Review Article

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KIDNEY RESEARCH AND CLINICAL PRACTICE

Expanding the potential therapeutic options of hemoperfusion in the era of improved sorbent biocompatibility

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Hemoperfusion has been considered a promising adjuvant treatment for chronic diseases and some acute states when specific removal of pathogenic factors from the bloodstream is desired. Over the years, advances in adsorption materials (e.g., new synthetic polymers, biomimetic coating, and matrixes with novel structures) have renewed scientific interest and expanded the potential therapeutic indications of hemoperfusion. There is growing evidence to suggest a prominent place for hemoperfusion as an adjuvant treatment in the setting of sepsis or severe coronavirus disease 2019 and as a therapeutic option for chronic complications associated with accumulated uremic toxins in patients with end-stage renal disease. This literature review will describe the principles, therapeutic perspectives, and the emerging role of hemoperfusion as a complementary therapy for patients with kidney disease.

Keywords: Adsorption, COVID-19, Hemodialysis, Renal dialysis, Kidney diseases

Introduction

The removal of unwanted plasma solutes and pathogens can be life-saving under certain conditions, such as sepsis, intoxication, and organ failure. Thus, the unique ability of hemoperfusion (HP) to adsorb specific molecules with large molecular weight (MW) and/or a high protein-binding affinity could explain why HP has been allured as a promising treatment for several diseases [1].

Whereas poisoning was once considered the classical indication of HP, advances in sorbents' biocompatibility and design have helped to expand its potential clinical indications to the treatment of inflammatory conditions (e.g., sepsis, pancreatitis, and hepatitis), autoimmune diseases, and chronic uremic symptoms [2].

The European Uremic Toxin Group classifies uremic toxins into three groups: small water-soluble toxins with an MW of <500 Da (e.g., urea and creatinine), middle molecules with an MW of ≥500 Da (e.g., parathyroid hormone [PTH], C-reactive protein, and β2-microglobulin [B2M]) that can be successfully removed by hemofiltration (HF) and high-flux hemodialysis (HD), and protein-bound solutes (e.g., homocysteine) which are not removed by classic HD or HF [3]. Moreover, as current dialysis techniques based on diffusion and convection show limitations due to membrane permeability characteristics [4], HP can be an attractive adjuvant modality for blood purification either alone or in combination with other renal- replacement therapies (RRTs). Besides, the high mortality rate attributed to cardiovascular disease and the outcomes of end-stage renal disease (ESRD) patients on HD have been correlated with blood levels of medium/large molecules insufficiently

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cleared by RRT [5].

Novel sorbents with greater biocompatibility and safety than before have renewed scientific interest in the broader implementation of HP [6]. Fig. 1 summarizes the advantages, disadvantages, and clinical conditions where HP can be considered.

Given the accumulation of encouraging data and the emerging new perspectives derived from research in HP as well as the current lack of consensus clinical guidelines, we aimed to conduct a literature review of the principles of HP, the evolution of sorbent materials, and the promising applications of HP in different clinical settings with a special focus on ESRD patients.

Principles of function and adsorption materials

According to the Consensus Conference on Biocompatibility, adsorption is the process of removing particles and toxins from the blood or plasma through their connection to the surface of the adsorbent, which lies in an extracorporeal purification machine [7].

Chemical and physical attraction forces are responsible for retaining the adsorbed molecules on the adsorbent. Physical forces include Van der Waals and hydrophobic interactions, whereas chemical interactions involve the formation of chemical bonds between the surface and the adsorbed species.

Adsorption materials can be found in nature or can be manufactured (e.g., synthetic polymers). Activated carbon produced from natural raw materials has shown a good adsorption capacity but poor biocompatibility [8,9]. Activated encapsulation technology or the use of activated carbon from other sources (resin-based) was considered for overcoming safety issues due mostly to the latter's rough surface [10]. With these modifications and alternatives, however, the adsorption capacity was influenced [11].

Inorganic porous materials present some important advantages, such as reusability and pore size variability, but adverse effects have been reported with their use [12–14]. Synthetic polymeric materials show remarkable functions, stability, and biocompatibility due to the tailor-made molecular design and/or surface modifications compared to natural polymeric materials. Notably, their low cost, hemocompatibility, and structure designability are their main advantages (Table 1) [15].

