acidemia from lactic acid production can produce an anion gap or decrease in bicarbonate value; however, a normal anion gap or bicarbonate does not preclude an elevation in lactate.[50] Liver transaminases, bilirubin and prothrombin time (PT)/ international normalized ratio (INR) should be evaluated as a test of hepatic dysfunction (Class III).

Urinalysis

Urinalysis is quick, inexpensive, noninvasive, and high-yield, because the urinary tract is the most common source of sepsis in patients over 65.[1] Urine should be collected for ED urinalysis of every patient with possible sepsis, formal microanalysis, and culture (Class III).

Lactate

Elevation of lactate in severe sepsis is correlated with increased mortality independent of shock or organ failure,[50] and early clearance of lactate is associ-

ated with improved mortality.[51] In an observational study of 166 patients, nonclearance of lactate was associated with a 60% mortality rate, while patients that had 10% or greater decrease on repeat measurements within 6 hours had a mortality of 19% ($P < 0.001$).[52] Peripheral venous lactate or arterial lactate measurement can be used.[53] Lactate can also be rapidly and accurately assessed with blood sampling from finger stick and a point-of-care testing device.[54] In the appropriate clinical setting, a serum lactate greater than or equal to 4 mmol/L strongly suggests a diagnosis of severe sepsis.[3] For patients with suspicion of sepsis, a rapid measurement of lactate should be made upon initial presentation and again within 6 hours of starting resuscitation as clinical conditions change (Class II).

Arterial Blood Gas

Although the presence of profound acidemia and acidosis has prognostic value, very little of the initial management of sepsis relies on information derived from a blood gas.[7,49] When there are signs of respiratory difficulty, it may be useful to determine the presence of hypercarbia and, after intubation, to follow the adequacy of ventilation. Given the many possible metabolic derangements possible in sepsis, normal or abnormal pH should not preclude directly testing lactate (Class III).[52]

Coagulation Markers

While not uniformly abnormal in sepsis, the laboratory presence of coagulopathy is related to poor outcome.[47,48] Prothrombin time and partial thromboplastin time (PTT) should be checked in all patients with severe sepsis and septic shock. Disseminated intravascular coagulation (DIC) occurs more commonly in Gram-negative sepsis, is associated with higher mortality, and is typically identified by decreased platelets, microangiopathic hemolytic anemia (ie, decreased hematocrit and shistocytes on peripheral smear), elevated fibrin split products, and decreased fibrinogen.[47] One simplified DIC score with good prognostic power requires only a platelet count and PT at the initial evaluation and one later interval (Class III).[55]

Cardiac Markers

Cardiac troponin and BNP are often elevated in cases of severe sepsis and septic shock.[31] As the critical organ in oxygen delivery, depressed cardiac function can profoundly worsen sepsis. In a retrospective study of 1036 patients, the recovery of cardiac function within 1 day of developing organ dysfunction was the single strongest predictor of good outcome.[30] In a prospective study of 75 patients, similar elevations of BNP were seen in severe sepsis and congestive heart failure, indicating that it may have prognostic value.[32] It is not clear yet what role BNP may play in ED evaluation of the septic patient but its rapidity and availability in many EDs make it an interesting area of future study (Class III).

Cultures

Expert consensus guidelines recommend performing blood cultures in all patients with suspected sepsis in order to identify bacteremia and narrow antibiotic choice.[7] Patients with positive blood cultures have a higher mortality.[33] A prospectively derived and validated rule, summarized in **Table 3**, suggests one possible decision path to draw cultures as they are not useful in patients with simple infection.[56] Using this decision rule, less than 1% of patients in the low-risk group had positive cultures. A total of 20 mL of blood should be drawn for cultures, as the number of sites is less important than total volume.[57] Cultures should be collected from every likely available infectious source, including sputum, urine, wound, catheters, and cerebrospinal fluid in the proper context.[58] Institutional rules for blood draws for culture should be developed in conjunction with microbiology to establish a practical, consistent, and effective protocol (Class III).[59]

Biomarkers

Nearly 100 biomarkers have been identified and studied in sepsis, many of which have demonstrated impressive prognostic accuracy. While few are well-standardized or readily available in the ED, powerful diagnostics tools may be on the horizon.[60,61]

Central Venous Oxygen Saturation

Decreases in $ScvO_2$ indicate a high percentage of extraction of oxygen from arterial blood by meta-

Table 3. Proposed Screening Tool For Blood Cultures[56]

Major Criteria
- Temperature > 39.5°C (103°F)
- Indwelling catheter
- Suspicion of endocarditis

Minor Criteria
- Temperature 38.4°C-39.4°C (101°F-102.9°F)
- Age > 65 years
- Hypotension (SBP < 90 mm Hg)
- Chills
- Vomiting

Laboratory data
- White blood cells > 18,000
- Bands > 5%
- Platelets < 150,000

Abbreviation: SBP, systolic blood pressure.
Note: Blood cultures should be drawn from patients with 1 major or 2 minor criteria (sensitivity 97%).

bolically demanding tissues. Detection of low $ScvO_2$ and resuscitation to normalize to 70% or higher is a central part of early goal-directed therapy (EGDT).[26] $ScvO_2$ can be measured continuously by catheter probe or intermittently by blood drawn from a centrally placed catheter and should be included in the evaluation of all patients with severe sepsis and septic shock (Class II).[7,61]

Central Venous Pressure

In the study by Rivers describing EGDT, obtaining a CVP of 8-12 cm H_2O by volume resuscitation was a primary endpoint.[26] However, in the initial trial there was not a difference in CVP measured in the control and intervention groups. A retrospective study of 96 patients demonstrated no value in using CVP to predict the improvement of cardiac output in response to fluid challenge.[62] The combination of CVP with pulmonary artery occlusion pressure did not improve the predictive power of cardiac filling parameters in predicting which patients respond to infusing IV fluids.[62] Still, current recommendations support the routine placement of central venous access and measurement of CVP in patients with severe sepsis and septic shock (Class III).[7,26,61] There is some developing evidence that dynamic measurements of preload may be superior. In a small study of mechanically ventilated patients, ultrasound measurements of dynamic change in inferior vena cava (IVC) diameter correlated with more invasive measures including CVP, extravascular lung water index, intrathoracic blood volume index, intrathoracic thermal volume, and the PaO_2/FiO_2 oxygenation index.[63] Emergency clinicians' familiarity with ultrasound provides an opportunity for leadership in developing dynamic IVC ultrasound as a reliable adjunct to sepsis management and as a replacement for invasive static measurement of CVP.

