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CLINICAL CHALLENGES:

- **What are the most recent changes to sepsis and septic shock screening guidelines?**
- **What are the current recommendations on sepsis treatment?**

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

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Prior to beginning this activity, see "CME Information" on page 2.

Abstract

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

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Goals: Upon completion of this activity, you should be able to: (1) identify areas in practice that require modification to be consistent with current evidence in order to improve competence and performance; (2) develop strategies to accurately diagnose and treat both common and critical ED presentations; and (3) demonstrate informed medical decision-making based on the strongest clinical evidence.
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Case Presentations

CASE 1

A 40-year-old woman with no past medical history presents with 3 days of fever, chills, dysuria, and flank pain…

- Her initial vital signs on ED triage are: temperature, 38.5°C; heart rate, 120 beats/min; blood pressure, 135/82 mm Hg; respiratory rate, 18 breaths/min; and oxygen saturation, 95% on room air.
- She is speaking in full sentences, demonstrating normal mentation, and is not in respiratory distress. Her lungs are clear to auscultation. Her abdomen is soft and minimally tender over the suprapubic region without rebound or guarding, with right costovertebral angle tenderness. She has brisk capillary refill. The patient has no recent hospitalizations.
- You believe she looks clinically well, but you wonder how concerned you should be about sepsis…

CASE 2

A 63-year-old man with a past medical history of right knee replacement 3 months ago, diabetes mellitus, and hypertension presents to the ED with fever, cough, and dyspnea…

- His initial vital signs are: temperature, 38.5°C; heart rate, 112 beats/min; blood pressure, 102/68 mm Hg; respiratory rate, 22 breaths/min; and oxygen saturation, 93% on room air.
- He is alert, but thinks it is 1997 and that Bill Clinton is the United States president. Physical examination reveals rales at the left lung base, no wheezing or respiratory distress, tachycardia, a benign abdomen, and well-healing surgical incisions.
- Laboratory findings include WBC of 14 $\times 10^3/mm^3$ with 5% bandemia, platelet count of 130 $\times 10^3/mm^3$, creatinine of 1.5 mg/dL (baseline of 0.85 mg/dL), and serum lactate of 2.5 mmol/L.
- Chest radiograph confirms left lower lobe infiltrate. After receiving ibuprofen and acetaminophen, the patient feels much better and requests to be discharged. His confusion has now resolved; he is oriented to person, place, time, and situation. The nurse asks whether she can remove the IV for the patient to be discharged, but something worries you…

CASE 3

A 35-year-old man with a past medical history of poorly controlled diabetes mellitus and IV drug use presents to the ED for right axillary pain and swelling…

- The paramedics report that he frequently presents for poorly controlled diabetes. He continues to complain of "20/10" pain despite 150 mcg of prehospital IV fentanyl. Prehospital vital signs include: temperature, 39.4°C; heart rate, 135 beats/min; blood pressure, 82/52 mm Hg; respiratory rate, 30 breaths/min; and oxygen saturation, 88% on room air. His initial glucose level is 342 mg/dL.
- The patient is alert and oriented but screaming in pain as he is transferred from the EMS stretcher. Physical examination reveals tachycardia; delayed capillary refill to 4 seconds; tachypnea; clear breath sounds; and erythema, swelling, and crepitus overlying the right axilla and chest wall.
- After 2 liters of isotonic crystalloid administration by EMS, repeat blood pressure is 70/45 mm Hg. You consider the best antibiotic(s) and are uncertain whether you should initiate vasopressors now, attempt another fluid bolus, or do both simultaneously…

Introduction

Sepsis is a life-threatening, dysregulated response to infection.[1] Biologically, sepsis is characterized by excessive inflammation, suppression of innate and adaptive immunity, and vascular injury.[2] Both host and pathogen factors influence the risk for developing sepsis. Annually in the United States, there are more than 850,000 emergency department (ED) visits related to sepsis.[3] Differences between federal reimbursement criteria, academic society guidelines, and cutting-edge literature have generated confusion for clinicians regarding the optimal management of sepsis in the ED. Although, in general, early, aggressive management of sepsis is recommended,[4-6] current controversies involve identifying ideal resuscitation targets; optimizing intravenous (IV) fluid resuscitation; clarifying the dosing, timing, and selection of vasoactive medications; and exploring novel targeted therapies. This issue of *Emergency Medicine Practice* reviews the recent updates in sepsis terminology, criteria, prognosticators, and quality metrics. It also offers recommendations for the recognition and treatment of sepsis and septic shock in the ED.

Critical Appraisal of the Literature

To evaluate recent clinically relevant articles regarding the diagnosis and early management of 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 2021 to 2025. Acknowledging the breadth of the sepsis literature, additional specific searches were performed and current consensus guidelines were also reviewed. The search identified 1052 articles. Five co-authors independently screened and eliminated irrelevant articles before full-text review.

Definitions and Terminology

The definition and diagnosis of sepsis has evolved substantially since the inception of standardized definitions in 1991.[7] "Sepsis-1" definitions (adopted in 1991) and "Sepsis-2" definitions (adopted in 2001) categorized sepsis as a systemic inflammatory response syndrome (SIRS) due to infection. *Severe sepsis* was defined as sepsis with organ dysfunction, and *septic shock* was defined as sepsis-induced hypotension despite fluid resuscitation.[7,8] SIRS criteria reflect only inflammation, which may involve an appropriate host response to an infection, and do not necessarily capture organ dysfunction or indicate a dysregulated response to an infection.[1] SIRS criteria were criticized for being overly sensitive, poorly specific, and having poor prognostic value for sepsis screening.[1] Shifting away from the focus on SIRS criteria,[8] in 2016, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force and agreed on updated definitions and clinical criteria.[1]

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 "a subset of sepsis in which underlying circulatory and cellular metabolic abnormalities are profound enough to increase mortality," clinically characterized by a persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) ≥65 mm Hg, and a lactate level >2 mmol/L, despite IV fluid resuscitation.[1] These new definitions were adopted by the 2016 Surviving Sepsis Campaign International Guidelines.[5] The 2016 guidelines did not include the term *severe sepsis*, although the updated definition of sepsis closely resembles the previous definition of severe sepsis.[1]

The updated definitions in Sepsis-3 emphasized organ dysfunction in the setting of infection, which can be quantified using the sequential (sepsis-related) organ failure assessment (SOFA) score. **See Table 1** for the SOFA score criteria. In Sepsis-3, the consensus definition of sepsis was clinically operationalized as a new (or presumed new) increase in the SOFA score of ≥2 points above baseline in the presence of infection.[11] Increasing SOFA scores are associated with increases in mortality.

Consensus Definitions and the United States Centers for Medicare & Medicaid Services Quality Measures

It is important to distinguish between the current understanding of sepsis consensus definitions versus federal compensation metrics and requirements. The United States Centers for Medicare & Medicaid Services (CMS) SEP-1 quality measures are currently used to evaluate institutional compliance with (1) the severe sepsis bundle, and (2) the septic shock bundle. Though the controversial CMS SEP-1 mandate has not adopted Sepsis-3 definitions of sepsis, the Sepsis-3 definition of sepsis closely resembles the prior "severe sepsis" definition, which is used in the severe

Table 1. Sequential (Sepsis-Related) Organ Failure Assessment Score[1,9,10]

Variables	SOFA Score				
	0	1	2	3	4
Respiratory (ratio)	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, 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 × $10^3/mm^3$)	≥150	<150	<100	<50	<20
Neurologic (Glasgow Coma Scale score)	15	13-14	10-12	6-9	<6

Abbreviations: 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.

sepsis bundle. The CMS SEP-1 mandate categorizes any infection with organ dysfunction or a lactate >2 mmol/L as *severe sepsis*, and defines *septic shock* as "hypotension (systolic blood pressure [SBP] <90 mm Hg) not responsive to fluids, or serum lactate ≥4 mmol/L, regardless of hypotension."[12,13] Notably, the CMS SEP-1 measures did not require vasopressor dependence as part of its definition for septic shock, which is a marked difference from consensus definitions. A comparison of the 2016 Sepsis-3 to the 2001 Sepsis-2 definitions, as well as to the CMS SEP-1 criteria, are presented in **Table 2**.

Screening

Early detection and treatment of sepsis are associated with improved outcomes.[14,15] Several early sepsis screening tools have been used, including SIRS criteria, quick SOFA (qSOFA), National Early Warning Score (NEWS), and Modified Early Warning Score (MEWS). However, due to their respective sensitivities and specificities **(see Table 3)** and ongoing discrepancies in identifying sepsis,[16-18] a comprehensive, consensus early screening tool to identify sepsis remains elusive. Nevertheless, to decrease morbidity and mortality, it is critical that each hospital formalize a screening process to identify patients with organ dysfunction in the setting of suspected infection.[1,19] One promising area in sepsis screening is the ongoing progress toward machine-learning and artificial intelligence tools that may outperform clinician judgment in recognizing more subtle presentations of sepsis.[20] See the "Controversies and Cutting Edge" section (page 13) for a detailed discussion of this topic.