In general, adsorption materials can be found as gran-

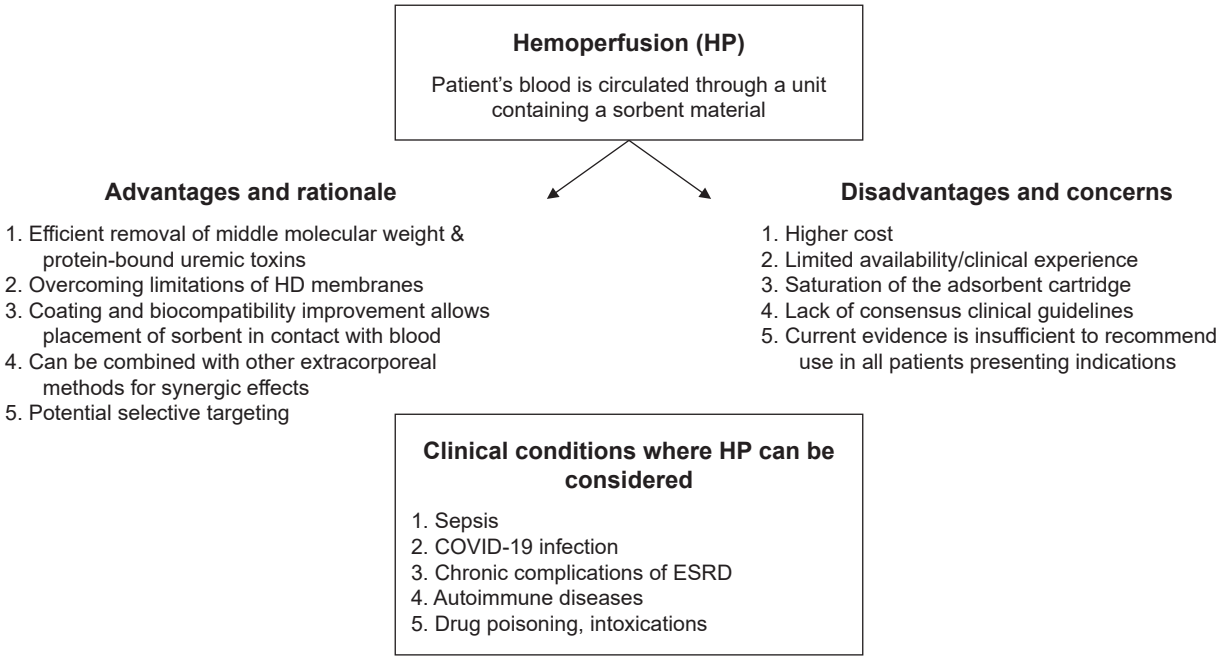

Figure 1. Overview of hemoperfusion technique.
HD, hemodialysis; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease.

Table 1. Summary of adsorbent types and their main advantages, disadvantages, and clinical indications

Adsorbent type	Advantage	Disadvantage	Example	Clinical availability	Clinical indication
Activated carbon (natural or resin-based) [8–11,15]	Low cost, high adsorption capacity	Poor biocompatibility	Adsorba (coated with cellulose acetate)	–	Intoxication
	Stable under physiological conditions	Lack of selective adsorption			
Inorganic porous material (e.g., mesoporous silica, silica gel) [12–15]	Reusability, pore size highly variable for different sizes of toxin molecules	High cost, variable results in biocompatibility, poor modifiability, limited structural design possibility	LiChroprep RP-18	–	Removal of bilirubin and uric acid, medicine removal
Natural (e.g., polysaccharide) or synthetic polymeric materials [15]	Hemocompatibility, high stability, bioinertia, structure designability and modifiability, low cost	Selectivity of natural polymeric materials not advantageous	CytoSorb, HA 330, Toraymyxin	+	Wide range

Data reproduced from references.

ules, spheres, fibers, cylindrical pellets, flakes, and powders. They are solid particles with diameters ranging from 50 μm to 1.2 cm. Their surface area to volume ratio is extremely high, with the surface area ranging from 300 to 1,200 m^2/g. Further classification of sorbents is based on their pore size, i.e., >500 Å (50 nm) (macroporous), 20 to 500 Å (mesoporous), and <20 Å (microporous).

Sorbents should also have favorable kinetics and transport properties. Isotherm equations and data from plotting curves known as adsorption isotherms during laboratory experiments provide information about the amount of sorbent required to remove a given amount of solute (Fig. 2) [1]. Moreover, packing sorbent particles into a cartridge requires a tortuous pathway (sorbent bed) through which blood or fluid must flow and be distributed uniformly. The mechanisms of solute adsorption in porous media include: 1) the external (interphase) mass transfer of the solute by convection from the bulk fluid and by diffusion through a thin film or boundary layer to the outer surface of the sorbent, 2) the internal (intra-phase) mass transfer of the solute by convection from the outer phase of the sorbent into the internal porous structure, and 3) surface diffusion along the surface of the internal pores and adsorption of the solute onto the porous surface (Fig. 3) [16].

