Opening the Debate on the New Sepsis Definition

Change Is Not Necessarily Progress: Revision of the Sepsis Definition Should Be Based on New Scientific Insights

In 1991, experts from diverse specialties developed the first consensus definition of sepsis (1). Sepsis was characterized as a systemic inflammatory response syndrome (SIRS) to infection, with three levels of severity: sepsis, severe sepsis, and septic shock (1). This definition arose from the belief that sepsis shares an underlying inflammatory pathway with other insults, such as trauma or pancreatitis (2). The expectation was that a "broad definition" might lead to early bedside detection; a better understanding of the processes that result in organ dysfunction, shock, and death; and early interventions with better outcomes (1). In 2001, a different set of experts expanded the SIRS criteria to a larger list of defining signs and symptoms (Figure 1) (3). Since that time, SIRS criteria have been fully embraced for identifying patients with sepsis for clinical practice, quality improvement initiatives, and research.

In a series of articles published in February 2016, an international task force presented a newly revised sepsis definition (4–6). Sepsis has been redefined as a "dysregulated" host response causing life-threatening organ dysfunction that is associated with the acute change of at least 2 points in the sequential organ failure assessment (SOFA) score (4). The "severe sepsis" nomenclature has been eliminated, and organ failure, as assessed by the SOFA score, must be present to define sepsis and septic shock (4). A quick SOFA score (qSOFA) was proposed for the non-intensive care unit setting. qSOFA requires the presence of two of three criteria (low blood pressure, high respiratory rate, and altered mentation) in the setting of a suspected infection. SIRS criteria have been deleted altogether (Figure 1).

SIRS criteria have long been criticized for being oversensitive and nonspecific. Furthermore, the inflammatory pathway construct has not resulted in new adjunctive therapies. Specifically, in sepsis trials, therapies that inhibit the host inflammatory response have not improved outcomes (7). Perhaps the host response to different infections is too complex to modulate with any single adjunctive therapy. It is also possible that bacterial pathogens, not the host response, may in some cases be the more important factors for worsened outcomes. Despite these limitations, the SIRS criteria have been practical and widely used for quality improvement initiatives (8, 9) and awareness campaigns (10) to educate clinicians and the public about the early signs and symptoms of sepsis and that delaying treatment can be lethal.

There is currently no test or gold standard to identify patients with sepsis. For 25 years, sepsis has been defined and redefined by consensus of expert opinion. Determining the diagnostic accuracy of a new or revised definition is not feasible without a gold standard to identify patients with the clinical syndrome. With this intrinsic limitation, one is left with evaluating the definition's value by other aspects of its operational usefulness: Does the sepsis construct lead to a treatment breakthrough or advances in the understanding of the pathobiology? The decision to revise the definition should reflect unambiguous new developments in the field, rather than expert opinion. Changes in the definition should be occasioned by true breakthroughs in scientific understanding or clinical evidence, and not by changes in task force members, their inclinations, or new consensus procedures.

What drove the decision to adopt the SOFA criteria instead of SIRS to define sepsis? The 2016 task force suggested that the recognition that sepsis involves activation of both pro- and anti-inflammatory responses required reconsideration of the definition (4). This concept is neither new nor justification for deleting the present clinical criteria. A process of validation of the SOFA score that was based on its ability to predict sepsis mortality was also undertaken. However, this test does not confirm diagnostic accuracy (5). One would expect that a set of diagnostic criteria for systemic inflammation would not predict mortality better than a score developed to predict outcome from changes in organ failure. Finally, establishing arbitrary cutoffs for SOFA and qSOFA can be potentially misleading by imposing a false image of homogeneity onto a heterogeneous disorder.

The new definition, requiring the presence of organ failure, may hinder general awareness of the importance of early recognition and treatment. Ideally, patients at risk for sepsis should be identified before organ dysfunction is established to prevent organ injury from occurring. The therapeutic triad of early initiation of appropriate antibiotics, source control, and supportive treatments (fluid resuscitation etc.) remains the cornerstone of sepsis care. The revised definition will likely identify a sicker population and could potentially delay treatment of patients who might benefit from an early approach. For example, using the new definition, a patient with an infection and fluid-responsive hypotension will be categorized as having "uncomplicated infection."

