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EDITORIAL

The new sepsis consensus definitions (Sepsis-3): the good, the not-so-bad, and the actually-quite-pretty

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I thank Drs. Sprung, Schein and Balk [1] for airing their concerns and encouraging debate; hopefully I can offer a persuasive rebuttal.

While we lack absolute answers to define and characterize sepsis, our understanding has advanced considerably. The excessive prior focus on 'systemic inflammation' has led to the multiple drug trial failures.

The imprecise characterization of "organ dysfunction" and "shock" in previous Consensus Definitions [2] has produced huge disparities in reported incidence and outcomes. Septic shock incidence varies tenfold and mortality fourfold [3]. "Severe sepsis" coded in a nationwide hospital sample in the USA rose from 300,270 to 781,725 within 8 years, with mortality nearly doubling [4]. This highlights the failure of current epidemiology to accurately assess the impact of sepsis.

The Sepsis-3 Task Force carefully balanced the desire to update definitions and offer robust, data-based clinical criteria against the necessary upheaval caused by usurping old friends ('SIRS', 'severe sepsis') and introducing a new lexicon [5]. Our improved knowledge base and the above examples stress the imperative for change.

Differentiating sepsis (infection-related organ dysfunction) from non-life-threatening mild infection is acknowledged as 'good'. Patients cannot die from infection without organ failure. Excessive overlap existed between infection and sepsis defined by the SIRS criteria. Ergo, 'new' sepsis describes a sicker patient, making 'severe sepsis' redundant.

Why was SIRS jettisoned? Its components remain useful when considering infection but less so for identifying the sick septic patient. Outcome benefit from manual or automated SIRS-based screening tools is unproved [6]; despite increasing delivery of management bundles, rates of ICU transfer and mortality are unaltered. High rates of false positives and alert fatigue are also commonplace. A patient fulfilling every SIRS criterion may simply have a bad cold. What literature justifies antibiotics for patients with three or four SIRS criteria alone, with no evidence of organ involvement/dysfunction? In contrast, many patients admitted to ICUs have SIRS-negative infection-related organ failure [7, 8]. Reliance on SIRS is neither failsafe nor specific.

Clinical markers of organ dysfunction underpin the rapid bedside quick Sepsis Related Organ Failure Assessment (qSOFA) tool to identify patients with possible sepsis and risk-prognosticate. We have stressed, however, that qSOFA requires prospective validation in varied healthcare settings [5].

The apparent inconsistency of mean blood pressure (BP) for shock and systolic BP for qSOFA is easily explained. Shock criteria were developed using the SSC database (systolic BP not recorded), and qSOFA from predominantly non-ICU-patient electronic health records where mean values were less frequently recorded. Pragmatically, systolic BP is more accurately and easily measured in non-ICU settings where qSOFA is intended; mean BP values are more accurate when electronically transduced.

SOFA is not complex––it uses standard physiological/biochemical tests and takes under a minute to score. There is zero expectation, or requirement, to score SOFA daily, or when the patient presents. Though needing an update (a task for Sepsis-4?), SOFA is well validated and provides the universal structure presently lacking to quantify the deterioration in organ function related

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to an infection episode. Prior definitions failed to precisely describe what organ dysfunction *is*, leading to current epidemiological confusion. Only a modest change in SOFA (≥2 points), qualifying as 'sepsis', is associated with a significant mortality risk. Notwithstanding missing Glasgow Coma Scores or blood gases, this modest rise is easily noticed; deterioration is often considerably more than 2 points.

SIRS criteria require blood tests (white count, blood gases) and thus equally challenging for low-income countries. qSOFA is a bedside tool requiring only sphygmomanometer and watch. If respiratory rate is identified as important, hospitals can easily mandate routine recording at zero cost. A seven-point National Early Warning Score (notably, including all qSOFA criteria) is used across the UK [9] and, in general, successfully delivered.

Sprung and colleagues fret that qSOFA may identify sick but not necessarily septic patients, leading to false alarms. Exactly the same applies to SIRS! Indeed, 50% of inpatients have ≥2 SIRS criteria at least once in their hospital stay, regardless of infection [10]. Are the authors not being self-contradictory? Surely we need to identify any sick patient, septic or otherwise, triggering a prompt summons to a clinical practitioner who can decide whether infection is causative.

The 'ugly' allegations are far prettier than appreciated. The cited 1995 paper [11] oddly reports little difference in mortality between patients with (severe sepsis) and those without (sepsis) organ dysfunction. Claimed improvements in outcome [12] are actually based on data from patients with *existing* organ dysfunction, who likely have the ≥2 SOFA point rise to describe 'new' sepsis. This blank ammunition does not support the arguments of Sprung et al. about early recognition and treatment *before* organ dysfunction has developed, nor does the lack of outcome benefit from the SIRS screening studies [6].

Earlier identification of infected patients who may benefit from prompt treatment is clearly desirable. However, maintaining proportionality is key. Of 850,000 patients cultured and treated for suspected infection, only 5% died in hospital [13], often from non-infection causes. Critical care witnesses the severe tip of the infection iceberg.

Sprung, Schein, and Balk also misunderstand the purpose of the shock definition (and clinical criteria). Like the mild–moderate–severe Berlin ARDS criteria [13], management should not differ depending on whether a sick patient falls within or outside the shock criteria thresholds. The "shock" criteria simply offer the necessary descriptor for more accurate coding and epidemiology. They are not intended as a clinical screening tool.

Sprung and co-authors fear mortality rates will be higher with Sepsis-3, precluding comparisons with old studies. As highlighted by our systematic review [4], between-study comparisons are already problematic. The *proportion* of patients dying will rise as the denominator shrinks, but the same *number* of patients will still die.

Sepsis advances have been incremental rather than seismic. No magic therapeutic bullet exists, nor is one likely as we now recognize that sepsis is more than just systemic inflammation. This in itself justifies the need for a new definition that takes us forward from an outdated paradigm that has served its purpose. Using the old definitions as the basis of entry criteria into trials has failed to deliver the breakthroughs Dr. Sprung and colleagues bemoan. This too undermines their argument for maintaining the status quo. We need better diagnostics but these will catalyze updated definitions and descriptors, not vice versa. For now, we should apply current the understanding of pathogenesis and solid data to provide a relevant scientific basis, improve consistency, reliability, and generalizability, and enhance patient selection for trials.

As per the recommendations of Sprung, Schein, and Balk, the big data analyses within Sepsis-3 have already compared the old and new criteria [14]. What randomized controlled trial can be performed on descriptors of a definition––what is being randomized? New biomarkers do need evaluation, but this is technology innovation upon which updated definitions will feed. We too recommended that SOFA be refined and a 'SOFA-lite' package developed for low-income nations [5]. Pending prospective validation, qSOFA could serve this purpose.

Compliance with ethical standards

Conflicts of interest

The corresponding author states that there is no conflict of interest.

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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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