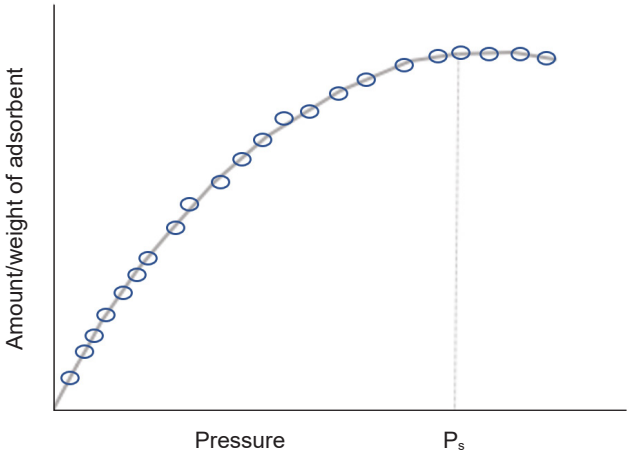

Figure 2. Example of adsorption isotherm graph. Adsorption increases steadily until it reaches equilibrium, which is when the concentration of the marker solute at the outlet of the unit is equal to the concentration at the inlet.
P_s, saturation pressure.

Biocompatibility

The ideal sorbent material for extracorporeal therapies is one that is biocompatible. Moreover, it should be characterized by hardness and mechanical strength to prevent crushing and erosion and to avoid any release of fragments into the systemic circulation. Additionally, since the blood is exposed to a larger surface in this context compared to other extracorporeal therapies, any cytotoxic reaction and immune system activation—clinically identifiable with the onset of rashes, shivers, leukopenia, and thrombocytopenia—must be prevented [17].

Therefore, surface coating is an attractive method to increase biocompatibility. Coating materials such as cellulose nitrate, albumin-collodion, cellulose acetate, and polyamide were initially evaluated by Chang [18], whereas

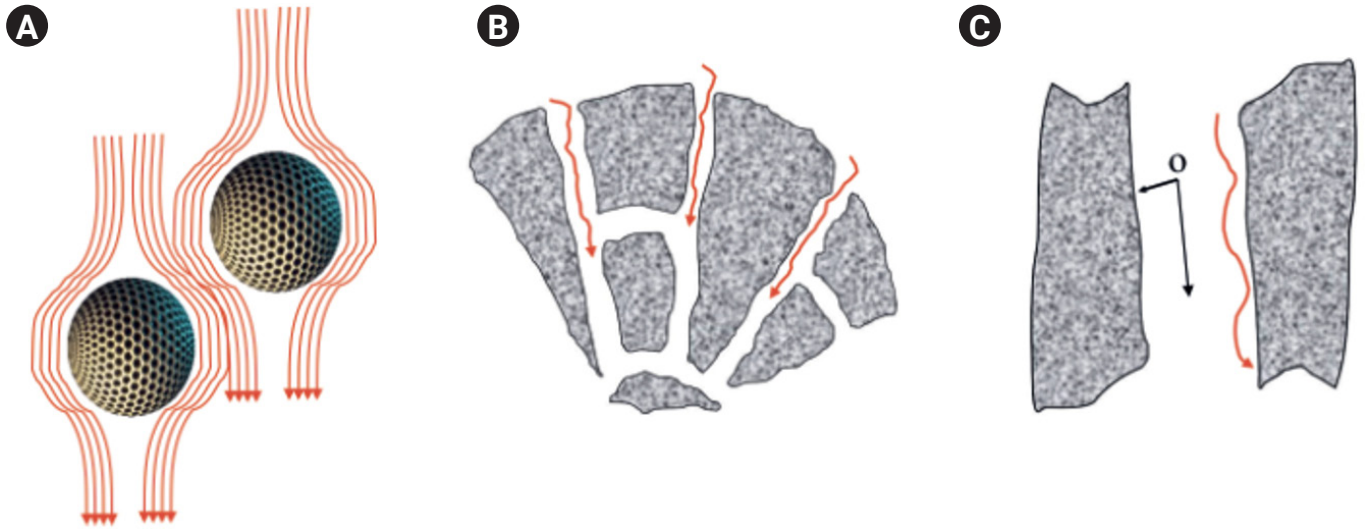

Figure 3. Mechanism of solute adsorption in porous media. Mechanisms of mass transport from the bulk solution to the sorbent surface. (A) External (interphase) mass transfer of the solute by convection from the bulk fluid by diffusion through a thin film of boundary layer to the outer surface of the sorbent. (B) Internal (intra-phase) mass transfer of the solute by pore convection from the outer surface of the adsorbent to the inner surface of the internal porous structure. (C) Surface diffusion along the porous surface and adsorption of the solute onto the porous surface. Reproduced from Clark et al. [16] with permission of Karger Publishers.

hydrogel was investigated by Andrade et al. [19]. Later on, various polymeric systems were developed to form stable protective coatings with better performances.

