

# ICU

MANAGEMENT & PRACTICE

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2024

VOLUME 24  
ISSUE 1

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# Haemoadsorption in Critically Ill Patients: The New Frontier

Haemoadsorption may represent the new frontier in extracorporeal blood purification. Haemoadsorption has demonstrated effective extraction of a variety of toxins and drugs during episodes of sepsis, acute kidney injury or intoxication. Selective haemoadsorption can be performed by endotoxin-binding polymyxin B functionalised polystyrene fibres. The clinical application of non-selective haemoadsorption in sepsis or other conditions with an evident cytokine release syndrome presents a clear rationale.

## Current Challenges

Critically ill patients present several challenges due to multiple organ involvement, complex clinical scenarios, increasing incidence of sepsis, and unmet diagnostic and therapeutic needs (Ronco et al. 2019; Clark et al. 2017). This determines a high demand for innovation and new paradigms. In the areas of sepsis and acute kidney injury (AKI), innovation is mandatory to improve current extracorporeal blood purification techniques (EBP), implement recent advances in technology and biomaterials, and cope with financial constraints. New areas of research include biomaterials, applied nanotechnology, microfluidics, new devices, new membranes and sorbents, transition from diffusion/convection to adsorption. Haemoadsorption (HA) may represent a new frontier in EBP (Ronco

and Bellomo 2022). Solute mass separation may occur by barrier (membrane) or by solid agent (sorbent). Diffusion is mainly used in haemodialysis (HD) to remove small solutes, but it becomes inefficient for molecules above 3-5 KDa. Convection is applied in haemofiltration (HF) and haemodiafiltration (HDF) to remove middle molecules up to 10 KDa using ultrafiltration and solvent drag. Still, clearance is limited by the permeability of the membrane (sieving). Even the most modern membranes cannot effectively remove uremic toxins or sepsis mediators with molecular weight above 10-15 KDa. Thus, HA represents a new and interesting option to overcome the limitations of dialysis techniques, providing the required removal of large-middle molecules (Ronco and Bellomo 2023a).

## Evolution of Sorbents

Sorbents have been used for two centuries. Natural carbons and allumo-silicates (to exchange ammonium and calcium) were recently substituted by synthetic polymers, chemically modified to become haemocompatible (Ricci et al. 2022). This allowed the clinical application of HA. Sorbents can be natural (zeolites and porous carbons) or synthetic (polymers). They may present high or low-density pores with a macro-, meso- or microporous structure (pore size > 500 Å, 20-500 Å or < 20 Å respectively) (Figure 1).

The pore density affects the amount of adsorbate (solute removed by the sorbent), while the pore size distribution affects the spectrum of molecules in the adsorbate. They may come in fibres, granules, beads, spheres, cylindrical pellets, flakes, or powder. They may operate by direct adsorption, anion or cation exchange, or immuno-adsorption. Recently, the expanded capacity of adsorption by new polymeric resins has spurred new interest in the use of HA in several clinical conditions in intensive care (Table 1) (Copelli et al. 2023).

## Rationale for Haemoadsorption

High levels of harmful molecules (solutes) in the blood are observed in the case of kidney or liver failure or in the case of exogenous intoxication and correlate with the severity of disease and mortality. This is the basis of life-saving treatments like EBP.

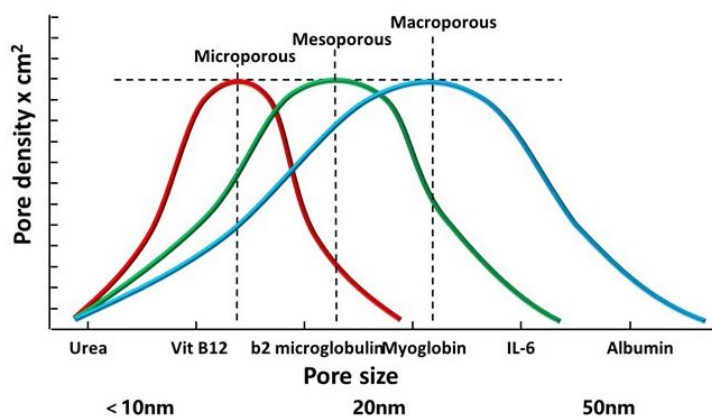


Figure 1. Pore density and pore size distribution in different polymeric resins. Adsorption of different molecular weight solutes depends on the pore size distribution curve that identifies micro-meso- and microporous structures.

