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REVIEW

Practical points of hemoperfusion in the intensive care unit

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ABSTRACT:

In cases of critical illness, some patients may experience adverse outcomes due to the excessive release of mediators or exposure to various toxins. These conditions can potentially lead to multi-organ failure and, ultimately, death. Hemoperfusion has emerged as an increasingly utilized method for blood purification, involving the removal of solutes by binding them to adsorbent materials. Currently, this technique is being employed in intensive care units to effectively clear many of the mediators and improve these critical conditions.

Hemoperfusion has demonstrated promising results in various conditions, including sepsis, severe Acute Respiratory Distress Syndrome (ARDS), acute liver failure, and severe Coronavirus Disease 2019 (COVID-19). Nonetheless, ongoing trials investigating various hemoperfusion techniques have yielded mixed results, necessitating further confirmation through additional studies.

Drawing upon my clinical experience and existing evidence, I advocate for a more personalized approach to initiating hemoperfusion therapy. I recommend evaluating each case individually and tailoring the treatment to optimize outcomes.

Keywords: Blood purification; Hemoperfusion; Severe COVID-19; Acute respiratory distress syndrome

INTRODUCTION

Immune dysregulation arises due to exposure to various toxins or the excessive release of certain mediators into the circulation. This process may cause the massive production of both pro-inflammatory cytokines, resulting in excessive hyperinflammatory responses, and anti-inflammatory cytokines, which can lead to relative immunoparalysis and trigger secondary infections. The overwhelming release of both types of cytokines can cause injury to both the infected and distant organs, ultimately resulting in life-threatening clinical conditions [1].

Hemoperfusion is an increasingly utilized modality for blood purification, where solute removal is achieved by binding molecules to adsorbent materials. This technique is currently employed in the intensive care unit to clear many of the mediators that drive immune dysregulation. It achieves this by binding specific molecules, such as endotoxins, or through the non-specific adsorption of pro-inflammatory mediators. Hemoperfusion has shown some positive effects in various conditions characterized by excessive systemic inflammatory responses, such as sepsis and severe Acute Respiratory Distress Syndrome (ARDS) [2,3]. However, trials involving several hemoperfusion techniques have yielded mixed results in conditions like septic shock [4], severe Coronavirus disease 2019 (COVID-19) [5], and other conditions associated with excessive cytokine release. These mixed results may necessitate further confirmation through additional studies.

Extracorporeal membrane oxygenation (ECMO) is increasingly employed to provide support for various life-threatening conditions, especially refractory shock and severe respiratory failure. In the context of ECMO use, many patients may experience an exaggerated hyper-inflammatory response, which is observed both during ECMO utilization and in critically ill patients [6]. Despite the recent introduction of numerous hemoperfusion devices designed to mitigate elevated levels of inflammatory molecules, there remains a lack of clinical evidence supporting their effectiveness.

Based on my clinical experiences and the current evidence [7], especially during the COVID-19 pandemic, I can introduce an innovative practical concept of hemoperfusion for clinical practice. In this paper, I provide a summary of the rationale behind hemoperfusion in the intensive care unit, available data, primary indications, technical aspects of hemoperfusion during ECMO support, and offer recommendations based on current studies and my clinical experience.

KEY MESSAGES:

- Several critical illnesses result from either the presence of various toxins or the excessive release of cytokines, contributing to multiple organ failures and increased mortality.
- Hemoperfusion is a recent technique developed for the selective and non-selective targeting of molecules, such as endotoxins and cytokines. It has demonstrated beneficial effects in various conditions, including septic shock, ARDS, substance overdose, acute liver failure, and severe COVID-19.
- This technique could be considered an adjuvant therapy for critically ill patients with specific indications, necessitating a tailored approach to achieve favorable outcomes.

RATIONALE OF HEMOPERFUSION

The mass separation process of blood purification can be performed using different extracorporeal techniques [8]. Diffusive solute transport, as seen in standard hemodialysis (HD), and convective solute transport are techniques based on semipermeable membrane separation, allowing for adequate correction of acid-base imbalances, electrolyte levels, and volume control. However, both techniques may have limitations for cytokine removal due to membrane permeability [9]. The other mechanism for mass separation is solute adsorption, which is based on using a solid agent called a 'Sorbent.' This technique can be carried out through direct hemoperfusion (HP) or plasma perfusion after plasma separation.

Hemoperfusion or hemoadsorption is a technique that involves circulating a patient's blood through a cartridge containing sorbents. Devices equipped with sorbent beds possess several advantages, including a notably high surface-to-volume ratio, excellent biocompatibility, and a substantial capacity for binding specific solutes. The process of solute adsorption is influenced not only by perfusion but also by the surface characteristics of the sorbent materials, their interactions with specific substances, and the potential for these interactions to take place on the surface of the sorbent particles [10].

