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EDITORIAL

The new sepsis consensus definitions: the good, the bad and the ugly

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Introduction

Despite improvements in diagnosis and management, sepsis and septic shock remain frequent causes of morbidity and mortality. Singer and colleagues [1–3] recently updated the consensus definitions of sepsis and septic shock to improve both sensitivity and specificity compared with the previous definitions [4]. We present here our opinions of the potential ramifications of this important work (Table 1).

The good

The work was performed by an internationally recognized, multidisciplinary group of experts in sepsis epidemiology, clinical trials, and basic or translational research. The new definitions were developed using objective data, including literature reviews, expert Delphi surveys, and studies of large databases [1–3]. Improvements in the new definitions include terms more specific for what is generally considered sepsis and development of the quick sequential organ failure assessment (qSOFA) score, a rapid, simple bedside score. The new definition is likely to be more specific in defining a septic patient than the less specific, but more sensitive systemic inflammatory response syndrome (SIRS) definition.

The bad

SIRS is important Singer et al. [1] unanimously considered SIRS unhelpful in identifying sepsis. In fact, SIRS is important [5] as a descriptor for infected and non-infected patients sharing similar characteristics [4]. It is a sensitive tool for the early recognition of risk for mortality and morbidity [6], identifying patients with increased prevalence of infections [7, 8] severity of disease [5, 8], organ failure [5] and mortality [5, 7, 9]. SIRS has been incorporated as inclusion criteria in many sepsis trials [10] and used in quality improvement initiatives and management bundles to improve sepsis care [11].

Definition of septic shock Septic shock is defined as hypotension requiring vasopressor therapy to maintain mean arterial pressures (MAP) ≥65 mmHg and having serum lactate levels >2 mmol/L after adequate fluid resuscitation [2]. The authors note that different systolic blood pressures (SBP) or MAP have been used for determining shock [2]. The authors should have used their databases to see which SBP or MAP best defines septic shock. It is inconsistent to use a MAP < 65 mmHg for septic shock and a SBP ≤ 100 mmHg for qSOFA. Earlier consensus definitions excluded lactate measurement because of its unavailability in low and middle income countries (LMICs).

SOFA problems The complexity of the components of SOFA makes it unsuitable for LMICs and poses obstacles even in the USA and Europe, where the score has not been widely adopted. In addition, calculating the Glasgow Coma Scale score (GCS) from medical records is problematic and frequently patients do not undergo blood gas measurements. Current vasopressor regimens no longer utilize dopamine. SOFA was developed as an acute organ dysfunction assessment and does not consider changes in patients with preexisting organ dysfunction [12].

qSOFA problems qSOFA includes ≥22 breaths per minute, altered mentation, and SBP ≤ 100 mmHg [1]. How can qSOFA be used in hospitals or countries where these data are not available? Eldicus developed an ICU triage score in 11 European countries and found respiratory rate to be missing in 44% of 6796 patients triaged for ICU and 50% of 794 septic patients [13]. Data are mostly from the USA, where two qSOFA components predict

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Table 1 The new sepsis consensus definitions: the good, the bad, and the ugly

1. The good
A. Internationally recognized, multidisciplinary group of sepsis experts
B. Definitions developed utilizing objective data
C. Easier-to-use terms and rapid bedside score without blood tests
2. The bad
A. SIRS is important
1. Descriptor to label infected patients versus non-infected patients with similar characteristics
2. Sensitive tool for the early recognition of septic patients at risk for mortality and morbidity
3. Increased prevalence of infection, sevee disease, organ failure, and mortality
4. Used for inclusion criteria in many sepsis trials
5. Use in quality improvement initiatives and management bundles
B. Definition of septic shock
1. Databases should have been used to determine which SBP or MAP best defines septic shock
2. Previous consensus definitions excluded lactate measurement because of its unavailability in some countries
C. SOFA problems
1. The complexity of SOFA means it is poorly suited for use in low and middle income countries and problematic even in the USA and Europe
2. Retrospective derivation of the SOFA score is problematic, as data may not be available
3. Current vasopressor regimens no longer utilize dopamine
4. SOFA is an acute organ dysfunction assessment.
D. qSOFA problems
1. Data are frequently not available
2. A qSOFA score with two of three components as a screening tool in LMICs will select a population with a higher mortality
3. qSOFA may identify sick patients but not necessarily septic ones
3. The ugly
A. Early sepsis recognition
1. The new definitions discard the sepsis spectrum
2. The new definitions do not expedite early recognition and treatment, and delay recognition and therapeutic intervention
3. Patients will be at a later stage of disease with less reversibility and a worse prognosis
4. Septic shock patients require vasopressor therapy and elevated lactates
5. The new definitions not useful for screening potentially septic patients who may benefit from early intervention
B. Sepsis study comparisons
1. Studies utilizing the new definitions will have higher mortality than those using prior definitions
2. The interpretation of the benefit of new therapeutic interventions will be hampered if they are compared with past outcome data using old definitions
C. Sepsis advances
1. No explanation of how the new definitions will improve the outcome of patients with sepsis
2. No biochemical, genetic, epigenetic, inflammatory, or anti-inflammatory components to the definitions
3. Wide gap between scientific advances in understanding and the clinical deployment of insights
4. Can we expect real benefits from a modest redefinition?