Renal	ICU	Liver	Intoxication
<ul style="list-style-type: none"> <li>Removal of middle-large &amp; protein-bound uremic toxins</li> <li>CHD complications: such as CVD, Pruritus, Hypertension</li> <li>Improvement of life quality</li> <li>Sepsis-Associated AKI</li> <li>Renal protection in CRS</li> </ul>	<ul style="list-style-type: none"> <li>Treatment of critical illness derived from cytokine release syndrome</li> <li>Removal of inflammatory mediators &amp; cytokines</li> <li>Hemodynamic stabilization</li> <li>Organ protections &amp; support</li> </ul>	<ul style="list-style-type: none"> <li>High bilirubin levels</li> <li>Severe hepatitis, liver failure and other diseases associated with hepatic encephalopathy</li> <li>HBV-ACLF</li> <li>Decompensated cirrhosis</li> </ul>	<ul style="list-style-type: none"> <li>Accelerate poisons or drug elimination</li> <li>Kidney and liver protection</li> <li>Reduce severity of illness</li> <li>Alleviate organ injury</li> <li>Shorten hospitalization</li> <li>Survival improvement</li> </ul>

Table 1. Critical illness conditions possibly addressed by HA

However, the efficiency of toxin removal with current systems may be inadequate to fully replace kidney or liver failure function or to compensate for the dramatic surge in endogenous pro-inflammatory immune toxins as in the case of cytokine release syndromes (CRS). In those conditions where adequate blood purification cannot be effectively obtained, HA application finds a logical rationale as an alternative or additional therapeutic option (Ronco and Bellomo 2022).

### Requirements for Safe and Effective Sorbent Therapy

Modern sorbent therapy requires an effective and haemocompatible sorbent material, a well-designed sorbent cartridge, and easy and simple implementation of related techniques with no or negligible side effects (Ronco and Bellomo 2023b).

Modern sorbents are derived from polymers that create a porous structure with a high surface/volume ratio. Adsorption

capacity is measured by experimental isotherms, specific curves that describe the maximal amount of solute that can be adsorbed by a unit of sorbent. Current sorbents demonstrate effective removal of molecules in the range between 10 and 55 KDa, including cytokines, chemokines, and protein-bound solutes, providing a new perspective on EBP. Porosity is regulated by the manufacturer, making it possible to target specific molecules. This results in a tridimensional sponge-like structure that can be analysed by electronic scanning microscopy (Figure 2). The forces involved in adsorption are 1) Hydrophobic bonds, generated by the hydrophobic affinity of the sorbent and the target molecules; 2) Ionic bonds, generated by electrostatic attraction between positively charged and negatively charged ions; and 3) Van der Waals forces, the interaction between electrons of one molecule and the nucleus of another molecule (Copelli et al. 2023).

New sorbents are highly haemocompatible, as recently demonstrated in static and dynamic tests performed to detect possible monocyte activation during contact with human blood (Bellomo and Ronco 2023). Biocompatibility characteristics are further improved by a surface coating that improves interparticle blood rheology during treatment. The flow of the fluid phase (blood) inside the sorbent cartridge (divided into inter-particle, extra-particle and intra-particle) is governed by Darcy's law and the Karman-Cozeny equation where the size of the beads, their porosity, the packing density, the length and diameter of the unit, the path tortuosity and Reynold's

