Editorial

Improving knowledge about sepsis 3 definition in critically ill patients: new insights

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Sepsis continues to be an important global public health problem with persisting elevated mortality rates. The reported incidence of sepsis is increasing, but considerable international variation in incidence (6–27%) of sepsis has been reported (1-4). Variations in the definition of sepsis and septic shock can explain differences in mortality rates among septic patients (as high as 80%) (5-7). Since the time of the original sepsis definitions in 1991 (and refinement in 2001, also known as sepsis-2 definition), clinical outcomes from sepsis have improved (1,2,8) because of their application and the interventions associated with their use. Nevertheless, all recent multinational trials assessing different treatments have failed to improve survival (9-11). Defining sepsis is often difficult because of the wide variation in patient characteristics, clinical presentation, and the varied standard-of-care found across the world. As suggested first in 2013 by Vincent (12), and later in 2014 by Gattinoni (13), it is time to change the sepsis definitions and create a better classification of sepsis severity. Following this, sepsis definitions were updated in "The Third International Consensus Definitions for Sepsis and Septic Shock" (sepsis-3) (7). Sepsis is now defined as 'a life-threatening organ dysfunction caused by a dysregulated host response to infection'. For identifying organ dysfunction, the authors stablished an increase in the Sequential [sepsis-related] Organ Failure Assessment (SOFA) score of 2 points, which is associated in international databases with an in-hospital mortality of more than 10% (14). Some patients with sepsis develop septic shock, a more severe stage characterized by circulatory and cellular metabolism abnormalities identified by the need of vasopressor therapy requirement to maintain a mean arterial pressure of 65 mmHg, and serum lactate level greater than 2 mmol/L (>18 mg/dL) after adequate fluid resuscitation (15). The new definition excludes the concept of systemic inflammatory response syndrome (SIRS) and introduces a new score named quick SOFA (q-SOFA) as tool for to identify infected patients with high risk of death.

In our opinion, the new sepsis definition is necessary since it provides uniformity in clinical practice as well as for epidemiological studies and future trials. In regular clinical practice, we continue considering the SIRS criteria as indicative of infection, and if they are present, we look for severity data using q-SOFA outside the ICU and the SOFA score inside the ICU. In fact, many of the studies that show that early treatment of sepsis decreases mortality are performed in patients with organ dysfunction (severe sepsis and septic shock) (16,17).

How this new sepsis definition is going to affect the epidemiology of sepsis remains to be seen. In this context, Shankar-Hari and colleagues (18), who participated prominently in the sepsis-3 definitions, analyzed the effect

that the new sepsis definition had on incidence, mortality, and another epidemiological variable by comparing sepsis-2 severe sepsis/septic shock and sepsis-3 sepsis/septic shock populations using a national ICU database of 654,918 consecutive admissions to 189 adult English ICUs (that covers 96% of the adult general ICUs). To define sepsis-2 severe sepsis, the authors defined a SOFA score of >1 for organ dysfunction, and to define sepsis-2 septic shock they used cardiovascular a SOFA score of >1 or a lactate level >4 mmol L^{-1}. The authors compared the epidemiology of sepsis based on sepsis-2 severe sepsis/septic shock and sepsis-3 sepsis/septic shock between January 2011 and December 2015.

Along the 5-year period of study, 654,918 patients were admitted in the participating ICUs, classified according the definitions as sepsis-2 severe sepsis 197,724 (30.2%) cases and as sepsis-3 197,142 (30.1%) cases. Sepsis-2 severe sepsis and sepsis-3 sepsis definitions were overlapped in 92% cases; these included a similar age, comorbidities, illness severity scores, infection source, and even a similar ICU and hospital mortality. In addition, when the epidemiology of sepsis-3 sepsis in the ICU setting is compared with the previously described for sepsis-2 severe sepsis the results were equivalent (3,14). Shankar-Hari and colleagues conclude that the new definition (sepsis-3) was reliable detecting a similar amount than the previous (sepsis-2) classification, with similar rates of mortality. These results are expected as diagnostic criteria are similar and the authors used the same score (SOFA) to identify severe sepsis (sepsis-2) and sepsis (sepsis-3). Recently, Williams and colleagues in a prospective study with 8871 patients from the emergency department, also found that overall organ dysfunction according to both definitions estimated similar mortality risk [12.5% (95% CI, 10.8–14.2%) *vs.* 11.4% (95% CI, 10.1–12.8%)]. In contrast, in this study 29% of patients with identified using the new criteria did not meet the previous criteria (19). Some authors argued about the lack of correlation between the previous concept of severe sepsis and the new definition of sepsis (20): some clinical situations could be included by the new definition, such as organ failure without hypotension or hyperlactatemia.

The new definition excludes the concept of SIRS and does not include the concept of sepsis without organ dysfunction. This has generated controversy since some authors suggest that, ideally, patients at risk of sepsis should be identified before organ dysfunction is established (21-24). In this regard, Shankar-Hari and colleagues described that only 4.1% of sepsis-2 severe sepsis patients do not meet the stricter criteria for sepsis-3 organ dysfunction and 4.0% of sepsis-3 patients were SIRS negative. In their analysis, as most patients with organ dysfunction also tend to have SIRS, discarding SIRS as the initial step for sepsis diagnosis (in patients in the first 24 h of ICU admission) does not alter the epidemiology of sepsis.

One important finding is that the proportion of patients with septic shock differs between sepsis-2 and sepsis-3 definitions. Among patients admitted with sepsis, there were 153,257 (77.5%) sepsis-2 septic shock and 39,262 (19.9%) sepsis-3 septic shock, being 0.01% negative for systemic inflammation criteria. The severity scores, lactate levels and hospital mortality were higher in sepsis-3 septic shock. Thus, the sepsis-3 septic shock definition selects a very critically ill subpopulation. Recently, Driessen and colleagues (25) prospectively analyzed a cohort of 632 ICU septic patients: 300 patients (48.4%) according to the new definition and 482 (76.3%) had septic shock according to the former criteria. Patients meeting the sepsis-3 septic shock criteria had a higher mortality than patients meeting the old septic shock definition (38.9% *vs.* 34.0%). The findings of these two recent studies support the objectives of the Task Force to select a very severe and homogeneous septic shock populations.

Shankar-Hari and colleagues also calculate trends and risk factors for adjusted and unadjusted hospital mortality using four logistic-regression models that include a large number of confusion factors as illness severity. They found an increase in sepsis incidence and an improvement in hospital mortality. In addition, age and comorbidity are factors that increase the incidence and mortality of Sepsis-3 sepsis and septic shock, similar to previous epidemiologic studies (26). In the regression models, the highest increment in predictive validity was for sepsis-3 septic shock, even when adjusting for severity.

In summary, Shankar-Hari and coworkers present us a well-designed study, using an observational high-quality database. They present one of the first direct comparisons of old and new sepsis epidemiology using in England. For adult ICU admissions with sepsis, the new sepsis-3 sepsis definition does not involve a big change in epidemiology data. This study confirms that new septic shock is a population with high risk of death. This can be interpreted as better predictive validity and argued as prognostic enrichment maybe resulting better patient selection for clinical trials, and therefore could be considered as a risk-stratification screening-tool. For designing clinical trials, will be important to assess the magnitude of mortality

risk reduction that is viable to be effectively reduced. This new definition will create different challenges for both clinicians and researchers. As we further explore a more uniform epidemiological description of sepsis, we will better understand it.

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Footnote

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

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