# Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

# 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.

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Author Affiliations: Author affiliations are listed at the end of this article.

**Group Information:** The Sepsis Definitions Task Force members are the authors listed above.

Corresponding Author: Clifford S. Deutschman, MD, MS, Departments of Pediatrics and Molecular Medicine, Hofstra-Northwell School of Medicine, Feinstein Institute for Medical Research, 269-0176th Ave, New Hyde Park, NY 11040 (cdeutschman@nshs.edu). epsis, 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.<sup>1</sup> The reported incidence of sepsis is increasing,<sup>2,3</sup> likely reflecting aging populations with more comorbidities, greater recognition,<sup>4</sup> and, in some countries, reimbursement-favorable coding.<sup>5</sup> Although the true incidence is unknown, conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide.<sup>6,7</sup> 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.<sup>8</sup>

A 1991 consensus conference<sup>9</sup> 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.<sup>10</sup> 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,<sup>11</sup> 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).<sup>12</sup> A systematic literature

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 Paco <sub>2</sub> <32 mm Hg (4.3 kPa)
White blood cell count >12 000/mm <sup>3</sup> or <4000/mm <sup>3</sup> or >10% immature bands
From Bone et al. <sup>9</sup>

review and Delphi consensus methods were also used for the definition and clinical criteria describing septic shock.<sup>13</sup>

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 lifethreatening state. Such early recognition is particularly important because prompt management of septic patients may improve outcomes.4

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.<sup>14,15</sup> 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,<sup>16</sup> along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation,<sup>14,17,18</sup> all of which have prognostic significance. Organ dysfunction, even when severe, is not associated with substantial cell death.<sup>19</sup>

The broader perspective also emphasizes the significant biological and clinical heterogeneity in affected individuals,<sup>20</sup> with age, underlying comorbidities, concurrent injuries (including surgery) and medications, and source of infection adding further complexity.<sup>21</sup> This diversity cannot be appropriately recapitulated in either animal models or computer simulations.<sup>14</sup> With further validation, multichannel molecular signatures (eg, transcriptomic, metabolomic, proteomic) will likely lead to better characterization of specific population subsets.<sup>22,23</sup> 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.<sup>24</sup> 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).<sup>25</sup> In addition, 1 in 8 patients admitted to criti-

Box 2. Key Concepts of Sepsis

 Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.

• Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.

• Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.

 The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.

• Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

cal 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.<sup>26</sup> 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<sup>27</sup>) (Table 1).<sup>28</sup> A higher SOFA score is associated with an increased probability of mortality.<sup>28</sup> The score grades abnormality by organ system and accounts for clinical interventions. However, laboratory variables, namely, Pao<sub>2</sub>, 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.<sup>13</sup> 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  $\pm$  diverse levels of hyperlactatemia  $\pm$  vasopressor use  $\pm$  concurrent new organ dysfunction  $\pm$  defined fluid resuscitation volume/targets), the data source and coding methods, and enrollment dates.

Table 1. Sequential [Sepsis-Related	I] Organ Failure Assessment Score <sup>a</sup>
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	Score					
System	0	1	2	3	4	
Respiration						
Pao <sub>2</sub> /Fio <sub>2</sub> , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support	
Coagulation						
Platelets, ×10 <sup>3</sup> /µL	≥150	<150	<100	<50	<20	
Liver						
Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)	
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) <sup>b</sup>	Dopamine 5.1-15 or epinephrine $\leq 0.1$ or norepinephrine $\leq 0.1^{b}$	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 <sup>b</sup>	
Central nervous system						
Glasgow Coma Scale score <sup>c</sup>	15	13-14	10-12	6-9	<6	
Renal						
Creatinine, mg/dL (µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)	
Urine output, mL/d				<500	<200	
Abbreviations: FIO2, fracti	on of inspired oxygen; M	AP, mean arterial pressure;	<sup>b</sup> Catecholamine doses are given as µg/kg/min for at least 1 hour.			
Pao <sub>2</sub> , partial pressure of c	oxygen.		<sup>c</sup> Glasgow Coma Scale so	<sup>c</sup> Glasgow Coma Scale scores range from 3-15; higher score indicates better		
<sup>a</sup> Adapted from Vincent et al. <sup>27</sup>			neurological function.			

Adapted from Vincent et al.

# A Need for Sepsis Definitions for the Public and for Health Care Practitioners

Despite its worldwide importance,<sup>6,7</sup> public awareness of sepsis is poor.<sup>29</sup> 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 highdependency 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.<sup>10</sup> 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)<sup>9</sup> or organ dysfunction (eg, SOFA,<sup>27,28</sup> Logistic Organ Dysfunction System<sup>30</sup>) (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.10

Full details are found in the accompanying article by Seymour et al.<sup>12</sup> 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 outcomeshospital 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

#### 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 ≥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 ≥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  $\leq 100 \text{ mm Hg}$ , or respiratory rate  $\geq 22/\text{min}$ .

 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 ≥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.

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<sup>9,27,30</sup> 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 Box 4. qSOFA (Quick SOFA) Criteria Respiratory rate  $\geq$ 22/min Altered mentation Systolic blood pressure  $\leq$ 100 mm Hg

mortality risk of approximately 10% in a general hospital population with presumed infection.<sup>12</sup> This is greater than the overall mortality rate of 8.1% for ST-segment elevation myocardial infarction,<sup>31</sup> 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.<sup>12</sup>

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.

#### 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.<sup>12</sup> 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, 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 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."<sup>10</sup> 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.<sup>13</sup> 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.<sup>32</sup> Hyperlactatemia is, however, a reasonable marker of illness severity, with higher levels predictive of higher mortality.<sup>33</sup> 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.<sup>34</sup> 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 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 fluidresistant 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 fluidresistant 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 = 54135) 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<sup>13</sup> 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 clinical 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.<sup>35</sup> 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

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology <sup>9,10</sup>	Severe sepsis Sepsis-induced hypoperfusion	Septic shock <sup>13</sup>
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis <sup>a</sup> and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation <sup>13</sup>
Recommended primary ICD codes <sup>a</sup>		
ICD-9	995.92	785.52
ICD-10 <sup>a</sup>	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infect for blood cultures and an specified period <sup>b</sup> Within specified period a 1. Identify sepsis by usin- life-threatening organ dy 2. Assess for shock criter vasopressors, MAP <65 n (18 mg/dL) <sup>d</sup>	ion by using concomitant orders tibiotics (oral or parenteral) in a round suspected infection <sup>c</sup> : g a clinical criterion for /sfunction ia, using administration of nm Hg, and lactate >2 mmol/L

Table 2. Terminology and International Classification of Diseases Coding

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

<sup>a</sup> Included training codes.

- <sup>b</sup> 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.<sup>12</sup>
- <sup>c</sup> 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.<sup>12</sup>
- <sup>d</sup> With the specified period around suspected infection, assess for shock criteria, using any vasopressor initiation (eg, dopamine, norepinephrine, epinephrine, vasopressin, phenylephrine), any 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.<sup>4</sup>

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.





The baseline Sequential [Sepsis-related] Organ Failure Assessment (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. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

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."<sup>32</sup> 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,<sup>34</sup> 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.<sup>3</sup> 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<sup>36</sup>) 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 agedependent 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 epidemiology is assessed and reported, operationalization will necessarily involve proxies such as antibiotic commencement or a clinically determined probability of infection. Future epidemiology studies should consider reporting the proportion of microbiologypositive sepsis.

Greater clarity and consistency will also facilitate research and more accurate coding. Changes to *ICD* coding may take several years to enact, so the recommendations provided in Table 2 demonstrate how the new definitions can be applied in the interim within the current *ICD* system.

The debate and discussion that this work will inevitably generate are encouraged. Aspects of the new definitions do indeed rely on expert opinion; further understanding of the biology of sepsis, the availability of new diagnostic approaches, and enhanced collection of data will fuel their continued reevaluation and revision.

# Conclusions

These updated definitions and clinical criteria should clarify longused 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, 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 (Annane); 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 Poll); Department of Intensive Care, Erasme University Hospital, Brussels, Belgium (Vincent); Department of Critical Care Medicine, University of Pittsburgh and UPMC Health System, Pittsburgh, Pennsylvania (Angus); Associate Editor, JAMA (Angus).

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# Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

**IMPORTANCE** The Third International Consensus Definitions Task Force defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." The performance of clinical criteria for this sepsis definition is unknown.

**OBJECTIVE** To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.

**DESIGN, SETTINGS, AND POPULATION** Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, we identified those with suspected infection in whom to compare criteria. Confirmatory analyses were performed in 4 data sets of 706 399 out-of-hospital and hospital encounters at 165 US and non-US hospitals ranging from January 1, 2008, until December 31, 2013.

EXPOSURES Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) criteria, Logistic Organ Dysfunction System (LODS) score, and a new model derived using multivariable logistic regression in a split sample, the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score (range, O-3 points, with 1 point each for systolic hypotension [≤100 mm Hg], tachypnea [≥22/min], or altered mentation).

MAIN OUTCOMES AND MEASURES For construct validity, pairwise agreement was assessed. For predictive validity, the discrimination for outcomes (primary: in-hospital mortality; secondary: in-hospital mortality or intensive care unit [ICU] length of stay  $\geq$ 3 days) more common in sepsis than uncomplicated infection was determined. Results were expressed as the fold change in outcome over deciles of baseline risk of death and area under the receiver operating characteristic curve (AUROC).

**RESULTS** In the primary cohort, 148 907 encounters had suspected infection (n = 74 453 derivation; n = 74 454 validation), of whom 6347 (4%) died. Among ICU encounters in the validation cohort (n = 7932 with suspected infection, of whom 1289 [16%] died), the predictive validity for in-hospital mortality was lower for SIRS (AUROC = 0.64; 95% CI, 0.62-0.66) and qSOFA (AUROC = 0.66; 95% CI, 0.64-0.68) vs SOFA (AUROC = 0.74; 95% CI, 0.73-0.76; P < .001 for both) or LODS (AUROC = 0.75; 95% CI, 0.73-0.76; P < .001 for both) or LODS (AUROC = 0.75; 95% CI, 0.73-0.76; P < .001 for both). Among non-ICU encounters in the validation cohort (n = 66 522 with suspected infection, of whom 1886 [3%] died), qSOFA had predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) that was greater than SOFA (AUROC = 0.79; 95% CI, 0.78-0.80; P < .001) and SIRS (AUROC = 0.76; 95% CI, 0.75-0.77; P < .001). Relative to qSOFA scores lower than 2, encounters with qSOFA scores of 2 or higher had a 3- to 14-fold increase in hospital mortality across baseline risk deciles. Findings were similar in external data sets and for the secondary outcome.

**CONCLUSIONS AND RELEVANCE** Among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was not significantly different than the more complex LODS but was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis. Among encounters with suspected infection outside of the ICU, the predictive validity for in-hospital mortality of qSOFA was statistically greater than SOFA and SIRS, supporting its use as a prompt to consider possible sepsis.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christopher W. Seymour, MD, MSc, Departments of Critical Care Medicine and Emergency Medicine, University of Pittsburgh School of Medicine, Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, 3550 Terrace St, Scaife Hall, Ste 639, Pittsburgh, PA 15261 (seymourcw@upmc.edu). A lthough common and associated with high morbidity and mortality,<sup>1,2</sup> sepsis and related terms remain difficult to define. Two international consensus conferences in 1991 and 2001 used expert opinion to generate the current definitions.<sup>3,4</sup> However, advances in the understanding of the pathobiology and appreciation that elements of the definitions may be outdated, inaccurate, or confusing prompted

EHR electronic health record

GCS Glasgow Coma Scale

ICU intensive care unit

**LODS** Logistic Organ Dysfunction System

**qSOFA** quick Sequential [Sepsis-related] Organ Function Assessment

**SIRS** systemic inflammatory response syndrome

**SOFA** Sequential [Sepsis-related] Organ Function Assessment the European Society of Intensive Care Medicine and the Society of Critical Care Medicine to convene a Third International Consensus Task Force to reexamine the definitions. Like many syndromes, there is no "gold standard" diagnostic test for sepsis. Therefore, the task force chose several methods to evaluate the useful-

ness of candidate clinical criteria, including clarity, reliability (consistency and availability), content validity (biologic rationale and face validity), construct validity (agreement between similar measures), criterion validity (correlation with established measures and outcomes), burden, and timeliness. Unlike prior efforts, the task force used systematic literature reviews and empirical data analyses to complement expert deliberations.

Based on clarity and content validity and after literature review and expert deliberation, the task force recommended elimination of the terms *sepsis syndrome, septicemia*, and *severe sepsis* and instead defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection."<sup>5</sup> Of note, the task force did not attempt to redefine infection. Rather, it next sought to generate recommendations for clinical criteria that could be used to identify sepsis among patients with suspected or confirmed infection. The purpose of this study was to inform this step by analyzing data from several large hospital databases to explore the construct validity and criterion validity of existing and novel criteria associated with sepsis.

# Methods

This study was approved with waiver of informed consent by the institutional review boards of the University of Pittsburgh, Kaiser Permanente Northern California (KPNC), Veterans Administration (VA) Ann Arbor Health System, Washington State Department of Health, King County Emergency Medical Services (KCEMS), University of Washington, and Jena University Hospital.

# Study Design, Setting, and Population

A retrospective cohort study was performed among adult encounters (age ≥18 years) with suspected infection. The primary cohort was all hospital encounters from 2010 to 2012 at 12 community and academic hospitals in the UPMC health care system in southwestern Pennsylvania. The cohort included all medical and surgical encounters in the emergency department, hospital ward, and intensive care unit (ICU). We created a random split sample (50/50) from the UPMC cohort, the derivation cohort for developing new criteria, and the validation cohort for assessment of new and existing criteria.

