Hemoadsorption

Rinaldo Bellomo[1,2,3,4] *Ravindra L. Mehta*[5] *Lui G. Forni*[6,7] *Alexander Zarbock*[8] *Marlies Ostermann*[9] *and Claudio Ronco*[10,11,12], *on behalf of the Acute Disease Quality Initiative Hemoadsorption Working Group**

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Introduction

Blood purification by dialysis is a nephrology cornerstone. However, despite its success, dialysis has not systematically moved to the treatment of other conditions, such as liver failure, intoxication with protein-bound toxins or drugs, poisoning with non–water-soluble toxins, and hyperinflammatory states. In these conditions, hemoadsorption (HA) may provide a possible therapy.

The Technology of HA

HA implies direct contact of blood or plasma with a sorbent. For this to occur safely, a sufficient level of biocompatibility is needed. Earlier technology from approximately 40 years ago used zeolites and charcoal with low biocompatibility and was marred by serious complications. Consequently, the clinical application of HA waned.[1]

However, evolving sorbent coating science and better materials have made HA potentially relevant again. Trials of endotoxin removal by polymyxin-bound cartridges have provided some impetus in this field. Finally, sorbent-based biocompatible synthetic porous polymers (styrene or acrylic acid based) have become commercially available, thus enabling the expansion of clinical experience.

Large polymers of cross-linked networks of divinylbenzene can be structured into beads and made more biocompatible with polysulfone coating. They deliver an adsorptive surface area >1000 m^2/g in cartridges containing 200–300 g and can bind multiple substances by van der Waals forces, strong hydrophobic bonds, and weak ionic bonds. Because of the above technological changes, adverse reactions have become relatively uncommon and can be further prevented by plasma separation, thus avoiding contact of cells with the sorbent.

Circuit Options

All extracorporeal HA circuits require vascular access. In acute situations, a central vein double lumen catheter is used. HA, however, can also be used in combination with hemodialysis *via* an arteriovenous fistula. The extracorporeal circuit typically requires a hemodialysis or continuous KRT (CKRT) machine. Heparin-based or regional citrate anticoagulation is necessary. There are several technical options. They include direct HA where blood is circulated directly through the sorbent cartridge. Blood flow may vary from 100 to 250 ml/min. HA can be added to hemodialysis or CKRT because sorbents have limited capacity to remove urea, creatinine, or ammonia. Plasma can also be separated, circulated through the sorbent, and then reinfused into the circuit. This approach can be added to intermittent hemodialysis (plasmafiltration-adsorption (PFAD)-hemodialysis) or CKRT (continuous PFAD [CPFA]-CKRT). Such separation may facilitate the use of less biocompatible and/or more densely packed cartridges, thus increasing the intensity and breadth of adsorption. This technique can be applied intermittently (intermittent PFAD) or continuously (CPFA). Different sorbent cartridges with specific characteristics can also be added to the circuit after plasma separation (double plasma molecular adsorption system). A schematic illustration of these circuits is presented in Figure 1. Finally, a sorbent cartridge can be added to the cardiopulmonary bypass circuit or an extracorporeal membrane oxygenation circuit. These circuit options highlight the technical versatility of HA.

Clinical Applications

Although technology has markedly evolved over the past two decades, clinical science has not evolved at the same speed.

Toxicology

HA has been used to treat several types of intoxication,[2] such as paraquat or organophosphates or natural toxins. Unfortunately, because of the unpredictable and uncommon nature of these conditions, no controlled studies exist.

Liver Disease

There are little data on HA for severe liver failure, but a report suggested an effect on severe cholestasis-associated pruritus.[3] Importantly, however, HA is ineffective at removing ammonia (a key liver failure–related toxin).

Kidney Disease

A variety of toxins, which accumulate in kidney failure are not adequately removed during dialysis (*e.g.*, β_2-microglobulin or solutes that contribute to CKD-associated pruritus). Such solutes may be removed by HA.[3]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence:
Prof. Rinaldo Bellomo, Department of Intensive Care, Austin Hospital, Heidelberg, Melbourne, VIC 3084, Australia. Email: Rinaldo.bellomo@austin.org.au

