

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 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.

Conflicts of interest

None

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