Managing Sepsis and Septic Shock: Current Guidelines and Definitions

Recent updates emphasize early recognition and prompt intervention.

ABSTRACT: Sepsis is a leading cause of critical illness and hospital mortality. Early recognition and intervention are essential for the survival of patients with this syndrome. In 2002, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) launched the Surviving Sepsis Campaign (SSC) to reduce overall patient morbidity and mortality from sepsis and septic shock by driving practice initiatives based on current best evidence. The SSC guidelines have been updated every four years, with the most recent update completed in 2016. The new guidelines have increased the focus on early identification of infection, risks for sepsis and septic shock, rapid antibiotic administration, and aggressive fluid resuscitation to restore tissue perfusion.

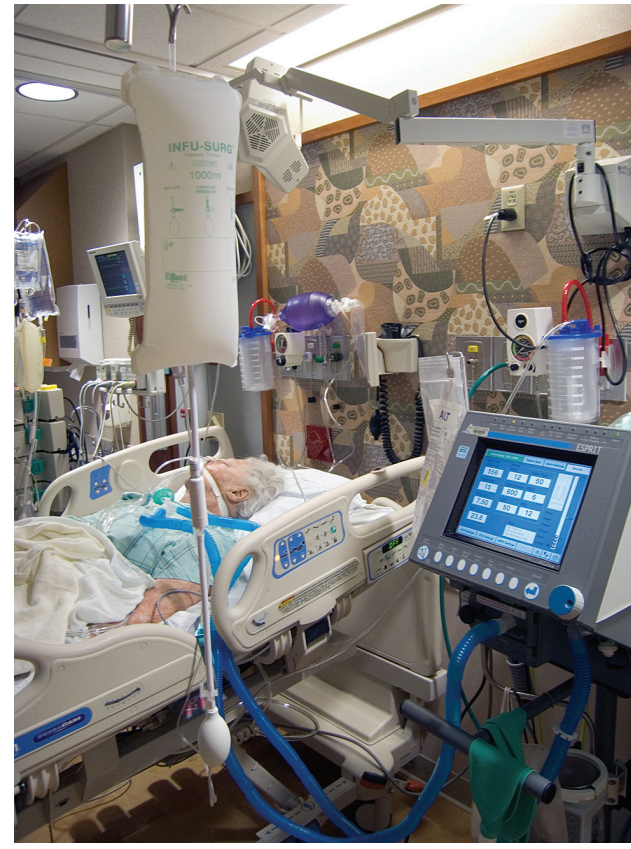
In 2014, the SCCM and the ESICM convened a task force of specialists to reexamine the definitions of terms used to identify patients along the sepsis continuum. In 2016, this task force published the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). The new definitions and recommendations included tools, based on an updated understanding of the pathobiology of sepsis, that can be used to predict adverse outcomes in patients with infection.

This article discusses the new SSC treatment guidelines, changes in the sepsis bundle interventions, and the Sepsis-3 definitions and tools, all of which enable nurses to improve patient outcomes through timely collaborative action.

Keywords: quick Sequential Organ Failure Assessment (qSOFA), sepsis, sepsis bundle, sepsis guidelines, septic shock, Sequential Organ Failure Assessment (SOFA), Surviving Sepsis Campaign, Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

While sepsis defies simple definition, it's generally understood to be a clinical syndrome caused by infection that may have profound adverse physiologic consequences.[1] Although its precise incidence is unknown, sepsis is believed to be a leading cause of critical illness and hospital mortality, accounting for more than one-third of all deaths in U.S. hospitals.[2-4] For patients with sepsis, early identification and rapid intervention are crucial to the restoration of tissue perfusion.

The Centers for Disease Control and Prevention recently partnered with clinical professional organizations and patient advocacy groups to launch a comprehensive campaign focused on prevention and rapid recognition of sepsis as critical components of patient safety programs.[5] Definitions of sepsis and septic shock are used to help clinicians identify patients with this complex clinical syndrome, to guide nursing and collaborative interventions, and to support research efforts. This article discusses the ways in which our understanding of sepsis and septic shock have changed over the years, the origin of the Surviving Sepsis Campaign (SSC), the latest revised SSC treatment guidelines, changes in the sepsis bundle interventions, and the new definitions and predictive tools introduced by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).



