Clinical Utility of Extracorporeal Cytokine Hemoadsorption Therapy: A Literature Review

Anthony Bonavia^a Andrew Groff^b Kunal Karamchandani^a Kai Singbartl^c

^aDepartment of Anesthesiology and Perioperative Medicine, Penn State College of Medicine, Hershey, PA, USA;

^bPenn State College of Medicine, Hershey, PA, USA; ^cDepartment of Critical Care Medicine, Mayo Clinic, Phoenix, AZ, USA

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Abstract

Cytokines play a critical role in coordinating and amplifying a host immune response to infection. The normal pattern of localized and systemic release of proinflammatory and anti-inflammatory cytokines varies on the basis of the disease process. A dysregulated cytokine response can lead to a hyper-inflammatory condition called a cytokine storm. This is believed to contribute to the pathophysiology of sepsis and septic shock, a condition carrying high morbidity and mortality in critically ill patients. Extracorporeal cytokine hemoadsorption is an emerging technology utilized in the treatment of dysregulated inflammatory states such as sepsis, although there is a paucity of clinical evidence supporting its outcomes benefits. We assess the peer-reviewed literature relating to cytokine hemoadsorption in the context of sepsis and suggest areas of future research incorporating this novel technology.

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A coordinated cytokine response is essential both for mounting an appropriate host immune response and for its timely abatement following resolution of the inflam-

matory trigger. Several disease states are associated with a dysregulated cytokine response, including autoimmune disorders and sepsis. By extension, cytokine adsorption technology is gaining momentum as a potential solution to the toxic “cytokine storm,” which may cause secondary organ injury in these disease states [1]. However, high-quality data showing the safety of this emerging therapy remains sparse. In this review, we will address the history behind cytokine adsorption therapy, describe the presently available technology, and discuss its clinical merits as reported in the peer-reviewed literature. Focusing on sepsis as a trigger for cytokine and immune dysregulation, we will also address potential concerns relating to the safety of nonspecific cytokine neutralization and consider the long-term potential for this therapy as a mainstay of treatment in hyper-cytokinemic disease states.

Cytokines and the Immune System

Cytokines broadly consist of small, soluble proteins (<40 kDa) involved in autocrine, paracrine, and endocrine signaling. They can cause the activation, proliferation, and/or motility of target cells [2]. Signaling is achieved by time- and space-compartmentalized processes and amplification cascades wherein the controlled release of certain

cytokines, in turn, stimulates the local or remote release of others [3]. Imbalances of pro- and anti-inflammatory cytokines lie at the center of systemic inflammatory responses and multi-organ dysfunction syndrome (MODS) [4, 5].

After innate immune antigen-presenting cells (macrophages and dendritic cells) phagocytose microbes, they present molecular fragments of their targets, via their major histocompatibility complex type II receptors, to T-cells of the adaptive immune system. Cytokines are used both by innate and adaptive immune cells to mount the initial immune response and, eventually, to downregulate it and create immunological memory. Proinflammatory cytokines normally produced during an infection include interleukin (IL)-1 β , IL-6, IL-12, and tumor necrosis factor (TNF)- α . These are released by host cells in response to damage-associated molecular patterns (DAMPs) released from necrotic cells, and pathogen-associated molecular patterns (PAMPs) on the surface of invading microorganisms. Cytokines are essential for neutrophil activation, thrombin formation, and for the enhanced vascular permeability necessary for leukocyte extravasation into infected tissue. Indeed, the host immune system cannot function without them. Serum proinflammatory cytokine levels peak within 2 h of cellular injury and return to almost undetectable levels within 6 h [3]. IL-6 is released by tissue macrophages and is an early and potent inflammatory mediator [6]. IL-1 β (catabolin) potentiates this early inflammatory response and amplifies the synthesis of other proinflammatory cytokines such as IL-6, IL-8, IL-12, and TNF- α [3].

Anti-inflammatory cytokines (e.g., IL-1RA, IL-4, and IL-10) form an equally important part of the host's response to infection. Their function is to reduce the overall production of proinflammatory cytokines and to restore homeostasis once an infection is eradicated [7, 8]. Besides initiating the host response to infection, antigen-presenting cells also participate in feedback inhibition pathways by expressing IL-4 and IL-10, which mitigate further inflammatory responses by macrophages [4]. As with proinflammatory cytokines, a dysregulated and hyperactive anti-inflammatory response can also harm the host. An over-exuberant IL-10 response, for example, is central to immunoparalysis following sepsis [9, 10] and major surgery [11], and it places the host at significant risk for developing secondary infections.

