CRITICAL CARE

COMMENTARY

Unrevealing culture-negative severe sepsis

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See related research by Phua et al., http://ccforum.com/content/17/5/R202

Abstract

Sepsis involves a wide array of sources and microorganisms, only a fraction of which are microbiologically documented. Culture-negative sepsis poses special diagnostic challenges to both clinicians and microbiologists and further questions the validity of sepsis definitions.

According to the 2012 Surviving Sepsis Campaign, sepsis is a 'systemic, deleterious host response to infection', characterized as 'suspected or documented', which can lead to severe sepsis as defined by an 'acute organ dysfunction secondary to infection' [1]. Central to this definition is the presence of an infectious process, which differentiates sepsis from other causes of severe inflammation. However, only about 40 to 60% of patients with severe sepsis or shock have a microbiologically documented infection. In a substantial proportion of patients, sepsis will remain only clinically suspected, raising the possibility of a non-infectious cause (that is, of severe systemic inflammatory response syndrome).

In this issue of *Critical Care*, Phua and colleagues reported on a large prospective cohort study of patients (n = 1,001) presenting with severe sepsis on ICU admission and compared the characteristics and outcomes of culture-negative versus culture-positive episodes [2]. Their main findings were that culture-negative sepsis occurred in 41.5% of the cohort, was associated with female gender, less comorbidities or organ failures, and more lung infection (74.5% vs. 59.9%) than their counterparts, and included lower serum procalcitonin levels and ICU mortality; however, identification of a pathogen was not independently associated with mortality in adjusted analyses.

Sepsis is a highly heterogeneous syndrome, affecting patients with various underlying conditions, and involving an array of infectious sources and microorganisms. Although the characteristics of infection were retained in attempts to better characterize sepsis through the PIRO (predisposition, infection, response and organ failure) concept [3], data are conflicting regarding their impact on outcome of patients [4,5]. The observations by Phua and colleagues [2] tend to confirm earlier epidemiological studies showing that patients with or without microbiological documentation were at similarly high risk of death [6-8]. Despite this apparent lack of influence on outcome of patients, nondocumented sepsis challenges both our understanding of sepsis and management strategy. Indeed, the highest possible rate of documentation is desirable, as this would allow for a more targeted therapy in many patients, possibly avoiding unnecessary prolonged administration of broad-spectrum antibiotics [1].

Why should patients presenting with a clinical syndrome of severe sepsis have nondocumented infection? Firstly, patients may have received antibiotics prior to the onset of organ dysfunction, thus obscuring conventional cultures. For example, patients with community-acquired respiratory tract infection often receive antibiotics before ICU admission, and not surprisingly Phua and colleagues report that respiratory tract infection was associated with culture-negative sepsis [2]. They did not, however, record information on prior antibiotic treatment, and this hypothesis cannot be substantiated.

Secondly, the diagnostic workup may be insufficient or incomplete, which does seem to apply to the current study because patients with positive or negative cultures appeared to have a similar number of samples taken [2].

A third possible explanation is sepsis caused by unusual organisms that are difficult to identify in routine practice. Conventional microbiological methods frequently fail to indentify a microorganism due to various reasons related to technical issues or intrinsic to the microorganism. Promising studies using PCR methods showed that microbial DNA could be rapidly detected in blood of septic patients [9], and could detect potentially

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significant bacteria and fungi not retrieved from blood culture [9,10]. In a recent meta-analysis, the overall sensitivity and specificity for such methods to detect bacterial or fungal DNA were 0.75 and 0.92 [11]. However, even in patients with severe sepsis, the rate of positive blood PCRs was only 34.7% [9]. Patients with culture-negative sepsis described by Phua and colleagues [2] having lower serum procalcitonin levels than others also suggests that at least some of them may have had severe viral infections. Indeed, a recent study showed that approximately one-third of ICU patients with severe pneumonia had viruses found by PCR assays on nasopharyngeal swabs or bronchoalveolar lavage fluid [12].

A fourth explanation is that some patients having culture-negative sepsis might actually have a noninfectious cause for the clinical syndrome. Indeed, Phua and colleagues report a few (n = 18) patients with culture-negative sepsis having an unknown source of infection [2], raising the question of whether these patients with severe systemic inflammatory response syndrome truly had an underlying infection. Indeed, numerous differential diagnoses of severe sepsis have been previously described, including various tissue injuries (for example, surgery/trauma, ischemia, and so forth), metabolic disorders (for example, thyroid storm), adverse effects of drugs, inflammatory diseases (for example, systemic lupus erythematosus, DRESS syndrome, and so forth), malignancies and subarachnoid hemorrhage [13,14]. One could reasonably hypothesize that some of these mimickers of sepsis accounted for some of the culture-negative severe sepsis in the study from Phua and colleagues [2].

Although the study by Phua and colleagues leaves several questions unanswered, it highlights the persisting gaps in our current understanding of sepsis and provides insightful information on the clinical features of nondocumented sepsis [2]. In the future, clinicians should strive to formalize strategies for managing such patients, probably combining clinical findings, imaging, and conventional bacterial cultures, but also the use of biomarkers and perhaps multiplex PCR-based assays to enhance our diagnostic ability.

Abbreviation

PCR: Polymerase chain reaction.

Competing interests

NdP and KR declare that they having no competing interests. CB-B was an investigator in a study on the Septifast® test in septic patients, sponsored by Roche-Diagnostics [10].

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