CRITICAL CARE

REVIEW

Clinical review: Blood purification for sepsis

Thomas Rimmelé and John A Kellum*

Abstract

Sepsis is the primary cause of death in the intensive care unit. Extracorporeal blood purification therapies have been proposed for patients with sepsis in order to improve outcomes since these therapies can alter the host inflammatory response by non-selective removal of inflammatory mediators or bacterial products or both. Recent technological progress has increased the number of techniques available for blood purification and their performance. In this overview, we report on the latest advances in blood purification for sepsis and how they relate to current concepts of disease, and we review the current evidence for high-volume hemofiltration, cascade hemofiltration, hemoadsorption, coupled plasma filtration adsorption, high-adsorption hemofiltration, and high-cutoff hemofiltration/hemodialysis. Promising results have been reported with all of these blood purification therapies, showing that they are well tolerated, effective in clearing inflammatory mediators or bacterial toxins (or both) from the plasma, and efficacious for improvement of various physiologic outcomes (for example, hemodynamics and oxygenation). However, numerous questions, including the timing, duration, and frequency of these therapies in the clinical setting, remain unanswered. Large multicenter trials evaluating the ability of these therapies to improve clinical outcomes (that is, mortality or organ failure), rather than surrogate markers such as plasma mediator clearance or transient improvement in physiologic variables, are required to define the precise role of blood purification in the management of sepsis.

Introduction

Sepsis is the primary cause of death in the intensive care unit [1], and more than 35% of patients are admitted with sepsis or develop it during their intensive care unit stay. Hospital mortality rates are 27%, reaching 54% in the case of septic shock [2].

Extracorporeal blood purification therapies have been proposed to improve outcomes for patients with sepsis. These therapies are based on the principle that removal of inflammatory mediators or bacterial toxins (or both) from the blood will favorably modulate the host inflammatory response. Recently, significant technological progress has greatly broadened the spectrum of techniques available for blood purification. Indeed, promising results have been reported with high-volume hemofiltration (HVHF), cascade hemofiltration, hemoadsorption, plasmapheresis, coupled plasma filtration adsorption (CPFA), high-adsorption hemofiltration, and high-cutoff (HCO) hemodialysis/hemofiltration. However, these techniques have not entered into mainstream clinical practice around the world.

This overview has three aims. First, we will report on the latest advances in blood purification for sepsis. Then, we will briefly describe each therapy and explain how they work and discuss how they relate to current concepts of disease. Finally, we will review the current evidence from the medical literature, highlighting the most important studies related to each therapy. To select articles from medical literature, we conducted a systematic review of the MEDLINE database using PubMed with the following search terms: blood purification, high-volume hemofiltration, sepsis, hemoadsorption, high-cutoff membranes, and coupled plasma filtration adsorption. The search included experimental and clinical studies.

Concept of blood purification

Systemic inflammatory states such as severe sepsis and septic shock result in immunologic disturbances with the release of numerous inflammatory mediators. The systemic inflammatory response, though a result of innate immunity, can become deleterious when excessive or uncontrolled, leading to the development of multi-organ failure syndrome and death. At least two mechanisms are identified to explain the potential harmful effects of this host inflammatory response: cytokines have the capacity to damage the cells (cytotoxic effects) [3], and the prolonged release of inflammatory mediators leads to severely impaired immunity [4]. This 'immunoparalysis'

*Correspondence: kellumja@ccm.upmc.edu
The CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Laboratory, Department of Critical Care Medicine, University of Pittsburgh Medical Center, 3550 Terrace Street, Pittsburgh, PA 15261, USA

state plays a major role in mortality because it favors severe secondary nosocomial infections. Secondary infections can be bacterial but also may be related to reactivation of dormant viruses [5,6].

The overall concept of blood purification is therefore to attenuate this overwhelming systemic expression of pro- and anti-inflammatory mediators. Restoration of immune homeostasis is thought to be able to improve outcomes and survival. Multiple mediators are involved in this inflammatory response [7], but past attempts to modulate it by targeting single components have failed, at least at the clinical phase [8]. Thus, over time, the blood purification concept and therapies have evolved toward the non-specific removal of a broad spectrum of inflammatory mediators, which can also include microbial toxins.