Although the SOFA score is part of the definition for sepsis, it has limited utility for initial screening. The SOFA score quantifies organ dysfunction, which is a familiar prognostic tool for intensive care unit (ICU) clinicians; however, several SOFA components (including arterial blood gases and total bilirubin) are not routinely obtained in ED patients with potential sepsis, limiting its utility for ED screening. SOFA may have utility in identifying decompensation and in-hospital mortality risk.[6,21] Due to the low sensitivity of qSOFA for identifying sepsis, the updated Surviving Sepsis Campaign 2021 guidelines for sepsis management recommend against using qSOFA for sepsis or sepsis-related mortality screening.[6] Patients who have a suspected source of infection and who have identified organ dysfunction or elevated lactate levels should be treated as having sepsis, regardless of whether they meet initial sepsis screening criteria, or whether they triggered a best-practice advisory.[6]

Online calculators for early sepsis screening tools are available at MDCalc.com:

- www.mdcalc.com/calc/691/sequential-organ-failure-assessment-sofa-score
- www.mdcalc.com/calc/2654/qsofa-quick-sofa-score-sepsis
- www.mdcalc.com/calc/1096/sirs-sepsis-septic-shock-criteria
- www.mdcalc.com/calc/1873/national-early-warning-score-news
- www.mdcalc.com/calc/1875/modified-early-warning-score-mews-clinical-deterioration

Table 3. Comparison of Screening Tools for Sepsis[21-23]

Screening Tool	Sensitivity	Specificity
Two systemic inflammatory response syndrome (SIRS) criteria	0.70-0.86	0.41-0.79
Sequential organ failure assessment (SOFA) score	0.61	0.76
Quick SOFA (qSOFA)	0.29-0.42	0.94-0.99
Modified early warning score (MEWS) ≥4	0.67	0.73
National early warning score (NEWS) ≥5	0.58-0.74	0.82-0.90

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

Sepsis Category	Sepsis-3 (2016)	Sepsis-2 (2001)	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 mHg or MAP <70 mm Hg, or an 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); and lactate >2 mmol/L (18.0 mg/dL).

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

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Epidemiology

Studies estimate that up to 850,000 ED visits for sepsis occur annually in the United States and 48.9 million cases occur worldwide.[3,24] Worldwide, there were approximately 11 million sepsis-related deaths in 2017.[24] Sepsis is 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.[25,26] Mortality due to sepsis and septic shock varies by definition. The mortality of sepsis is >10%, and the mortality of septic shock is approximately 40%.[1,27] The high mortality rate for sepsis and septic shock 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 mediators.[28,29] It was previously believed that the bacterial infection itself was the cause the clinical syndrome of sepsis, but the advent of modern antibiotic therapy showed that, despite treatment, many patients with sepsis died, implicating the host response's potential role in the pathogenesis of sepsis.[30] Blood cultures are positive in only approximately half of sepsis cases.[31,32] 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]

Differential Diagnosis

When encountering a patient with abnormal vital signs, consider both infectious and noninfectious etiologies to avoid premature closure in developing a differential diagnosis. Assessing each organ system systematically will ensure that an infectious source for sepsis is not overlooked. **Table 4** lists potential sources of infection associated with sepsis, by organ system. Although not exhaustive, it provides a framework for organizing this approach.

Prehospital Care

Emergency medical services (EMS) are the point of first medical contact in 40% to 70% of all sepsis hospitalizations.[34,35] Nonetheless, significant knowledge gaps exist regarding sepsis diagnosis and management among even advanced EMS providers. A retrospective study of 555 patients found that only 17% to 21% of confirmed septic patients transported by EMS had been suspected by EMS of having sepsis.[36] The implementation of local screening tools is essential to increase sepsis recognition by prehospital providers and improvement in prehospital ED notification of potential sepsis patients.[35]

Emergency Department Evaluation

History

When evaluating patients with potential sepsis, the initial history should focus on identifying the infectious source and any factors that could modify assessment and subsequent treatment, including IV crystalloid fluid resuscitation, antibiotic selection, and source control. The clinical history should include a review of home medications, allergies, comorbidities, recent antibiotics, surgeries, immunocompromise, hospitalizations, long-term care residence, indwelling devices or hardware, and IV drug use. Review of systems should address fever, headache, confusion, neck pain, respiratory symptoms, abdominal or back pain, urinary issues, extremity pain, rash, or warmth.

When a patient is unable to provide a history, seek collateral sources and search for clues on the physical examination to offer insight into the patient's presentation. One should be careful not to attribute

Table 4. Potential Sources of Infection Associated With Sepsis, by Organ System[33]

Organ System	Potential Source of Infection
Gastrointestinal	Infectious hepatitis, cholecystitis, appendicitis, perforated viscus, cholangitis, diverticulitis, abscess, pancreatitis, infectious colitis, spontaneous bacterial peritonitis
Genitourinary	Pyelonephritis, abscess, renal calculi, urinary tract obstruction, acute prostatitis
Pelvic	Peritonitis, abscess, septic abortion, endometritis
Lower respiratory tract	Pneumonia, empyema, septic emboli
Intravascular	Central-line–associated bloodstream infection, prosthetic device infection
Cardiovascular	Endocarditis, myocarditis
Dermatologic	Abscess, toxic shock syndrome, Stevens-Johnson syndrome, cellulitis, necrotizing soft tissue infection
Neurologic	Meningitis, epidural or intracranial abscess, discitis
Musculoskeletal	Osteomyelitis, septic arthritis, infected hardware, necrotizing soft tissue infection

sepsis to a relatively minor finding, such as a mild urinary tract infection or subtle pneumonia on chest radiography, without a broader diagnostic evaluation. In early sepsis, medications such as beta-blockers or calcium-channel blockers may mask vital sign abnormalities (eg, tachycardia).

Physical Examination

Initial evaluation should include a rapid assessment of airway, breathing, circulation, and vital signs to evaluate clinical stability. Patients with critical findings such as hypoxia, respiratory distress, hypotension or hypoperfusion, hypothermia/hyperthermia, or hypoglycemia should be treated immediately with appropriate interventions.

Next, a complete physical examination should be performed. Occult abdominal sepsis occurs frequently in older and diabetic patients, though they may exhibit minimal tenderness. Genitourinary and pelvic examinations are warranted in patients in whom pelvic infections are suspected. Thorough visual assessment and palpation of the skin and soft tissues of the back, pelvis, and perineum should also be conducted.

Current guidelines recommend that source identification and control be achieved "as rapidly as possible."[5] 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%.[37] In general, infected indwelling catheters should be removed as soon as alternative vascular access is obtained.[5,38] Blood cultures should be obtained from previously indwelling vascular catheters as well as from peripheral blood.

Frequent reassessments of perfusion and mentation should be undertaken to assess response to treatment. Pain out of proportion to examination may indicate diagnoses such as mesenteric ischemia or necrotizing soft tissue infections.

Patients should be assessed for tissue hypoperfusion, including altered mentation, delayed capillary refill, mottled or clammy skin, oliguria, and elevated serum lactate level.[39] Point-of-care ultrasound (POCUS) is a useful adjunct for assessing cardiac output and fluid status.[39] Although cardiac output is often normal or high in patients with distributive shock, sepsis can provoke acute decompensation of pre-existing cardiac dysfunction.

Diagnostic Studies

Laboratory Testing

Laboratory testing to identify organ dysfunction should include a complete blood cell count (CBC), which provides an assessment of coagulation function (platelet count); immune function (white blood cell and neutrophil count) and oxygen-carrying capacity (hemoglobin and hematocrit); and a basic metabolic panel, which assesses kidney function (creatinine), electrolyte abnormalities, hydration status (blood urea nitrogen/creatinine ratio), and acid/base status. Laboratory testing can help identify subtle signs of organ dysfunction that may be missed on initial vital signs and physical examination.

Routine acquisition of blood gas and hepatic panels exclusively for the purpose of SOFA score calculation is not recommended, as modified versions have similar predictive abilities.[10,40,41] However, blood gas testing may be useful in select patients to evaluate for acid/base status or lactic acidosis, and bilirubin levels may be informative in patients with suspected intra-abdominal sources of infection or suspected hepatic dysfunction. Guidelines recommend that 2 sets of blood cultures be obtained prior to antibiotic administration; however, this recommendation should be balanced with the severity of illness and should not delay the administration of antimicrobials.[42,43]

Trending Lactate Levels

Elevated lactate is thought to be due to tissue hypoxia and hypoperfusion in patients with shock; however, other causes of elevated lactate in shock patients include beta-adrenergic stimulation, hepatic dysfunction, and lactate generation by the lungs.[44,45] New literature suggests that 24-hour lactate clearance predicts 90-day mortality better than initial lactate clearance rates because initial lactate clearance is heavily impacted by underlying medical comorbidities.[45] The ANDROMEDA-SHOCK trial compared resuscitation guided by lactate clearance (decrease of 20% every 2 hours) with resuscitation guided by capillary refill normalization, and found significant improvement in SOFA scores at 72 hours but no statistically significant difference in mortality in the peripheral perfusion-targeted resuscitation group.[46] This suggests that clinical assessment of peripheral perfusion may be noninferior to lactate trending in septic shock. In clinical practice, if initial lactate is >2 mmol/L, we suggest obtaining a repeat level to ensure improvement after resuscitation. Although previous guidelines suggested using a normal lactate as a target of resuscitation,[5,47] the 2021 update softened this recommendation in favor of resuscitation strategies that decrease the lactate level more generally.[6] If repeat lactate is not improving, consider whether there may be additional unidentified pathology contributing to the aberrant metabolism.

