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Lemagnen I, Monard C, Palluau M, Bergamaschi L, Furukawa T, Bellomo R, Schneider A

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Drug Removal by Hemoadsorption

Authors: Ilona Lemagnen[a,d], Céline Monard[d], Maxime Palluau[a], Layla Bergamaschi[e], Taku Furukawa[b], Rinaldo Bellomo[c], Antoine Schneider[a-d]

[a]. Adult Intensive Care Unit, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.
[b]. Preclinical Critical Care Unit, Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Victoria, Australia
[c]. Department of Critical Care, Melbourne Medical School, University of Melbourne, Victoria, Australia
[d]. Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
[e]. Departement of Cardiovascular Surgery, Centre Hospitalier Universitaire Vaudois (CHUV)

Short Title: Drug Removal by Hemoadsorption

Corresponding Author:
Antoine Schneider, MD PhD
Adult Intensive Care Unit,
Centre Hospitalier Universitaire Vaudois,
1011 Lausanne, Switzerland.
Tel: 00 41 21 314 16 32
E-mail: antoine.schneider@chuv.ch

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Abstract

Background: There is growing interest in hemoadsorption (HA) therapies in critically ill patients although their precise indications remain to be established. Several devices are available on the market with heterogeneous properties and capabilities.

Summary: Due to the non-specific removal associated with most HA techniques, concerns have been raised on their unintended removal of drugs such as anti-infectives in sepsis. On the other hand, drug removal might be beneficial in certain situations for instance antithrombotic medications in patients requiring emergency surgery or in case of accidental or self-induced intoxication. In this review, we summarize available in vitro, in vivo, and clinical studies reporting on the influence of various HA techniques on drugs pharmacokinetics.

Key message: We conclude that further studies should aim at providing drug dosing recommendations during HA and confirm its safety, efficacy, and practicalities when used for intoxications.

Drug Removal by Hemoadsorption

Introduction

The term hemoadsorption (HA) describes blood purification techniques aiming to remove pathogens, proteins, and drugs from the plasma by their binding (adsorption) onto the surface of a material (sorbent). Adsorption is achieved through hydrophobic interactions, hydrogen, or covalent bonds formation or electrostatic or Van der Waals forces. HA techniques require the circulation of blood through a cartridge with adsorptive properties. The cartridge must be included within an extra-corporeal circuit, alone or in line with renal replacement therapy (RRT), cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) elements [1]. Cartridges are typically filled with sorbent, which, to optimize their adsorption capacity, exhibit a very high (300 to 1200 m^2/g) surface-to-mass ratio. According to their shape (granules, spheres, cylindrical pellets, flakes, or powders), size (from 50 µm to 1.2 cm) and pore size (from <2 nm to > 50 mm), sorbents exhibit different adsorptive properties and might be very targeted (for instance endotoxin or bilirubin) or non-specific (broad spectrum of potential targets) [2].

HA has been successfully used to treat drug poisoning, for instance with paraquat, antipsychotics or antiepileptics [3–10]. Since HA is a concentration dependant process, it may achieve a very high removal of a compatible drug provided its concentration is high. Non-specific HA is also sometimes proposed as an adjunct therapy in sepsis or sepsis-like syndromes where high circulating cytokines are thought to contribute to organ failure. In these situations, although strong evidence supporting its utilization is lacking, HA might remove circulating cytokines and restore their balance. However, given the very low specificity of the technique, HA might also be associated with the unintended removal of potentially beneficial molecules such as anti-infectives or antithrombotics drugs (Fig. 1). This removal, if present, should be quantified and accounted for during drug prescription. This is particularly relevant for antimicrobial drugs in sepsis as their uncontrolled removal, might lead to subtherapeutic drug levels, decreased efficacy, and potentially worsen patient's outcomes. Unfortunately, to date, our knowledge on the influence of HA on the pharmacokinetics of drugs commonly used in critically ill patients remains limited.

In this manuscript, we review the different types of HA devices available, their effect on drugs pharmacokinetics such as anti-infectives or antithrombotics, including beneficial removal in situations of intoxications or need for rapid undesirable drug removal.

Hemoadsorption devices

Several HA devices are available for clinical use and their respective influence on drug removal cannot necessarily be assumed to be equivalent. In this section, we briefly describe the different devices and their potential indications (Table 1).

Charcoal hemoperfusion (historical)

Charcoal hemoperfusion columns were developed in the 1940s and introduced in the 1970s for the treatment of poisoning and overdose. These columns contained activated charcoal which has adsorption capacities for certain drugs [11]. Today, this technique has become obsolete as new adsorbent cartridges with improved biocompatibility and effectiveness have been made available [12].

CytoSorb

CytoSorb (Cytosorbents, Princeton, USA) cartridges are made of highly porous polyvinylpyrrolidone-coated polystyrene-divinylbenzene beads ranging in size from 300 to 800 µm, with a total surface area of sorbent over 45 000 m^2 [13]. These beads are able to adsorb a large panel of substances, including cytokines, pathogen- and damage-associated molecular patterns, anaphylatoxins, myoglobin, bilirubin [14–17]. On the other hand, their affinity for endotoxin and IL-10 is low [18]. CytoSorb has been tested in patients with sepsis and septic shock, with, to date, controversial results [19–21]. In cardiac surgery, where the device could mitigate systemic inflammation associated with cardiopulmonary bypass, no efficacy was demonstrated in patients undergoing elective surgery or those with endocarditis [22–27]. Finally, in patients with COVID-19, CytoSorb led to a decreased cytokine levels and improved ventilation in a case series [14], but was associated with higher mortality in patients with ECMO [28,29].

Jafron HA Series

The Jafron (Jafron, Zhuhai, China) HA Series includes a range of cartridges of various size and content. All cartridges are filled with beads made of macroporous resin (styrene-divinylbenzene copolymers) with different pore sizes (smallest pores in the HA 130 cartridge, largest pores in the HA330 and HA380 series) [30–34]. Cartridges have been designed with specific indications in mind: poisoning (HA230) [3], cytokine removal (HA 330-380) [31–34], refractory uremic pruritus during chronic hemodialysis (HA130) [35] or bilirubin and biliary salts removal in liver failure (BS330, double plasma molecular adsorption system (DPMAS)) [30]. Thanks to its very small volume, HA130 may also be used in pediatric populations where minimization of extra-corporeal volume is of major importance. Similar to CytoSorb, the level of evidence supporting the use of Jafron Series remain limited. The HA380 has been shown to successfully remove inflammatory cytokines in COVID-19-induced acute respiratory distress syndrome (ARDS) [31,32] or during cardiac surgery [33]. In the latter situation, the therapy was associated with shorter length of stay. HA380 may also remove free hemoglobin during aortic dissection surgery [34].

oXiris

oXiris (Baxter, Deerfield, USA) is a modified continuous RRT (CRRT) membrane (AN69ST) with enhanced adsorption capabilities. A polyethyleneimine surface treatment confers a positive charge to the membrane. Together with a permanent heparin graft on the inner membrane surface, this positive charge enables the adsorption of negatively charged endotoxins. [18]. Negatives charges retained in the lower layer can adsorb inflammatory cytokines. Compared with other hemofilters used in conventional CRRT, oXiris hemofilter appears to effectively minimize inflammatory mediators and adsorb endotoxins, while enabling RRT [36].

In a recent randomized controlled trial (SIRAKIO2), oXiris was shown to decrease the rate of post-operative acute kidney injury (AKI) in 300 patients undergoing elective cardiac surgery with a bypass time of more than 90 minutes (28.4% versus 39.7% in the control group) [37]. A recent meta-analysis suggested that, in septic patients, oXiris could significantly reduce 28 day mortality and the ICU length stay compared to other CRRT filters [38]. In patients with coronavirus disease 2019 (COVID-19) or AKI, oXiris was associated with a significant reduction in interleukine-1beta (IL-1beta), IL-6, IL-10 and C reactive protein and in illness severity scores, contributing to a significant improvement in hemodynamic parameters [39]. In a pilot controlled randomized trial, RRT with oXiris was tested in patients with severe surgical septic shock and AKI. The therapy was associated with significant decrease in procalcitonin, IL-6, or lactates levels and lower norepinephrine requirement [40]. In a systematic review on 695 patients with sepsis and requiring RRT, oXiris was associated with lower 28-days mortality, SOFA score, lactates levels, vasopressors requirement and ICU length of stay [38].