Recently, a number of theories to explain the effects of blood purification have been proposed. First, Ronco and colleagues [9] hypothesized that eliminating the peaks of cytokine blood concentrations during the early phase of sepsis could stop the inflammatory cascade, limit organ damage, and consequently decrease the incidence of multi-organ failure syndrome. Second, Honoré and Matson [10] proposed the 'threshold immunomodulation hypothesis', postulating that the cytokine removal from the blood compartment leads to the removal of cytokines located at the tissue level because of an equilibration of their concentrations between these two compartments. This theory explains why numerous studies assessing blood purification techniques found an improvement of outcomes with no modification of cytokine blood concentrations as cytokines from the tissues replace those removed from the blood. Third, Di Carlo and Alexander [11] proposed the 'mediator delivery hypothesis', in which HVHF is responsible for an increase of the lymphatic flow because of the high amounts of crystalloid fluids used for replacement with this technique. This leads to a significant drag and displacement of inflammatory mediators to the blood compartment, making them available for removal [11].

Finally, Peng and colleagues [12] recently suggested that blood purification therapies act at the inflammatory cell level to restore the immune function through the regulation of monocytes, neutrophils, or even lymphocytes. This theory is supported by recent studies [13,14]. Indeed, it has been reported that polymyxin B hemoadsorption could increase the expression of leukocyte surface markers such as HLA-DR [13]. Thus, hemoadsorption would act as a 'reprogrammation system' for the leukocytes. However, the mechanism by which hemoadsorption stimulates HLA-DR expression remains unknown. If this 'cellular level' theory with immune response restoration is confirmed, timing indications for blood purification would need to be reconsidered since optimal timing for initiating a blood purification therapy would not be only in the early phase of septic shock as it is suggested today. Furthermore, a novel component of this hypothesis is that, by removing mediators from the plasma in the setting of systemic inflammation, one can restore the concentration gradient from plasma to infected tissues [12]. This gradient has significant effects on leukocyte trafficking and bacterial clearance [14]. Thus, the 'cytokinetic model' may be more relevant than cytotoxic models to explain the association between high cytokine levels and mortality (Figure 1).

High-volume hemofiltration

By increasing plasma water exchanges, HVHF appears to be an attractive therapy to remove a significant amount of inflammatory mediators from the plasma. First, these circulating molecules are predominately water-soluble and convection carries both plasma water and solutes across a semi-permeable membrane along a hydrostatic pressure gradient. Second, most inflammatory mediators are so-called middle-molecular-weight molecules with a wide range of mass (from 5 to 60 kDa) and convection is far more effective than diffusion in removing middle molecules [15,16]. Third, depending on their composition, most hemofiltration membranes also have some adsorptive properties. The ultrafiltrate contains the molecules from the plasma which are able to cross the membrane (molecular weight below the membrane cut-off), and adsorption allows the removal of some other molecules with a molecular weight higher than the membrane cutoff.

HVHF is not well defined in the medical literature. Recently, Honoré and colleagues [17] convened a consensus conference to clarify the definition of HVHF. They agreed that HVHF includes continuous high-volume treatment of 50 to 70 mL/kg per hour 24 hours a day and intermittent HVHF with brief, very-high-volume treatment at 100 to 120 mL/kg per hour for a short period of 4 to 8 hours, followed by conventional continuous veno-venous hemofiltration (CVVH). This latter strategy is also called 'pulse HVHF' [18]. However, for experts from the Acute Dialysis Quality Initiative workgroup, greater than 35 mL/kg per hour is already considered HVHF [19]. Indeed, given that 'renal dose' hemofiltration for acute kidney injury has been standardized at 25 to 30 mL/kg per hour (see reference [20] for justification), defining HVHF at greater than 35 mL/kg per hour seems reasonable.

Many animal studies have been performed to assess HVHF, especially in the 1990s, when HVHF was still very experimental in humans. Grootendorst and colleagues [21] reported an improvement in cardiac performance in pigs with endotoxin-induced shock when HVHF was applied. The authors hypothesized that some vasoactive mediators, responsible for the myocardial depression,

