Commentary

Sepsis without SIRS is still sepsis

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The host response to infection is pivotal to the clinical features observed in a patient with sepsis. Indeed, Sir William Osler noted that "*Except on few occasions, the patient appears to die from the body's response to infection rather than from it*". Importantly, evidence of the host response, in the form of the systemic inflammatory response syndrome (SIRS), during a documented or suspected infection is required criteria for sepsis diagnosis. Currently, the consensus for sepsis diagnosis, based on expert opinion, requires evidence of SIRS based on two or more of the following signs, abnormalities in white blood cell count, fever or hypothermia, tachycardia or elevated respiratory rate. Unfortunately, these criteria have never been validated and therefore the diagnosis of sepsis may include a heterogeneous population of patients, potentially with various pathophysiology and different outcomes, who may also benefit from distinct therapeutics. However, the mechanisms of sepsis remain uncertain. Given the need to standardize sepsis diagnostics, the SIRS plus infection criteria was embraced by the clinical and research community.

To better our understanding of the SIRS criteria in defining sepsis, Kaukonen *et al.* (1) conducted a retrospective investigation of patient data from a database available to the Australian and New Zealand Intensive Care Society (ANZICS). Specifically, they were interested in assessing how well the requirement of at least two SIRS criteria performed in diagnosing severe sepsis. They hypothesized that requiring two criteria to establish SIRS has low sensitivity and validity such that populations of patients, who ultimately have severe sepsis and organ dysfunction, are improperly diagnosed. To test this hypothesis they decided to quantify the number and clinical outcomes of patients admitted to an intensive care unit (ICU), who had an infection and organ dysfunction but lacked two or more SIRS signs. Additionally, they tested if there was a difference in the risk of death between patients who had two criteria *vs.* one, as is expected if the requirement of two criteria to establish a diagnosis has validity.

Data was reviewed from 1,171,797 patients admitted to 172 ICUs over a 14-year period. Records for patients admitted with a potential or proven infection using APACHE III information were included. Severely septic patients were determined from diagnostic admission codes for infection and organ failure. SIRS criteria were applied to the study data and in-hospital mortality was assessed. Patients with severe sepsis were divided into those who had two or greater SIRS criteria (SIRS-positive severe sepsis) *vs.* those who had less than two SIRS criteria (SIRS-negative).

Infection and organ dysfunction were identified in 109,663 patients, accounting for approximately 10% of patient records. SIRS-negative patients represented 12.1% of severe sepsis. Overall, the SIRS-negative population was older, less ill and had better overall mortality. One in five SIRS negative patients had no SIRS criteria while an abnormal white blood cell count was the most common single SIRS criteria found in the SIRS-negative group.

When they examined if two SIRS criteria significantly represented a transition point in patient outcome, they found that each criteria incrementally increased mortality by 13%, with no additional change when the level of two criteria was reached. Hence, diagnostically there is no data to support the requirement of two SIRS criteria for defining severe sepsis.

This trial is important evidence supporting what many researchers in the area have speculated for decades, namely that the sepsis syndrome is not well understood. In particular, this report generates a number of interesting possibilities. First, sepsis may not represent a gradient of severity starting as simple infection and progressing to septic shock. Each presentation may be due to different mechanisms. This is important, as different therapeutics

may be necessary for different variations of disease. Secondly, patients with the same level of sepsis severity may also have different underlying pathophysiology resulting in similar clinical phenotypes. As an analogy, acute coronary syndromes are defined by the presence or absence of blood troponins in conjunction with EKG changes. However, if patients were only categorized by the presence of chest pain and a number of clinical signs such as tachycardia or tachypnea without any additional diagnostic tests, the result would be a heterogeneous population of heart attacks, pulmonary embolisms, pneumonias, aortic dissections and chest wall pain. Treating this group with the same therapeutic, for example thrombolytics, could lead to some patients improving and may even result in a positive clinical trial. Clearly, this approach would lead to major issues, with some patients experiencing no benefit, or worse, harm. The addition of troponins have altered the way heart attacks are classified, risk stratified and treated, leading to patient improvements. The key component of this success is the fact that the diagnostic test is a directly related to the pathophysiology. In other words, cardiac ischemia leads to myocyte damage causing a leak of the troponin protein into the blood. This type of diagnostic advancement is a critical component missing in sepsis research and clinical care.

The article by Kaukonen and colleagues (1) proves what we have known for many years that clinical information alone will miss individuals with even severe sepsis. This strongly suggests that we should move beyond just clinical indicators of sepsis, moving into the realm of personalized or precision medicine to help include individuals who would otherwise be missed using clinical data only. Over the last 10-15 years, there have been many advances in the use of precision medicine for diagnosis and prognosis of disease (2). Although originally used for cancer diagnosis, prognosis and assisting in therapeutic decisions, it is now being used for a host of other diseases including sepsis (2). This type of investigation looking for phenotypic clusters or endotypes has yielded important information in sepsis, whether it is using just clinical data to determine phenotypes (3), using genomics data in children (4), using metabolomics data in adults (5,6) or children (7,8), or using cytokine-based risk stratification in adults (9,10).

Thus, there are tools being developed today to detect septic patients who may not show all the clinical features of sepsis, to help subclassify endotypes or phenotypes of sepsis for prognosis and help direct therapy or at least help in sepsis therapeutic research. There is great promise in this direction for the future of sepsis diagnosis and treatment.

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Footnote

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

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