Critical Care

REVIEW

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Use of extracorporeal blood purification therapies in sepsis: the current paradigm, available evidence, and future perspectives

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Abstract

Background Sepsis is the result of a dysregulated immune response to infection and is associated with acute organ dysfunction. The syndrome's complexity is contingent upon the underlying pathology and individual patient characteristics, including their immune response. The involvement of multiple organs and physiological functions adds complexity, with "organ cross-talk" emerging as a pivotal pathophysiological and clinical aspect. This narrative review to evaluate the rationale and available clinical evidence supporting the use of extracorporeal blood purification therapies as adjunctive therapy in patients with sepsis and septic shock.

Main body A search of the PubMed, Embase, Web of Science and Scopus databases for relevant literature from August 2002 to May 2024 has been conducted. The search was performed using the terms: 1) "blood purification" or "hemadsorption" or "plasma exchange" AND 2) "sepsis" or "septic shock". Therefore the authors have focused our discussion on several key areas such as conducting well-designed trials, developing more personalized protocols, ensuring optimal management and monitoring.

Conclusions Given the heterogeneity of patients with sepsis, conducting traditional randomized clinical trials in this domain can be a daunting task. However, statistical techniques such as Bayesian methods, propensity score analysis, and emulated clinical trials using clinical databases hold promise for enhancing comparability between the study groups. Indeed, to comprehend the clinical efficacy of extracorporeal blood purification techniques in patients with sepsis, it is imperative to assemble homogeneous groups of patients receiving uniform treatments. Clinical strategies should be individualized, signaling the end of the "one size fits all" approach in sepsis therapy and the need for personalized treatments.

Keywords Sepsis, EBPTs, Inflammatory mediators, Phenotypes, Microcirculation, Mortality, Inotropes, Propensity score, Organ cross talking, Antibiotics

Graphical abstract

Current suggested best practice for use of cytokine hemadsorption in sepsis.

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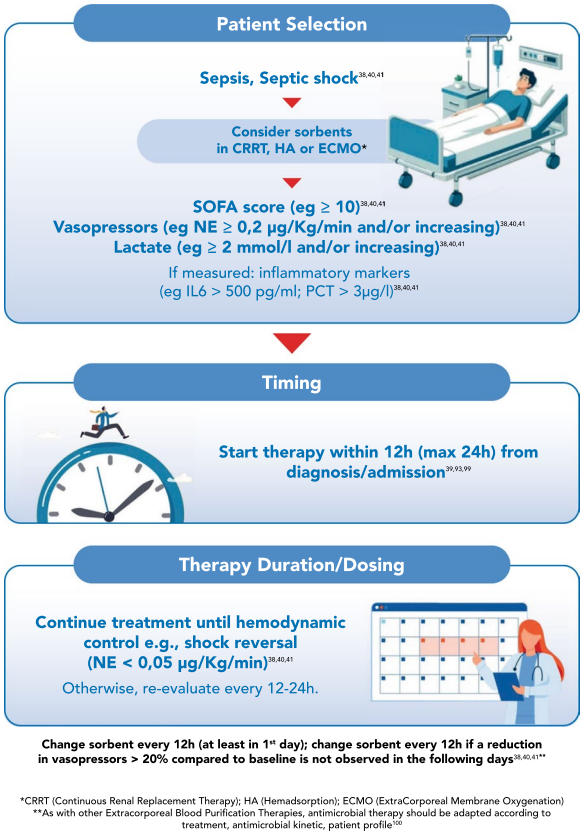

Background

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated response of the host to infection" [1]. This definition highlights two critical aspects: (a) the host response to infection is a normal and appropriate defense mechanism; (b) in some individuals the response becomes "dysregulated" and harmful, with tissue injury and failure to return to homeostasis. Sepsis pathogenesis therefore involves a "dysregulated" pro and an anti-inflammatory process that can occur quite early in the clinical course [2]. Such "dysregulated" release of pro-inflammatory and anti-inflammatory cytokines explains the "exacerbated response" that has been associated with the clinical picture of fulminant septic shock and premature death [3]. Recent data suggest that this complex biological response does not translate into a homogeneous clinical scenario as every patient follows their own immune response trajectory [2].