Toraymyxin

Toramyxin (Toray Industries, Tokyo, Japan) also known as Polymyxin B-immobilized hemoperfusion (PMX-HP), includes polypropylene-polystyrene fiber with covalently bound polymyxin B, which has a very high ability to selectively bind endotoxin [18]. The utilization of polymyxin B as an antibiotic is limited due to its renal toxicity and neurotoxicity. However, when bound to the fiber, it can selectively adsorb endotoxin without any systemic effect. PMX-HP is licensed in Japan and regularly used for septic shock management. Early data, coming predominantly from this country suggested that PMX-HP could decrease mortality in septic shock. In an observational study leveraging the Japanese national database, Fujimori et al. reported that the PMX-HP could be associated with a survival benefit in septic shock but only in patients with an average SOFA score between 7-9 and 10-12 [41]. In the multinational EUPHRATES RCT, this therapy was not associated with a survival benefit in 450 patients with septic shock and a high circulating endotoxin activity [42]. In a post-hoc analysis , however, the sub-group of patients with an endotoxin level of between 0.6 and 0.89 appeared to benefit from the therapy [43]. The TIRGRIS clinical trial is currently ongoing. This trial will focus on the subgroup of patients for which a significant reduction in mortality was observed in the EUPHRATE study. The primary objectives will be 28-day mortality [44].

Seraph 100

Seraph 100 Microbind Affinity (ExThera Medical, Martinez, CA, USA), is a hemoperfusion device made of polyethylene beads with end point-attached heparin. Seraph 100 is approved for the reduction of pathogens from the bloodstream as an adjunct to conventional anti-infective agents. Immobilized heparin mimics the surface of human cells with its heparan sulphate sequences necessary for the binding of viruses and bacteria, and this irreversible binding leads to their elimination [45]. During the COVID-19 pandemic, Seraph 100 was authorized for emergency use in the United States and a case series suggested that, at an early stage of the disease, it could avoid intubation and decrease the need for vasopressors by reducing the viral load [46,47].

Anti-infective drugs removal by hemoadsorption

In this section, we describe studies reporting on the clearance of anti-infective drugs. We begin with in vitro studies, reviewing them device by device, and subsequently delve into in vivo studies, following the same structure. A summary is provided in Table 2.

In vitro studies

CytoSorb

The in vitro removal capacity of CytoSorb was tested for β-lactams, quinolones, aminoglycosides, glycopeptides, and azole antimycotics. Either in a preparation of 1000 mL of 0.9% NaCl or 500 mL of 5% human albumin, their circulation through the CytoSorb device at a flow rate of 20 mL/min was associated with a very high removal particularly during the first 20 minutes. Rifampicin was completely adsorbed within 15 minutes of circulation. When reconstituted in blood and circulated for 18 hours, ciprofloxacin and meropenem were highly removed by the device. Both drugs showed a major decrease in their concentration (45% for meropenem and 52% for ciprofloxacin) within the first 30 min. No saturation effect was observed during the experiments, however, regardless of the support solution, and across all experiments conducted in this study, maximum adsorption occurred within the first 60 minutes [48].

Jafron Series

Vancomycin's removal was tested in vitro using a HA380 mini module (25% of the regular cartridge). A >90% removal ratio (RR) was observed when the drug was administered in repeated boluses of 100 mg every 20 minutes. In circuits containing vancomycin diluted in NaCl, the drug level presented a rapid exponential decrease, followed by a plateau phase. This study demonstrated that 244 mg of vancomycin were adsorbed per gram of sorbent, which, for an HA-380 cartridge, corresponds to a theoretical maximum adsorption of approximately 25 g of vancomycin. This data suggest, that, in a patient receiving 2g/24h of vancomycin and undergoing HA, a vancomycin level approaching zero should be obtained [49]. This very high removal was confirmed in a similar experiment which reported a 99% RR when vancomycin was diluted in either Ringer's lactate or blood. The experiment also included a control circuit (without hemoadsorber). Several cycles were performed with varying doses of vancomycin and administration methods further confirming these results [50].

Seraph 100

In an in vitro study, 18 anti-infective drugs were tested by adding them to human blood plasma, which was then pumped through the adsorber. The data suggested that the removal of anti-infective drugs by the device was neglectable except for aminoglycosides (gentamycin 54% and tobramycin 62%) [51]. Similarly, a simulation study using a pharmacokinetic and pharmacodynamic approach concluded that vancomycin, gentamycin, meropenem and imipenem clearances by the device were probably not clinically significant [52]

Other Hemoadsorbers

To the best of our knowledge, no in vitro study has evaluated the influence of other adsorbers on anti-infectives phamacokinetics (PK).

Limitations of in vitro studies

In light of these findings, it would appear that antibiotics are highly adsorbable molecules when exposed ex-vivo to the various HA devices available on the market, except, perhaps the Seraph 100. Unfortunately, the translation of in vitro data to in vivo performance is limited. Indeed, ex-vivo studies do not necessarily reflect in-vivo removal because microscopic clot formation, protein caking, and cell layering on the surface of the beads is likely greater during in-vivo therapy and may,

therefore, decrease beads performance. In addition, in vitro studies do not account for endogenous clearance, protein binding (if the study is not carried out on whole blood or plasma), volume of distribution, removal of potentially active metabolites or patient's clinical condition. In vivo studies are therefore needed to characterize the influence of HA on drugs pharmacokinetics.

In vivo studies

CytoSorb

An experimental controlled study involving 24 pigs, investigated the adsorption of 17 different molecules, including beta-lactams, antifungals, aminoglycosides, and other anti-infective agents [53]. Pigs were administered combinations of 3 to 5 drugs across 4 separate experiments. Blood samples were collected at various time points up to 6 hours after the administration. HA with CytoSorb was associated with a moderate increase in the clearance of fluconazole and linezolid, a slight increase for liposomal amphotericin B, posaconazole, and teicoplanin, and negligible effects for all other drugs, with even a negative adsorption observed for ganciclovir. Authors described non-linear clearance kinetics, with rapid removal in the first hour followed, for most drugs, by a plateau and decreased clearance in subsequent hours. A desorption phenomenon was even observed for beta-lactams.

Human data is very limited and restricted to case reports / case series [54]. In a single center observational study of 89 cardiac patients, CytoSorb HA was associated with a significant increase in the need for vancomycin and bivalirudin doses adjustments over the first three days of treatment. These adjustments were no longer required once a stable baseline concentration was achieved. Concomitant treatment with ECMO or RRT did not affect these results in subgroup analyses [55]. In case reports, peak levels of linezolid and meropenem were found to be well below therapeutic targets during CytoSorb treatment [56]. On the other hand, the clearance of ceftazidime, amikacin, levofloxacin, and meropenem did not seem to be influenced by the therapy in a pediatric series [57]. Similarly, clindamycin levels did not appear to be influenced by CytoSorb in a case report [58].

Jafron Series

The ability of the HA-380 hemoadsorber to remove vancomycin and gentamicin was studied in a sheep model. All six subjects received 2 g of vancomycin and 400 mg of gentamicin, combined with a continuous infusion of 20 mg/h of vancomycin. In this study the RR is calculated as: RR (%) = (1-C_{pre}/C_{post}) x 100 where C_{pre} is the concentration of drug in the pre-cartridge sample and C_{post} in the post-cartridge sample. The RR for vancomycin, which was 90% 10 minutes after the initiation of HA therapy, progressively decreased over time, reaching 28% after 4 hours. A similar trend was observed for gentamicin, though to a much lesser extent (96.6% at 10 minutes and 53% after 4 hours). Ultimately, the total elimination of both drugs was clinically significant, ranging from 25% to 35% of the total dose administered. These results suggest that dose adjustment should be performed in patients undergoing therapy with HA-380 [59]. However, the observed differences in the clearance of these two substances highlight the impact of drug protein binding and their lipophilic nature on adsorption with Jafron Series HA [60]. Indeed, distinct protein binding profiles of vancomycin and gentamicin may account for the significantly different adsorptive performance of HA-380 for these two antibiotics.

In a similar model, meropenem and piperacillin exhibited a similar pattern, with a very high initial RR followed by a progressive decrease. The overall clearance as well as the RR of piperacillin were significantly higher than those of meropenem ($p<0.0001$). These results also prompts for dose adjustment during HA therapy [61].

To date, human data is limited to case reports for instance, in a patient with pneumonia, ARDS, and Multiple organ dysfunction syndrome (MODS), hemoperfusion with HA-380, combined with continuous veno-venous hemofiltration (CVVH), enhanced the clearance of imipenem, removing 75.2% of the drug in 4 hours. A pharmacokinetic model suggested that 750 mg of imipenem would achieve the desired therapeutic concentration [62].

