The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

CONCLUSIONS AND RELEVANCE These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis.
Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a major public health concern, accounting for more than $20 billion (5.2%) of total US hospital costs in 2011. The reported incidence of sepsis is increasing, likely reflecting aging populations with more comorbidities, greater recognition, and, in some countries, reimbursement-favorable coding. Although the true incidence is unknown, conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide. Furthermore, there is increasing awareness that patients who survive sepsis often have long-term physical, psychological, and cognitive disabilities with significant health care and social implications.

A 1991 consensus conference developed initial definitions that focused on the then-prevailing view that sepsis resulted from a host’s systemic inflammatory response syndrome (SIRS) to infection (Box 1). Sepsis complicated by organ dysfunction was termed severe sepsis, which could progress to septic shock, defined as “sepsis-induced hypotension persisting despite adequate fluid resuscitation.” A 2001 task force, recognizing limitations with these definitions, expanded the list of diagnostic criteria but did not offer alternatives because of the lack of supporting evidence. In effect, the definitions of sepsis, septic shock, and organ dysfunction have remained largely unchanged for more than 2 decades.

The Process of Developing New Definitions

Recognizing the need to reexamine the current definitions, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine convened a task force of 19 critical care, infectious disease, surgical, and pulmonary specialists in January 2014. Unrestricted funding support was provided by the societies, and the task force retained complete autonomy. The societies each nominated cochairs (Drs Deutschman and Singer), who selected members according to their scientific expertise in sepsis epidemiology, clinical trials, and basic or translational research.

The group engaged in iterative discussions via 4 face-to-face meetings between January 2014 and January 2015, email correspondence, and voting. Existing definitions were revisited in light of an enhanced appreciation of the pathobiology and the availability of large electronic health record databases and patient cohorts.

An expert consensus process, based on a current understanding of sepsis-induced changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation (collectively referred to as pathobiology), forged agreement on updated definition(s) and the criteria to be tested in the clinical arena (content validity). The distinction between definitions and clinical criteria is discussed below. The agreement between potential clinical criteria (construct validity) and the ability of the criteria to predict outcomes typical of sepsis, such as need for intensive care unit (ICU) admission or death (predictive validity, a form of criterion validity), were then tested. These explorations were performed in multiple large electronic health record databases that also addressed the absence (missingsness) of missing elements of different organ dysfunction scores and the question of generalizability (ecologic validity). A systematic literature review and Delphi consensus methods were also used for the definition and clinical criteria describing septic shock.

When compiled, the task force recommendations with supporting evidence, including original research, were circulated to major international societies and other relevant bodies for peer review and endorsement (31 endorsing societies are listed at the end of this article).

Issues Addressed by the Task Force

The task force sought to differentiate sepsis from uncomplicated infection and to update definitions of sepsis and septic shock to be consistent with improved understanding of the pathobiology. A definition is the description of an illness concept; thus, a definition of sepsis should describe what sepsis “is.” This chosen approach allowed discussion of biological concepts that are currently incompletely understood, such as genetic influences and cellular abnormalities. The sepsis illness concept is predicated on infection as its trigger, acknowledging the current challenges in the microbiological identification of infection. It was not, however, within the task force brief to examine definitions of infection.

The task force recognized that sepsis is a syndrome without, at present, a validated criterion standard diagnostic test. There is currently no process to operationalize the definitions of sepsis and septic shock, a key deficit that has led to major variations in reported incidence and mortality rates (see later discussion). The task force determined that there was an important need for features that can be identified and measured in individual patients and sought to provide such criteria to offer uniformity. Ideally, these clinical criteria should identify all the elements of sepsis (infection, host response, and organ dysfunction), be simple to obtain, and be available promptly and at a reasonable cost or burden. Furthermore, it should be possible to test the validity of these criteria with available large clinical data sets and, ultimately, prospectively. In addition, clinical criteria should be available to provide practitioners in out-of-hospital, emergency department, and hospital ward settings with the capacity to better identify patients with suspected infection likely to progress to a life-threatening state. Such early recognition is particularly important because prompt management of septic patients may improve outcomes.

In addition, to provide a more consistent and reproducible picture of sepsis incidence and outcomes, the task force sought to integrate the biology and clinical identification of sepsis with its epidemiology and coding.
Identified Challenges and Opportunities

Assessing the Validity of Definitions
When There Is No Gold Standard
Sepsis is not a specific illness but rather a syndrome encompassing a still-uncertain pathobiology. At present, it can be identified by a constellation of clinical signs and symptoms in a patient with suspected infection. Because no gold standard diagnostic test exists, the task force sought definitions and supporting clinical criteria that were clear and fulfilled multiple domains of usefulness and validity.