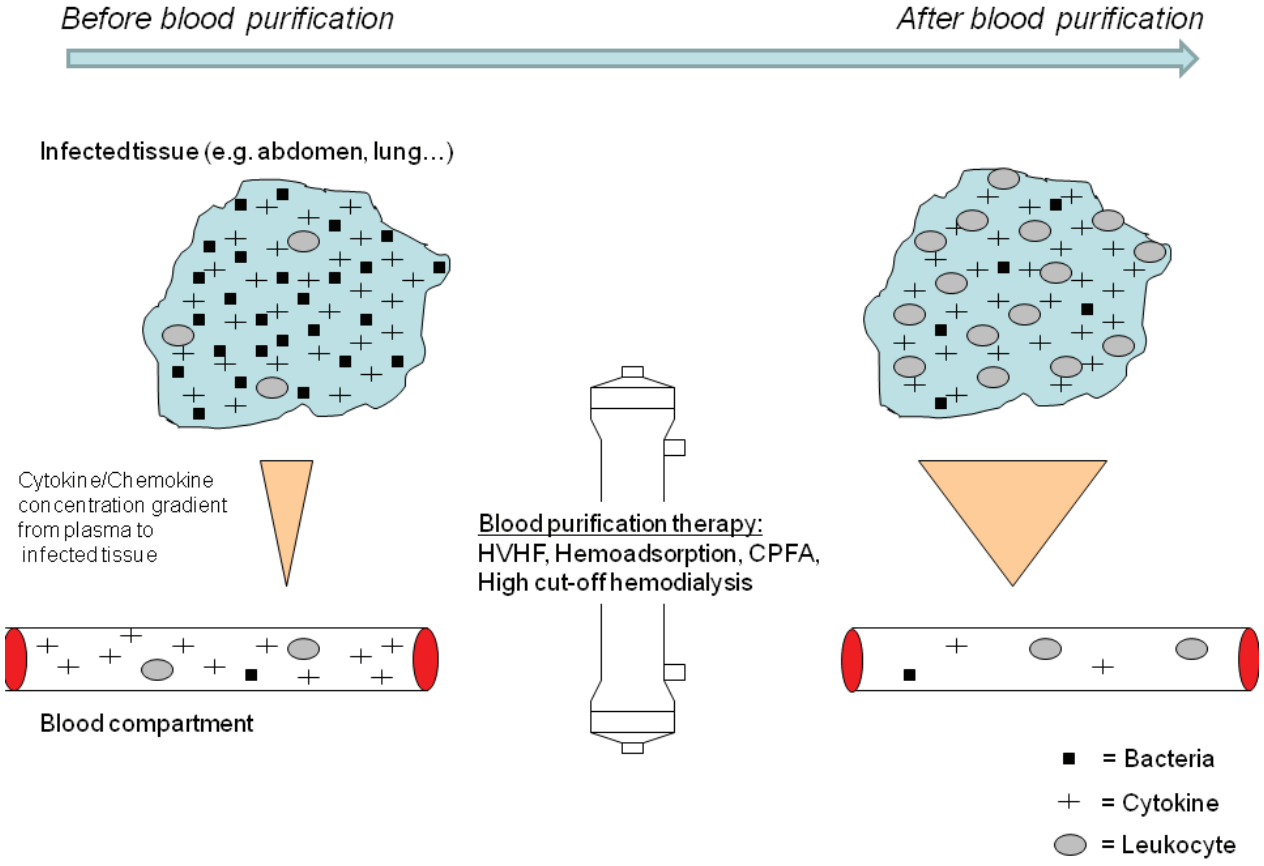

Figure 1. The 'cytokinetic model'. Blood purification therapies increase the cytokine/chemokine concentration gradient from plasma to infected tissue by removing those inflammatory mediators from the blood compartment. Consequently, leukocyte trafficking is driven toward the nidus of infection, allowing the increase of local bacterial clearance. CPFA, coupled plasma filtration adsorption; HVHF, high-volume hemofiltration.

were removed with HVHF. Even though other authors recently suggested a positive effect on the myocardial mitochondrial dysfunction [22], the pathophysiologic explanation of the hemodynamic improvement with HVHF remains unclear [23]. In septic dogs, Bellomo and colleagues [24] also found that HVHF improved hemodynamic parameters compared with a sham circuit with no hemofilter. Furthermore, some animal studies assessed HVHF by looking at ultrafiltrate obtained from either healthy donor or septic donor animals and infused into a healthy acceptor animal. The ability of HVHF to remove toxic mediators is suggested when ultrafiltrate obtained from septic animals leads to hemodynamic disturbances or even death in healthy animals. In a prospective randomized controlled study including 65 septic pigs, Lee and colleagues [25] reported an increase survival time in filtered animals compared with matched non-filtered ones. Increments in survival time even increased directly with filtration fraction. Moreover, ultrafiltrate concentrate obtained from septic pigs produced death in healthy ones whereas the infusion of 'clean' ultrafiltrate concentrate produced no response.

