Intensive Care Med (2016) 42:1851–1853
DOI 10.1007/s00134-016-4603-1

EDITORIAL

Sepsis: find me, manage me, and stop me!

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Introduction

Sepsis is always in our mind when we take care of severely ill patients. It is a cause of admission to the ICU, and a cause of clinical worsening of many of our patients. Although this syndrome is now well known, even among members of the public, it continues to kill, with an estimated 5.3 million deaths annually, increasing year on year [1].

New definitions of sepsis

Sepsis could be defined as an overreaction of the immune system with organ dysfunction related to infection. The old definitions of sepsis emphasized the role of systemic inflammatory response syndrome (SIRS) as a key element of the sepsis definition. However, SIRS is clearly non-specific and insensitive and has, hopefully, been abandoned as a key criterion of sepsis [2, 3].

The recent Sepsis-3 definition, proposed by an ESICM/SCCM taskforce, has only two grades: sepsis and septic shock. The members of the taskforce suggested that sepsis should be considered in the event of an infectious process associated with an increase in SOFA score of two points or more. Patients with septic shock would be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater, and serum lactate level greater than 2 mmol/l (>18 mg/dl) in the absence of hypovolemia [4].

This simplification is welcomed. However many problems in the wording, the cut-off points used, and the variables chosen have not been solved. Indeed, the cause of organ dysfunction and/or shock might not be directly related to infection. Moreover, this definition does not integrate the chronology of the infectious process, the chronology of the organ dysfunction, and the obvious differences in pathophysiology related to innate immunity, immune status, comorbid illnesses, and characteristics (source, micro-organism, inoculum) of the infection [5].

Sepsis: a change in epidemiology

The increases in incidence of sepsis and septic shock are probably multifactorial, partly due to a rising number of individuals at particularly high risk, such as the elderly, those with comorbid conditions, and the immunocompromised. There may also be over-registration of this syndrome. Indeed, the incidence of hospitalizations with sepsis codes has risen dramatically, while hospitalizations with the corresponding objective clinical markers have remained stable or decreased. Coding for sepsis has become more inclusive, and septicemia diagnoses are increasingly being applied to patients without positive blood cultures [6].

Despite a decrease in the mortality rate [7] of diagnosed sepsis reported by many studies, the dramatic increase in incidence has resulted in a rise of the absolute number of deaths [8, 9].

The cause of the decrease in mortality rate is probably due to earlier (over-)detection, earlier treatment of infections, and appropriate symptomatic treatment of tissue hypoperfusion. The early goal-directed therapy concept developed by Rivers et al. had a major impact on patient care and probably saved many lives. The fact that many RCTs, reproducing the original intervention of Rivers et al. [10], have failed adds spice to the situation [11]. We are convinced that we are making progress in improving the use of non invasive techniques and avoiding adverse events related to our care [12, 13], but we are unable to demonstrate which components of our therapeutic strategy are improving patients' outcomes.

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Why are there no specific therapies for sepsis?

Sepsis pathophysiology is extremely complex. Moreover, the patients are heterogeneous, with different sites of infection, different failing organ systems and varying co-morbidity, on top of their inborn and acquired genetic variability. Furthermore, sepsis care is complex; patients are cared for by many different healthcare professionals in different settings, and care differs among healthcare systems and countries. Urgent interventions are needed, and those we give are mainly based on physiology and tradition; many drugs are used off-label. In addition, it is very difficult to differentiate benefits and harms of interventions from the natural trajectory of this complex disease process, which in itself generates many adverse events. Together with the ethical challenges of managing patients who are unable to consent, these are the barriers to designing development programs for potential new therapeutic interventions.

All these elements may have introduced important random variability in the effect of interventions and may have largely decreased the chance to demonstrate that a new treatment is effective in reducing mortality [14, 15]. Furthermore, the superiority margins of the mortality risks that have been used in these heterogeneous populations may not be plausible [16].

How can we improve sepsis research?

In medical science in general, the design, conduct, and reporting of both commercial and academic research programs can be improved in all aspects, from the basic science to the final testing in trials [17]. Regarding clinical sepsis research, we need large cohort studies of unselected patients recruited in different settings to improve pheno- and genotyping, in order to guide the design of trials toward the right patients for the right interventions assessing the right outcomes. In addition, alternative models for trial design, including adaptive inclusion and conduct, may have advantages over traditional fixed, parallel-group designs [18]. Currently, collaborative trial groups in Europe, Australasia, and North America are very successful, and other groups in South America, Asia, and Africa are becoming more active. Such collaborative efforts are essential for clinical research to globally improve sepsis care. The exploitation of differing models for collaboration between academia and industry should be driven forward to increase the likelihood of success and the effectiveness of drug development programs. Increased interaction with patients, relatives, healthcare professionals, and society will be important to increase the overall acceptance of sepsis research and to improve the measurement of patient- and society-relevant outcomes.

Conclusion

In this issue of *Intensive Care Medicine*, many of these points are addressed extensively in editorials, short pieces, reviews, and original articles. Despite the many uncertainties, we are making progress in sepsis care. We now need to categorize pathophysiological and clinical phenotypes and genotypes in detail to offer optimal and timely care.

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Received: 17 October 2016 Accepted: 19 October 2016
Published online: 24 October 2016

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