Anti-adhesion properties are also important for biocompatibility since the contact of blood with an artificial surface triggers a number of processes, including protein and cell adsorption and platelets' adhesion to the artificial surface. Thus, anti-adhesion modifications and surface coating using new materials like zwitterionic groups have received increasing interest [20]. Indeed, zwitterionic materials are highly resistant to non-specific protein adsorption, bacterial adhesion, and biofilm formation [21].

Selective targeting

Selective targeting of a key molecule as an endotoxin has promoted the concept of surface grafting. Besides, in complex biological media such as blood, they will always exist molecules of different origins that compete for the chemical adsorption site against the target molecules. By immobilizing a molecule with a specific affinity for the target molecule on the surface, a high affinity is obtained, mainly via a combination of electrostatic and hydrophobic interactions plus steric complementarity of both molecules rather than a covalent chemical bond formation [22].

Polymyxin B, an antibiotic derived from *Bacillus polymyxa* that binds and neutralizes endotoxin (an outer membrane component of gram-negative bacteria), and protein A, which binds anthrax toxin (a specific exotoxin secreted by virulent strains of the bacterium *Bacillus anthracis*), are typical applications of the surface grafting concept in cases of sepsis [23,24]. Except for antibiotics, other ligands (e.g., amino acids) have also been used [25]. Technological achievements in the genomic area have inspired the use of grafted nucleic acid-based ligands on adsorbents for the treatment of patients with systemic lupus erythematosus and hepatitis B [26,27]. Synthetic ligands also exhibit resistance to biological degradation and similar selectivity [28]. Finally, computation simulation has enabled the design of affinity ligands based on the structure of Asp-Phe-Leu-Ala-Glu (DE5), a sequence of toxic peptides frequently found in uremic patients [29].

Technical aspects of hemoperfusion

HP alone does not achieve sufficient removal of small uremic toxins and fluid balance; however, when combined with other HD techniques, a synergistic effect can be ob-

tained [6].

In HP, the cartridge is placed in direct contact with the patient's blood, with the basic requirements being an HP cartridge, double lumen catheter, vascular access, and an anticoagulant (heparin or citrate) [30]. HP is effective in removing uncharged molecules through competitive binding, especially those that are significantly plasma protein-bound and lipophilic. Indeed, HP targets molecules that tend to be more difficult to remove with conventional HD or with continuous RRTs (CRRT) and has the capacity to remove molecules with MW up to 30,000 Da depending on the characteristics of the sorbent material [31]. When combined with HD/CRRT, the sorbent can be placed before or after the dialyzer and enhance the removal of middle molecules that are not sufficiently removed by HD, such as B2M [32].

In the process of plasma filtration adsorption, plasma is first separated from the whole blood and circulates through the sorbent [33], then is returned to the whole blood, which can be subjected to HD or CRRT in order to expand the clearance of small solutes such as urea and creatinine. In this case, the use of both methods maximizes solutes' removal [34].

In double plasma filtration molecular adsorption system, different cartridges exhibiting specific characteristics can be placed in the plasma filtration circuit [35]. Finally, HP can be combined with extracorporeal membrane oxygenation [36].

Potential clinical applications of hemoperfusion and ongoing trials

Poisoning

Extracorporeal therapies for drug or chemical intoxication are indicated when there is life-threatening toxicity, an inadequate response to standard supportive measures, or the poison's endogenous clearance is <4 mL/min/kg and the poison's volume distribution is <1–2 L/kg [37].

Nowadays, the use of high-flux and high-efficiency dialyzers and the higher blood flow rates achieved, have established intermittent HD as the preeminent extracorporeal modality for poisoning. Moreover, HD is easily accessible; it removes poisons rapidly and simultaneously corrects any electrolyte and acid-base disorders [38]. In contrast, HP requires greater systemic anticoagulation; flows that do not exceed 350 mL/min so as to avoid the risk of hemolysis; and nonselectively adsorbs platelets, calcium, glucose, and white blood cells [39,40]. The higher cost and the need to replace the cartridge every 2 hours due to saturation are also important disadvantages of HP [41]. Finally, for some metals like lithium and alcohols (e.g., methanol, ethylene glycol), HP is not indicated due to less efficiency [42,43].

While HP use for poisoning has declined to roughly 1% of HD utilization in the United States [44], HP seems to be more effective than HD for paraquat poisoning [45]. HP achieves enhanced clearance of paraquat, leading to higher survival rates compared to high-flux HD [46]. With paraquat poisoning being an important concern mostly in Asia, current recommendations do not mention the use of extracorporeal treatment for it [37].