LMICS low and middle income countries, *qSOFA* quick sequential organ failure assessment score, *SIRS* systemic inflammatory response syndrome

mortality [3] but where mortality rates are lower than in LMICs [14]. Perhaps only one rather than two qSOFA components should be necessary, especially in LMICs with a higher mortality. Finally, qSOFA may identify sick but not necessarily septic patients.

The ugly

Early sepsis recognition The new definitions apparently replace'severe sepsis' with 'sepsis' [1]. This discards the sepsis spectrum in which mortality increased stepwise from infection through sepsis and severe sepsis to septic shock [9]. By targeting greater severity, the new definitions may delay both recognition and therapeutic intervention. Patients will be at a later disease state with less reversibility and a worse prognosis using the new sepsis definitions of organ dysfunction with a $\geq$2 SOFA points increment rather than the less stringent definition of organ dysfunction, hypoperfusion, or hypotension.

Thus, a patient with hypotension, GCS of 13–14, and hyperlactatemia might be excluded. Similarly, septic shock now requires vasopressor therapy and elevated lactate rather than the previous hypotension and perfusion abnormalities. The new definitions are of limited utility for screening of potentially septic patients who may benefit from early intervention. Greater attention should be given to infected and septic patients without organ dysfunction who may benefit from prompt diagnosis and treatment. It is the early application of the Surviving Sepsis Campaign Bundles of Care that has improved outcomes [15].

Sepsis study comparisons Since the new sepsis definitions require more organ impairment than previous definitions, studies utilizing the new definitions should have a higher mortality than those using prior definitions. These differences will hinder comparisons of new therapeutic interventions to outcomes studied using old definitions.

Sepsis advances The most dispiriting aspect is what was beyond any contemporary consensus group's power to achieve, a truly new definition. The new definitions remain a clinical description based on vital signs and laboratory findings that, while somewhat refined, are not conceptually removed from the definitions proposed in 1991. There are no biochemical, genetic, epigenetic, inflammatory, or anti-inflammatory components to the definitions or their derivation. In the age of precision medicine, this represents a glaring deficiency in our progress. There remains a great gap between the numerous scientific advances in our understanding and the clinical deployment of these insights over the past decades. Can we expect real benefits from a modest redefinition?

Recommendations

1. Compare the old versus the new definitions using RCTs and epidemiological studies of sepsis and septic shock. The evaluation could demonstrate whether there is a need for the old definition of sepsis and whether SBP or MAP should be used.
2. Evaluate the role of single or multiple biomarkers or genetic, epigenetic, inflammatory or anti-inflammatory factors to enhance the definition and/or provide important surrogate end-points to guide management decisions.
3. Refine the SOFA score to define worsening organ dysfunction taking into account change from pre-existing organ dysfunction secondary to sepsis. Incorporate clinical parameters to define organ dysfunction for LMICs and thus expand the utility of the score globally.
4. Determine diagnostic methodologies to differentiate infected from non-infected patients.

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Compliance with ethical standards

Conflicts of interest
The three authors were members of the original ACCP-SCCM Sepsis Definitions Conference Committee and Drs. Balk and Sprung were members of the second 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.

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