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Hemoadsorption: One Name, Varied Techniques

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Abstract:
Background: Despite significant efforts to improve outcomes for patients with sepsis and septic shock, mortality rates remain alarmingly high.
Summary: Beyond standard management, novel adjuvant treatments seek to improve outcomes through a personalized approach. Among these, immunomodulation strategies aim to reestablish a balance in the dysregulated immune system, managing both pro-inflammatory and anti-inflammatory mediators. In recent years, various techniques utilizing extracorporeal circuits equipped with filters or cartridges, collectively referred to as blood purification therapies, have been developed and introduced to the market. Hemoadsorption, whether used alone or in conjunction with hemofiltration, may clear a broad range of substances from the blood, including inflammatory mediators, drugs, trace elements, bacteria, and viruses.
Key Messages: Understanding the fundamental principles of blood purification techniques is essential for enhancing survival probabilities, keeping in mind the principle of *primum non nocere* as a guiding tenet of our daily practice. This review aims to give an overview of hemoadsorption techniques by presenting current evidence and highlighting key areas that require further investigation.

Introduction:
Sepsis is a life-threatening syndrome caused by an immune response that leads to organ damage. Mortality from sepsis is estimated at around 11 million each year, with an incidence of nearly 50 million cases worldwide [1]. The origin of the infection leading to sepsis, characterized by organ damage indicated by a 2-point increase in the Sequential Organ Failure Assessment (SOFA) score, varies: pulmonary in half of the cases, abdominal and genitourinary infection in 15-30% of cases each, and bloodstream or skin/soft tissue in the remaining patients [2]. The type of infectious agent also varies, with Gram-positive and Gram-negative

bacteria being more common over fungal or viral infections (however, the incidence of viral sepsis can significantly increase during pandemics)[3]. Regardless of the origin of the infectious agent, sepsis can occur at any age, with incidence varying throughout life. It is characterized by a dysregulated immune response that leads to organ damage. This results from a complex interaction between the pathogen, its characteristics of quantity and virulence, and a multifaceted, elaborate, multi-component inflammatory response globally termed "maladaptive"[4]. Several components of the inflammatory system and its response to the infectious agent, such as the production of pro-inflammatory and anti-inflammatory cytokines, contribute to organ damage and the continuation of the dysregulated immune response[2,5]. The management and treatment of sepsis and septic shock aim to eradicate the infection (e.g., broad-spectrum combined antibiotics, source control), improve organ perfusion and mitochondrial oxygenation, and ensure organ support until a condition of immune balance is restored, enabling the gradual recovery of cellular, tissue, organ, and system functions [6]. Recommendations from the global guidelines, such as Surviving Sepsis Campaign [6], have significantly reduced treatment variability, contributing to a decrease in mortality from sepsis and septic shock [7]. Despite improvements, mortality remains consistently high, and additional treatments termed "adjuvant", have become available. Given the extreme heterogeneity of sepsis (host factors, pathogen type, immunocompetence, immune response, site of infection, chronic diseases, chronic therapies, acute treatments), it becomes crucial to identify subpopulations that would benefit more from specific treatments (such as immunosuppression, immune stimulation or immune modulation) [8]. Hemoadsorption (blood purification based on mass separation by a solid agent—i.e., sorbent) is the third blood purification mechanism, alongside techniques based on membrane separation: convection (e.g., CVVH, continuous veno-venous hemofiltration) and diffusion (CVVHD, continuous veno-venous hemodialysis) [9]. Some solutes are very large and cannot be removed by standard renal replacement therapies (RRT) techniques. In this context, hemoadsorption techniques are considered "adjuvant therapies" for sepsis, aiming to restore the immune balance through elimination of specific solutes that led to the deranged host-pathogen interaction occurring during the infection. Beyond traditional hemodialysis techniques for blood purification, hemoadsorption can also be used in conditions where traditional dialysis faces technical limitations: states of hyperinflammation (e.g., pancreatitis, sepsis, septic shock), liver failure, intoxication by drugs and protein-bound toxins, and intoxication by non-water-soluble toxins.