We also studied 4 external data sets: (1) all inpatient encounters at 20 KPNC hospitals from 2009 to 2013; (2) all encounters in 130 hospitals in the United States' VA system from 2008 to 2010; (3) all nontrauma, nonarrest emergency medical services records from 5 advanced life support agencies from 2009-2010 transported to 14 hospitals with community infection in King County, Washington (KCEMS)<sup>6</sup>; and (4) all patients from 2011-2012 at 1 German hospital enrolled with hospital-acquired infection in the ALERTS prospective cohort study.7 These cohorts were selected because they included patient encounters from different phases of acute care (out of hospital, emergency department, hospital ward) and countries (United States and Germany) with different types of infection (community and nosocomial). The UPMC, KPNC, and VA data were obtained from the electronic health records (EHRs) of the respective health systems; KCEMS data were obtained from the administrative out-of-hospital record; and ALERTS data were collected prospectively by research coordinators.

#### **Defining a Cohort With Suspected Infection**

For EHR data (UPMC, KPNC, and VA), the first episode of suspected infection was identified as the combination of antibiotics (oral or parenteral) and body fluid cultures (blood, urine, cerebrospinal fluid, etc). We required the combination of culture and antibiotic start time to occur within a specific time epoch. If the antibiotic was given first, the culture sampling must have been obtained within 24 hours. If the culture sampling was first, the antibiotic must have been ordered within 72 hours. The "onset" of infection was defined as the time at which the first of these 2 events occurred (eAppendix in the Supplement). For non-EHR data in ALERTS, patients were included who met US Centers for Disease Control and Prevention definitions or clinical criteria for hospital-acquired infection more than 48 hours after admission as documented by prospective screening.<sup>7</sup> For non-EHR data in KCEMS, administrative claims identified infection present on admission (Angus implementation of infection using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes).6

#### Determining Clinical Criteria for Sepsis Using Existing Measures

In UPMC derivation and validation data, indicators were generated for each component of the systemic inflammatory response syndrome (SIRS) criteria<sup>4</sup>; the Sequential [Sepsisrelated] Organ Failure Assessment (SOFA) score<sup>8</sup>; and the Logistic Organ Dysfunction System (LODS) score, <sup>9</sup> a weighted organ dysfunction score (**Table 1**). We used a modified version of the LODS score that did not contain urine output (because of poor accuracy in recording on hospital ward encounters), prothrombin, or urea levels. The maximum SIRS criteria, SOFA score, and modified LODS score were calculated for the time window from 48 hours before to 24 hours after the onset of infection, as well as on each calendar day. This window was used

Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)	Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)	Logistic Organ Dysfunction System (LODS) (Range, 0-22 Points)ª	Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) (Range, 0-3 Points)
Respiratory rate, breaths per minute	Pao <sub>2</sub> /Fio <sub>2</sub> ratio	Pao <sub>2</sub> /Fio <sub>2</sub> ratio	Respiratory rate, breaths per minute
White blood cell count, 10 <sup>9</sup> /L	Glasgow Coma Scale score	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial pressure, mm Hg	Systolic blood pressure, mm Hg	Systolic blood pressure, mm Hg
Heart rate, beats per minute	Administration of vasopressors with type/dose/rate of infusion	Heart rate, beats per minute	
Temperature, °C	Serum creatinine, mg/dL, or urine output, mL/d	Serum creatinine, mg/dL	
Arterial carbon dioxide tension, mm Hg	Bilirubin, mg/dL	Bilirubin, mg/dL	
	Platelet count, 10 <sup>9</sup> /L	Platelet count, 10 <sup>9</sup> /L	
		White blood cell count, 10 <sup>9</sup> /L	
		Urine output, L/d	
		Serum urea, mmol/L	
		Prothrombin time, % of standard	

Table 1. Variables for Candidate Sepsis Criteria Among Encounters With Suspected Infection

Abbreviation: Fio<sub>2</sub>, fraction of inspired oxygen.

<sup>a</sup> Measurement units for LODS variables per original description by Le Gall et al.<sup>9</sup>

for candidate criteria because organ dysfunction in sepsis may occur prior to, near the moment of, or after infection is recognized by clinicians or when a patient presents for care. Moreover, the clinical documentation, reporting of laboratory values in EHRs, and trajectory of organ dysfunction are heterogeneous across encounters and health systems. In a post hoc analysis requested by the task force, a change in SOFA score was calculated of 2 points or more from up to 48 hours before to up to 24 hours after the onset of infection.

#### **Deriving Novel Clinical Criteria for Sepsis**

In the derivation cohort (UPMC), new, simple criteria were developed according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) recommendations.<sup>10</sup> This entailed 2 steps: (1) assessing candidate variable quality and frequency of missing data and (2) developing a parsimonious model and simple point score.<sup>3,8,11</sup> Because of the subjective nature and complexity of variables in existing criteria, we sought a simple model that could easily be used by a clinician at the bedside.

Based on the assumption that hospital mortality would be far more common in encounters with infected patients who have sepsis than in those who do not, all continuous variables were dichotomized by defining their optimal cutoffs using the minimum 0/1 distance on the area under the receiver operating characteristic curve (AUROC) for in-hospital mortality.<sup>12</sup> Cutoffs were rounded to the nearest integer, and standard single-value imputation was used, with normal value substitution if variables were missing. The latter approach is standard in clinical risk scores<sup>8,13,14</sup> and mirrors how clinicians would use the score at the bedside. Multiple logistic regression was used with robust standard errors and forward selection of candidate variables using the Bayesian information criterion to develop the "quick SOFA" (qSOFA) model. The Bayesian information criterion is a likelihood-based stepwise approach that retains variables that improve the model's overall ability to predict the outcome of interest while incorporating a penalty for including too many variables. Favoring simplicity over accuracy, a point score of 1 was assigned to each variable in the final model, irrespective of the regression coefficients. Model calibration was assessed by comparing clinically relevant differences in observed vs expected outcomes, as the Hosmer-Lemeshow test may be significant due to large sample sizes.<sup>15</sup>

#### **Assessments of Candidate Clinical Criteria**

The test:retest or interrater reliability of individual elements was not assessed, in part because most elements have known reliability. However, the frequency of missing data was determined for each element because more common missing data for individual elements will potentially affect the reliability of integrated scores such as the SOFA score. Construct validity was determined by examining the agreement between different measures analogous to the multitrait-multimethod matrix approach of Campbell and Fiske, using the Cronbach a to measure agreement or commonality.<sup>16,17</sup> Confidence intervals were generated with the bootstrap method (100 replications).

Criterion validity was assessed using the predictive validity of the candidate criteria with outcomes (primary outcome: in-hospital mortality; secondary outcome: in-hospital mortality or intensive care unit [ICU] length of stay ≥3 days). These outcomes are objective, easily measured across multiple hospitals in US/non-US cohorts, and are more likely to be present in encounters with patients with sepsis than those with uncomplicated infection. To measure predictive validity, a baseline risk model was created for in-hospital mortality based on preinfection criteria using multivariable logistic regression. The baseline model included age (as a fractional polynomial), sex, race/ ethnicity (black, white, or other), and the weighted Charlson comorbidity score (as fractional polynomial) as a measure of chronic comorbidities.<sup>18,19</sup> Race/ethnicity was derived from UPMC registration system data using fixed categories consistent with the Centers for Medicare & Medicaid Services EHR

#### Table 2. Summary of Data Sets

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Characteristics	UPMC <sup>a</sup>	KPNC	VA	ALERTS	KCEMS
Years of cohort	2010-2012	2009-2013	2008-2010	2011-2012	2009-2010
No. of hospitals	12	20	130	1	14
Total No. of encounters	1 309 025	1 847 165	1 640 543	38 0 9 8	50727
Data source and study design	Retrospective study of EHRs	Retrospective study of EHRs	Retrospective study of EHRs	Prospective cohort study	Retrospective study of administrative records
Setting	Integrated health system in southwestern Pennsylvania	Integrated health system in northern California	All hospitals in the US VA system	Single university hospital, Jena, Germany	Out-of-hospital records from integrated emergency medical services system in King County, Washington
Definition of suspected infection	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR <sup>b</sup>	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR <sup>b</sup>	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR <sup>b</sup>	CDC criteria for hospital-acquired infections <sup>c</sup>	ICD-9-CM codes for infection, with present-on-admission indicators <sup>d</sup>
No. with suspected infection (% of total)	148 907 (11)	321 380 (17)	377 325 (23)	1186 (3)	6508 (13)
Location at onset of infection, No. (%) infected					
Intensive care unit	15 768 (11)	7031 (2)	73 264 (19)	300 (25)	0
Outside of intensive care unit	133 139 (89)	314 349 (98)	304 061 (81)	886 (75)	6508 (100)
In-hospital mortality, No. (%) infected <sup>e</sup>	6347 (4)	16 092 (5)	22 593 (6)	210 (18)	700 (11)
Abbreviations: KCEMS, King County Emergency Medical Services; KPNC, Kaiser Permanente Northern California; EHR, electronic health record; <i>ICD-9-CM</i> ,			<sup>c</sup> Patients were enrolled ir 48 hours and in-person	ALERTS if the in-hospital prospective screening reve	stay was longer than ealed hospital-acquired

International Classification of Diseases, Ninth Revision, Clinical Modification; VA, Veterans Administration.

(CDC) guidelines.<sup>7</sup> 4 453) <sup>d</sup> Required Angus implementation *ICD-9-CM* code for infection accompanied

 $^{\rm a}$  Referred to as the primary cohort, further divided into derivation (n = 74 453) and validation (n = 74 454) cohorts.

<sup>b</sup> See the eAppendix in the Supplement for details about time windows specified between body fluid cultures and antibiotic administration.

by present-on-admission indicator, as previously validated.<sup>6</sup> <sup>e</sup> Among UPMC encounters, 28 286 (19%) had in-hospital mortality plus

infection criteria according to Centers for Disease Control and Prevention

intensive care unit length of stay of 3 days or longer.

meaningful use data set.<sup>20</sup> Race/ethnicity was included in the baseline model because of its described association with the incidence and outcomes of sepsis.<sup>21</sup>

Encounters were then divided into deciles of baseline risk. Within each decile, the rate of in-hospital mortality ± ICU length of stay of 3 days or longer was determined comparing encounters with infection with 2 or more SIRS, SOFA, LODS, and qSOFA points vs encounters with less than 2 criteria of the same score (threshold of 2 points was determined a priori). Model discrimination was assessed with the AUROC for each outcome using the continuous score(s) alone, then added to the baseline risk model. Analyses were separately performed in ICU encounters and non-ICU encounters at the onset of infection. New, simple criteria in external data sets were assessed in both ICU and non-ICU encounters.

Because serum lactate is widely used as a screening tool in sepsis,<sup>22</sup> how its measurement would improve predictive validity of new criteria was assessed in post hoc analyses. Evaluation included qSOFA models that did and did not include serum lactate at thresholds of 2.0, 3.0, and 4.0 mmol/L (18, 27, and 36 mg/dL) and as a continuous variable.<sup>23</sup> Only KPNC data were used for these analyses because an ongoing quality improvement program promoting frequent serum lactate measurement across the health system minimized confounding by indication.<sup>24</sup>

Several sensitivity analyses were performed to assess robustness of the findings. These included a variety of restrictions to the cohort, more rigorous definitions of suspected or

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presumed infection, alternative ways to measure clinical variables (such as altered mentation in the EHR), and multiple imputation analyses for missing data. There are many possible time windows for criteria around the onset of infection. A variety of windows differing from the primary analysis were tested, including (1) 3 hours before to 3 hours after; (2) 12 hours before to 12 hours after; and (3) restricting to only the 24 hours after the onset of infection. Detailed descriptions are in the Supplement.

All analyses were performed with STATA software, version 11.0 (Stata Corp). All tests of significance used a 2-sided  $P \le .05$ . We considered AUROCs to be poor at 0.6 to 0.7, adequate at 0.7 to 0.8, good at 0.8 to 0.9, and excellent at 0.9 or higher.<sup>25</sup>

#### Results

#### **Cohorts and Encounter Characteristics**

At 177 hospitals in 5 US and non-US data sets between 2008 and 2013 (**Table 2**), 4 885 558 encounters were studied. In the primary cohort of 1 309 025 records (UPMC derivation and validation; **Figure 1**), 148 907 encounters had suspected infection, most often presenting outside of the ICU (n = 133 139 [89%]). As shown in **Table 3**, first infection was commonly suspected within 48 hours of admission (86%), most often presenting in the emergency department (44%) compared with the ward (33%) or ICU (11%), and mortality was low (4%). The

Assessment of Clinical Criteria for Sepsis

#### Figure 1. Accrual of Encounters for Primary Cohort



ED indicates emergency department; ICU, intensive care unit; PACU, postanesthesia care unit.

median time from the start of the encounter until the onset of suspected infection (defined as culture or antibiotics order) was 4.2 hours (interquartile range, 1.6-19.2 hours). In KPNC hospitals (eTable 1 in the Supplement), first suspected infections occurred outside the ICU (98%) with similar mortality (5%) and proportion identified within 48 hours of admission (81%). Serum lactate was measured in 57% of suspected infection encounters in KPNC hospitals compared with less than 10% in the other cohorts. In VA hospitals, encounters with suspected infection had similar mortality (6%) but were more likely to be first identified in the ICU (19%). A minority of first infection episodes occurred following surgery, and positive blood cultures were found in 5% to 19% of encounters. In the baseline risk model, using only demographics and comorbidities, there was a 10-fold variation for in-hospital mortality across deciles of baseline risk, ranging from 0.7% to 8% (eFigure 1 in the Supplement).

# Frequency of Missing Data Among Clinical and Laboratory Variables

In the UPMC derivation cohort, SIRS criteria and selected laboratory tests in SOFA and LODS were variably measured in the EHR near the onset of infection (eFigure 2 in the Supplement). Tachycardia, tachypnea, and hypotension, although present in less than 50% of encounters, were the most common clinical abnormalities. Encounters in the ICU were more likely to have SIRS and SOFA variables measured and values were more likely to be abnormal. For encounters outside of the ICU, laboratory data were less available, with total bilirubin, ratio of PaO<sub>2</sub> to fraction of inspired oxygen, and platelet counts absent in 62%, 74%, and 15% of encounters, respectively.

