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Updates and Controversies in the Early Management of Sepsis and Septic Shock

Abstract

Sepsis is a common and life-threatening condition that requires early recognition and swift initial management. Diagnosis and treatment of sepsis and septic shock are fundamental for emergency clinicians, and include knowledge of clinical and laboratory indicators of subtle and overt organ dysfunction, infection source control, and protocols for prompt identification of the early signs of septic shock. This issue is a structured review of the literature on the management of sepsis, focusing on the current evidence, guidelines, and protocols.

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Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentations

A 65-year-old man with COPD and diabetes presents from home with a productive cough (green sputum) for 1 week, dyspnea on exertion, and fever. Albuterol at home provided no relief. His vital signs are: heart rate, 102 beats/min; respiratory rate, 22 breaths/min; blood pressure, 130/89 mm Hg, and SpO_2, 94% on room air. He is speaking in full sentences and does not appear to be in respiratory distress. He has rales at the right lung base, mild wheezes, and tachycardia. Chest radiograph confirms right lower lobe pneumonia. The patient has no recent hospitalizations. You believe that he looks clinically well and may be able to be discharged home with antibiotics, but you are also concerned for sepsis and wonder if this would be a wise decision...

A 45-year-old man with hypertension and prostate cancer in remission presents complaining of 3 days of burning with urination, fevers, and chills. His vital signs are: heart rate, 110 beats/min; respiratory rate, 20 breaths/min; blood pressure, 130/90 mm Hg; SpO_2, 98% on room air; and temperature, 38.4°C (101.2°F). He is alert and fully oriented. His physical exam reveals mild suprapubic tenderness without rebound or guarding and bilateral costovertebral angle tenderness. Lab findings include a WBC count of 18,000 with 5% bands, a creatinine of 1.5 mg/dL, a platelet count of 130 x $10^3/mm^3$, 80 WBCs on urinalysis with positive nitrite and leukocyte esterase, and a serum lactate of 1.2 mmol/L. After receiving ibuprofen and a fluid bolus, the patient feels better and states, "I need to go get my dog!" The nurse asks you if she can remove the IV for the patient to be discharged, which sounds reasonable, but something worries you...

A 70-year-old woman with diabetes mellitus, hypertension, and colon cancer arrives via EMS from a local nursing home for right foot swelling and redness. Paramedics report 2 days of increasing confusion. Her initial blood pressure was 85/50 mm Hg, with a heart rate of 90 beats/min. Her initial glucose was 270 mg/dL. The patient is alert but unable to provide a history. During transfer into her bed, the patient screams in pain as her right leg bumps the bed rail. Your focused exam reveals tachycardia, clear breath sounds, and no acute distress. Her right foot and leg are extremely tender, warm, and erythematous. She has crepitus over the dorsum of the foot and right calf tenderness, but no pretibial edema. The nurse rechecks her vital signs, revealing a blood pressure of 70/40 mm Hg. You order and initiate a fluid bolus. You consider the best antibiotic(s) to start and whether you should initiate pressors before she has received a 30 mL/kg fluid challenge...

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Dr. Gupta and Dr. Nusbaum discuss the recent updates and controversies in sepsis treatment with Dr. Jeremy Rose of Mount Sinai Beth Israel Hospital. Tune in for insight on this important topic!

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Introduction

Sepsis is triggered by a systemic infection and is a life-threatening, dysregulated response to infection.[1] Immune abnormalities induced by invading pathogens or tissue damage produce both the inflammatory and immunosuppressive features of the disease, which causes organ dysfunction and can lead to death. Sepsis may lead to cellular abnormalities and perfusion deficits, causing septic shock. Optimal management strategies for sepsis have been an issue of intense research since a landmark study by Rivers and colleagues published in 2001 identified a 16% mortality reduction with randomization to an early aggressive care bundle termed *early goal-directed therapy* (EGDT). EGDT involves the administration of fluids, inotropes, and blood, and the achievement of hemodynamic goals to improve tissue oxygenation, as indicated by a central venous oxygen saturation ($ScvO_2$) > 70%.[2] After 3 recent multicenter trials failed to validate the results of that study, however, EGDT is no longer recommended.[3-5] Nonetheless, in general, early, aggressive management of sepsis is recommended and has been shown to improve outcomes.[6-9]

This issue of *Emergency Medicine Practice* reviews the recent changes in sepsis criteria, prognosticators, and quality metrics and offers recommendations on the recognition and treatment of sepsis, severe sepsis, and septic shock in the emergency department.

Definitions and Terminology

The diagnosis of sepsis has undergone a metamorphosis since the inception of standardized definitions in 1991.[10] Shifting away from the systemic inflammatory response syndrome (SIRS) criteria previously utilized,[11] in 2014 the Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force and, by an expert consensus process, agreed in 2016 on updated definitions and criteria to be tested clinically. The Third International Consensus Definitions for Sepsis and Septic Shock ("Sepsis-3") redefined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1]

Sepsis-3 also redefined septic shock as "hypotension not responsive to fluid resuscitation," with the added requirement for vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg and

a lactate > 2 mmol/L. These new definitions were adopted by the 2016 Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock.[9]

Sepsis-3 cited new insights into sepsis pathobiology, the lack of sensitivity and specificity of SIRS criteria, and the excessive focus on inflammation as some of the reasons for the changes. The updated definitions in Sepsis-3 emphasize organ dysfunction in the setting of infection, which can be quantified using the sequential (sepsis-related) organ failure assessment (SOFA) score. For expansion of the criteria for scoring SOFA, see **Table 1.**

Sepsis-3 also derived a bedside assessment tool for sepsis screening in patients with infection who are not in intensive care units (ICUs). Called the *quick SOFA* (qSOFA) score, it includes 1 point for each of 3 criteria: (1) respiratory rate ≥ 22 breaths/min, (2) altered mental status, or (3) systolic blood pressure (SBP) ≤ 100 mm Hg. A qSOFA score ≥ 2 is suggestive of sepsis.[12] Sepsis-3 recommends that, for a qSOFA score < 2, the full SOFA score, including laboratory results, should be used.[12]

Though the Sepsis-3 tool is more specific for sepsis, using SOFA may be problematic for the emergency clinician. SOFA components can be unfamiliar, with complex ICU-focused scoring on criteria not typically obtained routinely in potentially septic ED patients. These include arterial blood gases for respiratory evaluation and total bilirubin for hepatic dysfunction. In addition, qSOFA has been criticized as insensitive for sepsis screening,[13-21] though it may have increased specificity for mortality[22,23] and predicting organ dysfunction.[24]

Emergency clinicians should note that the current Centers for Medicare and Medicaid Services (CMS) SEP-1 quality measure, which is used to evaluate institutional sepsis bundle compliance, has not adopted Sepsis-3. The controversial CMS SEP-1 mandate is based on the presence of SIRS criteria, categorizes any infection with organ dysfunction as severe sepsis, and defines septic shock as "hypotension not responsive to fluids or serum lactate ≥ 4 mmol/L regardless of hypotension."[25,26] Therefore, hospital quality measures assess CMS quality metrics based on the 2001 International Sepsis Definitions Conference[11] and not Sepsis-3. There is no indication that this will change, so it is important to know the differing metrics and definitions. A comparison of Sepsis-3 to the 2001 Sepsis definitions as well as CMS SEP-1 criteria are presented in **Table 2, page 4**.

An online tool for calculating the SOFA score is available from MDCalc, at: www.mdcalc.com/sequential-organ-failure-assessment-sofa-score

An online tool for calculating the Glasgow coma scale score is available from MDCalc, at: www.mdcalc.com/glasgow-coma-scale-score-gcs

An online tool for calculating the quick SOFA score is available from MDCalc, at: www.mdcalc.com/qsofa-quick-sofa-score-sepsis

Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP ≥ 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

Critical Appraisal of the Literature

To evaluate clinically relevant articles regarding the diagnosis and early management of sepsis, severe sepsis, and septic shock, a search of the National Library of Medicine PubMed database was performed using the following search terms: *sepsis management, septic shock management,* and *clinical sepsis treatment guidelines*, with a date range of 2000 to 2018. Acknowledging the breadth of the sepsis literature, additional specific searches were performed including *intravenous fluids, antibiotics, vasopressors, corticosteroids, lactate, lactate clearance,* and *sepsis.* References relevant to prehospital and emergency department (ED) care of septic patients were included. Only adult, human studies were considered, and publications in English (with the exception of 3 Chinese studies on lactate clearance). Current consensus guidelines were also reviewed.

Guidelines have recently been augmented with high-powered randomized clinical trials of sepsis and septic shock that evaluated management strategies, adding to specific recommendations for treatment and resuscitative endpoints. Several studies have recently examined invasive (EGDT) versus less-invasive early resuscitation strategies, and these results have led to recommendations against routine use of invasive strategies that do not confer a mortality benefit. Recommendations for volume of intravenous (IV) fluids, early antibiotics, and infection source control are based on national metrics and observational studies and not randomized clinical trials of early sepsis patients. Randomized trials using serum lactate for both screening and as a resuscitative endpoint support a strong recommendation for its use. Norepinephrine is the current vasopressor of choice, given both randomized trial data and several observational studies. A recent large randomized trial of hydrocortisone for septic shock did not show mortality benefits, but did show improved secondary outcomes.

Epidemiology

Studies estimate that up to 850,000 ED visits for sepsis occur annually in the United States and 19 million cases occur worldwide.[27,28] The syndrome of sepsis is highly lethal and costly, resulting in death in approximately 1 of every 4 cases and costing nearly $17 billion per year in the United States alone.[29] Sepsis is also a leading cause of 30-day hospital readmissions, with a higher readmission rate and cost per admission than acute myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, and pneumonia.[30] In a study estimating the annual cost of readmissions in the state of California, sepsis readmissions accounted for nearly $500 million per year, more than double that of congestive heart failure.[31]

Mortality due to sepsis and septic shock varies by definition. Applying the Sepsis-3 definition, the mortality of sepsis is estimated at 10%, and the mortality of septic shock is approximately 40%.[1] Highly variable mortality rates are reported for septic shock using the 2001 versus the Sepsis-3 definition, with ranges of 14% to 34% and 28% to 39%, respectively.[32,33] Regardless of the definition used, patients meeting either criteria for septic shock have a high mortality rate that mandates urgent attention and aggressive intervention.

Etiology and Pathophysiology

When localized infections become systemic, they may incite aberrancies in immunity that trigger both inflammatory and immunosuppressive media-

Table 2. Definitions of Sepsis, Severe Sepsis, and Septic Shock

Sepsis Category	Sepsis-3	2001 Sepsis	CMS SEP-1
Sepsis	SOFA score ≥ 2 + suspected infection	2 of 4 SIRS criteria + suspected infection	2 of 4 SIRS criteria + suspected infection
Severe sepsis	Not applicable	Sepsis + organ dysfunction, hypoperfusion, or hypotension	Sepsis + sepsis-induced organ dysfunction*
Septic shock	Vasopressor requirement to maintain MAP ≥ 65 mm Hg + serum lactate level > 2 mmol/L in the absence of hypovolemia	Sepsis-induced hypotension persisting after adequate IV fluid resuscitation + presence of perfusion abnormalities or organ dysfunction	• Lactate > 4 mmol/L • SBP < 90 mm Hg, not responsive to IV fluids **or** • MAP < 70 mm Hg, not responsive to IV fluids

*Organ dysfunction variables according to CMS SEP-1 include: SBP < 90 mm Hg or MAP < 70 mm Hg, or a SBP decrease > 40 mm Hg or < 2 SD below normal for age or known baseline; creatinine > 2.0 mg/dL (176.8 mmol/L) or urine output < 0.5 mL/kg/hr for > 2 hr; bilirubin > 2 mg/dL (34.2 mmol/L); platelet count < 100,000; coagulopathy (INR > 1.5 or aPTT > 60 sec); lactate > 2 mmol/L (18.0 mg/dL).

