CME

Seeking a balanced approach to implementing sepsis guidelines

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ABSTRACT

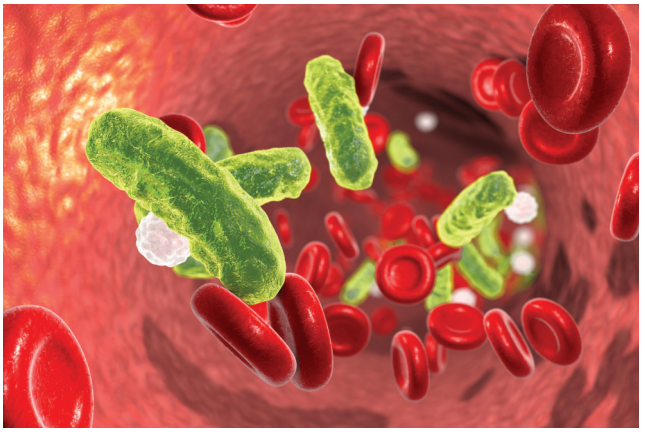
Sepsis, a life-threatening condition caused by an imbalanced response to infection, is a common diagnostic and therapeutic consideration for clinicians in acute care setting. The Surviving Sepsis Campaign (SSC) guidelines have increased awareness of sepsis and reduced mortality over the past 20 years. The Centers for Medicaid and Medicare Services created the SEP-1 core measure to ease and encourage implementation of the sepsis guidelines through financial incentives to hospitals. Still, the lack of clarity in sepsis diagnosis remains a concern. Many hospitals mandate sepsis care, forcing clinicians to provide treatment even if they consider it clinically unnecessary or harmful to the patient. This article describes a balanced approach to sepsis guideline implementation using clinical decision tools and educates clinicians on sepsis diagnosis and management.

Keywords: sepsis, septic shock, SOFA score, Surviving Sepsis Campaign guidelines, SEP-1 core measure, early goal-directed therapy

Learning objectives

- List the diagnostic criteria for SIRS and sepsis.
- Describe the SSC 1-hour bundle.
- Discuss the evidence related to sepsis care bundles.

Sepsis is a life-threatening condition caused by a dysregulated response to infection. The most common immediate cause of patient death in many US hospitals, sepsis is a common consideration in the evaluation and management of ED patients.[1] Since its inception in 2002, the Surviving Sepsis Campaign (SSC) has released four revisions of guidelines to improve diagnosis and recognition of sepsis, define and increase the use of appropriate treatment and care, and implement performance improvement programs.[2] The Centers for Medicaid and Medicare Services (CMS) created the SEP-1 core measure in 2015 to promote sepsis guidelines and bundled care implementation through hospital reimbursement and incentives.[3] Together, the SSC guidelines and SEP-1 core measure have made great strides to define and implement care of patients with severe sepsis and septic shock.



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The fourth revision of the SSC guidelines included input from key critical care organizations but departed from previous guidelines by leaving out comments from the American College of Emergency Physicians (ACEP).[4] Several academic leaders in emergency medicine expressed concern about the guidelines and core measure, including the directive nature of the use of a 1-hour bundle with an unclear sepsis diagnosis.[5] These physicians coauthored, signed, and circulated a petition to retire the SSC guidelines altogether, collecting more than 6,000 signatures.[5,6] In response, ACEP released a statement acknowledging the concerns about the 1-hour bundle and recommended against its implementation.[7] Nonetheless, CMS maintained its policy to encourage SEP-1 implementation.[8] Because of lack of clarity in diagnosis and the guidelines, finding a balance between sepsis guidelines and clinical reasoning is an essential skill for clinicians in acute care.[9]

DEFINING SEPSIS

In 1991, ACEP and the Society of Critical Care Medicine (SCCM) created the systemic inflammatory response syndrome (SIRS) criteria to help diagnose sepsis.[10,11] SIRS criteria are positive if a patient has two of the following four diagnostic signs:

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Key points

- The SSC guidelines and SEP-1 bundle have led to reductions in mortality, and recent sepsis literature calls for less-aggressive management than EGDT.
- The newest revisions of the SSC guidelines and SEP-1 call for measuring lactate, obtaining blood cultures, and delivering 30 mL/kg bolus of crystalloid fluids, broad-spectrum antibiotics, and vasopressors as needed, within 1 hour.
- Debate about these newest revisions addresses misapplication of the guidelines to questionable cases or cases in which this management is deemed unnecessary or inappropriate.