Currently, the strongly recommended method by the EXTRIP (Extracorporeal Treatments in Poisoning) group for the removal of most drugs is intermittent HD (https://www.extrip-workgroup.org/recommendations). In some cases, HP is an alternative option (1C or 1D) when HD cannot be performed (Table 2).

Sepsis

CRRT methods are widely used due to their capacity to retain body fluid balance and to correct electrolytic and acid-base imbalances in patients with sepsis and acute kidney injury (AKI). However, the removal of proinflammatory cytokines and complement fragments that promote kidney dysfunction and aggravate multiorgan dysfunction in the setting of septic shock is limited due to the limited permeability of the membranes [47]. Consequently, the use of high-flux HF and/or high cut-off membranes has been encouraged due to their removal capacity reaching up to 65 kDa. Unfortunately, their main disadvantage is the concomitant removal of important amounts of albumin. Therefore, HP and the design of biocompatible cartridges with the potential for customizing the target solutes have led to the increasing application of adsorption in sepsis and other inflammatory states such as coronavirus disease 2019 (COVID-19) (Table 3).

With selective HP being an alluring approach for removing circulating endotoxin and theoretically preventing the biological cascade in sepsis, research had focused on the

Table 2. List of drugs and the recommended extracorporeal therapy in case of acute poisoning

Drug	The first choice of extracorporeal modality	Acceptable alternatives
Acetaminophen	Intermittent HD (1D)	Intermittent HP (1D), CRRT (3D)
Baclofen	Not recommended (1D)	
Barbiturates	Intermittent HD (1D)	HP (1D) or CRRT (3D)
B-blockers		
Propranolol	Not recommended (1D)	
Atenolol	Intermittent HD (1D) only in severe poisoning with kidney impairment	
Sotalol		
Calcium channel blockers	Not recommended (1D)	
Carbamazepine	Intermittent HD (1D)	Intermittent HP (1D), CRRT (3D)
Digoxin	Not recommended (1D)	
Gabapentin/pregabalin	Intermittent HD (1D) only in severe poisoning with kidney impairment	
Isoniazid	Not recommended (2D), consider extracorporeal therapy where pyridoxine cannot be administrated (2D)	
Lithium	Intermittent HD (1D)	CRRT (1D)
Metformin	Intermittent HD (1D)	CRRT (2D)
Methanol	Intermittent HD (1D)	CRRT (1D)
Methotrexate	Not recommended (2D) when glucarpidase is not administrated, not recommended (1D) when glucarpidase is administrated, not recommended (1D) instead of administrating glucarpidase	
Phenytoin	Intermittent HD (1D)	Intermittent HP (1D)
Quinine/chloroquine	Not recommended (1D)	
Salicylates	Intermittent HD (1D)	Intermittent HP (1D), CRRT (3D)
Thallium	Intermittent HD (1D)	Intermittent HP (1D), CRRT (1D)
Theophylline	Intermittent HD (1C)	Intermittent HP (1C), CRRT (3D)
Tricyclic antidepressants	Not recommended (1D)	
Valproic acid	Intermittent HD (1D)	Intermittent HP (1D), CRRT (2D)

CRRT, continuous renal-replacement therapies; HD, hemodialysis; HP, hemoperfusion.

use of polymyxin-bound membranes. Besides, antiendotoxin drug therapies and intravenous polymyxin B have failed to prove a clinical benefit [48]. Therefore, direct HP with a polymyxin device (Toraymyxin; Today Industries Ltd.) was initially introduced and approved in Japan as an adjuvant sepsis therapy [49]. Later on, its use was expanded to other countries. Several randomized trials have provided conflicting results on the clinical benefit of polymyxin B in terms of mortality, hemodynamic parameters, and respiratory function of patients with septic shock due to an abdominal cause compared to conventional care [50–52]. Currently, the TIGRIS study (NCT03901807), a prospective, multicenter, randomized open-label trial, is investigating the effects of standard medical care plus polymyxin-based HP versus the standard care of treatment.

Regarding nonselective HP, extracorporeal cytokine adsorption with the CytoSorb cartridge (CytoSorbents Corporation) has been investigated in case series and small comparative studies [53–55]. CytoSorb consists of specially designed polymers with large surfaces, high flow, and low resistance. It is indicated for clinical situations with high plasma concentrations of cytokines. CytoSorb binds cytokines 10 to 50 kDa in size, with a removal rate of >90% to 95% [56]. However, in a multicenter randomized trial comparing conventional care with CytoSorb in ventilated patients with sepsis and either acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), no significant differences in interleukin (IL)-6 concentration were observed [57]. In a recent randomized controlled trial (RCT; the REMOVE trial), the authors failed to demonstrate a reduction in postoperative organ dysfunction or 30-day mortality with intraoperative use of CytoSorb in patients undergoing cardiac surgery for infective endocarditis. Even though CytoSorb achieved a lower level of plasma key cy-