# Performance of Existing Criteria in the ICU in the UPMC Cohort

Among ICU encounters with suspected infection in the UPMC validation cohort (n = 7932 [11%]), most had 2 or more LODS

the time of suspected infection, with mortality rates of 18% for all scores at this threshold (**Figure 2** and eFigure 3 in the <u>Supplement</u>). SOFA and LODS had greater statistical agreement with each other ( $\alpha = 0.87$ ; 95% CI, 0.87-0.88) but lower with SIRS ( $\alpha = 0.43$  [95% CI, 0.41-0.46] for SOFA;  $\alpha = 0.41$  [95% CI, 0.38-0.43] for LODS) (**Figure 3**). Encounters in the ICU with 2 or more vs less than 2 SIRS criteria were compared within decile of baseline risk and observed a 1- to 2-fold increased rate of hospital mortality compared with a 3- to 11-fold increase in mortality comparing those with 2 or more vs less than 2 SOFA points (**Figure 4**). The fold change in the LODS score was even greater than that for SOFA.

points (88%), SOFA points (91%), or SIRS criteria (84%) near

In the ICU, the predictive validity for hospital mortality using SOFA (AUROC = 0.74; 95% CI, 0.73-0.76) and LODS (AUROC = 0.75; 95% CI, 0.73-0.76; P = .20) were not statistically different but were statistically greater than that of SIRS (AUROC = 0.64; 95% CI, 0.62-0.66; *P* < .001 for either LODS or SOFA vs SIRS) (Figure 3 and eFigure 4 and eTable 2 in the Supplement). Results for a change in SOFA of 2 points or more were significantly greater compared with SIRS (AUROC = 0.70; 95% CI, 0.68-0.71; P < .001 vs SIRS criteria). The SOFA score was 2 or more in 98% of decedents (95% CI, 97%-99%); among survivors, the SOFA score was less than 2 in 10% (95% CI, 10%-11%). These proportions were similar for a LODS threshold of 2 or 3 (eTable 3 in the Supplement). Among decedents, 2 or more SIRS criteria were present in 91% (95% CI, 89%-92%). Results were consistent for the combined outcome (eFigures 5 and 6 in the Supplement).

# Performance of Existing Criteria Outside the ICU in the UPMC Cohort

For encounters with suspected infection outside of the ICU (n = 66 522 [89% of cohort]), 20 130 (30%) had no SIRS criteria, 27 560 (41%) had no SOFA points, and 29 789 (45%) had no LODS points (Figure 2). Agreement followed a pattern simi-

		Derivation Cohort		Validation Cohort	
Variables	All Encounters	ICU Encounters	Encounters Outside of ICU	ICU Encounters	Encounters Outside of ICU
Total encounters with suspected infection, No.	148 907	7836	66 617	7932	66 522
Infection type, No. (%) <sup>b</sup>					
Presumed	112 850 (76)	7282 (93)	49 287 (74)	7351 (93)	48 930 (74)
Confirmed bacteremia	6875 (5)	646 (8)	2780 (4)	652 (8)	2797 (4)
Age, mean (SD), y	61 (19)	62 (17)	61 (20)	62 (17)	60 (20)
Male, No. (%)	63 311 (43)	4192 (54)	27 418 (41)	4255 (54)	27 446 (41)
Race/ethnicity, No. (%)					
White	113 029 (76)	5774 (74)	50 843 (76)	5881 (74)	50 531 (76)
Black	20 892 (14)	808 (10)	9552 (14)	777 (10)	9755 (15)
Other	14 986 (10)	1254 (16)	6222 (9)	1274 (16)	6236 (9)
Weighted Charlson comorbidity index, median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Surgery prior to infection suspected, No. (%)	17 327 (12)	2153 (27)	6517 (10)	2171 (27)	6486 (10)
Onset of infection within 48 h of admission, No. (%)	128 358 (86)	6022 (77)	58 187 (87)	5993 (76)	58 156 (87)
Unit location at time infection suspected, No. (%)					
Emergency department	65 934 (44)		32 902 (50)		33 032 (50)
Ward	49 354 (33)		24787 (37)		24 567 (37)
ICU	15 768 (11)	7836 (100)		7932 (100)	
Postacute care unit or procedure unit	1965 (1)		960 (1)		1005 (2)
Step-down unit	15 662 (11)		7855 (12)		7807 (12)
Other or missing data	224 (<1)		113 (<1)		111 (<1)
SIRS near onset of suspected infection <sup>c</sup>					
Mean (SD)	1.3 (1.1)	2.5 (1.0)	1.2 (1.1)	2.5 (1.0)	1.2 (1.0)
Median (IQR)	1 (0-2)	3 (2-3)	1 (0-2)	3 (2-3)	1 (0-2)
SOFA near onset of suspected infection <sup>d</sup>					
Mean (SD)	2.0 (2.7)	6.3 (4.0)	1.4 (1.9)	6.2 (3.9)	1.4 (2.0)
Median (IQR)	1 (0-3)	6 (3-9)	1 (0-2)	6 (3-9)	1 (0-2)
LODS near onset of suspected infection <sup>e</sup>					
Mean (SD)	2.0 (2.8)	6.3 (3.9)	1.5 (2.1)	6.3 (3.8)	1.5 (2.1)
Median (IQR)	1 (0-3)	6 (4-9)	1 (0-3)	6 (3-9)	1 (0-3)
Serum lactate measured on day of infection, No. (%)	13 492 (9)	3187 (41)	3611 (5)	3067 (39)	3627 (5)
Serum lactate ≥2.0 mmol/L, No. (%)	6177 (4)	1643 (21)	1444 (2)	1555 (20)	1535 (2)
ICU admission, No. (%)	37 528 (25)	7836 (100)	10 935 (16)	7932 (100)	10 825 (16)
Hospital length of stay, median (IQR), d	6 (3-10)	12 (7-20)	6 (3-9)	12 (7-19)	6 (3-9)
Hospital mortality, No. (%)	6347 (4)	1298 (17)	1874 (3)	1289 (16)	1886 (3)

# Table 3. Characteristics of Encounters With Suspected Infection in the Primary Cohort at 12 UPMC Hospitals From 2010 to 2012 (N = 148 907)<sup>a</sup>

SI conversion: To convert serum lactate to milligrams per deciliter, divide by 0.111. Abbreviations: ICU, intensive care unit; IQR, interquartile range; LODS, Logistic Organ Dysfunction System; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Function Assessment.

<sup>a</sup> Data derived from electronic health records.

<sup>b</sup> Presumed infection is a subset of suspected infection in which encounters received 2 or more doses of an antibiotic within 96 hours of onset of infection. Confirmed bacteremia is a subset among which blood cultures were positive during the encounter.

<sup>c</sup> SIRS criteria range from 0 to 4, wherein 1 point is given for perturbations of the following variables: respiratory rate, white blood cell count/bands, heart rate, and temperature (see Table 1).<sup>29</sup> Maximum score is determined from 48 hours before to 24 hours after onset of infection.

<sup>d</sup> The SOFA score ranges from 0 to 24, where 0 to 4 points are assigned for 1 of 6 organ dysfunctions: hematologic, hepatic, respiratory, neurologic, cardiac, and renal.<sup>8</sup> A greater score corresponds to greater severity. Maximum score is determined from 48 hours before to 24 hours after onset of infection.

<sup>e</sup> The LODS score, modified for available data, ranges from 0 to 22 points, wherein points are assigned with increasing severity to hematologic, hepatic, pulmonary, neurologic, cardiovascular, and renal dysfunction.<sup>9</sup> Maximum score is determined from 48 hours before to 24 hours after onset of infection.

lar to that in the ICU encounters but with generally smaller Cronbach a statistics (Figure 3). Over deciles of baseline risk (Figure 4), encounters with 2 or more vs less than 2 SIRS criteria had a 2- to 7-fold increase in the rate of in-hospital mortality compared with up to an 80-fold change for 2 or more vs less than 2 SOFA points.

#### Figure 2. Distribution of Patient Encounters Over SIRS Criteria and SOFA, LODS, and qSOFA Scores Among ICU Patients and Non-ICU Patients With Suspected Infection in the UPMC Validation Cohort (N = 74 454)



ICU indicates intensive care unit; LODS, Logistic Organ Dysfunction System; qSOFA, quick Sequential [Sepsis-related] Organ Function Assessment; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Function Assessment. The x-axis is the score range, with LODS truncated at 14 points (of 22 points) and SOFA truncated at 16 points (of 24 points) for illustration.

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A ICU encounters (n = 7932)

# Figure 3. Area Under the Receiver Operating Characteristic Curve and 95% Confidence Intervals for In-Hospital Mortality of Candidate Criteria (SIRS, SOFA, LODS, and qSOFA) Among Suspected Infection Encounters in the UPMC Validation Cohort (N = 74454)

**B** Non-ICU encounters (n = 66 522)

	SIRS	SOFA	LODS	qSOFA		SIRS	SOFA	LODS	qSOFA
SIRS	0.64 (0.62-0.66)	0.43 (0.41-0.46)	0.41 (0.38-0.43)	0.46 (0.43-0.48)	SIRS	0.76 (0.75-0.77)	0.52 (0.51-0.53)	0.43 (0.42-0.44)	0.61 (0.61-0.62)
SOFA	<.001	0.74 (0.73-0.76)	0.87 (0.87-0.88)	0.65 (0.63-0.66)	SOFA	<.001	0.79 (0.78-0.80)	0.80 (0.80-0.81)	0.59 (0.58-0.60)
LODS	<.001	0.20	0.75 (0.73-0.76)	0.76 (0.75-0.77)	LODS	<.001	<.001	0.81 (0.80-0.82)	0.68 (0.68-0.69)
qSOFA	.01	<.001	<.001	0.66 (0.64-0.68)	qSOFA	<.001	<.001	.72	0.81 (0.80-0.82)

ICU indicates intensive care unit; LODS, Logistic Organ Dysfunction System; qSOFA, quick Sequential [Sepsis-related] Organ Function Assessment; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Function Assessment. The area under the receiver operating characteristic curve (AUROC) data in the blue-shaded diagonal cells derive from models that include baseline variables plus candidate criteria. For comparison, the AUROC of the baseline model alone is 0.58 (95% CI, 0.57-0.60) in the ICU and 0.69 (95% CI, 0.68-0.70) outside of the ICU. Below the AUROC data cells are *P* values for comparisons between criteria, while above the AUROC data cells are Cronbach a data (with bootstrap 95% confidence intervals), a measure of agreement.

The discrimination of hospital mortality using SOFA (AUROC = 0.79; 95% CI, 0.78-0.80), LODS (AUROC = 0.82; 95% CI, 0.81-0.83), or change in SOFA (AUROC = 0.79; 95% CI, 0.78-0.79) scores was significantly greater compared with SIRS criteria (AUROC = 0.76; 95% CI, 0.75-0.77; P < .01 for all) (Figure 3 and eFigure 4 and eTable 2 in the Supplement). Sixty-eight percent (95% CI, 66%-70%) of decedents had 2 or more SOFA points and 67% (95% CI, 66%-67%) of survivors had less than 2 SOFA points. In comparison, only 55% (95% CI, 53%-57%) of decedents had 2 or more SIRS criteria, whereas 81% of survivors had less than 2 SIRS criteria (95% CI, 81%-82%) (eTable 3 in the Supplement). Results were consistent for the combined outcome (eFigures 5 and 6 in the Supplement).

#### Performance of New, Simple Criteria

The final qSOFA model included Glasgow Coma Scale (GCS) score of 13 or less, systolic blood pressure of 100 mm Hg or less, and respiratory rate of 22/min or more (1 point each; score range, 0-3) (**Table 4**). Most encounters with infection (73%-90%) had less than 2 qSOFA points, and mortality ranged from 1% to 24% over the score range (eFigure 7 in the Supplement). Calibration plots showed similar observed vs expected proportion of deaths across qSOFA scores (eFigure 8 in the Supplement). The qSOFA agreed reasonably well with both SOFA ( $\alpha = 0.73$ ; 95% CI, 0.73-0.74) and LODS ( $\alpha = 0.79$ ; 95% CI, 0.78-0.79) and, unlike SOFA and LODS, also agreed more with SIRS ( $\alpha = 0.69$ ; 95% CI, 0.68-0.69) (Figure 3). The 24% of encounters with infection with 2 or 3 qSOFA points accounted for 70% of deaths, 70% of deaths or ICU stays of 3 days or longer.

In the ICU, the predictive validity for hospital mortality of qSOFA above baseline risk (AUROC = 0.66; 95% CI, 0.64-0.68) was statistically greater than SIRS criteria (P = .01) but significantly less than SOFA (P < .001) (Figure 3 and eFigure 4 and eTable 2 in the Supplement). Outside of the ICU, there was a 3- to 14-fold increase in the rate of hospital mortality across the entire range of baseline risk comparing those with 2 or more vs less than 2 qSOFA points (Figure 4). The predictive validity of qSOFA was good for in-hospital mortality (AUROC = 0.81; 95% CI, 0.80-0.82), was not statistically different from LODS (P = .77) and was statistically greater than SOFA or change in SOFA score (P < .001 for both) (Figure 3, Figure 4, and eFigure 4 and eTable 2 in the Supplement). Seventy percent (95% CI, 69%-72%) of decedents had 2 or more qSOFA points and 78% (95% CI, 78%-79%) of survivors had less than 2 qSOFA points (eTable 3 in the Supplement). Results were consistent for the combined outcome (eFigures 5 and 6 in the Supplement).

Among encounters with 2 or more qSOFA points, 75% also had 2 or more SOFA points (eFigure 9 in the Supplement). This proportion was greater among decedents (89%) and ICU encounters (94%) and increased as the time window for evaluation was extended to 48 hours (90%) and 72 hours (92%) after the onset of infection.