Improved Understanding of Sepsis Pathobiology
Sepsis is a multifaceted host response to an infecting pathogen that may be significantly amplified by endogenous factors.14,15 The original conceptualization of sepsis as infection with at least 2 of the 4 SIRS criteria focused solely on inflammatory excess. However, the validity of SIRS as a descriptor of sepsis pathobiology has been challenged. Sepsis is now recognized to involve early activation of both pro- and anti-inflammatory responses,16 along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation,14,17,18 all of which have prognostic significance. Organ dysfunction, even when severe, is not associated with substantial cell death.19

The broader perspective also emphasizes the significant biological and clinical heterogeneity in affected individuals,20 with age, underlying comorbidities, concurrent injuries (including surgery) and medications, and source of infection adding further complexity.21 This diversity cannot be appropriately recapitulated in either animal models or computer simulations.14 With further validation, multichannel molecular signatures (eg, transcriptomic, metabolomic, proteomic) will likely lead to better characterization of specific population subsets.22,23 Such signatures may also help to differentiate sepsis from noninfectious insults such as trauma or pancreatitis, in which a similar biological and clinical host response may be triggered by endogenous factors.24 Key concepts of sepsis describing its protean nature are highlighted in Box 2.

Variable Definitions
A better understanding of the underlying pathobiology has been accompanied by the recognition that many existing terms (eg, sepsis, severe sepsis) are used interchangeably, whereas others are redundant (eg, sepsis syndrome) or overly narrow (eg, septicemia). Inconsistent strategies in selecting International Classification of Diseases, Ninth Revision (ICD-9), and ICD-10 codes have compounded the problem.

Sepsis
The current use of 2 or more SIRS criteria (Box 1) to identify sepsis was unanimously considered by the task force to be unhelpful. Changes in white blood cell count, temperature, and heart rate reflect inflammation, the host response to “danger” in the form of infection or other insults. The SIRS criteria do not necessarily indicate a dysregulated, life-threatening response. SIRS criteria are present in many hospitalized patients, including those who never develop infection and never incur adverse outcomes (poor discriminant validity).25 In addition, 1 in 8 patients admitted to critical care units in Australia and New Zealand with infection and new organ failure did not have the requisite minimum of 2 SIRS criteria to fulfill the definition of sepsis (poor concurrent validity) yet had protracted courses with significant morbidity and mortality.26 Discriminant validity and convergent validity constitute the 2 domains of construct validity; the SIRS criteria thus perform poorly on both counts.

Organ Dysfunction or Failure
Severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions. Differences in these scoring systems have also led to inconsistency in reporting. The predominant score in current use is the Sequential Organ Failure Assessment (SOFA) (originally the Sepsis-related Organ Failure Assessment27) (Table 1).28 A higher SOFA score is associated with an increased probability of mortality.28 The score grades abnormality by organ system and accounts for clinical interventions. However, laboratory variables, namely, PaO2, platelet count, creatinine level, and bilirubin level, are needed for full computation. Furthermore, selection of variables and cutoff values were developed by consensus, and SOFA is not well known outside the critical care community. Other organ failure scoring systems exist, including systems built from statistical models, but none are in common use.

Septic Shock
Multiple definitions for septic shock are currently in use. Further details are provided in an accompanying article by Shankar-Hari et al.13 A systematic review of the operationalization of current definitions highlights significant heterogeneity in reported mortality. This heterogeneity resulted from differences in the clinical variables chosen (varying cutoffs for systolic or mean blood pressure ± diverse levels of hyperlactatemia ± vasopressor use ± concurrent new organ dysfunction ± defined fluid resuscitation volume/targets), the data source and coding methods, and enrollment dates.
A Need for Sepsis Definitions for the Public and for Health Care Practitioners

Despite its worldwide importance,6,7 public awareness of sepsis is poor.29 Furthermore, the various manifestations of sepsis make diagnosis difficult, even for experienced clinicians. Thus, the public needs an understandable definition of sepsis, whereas health care practitioners require improved clinical prompts and diagnostic approaches to facilitate earlier identification and an accurate quantification of the burden of sepsis.

Results/Recommendations

Definition of Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Box 3). This new definition emphasizes the primacy of the nonhomeostatic host response to infection, the potential lethality that is considerably in excess of a straightforward infection, and the need for urgent recognition. As described later, even a modest degree of organ dysfunction when infection is first suspected is associated with an in-hospital mortality in excess of 10%. Recognition of this condition thus merits a prompt and appropriate response.

Nonspecific SIRS criteria such as pyrexia or neutrophilia will continue to aid in the general diagnosis of infection. These findings complement features of specific infections (eg, rash, lung consolidation, dysuria, peritonitis) that focus attention toward the likely anatomical source and infecting organism. However, SIRS may simply reflect an appropriate host response that is frequently adaptive. Sepsis involves organ dysfunction, indicating a pathobiology more complex than infection plus an accompanying inflammatory response alone. The task force emphasis on life-threatening organ dysfunction is consistent with the view that cellular defects underlie physiologic and biochemical abnormalities within specific organ systems. Under this terminology, “severe sepsis” becomes superfluous. Sepsis should generally warrant greater levels of monitoring and intervention, including possible admission to critical care or high-dependency facilities.