Seraph-100

In vivo data evaluating the impact of Seraph 100 on anti-infectives pharmacokinetics is also very limited. An observational study conducted in 34 patients, suggested that the therapy might not

increase the clearance of seven antibiotics (azithromycin, cefazolin, cefepime, ceftriaxone, linezolid, piperacillin, and vancomycin) and one beta-lactamase inhibitor (tazobactam) [63]. Case reports suggested no removal of remdesivir [64] or vancomycin [65].

Limitations of In vivo studies

As discussed above, the best quality data on the influence of HA on anti-infective PK has been generated in animal models. These models, although highly informative, also have limitations and their translation to humans might not be completely possible. First, species-specific particularities might be present (absorption, volume of distribution, metabolism, excretion). Second, models included healthy animals while HA technics are likely to be utilized in critically ill patients with altered physiology. Several elements are known to significantly impact pharmacokinetics: the presence of acute kidney injury, which may modify endogenous clearance, increased capillary permeability and fluid shifts during medical resuscitation, which may increase volume of distribution, lowering the concentration of hydrophilic drugs, hypoalbuminemia and functional impairment of albumin which can may reduce protein binding, elevating the free fraction of drugs and potentially enhancing the risk of adverse effects [66,67]. Large-scale studies are required to define optimal drug monitoring and administration strategies during HA to reduce adverse outcomes and ensure adequate therapeutic drug levels.

Antithrombotic and anticoagulant drugs removal by hemoadsorption

Antithrombotic agents reduce the formation of clots in the blood and are used for primary and secondary prevention and treatment of acute thrombotic conditions including stroke, coronary or peripheral artery disease [68–71]. Similar to anti-infective drugs, their unintended removal by an extracorporeal blood purification device might increase the thrombotic risk and lead to potentially fatal complications such as myocardial infarction, stroke, pulmonary embolism or stent thrombosis. It is therefore important to understand the ability of HA devices to remove antithrombotics.

On the other hand, antithrombotics or anticoagulants removal might be desirable under certain circumstances. Indeed, those treatments are typically interrupted two (xabans), five (clopidogrel and ticagrelor), or seven days (prasugrel) [72] prior to an elective intervention. However, in case of life-threatening surgery, this delay cannot be respected, exposing patients to a major hemorrhagic risk during the procedure. Antithrombotics cannot be removed by standard hemodialysis due to their high protein binding, and no antidote is available, except perhaps for Andexanet alpha, a recombinant modified human factor Xa decoy protein, however, its cost and safety profile limits its routine utilization [73,74]. HA could represent an attractive option in these situations, particularly for emergent cardiac surgery procedures when the HA device can easily be inserted in the cardio-pulmonary bypass.

In this section, we discuss in vitro and in vivo studies investigating the clearance of antithrombotic and anticoagulant drugs by HA. To the best of our knowledge, only studies with Cytosorb have been conducted. These studies are summarized in Table 3.

In vitro data

A pre-clinical study has assessed CytoSorb's ability to remove Ticagrelor diluted in an albumin solution or human blood [75]. It was compared with an adsorbent mesh (Porapak Q 50-80 mesh). This study demonstrated that CytoSorb was able to remove ticagrelor from both bovine albumin solution and human blood with >99% efficiency (maximum removal 99.99% reached after 10h). A similar in vitro study with Dabigatran, a direct thrombin inhibitor, demonstrated complete removal with undetectable levels of Dabigatran after HA. In both experiments, the albumin concentration did not modify the adsorption efficiency suggesting the absence of interference of albumin with the process [76]. Similarly, CytoSorb might rapidly reverse the anticoagulant effect of rivaroxaban, a direct factor Xa inhibitor [77].

Clinical data

A few clinical studies have assessed the safety and efficacy of HA to clear antiplatelet and anticoagulant drugs. In an observational study including 55 patients treated with rivaroxaban or ticagrelor and undergoing emergent open-heart cardiac surgery, HA with CytoSorb, performed in 39 patients, was associated with lower drainage volumes, need for blood products transfusions and

shorter ICU (2 versus 4 days, p=0.01) and hospital (11 versus 16 days, p=0.02) length of stay [78]. Similarly, in 21 patients receiving Rivaroxaban or Ticagrelor and presenting with type A aortic dissection, HA with CytoSorb during the emergent surgery was associated with shorter procedure duration, lower post operative drainage and a lower need for redo thoracotomies [79]. More recently, the same team measured ticagrelor plasma levels in eleven patients on ticagrelor and undergoing urgent cardiac surgery with CytoSorb HA [80]. They found that ticagrelor plasma levels measured in the post operative period were lower (67.1% reduction) than pre-operative values. In these patients at high risk of bleeding complications, no re-operations, significant bleeding, or intracranial hemorrhage were observed. Of course, this data needs to be confirmed as, in the absence of a control group, the observed effect might be attributable to hemodilution and blood transfusions. In a before/after multicenter study including 25 patients treated with Apixaban and undergoing cardiac surgery, the 13 patients treated with CytoSorb had, despite a higher dose of apixaban and shorter interruption time, significantly lower 24 hour chest tube drainage and need for desmopressin compared with the previous 12 control patients [81]. Finally, case reports have suggested that intra-operative HA could lead to an effective reduction in specific anti-factor Xa activity in patients on apixaban [82].

Hence, HA with CytoSorb might be able to remove antithrombotics and anticoagulants in case of an overdose or need for an emergency surgery. However, more data is required before this therapy is taken to routine care. The ongoing STAR-T randomized, prospective, multicenter study including 120 patients will be the first prospective large-scale trial in the area. Hopefully, it will provide insights on the safety and efficacy of intraoperative HA to remove Ticagrelor [83].

Immunosuppressive agents

Studies reporting on immunosuppressive drugs and remaining drugs removal by HA are summarized in table 4.

To the best of our knowledge, only one experimental study conducted in sheep has evaluated the effect of CytoSorb on immunosuppressive agents' pharmacokinetics [84]. A negligible clearance was observed for prednisolone and basiliximab while an adsorption of less than 5% of the daily administered dosages was observed for tacrolimus, cyclosporin A, mycophenolate mofetil, everolimus and methyprednisolone.

In one case report, the Jafron Series HA-230 device was used in a child with acute lymphocytic leukemia after high-dose methotrexate chemotherapy to reduce toxicity in the event of delayed clearance. A single continuous veno-venous hemodiafiltration procedure combined with HA-230 adsorption reduced methotrexate levels from 540.7 to 79.60 µmol/L immediately, with a reduction rate of 85.27% over the course of 4 hours [85].

To our knowledge, no other device has been tested for the removal of immunosuppressive molecules. As such, reliable human data are lacking, and further studies are required to assess the safety of using HA in transplant patients or undergoing chemotherapy.

Intended drug removal by hemoadsorption: Intoxications

Poisoning, whether accidental or self-induced is a major health care issue. It may be caused by a wide variety of chemical agents, drugs, or endogenous molecules. In the Western world, drugs most commonly involved with poisoning include analgesics, household cleaning products, antidepressants, cosmetics, and personal care products [86]. Depending on the type of agent and the severity of the intoxication, the clinical presentation may range from asymptomatic to multiple organ failure leading to death. Many cases of poisoning can be managed conservatively, while some agents require the urgent administration of specific antidotes [87]. Hemodialysis is indicated for certain types of severe intoxications. However, not all substances, have adequate physico-chemical characteristics to enable their clearance by hemodialysis. Typically, lipophilic molecules with high protein binding are only mildly removed by hemodialysis. In these situations, HA might play a role. Data on the topic are scarce and mostly rely on case reports or small observational studies.

Paraquat

Paraquat, an herbicide banned from utilization in the European Union since 2007, is highly toxic to humans, and no specific antidote exists. It is still commonly utilized in developing countries. There,

accidental or voluntary ingestion of paraquat are common and associated with a mortality rate between 50% and 90% [3]. Treatment options for paraquat poisoning are generally ineffective [88], which is why extracorporeal purification therapies, particularly HA, have started to be investigated for this indication. In a retrospective study in 487 patients, those who received HA alone (with Jafron HA-330;1 to 3 sessions of 2 hours) or HA + CRRT (5 sessions of 2 hours) had lower 15 and 90 day mortality rates compared with those who received conventional therapy or CVVH [89]. Similarly, in a series of 189 patients, those treated with HA-330 + CVVH and those treated with HA-330 alone, had reduced their blood paraquat levels faster and had a higher survival rate compared to those receiving supportive therapy [90]. Unfortunately, this was not confirmed in a second similar size (213 patients) study [91].