• temperature greater than 38° C (100.4° F) or less than 36° C (96.8° F)
• heart rate greater than 90 beats/minute
• respirations greater than 20 or $PaCo_2$ less than 32 mm Hg
• white blood cell count greater than 12,000 cells/mm^3 or less than 4,000 cells/mm^3, or more than 10% immature white blood cell bands.[10,11]

Classically, these criteria in a patient with a known or suspected infectious source define *sepsis*. Sepsis with signs of new organ dysfunction, tissue hypoperfusion, or hypotension was referred to as *severe sepsis*. Signs of tissue hypoperfusion include lactic acidosis, oliguria, or altered mental status.[10,11] Hypotension (defined as systolic BP less than 90 mm Hg or a reduction of 40 mm Hg from baseline) despite adequate IV fluid resuscitation in the presence of severe sepsis is *septic shock*.[10,11] The definition of adequate IV fluid resuscitation, not specified in the original article defining sepsis, has since ranged from a 500-mL bolus of a crystalloid fluid every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg to the more recent SEP-1 recommendation of 30 mL/kg.[12,13]

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) updated sepsis classification and diagnosis based on new concepts in pathophysiology.[14] Singer and colleagues argued that SIRS criteria focus solely on inflammatory excess, although a more current understanding of sepsis recognizes not only pro- and anti-inflammatory responses but also noninflammatory pathways such as cardiovascular, neuronal, and metabolic.[14] As a result of Sepsis-3, there was no longer a distinction between sepsis and severe sepsis. Sepsis became classified as organ dysfunction in a patient with an infection as represented by a Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score increase of 2 points or more from the patient's baseline.[14] The score includes several laboratory findings and clinical data for end-organ dysfunction such as increased bilirubin for the hepatobiliary system (ranges from 0 points for less than 1.2 mg/dL to 4 points for 12 mg/dL or greater), increased creatinine for the renal system (ranges from 0 points for less than 1.2 mg/dL to 4 points for 5 mg/dL or greater), and Glasgow Coma Scale (GCS) score for the central nervous system (ranges from 0 points for GCS score of 15 to 4 points for a score of less than 6 points), among others.[15]

Because many of these laboratory values cannot be quickly obtained in the acute care setting, Sepsis-3 also proposed a quickSOFA (qSOFA) score assessed at the bedside with two of the following criteria suggesting a clinically significant risk for mortality:
• respirations of 22 or greater
• altered mental status, defined as a GCS score less than 15
• systolic BP of 100 mm Hg or less.[14]

Although Singer and colleagues recommended that qSOFA replace previous screening criteria for sepsis, it has not performed well in retrospective analyses.[14,16,17] Sterling and colleagues found patients who met previous SIRS criteria but not Sepsis-3 criteria still often demonstrated significant organ failure and 14% mortality.[18] Fang and colleagues showed that Sepsis-3 criteria achieved the goal of increased specificity, effectively narrowing the sepsis population.[19] However, it did so while compromising sensitivity.[19]

For a clinician, that means more misses—misdiagnosing or discharging a greater number of patients with sepsis. For some patients, the delay of diagnosis caused by a false-negative qSOFA score could prove devastating. Because of the high mortality of sepsis, perhaps striving for high sensitivity at the expense of false-positives is the best that can be achieved. Braun concluded that SIRS criteria along with clinical judgment should continue to be used until SOFA/qSOFA can be validated or until other decision rules are realized.[20] He emphasized that no replacement exists for a qualified clinician weighing all available factors at the bedside to make a clinical diagnosis.[20]

PROGRESS OF SSC GUIDELINES AND SEP-1

The initial 2004 guidelines were based on the idea proposed by Rivers and colleagues of early goal-directed therapy (EGDT) with monitoring of venous oxygen saturation through central venous catheterization.[12,21] Venous oxygen saturation through a central catheter was thought to be the best means to assess end-organ damage and hemodynamic response to resuscitation with crystalloid fluid boluses, with or without vasopressor administration. In this single-center, randomized controlled trial, EGDT reduced short-term mortality compared with standard resuscitation.[12]