### **External Data Sets**

The qSOFA was tested in 4 external data sets comprising 706 399 patient encounters at 165 hospitals in out-of-hospital (n = 6508), non-ICU (n = 619 137), and ICU (n = 80 595)

# Figure 4. Fold Change in Rate of In-Hospital Mortality (Log Scale) Comparing Encounters With ≥2 vs <2 Criteria for Each Decile of Baseline Risk in the UPMC Validation Cohort (N = 74 454)



ICU indicates intensive care unit; LODS, Logistic Organ Dysfunction System; qSOFA, quick Sequential [Sepsis-related] Organ Function Assessment; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Function Assessment. Panel A shows ICU encounters comparing fold change for SIRS, SOFA, LODS, and qSOFA. Panel B shows non-ICU encounters. Medians and ranges of baseline risk of in-hospital mortality within decile shown are below the x-axis.

Interpretive example: The x-axis divides the cohort into deciles of baseline risk, determined by age, sex. comorbidities, and race/ethnicity. For a young woman with no comorbidities (panel A, decile 2) admitted to the ICU with pneumonia, her chance of dying in the hospital is 10-fold greater if she has 3 SOFA points compared with 1 SOFA point. On the other hand, she has only a small increase in the chance of dying if she has 3 SIRS criteria compared with 1 SIRS criterion. For an older woman with chronic obstructive pulmonary disease admitted to the ward with pneumonia (panel B, decile 6), her chance of dying in the hospital is 7-fold higher if she has 3 qSOFA points compared with 1 gSOFA point. On the other hand, she has only a 3-fold increase in odds of dying if she has 3 SIRS criteria compared with 1 SIRS criterion

settings (eTable 1 in the Supplement). Among encounters with community infection (KCEMS) or hospital-acquired infection (ALERTS), qSOFA had consistent predictive validity (AUROC = 0.71 and 0.75, respectively) (**Table 5** and eFigure 4 in the Supplement). Results were similar in the VA data set (AUROC = 0.78), in which no GCS data were available.

#### Serum Lactate

During model building in UPMC data, serum lactate did not meet prespecified statistical thresholds for inclusion in qSOFA. In KPNC data, the post hoc addition of serum lactate levels of 2.0 mmol/L (18 mg/dL) or more to qSOFA (revised to a 4-point score with 1 added point for elevated serum lactate level) statistically changed the predictive validity of qSOFA (AUROC with lactate = 0.80; 95% CI, 0.79-0.81 vs AUROC without lactate = 0.79; 95% CI, 0.78-0.80; P < .001) (eFigure 10A in the Supplement). As shown in eTable 4 in the Supplement, this was consistent for higher thresholds of lactate (3.0 mmol/L [27 mg/dL], 4.0 mmol/L [36 mg/dL]) or using a continuous distribution (P < .001). However, the clinical relevance was small as the rates of in-hospital mortality comparing encounters with 2 or more vs less than 2 points across deciles of risk were numerically similar whether or not serum lactate was included in qSOFA (eFigure 10B in the Supplement).

Among encounters with 1 qSOFA point but also a serum lactate level of 2.0 mmol/L or more, in-hospital mortality was higher than that for encounters with serum lactate levels of less than 2.0 mmol/L across the range of baseline risk. The rate of in-hospital mortality was numerically similar to that for encounters with 2 qSOFA points using the model without serum lactate (eFigure 11 in the Supplement). Because serum lactate levels are widely used for screening at many centers, the distribution of qSOFA scores over strata of serum lactate level was investigated. The qSOFA consistently identified higherrisk encounters even at varying serum lactate levels (eFigure 12 in the Supplement). Table 4. Odds Ratios for Baseline Model and qSOFA Variables for In-Hospital Mortality in the UPMC Derivation Cohort (N = 74 453)

	Total No. With Categorical Variable	Deaths, No. (% of Total)	In-Hospital Mortality, Adjusted Odds Ratio (95% CI)
Baseline risk model <sup>a</sup>			
Age, y <sup>b</sup>			1.03 (1.03-1.03)
Charlson comorbidity index <sup>b</sup>			1.13 (1.11-1.15)
Race/ethnicity			
White	56617	2470 (4)	1 [Reference]
Black	10 360	319 (3)	0.89 (0.79-1.01)
Other	7476	383 (5)	1.37 (1.22-1.53)
Male			
No	42 843	1467 (3)	1 [Reference]
Yes	31610	1705 (5)	1.56 (1.45-1.68)
qSOFA model <sup>c</sup>			
Respiratory rate, /min			
<22	45 398	676 (1)	1 [Reference]
≥22	29 055	2496 (9)	3.18 (2.89-3.50)
Systolic blood pressure, mm Hg			
>100	44 669	789 (2)	1 [Reference]
≤100	29784	2383 (8)	2.61 (2.40-2.85)
Altered mental status, Glasgow Coma Scale score			
14-15	66 879	1677 (3)	1 [Reference]
≤13	7574	1495 (20)	4.31 (3.96-4.69)

Abbreviations: qSOFA, quick Sequential [Sepsis-related] Organ Failure Assessment; UPMC, University of Pittsburgh School of Medicine.

- <sup>a</sup> Fully parameterized using fractional polynomials in final analyses.
- <sup>b</sup> Odds ratios correspond to a comparison between encounters separated by 1 unit change in age or Charlson comorbidity index score.
- <sup>c</sup> Multivariable logistic regression model of qSOFA variables illustrates their association with in-hospital mortality. The odds ratios compare groups of encounters with vs without the specified criteria.

#### Table 5. AUROCs for In-Hospital Mortality for qSOFA in External Data Sets

	No. of Patients With	AUROC (95% CI)	
Data Set and Infection Type	Suspected Infection	Baseline Model	Baseline Model + qSOFA
KPNC (all suspected infections)	321 380	0.67 (0.67-0.67)	0.78 (0.78-0.78)
ICU patients	7031	0.64 (0.62-0.66)	0.72 (0.70-0.73)
Non-ICU patients	314 349	0.68 (0.67-0.68)	0.78 (0.78-0.79)
VA (all suspected infections) <sup>a</sup>	377 325	0.73 (0.73-0.74)	0.78 (0.78-0.79)
ALERTS (hospital-acquired infections)	1186	0.55 (0.51-0.60)	0.73 (0.69-0.77)
KCEMS (community-acquired infections)	6508	0.59 (0.57-0.62)	0.71 (0.69-0.73)

Abbreviations: AUROC, area under the receiver operating characteristic curve; ICU, intensive care unit; KCEMS, King County Emergency Medical Services; KPNC, Kaiser Permanente Northern California; qSOFA, quick Sequential [Sepsis-related] Organ Function Assessment; VA, Veterans Administration. <sup>a</sup> The VA data did not include Glasgow Coma Scale scores; the qSOFA is a modified 2-variable model (systolic blood pressure and respiratory rate only), with a range from 0 to 2 points.

#### Time Windows for Measuring qSOFA Variables

When qSOFA variables were measured in the time window from 3 hours before/after or 12 hours before/after the onset of infection in KPNC data (eTable 4 in the Supplement), results were not significantly different from the original model (P = .13for 3 hours and P = .74 for 12 hours). When qSOFA variables were restricted to only the 24-hour period after the onset of infection, the predictive validity for in-hospital mortality was significantly greater (AUROC = 0.83; 95% CI, 0.83-0.84; P < .001) compared with the primary model.

Additional sensitivity analyses are shown in eTable 4 in the Supplement. The predictive validity of qSOFA was not significantly different when using more simple measures, such as any altered mentation (GCS score <15 [P = .56] compared with the model with GCS score <13). The predictive validity was also not

significantly different when performed after multiple imputation for missing data and in a variety of a priori subgroups.

#### Discussion

The Third International Consensus Definitions Task Force defined sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection."<sup>5</sup> In the absence of a gold-standard test for sepsis, several domains of validity and usefulness were used to assess potential clinical criteria to operationalize this definition. Among encounters with suspected infection in the ICU (Figure 3), SOFA and LODS had statistically greater predictive validity compared with SIRS criteria. Outside of the ICU, a simple model (qSOFA) of altered menta-

tion, low systolic blood pressure, and elevated respiratory rate had statistically greater predictive validity than the SOFA score (Figure 3). The predictive validity of qSOFA was robust to evaluation under varied measurement conditions, in academic and community hospitals, in international locations of care, for community and hospital-acquired infections, and after multiple imputation for missing data. It was, however, statistically inferior compared with SOFA for encounters in the ICU and has a statistically lower content validity as a measure of multiorgan dysfunction. Thus, the task force recommended use of a SOFA score of 2 points or more in encounters with infection as criteria for sepsis and use of qSOFA in non-ICU settings to consider the possibility of sepsis.

### Criteria Outside of the ICU

For infected patients outside of the ICU, there is an increasing focus on early recognition of sepsis. Potential criteria for organ dysfunction like SOFA or LODS required clinical and laboratory variables that may be missing and difficult to obtain in a timely manner. These characteristics may increase measurement burden for clinicians. In comparison, a simple model (qSOFA) uses 3 clinical variables, has no laboratory tests, and has a predictive validity outside of the ICU that is statistically greater than the SOFA score (*P* < .001). The qSOFA and SOFA scores also had acceptable agreement in the majority of encounters.

However, 3 potentially controversial issues are worth noting. First, qSOFA was derived and tested among patient encounters in which infection was already suspected. The qSOFA is not an alert that alone will differentiate patients with infection from those without infection. However, at least in many US and European hospital settings, infection is usually suspected promptly, as evidenced by rapid initiation of antibiotics.<sup>26,27</sup>

Second, mental status is assessed variably in different settings, which may affect the performance of the qSOFA. Although the qSOFA appeared robust in sensitivity analyses to alternative GCS cut points, further work is needed to clarify its clinical usefulness. In particular, the model evaluated only whether mental status was abnormal, not whether it had changed from baseline, which is extremely difficult to operationalize and validate, both in the EHR and as part of routine charting. An alternative to the GCS (eg, Laboratory and Acute Physiology Score, version 2, in KPNC encounters)<sup>28</sup> found similar results.

Third, serum lactate levels, which have been proposed as a screening tool for sepsis or septic shock, were not retained in the qSOFA during model construction. One reason may be because serum lactate levels were not measured commonly in the UPMC data set. When serum lactate levels were added to qSOFA post hoc in the KPNC health system data set, in which measurement of lactate levels was common, the predictive validity was statistically increased but with little difference in how encounters were classified. This analysis assessed only how serum lactate levels at different thresholds contributed above and beyond the qSOFA model. However, among intermediaterisk encounters (qSOFA score = 1), the addition of a serum lactate level of 2.0 mmol/L (18 mg/dL) or higher identified those with a risk profile similar to those with 2 qSOFA points. Thus, areas for further inquiry include whether serum lactate levels could be used for patients with borderline qSOFA values or as a substitute for individual qSOFA variables (particularly mental status, given the inherent problems discussed above), especially in health systems in which lactate levels are reliably measured at low cost and in a timely manner.

#### Criteria in the ICU

Among ICU encounters, the diagnosis of sepsis may be challenging because of preexisting organ dysfunction, treatment prior to admission, and concurrent organ support. In this study, as others have reported in a distinct geographic region and health care system, <sup>29</sup> traditional tools such as the SIRS criteria have poor predictive validity among patients who are infected. Yet in our study, SOFA and LODS scores had superior predictive validity in the ICU and greater agreement, perhaps because more variables were likely to be measured, abnormal, and independent of ongoing interventions. These results are consistent with prior studies of SOFA and LODS in the ICU.<sup>30,31</sup> On average, only 2 of 100 infected decedents in the ICU had a SOFA or LODS score of less than 2. The qSOFA score had statistically worse predictive validity in the ICU, likely related to the confounding effects of ongoing organ support (eg, mechanical ventilation, vasopressors).

### **Advances Using EHRs**

The data from these analyses provided the Third International Consensus Task Force with evidence about clinical criteria for sepsis using EHRs from 3 large health systems with both academic and community hospitals. More than 60% of US nonfederal, acute care hospitals (and all US federal hospitals) now use advanced EHRs. Adoption of EHRs has increased 8-fold since 2009 in the United States and will continue to increase.<sup>32</sup> The EHR may present hospitals with an opportunity to rapidly validate criteria for patients likely to have sepsis, to test prompts or alerts among infected patients with specific EHR signatures suggestive of sepsis, and to build platforms for automated surveillance.<sup>33</sup> In addition, criteria such as in the qSOFA can be measured quickly and easily and assessed repeatedly over time in patients at risk of sepsis, perhaps even in developing countries without EHRs.

#### Limitations

This investigation has several limitations. First, we studied only patients in whom infection was already suspected or documented. We did not address how to diagnose infection among those in whom life-threatening organ dysfunction was the initial presentation. Therefore, these data alone do not mandate that hospitalized patients with SOFA or qSOFA points be evaluated for the presence of infection.

Second, we chose to develop simple criteria that clinicians could quickly use at the bedside, balancing timeliness and content validity with greater criterion validity. We acknowledge that predictive validity would be improved with more complex models that include interaction terms or serial measurements over time.<sup>3,34,35</sup> We tested how the change in SOFA score over time would perform, and although similar to the maximum SOFA score, the optimal time windows over which change should be measured are not known. Third, no organ dysfunction measurements evaluated in this study distinguish between chronic and acute organ dysfunction, assess whether the organ dysfunction has an explanation other than infection, or attribute dysfunction specifically to a dysregulated host response. For example, a patient with dementia with an abnormal GCS score at baseline will always have 1 qSOFA point but may not be as likely to have sepsis as a patient with a normal baseline sensorium. As such, we illustrated the predictive validity of various criteria across a full range of underlying risk determined from comorbidity and demographics.

Fourth, we chose 2 outcomes associated more commonly with sepsis than with uncomplicated infection. These outcomes have high content validity and were generalizable across data sets, but there are certainly alternative choices.<sup>36</sup>

Fifth, we compared predictive validity with tests of inference that may be sensitive to sample size. We found that statistically significant differences in AUROC were often present, yet these resulted in differences in classification with debatable clinical relevance. We reconciled these data by reporting the fold change in outcome comparing encounters of different scores to provide more clinical context. Sixth, the acute, life-threatening organ dysfunction in sepsis may also occur at different times in different patients (before, during, or after infection is recognized).<sup>37</sup> Results were unchanged over a variety of time windows, including both long (72-hour) and short (6-hour) windows around the onset of infection. Prospective validation in other cohorts, assessment in low- to middle-income countries, repeated measurement, and the contribution of individual qSOFA elements to predictive validity are important future directions.