Main text

Technology, materials, and techniques

Hemoadsorption technology involves direct contact between blood (or plasma) and an adsorbent surface (sorbent). Early applications (such as inorganic aluminosilicates (zeolites) and charcoal) used materials with poor biocompatibility, leading to serious complications (like thrombocytopenia, leukopenia, hypoglycemia, hypocalcemia). This caused a slowdown in the development of these technologies (e.g., organic polymer ion exchange resins and finally synthetic porous polymers—styrene or acrylic acid-based) that have found renewed interest in recent years[9,10]. Recent advancements in materials synthesis have produced potentially useful sorbents in clinical practice, particularly early experiences with polymyxin-B-coated cartridges for lipopolysaccharide (LPS) removal. These developments have sparked ongoing research and innovation in this field.

Sorbents are manufactured in many ways, including beads, particles, flakes, fibers, spheres, or cylindrical pellets with variable dimensions (from 50 μm to 1.2 cm). They possess a high surface area to mass ratio, varying from 300 to 1,200 m^2/g, which helps to magnify their adsorptive capacity [11]. Large polymers of divinylbenzene can be manufactured into beads and made more biocompatible by coating them with polysulfone. This structural design provides vast adsorption surface area (>1,000 m^2/g) in cartridges containing 200-300 g of material. Adsorbent materials are housed in cartridges with an inlet port (for the entry of plasma or blood) and an outlet port. Once blood comes into contact with the adsorbent material, solute removal occurs through various physical mechanisms, including van der Waals forces, hydrophobic bonds (the main mechanism), and weak ionic bonds, all contributing to the adsorption process. Some techniques separate the plasma from the blood corpuscular elements, preventing contact between the cells and the sorbent [11,12]. Optimal packing density generally ranges between 35% and 55% of the available space. Once the binding between the solute and the adsorbent material is complete, the cartridge becomes saturated and no longer available for the blood purification process. In clinical use, the global solute kinetics are influenced by various factors, including the extracorporeal blood flow and the initial concentration of the solute. A key aspect of hemoadsorption is the selectivity of target solutes. As discussed below, there are

systems specifically designed to bind certain solutes and systems that indiscriminately adsorb numerous substances. All these factors inevitably impact the clinical efficacy of treatment concerning the type of patient, the type of infection, and the characteristics of the host-pathogen interaction.

Technical aspects

To apply an adsorption technique, an extracorporeal circuit and a cartridge are required. The extracorporeal circuit typically involves a hemodialysis or a continuous RRT (CRRT) machine, or in certain instances, a basic blood pump equipped with pressure alarms. Blood is drawn from the vascular access (typically central venous access; double-lumen catheter) into the cartridge, allowing the purification process (chronic patients are also treated during dialysis via an A-V fistula)[13]. Anticoagulation (e.g., heparin, citrate, or other agents) of the extracorporeal circuit should be individualized based on patient characteristics, session duration, and the selected technique. Extracorporeal circuits can be exclusively dedicated to the hemoadsorption or be integrated elements in CRRT machines (figures 1-3). Blood pushed through a pump circulates within the cartridge at a rate of about 150 mL/min (100-200 mL/min)[11]. This process can also be associated with different extracorporeal circuits such as cardiopulmonary bypass systems or extracorporeal membrane oxygenation (ECMO) systems (figures 1-3)[9].

Technique #1: Hemoadsorption via a stand-alone hemoperfusion (figure 1 A): blood is pumped through a sorbent cartridge, coming into direct contact with the particles.

Technique #2: Hemoadsorption in a CRRT circuit (figure 1 B): hemoadsorption of combined with hemofiltration/hemodialysis. The adsorption cartridge is placed in series either before or after the dialyzer membrane.

Technique #3: Continuous Plasma Filtration and Adsorption (CPFA) (figure 2 A). In this method, plasma is extracted from blood, passed through the sorbent (cartridge), and then reinfused back into the circuit. The CPFA technique can be integrated into a CRRT machine (figure 2 B) to enhance the effectiveness of treatment for small solutes like urea and creatinine.

Technique #4: Hemoadsorption in combination with ECMO machine (figure 3). In patients receiving veno-venous or veno-arterial-ECMO, hemoperfusion can be linked to the ECMO circuit. Comparable circuits can also be established during cardiopulmonary bypass.