Clinical Criteria to Identify Patients With Sepsis

The task force recognized that no current clinical measures reflect the concept of a dysregulated host response. However, as noted by the 2001 task force, many bedside examination findings and routine laboratory test results are indicative of inflammation or organ dysfunction.10 The task force therefore evaluated which clinical criteria best identified infected patients most likely to have sepsis. This objective was achieved by interrogating large data sets of hospitalized patients with presumed infection, assessing agreement among existing scores of inflammation (SIRS)9 or organ dysfunction (eg, SOFA,27,28 Logistic Organ Dysfunction System30) (construct validity), and delineating their correlation with subsequent outcomes (predictive validity). In addition, multivariable regression was used to explore the performance of 21 bedside and laboratory criteria proposed by the 2001 task force.30

Full details are found in the accompanying article by Seymour et al.32 In brief, electronic health record data of 1.3 million encounters at 12 community and academic hospitals within the University of Pittsburgh Medical Center health system in southwestern Pennsylvania were studied. There were 148 907 patients with suspected infection, identified as those who had body fluids sampled for culture and received antibiotics. Two outcomes—hospital mortality and mortality, ICU stay of 3 days or longer, or both—were used to assess predictive validity both overall and across deciles of baseline risk as determined by age, sex, and comorbidity. For infected patients both inside and outside of the

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Scorea

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td>≥400</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100</td>
</tr>
<tr>
<td>(kPa)</td>
<td></td>
<td>(53.3)</td>
<td>(53.3)</td>
<td>(40)</td>
<td>(26.7)</td>
<td>(13.3)</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Platelets, ×10^9/μL</td>
<td></td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>(μmol/L)</td>
<td></td>
<td>(20)</td>
<td>(20-32)</td>
<td>(33-101)</td>
<td>(102-204)</td>
<td>(204)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or</td>
<td>Dopamine 5.1-15</td>
<td>Dopamine &gt;15 or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dobutamine (any dose)</td>
<td>epinephrine ≤0.1</td>
<td>epinephrine &gt;0.1</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td>Glasgow Coma Scale scorea</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>Creatinine, mg/dL</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(μmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FIO2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO2, partial pressure of oxygen.

<table>
<thead>
<tr>
<th>Scorec</th>
<th>01234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 13-14 10-12 6-9 &lt;6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver</th>
<th>Coagulation</th>
<th>Dopamine &lt;5 or dobutamine (any dose)</th>
<th>Dopamine 5.1-15 or epinephrine ≤0.1</th>
<th>Dopamine &gt;15 or epinephrine &gt;0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin, mg/dL (μmol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal</th>
<th>Central nervous system</th>
<th>Cardiovascular</th>
<th>Coagulation</th>
<th>Platelets, ×10^9/μL</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>glasgow comase scorea</td>
<td></td>
<td></td>
<td>&lt;1.2 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2-1.9 (20-32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0-5.9 (33-101)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.0-11.9 (102-204)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;12.0 (204)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Map</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70</td>
<td>&lt;70</td>
<td>MAP</td>
<td>MAP</td>
<td>Dopamine &lt;5 or dobutamine (any dose)</td>
<td>Dopamine 5.1-15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mm Hg</td>
<td>mm Hg</td>
<td></td>
<td>epinephrine ≤0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dopamine</th>
<th>5.1-15</th>
<th>&gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>epinephrine</td>
<td>≤0.1</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

b Catecholamine doses are given as μg/kg/min for at least 1 hour.

c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

- Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Scorea

Copyright 2016 American Medical Association. All rights reserved.
Screening for Patients Likely to Have Sepsis

A parsimonious clinical model developed with multivariable logistic regression identified that any 2 of 3 clinical variables—Glasgow Coma Scale score of 13 or less, systolic blood pressure of 100 mm Hg or less, and respiratory rate 22/min or greater—offered predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) similar to that of the full SOFA score outside the ICU. This model was robust to multiple sensitivity analyses including a more simple assessment of altered mentation (Glasgow Coma Scale score <15) and in the out-of-hospital, emergency department, and ward settings within the external US and non-US data sets.

For patients with suspected infection within the ICU, the SOFA score had predictive validity (AUROC = 0.74; 95% CI, 0.73-0.76) superior to that of this model (AUROC = 0.66; 95% CI, 0.64-0.68), likely reflecting the modifying effects of interventions (eg, vasoressors, sedative agents, mechanical ventilation). Addition of lactate measurement did not meaningfully improve predictive validity but may help identify patients at intermediate risk.

This new measure, termed qSOFA (for quick SOFA) and incorporating altered mentation, systolic blood pressure of 100 mm Hg or less, and respiratory rate of 22/min or greater, provides simple bedside criteria to identify adult patients with suspected infection who are likely to have poor outcomes (Box 4). Because predictive validity was unchanged (P = .55), the task force chose to emphasize altered mentation because it represents any Glasgow Coma Score less than 15. 

