Defining Septic Shock.

Anja K. Jaehne  
*Henry Ford Health System*, ajaehne2@hfhs.org

Namita Jayaprakash

Sam Langberg  
*Henry Ford Health System*

Follow this and additional works at: https://scholarlycommons.henryford.com/emergencymedicine_articles

**Recommended Citation**

Prior to rolling out the qSOFA, we would like it to be subjected to 2 challenges: (1) a comparison of its discrimination, calibration, and clinical usefulness in various settings with other models derived using subject matter knowledge or based on single vital signs and (2) a prospective trial of the effect, including patient outcomes, time burden, and costs, of using the qSOFA in clinical practice. If the qSOFA overcomes these challenges, then we too will be as optimistic as Seymour and colleagues.

Martin Gerdin, MD, PhD
Tim Baker, MB ChB, PhD

Author Affiliations: Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden.
Corresponding Author: Martin Gerdin, MD, PhD, Department of Public Health Sciences, Karolinska Institutet, Stockholm, 17177, Sweden (martin.gerdin@ki.se).
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


In Reply Both letters suggest misunderstandings about the scientific goal of the task force, which was to explore the predictive validity of diagnostic criteria for sepsis. There is no gold standard for sepsis, which precludes simple measures of validity based on the presence of true positives (cases with sepsis) and true negatives (controls without sepsis). Predictive validity permits assessment of the extent to which potential criteria, applied in a population at risk of the unmeasurable condition (sepsis), predict outcomes more common in the condition.

Outcomes such as hospital mortality were chosen because sepsis is life threatening, implying that death is more common in infected patients who have sepsis. However, mortality is not necessarily caused by sepsis. Therefore, not only was the AUROC used but also the fold change within each decile of baseline risk of death. This approach explores the consistency with which death occurs more frequently than expected among patients with potential criteria for sepsis. We agree with Drs Makam and Nguyen regarding the advantages of the NRI in the outcome prediction examples they cite, but the situation is not analogous.

The task force did not propose the qSOFA as a standalone criterion for sepsis but rather as a prompt among clinicians of patients with infection to identify those who might fare badly. This decision reflects consideration of more validity domains than just predictive validity. Makam and Nguyen’s comment about SIRS and early goal-directed therapy is also not relevant because more than half of the patients were outside the emergency department at the onset of infection, and no early goal-directed therapy protocols were uniformly adopted across all hospitals. Also, the proportion of patients with 2 or more SIRS criteria and signs of hypoperfusion was low (<5%).

Counter to the claims of Drs Gerdin and Baker, the task force had no a priori hypotheses regarding which criteria would have the greatest predictive validity. We do contend, however, that altered mentation, hypotension, and tachypnea are biologically and clinical plausible as criteria associated with increased odds of poor outcome. The threshold for respiratory rate was simply the cut point associated with the greatest explanatory power in the model.

The article encouraged prospective validation in other data sets, ideally in broader settings. Gerdin and Baker suggest that the reason for a need for validation is because the predictive score may not calibrate well. However, calibration is not a priority for this exercise: the reasons to test externally are to understand if the fundamental relationship endures, regardless of calibration, and then if prospective deployment can be integrated to improve care and outcomes.

A separate question is how to help clinicians manage patients in whom infection is not suspected. However, this blends 2 tasks: diagnosis of infection (beyond the remit of the task force) and a severity of illness assessment, regardless of cause. There are countless severity instruments, and it was not the goal to compare the qSOFA with all possible scores. Nonetheless, it is reassuring that the elements in the qSOFA were similar to those of other scores such as the CURB-65, yet dissimilar from SIRS.

Christopher W. Seymour, MD, MSc
Derek C. Angus, MD, MPH

Author Affiliations: Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.
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).
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Seymour reports receiving grants from the National Institutes of Health and personal fees from Beckman Coulter, Cytovale, and Edwards. Dr Angus is Associate Editor, JAMA. No other disclosures were reported.


Defining Septic Shock
To the Editor The proposed new definition of septic shock, part of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), requires the simultaneous presence of hypotension and hyperlactatemia for making the diagnosis, instead of hypotension or hyperlactatemia. In our opinion, this is a step backward compared with previous definitions.

First, including both hypotension and hyperlactatemia conflicts with the pathophysiology of shock. Shock is a
life-threatening, generalized form of acute circulatory dysfunction associated with inadequate oxygen utilization by the cells. The proposed definition does not consider the stages of shock starting with the initial hemodynamic insult followed by early compensatory mechanisms that, when overwhelmed, lead to progressive or refractory stages. The new consensus definition is, in practical terms, progressive or refractory septic shock. We understand that the intent was to select a very high-risk population but are concerned that, when widely applied, this definition may lead to the underdiagnosis of shock among patients who might benefit from early treatment.