Although these methods have had successful technical implementation without adverse events, clinical research detailing more extensive validation is required. Initially, it is essential to determine the solute kinetics and isotherms for specific solutes across various devices; secondly, additional investigation is required to establish the ideal treatment duration, cartridge saturation, and the risk of clotting; finally, in the clinical setting and daily practice, it is essential to accurately identify patient phenotypes, establish criteria for both the initiation and termination of hemoadsorption, determine the optimal "adsorption dose" for an individual patient, and identify marker molecules and clinical parameters that can assess the therapy's effectiveness and aid in designing future trials [9].

Clinical Use of Hemoadsorption

Although the predominant clinical use of adsorption systems is dedicated to patients with vasoplegia from sepsis, they can also be applied in other areas: adsorption of drug, both endogenous and exogenous toxins [9], acute liver failure (e.g. targeting ammonia or bilirubin or treatment of intractable cholestatic pruritus) [14] and kidney disease with the accumulation of substances that cannot be removed by dialysis (e.g., beta 2-microglobulin, or uremic toxins) [11,15]. Hemoperfusion was associated in better survival in previous studies on paraquat ingestion, showing that hemoperfusion may offer better clearance than high-flux hemodialysis [11]. Amanita phalloides, barbiturates, theophylline, aluminum, Hemoperfusion can also be indicated for other intoxications, including Amanita phalloides mushroom, carbamazepine, and valproic acid intoxications can also be treated with hemoperfusion [16]. To date there are no controlled studies on these applications.

The application of blood purification techniques in sepsis aims to attenuate the effect of soluble mediators of inflammation to restore immune system balance. This approach has been the primary objective of numerous studies to restore the pathophysiological balance in a dysregulated immune system. Hemoadsorption techniques fit within the framework of blood purification to ensure greater clearance of soluble mediators of inflammation.

In the area of hemoperfusion for sepsis treatment, two distinct approaches have been established: one that selectively targets a single specific molecule (such as endotoxin or lipopolysaccharide, LPS) and another that employs nonselective adsorption. While LPS adsorption has been tested in multiple studies (see below)

examining polymyxin B's capacity to bind endotoxin, the clinical effectiveness of broad adsorption strategies has not been evaluated in well-designed randomized control trials (RCTs), and clinical robustness is still lacking.

Selective Hemoadsorption: Polymyxin-B

The use of polystyrenic fibers bound to polymyxin-B (PMX®) cartridges, which can remove endotoxin or LPS (Toraymyxin; Toray Medical Co; Japan), has gained attention in modern hemoadsorption techniques. Endotoxin levels decrease in vitro within minutes after starting PMX® hemoperfusion (PMX-HP) [17]. This treatment typically involves a hemoperfusion duration of two hours, generally repeated twice. Anticoagulation is heparin-based, and the blood pump flow varies between 80 and 120 mL/min [11].

- The first RCT that generated interest toward this blood purification technique is the Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS) trial, which randomized 64 patients with septic shock (34 patients to PMX-B and 30 to standard care) and demonstrated the potential of this treatment in terms of hemodynamics (vasopressors and mean arterial pressure), respiratory function, sepsis-related organ failure scores (SOFA), and survival [18]. Specifically, PMX® was associated with a reduction in time to mortality[18].
- The second large RCT (ABDOMIX study) included 243 septic shock patients with peritonitis[19]. Patients were randomized to receive either PMX® or standard treatment (125 patients to PMX® and 118 to conventional treatment), regardless of the presence of abdominal infections due to Gram-negative bacteria. The study did not show a difference in mortality (mortality rate of 27% in the PMX-HP group and 19.5% in the conventional group). Emerging concerns were related to the low mortality in the control group and the limited proportion of patients who completed the PMX® treatment[19].
- The largest trial designed to investigate the clinical efficacy of polymyxin B is the Adult Treated for Endotoxemia and Septic Shock (EUPHRATES) study [20]. The EUPHRATES study compared standard treatment versus polymyxin-B in 450 adult patients with septic shock and Endotoxin Assay Activity (EAA) > 0.6 across 55 North American hospitals. The EUPHRATES study did not demonstrate an improvement in terms of survival.
- After the EUPHRATES study, a post-hoc analysis showed a 10% reduction in 28-day mortality after adjusting for organ failure scores and baseline mean arterial pressure in patients with EAA values ranging from 0.6 to 0.89 [21]. Additionally, patients who experienced a reduction in EAA of more than 13% showed improved mortality outcomes [21]. Crude data showed that at 28 days, 23 patients out of 88 (26.1%) in the PMX group died versus 39 out of 106 (36.8%) in the sham group [risk difference 10.7%, OR 0.52, 95% CI (0.27, 0.99), P = 0.047]. Even if encouraging, these, still weak, results have pushed the investigators and researches to design a new and more targeted trial (see the following point).
- Consistent with these findings, a new North American study (the TIGRIS trial, ClinicalTrials.gov Identifier: NCT03901807) is enrolling 150 patients with EAA between 0.6 and 0.9 and septic shock, aiming to determine whether this range of EAA may represent an optimal therapeutic window [22].