Procalcitonin

Procalcitonin (PCT) is a biomarker that is typically elevated in patients with bacterial pneumonia and bacteremia.[48,49] While PCT may have specific clinical applications, its routine use for diagnosing or guiding initial antibiotic therapy in sepsis in the ED is not recommended.[6] PCT has a pooled sensitivity of 77% for sepsis in critically ill patients, which is insufficient for reliably excluding sepsis.[50] PCT levels peak 12

to 48 hours after onset of bacterial infection, which limits its utility during early ED presentations.[51,52] The strongest evidence for PCT lies in its role in guiding early antibiotic de-escalation in the inpatient setting.[49,50,53,54] Emergency clinicians should not use PCT for diagnosis of sepsis or for initial antibiotic decision-making.

Imaging

Imaging can be useful to identify the source of infection in combination with history, physical examination, and laboratory testing. A single-center retrospective study of 76 computed tomography (CT) studies in a German operative ICU found that CT changed management in 85.5% of cases.[55] In a 2017 clinical trial, POCUS of the lungs, heart, abdomen, joints, and soft tissues increased diagnostic sensitivity by 25% when added to the bedside history and physical examination.[56] Based on these studies and our own experience, we recommend that focused diagnostic imaging be performed in undifferentiated cases of sepsis and septic shock, tailored toward the most likely source of infection, based on history and physical examination.

Treatment

Initial Management

Both the CMS SEP-1 severe sepsis and septic shock management bundle and the 2021 Surviving Sepsis Campaign consensus guidelines provide recommendations for the management of patients with sepsis and septic shock. Though similar, some variation exists between CMS SEP-1 and the consensus guidelines. These differences are clarified in the following sections, and available evidence for each of the recommendations is assessed critically.

The CMS SEP-1 severe sepsis and septic shock management bundle recommends the following for the initial management of patients with sepsis and septic shock.[6,57,58]

In the first 3 hours:

- Measure serum lactate,
- Obtain 2 sets of blood cultures prior to antibiotic administration (when possible),
- Administer IV antibiotics (within the first hour when possible), and
- If patient is hypotensive or lactate >4 mmol/L:
  - Give isotonic IV fluid challenge with 30 mL/kg.
- Caveats:
  - Resuscitation based on ideal body weight is acceptable for patients with body mass index (BMI) >30.
  - CMS also permits clinician documentation of administration of a lesser volume of IV fluid when accompanied by documentation of clinician reasoning.

In the first 6 hours:

- Remeasure lactate if the initial lactate is >2 mmol/L or increasing.
- If patient is hypotensive or lactate ≥4 mmol/L in the first 6 hours:
  - Administer IV vasopressors as needed to achieve MAP of at least 65 mm Hg, and
  - Reassess intravascular volume status and tissue perfusion.

Intravenous Fluids

Positive Fluid Balance

Concerns regarding harm associated with positive fluid balance and the lack of nuance associated with a fixed volume recommendation for all patients is the focus of significant research and controversy. Current literature remains neutral regarding restrictive versus liberal fluid strategies.[6,59-61] The CLOVERS trial compared restrictive versus liberal fluid strategies in patients with sepsis-induced hypotension. After receiving an initial fluid bolus before randomization, patients randomized to the restrictive fluid strategy (early vasopressor administration with "rescue fluids") experienced similar mortality and secondary outcomes as the patients randomized to a liberal fluid strategy (additional fluid boluses with "rescue vasopressors").[61] The CLASSIC trial also had similar findings.[59] An updated meta-analysis of 13 trials comparing lower versus higher IV fluid volumes found no statistically significant difference in all-cause mortality or serious adverse events.[62] Taken together, a liberal fluid strategy does not appear to be associated with higher or lower mortality compared with a restrictive fluid strategy.

Early and adequate IV crystalloid fluid administration remains a crucial component of the resuscitation of patients with sepsis and septic shock. In the absence of better evidence, we recommend timely administration of a 30-mL/kg IV crystalloid fluid bolus for patients who do not have contraindications to administration of that fluid volume and who have evidence of hypotension or hypoperfusion.

Patients With Obesity

Special attention should be directed to patients with obesity in order to ensure appropriate fluid volume administration. A 2018 study evaluating fluid volume in patients with obesity found improved mortality when using adjusted body weight as opposed to actual body weight for fluid volume calculation.[63] Updates to the CMS SEP-1 core measure allow clinicians to document that they are administering IV fluids based on ideal body weight for patients with BMI >30 if the clinician documents that the patient is obese or has a BMI >30.

Patients at Risk for Fluid Overload

Although most patients with evidence of hypoperfusion or hypotension require IV crystalloid administration, this should be balanced with consideration of the risk for fluid overload in certain clinical conditions and scenarios.[6] Updates to CMS SEP-1 allow for administration of <30 mL/kg in specific situations (such as when there is concern for fluid overload) if both the lesser volume and the rationale are documented (eg, 1 liter IV fluid administered rather than 30 mL/kg, due to concerns for volume overload in the setting of severe congestive heart failure).

Fluid Type

Two landmark trials evaluated clinical outcomes between resuscitation with balanced crystalloids versus 0.9% sodium chloride in adults. The SALT-ED study, published in 2018, compared balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) with 0.9% sodium chloride in ED patients who were subsequently admitted to a non-ICU bed.[64] SALT-ED found decreased major adverse kidney events in patients receiving balanced crystalloids, though there was no difference in hospital-free days between the 2 groups at 28 days. The SMART trial found that the use of balanced crystalloids resulted in a lower rate of the composite outcome of death, new renal replacement therapy, or persistent renal dysfunction at 30 days.[65] A preplanned secondary analysis of the SMART cohort found lower 30-day mortality and greater number of vasopressor-free days among critically ill patients with sepsis who received balanced crystalloids versus 0.9% sodium chloride.[66] When available, balanced crystalloid solutions rather than 0.9% sodium chloride should be used for IV fluid resuscitation in patients with sepsis.

Fluid Status Assessment

Fluid administration should be tailored to the patient's fluid volume status.[6] Dynamic measures for assessing fluid status are preferred.[6] There are several methods to assess fluid status. Passive leg raise is a noninvasive method to test for potential fluid bolus responsiveness.[67,68] Point-of-care limited echocardiography in conjunction with inferior vena cava (IVC) ultrasound is another approach familiar to many emergency clinicians. The sensitivity and specificity of IVC ultrasound for fluid responsiveness have been reported at 76% and 86%, respectively, but may be confounded by clinical scenarios that affect intrathoracic or intra-abdominal pressure.[67,68] We recommend against the routine use of invasive measures, such as central venous pressure measurement, in the ED.[69]

Antibiotics

Timing of Antibiotic Administration

Early empiric broad-spectrum IV antibiotic coverage is recommended for patients with sepsis, and has been associated with reduced mortality.[15,70] Blood cultures should be obtained prior to antibiotic administration, when possible, to maintain compliance with CMS metrics. The CMS SEP-1 3-hour bundle includes administration of broad-spectrum antibiotics. The Surviving Sepsis Campaign 2021 guidelines stratify antibiotic urgency for patients without shock by their overall likelihood of infection: antibiotics should be administered within the first hour of presentation for patients with *high suspicion* for either sepsis or septic shock, but a more lenient 3-hour recommendation exists for patients if (1) infectious etiology is perceived to be less likely, and (2) there are no signs of shock.[6] Patients with only *possible* infection and no signs of shock may be monitored, and the decision on antibiotic administration may be delayed until more clinical information is available.

A retrospective cohort study of 166,559 patients with suspected serious infection found that using Surviving Sepsis Campaign 2021 categories of "definite/probable sepsis or septic shock" (with a 1-hour antibiotic timing target) and "possible sepsis" without shock (with a 3-hour antibiotic target) to guide antibiotic timing was safe.[71] Patients with "definite/probable sepsis or septic shock" were treated within 1 hour, while those with "possible sepsis" without shock had a 3-hour target. Mortality was very low in patients with only possible sepsis and no evidence of septic shock.

The benefit of early antibiotics is greatest in septic patients with hypotension or shock. For patients with septic shock, administration of antibiotics after the onset of shock has been associated with increased mortality (odds ratio [OR] 2.4; 95% confidence interval [CI]: 1.1,4.5).[70] Several studies have failed to demonstrate the benefit of early antibiotics for patients with sepsis without shock or hypotension.[72,73] Nonetheless, 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, because sepsis mortality increases significantly with inadequate antimicrobial coverage.[74,75] The choice of antimicrobials should take into account the anatomic site of suspected infection and its associated causative organisms, local antibiotic resistance patterns and susceptibilities, the presence of immunosuppression, patient comorbidities, and prior cultures and susceptibilities.[5] Antibiotic recommendations based on infection type or source are listed in **Table 5, pages 10 and 11**.