# Conclusions

Among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was not significantly different than the more complex LODS but was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis. Among encounters with suspected infection outside of the ICU, the predictive validity for inhospital mortality of qSOFA was statistically greater than SOFA and SIRS, supporting its use as a prompt to consider possible sepsis.

#### **ARTICLE INFORMATION**

Author Affiliations: Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Seymour, Kahn, Angus): Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, Pittsburgh, Pennsylvania (Seymour, Kahn, Angus); Division of Research. Kaiser Permanente. Oakland. California (Liu); Department of Internal Medicine, University of Michigan, Ann Arbor (Iwashyna, Escobar): Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan (Iwashvna, Escobar): Australia and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (Iwashyna, Escobar); Center for Clinical Studies, Jena University Hospital, Jena, Germany (Brunkhorst); Division of General Internal Medicine, University of Washington, Seattle (Rea): Research Group Clinical Epidemiology, Integrated Research and Treatment Center, Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany (Scherag); Trauma, Emergency, and Critical Care Program, Sunnybrook Health Sciences Centre; Interdepartmental Division of Critical Care, University of Toronto, Toronto, Ontario, Canada (Rubenfeld); Critical Care Medicine, Guy's and St Thomas' NHS Foundation Trust, London, England (Shankar-Hari): Bloomsbury Institute of Intensive Care Medicine, University College London, London, England (Singer); Feinstein Institute for Medical Research, Hofstra-North Shore-Long Island Jewish School of Medicine, Steven and Alexandra Cohen Children's Medical Center, New Hyde Park, New York (Deutschman).

Author Contributions: Dr Seymour had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Seymour, Iwashyna, Rubenfeld, Kahn, Shankar-Hari, Deutschman, Escobar, Angus. Acquisition, analysis, or interpretation of data: Liu, Iwashyna, Brunkhorst, Rea, Scherag, Kahn, Singer, Escobar, Angus.

*Drafting of the manuscript:* Seymour, Singer, Deutschman, Angus.

Critical revision of the manuscript for important intellectual content: Liu, Iwashyna, Brunkhorst, Rea, Scherag, Rubenfeld, Kahn, Shankar-Hari, Singer, Deutschman, Escobar, Angus.

*Statistical analysis:* Seymour, Liu, Iwashyna, Scherag.

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# Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Developing a New Definition and Assessing New Clinical Criteria for Septic Shock For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPh; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

**IMPORTANCE** Septic shock currently refers to a state of acute circulatory failure associated with infection. Emerging biological insights and reported variation in epidemiology challenge the validity of this definition.

**OBJECTIVE** To develop a new definition and clinical criteria for identifying septic shock in adults.

**DESIGN, SETTING, AND PARTICIPANTS** The Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force (19 participants) to revise current sepsis/septic shock definitions. Three sets of studies were conducted: (1) a systematic review and meta-analysis of observational studies in adults published between January 1, 1992, and December 25, 2015, to determine clinical criteria currently reported to identify septic shock and inform the Delphi process; (2) a Delphi study among the task force comprising 3 surveys and discussions of results from the systematic review, surveys, and cohort studies to achieve consensus on a new septic shock definition and clinical criteria; and (3) cohort studies to test variables identified by the Delphi process using Surviving Sepsis Campaign (SSC) (2005-2010; n = 28 150), University of Pittsburgh Medical Center (UPMC) (2010-2012; n = 1309 025), and Kaiser Permanente Northern California (KPNC) (2009-2013; n = 1847 165) electronic health record (EHR) data sets.

MAIN OUTCOMES AND MEASURES Evidence for and agreement on septic shock definitions and criteria.

**RESULTS** The systematic review identified 44 studies reporting septic shock outcomes (total of 166 479 patients) from a total of 92 sepsis epidemiology studies reporting different cutoffs and combinations for blood pressure (BP), fluid resuscitation, vasopressors, serum lactate level, and base deficit to identify septic shock. The septic shock–associated crude mortality was 46.5% (95% CI, 42.7%-50.3%), with significant between-study statistical heterogeneity ( $l^2$  = 99.5%;  $r^2$  = 182.5; P < .001). The Delphi process identified hypotension, serum lactate level, and vasopressor therapy as variables to test using cohort studies. Based on these 3 variables alone or in combination, 6 patient groups were generated. Examination of the SSC database demonstrated that the patient group requiring vasopressors to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L (18 mg/dL) after fluid resuscitation had a significantly higher mortality (42.3% [95% CI, 41.2%-43.3%]) in risk-adjusted comparisons with the other 5 groups derived using either serum lactate level greater than 2 mmol/L alone or combinations of hypotension, vasopressors, and serum lactate level 2 mmol/L or lower. These findings were validated in the UPMC and KPNC data sets.

**CONCLUSIONS AND RELEVANCE** Based on a consensus process using results from a systematic review, surveys, and cohort studies, septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. Adult patients with septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.

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Author Affiliations: Author affiliations are listed at the end of this article.

**Group Information:** Members of the Sepsis Definitions Task Force are listed at the end of this article.

Corresponding Author: Manu Shankar-Hari, MD, MSc, Department of Critical Care Medicine, Guy's and St Thomas' NHS Foundation Trust, London SE17EH, United Kingdom (manu.shankar-hari@kcl.ac.uk).

onsensus definitions, generated in 1991<sup>1</sup> and revisited in 2001,<sup>2</sup> describe septic shock as a state of cardiovascular dysfunction associated with infection and unexplained by other causes. The increasing availability of large electronic health record (EHR) data sets, registries, national case mix programs, trial data sets, and claims databases using International Classification of Diseases codes have since generated multiple observational studies reporting septic shock epidemiology. However, variable interpretation and application of the consensus definitions<sup>1,2</sup> have contributed to variable estimates of both incidence and outcomes.<sup>3-8</sup> It is unclear to what extent these variations represent true differences or an artifact attributable to inconsistent use of definitions.<sup>8,9</sup> Furthermore, emerging insights into sepsis pathophysiology<sup>10-13</sup> warrant a review of the current septic shock definition and the criteria used to identify it clinically.

Against this background, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Med (ESICM) convened an international task force to review definitions of sepsis and septic shock in January 2014. To support the task force deliberations on redefining septic shock, a series of activities was performed: a systematic review and metaanalysis of criteria used in observational studies reporting sepsis epidemiology in adults; a Delphi study to achieve consensus; cohort studies using the Surviving Sepsis Campaign (SSC) registry; and subsequent testing of the applicability of the new criteria in patients with suspected infection from 2 large EHRderived data sets. The aims of this study were to develop an updated septic shock definition and to derive clinical criteria for identifying patients with septic shock meeting this updated definition. Specifically, this updated definition and these criteria are intended to provide a standard classification to facilitate clinical care, future clinical research, and reporting.

### Methods

In this article, "definition" refers to a description of septic shock and "clinical criteria" to variables used to identify adult patients with septic shock.

#### **Task Force**

The SCCM and ESICM each nominated cochairs of the task force and provided unrestricted funding support toward the work conducted. The 2 cochairs then selected 17 other task force participants based on their scientific expertise in sepsis epidemiology, clinical trials, and basic or translational research. Task force participants are listed at the end of the article. The task force retained complete autonomy for all decisions. ESICM and SCCM had no role in study design, conduct, or analysis but were consulted for peer review and endorsement of the manuscript.<sup>14</sup>

#### Systematic Review and Meta-analysis

The aims of the systematic review were to assess the different criteria used to identify adult patients with septic shock and whether these criteria were associated with differences in reported outcomes. MEDLINE was searched using search terms, MeSH headings, and combinations of *sepsis, septic shock*, and *epidemiology* and limits of human studies; adults 19 years or older; English-language publications; and publication dates between January 1, 1992 (1991 definitions<sup>1</sup>), and December 25, 2015. For full-text review, only noninterventional studies reporting sepsis epidemiology and all-cause mortality were included. Randomized clinical trials were excluded, because the additional inclusion and exclusion criteria might confound the effect of criteria on mortality (the study objective).<sup>8</sup> To avoid variability in outcomes related to specific pathogens, specific patient groups, and interventional before-and-after studies, studies reporting these populations were also excluded. Data were extracted on cohort recruitment period, cohort characteristics, setting, criteria used to identify septic shock, and acute mortality. Detailed methods, including search strategy, are presented in eMethods 1 and eTable 1 in the Supplement.

#### **Delphi Study**

To generate consensus on the septic shock definition and criteria, 3 face-to-face meetings, 3-round sequential pretested questionnaires, and email discussions among the task force participants were conducted. One task force member did not participate in these surveys because of lack of content expertise, and 1 did not respond to the first 2 surveys. Questionnaires were developed, refined, and administered consisting of single- and multiple-answer questions, free-text comments, and a 5-point Likert agreement scale. For consensus discussions and noting agreement, the 5-point Likert agreement scales were grouped at the tails of the scale choices (ie, "strongly disagree" grouped with "disagree"; "strongly agree" grouped with "agree"). All outputs from the systematic review, surveys, and the results of cohort studies were made available to participants throughout the Delphi study.

In the first round (August 2014), using 26 questions in 4 domains, agreement and opinions were explored on (1) components of the new septic shock definition; (2) variables and their cutoffs identified by the systematic review; (3) definitions of, and criteria for, hypotension, persistent hypotension, adequacy of resuscitation, and resuscitation end points; and (4) septic shock severity scoring. In the second round (November 2014), 4 questions were used to generate statements for key terms (persistent hypotension, adequacy of resuscitation, and septic shock) and to reach agreement on test variables and outcomes for subsequent analysis of predictive validity. The objectives of the third round (January 2015) were to establish a consensus definition of septic shock and related clinical criteria. In the third survey, the task force members were given 4 choices for the septic shock updated criteria ([1] serum lactate level alone; [2] hypotension alone; [3] vasopressor-dependent hypotension or serum lactate level; [4] vasopressor-dependent hypotension and serum lactate level) and were asked to provide their first and second choices. The cumulative first or second choices were used to agree on the reported septic shock criteria.

Questionnaire items were accepted if agreement exceeded 65%. Choices for which agreement was less than 65% were rediscussed to achieve consensus or were eliminated, as appropriate to achieve the project aims. The survey questionnaires are presented in eMethods 2 in the Supplement.

#### **Cohort Studies**

The institutional review boards of Cooper University Hospital (Camden, New Jersey),<sup>15</sup> University of Piitsburgh Medical Center (UPMC; a network of hospitals in western Pennsylvania), and Kaiser Permanente Northern California (KPNC)<sup>16</sup> provided ethics approvals for research using the SSC and EHR data sets, respectively.

The SSC registry includes data collected from 218 hospitals in 18 countries on 28 150 patients with suspected infection who, despite adequate fluid resuscitation as judged by the collecting sites, still had 2 or more systemic inflammatory response syndrome criteria and 1 or more organ dysfunction criteria (eMethods 3 in the Supplement). The SSC database setup, inclusion, and reporting items are described in detail elsewhere.<sup>6,17</sup> To select clinical criteria for the new septic shock definition, an analysis data set was created that included all patients with a serum lactate level measurement or a mean arterial pressure less than 65 mm Hg after fluids, or who received vasopressors.

For external validation, mortality was determined using the same clinical criteria in patients with suspected infection (cultures taken, antibiotics commenced) within 2 large EHR databases from UPMC (12 hospitals, 2010-2012, n = 1309 025) and KPNC (20 hospitals, 2009-2013, n = 1847165). Three variables (hypotension, highest serum lactate level, and vasopressor therapy as a binary variable [yes/no]) were extracted from these 2 data sets during the 24-hour period after infection was suspected. Descriptive analyses, similar to those performed on the SSC data set, were then undertaken. Because of constraints on data availability, hypotension was considered present if systolic blood pressure was 100 mm Hg or less for any single measurement taken during the 24-hour period after infection was suspected. Serum lactate levels were measured in 9% of infected patients at UPMC and in 57% of those at KPNC after implementation of a sepsis quality improvement program.

#### **Statistics**

#### Meta-analysis

A random effects meta-analysis of septic shock mortality by study-specific septic shock criteria and sepsis definitions was performed. Two meta-regression models of septic shock mortality were tested with the covariates: sepsis definition, criteria for shock, mid-cohort-year of study population, single center or multicenter, and World Health Organization member state regions.<sup>18</sup> These 2 models (with and without per capita intensive care unit beds) were generated to account for international cohorts and countries for which per capita intensive care unit bed data were unavailable (See eMethods 1 in the Supplement for details).

#### **Cohort Studies**

Hospital mortality was used as the primary outcome for derivation and descriptive validation analysis. Using the 3 dichotomous variables identified in round 2 of the Delphi process, the SSC cohort was divided into 6 groups and the variables tested either alone or in combination: (1) hypotension (mean arterial pressure <65 mm Hg) after fluid administration; (2) vasopressor therapy; and (3) serum lactate level greater than

in the Systematic Review 1017 Records identified and screened 982 MEDLINE 35 Other sources<sup>a</sup> 915 Excluded 894 Did not meet screening criteria 21 Duplicate 102 Met full-text review criteria 36 Excluded<sup>b</sup> 16 Specific population 10 Included all age groups 10 Interventional study 26 New records included from reference search of full-text articles 92 Included for gualitative synthesis of definitions and criteria

Figure 1. Study Identification and Selection Process Used

**44** Reported septic shock-specific mortality for quantitative synthesis<sup>c</sup>

<sup>a</sup> Nonduplicate references from other sources included review articles.<sup>3,108-110</sup> See eMethods 1 in the Supplement for further details of search strategy.