Numerous human studies have shown beneficial hemodynamic effects of HVHF. In a randomized crossover study of 11 patients with septic shock and multiorgan failure, an 8-hour period of HVHF (6 L/hour) was associated with a greater reduction in norepinephrine requirements in comparison with a similar period of CVVH (1 L/hour) [26]. Reduction of vasopressor requirements with HVHF was also found more recently in a pilot randomized study comparing CVVH at 65 mL/kg per hour versus 35 mL/kg per hour in 20 septic shock patients with acute kidney injury [27]. Large randomized controlled studies of HVHF in septic shock which use mortality as the primary outcome are lacking. One such study, known as the IVOIRE (High Volume in Intensive Care) study, which compares 70 mL/kg per hour versus 35 mL/kg per hour, is currently ongoing in Europe. Although results from this study have not yet been released, the investigators have reported that the enrollment process was very slow and therefore the number of patients included is likely to be less than 150, making conclusions regarding mortality difficult to establish. Thus, the only available studies regarding mortality have

relied on comparisons with expected mortality based on the patients' severity scores at admission. Though uncontrolled, at least six studies have found significant (and sometimes spectacular) reductions in mortality rate with HVHF compared with predicted mortality [28-33]. Honoré and colleagues [29] reported a reduction of the mortality rate from 79% (expected mortality based on APACHE II [Acute Physiology and Chronic Health Evaluation II] score and SAPS II [Simplified Acute Physiology Score II]) to 55%. Several years later, Joannes-Boyau and colleagues [30] obtained a similar result with a predicted 28-day mortality of 70% and an observed mortality of 46% in a study assessing the effect of 40 to 60 mL/kg per hour maintained for 96 hours in patients with septic shock. In patients without sepsis but with systemic inflammation, the effect of HVHF on mortality was evaluated in two randomized controlled trials [34,35]. In 61 resuscitated cardiac arrest patients, very-high-volume hemofiltration (200 mL/kg per hour during 8 hours) was associated with improved 6-month survival and a decreased risk of death from early intractable shock [35]. The most important recent studies assessing mortality with HVHF as a blood purification therapy are summarized in Table 1. Unlike HVHF, standard 'renal dose' continuous renal replacement therapy (CRRT) appears to be ineffective as an immune modulating therapy. Like Cole and colleagues [36] in 2002, Payen and colleagues [37] found no difference (and even a trend toward worse outcomes) between septic shock patients who did not have acute kidney injury and who underwent CVVH (25 mL/kg per hour for a 96-hour period) at the early phase of sepsis and those who were managed conventionally.

HVHF has important limitations such as a theoretical depletion of low-molecular-weight molecules (nutrients, vitamins, trace elements, and drugs such as antibiotics), an elevated cost due mainly to the requirement of large replacement fluid amounts, and a high nursing workload [38,39]. Cascade hemofiltration was recently developed to limit some of these drawbacks [40]. It allows application of HVHF selectively on middle-molecular-weight molecules with a low replacement fluid flow rate because of a particular circuit that combines two hemofiltration membranes having different cutoffs (Figure 2).

Hemoadsorption

Hemoadsorption places sorbents in direct contact with blood via an extracorporeal circuit. The sorbent attracts solutes through hydrophobic interactions, ionic attraction, hydrogen bonding, and van der Waals interactions [41]. Until recently, poor biocompatibility has been the main clinical limitation of hemoadsorption, as evidenced by severe thrombocytopenia and leukopenia [41]. The interesting feature of hemoadsorption is its high-molecular-weight adsorption potential, allowing it to target large molecules, exceeding the cutoff of conventional synthetic high-flux hemofilters.

Polymyxin B is a cyclic basic polypeptide that disrupts the permeability of the cell membrane of Gram-negative bacteria. It was developed as an antibiotic but its severe renal toxicity precludes systemic use. However, polymyxin B-immobilized polystyrene-derived fibers have been developed for use in extracoporeal therapy as a means to remove endotoxin from the blood. Though still under evaluation in Europe and the US, polymyxin B hemoadsorption (Toraymyxin; Toray Industries, Inc., Tokyo, Japan) is widely used in Japan as a blood purification therapy and is covered by the Japanese national health insurance [42]. The EUPHAS (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis) study was a prospective, multicenter randomized controlled study that was performed in 10 Italian intensive care units [43]. Sixty-four patients with severe sepsis or septic shock were randomly assigned to one of two groups (either conventional therapy or conventional therapy along with two sessions of polymyxin B hemoadsorption) within the 6 hours following emergency surgery for intra-abdominal infection. Hemodynamics, the PaO_2/FiO_2 (arterial partial pressure of oxygen/fraction of inspired oxygen) ratio, and the SOFA (Sequential Organ Failure Assessment) score of patients from the hemoadsorption group improved within 72 hours, whereas the conventional group did not. The main result (though not the primary outcome) of this study was the 28-day mortality rate, which was drastically reduced to 32% in the hemoadsorption group compared with 53% in the control group ($P = 0.03$). However, the conclusions of this study should be taken with caution. Indeed, although mortality was only a secondary endpoint, the study was prematurely stopped because it was judged to be unethical to deprive patients of hemoadsorption. The decision to halt the study seems extremely debatable because it was based upon a secondary analysis of an underpowered study and a different outcome in a single patient would have abolished the statistical difference in mortality [44]. Moreover, the fact that the study was controlled is also debatable since hemodynamic and respiratory parameters were only analyzed independently within each group, comparing 72-hour to baseline levels. No statistical comparison was performed between the two groups at 72 hours. No statistical comparison was performed between the two groups at 72 hours.