TECHNICAL ASPECTS OF HEMOPERFUSION

Hemoperfusion can be performed through an extracorporeal circuit, necessitating vascular access via a catheter inserted into a central vein. Various techniques can be employed for this procedure (as depicted in Figure 1A-1D), which include:

1. *Direct hemoperfusion (HP):* In this approach, the patient's blood or plasma is directly circulated through a cartridge, allowing it to come into contact with sorbent beds. The blood flow rates vary depending on the cartridge's size and type, typically ranging from 100 to 250 ml/min (as shown in Figure 1A).

2. Hemoperfusion Combined with Dialysis or Continuous Renal Replacement Therapy (CRRT) Machine: Hemoperfusion can be seamlessly integrated with hemodialysis or CRRT by positioning the sorbent either before or after the dialyzer (as depicted in Figure 1B). Some specific membrane filters, such as modified surface-treated polyacrylonitrile (AN69) named oXiris® (Baxter, Meyzieu, France), can execute both hemofiltration and hemoperfusion within the same cartridge when employed with a CRRT machine (as illustrated in Figure 1C).

3. *Plasmafiltration-adsorption (PFAD)*: This technique involves separating plasma from the blood, routing the patient's plasma through the sorbent, and subsequently returning it to the circuit (as illustrated in Figure 1D). Another related method is coupled plasma filtration adsorption (CPFA), which combines initial plasma separation with the adsorption of cytokines and inflammatory mediators, followed by a second stage of hemofiltration to manage volume and eliminate small water-soluble mediators.

TYPES OF HEMOPERFUSION CARTRIDGES

Recently, sorbents have undergone development to enhance their biocompatibility and potential efficiency as biomaterials. They are typically formulated as beads, granules, fibers, spheres, or cylindrical pellets, with diameters typically ranging from 50 μm to 1.2 cm. These sorbents exhibit an exceptionally high surface-area-to-volume ratio (S/V), with surface areas spanning from 300 to 1,200 m^2/g. Multiple factors, including the type of polymer, sorbent design, packing, flow characteristics, and saturation levels, collectively contribute to the diverse array of sorbents available, each with distinct clinical effects and indications. Refer to Table 1 for a comprehensive list of currently accessible extracorporeal blood purification cartridges.

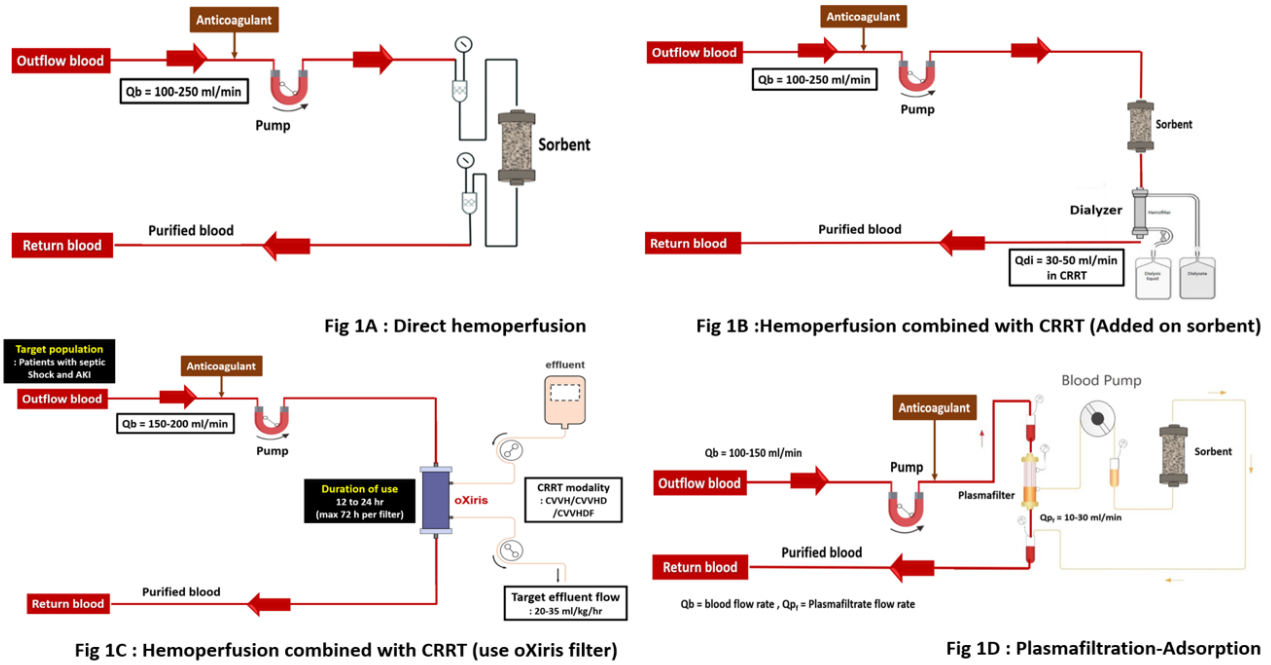

Figure 1A-1D. Schematic configuration of possible aspects of hemoperfusion (Modified from reference No 3)
Abbreviation: Qb: blood flow rate; Qpf: plasma-filtrate flow rate; CRRT: Continuous renal replacement therapy.