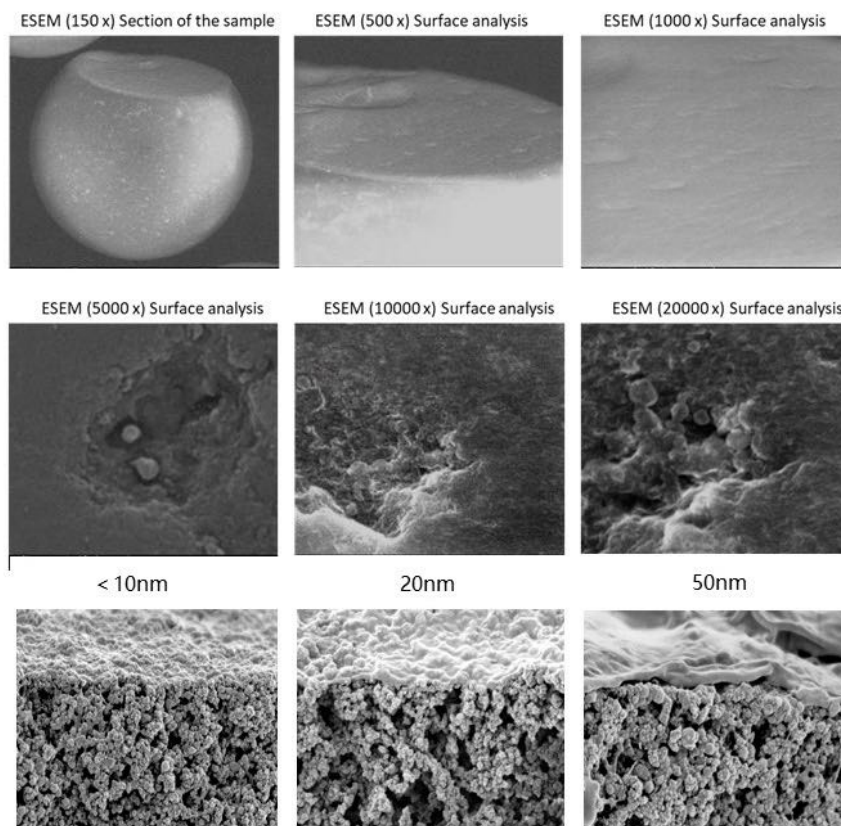
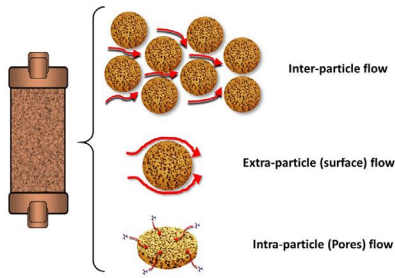
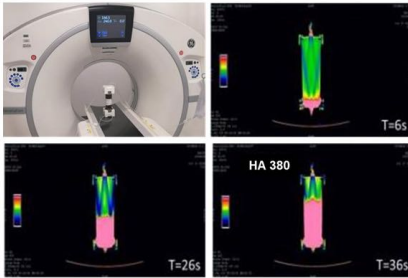


Figure 2. Electron scanning microscopy of sorbent beads at various magnifications. In the lower section, typical micro- meso- and microporous structures can be identified.





**Figure 3.** When a liquid mixture is brought into contact with a microporous solid, adsorption of certain components of the mixture takes place on the surface of the solid. The fluid phase flows in the interparticle space, on the surface of the sorbent beads, and finally inside the porous structure. The maximum extent of adsorption occurs when equilibrium is reached, as described by a curve defined "isotherm".



**Figure 4.** Flow distribution analysis by helical scanning inside a sorbent cartridge HA380. The distribution of the dye injected during blood flow circulation describes a homogeneous pathway with complete exposure of the available sorbent to the fluid phase [blood].

number are the involved variables (**Figure 3**) (Ronco and Bellomo 2023c). Helical scanning techniques reported in **Figure 4** (Lorenzin et al. 2019) demonstrate a homogeneous distribution of blood flow.