Other trials showed interesting results with polymyxin B hemoadsorption. Vincent and colleagues [45] conducted a multicenter randomized controlled study that enrolled 36 postsurgical patients with septic shock. Nineteen patients were allocated to standard treatment, and 17 were given an additional polymyxin B hemoadsorption

Table 1. Summary of recent human studies that assessed the effects of high-volume hemofiltration as a blood purification technique on hemodynamics and survival

Study	Design	Number of patients	Clinical setting	Dose, mL/kg per hour	Improved hemodynamics with HVHF	Improved survival with HVHF	*P* value (survival)
Honoré, *et al.* [29] 2000	Prospective, cohort, uncontrolled	20	Refractory septic shock	115	Yes	Yes. 28-day survival: 21% (expected) to 45% (observed)	<0.05
Cole, *et al.* [26] 2001	Randomized, crossover	11	Septic shock with multi-organ failure	6,000 mL/hour	Yes	Not assessed	N/A
Joannes-Boyau, *et al.* [30] 2004	Prospective, cohort, uncontrolled	24	Septic shock	40-60	Yes	Yes. 28-day survival: 30% (expected) to 54% (observed)	<0.075
Laurent, *et al.* [35] 2005	RCT	61	Resuscitated cardiac arrest	200	Yes	Yes. Six-month survival: 21% to 45%	0.026
Jiang, *et al.* [34] 2005	RCT	37	Severe acute pancreatitis	4,000 mL/hour	Yes	Yes. 14-day survival: 68.4% to 94.4%	<0.01
Ratanarat, *et al.* [33] 2005	Prospective, cohort, uncontrolled	15	Severe sepsis	85 (pulse HVHF)	Yes	Yes. 28-day survival: 30% (expected) to 53% (observed)	N/A
Piccinni, *et al.* [32] 2006	Retrospective, uncontrolled	80	Septic shock	45	Yes	Yes. 28-day survival: 27.5% to 55%	0.005
Cornejo, *et al.* [28] 2006	Prospective, cohort, uncontrolled	20	Refractory septic shock	100	Yes	Yes. Hospital survival: 37% (expected) to 60% (observed)	<0.03
Boussekey, *et al.* [27] 2008	RCT	20	Septic shock	65	Yes	No	0.65
Zhu, *et al.* [77] 2009	Retrospective	63	Severe acute pancreatitis	60-80	No	Yes. 28-day survival: 65.5% to 91.2%	0.014
IVOIRE study, ongoing	RCT	Approximately 150	Septic shock	70	Not reported	Not reported	Not reported

HVHF, high-volume hemofiltration; IVOIRE, High Volume in Intensive Care; N/A, not applicable; RCT, randomized controlled trial.

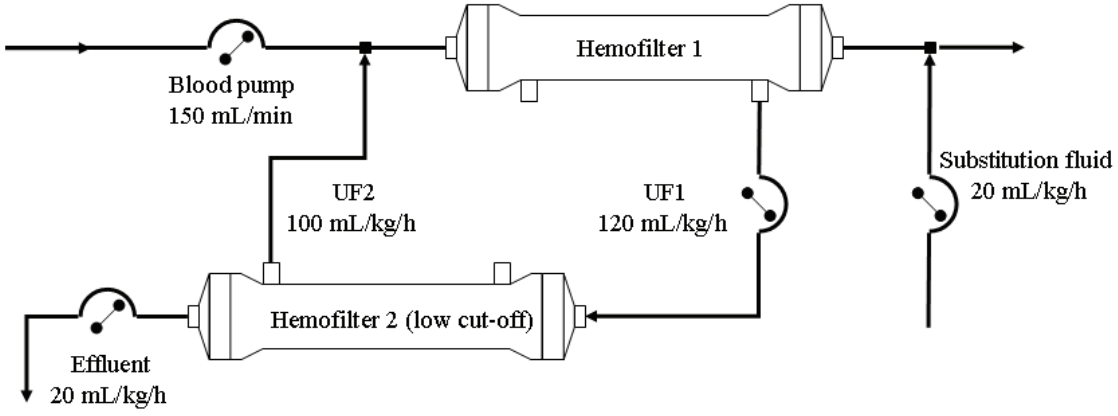

Figure 2. Cascade hemofiltration circuit.