Table 3. Summary of characteristics and main results of the most frequently used HP filters in the field of sepsis and COVID-19 infection

Filter	Selectivity	Targets	Indications	Combined treatment	Results
Toraymyxin (Today Industries Ltd.) [49–52,69]	+	Endotoxins, inflammatory mediators, cytokines	Sepsis with positive culture for Gram-negative bacteria/high endotoxin activity assay level, severe sepsis or septic shock from an abdominal cause, COVID-19 infection with septic shock		Higher hemodynamic and ventilation parameters Unclear results for mortality
CytoSorb (CytoSorbents corporation) [53–58,69–78]	-	Inflammatory mediators, cytokines, albumin-bound substances and pathogenic toxins but not effective removal of endotoxin	Severe sepsis or septic shock (cytokine storm) and ARDS, COVID-19 infectiona	HD SCUF CRRT ECMO	Higher hemodynamic parameters and improved respiratory distress Unclear results for mortality and for reduction of IL-6
HA series (Jafron Biomedical Company) [59–62,69]	-	Inflammatory mediators, cytokines, complement, free hemoglobin and myoglobin	Severe sepsis or septic shock +/– acute lung injury, COVID-19 infection	CRRT ECMO	Reduction of inflammatory cytokine levels and improved hemodynamic parameters Unclear results for mortality
oXiris (Baxter Inc.) [64–68,70,83–85]	-	Endotoxins, inflammatory mediators and cytokines with potential antithrombogenic properties	COVID-19 infection[a], sepsis with AKI	Stand-alone filter for SCUF and CRRT	Reduction in inflammatory markers and improved hemodynamics Limited experience on mortality
Seraph 100 Microbind Blood Affinity Filter (ExThera Medical Corporation) [70,79–82]	-	Pathogens and proinflammatory cytokines	COVID-19[a]	HD CRRT	Improvement in circulatory dysfunction and in inflammatory markers (CRP and IL-6), initial results showing lower mortality
Spectra Optia Apheresis and Depuro D2000 Adsorption Cartridge (Terumo BCT) [70,86]	-	Endotoxins, inflammatory mediators and cytokines	COVID-19[a]	Therapeutic apheresis	Limited experience

Data reproduced from references.
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRRT, continuous renal-replacement therapy; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; IL, interleukin; SCUF, slow-continuous ultrafiltration.
[a]Devices approved by U.S. Food and Drug Administration for the treatment of severe COVID-19 infection.

tokines, no clinical benefit was obtained [58].

HP with the Jafron HA cartridges (Jafron Biomedical Company) has also been tested in acute respiratory failure caused by sepsis, with prominent results concerning hemodynamic parameters, respiratory function, and mortality within 28 days of hospitalization [59]. The HA 330 cartridge has an electrically porous resin that specifically removes cytokines, complements, and other endotoxins with MWs of 10 to 60 kDa. HA 330-based HP was studied in multiple cohorts in the context of inflammatory conditions such as sepsis, ALI, hepatitis, and pancreatitis [2]. In a small nonrandomized study, intensive care unit (ICU) mortality and length of ICU stay were found to be better in septic patients receiving HA 330-based HP compared to those given standard therapy, albeit with no effect on mortality [60]. Encouraging results come from a case series of children with sepsis and underlying hematological disorders receiving HA 330-based HP as an adjunctive treatment to counterbalance the cytokine storm [61]. In another study, patients with ALI induced by extrapulmonary sepsis were randomized to HA 330-based HP or standard therapy. In the HP group, significant reductions in the duration of mechanical ventilation and ICU stay and the ICU mortality rate were observed. Improved respiration parameters were also observed and correlated with the significant removal of inflammatory cytokines (tumor necrosis factor [TNF] and IL-1). In a recent study by Chu et al. [62], the combination of the same cartridge with pulse high-volume HF in

patients experiencing septic shock led to beneficial effects on cardiovascular physiology and greater decreases in IL-6, IL-10, and TNF-α concentration when compared to patients who received continuous venous-venous HF.

Finally, the AN69-based oXiris membrane (Baxter Inc.), which is a heparin-grafted membrane specifically designed for cytokine and endotoxin adsorption, alongside RRT, presents three layers: 1) AN69 copolymer hydrogel structure that adsorbs cytokines and removes solutes via convection through membrane pores, 2) a multilayer structure of polyethyleneimine that adsorbs endotoxin and offers better biocompatibility, and 3) a heparin graft that reduces local thrombogenicity [63]. *In vitro* comparison of oXiris with Toraymyxin and CytoSorb revealed similar efficacies in lipopolysaccharide clearance and inflammatory mediator clearance, respectively [64]. However, there are a limited number of studies to support its action in septic shock compared to the above-mentioned products [65–67].

