EDITORIAL

Focus on sepsis

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Despite extensive research and several thousands of publications each year, sepsis remains a major challenge to patients, clinicians and healthcare systems globally [1]. In this context, recent research provided new insights aiming at improving care of these patients (Fig. 1).

Present strategies and future research to improve sepsis care

The use of a single biomarker to diagnose or characterize patients or to assess their response to intervention in a complex disease as sepsis is probably both too simplistic and illusory, as has been shown for lactate levels [2]. The more detailed systemic inflammatory response syndrome (SIRS) criteria, combining clinical and biological data, were also challenged. Using a Bayesian network model, Zampieri et al. [3] suggested that the performance of this screening tool may differ depending on the population, the infectious source and other confounders, and it should therefore be used with caution.

Large randomized controlled trials (RCTs) in sepsis continue to be performed [4, 5]. However, decades of neutral clinical trials forced us to realize that sepsis is a complex syndrome encompassing a vast, multidimensional array of clinical and biological features and that all patients should probably not be treated the same way. Artificial intelligence may be a valuable tool to achieve personalized treatment. In this regard, Seymour et al. [6] used machine learning methods in a large cohort of Sepsis-3 patients to derive and validate four clinical phenotypes (α , β , γ and δ) with different biological and clinical data and showed a correlation with host–response patterns and mortality. Komorowski et al. [7] used reinforcement learning in the MIMIC-III database to derive

an “artificial intelligence clinician” that advises about optimal fluid volume and vasopressor dose and showed, in the eICU database, that patients receiving the treatment suggested by the artificial intelligence clinician had the lowest mortality. Geri et al. [8] made a further step toward clustering of patients, which potentially may be used for more personalized hemodynamic support in septic shock patients. The authors collected data from transthoracic echocardiography performed within the first 12 h of septic shock diagnosis and after initial resuscitation with fluids and vasopressors. They identified five cardiovascular phenotypes (the “well-resuscitated” patients, those with left ventricular systolic dysfunction, a hyperkinetic profile, right ventricular failure or sustained hypovolemia) and suggested that these might change the management by allowing more personal and adequate hemodynamic support optimization. Whether a specific cardiovascular phenotype-based resuscitation algorithm improves patient outcome remains to be evaluated.

As far as sepsis treatment is concerned, a core task for intensivists is hemodynamic resuscitation. Although norepinephrine is recommended as the first-line vasopressor agent using a mean arterial pressure target of at least 65 mmHg, the optimal choice, timing, dose and individualized pressure target remain subject of debate [9, 10]. The use of non-catecholaminergic vasopressors was therefore proposed to spare catecholamines and reduce adverse events, such as tachyarrhythmias and excess vasoconstriction, resulting in tissue ischemia. Vasopressin use is highly variable among countries (from 0 to 20%). An individual patient data meta-analysis of 4 RCTs (1453 patients) aimed at assessing its effect in septic shock [11]. Compared with other vasoactive substances, vasopressin had no obvious effect on 28-day mortality in general and in predefined subgroups (baseline kidney injury severity, baseline lactate, baseline norepinephrine requirement and time to study inclusion). On the other hand, vasopressin appeared safe, although its side effects differed from those of

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norepinephrine (more digital ischemia and fewer arrhythmias).

Sepsis-induced myocardial dysfunction is also an interesting resuscitation target. While dobutamine is the recommended inotropic agent, its deleterious side effects—likely increased risk of myocardial ischemia and arrhythmias—are of concern. In a subgroup analysis of the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) randomized trial [12], Antcliffe et al. evaluated the effects of levosimendan, a calcium-sensitizing drug with inotropic and vasodilating properties in patients with biochemical evidence of cardiac dysfunction. Despite its capacity to increase cardiac output and appealing anti-inflammatory and anti-oxidative properties, levosimendan, added to standard therapy, failed to improve severe organ dysfunction or mortality in these patients. But hemodynamic optimization is not the only target in septic shock.

Another component of the treatment of patients with sepsis is fever management [13]. Whether fever should be treated in critically ill patients remains a matter of debate. The REACTOR trial, a feasibility trial in preparation of a larger RCT, showed that active temperature control reduces body temperature compared with ordinary temperature management in critically ill patients with fever and high illness severity.

Among patients who survive the initial acute phase of sepsis, a proportion will die in the weeks or months thereafter due to secondary complications. Secondary infections like reactivation of latent viruses or secondary hospital-acquired infections may occur because of a compensatory anti-inflammatory response following the initial SIRS resulting in postseptic immunosuppression. Blockade of programmed cell death protein (PD-1) and its corresponding ligand (PD-L1) may reverse T cell exhaustion-mediated immunosuppression in patients with sepsis by restoring some immune cell effector functions and thus may improve survival [14]. In this context, a phase 1b study assessed the safety of nivolumab, an anti-PD-1 antibody that binds to PD-1 on T-cells, in participants with sepsis and low lymphocyte count [15]. The authors indeed showed that the administration of nivolumab did not result in serious adverse events and did not worsen fever, shock or other signs or symptoms of cytokine storm. These results may pave the way for new studies on inhibitory immune checkpoint molecules like in cancer patients.

While the development of ICU therapy continues and entails new hopes [16], it also represents ethical challenges requiring interactions between the different stakeholders. Nurses play a major role in the early identification, alert and management of sepsis. Four

international critical care organizations therefore issued specific guidelines for nursing care based on the revised Surviving Sepsis Campaign guidelines [17] to raise the awareness of the therapeutic emergency of septic shock.

Finally, postsepsis rehabilitation including prevention of long-term morbidity has been identified as one of the emerging health issues. Cardiovascular disease after sepsis, potentially related to inflammation and coagulation, appears to be a leading cause of hospital readmission [18]. Better organization of long-term follow-up may be warranted.

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Compliance with ethical standards

Conflicts of interest

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