EDITORIAL

New Definitions for Sepsis and Septic Shock
Continuing Evolution but With Much Still to Be Done

Edward Abraham, MD

The diagnosis of sepsis is not a new concern. Indeed, as early as 700 BCE, the Greeks recognized Σήψις (sepsis), referring to decomposition or rot, as a life-threatening condition associated with infection and high risk of death. The primary criterion for sepsis has historically been progressive organ system dysfunction resulting from infection. Because the only available therapies for this condition, antimicrobials and supportive care, are not specific, there was little concern about developing more detailed standards for diagnosis.

Related articles pages 762, 775 and 801

Over the past 30 years, 2 major factors have led to a perceived need for better definitions. In particular, the increasing sophistication, at least in high-income countries, of modalities available for organ support in critical care units, including ventilators and dialysis, has resulted in growing numbers of patients with sepsis receiving care in intensive care units (ICUs) and enhanced awareness of the frequency and high costs associated with this condition. In addition, greater understanding of the underlying pathophysiologic mechanisms responsible for cellular dysfunction in experimental models and in patients with severe infection has accelerated the need for better entry criteria in clinical trials using therapies specifically directed toward molecular events thought to contribute to sepsis-associated morbidity and mortality.

In this issue of *JAMA*, the Sepsis Definitions Task Force presents 3 articles: the updated definitions for sepsis and sepsis shock[1] and 2 supporting reports with evidence for derivation and validation of these new definitions.[2,3] In their Special Communication, Singer and colleagues[1] describe the importance, process used, issues addressed, key findings from the evidence, and synthesis to develop the third iteration of consensus conference definitions for sepsis and septic shock and present the new definitions in detail. Previous versions of these definitions date from 1992 and 2003.[4,5] A major underpinning for the present effort was the use of analyses in large cohorts to provide quantitative information in support of the revised criteria.

The accompanying report by Seymour and colleagues[2] assesses the predictive validity of the Sequential [Sepsis-related] Organ Failure Assessment score (SOFA), systemic inflammatory response syndrome (SIRS) criteria, and the Logistic Organ Dysfunction System (LODS) score and derived a new score called quickSOFA (qSOFA) in a primary cohort that included 148 907 patient encounters with suspected sepsis and a confirmatory analysis that included 706 399 out-of-hospital and hospital patient encounters at 165 US and non-US hospitals. The investigators found that among ICU encounters with suspected infection (n = 7932), the predictive validity for in-hospital mortality of SOFA (area under the receiver operating characteristic curve [AUROC], 0.74 [95% CI, 0.73-0.76]) was not significantly different than that derived from the more complex LODS (AUROC, 0.75 [95% CI, 0.73-0.76]) but was superior to that from SIRS (AUROC, 0.64 [95% CI, 0.62-0.66]), supporting use of SOFA in clinical criteria for sepsis. Among patient encounters with suspected infection outside the ICU (n = 66 522), qSOFA had high predictive validity for in-hospital mortality (AUROC, 0.81 [95% CI, 0.80-0.82]) that was statistically greater than that for SIRS (AUROC, 0.76 [95% CI, 0.75-0.77]), suggesting that it may have utility as a prompt to consider possible sepsis.

In the other accompanying report, Shankar-Hari and colleagues[3] describe the process of developing a new definition and clinical criteria for identifying septic shock in adults. The authors conducted a systematic review and meta-analysis of 92 studies informing a Delphi process that created the new definition, then tested the variables identified by the Delphi process in cohort studies (Surviving Sepsis Campaign [n = 28 150; University of Pittsburgh Medical Center [n = 1 309 025], and Kaiser Permanente Northern California [n = 1 847 165]).

According to the new definitions, sepsis is now defined as evidence of infection plus life-threatening organ dysfunction, clinically characterized by an acute change of 2 points or greater in the SOFA score. The new clinical criteria for septic shock include sepsis with fluid-unresponsive hypotension, serum lactate level greater than 2 mmol/L, and the need for vasopressors to maintain mean arterial pressure of 65 mm Hg or greater. A major change in the new definitions is the elimination of mention of SIRS. Components of SIRS include tachycardia, tachypnea, hyperthermia or hypothermia, and abnormalities in peripheral white blood cell count. Many studies have shown that the presence of SIRS is nearly ubiquitous in hospitalized patients and occurs in many benign conditions, both related and not related to infection, and thus is not adequately specific for the diagnosis of sepsis.[6] It is a strength of the consensus definition that it no longer includes SIRS.