Abbreviations: aPTT, activated partial thromboplastin time; CMS, Centers for Medicare and Medicaid Services; INR, international normalized ratio; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

tors.[34-37] Previously, the bacterial infection itself was believed to cause the clinical syndrome of sepsis, but the advent of modern antibiotic therapy showed that systemic symptoms may persist even after eradication of the source of infection.[38] The degree and severity of the immune response in patients with systemic infection vary, but in some patients, normal immune regulatory safeguards fail and manifest clinically as organ dysfunction. This constitutes sepsis. When a systemic infection becomes severe enough to result in persistent cellular and metabolic abnormalities with the presence of arterial hypotension, septic shock is the result.[1]

The most common inciting infections leading to sepsis, in descending order, are:[29,39-41]

- Pneumonia
- Intra-abdominal infections
- Urinary tract infections

Blood cultures are positive in up to one-third of cases, while about one-third have no causative organism cultured from any source.[29,40,42,43] Generally, gram-positive infections predominate over gram-negative infections, particularly for community-acquired infections.[44] However, in ICU populations worldwide, gram-negative infections of increasing resistance appear to have overtaken gram-positive infections.[41]

Many of the signals mediating the clinical syndrome of sepsis are the result of damage to either endogenous tissues, called *damage-associated molecular patterns* (DAMPs), or a response to the molecular patterns associated with invading pathogens, called *pathogen-associated molecular patterns* (PAMPs).[45-47] Both patterns trigger the upregulation of genes leading to the release of inflammatory cytokines and the migration of cells of innate immunity, which lead to the release of toxic mediators and ongoing tissue damage. Conversely, the attempt at balancing the systemic inflammatory response is also mediated by regulatory processes, including neural, humoral, and cellular mechanisms to blunt the inflammatory response.[47] Several studies have shown that inflammation and immunosuppression occur concurrently, and that critically ill septic patients experience reactivation of specific viruses that are typically limited to patients with severe immunosuppression.[37,48,49]

Table 3. Noninfectious Conditions That May Mimic Sepsis[50]

Organ System/ Category	Noninfectious Condition
Cardiovascular	Dysrhythmia, pulmonary embolism, myocardial infarction, ventricular pseudoaneurysm, congestive heart failure, acute pulmonary edema
Endocrine	Diabetic ketoacidosis, thyroid storm, pancreatitis, adrenal insufficiency
Circulatory	Hypovolemia from diuretic use, gastrointestinal hemorrhage, burns, poor oral intake
Respiratory	Massive aspiration, atelectasis
Trauma	Spinal cord injury, massive burn, hemorrhage
Immune	Anaphylaxis
Obstetric	Hemorrhage
Toxicologic	Intoxication, sympathomimetic use, cholinergic crisis, serotonin syndrome, snakebite, alcohol withdrawal

Differential Diagnosis

When encountering a patient with abnormal vital signs and concern for infection, first consider infectious versus noninfectious conditions that cause the clinical presentation. By reviewing noninfectious conditions causing similar clinical findings, unlikely causes of the presentation can be eliminated. Assessing each organ system systematically will ensure that an infectious source for sepsis is not overlooked. While **Tables 3** and **4** are not exhaustive, they provide a framework for organizing this approach.

Prehospital Care

The prehospital period provides an opportunity to improve early intervention for sepsis. The incidence of severe sepsis in emergency medical services (EMS) encounters in the United States is 3.3 per 100,

Table 4. Potential Sources of Infection Associated With Sepsis, by Organ System[50]

Organ System	Potential Source of Infection
Gastrointestinal	Infectious hepatitis, cholangitis, diverticulitis, abscess, intestinal instrumentation, bowel obstruction, pancreatitis, infectious colitis
Genitourinary	Pyelonephritis, abscess, renal calculi, urinary tract obstruction, acute prostatitis, renal insufficiency, instrumentation
Pelvic	Peritonitis, abscess, septic abortion, endometritis
Lower respiratory tract	Pneumonia, empyema, lung abscess
Intravascular	Central-line-associated bloodstream infection, prosthetic device infection, acute bacterial endocarditis
Cardiovascular	Endocarditis, myocarditis, myocardial/ perivalvular ring abscess
Dermatologic	Abscess, toxic shock syndrome, Stevens-Johnson syndrome, meningococcemia, cellulitis, necrotizing fasciitis
Neurologic	Meningitis, epidural abscess, discitis

and 40% to 70% of all severe sepsis hospitalizations arrive to the ED via EMS.[51-53] In a large metropolitan area, 54% were transported by paramedics; the prehospital care time for these patients was, on average, > 45 minutes; and < 37% arrived with IV access established.[54] In a survey of German prehospital systems using the European model of prehospital care (with physicians on scene), only 10.3% of rescue districts used an algorithm for sepsis, severe sepsis, or septic shock.[55]

While one study showed that out-of-hospital shock index and respiratory rate were highly predictive of ICU admission, others revealed significant knowledge gaps related to diagnosis and management of sepsis among advanced EMS providers in a variety of agencies.[56,57] In fact, only 18% to 21% of confirmed septic patients transported by EMS had been suspected of having sepsis by the EMS providers.[58,59] Out-of-hospital fluid was administered in only half of patients with severe sepsis.[60] Recognition of sepsis and early protocolized treatment may be improved by prehospital-specific scores, but thus far in the United States, only single-site derivations have been published.[52,61]

Prehospital IV fluid resuscitation has not been associated with improved mortality, but has been associated with shorter hospital stays.[51] Prehospital venous lactate measurements and sepsis protocols have been described, with preliminary data showing improvements in in-hospital mortality for patients identified or treated by EMS, though further research is needed to determine their long-term feasibility and influence on sepsis outcomes.[62]

All EMS systems can improve the care of patients with sepsis by focusing on stabilization of vital signs and providing efficient transport. Though prehospital care has not been shown to improve the prognosis of septic patients, patients presenting via EMS do have shorter delays to initiation of antibiotics, IV fluids, and early-care bundles.[52,58,63] Prehospital caregivers should recognize that vital sign instability may indicate early stages of septic shock. While care should be given to not delaying transport, establishing IV access and judiciously initiating IV fluids as well as administering oxygen to patients with hypoxia have the potential to improve outcomes.

Emergency Department Evaluation

History

Expeditious evaluation and treatment can change a sepsis patient's trajectory from a worsening clinical syndrome to organ support and recovery. When evaluating a patient for sepsis, the initial history must focus on identifying an infectious source of the patient's symptoms. **(See Table 5.)** When a patient is unable to provide a cohesive history, seek collateral sources and search for clues on the physical examination to offer insight into the patient's presentation. Similarly, consider the patient symptoms and be careful not to attribute sepsis to a relatively minor finding, such as a mild urinary tract infection or subtle pneumonia on chest radiography.

Physical Examination

Initial evaluation should include a rapid assessment of airway, breathing, and circulation, followed immediately by assessment of vital signs and point-of-care glucose testing to evaluate clinical stability. Patients with critical findings such as hypoxia, respiratory distress, hypotension, signs of hypoperfusion, hypothermia/hyperthermia, or hypoglycemia should be treated immediately with appropriate interventions such as oxygen, endotracheal intubation, IV fluid resuscitation, vasopressors, warming or antipyretics, and dextrose.

Next, a complete physical examination should be performed. An initial Glasgow Coma Scale (GCS) score may be calculated as a measure of neurologic dysfunction. **Table 5** provides a guide for system-

Table 5. Historical and Physical Examination Findings Concerning for Sepsis

Historical Findings	
Clinical history	Allergies, chronic illness, recent antibiotic use, surgery or procedures, corticosteroid use, HIV or other immune compromise, recent hospitalization or long-term care residence, indwelling devices, intravenous drug use
Review of systems	Fever; headache; confusion; neck pain; cough, shortness of breath; abdominal pain; back pain; flank pain; dysuria, urinary frequency, hematuria; extremity pain, rash, warmth
Physical Examination Components to Assess for Occult Infection	
Body System	**Finding**
Central nervous system	Altered mental status, seizure
Head and neck	Airway, oropharyngeal infection, scalp, ears, cervical soft tissue, lymphadenopathy, neck mobility
Heart	New murmurs, rubs, distant heart sounds, crackles
Lung	Rhonchi, rales, reduced breath sounds
Abdomen	Focal tenderness, guarding, rebound, fluid wave, organomegaly, oliguria
Genitourinary	Skin lesions or redness, abscess, discharge, bleeding
Extremities	Color, temperature, perfusion, erythema, swelling, warmth
Skin	Rash, erythema, crepitus, mottling
Indwelling devices	Tenderness, erythema, warmth, purulent discharge

atic evaluation of each organ system to assess for sources of sepsis. Occult abdominal sepsis occurs frequently in older and diabetic patients, though they may exhibit minimal tenderness. Genitourinary and pelvic examination is warranted in cases where pelvic infections are suspected. Visual assessment and palpation of the skin and soft tissues of the back, pelvis, and perineum should also be conducted.

Missing an occult infection in a critically ill septic patient can have lethal consequences, but diagnostic accuracy for identifying an infectious source can be as low as 65% to 85%.[64] Current guidelines recommend that source identification and control be achieved "as rapidly as possible."[9] The least invasive method for source control should be utilized, and infected indwelling catheters should be removed as soon as alternative vascular access is obtained.[9,65,66] Blood cultures should be obtained from previously indwelling vascular catheters as well as from peripheral blood, as early positive blood cultures from the vascular access site (2 hours in advance of peripheral) are suggestive of line sepsis.[9] Frequent reassessments of perfusion and mental status should be undertaken to assess response to treatment. Give significant credence to the finding of pain out of proportion to examination, which may indicate diagnoses such as mesenteric ischemia or necrotizing soft-tissue infections. In these and other cases, point-of-care ultrasound (POCUS) may be an important extension of the physical examination to rapidly identify potential sources of infection.[67,68]

In patients with shock, the history and physical examination findings, along with physiologic parameters, will allow identification of the shock etiology. First, when arterial hypotension is present, signs of tissue hypoperfusion should be assessed, including altered mentation, mottled or clammy skin, oliguria, and elevated serum lactate level.[69] Next, cardiac output should be evaluated, as well as fluid status, which can be rapidly assessed with POCUS. In cases where cardiac output is normal or high, the most likely diagnosis is distributive shock. In the setting of other sepsis indicators (including the absence of an alternative cause), septic shock is diagnosed and treatment can be initiated.

Diagnostic Studies

Laboratory Testing

Laboratory testing is aimed at identifying organ dysfunction or evaluating infectious sources. Complete blood cell counts provide an assessment of coagulation function (platelet count) as well as immune function (white blood cell and neutrophil count) and oxygen-carrying capacity (hemoglobin and hematocrit). Basic metabolic panels should be obtained to assess kidney function (creatinine), electrolyte abnormalities, hydration status (blood urea nitrogen/creatinine ratio), and acid/base status.

Though blood gas testing may be useful for assessing acid/base status or lactic acidosis, we do not advocate routine blood gas testing to calculate the respiratory SOFA score. Instead, we recommend use of pulse oximetry to calculate the SpO_2/FiO_2 (oxygen saturation/fraction of inspired oxygen) ratio, which has been validated.[70] We also do not advocate for routine testing of total bilirubin for the hepatic SOFA score unless history or physical examination findings (eg, icterus, jaundice, or abdominal pain) suggest hepatic dysfunction, as this does not improve the prognostic ability of SOFA.[71] In addition, though guidelines recommend that 2 sets of blood cultures be obtained prior to the administration of antibiotics, this recommendation should be balanced with the severity of illness of the patient and should not cause a significant delay in the administration of antimicrobials (> 45 minutes).

Lactate Versus Central Venous Oxygen Saturation

Currently, lactate normalization or clearance as a goal of sepsis resuscitation is recommended in the management of patients with sepsis and elevated lactate levels.[9] Achievement of $ScvO_2 > 70\%$ as a goal of sepsis resuscitation can still be used, but it is no longer recommended by the Surviving Sepsis Campaign after trials failed to establish benefit over standard care.[3-5] In addition, $ScvO_2$ monitoring requires a central venous catheter in the neck or chest and specialized monitoring for continuous measurements. Lactate, however, can be measured more conveniently in the ED from peripheral venous or arterial blood.