Other drugs

Many other drugs typically associated with poisoning may theoretically be removed by HA. As mentioned earlier, charcoal hemoperfusion was found to be effective in case of poisoning with calcium channel antagonists [9,10], baclofen [92], chloroquine, hydroxychloroquine and quinine [93] and theophylline poisoning [94]. More recently, quetiapine has shown a positive response to CytoSorb HA combined with hemodiafiltration, reducing blood quetiapine levels by 65% after the first 12 hours of treatment. Complete elimination of plasma quetiapine was observed after 72 hours and the patient could be extubated 96 hours after the start of hemoperfusion[4]. Similarly, clozapine was rapidly eliminated by CytoSorb in combination with hemodiafiltration in a 56-year-old patient who had intentionally ingested 10 times the toxic dose of clozapine. He received, within 6 hours of suspected clozapine ingestion, two 12 hours treatments with Cytosorb combined with continuous veno-venous hemodiafiltration. He could be successfully extubated 3 days after his admission without neurological abnormalities [5]. Antiepileptic drugs, such as carbamazepine [6], and lamotrigine [7] were eliminated from the body more rapidly and effectively through extracorporeal purification therapies, combining HA devices and RRT. In a prospective study, 104 patients with carbamazepine intoxication were treated with *early* (emergency department), *delayed* HA with Jafron HA-230 or no HA at all. Patients who received HA had significantly less respiratory depression and seizure and higher Glasgow scores than the others. Early HA was associated with a shorter hospital length of stay compared with delayed or no HA [6]. In a 60-year-old woman found unconscious with a significantly elevated (85.8 mg/L) lamotrigine plasma level, Cytosorb HA was initiated on day 8 in line with continuous veno-venous hemodialysis. Significant reduction of plasma lamotrigine levels were achieved within 8 hours of therapy, and associated with improved neurological condition. [7].

Cardiovascular drugs, which also carry a high risk of morbidity and mortality in the event of overdose, can be eliminated by HA. In a case of severe amlodipine overdose, a HA 230 cartridge, inserted in a RRT circuit, significantly improved hemodynamic parameters within 6 hours of treatment and enabled complete weaning from vasopressors [8].

A recent in vitro study aimed to evaluate the adsorption kinetics of iohexol, an iodinated contrast medium by HA-380 Jafron. A solution spiked with iohexol was recirculated in a closed loop for 60 minutes, and the experiment repeated twice. In both experiments, the iohexol concentration decreased by approximately 53%. Initial Iohexol clearance was 46.8 mL/min and decreased to 3.6 mL/min in the last 20 minutes. Sorbent saturation calculations indicated that each gram of sorbent removed 155 mg of iohexol. The clinical implication of these findings, in particular, its potential utilization for acute kidney injury (AKI) prevention should be assessed in prospective human studies [95].

As it stands, the place of HA for the management of intoxication remains to be clarified. However, this indication carries a strong rationale for compatible molecules. Further studies should be conducted to confirm or refute the efficacy of HA in drug poisoning.

Future Studies

Ongoing clinical trials evaluating drugs' pharmacokinetics during HA are presented in table 5. More studies are required to establish the impact of extracorporeal purification treatments on drug removal. These studies should be prospective, include a control group and thorough evaluation of

drugs' pharmacokinetics. Their final aim should be to develop kinetic models enabling therapeutic levels estimation and drug dosage recommendations. For intoxications, studies should aim at confirming the safety of the procedure, but also at establishing the right timing as well as the right dose (duration of therapy and number of therapies) required.

Conclusions

Our knowledge on the influence of different HA devices on drugs pharmacokinetics remains limited. Further studies should aim at providing drug dosing recommendations during HA and confirm its safety, efficacy and practicalities when used for intoxications.

4670 Words

Statements

Conflict of Interest Statement

Antoine Schneider has received speaker and/or consulting honoraria from Fresenius Medical Care, CytoSorbents SA, Jafron and B. Braun Avitum.
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Ilona Lemagnen and Antoine Schneider drafted the manuscript. Dr Céline Monard, Mr. Maxime Palluau, Ms. Layla Bergamaschi, Dr Taku Furukawa and Prof. Rinaldo Bellomo critically revised this review and approved the final version.

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Figure Title and Legend

Figure 1 Hemoadsorption risk-benefit balance

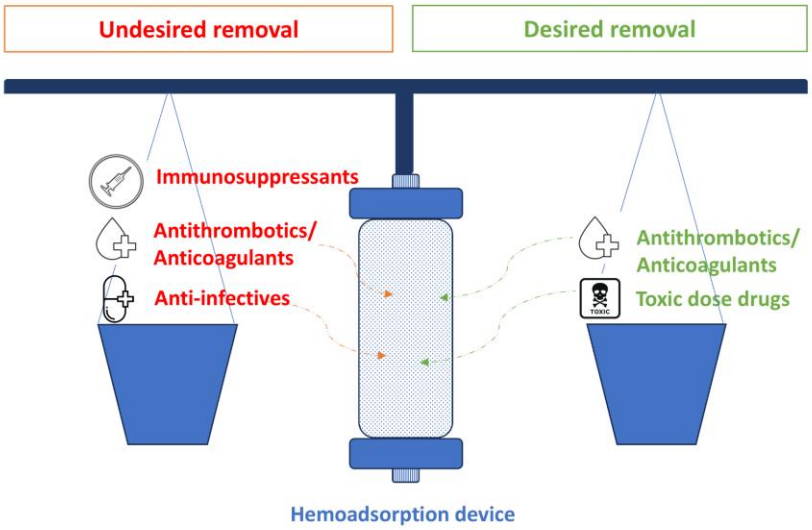

Table 1 - Main Hemoadsorption Devices

Device	Adsorption material	Connection options	Potential Targets	Potential indication(s)	Major clinical evidence
CytoSorb	Highly porous polyvinylpyrrolidone-coated polystyrene-divinylbenzene beads	ECMO CRRT CPB	Cytokines PAMP & DAMPs Myoglobin Bilirubin Drugs (P2Y12, Thrombin inhibitor and Factor Xa inhibitor)	Septic shock	- Substantial lower plasma level of IL-6 [19] - Lower plasma levels of IL-8 + improvement of microcirculation despite no significant variation in macro-hemodynamics [20] - No reduction level of IL-6 and increased risk of death [21]
Jafron Series	Macroporous resin styrene-divinylbenzene copolymers	ECMO CRRT CPB	Cytokines DAMPs Bilirubin Uremic toxins Drugs (paraquat, carbamazepine) β2-microglubuline Myoglobin	Septic shock Cardiac surgery	- Improved of the SOFA score and mortality rate at day 28 [31] - Improved CRP avec PCT levels but no effect on mortality rate [32] - Lower levels of IL-6, IL-8 and IL-10. Shorter mechanic ventilation time and ICU stay + less vasopressors requirement [33]
oXiris	Modified continuous RRT membrane: AN69ST	CPB ECMO Stand Alone	Cytokines Endotoxins Some antimicrobials Some immunosuppressive drugs	Systemic inflammatory response syndrome (SIRS)	- Decreased rate of post-operative acute kidney injury (AKI) in the first seven days [37] - Lower levels of IL-1β, IL-6, IL-10 and CRP + improvement of APACHE II and SOFA score [39] - Decrease28-days mortality, SOFA score, lactates levels, vasopressors requirement and ICU length of stay [38]
Toraymyxin PMX-20R	Polypropylene-polystyrene fiber with covalently bound polymyxin B (a cationic polypeptide that binds endotoxins)	CRRT CPB ECMO	PAMPs Endotoxins: Lipopolysaccharides	Septic shock with gram negative bacteria	- No differences on 28-days mortality rate [42] - Post-hoc analysis of EUPHRATES Trial with patients with endotoxin activity between 0.6-0.89. Suggest an impact of PMX-20R on mean arterial pressure, ventilator free-days and mortality rate[43].
Seraph-100	Polyethylene beads with end point-attached heparin	CRRT ECMO Alone	Cytokines PAMPs Some bacteria, viruses Some antimicrobials	Bacteremia, viremia, toxemia	- Improvement of hemodynamic stability on patient with COVID-19 and ventilator and vasopressors requirement [46]