Viral infections, including severe acute respiratory syndrome coronavirus 2

Uncontrolled cytokine response was considered the hallmark of severe COVID-19 during the first months of the pandemic [68]. Several extracorporeal blood-purification techniques have been used in COVID-19 patients to restore "immune homeostasis" by removing inflammatory molecules [69].

Recently, experts' recommendations state that, in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and cytokine release syndrome, cytokine-removal strategies should be reserved for COVID-19 patients with evidence of high levels of circulating cytokines like IL-6 and IL-8, a biochemically determined inflammatory status, a high SOFA (Sequential Organ Failure Assessment) score, clinical symptoms of hemodynamic instability requiring vasopressors, and initial signs of immune dysregulation or coagulation disorders [69]. Polymyxin-based HP is indicated in the early phase for suspected sepsis (indicated by a high procalcitonin level and/or positive bacterial culture) or an elevated endotoxin level proven by activity assay. If HP is indicated for cytokine removal, sessions with CytoSorb or HA 380 might follow.

In fact, the U.S. Food and Drug Administration (FDA) has approved four blood-purification devices to treat COVID-19, including 1) CytoSorb, 2) the Seraph 100 Microbind Affinity Blood Filter (ExThera Medical Corporation), 3) the oXiris Filter, and 4) the Spectra Optia Apheresis System (Terumo BCT) [70].

The first case of CytoSorb use in conjunction with CRRT in a critically ill patient with COVID-19 was reported by Rizvi et al. [71], underlining a plausible contribution to early improvement in inflammatory markers. Other case-control and retrospective studies followed, highlighting a potentially beneficial role of adjuvant HP with CytoSorb in the early phase of COVID-19 in terms of cytokine reductions (mainly IL-6 levels), a better clinical course with less need for vasoactive agents, and the improvement of respiratory distress. However, data on mortality rates were inconsistent [72–77]. Indeed, in a recent prospective, randomized pilot study with 50 COVID-19 patients receiving CytoSorb for 3 to 7 days or standard therapy, HP did not improve the resolution of vasoplegic shock (primary outcome) or the predefined secondary endpoints, which included mortality, IL-6 concentration, and catecholamine requirement [78]. Ongoing randomized trials and a large registry of CytoSorb therapy in COVID-19 ICU patients (NCT04391920) aim to enrich the current literature regarding the role of CytoSorb as a potential therapy in severe COVID-19 [70].

HP with the Seraph 100 Microbind Affinity Blood Filter, a biomimetic adsorber that has been shown to bind pathogens, including SARS-CoV-2, from the blood using ultra-high MW adsorptive beads [79], received Emergency Use Authorization for severe COVID-19 from the FDA. Olson et al. [80] were the first to report its use in COVID-19 patients with ARDS and septic shock who required mechanical ventilation. Rapid improvement in vasopressor needs, overall circulatory dysfunction as well as C-reactive protein and IL-6 levels were noticed following the initiation of HP. Similar results were documented by Sandoval et al. [81] who used Seraph 100 in four elderly, multimorbid ESRD patients on HD with severe COVID-19. Data from the COSA (COVID-19 patients treated with the Seraph 100 Microbind Affinity filter) registry support that Seraph 100 treatment is easy to deploy either as a stand-alone HP treatment or in combination with RRT. The observed mortality rate was lower than that calculated by established scores, but the data are limited due to the lack of a control group [82]. Initial data from an observational retrospective study (PURIFY-OBS-1; NCT04606498) suggest improvements in

the survival of severely ill COVID-19 patients treated with Seraph 100.

Evidence of significant reductions in inflammatory markers and improved hemodynamics, organ function, and clinical outcomes with oXiris comes mostly from case series, the oXirisNet registry, and small observational studies [83–85]. An RCT (oXAKI-COV Study; NCT04597034) is ongoing and aims to demonstrate the clinical efficacy of AN69-oXiris compared to the AN69 standard membrane in decreasing vasopressor requirements to sustain a stable mean arterial pressure in critically ill patients with COVID-19 and AKI requiring CRRT.

Finally, the Spectra Optia Apheresis System provides therapeutic apheresis in combination with HP with the Depuro D2000 adsorption cartridge. The Depuro D2000 cartridge is composed of activated uncoated coconut shell charcoal and the non-ionic resins Amberlite XAD-7HP and Amberchrom GC300C, and its placement downstream in the apheresis circuit allows for cytokine removal with subsequent return of the treated plasma to the patient. Its use as a rescue therapy for cardiogenic shock due to stress-cardiomyopathy in severe COVID-19 has been reported only in a single patient by Faqihi et al. [86]. An ongoing large multicenter single-arm clinical trial (Plasma Adsorption in Patients With Confirmed COVID-19; NCT04358003) of the United States is expected to provide information about the effects of the D2000 cartridge with the Optia protocol on morbidity and mortality rates of COVID-19 patients admitted to the ICU.