Elevated lactate is thought to be due to tissue hypoxia and impaired aerobic respiration leading to anaerobic glycolysis in patients with shock; however, there may be several causes of elevated lactate in shock patients. These include beta-adrenergic stimulation causing accelerated aerobic glycolysis, hepatic or renal failure, and lactate generation by the lungs.[72]

In 2010, a randomized controlled noninferiority study compared 10% lactate clearance to traditional EGDT with goal $ScvO_2 > 70\%$ in patients with severe sepsis, and it demonstrated no difference in mortality.[73] An ICU study of septic shock patients used a lactate clearance goal of 20%, compared with standard therapy, and it demonstrated a significantly reduced mortality in the lactate clearance group (33.9%) compared with the standard care group (43.5%).[74] A study in ICU patients with septic shock used lactate clearance goals of 10% or 30% in 2 experimental groups, compared with a standard (EGDT) group, and found reduced APACHE II scores, shorter ICU lengths of stay, and lower 28-day mortality rates for both lactate clearance groups.[75] The mortality reduction was particularly significant in the group with the lactate clearance goal of 30%.

Other studies have demonstrated similar findings using a lactate clearance goal of 10%.[76,77] Finally, a randomized controlled trial of 360 ICU patients with sepsis and refractory hypotension or a lactate > 4 mmol/L was performed, comparing traditional EGDT to stepwise lactate kinetics.[78] Stepwise lactate kinetics used target thresholds for lactate clearance of up to 10% at 2 hours, up to 20% at 4 hours, and up to 30% at 6 hours. The stepwise lactate kinetics group had a significantly lower in-hospital mortality rate compared with the EGDT group (18.3% vs 27.9%, $P = .033$), as well as a lower 60-day mortality rate, though they received more fluids. Based on the best available evidence, in patients with initially elevated lactate levels, we recommend serial lactate testing for sepsis until there is a reasonable trend toward improvement.

Procalcitonin

Procalcitonin is a peptide precursor of calcitonin that becomes elevated in patients with bacterial infections, but not viral infections. It is not currently recommended to use procalcitonin as a biomarker for diagnosing sepsis because it lacks negative predictive value to justify withholding lifesaving antibiotics from a potentially septic patient.[9,79-81] The strongest body of literature in support of procalcitonin is with regard to diagnosis of pulmonary infections[82-84] and early antibiotic de-escalation.[80,85-88]

Imaging

Imaging can be used to identify the source of infection when it cannot be identified on history, physical examination, or laboratory testing. In a single-center retrospective study of septic surgical ICU patients, 144 computed tomographic (CT) scans were reviewed, of which 76 (52.8%) identified a causative source of infection, changing management in 65 (85.5%) cases.[89] In addition, in a 2017 clinical trial, POCUS was shown to increase diagnostic sensitivity when added to the bedside history and physical examination.[68] In this study, POCUS examinations included evaluations of lung, abdominal, cardiac, joint, and soft-tissue organs to identify the source of infection, demonstrating a 25% improvement in sensitivity from clinical impression alone.[68] Based on these studies and our own experience, we recommend that focused diagnostic imaging, tailored toward the most likely source of infection, be performed in cases of occult infection causing sepsis or septic shock.

Scoring Systems

Clinical recognition of early sepsis in the ED requires a high degree of suspicion. The lack of a "gold standard" biomarker for sepsis has led to the development of numerous scoring systems, none of which possesses ideal test characteristics. Therefore, we recommend that screening tools for sepsis be highly sensitive and moderately specific, given the lethality of the disease when the diagnosis is not treated urgently or is missed. Though recent literature has demonstrated a lack of sensitivity and specificity for SIRS criteria in diagnosing severe sepsis,[90] there may still be a role for SIRS criteria in initial ED screening for sepsis, given staff familiarity with the criteria and their ease of use. We also recommend that institutions develop sepsis screening protocols and consider implementing automated systems for sepsis recognition, as these may improve outcomes.[91]

Upon initial arrival, if infection is suspected based on chief complaint, qSOFA is applied. In most cases, qSOFA-positive patients should be transferred rapidly to a monitored bed within the ED where assessment and treatment for sepsis can be initiated. For qSOFA-negative patients for whom sepsis is still suspected, initial screening should include laboratory testing to diagnose organ dysfunction and radiography to identify the source of infection. Consideration should be given to calculating a full SOFA score to assess for organ dysfunction. Patients with a suspected source of infection who are qSOFA-positive, have a lactate > 2 mmol/L, or have newly diagnosed organ dysfunction should be treated as having sepsis.

Treatment

Initial Management

Current national metrics (ie, CMS) and the Surviving Sepsis Guidelines recommend the following for the initial management of patients with sepsis and septic shock.[25]

In the first 3 hours:

- Measure serum lactate,
- Obtain 2 sets of blood cultures prior to antibiotics (when possible),
- Administer IV antibiotics (within the first hour when possible), and
- Give isotonic IV fluid challenge with 30 mL/kg to patients with hypotension or lactate > 4 mmol/L. Ideal body weight is acceptable for patients with body mass index (BMI) > 30.

In the first 6 hours:

- Administer IV vasopressors to achieve MAP of at least 65 mm Hg,
- Reassess intravascular volume status and tissue perfusion, and
- Remeasure lactate (when initial lactate > 2 mmol/L).

The available evidence for each of these recommendations is assessed critically in the following sections.

In order for initial care to be as efficient as possible, care maps are recommended to facilitate rapid

IV access, simultaneously obtain lactate and blood cultures from 2 sources, and administer IV antibiotics and crystalloid IV fluids as soon as practical.[9] Though guidelines allow for the administration of antibiotics without cultures in cases where cultures cannot be obtained rapidly, this should occur infrequently and is inconsistent with national metrics.

Intravenous Fluids

Fluid Volume and Timing

Current recommendations include administration of at least 30 mL/kg of isotonic IV fluids for septic patients presenting with hypotension or a lactate > 4 mmol/L.[9] Three large randomized controlled studies of early sepsis resuscitation administered approximately this volume of fluids to patients with sepsis, without adverse effects.[3-5]

A 2017 prospective multicenter observational study of timeliness of crystalloid IV fluid administration in patients with sepsis (defined as 2 of 4 SIRS criteria, infection, plus lactate > 2.2 mmol/L or acute organ dysfunction) or septic shock compared outcomes of "early" fluid bolus administration (≤ 120 minutes) to later administration (> 120 minutes). The results showed that administering fluid boluses in ≤ 120 minutes was associated with lower rates of hospital mortality, mechanical ventilation, and ICU admission as well as reduced length of stay and fewer ICU days (after controlling for confounders) compared with patients receiving IV fluid boluses later. The study also showed that mortality odds increased by 1.09 for each hour of delay to fluid administration.[92] Importantly, the mean volume of fluid in the < 30-minute and 31- to 120-minute groups that showed improved outcomes were 29 mL/kg and 27 mL/kg, respectively. This study also demonstrated that patients with chronic renal disease or congestive heart failure were more likely to experience delays to fluid administration and to receive lower fluid volumes, though they did not have increased mortality compared to the rest of the cohort.

A multicenter prospective observational study of 49,331 patients demonstrated reduced mortality for patients with sepsis who were treated with the 3-hour sepsis bundle.[93] However, in that study, timeliness of fluid bolus administration was not associated with a mortality benefit.

In a 2018 study of 4157 patients, of whom 31.3% were obese (BMI > 30), fluid dosing based on adjusted weight (ideal weight plus 40% of the difference of actual and ideal body weight) versus actual body weight in obese patients was associated with decreased mortality.[94] Though this study was observational, it highlights the need for well-controlled trials evaluating mandated weight-based fluid dosing in special populations. Most recently in the v5.3a update to CMS SEP-1, an adjustment was made to weight-based fluid dosing such that if the patient is obese (BMI > 30), the clinician can choose to use the patient's ideal body weight for fluid dosing as long as this is stated and the ideal weight is documented clearly.

Overall, based on these data, it is likely that the recommendation for an initial dose of 30 mL/kg IV fluids is safe for most sepsis patients, particularly those with hypotension and lactate > 4 mmol/L. We also recommend initial individualized fluid challenge in patients with sepsis without hypotension but with lactate > 2 mmol/L or with acute organ dysfunction.

Fluid Status Assessment

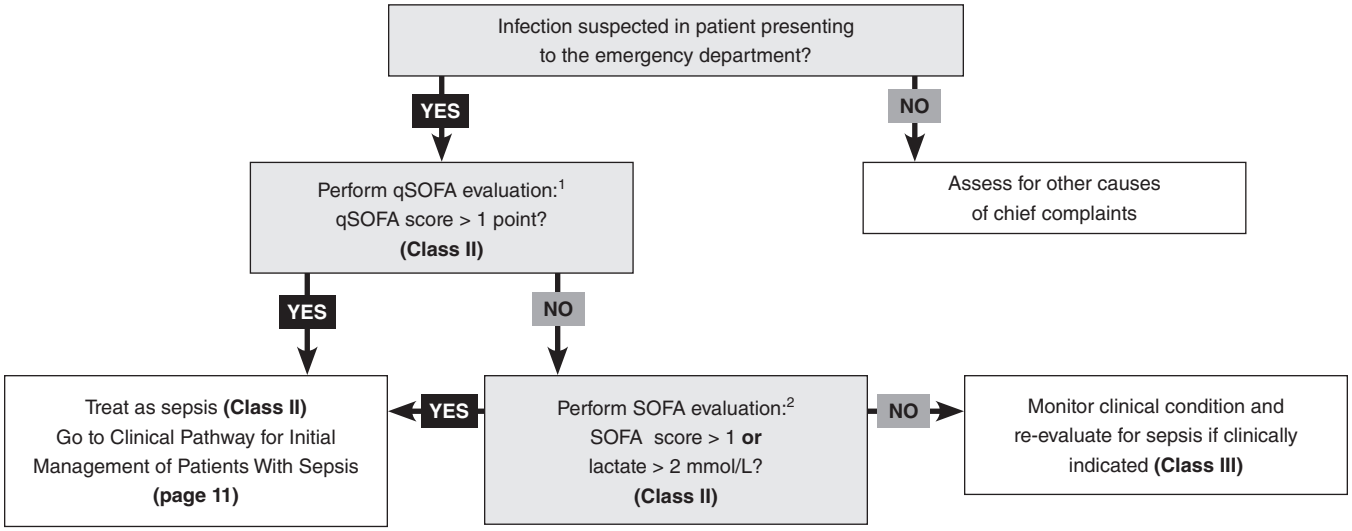
Beyond the initial IV fluid bolus, objective measures should be utilized to tailor further volume administration to the patient's fluid status.[9] Patients without signs and symptoms of overt fluid loss in the setting of sepsis (eg, vomiting, diarrhea, polyuria from hyperglycemia, or insensible losses from diaphoresis or respiratory distress) may not necessarily benefit from additional fluids.[95]

Though there are several methods to assess fluid status, for practical reasons, we recommend the early use of limited echocardiography in conjunction with inferior vena cava (IVC) ultrasound whenever feasible, though studies have not convincingly demonstrated improved outcomes using this approach.[96-99] The sensitivity and specificity of IVC ultrasound for fluid responsiveness have been reported at 76% and 86%, respectively.[100] IVC ultrasound may be confounded by various clinical scenarios, including the following:[101]

- High positive end-expiratory pressure (PEEP) or low-tidal-volume mechanical ventilation
- Assist modes of ventilation, including pressure support or continuous positive airway pressure
- Varying respiratory patterns in spontaneous breathing patients
- Asthma or chronic obstructive pulmonary disease exacerbations
- Chronic right ventricular dysfunction or right ventricular myocardial infarction
- Cardiac tamponade
- Intra-abdominal hypertension
- Pronounced IVC lateral displacement during inspiration
- Mechanical factors affecting the IVC