Imaging Tests

Chest x-ray should be obtained in every patient suspected of having sepsis, because pneumonia is the most commonly identified infection leading to sepsis.[35] Chest computed tomography (CT) may be necessary to differentiate pulmonary embolism, and CT may be needed to evaluate for CNS infection, abdominal source, or deep-tissue abscess.[40]

Illness Severity Scores

The majority of research protocols use a calculated metric to determine illness severity. The Acute Physiology and Chronic Health Evaluation (APACHE) score is one of the most commonly used in research protocols.[49] The APACHE metric has a dozen physiologic measurements, although calculators require the entry of more than 30 data points. In a study of 81 patients, the APACHE II score changed rapidly in the first few hours in the ED, and its ability to accurately predict mortality was not apparent until 12 hours after ED arrival.[64]

The Mortality in Emergency Department Sepsis (MEDS) score **(see Table 4)** uses 9 historical, examination, and laboratory findings in a simple additive point scale.[65] The MEDS score is limited in its ability to parse out mortality along as broad a spectrum as APACHE II, but it does identify a group of patients at "high risk of death;" a MEDS score greater than 15 has a predicted mortality of 50%, approximately the same as an APACHE II score of 25 or higher. The MEDS score has been shown to predict outcomes at 28 days.[66] Subsequent studies and meta-analysis have been less positive, however, concluding that the MEDS score performs reasonably well at predicting mortality versus individual biomarkers and other sepsis scoring but is less powerful in predicting mortality within the group with severe sepsis.[6]

Summary Of Diagnostic Studies Recommendations

In conclusion, for patients with suspected sepsis, acquire a complete blood count; a comprehensive metabolic panel including electrolytes, liver panel, and creatinine; coagulation studies (PT/INR and PTT); lactate; blood cultures, urinalysis and urine culture; cultures of any indwelling device; troponin; and chest x-ray with additional imaging as needed. If there is strong suspicion of severe sepsis or septic shock, or if the lactate is elevated, a central line should be placed for the additional tests of CVP and $ScvO_2$. Low platelets, elevated INR, or bleeding problems should prompt an investigation for DIC with fibrinogen and fibrin split products (Class III).

Table 4. Mortality In Emergency Department Sepsis (MEDS) Score[65]

Historical Or Physiologic Variable	Points
Terminal illness (< 30 days expected survival)	6
Tachypnea or hypoxia	3
Septic shock	3
Platelets < 150,000/mm^3	3
Bands > 5%	3
Age > 65	3
Lower respiratory infection	2
Nursing home resident	2
Altered mental status	2
Predicted Mortality (28 Days)	**Point Totals**
1%	0-4
2% to 4%	5-7
7% to 9%	8-12
15% to 20%	13-15
40% to 50%	> 15

Treatment

The majority of patients with sepsis without signs of organ failure are admitted to general medicine wards and have minor systemic disturbances requiring vigilance but not necessarily aggressive interventions.[1,68] There continues to be disagreement about optimal diagnosis and management of sepsis, perhaps due to the heterogeneity of sepsis physiology; therefore, little of the evidence even from very large trials and meta-analysis can be used to support the highest levels of recommendations. Nonetheless, there is clear evidence that organizational effort can improve care. A study of 400 patients before and after implementation of a hospital-wide protocol demonstrated an increase in appropriate antibiotics, decreased organ failure, and improved survival.[69] The Surviving Sepsis Campaign® guideline committee evaluated just over 15,000 patients in hospitals that adapted hospital-wide protocols and found improved survival that persisted and further improved the longer a hospital participated.[4] Experience seems to matter, as EDs with the highest volume of patients with severe sepsis and septic shock seemed to have the best performance (in terms of mortality), despite having patients with more comorbidities.[39]

Initial Resuscitation

Patients with severe sepsis and septic shock need rapid stabilization with management of airway and breathing as well as establishment of IV access for fluid resuscitation and possibly blood products and vasoactive medications. **(See the Clinical Pathway For Initial Resuscitation Of Severe Sepsis, page 12.)** In the decade since publication of Dr. Emanuel Rivers' original *New England Journal of Medicine* article describing EGDT, the strategy has been widely incorporated into consensus guidelines and applied in practice.[7] A meta-analysis of almost 6000 patients treated with EGDT concluded clear mortality benefit, with a number needed to treat of only 6 for a life saved.[70] The presence of hypotension (MAP < 65 mm Hg) after initial fluid challenge, elevated lactate (> 4 mmol/L), clinical evidence of hypoperfusion, or organ failure strongly suggests severe sepsis or septic shock and should lead to rapid institution of intervention, including EGDT (Class II).

Antimicrobials

Time-to-antibiotics is a primary determinant of mortality, with a clear benefit for those patients receiving appropriate broad-spectrum antibiotics within an hour of identification of severe sepsis or septic shock.[71,72] Guidelines for appropriate antibiotics for initial ED therapy should be developed in individual institutions in conjunction with microbiology and infectious disease departments, taking into account local patterns of resistance and availability.[7] **Table 5 (see page 10)** presents a proposed selection of empiric antibiotics (Class III).[73]

Source Control

Source control, which is the physical removal of a potential ongoing source of microbes, necrotic tissue, and the associated inflammatory cells, should be done when possible.[45] Methods of source control include abscess drainage and debridement of necrotic tissue in skin and soft tissue infections, with amputation in extreme cases. Abscess drainage should be undertaken percutaneously, when possible. Any indwelling vascular devices should be carefully examined, and if there are skin changes around the device that suggest infection, the device should be removed and sent for culture. If left in place, blood cultures indicating the device or vascular site should be sent. If the skin is intact and does not appear infected, vascular catheters can be changed over a wire (Class III).[45] Indwelling urinary catheters should be replaced, with urine cultures collected from a newly placed catheter (Class II).[45]

Even though vascular access devices are common nosocomial sources of infection, all patients with severe sepsis or septic shock should have central venous access. The use of chlorhexadine scrubs instead of povidone-iodine, antimicrobial impregnated catheters, and institutionally enforced improvements in sterile technique are capable of significantly reducing or eliminating catheter-associated infections.[78,79] Unless placed in a truly emergent situation, central venous access should be placed in patients with severe sepsis or septic shock only after hand washing, and with cap, gown, and full sterile preparations (Class II).[78]

Hemodynamic Management: Early Goal-Directed Therapy

Most patients with sepsis will be volume-dependent in the initial stages of sepsis and will likely need an initial fluid challenge of 1-2 L of fluid.[80] Patients without severe sepsis will often respond to this initial fluid, normalizing blood pressure, oxygen delivery, and organ function. For severe sepsis and septic shock, fluid resuscitation and optimization of oxygen delivery require the placement of a central venous catheter and measurement of CVP and $ScvO_2$. After an initial bolus, the fluid therapy should be guided toward establishing and maintaining a CVP of 8-12 cm H_2O.[26] There has been no demonstrated difference in outcomes whether crystalloid or colloid was used in resuscitation.[81] Low venous saturations, indicated by $ScvO_2$ less than 70%, indicate metabolically active tissues extracting a high percentage of available oxygen, hypoxemia, diminished oxygen carrying capacity, or low cardiac output. As shown in **Figure 1 (see page 4)**, lower amounts of delivered oxygen (due to low arterial saturation or low

hemoglobin) can be reflected in low venous oxygen saturation after abundant tissue oxygen extraction. Oxygen delivery can be improved by supplemental O_2 and by transfusing packed red blood cells to achieve a hematocrit of greater than or equal to 30% if $ScvO_2$ is less than 70% (Class II).[26]