Maximizing toxin removal and clinical benefits in patients with end-stage renal disease

ESRD has been increasingly recognized as an inflammatory state with protein-bound uremic toxins (PBUTs) and middle molecules like B2M being key factors and inducing various cardiovascular complications. Therefore there is a rationale for the increasing research on synergic approaches that combine HP with other dialytic techniques to achieve complementary elimination of metabolites and effectively prevent and treat complications and improve clinical outcomes [6,87].

Regarding overall survival, a systematic review and meta-analysis showed that the combination of HD with HP improves survival rates [88].

Important ameliorations of blood pressure—even in dialysis patients with refractory hypertension—and left ventricular mass index, reduced dosages of epoetin, and higher hemoglobin levels, have been reported when HD with HP are combined compared to HD alone [89–91]. Considering the more pronounced decrease in levels of myocardial enzymes associated with the combination of HP and HD, it was speculated that their concurrent use can lighten the cardiovascular burden and protect the myocardium [92]. Besides, the improvement of microinflammatory indicators associated with the combination of these therapies could partially explain the lower incidence of cardiocerebrovascular events and the improvement of anemia in patients who had received both HP and HD treatment [93].

Along the same lines, in a study by Raine et al. [94], apart from the greater reduction in inflammation markers, an important improvement in the indices of nutritional status occurred in the HD plus HP group.

Greater benefits in terms of B2M and PTH reductions have been shown by several studies when HP and HD were combined.

Hence, there are potential to improve secondary hyperparathyroidism, pruritus, and dialysis-related amyloidosis [95–97].

Interestingly, based on the reported relationship between the intestinal environment and renal disease, HP combined with dialysis showed encouraging results with respect to the potential improvement of microbiota disorders. Indeed, significantly higher levels of beneficial bacteria like *Lactobacillus acidophilus* and lower levels of harmful bacteria such as *Escherichia coli* were reported in colony distributions of patients receiving HP combined with HD plus hemodiafiltration compared to patients receiving HD plus HF [98]. Research is now focusing on promising sorbent materials—such as a divinylbenzene sorbent coated with polyvinylpyrrolidone (DVB-PVP) and cellulose with hexadecyl chains—which show a high adsorption ability of PBUTs or hydrophobic cytokines. A synergistic effect on the reduction of PBUTs was recently demonstrated during HD therapy combined with DVB-PVP resins and symbiotic formulation [99].

Moreover, improved sleep disturbance and sleep efficiency accompanied by an increase in nocturnal melatonin levels were reported with HP therapy (1–2 times/wk) for 2 years [100].

Finally, there is some evidence that the combination of HP with HD can improve the life quality of ESRD patients [97,101]. Symptoms like skin itching, fatigue, sleep quality, and sexual function were significantly improved by adding HP, probably due to the greater clearance of middle and large molecular toxins such as PTH and B2M [88].

Experimental indications of sorbent use in systemic diseases with kidney involvement

Some interesting results have arisen from case series of patients with systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and vasculitis with and without renal involvement [102,103]. Improvements in renal function and dialysis independence following HP sessions in combination with chemotherapy have also been reported in a patient with cast nephropathy [104]. Finally, AKI can occur as a side effect of medications used in autoimmune disease; thus, HP could also be of value in this context. A recent small case series of patients with high-dose methotrexate-induced AKI showed a possibly positive effect of using charcoal HP as a rescue therapy until glucarpidase is available [105].

Conclusion

Whereas HP was once only indicated for treating poisoning from certain substances, emerging evidence suggests that other indications might be also considered. Advances in the biocompatibility of new cartridges and the selective removal of key molecules in different clinical settings and diseases like sepsis, hepatitis, and SARS-CoV-2 infection have been considered as the triggering force in that direction. With the increasing research interest in the removal of PBUTs and their involvement in CKD-related systemic complications, HP is also regaining its place as a vital accessory to dialysis treatment.

Despite this progress, current clinical use of HP remains limited, with possible reasons including the cost of performance, local practice or physician preference, a lack of consensus clinical guidelines and established indications for HP, and the absence of consistent data derived from RCTs.

In conclusion, the role of HP remains a point of discussion until its clinical effectiveness can be verified by further positive RCTs. Although in this era of disease-targeting treatments new indications are being investigated, efforts to better evaluate the applicability of HP and to shed light on the role of HP in current clinical practice are needed.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: All authors
Investigation: AD, ES, ZA
Supervision: AD, DP
Writing–original draft: AD, ES, ZA
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