Passive leg raise is another noninvasive method for fluid status assessment.[96,100] Though more accurate dynamic methods of fluid status evaluation are available, most are invasive and difficult to use in the ED setting. We recommend against the routine use of invasive measures such as central venous pressure to gauge fluid status, as these are unlikely to change management.[102]

Clinical Pathway for Sepsis Screening in the Emergency Department



[1]Quick SOFA (qSOFA) score components:
(Assess 1 point for each component)
1. Altered mental status: GCS score < 15 (1 point)
2. Respiratory rate: ≥ 22 breaths/min (1 point)
3. Systolic blood pressure: ≤ 100 mm Hg (1 point)

A score of ≥ 2 suggests high risk of poor outcome in patients with suspected infection.
- Link to MDCalc calculator for Quick SOFA score for sepsis: www.mdcalc.com/qsofa-quick-sofa-score-sepsis
- Link to MDCalc calculator for GCS score: www.mdcalc.com/glasgow-coma-scale-score-gcs

[2]Sequential organ failure assessment (SOFA) score components:
(Point values are based on clinical data for each organ system)
1. Respiration: SpO_2/FiO_2 < 302 **or** overt hypoxia
2. Coagulation: platelets < 150 x $10^3/mm^3$
3. Neurologic function: GCS score < 15
4. Liver function: total bilirubin ≥ 1.2 mg/dL
5. Cardiovascular function: MAP < 70 mm Hg or on vasopressors
6. Renal: creatinine ≥ 1.2 mg/dL

- Link to MDCalc calculator for SOFA score for sepsis: www.mdcalc.com/sequential-organ-failure-assessment-sofa-score

Abbreviations: FiO_2, fraction of inspired oxygen; GCS, Glasgow coma scale; qSOFA, quick sequential organ failure assessment; SOFA, sequential organ failure assessment; SpO_2, 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
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

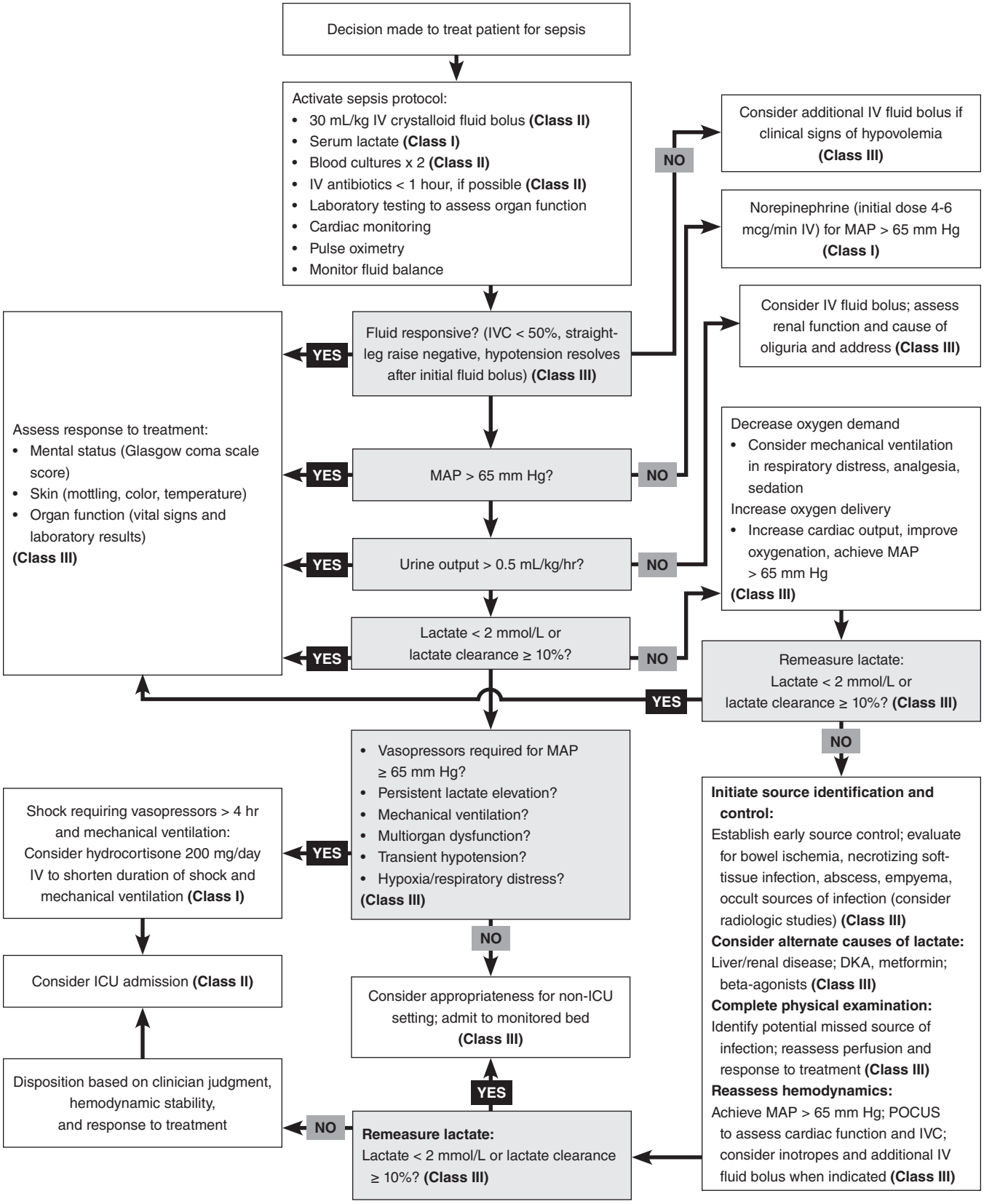
Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

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

Clinical Pathway for Initial Management of Patients With Sepsis



Abbreviations: DKA, diabetic ketoacidosis; ICU, intensive care unit; IV, intravenous; IVC, inferior vena cava; MAP, mean arterial pressure; POCUS, point-of-care ultrasound.

For class of evidence definitions, see page 10.

Antibiotics

Antibiotic Timing

Early empiric broad-spectrum IV antibiotic coverage is recommended in sepsis, and has been associated with reduced mortality.[103,104] Current guidelines recommend that antibiotics be administered within the first hour of presentation for patients with sepsis or septic shock, though this may not be feasible in some settings or in atypical presentations of sepsis.[9] Blood cultures should be obtained prior to antibiotics, when possible. A study published in 2006 showed that every hour of delay in the administration of antibiotics to patients presenting with sepsis and hypotension was associated with an increased mortality of approximately 8%.[103] A large retrospective study including 35,000 patients with sepsis across 21 EDs recently corroborated these findings.[105] Hourly delays in antibiotics in patients with sepsis were associated with increased odds of death (1.09, 95% confidence interval [CI], 1.05-1.13). Another large retrospective multicenter study demonstrated a similar increase in the odds of death with the longer time to antibiotics in patients treated with a 3-hour sepsis bundle.[93]

It is likely that the benefit of early antibiotics is greatest in patients with sepsis and hypotension, or septic shock. In patients with septic shock, administration of antibiotics after the onset of shock has been associated with increased mortality.[104] Conversely, some studies have failed to demonstrate the benefit of early antibiotics, particularly in sepsis without shock or hypotension.[106-108] However, in general, we recommend early administration of antibiotics in sepsis or septic shock, when feasible.

Antibiotic Coverage

Appropriate coverage of the causative organism is vital to improving outcomes, as significant increases in sepsis mortality are seen with inadequate antimicrobial coverage.[109-111] The choice of antimicrobials should take into account several factors: (1) The anatomic site of infection and the causative organisms associated with that site; (2) local bacterial resistance patterns and susceptibilities; (3) the presence of immunosuppression from neutropenia, splenectomy, or poorly controlled HIV; and (4) the patient's age and comorbidities, including diabetes mellitus, chronic liver or kidney disease, and indwelling devices (vascular catheters or urinary catheters).[9] In general, multidrug therapy—including extended-spectrum beta-lactam therapy—as well as the addition of vancomycin or linezolid for methicillin-resistant *Staphylococcus aureus* (MRSA) coverage, may be required. Additional gram-negative coverage may also be appropriate in severely ill septic patients at high risk for multidrug-resistant pathogens (eg, *Pseudomonas, Acinetobacter*).[112] Combination therapy, in which 2 antimicrobial agents of differing classes are given concomitantly to increase bacterial clearance, is currently recommended only for patients with septic shock,[113] and is not generally recommended in patients with bacteremia, neutropenic fever, or sepsis without shock.[114,115] However, we advise that, in cases in which the offending organism is unknown and the patient is critically ill, providing 2 antimicrobial agents in order to broaden the spectrum of antimicrobial coverage to ensure the best outcome is still recommended. Antibiotic recommendations based on infection type or source are listed in **Table 6, pages 14 and 15.**

Vasopressors and Inotropes

Peripheral infusion of catecholamine vasopressors may be safe for brief periods in settings where close monitoring for extravasation can be provided until central venous access is established.[120] Vasopressin should be administered only through a central vein, as extravasation in a peripheral vein cannot be reversed using phentolamine as it can with catecholamine vasopressors.

Norepinephrine Versus Dopamine

Norepinephrine is the recommended first-line vasopressor for septic shock.[9] It can be initiated at a dose of 4 to 6 mcg/min IV and titrated incrementally by 4 to 6 mcg/min (recommended max dose, 30-50 mcg/min) to achieve MAP > 65 mm Hg. Weight-based dosing for norepinephrine can also be used, with a range of 0.01 to 3 mcg/kg/min. It has primarily alpha-adrenergic properties and also modest beta-adrenergic effects, and reliably increases systemic vascular resistance while supporting cardiac function.[9,69] Nonetheless, patient physiology should be taken into account (including cardiac function and peripheral perfusion) with any choice of vasopressor.[69]

A double-blind multicenter randomized controlled trial of 1679 patients that compared norepinephrine and dopamine in undifferentiated shock (60% had septic shock) demonstrated an increased rate of arrhythmias with dopamine as well as increased mortality in patients with cardiogenic shock, compared with norepinephrine.[121]

A meta-analysis also compared norepinephrine to dopamine in septic shock. Of the 5 observational studies (after the removal of 1 study that accounted for data heterogeneity), dopamine was associated with an increased risk of death (relative risk [RR], 1.23; CI, 1.05-1.43, $P < .01$) compared with norepinephrine. Of the 6 randomized trials, dopamine was associated with increased risk of death (RR, 1.12; CI, 1.01-1.20, $P = .035$).[122] A study including 502 United States hospitals and 61,122 patients compared norepinephrine to dopamine and showed dopamine was, again, associated with increased odds of death (odds ratio, 1.08; 95% CI, 1.02-1.14).[123] Another trial comparing multiple vasopressor combinations also

found that norepinephrine was superior to dopamine.[124] Therefore, norepinephrine is recommended as first-line, and dopamine is recommended for use only in "highly selected" patients at low risk for tachyarrhythmia or with bradycardia.[9]

Vasopressin

Vasopressin is currently a second-line vasopressor for septic shock.[9] A major study designed to evaluate vasopressin, the Vasopressin and Septic Shock Trial (VASST), demonstrated low-dose vasopressin to be noninferior to norepinephrine.[125] In a subsequent secondary analysis of VASST data, a potential benefit in patients with acute kidney injury plus septic shock was identified.[126] This was important preliminary data, given that vasopressin is known to selectively vasoconstrict efferent arterioles, leading to increased glomerular filtration rate,[127,128] and that patients with septic shock are known to be relatively vasopressin-deficient.[129] However, a subsequent randomized trial, the Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial, failed to demonstrate benefit to vasopressin titration with regard to renal outcomes in septic shock.[130]

Though vasopressin does not appear to offer a mortality benefit or to definitively improve kidney function in septic shock, its use has been shown to reduce the norepinephrine dose when administered at fixed doses of 0.03 to 0.04 units/min IV.[131,132]

Epinephrine

Two important studies have compared the efficacy of epinephrine to norepinephrine directly. Epinephrine can be initiated at 0.05 to 2 mcg/kg/min IV and increased by 0.05 to 0.2 mcg/kg/min every 10 to 15 minutes to achieve MAP goals. Epinephrine can also be dosed starting at 2 to 4 mcg/min initially and titrated to effect (recommended max dose of 15-20 mcg/min). One study demonstrated that epinephrine and norepinephrine were equivalent in achieving MAP goals in ICU patients with shock.[133] However, 18 of the 139 patients had epinephrine withdrawn due to the development of significant tachycardia, lactic acidosis, or an increased insulin requirement. Another study demonstrated that epinephrine versus norepinephrine plus dobutamine (when needed) were no different with regard to mortality.[134] Therefore, we recommend consideration of epinephrine in patients with diminished cardiac contractility who are in need of additional support to achieve MAP goals.