At a molecular level, the processes underlying hyperinflammation and septic shock are quite similar. They are driven by the release of endogenous or exogenous mediators formerly intended to protect the host. The result of an overzealous defense mechanism, however, turns a physiologic response into a pathologic one. Sepsis, for example,

is characterized by life-threatening end-organ failure resulting from a dysregulated immune response to infection [12]. The term "dysregulated" implies that the cytokine profile in sepsis can differ significantly between individuals. In fact, a large body of evidence suggests that some patients with sepsis rapidly produce both proinflammatory and anti-inflammatory cytokines, whereas other patients have either a predominance of anti-inflammatory cytokines or globally depressed cytokine production [13].

The Cytokine Storm and Sepsis

There is no established definition of what a "cytokine storm" is, although the term was first coined in 1993 to describe the dramatic effects of IL-1 in graft-versus-host disease [14]. Its use in this context persisted until 1996 when Aikawa used the term in the context of post-surgical sepsis and MODS [15]. At present, "cytokine storm" encompasses a heterogeneous group of disorders characterized by life-threatening hyperinflammation [16]. Many cytokine storm syndromes are triggered by infection, and sepsis remains the largest catch-all term used to categorize these conditions [16]. Noninfectious conditions that may trigger a cytokine storm include active rheumatic diseases (e.g., macrophage activation syndrome) and certain malignancies (e.g., malignancy-associated syndrome of hyperinflammation) [16, 17]. Clinical manifestations of a cytokine storm may include refractory fevers, cytopenias, coagulopathy, MODS, and death [17]. For the purposes of this review, we will focus on sepsis and septic shock, since the most available research into cytokine adsorption therapy has historically been performed in this setting. Furthermore, with an estimated mortality of 40–60% and a limited understanding of the underlying disease pathophysiology, septic shock remains a central focus of adult critical care medicine, yet one in which limited effective therapeutic interventions exist [4].

There is increasing evidence that elevated circulating levels of proinflammatory cytokines are associated with increased morbidity in septic patients [18–22]. Specifically, elevated serum IL-6 and resistin levels appear to correlate with sepsis severity and end-organ damage [23]. By extension, serum levels of key anti-inflammatory cytokines such as IL-10, as well as PAMPs and DAMPs also appear to predict outcomes, presumably due to poor regulation of the proinflammatory response [19]. While additional prospective investigations into the diagnostic utility of cytokine levels are needed, the blockade or removal of these cytokines may provide a therapeutic op-

portunity to ameliorate sepsis-associated organ dysfunction [24]. This technique has shown some success in removing inflammatory mediators from septic plasma and thus reducing renal tubular cell injury [25]. The results of randomized clinical trials utilizing cytokine targeted therapies have, however, thus far been disappointing.

An early target of immunomodulation therapy was the TLR-4 receptor, a specific pattern recognition receptor believed to control the initial amplification cascade of the inflammatory response [26]. It was targeted by using the MD2-TLR-4 antagonist, Eritoran [27, 28]. The ACCESS (A Controlled Comparison of Eritoran tetrasodium and placebo in patients with Severe Sepsis) trial studied 2,000 patients with severe sepsis [29], randomizing patients to receive a 6-day course of Eritoran tetrasodium or placebo within 12 h of the first evidence of end-organ dysfunction. The results did not show a significant difference in the primary outcome (28-day all-cause mortality) when treatment with Eritoran was compared to placebo. The ACCESS trial also showed that there was no significant improvement in all-cause mortality at 3, 6, and 12 months following treatment [29].

Similarly, anti-IL-1RA, anti-IL-1 β , anti-TNF- α , and anti-lipopolysaccharide have all had disappointing results in both animal and human trials, despite their ability to significantly reduce serum cytokine concentrations [30–37]. Although the clinical efficacy of anti-TNF- α therapy remains disputed, there is some evidence that it may reduce the number of days of mechanical ventilation and days in the intensive care unit in patients with severe sepsis [38]. Two meta-analyses also demonstrated that anti-TNF- α therapy is associated with a significant decrease in sepsis-related mortality [39, 40]. A large, multicenter randomized follow-up trial may be warranted to confirm these benefits and to evaluate the incidence of drug-related side effects. When attempting to regulate a system-wide inflammatory response, the short-term and long-term risks of generalized immunosuppression (such as secondary infections and malignancy) need to be considered and explicitly assessed. This is especially true when one is altering the serum levels of not just one, but a broad range of cytokines, as is the case with cytokine adsorption therapy.