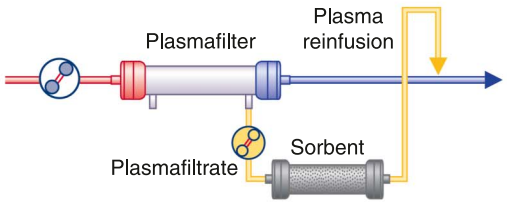
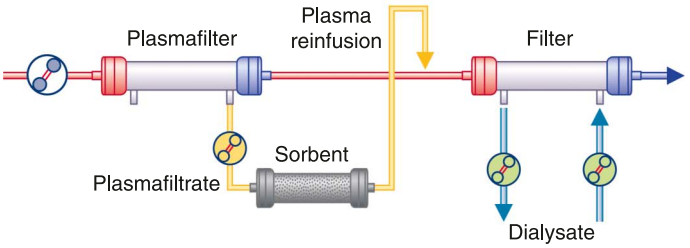
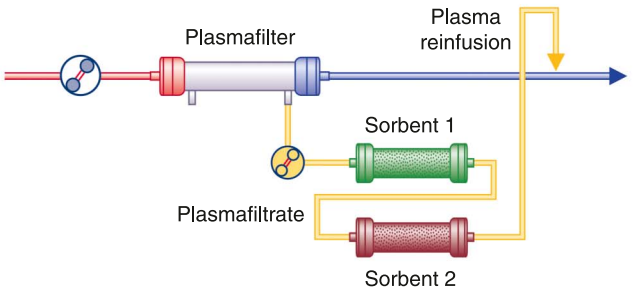
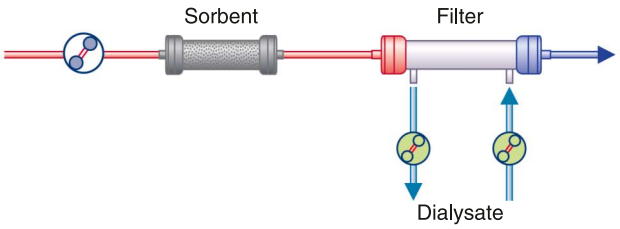
Technique - Abbreviation Intended indications	Extracorporeal layout and design
Hemoadsorption (HA) Removal of various molecules not cleared by other extracorporeal blood purification techniques, using a hemocompatible sorbent	
Plasmafiltration-adsorption (PFAD) Removal of bilirubin and bile acids using sorbents that cannot be placed in direct contact with blood	
Plasmafiltration-adsorption and hemodialysis or CRRT (PFAD-HD/CRRT) Combination of removal or uremic toxins and protein-bound solutes	
Double plasmafiltration and molecular adsorption system (DPMAS) Combined removal of protein-bound solutes, bilirubin and bile acids, and cytokines/inflammatory mediators	
Hemoadsorption and HD/CRRT (HA-HD/CRRT) Removal of various molecules in case of CKD (HA-HD) or AKI/sepsis (HA-CRRT) that are not sufficiently cleared by classic dialysis techniques	

Figure 1. Schematic representation of various extracorporeal techniques that use isolated or combined HA mechanisms and principles. The first panel shows isolated direct HA. The second panel shows the combination of plasmafiltration, plasma adsorption, and reinfusion. The third panel shows the combination of plasmafiltration with plasma adsorption and reinfusion with additional in series CKRT or hemodialysis. The fourth panel shows plasmafiltration with double adsorption using sorbents with different specificity for different solutes. The fifth panel shows direct HA followed by CKRT or hemodialysis in series. CKRT, continuous KRT; HA, hemoadsorption; DPMAS, double plasma molecular adsorption system.

Sepsis

Selective HA

Polymixin B-based HA is an endotoxin-selective form of HA, which has been investigated in sepsis using the Toraymyxin (Toray Medical Co., Ltd., Tokyo, Japan) cartridge.[4,5]

The first multicenter randomized controlled trial (RCT) was the Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS), which randomized 64 patients with septic shock to polymyxin B HA or usual care.[3,6] HA improved several physiological parameters and lengthened survival times. The second multicenter RCT involved 243 patients with peritonitis. In contrast to EUPHAS, it demonstrated a trend to shorter survival times with polymyxin B HA. The third multicenter RCT was the Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic Shock (EUPHRATES) trial,[4,5] which compared polymyxin B HA with usual care in 450 adult patients with septic shock with an endotoxin assay activity (EAA) level of ≥0.60 in 55 North American hospitals. This trial found no survival advantage. However, in a secondary assessment focused on those patients with midlevel EAA, polymyxin B-based HA achieved longer survival times. Thus, a North American RCT is currently studying polymyxin B HA in 150 patients with endotoxemic (EAA: 0.60–0.90) septic shock (ClinicalTrials.gov identifier: NCT03901807). Unfortunately, at this stage, no data exist to guide timing, number, and duration of treatment. These aspects of HA may have influenced trial results so far.