Vasopressors and Inotropes

Central Versus Peripheral Access

The 2021 Surviving Sepsis Campaign guidelines support initiating vasopressors through a peripheral IV to prevent delays associated with obtaining central venous access.[6] This updated recommendation is based on literature showing more rapid correction of hypoperfusion, as well as improved safety, when used peripherally for <6 hours, with close monitoring.[77,78]

Norepinephrine

Norepinephrine continues to be the recommended first-line vasopressor for septic shock.[42] It can be initiated at a dosage of 0.05 mcg/kg/min (4-6 mcg/min) IV and titrated incrementally by 0.02 to 0.05 mcg/kg/min (2-6 mcg/min) to achieve MAP ≥65 mm Hg. Norepinephrine has more alpha-adrenergic properties than beta-adrenergic effects, but it reliably increases systemic vascular resistance while supporting cardiac function.[5,39]

Norepinephrine Versus Dopamine

Dopamine has dose-dependent effects on dopaminergic, beta-1, beta-2, and alpha-1 receptors. A double-blind multicenter randomized controlled trial of 1679 patients that compared norepineph-

Table 5. Initial Antibiotic Recommendations for Patients With Sepsis, by Source of Infection (Continued on page 11)

Infection Type or Source	Recommended Antibiotics	Penicillin-Anaphylactic Patient*	Additional Circumstances
Pneumonia, community-acquired, nonsevere	Ceftriaxone 2 g IV **PLUS** Azithromycin 500 mg IV or PO **OR** Doxycycline 100 mg IV	Levofloxacin 750 mg IV	• Prior MRSA respiratory isolate: add vancomycin 20-25 mg/kg IV. • Prior pseudomonal respiratory isolate: use cefepime 2 g IV in place of ceftriaxone 2 g IV.
Pneumonia, community-acquired, severe	Ceftriaxone 2 g IV **PLUS** Azithromycin 500 mg IV or PO **OR** Doxycycline 100 mg IV	Levofloxacin 750 mg IV	• Prior MRSA respiratory isolate **OR** hospitalization **AND** IV antibiotics in prior 90 days with local risk for MRSA: add vancomycin 20-25 mg/kg IV. • Prior pseudomonal respiratory isolate **OR** hospitalization **AND** IV antibiotics in prior 90 days, with local risk for *Pseudomonas*: use cefepime 2 g IV in place of ceftriaxone 2 g IV.
Intra-abdominal	Ceftriaxone 2 g IV **PLUS** Metronidazole 500 mg IV	Levofloxacin 750 mg IV **PLUS** Metronidazole 500 mg IV	• Gram-negative bacilli (including *Pseudomonas*): infections involving the hepatobiliary tree or in patients with prior surgery or prosthetics (eg, surgical mesh, gastrostomy tubes, etc) should be covered for *Pseudomonas aeruginosa*. Recommended agents include piperacillin/tazobactam 4.5 g IV **OR** cefepime 2 g IV **PLUS** metronidazole 500 mg IV.
Urinary tract	Ceftriaxone 2 g IV	Ciprofloxacin 500 mg IV if local uropathogen resistance patterns do not exceed 20%. If local resistance patterns indicate significant resistance, consider gentamycin or meropenem.[76]	• ESBL-producing infections ○ ESBL-producing infections are increasingly prevalent. Prior cultures should be reviewed, when available. Recommended agents include fluoroquinolones or trimethoprim/sulfamethoxazone, if susceptible. Carbapenems should be reserved for resistant bacteria. • 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 for *Pseudomonas* and multidrug-resistant gram-negative bacteria and should be treated based on prior culture results, when available. Recommended agent: cefepime 2 g IV. • Consider prostatitis in the correct clinical scenario. Treatment of prostatitis should be tailored to suspected organisms and current guidelines for prostatitis management.
Pelvic (including pelvic inflammatory disease, tubo-ovarian abscess)	Cefoxitin 2 g IV **PLUS** Doxycycline 100 mg IV	Clindamycin 900 mg IV **PLUS** Gentamicin loading dose (2 mg/kg IV)	• For endometritis or infection of retained products, ampicillin 2 g IV + gentamicin + clindamycin, at the doses indicated, are recommended.

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

Abbreviations: ESBL, extended-spectrum beta-lactamase; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*, PO, oral.

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rine 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.[79] Multiple meta-analyses have shown a statistically significant increased risk for death (risk ratio [RR], 1.08-1.23) associated with the use of dopamine compared to norepinephrine.[80-82] Dopamine is not recommended as a vasopressor for sepsis-related hypotension or hypoperfusion.

Vasopressin

Vasopressin is currently a second-line vasopressor for septic shock.[5] Vasopressin is a non-adrenergic vasopressor that causes vasoconstriction and increased systemic vascular resistance by stimulating V_1 receptors in vascular smooth muscle cells.[83] It also acts on V_2 receptors in the kidney.[83] 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.[84] Vasopressin does not appear to offer a mortality benefit, impact new-onset arrhythmias, or definitively improve kidney function as a single, first-line agent.[85] However, fixed-dose vasopressin use at a dose of 0.03 units/min IV as a second-line agent after norepinephrine initiation has been shown to reduce the dose of norepinephrine required.[86,87] There may be an association between the initiation of vasopressin at lower norepinephrine doses and lower mortality, based on limited, observational data.[88,89]

Table 5. Initial Antibiotic Recommendations for Patients With Sepsis, by Source of Infection (Continued from page 10)

Infection Type or Source	Recommended Antibiotics	Penicillin-Anaphylactic Patient*	Additional Circumstances
Intravascular or catheter-associated bloodstream infections	Vancomycin 20-25 mg/kg IV **PLUS** Cefepime 2 g IV	Vancomycin 20-25 mg/kg IV **PLUS** Aztreonam 2 g IV	When possible, treatment based on cultures is recommended.
Cardiovascular (including endocarditis and valvular infections)	Vancomycin 20-25 mg/kg IV **OR** Daptomycin 8-12 mg/kg IV if concern for *Enterococcus* **PLUS** Cefepime 2 g IV if concern for *Pseudomonas*	Vancomycin 20-25 mg/kg IV **PLUS** Gentamicin 3 mg/kg IV	• When available, treatment based on cultures is recommended. • 3 sets of blood cultures should be drawn prior to the administration of antibiotics, whenever possible. • Gentamicin 3 mg/kg/day IV may be considered in patients with prosthetic valves, enterococcal endocarditis, and other special circumstances. • Rifampin 300 mg IV or PO may also be considered in prosthetic valve endocarditis (infectious disease consultation may be indicated).
Skin/soft tissue	Vancomycin 20-25 mg/kg IV		• Necrotizing soft tissue infections 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, add piperacillin/tazobactam (4.5 g IV) and clindamycin 900 mg IV (for its antitoxin effects). • Linezolid also possesses antitoxin effects; if used in place of vancomycin, clindamycin can be held.
Meningitis	Ceftriaxone 2 g IV **PLUS** Vancomycin 20-25 mg/kg IV	Vancomycin 20-25 mg/kg IV **PLUS** Moxifloxacin 400 mg IV	• For suspected meningitis patients with impaired cellular immunity, risk for *Listeria*, or age >50 yr, add ampicillin 2 g IV (meropenem can be used for penicillin-anaphylactic patients). • If viral encephalitis due to herpes simplex virus is suspected, acyclovir 10 mg/kg IV should also be given.

*Most penicillin-allergic patients (not anaphylactic) may safely receive third- and fourth-generation cephalosporins; 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: IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral.

Epinephrine

Epinephrine is a nonselective alpha-adrenergic and beta-adrenergic agonist. In addition to its vasopressor activity due to alpha-adrenergic stimulation, it is also a powerful beta-1 and beta-2 agonist, thereby exerting more inotropy and chronotropy than norepinephrine.[90] Epinephrine can be initiated at 0.05 mcg/kg/min IV and increased by 0.02-0.05 mcg/kg/min to achieve a MAP goal of ≥65 mm Hg. Hyperlactatemia caused by epinephrine infusion may obscure the use of serial lactate monitoring. A randomized controlled trial with 280 patients did not show benefit of epinephrine over norepinephrine.[91] Another trial with 330 patients demonstrated that epinephrine versus norepinephrine plus dobutamine, when needed, demonstrated no difference in mortality.[92]

Dobutamine

Dobutamine is a beta-adrenergic agonist that increases cardiac contractility; however, reflex hypotension may occur with its use.[6] Dobutamine is an inotrope, not a vasopressor. For stabilized vasopressor-dependent patients with the need for additional inotropy, dobutamine can be added instead of epinephrine at a starting dose of 2 to 5 mcg/kg/min IV to a maximum of 20 mcg/kg/min. We recommend caution and judicious monitoring, with a low threshold for discontinuing the agent if hypotension occurs after dobutamine initiation.

Phenylephrine

Phenylephrine has pure alpha-adrenergic properties, acting only as a vasoconstrictor, with no direct effects on myocardial function except for increased afterload. Phenylephrine can be 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. If norepinephrine is rapidly available, it is preferable to use norepinephrine rather than push-dose phenylephrine. However, given variations in what is rapidly available in different EDs, push-dose phenylephrine may be considered as a temporizing option in some circumstances. Phenylephrine infusion is not currently recommended as a first- or second-line vasopressor for sepsis.