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CHANGING DEFINITIONS OF SEPSIS AND SEPTIC SHOCK

The first working definition of sepsis was developed in 1991 to guide research and practice.[6] Bone and colleagues introduced a broad definition of sepsis and the concept of systemic inflammatory response syndrome (SIRS), which is characterized by a cluster of symptoms triggered by an inflammatory response that may or may not be due to an infectious process. SIRS was said to be characterized by, though not limited to, more than one of the following clinical symptoms[6]:

- abnormally high or low temperature
- abnormally high or low white blood cell count
- elevated heart rate
- elevated respiratory rate

In the presence of infection and at least two clinical symptoms of SIRS, the systemic response was identified as sepsis.[6] While clinical treatment of sepsis and sepsis research continued to evolve, resulting in several practice guideline updates, SIRS remained part of the continuum of the sepsis syndrome.[7-10]

The SSC was launched in 2002 by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), with the goal of reducing mortality from sepsis by increasing awareness, improving diagnosis and treatment, educating health care providers, developing management guidelines, implementing a performance improvement plan, and improving post-ICU care (see www.survivingsepsis.org). A major goal of the campaign has been to encourage clinicians to recognize symptoms along the continuum from SIRS to sepsis and septic shock in order to facilitate early identification and aggressive treatment of sepsis, thereby improving patient outcomes. The SSC released its first management guidelines in 2004, and these have been updated every four years, with the most recent update completed in 2016.

The Sepsis-3 task force, convened in 2014 by the SCCM and the ESICM, introduced new definitions for *sepsis* and *septic shock* based on advances in the scientific understanding of this complex syndrome.[1, 11, 12] A principal change in the new definitions was the requirement that sepsis be triggered by infection.[1] This pathobiological understanding removes SIRS from the definition of sepsis, as numerous conditions other than infection may cause SIRS.

The Sepsis-3 definitions focus on the understanding that sepsis is a multifaceted patient response to infection and results in organ dysfunction.[1, 11] The new definitions thus focus on organ dysfunction and hypoperfusion in the presence of infection, rather than on inflammation (specifically SIRS). Furthermore, the term *severe sepsis* is no longer recommended, as it is hard to identify clinically and is not helpful in guiding clinical treatment interventions.[1, 11] *Septic shock* is now defined as a subset of sepsis in which the patient has profound hypoperfusion. Four years following publication of the SSC 2012 guidelines, Sepsis-3 published its new and refined definitions.[1] (For a comparison of

the guidelines, see Table 1.[1, 9, 13]) Although there is some debate about the Sepsis-3 definitions, the changes were proposed to aid clinicians in rapidly identifying and treating patients with sepsis, with the goal of reducing morbidity and mortality.

EARLY RECOGNITION OF SEPSIS: SOFA AND qSOFA

The emphasis in the Sepsis-3 definitions on organ dysfunction caused by infection requires clinicians to take a more concentrated, objective approach to the assessment of organ function. The Sepsis-3 recommendation is to use an organ dysfunction assessment tool to identify patients with sepsis. The Sequential Organ Failure Assessment (SOFA), most commonly used in ICUs, is effective in quantifying the severity of organ dysfunction and morbidity and estimating mortality risk.[14, 15]

The SOFA evaluates the following physiologic functions: respiration, coagulation, hepatic, cardiovascular, central nervous system, and renal.[15] In order to calculate a patient's SOFA score, it is necessary to obtain the following laboratory values: bilirubin, creatinine, coagulation studies, and arterial blood gases. However, while these can reveal organ dysfunction, they may not accurately reflect the patient's perfusion status. The higher the SOFA score, the greater the patient's risk of morbidity and mortality.[16] (See *The Sequential Organ Failure Assessment (SOFA) Score*.[15])

The quick SOFA (qSOFA), an abbreviated organ dysfunction assessment, was introduced in Sepsis-3.[1] The qSOFA relies on only three variables: systolic blood pressure, respiratory rate, and mentation.[1] In non-ICU patients, the qSOFA score predicts elevated risk of death and extended ICU stay, but it is not designed to stand alone as an early warning of sepsis or to identify which patients should be transferred to the ICU.[17, 18] (See *The Quick Sequential Organ Failure Assessment (qSOFA) Score*.[1])

The information imparted by serum lactate levels can also play an important role in guiding clinical decision making. A serum lactate level greater than 2 mmol/L suggests hypoperfusion, with higher lactate levels indicating more severe hypoperfusion. Normalization of lactate in patients with elevated lactate