### Molecular Targets: Selective and Non-Selective Haemoadsorption

Soluble mediators in the middle-large molecular weight range contribute significantly to organ injury, severity of disease and mortality in septic patients. As in the case of other clinical conditions derived from a cytokine release syndrome (infections, pancreatitis, burns, trauma, etc), sepsis mediators represent logical targets for removal by haemoperfusion. In sepsis, two approaches have been suggested: one based on selective targeting of a key molecule (e.g. endotoxin) and the other based on non-selective, broad molecular spectrum adsorption (Ronco and Bellomo 2022).

In case of the presence of the microbial agent, removal of circulating bacteria or viral particles can be obtained by special affinity binder cartridges. This treatment has been used in combination with special adsorbing membranes such as modified AN69 or adsorbing cartridges (Bellomo et al. 2024). In case of the presence of endotoxin in blood, detected by endotoxin activity assay, extracorporeal removal of endotoxin with polymyxin-B cartridge (PMX-HA) can be indicated alone or in conjunction with other adsorption or CRRT techniques (Kellum and Ronco 2023; Cruz et al. 2009; Dellinger et al. 2018; Klein et al. 2018). We should mention that different endotypes may also be a reflection of different conditions of the same patient in different time windows of the ICU stay. In these circumstances, the application of different adsorption and blood purification techniques can be time-sensitive, as suggested in a recent proposal for the sequential application of extracorporeal techniques (Ronco et al., 2023a).

On the other side, from selective potential, are non-selective sorbents capable of removing a broad range of molecules, including mediators and protein-bound solutes. Sepsis induces the expression of a dozen inflammatory mediators where no single molecule is responsible for the entire syndrome. In such circumstances, non-specific removal of the various mediators by haemoadsorption may represent the ideal condition to restore immune homeostasis (Ronco and Bellomo 2022; Ronco et al. 2023b). The cytokine release syndrome (CRS) is a systemic inflammatory response induced by bacteria, viruses, blood exposure to non-biocompatible materials, drugs, and antibody-based therapies or chimeric antigen receptor (CAR)-T cell therapy. Cytokines trigger a cascade with the activation of innate immune cells (macrophages and endothelial cells) with further cytokine release (Cobb and Lee 2021). The presence of a CRS may be demonstrated by biochemical measurements in the presence of the typical clinical picture characterised by hypotension and organ dysfunction. Therefore, it makes no sense to apply a cytokine removal technique if there is no evidence of systemic

inflammation or elevated biochemical levels of cytokines. On the other hand, there is a specific time window for this type of intervention, which may prove beneficial in preventing the development of cytokine-mediated organ dysfunction or in protecting the kidney from disease and damage progression. Recently, special cartridges with microporous biocompatible resin have been made available with high capacity of cytokine adsorption (Bellomo and Ronco 2023). According to the peak concentration hypothesis (Ronco et al. 2004; Ronco et al. 2003), higher removal will occur for molecules with the highest concentration in blood and likely with the more impactful action on immunodysregulation. In such conditions, patients with impending or overt cytokine storm induced by different causes represent the ideal population for extracorporeal cytokine removal by haemoadsorption (Peng et al. 2008).