Vasopressor Timing

The ideal timing of vasopressor initiation, as well as the ideal balance between IV crystalloid fluid resuscitation and vasopressor initiation, remains controversial. Though hypotension is harmful and associated with adverse outcomes,[93,94] early vasopressors have not been convincingly shown to improve mortality compared to usual care. Based on the current literature, it may be reasonable to promptly address hemodynamic instability with a hybrid approach of IV crystalloid fluid administration for volume resuscitation while simultaneously administering vasopressors for hemodynamic support, with the goal of weaning vasopressors as fluid resuscitation is accomplished.[95] Similarly, the traditional sequenced approach of IV crystalloid fluid resuscitation followed by vasopressors is also reasonable. Though there is limited evidence, in a peri-arrest situation, or for the rapidly decompensating patient, we recommend stabilizing the patient with simultaneous administration of vasopressors and IV fluids. For example, a hypotensive patient with sepsis who requires emergent intubation and represents a physiologically difficult airway may require simultaneous administration of vasopressors and IV crystalloid to optimize hemodynamics prior to intubation.

Corticosteroids

For patients on vasopressors for septic shock, the Surviving Sepsis Campaign and current consensus guidelines recommend administering hydrocortisone at a dose of either 50 mg IV bolus every 6 hours or 200 mg IV per day continuous infusion.[6,96] Two meta-analyses of randomized clinical trials of corticosteroids in septic shock demonstrated a shorter duration of shock in patients who received corticosteroids.[97,98] A meta-analysis of corticosteroids in patients with severe community-acquired pneumonia found reduced mortality and need for mechanical ventilation.[99] Recent studies show that outcomes may be improved by the addition of fludrocortisone to hydrocortisone in early septic shock;[100,101] however, this recommendation has not been adopted by consensus guidelines.

Blood Transfusion

For patients with a hemoglobin ≥7 g/dL, outside of special circumstances (such as obvious blood loss), current recommendations do not support blood transfusion.[6]

Special Populations and Circumstances

A variety of patient physiologic processes and states may present challenges to recognizing and treating sepsis.

- Elderly patients with septic shock have worse outcomes, likely due to chronic inflammation, impaired cardiovascular function, and differing inflammatory responses compared with younger patients with septic shock.[102,103]
- In patients with cirrhosis, 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.
- In patients with end-stage renal disease, bacteremia is common, and one must remain vigilant for sepsis from intravascular devices. Large, frequent fluid shifts may limit the patient's physi-

ologic 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.[65,66,104,105]

- The physiologic changes of pregnancy make sepsis recognition more difficult because these patients, at baseline, typically have decreased blood pressure and platelet count with increased heart rate, white blood cell count, and respiratory rate. Pregnancy can also increase a patient's risk for pneumonia and a variety of genitourinary infections, and sepsis in pregnancy can increase the risk for perinatal infection and maternal and fetal morbidity.[106]

Controversies and Cutting Edge

The Evidence Basis for CMS Bundle Metrics

The CMS SEP-1 core measure brought needed attention to sepsis; however, there remains considerable controversy surrounding whether bundle compliance improves outcomes, the strength of the evidence underlying recommended elements, and whether its unintended consequences exceed its benefits.[107,108] CMS SEP-1 has been a pay-for-reporting measure since 2015. It is slated to become a pay-for-performance measure in 2026, becoming incorporated into the Hospital Value-Based Purchasing Program.[107] This change prompted numerous professional societies, including the American College of Emergency Physicians, to issue a jointly written position paper.[107] Concerns included: (1) that antibiotic stewardship and the requirement for antibiotic administration within 3 hours are in tension, and (2) the lack of nuance regarding the 30 mL/kg IV crystalloid fluid bolus and potential concerns for harm associated with excess fluid administration. Though the core measure remains unchanged at this time, we recommend individualizing care to the patient while still adhering to hospital policies, when possible.

Sepsis Screening

Because hospitals are increasing the utilization of electronic health records (EHRs) and artificial intelligence-based screening tools and models, there is a need for an accurate and practical screening tool that balances sensitivity and specificity. Though these tools are likely the future of sepsis screening, in their current state, there is still significant opportunity for improvement. EPIC has a proprietary screening tool, the "EPIC Sepsis Model" (ESM). Although a recent external validation of the ESM found it to be poorly sensitive (area under the curve [AUC], 0.63), other studies have been more positive.[109,110] A before-and-after study of ESM implementation found a 44% reduction in the odds of sepsis-related mortality, a sensitivity of 86%, and a specificity 81%, though the use of different score thresholds for triggering the alerts may have contributed to some differences.[111] Models such as this are likely the future of sepsis screening, but currently, the incremental benefit they provide to gestalt may be limited. Sepsis screening tools and best-practice advisories should balance sensitivity with the very real concern for alert fatigue.[112]

Methylene Blue

Methylene blue, which is catecholamine-independent, exerts indirect vasopressor effects by inhibiting inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS), thereby restoring vascular tone in conditions of nitric oxide upregulation. A randomized controlled trial of 91 patients compared septic shock patients already receiving norepinephrine in a medical-surgical ICU who were then treated with early adjunctive methylene blue (<24 hours after norepinephrine initiation) versus placebo.[113] The study found that patients who received earlier methylene blue treatment experienced a significantly shorter time to vasopressor discontinuation, more vasopressor-free days, and shorter ICU and hospital lengths of stay, without any significant adverse events.[113] A systematic review and meta-analysis of the use of methylene blue that incorporated data from 556 patients noted reduced mortality and decreased ICU and hospital length of stay for patients with catecholamine-refractory shock who received methylene blue.[114]

Hydroxocobalamin

Hydroxocobalamin is currently being explored as a potential agent to ameliorate vasodilatory shock.[115] It is theorized that hydroxocobalamin may scavenge vasodilatory molecules such as H_2S, helping to reverse vasoplegia and improve vascular tone. A promising feasibility study in 20 ICU patients demonstrated lower vasopressor requirements and lower H_2S levels in patients receiving high-dose hydroxocobalamin, compared to placebo.[115] More research needs to be done to clarify best practices surrounding its use.

Disposition

Patients with sepsis, septic shock, or organ dysfunction due to an infection should be admitted. Septic patients requiring mechanical ventilation or vasopressor support clearly warrant intensive care; however, other patients may require ICU admission due to the risk for progressing from sepsis to septic shock. Risk factors for progression to septic shock may include intermittent hypotension and lactic acidosis of ≥4 mmol/L.[116] Careful consideration of potential ICU needs is recommended, and we recommend considering ICU consultation or admission in the setting of multiple organ system involvement or anticipated need for organ support.

Risk Management Pitfalls for Managing Emergency Department Patients With Sepsis

1. **"I prioritized intubation without optimizing hemodynamics because the patient was altered and not protecting their airway."** Patients with sepsis can present with acidosis, hypoxemia, hypoperfusion, and/or hypotension, which should be addressed prior to intubation, if possible. For example, a patient with a blood pressure of 60/40 mm Hg and hypoxia should have their hemodynamics and oxygen saturation optimized prior to intubation to prevent peri-intubation cardiac arrest.

2. **"I did not think the patient was septic because he was not hypotensive."** The diagnosis and management of sepsis is not based on hypotension, but on the presence of organ dysfunction. Hypotension is a late marker of hypoperfusion. Late recognition of sepsis results in late treatment, which results in increased mortality.

3. **"I was afraid to give fluids because the patient had congestive heart failue."** Even patients with congestive heart failure or end-stage renal disease may benefit from fluids on an individualized basis. CMS allows for delivery of less than the 30 mL/kg IV crystalloid fluid bolus when a specific concern for harm is documented. We recommend an individualized approach and frequent reassessment of volume status to guide fluid resuscitation.

4. **"I forgot to review past medical history and prior culture results prior to antibiotic selection."** Failure to consider prior culture results and recent medical history can result in inappropriate antibiotic coverage. Antibiotic regimens should be tailored to prior resistance patterns, when available. It is important to note that extended-spectrum beta-lactamase (ESBL) producing urinary tract infections are increasingly common, and reviewing prior cultures can improve antibiotic selection.

5. **"I called the cardiologist because the patient's troponin was elevated."** Sepsis is defined by end-organ dysfunction. It is important not to mistake sepsis-induced organ dysfunction as the patient's primary pathology (eg, type II NSTEMI from appendicitis).

6. **"I did not reassess the patient."** It is important to reassess a patient's clinical status after treatment to ensure improvement. For example, assessing lactate clearance, mentation, and perfusion status help guide further management. It is necessary to maintain a high degree of suspicion for decompensation and to perform frequent reassessments of patients with sepsis.

7. **"I found a urinary tract infection and I treated it. I did not realize the patient also had a renal abscess."** It is important not to prematurely anchor on the source of infection. Similarly, it is important not to exclude sepsis prematurely. For example, attributing septic shock to a relatively minor source of infection (eg, mildly positive urinalysis) without comprehensively investigating other sources of infection could result in delayed diagnosis.

