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FOCUS EDITORIAL

Focus on sepsis: new concepts and findings in sepsis care

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. It affects over 30 million people worldwide and represents one of the top causes of death. The Surviving Sepsis Campaign (SSC) guidelines undoubtedly improved the process of care and outcomes in the past decade. The last version of the guidelines was recently published in the journal [1]. As key messages, the Surviving Sepsis Campaign recommends "antimicrobial therapy in the first hour", and "aggressive fluid resuscitation during the first 24 h of management". Hypotensive patients with lactate level of 4 mMol/L or more should receive an immediate crystalloid of more than 30 mL/kg within 3 h and repeated bolus as needed.

Translation of the guidelines to resource-limited settings is hampered by the limited availability of skilled staff, equipment, and laboratory support, compounded by infrastructure and logistical challenges. Subsequently, recommendations relating to core elements of general supportive care for patients with sepsis in these settings have been developed [2]. However, evidence of their efficacy in resource-limited settings are lacking and may differ from trials conducted in other settings.

As a recent example, Andrews et al. [3] randomly assigned patients with sepsis and hypotension in Zambia to be treated using either (1) an early resuscitation protocol including intravenous fluid bolus administration with monitoring of jugular venous pressure, respiratory rate, and arterial oxygen saturation and treatment with vasopressors targeting mean arterial pressure ($\geq$65 mmHg) and blood transfusion (for patients with a hemoglobin level $<$7 g/dL), or (2) usual care in which treating clinicians determined hemodynamic management. Paradoxically the early resuscitation protocol increased hospital mortality from 34/103 (33%) to 51/106 patients (48.1%) [between-group difference, 15.1% (95% CI 2.0%–28.3%)].

Even in high income countries, gaps in the data frequently exist, leading to insufficient clarity on many elements of sepsis management and precluding recommendations on many topics (Table 1). In a retrospective analysis of a large multicenter US database, Marik et al. questioned the impact of a large fluid loading after initial resuscitation on prognosis [4]. They evaluated 35,135 patients with a diagnosis of severe sepsis or septic shock, and identified that a low volume resuscitation (1–4.99 L) was associated with a reduction in mortality of $-$0.7% per litre (95% CI $-$1.0%, $-$0.4% $p=0.02$). However, in patients receiving high volume resuscitation (5 to $\geq$9 L), the mortality increased by 2.3% (95% CI 2.0, 2.5%; $p=0.0003$) for each additional liter above 5 L. This result strongly questioned the dogma of an extra-large fluid loading during the first hours. Another large epidemiological study in the emergency department was not able to demonstrate a survival benefit of an increase of the amount of fluid received in case of severe sepsis and septic shock [5]. Finally, severe weight gain in patients with shock was independently associated with increased mortality in patients who survived the first 3 days [6].

These results altogether suggested that fluid overload is rapidly deleterious and that fluid loading after initial resuscitation should be lower than usually recommended, and guided not only on macrocirculatory, but also microcirculatory parameters.

In an attempt to determine priorities for research within the field of sepsis, the SSC created a new research committee which came up with a list of six questions to be answered in the near future [7], that were quite consistent with priorities set up by another recent

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Table 1 Uncertainties in sepsis

1.	Optimal amount of initial fluids in sepsis-induced hypoperfusion
2.	Ideal clinical parameters and endpoints for volume resuscitation
3.	Time-to-initiation of empirical antibiotics in patients with sepsis without shock
4.	Role of rapid microbiological diagnostic tests in the management of sepsis
5.	Selection of patients for treatment with adjunctive therapies
6.	Efficacy and feasibility of treatment recommendations in resource-limited countries

international expert consensus [8]. Among the top six priorities, five included the ICU stay and included scoring/identification, appropriate therapy of infection, fluids and vasoactive agents, and adjunctive therapy.

Some recent developments are targeting the adjunctive therapy. Several extracorporeal devices have been developed to remove endotoxin, cytokines and other sepsis mediators from the circulation. However, the studies evaluating these devices have been limited and heterogeneous; therefore, further research is warranted [9]. Another potentially interesting therapeutic target in sepsis might be the blood coagulation, in order to counteract excessive coagulation activation. In that perspective, thrombomodulin, which combines anticoagulant and anti-inflammatory effects, represents a promising therapeutic option [10]. Interestingly, in the different clinical trials that evaluate this drug, the rate of bleeding complications was generally relatively low, suggesting that despite major coagulation disorders, anticoagulation of patients with sepsis is quite safe. Thrombomodulin trials have so far allocated anticoagulant treatments to a selected subset of septic patients on the basis of coagulopathy criteria. Following encouraging results of a phase II trial, a larger Phase III study with 800 randomized patients (SCARLET trial, EudraCT number 2012-002251-42) was recently completed, and its results are pending.

In before-after studies, educational and training programs are able to improve the appropriateness of antimicrobial therapy in sepsis [11]. These initiatives clearly improved the process of care, but have not demonstrated any positive impact on outcome. The reduction of the time before initiation of antimicrobial therapy by means of a multifaceted intervention was tested in a cluster-randomized trial involving 4183 patients with sepsis or septic shock [12]. Although the risk of death increased by 2% per hour of delay of the antimicrobial therapy start, and by 1% per hour of delay of the source control, the intervention was not able to reduce neither the median time to antimicrobial therapy (1.5 vs. 2.0 h, $p = 0.41$), nor the mortality. One possible explanation is that immediate antimicrobial therapy may be instrumental in septic shock but of a lesser importance in sepsis, as suggested by two large epidemiological studies [5, 13]. The absence of benefit of early antimicrobial therapy may have been related with the diagnostic uncertainty regarding sepsis and the possible harm associated with unnecessary antibiotics such as toxic or allergic reactions and emergence of bacterial resistance.

The management of multidrug-resistant bacteria (MDRB) in the intensive care setting is more than ever challenging due to their sustained diffusion in healthcare settings and, for some of them, in the community setting [14]. The control of MDRB requires antibiotic stewardship programs that should include faster diagnostic spanning antibiotic resistance, in addition to pathogen identification, and a better assessment of pharmacokinetics parameters. New antibiotics active on MDRB (especially Gram-negative rods) are also urgently needed [15].

The resident microbes of the gut serve essential metabolic and immunomodulatory functions. Profound alterations of richness and diversity of the gut microbiota have been described in ICU patients largely due to antimicrobial exposure [16], but also to many other drugs including antiviral and antiprotozoan therapies [17]. These alterations may favor the emergence of pathogenic bacteria (so called pathobiota) and may contribute to immune dysregulation and multiple organ failure in sepsis.

In a recent cohort, Freedberg et al. showed that at admission in ICU, the intestinal dominance of *Enterococcus* as determined by 16S profiling was associated with a higher risk of infections and increased mortality [18]. In addition, they also observed that the detection of reads assigned to *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* spp. and *Clostridium difficile* was associated with a higher risk of infections caused by those bacteria. While assessing the risk of infections caused by MDRB using clinical parameters remains unsatisfactory [19], the findings of Freedberg et al. suggest that considering specific microbiological traits of the patients could be of help.

Hence, the control and modulation of the intestinal microbiota is a promising approach. As an unaltered microbiota could be associated with a better outcome in ICU patients, some drugs aiming at preventing the impact of antibiotics on the intestinal microbiota could be made available in the coming years, such as gut-delivered active charcoal [20] or recombinant beta-lactamases.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interests.

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