### Adsorption Techniques and Relevant Indications

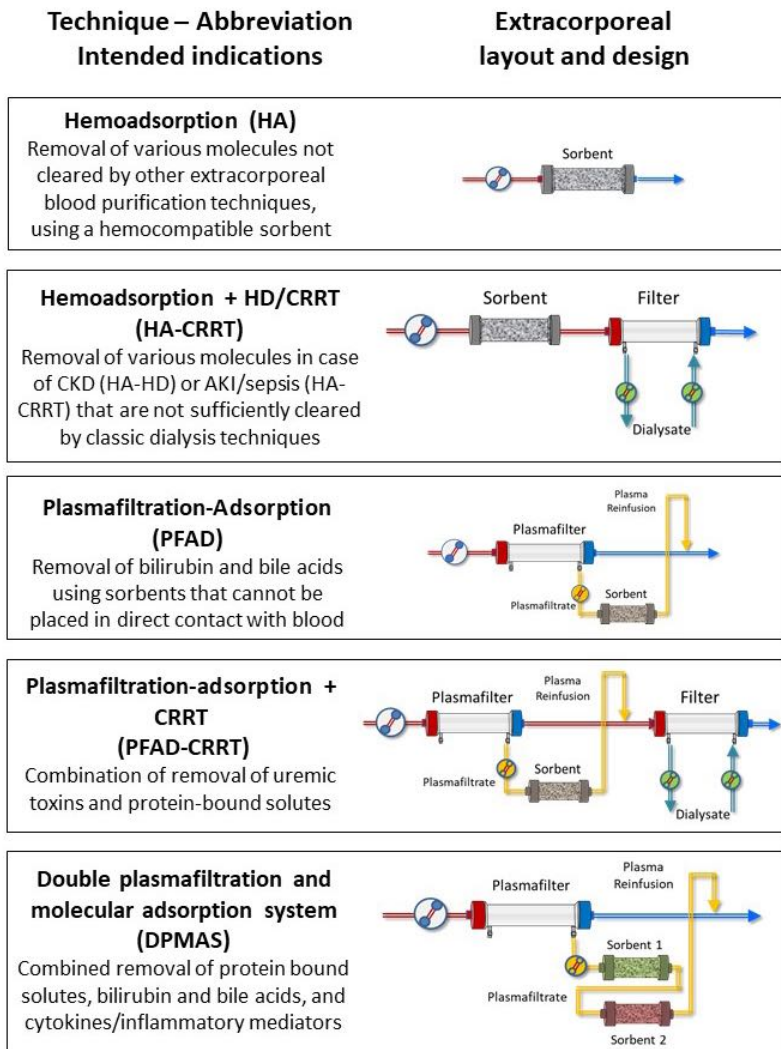
Modalities and indications for the clinical use of adsorption are reported in **Figure 5** (Ostermann et al. 2023).

**Haemoadsorption (HA):** indicated in sepsis and other cytokine-release syndromes, intoxications and poisoning, the technique is generally applied for repeated sessions of 6 to 12 hours each with a blood flow between 100 and 300 ml/min.

**Haemoadsorption + CRRT (HA-CRRT):** indicated in sepsis-associated AKI for removal of cytokines and uremic toxins, this technique combines a sorbent cartridge in series with a CRRT filter. The complete saturation of the sorbent occurs between 6 and 12 hours.

**Plasmafiltration-Adsorption (PFAD):** This technique utilises a plasmafilter in the extracorporeal circuit. The filtered plasma, processed through a sorbent cartridge, is subsequently reinfused in the venous bloodline, reconstituting the whole blood. The technique is indicated to remove bilirubin, bile acids and other protein-bound solutes in acute liver failure or decompensated cirrhosis.

### Extracorporeal techniques using isolated or combined adsorption mechanisms



**Figure 5.** Schematic representation of the sepsis population subdivided into different clinical phenotypes and specific endotypes describing the interaction between the pathophysiological mechanism and the patient response. If an infection is documented, antibiotic therapy is a priority, together with remediation of the infectious focus. When bacteria or viral particles are overwhelmingly high in the bloodstream, extracorporeal removal with affinity binders may be considered [11]. If endotoxin activity assay (EAA) shows a value between 0.6 and 0.9 units, extracorporeal removal with polymyxin-B haemoperfusion (PMX-HA) is indicated. If the phenotype is characterised by a cytokine release syndrome (CRS), haemoadsorption with cytokine adsorbers (HA) can be utilised in sequence with PMX-HA or isolated for repeated sessions of minimum 6 hours. In case of the presence of Stage-1 AKI, HA can be indicated to mitigate the severity of the CRS and progression towards stages 2 and 3 AKI. When organ failure (i.e. AKI stage 3 or acute liver failure) is present and due to persistent CRS, HA and extracorporeal organ support (CRRT, TPE or other ECOS therapies) can be combined with HA.