- <sup>b</sup> Refers to records that were excluded after reference screening of full text articles. The screening criteria for full text inclusion were reporting of all case sepsis epidemiology in adult populations without specific assessment of interventions. The qualitative review assessed sepsis and septic shock definitions and criteria. The records included in the qualitative review (92 studies<sup>5-7,19-107</sup>) are presented in eTable 2 in the Supplement. The quantitative review assessed septic shock criteria and mortality.
- <sup>c</sup> Refers to the records included for quantitative assessment of septic shock mortality and the heterogeneity by criteria using random-effects meta-analysis (44 studies<sup>5-7;19-59</sup>) (eTable 2 in the Supplement).

2 mmol/L or 2 mmol/L or less (to convert serum lactate values to mg/dL, divide by 0.111). Hypotension was assumed when vasopressor therapy was being administered, generating 6 distinct potential septic shock patient groups using the 3 selected variables (eTable 5 in the Supplement). Analyses were performed using either the 6 groups or the 3 dichotomous variables as the risk factor. Subsequent analyses using the serum lactate level as a categorical variable were performed using a  $\chi^2$  test of trend for mortality.

Currently, there are no gold standard septic shock criteria for predictive validity comparisons.<sup>8</sup> Thus, these analyses aimed to identify a patient population that has the attributes of the newly proposed definition, which includes higher mortality compared with other patient populations commonly reported as having septic shock in the literature identified by the systematic review. Therefore, the independent relationship between the 3 potential criterion variables (hypotension, serum lactate level, and vasopressor therapy) agreed on the second round of the Delphi process and a future outcome (hospital mortality) was tested using

	Septic Shock Case Definiti	ons and Corresponding Varial	bles Reported in Literature		
	<b>Consensus Definitions</b>		Other Definitions		Other Description
Criteria	Bone et al <sup>1</sup>	Levy et al <sup>2</sup>	SSC <sup>111</sup>	Trial-based <sup>112</sup>	of Criteria Variables
Infection	Suspected or proven	Suspected or proven	Suspected or proven	Suspected or proven	Bacteremia, culture positive; CDC definitions for infection
SIRS criteria, No.	2	One or more of 24 variables <sup>b</sup>	2	3	NA
Septic shock description	Sepsis-induced hypotension despite adequate resuscitation OR receiving vasopressors/Inotropes plus presence of perfusion abnormalities	State of acute circulatory failure characterized by persistent arterial hypotension after adequate resuscitation unexplained by other causes	Sepsis-induced hypotension persisting despite adequate fluid resuscitation	Cardiovascular dysfunction defined as hypotension despite adequate resuscitation or need for vasopressors	Precoded data using ICD-9 and ICD-10 codes <sup>c</sup>
Hypotension, mm Hg					
Systolic BP	<90	<90	<90	<90	<100
Decrease in systolic BP	Decrease >40	Decrease >40	Decrease >40	NA<70	>50% decrease in hypertension
MAP	No	<60	<70	Hypotension lasting >1 h after resuscitation	<65
Adequate resuscitation definition	Not defined	Not defined	Goals set as CVP 8-12 mm Hg; urine output ≥0.5 mL/kg/h; ScvO <sub>2</sub> >70%	Not defined	After resuscitation fluids (0.5 L; 1 L; 1.5 L; 20 mL/kg ideal body weight
Vasopressor use	Yes (not absolute requirement)	Yes (CVS SOFA score)	Yes (not absolute requirement)	Yes (not absolute requirement)	Vasoactive drugs required for >30 min
Hypoperfusion abnormalities	Hypoperfusion abnormality defined as lactic acidosis; oliguria; low Glasgow Coma Score	Tissue hypoperfusion defined as serum lactate >1 mmol/L or delayed capillary refill	Tissue hypoperfusion defined as infection-induced hypotension, elevated serum lactate (>4 mmol/L), or oliguria	No description	Serum lactate >2.5 mmol/L; base deficit >5 mEq/L, alkaline reserve <18 mEq/L; CVP <8; PCWP <12
Data points from included studies, No. (%) <sup>d</sup>	39 (75)		13 (25)		
Sample size, No.	158 354		8125		
Mortality by septic shock definition using random-effects meta analysis, % (95% CI)	47.2 (42.	7-51.7)	44.2 (3	8.5-49.9)	
l <sup>2</sup> , % <sup>e</sup>	99.6		95.9		
$\tau^{2f}$	191.21		94.9		
P value heterogeneity	<.001		<.001		
Abbreviations: BP, blood Prevention; CVP, central <i>ICD, International Classif</i> NA, not applicable; PCW blood pressure; ScvO <sub>2</sub> , c	l pressure; CDC, Centers for l venous pressure; CVS, cardi <i>ication of Diseas</i> es; MAP, me P, pulmonary capillary wedg entral venous oxygen satura	Disease Control and ovascular system; an arterial pressure; e pressure; SBP, systolic tion; SIRS, systemic	<sup>c</sup> Different <i>ICD-9</i> codes a These include shock w 785.52, 785.59), hypo cardiovascular failure o code 796.3.	are reported to identify sept ithout trauma code 785.50 tension code 458 with subc code 427.5 and the nonspeci	ic shock in the literature. with all subcodes (785.51, odes (458.0, 458.8 458.9), fic low blood pressure
inflammatory responses Failure Assessment: SSC	syndrome; SOFA, Sequential	[Sepsis-related] Organ	<sup>d</sup> Studies reporting 2 or	more subsets, <sup>6,7,30,32</sup> currer	nt study (whole population

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

<sup>a</sup> The summary table was generated from eTable 2 data from 92 studies.<sup>5-7,19-107</sup>

<sup>b</sup> Levy et al highlight an extended variable list as a replacement for SIRS criteria consisting of general (n = 7); inflammatory (n = 5); hemodynamic (n = 3); organ dysfunction (n = 7) and tissue perfusion (n = 2) variables.<sup>2</sup>

and Group 1), and GiViTI database account for 52 data points from 44 studies. See Figure 2 notes for further details. <sup>e</sup> I<sup>2</sup> is the percentage of between-study heterogeneity that is attributable to a true variability in septic shock mortality, rather than sampling variation,

implying heterogeneity.

 $^{\rm f}$   $\tau^2$  refers to the between-study variance within groups in random-effects meta-analysis.

2 generalized estimating equation population-averaged logistic regression models with exchangeable correlation structure, where hospital site was the panel variable.

The first model used the potential septic shock groups 1 to 6 derived from these variables (eTable 5 in the Supplement), with group 1 as the referent group and adjusted for other covariates to assess true mortality difference between these groups. The second model assessed the independent association of these 3 potential criterion variables on hospital mortality adjusted for other covariates. These models also included an a priori adjustment variable for covariates including region (United States and Europe), location where sepsis was suspected (emergency department, ward, or critical care unit), antibiotic administration, steroid use, organ dysfunction (pulmonary, renal, hepatic, and acutely altered mental state), infection source (pneumonia, urinary tract infection, abdominal, meningitis and other), hyperFigure 2. Random-Effects Meta-analysis of Studies Identified in the Systematic Review, **Reporting Septic Shock Mortality** 

		Patients With		
	Septic Shock	Septic Shock,	Mortality, %	
Source	Deaths, No.	No.	(95% CI)	
Consensus Definition				
Degoricija et al, <sup>46</sup> 2006	90	125	72.0 (64.1-79.9)	-
Angkasekwinai et al, <sup>38</sup> 2007	41	78	52.6 (41.5-63.6)	
Nesseler et al. <sup>27</sup> 2013	30	93	32.3 (22.8-41.8)	
Sakr et al. <sup>25</sup> 2013	85	145	58.6 (50.6-66.6)	
Goncalves-Pereira et al. <sup>23</sup> 2014	418	856	48.8 (45.5-52.2)	
Leliadowicz et al <sup>5</sup> 2014	4146	7974	52 0 (50 9 -53 1)	
Ortiz et al <sup>19</sup> 2014	144	310	45 1 (30 7-50 6)	
Hypotension	144	515	45.1 (55.7-50.0)	
Laupland et al 47 2004	81	150	50 0 (13 2-58 7)	
	01	139	30.9 (43.2-36.7)	
	44	129	34.1 (25.9-42.3)	
Shapiro et al, 44 2006	15	53	28.3 (16.2-40.4)	
Povoa et al, <sup>33</sup> 2009	202	458	44.1 (39.6-48.7)	
Klein Klowenberg et al, <sup>7</sup> 2012	52	98	53.1 (43.2-62.9)	
Kaukonen et al, <sup>22</sup> 2014	14609	51079	28.6 (28.2-29.0)	
Hypotension + Perfusion Abnormalities and/or	Vasopressor The	erapy		
Rangel-Frausto et al, <sup>56</sup> 1995	51	110	46.4 (37.0-55.7)	
Salvo et al, <sup>55</sup> 1995	27	33	81.8 (68.7-95.0)	
Alberti et al, <sup>52</sup> 2002	752	1180	63.8 (60.7-67.0)	
Hypotension + Vasopressor Therapy				
Rodriguez et al. <sup>31</sup> 2001	129	283	45.6 (39.8-51.4)	
Silva et al. <sup>48</sup> 2004	106	203	52.2 (45.3-59.1)	
Laupland et al. <sup>49</sup> 2005	28	57	49.1 (36.5-61.8)	
Vincent et al. <sup>43</sup> 2006	250	462	54 1 (49 6-58 7)	
Karlsson et al <sup>40</sup> 2007	250	363	24.8 (20.4-20.2)	
Sale at al 39 2007	250	462	54.1 (40.6-58.7)	
	105	402	72 5 (67 1 78 0)	
	165	200	72.5 (07.1-78.0)	
Levy et al,° 2010	915	2494	36.7 (34.8-38.6)	
Phua et al, <sup>32</sup> 2011	441	939	47.0 (44.3-49.7)	
Ogura et al, <sup>20</sup> 2014	117	282	41.5 (35./-4/.2)	
GiViTI database, 2015 <sup>a</sup>	15935	26295	60.6 (60.0-61.2)	
Hypotension + Vasopressor Therapy + Serum L	actate Level >2 r	nmol/L		
Group 1 <sup>b</sup>	3602	8520	42.3 (41.2-43.3)	
Hypotension + Perfusion Abnormalities + Vaso	pressor Therapy			
Lundberg et al, <sup>54</sup> 1998	19	41	46.3 (31.1-61.6)	
Levy et al, <sup>6</sup> 2010	3428	7436	46.1 (45.0-47.2)	<b>İ</b>
Quenot et al, <sup>26</sup> 2013	728	1495	48.7 (46.2-51.2)	
Hypotension ± Vasopressor Therapy or Metabo	lic Abnormalities	5		
Peake et al. <sup>36</sup> 2009	75	324	23.1 (18.6-27.7)	
Hypotension or Vasopressor Therapy				
Dahmash et al <sup>59</sup> 1993	14	36	38 9 (23 0-54 8)	
McLauchlan et al <sup>58</sup> 1995	73	101	72 3 (63 5-81 0)	
Pittot of al 57 1995	7	17	58 3 (30 4-86 2)	
Schoophorg et al 53 1008	22	00	40.0 (20.2 50.7)	
	32	100	40.0 (29.3-30.7)	
	119	190	62.6 (55.8-69.5)	
	27	59	45.8 (33.1-58.5)	
Khwannimit and Bhuayanontachai, 37 2009	164	303	54.1 (48.5-59.7)	
Moore et al, 33 2011	22	61	36.1 (24.0-48.1)	
Zahar et al, <sup>30</sup> 2011 (community)	215	530	40.6 (36.3-44.8)	. 💻
Zahar et al, <sup>30</sup> 2011 (ICU)	123	232	53.0 (47.1-59.0)	
Zahar et al, <sup>30</sup> 2011 (nosocomial)	233	580	40.2 (36.1-44.2)	
Klein Klowenberg et al, <sup>7</sup> 2012	29	47	61.7 (47.8-75.6)	
Park et al, <sup>28</sup> 2012	228	740	30.8 (27.5-34.1)	
Hypotension or Serum Lactate Any Value or Va	sopressor Therag	ργ		
Liu et al. <sup>21</sup> 2014	827	2536	32.6 (30.8-34.4)	
SSC database. <sup>16</sup> 2016 <sup>b</sup>	6556	18840	34.8 (34.1-35.5)	
International Classification of Diseases Codes	0000	10010	5 110 (5 112 5515)	
Annano et al 51 2003	13 260	26172	50 7 (50 1-51 3)	
Flaatten 50 2004	15205	1562	20.2 (27.1.21.6)	
Fladileii, 2004	437	1502	29.5 (27.1-51.0)	
	11/	521	30.4 (31.2-41.7)	
Serum Lactate Level >4 mmol/L	242	011	20.0 (26.7.22.5)	
Levy et al,º 2010	242	811	29.8 (26.7-33.0)	
Phua et al, <sup>32</sup> 2011	219	466	47.0 (42.0-52.0)	.   👎
Overall (I <sup>2</sup> = 99.5%; P = .000)			46.5 (42.7-50.3)	
				0 20 40 60
				0 20 40 00



80 100 Mortality, % (95% CI)

Forty-four studies report septic shock-associated mortality<sup>5-7,19-59</sup> and were included in the quantitative synthesis using random-effects meta-analysis. The Surviving Sepsis Campaign (SSC) database analyses with similar data are reported in 2 studies<sup>6,29</sup>; therefore,

only one of these was used in the meta-analysis reported.<sup>6</sup> Levy et al report 3 septic shock subsets,<sup>6</sup> Klein Klowenberg et al report 2 (restrictive and liberal),<sup>7</sup> Zahar et al report 3 (community-acquired, ICU-acquired, and nosocomial infection-associated septic shock),<sup>30</sup> and Phua et al report 2 groups,<sup>32</sup> which were treated as separate data points in the meta-analysis. Studies under "consensus definition" cite the Sepsis Consensus Definitions.<sup>1,2</sup> The categorization used to assess heterogeneity does not fully account for septic shock details in individual studies.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

<sup>a</sup> Data obtained from GiViTI database provided by Bertolini et al (published 2015<sup>8</sup>).