Table 1. Selection of currently available extracorporeal blood purification devices.

Devices	Material	Adsorption spectrum	Treatment type	Blood flow (ml/min)	Duration of single device
Toraymyxin (PMX-HP)	Polystyrene-based woven fibers with immobilized polymyxin B	Endotoxins	HP	100-120	2 hr
Seraph-100	Polyethylene beads with end-point-attached heparin	Bloodstream pathogen	HP	250-300	3-4 hr
oXiris	Hollow fibers (AN69 coated with PEI and unfractionated heparin)	Endotoxins and Cytokines	CRRT (Adsorption and convection)	120-200	72 hr
Cytosorb	Polystyrene divinylbenzene microporous beads	Cytokines	HP	150-500	12-24 hr
HA-Jafron Series	Styrene -divinylbenzene copolymer	Cytokines	HP	100-250	2-4 hr (may be up to 24 hr depends on hybrid Rx)

(Modified from reference No 2,4) Abbreviation: AKI: Acute kidney injury; AN69: Acrylonitrile and sodium methylal sulfonate copolymer membrane; PEI: polyethyleneimine; HP: hemoperfusion; CRRT: Continuous renal replacement therapy.

GENERAL INDICATIONS OF HEMOPERFUSION IN THE INTENSIVE CARE UNIT (ICU)

Recently, there have been no absolute indications for hemoperfusion in the intensive care unit (ICU) due to the limited availability of strong evidence supporting the real and effective role of extracorporeal blood purification therapies in the critical care setting [2,3]. Nevertheless, our understanding of specific biologically and pathophysiologically rational indications has advanced. I can summarize the potential indications for hemoperfusion as follows:

1. *Intoxication*

Hemoperfusion can be employed for patients who have been exposed to intoxication with various substances, including drugs [11,12,13] such as valproate, carbamazepine, benzodiazepines, and metformin, toxic chemical compounds [14,15] like paraquat or organophosphates, or toxic natural products [16] such as mushroom-related toxins. However, it's important to note that the current evidence primarily stems from observational studies and case reports, with a lack of existing randomized controlled trials.

At present, the most commonly used hemoperfusion devices are non-specific polystyrene divinyl benzene resin-based systems, such as Cytosorb® (CytoSorbents

Corp., Monmouth Junction, NJ, USA) or the HA230 cartridges (Jafron Biomedical, Guangdong, China). These devices have demonstrated more benefits than other blood purification techniques like dialysis or hemofiltration in certain cases involving toxic substances, such as Amanita, Paraquat, Isoniazid, Barbiturate, Digitoxin, Methotrexate, and others [17,18,19].

2. *Liver failure*

There is potential for hemoperfusion to be used in conjunction with the double plasmafiltration molecular adsorption system (DPMAS) to lower total bilirubin levels and mitigate inflammatory agents. A recent meta-analysis has shown that when DPMAS is combined with plasma exchange, it can decrease the occurrence of adverse reactions, enhance the effectiveness of treatment, and improve the 90-day survival rate [20]. Furthermore, an observational study has suggested that hemoperfusion may also play a role in the treatment of refractory cholestatic pruritus [21]

3. *Conditions with uncontrolled cytokine release (Cytokine storm)*

Hemoperfusion may be recommended for a wide range of critical conditions characterized by hyperinflammatory mediators and uncontrolled cytokine release [2,3,4]. These conditions include severe pancreatitis, ARDS, sepsis/septic shock, severe burns, post-cardiac surgery, multiple traumas, and more. However, the implementation of these strategies presents several challenges, primarily due to the presence of numerous targets and variations in patients' conditions. In the following sections, I will examine the specific indications for each of these conditions, as outlined below.

(1) Sepsis/Septic shock

The primary approach for treating sepsis has traditionally centered around administering timely and effective antibiotics, ensuring proper hydration, managing vasoactive agents, and implementing standard source control procedures. Nevertheless, despite these adequate therapeutic measures, some patients still experience a high mortality rate from sepsis and septic shock. In these cases, the presence of the pathogen itself, molecules derived from the pathogen (referred to as Pathogen-associated molecular patterns, or PAMPs), and elevated plasma levels of cytokines may directly contribute to unfavorable outcomes [4,22]. It is noteworthy that every stage of septic pathogenesis presents potential targets for specific extracorporeal interventions. Therefore, I should consider employing various hemoperfusion techniques at different stages to address distinct factors and ultimately achieve the desired outcome, as illustrated in Figure 2.