Given the high mortality rates associated with sepsis, there is a continuing need for active research into potential therapies to improve patient outcomes. Multiple avenues have been explored over the past decades, targeting individual components or pathways of the immune response, with limited success [4–6]. Cavaillon and collaborators have suggested that the "exacerbated response" may be associated with a reprogramming of circulating leukocytes, which induces immune-paralysis to endotoxins and a remodulation of metabolism that can translate into immune dysfunction, with a high risk of secondary infections, organ function failure, and death [7]. In an early pilot study, Ronco and collaborators noted that this phenomenon of leukocytes being "deaf" to the stimulus of endotoxins could be reversed by eliminating cytokines by adsorption [8], raising a potential role for blood purification in the treatment of septic shock. In this context, Extracorporeal Blood Purification Therapies (EBPTs) are increasingly employed in critical care settings. In an area still affected by considerable uncertainty, the current paradigm of their clinical application is to dedicate these treatments to patients with concomitant Acute Kidney Injury, or as "final rescue therapies" [9].

This manuscript details a narrative review among European clinical scientists from various specialties, including intensive care, critical care nephrology, and physiology.

The authors convened to examine the critical aspects of implementing EBPTs in septic patients. Topics included have been practical challenges, limitations, and future research directions, with a focus on improving patient selection criteria, optimizing treatment strategies, and exploring innovative research methodologies. The narrative review has been enriched with a comprehensive search of the PubMed, Embase, Web of Science, and Scopus databases between August 2002 and May 2024 using the search terms ["blood purification" or "hemadsorption" or "plasma exchange"] AND ["sepsis" or "septic shock"]. We searched for EBPTs studies data in critically ill patients with sepsis, septic shock, refractory septic shock, Covid-19, collecting more than 30 studies and 4.000 recruited patients (supplementary Table 1).

Rationale for use of extracorporeal therapies in sepsis

Renal replacement therapies (RRTs), such as hemodialysis or hemofiltration, are used to reinforce or replace renal function in critically ill patients with acute kidney injury (AKI), acting to ensure fluid and chemical balance in the body and eliminate waste products. Use of RRT is essential for patients with AKI, including sepsis-associated AKI, and is associated with an improvement in various hemodynamic parameters [10]. As the complex pathophysiology of sepsis became better understood, it was proposed that some forms of RRT could have additional benefits in patients with sepsis, by removing (some of) the excess sepsis mediators. The "peak concentration" hypothesis was proposed in 2003, suggesting that the partial removal of cytokines from circulating blood could reduce peak concentrations during the early stages of sepsis, thus helping to regulate the inflammatory cascade [11]. The potential benefits of such extracorporeal blood purification therapies have been further emphasized by recognition of the importance of "organ crosstalk" during sepsis, in which dysfunction of one organ can affect other organ systems, particularly in the context of multiple organ dysfunction syndrome (MODS). Ronco and Bellomo first introduced the concept of multi-organ support therapy (MOST) in 2002 [12, 13], which later evolved into the concept of extracorporeal organ support (ECOS) [14, 15]. However, no randomized controlled trial (RCTs) has yet shown a significant improvement in clinical outcomes associated with the use of these techniques.