If the goal of $ScvO_2$ of 70% is not achieved despite CVP 8-12 cm H_2O and hematocrit of 30% or greater, inotropes can be added to increase cardiac output, specifically, dobutamine in doses starting at 2.5 mcg/kg min and increasing to a maximum of 20 mcg/kg min (Class II).[6,26] Higher doses and attempts to maximize cardiac output any further or to reach a preset cardiac index are not effective.[78] New tachycardia or heart rates above 120 should prompt discontinuation of dobutamine.[61] Drops in blood pressure when initiating dobutamine often indicate inadequate preload, and volume resuscitation should be considered. Transfusion of red blood cells to improve oxygen-carrying capacity and improve cardiac output with inotropes can effectively reverse tissue hypoxia, as reflected in improved $ScvO_2$ and

Table 5. Antimicrobial Therapy For Severe Sepsis And Septic Shock (Class III)

Source	Initial Antibiotic Choice
Unknown*	Carbapenem (imipenem/cilastin 500 mg IV every 6 h) ***Or*** Third- or fourth-generation cephalosporin (ceftazidime 1 g IV every 8 h) ***Or*** Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h)
Community-acquired pneumonia[74]	Beta-lactam (ceftriaxone 1 g IV every 12 h) ***Plus*** Respiratory quinolone (moxifloxacin 400 mg IV every 24 h) ***Or*** Macrolide (azithromycin 500 mg IV every 24 hours) **For penicillin-allergic patients:** Aztreonam 1-2 g IV every 8-12 h ***Plus*** Respiratory quinolone (moxifloxacin 400 mg IV every 24 h)
Hospital-acquired, healthcare- or ventilator-associated pneumonia[75]	Anti-pseudomonal cephalosporin (ceftazidime 1 g IV every 8 h) ***Or*** Carbapenem (imipenem/cilastin 500 mg IV every 6 h) ***Or*** Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h) ***Plus*** Anti-pseudomonal fluoroquinolone (levofloxacin 750 mg IV every 12 h) ***Or*** Aminoglycoside (amikacin 7.5 mg/kg IV every 12 h)
Urinary tract[76]	Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h) ***Or*** Carbapenem (imipenem/cilastin 500 mg IV every 6 h)
Abdominal[77]	Carbapenem (meropenem 1 g IV every 8 h) ***Or*** Tigecycline 50 mg IV every 12 h after a 100 mg initial dose
Skin/soft tissue[77]	Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h)
For all above, institutions/ communities with resistant Gram-positive bacteria (ie, MRSA) should consider:	Glycopeptide (vancomycin 1 g IV every 12 h) ***Or*** Oxazolidinone (linezolid 600 mg IV every 12 h)
Fungal infection†[73]	Azole (fluconazole 400 mg IV every 24 h) ***Or*** Echinocandins (caspofungin 70 mg IV on day 1, then 50 mg IV every 24 h)

Note: Recommended drug classes are listed and examples included in parenthesis for illustration, not as a recommendation of a particular agent.

* Monotherapy is as efficacious as combination therapy with beta-lactam and aminoglycoside.[73]

†Empiric antifungal therapy limited to patients at high risk (current/recent broad spectrum antibiotics, colonized with *Candida* at several sites, damaged physiologic barriers, immunosuppression.[73]

Abbreviations: g, gram; h, hour; IV, intravenously; mg, milligram; MRSA, methicillin-resistant *Staphylococcus aureus.*

decreased lactate in the early, delivery-dependent phase of sepsis. In a randomized trial of 300 patients, additional management to normalize lactate after normalization of $ScvO_2$ did not improve mortality.[83] In direct contrast, a prospective cohort study of 166 patients demonstrated a large percentage of patients that did not clear lactate and had increased mortality despite normalized $ScvO_2$.[52] Further study is needed to answer this particular question.

In the original EGDT study,[26] hypotension persisting after CVP goals were met was treated with dopamine or norepinephrine to maintain a mean arterial pressure (MAP) above 65 mm Hg. A recently published multicenter trial by De Backer et al (SOAP II) randomized 1679 patients with shock to norepinephrine or dopamine. The 2 vasopressors were equally efficacious at reversing hypotension with similar overall IV fluid volumes, additional pressors, and inotropes, and overall mortality was not significantly different at 28 days, 6 months, or 12 months.[84] However, there were significantly more adverse events with dopamine, primarily arrhythmias. In subgroup analysis of patients receiving steroids with dopamine, there was a statistically significant increase in mortality versus norepinephrine (55.8% vs 48.8%; odds ratio [OR] 1.33; 95% confidence interval [CI], 1.01-1.74; $P < .05$), prompting the author to conclude that norepinephrine is a superior drug in septic patients. Mean arterial pressure should be maintained above 65 mm Hg throughout the resuscitation; do not wait for the CVP to be optimized first before using vasopressors.[7]

Patients with refractory hypotension, despite meeting the goals of EGDT and receiving norepinephrine, may benefit from the addition of vasopressin. Studies of critically ill patients have demonstrated low serum vasopressin levels.[85] Very low doses should be used, as sepsis patients seem to be very sensitive to vasopressin. In doses of 0.01–0.04 units per minute, study patients have shown improvements in blood pressure and renal function.[86-88] These studies had also reported decreased requirement of other vasopressors, and a prospective randomized trial of 778 patients (VASST) did support this finding but showed no overall difference in mortality in patients receiving vasopressin in addition to norepinephrine.[89] In this study, MAP in the patients studied was already above 65 mm Hg and the overall mortality was lower than reported in previous large studies; therefore, it did not sufficiently study the question of patients refractory to maximum doses of catecholamines (norepinephrine at doses of 0.19 mcg/kg/min — a 14 mcg/min infusion for the typical 75 kg patient). In a small study of 16 patients all with shock refractory to norepinephrine and with a very high mortality, vasopressin was found to immediately improve MAP and renal function.[86] Doses higher than 0.04 units per minute have not been shown to be effective and may be harmful.[83] In studies using vasopressin, digital necrosis was the most common adverse effect of the drug and was not rare.[89] In patients with MAP less than 65 mm Hg despite CVP 8-12 cm H_2O and maximum-dose norepinephrine, consider the addition of vasopressin 0.01-0.04 units per minute (Class III).