Nonselective HA

Nonselective hemoadsoprtion has been under investigation for more than a decade. An initial trial of HA in septic shock was stopped for futility.[4] Similarly, a trial of CPFA in sepsis was stopped because of harm.[5] Nonselective HA has also been attempted with the CytoSorb cartridge (CytoSorb, Cytosorbents Inc., NJ) with almost 1300 patients reported so far.[7]

One multicenter RCT compared CytoSorb HA (6 hours daily for 7 days) with usual care[7] in 100 patients with septic ARDS. CytoSorb did not decrease IL-6 levels or improve clinical outcomes. Subsequently, CytoSorb HA was tested in patients with coronavirus disease 2019 receiving extracorporeal membrane oxygenation and in patients with endocarditis where it did not achieve clinical benefits.[7] These disappointing findings may, among other reasons, have been related to technical inadequacy, late intervention, inability to address tissue cytokines levels, and lack of knowledge regarding targets.

A Chinese company (Jafron Biomedical, Guangdong, China) has also developed sorbents for clinical application.[3] The Jafron HA cartridge series has been used for the treatment of sepsis in small case series. In a nonrandomized controlled study of 24 patients who received HA (one treatment per day for 3 days), investigators reported hemodynamic benefits, reduced IL-8 and IL-6 levels, and beneficial effects on ICU length of stay and mortality. Jafron sorbents (like CytoSorb) also remove antimicrobials with vancomycin and gentamicin clearances of >80 ml/min at the start of treatment decreasing to 30 and 50 ml/min, respectively, after 4 hours.[8]

HA can also be achieved by modifying dialysis membranes. A membrane called oXiris (Baxter, Chicago, IL) has been used to treat patients with combined sepsis and kidney injury.[9] Short-term ex vivo studies have shown this membrane to perform similarly to polymyxin B-bound sorbents for endotoxin adsorption and similarly to CytoSorb in terms of cytokine removal.[9] However, so far, only small clinical studies have been published.

Finally new approaches (*e.g.*, Seraph 100 Microbind Affinity Blood Filter) are being studied to adsorb bacteria and viruses.[10]

At this time, the clinical efficacy of HA has not been demonstrated. Yet, the rationale remains. Although, no recommendations can be made, we support more preclinical and clinical research with randomized trials and the development of registries and a focus on identifying appropriate phenotypes for intervention. Unless these studies are conducted in a systematic way, the role of HA will remain uncertain and inadequately understood, and this modality of treatment will likely wane once more.

Disclosures

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Author Contributions

Conceptualization: Rinaldo Bellomo, Lui G. Forni, Ravindra L. Mehta, Marlies Ostermann, Claudio Ronco, Alexander Zarbock.
Formal analysis: Rinaldo Bellomo, Marlies Ostermann.
Methodology: Rinaldo Bellomo, Lui G. Forni, Ravindra L. Mehta, Claudio Ronco, Alexander Zarbock.
Supervision: Lui G. Forni.
Writing – original draft: Rinaldo Bellomo, Lui G. Forni, Ravindra L. Mehta, Marlies Ostermann, Claudio Ronco, Alexander Zarbock.
Writing – review & editing: Rinaldo Bellomo, Ravindra L. Mehta, Marlies Ostermann, Claudio Ronco, Alexander Zarbock.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B852.

Supplemental Summary 1. Acute Disease Quality Initiative Hemoadsorption Working Group members.

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*The list of nonauthor contributors is extensive and has been provided in Supplemental Summary 1.

AFFILIATIONS

[1]Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[2]Department of Critical Care, University of Melbourne, Melbourne, Victoria, Australia
[3]Department of Intensive Care, Austin Hospital; Melbourne, Victoria, Australia
[4]Department of Intensive Care, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[5]Department of Medicine, University of California San Diego, La Jolla, California
[6]Department of Critical Care, Royal Surrey Hospital Foundation Trust, Guilford, United Kingdom
[7]Faculty of Health Sciences, University of Surrey, Guilford, United Kingdom
[8]Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital, Muenster, Germany
[9]Department of Intensive Care, King's College London, Guy's and St Thomas' Hospital, London, United Kingdom
[10]Department of Medicine, University of Padua, Padua, Italy
[11]International Renal Research Institute of Vicenza (IRRV), Vicenza, Italy
[12]Department of Nephrology, San Bortolo Hospital, Vicenza, Italy