Renal replacement therapy

Following the early pilot study by Ronco and colleagues mentioned earlier [8], various clinical trials using different forms of RRT in sepsis were conducted. Ratanarat et al. [16] evaluated the effects of prolonged intermittent high-volume hemofiltration (PHVHF) in 15 critically ill patients with sepsis and reported that hemodynamics improved with treatment, enabling the dose of norepinephrine to be reduced. Tapia et al. [17] evaluated the efficacy of high-volume hemofiltration (HVHF) in 31 patients with refractory septic shock, and reported an improvement in hemodynamic, metabolic, and respiratory parameters; there was a trend toward a reduction in hospital mortality. However, the three main RCTs [18–20] carried out in adults did not show an advantage of HVHF over standard volume hemofiltration (SVHF) in terms of mortality or vasopressor requirement. For these reasons, the minimum effective dose for venovenous haemofiltration remains 35–40 ml/kg/h, with an increased risk of loss of micronutrients, vitamins, trace elements, drugs such as antibiotics at higher doses [21].

Plasma exchange and coupled plasma filtration and adsorption

Therapeutic Plasma Exchange (TPE) involves the removal of a patient's plasma, followed by replacement with fluids such as 5% albumin or fresh frozen plasma (FFP). This procedure aims to reduce harmful substances in the plasma, including autoantibodies, proinflammatory cytokines, other inflammatory mediators such as chemokines, and clotting factors. In critical care settings, TPE can help restore immune homeostasis, decrease systemic inflammation, and improve microcirculation. There are two main techniques for performing plasma exchange: membrane plasma exchange (mTPE) and centrifugal plasma exchange (cTPE). mTPE uses specialized hollow-fiber filters to separate plasma from blood based on molecular size, whereas cTPE relies on centrifugal force to separate plasma based on differences in density between blood components. While both techniques are effective, mTPE is often preferred in critically ill patients with hemodynamic instability because it can be integrated with continuous renal replacement therapy (CRRT). On the other hand, cTPE may offer advantages in terms of higher plasma removal rates and is typically performed in stable patients. Several studies [22–25], while promising, do not provide definitive evidence that PEX improves outcomes in critically ill children, and further clinical investigation is required. Although TPE has shown promise in modulating the immune and coagulation systems in septic shock, its role in patients with multiorgan failure remains uncertain. The American Society for Apheresis (ASFA) has classified TPE for septic shock as Category III, Grade 2B. This classification indicates that the evidence for TPE's effectiveness is conflicting or uncertain, and its use is not yet fully endorsed as a standard treatment [26] (Fig. 1).

CPFA (Continuous Plasma Filtration Adsorption) is an extracorporeal blood purification therapy designed

Product	Technique	Mode	Indications and take-aways
CytoSorb	CytoSorb was incorporated into the continuous venovenous hemodialysis/hemodialysis circuit, extracorporeal membrane oxygenation system, or cardiopulmonary bypass system during surgical procedures	HP, CRRT, CPB, ECMO	Elevated levels of cytokines and/or bilirubin and/or myoglobin exist. Indicated for use intraoperatively during cardio pulmonary bypass surgery for the removal of P2Y12-Inhibitor Ticagrelor and/or Factor Xa-Inhibitor Rivaroxaban
Jafron	HA330 adsorbent, a neutro-macroporous resin column used for hemoadsorption, was administered alone for 2hr of hemoperfusion over a period of 3 d. It could also be used in combination with continuous kidney replacement therapy (CKRT)	HP, CRRT, CPB	Used in extracorporeal blood circuits, it is indicated to remove endogenous and exogenous molecules including inflammatory mediators and cytokines, bilirubin, metabolic toxins, protein-bound toxins, residual drugs
Toraymyxin	Polymyxin-B hemoperfusion using Toraymyxin was conducted according to the most com monly used protocol, which involved 2 sessions administered on 2 consecutive days, with each session lasting 2 hr	Stand Alone	Selective removal of endotoxin from circulating blood through direct hemoperfusion (DHP)
PEX	Plasma exchange was performed either with a fixed volume (12 units of plasma, 2,000mL) or calculated based on body weight (30–40 to 100mL/kg) for each session	Stand Alone	Treatment of Guillain-Barré syndrome, Thrombotic Thrombocytopenic Purpura (TTP), Myasthenia Gravis and Goodpasture syndrome. Removal of large-molecular weight substances such as pathogenic auto-antibodies, immune complexes, cryoglobulins,
CPFA	Coupled plasma filtration and adsorption (CPFA) involved the treatment of more than 0.2L/kg or 10L of plasma per day through a series of 3–5 sessions	Stand Alone	Plasma separation and adsorption of inflammatory mediators and/or toxins