History of Cytokine Adsorption Therapy

The use of blood purification to improve clinical outcomes is not a novel concept. An increased understanding of the cell signaling pathways involved in sepsis has led to research efforts focused on reducing systemic cyto-

kine levels by using extracorporeal blood purification [41]. In fact, extracorporeal filtration techniques such as coupled plasma filtration adsorption have shown promise as a potential adjuvant therapy in sepsis and septic shock [41–43].

The 3 main blood purification techniques available are filtration, dialysis (diffusion), and adsorption [24, 44, 45]. Continuous venovenous hemofiltration (CVVH) with dialysis or continuous hemodiafiltration (CHDF) was first used for the treatment of hyper-cytokemia in 1993 [46], and many of the subsequent efforts focused on this approach to improve outcomes in sepsis [46–51]. However, randomized controlled trials (RCTs) were unable to demonstrate clear outcome benefits with dialysis in patients with sepsis [52, 53], and the inability to remove middle molecular weight toxins led to the need for supplementary hemoadsorption therapy [50, 54, 55].

Ensuing studies investigated the use of increased filtration volumes by using high-volume hemofiltration (HVHF) with high cutoff membranes. Although both of these therapies have demonstrated substantial cytokine removal [56, 57], there were associated concerns about the exaggerated removal of beneficial molecules such as nutrients, proteins, and antimicrobial peptides [49]. Furthermore, trials using HVHF have also had mixed results in septic patients [53, 58, 59]. A recent Cochrane Review found low-quality evidence for HVHF in the treatment of critically ill patients with sepsis, and suggested that more multicenter RCTs are required before these therapies can be recommended for routine use [60].

Contemporary research efforts have focused almost exclusively on the use of biocompatible adsorption hemofilters, which remove molecules such as cytokines from the bloodstream based on their physical properties [55, 61–63]. Porous polymer beads of different sizes and with different side chains, for example, can be used to build adsorbent columns for extracting particles within a particular molecular weight range [43, 64–66]. Physical modification of the size of the beads and chemical modification of the molecular side chains allow cytokines such as bacterial endotoxins and lipopolysaccharides to be targeted [43, 67].

Direct hemoperfusion using a polymyxin B endotoxin-adsorbing column (PMX-DHP) is one such modality, developed in Japan to treat gram-negative septic shock. It is marketed as Toraymyxin[®] (Toray Industries, Tokyo, Japan) and is a polycationic antibiotic column containing multiple polymyxin B-immobilized fibers, which have been shown to neutralize bacterial endotoxins [68–70]. A randomized, controlled study by Cruz et al. [71] in

2009 demonstrated that the addition of this device to conventional medical therapy significantly improved hemodynamic status and organ dysfunction and reduced 28-day mortality in patients with gram-negative sepsis. However, a subsequent randomized, controlled trial (the ABDOMIX study) failed to confirm its clinical efficacy and actually showed an increased mortality in the treatment group, although this finding did not reach statistical significance [72]. Although polymyxin B can be nephrotoxic, Toraymyxin is considered relatively safe even in patients with renal dysfunction, since the antibiotic is immobilized in a column [73]. A major concern related to polymyxin B hemoperfusion, however, is the risk of cartridge clotting, which can cause premature interruption of the treatment and acute blood loss in patients who are already critically ill [71, 72].

There are a multitude of adsorption hemofilters currently being investigated including, but not limited to, polymethyl-methacrylate (PMMA) membranes, AN69 surface-treated (AN69ST) membranes, and modified AN69ST membranes (oXiris®). The PMMA membrane is a hydrophobic, synthetic, polymeric membrane having a microporous structure [46]. Historically, PMMA hemofilters were used as an adjunct to maintenance hemodialysis [49, 74] and utilized PMMA molecules bound to a synthetic, polymeric membrane as a filter. The hydrophobic nature of the polymer permits ample diffusion of small- and medium-size solutes across the membrane while extracting cytokines and larger solutes such as proteins (e.g., albumin, uremic toxins, and immunoglobulin light chains) [7, 49, 75]. PMMA hemofiltration is currently indicated for the treatment of chronic kidney disease dependent on hemodialysis. However, the absorptive properties of the membrane make it an attractive adjunctive option in the treatment of sepsis-related organ dysfunction [49].

Continuous hemodiafiltration using a PMMA membrane (PMMA-CHDF) has been used in critically ill patients with severe acute pancreatitis and has been associated with reduced abdominal pain and a rapid improvement of symptoms [76]. It has also been reported that early PMMA-CHDF in addition to early goal-directed therapy in patients with septic shock resolved the shock and improved the 28-day survival rate [77]. Multicenter trials are needed to establish the feasibility of routine use of PMMA-CHDF in patients with septic shock, although these initial results are certainly encouraging. The greatest disadvantage of PMMA membranes is their propensity to clot because of the nature of their adsorptive properties. It is thus recommended that they are replaced every 24 h for the duration of treatment.