ICU, predictive validity was determined with 2 metrics for each criterion: the area under the receiver operating characteristic curve (AUROC) and the change in outcomes comparing patients with a score of either 2 points or more or fewer than 2 points in the different scoring systems across deciles of baseline risk. These criteria were also analyzed in 4 external US and non-US data sets containing data from more than 700 000 patients (cared for in both community and tertiary care facilities) with both community- and hospital-acquired infection.

In ICU patients with suspected infection in the University of Pittsburgh Medical Center data set, discrimination for hospital mortality with SOFA (AUROC = 0.74; 95% CI, 0.73-0.76) and the Logistic Organ Dysfunction System (AUROC = 0.75; 95% CI, 0.72-0.76) was superior to that with SIRS (AUROC = 0.64; 95% CI, 0.62-0.66). The predictive validity of a change in SOFA score of 2 or greater was similar (AUROC = 0.72; 95% CI, 0.70-0.73). For patients outside the ICU and with suspected infection, discrimination of hospital mortality with SOFA (AUROC = 0.79; 95% CI, 0.78-0.80) or change in SOFA score (AUROC = 0.79; 95% CI, 0.78-0.79) was similar to that with SIRS (AUROC = 0.76; 95% CI, 0.75-0.77).

Because SOFA is better known and simpler than the Logistic Organ Dysfunction System, the task force recommends using a change in baseline of the total SOFA score of 2 points or more to represent organ dysfunction (Box 3). The baseline SOFA score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population with presumed infection. This is greater than the overall mortality rate of 8.1% for ST-segment elevation myocardial infarction, a condition widely held to be life threatening by the community and by clinicians. Depending on a patient’s baseline level of risk, a SOFA score of 2 or greater identified a 2- to 25-fold increased risk of dying compared with patients with a SOFA score less than 2.

As discussed later, the SOFA score is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient. Components of SOFA (such as creatinine or bilirubin level) require laboratory testing and thus may not promptly capture dysfunction in individual organ systems. Other elements, such as the cardiovascular score, can be affected by iatrogenic interventions. However, SOFA has widespread familiarity within the critical care community and a well-validated relationship to mortality risk. It can be scored retrospectively, either manually or by automated systems, from clinical and laboratory measures often performed routinely as part of acute patient management. The task force noted that there are a number of novel biomarkers that can identify renal and hepatic dysfunction or coagulopathy earlier than the elements used in SOFA, but these require broader validation before they can be incorporated into the clinical criteria describing sepsis. Future iterations of the sepsis definitions should include an updated SOFA score with more optimal variable selection, cutoff values, and weighting, or a superior scoring system.

ICU, predictive validity was determined with 2 metrics for each criterion: the area under the receiver operating characteristic curve (AUROC) and the change in outcomes comparing patients with a score of either 2 points or more or fewer than 2 points in the different scoring systems across deciles of baseline risk. These criteria were also analyzed in 4 external US and non-US data sets containing data from more than 700 000 patients (cared for in both community and tertiary care facilities) with both community- and hospital-acquired infection.

In ICU patients with suspected infection in the University of Pittsburgh Medical Center data set, discrimination for hospital mortality with SOFA (AUROC = 0.74; 95% CI, 0.73-0.76) and the Logistic Organ Dysfunction System (AUROC = 0.75; 95% CI, 0.72-0.76) was superior to that with SIRS (AUROC = 0.64; 95% CI, 0.62-0.66). The predictive validity of a change in SOFA score of 2 or greater was similar (AUROC = 0.72; 95% CI, 0.70-0.73). For patients outside the ICU and with suspected infection, discrimination of hospital mortality with SOFA (AUROC = 0.79; 95% CI, 0.78-0.80) or change in SOFA score (AUROC = 0.79; 95% CI, 0.78-0.79) was similar to that with SIRS (AUROC = 0.76; 95% CI, 0.75-0.77).

Because SOFA is better known and simpler than the Logistic Organ Dysfunction System, the task force recommends using a change in baseline of the total SOFA score of 2 points or more to represent organ dysfunction (Box 3). The baseline SOFA score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population with presumed infection. This is greater than the overall mortality rate of 8.1% for ST-segment elevation myocardial infarction, a condition widely held to be life threatening by the community and by clinicians. Depending on a patient’s baseline level of risk, a SOFA score of 2 or greater identified a 2- to 25-fold increased risk of dying compared with patients with a SOFA score less than 2.