In 2014 and 2015, three large, multicenter, randomized controlled trials showed that this protocol of aggressive monitoring significantly increased use of ICU resources but did not improve outcomes compared with less-aggressive monitoring and care for patients with septic shock.[22-25] As a result, the 2016 SSC guidelines recommended more conservative dynamic measures for hemo-

dynamic monitoring and assessing fluid responsiveness, such as passive leg raise.[26] During this examination, a patient is lowered from a semirecumbent to horizontal supine position with their legs then raised passively to 45 degrees. The clinician observes for a 10% increase in stroke volume (via cardiac output monitor) or pulse pressure (using an arterial line).[27] Other dynamic variables include variation in mean arterial pressure or serial serum lactate measurements.[26]

Despite the lack of clear sepsis diagnostic criteria, Levy and colleagues as well as Miller and colleagues demonstrated improved outcomes with implementation of the 2004 and 2008 versions of the SSC guidelines and sepsis performance bundles.[21,28] In a large prospective cohort study, Levy and colleagues demonstrated a 25% relative risk reduction in mortality associated with increased compliance with the 2004 SSC guidelines.[21] Mukherjee and Evans cited these two studies as evidence of the value of the SSC guidelines.[29] They contend that persistent lack of adherence among clinicians is due to unfamiliarity or disagreement with guidelines and the inability to overcome inertia of existing behavior.[29] They further argued that greater adherence would lead to more improved outcomes.[29]

Motzkus and Lilly noted that SEP-1, compared with hospital quality initiative core measures for acute coronary syndrome and cerebrovascular accident, has faced additional challenges because of its complexity, measurement difficulty, and disappointing adherence.[30] In response to criticism, CMS produced several revisions of the core measure to address nuances in sepsis care. For example, one revision acknowledges that a patient's baseline creatinine may be elevated in chronic kidney disease, and acute kidney injury in these patients would be an increase of 0.5 mg/dL from baseline.[31]

CONCERNS FOR SSC GUIDELINES AND SEP-1

The 2016 SSC guidelines continue to recommend crystalloid fluid boluses and broad-spectrum IV antibiotics, as did previous guidelines.[26] However, the SSC bundle and SEP-1 core measure recommend administering treatment within 1 hour of ED triage (**Table 1**).[13,30] Many hospitals still use SIRS criteria to dictate whether treatment should be delivered this early. Three criteria (heart rate, respirations, and temperature) can be assessed at the bedside within 1 hour but are nonspecific for sepsis. Pressure from hospitals to meet the 1-hour bundle may prompt clinicians to deliver fluid boluses and broad-spectrum antibiotics based on these three SIRS criteria even when they deem treatment unnecessary or potentially harmful and the diagnosis unclear.[5]

TABLE 1. SSC 1-hour bundle

- Measure lactate. Remeasure if initial lactate is greater than 2 mmol/L
- Obtain blood cultures before administering antibiotics
- Administer broad-spectrum antibiotics
- Administer 30 mL/kg crystalloid fluid bolus for hypotension or lactate of 4 mmol/L or greater
- Administer vasopressor to maintain a mean arterial pressure of 65 mm Hg or greater if the patient is hypotensive during or after fluid administration.

Reprinted with permission from Springer Publishing: Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign bundle: 2018 update. *Intensive Care Med.* 2018;44(6):925-928.

Rivers and colleagues along with Angus and colleagues showed improved outcomes with IV fluid and antibiotic administration in patients with severe sepsis and septic shock, but not in patients with mild infectious disease or undifferentiated SIRS.[12,25] Farkas and colleagues noted that indiscriminate fluid administration in many patients can lead to patient harm, and overuse of antibiotics contributes to antibiotic resistance.[5] Regulation of sepsis management through bundled care becomes especially controversial in unclear cases and frustrates the diagnostic process. The guidelines attempt to simplify diagnosis and management that often are not simple.[5] As a result, clinicians sometimes are caught between following guidelines to appease hospital interests and following their clinical intuition to benefit and not harm the patient.

