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# Extracorporeal Blood Purification Therapies in Sepsis


Sepsis is a life-threatening condition caused by a dysregulated host response to infection, leading to organ dysfunction. Sepsis involves both pro-inflammatory and anti-inflammatory processes, which can occur early in the disease and explain the severe clinical outcomes such as septic shock and premature death. However, each patient follows a unique immune response trajectory.

Despite significant research, therapies targeting specific components of the immune response have shown limited success. One hypothesis suggests that the exacerbated response in sepsis could be linked to a reprogramming of circulating leukocytes, leading to immune paralysis and increased risk of secondary infections, organ failure, and death. Blood purification methods, such as Extracorporeal Blood Purification Therapies (EBPTs), have been explored, particularly in patients with Acute Kidney Injury or as a final rescue therapy.

A narrative review conducted by European clinical scientists from various specialties discusses the challenges and limitations of implementing EBPTs in sepsis treatment. It emphasises the need for better patient selection, optimised treatment strategies, and innovative research to improve patient outcomes.

Renal replacement therapies (RRTs), such as haemodialysis and haemofiltration, are used to manage acute kidney injury (AKI) in critically ill patients, ensuring fluid balance and eliminating waste. These therapies are crucial in sepsis-associated AKI and can improve haemodynamic parameters. Some studies suggest that RRTs might also benefit sepsis patients by removing excess sepsis mediators, potentially helping regulate the inflammatory response.

The "peak concentration" hypothesis proposes that removing cytokines early in sepsis can control the inflammatory cascade. The concept of multi-organ support therapy (MOST) and extracorporeal organ support (ECOS) was introduced to address organ dysfunction in sepsis, though no randomised controlled trials have shown significant improvements in clinical outcomes with these therapies.

Various trials have tested RRTs in sepsis. For example, prolonged intermittent high-volume haemofiltration (PHVHF) and high-volume haemofiltration (HVHF) showed some improvements in haemodynamics, metabolic, and respiratory parameters, but larger RCTs did not show clear advantages in terms of mortality or vasopressor use. The optimal dose of haemofiltration remains unclear, with risks of nutrient loss at higher doses.

Plasma exchange (TPE) is another therapy that removes harmful substances from the plasma, aiming to reduce inflammation and improve microcirculation. Techniques include membrane plasma exchange (mTPE) and centrifugal plasma exchange (cTPE), with mTPE often preferred for unstable patients. However, the effectiveness of TPE in critically ill patients, particularly those with multiorgan failure, is still uncertain, and evidence remains inconclusive, leading to its classification as Category III, Grade 2B by the American Society for Apheresis.

Continuous plasma filtration adsorption (CPFA) targets inflammatory mediators and toxins but did not show mortality reduction in large studies, despite early haemodynamic benefits. High doses of CPFA raised concerns, with one study even showing higher mortality in non-AKI patients, highlighting the need for further investigation.

Haemadsorption has become one of the most studied treatments for sepsis. Studies have shown that haemadsorption can reduce circulating cytokines and other sepsis mediators, such as endotoxins, mycotoxins, and damage-associated molecular patterns (DAMPs). Research has demonstrated its ability to improve haemodynamic parameters, organ support, and microcirculation, with some retrospective studies suggesting improved short- and long-term survival in patients treated with haemadsorption.

However, RCTs have yielded conflicting results. For example, large multicentre RCTs examining endotoxin removal with polymyxin-B haemadsorption in peritonitis-induced septic shock found no significant reduction in mortality or improvement in organ failure. Similarly, other RCTs on haemadsorption for broad cytokine removal have shown mixed results, with issues such as patient heterogeneity and confounding factors affecting the studies' validity. Some studies suggest that haemadsorption may be more effective in severely ill patients at high risk of death, but results are inconsistent.

Meta-analyses have provided controversial conclusions, with some studies suggesting blood purification therapies, including haemadsorption, reduce mortality, while others found no evidence of benefit and raised concerns about the risk of increased mortality. Despite these uncertainties, recent guidelines have recommended haemadsorption for septic AKI patients, but its effectiveness remains uncertain, with the evidence being of low quality due to imprecision, bias, and study heterogeneity.