The AN69ST (surface-treated) hemofiltration membrane is a derivative of AN69 (native AN69), which was originally developed in 1969 as the world's first synthetic polymeric membrane prepared by surface treatment of polyethyleneimine (PEI) [49]. It was approved in Japan in 2014 for the treatment of severe sepsis [49, 78], but it may also be used in the treatment of sepsis-related acute kidney injury [79]. AN69 is a co-polymer membrane that integrates a hydrophobic molecule (acrylonitrile) with a hydrophilic molecule (sodium methallylsulfonate) [49]. The membrane is negatively charged due to methallylsulfonate, enabling the high-capacity binding of positive charged cytokine amino groups [78]. The surface of the membrane is then treated with the cationic molecule PEI to enhance removal of negatively charged endotoxins [80]. The membrane is also coated with immobilized heparin in order to reduce the risk of thrombogenic events with treatment and to lengthen the life of the filter.

As the AN69 membrane has a hydrogel structure, adsorption to this membrane is considered to take place not only on the membrane surface but also within the bulk layer, explaining its high adsorptive capacity [49]. De Vriese et al. [81] reported a decrease in blood cytokine levels and improvement in hemodynamic parameters in patients with sepsis-associated acute kidney injury who underwent this hemofiltration method. However, they also found that besides needing to replace the hemofilter frequently, cytokine levels soon increased again following their initial decline [81]. Native AN69 is also known to generate bradykinin when it comes in contact with blood. When a patient takes angiotensin-converting enzyme inhibitors, kininase II (which inactivates bradykinin) is also inhibited, and this causes significant hypotension [49]. This has been a further disadvantage of AN69 membrane.

Compared with the AN69ST membrane, the modified AN69ST membrane oXiris® (Baxter, Meyzieu, France) uses 3 times the amount of PEI to enhance endotoxin adsorption and 10 times the amount of immobilized heparin to reduce thrombogenicity [49]. The oXiris membrane is intended to adsorb both endotoxin and cytokines, and it has been shown to adsorb more of both when compared with the AN69 membrane [82]. However, there are limited clinical trials utilizing this device. Shum et al. [80] utilized a combination of oXiris and CVVH in 6 patients with sepsis-associated acute kidney injury, comparing these patients with 24 severity-matched historical controls undergoing PS-CVVH. They found that, after 48 h, the SOFA score of patients undergoing concurrent oXiris therapy decreased by 38% compared to their admission score. Conversely, the SOFA score increased by 3% in the control group. There

were no significant differences in intensive care unit and in-hospital mortality between the groups [80].

CytoSorb® (CytoSorbents Corporation, Monmouth Junction, NJ, USA) is a recently developed, commercially available hemoadsorption device that utilizes extracorporeal blood purification to reduce serum level of both pro- and anti-inflammatory cytokines. While not specific for sepsis management, it is currently marketed to address this disease among several others. Specifically, CytoSorb is reported to work most effectively when treatment is initiated within 24 h of diagnosed sepsis [83]. It is designed to reduce the systemic cytokine burden in generalized inflammatory states to a “normal” level. As a result, it is inferred that hemodynamic and metabolic stabilization will follow. A recently published *in vitro* study performed a head-to-head comparison between the adsorptive capacities of Toraymyxin, oXiris and CytoSorb [84]. oXiris was the only device that removed both endotoxin and cytokines. oXiris showed similar removal of 27 pro- and anti-inflammatory mediators (including IL-6, TNF- α , IL-1 β , IL-4 and IL-10) as CytoSorb, and similar endotoxin removal to Toraymyxin.

CytoSorb therapy has recently gained momentum in Europe in the treatment of sepsis, burn injuries, trauma, and acute respiratory distress syndrome. CytoSorb is CE Mark approved under the Medical Devices Directive, is ISO 10993 biocompatible, and is manufactured in the United States under ISO 13485 certification [85]. It is the only specifically approved extracorporeal cytokine adsorber in the European Union and is approved for all indications in which increased levels of cytokines occur (Intended Use) [86]. As of 2018, according to the manufacturer, over 40,000 CytoSorb treatments have been reported thus far in more than 700 medical centers throughout the world [87].