Aaronson and colleagues provided specific clinical challenges to SEP-1 based on an analysis of a random sample of 50 possible sepsis cases.[32] They acknowledged that SEP-1 is an important move forward in improving outcomes for patients with severe sepsis, septic shock, and high risk for mortality. However, the current incentive-based approach enforces clinical decisions, and the complexity of current reporting requirements detracts from patient care.[32] Particular clinical challenges include the ambiguous definition of sepsis, complications developed from prescriptive fluids requirement, and the "all or nothing" requirements of the SEP-1 core measure.[32]

Levy and colleagues and Miller and colleagues retrospectively demonstrated improved outcomes associated with the SSC guidelines and bundles based on about 30% guideline adherence.[21,28] Aaronson and colleagues pointed out that the 30% adherence in these retrospective studies represents 30% of patients for whom clinicians were comfortable providing sepsis bundle care.[32] The clinical effect of implementing care to the remaining 70% of patients is unclear. Aaronson and colleagues noted that linking guideline adherence to payment might risk promoting inappropriate care.[32] ACEP released a statement that recommends hospitals not implement the 1-hour bundle, noting that a multiorganizational task force will release evidence-based recommendations in 2020.[7]

DIRECTIONS FORWARD

Levy and colleagues defined a bundle as a set of interventions or care processes based on evidence-based

guidelines that, when implemented collectively, contribute positively to quality care.[33] Bundle use has been particularly important in application of sepsis guidelines over the previous decade.[29] One of the primary goals of the SSC bundle and the SEP-1 core measure has been to facilitate clinical translation of sepsis research to bedside practice.[33] Other important aspects of clinical translation of sepsis guidelines include education of clinicians and medical staff, early warning systems, clinical decision support tools, and sepsis champions who manage quality improvement initiatives. SEP-1 encourages guideline implementation by providing reimbursement to hospitals that meet all aspects of the core measure. However, mandating care can sometimes promote harmful treatment in the interest of financial gain rather than patient benefit. Educating clinicians and providing resources rather than mandating care preserves clinician autonomy to provide care based on what they believe will benefit patients.

More hospitals are instituting a sepsis alert system for implementing the 1-hour sepsis bundle, similar to previous alert systems used in the management of trauma, stroke, and myocardial infarction. The benefits of an early-alert system include the mobilization of key personnel (such as clinicians, nurses, pharmacists, and respiratory therapists) and quick implementation of bundle elements through a standardized protocol.[34] In many of these systems, a sepsis alert is automatically called if a patient presents with two of four SIRS criteria with a suspected infectious source plus a sign of end-organ damage such as respiratory distress or altered mental status. A sepsis alert can also be called for patients without signs of end-organ damage at the clinician's discretion. Whether these alerts are helpful in improving clinically significant end points has not been well-validated.[35] Harrison and colleagues noted that successful alert systems should minimize alert fatigue, interruption, and information overload.[35]

Quality improvement measures are targeting increased compliance to SEP-1 bundle measures for patients who meet SIRS criteria with a documented infectious source, effectively using an imperfect diagnostic tool as a reference standard for sepsis diagnosis.[32] More accurate reference standards include *ex post facto* methods such as administrative claims data or internal medicine physician chart review.[36] Positive outcomes for patients with nonsevere sepsis or questionable sepsis are thought to be associated with bundle care. However, because of the retrospective nature of the studies and the possibility that a positive outcome may have resulted without care, this association often is unclear. Quality improvement measures are less adept at identifying the large number of patients without sepsis who receive bundle care and the potential harms of this widespread treatment.

CONCLUSION

SSC guidelines and sepsis performance bundles have revolutionized sepsis care and reduced mortality. When sepsis bundles are applied to patients with severe sepsis or septic shock, adherence is associated with significant reduction in hospital mortality. Positive outcomes have been demonstrated based on 30% adherence, but greater compliance may not necessarily mean better outcomes. These results have not been validated in patients with less severe infectious disease, questionable sepsis, or those at risk of being harmed by interventions. A risk-benefit analysis for these patients considers the potential harm of implementing SSC guidelines and the SEP-1 core measure. Mandating care takes away autonomy from this analysis and the diagnostic process, and often encourages clinicians to provide care that they do not trust. Educating clinicians and providing resources such as clinical decision tools promote guidelines without mandating them. Sepsis diagnosis, like much of medicine, often is complex and requires skill in the clinical decision-making process. Guidelines and bundles should help clinicians navigate the gray areas rather than encourage the application of the same care for several nuanced clinical situations.

Finding a balance between sepsis guidelines and clinical reasoning at the bedside is an essential skill for acute care clinicians. Ultimately, the goal of clinicians and guidelines are the same—keeping patients safe. **JAAPA**

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