Editorial

Life ain't no SOFA—considerations after yet another failed clinical sepsis trial

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Sepsis and septic shock account for a considerable amount of ICU admissions with high morbidity and mortality rates. Thus, sepsis and septic shock represent a major burden to healthcare systems worldwide (1-3). Importantly, the incidence of sepsis is rising which may be due to aging populations, advances in medical treatment, and increased medical awareness (2). Nevertheless, despite its paramount importance, the ICU community seems insecure in regard to both definition and design of effective therapeutic approaches for this complex heterogeneous syndrome.

The terms "sepsis" and "septic shock" embrace all clinically apparent forms of organ dysfunction induced by a dysregulated host response to severe infection. Initially, respective terms were designed to facilitate clinical recognition, prognostication, and treatment (3). Although recent coining of the new ("sepsis-3") definitions may provide benefits regarding e.g., recognition at the bedside, it may not overcome the universal problem that arises from the biological diversity of the host response and the lack in disease specificity when patients with "sepsis" are assessed. E.g., recent mounting data convincingly demonstrates that there is no universal host response to sepsis and that e.g., patients with acquired sepsis-associated immunosuppression may need tailored treatment that may substantially differ from that of patients in the hyper-inflammatory early phase of the disease (4-7). This resulting heterogeneity of patient populations may at least partially explain the continued failure of recent large-scale clinical sepsis trials.

The LeoPARDS trial, recently published in *the New England Journal of Medicine* (8), must most likely be interpreted in this context. In fact, compared to traditional inotropic drugs, levosimendan is a calcium-sensitizer with positive lusitropy that increases myocardial contractility at (when compared to other inotropic drugs) reduced myocardial oxygen consumption. Few previous smaller trials showed direct beneficial hemodynamic and anti-inflammatory effects (8) for levosimendan, with a small meta-analysis showing a mortality benefit in severe sepsis/septic shock (9). Thus, hopes were high for LeoPARDS.

Gordon and colleagues conducted a double-blind, randomized, multicenter clinical trial including 516 patients in 34 ICUs in the United Kingdom. The authors investigated whether adjunctive (24-hour-) treatment with levosimendan would reduce the severity of organ dysfunction [assessed as mean sepsis-related organ failure assessment (SOFA) score; primary endpoint] in adults with early septic shock (8). Over the ICU stay, mean daily SOFA scores did not differ between the two groups [6.68±3.96 (levosimendan) *vs.* 6.06±3.89 (placebo group) (mean difference 0.61; 95% CI, –0.07 to 1.29; P=0.053)] (8). Mortality at 28 days did not differ between the two groups also [34.5% in the levosimendan group *vs.* 30.9% in the placebo group (mean difference, 3.6 percentage points; 95% CI, –4.5 to 11.7; P=0.43)]. In the levosimendan group, patients requiring mechanical ventilation at inclusion were less likely to be weaned from MV successfully within

28 days (hazards ratio 0.77; 95% CI, 0.60–0.97; P=0.03). Moreover, in the levosimendan group, mean arterial blood pressure was lower, higher doses of vasopressors were needed, and more arrhythmias observed when compared to placebo (8).

So is LeoPARDs just another one trial in a large series of failed clinical sepsis investigations? When looking at the data, it seems apparent that the inclusion criteria in LeoPARDS were based on the 1992 international consensus definitions for severe sepsis and septic shock, which incorporate the systemic inflammatory response syndrome (10). Thus, LeoPARDS and other previous clinical sepsis trials included a rather heterogeneous group of patients with differing sources and sites of infection, different underlying states of the hosts' response, and different severities (8).

Moreover, inclusion of "septic shock" patients currently relies on the need for vasopressor treatment to correct hypotension after adequate fluid resuscitation (8,10). In most clinical trials on septic shock, mean arterial blood pressures below 65 mmHg served as inclusion criterion. This issue seems not resolved in the new sepsis-3 definitions for septic shock (11) and recommended targeted mean arterial pressures may lack a clear-cut basis (12), may not reflect the state of end-organ tissue perfusion (11), and inotropes treatment to achieve such targets may per se have negative effects on outcome (12-14). Moreover, all inotropes and vasopressors suffer from substantial side effects and the preferable substance is unknown (14,15). Optimal hemodynamic targets are thus unknown and should most likely be set in the light of the individual patient and the underlying medical condition. In addition, after two decades of adherence to an early goal directed approach (16), large multicenter randomized controlled trials (RCT) could not verify the benefit of this practice (17-19) and no consensus exists on which type of fluids should be used for resuscitation (3). In fact, "standard" treatment of septic shock is complex, involves fluid resuscitation, vasopressors, inotropes, various interventions for source control including anti-microbial drugs, and in severe cases, organ-support therapy such as mechanical ventilation or renal replacement therapy. Thus, the term "septic shock" encompasses highly variable degrees of disease severity, introducing yet another source of heterogeneity.

In LeoPARDS (8), this may become apparent in several ways. First, based on baseline lactate levels [levosimendan group 2.2 (interquartile range, 1.4–3.5) mmol/L *vs.* placebo group 2.3 (interquartile range, 1.5–3.9) mmol/L] (8), the degree of hemodynamic shock does not seem very severe generally. However, specific selection of patients at high risk for death within a given group of septic shock patients did previously demonstrate treatment benefits (11). An example is the success of prone positioning in acute respiratory distress syndrome (ARDS), when it took several larger trials to define the subgroup of ARDS patients that benefit from this treatment strategy (20). Second, multiple interventions in the control group can obscure true effects of a given intervention. Gordon and colleagues provide an excellent characterization of the respective control group (8). Still, control groups reporting RCT of septic shock may often fail to adequately portray control groups and few emerging calls advocate standardized reporting (11,21).

In conclusion, the field of sepsis faces dynamic times. After a series of failed interventional large scale RCTs including LeoPARDS, optimum treatment strategies remain largely unknown (22). The new sepsis-3 definitions (23) may most likely not overcome the underlying problem of heterogeneity. Thus, the "sepsis syndrome" calls for clinical trials performed in more specific patient subgroups while keeping the etiology, the host response, and respective disease severity in mind (5,24,25). Personalized medicine aims to improve patient outcome via this concept and should also be pursued in critical illness and sepsis.

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Footnote

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

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