ECMO: Extracorporeal Membrane Oxygenation
CRRT: Continuous Renal Replacement Therapy
CPB: Cardiopulmonary bypass
PAMPs: Pathogen-Associated Molecular Patterns
DAMPs : Damage-Associated Molecular Patterns
IL-: Interleukine –
CRP: C-Reactive Protein
PCT: Procalcitonin
ICU: Intensive Care Unit

Table 2 – Overview of studies evaluating anti-infective removal

			Type of device	Type of study	Results	References
Antibiotics	Beta-lactams	Meropenem	Cytosorb	In vivo study on pigs vs control group	- Dose of 2g injected IV over 30 min one hour before initiation of extracorporeal circulation - Total clearance of approximately 2 L/h with additional clearance by adsorber of +6.3 % compared with endogenous clearance alone - Negative clearance from the sixth hour of treatment onwards	[53]
			Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- Clearance of 1.32 L/h in NaCl, 95% of drug removed in 1.5h - Clearance of 1.29 L/h in HA, 85% of drug removed in 1.5h No significant difference was observed for clearance values by hemoadsorption in these two solutions. - On an initial dose of 46.4 mg + (192 mg/h x 18h) = 3492 mg, 400 mg of meropenem was eliminated in 18h with an initial clearance of 5.4L/h (vs 2L/h with CRRT).	[48]
			Jafron HA-380	In vivo study on healthy sheep	- 2g meropenem IV over 30 min RR > 90% at 10 min, 74% at 30 min, 59.2% at 60 min then <20% at 4h. - Cumulative elimination of meropenem on sorbent over 4 hours was 386.6 mg, representing 19.3% of the total dose administered.	[61]
			Cytosorb	Case report	- Patient with septic shock - 6g meropenem on day 2, peak meropenem levels were lower during Cytosorb therapy (around 40 mg/L vs. 65 mg/L without Cytosorb)	[56]
			Cytosorb	Prospective observational study on 10 children with no control group	- Observation of negative clearance: -1.5 L/h of meropenem by Cytosorb suggesting an increase in the rate of antibiotic leaving the Cytosorb probably linked to a desorption phenomenon. - The non-linear saturation kinetics of the cartridge during the 24 hours of treatment with Cytosorb: Saturation during the first 12 hours then desorption during the following 12 hours.	[57]
			Seraph-100	In vitro study with human plasma	- Injection of 500 mg meropenem - Initial concentration C_0 de 125.6 +/- 17.9 mg/L - RR= 15% between 0 to 60 min	[51]
		Piperacillin	Cytosorb	In vivo study on pigs vs control group	- 6000/750 mg injected IV over 30 min one hour before initiation of extracorporeal circulation - Total clearance of approximately 2.5 L/h with additional clearance by adsorber of +19.6 % compared with endogenous clearance alone - Negative clearance from the sixth hour of treatment onwards	[53]
			Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 80 mg/L piperacillin - Clearance of 1.29 L/h in NaCl, 94% of drug eliminated in 1.5h - Clearance of 1.44 L/h in HA, 90% of drug eliminated in 1.5h	[48]
			Jafron HA-380	In vivo study on healthy sheep	- 4g piperacillin IV over 30 min - RR = 98.4% at 10 min and 37.4% at 4h - Cumulative elimination of piperacillin mass on sorbent over 4 hours was 647.4 mg, or 16.2%, with 63.4% occurring in the first 60 minutes.	[61]
			Seraph-100	In vitro study with human plasma	- Injection of 4000 mg of piperacillin - Initial concentration C_0 de 1364.3+/- 193 mg/L - RR= 16% between 0 to 60 min	[51]
		Ceftriaxone	Cytosorb	In vivo study on pigs vs control group	- 4000 mg over 30 min one hour before initiation of extracorporeal circulation - Total clearance of approximately 0.8L/h with an additional clearance by the adsorber of +5.2 % compared with endogenous clearance alone. - Negative clearance from the second hour onwards	[53]
		Cefepime	Cytosorb	In vivo study on pigs vs control group	- 2000 mg over 30 min one hour before initiation of extracorporeal circulation	[53]

					- Total clearance of approximately 1L/h with an additional clearance by the adsorber of +1.2% compared with endogenous clearance alone. - Negative clearance from the second hour.	
		flucloxacillin	Cytosorb	In vivo study on pigs vs control group	- 4000 mg over 30 min one hour before initiation of extracorporeal circulation - Total clearance of approximately 2.6 L/h with an additional clearance by the adsorber of +15.9 % compared with endogenous clearance alone. - Negative clearance from the third hour.	[53]
			Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 80 mg/L flucloxacillin - Clearance of 1.17 L/h in NaCl, 100% of drug removed in 1.5h - Clearance of 1.20 L/h in HA, 100% of drug removed in 1.5h - No significant difference in clearance values between NaCl solution and 5% human albumin solution.	[48]
		Ceftazidime	Cytosorb	Prospective observational study on 10 children with no control group	- Positive clearance: 1.5 L/h of ceftazidime by Cytosorb vs 2L/h for the hemofilter - Cytosorb is associated with an increase in total clearance with a moderate impact: 43%. - As with meropenem, a mass removal by Cytosorb = -4.1 mg/h was observed, suggesting an increase in the ceftazidime rate at the cytosorb outlet due to desorption. - The non-linear saturation kinetics of the cartridge during the 24 hours of treatment with Cytosorb: Saturation during the first 12 hours then desorption during the following 12 hours.	[57]
			Seraph-100	In vitro study with human plasma	- Injection of 2000 mg of ceftazidime - Initial concentration C_0 de 276 +/- 22.8 mg/L - RR= 11% between 0 to 60 min	[51]
		Cefazoline	Seraph-100	In vitro study with human plasma	- Injection of 2000 mg of cefazolin - Initial concentration C_0 de 828.8 +/- 86.7 mg/L - RR= 15% between 0 to 60 min	[51]
	Aminoglycosides	Amikacin	Cytosorb	Prospective observational study on 10 children with no control group	- Positive clearance of 0.1 and 0.2 L/h for min and max concentration respectively. - Clearance for Cmin increased between day 0 and day 1 but a reduction was seen for Cmax over the same period. - Cytosorb is associated with an increase in total clearance with a low impact of 6 to 12%. - Mass removal Cmin = 0.3 mg/h and Cmax = 2.5 mg/h	[57]
		Gentamicin	Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 20 mg/L gentamicin - Clearance of 1.13 L/h in NaCl, 67% of drug removed in 1.5h - Clearance of 1.25 L/h in HA, 99% of drug removed in 1.5h - No significant difference in clearance values between NaCl solution and 5% human albumin solution.	[48]
			Jafron HA-380	In vivo study on 6 healthy sheep	- 400 mg gentimicin bolus IV over 30 min then onset of hemoadsorption 45 min later - As with vancomycin, there is a progressive decline in the RR and clearance of gentamicin as a function of time - RR = 96.9% at 10 min and >50% at 4h. - The cumulative mass removal of gentamycin over the 4h period was 138 mg accounting for 34.6% of the total dose with 49% in the first 60 min.	[59]
			Seraph-100	In vitro study with human plasma	- Injection of 20 mg of gentamicin - Initial concentration C_0 de 6.5 +/- 0.1 mg/L - RR= 59% between 0 to 60 min	[51]
		Tobramycin	Cytosorb	In vivo study on pigs vs control group	- 320 mg over 30 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 0.4 L/h with an additional clearance by the adsorber of +5.5 % compared with endogenous clearance alone. - Negative clearance from the first hour.	[53]
			Seraph-100	In vitro study with human plasma	- Injection of 80 mg of tobramycin - Initial concentration C_0 de 18.8 +/- 6.5 mg/L	[51]

