LETTER TO EDITOR

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

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a major public health concern, accounting for more than $20 billion (5.2%) of total US hospital costs in 2011.The reported incidence of sepsis is increasing, likely reflecting aging populations with more comorbidities, greater recognition, and, in some countries, reimbursement-favorable coding. Although the true incidence is unknown, conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide.

Identified Challenges and Opportunities

Assessing the Validity of Definitions When There Is No Gold Standard

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

Improved Understanding of Sepsis Pathobiology

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

Variable Definitions

Sepsis - The current use of 2 or more SIRS criteria 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

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. A higher SOFA score is associated with an increased probability of mortality.

Septic Shock Multiple definitions for septic shock are currently in use. Further details are provided in an accompanying article by Shankar-Hari et al. A systematic review of the operationalization of current definitions highlights significant heterogeneity in reported mortality.

Results/Recommendations

Definition of Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This

Correspondence
Dr. Adil Rafiq Rather, M.D.
Department of Medicine, SKIMS
Srinagar, Kashmir

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.

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. 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) or organ dysfunction (eg, SOFA, Logistic Organ Dysfunction System) (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.

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 2.12

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

Screening for Patients Likely to Have Sepsis

A parsimonious clinical model developed with multivariable logistic regression identified that any 2 of 3 clinical variablesGlasgow 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 similar to that of the full SOFA score outside the ICU.

For patients with suspected infection within the ICU, the SOFA score had predictive validity superior to that of this model, likely reflecting the modifying effects of interventions (eg, vasopressors, 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.

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. The 2001 task force definitions described septic shock as "a state of acute circulatory failure." The task force favored a broader view to differentiate septic shock from cardiovascular dysfunction alone and to recognize the importance of cellular abnormalities. There was unanimous agreement that septic shock should reflect a more severe illness with a much higher likelihood of death than sepsis alone.

Key concepts :-

- 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 SOFAscore ≥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 tuted.

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- A SOFAscore ≥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 ≤ 100mmHg, or respiratory rate ≥22/min.
- **Septic shock** is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintainMAP_65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation.

REFERENCES

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2. Vincent J-L, Opal SM, Marshal JC, Tracey KJ. Sepsis definitions: time for change. Lancet 2013; 381 (9868): 774-775

Adil Rafiq, M.D., Basharat Kasana, M.D.

Senior Residents Department of General Medicine (Division Infectious Disease) SKIMS, Soura, Srinagar