Second, diagnosis of shock is based on a combination of clinical, hemodynamic, and biochemical signs. To rely only on hypotension and hyperlactatemia misses the opportunity to interpret other relevant signs of clinical hypoperfusion, such as peripheral perfusion, which have been validated in recent years.

Third, a recent study highlighted the relevance and drawbacks of adding lactate to the septic shock definition, but progressive hyperlactatemia, including lactate levels in the high normal range, even without hypotension, is associated with a stepwise increase in mortality. So a diagnosis of septic shock in normotensive patients should not be dismissed.

Fourth, defining septic shock as hypotension and hyperlactatemia vs hypotension or hyperlactatemia can lead to very different physiological scenarios with unpredictable consequences on patient care and outcome. The implications of the change in definition might even be more important in low- and middle-income settings, where awareness of and sensitivity about an early diagnosis of shock need to be increased.

Gustavo Ospina-Tascón, MD, PhD
Flávia Machado, MD
Glenn Hernández, MD, PhD

To the Editor

A panel of 19 experts conducted an extensive and complex analysis of current literature and sepsis databases to develop new SEPSIS-3 definitions and clinical criteria for sepsis and septic shock. Despite this effort, some concerns remain in regard to these definitions.

The new definition of septic shock states that “Adult patients with septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean [blood pressure] of 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.” This definition excludes a number of patients with septic shock who are alactatemic (lactate level <2 mmol/L).

Studies show patients who remain hypotensive after administration of fluids and vasopressors with lactate levels less than 2 mmol/L comprise as many as 50% of patients with septic shock and that mortality among these patients is as high as 30%. Many patients may develop multisystem organ failure and die without ever having abnormal lactate levels. The variable mortality may be related to inconsistent vasopressor use among clinicians, sometimes before adequate volume resuscitation. In the article by Dr Shankar-Hari and colleagues, there was no expert consensus for serum lactate cutoff level derived from the Delphi method, so the 2 mmol/L in the definition appears to be based on the highest crude mortality rate in the validation cohort study. Patients without elevated lactate levels comprised 21.2% of patients in the Surviving Sepsis Campaign database, with a mortality of 30.1%. Shankar-Hari and colleagues also provided a baseline septic shock mortality rate of 46.5% in 2001-2015, identical to the control group mortality in the original early goal-directed therapy trial but in contrast to the mortality rates of 18% to 26% observed in recent randomized clinical trials.

The adoption of the SEPSIS-3 definition should be received with caution when it does not address hypotensive patients with normal lactate levels who are receiving vasopressors.

Anja Kathrin Jaehne, MD
Namita Jayaprkash, MD, MB BCh BAO, MRCEM
Sam Langberg, MD

Anja Kathrin Jaehne, MD, Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan (Jaehne, Langberg); Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota (Jayaprkash).

Corresponding Author: Anja Kathrin Jaehne, MD, Department of Emergency Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (ajaehe2@hfhs.org).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported being members of the Latin America Intensive Care Network. No other disclosures were reported.

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 recommendations1 cited by Dr Hernández and colleagues. This change in clinical criteria describing this definition will alter the epidemiology of septic shock because of reclassification2 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.2 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 hypotension after fluids without hyperlactatemia; 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,3 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 sets3 and in 12,004 critical care patients in England.4

Although patients without both cardiovascular dysfunction and elevated lactate levels would not meet the new definition of septic shock, we would expect a hypotensive acalcaemic patient (suggested by Jaehne and colleagues), a normotensive hyperlactatemic patient, or a normotensive acalcaemic 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.2 The framework, which emphasizes reliability and at least 1 form of validity, is a step forward from a simple consensus statement.

Manu Shankar-Hari, MD, MSc
Mervyn Singer, MD, FRCP

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Singer reported serving on the advisory boards of Infabio, Bayer, Biotest, and Merck and that his institution has received grants from the European Commission, UK National Institute of Health Research, Immunexpress, DSTL, and Wellcome Trust. No other disclosures were reported.


Definitions for Sepsis and Septic Shock

To the Editor Dr Singer and colleagues2 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.2 In the original sepsis definition,3 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 colleagues4 found that mortality rates were 16% (not low) for SIRS and 20% for severe sepsis.