8. **"I ignore best practice advisory (BPA) alerts in the EMR because they are usually wrong and alert too often."** Institutional screening tools (eg, NEWS, SIRS), while not perfect, are effective tools to identify occult sepsis. Clinicians should not minimize the value of early recognition scores, though they have room for improvement. It is important for clinicians to assess undifferentiated potentially septic patients as quickly as possible to diagnose and manage critically ill patients expeditiously.

9. **"I did not fully undress the patient and missed the toe necrosis."** Source control is a key component of sepsis management. Maintaining a broad differential and providing a thorough history and physical examination can help to decrease surreptitious or "hidden" sepsis. Prioritize prompt consultation to services who can facilitate source control procedures (eg, surgical consultation for debridement, ureteral stent for a septic patient with an infected stone, etc).

10. **"The patient did not meet SIRS criteria, so I did not think she was septic."** SIRS is not synonymous with sepsis. Not all patients with sepsis meet SIRS criteria, nor are all patients with SIRS criteria septic. Patients with organ dysfunction in the setting of a suspected infection should be evaluated for sepsis.

Case Conclusions

CASE 1

For the 40-year-old woman with no past medical history who presented with 3 days of fever, chills, dysuria, and flank pain…

You suspected that this patient had an infection and possible sepsis. While waiting for laboratory results that might identify end-organ dysfunction, you empirically started sepsis management. You administered IV ceftriaxone to cover the suspected urinary source, a 1-liter IV crystalloid fluid bolus, and acetaminophen for her fever. Her laboratory workup demonstrated a lactate of 1.2 mmol/L, normal renal function, and a nitrite-positive urinalysis. Her vital signs normalized with antipyretics and fluids. She had an infection, but no organ dysfunction, and she was not septic. She was discharged on oral cephalexin for treatment of her pyelonephritis.

CASE 2

For the 63-year-old man with past medical history of right knee replacement 3 months ago, diabetes mellitus, and hypertension who presented to the ED with fever, cough, and dyspnea…

Based on his history of recent hospitalization and the potential for healthcare-associated infection, you suspected infection and possible sepsis. While awaiting laboratory results that might identify end-organ dysfunction, you empirically started sepsis management. You administered IV ceftriaxone and IV vancomycin to cover a potential pulmonary source, as well as a 30 mL/kg IV crystalloid fluid bolus. His chest x-ray demonstrated lobar pneumonia. His creatinine was 1.5 mg/dL, from a baseline of 0.9 mg/dL, consistent with end-organ dysfunction in the form of acute kidney injury. His blood pressure improved to 115/76 mm Hg after IV fluid administration, and his repeat lactate had down-trended from 2.5 to 2.1 mmol/L, but he was noted to be requiring 3 liters of oxygen via nasal cannula, and had a respiratory rate of 23 breaths/min. He was admitted to the floor for sepsis due to pneumonia and discharged on hospital day 3.

CASE 3

For the 35-year-old man with a past medical history of poorly controlled diabetes mellitus and IV drug use who presented to the ED for right axillary pain and swelling…

You recognized this patient's refractory hypotension, hypoperfusion, and hypoxia as well as the potential soft tissue infection with crepitus as being highly concerning for septic shock due to necrotizing soft tissue infection. You administered IV vancomycin, IV piperacillin/tazobactam, and IV clindamycin for his necrotizing soft tissue infection, in addition to giving a 30 mL/kg IV crystalloid fluid bolus. His initial lactate was 6.0 mmol/L. Given his persistent hypotension after administration of the IV fluid bolus, you started him on peripheral norepinephrine while central venous access was obtained. Hydrocortisone IV was also administered due to his persistent hypotension requiring vasopressor use. You consulted general surgery for source control with operative debridement of his necrotizing soft tissue infection. He was admitted to the ICU following debridement and required a prolonged hospital course.

End-of-Life Care

Aggressive treatment may not align with patient or family goals of care for those with end-stage conditions. When resuscitative efforts could be considered futile or contrary to the patient's wishes, hospice and advance directives should be addressed. Nonetheless, "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.[117] If desired by the patients and their families, it is reasonable to proceed with a time-limited trial of potentially helpful resuscitative efforts without committing them to prolonged and burdensome therapies.[118]

Summary

The diagnosis of sepsis should be considered in patients presenting with suspected infection and organ dysfunction; prompt and appropriate management should be undertaken to correct hypoperfusion. We recommend institutional protocols and directed education for sepsis screening and recognition. For patients with sepsis, development and utilization of institutional protocols for initial care should include obtaining a serum lactate, 2 sets of blood cultures (prior to antibiotics whenever practical), administration of broad-spectrum IV antibiotics to cover the suspected organisms, and a 30 mL/kg IV crystalloid fluid bolus in patients with hypotension or a lactate ≥4 mmol/L unless the potential harm of large-volume fluid resuscitation outweighs the benefit. Infectious source control is also recommended to be undertaken as quickly as possible. For patients with septic shock not responsive to an initial

IV crystalloid fluid bolus, norepinephrine should be initiated and titrated to achieve MAP >65 mm Hg, and may be safely started peripherally while obtaining central venous access. IV corticosteroids are recommended for patients with septic shock who are on vasopressors.

Time- and Cost-Effective Strategies

- For patients with sepsis, utilizing bundled care and quality improvement initiatives may decrease healthcare costs and length of stay.[119,120]
- Hospital admissions due to sepsis have increased significantly and are among the most expensive reasons for hospitalization.[121] Unnecessary ordering of blood cultures in immunocompetent febrile patients without acute organ dysfunction, stable patients with viral illnesses, or patients who do not have sepsis and are likely to be discharged can be costly, and this testing is unlikely to change management. Nonetheless, any patient with suspected sepsis should be cultured.

Disclaimer

Authors Elisabeth H. W. Hwang, MD, Captain, United States Air Force, MC; and Charles W. Hwang, MD, Major, United States Air Force, MC advise that the opinions and assertions expressed herein are those of the authors and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, the United States Air Force, the United States Department of Defense, or the United States government.

5 Things That Will Change Your Practice

1. Sepsis is infection plus organ dysfunction and is not synonymous with SIRS. However, there may be some utility of SIRS, NEWS, or MEWS for initial sepsis screening.
2. Identifying and achieving infection source control can improve patient outcomes.
3. Early, appropriate, broad-spectrum antibiotics for critically ill patients with sepsis confers mortality benefit.
4. Patients predisposed to fluid overload (eg, those with congestive heart failure or end-stage renal disease) may benefit from fluid resuscitation in septic shock and should be treated with an individualized clinical assessment to guide fluid resuscitation.
5. Balanced crystalloid fluids are likely superior to 0.9% sodium chloride for the resuscitation of patients with sepsis.

References

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

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

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1. **What is the clinical definition of septic shock, according to Sepsis-3?**
   a. 2 systemic inflammatory response syndrome (SIRS) criteria with initial systolic blood pressure <90 mm Hg
   b. Infection-associated elevated lactate level
   c. Hypotension of unclear etiology
   d. Hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mm Hg or lactate >2 mmol/L despite IV fluid

2. **What lactate level threshold does the Centers for Medicare & Medicaid Services (CMS) Core Measure use to determine septic shock?**
   a. 2 mmol/L
   b. 4 mmol/L
   c. No threshold exists
   d. Any elevated lactate that does not decrease after fluids

3. **How is qSOFA used for sepsis screening?**
   a. It is the sole screening tool for potential sepsis patients.
   b. qSOFA replaces SIRS for screening.
   c. qSOFA-negative patients should be discharged.
   d. qSOFA should not be used for screening.

4. **For patients for whom there is concern for sepsis and no evidence of shock, how quickly should antibiotics be administered?**
   a. within 1 hour
   b. within 3 hours
   c. within 6 hours
   d. within 24 hours

5. **For which of the following patients with suspected infection is the standard 30 mL/kg IV crystalloid fluid bolus required by CMS?**
   a. A 43-year-old patient with cellulitis and a history of end-stage renal disease who has missed dialysis
   b. A 49-year-old patient with lactate, 3.5 mmol/L; creatinine, 3 mg/dL; bilirubin, 4.3 mg/dL; SpO_2, 90%; and SBP, 110 mm Hg
   c. A 65-year-old patient with pneumonia with lactate, 4.1 mmol/L; SpO_2, 80% on room air; and SBP, 90 mm Hg
   d. A 55-year-old patient weighing 200 kg

6. **At what time point should a second serum lactate measurement be made, according to CMS guidelines?**
   a. 1 hour
   b. 3 hours
   c. 6 hours
   d. 24 hours

7. **Which fluid type should be used for sepsis resuscitation?**
   a. Lactated Ringer`s solution
   b. 0.9% sodium chloride
   c. Orange juice drink
   d. Albumin