For the purpose of pathogen removal, Seraph®-100 (ExThera Medical in Martinez, CA) employs heparin as a surface to capture pathogens effectively, displaying a broad capability to remove various pathogens. Studies have shown a substantial reduction in bacterial load in patients with bacteremia following Seraph®-100 hemoperfusion [23]. Furthermore, the Seraph®-100 heparinized medium has demonstrated the ability to bind several damage-associated molecular patterns (DAMPs), including histones, nucleosomes, high mobility group box 1 (HMGB1), and platelet factor 4 (PF4) [24].

Endotoxin, specifically Lipopolysaccharides (LPS), can initiate all the fundamental aspects of sepsis and induce direct cytotoxic effects that contribute to organ failure. Polymyxin B hemoperfusion is a recognized method for removing endotoxins [4]. However, the results of the two largest studies conducted so far, namely the Effects of Hemoperfusion with Polymyxin B in Peritonitis-induced Septic Shock, or ABDOMIX trial, and the Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock, or EUPHRATES trial, did not demonstrate a survival advantage with this hemoperfusion technique. Nevertheless, upon reanalyzing a subgroup of EUPHRATES study patients who had endotoxin activity assay (EAA) levels between 0.6 and 0.9, improvements were observed in hemodynamics, ventilator-free days, and mortality [25]. These findings are set to be confirmed through a forthcoming large-scale study (ClinicalTrials.gov identifier: NCT03901807). Notably, a recent prospective observational case series explored the use of adjunctive polymyxin B hemoperfusion in children with refractory septic shock. After undergoing two hemoper-

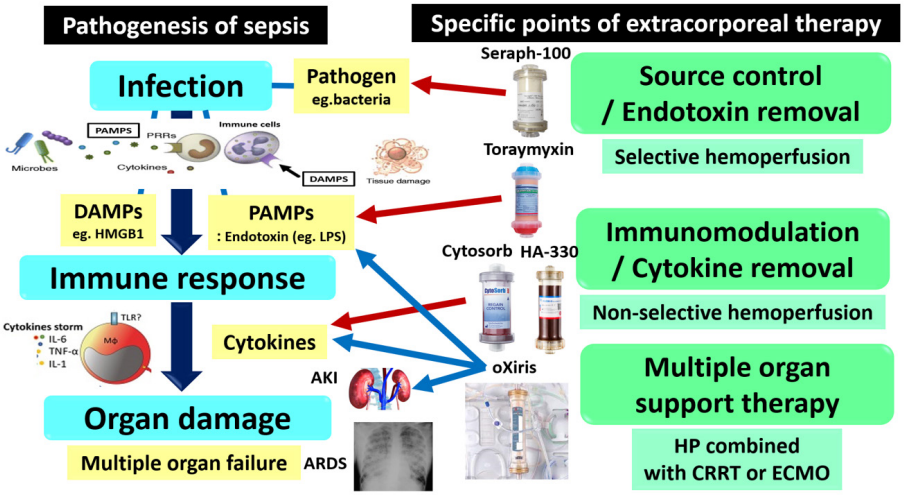

Figure 2. Pathogenesis of sepsis and specific points of available extracorporeal therapy devices (Modified from reference No 4)
Abbreviation: AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; DAMPs: Damage-associated molecular pattern; PAMPs: Pathogen-associated molecular pattern molecules; HP: Hemoperfusion; CRRT: continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation.

fusion sessions, clinical hemodynamics improved significantly, along with reductions in severity of illness scores, and importantly, no device-related adverse events were recorded [39].

Sepsis is typically characterized by elevated cytokine levels, significantly increasing the risk of death. This concept forms the basis for extracorporeal therapies designed for cytokine removal. Due to the larger molecular sizes of cytokines, which exceed the capacity of dialysis membranes, nonspecific hemoadsorption is recommended and can be carried out through direct hemoperfusion or by connecting it to a Continuous Renal Replacement Therapy (CRRT) machine.

In recent times, direct hemoadsorption has been performed using two types of sorbent units [4]: Cytosorb® (CytoSorbents Corp., Monmouth Junction, NJ, USA) and Jafron HA-330 or 380 (Jafron Biomedical, Guangdong, China). A multicenter open-label randomized trial was conducted, which included 100 mechanically ventilated patients diagnosed with sepsis or septic shock, and acute respiratory distress syndrome. In this trial, Cytosorb® hemoperfusion was compared to conventional therapy, with hemoperfusion administered for 6 hours per day for up to 7 consecutive days. While the study showed a significant reduction in interleukin-6 (IL-6) levels, with approximately 5-18% IL-6 elimination observed during single-pass IL-6 extraction, there were no notable differences in IL-6 levels, the multiple organ dysfunction score, ventilation duration, or the trajectory of oxygenation improvement [26].

