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

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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.

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 and cellular abnormalities 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 septic shock1 and 2 supporting reports with evidence for derivation and validation of these new definitions.2,3 In their Special Communication, Singer and colleagues1 describe the process of developing a new definition, then tested the variables identified by the Delphi process in cohort studies (Surviving Sepsis Campaign [n = 28150; University of Pittsburgh Medical Center [n = 1309025], and Kaiser Permanente Northern California [n = 1847165]).

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.4 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.5 The updated definition for sepsis,
like the previous versions, is broad with respect to diagnostic
criteria and will not help in segmenting patients into sub-
groups based on underlying microbiology, pathophysiology,
or cellular alterations. For example, a previously healthy
18-year-old with meningococemia, coagulopathy, and
hypoxemia; a 45-year-old tourist returning from Southeast
Asia with malaria, new-onset renal dysfunction, and hyper-
bilirubinemia; and a 90-year-old with a medical history of
Alzheimer disease, diabetes, and congestive heart failure
who presents with worsening mental status, decreased uri-
inary 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, infec-
tion, organ system dysfunction of multiple types, and a vari-
ety 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 up-
dated criteria. In particular, the patient data are all almost ex-
clusively 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 set-
tings that are less resource replete, and among pediatric popu-
lations is presently unknown. As noted by the authors of these
articles, the ability of the new definitions to predict morbid-
ity 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 con-
cern relates to the inclusion of serum lactate levels in the defi-
nition 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 out-
side 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 retrospec-
tively 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,2,4 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 heteroge-
neous in terms of their underlying microbiology, medical
history, and clinical characteristics, so are the alterations in
cellular function that accompany this condition.9,10 Devel-
opments in genetics, genomics, immunology, and cellular
biology have led to increased understanding of the derange-
ments 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 intra-
cellular 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 con-
ference definitions of sepsis and septic shock are accompa-
nied by weaknesses in their ability to be used in the treat-
ment of individual patients or in clinical trials. Although the
new definitions provide a broad view of the universe of sep-
sis and may help in facilitating early identification of patients
with this condition, they will be of only limited help in direct-
ing 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 cellu-
ar alterations accompanying their disease process, is revolu-
tionizing 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 sep-
sis, given the heterogeneity of cellular responses associated
with this condition. However, the lack of molecular compo-
nents 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

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REFERENCES


The Acute Respiratory Distress Syndrome
Dialing in the Evidence?

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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-expiratory 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.

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 of 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