Of note, hyperlactatemia caused by epinephrine infusion may obscure the use of serial lactate monitoring as an endpoint of sepsis resuscitation. For stabilized vasopressor-dependent patients with the need for additional inotropy, dobutamine can be added instead of epinephrine at a starting dose of 0.5 to 1 mcg/kg/min IV to a maximum dose of 40 mcg/kg/min. However, the potential for hypotension is higher with dobutamine than with epinephrine; therefore, we recommend initiation at a low dose, with caution and judicious monitoring.

Phenylephrine

Phenylephrine is another vasopressor agent with pure alpha-adrenergic properties, acting only as a vasoconstrictor, with no direct effects on myocardial function except for increased afterload. Phenylephrine can be conveniently used in IV bolus (or "push") doses at 100 to 200 mcg/dose, making it a convenient option while IV vasopressor infusions are being prepared. Initial IV infusion doses of 100 to 180 mcg/min are recommended, with previous studies showing safety at doses up to a maximum of 9.1 mcg/kg/min.[135] Phenylephrine is not currently recommended as a first or second-line vasopressor, but is considered safe. Studies on phenylephrine in septic shock have not shown major differences in comparison to norepinephrine with regard to mortality or organ function.[136,137]

Angiotensin II

A study published in 2017 evaluated the use of angiotensin II as a vasopressor for septic shock.[138] Adult patients requiring doses of norepinephrine of ≥ 0.2 mcg/kg/min were randomized to receive angiotensin II or placebo to assess its use in vasodilatory shock. The primary endpoint of the study was hemodynamic improvement 3 hours after study drug initiation, and secondary outcomes included improvement in cardiovascular SOFA score at 48 hours. Significant improvements in both the primary outcome of MAP ≥ 75 mm Hg ($P < .001$) as well as cardiovascular SOFA at 48 hours ($P = .01$) were found with angiotensin II. There were no significant differences in mortality. Though the findings of improved MAP and cardiovascular SOFA score are compelling, it is unclear where angiotensin II will fall within the vasopressor armamentarium for the emergency clinician. Furthermore, angiotensin II may increase risk of venous or arterial thrombosis and, potentially, thromboembolism. More studies are needed to determine the effects of this drug on patient-centered outcomes.

Table 6. Antibiotic Recommendations by Source of Infection (Continued on page 15)

Infection Type or Source	Recommended Antibiotics	Penicillin-Anaphylactic Patient*	Additional Circumstances
Pneumonia, community-acquired	Ceftriaxone 2 g IV q24 hr **plus** Azithromycin 500 mg IV q24 hr **or** Levofloxacin 750 mg IV q24 hr **or** Moxifloxacin 400 mg IV q24 hr	Levofloxacin 750 mg IV q24 hr **or** Moxifloxacin 400 mg IV q24 hr	Treatment for patients with increased MRSA risk: • Vancomycin 25 mg/kg IV loading dose (max 2.5 g) followed by 15 mg/kg q12 hr (max 2 g per dose) or linezolid 600 mg IV q12 hr. • Patients at increased risk due to increased colonization include those with end-stage renal disease, contact sport participants, injection drug users, those living in crowded conditions, and men who have sex with men. • Other risk factors for increased MRSA risk include recent influenza-like illness, antimicrobial therapy in the prior 3 months, necrotizing or cavitary pneumonia, presence of empyema, and gram-positive cocci in clusters seen on sputum Gram stain. Treatment for patients with increased *Streptococcus pneumoniae* risk: • Generally, ceftriaxone 2 g IV q12 hr provides adequate coverage. Penicillin-allergic patients can receive vancomycin (same dosing as for MRSA). • Risk factors for drug-resistant *S pneumoniae* include age > 65 years; beta-lactam, macrolide, or fluoroquinolone therapy within the past 3-6 months; alcoholism; comorbidities; immunosuppressive illness or therapy; exposure to a child daycare center; residence in a long-term care facility.[115]
Pneumonia, healthcare-associated or hospital-acquired (gram-negative bacilli, including *Pseudomonas*)	Piperacillin/tazobactam 4.5 g IV q6 hr **or** Cefepime 2 g IV q8 hr **plus 1 of the following:** • Levofloxacin 750 mg IV q24 hr • Ciprofloxacin 400 mg IV q8 hr • An aminoglycoside	Levofloxacin 750 mg IV q24 hr **plus** Aztreonam 2 g IV q8 hr **plus** An aminoglycoside (gentamicin, tobramycin, or amikacin)	• Risk factors include recent antibiotics or hospitalization; immunosuppression; end-stage renal disease; structural lung disease including cystic fibrosis, bronchiectasis, or repeated exacerbations of COPD requiring antibiotics and glucocorticoids; aspiration; and multiple medical comorbidities.[116-118] • The risk factors and treatment for patients with MRSA risk are the same as per community-acquired pneumonia (above).
Intra-abdominal	Ceftriaxone 2 g IV q24 hr **plus** Metronidazole 500 mg IV q8 hr	Ciprofloxacin 400 mg IV q12 hr **plus** Metronidazole 500 mg IV q8 hr	Gram-negative bacilli (including *Pseudomonas*): • Infections involving the hepatobiliary tree or in patients with prior surgery, prosthetics (eg, surgical mesh, gastrostomy tubes, etc) should be covered for *Pseudomonas aeruginosa.* Recommended agents include piperacillin/tazobactam 4.5 g IV q6 hr **or** cefepime 2 g IV q8 hr **plus** metronidazole 500 mg IV q8 hr. • Specific attention should be given to risk of MRSA, which should be treated with vancomycin 25 mg/kg IV loading dose (max 2.5 g) followed by 15 mg/kg q12 hr (max 2 g per dose) or linezolid 600 mg IV q12 hr.
Urinary tract	Ceftriaxone 2 g IV q24 hr	Gentamicin 5 to 7 mg/kg/day, q24 hr	Gram-negative bacilli (including *Pseudomonas*): • Patients with indwelling catheters (urethral or suprapubic), ureteral stents, recent instrumentation, or multiple recurrent urinary tract infections are at increased risk of *Pseudomonas* and multidrug-resistant gram-negative bacteria and should be treated based on prior culture results, when available. Recommended agents include piperacillin/tazobactam 4.5 g IV q6 hr or cefepime 2 g IV q8 hr.

*Most penicillin-allergic (not anaphylactic) patients may safely receive third- and fourth-generation cephalosporins (as per "Recommended Antibiotics"); however, penicillins such as piperacillin should be avoided in patients with penicillin allergy.

Recommendations are empiric and based on likely pathogens and guideline recommendations. Clinicians should follow local institutional antibiograms regarding the prevalence and sensitivity of suspected pathogens causing sepsis. In particular, some institutions have increased *Pseudomonas* resistance to fluoroquinolones, in which case alternative agents should be used if *Pseudomonas* is suspected. Initial doses of antibiotics can be dosed safely in patients with renal impairment; subsequent doses of antibiotics may require adjustment based on renal impairment.

Abbreviations: COPD, chronic obstructive pulmonary disease; IV, intravenous; q, every; MRSA, methicillin-resistant *Staphylococcus aureus.*

Table 6. Antibiotic Recommendations by Source of Infection (Continued from page 14)

Infection Type or Source	Recommended Antibiotics	Penicillin-Anaphylactic Patient*	Additional Circumstances
Pelvic (including pelvic inflammatory disease)	Cefoxitin 2 g IV q6 hr **or** Cefotetan 2 g IV q12 hr **plus** Doxycycline 100 mg IV q12 hr	Clindamycin 900 mg IV q8 hr **plus** Gentamicin loading dose (2 mg/kg IV) followed by maintenance dose 1.5 mg/kg q8 hr (alternatively, may use once-daily gentamicin dosing)	Gram-negative bacilli (including *Pseudomonas*): • If concern for *Pseudomonas* or multidrug-resistant gram-negative infections due to special circumstances or indwelling devices, use gastrointestinal antibiotic regimens.
Intravascular or catheter-associated bloodstream infections	Empiric therapy: Vancomycin 25 mg/kg IV loading dose (max 2.5 g) followed by 15 mg/kg q12 hr, (max 2 g per dose) **or** Linezolid 600 mg IV q12 hr **plus** Piperacillin/tazobactam 4.5 g IV q6 hr **or** Cefepime 2 g IV q8 hr	Vancomycin **or** linezolid (as for non-anaphylactic patient) **plus** Ciprofloxacin 400 mg IV q12 hr **or** Aztreonam 2 g IV q8 hr **plus** An aminoglycoside (gentamicin, tobramycin, or amikacin)	When possible, treatment based on cultures is recommended.
Cardiovascular, including endocarditis and valvular infections or abscesses	Vancomycin 25 mg/kg IV loading dose (max 2.5 g) followed by 15 mg/kg q12 hr (max 2 g per dose) **or** Daptomycin 8-12 mg/kg IV q24 hr if concern for *Enterococcus* **plus** Cefepime 2 g IV q8 hr if concern for *Pseudomonas*	Vancomycin 25 mg/kg IV loading dose (max 2.5 g) followed by 15 mg/kg q12 hr (max 2 g per dose) **plus** Gentamicin 3 mg/kg IV q24	• When available, treatment based on cultures is recommended. • Three sets of blood cultures should be drawn prior to the administration of antibiotics, whenever possible. • Gentamicin 3 mg/kg/day IV q24 hr may be considered in patients with prosthetic valves, enterococcal endocarditis, and other special circumstances. • Rifampin 300 mg IV or by mouth q8 hr may also be considered in prosthetic valve endocarditis. (Infectious Disease consultation may be indicated.)
Skin/soft tissue	Vancomycin 25 mg/kg loading dose (max 2.5 g) followed by 15 mg/kg q12 hr (max 2 g per dose)	Same as for non-anaphylactic patient	• Necrotizing soft-tissue infections, including necrotizing fasciitis, should include broad-spectrum antibiotics with activity against MRSA, group A *Streptococcus* and *Clostridium perfringens*, as well as gram-negative and anaerobic coverage, as these are frequently polymicrobial. • For necrotizing soft-tissue infections, give vancomycin or linezolid plus either meropenem (1 g IV q8 hr), imipenem (1 g IV q8 hr), or piperacillin/tazobactam (4.5 g IV q6 hr). • Clindamycin 900 mg IV should also be given for its effects against toxin-producing strains of streptococci and staphylococci except in cases where linezolid is given.
Meningitis	Ceftriaxone 2 g IV q12 hr **plus** Vancomycin 25 mg/kg IV loading dose (max 2.5 g), followed by 15 mg/kg q12 hr (max 2 g per dose)	Vancomycin **plus** Moxifloxacin 400 mg IV q24 hr If *Listeria* is suspected, trimethoprim-sulfamethoxazole at 5 mg/kg (based on trimethoprim component), IV q8 hr	• For meningitis patients with impaired cellular immunity, ampicillin 2 g IV q4 hr in addition to cefepime plus vancomycin are recommended. • For healthcare-associated meningitis, cefepime or meropenem (2 g IV q8 hr) should be substituted for ceftriaxone, particularly in patients with recent surgery (eg, ventriculoperitoneal shunt). • If viral encephalitis due to herpes simplex virus is suspected, acyclovir 10 mg/kg IV q8 hr should be given.