					- RR= 62% between 0 to 60 min	
	Fluoroquinolones	Ciprofloxacin	Cytosorb	In vivo study on pigs vs control group	- 400 mg over 60 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 2 L/h with an additional clearance by the adsorber of +14.5 % compared with endogenous clearance alone. - Negative clearance from the sixth hour.	[53]
			Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 15 mg/L Vancomycin - Clearance of 1.32 L/h in NaCl, 94% of drug removed in 1.5h - Clearance of 1.24 L/h in HA, 99% of drug removed in 1.5h No significant difference in clearance values between NaCl solution and 5% human albumin solution. - On an initial dose of 7.25 mg + (30 mg/h x 18h) = 540 mg, 235 mg of ciprofloxacin were eliminated in 18h with an initial clearance of 6.3 to 4.3L/h (vs 1.7L/h with CRRT).	[48]
		Levofloxacin	Cytosorb	Prospective observational study on 10 children with no control group	- Positive clearance of 1.9 and 4.7 L/h for min and max concentration respectively. - Clearance for Cmin increased between day 0 and day 1 but a reduction was seen for Cmax over the same period. - Cytosorb is associated with an increase in total clearance with a moderate to high impact of 52 to 72%. - Mass removal Cmin = 4.5 mg/h and Cmax = 26 mg/h	[57]
			Seraph-100	In vitro study with human plasma	- Injection of 250 mg of levofloxacin - Initial concentration C_0 de 89.6 +/- 37.5 mg/L - RR= 9% between 0 to 60 min	[51]
		Moxifloxacin	Seraph-100	In vitro study with human plasma	- Injection of 400 mg of moxifloxacin - Initial concentration C_0 de 67.4 +/- 7.1 mg/L - RR= 11% between 0 to 60 min	[51]
	Glycopeptides	Teicoplanin	Cytosorb	In vivo study on pigs vs control group	- 800 mg over 30 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 2.1 L/h with an additional clearance by the adsorber of +30.7 % compared with endogenous clearance alone.	[53]
			Cytosorb	Clinical study of 3 patients with septic shock	- 800 mg Teicoplanin injected IV more than 60 min before the start of hemoadsorption - After 6 hours of hemoperfusion, serum levels were within the therapeutic range - Elimination > 50% at 60 min from the start of hemoadsorption therapy	[54]
		Vancomycin	Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 40 mg/L Vancomycin - Clearance of 1.19 L/h in NaCl, 70% of drug removed in 1.5h - Clearance of 1.28 L/h in HA, 95% of drug removed in 1.5h No significant difference in clearance values between the NaCl solution and the 5% human albumin solution.	[48]
			Jafron HA-380	In vitro study with a 500 mL blood mixture solution and a balanced solution	- Total elimination of vancomycin at a minimum baseline concentration of 23.0 +/- 7.4 mg/L achieved in 5 of treatment by hemoadsorption. - In the model with the very high concentration of Vancomycin (777.0 +/- 62.2 mg/L), RR = 90.1 +/- 0.6 % at 5 min and 99.2 +/- 0.6 % at the end of the experiments. - The total quantity of 2000 mg, corresponding to the loading dose in a patient with normal function, resulted in adsorption of 1919 mg without saturation.	[50]
			Jafron HA-380	In vivo study on 6 healthy sheep	- Loading dose of 2g vancomycin followed by continuous infusion of 20 mg/h vancomycin. - Progressive decline in RR and gentamicin clearance as a function of time - RR > 90% but declines, 68% at 30 min, 52.8% at 1 h, reaching 28% at 4 h. - Cumulative massive elimination of vancomycin over the 4-hour period was 556 mg, representing 26.7% of the total dose, 46.7% of which occurred during the first 60 minutes.	[59]
			Cytosorb	Clinical study of 3 patients with septic shock	- Patient 1 received a bolus dose of 1g vancomycin injected IV more than 60 min before the onset of hemoadsorption and patient 3 received a loading dose of 15mg/kg followed by a continuous infusion of 25mg/kg.	[54]

					- At 15 min after the start of hemoadsorber therapy, patient 1's vancomycin was virtually indosable. After 120 min, serum levels were sub-therapeutic (<15 mg/dL). - Patient 3's equilibrium concentration was 22 to 24 mg/dL; after the start of adsorbent therapy, this level fell but remained above the recommended limit.	
			Seraph-100	In vitro study with human plasma	- Injection of 500 mg of Vancomycin - Initial concentration C_0 de 179.8 +/- 23.8 mg/L - RR= 23% between 0 to 60 min	[51]
	Macrolides	Clarithromycin	Cytosorb	In vivo study on pigs vs control group	- 500 mg over 60 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 3.3 L/h with an additional clearance by the adsorber of +4.7 % compared with endogenous clearance alone.	[53]
	Oxazolidinones	Linezolid	Cytosorb	In vivo study on pigs vs control group	- 600 mg over 30 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 4.6 L/h with an additional clearance by the adsorber of +114.6 % compared with endogenous clearance alone.	[53]
			Cytosorb	Case report	- Patient with septic shock - 600mg of linezolid on day 2, the peak level was lower during Cytosorb therapy (around 12 mg/L vs. 16 mg/L without Cytosorb on the same day) On day 3 same observation: 12 mg/L vs. 18 mg/L without Cytosorb.	[56]
			Seraph-100	In vitro study with human plasma	- Injection of 600 mg of Linezolid - Initial concentration C_0 de 109.4 +/- 10.9 mg/L - RR= 14% between 0 to 60 min	[51]
	Others	Clindamycin	Cytosorb	In vivo study on pigs vs control group	- 1200 mg over 40 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 3.9 L/h with an additional clearance by the adsorber of +6.4 % compared with endogenous clearance alone.	[53]
			Cytosorb	Case report	- First 2 cytosorb sessions, clindamycin clearance of 3.6 and 4.1 L/h respectively - Which subsequently increased to 6.1 L/h at the third session - Unlikely that cytosorb was responsible for the drop in clindamycin concentration according to the authors.	[58]
			Seraph-100	In vitro study with human plasma	- Injection of 600 mg of clindamycin - Initial concentration C_0 de 9.9 +/- 3.3 mg/L - RR= 20% between 0 to 60 min	[51]
		Metronidazole	Cytosorb	In vivo study on pigs vs control group	- 2000 mg over 30 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 0.3 L/h with an additional clearance by the adsorber of +15.4 % compared with endogenous clearance alone.	[53]
		Daptomycin	Seraph-100	In vitro study with human plasma	- Injection of 350 mg of daptomycin - Initial concentration C_0 de 68.5 +/- 3.5 mg/L - RR= 15% between 0 to 60 min	[51]
		Fosfomycin	Seraph-100	In vitro study with human plasma	- Injection of 2000 mg of fosfomycin - Initial concentration C_0 de 953.9 +/- 487.8 mg/L - RR= 13% between 0 to 60 min	[51]
		Rifampicin	Seraph-100	In vitro study with human plasma	- Injection of 600 mg of rifampicin - Initial concentration C_0 de 109.4 +/- 4.4 mg/L - RR= 7% between 0 to 60 min	[51]
		Tazobactam	Seraph-100	In vitro study with human plasma	- Injection of 500 mg of tazobactam - Initial concentration C_0 de 142.3 +/- 16.7 mg/L - RR= 17% between 0 to 60 min	[51]
Antifungals		Fluconazole	Cytosorb	In vivo study on pigs vs control group	- 800 mg over 40 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 4.2 L/h with an additional clearance by the adsorber of +282.2 % compared with endogenous clearance alone.	[53]

			Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 40 mg/L fluconazole - Clearance of 1.12 L/h in NaCl, 92% of drug removed in 1.5h - Clearance of 1.22 L/h in HA, 92% of drug removed in 1.5h - No significant difference in clearance values between the NaCl solution and the 5% human albumin solution.	[48]
			Seraph-100	In vitro study with human plasma	- Injection of 200 mg of fluconazole - Initial concentration C_0 de 28.5 +/- 4.9 mg/L - RR= -1% between 0 to 60 min	[51]
		Posaconazole	Cytosorb	In vivo study on pigs vs control group	- 300 mg over 30 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 4.8 L/h, with additional clearance by the adsorber of +32% compared with endogenous clearance alone.	[53]
		Voriconazole	Cytosorb	In vitro study with a solution of NaCl, 5% human albumin and a solution of reconstituted blood	- 10 mg/L voriconazole - Clearance of 1.18 L/h in NaCl, 100% of drug removed in 1.5h - Clearance of 1.41 L/h in HA, 100% of drug removed in 1.5h No significant difference in clearance values between NaCl solution and 5% human albumin solution.	[48]
		Anidulafungin	Cytosorb	In vivo study on pigs vs control group	- 200 mg over 60 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 0.7 L/h with an additional clearance by the adsorber of +22.7 % compared with endogenous clearance alone.	[53]
		Liposomal amphotericin B	Cytosorb	In vivo study on pigs vs control group	- 150 mg over 30 min, one hour before initiation of extracorporeal circulation - Total clearance of approximately 2.4 L/h, with additional clearance by the adsorber of 74.9% compared with endogenous clearance alone.	[53]
			Seraph-100	In vitro study with human plasma	- Injection of 50 mg of amphotericin B - Initial concentration C_0 de 13 +/- 2.1 mg/L - RR= 26% between 0 to 60 min	[51]
Antivirals		Ganciclovir	Cytosorb	In vivo study on pigs vs control group	- 400 mg over 60 min, one hour before initiation of extracorporeal circulation - Total negative clearance -0.3 L/h with an additional clearance by the adsorber of -3.4 % compared with endogenous clearance alone. - This negative clearance suggests drug release into the circulation which appears to be due to drug release from red blood cells.	[53]
		Aciclovir	Seraph-100	In vitro study with human plasma	- Injection of 250 mg of aciclovir - Initial concentration C_0 de 58.6 +/- 8.3 mg/L - RR= 22% between 0 to 60 min	[51]