Fig. 1 The figure reports a summary of the device available on the market, mechanism of function and clinical indication of extracorporeal blood purification techniques including hemoadsorption, plasma exchange, coupled plasma filtration and adsorption

to address the inflammatory mediators and toxins that contribute to the systemic inflammation in conditions like septic shock. The therapy operates in two stages plasma separation and adsorption. In a Prospective Multicenter Trial, Livigni et al. [27] included 330 septic shock patients and found that CPFA did not reduce mortality or improve other major clinical outcomes, despite the early hemodynamic benefits. Interestingly, a subgroup of patients receiving a higher CPFA dose (greater than 0.18 L/kg/day) showed a potential mortality reduction, but this was not sufficient to alter the overall study outcome. Consequently, Garbero et al. [28] enrolled 115 septic shock patients and assessed the efficacy of high-dose CPFA. Surprisingly, the study found higher mortality in the CPFA group compared to controls, especially in patients without severe renal failure (non-AKI) (Fig. 1).

Hemoadsorption

More recently, hemadsorption, with sorbents specifically incorporated to remove cytokines and other inflammatory mediators, has established itself as the most widely studied extracorporeal intervention in the context of clinical sepsis [29]. In vitro and ex vivo studies have recently demonstrated the effectiveness of hemadsorption in reducing circulating mediators, in particular cytokines, in sepsis [30–47]. Gruda et al. [48] have shown that hemadsorption through porous polymer bead devices have reduced the levels of a broad spectrum of cytokines (MIP1-α, IL-6, and IFN-γ, TNF-α DAMPS (C5a, HMGB-1, procalcitonin, and S100-A8), PAMPS (α-toxin, SpeB, and TSST-1) and mycotoxins (aflatoxin, T-2 toxin). Malard et al. [49] have investigated endotoxins and cytokines hemoadsorption using different devices and showing a different removal depending on the device selected and the target mediators. Harm et al. [50] have demonstrated that sorbents can remodulate several cytokines as ICAM-1, E-selectin, and secreted cytokines IL-8 and IL-6. Nierhaus et al. [31] performed an analysis of two blood purification systems to determine their performance for removing interleukins (ILs)-6 and 10, tumor necrosis factor (TNF)-a and monocyte chemoattractant protein (MCP)-1 from blood. Both the CytoSorb and the Jafron HA 380 devices are capable of removing cytokines from blood in a benchtop model.

In healthy volunteers challenged with lipopolysaccharide, Jansen et al. [30] used pre–post sorbent measurements, a procedure that enables calculation of mass balance as well as clearance, to determine the effects of hemadsorption on cytokine levels, notably interleukin (IL)-6, IL-8, IL-10 and tumor necrosis factor (TNF)-alpha. Cytokine levels were significantly lower in subjects who received hemadsorption. Many clinical studies have shown beneficial effects of hemadsorption on hemodynamics [33–52], need for organ support [53–56], and

the microcirculation [57–59]. The use of statistical tools, such as propensity score matching, has made it possible to form as much as possible homogeneous groups of patients to enable analyses of effects on mortality to be conducted, albeit retrospectively [52, 60, 61]; results have suggested short and long-term improvement in survival with hemadsorption. These statistical methods were performed in single-center, retrospective studies that included low sample sizes [52, 60, 61].

Attempts to confirm these results in removing cytokines and endotoxin, by designing RCTs, has led to contradictory results [62, 63]. Two large multicenter RCTs referring to endotoxins' removal comparing polymyxin-B hemadsorption, to conventional treatment in peritonitis induced septic shock [64, 65], demonstrated a non-significant increase in mortality and no improvement in organ failure. However, doubts were raised related to the heterogeneity of the study populations, the mode of application of the therapies, and the patient selection in these studies [66, 67].