To further improve oxygen delivery, low arterial saturations in patients without underlying lung disease despite supplemental oxygen delivery can be improved with intubation and mechanical ventilation.[7,26] There is not compelling evidence that "early" intubation decreases metabolic demand (and thus O_2 extraction), but this is frequently recommended, as delayed intubation in patients eventually requiring intubation does worsen outcomes.[33]

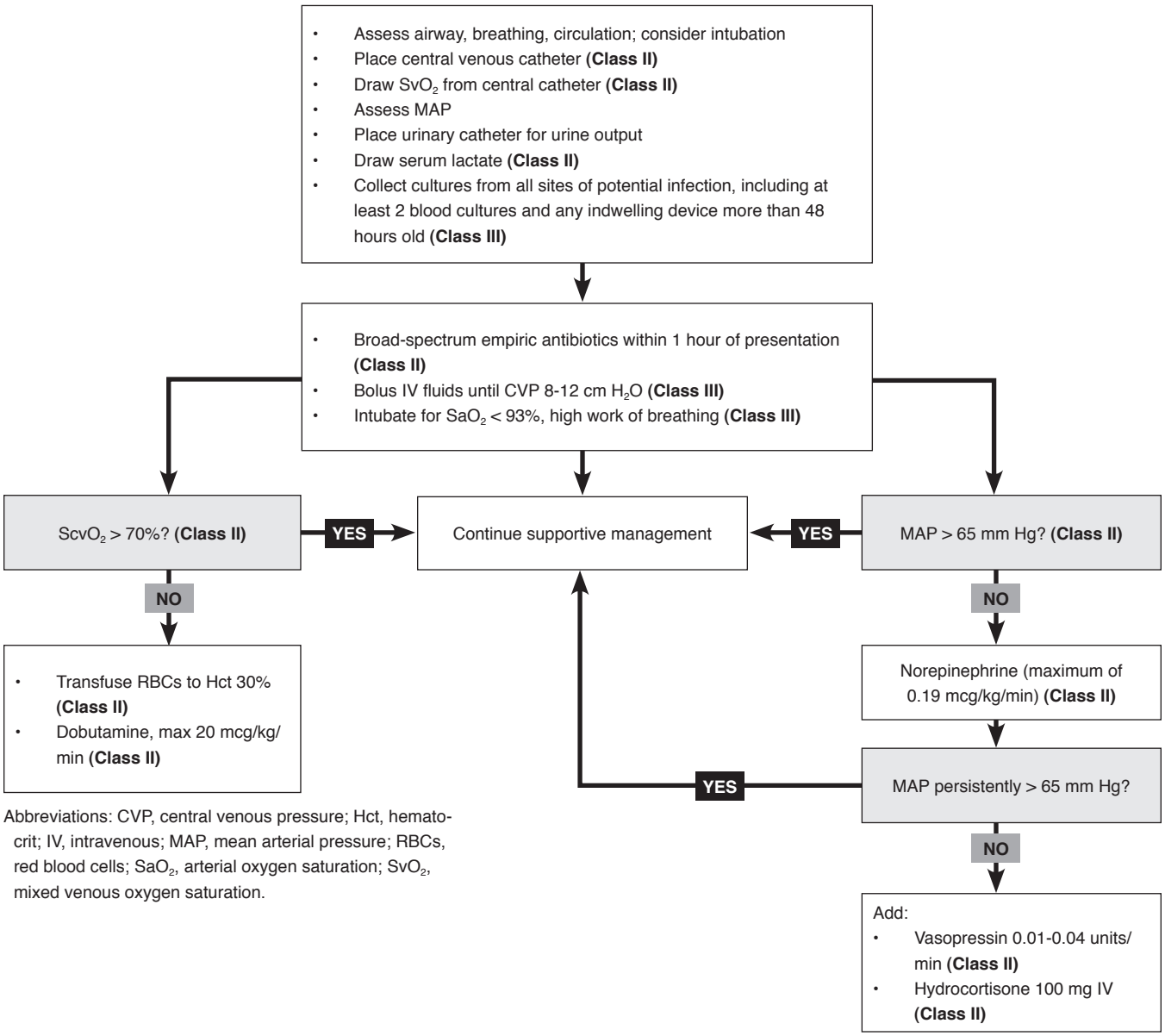
Again, it is worth comment that the survival benefit of EGDT is likely derived from its uniform, consistent application rather than large benefit from any single intervention.[4,70] While there continues to be debate about the ideal goals and measurement for any single element, its power lies in the combination of goals, the development of an orderly process, and the recruitment of a team to continue care even if the directing physician is not at the bedside.

Mechanical Ventilation

Most patients with severe sepsis and septic shock require intubation and ventilation, and 50% go on to develop acute lung injury or ARDS.[90] The lung is both a fragile end organ and also a metabolically active area with an enormous area of endothelium for the production of inflammatory cytokines.[20] There is survival benefit in limiting tidal volumes in mechanical ventilation of ARDS patients to 6 cc/kg and allowing hypercapnia, if needed to avoid barotrauma, by limiting plateau pressure (Class I).[91]

Initial inspired fractions of oxygen (FiO_2) may be high but should be reduced when possible to avoid oxygen toxicity, and a minimum amount of positive end-expiratory pressure (PEEP) should be set to maintain open alveoli at end exhalation.[90] Ideal settings for PEEP are dependent on thoracic compliance and volume. The relationship between elevated PEEP in attempts to increase or maintain oxygenation and decreased cardiac output in the preload-dependent patient should be kept in mind. When supine, body position is still important; a prospective randomized trial demonstrated decreased ventilator-associated pneumonia with the head elevated 30° to 45° (Class II).[92] Noninvasive positive pressure ventilation (NIPPV) may be considered in patients with mild ventilatory derangements who have normal mental status and predicted recovery within 24 hours (Class II).[90] However, NIPPV is not indicated in patients with depressed mental status, septic shock, signs of fatigue, or impaired oxygenation, making it a poor choice for many sepsis patients. In trials evaluating its use, sepsis patients

Clinical Pathway For Initial Resuscitation Of Severe Sepsis



Abbreviations: CVP, central venous pressure; Hct, hematocrit; IV, intravenous; MAP, mean arterial pressure; RBCs, red blood cells; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