*Most penicillin-allergic (not anaphylactic) patients may safely receive third- and fourth-generation cephalosporins (as per "Recommended Antibiotics"); however, penicillins such as piperacillin should be avoided in patients with penicillin allergy.

Recommendations are empiric and based on likely pathogens and guideline recommendations. Clinicians should follow local institutional antibiograms regarding the prevalence and sensitivity of suspected pathogens causing sepsis. In particular, some institutions have increased *Pseudomonas* resistance to fluoroquinolones, in which case alternative agents should be used if *Pseudomonas* is suspected. Initial doses of antibiotics can be dosed safely in patients with renal impairment; subsequent doses of antibiotics may require adjustment based on renal impairment.

Abbreviations: COPD, chronic obstructive pulmonary disease; IV, intravenous; q, every; MRSA, methicillin-resistant *Staphylococcus aureus.*

Corticosteroids

Several randomized trials have evaluated the effectiveness of corticosteroids in sepsis. When utilized, we suggest a dose of hydrocortisone 200 mg IV per day (continuous infusion) or a 50 mg IV bolus every 6 hours. Current guidelines weakly recommend against the use of corticosteroids in patients in whom hemodynamic stability can be established on a single vasopressor agent alone.[8] In patients requiring multiple vasopressors to achieve stability, corticosteroids may be given. In a placebo-controlled randomized double-blind study performed by Annane et al in the late 1990s, 300 patients were randomized to either hydrocortisone (50 mg IV bolus every 6 hours) and fludrocortisone (50 mcg tablet administered via nasogastric tube once daily) or to placebo for 7 days after undergoing a short corticotropin test. In nonresponders to the test, there was a significant reduction in mortality for those who received steroids compared with those who did not.[139] Similar results were found in an earlier study in which shock reversal (sustained SBP > 90 mm Hg for at least 24 hours) was achieved more frequently in vasopressor-dependent septic shock patients who received hydrocortisone rather than placebo.[140]

Another study showed a shorter time to vasopressor cessation with hydrocortisone for septic shock.[141] However, the randomized controlled CORTICUS study did not identify an improvement in mortality among septic shock patients given hydrocortisone, and it showed an increased rate of superinfections, including new sepsis and septic shock.[142] Although the patients in this study had lower disease severity than those in the previous trials, it contributed to the body of literature that argues against the use of corticosteroids in less critically ill septic shock patients. A recent task force was convened to address these uncertainties, and it recommended IV hydrocortisone at < 400 mg per day only in patients with septic shock not responsive to fluids that required moderate- to high-dose vasopressor therapy.[143]

The recent ADRENAL trial[144] was designed to provide answers to questions raised by the Annane et al and CORTICUS trials. In the ADRENAL trial, there were 3800 patients randomized to either hydrocortisone 200 mg/day (continuous infusion) for up to 7 days or until ICU discharge versus placebo. Enrolled patients were adult septic shock patients on mechanical ventilation (including noninvasive ventilation) being treated with vasopressors for at least 4 hours. Though there were no differences in 90-day mortality between patients given hydrocortisone (27.9%) or placebo (28.8%), the patients given hydrocortisone had shorter time to shock resolution (3 vs 4 days), shorter time to discharge from ICU (10 vs 12 days), shorter time to cessation of initial mechanical ventilation (6 vs 7 days), and fewer blood transfusions. There was no increase in new-onset bacteremia/fungemia. Though this trial provided compelling evidence for the use of hydrocortisone in septic shock, the primary indication for corticosteroids is unlikely to change; namely, arterial hypotension requiring moderate- to high-dose vasopressors or more than 1 vasopressor to achieve hemodynamic stability.

The APROCCHSS trial, published by Annane et al in 2016, demonstrated a decreased 90-day mortality for patients receiving hydrocortisone plus fludrocortisone (43%) compared with placebo (49.1%). Hydrocortisone was given as a 50 mg IV bolus every 6 hours, and fludrocortisone was given as a 50 mcg tablet every 6 hours orally or via nasogastric tube; both drugs were given for 7 days. However, this trial had several limitations. Patients were enrolled from 2008 to 2015, and it was stopped twice during that period. It was first suspended after 1 of the study drugs (activated protein C) was removed from the market by the manufacturer. Following this, the study continued with only 2 parallel groups. The study was again stopped to evaluate for adverse events, after which it was restarted until study completion in 2015.[145]

Blood Transfusion

Previous guidelines recommended the administration of blood in severe sepsis patients to achieve $ScvO_2 > 70\%$.[146] This was based on the original Rivers et al study that included the transfusion of packed red blood cells to a goal hematocrit of 30% to achieve this resuscitative endpoint.[2] However, more recently, the TRISS trial (a multicenter parallel group trial) compared transfusion to a hemoglobin goal of 9 g/dL versus 7 g/dL in septic shock patients and found no difference in outcomes. Therefore, it is not recommended to transfuse patients with a hemoglobin ≥ 7 g/dL unless other indications arise.[147]

Special Populations

A variety of physiologic processes and states may challenge a clinician's ability to recognize and treat sepsis. In one study, female sepsis patients experienced higher mortality.[148] Elderly patients also have worse outcomes, due to chronic inflammation, impaired cardiovascular function, and differing inflammatory responses compared to younger patients with septic shock.[149,150] In patients with cirrhosis, chronic decreases in blood pressure and platelet count—along with tachycardia and impaired lactate clearance—could be misinterpreted as normal physiologic variations rather than correctly identified as sepsis.

Pregnant Patients

The physiologic changes of pregnancy make sepsis recognition and treatment more difficult, as patients typically have baseline decreased blood pressure and platelet count and increased heart rate, white blood cell count, and respiratory rate. Pregnancy can also increase the risk of pneumonia and a variety of genitourinary infections, and sepsis in pregnancy can increase risk of perinatal infection and maternal and fetal morbidity.[151] Bacteremia may occur in up to 9% of all pregnancies, though a recent study of peripartum patients showed that few cases of septic shock developed.[152]

Patients With End-Stage Renal Disease

In patients with end-stage renal disease (ESRD), bacteremia is common, and one must remain vigilant for sepsis from intravascular devices. ESRD sepsis patients also have a higher mortality than non-ESRD sepsis patients.[153] Renal patients often take medications for comorbid conditions that may mask subtle clues to sepsis. Furthermore, frequent large fluid shifts may limit the patient's physiologic response to acute illness. While many clinicians have concern for volume overload in these patients, current evidence supports administering the same initial IV fluid boluses.[154-157]

Controversies and Cutting Edge

Controversies

Fluid Volume

Controversies regarding the correct volume of fluids for special patient populations (congestive heart failure, ESRD, obesity) exist. As discussed previously, there is some indication from the literature that adjusted body weight for obese patients may be superior to actual or ideal body weight fluid dosing. There is also the suggestion that congestive heart failure and ESRD patients are treated with smaller volumes of fluids, though this has not demonstrated differences in mortality. We recommend that initial fluid volumes adhere generally to quality metrics of 30 mL/kg in hypotensive patients or those with lactate > 4 mmol/L, with the caveat that the assessment of individual patient fluid needs takes precedence over guideline recommendations.

Etomidate

The use of etomidate for endotracheal intubation of septic patients has been long debated. Though etomidate is known to cause adrenal suppression, the degree to which this is clinically relevant has not been established. A recent retrospective propensity-matched study of septic patients intubated with etomidate versus ketamine demonstrated significantly increased hypotension in the 6 to 12 hours following intubation in the etomidate group compared with the ketamine group.[158] A previous meta-analysis also demonstrated increased mortality and adrenal insufficiency related to etomidate use in sepsis, though the study raised significant methodologic issues.[159,160] Of note, the recent ADRENAL trial excluded patients who had received etomidate, indicating the investigators' concerns that etomidate may cause clinically relevant adrenal suppression.[144] In light of alternatives such as ketamine, it is our opinion that etomidate should be considered a second-line induction agent.

Cutting Edge

Currently, there are no specific treatments for sepsis, though there are several potential therapies and new areas of investigation:[161]

- The recently completed (and soon to be published) Rapid Administration of Carnitine in sEptic Shock (RACE) trial tested the hypothesis that L-carnitine administration might reduce cumulative organ failure in patients with septic shock.[162]
- A provocative before-and-after study of vitamin C, thiamine, and corticosteroids for the treatment of sepsis showed an improved mortality in patients given this novel treatment.[163] A multicenter randomized controlled trial (VICTAS, NCT03509350) is currently enrolling patients, with estimated study completion in October 2021.
- Immunostimulant therapies (such as IL-7) in immunosuppressed patients with sepsis are being investigated.[164]
- A comparison of a crystalloid liberal versus early vasopressor approach to early septic shock patients is also underway (CLOVERS, NCT03434028).

Disposition

Not all patients who have a suspected infection and SIRS require inpatient admission. SIRS criteria may represent an appropriate host response to infection and are not necessarily indicative of a dysregulated or life-threatening response to infection.[1]

Patients who have a qSOFA score ≥ 2 represent a subset of septic patients with increased mortality in whom ICU admission should be considered. However, those with a qSOFA < 2 may still require a higher level of care. Patients who have a qSOFA score of 1 but a lactate ≥ 2 mmol/L have a mortality risk similar to patients with qSOFA ≥ 2.[12] A recent prospective study of patients in the ED or wards who were subsequently admitted to the ICU demonstrated a 6% mortality for patients with qSOFA score < 2.[165]

Septic patients requiring mechanical ventilation or vasopressor support clearly warrant intensive care; however, other patients may require ICU ad-

Risk Management Pitfalls for Sepsis Management in the Emergency Department

1. **"I didn't reassess the patient's lactate."**
   Lactate clearance can aid in assessing a patient's response to treatment. Persistently elevated lactate may indicate inadequate resuscitation or alternative diagnoses. Particular attention should be given to patients with limited lactate clearance, as persistent elevation is associated with poor outcomes.

2. **"I was afraid to give the initial 30 mL/kg IV fluid bolus to my hypotensive septic patient."**
   While a fluid bolus in the first 6 hours for all patients with septic shock (lactate > 4 mmol/L or hypotension not responsive to fluids) is recommended, often practitioners are uncertain whether to give these boluses to patients with ESRD, congestive heart failure, or other stable chronic medical conditions. In the absence of overt hypervolemia, emergency clinicians should recognize that administering this volume of fluids to most patients with sepsis is safe and, when concern for fluid overload exists, the initial IV fluid bolus may be given more slowly.

3. **"I overlooked the patient's mental status."**
   Mental status is an important sign of end-organ dysfunction in sepsis. A careful evaluation is essential to avoid attributing altered mental status from sepsis to dementia or other causes.

4. **"I didn't notice the subtle signs of organ dysfunction."**
   Minor laboratory abnormalities, decreased capillary refill, and limited urine output can be easily overlooked; however, careful assessments of each organ system can help identify clues to making the diagnosis of sepsis.

5. **"I wasn't sure of the patient's source of infection, so I waited to give antibiotics."**
   Patients with presumed sepsis and hypotension have an increased mortality when antibiotics are delayed. In such cases, administering broad-spectrum antibiotics prior to source confirmation is recommended. For stable patients in whom sepsis is being considered, source-directed antibiotics should be administered as soon as practical and, ideally, within 1 hour of sepsis recognition.

6. **"I didn't choose or dose the antibiotics correctly."**
   Empiric antibiotics should be chosen based on the anatomic site of infection, local bacterial resistance and susceptibilities, immunosuppression, age, comorbidities, and indwelling devices. Full loading doses of antibiotics should be given in the ED regardless of renal function.

7. **"I didn't perform a complete evaluation to identify an occult source of infection prior to admission."**
   Always evaluate for occult sources of infection by performing a complete history and physical examination. When concern for occult infections exists, advanced imaging may be necessary to diagnose the source of infection. Meningitis, skin and soft-tissue infections, as well as intra-abdominal infections should also be considered.

8. **"I thought the patient would be appropriate for the general ward."**
   qSOFA-positive patients or patients with significant organ dysfunction are at risk of poor outcomes from sepsis. Patients with multiple organ dysfunction usually require increased resources while admitted, and ICU admission should be considered.