Hemoperfusion using the Jafron HA cartridge series has been employed in the treatment of sepsis and has been the focus of several randomized studies. In one open-label randomized study, 46 septic patients with acute lung injury were included. This study compared daily treatment with HA-330 cartridges for three consecutive days to standard sepsis care. The benefits of HA-330 hemoperfusion were significant, encompassing substantial reductions in Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 (IL-1) levels. Additionally, improvements were observed in lung function, duration of mechanical ventilation, the necessity for continuous renal replacement therapy (CRRT), and even 28-day mortality rates (67% in the hemoperfusion group compared to 28% in the control group) [27]. In another randomized study, the objective was to assess the clinical efficacy of combining HA-330 hemoperfusion with pulse high-volume hemofiltration in 30 septic shock patients. The interventional group demonstrated significant reductions in cytokine levels and doses of norepinephrine. However, it's important to note that this approach did not lead to a significant impact on mortality rates [28].

The heparin-coated oXiris ® hemofiltration membrane has been improved by adding a layer of positively charged polyethyleneimine (PEI) polymer. This modification enables the adsorption of endotoxins in the second layer, placed on top of an enhanced AN69 membrane that simultaneously adsorbs cytokines and toxins. Furthermore, oXiris® serves as a versatile CRRT membrane capable of performing dialysis, hemofiltration, and hemoadsorption. In a small randomized crossover double-blind design study involving patients with septic shock-associated acute kidney injury (AKI) and endotoxin levels exceeding 0.03 EU/ml, CRRT using oXiris® was compared to CRRT employing a standard high-flux hemofilter. The results indicated that oXiris® led to more significant reduction in endotoxin levels, TNF-alpha, and IL-6 levels compared to the standard filter groups. Moreover, the infusion rate of norepinephrine was reduced during oXiris® CRRT but remained unchanged during standard filter CRRT [29]. In another retrospective cohort study examining the clinical outcomes of oXiris-CRRT in comparison to standard filter-CRRT in septic shock patients, the use of oXiris® was associated with lower mortality. Additionally, it appeared to result in reduced lactate levels, lower norepinephrine dosages, decreased procalcitonin levels, and lower white blood cell counts when compared to standard filter CRRT [30].

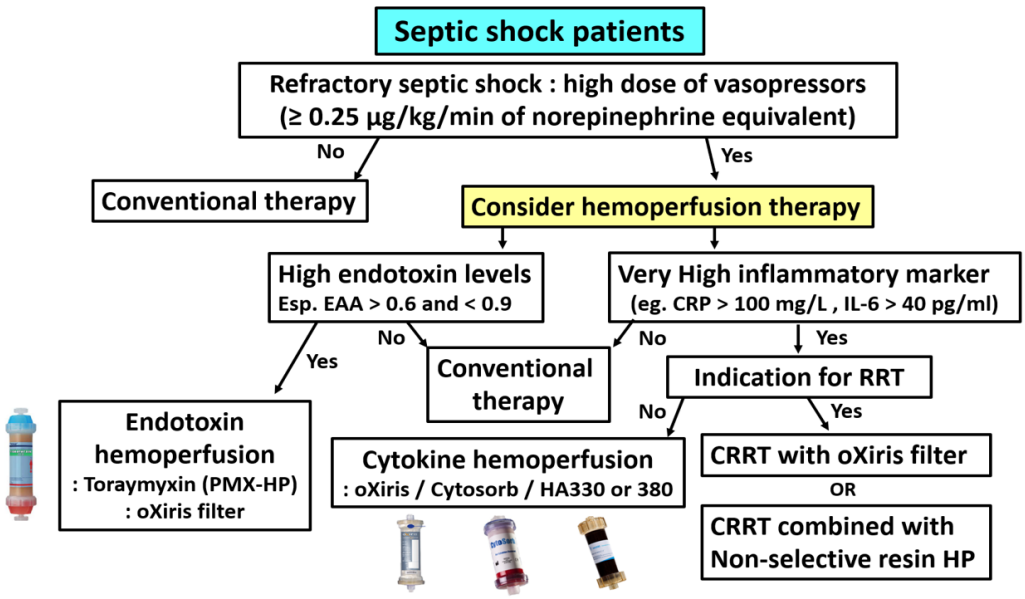

Figure 3. Potential applications of cytokine and endotoxin hemoadsorption in sepsis (Modified form reference No 34)
Abbreviation: PMX-HP: polymyxin B hemoperfusion; CRRT: continuous renal replacement therapy; EAA: endotoxin activity assay; HP: hemoperfusion; CRP: C-reactive protein; IL-6: Interleukin-6.

