Commentary

New definitions for septic shock—a roadmap for a better clinical outcome?

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Worldwide septic shock represents one of the most common causes for admission to intensive care units (ICU) (1). From a historical point of view, the primary criterion for the diagnosis of sepsis was progressive dysfunction of organ systems resulting from a proven infection. In 1991, a new set of terms and definitions was developed to define sepsis more precisely (2,3). The concept of the systemic inflammatory response syndrome (SIRS) was introduced with predefined diagnostic criteria. However, the SIRS definition reveals several major concerns. SIRS criteria are very common and therefore up to 90% of all patients being admitted to an ICU might fulfil them. Furthermore, SIRS criteria might be caused by several non-infectious diseases, such as a severe trauma, burns, pancreatitis, and ischemic reperfusion syndromes (4). In addition, septic shock was defined as a sepsis-induced arterial hypotension persisting despite adequate fluid substitution. The discrimination between severe sepsis and septic shock is critically important as it stratifies patients into groups with low and high risk of death. Especially septic shock reveals a highly variable mortality ranging from 30% to 80% across epidemiologic and therapeutic studies (1). This extreme variability has been attributed to an intrinsic heterogeneity of the different patients suffering from septic shock (1,5). Also non-equivalent definitions of severe sepsis or septic shock being applied in different studies might have influenced mortality rates (6-8). Due to the described inconsistencies the definitions of sepsis and septic shock were revised in 2001 (6).

The current management of patients with septic shock aims to control directly the cause of infection in order to modulate immune response, to counterbalance metabolic and organ dysfunction as well as to achieve hemodynamic stabilisation. Over the last decades considerable advances have been achieved in the understanding of the pathophysiology, epidemiology and management of septic shock revealing an urgent need to re-constitute the concept and definition of septic shock (9,10). Within the last issue of the *Journal of the American Medical Association* (*JAMA*) a triplet of articles were published developing new definitions of sepsis and septic shock (11-13).

We read with great interest the work of Shankar-Hari and colleagues (11) investigating new definitions of septic shock within a three stepped analysis as follows: (I) a systematic review and meta-analysis of 44 different observational studies (i.e., a total of 166.479 patients). These studies revealed a huge heterogeneity and varying cut-off levels of clinical markers, such as decreasing systolic or mean arterial blood pressure, increasing lactate levels or base deficits and vasopressor definitions. As a consequence, the septic shock related mortality varied extremely from 23% to 81%; (II) according to the applied Delphi study protocol a task force consisting of 19 experts in the field of sepsis-related research were asked to vote for different combinations of septic shock criteria being derived from the initial systematic review. The task force members were guided by three rounds of face-to-face meetings, email discussions and pretested sequential questionnaires. An agreement rate of at least 65% was regarded as sufficient to define expert consensus for a certain combination of septic shock criteria, whereas a lower agreement rate lead to re-evaluation or final elimination. Agreement was

achieved for the following three criteria being critical for septic shock: fluid resuscitation, need for vasopressors and serum lactate levels above or lower than 2 mmol/L; (III) 6 groups of different combinations of the above criteria were then transferred on a subset of the Surviving Sepsis Campaign (SSC) study cohort including 18.840 patients.

The most endangered patient group was defined as suffering from arterial hypotension, need for vasopressors and revealed serum lactate levels above 2 mmol/L. This group was associated with the highest in-hospital mortality rate of 42.3% compared to patients with persisting hypotension after fluids and vasopressor therapy with lactate levels lower than 2 mmol/L (mortality 30.1%) and compared to patients with lactate levels above 2 mmol/L being normotensive after fluids without vasopressors (mortality 25.7%).

Shankar-Hari and colleagues define septic shock being present in a subset of patients in which circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone (11). The new clinical criteria representing septic shock are the need for vasopressor therapy to maintain a mean arterial pressure of 65 mmHg or greater and having a serum lactate level greater than 2 mmol/L persisting after fluid resuscitation (11).

From a critical point of view, the main finding of the new definition of septic shock is the upgrading of serum lactate levels above 2 mmol/L. Being based on Shankar-Hari's comprehensive analyses, lactate levels turned out as a most robust and independent prognostic biomarker being associated with increased in-hospital mortality due to septic shock, moving serum lactate up to an independent criterion of septic shock itself. Formerly, lactate levels of 1.5 times higher than the local laboratory references defined metabolic acidosis besides an increased base excess, and characterized only one out of five organ dysfunctions defining severe sepsis (3,14). Furthermore, the distribution of data on patients with septic shock to five subgroups with defined combinations of diagnostic criteria lead to clear improvement and ordering of the initial varying range of mortality rates, demonstrating that the highest risk group revealed the highest in-hospital mortality rate of 42.3%.

Although the use of large data sets, systematic reviews and meta-analysis provides support for the new consensus definitions of septic shock, the study by Shankar-Hari and colleagues reveals several limitations concerning the information used to generate the updated criteria. Firstly, the data are almost all from adult patients in the United States, so the utility of the new definitions in pediatric populations or in other geographic regions, which are not high income countries, is unknown at present. Secondly, only the Delphi-derived variables were tested in multiple data sets to generate the proposed septic shock criteria, meanwhile variables such as tissue perfusion markers, acute alteration of mentation and numerous biomarkers reported in the literature (15), which could improve the proposed septic shock criteria were not included. Third, measurements of serum lactate levels are not available in resource-limited environments.

Shankar-Hari *et al*. chose an iterative approach for their comprehensive analyses constituting to the above described three analytic steps. The authors were dependent on available data being published on MEDLINE, including only observational and non-randomized studies with a varying number of patients and inclusion criteria. The major obstacle of sepsis-related research represents in the lack of large-scaled prospective randomized controlled trials comparatively evaluating combinations of different diagnostic and prognostic criteria for all stages of sepsis severity. Trying to alleviate this selection bias, which represents the most important disadvantage of such a comprehensive meta-analysis, the authors investigated the described three-armed analytic approach, which for sure increases their data quality, generalizability and clinical utility (11).

However, over the last decades there has been accumulating scientific evidence in the field of other clinical parameters and biomarkers apart from fluid resuscitation, vasopressor therapy and serum lactate. Clinical parameters, blood-derived or even molecular biomarkers, such as base-excess, central venous pressure, interleukin-6, procalcitonin, presepsin, or specific genomic and cellular alterations have been evaluated in the same kind of prospective non-randomized clinical studies with comparable numbers of patients with septic shock or are currently under investigation (15-19). However, these new biomarkers were not measured routinely within the 44 studies being included in the work of Shankar-Hari et al., whereas their increasing diagnostic and prognostic capacity in patients with septic shock was proven recently (15,18,19). Although the present definition for septic shock provides needed evolution and update of current knowledge of this syndrome, incorporating more information based on expression of specific new biomarkers, including cellular receptors, activation of intracellular pathways, and genomic alterations would be helpful. Such characterization would enable development of therapies targeted to specific septic patients, with the potential of remarkable improvements in

outcome.

Hopefully, the next iteration of these guidelines for sepsis will take full advantage of the rapidly advancing understanding of molecular processes that lead from infection to organ failure and death, so that septic shock can be defined as a separate disease being characterized by specific cellular alterations and linked biomarkers. Millions of patients developing this life-threatening condition would benefit worldwide from such an evolution.

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Footnote

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