RR: Removal Ratio
Cmin and Cmax: Minimal concentration and maximal concentration respectively
HA: Hemoadsorption
CRRT : Continuous renal replacement therapy

Table 3 –Studies evaluating antithrombotic drugs removal

		Type of device	Type of study	Results	References
Antithrombotics	Ticagrelor (P2Y12 inhibitor)	Cytosorb and Porapak Q 50-80 mesh	In vitro study with two solutions of bovin serum albumin solution (BSA) one at 0.4% and one at 4% or human blood solution	- In experiment with BSA solution at 4%: 99% of Ticagrelor was removed from the Cytosorb and 100 % from the Porapak Q50-80 mesh. There was no statiscal differencies between BSA 0.4 or 4% using Cytosorb. - In experiments with human blood, 3 models were used: o In model 1: 14 10-ml columns mounted in series removed at maximum 96% of the Ticagrelor concentration o In model 2: 1 300 mL column removed >99% of Ticagrelor in the first 3 hours o In model 3: 99.99% of ticagrelor was removed from the whole blood and plasma after 10 hours.	[75]
		Cytosorb	Prospective study on 55 patients underwent emergency cardiac surgery and receiving therapy with either Ticagrelor or Rivaroxaban	- 32 Patient receiving Ticagrelor in group Cytosorb and 11 without adsorption - The rate of rethoracotomy was significantly different between the two groups in favor of Cytosorb (p= 0.0003), as was the 24-hour drainage volume (p=0.0037) (300-450 mL VS 630-1025 mL). - ICU and hospital LOS were significantly different to (2 versus 3 days, p=0.01 and 11 versus 14 days, p=0.02 respectively)	[78]
		Cytosorb	Retrospective study on 21 patients underwent emergency cardiac surgery for acute type A aortic dissection 9 Patients pretreated with Rivaroxaban and 12 with ticagrelor	- 10 in adsorber group and 11 in control group - 24-hour drainage volume is significantly different between the two groups (p<0.001; 750 mL [635,695] in control group VS. 475 mL [428,508] in adsorber group) - No statistical difference between the two groups on rethoracotomies, need for red blood cells transfusion. However, patients without adsorption needed significantly mor platelet transfusions (10 VS. 6 p= 0.049).	[79]
		Cytosorb	Prospective study on 11 patients on ticagrelor who underwent nondeferrable CABG surgery No control group	- Mean ticagrelor pre-CPB compared with mean post-CPB levels represent a statistically significant reduction of 67.1% (p<0.001) - No reoperation performed for bleeding - No BARC-4 bleeding events - Median thoracic drainage over 24 hours was 520 mL (375,930 mL)	[80]
	Dabigatran (Thrombin inhibitor)	Cytosorb	In vitro study with 100 mL of 0.4% and 4% BSA solution passed through 10-, 20- and 40-mL sorbent colums.	- Removal efficiency was the same with the two albumin dilutions = 94%, p=0.5. - Maximum removal of Dabigatran > 99% with 40 mL column in 100 minutes first-pass experiment. - In this experience 0.35 mg de dabigatran was eliminated with 40 mL Cytosorb column. To remove 21 mg in a human body for a distribution volume of 60 L, 2400 mL of Cytosorb column could potentially remove the drug.	[76]
	Rivaroxaban (Factor Xa inhibitor)	Cytosorb	In vitro study with 1000 mL of human whole blood in Cytosorb during 120 min hemoperfusion.	- Initial concentration of Rivaroxaban in human whole blood: 571+/-20 µg/L. - 91.6% of Rivaroxaban was eliminated in the first hour - At 120 minutes, the plasma concentration of Rivaroxaban was 46.8 µg/L. This final value is above the threshold of 30 µg/L. However, since normal therapeutic concentrations are below 300 µg/L, the plasma concentration of Rivaroxaban could potentially be reduced below the critical threshold with the use of Cytosorb	[77]
		Cytosorb	Prospective study on 55 patients underwent emergency cardiac surgery and receiving therapy with either Ticagrelor or Rivaroxaban	- 7 Patient receiving rivaroxaban in group Cytosorb and 5 without adsorption - The rate of rethoracotomy was significantly different between the two groups in favor of Cytosorb (p= 0.0003), as was the 24-hour drainage volume (p=0.0037) (310-430 mL VS 590-1000 mL). - ICU and hospital LOS were significantly different to (2 versus 6 days, p=0.01 and 11 versus 18 days, p=0.02 respectively)	[78]
		Cytosorb	Retrospective study on 21 patients underwent emergency cardiac surgery for acute type A aortic dissection	- 10 in adsorber group and 11 in control group - 24-hour drainage volume is significantly different between the two groups (p<0.001; 750 mL [635,695] in control group VS. 475 mL [428,508] in adsorber group) - No statistical difference between the two groups on rethoracotomies, need for red blood cells transfusion. However, patients without adsorption needed significantly mor platelet transfusions (10 VS. 6 p= 0.049).	[79]

			9 Patients pretreated with Rivaroxaban and 12 with ticagrelor		
	Apixaban (Factor Xa inhibitor)	Cytosorb	Case report of an 83-year-old-women	- Patient admitted for emergent mitral valve replacement for prosthetic valve endocarditis - The last dose of apixaban was taken 7 hours before surgery - 50% decrease in AFXaA levels between the start and weaning of CPB. However, this should be interpreted with caution due to the indirect inhibition of factor Xa by heparin.	[82]
		Cytosorb	Non randomized, prospective, multicentric study on 25 patients undergoing cardiac surgery	- Patients under Apixaban and admitted for urgent cardiac surgery - 12 without HA and 13 with Cytosorb - 24h hours chest tube drainage lower in HA group 510 (450,550) vs. 705 mL (588,902) p=0.03 - Desmopressin 10 +/- 13.6 mg for control group and none of the patients in the HA group required desmopressin.	[81]

BSA: Bovin Serum Albumin
ICU: Intensive Care Unit
LOS: Length of stay
CABG: Coronary artery bypass grafting
CPB: Cardio-pulmonary bypass
BARC-4: Bleeding academic research consortium category 4
HA: Hemoadsorption