9. **"I used dopamine as the first-line vasopressor for septic shock."**
   Recent literature and guidelines support norepinephrine as the first-line vasopressor for septic shock. Dopamine is associated with increased risk of arrhythmias and mortality compared with norepinephrine.

10. **"Our hospital has not instituted a program for early sepsis recognition and management."**
    Institution-wide programs facilitate sepsis recognition and rapid treatment and may improve outcomes in patients at risk for sepsis and septic shock.

mission due to risk of progressing from sepsis to septic shock. Careful consideration of potential ICU needs is recommended, as some evidence suggests that patients admitted to a general medicine floor and subsequently transferred to ICUs have worse outcomes.[166-168] One study showed that factors associated with progression to septic shock within 4 to 48 hours of ED arrival included nonpersistent hypotension, female gender, bandemia of at least 10%, lactate of at least 4 mmol/L, and history of coronary artery disease.[169]

End-of-Life Care

Aggressive treatment may not align with patient or family goals of care for those with end-stage conditions such as metastatic cancer, end-stage liver disease, and other similar conditions. When resuscitative efforts could be considered futile or contrary to the patient's wishes, hospice and advanced directives should be addressed. However, "allow-natural-death" orders should not be considered a contraindication to initial resuscitation. Recent studies have shown similar rates of resuscitation for septic patients with do not resuscitate/do not intubate status, with initial survival rates of 50% or more.[170] In some cases, it is reasonable to proceed with aggressive resuscitation of these patients, if desired by the patients and their families. A discussion of likely outcomes for various treatment strategies may help patients and their decision-makers determine which course is most appropriate.

Summary

In patients presenting with infection and suspected organ dysfunction after clinical assessment, the diagnosis of sepsis should be considered seriously. SIRS criteria are still useful for sepsis screening, and patients with infection plus a qSOFA score ≥ 2 should be managed urgently, placed in a monitored bed, and treated with a sepsis care bundle, if possible. In patients with qSOFA scores < 2, after laboratory assessment, a full SOFA score may be calculated to assess for organ dysfunction. Patients with a SOFA score ≥ 2 or with end-organ dysfunction should be diagnosed as having sepsis and treated.

For patients with sepsis, we recommend the development and utilization of institutional protocols for initial care. These should include obtaining a serum lactate and 2 sets of blood cultures (prior to antibiotics whenever practical) as well as the administration of IV antibiotics to cover the suspected organism and a 30 mL/kg IV fluid bolus in patients with hypotension or a lactate > 4 mmol/L. Infectious source control is also recommended to be undertaken as quickly as possible. Lactate clearance by 10% to 20% or normalization (< 2 mmol/L) are literature-supported goals of resuscitation, while $ScvO_2$ and central venous pressure monitoring are no longer routinely recommended but may be indicated in select patients. In patients with septic shock not responsive to an initial IV fluid bolus, norepinephrine should be initiated at a starting dose of 0.1 to 0.5 mcg/kg/min IV and titrated to achieve MAP > 65 mm Hg up to a maximum of 1 mcg/kg/min. Second-line vasopressors, including vasopressin and epinephrine, may be added, depending on the patient's cardiac function and peripheral perfusion. IV hydrocortisone is recommended only in patients with septic shock that is not responsive to IV fluids and is requiring moderate- to high-dose vasopressors. Blood transfusion is also not generally recommended unless the patient has a hemoglobin of ≤ 7 g/dL, outside of special circumstances or obvious blood loss.

Case Conclusions

The 65-year-old man with COPD had a WBC of 13.4 with 80% PMNs, a creatinine of 1.0 mg/dL, and a normal platelet count. You treated his wheezing with albuterol and ipratropium and administered acetaminophen for fever. Repeat vital signs were: heart rate, 80 beats/min; blood pressure, 128/86 mm Hg; respiratory rate, 14 breaths/min; and SpO_2, 98% on room air. The patient had a qSOFA score of 1 for respiratory rate, but no organ dysfunction, and a normal lactate. He tolerated oral medications and had inhalers for COPD at home. You initiated oral antibiotics for his community-acquired pneumonia, ensured that he could follow up with his primary care provider within a few days and that his wife could properly care for him, and discharged him home.

The 45-year-old man with the urinary tract infection had a SOFA score of 2 and met the Sepsis-3 definition of sepsis, due to pyelonephritis. The patient was convinced to stay in the hospital, had 2 sets of blood cultures drawn, 30 mL/kg of IV fluids administered, and a dose of ceftriaxone 2 grams IV administered. His vital signs remained stable, and the patient was admitted to a monitored hospital bed. He was discharged 2 days later to continue oral antibiotics.

The 70-year-old woman with the painful foot was qSOFA-positive. She was rapidly moved to the resuscitation bay, where 2 large-bore IV catheters were placed. Two sets of blood cultures, complete labs, and a lactate level were drawn, and an initial IV fluid bolus with 30 mL/kg of isotonic fluids was initiated. Piperacillin/tazobactam 4.5 g IV was given in the first hour of arrival to the ED, followed by clindamycin 900 mg IV and vancomycin 25 mg/kg IV. The patient remained hypotensive after IV fluid resuscitation and required norepinephrine initiated at 10 mcg/min IV to maintain a MAP > 65 mm Hg. Her lactate level was 4 mmol/L. After obtaining plain radiographs of the right foot and leg that demonstrated soft-tissue gas, the patient was taken emergently to the operating room for necrotizing fasciitis. Postoperatively, the patient was admitted to the surgical ICU for continued care, where she remained for 10 days. After a 2-week stay in the hospital, she was discharged back to her facility.

Time- and Cost-Effective Strategies

- Hospital admissions due to sepsis have increased significantly in recent years and are now the most expensive reason for hospitalization.[171] Unsurprisingly, this has led to increased focus on potential cost-saving strategies for improving care for septic patients. Institutional protocols for the initial care of septic patients have been associated with lower costs and improved mortality rates.[91,172]
- Unnecessary blood cultures in immunocompetent febrile patients, patients without significant comorbidities, stable patients with viral illnesses, or patients who do not have sepsis and are likely to be discharged can be costly to an institution. Nonetheless, any patient with sepsis should be cultured.
- Point-of-care lactate testing is a cost-effective method to allow for rapid reporting of critical lactate values in the septic patient and may be useful for streamlining processes of care.

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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 is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

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1. Which of the following is part of the Centers for Medicare and Medicaid Services definition of septic shock?
   a. Hypotension not responsive to fluids and requiring vasopressors to maintain a mean arterial pressure > 65 mm Hg
   b. White blood cell count > 20,000
   c. Lactate > 4 mmol/L
   d. Altered mental status

2. A 70-year-old woman with congestive heart failure presents complaining of shortness of breath and is diagnosed with pneumonia. Initial vital signs are: heart rate, 88 beats/min; blood pressure, 98/65 mm Hg; respiratory rate, 22 breaths/min; SpO_2, 97%; and temperature, 37.5°C (99.5°F) After IV antibiotics and fluids, her repeat vitals signs are: heart rate, 90 breaths/min; blood pressure, 90/50 mm Hg; respiratory rate, 20 breaths/min; and SpO_2, 95%. Which of the following most strongly influences your decision to admit her to the ICU?
   a. Pneumonia as the infectious etiology
   b. Her age
   c. Systolic blood pressure < 100 mm Hg
   d. Her history of congestive heart failure

3. Which of the following infections is the most common source of sepsis in an immunocompetent patient?
   a. Urinary tract infection
   b. Other intra-abdominal infection
   c. Pneumonia
   d. Cellulitis

4. **A 38-year-old man with diabetes presents with fever, altered mental status, and hypotension. Which of the following is the best next action while initiating the institutional sepsis protocol?**
   a. Place a Foley catheter to monitor resuscitation.
   b. Administer acetaminophen for fever.
   c. Perform a complete bedside physical examination to identify the source of infection.
   d. Perform a lumbar puncture when hemodynamically stable.

5. **Point-of-care ultrasound is particularly useful in sepsis for:**
   a. Diagnosing distributive shock by recognizing low cardiac output.
   b. Assessing cardiac output or fluid status at the bedside in a noninvasive manner.
   c. Measuring the aorta to determine whether the patient is volume depleted.
   d. Placement of central venous catheter for routine central venous oxygen saturation monitoring.

6. **A 60-year-old man presents with 3 days of fevers, chills, and abdominal pain. Vital signs are: blood pressure, 90/60 mm Hg; heart rate, 115 beats/min; respiratory rate, 20 breaths/min; temperature, 38.5°C (101.5°F); oxygen saturation, 96%; and glucose, 220 mg/dL. He has left lower quadrant abdominal tenderness and his urinalysis shows +nitrite and 12 WBCs. He has no costovertebral angle tenderness. Which of the following are appropriate initial steps in management?**
   a. Obtain a urinalysis and urine culture and reassess after test results come back.
   b. Obtain IV access and obtain labs for assessing organ dysfunction while administering 1 L of normal saline.
   c. Obtain IV access and obtain labs for assessing organ dysfunction and a lactate, administer a fluid bolus and antibiotics to cover an abdominal source of infection, and order a CT scan of the abdomen and pelvis.
   d. Obtain IV access, administer an IV fluid bolus, give IV piperacillin/tazobactam and vancomycin, and consult surgery.

7. **Regarding the patient in the previous question, which of the following has the best evidence for improved mortality?**
   a. Early administration of norepinephrine
   b. Administration of broad-spectrum antibiotics as soon as it is practical
   c. Initial IV fluid bolus
   d. Obtaining blood cultures

8. **A 65-year-old woman presents with cough, fever, hypotension and tachypnea. Chest x-ray reveals pneumonia, and she is treated with a sepsis bundle, including appropriate antibiotics. After IV fluids, her blood pressure is 80/56 mm Hg. What is the next step in management?**
   a. Administer additional IV fluids and reassess blood pressure and mean arterial pressure.
   b. Administer vasopressin at 0.04 units/min, give an additional IV fluid bolus, and admit to the ICU.
   c. Initiate IV norepinephrine at 5 mcg/min and admit to the ICU.
   d. Administer low-dose IV dopamine, give additional IV fluids, and admit to intermediate care.

9. **Regarding sepsis in special populations, which of the following is TRUE?**
   a. Men experience higher mortality than women.
   b. Elderly patients respond physiologically to inflammation in the same way as younger patients.
   c. Patients with end-stage renal disease should receive initial IV fluid boluses of 20 mL/kg
   d. Cirrhotic patients may have elevated lactate levels due to impaired liver clearance, even without acute infection.

10. **Regarding the qSOFA score, which of the following is TRUE?**
    a. Patients with a score < 2 should be discharged home
    b. Patients with a lactate of ≥ 2 mmol/L and a qSOFA score of 1 have similar mortality to patients with a score of ≥ 2.
    c. Patients with suspicion of infection plus qSOFA score of 1 require treatment with a sepsis bundle upon arrival.
    d. The full SOFA score should be calculated routinely in patients with a qSOFA score of ≥ 2.

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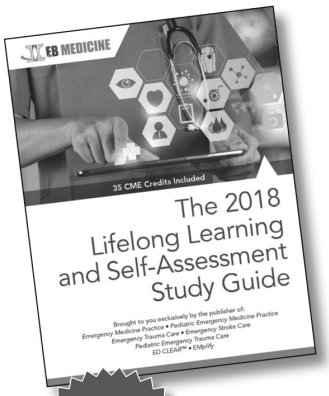

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Objectives: Upon completion of this article, you should be able to: (1) describe potential methods for early sepsis recognition in a patient presenting with signs and symptoms of infection, (2) list the elements of the Sequential (Sepsis-related) Organ Failure Assessment score and its utility in clinical practice, (3) provide specific recommendations for early management of severe sepsis and septic shock, and (4) explain the implications of national quality metrics for sepsis care.