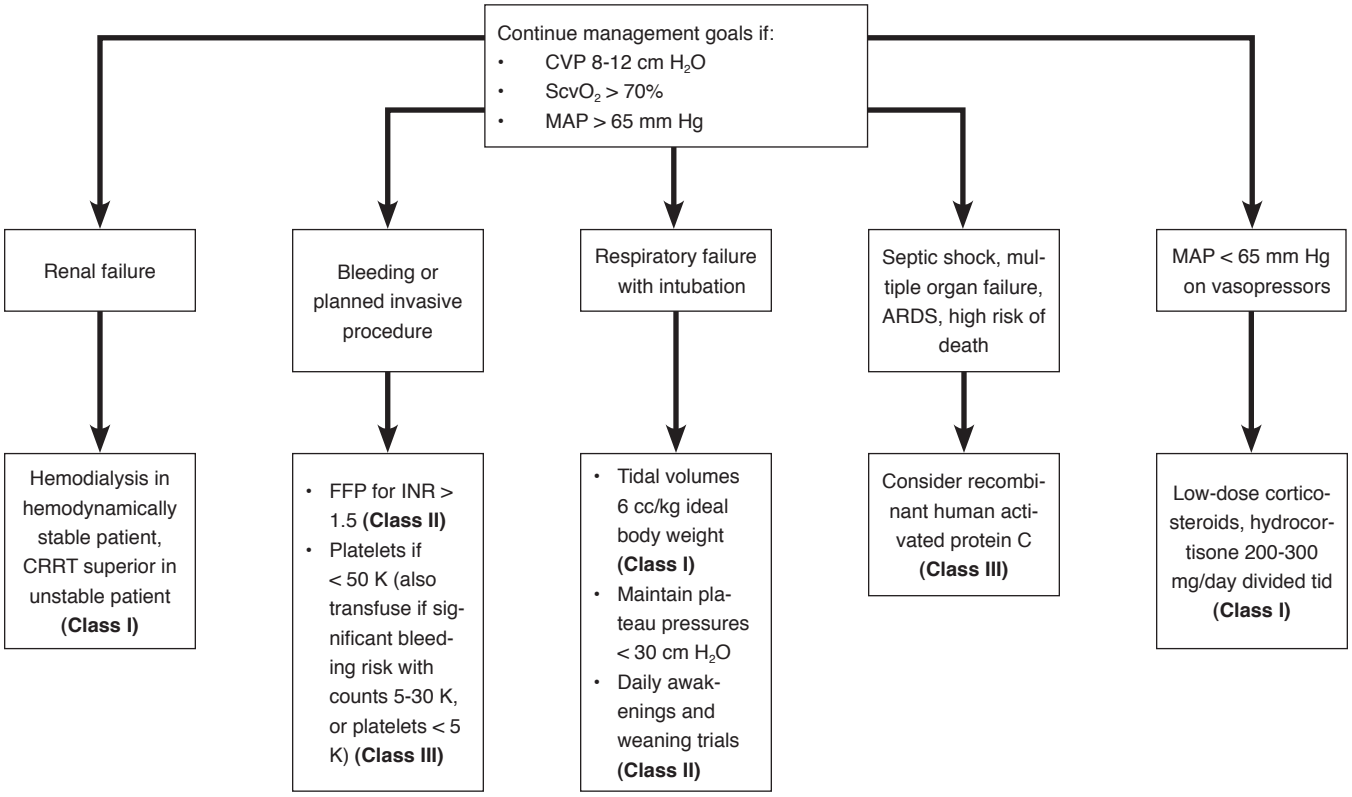
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

Clinical Pathway For Management Of Severe Sepsis And Septic Shock



Abbreviations: ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; CVP, central venous pressure; FFP, fresh frozen plasma; INR, international normalized ratio; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation; tid, 3 times per day.

had a considerably higher rate of failure and need for intubation than patients treated with NIPPV for chronic obstructive pulmonary disease or congestive heart failure.[93] NIPPV cannot currently be recommended as standard treatment in sepsis. The above strategy of permissive hypercapnia and pressure-limited and low tidal volume ventilation has been demonstrated to decrease mortality.[94]

Induction And Intubation

Patients requiring mechanical ventilation should be committed to the therapy early, and thus induction of anesthesia and sedation as part of a strategy of mechanical ventilation are critical components of ED management. The selection of an induction agent is an area of ongoing controversy. The use of etomidate, even in single doses as low as 0.04 mg/kg, has been associated with as much as 24 hours of adrenocortical suppression.[95] The Corticosteroid Therapy of Septic Shock (CORTICUS) study demonstrated that patients that received etomidate as an induction agent had a 60% rate of adrenal suppression versus 43% for patients not receiving etomidate.[96] The study further demonstrated an increased risk of death at 28 days among patients who received etomidate (40%-45% mortality versus 30%-32%).[96] Two retrospective cohort studies totaling 344 patients intubated with either etomidate or a variety of other medications including benzodiazepines, propofol, and ketamine demonstrated that patients receiving etomidate (187 of the total 344 patients studied) were more likely to receive steroids for adrenal replacement therapy but did not demonstrate any outcome differences in mortality, intensive care unit (ICU) length of stay, ventilator days, or vasopressor use.[97,98] A prospective, randomized trial comparing 355 acutely ill patients who received etomidate (0.3 mg/kg) or ketamine (2 mg/kg) for intubation demonstrated statistically significant higher rates of adrenal sufficiency in patients receiving etomidate but did not demonstrate overall differences in peak Sequential Organ Failure Assessment (SOFA) score or mortality.[99] Subgroup analysis of patients with sepsis showed a trend towards high mortality but did not reach statistical significance. A prospective, observational trial of 106 patients comparing midazolam (0.1 mg/kg, notably lower than typical induction dose) to etomidate (0.3 mg/kg) also demonstrated a trend towards higher mortality but was not sufficiently powered.[100]

There is no strong evidence to retire etomidate in favor of an alternative, and the studies discussed above suggest it is still the primary agent used in EDs, but suggestive trends should prompt very close attention to the choice of induction agent in the ED. Ketamine (2 mg/kg IV) may have particular advantages, as it has been demonstrated in vitro to decrease activity of IL-6 and TNF-alpha, 2 potent inflammatory cytokines in sepsis, and may be a good alternative without the risk of increased intracranial pressure.[101] Propofol (1-2.5 mg/kg IV, given 40 mg every 10 sec until induction) has not been studied independently, but it has large clinical experience as a long-term sedative without adverse events.[102]

Sedation For The Mechanically Ventilated Patient

In addition to managing the pulmonary mechanics of intubated, ventilated septic patients, the emergency clinician must provide sedation. A number of different pharmacotherapies and protocols have been employed with essentially no significant difference with regard to choice of agent for sedation nor continuous or intermittent dosing (Class II).[102] Propofol (5-50 mcg/kg/min IV) and midazolam (0.02-0.1 mg/kg/min IV) are frequent choices, with the addition of fentanyl (50-100 mcg IV) and hydromorphone (0.5-4 mg IV) as needed for analgesia. Neuromuscular blockade should be avoided to prevent neuropathy; if it must be used, depth of paralysis should be followed closely (Class II).[102]

Renal Replacement Therapy

Acute renal failure occurs in 23% of patients with severe sepsis and 51% with septic shock; acute renal failure combined with sepsis has a mortality of 70%.[103] Like other organ dysfunction in sepsis, this is a functional and not structural failure, and survivors often recover to normal renal function. Acute intermittent dialysis is indicated for patients with renal failure and stable hemodynamics. Continuous renal replacement therapy (CRRT), with its smaller volume shifts, can be used in place of intermittent hemodialysis in unstable patients with renal failure. There is no difference in efficacy and safety between intermittent hemodialysis and CRRT in stable patients (Class I).[104] While it has been attempted in trials aimed at removing toxins, inflammatory cytokines, and volume in sepsis, there is currently no role for hemodialysis in sepsis except as renal replacement therapy.[105,106]

Blood Products

Figure 1 (see page 4) demonstrates the effect of oxygen delivery and tissue utilization on venous oxygen saturation. One of the fundamental derangements of sepsis is tissue hypoxia due to a lack of oxygen delivery at the tissue level. Maintaining adequate oxygen-carrying capacity by transfusion of packed red blood cells to a hematocrit of 30% in patients with $ScvO_2$ less than 70% is a fundamental portion of EGDT (Class II).[26] In the absence of tissue hypoxia (ie, patients with an $ScvO_2 > 70\%$), active bleeding, or significant cardiac disease, a restrictive protocol for transfusion of red blood cells should be employed to maintain hemoglobin above 7 g/dL.