Limiting factors for the lack of guidance on the use of polymyxin B include optimal disease phase (timing) and the number and duration of treatments. Altering these parameters could impact disease outcomes. Unlike other techniques, the use of polymyxin B can be guided through a laboratory test (i.e., EAA). EAA is particularly valuable because it enables a targeted approach using a laboratory biomarker, improving patient stratification for endotoxin removal techniques. EAA might assist clinicians in monitoring treatment effects, determining the number and duration of hemoadsorption sessions, and allowing timely cessation of extracorporeal circulation. It should also underlined that polymyxin B, differently from other devices (see later), only removes LPS.

The data available from the published studies, suggest that the beneficial effects of PMX-HP on mortality still need confirmation.

Unselective hemoadsorption (1): coupled plasma filtration adsorption (CPFA)

The CPFA technique is based on separating the corpuscular elements of blood from plasma and passing plasma through an adsorption system. Red blood cells, white blood cells, and platelets never come into contact with the sorbent surface, thus avoiding bio-incompatibility reactions. Although initial results were encouraging, the latest COMPACT-2 study led to the discontinuation of the marketing of circuits for CPFA due to potential harms [23].

Unselective hemoadsorption (2): CytoSorb®

One of the most widely used techniques to date, although lacking large positive RCTs, is based on the CytoSorb® cartridge (CytoSorb®, CytoSorbents, NJ, USA), a generic anti-inflammatory strategy [24]. The device has demonstrated a high safety profile regarding biocompatibility and ease of use and removes a many different of cytokines (e.g. IL-6, MIP1-α, and IFN-γ, TNF-α DAMPS (procalcitonin, C5a, HMGB-1, and S100-A8), PAMPS (α-toxin, SpeB, and TSST-1) and mycotoxins (aflatoxin, T-2 toxin)[25,26]. It is made from polystyrene divinylbenzene and polyvinylpyrrolidone copolymers and targets molecules in the 5–50 kDa range, which includes the molecular mass of several cytokines [27]. According to the Food and Drug Administration, CytoSorb® can be used for up to 24 hours, although maximum efficacy, in terms of sorbent saturation, has been reported to be about 12 hours [https://www.fda.gov/media/136866/download]. The recommended blood flow is between 150 and 500 mL/min, and the device can be used either as a stand-alone or inserted in series in CRRT machines. The cartridge can also be applied to an ECMO system or a cardiopulmonary bypass machine. Reductions in plasma cytokine concentrations in septic patients treated with CytoSorb® have been reported in the literature, particularly with IL-6 identified as a diagnostic marker of device efficacy[28,29]. Nevertheless, an RCT compared CytoSorb with standard treatment in 100 patients with Acute Respiratory Distress Syndrome (ARDS) sepsis[24] showed no reduction in IL-6 levels or improvement in clinical outcomes. Subsequently, CytoSorb® was used in patients with COVID-19 undergoing ECMO, but it did not demonstrate any clinical benefit[24]. A recent randomized study on cytokine adsorption in severe, refractory septic shock indicated that the CytoSorb® cartridge hemoadsorption technique was neither associated with reduced IL-6 levels nor vasopressor requirements and led to an increased hazard of death [30]. Although the literature reports some positive and promising results in small case series [27,31], RCTs have shown no mortality benefit, and prospective, matched controlled, and randomized studies have reported potential harm[11,29,32,33]. These findings, possibly due to suboptimal applications in terms of timing, patient selection, treatment duration, and non-beneficial removal of “good” solutes (e.g., antibiotics, efficient mediators of inflammation), must prompt clinicians to exercise caution before applying these techniques.