Patients with infections and organ dysfunction are exceptionally heterogeneous in terms of demographic characteristics, underlying conditions, microbiology, and other clinically relevant factors.[7] The updated definition for sepsis,

like the previous versions, is broad with respect to diagnostic criteria and will not help in segmenting patients into subgroups based on underlying microbiology, pathophysiology, or cellular alterations. For example, a previously healthy 18-year-old with meningococcemia, coagulopathy, and hypoxemia; a 45-year-old tourist returning from Southeast Asia with malaria, new-onset renal dysfunction, and hyperbilirubinemia; and a 90-year-old with a medical history of Alzheimer disease, diabetes, and congestive heart failure who presents with worsening mental status, decreased urinary output, and a urinary tract infection related to an indwelling bladder catheter will all be categorized as septic, and all will have septic shock if they demonstrate an elevated serum lactate level and require vasopressors to maintain blood pressure. The inclusion of such a wide variety of patients with suspected, but not necessarily proven, infection, organ system dysfunction of multiple types, and a variety of underlying medical conditions ensures that even though the new definitions may be helpful in evaluating the epidemiology and economics relating to sepsis, they will be limited in their utility to strengthen the design of clinical trials and, most importantly, in directing care for individual patients.

Although the use of large databases provides support for the new consensus definitions of sepsis and septic shock, there remain concerns with the information used to generate the updated criteria. In particular, the patient data are all almost exclusively from adults in high-income countries and primarily contain information from patients in the United States, so the utility of these definitions in other geographic regions, in settings that are less resource replete, and among pediatric populations is presently unknown. As noted by the authors of these articles, the ability of the new definitions to predict morbidity and mortality in low- and middle-income countries, where levels of patient monitoring and supportive care commonly used in the United States and developed world are often not available, remains an unanswered question. An additional concern relates to the inclusion of serum lactate levels in the definition of septic shock, because such measurements may not be available in resource-limited settings.

The consensus document also introduces a new bedside index, called the qSOFA, which is proposed to help identify patients with suspected infection who are being treated outside of critical care units and likely to develop complications of sepsis. The qSOFA requires at least 2 of the following 3 risk variables: respiratory rate of 22 or more breaths per minute, systolic blood pressure of 100 mm Hg or less, and altered mental status. However, because this index was retrospectively derived from databases that had substantial gaps in clinical information for patients treated outside of ICUs, qSOFA will require prospective, real-world validation before it can enter routine clinical practice. In addition, because analysis of the Veterans Affairs database appeared to show little additional predictive value in qSOFA from the inclusion of mental status changes, further simplification of this index may be possible.

A fundamental component of the new definitions for sepsis and septic shock remains the presence of infection. Yet negative microbiologic cultures from blood or relevant anatomic sites are frequent in patients clinically identified as being septic.[7] While new techniques, such as those using matrix-associated laser desorption ionization-time of flight (MALDI-TOF) or polymerase chain reaction (PCR), are likely to enhance the current ability to diagnose infections,[7,8] a major limitation continues to be the identification of patients whose organ system dysfunction is truly secondary to an underlying infection rather than other causes. This is a particularly important issue in critical care, where many noninfectious conditions, such as trauma and pancreatitis, are accompanied by the acute onset of organ failure, with the contributory role of concomitant infection often being extremely difficult to determine.

In the same way that patients with sepsis are heterogeneous in terms of their underlying microbiology, medical history, and clinical characteristics, so are the alterations in cellular function that accompany this condition.[9,10] Developments in genetics, genomics, immunology, and cellular biology have led to increased understanding of the derangements that contribute to organ dysfunction and death in experimental models and patients with severe infections. Pathways involving inflammatory and anti-inflammatory signaling, innate and adaptive immune response, apoptosis, mitochondrial function, translational and transcriptional regulation, and oxidative biology, as well as additional intracellular and extracellular events, are activated with differing kinetics in individuals with sepsis. Enhanced understanding of the range of underlying cellular events contributing to organ dysfunction associated with severe infection has highlighted the need to develop biomarkers that identify the alterations present in patients with sepsis so specific therapies can be used in an appropriate manner.

The epidemiologic strengths of the new consensus conference definitions of sepsis and septic shock are accompanied by weaknesses in their ability to be used in the treatment of individual patients or in clinical trials. Although the new definitions provide a broad view of the universe of sepsis and may help in facilitating early identification of patients with this condition, they will be of only limited help in directing specific therapies to individual patients or in designing clinical trials focused on specific mechanisms of sepsis-induced organ dysfunction.