Transfusion above 9 g/dL is not warranted (Class II).[107] Fresh frozen plasma should be transfused for patients with a prolonged PT (INR > 1.5) for whom invasive procedures are necessary (Class II).[108] Platelets should also be transfused for planned invasive procedures in patients with thrombocytopenia and platelets less than 50,000/dL. Patients with less than 30,000 platelets and a high risk of bleeding should be transfused. Any patient with less than 5000 platelets should be transfused (Class III).[108]

Pharmacotherapy

Corticosteroids

Patients with refractory hypotension after fluids and vasopressors should receive corticosteroids; there is no value in patients with MAP greater than 65 mm Hg. In a large meta-analysis, low-dose steroids (200-300 mg/day of hydrocortisone either continuously infused or divided 3 times per day to 4 times per day) for at least 7 days were found to decrease mortality in severe sepsis and septic shock.[109] The CORTICUS trial of 499 patients demonstrated no difference in mortality when steroids were used in all sepsis patients receiving vasopressors for any length of time.[96] However, when the same inclusion criteria were used to define a subset similar to the population in the earlier studies (longer period of hypotension, longer requirement for vasopressors, and a much higher overall mortality), subset analysis showed the same mortality benefit. The use of corticosteroids as an immunosuppressive (ie, hydrocortisone doses higher than 300 mg/day) in sepsis patients has not been shown to be effective.[110] There is no evidence in support of stimulation testing for adrenal response.[96,109] The addition of a mineralocorticoid, such as 0.05-0.2 mg of fludrocortisone, has been suggested but has no compelling evidence in its favor.[110] Stress-dose steroids should be given to patients on chronic steroid therapy, as they have been shown to accelerate improvements in hemodynamic stability and reduce mortality without any significant increase in infectious complications.[111] A review of the PROGRESS (Promoting Global Research Excellence in Severe Sepsis) registry of 8968 sepsis patients would suggest that steroids are used by clinicians far more often than is supported by the literature.[112] In summary, septic patients with persistent hypotension despite EGDT and vasopressors should receive dexamethasone 4 mg IV or hydrocortisone 100 mg IV in the ED to provide a physiologic level of glucocorticoid in the setting of adrenal failure. It is not indicated in patients without shock or organ failure or in patients who have responded to vasopressors (Class II).

Insulin

A single study by van den Berghe et al in 2001 demonstrated a mortality benefit from intensive control of glucose in critically ill patients.[113] In the prospective, randomized trial of over 1500 patients, subjects in the treatment arm maintained blood glucose from 80-110 mg/dL using a combination of continuous infusions of insulin and glucose and bolus medications. Subjects in the standard therapy arm did not have any management of blood glucose until levels were greater than 215 mg/dL, and they had blood glucose levels from 180-200 mg/dL throughout the study. The study showed a decrease in length of ICU stay, number of days requiring a ventilator, bacteremia, renal failure requiring dialysis, requirements for red blood cell transfusion, polyneuropathy, and an overall 34% decrease in mortality. Subsequent studies demonstrated similar outcomes in medical ICUs.[114] However, a study released in January 2008 by Brunkhorst et al showed no improvement in patients receiving an intensive insulin regimen with a resultant mean blood glucose of 112 mg/dL versus standard therapy in which patients had a mean blood glucose of 151 mg/dL.[115] The study was terminated early due to a high number of adverse events from hypoglycemia in the intensive group. It is possible that the differences in outcomes can be explained by the higher mean glucose in van den Berghe's control arm. However, there is agreement in the trials that normal or near-normal blood glucose is associated with better outcomes. In summary, insulin should be administered in a systematic way while monitoring blood glucose regularly to maintain normal or near-normal levels without hypoglycemic episodes. An intensive regimen cannot be strongly recommended based on the available evidence (Class III).

Recombinant Human Activated Protein C

Recombinant human activated protein C (rhAPC) is the only drug with U.S. Food and Drug Administration (FDA) approval specifically for treatment of sepsis. Prospective observational studies demonstrated increased mortality in sepsis patients with an absolute decrease in the level of activated protein C.[23] The PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial enrolled a total of 1690 patients internationally into a database to prospectively compare rhAPC with placebo. In 1271 patients analyzed, the investigators reported a statistically significant decrease in mortality in patients in the highest quartile of illness (approximately 50% predicted mortality) when treated.[116] There were subsequent reports to support rhAPC as a cost-effective treatment[117] and to demonstrate that these survivors of sepsis made meaningful recoveries with decreased resource utilization (continued ICU care, hospital stays, long-term care facilities, etc).[118] There was a change in study protocol after 43% of the enrollment was completed. Prior to this protocol change, the mortality of the study and placebo arms was not different. The sur-

Risk Management Pitfalls For Management Of Sepsis

1. **"She isn't febrile, so this can't be sepsis."**
Particularly in the elderly, the febrile response to infection – even major infection – can be blunted.[50,56]

2. **"He has a history of congestive heart failure and was dyspneic and edematous, so I put him on BiPAP, and since his blood pressure was kind of low, I just gave him a little furosemide. The lab just called with a BNP of 550, so this is definitely congestive heart failure."**
Dyspnea, peripheral edema, hypotension, and elevations in troponin and BNP could all be present in sepsis; in elderly patients, fever is not universal.[30,31,37]

3. **"This guy was really sick, so I just threw in the central line quickly."**
The Institute for Healthcare Improvement's 100,000 Lives campaign identified a number of interventions that hospitals could institute to decrease mortality. Among the interventions with a noticeable impact on morbidity and mortality was adoption of a hospital-wide policy on central line placement, encouraging full sterile technique with full sterile drape, sterile gown, masks, and surgical caps.[79]