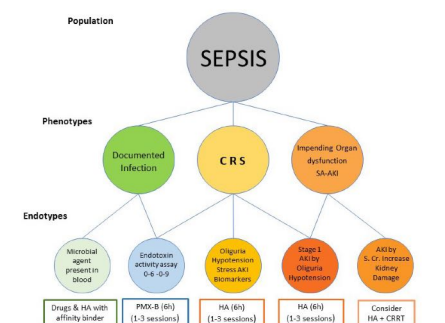
**Plasmafiltration-Adsorption + CRRT (PFAD-CRRT):** This technique combines PFAD with CRRT and is indicated to remove bilirubin, protein-bound solutes and uremic toxins in patients with combined liver and kidney failure.

**Double plasmafiltration and molecular adsorption system (DPMAS):** This technique utilises a plasmafilter in the extracorporeal circuit. The filtered plasma is processed through two different sorbent cartridges in series and is subsequently rein-

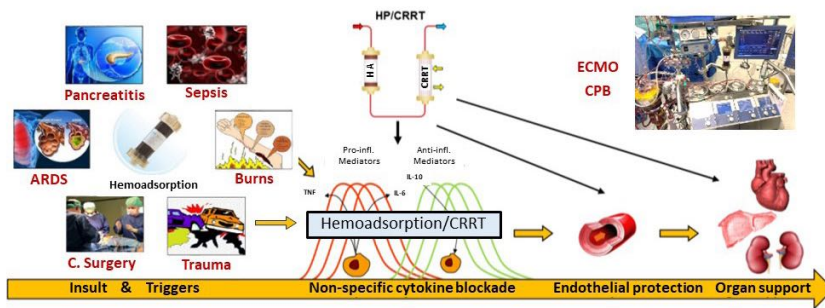
fused in the venous bloodline, reconstituting the whole blood. The technique is indicated in acute liver failure and decompensated cirrhosis to remove bilirubin, bile acids and other protein-bound solutes, together with circulating inflammatory mediators.

### Haemoadsorption in ICU: Who is the Ideal Candidate?

Current EBP applied to AKI and septic patients presents important limitations (White et al. 2023). As such, new and more effective techniques are needed. Studies on the application of HA have been limited to small populations, producing sometimes controversial results (Zarbock et al. 2023; Zarbock et al. 2023b; Virág et al. 2021; Houschyar et al. 2017). This is in part due to the heterogeneity of the study patients. HA can, in fact represent an effective treatment for critically ill patients characterised by peculiar phenotypes (Figure 6). It is now evident that both sepsis and SA-AKI are a mixture of syndromes in which the cause and the response of the host play an important role in creating specific endotypes with peculiar characteristics and clinical pictures (Kellum and Ronco 2023; Cruz et al. 2009; Dellinger et al. 2018). Among them are haemodynamic instability, variations in temperature and leucocyte/platelet count, microthrombotic/microangiopathic profiles, and oliguria



**Figure 6.** According to the peak concentration hypothesis, the figure suggests the potential role of HA in several clinical conditions. The presence of immune-dysregulation and cytokine release syndrome caused by infections, pancreatitis, burns, trauma, or cardiac surgery (including ECMO or CPB= cardiopulmonary bypass conditions). Non-specific cytokine blockade by HA or HA+CRRT may protect the endothelium and restore a certain degree of immuno-homeostasis with improvement in organ function.



**Figure 7.** Different pathological conditions may be at the origin of a cytokine release syndrome. In such conditions, a disruption of the host immune-response occurs with peaks of inflammatory and anti-inflammatory humoral mediators present in blood at different times. Since a targeted extracorporeal removal is impossible in the absence of a real-time cytokine measurement, the non-selective nature of haemo-adsorption with cytokine adsorber cartridges is indicated to restore immune-homeostasis and produce endothelial and organ protection effects.