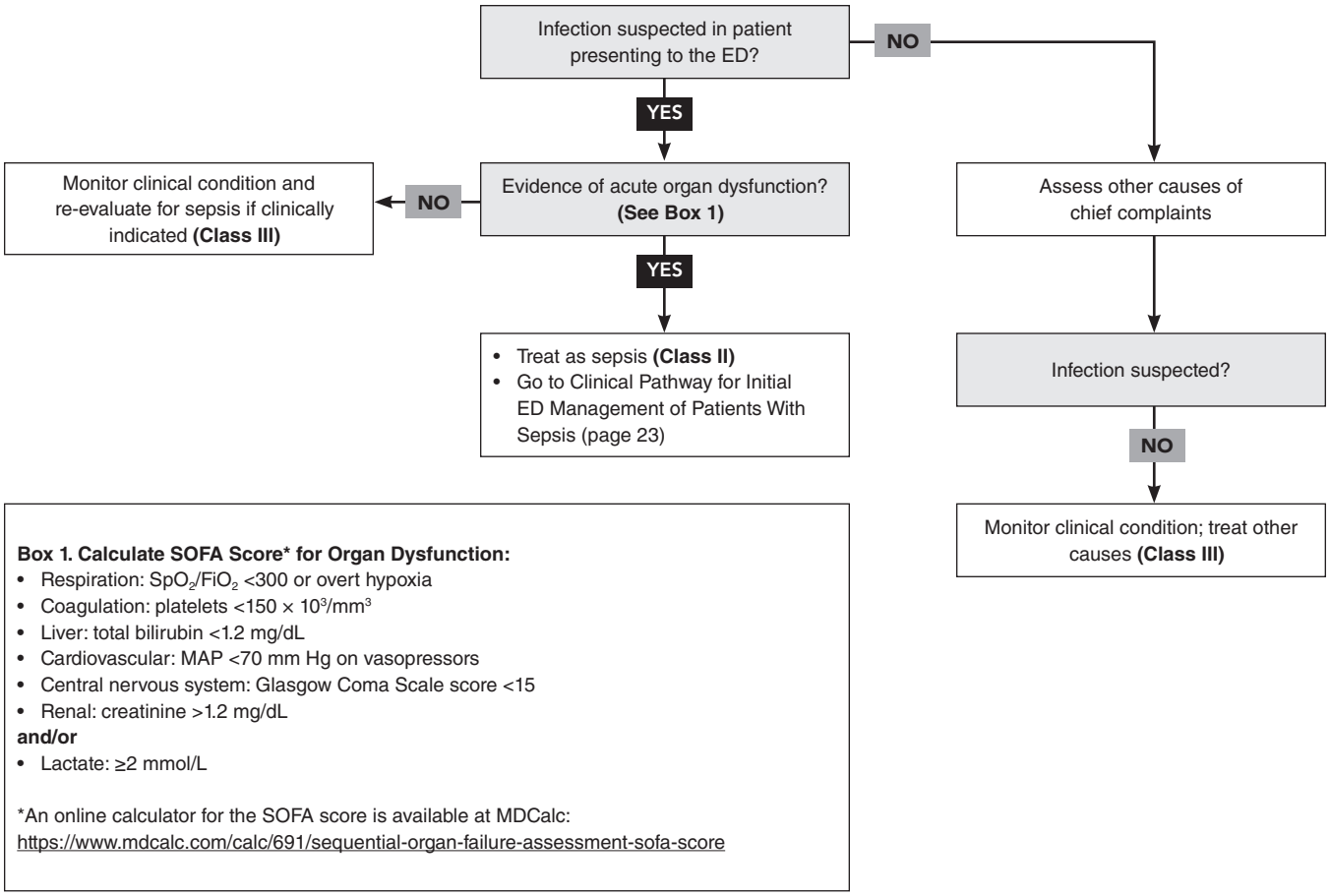
8. **For a hypotensive patient requiring vasopressors, which initial vascular access for vasopressor administration is most appropriate?**
   a. Set up for right internal jugular central venous line
   b. Place a left tibial intraosseous line
   c. Consult the peripherally inserted central catheter (PICC) line team
   d. Administer through already established 18-gauge PICC in the right antecubital fossa

9. **What is the recommended first-choice antibiotic for a non–penicillin-anaphylactic patient who is septic from a urinary tract infection?**
   a. Ceftriaxone
   b. Trimethoprim/sulfamethoxazole
   c. Vancomycin and piperacillin/tazobactam
   d. Wait for cultures

10. **Which patient should receive hydrocortisone?**
    a. Patient with 3 SIRS criteria
    b. Patient with evidence of end-organ dysfunction but who is normotensive
    c. Patient with hypotension requiring vasopressors
    d. Patient with initial hypotension that resolves after fluids

Clinical Pathway for Sepsis Screening in the Emergency Department

Click here or scan for interactive pathway



Box 1. Calculate SOFA Score* for Organ Dysfunction:

- Respiration: SpO_2/FiO_2 <300 or overt hypoxia
- Coagulation: platelets <150 × $10^3/mm^3$
- Liver: total bilirubin <1.2 mg/dL
- Cardiovascular: MAP <70 mm Hg on vasopressors
- Central nervous system: Glasgow Coma Scale score <15
- Renal: creatinine >1.2 mg/dL

and/or

- Lactate: ≥2 mmol/L

*An online calculator for the SOFA score is available at MDCalc: https://www.mdcalc.com/calc/691/sequential-organ-failure-assessment-sofa-score

Abbreviations: ED, emergency department; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; MAP, mean arterial pressure; 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

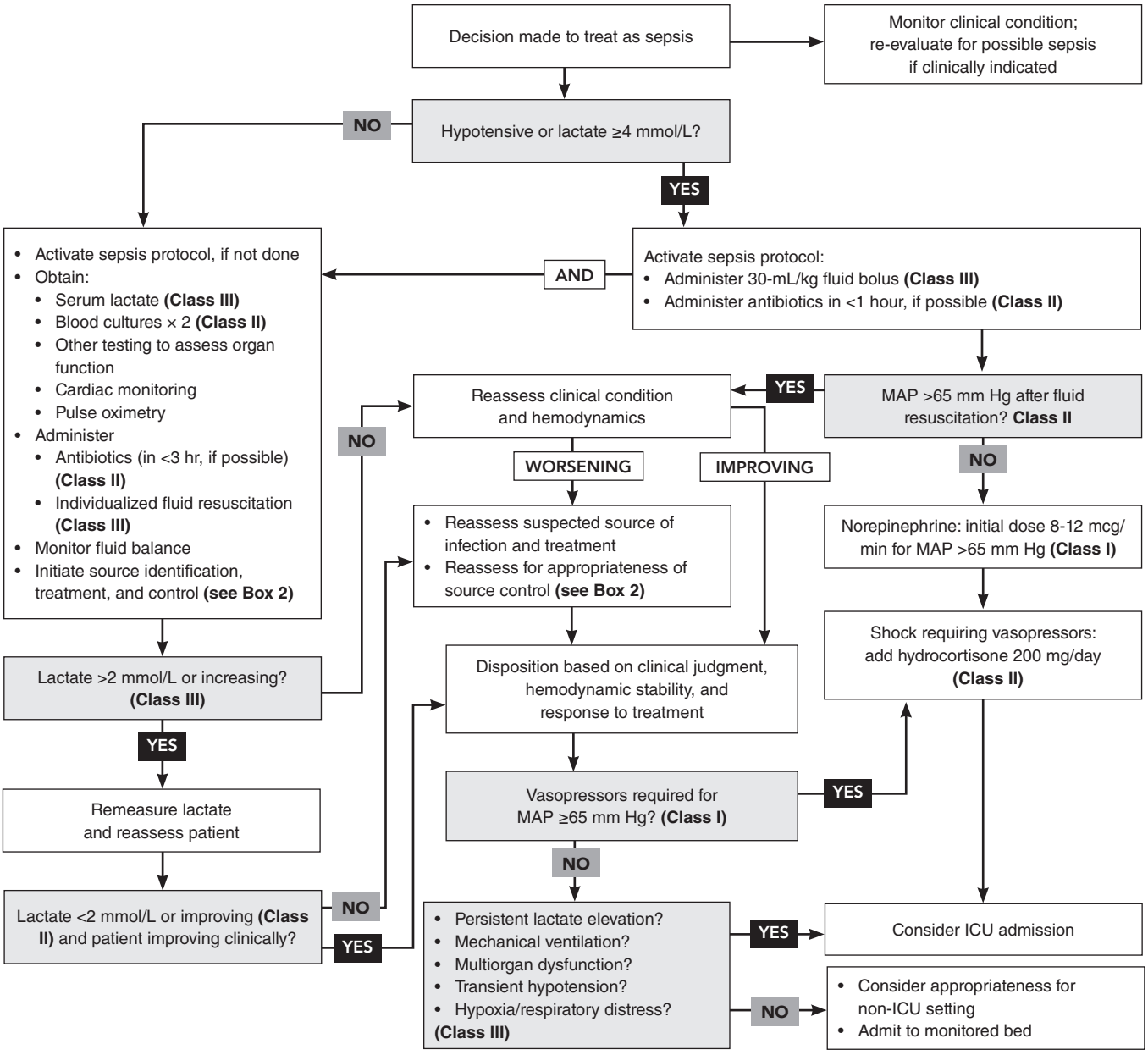
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

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 Emergency Department Management of Patients With Sepsis

Click here or scan for interactive pathway



Box 2. Perform Early Source Identification, Treatment, and Control:

- Evaluate for bowel ischemia, necrotizing soft tissue infection, abscess, empyema, or occult sources of infection (consider radiologic studies) **(Class III)**
- Consider alternative causes of lactate elevation: liver/renal disease, diabetic ketoacidosis, metformin or beta agonist use **(Class III)**
- Perform complete physical examination to identify potential missed source of infection
- Reassess perfusion and response to treatment **(Class III)**
- Reassess hemodynamics
- Achieve MAP >65 mm Hg
- Perform POCUS to assess cardiac and inferior vena cava function
- Consider inotropes and additional fluid bolus when indicated **(Class III)**

Abbreviations: ICU, intensive care unit; MAP, mean arterial pressure; POCUS, point-of-care ultrasound.