The same limitations (e.g. heterogeneity of patients) are present in other RCTs in critically ill patients and sepsis regarding hemoadsorption to remove broad spectrum cytokines [13, 68–74]. Important confounding factors in population selection between the treatment and control groups resulting in unbalanced groups, with more severe patients in the intervention groups, is a common finding among studies [75, 76]. In several studies significative differences at baseline between control and study group in the inclusion criteria (e.g. CVVH or non CVVH patients) of septic patients may have led to confounding results (e.g. 63–64). This type of bias is not surprising given that current data, and clinical experience, suggest that hemadsorption may be most effective in the most severely ill patients at high risk of death (e.g., high sequential organ failure assessment [SOFA] score) [77], although propensity matched studies have suggested that patients with lactate levels higher than 6–7, 5 mmol/l had worse outcome [52, 61].

Given these caveats, it is not surprising that meta-analyses based on these RCTs have also provided controversial results on the effectiveness of extracorporeal blood purification therapies on survival [78–80]. Nevertheless, in a meta-analysis of 16 RCTs, Zhou et al. [81] reported that blood purification reduced mortality compared to no blood purification, and, in a meta-analysis of 37 RCTs, Putzu and coauthors [82] concluded that, despite the very low quality of the evidence analyzed, hemoperfusion, hemofiltration, and plasmapheresis were associated with lower mortality compared to conventional therapy. Similar results were reported in a more recent network meta-analysis of 60 RCTs [83]. Focusing specifically on hemadsorption, while recent consensus guidelines have recommended the use of hemadsorption even as a standalone modality for immunomodulatory support in septic AKI patients [84], some systematic reviews and meta-analyses [78–80] have concluded that there is no evidence that this technique has positive effects on outcomes in sepsis and insufficient evidence to support a recommendation for its use, and it may even increase mortality. However, once again, the meta-analyses reported that some of the included trials were of very low quality due to imprecision, risk bias and study heterogeneity [75](Fig. 1).

Future research of extracorporeal blood purification in sepsis

As previously noted, the available evidence regarding the use of extracorporeal blood purification therapies is inconclusive. Given the limitations of RCTs in this field, associated with heterogeneity in populations and modes and dosing of blood purification therapies, the future of extracorporeal blood purification in sepsis lies in a move from large-scale randomized trials to tailored and adaptive studies targeting specific and objective patient criteria with standardized therapeutic protocols. Personalization should be integrated into trial protocols so that more specific patient groups and subgroups are defined in which a particular treatment has proven beneficial. However, designing randomized trials that adequately address the heterogeneity of sepsis while maintaining scientific rigor is challenging. Ensuring adequate patient selection, standardizing interventions, including dosing and timing, and controlling confounding variables are critical but difficult tasks. Creating groups of comparable patients is essential to evaluate the effectiveness of any intervention. In this context, statistical techniques such as Bayesian methods, propensity score analysis and emulated clinical studies using clinical databases seem promising to improve comparability between groups [60, 61]. Non-interventional studies may allow precise targeted population, with long term standardized data assessment, although without randomization [85]. Addressing these challenges requires collaboration between researchers, clinicians, and policymakers to design and implement studies that better reflect the complexity of real-world sepsis.

Heterogeneity in study populations

Patient selection using endotyping with genomic analysis is still in its infancy and is primarily limited to sepsis research [86]. Recently, the authors have examined this issue, concluding that a more personalized approach based on "omics" techniques that focus on a specific class of compounds (DNA, RNA, proteins, metabolites, lipids, epigenetic modifications, microbial communities),

will be possible in the near future [87]. These techniques will enable the simultaneous characterization of multiple patient factors, providing a more complete understanding of the biological processes, and it is hoped that with advances in computing power and technology, the real-time analysis of data collected from patients will also become feasible in the clinic.