I can summarize and visually represent the potential applications of cytokine and endotoxin hemoadsorption in septic shock, as illustrated in Figure 3, as follows:

(2) Severe COVID-19

Patients with severe forms of COVID-19 may develop serious conditions characterized by uncontrolled systemic hyperinflammation due to the excessive production of pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and IL-6. This hyperinflammation can lead to complications such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), multiple organ failure (MOF), and even death [31]. Recently, the treatment strategies for severe COVID-19 have shifted their focus towards reducing viral load and mitigating inflammation, which includes the use of corticosteroids, IL-6 inhibitors, and Janus kinase (JAK) inhibitors [32]. Extracorporeal blood purification (EBP) methods, employing various techniques, have emerged as promising adjunctive therapies for mitigating excessive inflammation in COVID-19 patients at high risk of organ dysfunction. These methods have been recommended during the recent consensus conference of the Acute Disease Quality Initiative as potential adjunctive therapeutic tools for critically ill COVID-19 patients [33].

Due to the diverse clinical presentations of COVID-19, it's important to recognize that potential hemoadsorption therapy may not be suitable for all COVID-19 patients. The decision to use this technique with critically ill patients should be based on an individualized assessment. Hemoadsorption therapy may be especially suitable for COVID-19 patients who manifest a hyperinflammatory phenotype, marked by elevated levels of biomarkers such as IL-6, ferritin, C-reactive protein (CRP), and D-dimer [34].

The devices utilized for hemoperfusion in severe COVID-19 patients have primarily included Cytosorb® and Jafron HA330 or 380. However, clinical experiences are limited and mainly stem from case reports and small observational studies. Notably, there is a notable absence of large-scale studies, particularly randomized trials assessing cytokine hemoadsorption in critically ill COVID-19 patients. Stockmann et al. [35] conducted a prospective, randomized controlled pilot study involving 49 COVID-19 patients experiencing vasoplegic shock necessitating a high dose of norepinephrine with C-reactive protein levels exceeding 100 mg/L. These patients were randomized into two groups: one receiving CRRT with Cytosorb® (N=23), and the other receiving CRRT without an adsorbent cartridge (N=26). The study observed no significant differences in the effects on inflammatory markers, catecholamine requirements, or the incidence of adverse events between the two groups. As a result, they reported that Cytosorb® hemoperfusion did not lead to improved resolution of vasoplegic shock or a reduction in mortality. In another open-label randomized controlled study conducted by Supady et al. [36], patients with severe COVID-19 pneumonia requiring veno-venous (VV)-ECMO were compared. Seventeen patients received Cytosorb® hemoadsorption for 72 hours, while another 17 patients received standard therapy with ECMO support alone. The authors found that early initiation of cytokine adsorption in severe COVID-19 patients undergoing VV-ECMO did not result in a reduction of serum IL-6 levels and was associated with an increased risk of mortality within 30 days.

Conversely, I conducted a single-center prospective cohort study [7] to compare the early use of HA-330 hemoperfusion in conjunction with standard therapy in severe COVID-19 patients characterized by an excessive hyperinflammatory state and severe pneumonia, in contrast to standard treatment alone. Hemoperfusion with the Jafron (HA-330) machine was administered for 4 hours per session daily for three consecutive days. My study revealed that HA-330 hemoperfusion led to improvements in C-reactive protein levels, chest X-ray infiltration scores, outcomes related to organ failure (measured by the Sequential Organ Failure Assessment Score or SOFA score), and an increase in the number of mechanical ventilator-free days. Furthermore, it showed potential for significantly reducing 28-day mortality rates. My study underscores the importance of initiating hemoperfusion during the early stages of hyperinflammatory states, before the onset of multiple organ failures, and the careful selection of patients, particularly those exhibiting high inflammatory markers, as crucial factors in patient selection.

Seraph®-100 has also recently demonstrated the ability to effectively clear the nucleocapsid protein (N-protein) of the SARSCoV-2 virus [40] from the bloodstream, potentially offering benefits for severe COVID-19 patients. In a retrospective cohort study [41], efficacy outcomes were compared among COVID-19 patients with critical illnesses, with 53 patients treated with Seraph® and 53 patients receiving no treatment. The study initially indicated that Seraph®-100 led to improvements in vasopressor-free days and a reduction in in-hospital mortality. However, upon conducting further analysis and making adjustments, it was determined that the significant difference in vasopressor-free survival was not achieved, and the observed mortality benefit did not persist when compared to an external control group in post-hoc analysis.

I can summarize the potential applications of cytokine and endotoxin hemoadsorption in severe or critically ill COVID-19 patients in Figure 4 as follows:

CYTOKINE ADSORPTION THERAPY DURING EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Why we need to combine hemoperfusion with ECMO ?