Table 4 –Studies evaluating other drugs removal

		Type of device	Type of study	Results	References
Immunosuppressive Agents	Prednisolone	Cytosorb	Interventional study on 15 sheep Cytosorb versus control group	- Initial dose of Prednisolone: 10 mg - Negligible clearance for prednisolone	[84]
	Basiliximab			- Initial dose of Basiliximab: 20 mg - Negligible clearance for Basiliximab	
	Tacrolimus			- Initial dose of Tacrolimus: 2x 10-12 mg - Maximum absolute adsorbed amount = 0.040 (0.028-0.053) - Clearance max: CL_{max}: 0.04mg/4.02L/h	
	Cyclosporine A			- Initial dose of Cyclosporine A: 2x 600-1000 mg - Maximum absolute adsorbed amount: 1.15(0.39-1.91) - Clearance max: CL_{max}: CLmax1.15 mg/2.80L/h	
	Mycophenolate mofetil			- Initial dose of Mycophenolate mofetil: 2x 1g - Maximum absolute adsorbed amount: 4.17(2.00-6.35) - Clearance max: CL_{max}: 4.17 mg/3.71L/h	
	Everolimus			- Initial dose of Everolimus: 2x 3-8.25 mg - Maximum absolute adsorbed amount: 0.0163 (0.007-0.026) - Clearance max: CL_{max}: 0.0163mg/3.23L/h	
	Methylprednisolone			- Initial dose of Methylprednisolone: 2 sheep = 2x1g and 2 sheep = 1x1.5g (control) - Maximum absolute adsorbed amount: 53.4 (20.9-85.9) - Clearance max: CL_{max}: 53.4mg/8.21L/h	
	Metothrexate	Jafron HA-230	Case report	- Patient of 8 years old with acute lymphocytic leukemia. HA was used to reduce methotrexate toxicity after high-dose chemotherapy - HA treatment has taken place during 4 hours - Reduction of methotrexate level from 540.7 to 79.60 µmol/L, so reduction rate = -85.27% - 12 hours after the procedure methotrexate level was 49.04 µmol/L - This rate continued to fall, reaching 14.60 µmol/L, 48 hours after the procedure.	[85]
Others	Paraquat	Jafron HA-330	Retrospective cohort study of 487 patients with acute paraquat poisoning	- Patients was separate in 5 groups: control, CVVH, HA, SHP, SHP + CVVH - Differences in ninety-day survival curves: o SHP + CVVH versus Control group: χ^2=118.084, p=0.000 o SHP + CVVH versus HA: χ^2 = 11.003, p = 0.001 o SHP + CVVS versus CVVH: χ^2 =28.549, p=0.000 o SHP+ CVVH versus SHP: χ^2 =5.740, p=0.017 - Statistically significant difference between SHP+CVVH group and the other groups on organ damages (respiratory failure, mechanical ventilation, acute renal injury)	[89]
		Jafron HA-330	Multicenter retrospective study on 183 patients with acute paraquat poisoning	- 3 groups of patients: 75 with conservative treatment (Control), 65 with HA treatment and 43 with HA + CVVH - Blood levels of paraquat comparison at 72 hours: Differences are statistically significant p <0.001 o Control: 6.02 +/- 3.29 o HA: 2.50+/-1.34 o HA + CVVH: 2.11 +/- 1.67 - No statistically significant differences on the SOFA at 24 hours but ΔSOFA values in HA group and HA + CVVH group were significantly lower than control group - Median survival was significantly longer in the HP (p = 0.003) and HP + CVVH (p = 0.001) groups compared with the conservative treatment group, but without difference between the HP and HP + CVVH groups (p = 0.535).	[90]
	Quetiapine	Cytosorb	Case report of a 27-year-old patient	- Women admitted in emergency department with worsening mental status and seizures after a voluntary intake of 15g of quetiapine to attempt suicide - Start of HA treatment for 48 hours with CVVH. - After 12 hours quetiapine levels reduced from 1850 to 648 µg/L with a removal rate = 65% - Clinicians observed a desorption phenomenon and therefore decided to start a second treatment session after first-24h session - Quetiapine has totally disappeared from the blood stream 120 hours after the patient's admission	[4]
	Clozapine	Cytosorb	Case report of a 56-year-old patient	- Men admitted to the emergency department after being found to have generalized epileptic seizures and arrhythmias. The presume ingested dose of clozapine was 5000 mg. - CVVH + Cytosorb HA therapy were begin 4 to 6 hours after the presume ingestion for 2 sessions of 12h - Systemic clozapine drug concentration before was 4.779 ng/mL. After the first 12h session clozapine concentration has been cut by around half. - Patient could be extubated 3days after his admission	[5]
	Carbamazepine	Jafron HA-230	Prospective study of 104 patients with acute carbamazepine poisoning	- 3 groups of patients: Group A received HA treatment in Emergency department, Group B HA treatment in the blood purification room and group C received conservative treatment without HA. - Mean retention times: 0.85 +/- 0.08; 1.20 +/- 0.15; 2.52 +/- 0.29 days for groups A, B and C respectively. Lower in group A than in group B, p<0.05	[6]

				- Improvements in respiratory depression and seizure significantly greater in goup A than in group B and C. - Glasgow coma scale score at 4h is significantly higher in group A than other groups, p<0.05.	
	Lamotrigine	Cytosorb	Case report of a 60-year-old woman patient	- Women admitted to the emergency department after being found unconscious by her husband - On admission lamotrigine plasma level = 85.8 mg/L (reference therapeutic range = 3-15 mg/L - Cytosorb treatment was started on day 8 with CVVH for 44 consecutive hours with adsorber used - During the first 12 hours lamotrigine plasma level decreased around 50% with further clinical improvement like the vigilance	[7]
	Amlodipine	Jafron HA-230	Case report of 20-year-old patient	- Patient admitted to the intensive care unit with hemodynamic instability and shock after an overdose of amlodipine and risperidone. - First HA treatment was beginning 24 hours after admission for 6 hours. And 18 hours after the first session, the patient received a second session of 6 hours. - During the first session: MAP increased from 60 mmHg to 73 + methylene blue, insuline and calcium infusions was stopped + Lactates levels decreased from 7.6 mmol/L to 3.6 mmol/L. - During the second session: Adrenaline was weaned to 0.6 µg/kg/min (from 1 µg/kg/min) and stopped 8 hours after + MAP maintained at 70 mmHg - Patient was extubated 48 hours later.	[8]
	Iohexol	Jafron HA-380	In vitro study with 1000 mL solution of NaCl + Iohexol	- This solution contained 40 mL of OMNIPAQUE in 960 mL NacL for a final Iohexol concentration of 30.2 g/L and this solution was recirculated in a closed loop circuit with Jafron HA-380 for 60 min. - Experiment 1: RR of 53.0% and Cl decreased from 46.79 mL/min to 3.57 mL/min. Total mass adsorbed at 60 min = 16.29g. - Experiment 2: RR of 53.1% and Cl decreased from 46.72 mL/min to 3.87 mL/min. Total mass adsorbed at 60 min = 16.37g. - Each cartridge contained 105g of sorbent, the ratio of adsorbate/sorbent is 155 mg/g so, for each gram of the sorbent can remove 155 mg of iohexol dissolved in saline solution.	[95]

CVVH: Continuous veno-venous hemofiltration
SHP: Strengthened hemoperfusion: HA was performed 5 times continuously, each perfusion lasted 2 hours for a total time of 10 hours
RR: Reduction Ratio = $C_i - C_t$ / C_i ou C_i is the initial concentration and C_t the concentration at different timepoints.
Cl: Clearance (mL/min) = Elimination rate (g/min) / Concentration (g/mL)

Table 5- Ongoing trials registered in clinicaltrials.gov and evaluating drug removal by hemoadsorption

Name of study	Population	Intervention	Main outcome	Number of subjects
STAR registry NCT05077124	STAR Registry will collect patient-level clinical data on antithrombotic removal with CytoSorb	Cytosorb	Bleeding complications including requirements for transfusions and other blood products	NI
VITAL NCT06109142	Patients with vasoplegic shock and an indication for renal replacement therapy	oXiris	50% reduction in vasoinotropic score within 24 hours of initiation on oXiris.	30
NCT04033029	Sepsis patients undergoing continuous renal replacement therapy and admitted in Intensive care Unit	oXiris	Time above minimum inhibitory concentration (%fT > k× MIC) for betalactams, and total-drug AUC24/MIC ≥ 666 for daptomycin	NI
NCT06261164	Patients with a diagnosis of SIRS, sepsis and/or septic shock treated with amikacin and/or vancomycin	Cytosorb oXiris	Measurement of amikacin and vancomycine serum concentrations in several time points in order to gain pharmacokinetic profiles of previously mentioned drugs and to develop population pharmacokinetic model of amikacin and vancomycin by nonlinear modeling of combined effects in critically ill patients on veno-venous hemodiafiltration with two types of adsorbents.	20
NCT06602245	Patients with sepsis and/or septic shock presumed to be of Gram-negative aetiology requiring, in the opinion of the investigator, isolated lipopolysaccharide hemoperfusion.	Efferon LPS	Adsorption clearance of antibacterial drugs by the Efferon LPS device, mL/min	30
NCT06710834	20 patients, stable on a thrice-weekly hemodialysis program. Prospective collection of two dialysis sessions.	Jafron HA-130	Uremic toxins reduction ratios (RR)	20
NCT06807151	Patients with acute Diquat poisoning	Extracorporeal treatment included hemoperfusion and CVVH	This primary outcome measure evaluates patient survival status within 28 days following their presentation at the emergency department.	163
NCT06798129	Patients with acute paraquat poisoning	Extracorporeal treatment included: Intermitent hemodialysis, CRRT, plasma exchange, HA	Survival at 28 days	4178

HA= Hemoadsorption
SIRS= Systemic Inflammatory Response Syndrom
CVVH= Continuous veno-venous hemofiltration
CRRT= Continuous Renal Replacement Therapy