4. **"My nurses always struggle measuring CVP, and he had good peripheral access, so I didn't want to risk a central line."**
While it may not be the absolute best predictor of response to fluids, multiple studies have demonstrated a survival benefit from goal-directed therapy that relies upon establishing an adequate CVP as a surrogate for cardiac filling pressures.[70] Central venous oxygen saturations are also critical to demonstrating the success of interventions intended to reverse the oxygen delivery derangements seen in sepsis.[26]

5. **"He wasn't in the hospital long, so I treated the pneumonia with my usual regimen."**
Patients with pneumonia who have had any recent contact with hospitals or nursing homes have risk of MRSA. Community-acquired MRSA is on the rise and is an emerging entity as a cause of pneumonia.[72]

6. **"She is a dialysis patient, so I didn't want to give her too much fluid."**
Dialysis patients require the same volume resuscitation as other patients even if it leads to a higher rate of intubation. The initial studies on EGDT demonstrate that patients receiving "standard" therapy eventually get as much or even more fluid in the first 36 hours of care.[80]

7. **"I've been taking care of sepsis patients for years. I don't need a bundle."**
Clinical experience is invaluable, and high-volume EDs do seem to perform better in decreasing mortality of even very sick patients,[39] but the hospital-wide adoption of guidelines for the care of the sepsis patient has demonstrated mortality benefit, and the benefit seems to increase with level and duration of compliance.[4]

8. **"He has a vascular catheter for dialysis and had been getting vancomycin for persistent fevers at dialysis, so I added gentamicin and switched to linezolid for Gram-positives."**
Candida is the fourth most common causative agent cultured from the blood of septic patients. Patients at increased risk for fungemia include those with central lines and those receiving antibacterials. Patients with persistent illness despite antimicrobials should prompt investigation for fungal sources and in the ED may benefit from empiric coverage with fluconazole or caspofungin.[36,38,43]

9. **"He didn't have a history of heart failure, so there was no need for dobutamine."**
In patients with a CVP of 8-12 cm H_2O, a hematocrit of greater than 30%, and $ScvO_2$ still less than 70%, oxygen delivery is inadequate for demand and an inotrope is indicated to improve cardiac output.[26] Also, circulating myocardial depressants and nitric oxide cause functional changes within the myocardium and decreased ejection fraction.[29]

10. **"The patient's family said they wanted everything done, so I did 20 minutes of CPR."**
There is no universal understanding amongst medical professionals – much less laypersons – about what "doing everything" means. Cardiac arrest in sepsis is end-organ failure, and resuscitation techniques developed for primary cardiac arrest and dysrhythmia are very unlikely to be successful in the short-term or allow survival to discharge. It is possible that "doing everything" means ensuring comfort and not applying therapies that are painful and unlikely to affect the outcome.

vival benefit was present but no longer statistically significant at 1 year.[119] The positive mortality benefit shown by PROWESS was not reproduced in a large trial of pediatric patients.[120] The subset of patients with improved survival in the PROWESS trial was prospectively identified in a single-arm study (ENHANCE US) that enrolled 273 patients with severe sepsis and had an all-cause 28-day mortality of 26.4%.[121] The study authors compared this outcome with the placebo group from the PROWESS trial and concluded a survival benefit. There was an increased risk of bleeding in all patient groups.

Based on these trial results, the FDA approved rhAPC for patients with severe sepsis or septic shock with high predicted mortality.[122] The ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) trial, a double-blind, placebo-controlled, multicenter trial of over 2600 patients, performed at the behest of the FDA to evaluate the drug in patients with severe sepsis but lower risk of death, was halted due to bleeding complications and no demonstrated benefit.[123] Subsequent meta-analysis of the available trials showed significant adverse effects and did not demonstrate mortality benefit, including in patients with the most severe illness.[124] The drug maker is sponsoring a large, placebo-controlled trial, the PROWESS-SHOCK trial, to answer calls for a definitive study. Currently, rhAPC has very limited utility in the ED, and its use should be discussed with an intensivist (Class III).

Prophylaxis Of Inpatient Complications

Deep venous thromboembolism (DVT) prophylaxis should be instituted for all patients treated for sepsis. Studies of general ICU patients – including sepsis patients – treated with low-molecular-weight heparin showed a decrease in DVT from 25% to 30% to less than 5%, a decrease in pulmonary embolism, and an absolute risk reduction in overall mortality of 2% to 3%, similar to other more widely touted interventions.[125] Low-molecular-weight heparin has not been shown to increase bleeding risk; however, in patients already at high risk of bleeding, it should be withheld in favor of sequential compression devices. Institution of these measures should take place within the first 24 hours of care, so they should be considered in patients remaining in the ED for an extended period of time (Class II).

Stress ulcer prophylaxis can be instituted with either a proton pump inhibitor or H-2 blocker and in the ED. This is a Class I recommendation in mechanically ventilated patients or patients with coagulopathy or hypotension. It is a Class III recommendation in all others.[125]

Special Circumstances

End-Stage Renal Failure

Patients with end-stage renal disease and sepsis are a special challenge to the emergency clinician. Often, the patient on dialysis has a number of other comorbidities. In addition, they may have indwelling vascular devices that are accessed several times a week, giving them increased risk for bacteremia with MRSA and unusual pathogens including anaerobes and *Candida*.[43] Oliguric or anuric renal failure makes them intolerant to aggressive fluid resuscitation. There are no good studies on the safety and efficacy of using dialysis access for resuscitation and EGDT, but for patients in shock, using a dialysis catheter to provide immediate resuscitation can be life-saving. Patients with end-stage renal failure should receive the same resuscitation with the same goals for CVP, MAP, and $ScvO_2$, because they have the same mortality benefit, although more patients on dialysis will require intubation and mechanical ventilation (Class III).[1,7]

Diabetes Mellitus

In a survey of 12.5 million sepsis hospitalizations between 1979 and 2003, 17% of patients had diabetes mellitus.[126] In Type II diabetes mellitus, there is abnormal immune response; specifically, an impaired cytokine response to the initial presence of bacteria.[127] Diabetics have a higher incidence of blood stream infection once in the hospital as well, despite tight glycemic control.[128] Despite the increased incidence of sepsis in diabetics, a review of 837 patients with severe sepsis indicated no difference in mortality for diabetics versus non-diabetics.[129] Hyperglycemia at presentation in patients without diabetes is independently associated with increased mortality, but this is not true in diabetics.[129]

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation represents an extreme derangement of the coagulation system and occurs in the sickest sepsis patients.[47] Organ dysfunction results from microvascular thrombosis, a result of fibrin deposition coupled with inadequate fibrinolysis. The coagulation cascade generates a prothrombotic state along with a general inhibition of fibrinolysis, and in the face of a continued inflammatory state, there is consumption of coagulation inhibitors.[130] The presence of DIC is independently prognostic of mortality.[47] Treatment of patients with DIC is directed at correcting the underlying cause. The routine use of platelets, fresh frozen plasma, or cryoprecipitate is discouraged, and heparin is only recommended when there is a clear thromboembolic disease. Retrospective analysis of the PROWESS database of 1568 patients with sepsis demonstrated a nonsignificant trend towards decreased mortality in patients with overt DIC who received rhAPC versus placebo, but there was

also increased bleeding.[131] The use of rhAPC in septic patients with DIC cannot be recommended based on currently available literature.