Precision medicine, in which individualized therapies are provided to patients based on the specific genomic and cellular alterations accompanying their disease process, is revolutionizing the treatment of cancer and other conditions.[11] Such targeted treatment has been shown to be associated with enhanced clinical response among patients with cancer, often with diminished toxicity. There would appear to be substantial potential for a similarly tailored approach to sepsis, given the heterogeneity of cellular responses associated with this condition. However, the lack of molecular components in the new consensus definitions does not advance this exciting possibility.

An ongoing issue, discussed in the articles in this issue of *JAMA*, is that sepsis is a syndrome and not a specific disease. The new definitions do not alleviate this concern. Other con-

ditions, most notably cancer, were previously described in a similar manner but are now further characterized based not just on anatomic location and cell type but most recently on expression of specific biomarkers, including cellular receptors, activation of intracellular pathways, and genomic alterations. Such characterization has enabled development of therapies targeted to specific patients, with remarkable improvements in outcome. Although the present definition for sepsis provides needed evolution in categorization of this syndrome, incorporation of more information about the molecular and cellular characterization of sepsis may have been helpful. Hopefully, the next iteration of this consensus process will take full advantage of the rapidly advancing understanding of molecular processes that lead from infection to organ failure and death so that sepsis and septic shock will no longer need to be defined as a syndrome but rather as a group of identifiable diseases, each characterized by specific cellular alterations and linked biomarkers. Such evolution will be required to truly transform care for the millions of patients worldwide who develop these life-threatening conditions.

ARTICLE INFORMATION

Author Affiliation: Wake Forest School of Medicine, Winston Salem, North Carolina.

Corresponding Author: Edward Abraham, MD, Wake Forest School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157 (eabraham@wakehealth.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. doi:10.1001/jama.2016.0287.

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*. doi:10.1001/jama.2016.0288.

3. Shankar-Hari M, Phillips GS, Levy ML, 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*. doi:10.1001/jama.2016.0289.

4. Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20(6):864-874.

5. Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.

6. Vincent J-L, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. *Lancet*. 2013;381(9868):774-775.

7. Cohen J, Vincent J-L, Adhikari NK, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis*. 2015;15(5):581-614.

8. Buehler SS, Madison B, Snyder SR, et al. Effectiveness of practices to increase timeliness of providing targeted therapy for inpatients with bloodstream infections: a laboratory medicine best practices systematic review and meta-analysis. *Clin Microbiol Rev*. 2016;29(1):59-103.

9. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. *Immunity*. 2014;40(4):463-475.

10. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest*. 2016;126(1):23-31.

11. Jameson JL, Longo DL. Precision medicine—personalized, problematic, and promising. *N Engl J Med*. 2015;372(23):2229-2234.

The Acute Respiratory Distress Syndrome
Dialing in the Evidence?

Brendan J. Clark, MD; Marc Moss, MD

Acute respiratory distress syndrome (ARDS) could be regarded as a prototypical disorder that has benefited from a bench to bedside research approach. After its original description in 1967, the complex pathophysiology of ARDS has been slowly unraveled through extensive basic and translational research. Based on this improved understanding of the mechanisms responsible for ARDS, a variety of major clinical trials were subsequently designed and conducted. Several of these clinical trials identified relatively simple and biologically plausible interventions that reduced mortality for patients with ARDS. For example, the ARDS network trial established that low tidal volume ventilation (6 mL/kg of predicted body weight) reduced mortality from 40% to 31%.[1] A meta-analysis of 3 other trials demonstrated that a strategy of high positive end-expository pressure (PEEP) was associated with decreased mortality for patients with moderate to severe ARDS.[2] In addition, ventilation in the prone position early in the course of moderate to severe ARDS resulted in a 16% absolute risk reduction in mortality.[3] In theory, these beneficial therapies should be relatively easy to implement. They are essentially free, involve adjusting the dials on the ventilator or positioning patients, and are relatively safe.

Related article page 788

As the mechanistic and clinical understanding of ARDS advanced, concerns arose about the diagnostic criteria used to define ARDS. A panel of experts was convened to evaluate the objective performance of various diagnostic criteria for ARDS using a consensus process. The result was that the 2012 Berlin Definition changed several the diagnostic criteria for ARDS. The Berlin criteria included a graded severity based on the degree of hypoxemia was created (mild, moderate, or severe ARDS), a minimal amount of PEEP was added as a specific diagnostic criterion, and the intubation requirement was removed for patients with mild ARDS.[4]

Until the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study, reported by Bellani and colleagues in this