<sup>b</sup> The mortality data of Group 1 patients (new septic shock population) and the overall potential septic shock patient populations (n = 18 840) described in the manuscript from the current study using the Surviving SSC database are also included in the meta-analysis. Septic shock-specific data were obtained from Australian & New Zealand Intensive Care Society Adult Patient Database (ANZICS), from a previously published report.<sup>22</sup> This results in 52 data points for random-effects meta-analysis.

thermia (>38.3°C), hypothermia (<36°C), chills with rigor, tachypnea (>20/min), leukopenia (<4000 cells/µL), hyperglycemia (plasma glucose level >120 mg/dL [6.7 mmol/L), platelet count  $<100 \times 10^{3}/\mu$ L, and coagulopathy.

#### Table 2. Random Effects Meta-Analysis by Septic Shock Criteria Groups

, ,	•	•					
Septic Shock Case Definition Criteria <sup>a</sup>	No. <sup>b</sup>	Mortality, No. of Events/ No. of Patients (%) [95% CI] <sup>c</sup>	Heterogeneity Statistic <sup>d</sup>	df	P Value	I <sup>2</sup> , % <sup>e</sup>	$\tau^{2f}$
Consensus definitions cited (no description)	7	4954/9590 (51.6) [46.3-56.9]	53.2	6	<.001	88.7	39.9
Hypotension	6	15 003/51 976 (39.8) [30.1-49.5]	100.5	5	<.001	95.0	129.5
Hypotension + perfusion abnormalities and/or vasopressor therapy	3	830/1323 (63.3) [48.3-78.4]	20.4	2	<.001	90.2	155.8
Hypotension + vasopressor therapy	11	18 446/32 095 (48.9) [40.5-57.4]	919.8	10	<.001	98.9	195.8
Hypotension + vasopressor therapy + serum lactate level >2 mmol/L	1	3602/8520 (42.3) [41.2-43.3]		0			
Hypotension + perfusion abnormalities + vasopressor therapy	3	4175/8972 (47.0) [45.0-49.0]	3.4	2	.19	40.5	1.33
Hypotension ± vasopressor therapy or metabolic abnormalities	1	75/324 (23.1) [18.6-27.7]		0			
Hypotension or vasopressor therapy	13	1286/2971 (48.4) [41.3-55.5]	165.3	12	<.001	92.7	142.3
Hypotension or serum lactate any value or vasopressor therapy	2	7383/21 376 (33.9) [31.8-36.0]	4.9	1	.03	79.4	1.9
International Classification of Diseases codes	3	13 843/28 055 (38.9) [22.5-55.2]	343.8	2	<.001	99.4	205.6
Serum lactate level >4 mmol/L	2	461/1277 (38.3) [21.5-55.1]	32.6	1	.005	96.9	142.6
Overall	52	70 058/166 479 (46.5) [42.7-50.3]	11026.7	51	<.001	99.5	182.5

Abbreviation: df, degree of freedom.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

<sup>a</sup> Interpretation of the operationalization described for criteria to detect a septic shock case in individual studies reporting septic shock mortality.

<sup>b</sup> Number of data points from studies included in the systematic review shown in Figure 2 (see Figure 2 legend).

<sup>c</sup> Septic shock mortality was reported by 44 studies. Four studies report septic shock subsets<sup>6,7,30,32</sup>; data obtained from GiViTi database provided by

These models were used to estimate acute hospital mortality odds ratios (ORs) and adjusted ORs for mortality per-unit increase in the serum lactate level using continuous natural log-transformed serum lactate level. The operating characteristics (sensitivity/specificity over hospital mortality curves; positive and negative predictive values) of different serum lactate cutpoints (2, 3, and 4 mmol/L) were also tested using the logistic regression model. Multiple imputations (n = 20) were used to assess the statistical effect of missing serum lactate values.

*P* < .05 (2-sided) was considered statistically significant. All analyses were performed using Stata version 13.1 (StataCorp).

# Results

#### Systematic Review and Meta-analysis

The systematic review identified 44 studies (166 479 patients) reporting septic shock mortality<sup>5-7,19-59</sup> from a total of 92 studies reporting sepsis cohorts between 1987 and 2015<sup>5-7,19-107</sup> (**Figure 1**; eTable 2 in the Supplement). Different shock criteria were used for systolic blood pressure (<90 mm Hg; <100 mm Hg; decrease >40 mm Hg; or decrease >50% of baseline value if hypertensive), mean arterial pressure (<70; <65; <60 mm Hg), serum lactate level (>4, >2.5, >2, >1 mmol/L) and base deficit (-5 mmol/L) (**Table 1**; eTable 2 in the Supplement). Temporal relationships

Bertolini et al<sup>8</sup> and the current septic shock study resulting in 52 data points (further information provided in Figure 2 legend).

<sup>d</sup> The categorization used to assess heterogeneity does not fully account for septic shock details in individual studies.

<sup>e</sup> Percentage of between-study heterogeneity attributable to true variability in septic shock mortality, rather than sampling variation, implying heterogeneity.

 $^{\rm f}$   $\tau^2$  refers to the between-study variance within groups in random-effects meta-analysis.

between resuscitation status and end points to shock diagnosis were seldom reported. The studies differed in the description of resuscitation, persistent hypotension, and in their vasopressor definitions when using the cardiovascular Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score categories.<sup>113</sup> Diverse infection and organ dysfunction codes were also used in the *International Classification of Diseases*-based derivations.<sup>63,70,79,90</sup> Variables highlighted in Table 1 and in eTable 2 in the Supplement informed the Delphi survey questions.

The random-effects meta-analysis showed significant heterogeneity in septic shock mortality (mean mortality, 46.5% [95% CI, 42.7%-50.3%], with a near 4-fold variation from 23.0% to 81.8%;  $I^2 = 99.5\%$ ;  $\tau^2 = 182.5$ ; and P < .001) (**Figure 2**). Statistically significant heterogeneity was also observed in random-effects meta-analysis by clinical criteria reported for septic shock case definition in studies (**Table 2**). The meta-regression models described could not explain this heterogeneity (eTable 3A and eTable 3B in the Supplement).

#### **Delphi Study**

In the first round, informed by the systematic review, 15 task force members (88%) voted to include persistent hypotension, vasopressor therapy, and hyperlactatemia in the updated criteria. There was no agreement on the lower cutoff for serum lactate level in this round. Eleven members (65%) voted that including fluid resuscitation would improve the

Cohorts <sup>a</sup>	Lactate Category, mmol/L <sup>b</sup>	No. (% of total) [n = 18 840]	Acute Hospital Mortality, No. (%) [95% CI]	χ² Test for Trend	Mortality, Adjusted OR (95% CI) <sup>c</sup>	<i>P</i> Value <sup>c</sup>
Group 1 (hypotensive after fluids						
and vasopressor therapy and serum lactate levels >2 mmol/L)	>2 to ≤3	2453 (13.0)	818 (33.3) [31.5-35.3]	<.001	1 [Reference]	
	>3 to ≤4	1716 (9.1)	621 (36.2) [33.9-38.5]			
	>4	4351 (23.1)	2163 (49.7) [48.2-51.2]			
	All	8520 (45.2)	3602 (42.3) [41.2-43.3]			
Group 2 (hypotensive after fluids and vasopressor therapy and serum lactate levels ≤2 mmol/L)	≤2	3985 (21.2)	1198 (30.1) [28.6-31.5]	NA <sup>d</sup>	0.57 (0.52-0.62)	<.001
Group 3 (hypotensive after fluids						
and no vasopressors and serum lactate levels >2 mmol/L)	>2 to ≤3	69 (0.4)	15 (21.7) [12.7-33.3]	.04	0.65 (0.47-0.90)	.009
	>3 to ≤4	57 (0.3)	14 (24.6) [14.1-37.8]			
	>4	97 (0.5)	35 (36.1) [26.6-46.5]			
	All	223 (1.2)	64 (28.7) [22.9-35.1]			
Group 4 (serum lactate levels >2 mmol/L						
and no hypotension after fluids	>2 to ≤3	860 (4.6)	179 (20.8) [18.1-23.7]	<.001	0.71 (0.62-0.82)	<.001
	>3 to ≤4	550 (2.9)	105 (19.1) [15.9-22.6]			
	>4	1856 (9.9)	555 (29.9) [27.8-32.0]			
	All	3266 (17.3)	839 (25.7) [24.2-27.2]			
Group 5 (serum lactate levels between						
2-4 mmol/L and no hypotension before fluids and no vasopressors)	>2 to ≤3	1624 (8.6)	489 (30.1) [27.9-32.4]	NA <sup>d</sup>	0.77 (0.66-0.90)	.001
	>3 to ≤4	1072 (5.7)	313 (29.2) [26.5-32.0]			
	>4	790 <sup>e</sup>				
	All	2696 (14.3)	802 (29.7) [28.0-31.5]			
Group 6 (hypotensive after fluids and no vasopressors and serum lactate ≤2 mmol/L)	≤2	150 (0.8)	28 (18.7) [12.8-25.8]	NA <sup>d</sup>	0.32 (0.20-0.51)	<.001

Abbreviations: NA, not available; OR, odds ratio.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

<sup>a</sup> Mean arterial pressure less than 65 mm Hg was used to define hypotension.

"After fluids" was defined using the field "crystalloids" coded as a binary term within the Surviving Sepsis Campaign database.

 $^b$  Using  $\chi^2$  tests, trends in mortality across serum lactate categories within groups (>2 to  ${\leq}3$  mmol/L; >3 to  ${\leq}4$  mmol/L and >4 mmol/L) were assessed.

<sup>c</sup> Refers to the adjusted OR generated using generalized estimating equation regression model (eTable7 in the Supplement).

 $^d\chi^2$  test for trend could only be performed if there were 3 or more serum lactate categories.

<sup>e</sup> Excluded from full case analysis.

criteria. The task force determined that neither a severity grading for septic shock nor criteria for either adequacy of fluid resuscitation or persistent hypotension should be proposed because of the nonstandardized use of hemodynamic monitoring, resuscitation protocols, and vasopressor dosing in clinical practice. (Other results are reported in eTable 4 in the Supplement.)

In Delphi round 2, the task force was provided with a preliminary descriptive analysis from the SSC database. With agreement on the description of the septic shock illness concept, 3 test variables (hypotension after fluid resuscitation, vasopressor therapy, and serum lactate level) were agreed on for predictive validity analyses. The "after fluids" field in the SSC database was used as a proxy for resuscitation. The need for vasopressors was agreed as a proxy for persistent hypotension by 95% of the task force. Twelve members (71%) voted that a minimum vasopressor dose should not be proposed in view of the variability in blood pressure targets and resuscitation protocols identified by the systematic review, and because of variable sedation use. Vasopressor therapy was therefore treated as a binary variable within the analysis. To derive an optimal cutoff for serum lactate level, 13 task force members (77%) agreed on acute hospital mortality as the outcome variable. The test variables could be present either alone or in combinations, thus identifying 6 potential groups of patients with septic shock (**Table 3**; eTable 5 in the Supplement).

Prior to the final round of the Delphi process, all analyses from the SSC data set and the EHR data sets were provided. These findings generated the new definition—"septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone"—and the clinical criteria described below.

### **Cohort Studies**

#### SSC Database

Patients with serum lactate levels greater than 4 mmol/L who did not receive fluids as recommended by the SSC guidelines<sup>111</sup> (n = 790 [2.8%]) were excluded. Patients without any serum lactate values measured were excluded initially for full case analysis (n = 4419 [15.7%]) but were reassessed in the missing data analysis. Of the 22 941 remaining patients, 4101 coded as having severe sepsis were excluded from this analysis, generating the analysis set of 18 840 patients who were either hy-





Hypotension was defined as mean arterial pressure less than 65 mm Hg. Vasopressor therapy to maintain mean arterial pressure of 65 mm Hg or higher is treated as a binary variable. Serum lactate level greater than 2 mmol/L (18 mg/dL) is considered abnormal. The "after fluids" field in the Surviving Sepsis Campaign (SSC) database was considered equivalent to adequate fluid resuscitation. "Before fluids" refers to patients who did not receive fluid resuscitation. Serum lactate level greater than 2 mmol/L after fluid resuscitation but without hypotension or need for vasopressor therapy (group 4) is defined

potensive after fluids or required vasopressors or had a serum lactate level measurement (**Figure 3** and Table 3). Hypotension was reported in 83.1%, serum lactate level greater than 2 mmol/L in 78.1%, and receipt of vasopressors in 66.4%. Overall, crude hospital mortality was 34.7%. Cohort characteristics by setting are shown in eTable 6 in the Supplement.

#### Predictive Validity of Potential Septic Shock Groups

Of the 6 groups of potential patients with septic shock (Table 3), the most prevalent was group 1 (hypotension + vasopressor therapy + serum lactate level >2 mmol/L) (n = 8520); followed by groups 2 (n = 3985) and 4 (n = 3266). Crude hospital mortality rates in these 3 groups were 42.3%, 30.1%, and 25.7%, respectively. Statistically significant increasing trends in crude mortality were observed over increasing serum lactate level categories within groups ( $\chi^2$  test of trend: P < .001 for groups 1 and 4, *P* = .04 for group 3). The adjusted OR for hospital mortality using group 1 for reference was significantly lower in all other groups (P < .01 for groups 2 to 6), suggesting that group 1 represents a distinct subpopulation with a significantly greater risk of death (eTable 7 in the Supplement). By a majority (cumulative first choice, 72.2%; second choice, 55.6%) (eTable 4 in the Supplement), the task force agreed that group 1 was most consistent with the proposed septic shock definition, thus generating the new septic shock criteria.

as "cryptic shock." Missing serum lactate level measurements (n = 4419 [15.7%]) and patients with serum lactate levels greater than 4 mmol/L (36 mg/dL) who did not receive fluids as per SSC guidelines (n = 790 [2.8%]) were excluded from full case analysis. Of the 22 941 patients, 4101 who were coded as having severe sepsis were excluded. Thus, the remaining 18 840 patients were categorized within septic shock groups 1 to 6.

<sup>a</sup>Patients with screening serum lactate levels coded as greater than 2 mmol/L (n=3342) were included in the missing-data analysis.