Table 1. A Comparison of the SSC and Sepsis-3 Definitions

Terminology	SSC Definitions[9, 13]	Sepsis-3 Definitions[1]
SIRS	The presence of at least two of the following clinical criteria: • Temperature, < 36°C or > 38.3°C • Heart rate, > 90 bpm • Respiratory rate, > 20 bpm, or $PaCO_2$, < 32 mmHg • WBC count, < 4,000 mm^3 or > 12,000 mm^3	Not part of the definition
Sepsis	The presence of at least two SIRS criteria and known or suspected infection	• Sepsis is a life-threatening organ dysfunction caused by a dysregulated patient response to infection. • In lay terms, sepsis is a life-threatening condition that arises when the body's response to infection causes injury to itself and its organs.
Severe Sepsis	• Sepsis-induced hypotension • SBP, < 90 mmHg • MAP, < 70 mmHg, or an SBP reduction of 40 mmHg from baseline • Serum lactate, > 2 mmol/L • Signs of organ dysfunction (acute oliguria, for example)	Not part of the definition
Septic Shock	Sepsis-induced hypotension that persists despite adequate fluid resuscitation and requires vasopressors to support perfusion	Septic shock is seen in patients with sepsis who develop underlying circulatory and metabolic abnormalities resulting in hypotension that require vasopressors to maintain a MAP of ≥ 65 mmHg and having a serum lactate level of ≥ 2 mmol/L despite adequate volume resuscitation, resulting in a higher risk of mortality.

MAP = mean arterial pressure; $PaCO_2$ = partial pressure of arterial carbon dioxide; SBP = systolic blood pressure; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock; SIRS = systemic inflammatory response syndrome; SSC = Surviving Sepsis Campaign; WBC = white blood cell.

The Sequential Organ Failure Assessment (SOFA) Score[15]

A clinical evaluation of the patient that includes laboratory values (bilirubin, creatinine, coagulation studies, and arterial blood gases) is needed to calculate a SOFA score. The SOFA score is most commonly used in the ICU practice setting.

The following are the abnormal physiologic SOFA parameters, each of which receives a score of 2 or higher:

- PaO_2:FiO_2, < 300 mmHg
- platelets, < $100 \times 10^3/mm^3$
- bilirubin, ≥ 2 mg/dL
- hypotension requiring vasopressor support
- Glasgow Coma Scale score, ≤ 12
- creatinine, ≥ 2 mg/dL, or urine output < 500 mL/day

Physiologic parameters are scored from 0 (normal function) to 4 (organ failure). Each parameter is scored individually, after which a total score is derived to suggest severity of illness. The higher the cumulative score, the greater the patient's risk. A score of 2 or higher in any system indicates an elevated risk of organ dysfunction, poor outcome, or death.

An online SOFA calculator can be found at www.mdcalc.com/sequential-organ-failure-assessment-sofa-score.

FiO_2 = fractional inspired oxygen; PaO_2 = partial pressure of arterial oxygen.

levels remains a recommendation in the current SSC guidelines.[13] That said, adding serum lactate levels to the parameters used to determine the qSOFA score has been found to do little to improve its predictive validity for mortality.[11]

The advantages of the qSOFA are that it is easy to use and enables clinicians to identify at-risk patients in the absence of laboratory values. The qSOFA score is not a component of the new sepsis definition; rather, it should alert clinicians to patients in need of further assessment for organ dysfunction, which may escalate care for those with previously unrecognized infection or possible sepsis.[19] Patients presenting with even modest organ dysfunction associated with infection can deteriorate rapidly; this underscores the importance of early recognition and intervention.[13, 20, 21] Recent commentaries[21, 22] and recommendations from the SSC[23] provide examples of how to integrate the SOFA and qSOFA into the assessment of patients at risk for sepsis. For a composite clinical example from our practice, see *Assessing Risk of Organ Failure in Patients with Infection*.