Extracorporeal membrane oxygenation (ECMO) is increasingly utilized to provide support for individuals facing severe respiratory and cardio-circulatory failure. During ECMO treatment, a significant systemic response is often observed in many patients [6, 37]. This systemic reaction can be attributed to various factors, encompassing situations where ECMO is employed to manage systemic inflammatory responses, such as cardiogenic shock, the

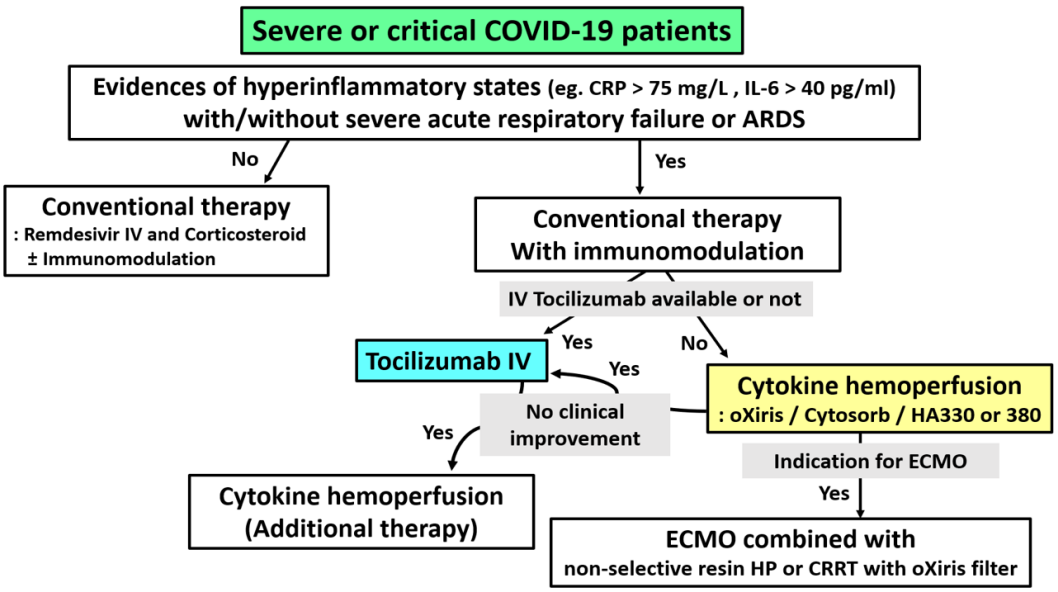

Figure 4. Potential applications of cytokine hemoadsorption in severe and critical COVID-19 patients (Modified form reference No 34) Abbreviation: CRRT: continuos renal replacement therapy; HP: hemoperfusion; CRP: C-reactive protein; IL-6: Interleukin-6; ECMO: Extracorporeal membrane oxygenation.

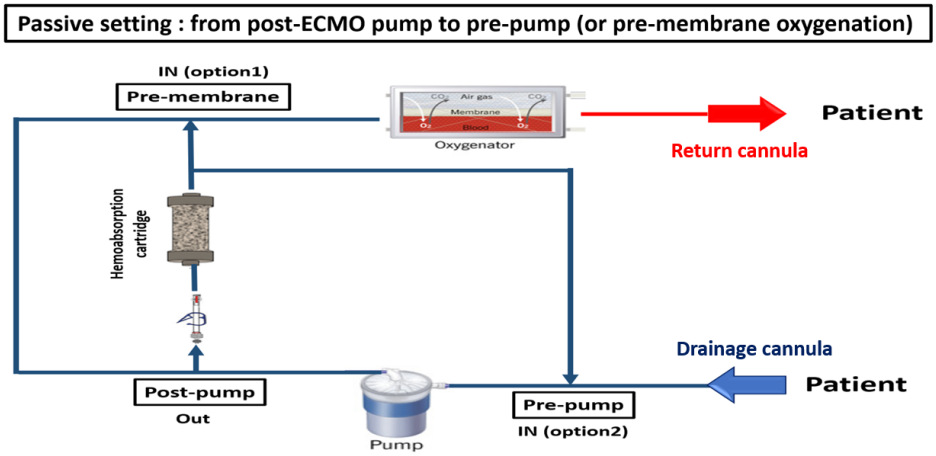

Figure 5A.

Figure 5A. Integration of hemoperfusion system in passive setting : Venous blood of the patients get drawn before post-ECMO pump and return to pre-ECMO pump or pre-membrane oxygenation (Adapted from reference No 6)