As discussed later, the SOFA score is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient. Components of SOFA (such as creatinine or bilirubin level) require laboratory testing and thus may not promptly capture dysfunction in individual organ systems. Other elements, such as the cardiovascular score, can be affected by iatrogenic interventions. However, SOFA has widespread familiarity within the critical care community and a well-validated relationship to mortality risk. It can be scored retrospectively, either manually or by automated systems, from clinical and laboratory measures often performed routinely as part of acute patient management. The task force noted that there are a number of novel biomarkers that can identify renal and hepatic dysfunction or coagulopathy earlier than the elements used in SOFA, but these require broader validation before they can be incorporated into the clinical criteria describing sepsis. Future iterations of the sepsis definitions should include an updated SOFA score with more optimal variable selection, cutoff values, and weighting, or a superior scoring system.
Scale score less than 15 and will reduce the measurement burden. Although qSOFA is less robust than a SOFA score of 2 or greater in the ICU, it does not require laboratory tests and can be assessed quickly and repeatedly. The task force suggests that qSOFA criteria be used to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring, if such actions have not already been undertaken. The task force considered that positive qSOFA criteria should also prompt consideration of possible infection in patients not previously recognized as infected.

**Definition of Septic Shock**

Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality (Box 3). The 2001 task force definitions described septic shock as “a state of acute circulatory failure.” The task force favored a broader view to differentiate septic shock from cardiovascular dysfunction alone and to recognize the importance of cellular abnormalities (Box 3). There was unanimous agreement that septic shock should reflect a more severe illness with a much higher likelihood of death than sepsis alone.

**Clinical Criteria to Identify Septic Shock**

Further details are provided in the accompanying article by Shankar-Hari et al. First, a systematic review assessed how current definitions were operationalized. This informed a Delphi process conducted among the task force members to determine the updated septic shock definition and clinical criteria. This process was iterative and informed by interrogation of databases, as summarized below.

The Delphi process assessed agreements on descriptions of terms such as “hypotension,” “need for vasopressor therapy,” “raised lactate,” and “adequate fluid resuscitation” for inclusion within the new clinical criteria. The majority (n = 14/17; 82.4%) of task force members voting on this agreed that hypotension should be defined as a mean arterial pressure less than 65 mm Hg according to the pragmatic decision that this was most often recorded in data sets derived from patients with sepsis. Systolic blood pressure was used as a qSOFA criterion because it was most widely recorded in the electronic health record data sets.

A majority (11/17; 64.7%) of the task force agreed, whereas 2 (11.8%) disagreed, that an elevated lactate level is reflective of cellular dysfunction in sepsis, albeit recognizing that multiple factors, such as insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, and reduced hepatic clearance, also contribute. Hyperlactatemia is, however, a reasonable marker of illness severity, with higher levels predictive of higher mortality. Criteria for “adequate fluid resuscitation” or “need for vasopressor therapy” could not be explicitly specified because these are highly user dependent, relying on variable monitoring modalities and hemodynamic targets for treatment. Other aspects of management, such as sedation and volume status assessment, are also potential confounders in the hypotension-vasopressor relationship.

By Delphi consensus process, 3 variables were identified (hypotension, elevated lactate level, and a sustained need for vasopressor therapy) to test in cohort studies, exploring alternative combinations and different lactate thresholds. The first database interrogated was the Surviving Sepsis Campaign’s international multicenter registry of 28 150 infected patients with at least 2 SIRS criteria and at least 1 organ dysfunction criterion. Hypotension was defined as a mean arterial pressure less than 65 mm Hg, the only available cutoff. A total of 18 840 patients with vasopressor therapy, hypotension, or hyperlactatemia (>2 mmol/L [18 mg/dL]) after volume resuscitation were identified. Patients with fluid-resistant hypotension requiring vasopressors and with hyperlactatemia were used as the referent group for comparing between-group differences in the risk-adjusted odds ratio for mortality. Risk adjustment was performed with a generalized estimating equation population-averaged logistic regression model with exchangeable correlation structure.

Risk-adjusted hospital mortality was significantly higher (P < .001 compared with the referent group) in patients with fluid-resistant hypotension requiring vasopressors and hyperlactatemia (42.3% and 49.7% at thresholds for serum lactate level of >2 mmol/L [18 mg/dL] or >4 mmol/L [36 mg/dL], respectively) compared with either hyperlactatemia alone (25.7% and 29.9% mortality for those with serum lactate level of >2 mmol/L [18 mg/dL] and >4 mmol/L [36 mg/dL], respectively) or with fluid-resistant hypotension requiring vasopressors but with lactate level of 2 mmol/L (18 mg/dL) or less (30.1%). With the same 3 variables and similar categorization, the unadjusted mortality in infected patients within 2 unrelated large electronic health record data sets (University of Pittsburgh Medical Center [12 hospitals; 2010-2012; n = 5984] and Kaiser Permanente Northern California [20 hospitals; 2009-2013; n = 54 135]) showed reproducible results. The combination of hypotension, vasopressor use, and lactate level greater than 2 mmol/L (18 mg/dL) identified patients with mortality rates of 54% at University of Pittsburgh Medical Center (n = 315) and 35% at Kaiser Permanente Northern California (n = 8051). These rates were higher than the mortality rates of 25.2% (n = 147) and 18.8% (n = 3094) in patients with hypotension alone, 17.9% (n = 1978) and 6.8% (n = 30 209) in patients with lactate level greater than 2 mmol/L (18 mg/dL) alone, and 20% (n = 5984) and 8% (n = 54 135) in patients with sepsis at University of Pittsburgh Medical Center and Kaiser Permanente Northern California, respectively.