For Class of Evidence definitions, see page 22.

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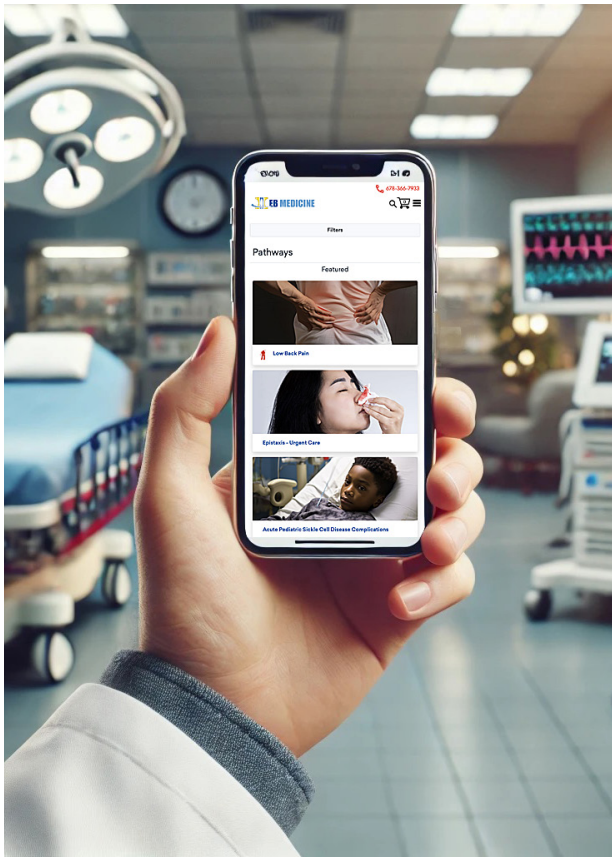

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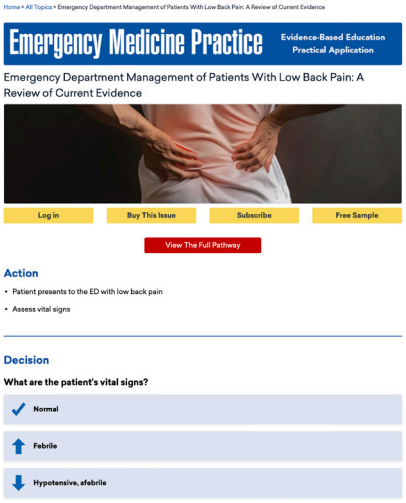

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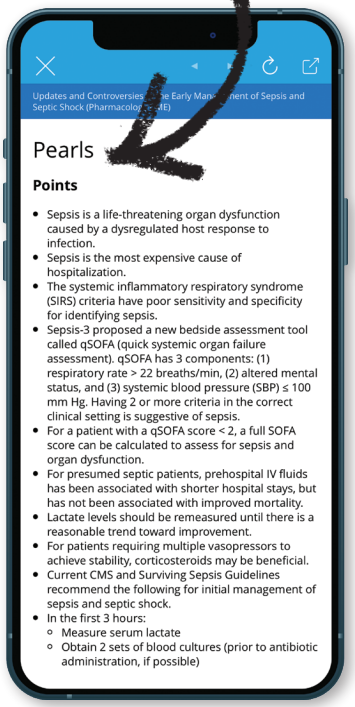

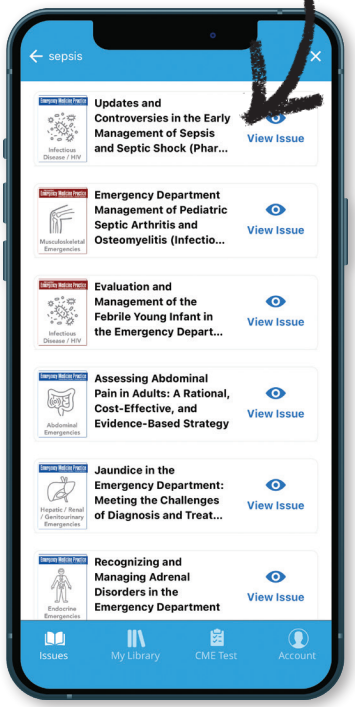

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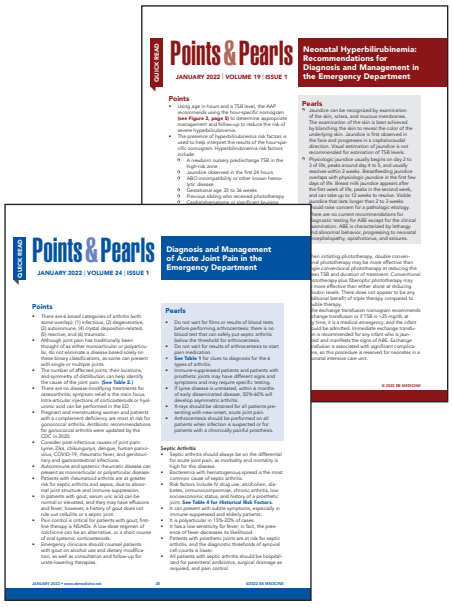

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QUICK READ

Points & Pearls

AUGUST 2025 | VOLUME 27 | ISSUE 8

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

Points

Definitions and Screening Tools

- Sepsis is characterized by excessive inflammation, suppression of innate and adaptive immunity, and vascular injury.[2]
- The definitions of sepsis have evolved substantially. Sepsis-3 is the most current definition (Third International Consensus Definitions), adopted in 2016.[1] It redefined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1]
- Updated definitions in Sepsis-3 emphasized organ dysfunction in the setting of infection, which can be quantified using the sequential (sepsis-related) organ failure assessment (SOFA) score.
- **Table 1** outlines the definitions of Sepsis-3 and summarizes the U.S. Centers for Medicare & Medicaid Services (CMS) SEP-1 definitions.
- Sepsis-3 consensus definition of sepsis was clinically operationalized as a new (or presumed new) increase in the SOFA score of ≥2 points above baseline in the presence of infection.[11]
- The SEP-1 quality measures are currently used to evaluate institutional compliance with (1) the severe sepsis bundle, and (2) the septic shock bundle.
- Tools for early sepsis screening include SOFA, qSOFA, SIRS criteria, NEWS, and MEWS. Online calculators for these tools can be found at www.MDcalc.com **Table 3** compares the sensitivity and specificity of these tools.
- Although the SOFA score is part of the definition for sepsis, it has limited utility for initial screening in the ED.

Diagnosis

- Identify the infectious source and any factors that could modify assessment and treatment (eg, beta blockers masking tachycardia, minor findings, etc).
- **Table 4** lists potential sources of infection associated with sepsis, by organ system, which can be a framework for diagnosis.[33]
- Assess perfusion, mentation, and pain levels.[39]
- Sepsis can provoke acute decompensation of pre-existing cardiac dysfunction.
- Obtain 2 sets of blood cultures, but this should not delay administration of antimicrobials.[42,43]
- The ANDROMEDA-SHOCK trial results suggest that clinical assessment of peripheral perfusion may be noninferior to lactate trending in septic shock.[46] If initial lactate level is >2 mmol/L, obtain a repeat level to ensure improvement after resuscitation.
- Focused diagnostic imaging tailored toward the most likely source of infection can be performed in undifferentiated cases of sepsis or septic shock.

Treatment

- Early empiric broad-spectrum IV antibiotic coverage is recommended, and has been associated with reduced mortality.[17,70]
- **See Table 5** for antibiotic recommendations.
- Norepinephrine continues to be the recommended first-line vasopressor for septic shock.[42] Vasopressin is second-line.[5]

Pearls

- Patients who have a suspected source of infection and identified organ dysfunction or elevated lactate levels should be treated as having sepsis, regardless of whether they meet initial sepsis screening criteria, or whether they triggered a best-practice advisory.[6]
- Infectious source identification and control should be achieved as rapidly as possible.[5]
- The CMS SEP-1 management bundle for severe sepsis and septic shock is outlined in the "Initial Management" section on **page 8**.
- Current literature remains neutral regarding restrictive versus liberal IV fluid strategies.[6,59-62]
- Fluid administration should be tailored to the patient's volume satus.[6] Dynamic assessment measures are preferred.[6]
- Based on current literature, it may be reasonable to promptly address hemodynamic instability with a hybrid approach of IV crystalloid fluid administration for volume resuscitation while simultaneously administering vasopressors for hemodynamic support, with the goal of weaning vasopressors as fluid resuscitation is accomplished.[95]