SEPSIS BUNDLE CHANGES

In 2017, the new SSC guidelines were published, containing major changes to the sepsis bundles.[13, 24] The new SSC guidelines briefly discuss the Sepsis-3 definitions, but acknowledge that the research informing the guidelines incorporated the earlier definitions of sepsis and septic shock that included SIRS.[13] Furthermore, the new SSC guidelines do not include qSOFA or SOFA as clinical requirements for assessing patients with suspected sepsis or septic shock, as some studies suggest additional research is needed to evaluate the benefits of including these organ assessment tools in the efforts to identify and treat patients with sepsis as early as possible.[16, 25]

The elements of the new SSC guidelines that most affect nursing practice focus on the following actions:

The Quick Sequential Organ Failure Assessment (qSOFA) Score[1]

The following are the abnormal physiologic qSOFA parameters:

- systolic blood pressure, ≤ 100 mmHg
- respiratory rate, ≥ 22 breaths per minute
- any change in mental status

Patients are assigned one point for each abnormal parameter. Non-ICU patients with a total score of 2 or 3 are considered at elevated risk for an extended ICU stay or death and should be assessed for evidence of organ dysfunction using the SOFA. An online qSOFA calculator can be found at www.mdcalc.com/qsofa-quick-sofa-score-sepsis.

- early identification of patients with possible infection and sepsis
- rapid and aggressive fluid resuscitation (at least 30 mL/kg within three hours of sepsis-induced hypoperfusion)
- frequent hemodynamic reassessment of patient response to fluids
- administration of IV antibiotics within one hour of suspected sepsis or septic shock

Readers are encouraged to review the new guidelines—Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016[13]—as well as the three- and six-hour SSC bundles. All are available for download on the

Assessing Risk of Organ Failure in Patients with Infection

How to use the SOFA and the qSOFA.

A 69-year-old man presents to the ED, reporting increased pain, redness, and tenderness in the palm of his left hand near the base of his thumb. He says he sustained a cut of roughly 2 cm from his fishing knife three days prior, after which he washed the cut in the stream and applied an antibiotic ointment along with over-the-counter suture strips. He has had general malaise and possibly a low-grade fever for the past two days, and does not recall when he had his last tetanus shot. He answers questions appropriately, showing no sign of cognitive dysfunction. His medical history includes hypertension controlled with metoprolol and lisinopril, and type 2 diabetes treated with metformin. On admission, his vital signs are as follows:

- BP, 102/58 mmHg
- MAP, 73 mmHg
- HR, 118 beats per minute
- RR, 28 breaths per minute
- SpO_2, 92% on room air
- TAT, 100.7°F

The patient is triaged to a lower level of care and taken to a room to have his wound cleaned and redressed. The nurse checks on him 45 minutes later and finds that his face is flushed, he is somewhat confused, and he appears to be anxious. His vital signs are now: BP, 98/50 mmHg; MAP, 66 mmHg; HR, 128 beats per minute; RR, 32 breaths per minute; and TAT, 101.1°F.

The nurse performs a qSOFA and alerts the primary provider that the patient may have sepsis based on the fact that on admission he had a suspected infection and his qSOFA indicates a RR of ≥ 22 breaths per minute, giving him a qSOFA score of 1. Shortly after the initial qSOFA, however, his clinical condition deteriorated and his qSOFA score increased to 3 (RR, ≥ 22 breaths per minute; systolic BP, ≤ 100 mmHg; and altered mentation). When a patient's qSOFA score is 2 or higher, the next steps are to alert the primary provider of the change in the patient's condition and to assess the patient for organ dysfunction using the SOFA score. This patient's SOFA clinical and laboratory data are as follows:

Physiologic Parameter	SOFA Score
• PaO_2:FiO_2, 295 mmHg[a]	2
• platelets, $180 \times 10^3/mm^3$	0
• bilirubin, 1.1 mg/dL	0
• MAP, 66 mmHg	1
• Glasgow Coma Scale score, 14[b]	1
• creatinine, 1.4 mg/dL	1

The patient's overall SOFA score is 5, and he has a SOFA score of at least 2 in one system. The results of this assessment, in addition to the patient's history and clinical presentation, support the rapid implementation of the three- and six-hour sepsis bundles, including fluid resuscitation, rapid antibiotic administration, frequent reassessment, and targeted organ support to prevent further clinical deterioration.

BP = blood pressure; FiO_2 = fractional inspired oxygen; HR = heart rate; MAP = mean arterial pressure; PaO_2 = partial pressure of arterial oxygen; qSOFA = quick Sequential Organ Failure Assessment; RR = respiratory rate; SOFA = Sequential Organ Failure Assessment; SpO_2 = peripheral capillary oxygen saturation; TAT = temporal artery temperature.

[a] PaO_2 is 62 mmHg on room air; FiO_2 is 21%.

[b] Best eye response, 4; best verbal response, 4; obeys commands, 6.

SSC website, along with supplemental educational materials and related editorials (see www.survivingsepsis.org/Guidelines/Pages/default.aspx).