Unselective hemoadsorption (3): Jafron® HA

A recent cartridge for hemoadsorption (neutro-macroporous resins made of styrene–divinylbenzene copolymer; HA130, HA230, and HA330) has been developed by a Chinese company (Jafron® Biomedical, China)[12]. The pore size distributions of the resins are 500 D–40 kD in HA130, 200 D–10 kD in HA230, and 500 D–60 kD in HA330/HA380. CA 330 for the treatment of inflammation and sepsis has been recently introduced into the market. The HA130 cartridge is primarily used in chronic disease conditions in combination with dialysis during one or more weekly sessions. The role of hemoadsorption in these clinical conditions is to reduce itching, muscle weakness, inappetence, and anemia. The HA230 cartridge is also used in intoxication conditions related to drug overdose, pesticide, and industrial poison intoxication. The two cartridges, HA330 and HA380, are mainly employed in acute hyper-inflammatory conditions such as sepsis, trauma, burns, pancreatitis, and cases of cytochemical release syndrome [11]. The recommended blood flow is between 150 and 250 mL/min, and the cartridge is typically applied during CRRT treatment. Currently, only small studies in septic patients are available. Importantly, this cartridge, as well as the previous one, removes antibiotics with substantial avidity (e.g., Vancomycin and Gentamicin)[12,34].

Unselective hemoadsorption (4) plus hemofiltration: oXiris®

The oXiris® membrane is made of hollow fibers composed of polyacrylonitrile copolymer (AN69) and features a negatively charged hydrogel core that can adsorb humoral factors, including cytokines. To enhance biocompatibility, the surface of the hollow fiber is treated with polyethyleneimine, which carries a slight positive charge. This enables the membrane to be pre-grafted with heparin, effectively reducing local thrombogenicity. Furthermore, the positive charge of the polyethyleneimine facilitates the adsorption of endotoxin, allowing oXiris® to adsorb both endotoxin and cytokines at rates similar to those of existing devices[35,36]. A recent meta-analysis including 10 studies (481 patients: 234 oXiris® group and 247 control group), consisting of 2 RCTs and 8 non-randomized studies of interventions, showed that the use of oXiris® was significantly associated with reduced overall mortality compared to the control group. The infusion rate of norepinephrine after treatment was significantly lower in the oXiris® group compared to control group, and the SOFA score was significantly reduced in the oXiris® group after treatment. After 72 hours of treatment, the oXiris® group demonstrated significantly lower CRP, IL-6, and lactate levels. Even if the results were positive, the certainty of evidence is very low, highlighting the need for high-quality RCTs to further evaluate its efficacy in this population[35]. Interestingly, a recent application of this membrane during

cardiopulmonary bypass through a CRRT machine during elective cardiac surgery was able to show, in a randomized controlled trial in 343 patients, a significant reduction of cardiac surgery associated acute kidney injury[37]. The authors imply that the modulation of intense inflammation during extracorporeal circulation was able to blunt organ damage.

Unselective hemoadsorption (5): Seraph 100

The Seraph 100® cartridge (ExThera, Martinez, CA), designed to remove pathogens from the bloodstream, represents the latest advancement in adsorption technology. Preliminary studies have shown the ability to adsorb bacteria and viruses [38]. It contains ultra-high molecular weight polyethylene beads with end-point-attached heparin, which is believed to immobilize pathogens similarly to the action of heparan sulfate on the cell [39]. It can be run both as a stand-alone treatment or in series with a CRRT machine, with a blood flow rate of 150-350 mL/min and a treatment time of up to 24 hours [https://www.fda.gov/media/137105/download]. A recent retrospective cohort study aimed at evaluating the safety and efficacy of Seraph 100 treatment for COVID-19 showed some clinical benefit across all endpoints (e.g., vasopressor-free days) in 53 COVID-19 patients compared to controls, opening the possibility of applying blood purification to treat pathogen threats while awaiting targeted therapies [38]. A more recent study on the application of the Seraph 100 filter in COVID-19 patients did not demonstrate a reduction in viral RNA titers in plasma. Nevertheless, circulating proteins (with roles in inflammation, endothelial/epithelial damage, and/or angiogenesis) decreased under treatment [40].