session. Endotoxin and interleukin-6 concentrations were not different between the two groups within the 24 hours following the start of treatment. However, patients treated with hemoadsorption had a marked improvement in hemodynamics and oxygen transport function, and the need for CRRT after the study was less important in the hemoadsorption group. These beneficial effects were also reported in a systematic review of 28 publications (1,425 patients) [46]. Indeed, although Cruz and colleagues [46] highlighted the suboptimal quality of the studies, favorable effects regarding blood pressure, vasopressor requirement, gas exchanges, and even mortality were

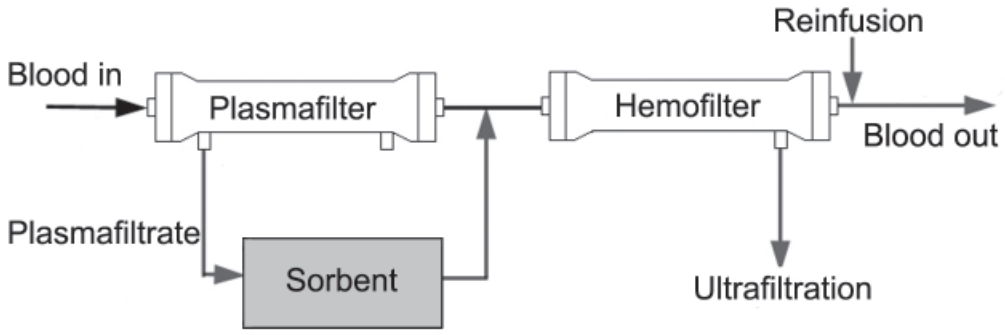

Figure 3. Coupled plasma filtration adsorption circuit.

reported. Importantly, this review points out the need for further rigorous studies of this therapy. Two large multicenter studies, similar to the EUPHAS study, were expected to be started in the US and Europe in 2010.

The CytoSorb™ technology (CytoSorbents Corporation, Monmouth Junction, NJ, USA) is composed of cartridges containing biocompatible polystyrene divinyl benzene copolymer beads. This technology does not target endotoxin but has been shown to result in rapid *in vitro* and *in vivo* elimination of several key cytokines [47]. Recently, 33 septic rats were randomly assigned to receive either hemoadsorption or sham treatment for 3 hours [48]. Cytokine concentrations were lower in the hemoadsorption group at the end of the treatment and this difference lasted 6 hours after treatment. Blood pressure of the rats from the hemoadsorption group was higher than that of the sham group. Finally, the overall survival rate (defined at 12 hours after randomization) was also significantly greater in the hemoadsorption group (11/17 versus 2/16; P <0.01).

The resin referred to by its manufacturer as "CTR resin" (Kaneka Corporation, Osaka, Japan) is an adsorbent composed of porous cellulose beads. Taniguchi and colleagues [49] reported that CTR effectively adsorbed small- to middle-sized proteins such as cytokines, enterotoxins, and toxic shock syndrome toxin-1 *in vitro*. Additionally, in an endotoxemic rat model, hemoadsorption with CTR dramatically reduced the mortality rate 8 hours after endotoxin injection (14% versus 92% for endotoxemia alone) [49]. Interestingly, the same authors further demonstrated in rats the dose-related effects of hemoadsorption with CTR on mortality [50].

Plasmapheresis and coupled plasma filtration adsorption

Only very limited data are available in the medical literature regarding plasmapheresis, plasma exchanges, and related techniques for this indication [51-55]. Nevertheless, it has been suggested that these therapies might be beneficial, especially for patients with Gram-negative sepsis [52,54,56,57] and when implemented as early as possible [58]. Additional studies are therefore warranted to better assess these therapies for blood purification [59].

CPFA first separates plasma from the blood by means of a plasma filter. The plasma then circulates through a sorbent, allowing inflammatory mediator adsorption, and finally returns to the blood, where a second blood filter is used for renal support (hemofiltration, hemodialysis, or hemodiafiltration) (Figure 3). Performing adsorption with plasma, rather than with blood, avoids coagulation issues, platelet aggregation, and hemolysis and allows the use of a low flow rate, extending the time of contact between the inflammatory mediators and the sorbent and consequently maximizing their adsorption.

