Definitions for Sepsis and Septic Shock.

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In Reply Sepsis-3 defines septic shock as a life-threatening, generalized form of acute circulatory dysfunction (represented as vasopressor-dependent hypotension) associated with inadequate oxygen utilization (represented as hyperlactatemia), but with the important caveat of adequate fluid resuscitation. This definition has strong similarities to the consensus recommendations cited by Dr Hernández and colleagues. This change in clinical criteria describing this definition will alter the epidemiology of septic shock because of reclassification but should offer greater consistency, as the current incidence varies 10-fold and mortality 4-fold.

An accepted framework was applied to evaluate complex syndromes that incorporated content, criterion, predictive, and construct validity principles. The task force considered patients with septic shock as representing a population with a higher risk of dying than those with sepsis alone. Using the Surviving Sepsis Campaign database, crude mortality for patients with a combination of vasopressor-dependent hypotension and hyperlactatemia (>2 mmol/L) after fluids was 42.3%. This compares with 30.1% for patients with hypotension after fluids without hyperlactatemia and 25.7% for hyperlactatemia after fluids without hypotension; these differences persisted after risk adjustment. Importantly, mortality in the latter 2 groups, which perhaps represent a state of “pre-shock” rather than “early shock,” was similar to that for patients without hyperlactatemia or vasopressor-dependent hypotension (25.0%).

Hernández and colleagues also raise concerns about the availability of lactate measurement in low- and middle-income settings. We too proposed clinical assessment of the peripheral circulation as an alternative to detect other signs of shock, although such a tool must be validated and readily reproducible.

In response to Dr Jaehne and colleagues, several factors explain the lower mortality in trials evaluating early goal-directed therapy. Multiple exclusion criteria were operant; patients could be enrolled with hyperlactatemia (>4 mmol/L), irrespective of fluid resuscitation, many of whom respond quickly to fluid therapy or could have fluid-refractory hypotension, and only 16% of enrolled cases had the more life-threatening combination of hypotension and hyperlactatemia. The mortality data we derived using the Surviving Sepsis Campaign database were confirmed in 2 additional data sets and in 12,004 critical care patients in England.

Although patients without both cardiovascular dysfunction and elevated lactate levels would not meet the new definition of septic shock, we would expect a hypotensive alactatemic patient (suggested by Hernández and colleagues), a normotensive hyperlactatemic patient, or a normotensive alactatemic patient with other clinical signs of unwellness (suggested by Hernández and colleagues) to receive prompt, appropriate management. Caring for a sick patient should not be delayed simply because they do not meet specific criteria—this is just as true for the old definitions as for the new.

We do not agree that the updated septic shock definition will worsen patient outcomes or endanger patient care. The redefinition of a syndrome aims to provide an updated illness concept. We contend that the new definition, offering clearly articulated clinical criteria, will provide a stronger platform on which to build research, education, and quality improvement studies by harmonizing the multiple septic shock case definitions currently in use. The framework, which emphasizes reliability and at least 1 form of validity, is a step forward from a simple consensus statement.

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Definitions for Sepsis and Septic Shock

To the Editor Dr Singer and colleagues reevaluated and updated the definitions of sepsis and septic shock using literature reviews, Delphi surveys of experts, and studies of several large databases. Despite some improvements, such as easier-to-use terms (ie, sepsis rather than severe sepsis) and development of the quick Sequential Organ Failure Assessment (qSOFA) score, a rapid bedside score without blood tests, we have several concerns.

First, the current definitions have been successfully used for more than 20 years. Before changing them, new definitions should be shown to be superior to the old ones. Although the methodology purportedly found the best definition, a comparison of the old vs the new definitions could have demonstrated which was superior for different patient groups.

Second, we disagree that the systemic inflammatory response syndrome (SIRS) is unhelpful. SIRS describes a similar clinical response for infected (septic) or noninfected patients. The term helps physicians not to refer to noninfected patients as “septic.” More importantly, noninfected patients with 3 or 4 SIRS criteria as opposed to 1 or 2 criteria subsequently develop severe sepsis or septic shock more frequently.

In the original sepsis definition, SIRS was used to describe the “systemic response to an infection” and severe sepsis to describe “sepsis associated with organ dysfunction, hypoperfusion or hypotension.” Rangel-Frausto and colleagues found that mortality rates were 16% (not low) for SIRS and 20% for severe sepsis.
Third, the new definitions replace severe sepsis with sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This definition eliminates the sepsis spectrum with increasing mortality from infection to sepsis, severe sepsis, and septic shock.4 Contrary to the authors’ claim, the new definitions will likely not facilitate earlier sepsis recognition and treatment but rather delay it. By requiring organ dysfunction as part of the definition of sepsis, patients may be in a more advanced stage when discovered. Emphasis rather should be placed on infected patients and septic patients by the old definition as these patients are at an earlier stage of sepsis and can benefit from early recognition and treatment before organ dysfunction with its attendant increased mortality.