The task force recognized that serum lactate measurements are commonly, but not universally, available, especially in developing countries. Nonetheless, clinical criteria for septic shock were developed with hypotension and hyperlactatemia rather than either alone because the combination encompasses both cellular dysfunction and cardiovascular compromise and is associated with a significantly higher risk-adjusted mortality. This proposal was approved by a majority (13/18; 72.2%) of voting members but warrants revisiting. The Controversies and Limitations section below provides further discussion about the inclusion of both parameters and options for when lactate level cannot be measured.

**Recommendations for ICD Coding and for Lay Definitions**

In accordance with the importance of accurately applying diagnostic codes, Table 2 details how the new sepsis and septic shock clini-
cal criteria correlate with ICD-9-CM and ICD-10 codes. The task force also endorsed the recently published lay definition that “sepsis is a life-threatening condition that arises when the body’s response to infection injures its own tissues,” which is consistent with the newly proposed definitions described above. To transmit the importance of sepsis to the public at large, the task force emphasizes that sepsis may portend death, especially if not recognized early and treated promptly. Indeed, despite advances that include vaccines, antibiotics, and acute care, sepsis remains the primary cause of death from infection. Widespread educational campaigns are recommended to better inform the public about this lethal condition.

### Controversies and Limitations

There are inherent challenges in defining sepsis and septic shock. First and foremost, sepsis is a broad term applied to an incompletely understood process. There are, as yet, no simple and unambiguous clinical criteria or biological, imaging, or laboratory features that uniquely identify a septic patient. The task force recognized the impossibility of trying to achieve total consensus on all points. Pragmatic compromises were necessary, so emphasis was placed on generalizability and the use of readily measurable identifiers that could best capture the current conceptualization of underlying mechanisms. The detailed, data-guided deliberations of the task force during an 18-month period and the peer review provided by bodies approached for endorsement highlighted multiple areas for discussion. It is useful to identify these issues and provide justifications for the final positions adopted.

The new definition of sepsis reflects an up-to-date view of pathobiology, particularly in regard to what distinguishes sepsis from uncomplicated infection. The task force also offers easily measurable clinical criteria that capture the essence of sepsis yet can be translated and recorded objectively (Figure). Although these criteria cannot be all-encompassing, they are simple to use and offer consistency of terminology to clinical practitioners, researchers, administrators, and funders. The physiologic and biochemical tests required to score SOFA are often included in routine patient care, and scoring can be performed retrospectively.

The initial, retrospective analysis indicated that qSOFA could be a useful clinical tool, especially to physicians and other practitioners working outside the ICU (and perhaps even outside the hospital, given that qSOFA relies only on clinical examination findings), to promptly identify infected patients likely to fare poorly. However, because most of the data were extracted from extracted US databases, the task force strongly encourages prospective validation in multiple US and non-US health care settings to confirm its robustness and potential for incorporation into future iterations of the definitions. This simple bedside score may be particularly relevant in resource-poor settings in which laboratory data are not readily available, and when the literature about sepsis epidemiology is sparse.

Neither qSOFA nor SOFA is intended to be a stand-alone definition of sepsis. It is crucial, however, that failure to meet 2 or more qSOFA or SOFA criteria should not lead to a deferral of investigation or treatment of infection or to a delay in any other aspect of care deemed necessary by the practitioners. qSOFA can be rapidly scored at the bedside without the need for blood tests, and it is hoped that it will facilitate prompt identification of an infection that poses a greater threat to life. If appropriate laboratory tests have not already been undertaken, this may prompt testing to identify biochemical organ dysfunction. These data will primarily aid patient management but will also enable subsequent SOFA scoring. The task force wishes to stress that SIRS criteria may still remain useful for the identification of infection.

Some have argued that lactate measurement should be mandated as an important biochemical identifier of sepsis in an infected patient. Because lactate measurement offered no meaningful change in the predictive validity beyond 2 or more qSOFA criteria in the identification of patients likely to be septic, the task force could not justify the added complexity and cost of lactate measurement alongside these simple bedside criteria. The task force recommendations should not, however, constrain the monitoring of lactate as a guide to therapeutic response or as an indicator of illness severity.
Our approach to hyperlactatemia within the clinical criteria for septic shock also generated conflicting views. Some task force members suggested that elevated lactate levels represent an important marker of “cryptic shock” in the absence of hypotension. Others voiced concern about its specificity and that the nonavailability of lactate measurement in resource-poor settings would preclude a diagnosis of septic shock. No solution can satisfy all concerns. Lactate level is a sensitive, albeit nonspecific, stand-alone indicator of cellular or metabolic stress rather than “shock.” However, the combination of hyperlactatemia with fluid-resistant hypotension identifies a group with particularly high mortality and thus offers a more robust identifier of the physiologic and epidemiologic concept of septic shock than either criterion alone. Identification of septic shock as a distinct entity is of epidemiologic rather than clinical importance. Although hyperlactatemia and hypotension are clinically concerning as separate entities, and although the proposed criteria differ from those of other recent consensus statements, clinical management should not be affected. The greater precision offered by data-driven analysis will improve reporting of both the incidence of septic shock and the associated mortality, in which current figures vary 4-fold. The criteria may also enhance insight into the pathobiology of sepsis and septic shock. In settings in which lactate measurement is not available, the use of a working diagnosis of septic shock using hypotension and other criteria consistent with tissue hypoperfusion (eg, delayed capillary refill) may be necessary.