Derivation of Serum Lactate Cutoff Value and Missing Data Analysis In the generalized estimating equation model (shown in eTable 8 in the Supplement), serum lactate level was associated with mortality, and the adjusted OR for hospital mortality increased linearly with increasing serum lactate level. An increase in serum lactate level from 2 to 10 mmol/L increased the adjusted OR for hospital mortality from 1.4 (95% CI, 1.35-1.45) to 3.03 (95% CI, 2.68-3.45) (referent lactate = 1; Figure 4). A serum lactate level greater than 2 mmol/L was chosen as the preferred cutoff value for the new septic shock criteria, the rationale being the trade-off between highest sensitivity (82.5% when using the n = 18 840 subset, and 74.9% when using patients in groups 1 and 2 combined [n = 12475]), and the decision from the Delphi process to identify the lowest serum lactate level independently associated with a greater risk of death (OR of 1.4 at a lactate value of 2 mmol/L) (Table 4; eTable 9, eFigure 1, and eFigure 2 in the Supplement).

Predicated on this understanding of the SSC database structure and the regression analyses completed (eTable 6, eTable 7, and eTable 8 in the Supplement), we assumed that data were missing at random; ie, any difference between observed values and missing values did not depend on unobserved data. Complete case analysis was therefore performed, followed by multiple imputation analysis to support the missing-atrandom assumption.<sup>114</sup> The ORs for mortality per unit increase in serum lactate level using complete case analysis (n = 18 840) and imputed analyses (n = 22 182) were similar (1.09 [95% CI, 1.08-1.10]; P < .001 vs 1.09 [95% CI, 1.08-1.09]; P < .001, respectively). The imputed and complete case analysis probabilities of hospital mortality were also similar (36.4% and 35.5%, respectively).

#### **EHR Data Sets**

The UPMC and KPNC EHRs included 148 907 and 321 380 adult patients with suspected infection, respectively (eTable 10 in the Supplement). Forty-six percent (n = 5984) of UPMC patients and 39% (n = 54 135) of KPNC patients with 1 or more SOFA score points and suspected infection fulfilled criteria for 1 of the 6 potential septic shock groups described. Patients meeting group 1 criteria (hypotension + vasopressor therapy + serum lactate level >2 mmol/L) comprised 5.3% (UPMC) and 14.9% (KPNC) of the EHR population of patients with suspected infection and had a mortality of 54% and 35%, respectively. Similar to the SSC database, crude mortality rates within each group were higher among those with higher serum lactate levels (**Table 5**).

### Discussion

The systematic review illustrated the variability in criteria currently used to identify septic shock, whereas the metaanalysis demonstrated the heterogeneity in mortality. Informed by this systematic review, a Delphi process was used to reach a consensus definition of septic shock and related clinical criteria. Three large data sets were then used to determine the predictive validity of these criteria. Septic shock was defined as a subset of sepsis in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. The clinical criteria representing this definition were the need for vasopressor therapy to maintain a MAP of 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L persisting after fluid resuscitation.

The proposed definition and criteria of septic shock differ from prior definitions<sup>1,2,111</sup> in 2 respects: (1) the need for both a serum lactate level and vasopressor-dependent hypotension (ie, cardiovascular SOFA score  $\geq$ 2) instead of either alone and (2) a lower serum lactate level cutoff of 2 mmol/L vs



Adjusted odds ratio for actual serum lactate levels for the entire septic shock cohort (N = 18 840). The covariates used in the regression model include region (United States and Europe), location where sepsis was suspected (emergency department, ward, or critical care unit), antibiotic administration, steroid use, organ failures (pulmonary, renal, hepatic, and acutely altered mental state), infection source (pneumonia, urinary tract infection, abdominal, meningitis, and other), hyperthermia (>38.3°C), hypothermia (<36°C), chills with rigor, tachypnea (>20/min), leukopenia (<4000 cells/µL), hyperglycemia (plasma glucose >120 mg/dL [6.7 mmol/L]), platelet count <100 ×10<sup>3</sup>/µL, and coagulopathy (eMethods 3 in the Supplement). The adjusted odds ratio (OR) for the 6 groups presented in eTable 7 in the Supplement and the adjusted OR for the individual variables (lactate, vasopressor therapy, and fluids) are reported in eTable 8 in the Supplement. To convert serum lactate values to mg/dL, divide by 0.111.

Table 4. Characteristics of Serum Lactate Level Cutoff Values for Complete Case Analysis and Imputation Analysis Using Surviving Sepsis Campaign Database

	Serum Lactate Level, mmol/L									
	>2		>3		>4					
Characteristic	Died/Total	% (95% CI)	Died/Total	% (95% CI)	Died/Total	% (95% CI)				
Complete Case Analysis (n = 18 795)										
Hospital mortality, %	5757/18795	30.6 (29.9-31.4)	6101/18 795	32.5 (31.8-33.2)	6456/18975	34.3 (33.7-35.0)				
Sensitivity, %	5372/6509	82.5 (81.6-83.4)	3779/6509	58.1 (56.8-59.3)	2811/6509	43.2 (42.0-44.4)				
Specificity, %	2748/12286	22.4 (21.6-23.1)	6418/12 286	52.2 (51.4-53.1)	8564/12 286	69.7 (68.9-70.5)				
PPV, %	5372/14910	36.0 (35.3-36.8)	3779/9647	39.2 (38.2-40.2)	2811/6533	43.0 (41.8-44.2)				
NPV, %	2748/3885	70.7 (69.3-72.2)	6418/9148	70.1 (69.2-71.1)	8564/12 286	69.8 (69.0-70.7)				
Imputed Missing Serum Lactate Level (n = 22 182)										
Hospital mortality, %	6965/22 182	31.4 (30.8-32.0)	7363/22 182	33.2 (32.6-33.8)	7772/22 182	35.0 (34.4-35.7)				
Sensitivity, %	6457/7748	83.3 (82.5-84.2)	4461/7748	57.6 (56.5-58.7)	2931/7748	37.8 (36.7-38.9)				
Specificity, %	3341/14434	23.1 (22.5-23.8)	7833/14 434	54.3 (53.5-55.1)	10801/14434	74.8 (74.1-75.5)				
PPV, %	6457/17 550	36.8 (36.1-37.5)	4461/11062	40.3 (39.4-41.2)	2931/6564	44.6 (43.4-45.8)				
NPV, %	3341/4634	72.1 (70.8-73.4)	7833/11 120	70.4 (69.6-71.3)	10801/15618	69.2 (68.4-69.9)				

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

#### Table 5. Crude Mortality in Septic Shock Groups From UPMC and KPNC Data sets

Variable <sup>a</sup>	Highest Serum Lactate Levels 24 h After Infection Identified, mmol/L	UPMC			KPNC			
		No. (%) (n = 5984)	Acute Hospital Mortality		 No. (%)	Acute Hospital Mortality		
			No.	% (95% CI)	(n = 54 135)	No.	% (95% CI)	
Group 1	>2 (all)	315 (5.3)	171	54.3 (48.6-59.9)	8051 (14.9)	2835	35.2 (34.2-36.3)	
	>3	246 (4.1)	147	59.8 (53.3-65.9)	6006 (11.1)	2355	39.2 (38.0-40.5	
	>4	189 (3.2)	120	63.5 (56.2-70.4)	4438 (8.2)	1939	43.7 (42.2-45.2)	
Group 2	≤2	147 (2.5)	37	25.2 (18.4-33.0)	3094 (5.7)	582	18.8 (17.4-20.2)	
Group 3	>2 (all)	3544 (59.2)	1278	36.1 (34.5-37.7)	12 781 (23.6)	2120	16.6 (15.9-17.2)	
	>3	2492 (41.6)	1058	42.5 (40.5-44.4)	6417 (11.9)	1381	21.5 (20.5-22.5)	
	>4	1765 (29.5)	858	48.6 (46.3-51.0)	3316 (6.1)	914	27.6 (26.0-29.1)	
Groups 4 and 5	>2 (all)	1978 (33.1)	355	17.9 (16.3-19.7)	30 209 (55.8)	2061	6.8 (6.5-7.1)	
	>3	1033 (17.3)	224	21.7 (19.2-24.3)	12 450 (23.0)	1138	9.1 (8.6-9.7)	
	>4	566 (9.4)	146	25.8 (22.2-29.6)	5394 (9.9)	637	11.8 (11.0-12.7)	

Abbreviations: KPNC, Kaiser Permanente Northern California; SSC, Surviving Sepsis Campaign; UPMC, University of Pittsburgh Medical Center.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111. <sup>a</sup> Group 1 refers to patients with hypotension + vasopressors + serum lactate levels greater than 2 mmol/L. Group 2 refers to patients with hypotension +

vasopressors + serum lactate levels less than 2 mmol/L. Group 3 refers

to patients with hypotension and serum lactate levels greater than 2 mmol/L. Groups 4 and 5 refer to isolated serum lactate level greater than 2 mmol/L. Counts within a group are not mutually exclusive, as those with serum lactate levels greater than 2 mmol/L will include those in the higher serum lactate cutoffs.

4 mmol/L as currently used in the SSC definitions. In the new septic shock definition, an increase in serum lactate level is positioned as a proxy for a cellular metabolic abnormality, and as a variable independently associated with acute mortality (predictive validity), which is consistent with the published literature.<sup>115-118</sup> An elevated serum lactate level is not specific for cellular dysfunction in sepsis<sup>118,119</sup> but has face validity given the lack of a superior yet readily available alternative. This present study identifies a lower serum lactate level cutoff as an independent prognostic variable when compared with a recent analysis of the entire SSC database. This disparity is explained by using a data set of 18 840 patients in the analysis in this study rather than the total 28150-patient SSC data set used by Casserly et al.<sup>17</sup> From this subpopulation 6 groups were identified and analyzed as risk strata within the generalized estimating equation model and performance-tested for various serum lactate level cutoffs. The group with a significantly greater risk of death was then selected. In contrast, Casserly et al<sup>17</sup> reported the independent relationship of hypotension and serum lactate levels with mortality in severe sepsis.

The 6 potential septic shock patient groups analyzed in this study also provide an explanation for the heterogeneity in septic shock mortality highlighted by the meta-analysis. Depending on the group selected, septic shock mortality ranged from 12.8% to 51.2% within the SSC data set and from 7.0% to 64.0% in the EHR data sets. The KPNC EHR data set corroborated the consistent trends of higher mortality associated with a higher serum lactate level, even in a population with a wider range of illness severity captured by more prevalent measurement of serum lactate levels.

The key strengths of the present study are in the methodology used to arrive at the new definition and clinical criteria for septic shock, a clinical syndrome with a range of signs, symptoms, and biochemical abnormalities that are not pathognomonic. Furthermore, the supporting studies (systematic review, Delphi process, and analyses of the SSC and EHR cohorts) were iterative and concurrent with the consensus process, a significant step forward from previous definitions.

This study also has several limitations. First, the systematic review did not formally assess study quality and was restricted to MEDLINE publications, adult populations, and observational studies reporting epidemiology. Second, only the Delphi-derived variables were tested in multiple data sets to generate the proposed septic shock criteria. Other variables, including tissue perfusion markers (eg, base deficit, oliguria, acute alteration in mentation), blood pressure characteristics (eg, diastolic pressure), resuscitation end points (eg, central venous saturation, lactate clearance), and numerous biomarkers reported in the literature,<sup>17</sup> could potentially improve on the proposed septic shock criteria but were not included. However, operationalizing the definition of septic shock with 3 commonly measured variables should increase both generalizability and clinical utility. Third, the lack of a gold standard diagnostic criteria for septic shock<sup>8</sup> precludes comparative assessment of these proposed criteria. Fourth, all data sets had missing data that could potentially introduce a form of selection bias.<sup>120</sup> In the primary data set (SSC database) this issue was addressed by demonstrating that full case analysis is an appropriate method (see "Derivation of Serum Lactate Cutoff Value and Missing Data Analysis"). Fifth, serum lactate measurements are not universally available, especially outside of a critical care setting or in resource-limited environments. Although feasibility is a quality indicator for a definition,<sup>8</sup> identification of a critically ill patient would generally trigger obtaining a serum lactate measurement, both to stratify risk and to monitor the response to treatment.<sup>17</sup> Sixth, although the proposed new definition and clinical criteria for sepsis are arbitrary, these do have predictive validity for mortality, alongside face and content validity.8

This study represents one step in an ongoing iterative process and provides a resourceful structure and a predictive validity standard for future investigations in this area. Prospective validation of the clinical criteria may improve on the variables and cutoffs proposed herein, and identification and validation of novel markers of organ dysfunction and shock may replace lactate level.  $^{\rm 8}$ 

# Conclusions

Based on a consensus process using results from a systematic review, surveys, and cohort studies, septic shock is

#### **ARTICLE INFORMATION**

Author Affiliations: Division of Asthma, Allergy, and Lung Biology, King's College London, London, United Kingdom (Shankar-Hari); Department of Critical Care Medicine, Guy's and St Thomas' NHS Foundation Trust, London SE17EH, United Kingdom (Shankar-Hari); The Ohio State University College of Medicine, Department of Biomedical Informatics, Center for Biostatistics, Columbus (Phillips); Rhode Island Hospital, Brown University School of Medicine, Providence, Rhode Island (Levy); Clinical Research, Investigation, and Systems Modeling of Acute Illness Center, Department of Critical Care and Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Seymour, Angus); Division of Research, Kaiser Permanente, Oakland, California (Liu); Department of Pediatrics, Hofstra-North Shore-Long Island Jewish-Hofstra School of Medicine, Steven and Alexandra Cohen Children's Medical Center, New Hyde Park, New York (Deutschman); Department of Molecular Medicine, Hofstra-North Shore-Long Island Jewish-Hofstra School of Medicine, Steven and Alexandra Cohen Children's Medical Center, New Hyde Park, New York (Deutschman); Feinstein Institute for Medical Research, Manhasset, New York (Deutschman); Associate Editor, JAMA (Angus); Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada (Rubenfeld); Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Rubenfeld): Bloomsbury Institute of Intensive Care Medicine, University College London, London, United Kingdom (Singer).

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