The evidence surrounding the use of EBPTs in sepsis remains inconclusive. To improve future studies, researchers propose moving away from large-scale randomiaed trials to more personalised, adaptive studies that target specific patient subgroups with standardised protocols. Key challenges in designing such trials include patient selection, intervention standardisation, and controlling confounding variables.

Heterogeneity in patient populations is a significant issue. Using "omics" techniques, such as genomic analysis and biomarker profiling, could allow for more personalised treatment based on a better understanding of biological processes. Real-time biomarker levels and microcirculatory assessments could further refine patient selection.

Additionally, the heterogeneity in dosing of EBPTs, including the amount of blood purified and treatment duration, remains underexplored. Under- or overdosing could diminish therapeutic efficacy, and studies suggest higher doses may lead to improved outcomes, especially in paediatric patients. Optimising dosing strategies, including blood flow rates and treatment duration, is essential for effective therapy.

Finally, determining the optimal timing for starting EBPTs in sepsis is challenging due to the diversity in patient conditions. The timing should be personalised based on factors like organ dysfunction scores, perfusion indexes, vasopressor load, and biomarkers. Some studies suggest that starting therapy within 24 hours of sepsis diagnosis may lead to better outcomes, including improved haemodynamics and reduced mortality. Personalised approaches to timing and dosing are crucial to enhancing the effectiveness of EBPTs in sepsis.

Focusing solely on mortality as the endpoint in trials of blood purification therapies for sepsis may not effectively demonstrate their impact. Blood purification is an adjunctive therapy aimed at supporting primary treatments like antibiotics and vasopressors. If these primary treatments are ineffective, adjunct therapies are unlikely to improve outcomes. Additionally, the heterogeneous nature of sepsis patients means a single therapy may not be effective for everyone, and mortality is influenced by numerous factors that vary among patients.

Instead, shifting focus to morbidity-related endpoints—such as vasopressor use, mechanical ventilation needs, ICU length of stay, prevention of chronic kidney disease, and quality of life—may provide more meaningful insights. However, these endpoints are harder to measure objectively and consistently across studies. Physiologically, restoring microvascular blood flow for adequate organ perfusion is a key goal in septic shock. While surrogates like mean arterial pressure, lactate levels, and venous oxygen saturation are used to monitor tissue perfusion, they are not always direct or reliable indicators. These factors should be included in future studies of extracorporeal blood therapies for sepsis.

The most effective current approach for extracorporeal blood purification in sepsis is personalised treatment, focusing on careful patient selection, tailored therapy based on individual patient evolution, and appropriate dosing. Key factors to consider in choosing the right therapy include haemodynamic and metabolic parameters such as inotrope dosages, vasoactive inotropic score (VIS), mean arterial pressure (MAP), lactate levels, and pH. Effects on microcirculation should also be considered, though routine monitoring is not yet widely available.

A pragmatic approach involves escalating to adjuvant therapy like extracorporeal blood purification when there is clinical deterioration despite optimal primary therapy. Important factors for escalation include worsening organ dysfunction, perfusion indexes, vasopressor load, and rising biomarker levels.

Extracorporeal therapies can alter the dosing of other drugs, such as antibiotics. Careful adjustment of antibiotic administration is crucial when combined with extracorporeal blood purification therapies. Therapeutic drug monitoring should be done when possible, and pharmacokinetic/pharmacodynamic evaluations should be based on the patient's condition and the type of therapy being used.

There is an urgent need for clearer guidelines on the use of adjunctive extracorporeal therapies in sepsis. A single therapy is unlikely to drastically reduce sepsis mortality due to the complex nature of the condition. However, integrating extracorporeal blood purification within treatment protocols, when applied at the correct time and dose, can optimise patient care and improve outcomes. It's important to consider the potential interference of these therapies with drugs, particularly antibiotics. The era of "one size fits all" in sepsis treatment is over, and a shift towards more personalised approaches in both clinical practice and research is necessary.

Source: Critical Care

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