The task force focused on adult patients yet recognizes the need to develop similar updated definitions for pediatric populations and the use of clinical criteria that take into account their age-dependent variation in normal physiologic ranges and in pathophysiologic responses.

Implications

The task force has generated new definitions that incorporate an up-to-date understanding of sepsis biology, including organ dysfunction (Box 3). However, the lack of a criterion standard, similar to its absence in many other syndromic conditions, precludes unambiguous validation and instead requires approximate estimations of performance across a variety of validity domains, as outlined above. To assist the bedside clinician, and perhaps prompt an escalation of care if not already instituted, simple clinical criteria (qSOFA) that identify patients with suspected infection who are likely to have poor outcomes, that is, a prolonged ICU course and death, have been developed and validated.

This approach has important epidemiologic and investigative implications. The proposed criteria should aid diagnostic categorization once initial assessment and immediate management are completed. qSOFA or SOFA may at some point be used as entry criteria for clinical trials. There is potential conflict with current organ dysfunction scoring systems, early warning scores, ongoing research studies, and pathway developments. Many of these scores and pathways have been developed by consensus, whereas an important aspect of the current work is the interrogation of data, albeit retrospectively, from large patient populations. The task force maintains that standardization of definitions and clinical criteria is crucial in ensuring clear communication and a more accurate appreciation of the scale of the problem of sepsis. An added challenge is that infection is seldom confirmed microbiologically when treatment is started; even when microbiological tests are completed, culture-positive “sepsis” is observed in only 30% to 40% of cases. Thus, when sepsis epide-
Conclusions

These updated definitions and clinical criteria should clarify long-used descriptors and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing it. This process, however, remains a work in progress. As is done with software and other coding updates, the task force recommends that the new definition be designated Sepsis-3, with the 1991 and 2001 iterations being recognized as Sepsis-1 and Sepsis-2, respectively, to emphasize the need for future iterations.

ARTICLE INFORMATION

Author Affiliations: Bloomsbury Institute of Intensive Care Medicine, University College London, London, London, United Kingdom (Singer); Hofstra-Northwell School of Medicine, Feinstein Institute for Medical Research, New Hyde Park, New York (Deutschman); Department of Critical Care and Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Seymour); Department of Critical Care Medicine, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom (Shankar-Hari); Department of Critical Care Medicine, University of Versailles, France (Annan); Center for Sepsis Control and Care, University Hospital, Jena, Germany (Bauer); Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, and Austin Hospital, Melbourne, Victoria, Australia (Bellomo); Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University, Nashville, Tennessee (Bernard); Réanimation Médicale-Hôpital Cochin, Descartes University, Cochin Institute, Paris, France (Chiche); Critical Care Center, Emory University School of Medicine, Atlanta, Georgia (Coopersmith); Washington University School of Medicine, St Louis, Missouri (Hotchkiss); Infectious Disease Section, Division of Pulmonary and Critical Care Medicine, Brown University School of Medicine, Providence, Rhode Island (Levy, Opal); Department of Surgery, University of Toronto, Toronto, Ontario, Canada (Marshall); Emory University School of Medicine and Grady Memorial Hospital, Atlanta, Georgia (Martin); Trauma, Emergency & Critical Care Program, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Rubenfeld); Interdepartmental Division of Critical Care, University of Toronto (Rubenfeld); Department of Infectious Diseases, Academisch Medisch Centrum, Amsterdam, the Netherlands (van der Pol); Department of Intensive Care, Erasmus University Hospital, Brussels, Belgium (Vincent); Department of Critical Care Medicine, University of Pittsburgh and UPMC Health System, Pittsburgh, Pennsylvania (Angus); Associate Editor, JAMA (Angus).

Author Contributions: Drs Singer and Deutschman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Singer, Deutschman, Seymour, Shankar-Hari, Angus.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shankar-Hari, Seymour.

Obtained funding: Deutschman, Chiche, Coopersmith.

Administrative, technical, or material support: Singer, Deutschman, Chiche, Coopersmith, Levy, Angus.

Study supervision: Singer, Deutschman.