Finally, the new definitions will not reduce variation in the incidence or mortality of sepsis and septic shock, as using the same definitions led to different mortality rates in the different databases used in the study.

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To the Editor The new consensus definition for sepsis (Sepsis-3)1 relies on interpretation of a study on the performance of several scores in patients with suspected infection for mortality prediction.2 Although this is a commendable step forward compared with previous expert opinion-based criteria definitions,3 we fear unintended adverse effects. Unsurprisingly, as the SOFA score was developed for predicting mortality, it outperformed SIRS in the hospital setting.4 Based on this result, the authors abandoned SIRS from the sepsis definition, eliminated the first stage of the former sepsis-continuum4 (previously called sepsis), and reclassified it as infection.1

We anticipate that this repositioning of sepsis may negatively affect early clinical diagnosis of worsening, potentially life-threatening infections. Clinicians now will not only lack adequate vocabulary but also motivation for close monitoring of patients or intervention before the onset of life-threatening organ dysfunction. Consequently, the new definition may not improve care of patients with infections but may rather cost lives and jeopardize progress in sepsis awareness and therapy.

In our view, the new sepsis definition also represents a misleading signal to the research community, discouraging efforts to improve early detection of sepsis because the criterion for its measurement no longer exists. This definition may hinder development of more specific sepsis-related measures and concepts as well as identification of relevant patient subgroups early in the disease course for clinical trials. Resulting delay in innovation may cost lives.

Excluding an early, less-fatal stage from the sepsis definition may increase overall sepsis mortality statistics, although true mortality would not change. Patients would not be directly harmed, but artificially increased sepsis mortality could motivate misallocation of resources for mitigation of a nonexistent problem.

Therefore, we believe that the definition of sepsis should remain an infection triggering a systemic host response, marking the onset of a sepsis continuum.4 Only longitudinal studies can assist in defining clinically as well as epidemiologically meaningful steps along this spectrum.

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To the Editor The Sepsis Definitions Task Force published a series of articles that proposed a new definition of sepsis and septic shock, including revision of the current definitions of severe sepsis and septic shock.1 Because the definitions of sepsis and septic shock are integral to the recently implemented Centers for Medicare & Medicaid Services (CMS) sepsis measure (SEP-1: Early Management Bundle, Severe Sepsis/Septic Shock), clinicians and hospital stakeholders...
have questioned how the proposed definitions may affect the SEP-1 measure specifications.

CMS welcomes new research and innovative thinking to inform a transparent and iterative measure development and maintenance process. This careful and thoughtful process necessarily means any potential change developed from even the best research cannot immediately translate into actual measurement of clinical practice. Extensive real-world field testing must be completed to assess reliability, usability, and feasibility of measures and definitions. The SEP-1 measure underwent more than 8 years of development and critical review and has a robust body of evidence supporting its utilization. There is risk that changing these effective definitions and identification criteria could impede ongoing quality improvement efforts.

The existing sepsis definitions, including the use of SIRS criteria, have been instrumental in training clinicians and nurses on how best to identify the earliest stages of sepsis. The widespread teaching of these sepsis criteria and the adoption of screening and protocolized care processes have resulted in an unprecedented reduction in sepsis mortality. As such, the existing sepsis definitions have helped clinicians to identify, diagnose, and treat sepsis early, before a patient's condition worsens.

As opposed to early identification, the proposed task force definitions may delay the diagnosis of sepsis until patients are much sicker. Although the task force's definition structure may identify patients with the highest likelihood of poor outcomes, it does not clearly identify patients in the early stages of sepsis when rapid resuscitation provides the greatest patient benefit and improves survival. A change to the existing definition could disrupt the 15-year trend toward further reduction in sepsis mortality. Prior to changing the widespread and understood definitions used in SEP-1, rigorous clinical investigation will be required of the task force's proposed definitions. In the coming years, CMS will track the research and field testing that the proposed definitions will inspire.

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To the Editor The Sepsis-3 definition of sepsis includes the SOFA score. The SOFA scoring system has stood the test of time as a simple, readily reproducible scoring system to monitor the progression of sepsis patients, and its place in clinical evaluation is undisputed.

The Surviving Sepsis Campaign guidelines recommend norepinephrine as the first-choice vasopressor to maintain mean arterial pressure 65 mm Hg or higher, with epinephrine used when an additional agent is needed to maintain adequate blood pressure. Dopamine is not recommended except in selected circumstances. Dobutamine infusion can be administered or added to other vasopressors in the presence of myocardial dysfunction or ongoing signs of hypoperfusion despite achieving adequate intravascular volume and mean arterial pressure. The vasopressor of first choice in septic shock is norepinephrine followed by epinephrine.