Several studies have demonstrated the safety and the effectiveness of CPFA for removing inflammatory mediators from the circulation [60,61]. Moreover, CPFA was able to increase the survival of a rabbit model of endotoxic shock and to improve hemodynamics and the pulmonary function of patients with septic shock [62,63]. Recently, CPFA was compared with other extracorporeal blood purification techniques. In a small pilot study, Lentini and colleagues [64] reported no difference in hemodynamic effects between pulse HVHF and CPFA in patients with septic shock. In pigs with hyperdynamic septic shock, continuous hemofiltration, unlike CPFA, was able to remove some inflammatory mediators involved in delayed cardiac repolarization [65]. Conversely, Ronco and colleagues [61] reported in patients with septic shock that CPFA combined with hemodialysis was associated with greater improved hemodynamics compared with continuous hemodiafiltration. The authors hypothesized that this result could be due to the ability of CPFA to restore leukocyte responsiveness to lipopolysaccharide. Interestingly, effects of CPFA on immune function were also shown by Mao and colleagues [66] in a small crossover study comparing CPFA with HVHF in septic patients with multiple organ dysfunction syndrome. HLA-DR expression increased after CPFA but

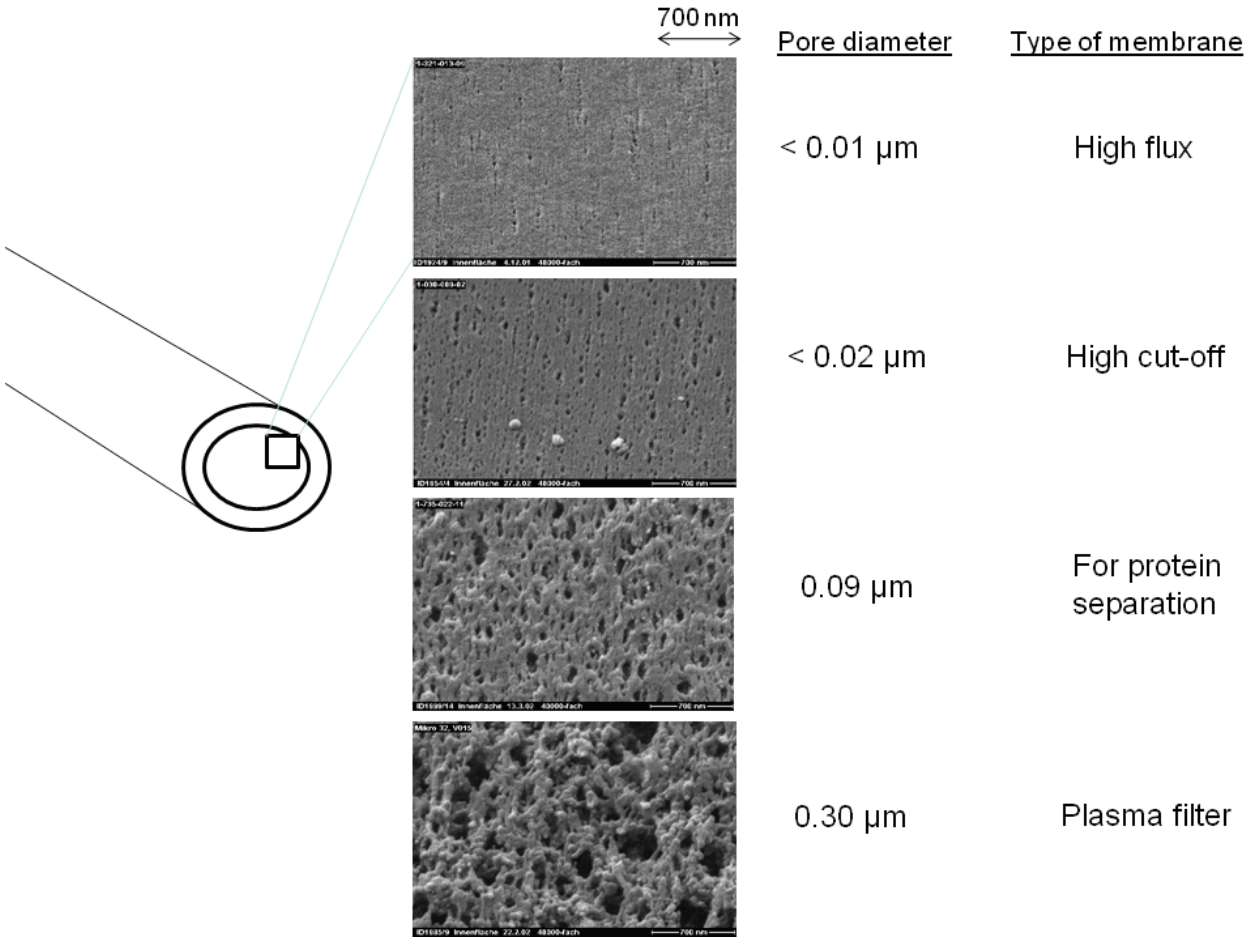

Figure 4. Electronic microscopy images of the internal surface of different filters.

there was no change after HVHF. In addition, spontaneous and lipopolysaccharide-induced tumor necrosis factor production increased over time with CPFA but did not change with HVHF. The authors therefore suggested that CPFA was superior to HVHF in restoring leukocyte responsiveness.