Disposition

Seventy-four percent of patients with non-trivial infections have minimal or no systemic derangements, have low risk of mortality, and can effectively be treated with minimal supportive care and appropriate antibiotics either as outpatients or in medical wards.[38] Before the decision to send a patient to a regular medical ward is made, however, serious consideration should be given to the possibility of severe sepsis. In a study of more than 15,000 patients, progression from sepsis to severe sepsis and septic shock was seen over the course of 1 to 2 days.[132] Patients subsequently transferred from regular wards to an ICU for care of sepsis have a much higher mortality than patients initially treated in an ED or ICU, so patients with severe sepsis or high suspicion of sepsis should be admitted to an ICU (Class II). The calculation of simple prognostic scores (such as the MEDS score) may be useful in identifying patients with a higher risk of mortality. Nationwide, 97% of sepsis patients are admitted.[38]

End-Of-Life Care

Sepsis is a disease with a very high mortality, and survivors can have significant decreases in quality of life.[133] Many patients with the comorbidities that predispose to severe sepsis and high mortality have diminished quality of life prior to the acute illness.[134] In this circumstance, there may be patients for whom aggressive therapy would be futile and not desired by the patient. The SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment) trial reported that 50% of conscious patients dying in hospitals reported moderate to severe pain, and few families reported a discussion with a physician describing likely outcomes.[135] A large percentage of seriously ill patients also report a preference for comfort care, and many of these patients report that their care is not consistent with the goals of comfort.[136] In an era when the cost of medical care is under ever-growing scrutiny, quality research and clinician effort should be directed at providing quality interventions, when indicated, and providing high-quality, evidence-based comfort-directed care when appropriate.

Summary

Caring for septic patients ultimately depends on the judgment of the treating clinician. An understanding of the pathophysiology, consistent attention to the literature, and the flexibility to adapt novel therapies that achieve a level of good evidence can guide the clinician in care, but the art of medicine still lies in balancing the analytical with the personal, and blending quality evidence into personal practice. Hospital-wide adaptation of rigorous guidelines for care, whether adopted from large consensus statements such as the Surviving Sepsis Campaign® or developed at an institutional level, help clinicians and institutions maintain high levels of care for every patient and help improve mortality.[4,70] There are many questions still to be answered regarding the treatment of sepsis. The ED is likely to be the cauldron in which many of these questions are brewed, and emergency clinicians should take a lead role in investigating and applying the next generation of advances.

Case Conclusions

For the first patient, the decision to admit a nursing home patient to a medical ward after therapy in the ED was informed by the use of a MEDS score[66] and a lactate level[52] to identify low risk of mortality and a patient unlikely to benefit from more aggressive interventions or who may need subsequent transfer to the ICU.

In the second case, increasing rather than improving lactate, altered mental status, DIC, and multiorgan failure predicted high mortality. The application of a goal-directed therapeutic plan with aggressive volume correction, optimized oxygen delivery, prompt delivery of broad-spectrum antibiotics, support of cardiac output, and possibly the addition of specific medications for reversal or moderation of sepsis physiology may result in improvement. The hoped-for road signs to recovery include a decreasing lactate,[52] preserved or improving cardiac performance,[30] a normal or near-normal glucose,[110] MAP > 65 mm Hg through the use of IV fluids and vasopressors, $ScvO_2$ > 70% by maintaining Hct > 30% and adding inotropes if needed, urine output > 0.5 cc/kg/hr, and the clinical appearance of improved perfusion, organ function, and clearing mental status.[7,26]

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. **In sepsis, the lifespan of neutrophils is:**
   a. Unchanged
   b. Increased
   c. Decreased

2. **The most common source of infection in sepsis is:**
   a. Pulmonary
   b. Urinary tract
   c. Skin
   d. CNS

3. **The recovery of which organ system function is best associated with improved survival:**
   a. Renal
   b. Hematopoietic
   c. Cardiovascular
   d. Pulmonary

4. **Sixty percent of cases of sepsis occur in patients over 65. Compared to younger patients, sepsis patients over 65 years of age have a greater chance of:**
   a. Urinary source of infection
   b. Death early in hospital stay
   c. Discharge to skilled nursing facility
   d. All of the above

5. **Elevations in brain natriuretic peptide essentially rule out sepsis.**
   a. True
   b. False

6. **Mortality from septic shock is:**
   a. 5% to 10%
   b. 20% to 25%
   c. 40% to 50%
   d. 65% to 70%

7. **Central venous oxygen saturation in septic patients is best used to monitor:**
   a. Acute lung injury
   b. Cardiac end-diastolic filling pressure
   c. Cardiac output
   d. Hypoxia and oxygen delivery at the tissue level

8. **After fluid resuscitation, a septic patient has a CVP of 9 cm H_2O, MAP of 60 mm Hg, a hematocrit of 26%, and an $ScvO_2$ of 65%. In addition to antibiotics, which of the following therapies should be considered?**
   a. Dobutamine and vasopressin
   b. Norepinephrine and pRBCs transfused to a hematocrit of 30%
   c. Additional fluid boluses
   d. Recombinant human activated protein C

9. **In adults, an APACHE II score can accurately predict mortality upon arrival in the ED.**
   a. True
   b. False

10. **In patients with severe sepsis who are intubated, there is a 50% chance of developing acute lung injury. In these patients, ventilator management should include:**
    a. 6 cc/kg tidal volumes and plateau pressures less than 30 cm H_2O
    b. Highest possible FiO_2
    c. The patient lying perfectly flat
    d. No positive end-expiratory pressure

In This Month's *Pediatric Emergency Medicine Practice*

An Evidence-Based Approach To The Evaluation And Treatment Of Child Physical Abuse

by Megan Bair-Merrit, MD, MSCE
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Wendy Lane, MD
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Emergency clinicians frequently face diagnostic and management challenges when assessing the "irritable infant" and managing traumatic injuries with vague or inconsistent histories. Determining whether these presentations are consistent with child physical abuse is difficult, and some emergency clinicians believe that their training has not adequately prepared them for the task. The diagnosis of maltreatment can be critical, because physical abuse is associated with significant morbidity and mortality. A correct diagnosis may also protect a child from further harm. Research has documented that many children who die from maltreatment had been seen by a medical provider prior to their death. Given that abused children are most often taken to the emergency department for medical care, it is imperative that emergency clinicians be familiar with the signs of maltreatment. This issue of Pediatric Emergency Medicine Practice *provides emergency clinicians with a comprehensive, up-to-date, and empirically based approach for assessing, diagnosing, and managing suspected child physical abuse.*

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