Early recognition and treatment of sepsis is currently accepted as a general principle, and has been deemed especially important in low- and middle-income regions (11). However, the 2016 task force failed to include representatives from any of these regions, where the underlying infections and the priorities for improving quality of care may differ from those in high-income regions. Some professional societies of emergency medicine and low- and middle-income regions have already voiced this concern and have not endorsed this new definition (12, 13).

Despite 25 years of clinical trials, using the sepsis construct to enroll study patients has not resulted in a single new therapy. This failure does not necessarily condemn the diagnostic criteria. Combining heterogeneous infectious diseases under one umbrella and assuming that all should receive the same new adjunctive therapy has been unproductive. An alternative approach might be to study new therapeutic approaches in patients with well-defined severe infectious diseases and only combine different severe infections into a revised

C.S.H. is partially funded by the German Federal Ministry of Education and Research via the integrated research and treatment Center for Sepsis Control and Care (grant 01EO1002). I.C.-P. is funded by intramural funding from the National Institutes of Health.

The opinions expressed in this article are the authors' own and do not represent any position or policy of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

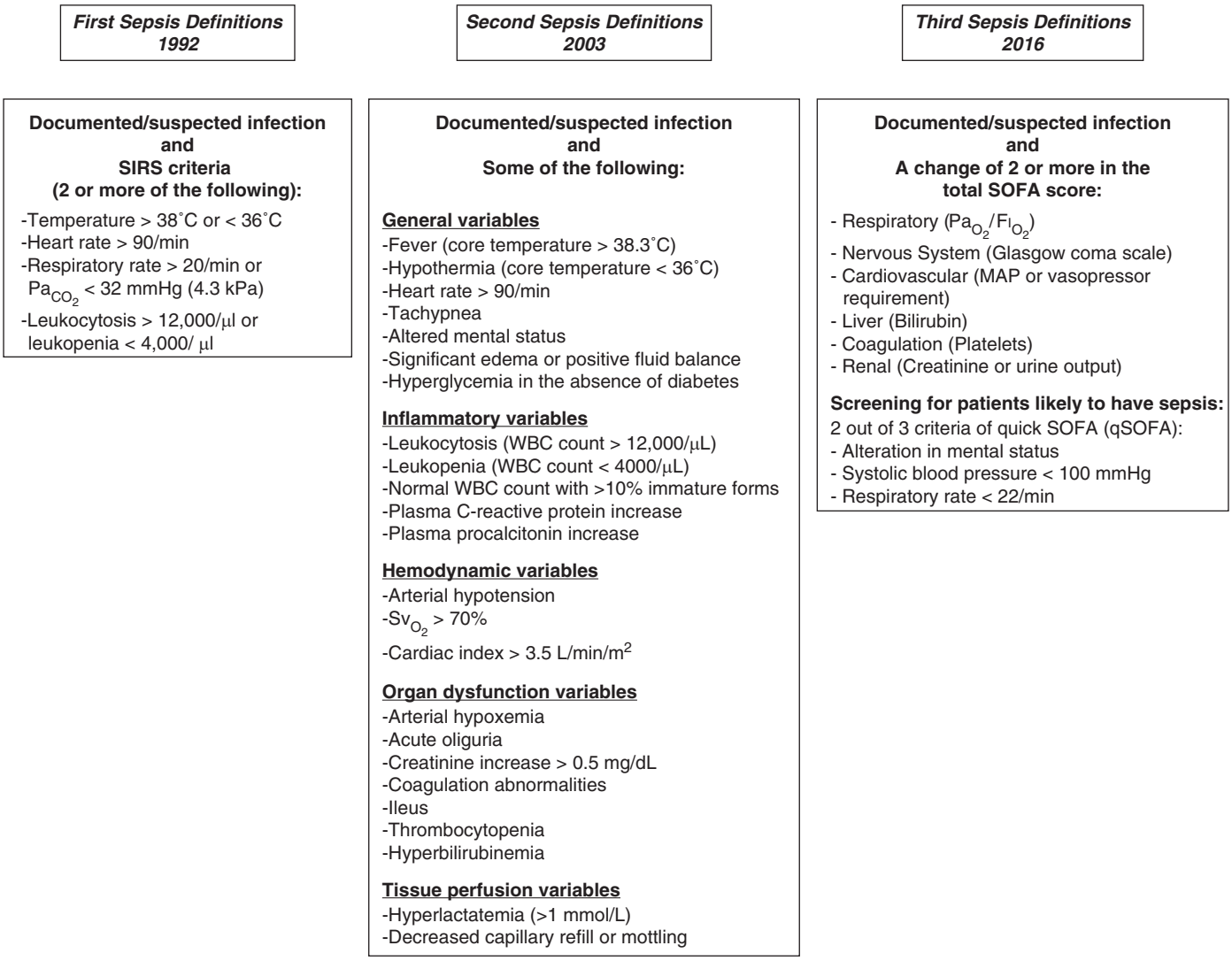

Figure 1. Consensus definitions of sepsis as published in 1992, 2003, and 2016. MAP = mean arterial pressure; SIRS = systemic inflammatory response syndrome; SOFA = sequential organ failure assessment; WBC = white blood cells.

sepsis construct once there is proof of a shared pathobiology and treatment. A new "umbrella definition" should be based on improved scientific understanding. It is not helpful to replace a widely accepted and used sepsis construct with a newer one that might delay diagnosis and treatment. Change should always reflect progress.

A compelling argument for needing new sepsis definitions has not been made. For now, and until a new characterization derived from true scientific advances can be developed, clinicians should consider continued use of the criteria that are currently used by quality improvement initiatives to screen patients for sepsis. In contrast to the sepsis 3 definition, the first two definitions did not require organ failure to be present. Therefore, they are more likely to capture patients earlier, before organ failure takes place, prompting more rapid initiation of life-saving interventions. Moreover, these previous definitions and the SIRS criteria have been widely adopted for use at the bedside and for hospital- and statewide quality improvement initiatives worldwide. Numerous controlled trials have relied on them, and this scientific database should not be discarded until unequivocal evidence indicates that superior diagnostic criteria exist. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Irene Cortés-Puch, M.D.
Critical Care Medicine Department
National Institutes of Health
Bethesda, Maryland

Christiane S. Hartog, M.D.
Center for Sepsis Control and Care
and
Department of Anesthesiology and Intensive Care Medicine
Jena University Hospital
Jena, Germany

ORCID ID: 0000-0002-3639-5046 (I.C.-P.).

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ; The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–1655.
2. Bone RC, Sprung CL, Sibbald WJ. Definitions for sepsis and organ failure. *Crit Care Med* 1992;20:724–726.
3. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31:1250–1256.
4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:801–810.
5. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, *et al*. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315: 762–774.
6. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, Angus DC, Rubenfeld GD, Singer M; Sepsis Definitions Task Force. Sepsis definitions task F: developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:775–787.
7. Suffredini AF, Munford RS. Novel therapies for septic shock over the past 4 decades. *JAMA* 2011;306:194–199.
8. Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, Divatia J, Du B, Evans L, Ferrer R, *et al*. The surviving sepsis campaign bundles and outcome: results from the international multicentre prevalence study on sepsis (the impress study). *Intensive Care Med* 2015;41:1620–1628.
9. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014;42:1749–1755.
10. Burrell AR, McLaws ML, Fullick M, Sullivan RB, Sindhusake D. SEPSIS KILLS: early intervention saves lives. *Med J Aust* 2016; 204:73.
11. Cheng AC, West TE, Limmathurotsakul D, Peacock SJ. Strategies to reduce mortality from bacterial sepsis in adults in developing countries. *PLoS Med* 2008;5:e175.
12. Machado FR, Salomão R, de Azevedo LC, Lisboa T, Filho RC; on behalf of the Latin American Sepsis Institute. Why LASI did not endorse the new definitions of sepsis published today in JAMA. Brazil: Instituto Latino Americano da Sepse; 2016 [accessed 2016 Apr 1]. Available from: http://ilas.org.br/upfiles/arquivos/statement-en.pdf
13. Simpson SQ. New sepsis criteria: a change we should not make. *Chest* 2016;149:1117–1118.