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Rethinking caution: a critical appraisal of extracorporeal blood purification in sepsis

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Dear Editor,

We thank Stahl and colleagues for their commentary [1] on our paper [2]. Their observations provide an opportunity to further analyze and discuss key aspects of extracorporeal therapies in sepsis, as well as recently emerging data.

Stahl expresses concerns and disagreement with our conclusions on "considerations for current clinical practice," citing potential harm and suggesting that extracorporeal therapies should be used only in clinical studies. Their position is primarily based on two distinct clinical studies: one on Continuous Plasma Filtration Adsorption (CPFA) [3] and the other on Hemoadsorption (HA), specifically the study by Wendel Garcia et al. (Intensive Care Med, 47(11):1334–1336, 2021) [4].

The latter study [4] is a retrospective, single-center observational study with a historic control group. This design inherently limits the conclusiveness of its findings and does not meet the standard of a randomized controlled trial (RCT), which, as the authors themselves note, remains the gold standard for clinical practice evidence. Furthermore, the study's supplementary material raises concerns about the robustness of the data, even within an observational framework. For example, all Cytosorb patients underwent Continuous Veno-Venous Hemofiltration (CVVH), but the study does not provide data on how many control patients also received CVVH. In fact, there is no mention of whether any sepsis patients in the control group underwent CVVH, nor is there an analysis of whether CVVH itself could have contributed to the increased mortality observed in the Cytosorb group. This potential confounding factor is neither discussed nor accounted for in the study's extensive statistical analysis.

Conversely, the authors express confidence in the superiority of Therapeutic Plasma Exchange (TPE), citing clinical studies that also warrant caution. The study by David et al. (cited in the commentary) [5] was a randomized controlled trial with early hemodynamic stabilization as its primary outcome, measured by norepinephrine reduction at six hours of TPE treatment. However, secondary outcomes such as mortality and changes in the SOFA score were not significant [5]. Notably, the mortality rate in the TPE arm was 60%, compared to 50% in the control group [5]. Similarly, the study by Knaup et al. [6], also cited by the authors, focused on the technique's tolerance, with secondary endpoints assessing

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only short-term (< 6 h) hemodynamic effects. The 28-day mortality rate in this study was 65% [6].

While these studies suggest potential benefits, their findings should be interpreted cautiously, especially given the lack of significant clinical outcomes, including mortality. Likewise, the Wendel-Garcia study should not be considered the definitive reference for evaluating HA, as previous studies involving similar patient populations and statistical methods have reported contradictory findings, including in long-term follow-ups [7–9]. While we do not claim these studies are of superior quality—since they, too, are retrospective—they serve as a reminder that careful interpretation is always necessary. As our review emphasized in its critical appraisal of current evidence, rigorous scrutiny is essential when evaluating these findings [10].

We agree with the authors on the need for further studies to explore patient-specific approaches, such as biomarker-driven identification of inflammatory sepsis phenotypes. However, we also believe that large observational studies, like those we have reported, can help identify clinical patterns that guide therapy at the time of treatment. This approach helps prevent delayed use of these techniques, which has historically led to selection biases. As noted in our review, propensity-matched studies suggest that patients with lactate levels above 6–7.5 mmol/L have worse outcomes [10]. While RCTs provide the most robust evidence on treatment effectiveness, observational studies, when properly analyzed, allow us to better understand the natural history of patients, risk factors, and outcomes.

Regarding Stahl's concerns about cartridge changes, Jansen and colleagues demonstrated, using an ex vivo model, a real reduction in cytokine levels by measuring mediators before and after the cartridge [11]. They also reported that the cartridge undergoes saturation and potential de-adsorption, with different kinetics depending on the mediator [11]. This is unsurprising, as previous studies on HA in rhabdomyolysis highlighted similar membrane saturation kinetics, dependent on target mediator concentrations in the bloodstream [12]. Understanding these dynamics is valuable for optimizing extracorporeal treatments. We agree that there is no "magic number" for cartridge replacement; rather, it should be tailored to the patient's clinical picture, which depends on endogenous mediator production rates that vary throughout the clinical course [13]. This approach could be further refined by bedside theranostic biomarkers monitoring. However, we disagree with the notion that de-adsorption, based on Jansen's studies and other clinical data, causes a significant "rebound" in target molecule levels [11–13]. This phenomenon is more commonly associated with techniques like TPE, where mediators redistribute from the tissue compartment to the bloodstream between sessions. In contrast, continuous and effective removal prevents such fluctuations.

Finally, we agree with Stahl that these techniques are distinct. We acknowledge the potential role of TPE as an adjunctive therapy in septic shock under specific conditions, such as thrombocytopenia associated with multiple organ dysfunction. However, broad implementation is not justified by current evidence [14]. TPE functions through the non-selective removal of plasma components, particularly via plasmapheresis by centrifugation. Plasma reinfusion during exchange is not always performed at a 1:1 ratio (which would require high volumes of fresh frozen plasma) and does not mitigate drug removal concerns, making therapeutic drug monitoring advisable during treatment. Conversely, HA techniques target high mediator concentrations, aiming to restore immune homeostasis by "modulating peaks" of pro- and anti-inflammatory mediators while preserving physiological levels [15].

In conclusion given that intensive care is an inherently complex field, caution is always a commendable approach. However, it is important to note that this cautious stance, based on current evidence, applies to the majority of sepsis treatments proposed to date. Aim of our paper has been to promote through a critical appraisal of existing evidences on extra-corporeal therapies in sepsis a different approach to the skeptical one, where generalizations and simplifications do not contribute to improving knowledge or patient care. Today, we can start from the preliminary results that we have reached with some available scientific evidences, and tomorrow we will plan future studies following this paradigm shift.

Abbreviations

CPFA	Continuous plasma filtration adsorption
HA	Hemoadsorption
RCT	Randomized controlled trial
CVVH	Continuous veno-venous hemofiltration
TPE	Therapeutic plasma exchange

Author contributions

GB and VMR conceptualized the manuscript. CI, AP, FA, AMS, CR, JLV reviewed the manuscript giving a substantial contribution to the final version. All the authors have approved the submitted version (and any substantially modified version). All authors read and approved the final manuscript

Availability of data and Materials

No datasets were generated or analysed during the current study.

Declarations

Conflict of interest

Professor Jean Louis Vincent is a journal editor. The others authors declare that they have no competing interests

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