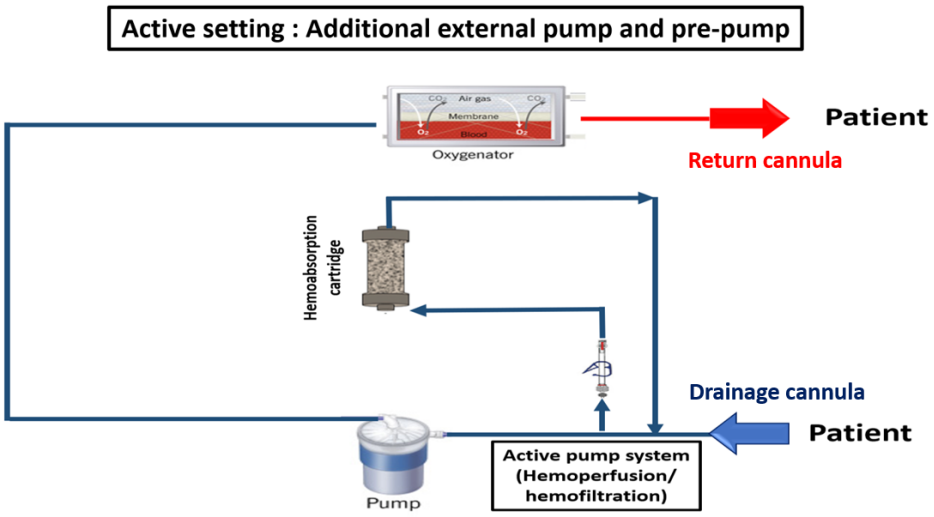

Figure 5B.

Figure 5B. Integration of hemoperfusion system in active setting : Venous blood of the patients get drawn and returned before ECMO pump by using active pump of hemoperfusion systems (Adapted from reference No 6)

post-cardiac arrest state, severe acute respiratory distress syndrome, and severe COVID-19 with cytokine release syndrome. Additionally, it includes the systemic inflammatory responses that can occur during ECMO itself [37]. These responses involve processes like cellular activation, fibrinolysis, complement activation, secondary von-Willebrand syndrome, hemolysis, and end-organ hyperperfusion. Notably, this process is marked by an elevation in IL-6 levels, which, in turn, results in increased vascular permeability. Ultimately, this can lead to high mortality rates and unfavorable neurological outcomes [38]. Consequently, the consideration of cytokine adsorption therapy may emerge as an appealing treatment option in these complex clinical settings [6].

Technical aspects of connecting hemoadsorption with ECMO

Hemoperfusion devices can be integrated with ECMO devices through two options as follows:

1. Integration of a hemoadsorption system to ECMO circuit

When combining hemoadsorption devices with an ECMO device, they can be integrated using a low blood flow rate within a CRRT circuit and/or a direct hemoperfusion circuit system. The potential connection of the hemoperfusion system can be carried out actively or passively, as illustrated in Figure 5A-5B. It is crucial to take safety considerations into account, particularly the potential impact on ECMO flow rate reduction and the risk of accidental disconnection of a high-flow circuit, which could have adverse consequences [6, 37].

2. Separation of hemoperfusion systems from the ECMO circuit

The cytokine hemoperfusion system can be operated using other readily available venous access points. This technique may not necessitate a complex setup, requires less expertise, and can be easily performed without concerns related to ECMO circuit issues.

At present, there is a lack of definitive recommendations and conclusive evidence regarding the preferred techniques that should be the primary choice. Achieving optimal performance in this context requires personalized management, which involves considering factors such as the type of hemoperfusion, timing, duration, dosing, and the elimination of adsorptive drugs, with a particular emphasis on antibiotics [6].

Evidences of cytokine adsorption therapy and ECMO

1. Severe COVID-19

Hemoperfusion can be performed in severe COVID-19 patients with cytokine release syndrome, particularly when contemplating ECMO support. Some case studies have reported swift reductions in vasopressor demand, rapid hemodynamic stabilization, decreases in IL-6 levels, enhancements in chest X-rays, and improvements in acute kidney injury outcomes [39]. However, as mentioned earlier in the randomized study [36], the use of Cytosorb® hemoperfusion during ECMO support did not result in reduced IL-6 concentrations. Furthermore, it may increase the risk of mortality within 30 days after initiating ECMO. Therefore, before initiating cytokine hemoadsorption, careful consideration of the risk-benefit ratio, optimal timing for initiation, and specific patient conditions is crucial.

2. Other critical conditions with cytokine releasing syndromes

There is a rapidly growing body of published cases and case series that highlight the promising efficacy and safety of hemoadsorption during ECMO. These benefits encompass improvements in hemodynamics, reductions in vasopressor usage, and the stabilization of metabolic parameters. Potential indications for the use of cytokine hemoadsorption during ECMO include sepsis/septic shock, post-cardiac arrest syndrome, post-cardiotomy cardiogenic shock, ARDS, severe rhabdomyolysis, acute liver failure, and more [37]. However, as of now, there is no standard guideline recommending the routine use of cytokine hemoadsorption in clinical practice. Therefore, the decision to employ hemoperfusion should be meticulously considered on a case-by-case basis.

CONCLUSION

Hemoperfusion techniques now exist to remove inflammatory and other mediators from circulation. Recent studies have shown that sorbent-based hemoperfusion therapies can yield positive outcomes, including a reduction in inflammatory markers, improved organ function, and lower mortality rates. These evolving treatments demand a tailored approach, necessitating further research for specific patient selection and desired outcomes.

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