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EDITORIAL

Hemoadsorption in septic shock – CON

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Sepsis is a life-threatening condition caused by a dysregulated host response to infection that leads to systemic inflammation, organ dysfunction, and high mortality. Although, there is a lack of precise criteria for recognising a dysregulated immune response, septic patients have worse clinical outcomes when bacterial burden, endotoxin levels, and pro- and anti-inflammatory cytokine/chemokine levels are elevated in tissues and blood [1].

The term 'hemoadsorption' encompasses various extracorporeal treatments that utilise both selective and non-selective adsorbents to remove circulating inflammatory mediators and other harmful substances, with the objective of increasing the tolerance of the host's immune response to infectious insults. Furthermore, the mechanisms underlying molecular removal may vary across different methodologies, with some approaches employing solely hemoadsorption, while others integrate hemoadsorption with diffusion and convection techniques. While biological hypotheses and clinical observations have indicated potential benefits, there is a lack of definitive evidence. Additionally, recent concerns about their application have drawn significant attention (Fig. 1).

Heterogeneity of the immune response to infections

The host immune response to infection simultaneously encompasses both pro- and anti-inflammatory pathways, which typically interact and combine during the clinical course of sepsis. The former plays a fundamental role in pathogen clearance, while the latter is involved in attenuating and controlling pro-inflammatory reactions, aiming to restore tissue homeostasis after infection is controlled. In theory, the equilibrium between these two components may determine a favourable clinical outcome. Conversely, an uncontrolled and imbalanced response could lead to organ damage and immune suppression, thereby increasing the risk of secondary infections [1]. It becomes obvious that any modulation within this complex matrix through hemoadsoprtion may yield variable results depending on the patient's immune phenotype. This issue is further exacerbated by the absence of a validated approach to assess the structure and trajectory of the host immune response, despite significant efforts having been made in recent years to investigate the use of various biomarker in the identification of immune dysfunction [1]. Moreover, the measurements of the immune condition based on circulating surrogates in the blood are further complicated by (a) dynamic changes over time, (b) the high heterogeneity among clinical, biomarkers and transcriptomic data, and (c) compartmentalisation of these inflammatory responses; for example, what might be detectable in the blood does not necessarily reflect the immune status at the tissue level [2, 3]. All this contributes to the uncertain results observed in clinical trials with various hemoadsorption techniques for sepsis [4].

Lack of molecular selectivity of hemoadsorption techniques

The mode of action of different hemoadsorption techniques results in varying degrees of selectivity for the removal of molecules. Certain methods, such as high cut-off membranes, exhibit low intrinsic selectivity and non-specifically remove any medium-to-high molecular weight molecules, including cytokines, as well as numerous plasma proteins. This lack of selectivity may result in the removal of beneficial mediators, potentially compromising the host's capacity to combat infection or developing an evolutionarily preserved compensatory response. Even the more selective techniques, such as polymyxin

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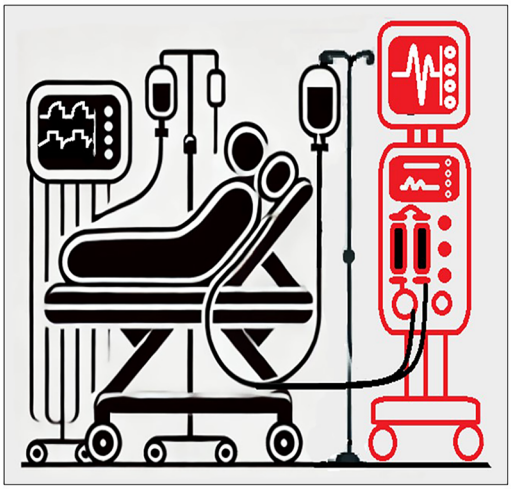

INTERACTION WITH IMMUNE RESPONSE	– Modulation of specific inflammatory pathways may yield varying results depending on the patient's immune response phenotype. – They are frequently applied in patients whose immunological status is unknown
LACK OF SELECTIVITY	– Risk of removing useful mediators involved in the inflammatory immune response. – Due to the redundancy of the immune pathways, removal of specific immune molecules may fail to provide complete control over the broader immune response
LACK OF CLINICAL EVIDENCE	– Randomized clinical trials and meta-analyses failed to demonstrate benefits in patient survival
POTENTIAL SIGNALS OF HARM	– Removal of antibiotics and other life-saving drugs – Some studies have raised concerns about the safety, highlighting increased mortality rates