Drs Singer and Deutschman are joint first authors.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Singer reports serving on the advisory boards of Inflax, Bayer, Biokont, and Merck and that his institution has received grants from the European Commission, UK National Institute of Health Research, Immunexpress, DSTL, and Wellcome Trust. Dr Deutschman reports holding patents on materials not related to this work and receiving travel/ accommodations and related expenses for participation in meetings paid by the Centers for Disease Control and Prevention, World Federation of Societies of Intensive and Critical Care, Pennsylvania Assembly of Critical Care Medicine/PA Chapter, Society of Critical Care Medicine, Northern Ireland Society of Critical Care Medicine, International Sepsis Forum, Department of Anesthesiology, Stanford University, Acute Dialysis Quality Initiative, and European Society of Intensive Care Medicine (ESICM). Dr Seymour reports receiving personal fees from Beckman Coulter and a National Institutes of Health (NIH) grant awarded to his institution. Dr Bauer reports support for travel to meetings for the study from ESICM, payment for speaking from CSL Behring, grants to his institution from Jena University Hospital, and patents held by Jena University Hospital. Dr Bernard reports grants from AstraZeneca for activities outside the submitted work. Dr Chiche reports consulting for Nestle and Abbott and honoraria for speaking from GE Healthcare and Nestle. Dr Coopersmith reports receiving grants from the NIH for work not related to this article. Dr Coopersmith also reports bringing president-elect and president of SCCM when the task force was meeting and the article was being drafted. A stipend was paid to Emory University for his time spent in these roles. Dr Hotchkiss reports consulting on sepsis for GlaxoSmithKline, Merck, and Bristol-Meyers Squibb and reports that his institution received grant support from Bristol-Meyers Squibb and GlaxoSmithKline, as well as the NIH, for research on sepsis. Dr Marshall reports serving on the data and safety monitoring board (DSMB) of AKPA Pharma and Spectral Medical Steering Committee and receiving payment for speaking from Toray Ltd and Uni-Labs. Dr Martin reports serving on the board for SCCM and Project Help, serving on the DSMB for Cumberland Pharmaceuticals and Vanderbilt University, serving on the medical advisory board for Grifols and Pulsion Medical Systems, and grants to his institution from NIH, the Food and Drug Administration, Abbott, and Baxter. Dr Opal reports grants from GlaxoSmithKline, Atoxibio, Asahi-Kasei, Ferring, Cardeas, and Arsanis outside the submitted work; personal fees from Arsanis, Aribis, Bioequis, Cyn, and Battelle; and serving on the DSMB for Achaogen, Spectral Diagnostics, and Paratek. No other disclosures were reported.

Funding/Support: This work was supported in part by a grant from the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM).

Role of the Funder/Sponsor: These funding bodies appointed cochairs but otherwise had no role in the design and conduct of the work; the collection, management, analysis, and interpretation of the data; preparation of the manuscript; or decision to submit the manuscript for publication. Other national and international societies, they were asked for comment and endorsement.

Disclaimer: Dr Angus, JAMA Associate Editor, had no role in the evaluation of or decision to publish this article.

Endorsing Societies: Academy of Medical Royal Colleges (UK); American Association of Critical Care Nurses; American Thoracic Society (endorsed August 25, 2015); Australian–New Zealand Intensive Care Society (ANZICS); Asia Pacific Association of Critical Care Medicine; Brazilian Society of Critical Care, Central American and Caribbean Intensive Therapy Consortium; Chinese Society of Critical Care Medicine; Chinese Society of Critical Care Medicine–China Medical Association; Critical Care Society of South Africa; Emirates Intensive Care Society; European Respiratory Society; European Resuscitation Council; European Society of Clinical Microbiology and Infectious
Diseases and its Study Group of Bloodstream Infections and Sepsis; European Society of Emergency Medicine; European Society of Intensive Care Medicine; European Society of Paediatric and Neonatal Intensive Care; German Sepsis Society; Indian Society of Critical Care Medicine; International Pan Arabian Critical Care Medicine Society; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Pan American/Pan Iberian Congress of Intensive Care; Red Intensiva (Sociedad Chilena de Medicina Critica y Urgencias); Sociedad Peruana de Medicina Critica; Shock Society; Sociedad Argentina de Terapia Intensiva; Society of Critical Care Medicine; Surgical Infection Society; World Federation of Pediatric Intensive and Critical Care Societies; World Federation of Critical Care Nurses; World Federation of Societies of Intensive and Critical Care Medicine.

Additional Contributions: The task force would like to thank Frank Bankhurst, MD, University Hospital Jena, Germany; Theodore J. Iwashyna, MD, PhD, University of Michigan; Vincent Liu, MD, MSC, Kaiser Permanente Northern California; Thomas Rea, MD, MPH, University of Washington; and Gary Phillips, MAS, Ohio State University; for their invaluable assistance, and the administrations and leadership of SCCM and ESICM for facilitating its work. Payment was provided to the Center for Biostatistics, Ohio State University, to support the work of Mr. Phillips.

REFERENCES


