Clinical implications of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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Many physicians may not be aware that the term "sepsis" has undergone a change in definition that is important for research and for our understanding of its management. A joint task force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine recently re-examined long-standing definitions of sepsis and septic shock, and generated the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[1–3] Sepsis is common and has a large impact worldwide, resulting in an estimated 8 million deaths annually; experts have emphasized that rapid detection and treatment are needed to reduce the number of deaths.[4] The updated definitions have moved away from a broad characterization of infection and systemic inflammatory response to a more specific subset of severe illness with infection characterized by organ dysfunction. Although the novel definitions are helpful to provide a more accurate description of the pathologic condition of sepsis, it is important to note that the definition and the criteria derived to operationalize them have not yet been shown to be useful in the management of individual patients, and screening based on the traditional definition should not be abandoned.

Original definitions of sepsis required the presence of two or more of the systemic inflammatory response syndrome (SIRS) criteria, coupled with suspicion of infection.[5] Clinical use of the SIRS criteria became pervasive, and sepsis treatment protocols were developed based on these criteria. Rapid treatment protocols have translated into improved survival for patients[6,7] and reinforced widespread use of SIRS-based criteria. However, the low specificity of the SIRS criteria, and new evidence that questioned their sensitivity,[8] generated concern that the broad definition did not adequately signify the severity of sepsis as an illness.

In response, the authors of Sepsis-3 used large-scale, national databases to derive evidence-based, updated consensus definitions for sepsis and septic shock. The SIRS criteria were discarded, because inflammatory response was not considered to be specific to sepsis. Instead, Sepsis-3 defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1] Although this new definition explains what sepsis is, applying it at the bedside is challenging. Therefore, objective clinical criteria were also identified for making the diagnosis of sepsis, using the Sequential Organ Failure Assessment (SOFA) score. This assessment assigns points based on the magnitude of dysfunction in six organ systems and has been used for decades to predict mortality in patients with infection.[9] Sepsis is now defined as an acute increase in SOFA score of 2 or more from baseline in a patient with suspected infection,[1] and is associated with a minimum twofold increased risk of death.

This revised definition of sepsis is more consistent with recognized pathophysiology, carries an incremental increase in mortality risk, and thus is associated with more face validity than SIRS. However, the inclusion of the subjective words "life-threatening" and "dysregulated," as well as the subjective threshold of an increase in SOFA score of two points, makes clinical interpretation challenging. Use of SOFA for routine diagnosis in individual patients can prove burdensome, as laboratory values are not always easily obtained, particularly in low-resource settings. Furthermore, the mortality risk-stratification score used

KEY POINTS

- The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Sepsis-3 replaced systematic inflammatory response syndrome (SIRS) criteria from the definition of sepsis with clinical criteria based on the Sequential Organ Failure Assessment (SOFA) score; these criteria should be used only for prognostication of mortality and not for start of treatment.
- Quick SOFA clinical criteria were proposed for rapid risk-stratification of patients with suspected infection, but existing evidence suggests that these criteria are poorly sensitive for prediction of mortality outside of the intensive care unit.
- Clinicians should continue to use SIRS criteria and clinical gestalt in screening, treating and risk-stratifying patients with infection.

in Sepsis-3 indicates severe illness; it is not clinically equivalent to a screening test (i.e., a trigger for the start of treatment). Clinicians should clearly not use the SOFA score to guide initiation of treatment in patients with infection as treatment should be started earlier in the course of illness.

Sepsis-3 also derived alternative criteria for the identification of patients at increased risk of death, using clinical parameters alone and in the absence of laboratory data. The quick SOFA (qSOFA)[2] uses three criteria: systolic blood pressure of 100 mm Hg or less, respiratory rate of 22 breaths/min or greater, and Glasgow Coma Scale score of less than 15. Presence of two or more of these criteria indicates increased risk of death and alerts the clinician to a patient who may require closer attention. The quick SOFA is not intended to define sepsis, but rather acts as a risk-stratification tool to identify patients at increased risk of death.[1] Risk of death may already be clear, however, based on the presence of tachypnea, hypotension and altered consciousness, which are all alarming signs without need for a scoring system. The quick SOFA does not replace or eliminate the clinical utility of SIRS,[10] and it was not intended to inform treatment decisions in patients with infection. A patient who meets fewer than two qSOFA criteria may still require aggressive treatment, because sensitivity of this tool for prediction of mortality is poor, particularly when compared with SIRS,[11] and clinicians managing at-risk patients with infection outside of the intensive care unit (ICU) should continue to use the SIRS criteria as a prompt for the start of treatment.

Sepsis-3 also updated the definition of "septic shock," identifying criteria that characterize this high-risk subset of patients with sepsis.[3] Previously, septic shock was defined as sepsis in addition to the presence of hypotension or start of vasopressors or inotropes (with evidence of perfusion abnormalities).[5] Sepsis-3 defines septic shock more specifically as sepsis in addition to shock requiring the start of vasopressors to maintain a mean arterial pressure 65 mm Hg or greater, and a serum lactate level greater than 2.0 mmol/L following "adequate fluid resuscitation."[3] Initial operationalization of this new definition suggested a lack of sensitivity, given its strict criteria; an appreciable proportion of patients who would have been identified using the old definitions ultimately died.[12]

Although the Sepsis-3 definitions reflect our updated understanding of the pathophysiology of sepsis, they are not actionable and do not replace existing protocols for the management of sepsis, which are associated with improved outcomes.[6,7] To be fair, the revised definitions are not intended to be actionable, but rather prognostic. For clinicians, Sepsis-3 criteria do not guide treatment and should not be used to rule out risk of deterioration. When assessing patients with infection in non-ICU settings (e.g., the emergency department), the SIRS criteria have superior sensitivity to qSOFA[11] and therefore should be used preferentially as a prompt for treatment, as per existing protocols.[6] Clinical impression is still key in the care of patients with infection, who, even in the absence of SIRS criteria, may still require treatment for sepsis. The Sepsis-3 criteria may be useful for identification of patients at highest risk of death, but should not be used to form a clinical impression, particularly when they are absent. Prospective validation of the criteria is required. Ultimately, the label "sepsis" may be less important than being able to identify patients at risk of deterioration quickly.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
2. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:762-74.
3. Shankar-Hari M, Phillips GS, Levy ML, et al.; Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:775-87.
4. Dugani S, Veillard J, Kissoon N. Reducing the global burden of sepsis. *CMAJ* 2017;189:E2-3.
5. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644-55.
6. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017;376:2235-44.
7. Levy MM, Rhodes A, Phillips GS, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015;43:3-12.
8. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015;372:1629-38.
9. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-10.
10. Vincent JL, Martin GS, Levy MM. qSOFA does not replace SIRS in the definition of sepsis. *Crit Care* 2016;20:210.
11. Fernando SM, Tran A, Taljaard M, et al. Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected infection: a systematic review and meta-analysis. *Ann Intern Med* 2018;168:266-75.
12. Sterling SA, Puskarich MA, Glass AF, et al. The impact of the Sepsis-3 septic shock definition on previously defined septic shock patients. *Crit Care Med* 2017;45:1436-42.

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