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EDITORIAL

In sepsis, everything old is new again

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Physicians have recognised the clinical syndrome of sepsis from the time of Hippocrates and Galen [1]. Across the globe, in intensive care units, in emergency departments, in general medical and surgical wards, and even in the community, clinicians regularly diagnose patients with sepsis. However, attempts to define sepsis in a fashion that allows the syndrome to be reliably studied have proven more elusive. Some of these issues regarding the definition of sepsis are well illustrated in the INSEP study, the report of which was recently published in *Intensive Care Medicine*.

The SepNet investigators conducted a prospective cohort study in 133 ICUs in 95 hospitals across Germany [2]. More than 11,000 patients admitted to the participating ICUs were screened for sepsis using the definition of sepsis current when the study was conducted in 2013 [3]. This definition relied upon a suspicion of, or a proven source of infection and the presence of at least two of the four systemic inflammatory response syndrome (SIRS) criteria, to define a case of sepsis. Using these criteria, the SepNet investigators were able to define an incidence of sepsis within the ICU, as well as the prevalence of sepsis during the study period as well as demonstrating that patients with sepsis still have a high mortality rate, even in a high-income country.

The INSEP study highlights some of the issues that will play out as researchers and clinicians transition from the older SIRS-based definition of sepsis [4] to the new definitions suggested in Sepsis 3 [5]. For example, as a result of applying the revised criteria for septic shock, approximately 34 % of the patients who had previously been considered as having septic shock did not be meet the new threshold. Those that did meet this new threshold were noted to have a significantly higher mortality rate. In this sample of patients, in a structured clinical study, in a healthcare system without significant resource constraints, 5 % of patients did not have a lactate measurement and therefore may not meet all requirements for the new definition of septic shock. By straddling the old and the new definitions of septic shock, the SepNet investigators provide an initial insight into the changing landscape that will be brought about following Sepsis 3 [5].

There were some limitations to the use of the SIRS-based criteria for defining sepsis and septic shock, including the fact that SIRS occurs in patients without infection [6], and that some patients who have been classified by clinicians as having an infection associated with significant organ dysfunction did not meet the SIRS criteria [7]. Even with these limitations, the SIRS-based definition of sepsis has been utilised in clinical practice for almost a quarter of a century and, contrary to assertions of some [8], these criteria have enabled improvements in clinical practice, with the rapid detection of patients with life-threatening infection and the implementation of large-scale quality improvement programs that have led to improved outcomes for patients with sepsis worldwide [9–12]. While the new definition of sepsis as "Life threatening organ dysfunction caused by a dysregulated host response to infection" [5] appears to better encapsulate the current understanding of the pathophysiology, the operationalisation of this, as an increase in the Sequential (Sepsis) Organ Failure Assessment (SOFA) [13] score of 2 or more points may lead to problems in both the research and clinical arenas. One concern is the relative complexity of the SOFA score [13] which has six domains, each one with five separate cut-off levels, and the requirement for an arterial blood gas, and laboratory measurement of serum creatinine, platelet levels and bilirubin to calculate the SOFA score and thus make the diagnosis of sepsis. To add to this complexity, under the Sepsis 3 system, a baseline SOFA is required to ascertain whether the cases meet the two-point increase in the SOFA score that is needed to make the diagnosis of sepsis.

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There are other potential issues with the Sepsis 3 definitions. The increase in two points in the SOFA score was selected as the new operational definition because its predictive value for mortality was superior to the SIRS criteria [14]. However, there was no comparison with the previous severe sepsis definition, SIRS plus one organ dysfunction. It is notable that the SOFA scoring system is rarely used outside of the ICU. This may be a barrier to the widespread adoption of the SOFA-based operational definitions of sepsis in clinical practice. The requirement to wait for blood test results to determine if a patient meets the criteria for sepsis may delay the recognition and early intervention for patients with sepsis in clinical practice and will potentially delay recruitment into clinical trials that seek to assess the early management of patients with sepsis. One of the criticisms of the previous septic shock definition was that the heterogeneity of the criteria used to identify cases of septic shock was associated with a four-fold difference in the reported mortality [15]. Sepsis 3 may only serve to add additional confusion as the diagnosis of septic shock requires both the use of vasopressors for hypotension *and* a lactate measurement. Unfortunately, lactate is not widely sampled in septic patients, even in high-income countries. In the INSEP study lactate values were missing in 5 % of patients. Similar observational studies conducted in low- and middle-income countries may have even lower rates of lactate sampling. The Sepsis 3 definition of septic shock does not clearly define the status of patients who require vasopressors but in whom a lactate measurement is unavailable. There is clearly a risk of ongoing heterogeneity in the implementation of the definition of septic shock with the associated reported mortality hinging upon the availability of the lactate measurement. Studies that seek to enrol patients with septic shock may enrol different populations of patients depending on the availability of lactate measurements, with the potential for systematic bias with studies conducted in settings with low availability of lactate reporting lower mortality rates.

As the SepNET investigators have demonstrated, sepsis remains an ongoing concern for clinicians because of the relatively high incidence of the syndrome and the continued high mortality rates. The original sepsis definitions were a significant step forward, allowing the development of co-ordinated research efforts and widespread implementation of quality improvement projects that have led to a significant reduction in mortality over the last 25 years. The men who have delivered the new Sepsis 3 definitions have done so to take into account advances made in the understanding of the pathophysiology of sepsis over the subsequent decades. It may take some time to determine whether the new definitions lead to greater consistency for epidemiological studies and more timely management of patients with sepsis.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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