LIMITATIONS OF THE SEPSIS-3 DEFINITIONS

The new Sepsis-3 definitions are not without controversy. There is debate about whether the exclusion of SIRS and the inclusion of the new sepsis definitions will expedite identification of patients with sepsis.[20, 26, 27] Bear in mind that the qSOFA score is a predictor of mortality risk and not a defining characteristic of sepsis. It should be used to identify patients who require further assessment for organ failure.[11, 13, 17, 20, 21] Clinical deterioration in patients with a positive qSOFA score may be due to causes other than sepsis. On the other hand, in the study used to develop the new Sepsis-3 definitions, more than 75% of the patients with a suspected infection who scored 2 or higher on the qSOFA also had a positive SOFA score, indicating the presence of organ dysfunction and suspected sepsis.[11]

IMPLICATIONS FOR NURSING PRACTICE

Although the changes in the definitions of sepsis and septic shock may have little effect on the way nurses provide care to patients, one argument in their favor is that the simplification of terms used to describe suspected sepsis syndrome will expedite intervention. Encouraging nurses to "think sepsis" when subtle changes occur in patients with possible infection is key to early intervention and improved patient outcomes. While the value of the qSOFA in predicting risk of sepsis has not yet been well studied, it is a simple tool that can point to the need for additional focused assessment and intervention. ▼

For seven additional continuing nursing education activities on the topic of sepsis, go to www.nursingcenter.com/ce.

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REFERENCES

1. Singer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315(8):801-10.
2. Cohen J, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis* 2015;15(5):581-614.
3. Finfer S, Machado FR. The global epidemiology of sepsis. Does it matter that we know so little? *Am J Respir Crit Care Med* 2016;193(3):228-30.
4. Liu V, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA* 2014;312(1):90-2.
5. Novosad SA, et al. Vital signs: epidemiology of sepsis: prevalence of health care factors and opportunities for prevention. *MMWR Morb Mortal Wkly Rep* 2016;65(33):864-9.
6. Bone RC, 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(6):1644-55.
7. Dellinger RP, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32(3):858-73.
8. Dellinger RP, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36(1):296-327.
9. Dellinger RP, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41(2):580-637.
10. Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31(4):1250-6.
11. Seymour CW, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315(8):762-74.
12. Shankar-Hari M, et al. 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(8):775-87.
13. Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45(3):486-552.
14. Vincent JL, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998;26(11):1793-800.
15. Vincent JL, 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(7):707-10.
16. Raith EP, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. *JAMA* 2017;317(3):290-300.
17. Donnelly JP, et al. Application of the third international consensus definitions for sepsis (Sepsis-3) classification: a retrospective population-based cohort study. *Lancet Infect Dis* 2017;17(6):661-70.
18. Seymour CW, et al. Application of a framework to assess the usefulness of alternative sepsis criteria. *Crit Care Med* 2016;44(3):e122-e130.
19. Vincent JL, et al. qSOFA does not replace SIRS in the definition of sepsis. *Crit Care* 2016;20(1):210.
20. Singer M. The new sepsis consensus definitions (Sepsis-3): the good, the not-so-bad, and the actually-quite-pretty. *Intensive Care Med* 2016;42(12):2027-9.
21. Vincent JL, et al. Sepsis: older and newer concepts. *Lancet Respir Med* 2016;4(3):237-40.
22. Kleinpell RM, et al. The new sepsis definitions: implications for critical care practitioners. *Am J Crit Care* 2016;25(5):457-64.
23. Antonelli M, et al. *Surviving Sepsis Campaign responds to Sepsis-3*. Arlington Heights, IL; 2016 Mar 1. Surving Sepsis Campaign; http://www.survivingsepsis.org/SiteCollectionDocuments/SSC-Statements-Sepsis-Definitions-3-2016.pdf.
24. Dellinger RP, et al. A users' guide to the 2016 Surviving Sepsis guidelines. *Crit Care Med* 2017;45(3):381-5.
25. Fullerton JN, et al. New sepsis definition changes incidence of sepsis in the intensive care unit. *Crit Care Resusc* 2017;19(1):9-13.
26. Sprung CL, Reinhart K. Definitions for sepsis and septic shock. *JAMA* 2016;316(4):456-7.
27. Verdonk F, et al. The new sepsis definition: limitations and contribution to research and diagnosis of sepsis. *Curr Opin Anaesthesiol* 2017;30(2):200-4.