



“Shifting goal posts in sepsis, shoot carefully”

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Comment on: Shankar-Hari M, Harrison DA, Rubenfeld GD, *et al.* Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. *Br J Anaesth* 2017;119:626-36.

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Sepsis is a leading cause of mortality and critical illness worldwide (1). In recognising the significant disease burden, the World Health Assembly, the World Health Organisation's decision-making body, adopted a resolution on improving the diagnosis, management and prevention of sepsis in May 2017 (2).

To improve the diagnosis and classification of sepsis, a task force convened by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine published new definitions for sepsis and septic shock (Sepsis-3) (3). Based on the new definitions, sepsis is now defined as evidence of infection plus life-threatening organ dysfunction, clinically characterized by an acute change of two points or greater in the Sequential (Sepsis-related) Organ Failure Assessment score (SOFA). Septic shock refers to sepsis with hypotension unresponsive to fluid resuscitation, serum lactate level greater than 2 mmol/L, and the need for vasopressors to maintain mean arterial pressure of 65 mmHg or greater. In contrast, the older Sepsis-2 definitions employed the use of the systemic inflammatory response syndrome (SIRS) criteria, which include elements such as tachycardia, tachypnoea, hyperthermia or hypothermia, and abnormal peripheral white cell counts; sepsis was defined as SIRS associated with an infection, severe sepsis defined as sepsis complicated by organ dysfunction (including acute lung injury, acute oliguria/renal dysfunction, coagulopathy, ileus, hyperbilirubinaemia), and septic shock defined as severe sepsis with persistent hypotension and/or lactate level greater than 4 mmol/L despite adequate fluid resuscitation

(4,5). Significantly, the new Sepsis-3 definitions have eliminated the use of the SIRS criteria, as well as abandoned the term “severe sepsis”, incorporating the component of organ dysfunction under “sepsis” and according the latter greater emphasis and clinical importance.

Proponents of the new definitions have argued that the use of SIRS in defining sepsis is not adequately specific for diagnosis, as features of SIRS are commonly seen in hospitalised patients, with or without infections (6). In one of the largest epidemiologic study by Kaukonen *et al.*, the need for two or more SIRS criteria to define severe sepsis excluded 1 in 8 patients with infection, organ failure and substantial mortality and failed to define a transition point in the risk of death, challenging its sensitivity, face validity and construct validity (7). On the other hand, critics of the new Sepsis-3 definitions have several concerns with the clinical utility of the updated definitions. One, the patient data on which the new definitions are based on are almost exclusively from high-income countries and primarily from the United States and thus, there are reservations with respect to the utility in other geographical regions and in resource-limited settings with lower levels of patient monitoring and supportive care, and in settings with limited access to serum lactate measurement in defining septic shock. More importantly, while the new definitions have better predictive ability for mortality than does infection with SIRS, data suggest that they do so by an increased specificity that comes at the cost of compromising sensitivity and hence early detection (8). This is especially pertinent as early recognition and initiation of treatment in

sepsis are instrumental in reducing mortality (9-11).

Shankar-Hari *et al.* in their study, “*Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database*” published in *British Journal of Anaesthesia* (12), have advanced our understanding of this ongoing clinical controversy. This was a descriptive epidemiological study utilising a high-quality, national, intensive care unit (ICU) database of 654,918 consecutive admissions to 189 ICUs in England from January 2011 to December 2015. The authors tested the impact of the new Sepsis-3 definitions on epidemiology, comparing Sepsis-2 severe sepsis/septic shock and Sepsis-3 sepsis/septic shock populations identified from the same database following the first 24 hours of ICU admission. Over the 5-year study period, there were 197,724 (30.2%) Sepsis-2 severe sepsis and 197,142 (30.1%) Sepsis-3 sepsis cases. Among the sepsis cases, 92% met criteria for both definitions, indicating that both Sepsis-2 and Sepsis-3 definitions were able to identify similar populations of sepsis cases. Sepsis-3 also identified a SIRS-negative population (4.1% in Sepsis-3 sepsis cases, 1.0% in Sepsis-3 septic shock cases). While there was a much smaller septic shock subpopulation identified by Sepsis-3 (19.9%) compared with Sepsis-2 (77.5%) criteria, this group of patients had a much higher Acute Physiology And Chronic Health Evaluation II (APACHE II) score, greater mortality and no risk-adjusted trends in mortality improvement compared with Sepsis-2 septic shock, implying a significantly better predictive validity of the new Sepsis-3 definitions.

The strength of this study lies in its use of a large, high-quality database in making direct comparisons of old and new sepsis epidemiology. The authors had sought to operationalise both Sepsis-2 severe sepsis/septic shock and Sepsis-3 sepsis/septic shock definitions which were used in recent resuscitation trials (13), enabling a common basis for comparison and interpretation. The study also confirmed the findings of the superior predictive validity of the Sepsis-3 SOFA score for in-hospital mortality as compared to the SIRS criteria (14-16). However, while the Sepsis-3 definitions perform better in identifying sick patients at high-risk for organ dysfunction and mortality, the fundamental question is whether they are useful in facilitating the early diagnosis of patients with sepsis, as early as possible in the continuum of illness in order to initiate prompt treatment and minimise the risk of disease progression (17). Although this study revealed that both descriptive criteria identified a similar population with a high degree of overlap and did not significantly alter

the incidence of sepsis, it does not directly answer the above clinical question. In addition, this study utilised a database of patients admitted to the ICUs and may have limited generalizability to sepsis in the general wards or emergency room setting, as well as in resource-limited settings. Previous studies have suggested that abandoning the Sepsis-2 and SIRS criteria may result in delayed identification of high-risk sepsis population (18,19). A recent meta-analysis by Serafim *et al.* also found that the sensitivity for the diagnosis of sepsis comparing the quick SOFA (qSOFA) and SIRS was in favour of SIRS [risk ratio (RR), 1.32; 95% CI, 0.40–2.24; $P < 0.0001$; $I^2 = 100\%$] (20).

Taken together, the rather conflicting evidence from various studies contribute to clinical equipoise and require further answers from good quality randomised controlled trials. This is a syndrome without, at present, a validated standard diagnostic test or criteria. The litmus test for any diagnostic investigation or definition lies in its ability to accurately identify patients with sepsis early, in order to prompt therapy that will be effective in preventing organ dysfunction and in reducing mortality. We hope such clinical controversies will spur continued research in improving the early detection of sepsis, especially in the emergency department and general ward settings, and directing specific treatment of patients who matter the most, in the fight against sepsis so as to truly transform patient care. For now, physicians managing patients with sepsis will need to be familiar with the new sepsis definitions, including the SOFA and qSOFA scores. Taking into consideration the various implications discussed above, physicians will need to apply these definitions and scores in conjunction with all other available clinical information on a case-by-case basis, with continuous monitoring of response to resuscitation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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