However, in the SOFA score for assessment of the cardiovascular system, a score of 2 is given if the patient is placed on dopamine or dobutamine, and scores of 3 and 4 include escalating doses of dopamine with the addition of norepinephrine and epinephrine. This is not in agreement with the Surviving Sepsis Campaign guidelines recommending dopamine in only selected circumstances. We would therefore solicit the authors’ comments on the relevance of the SOFA score in the new definition of sepsis. If the SOFA score is to be used in the definition of sepsis, it needs to be validated with the use of norepinephrine and epinephrine as in the present guidelines.

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That is not the case. Rather, SIRS may be useful in the presumptive diagnosis of infection. However, SIRS is not specific nor particularly sensitive for infection. As an example, Churpek and colleagues reported that 50% of hospital inpatients have SIRS at least once in their hospital stay, and many of these patients will not have infection nor require antibiotic therapy. Conversely, 64% of the 66,522 non-intensive care unit (ICU) patients in the University of Pittsburgh Medical Center validation cohort had 0 or 1 SIRS criteria at the time they were cultured and treated for suspected infection. The article also did not suggest that what was previously called “sepsis” be eliminated from the diagnostic spectrum. Rather, it should be simply and correctly identified as “infection.”

We are surprised by the concern expressed by these authors and Dr Townsend and colleagues that the new definitions will delay the diagnosis of sepsis and negatively affect survival. Treatment should not be delayed until patients deteriorate to fulfill 2 or more qSOFA criteria. We would expect management to be similar to that provided to the 1 in 8 infected patients with new-onset organ failure who were admitted to Australasian ICUs despite having fewer than 2 SIRS criteria and previously would not have qualified as “septic.” The new criteria were based on analysis of more than 850,000 hospitalized patients with suspected infection. Such an exercise has not previously been undertaken and SIRS has never been scrutinized so comprehensively. This analysis underpinned the development of the qSOFA criteria for rapid assessment of patients with suspected infection likely to have poor outcomes. Both SIRS and qSOFA were compared using data abstracted from varying time windows both before and after cultures were sent and antibiotics started. In this analysis, qSOFA showed superior predictive validity. Nonetheless, we encourage prospective confirmation of these findings in different health care settings. We are also unaware of any prospective interventional studies using SIRS alone as an entry criterion. All the cited studies showing mortality benefits through quality improvement programs involved patients who had established organ dysfunction (ie, “sepsis” in the new definition).

To die from infection requires development of organ dysfunction; therefore the new definition cannot increase absolute mortality. The large increase in discharge coding for sepsis has lowered relative mortality but increased absolute numbers of patients dying. This trend was observed irrespective of the coding method used, but the choice of method affected estimates of incidence and absolute mortality. A major aim of the new definitions is to reduce this inconsistency.

Townsend and colleagues share the concerns of CMS about the new definitions. We are encouraged that CMS will track and test application of a SOFA score of 2 or greater and qSOFA. Multiple groups worldwide are already engaged in this process. We are confident that this measured approach will lead to a reconciliation of any differences with existing quality improvement parameters, improving the care of septic patients.

We agree with Dr Singh and colleagues that an updated SOFA score should be developed as part of the next iteration of the definitions. The SOFA score simply records vasopressor usage and dosage that are decided at the local (hospital) level, notwithstanding consensus recommendations.

Rather than discouraging efforts to detect sepsis early in its course, as voiced by Schneider-Lindner and colleagues, the new definition specifically highlights the 2 key characteristics of sepsis—namely, organ dysfunction and a dysregulated host response. Use of this new definition should lead researchers to focus on developing early, more-sensitive means to detect the presence of these 2 key components that differentiate infection from sepsis.

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Composition of the Sepsis Definitions Task Force

To the Editor Dr Singer and colleagues, in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), focused on organ dysfunction as an integral component of the pathobiology of sepsis. Incorporation of the Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score to identify organ dysfunction makes the definition more objective for clinicians and researchers.

Identification of hyperlactatemia in patients with fluid-resistant hypotension may help to identify those with higher risk of hospital mortality. The simple bedside quick SOFA (qSOFA) measure in patients with suspected infection can potentially help in the early detection of a sicker subgroup of patients.

The definitions were endorsed by 31 societies; however, low- and middle-income countries seem to be underrepresented. Low- and middle-income countries bear the largest part of the global sepsis burden and have higher morbidity and mortality. Low- and middle-income countries may also face diffi-