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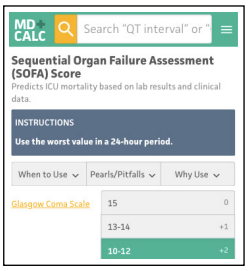

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Sequential Organ Failure Assessment (SOFA) Score

Introduction: The SOFA score predicts mortality risk for patients in the intensive care unit based on lab results and clinical data.

Points & Pearls

- The Sequential Organ Failure Assessment (SOFA) is a mortality prediction score that is based on the degree of dysfunction of 6 organ systems.
- The score is calculated at admission and every 24 hours until discharge, using the worst parameters measured during the prior 24 hours.
- The scores can be used in several ways, including:
  - » As individual scores for each organ to determine the progression of organ dysfunction.
  - » As a sum of scores on a single intensive care unit (ICU) day.
  - » As a sum of the worst scores during the ICU stay.
- The SOFA score stratifies mortality risk in ICU patients without restricting the data used to admission values.

Critical Actions

Clinical prediction scores such as the SOFA and the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) can be measured on all patients who are admitted to the ICU, to determine the level of acuity and mortality risk. This information can then be used in various ways, such as to provide the family with a prognosis, for clinical trials, and/or for quality assessment.

The SOFA score is not designed to influence medical management. It should not be used dynamically or to determine the success or failure of an intervention in the ICU.

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Why to Use

The SOFA score can be used to determine the level of organ dysfunction and mortality risk in ICU patients.

When to Use

- The SOFA can be used on all patients who are admitted to an ICU.
- It is not clear whether the SOFA is reliable for patients who were transferred from another ICU.

Instructions

Calculate the SOFA score using the worst value for each variable in the preceding 24-hour period.

Next Steps

Even though it is calculated sequentially based on the worst value for each variable in the past 24 hours, the SOFA score is not meant to indicate the success or failure of interventions or to influence medical management.

Abbreviations: ICU, intensive care unit; SOFA, sequential organ failure assessment.

Evidence Appraisal

The SOFA variables were selected by a working group of the European Society of Intensive Care Medicine (Vincent 1996). In the initial validation study, 1449 patients were enrolled over a period of 1 month from 40 ICUs in 16 countries (Vincent 1998). The study found that the SOFA score had a good correlation to organ dysfunction/failure in critically ill patients.

The SOFA score was also prospectively validated in an observational cohort study conducted by Ferreira et al (2001) at the ICU of a university hospital in Belgium. The study included 352 patients and found that the SOFA score was a good indicator of prognosis.

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Calculator Creator

Jean-Louis Vincent, MD, PhD
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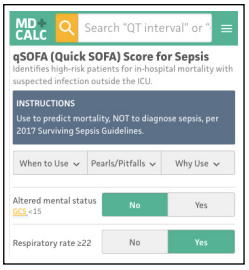

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qSOFA (Quick SOFA) Score for Sepsis

Introduction: The qSOFA score identifies patients with suspected infection who are at high risk for in-hospital mortality outside of the intensive care unit.

Points & Pearls

- The quick Sequential Organ Failure Assessment (qSOFA) was introduced by the Third International Consensus Definitions for Sepsis and Septic Shock ("Sepsis-3") as a simplified version of the Sequential Organ Failure Assessment (SOFA). The SOFA is a validated intensive care unit (ICU) mortality prediction score; the qSOFA was derived by Sepsis-3 to help identify patients with suspected infection who are at high risk for poor outcome (defined as in-hospital mortality or an ICU stay of ≥ 3 days) outside of the ICU.
- The qSOFA simplifies the SOFA significantly by including only 3 clinical criteria, each of which are easily assessed at the bedside.
- Calculation of the qSOFA score can be repeated serially if there is a change in the patient's clinical condition.
- The qSOFA score predicts mortality but does not diagnose sepsis, and it still has an unclear role in the sequence of events from screening to diagnosis to the triggering of sepsis-related interventions.
- At this time, no prospective studies have demonstrated that clinical decisions based on the qSOFA lead to better patient outcomes.
- The most recent Surviving Sepsis Campaign guidelines, published in March 2017, do not integrate the qSOFA into recommendations for screening or diagnosis of sepsis.

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Why to Use
The qSOFA score identifies patients with suspected infection who are at high risk for in-hospital mortality outside of the ICU. It may help increase suspicion or awareness of a severe infectious process and prompt further testing and/or closer monitoring of the patient.

When to Use
Use the qSOFA for patients aged ≥18 years who have a confirmed or suspected infection and are in a non-ICU setting (ie, prehospital, ward, emergency department, or step-down unit).

Instructions
The qSOFA score should be used to predict mortality, not to diagnose sepsis, per the 2016 Surviving Sepsis Campaign guidelines.

Next Steps
A "positive" qSOFA score (≥ 2) suggests high risk of poor outcomes in patients with suspected infection. These patients should be more thoroughly assessed for evidence of organ dysfunction. A positive qSOFA score by itself should not trigger sepsis-directed interventions such as the initiation of broad-spectrum antibiotics; rather, it should prompt clinicians to further investigate for the presence of organ dysfunction or increase the frequency of patient monitoring.

Abbreviations: ICU, intensive care unit; qSOFA, quick sequential organ failure assessment.

Advice
The Sepsis-3 task force recommended that a positive qSOFA score should prompt the calculation of a SOFA score to confirm the diagnosis of sepsis. This recommendation remains controversial, as the qSOFA has been shown to be more predictive than the SOFA outside of the ICU setting. Even if the patient's qSOFA score is initially "negative" (< 2), it can be repeated if there is a change in the patient's clinical status.

Critical Actions
The qSOFA is a mortality predictor, not a diagnostic test for sepsis. It is still not clear how it will be used in the sequence of events from screening to diagnosis of sepsis to the triggering of sepsis-related interventions. The management of sepsis is continuously evolving and is detailed in the 2016 Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock (Rhodes 2017).

Evidence Appraisal
The qSOFA was introduced in February 2016 by the Sepsis-3 task force as a rapid, bedside clinical score to identify patients with suspected infection who are at greater risk for poor outcomes. The primary outcome was in-hospital mortality, and the secondary outcome was an ICU length of stay of ≥ 3 days. The qSOFA was meant to replace the systemic inflammatory response syndrome (SIRS) criteria, which were believed to be less sensitive and specific, although this remains controversial.

Seymour et al retrospectively derived and internally validated the qSOFA in a 2016 study that included 148,907 patients with suspected infection, either inside or outside of the ICU setting. For patients outside of the ICU with a qSOFA score ≥ 2, there was a 3- to 14-fold increase in the rate of in-hospital mortality. Among ICU patients, however, the predictive validity of the SOFA for in-hospital mortality was statistically greater than the qSOFA.

The qSOFA was prospectively validated in an emergency department population in a study by Freund et al published in 2017. The study, which included 879 patients across 30 emergency departments in 4 countries, found that use of the qSOFA resulted in greater prognostic accuracy for in-hospital mortality than either SIRS or severe sepsis.

Raith et al (2017) externally validated the SOFA and the qSOFA in a retrospective cohort analysis of 184,875 patients who had an infection-related admission diagnosis. The study found that, in an ICU population, an increase in the SOFA score of ≥ 2 points had greater prognostic accuracy for in-hospital mortality than the SIRS criteria or the qSOFA.

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Calculator Creator
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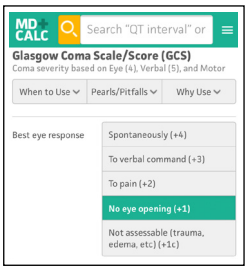

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Glasgow Coma Scale

Introduction: The Glasgow coma scale (GCS) estimates coma severity based on eye, verbal, and motor criteria.

Points & Pearls

- The Glasgow coma scale (GCS) allows providers in multiple settings and with varying levels of training to communicate succinctly about a patient's mental status.
- The GCS score has been shown to have statistical correlation with a broad array of adverse neurologic outcomes, including brain injury, need for neurosurgery, and mortality.
- The GCS score has been incorporated into numerous guidelines and assessment scores (eg, Advanced Cardiac Life Support, Advanced Trauma Life Support, Acute Physiology and Chronic Health Evaluation I-III, the Trauma and Injury Severity Score, and the World Federation of Neurologic Surgeons Subarachnoid Hemorrhage Grading Scale)

Points to keep in mind:

- Correlation with outcome and severity is most accurate when the GCS is applied to an individual patient over time; the patient's trend is important.
- A GCS score of 8 should not be used in isolation to determine whether or not to intubate a patient, but does suggest a level of obtundation that should be evaluated carefully.
- Reproducibility of the GCS score can be low; if individual institutions have concerns about agreement between providers, training and education are available online from the GCS creators at www.glasgowcomascale.org.
- There are simpler scores that have been shown to perform as well as the GCS for initial evaluation in the prehospital and emergency department setting; these are often contracted versions of the GCS itself. For example, the simplified motor score (SMS) uses only the motor portion of the GCS. THE SMS and other contracted scores are less well studied than the GCS for outcomes like long-term mortality, and the GCS has been studied as trended over time, while the SMS has not.

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Critical Actions

Although it has been adopted widely and in a variety of settings, the GCS score is not intended for quantitative use. Clinical management decisions

Why to Use

The GCS is an adopted standard for mental status assessment in the acutely ill trauma and nontrauma patient and assists with predictions of neurological outcomes (complications, impaired recovery) and mortality.

When to Use

- The GCS is designed for use in serial assessments of patients with coma from either medical or surgical causes and is widely applicable.
- The GCS is commonly used in the prehospital and acute care setting as well as over a patient's hospital course to evaluate for mental status assessment in both traumatic and nontraumatic presentations.

Next Steps

- The GCS can indicate the level of critical illness.
- Trauma patients presenting with a GCS score < 15 warrant close attention and reassessment.
- A declining GCS score is concerning in any setting, and should prompt airway assessment and possible intervention.
- Conversely, a GCS score of 15 should not be taken as an indication that a patient (trauma or medical) is not critically ill. Decisions about the aggressiveness of management and treatment plans should be made based on clinical presentation and context, and should not be overridden in any way by the GCS score.
- Clinical management decisions should not be based solely on the GCS score in the acute setting.
- If a trauma patient has a GCS score < 8 and there is clinical concern that the patient is unable to protect his or her airway or there is an expected worsening clinical course based on examination or imaging findings, then intubation can be considered.
- In any patient, a rapidly declining or waxing and waning GCS score is concerning and intubation should be considered in the context of the patient's overall clinical picture.

Abbreviation: GCS, Glasgow Coma Scale.

should not be based solely on the GCS score in the acute setting.

Evidence Appraisal

The modified Glasgow coma scale (modified GCS) is a 15-point scale that has been widely adopted, including by the original unit in Glasgow, as opposed to the 14-point scale. The modified GCS was developed to be used in a repeated manner in the inpatient setting to assess and communicate changes in a patient's mental status and to measure the duration of coma (Teasdale 1974).

In the acute care setting, the GCS has been shown to have highly variable reproducibility and interrater reliability (ie, 56% among neurosurgeons in 1 study, 38% among emergency department physicians in another study). In its most common usage, the 3 sections of the GCS are often combined to provide a summary of severity. The authors themselves have explicitly objected to the score being used in this way, and analysis has shown that patients with the same total score can have huge variations in outcomes, specifically mortality. A GCS score of 4 predicts a mortality rate of 48% if calculated 1 (eye) + 1 (verbal) + 2 (motor), and a mortality rate of 27% if calculated 1 (eye) + 2 (verbal) + 1 (motor), but a mortality rate of only 19% if calculated 2 (eye) + 1 (verbal) + 1 (motor) (Healey 2014).

In summary, the modified GCS provides an almost universally accepted method of assessing patients who have acute brain damage. The summation of the GCS components into a single overall score results in information loss and provides only a rough guide to severity. In some circumstances, such as early triage of severe injuries, an assessment of only a contracted version of the motor component of the scale (such as the SMS), can perform as well as the GCS and is significantly less complicated. However, the SMS may be less informative in patients with less severe injuries.

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Calculator Creator

Sir Graham Teasdale, MBBS, FRCP
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