(Klein et al. 2018). In recent years, the possibility of measuring endotoxin activity using a specific assay (EAA) has allowed clinicians to identify a specific patient endotype in which endotoxin is detectable in blood and may represent a target for extracorporeal removal. Polymyxin-B-coated polystyrene fibres have been included in a special adsorption cartridge and are capable of removal of circulating endotoxin up to approximately 20 µg in a two-hour treatment (Cruz et al. 2009; Dellinger et al. 2018). Analyses have demonstrated that positive results are more likely in patients with significant organ failure and in patients with endotoxin activity between 0.6 and 0.9 (Klein et al. 2018). New studies should, therefore, be focused on this specific phenotype (Iba and Klein 2019).

The same approach can be utilised to identify the right population affected by sepsis and/or sepsis-associated AKI. As described in **Figure 7**, sepsis and AKI are multifactorial syndromes, and only when presenting a specific endotype (Oliguria-based Stage 1 with sepsis or CRS-induced hypotension), there is a rationale for application of HA, even in the absence of any other RRT. In other stages, HA can be combined with CRRT if immunomodulation or cytokine removal beyond renal support is desired (Zarbock et al. 2023b; Ronco and Kellum 2024).

### Endpoints for Haemoadsorption Trials?

Once the right population has been identified, the endpoints for clinical trials should be clearly defined with a hierarchy of importance. For extracorporeal therapies such as HA, a progression from biochemical endpoints (removal of molecules) to biological endpoints (cellular effects of molecule removal such as enzymatic reactions, cellular functions, and immunological response) would be appropriate. Furthermore, pathophysiological endpoints (life parameters such as blood pressure, heart rate, PaO<sub>2</sub>/FiO<sub>2</sub>, diuresis, cardiac output, etc.) and then clinical endpoints (clinical outcomes including organ function and disease severity, need for dialysis, hospital-free days, mechanical ventilation free days, survival) should be considered. Survival represents the ultimate endpoint, but while trying to achieve sufficient evidence for this measure, it is important to avoid dismissing a treatment as ineffective because the right study has not yet been conducted. Evidence is a wall, and every small brick represents an addition to current knowledge. To advance in the acquisition of new evidence, it is important to share consensus on a structured research agenda (Bellomo et al. 2023) and proceed with collaborative efforts to build registries, well-designed studies, and big data collection.

### Available Clinical Data

Several studies have reported the use of HA in the setting of intoxication, poisoning or drug overdose (e.g. paraquat or organophosphates, mushroom-related toxins, pesticides, valproate, carbamazepine and other) (Ghannoum et al. 2014; Kawasaki et al. 2005). Studies report information concerning clearance and mass removal when sorbents are used in isolation or in series with continuous haemodialysis. Extraction rates vary from 20 to 90% (Baylis et al. 2022), and mitigation of severity of the clinical picture has been reported.

There is limited information on the use of HA and plasma-filtration adsorption for severe liver failure, even though there is a robust rationale for targeting ammonia or bilirubin in this setting (Kittanamongkolchai et al. 2017; Santoro et al. 2007). Few studies confirm the utility of the DPMAS in comparison to plasma exchange (Marcello and Ronco 2023; Guo et al. 2020; Wang et al. 2023), and a large study on more than 1400 patients seems to confirm these results (Chen et al. Ongoing trial).

Several trials have addressed the possible effectiveness of PMX-HA for the removal of endotoxin in patients with sepsis. The first trial was reported in 2009 under the name of the EUPHAS (Cruz et al. 2009). This study reported physiological advantages on blood pressure, gas exchange, and use of vasopressors with polymyxin B haemoperfusion. In addition, it found that polymyxin haemoperfusion decreased time to mortality. The second study was a multicentre randomised controlled trial of the early use of polymyxin B haemoperfusion in patients with septic shock due to peritonitis (Payen et al. 2015). A larger study was the EUPHRATES trial (Dellinger et al. 2018). This multicentre randomised controlled trial compared polymyxin B haemoperfusion to conventional therapy in 450 adult critically ill patients with septic shock and an endotoxin assay activity of 0.60 or higher in 55 North American hospitals. This trial found no survival advantage among all participants or in



the pre-specified subgroup of patients with a multiorgan dysfunction score > 9, both on intention to treat analysis or pre-protocol analysis.