High-adsorption hemofiltration and high-cutoff membranes

Other approaches proposed for blood purification therapies consist of optimizing the performances of the hemofilters regarding cytokine or endotoxin removal (or both) by manipulating their composition or structure. High-adsorption hemofiltration is a technique whereby the adsorption properties of a hemofilter are enhanced. Positive hemodynamic effects of a polyacrylonitrile hemofiltration membrane having endotoxin adsorption properties were recently reported in septic pigs [67]. The membrane surface polarity was modified by adjunction of a polyethylenimine coating, a positively charged polymer, allowing it to catch negatively charged endotoxins via surface adsorption. This study highlights another potentially important aspect of blood purification for the future: the synergy between different blood purification mechanisms (HVHF + high adsorption) [67,68]. In the same line, other models in which HVHF and high-permeability hemofiltration work synergistically have shown promising results [69].

The use of HCO membranes represents another logical strategy to increase mediator removal. When the membrane pore size is increased from 0.01 to 0.02 µm (Figure 4), the spectrum of molecules affected by the therapy is significantly broadened [70]. In experimental models of sepsis, HCO membranes improve hemodynamics and prolong survival [71]. In patients with sepsis-induced acute kidney injury, Morgera and colleagues [72] reported a reduction in vasopressor requirements with the use of HCO hemofiltration and not with conventional CVVH. Additionally, cytokine clearance rates were significantly higher in the HCO hemofiltration group. In another randomized study, HCO hemofiltration restored the monocyte proliferation

capacity of septic patients, probably by eliminating immunomodulatory mediators [73]. However, the use of HCO hemofiltration has been challenged by the albumin loss, which can be up to 15 g per 4-hour session [74]. Consequently, HCO membranes are now proposed for use with hemodialysis. Indeed, the use of diffusion rather than convection is suggested to reduce the albumin loss without significantly impacting cytokine clearances, especially in cases of elevated dialysate flow rates [74]. Haase and colleagues [75] showed that HCO hemodialysis was more efficient than standard hemodialysis in regard to diffusive cytokine clearances. While some decreases in plasma cytokine levels were even reported after only 4 hours of treatment, the albumin loss was limited and plasma albumin concentrations remained stable. Conversely, Lee and colleagues [76] recently highlighted reductions in serum albumin levels after HCO hemodialysis sessions, leaving this question open to further clinical investigation. To address this issue, membrane parameters and aspects other than the type of modality (diffusion versus convection) – for example, membrane homogeneity in terms of pore size, membrane surface, the use of super-high-flux hemofilters that have a slightly lower cutoff, and the use of the association HVHF-high permeability – certainly need to be taken into account [69]. Finally, it should be mentioned that the medical literature regarding HCO membranes contains significant heterogeneity due to differences in terms of type of HCO membrane (cutoff points, surface area, and composition), modality used, and type of cytokines measured, making conclusions regarding this strategy difficult to establish.

Conclusions

Considerable work remains in order to find and optimize the best blood purification strategy for treatment of sepsis. A better understanding of how these therapies work by modulating the cytotoxic and cytokinetic effects of inflammatory mediators is essential. Convection, diffusion, and adsorption should probably not be seen as competitive mechanisms for blood purification but rather as complementary ones. Many experimental and clinical studies have reported promising results showing that blood purification therapies are well tolerated, effective in clearing inflammatory mediators or endotoxins (or both) from the plasma, and responsible for an improvement of different physiologic parameters (hemodynamics and oxygenation). However, important questions, including timing, duration, and frequency of these therapies in the clinical setting, remain unanswered. Large multicenter trials evaluating the ability of these therapies to improve clinical outcomes (that is, mortality or organ failure), rather than focusing on surrogate markers such as plasma mediator clearance or transient improvement in physiologic variables, are required to define the precise role of blood purification in the management of sepsis.

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Abbreviations

CPFA, coupled plasma filtration adsorption; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; EUPHAS, Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis; HCO, high cutoff; HVHF, high-volume hemofiltration.

Competing interests

TR has received research funding from Gambro (Stockholm, Sweden) and Fresenius Medical Care (Bad Homburg, Germany) as well as consulting fees from Gambro. JK has received research funding from Gambro, CytoSorbents Corporation (Monmouth Junction, NJ, USA), and Kaneka Corporation (Osaka, Japan) as well as consulting fees from Gambro, Baxter (Deerfield, IL, USA), and CytoSorbents Corporation.

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