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.


Copyright 2016 American Medical Association. All rights reserved.
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 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, reimbursements of 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 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, reimbursements of 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.

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 (missingness) of individual elements of different organ dysfunction scores and the question of generalizability (ecologic validity).

Box 1. SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:
- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or Paco₂ <32 mm Hg (4.3 kPa)
- White blood cell count >12,000/mm³ or <4000/mm³ or >10% immature bands

From Bone et al. 9

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. 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, along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, and coagulation, all of which have prognostic significance. Organ dysfunction, even when severe, is not associated with substantial cell death.

The broader perspective also emphasizes the significant biological and clinical heterogeneity in affected individuals, with age, underlying comorbidities, concurrent injuries (including surgery) and medications, and source of infection adding further complexity. This diversity cannot be appropriately recapitulated in either animal models or computer simulations. With further validation, multichannel molecular signatures (eg, transcriptomic, metabolomic, proteomic) will likely lead to better characterization of specific population subsets. 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. 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). 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.

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 Assessment) (Table 1). A higher SOFA score is associated with an increased probability of mortality. 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. 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. \(^8^9\) 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 System \(^30\) ) (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. \(^12\) 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 Score

<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>Respiration</td>
<td></td>
<td>PaO2/FIO2 (mm Hg (kPa))</td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td>Platelets, ×10^5/μL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<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>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td>Glasgow Coma Scale score</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 (μmol/L)</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>Urine output, mL/d</td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* Adapted from Vincent et al. \(^27\)

\(^b\) 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. 

Copyright 2016 American Medical Association. All rights reserved.
Box 3. New Terms and Definitions

- **Sepsis** is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score $\geq$ 2 points consequent to the infection.
- The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- A SOFA score $\geq$ 2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure $\leq$ 100 mm Hg, or respiratory rate $\geq$ 22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP $\geq$ 65 mm Hg and having a serum lactate level $>$ 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.
- With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Box 4. qSOFA (Quick SOFA) Criteria

| Respiratory rate $\geq$ 22/min |
| Altered mentation |
| Systolic blood pressure $\leq$ 100 mm Hg |

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 $\leq$ 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, vaso-pressors, 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 Scale 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.
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 denoted 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 = 30209) 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-
Consensus Definitions for Sepsis and Septic Shock

Special Communication Clinical Review & Education

Table 2. Terminology and International Classification of Diseases Coding

<table>
<thead>
<tr>
<th>Current Guidelines and Terminology</th>
<th>Sepsis</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 and 2001 consensus terminology9,10</td>
<td>Severe sepsis Sepsis-induced hypoperfusion</td>
<td>Septic shock14</td>
</tr>
<tr>
<td>2015 Definition</td>
<td>Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection</td>
<td>Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality</td>
</tr>
<tr>
<td>2015 Clinical criteria</td>
<td>Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)</td>
<td>Sepsisa and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate &gt;2 mmol/L (18 mg/dL) despite adequate fluid resuscitation13</td>
</tr>
<tr>
<td>Recommended primary ICD codesa</td>
<td>ICD-9 995.92 785.52</td>
<td></td>
</tr>
<tr>
<td>ICD-10a</td>
<td>R65.20 R65.21</td>
<td></td>
</tr>
<tr>
<td>Framework for implementation for coding and research</td>
<td>Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified periodd</td>
<td></td>
</tr>
<tr>
<td>Within specified period around suspected infectiond:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Assess for shock criteria, using administration of vasopressors, MAP &lt;65 mm Hg, and lactate &gt;2 mmol/L (18 mg/dL)d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICD, International Classification of Diseases; MAP, mean arterial pressure; SOFA, Sequential [Sepsis-related] Organ Failure Assessment.27

a Included training codes.

b Suspected infection could be defined as the concomitant administration of oral or parenteral antibiotics and sampling of body fluid cultures (blood, urine, cerebrospinal fluid, peritoneal, etc). For example, if the culture is obtained, the antibiotic is required to be administered within 72 hours, whereas if the antibiotic is first, the culture is required within 24 hours.10

c Considers a period as great as 48 hours before and up to 24 hours after onset of infection, although sensitivity analyses have tested windows as short as 3 hours before and 3 hours after onset of infection.12

d With the specified period around suspected infection, assess for shock criteria, using any vasopressor initiation (eg, dopamine, norepinephrine, epinephrine, vasopressin, phenylephrine). Lactate level >2 mmol/L (18 mg/dL) and mean arterial pressure <65 mm Hg. These criteria require adequate fluid resuscitation as defined by the Surviving Sepsis Campaign guidelines.4

Copyright 2016 American Medical Association. All rights reserved.
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.”\(^{32}\) 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,\(^{34}\) 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.\(^{3}\) 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\(^{38}\)) 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-
Consensus Definitions for Sepsis and Septic Shock

Special Communication Clinical Review & Education

Articles Information

Author Affiliations: Bloomsbury Institute of Intensive Care Medicine, University College 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, Academic Medisch Centrum, Amsterdam, the Netherlands (van der Poll); 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 Inflixa, Bayer, Bioteest, 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 Seymor 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, Atoxlib, Asahi-Kasei, Ferring, Cardeas, and Arsanis outside the submitted work; personal fees from Arsanis, Ardis, Bioeqis, 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: The 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. 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 Societies; International Congress on Sepsis; International Critical Care Nurses Association; International Sepsis Forum; International Society of Critical Care Medicine; Long Island Society of Critical Care Medicine; National Association of Intensive Care Units; Northern New England Emergency Services; Northern New England Intensive Care Nurses Association; Northern New England Chapter, Society of Critical Care Medicine; Society of Critical Care Medicine/PA Chapter; French Academy of Medicine; German Society of Critical Care Medicine; Hungarian Society of Critical Care Medicine; Icelandic Society of Critical Care Medicine; Israeli Society of Critical Care Medicine; Italian Society of Critical Care Medicine; Japanese Society of Critical Care Medicine; Korean Society of Critical Care Medicine; Mathematical and Computational Biology Society; Mexican Society of Critical Care Medicine; Netherlands Society of Critical Care Medicine; New Zealand Society of Critical Care Medicine; Nordic Society of Critical Care Medicine; Polish Society of Critical Care Medicine; Portuguese Society of Critical Care Medicine; Russian Society of Critical Care Medicine; Saudi Society of Critical Care Medicine; Spanish Society of Critical Care Medicine; South African Society of Critical Care Medicine; Swiss Society of Intensive Care Medicine; Taiwan Society of Critical Care Medicine; Thai Society of Critical Care Medicine; Turkish Society of Critical Care Medicine; United Arab Emirates Society of Critical Care Medicine; and World Federation of Societies of Intensive and Critical Care Medicine.

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.

JAMA February 23, 2016 Volume 315, Number 8 809

Copyright 2016 American Medical Association. All rights reserved.
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 Brunekhorst, 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 ESMIC for facilitating its work. Payment was provided to the Center for Biostatistics, Ohio State University, to support the work of Mr Phillips.

REFERENCES