Meanwhile, personalization of treatments can be improved, as a basis for more meaningful RCTs [86], by using specific biomarker profiles at the bedside to select more homogeneous populations. Real-time biomarker levels, in combination with other important mediators of sepsis (DAMPs, PAMPs, cytokines) and the clinical picture, can already provide a rapid indication of patient phenotypes. Physiological biomarkers such as the presence of microcirculatory alterations can also be considered.

Heterogeneity in dosing of extracorporeal blood purification therapies

Different extracorporeal blood purification therapies have different mechanisms of action and a good understanding of these mechanisms is fundamental to enable critical evaluation of the existing scientific literature on this topic and correct application in clinical practice. The dose–response characteristics of extracorporeal therapy in sepsis have not been fully explored and, as with other "drugs", underdosing or overdosing could reduce its efficacy. Experience in patients with chronic kidney disease, indicates that as long as we are unable to define the purifying capacity of extracorporeal therapy by measurement of mass balances normalized to a patient's characteristics (Kt/V), it is not possible to understand how this intervention can influence patient outcomes [88]. This theory is much more than probably true also in overwhelming inflammatory diseases, such as sepsis. Many in vitro and in vivo studies have linked the "quantity" of therapy administered to its clinical effects. In a cohort of severely ill patients, Schultz et Al. have shown that the observed mortality rate was reduced if the blood purification volumes had inadvertently exceeded 6 l/kg BW (Body Weight). ABP (Amount of Blood Purified) was associated with survival [89]. Of particular interest, studies in pediatric patients [90, 91], in whom the treatment dose is generally higher than in adults, have shown more positive results than studies in adults. Of note, dose considerations include not only the duration of the treatment but also the blood flow and how often to change the sorbent filters. The existing evidence often correlates negative results on outcomes to "underdosed" extracorporeal blood purification or inhomogeneous delivery of extracorporeal treatment (the same techniques but different devices, over-short delivery times, session times incorrectly programmed, etc.) [78]. Further study is needed to better define optimal dosing strategies.

Heterogeneity in the timing of extracorporeal blood purification therapies

Extracorporeal blood purification is currently an adjunct therapy, therefore there is no clearly defined "correct" time to start it. A pragmatic approach to escalating to adjuvant therapies, including extracorporeal treatments, in sepsis involves assessment of the evolving clinical course [92, 93]. Important parameters to be considered in the patient trajectory could include escalation of organ dysfunction scores, perfusion indexes, vasopressor load, and increasing biomarker levels [92, 93]. Importantly, given the heterogeneity of sepsis populations, e.g., in terms of delay since sepsis diagnosis, degree of immune response, etc., extracorporeal blood purification should not be started at the same set time period in all patients in large clinical trials, but in a more personalized manner. Kogelmann et al. have found that, in the hemadsorption patient, actual mortality was lower than mortality predicted by APACHE II score (Acute Physiology And Chronic Health Evaluation) and associated with hemodynamic stabilization and a reduction in blood lactate levels. These effects are more pronounced in patients in whom therapy started within 24 h of sepsis diagnosis [94].

Endpoints for future studies

Focusing on mortality as the endpoint for trials of blood purification in sepsis will likely lead to failure to demonstrate a consistent effect for several reasons [95]. First, blood purification is an adjunct intervention aimed at gaining time for primary therapies, such as antibiotics, vasopressors, etc., to act. If the primary therapy is not appropriate or effective in a particular patient, then any adjunct therapy will not improve outcomes either. Moreover, given the heterogeneous nature of patients with sepsis, one intervention is unlikely to be effective in all. Second, multiple factors influence mortality, which will vary across individual patients. Third, randomized studies provide an estimate of the average effect on the population tested and do not inform us about which patients in particular will benefit from the treatment or to what extent [2, 96].