Fig. 1 Key factors restricting the use of hemoadsorption in septic patients

B hemoperfusion adsorbers designed for specific endotoxin adsorption, have been shown to adsorb inflammatory cells (e.g. activated monocytes and neutrophils) and inactivate renal pro-apoptotic factors. Furthermore, it is imperative to consider that although blood purification techniques target several pathways of the inflammatory response, the endogenous immune response relies on a significantly more complex interplay of molecular mechanisms, many of which are redundant and not yet fully elucidated.

Lack of supporting clinical evidence

Numerous uncontrolled case series across various hemoadsorption techniques have reported anecdotal clinical improvements and some randomised controlled trials (RCT) have demonstrated effective endotoxin, cytokine, and blood lactate clearance along with haemodynamic stabilisation [5]. However, when examined under controlled conditions, dynamic systems such as post-adsoprtion cytokine networks do not differ significantly from the natural progression of the disease [6, 7]. Moreover, conclusive evidence regarding the outcome endpoints remains elusive. A recent network meta-analysis investigating several types of blood purification techniques found no effect of any unselective adsorption, but potential benefits for plasma exchange and Polymyxin-B hemoperfusion, although most comparisons were based on low or very low certainty evidence [4].

Polymyxin B hemoperfusion has been mainly studied in the EUPHAS, ABDOMIX, and EUPHRATES RCTs [5, 8, 9]. Although the oldest trial reported survival benefits, these findings were not confirmed in subsequent multicentre RCTs. Coupled plasma filtration adsorption (CPFA) treatments were investigated in COMPACT 1 and 2, and the ROMPA trials [10–12].The first failed to show a benefit in mortality, the second was stopped early because of a signal of harm and the third was interrupted early without showing differences in mortality between the two study groups. Cytosorb, a filter with polymer beads of polystyrene divinylbenzene adsorbing molecules with molecular weight up to 60 kDa including cytokines, has been primarily investigated in RCTs which demonstrated no significant survival benefit and suggested potential adverse effects [6, 13, 14]. The pooled effects of Cytosorb were further assessed by various meta-analyses which did not show any mortality benefit [15, 16].

Potential signals of harm

In addition to the—by itself potentially injurious—removal of endogenous molecules, hemoadsorption may also remove pharmacological agents. This phenomenon can potentially compromise patient outcomes by reducing the circulating and tissue levels of antibiotics. The studies have demonstrated that hemadsorption with Cytosorb is associated with enhanced clearance of the antimicrobial drugs tested, with certain drugs exhibiting additional body clearance exceeding 100% (e.g. linezolid) and others (teicoplanin, posaconazole, and liposomal amphotericin B) undergoing more than 30% additional clearance [17]. Notably, the Oxiris filter, which integrates diffusion and convection with adsorption, enhanced the clearance of cefiderocol by approximately 50% compared to the standard filter employed in continuous renal replacement therapy [18].

The effects of hemoadsorption on antibiotics and other drugs may elucidate negative outcomes in certain trials. A

small RCT on COVID patients undergoing ECMO demonstrated significantly higher mortality among patients receiving Cytosorb [6] and in a propensity-matched study of patients with refractory septic shock, high IL-6, and high-dose vasopressors, cytokine adsorption led to an increased hazard for mortality (HR 1.82) [7].

These data suggest that caution is warranted and further investigations into early therapeutic drug monitoring strategies for antibiotics as a potential solution are recommended.

Conclusions

Pathophysiological considerations and evidence-based data argue against the routine utilisation of hemoadsorption in sepsis. Indeed, current guidelines recommend against the use of any blood purification technique outside the experimental context [19]. In light of the recent indication of potential harm, it is incumbent upon the intensive care community to conduct further high-quality research and adhere to the Hippocratic principle: 'Primum non nocere.'

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Declarations

Conflicts of interest

MG has received honoraria for speaking at conferences from Estor and Fresenius; MT and SD have no conflict of interest to declare.

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