A crucial aspect of blood purification (including all available techniques) is that they are not selective, and such methods may lead to the unwanted removal of beneficial solutes (e.g., antibiotics, anti-inflammatory substances, protective cytokines, amino acids, macro- and micronutrients, and other potentially protective circulating metabolites). This removal could be clinically significant or could theoretically imply harm in specific instances. In the context of sepsis, the major protective agents to consider are antimicrobial drugs. Therapeutic drug monitoring should be part of common clinical practice in septic patients, especially when any form of blood purification technique is applied. While extensive data exist on the clearance of various substances during different forms of RRT, there is a noticeable lack of information regarding the clearance of antibiotics and antifungals during hemoperfusion [41–44]. Finally, also the measurement of the production/removal of the target solutes is a complex issue. The decrease in plasma concentration of the solute targets (e.g. CKs, LPS) depends on many pathophysiological and technical factors (e.g. plasma concentration of the solutes, continuous release of them from the tissues to blood, blood flow toward the cartridge, cartridge saturation kinetics, duration of the treatment, clotting and clogging processes, set of the CRRT machine - e.g. pre-dilution). RCTs coupled with careful measurement and control of solute removal are necessary before considering the routine use of cartridges of this type for daily clinical practice.

Conclusions

Blood purification techniques are both fascinating and arguably necessary as part of innovative strategies to reduce mortality in patients with sepsis and septic shock but the existing evidence concerning the use of extracorporeal blood purification therapies is ambiguous and inconclusive. The evolution of these techniques has seen impressive advancements over the past two decades, providing clinicians with various tools characterized by different properties while definitive evidence of benefits in sepsis/septic shock is awaited. Current cartridges have high biocompatibility but remain limited by poor selectivity regarding targets. Some can combine diffusion, convection, and fluid removal with adsorption, while others are limited to the adsorption process. Our understanding of the pathophysiology of sepsis, septic shock, and hyperinflammatory states is steadily improving. The ability to identify sub-phenotypes and sub-genotypes of patients with unique and individual immune system responses is also advancing. Research on hemoadsorption must progress alongside a deeper understanding of critically septic and hyper-inflamed patients to apply individualized and safe treatments aimed at restoring a balance between infection and a dysregulated immune system response. Until these treatments demonstrate safety and efficacy without the risk of harm to specific patients, clinicians must exercise utmost attention to their application during the treatment of patients who continue to experience high mortality rates. Considering the limitations of RCTs in this area, which are compounded by heterogeneity in patient populations and variations in the methods, technologies and dosages, the future of these applications in sepsis should shift from large-scale randomized trials to more tailored and adaptive studies. These studies should focus on specific and defined patient criteria while implementing standardized therapeutic protocols. These protocols must ensure

appropriate patient selection, standardize interventions and control for confounding variables. In particular it is essential to define the technical parameters (such as blood flow, cartridge size, length and composition, and duration of use) that determine the optimal operating conditions for this technology. These adaptive studies may be pivotal in clarifying the role of hemoadsorption and improving our understanding of the application of this important therapy. Lastly it is important to remain cognizant of any current uncertainty and the potential to impact negatively on patient outcomes.

Conflict of Interest Statement

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Author Contributions

SR has conceived the manuscript and written the first draft. ZR, GV and FB have reviewed and modified the text.

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Figure Legends

Figure 1 – Stand-alone hemoperfusion extracorporeal circuits (A); hemoperfusion (for hemoadsorption)-hemofiltration/hemodialysis combined in a continuous renal replacement circuit (B).

Figure 2 - Stand-alone Coupled Plasma Filtration Adsorption (CPFA) (A); CPFA- hemofiltration/hemodialysis (B).

Figure 3 - Configuration of an Extracorporeal Membrane Oxygenation circuit with an hemoperfusion cartridge.