Endpoints other than mortality may offer greater or additional clarity in terms of a therapy's effectiveness. A shift in attention towards morbidity endpoints (such as the use of vasopressors, the need for mechanical ventilation, the length of stay in the intensive care unit, the prevention of chronic kidney disease, quality of life) is needed. However, some of these are more difficult to measure objectively and homogeneously,

making comparisons across studies more difficult. From a physiological point of view, one of the first objectives in resuscitation in septic shock should be restoration of microvascular blood flow to enable adequate organ perfusion. Currently, mean arterial pressure, venous oxygen saturation, or lactate levels are used as surrogate indicators of tissue perfusion, as a direct and reliable measurement is not yet widely available [97, 98]. These variables should be routinely included in new studies of extracorporeal blood therapies in sepsis.

Considerations for current clinical practice

The most rational approach currently, while awaiting definitive results, seems to be to adopt a personalized approach, with careful patient selection, personalized treatment starts according to patient evolution, and adequate dosing. Defining the most appropriate therapy for individual patients should take into account hemodynamic and metabolic results, such as inotrope dosages, vasoactive inotropic score (VIS), mean arterial pressure (MAP), lactate levels, pH, etc. Given the important contributions of cytokines to endothelial dysfunction, a central factor in the pathophysiology and etiology of sepsis, effects on microcirculatory aspects should also be considered, although routine monitoring of the microcirculation is not yet widely available.

A pragmatic approach to determine when to escalate to an adjuvant therapy in sepsis, such as extracorporeal blood purification, involves assessment of a worsening clinical course despite optimal primary therapy [92, 93]. Important parameters to be considered for this purpose include escalation of organ dysfunction scores, perfusion indexes, vasopressor load, and increasing biomarker levels [92, 93].

Importantly extracorporeal therapies can influence doses of other drugs administered concomitantly, including antibiotics. Antibiotic administration must therefore always be carefully adjusted when used in conjunction with an extracorporeal blood purification therapy. Therapeutic drug monitoring should be performed when possible and if laboratory support is not available, PK/PD (pharmacokinetic/pharmacodynamic) evaluations should be based on patient condition and the type of EBPT being used [99, 100].

Conclusions

There is an urgent need for greater clarity regarding use of adjunctive extracorporeal therapies in sepsis. Expecting a single therapy to drastically reduce mortality from sepsis is not realistic, primarily due to the multifaceted nature of the septic syndrome. Integration of additional therapies, such as extracorporeal blood purification, within treatment protocols can optimize patient care and improve outcomes, but these must be applied at the correct time and dose, also taking into account the interference that all such therapies have with drugs, and with antibiotics in particular. The era of "one size fits all" in sepsis therapy is over, and the time has come for a paradigm shift toward more focused approaches in both clinical practice and research.

Abbreviations

EBPTs	Extracorporeal blood purification therapies
sIPTW	Inverse probability of treatment weights
RRT	Renal replacement therapies
AKI	Acute kidney injury
MODS	Multiple organ dysfunction syndrome
MOST	Multi-organ support therapy
ECOS	Extracorporeal organ support
PHVHF	Prolonged intermittent high-volume hemofiltration
HVHF	High-volume hemofiltration
RCTs	Randomized control trials
IL	Interleukin
TNF	Tumor necrosis factor
CVVH	Continuous veno-venous hemofiltration
SOFA score	Sequential organ failure assessment score
DAMPS	Damage-associated molecular patterns
PAMPS	Pathogen-associated molecular patterns
BW	Body weight
ABP	Amount of blood purified
APACHE	Acute physiology and chronic health evaluation
VIS	Vasoactive inotropic score
MAP	Mean arterial pressure
PK/PD	Pharmacokinetic/pharmacodynamic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05220-7.

Additional file 1 (DOCX 31 KB)

Acknowledgements
Not Applicable

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

Funding
No funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not Applicable.

Consent for publication
Not Applicable.

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

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Received: 11 October 2024 Accepted: 16 December 2024
Published online: 25 December 2024

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