A subsequent post-hoc assessment of the EUPHRATES study, however, has been conducted with a focus on the specific group of patients without extreme endotoxemia (Klein et al. 2018). In this subgroup of patients, haemoperfusion with polymyxin B appeared to carry a survival advantage on time-to-event analysis. A new study is currently underway in patients with endotoxaemic septic shock called TIGRIS (*Clinical Trials.gov identifier: NCT03901807*). This is a prospective, multicentre, randomised, open-label trial of standard medical care plus the PMX cartridge versus standard medical care alone in subjects with endotoxaemia and septic shock. Subjects in critical care areas will be assessed for septic shock using known or suspected infection, multiple organ failure, fluid resuscitation and hypotension requiring vasopressor support as primary criteria. Subjects will meet all entry criteria for study if endotoxin activity is within the range of  $\geq 0.60$  to  $<0.90$ . This study is scheduled to recruit 150 patients.

HA with non-selective cartridges represents a form of generic anti-inflammatory/immunomodulation HA strategy and has been studied in sepsis in the form of case series and comparative studies (Nassiri et al. 2021; Boss et al. 2021; Paul et al. 2021; Alharthy et al. 2021; Brouwer et al. 2019;

Schädler et al. 2017; Supady et al. 2021; Esmaeili Vardanjani et al. 2021; Sazonov et al. 2021; Huang et al. 2010; Huang et al. 2013; Chu et al. 2020; Sánchez-Morán et al. 2023; Lertussavivat et al. 2023; Becker et al. 2023).

Typical observations in the majority of studies were a remarkable reduction in Interleukin-6, tumour necrosis factor-alpha and other cytokines, significant reduction of inflammatory biomarkers (biochemical endpoints), Improved HLA-DR expression and monocyte function (biological endpoints), improved haemodynamic stability with reduction of vasopressor requirement (physiological endpoint), improvement in SOFA and other severity scores (clinical endpoints) and, in some studies, improvement of survival (ultimate endpoint). Data need to be further confirmed in larger trials and selected populations with homogeneous endotypes (Bellomo et al. 2024).

### The Haemoadsorption Research Agenda

The state of research in the field of haemoadsorption resembles that of continuous renal replacement therapy (CRRT) in the 1980s. Studies need to be done to establish the biological, physiological, and clinical effects of sorbent-based techniques. Just like diffusion and convection across semipermeable membranes have been extensively studied over a period of more than 50 years, the third approach of mass separation based

on the utilisation of solid agents (sorbents) should be explored to expand the future options provided by EBP. First, such research should first focus on achieving a better understanding of the basic aspects of the adsorption process. We need to understand the basic properties of each sorbent material, the mechanisms of adsorption and the potential side effects, including the unwanted removal of protective solutes such as antibiotics or nutrients (Bellomo et al. 2024; Migliorini et al. 2018; Ronco et al. 2001; Godi et al. 2021). We, therefore, need to establish a well-structured research agenda, in particular, the need to identify patient's endophenotypes that are likely to benefit from HA. We need to establish adequate dose, frequency, and criteria for HA application. We need to identify target molecules and biomarkers and find a way to perform effective biomonitoring; we need to identify adequate endpoints for clinical trials to establish solid evidence, and we need to consider potential side effects and contraindications for this therapy promoting a medical-industry alliance for the development of new and more safe and effective devices. Another area of research will be the thorough analysis of the cost-benefits of HA, possibly moving from a strict budget-oriented approach to a more ethically oriented strategy. All these steps will allow significant progress in the field for the benefit of the patients.

### Conflict of Interest

None.

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