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EDITORIAL

Refining trial design in sepsis management: balancing realism with ideal outcomes

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Freund and colleagues conducted a large, multicenter, binational stepped wedge cluster randomized clinical trial investigating the impact of a 1 h sepsis bundle in emergency departments in patients with suspected sepsis [1]. Their findings demonstrated that this intervention did not improve 28-day in-hospital mortality compared to standard care. While some may view this as another addition to the list of negative sepsis trials, Freund et al. deserve commendation for executing such an extensive trial within a few months, highlighting the pragmatic nature of its design. In addition, this trial warrants attention and discussion, especially considering the significant challenge of designing future clinical trial in sepsis.

(1) Tailoring treatment to individual needs

The complexity and diverse presentations of sepsis have long suggested that it is unlikely a one-size-fits-all intervention will be effective. A more nuanced approach, potentially involving the combination of synergistic therapies or adopting a strategy like the 1 h bundle, might offer better results. While the 2021 Surviving Sepsis Campaign recommended antibiotic administration within a 3 h window for suspected sepsis cases [2]. Freund et al.'s trial [1] assessed the efficacy of a multifaceted strategy—considering the severity of the patient—which included microbiological cultures, lactate measurement, broad-spectrum antibiotic administration, and, when necessary, crystalloid intravenous fluid resuscitation, all within 1 h.

(2) Temporal dynamics of intervention

However, as assessed by this trial, the discrepancy between ideal timeframes recommended by guidelines and real-life implementation highlights the challenges in translating evidence into practice. Despite efforts to initiate interventions promptly, Freund's trial [1] revealed significant delays, questioning the feasibility of strict timeframes. Only 63.5% of patients received antibiotics within 1 h, and 73.6% received fluid resuscitation within 1 h when indicated, despite the trial's stepped wedge cluster randomized design intended to facilitate this. The low compliance with the bundle and minimal clinical differences between arms may have diminished the likelihood of detecting a significant effect.

In addition, the initiation window of 1 h post-presentation contrasts with one of the trial's inclusion criteria permitting assessment of eligibility within 6 h of triage, potentially elongating the assessment-to-initiation interval to 7 h. This prompts a reevaluation of the concept of time-based intervention. Another example is the SCARLET trial [3], which experienced enrollment difficulties leading to a prolonged inclusion period. As a result, 21% of the 800 patients no longer had disseminated intravascular coagulation by the time they received treatment, due to the excessively large time-window for enrollment.

(3) Population selection challenges

One of the problems with very short time-window to enroll patients is that patients must be assessed quickly, and their severity might be underscored, or the diagnosis of sepsis inappropriate, leading to enrollment of patients without confirmed sepsis. In the present trial, over 70% of the patients finally did not have a sepsis (346/485 = 71% had a Sequential Organ Failure Assessment (SOFA) score < 2 points

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at baseline, and 279/387 = 72% in the intervention group). Many patients may, therefore, have received unnecessary treatments, with for example more than 15% of the patients receiving undue antibiotics, which is likely to be deleterious [4]. This is the reason why the 2021 Surviving Sepsis Campaign recommended that the patients with suspected sepsis should receive antibiotics within a 3 h time-window [2], preferring more reliable diagnosis to rapidity in patients without shock.

On the other hand, while targeting a very specific population might lead to inclusion of a homogeneous population (for example sepsis with sepsis-induced coagulopathy, like in SCARLET trial [3]) and allow targeted and personalized intervention, it may also lead to the observed recruitment difficulties and prevent generalizability of the results. Striking a balance between inclusivity and specificity in patient selection is therefore crucial to ensure both generalizability and relevance of trial findings in real-world settings.

(4) Choosing appropriate endpoints

While 28-day in-hospital mortality is a commonly used endpoint in sepsis trials, it may not capture early treatment responses or account for confounding factors such as secondary infections or other late complications. Consideration of alternative endpoints, such as day 7 mortality or composite outcomes, could provide a more comprehensive assessment of intervention efficacy. In addition, alternative endpoints such as resolution of disseminated intravascular coagulation (DIC) in septic shock or improvement in organ failure (SOFA) could offer complementary perspectives on treatment efficacy. While other endpoints could be chosen, like resolution of disseminated intravascular coagulation, organ failure (SOFA) improvement, composite outcomes might also be preferred.

(5) Considerations on trial design

The trial's premature conclusion and underpowered sample size may raise concerns about its ability to detect statistically significant differences between groups. In addition, the discrepancy between the anticipated mortality rates and observed outcomes, but also the expectation of an important effect of the bundle (expected relative risk reduction of 38% and absolute risk reduction of 10%) underscores the complexities of sepsis management and the need for realistic outcome expectations in clinical trials.

In conclusion, while the trial by Freund et al. [1] may not have demonstrated a significant improvement in outcomes, its findings prompt valuable reflections on the challenges and complexities of sepsis management. Addressing these complexities necessitates a nuanced approach, balancing pragmatic considerations with the pursuit of ideal outcomes as well as strategies to account for patient and disease heterogeneity and increase the efficiency of trial conduct [5].

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Declarations

Conflicts of interest

JH has received honoraria for lectures from Diagnostica Stago, Pfizer PFE France, Sanofi Aventis France, Inotrem, MSD, Shionogi and Asahi Kasei. PP has received honoraria for lectures from Gilead, Pfizer, Mundipharma, MSD and is part of the Advisory board from Biocodex, Gilead. SJ reports receiving consulting fees from Drager, Medtronic, Mindray, Fresenius, Baxter, and Fisher & Paykel.

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