The technology at the core of CytoSorb is a single-use, whole blood perfusion cartridge that can be utilized as stand-alone therapy or in conjunction with continuous renal replacement therapy (CRRT, either pre- or post-dialyzer), cardiopulmonary bypass machines, or extracorporeal membrane oxygenation (Fig. 1) [88]. After establishing large-bore intravenous access (as with a hemodialysis catheter, for example), the cartridge is attached in a series with a pump and a closed-loop circuit with the patient. In its simplest form, the circuit extracts venous blood from the patient at one end, drives it into the hemoadsorption cartridge, and re-infuses it into the patient at the other end. Following systemic anticoagulation to aPTT of 60–80 s, the patient’s blood is continuously circulated through the extracorporeal CytoSorb cartridge at blood flow rates of 150–500 mL/min [89]. Cytokines and

inflammatory mediators are irreversibly extracted from the bloodstream, effectively diminishing serum concentrations of these compounds. A single cartridge can be used for up to 24 h at a time, after which a new cartridge can be replaced daily for up to 7 consecutive days [87].

CytoSorb hemoadsorption is unique in that its efficacy is concentration dependent, that is, cytokines found at high concentrations in the blood will be removed more quickly in comparison to blood with lower cytokine levels. Furthermore, with a large surface area (approximately 40,000 m²), cytokines can be rapidly extracted from serum. At the particulate level, each hemoadsorption cartridge is composed of biocompatible, sorbent, polystyrene, and divinylbenzene polymer beads. Each polymer bead is between 300 and 800 μ m in size and has a network of pores and channels, giving it a large effective surface area for binding of hydrophobic molecules between 5–60 kDa in size [90]. This size range (referred to as the “cytokine sweet spot”) targets many of the key inflammatory mediators involved in the sepsis-triggered cytokine storm, such as: IL-1 β , IL-6, TNF- α , IL-10, and potentially PAMPs and DAMPs [91]. Particles outside this size range, including larger immune cells and smaller serum electrolytes recirculate unchanged. While the manufacturer states that bacterial endotoxins are not removed with CytoSorb, a study has shown some efficacy in removing toxins within the 5–60 kDa range [92].

While the reported indications of CytoSorb therapy are many (refractory septic shock, vasoplegic shock, toxic shock syndrome, necrotizing fasciitis, meningococcal sepsis, pancreatitis, burns, trauma, liver failure, and rhabdomyolysis among others) [93, 94], these authors were unable to identify significant reported contraindications outside of the standard contraindications for extracorporeal blood purification such as the requirement for systemic anticoagulation. There is some evidence that platelet and albumin levels can also be affected by hemoadsorption therapy, although these decreases were reported to be clinically insignificant [94].

Literature Evidence for Cytokine Adsorption Therapy

Our group and others have demonstrated that CytoSorb effectively extracts serum resistin, an early-phase 12.5 kDa inflammatory cytokine associated with increased sepsis severity, impaired neutrophil migration, and intracellular bacterial clearance [22, 23, 95, 96]. Furthermore, this therapy reverses neutrophil dysfunction

Fig. 1. Schematic illustrating the use of extracorporeal cytokine hemoabsorption in conjunction with continuous renal replacement therapy via the right internal jugular vein.

and restores their bacterial killing function, suggesting a direct benefit to the innate immune system [22]. Preclinical animal data for cytokine adsorption therapy showed positive results in its ability to reduce circulating cytokine levels and to improve sepsis-related survival. Rats injected with endotoxin who underwent CytoSorb therapy demonstrated up to 50% decreases in the levels of IL-6, IL-10, and TNF- α , within 2 h of treatment initiation, with increased short-term survival and improved hemodynamic stability [97–100]. A more recent rat model of sepsis utilizing cecal ligation and puncture exposed experimental animals to 3 different amounts of hemoabsorption beads (0.75, 1.6, and 3 mg) and one sham treatment. Although the selected sample size was too small to compare survival benefits, rats in the treatment groups had trends indicating improved renal and hepatic function compared to the sham group [100, 101].

Numerous case reports and case series have suggested improved clinical outcomes with hemoabsorption de-

vices such as the CYT-860-DHP membrane [102, 103], AN69ST [49, 78], modified AN69ST [80], PMMA [77], and CytoSorb [83, 104]. The conclusions of many of these reports, however, are hindered by small sample sizes and, at best, they advocate for larger, RCTs to evaluate any potential benefits in septic patients. The CYT-860-DHP membrane, for example, has been shown to effectively reduce cytokine levels and to improve general respiratory and circulatory status in 7 patients with SOFA scores ≥ 5 [103].

More recent clinical research has focused on the use of the CytoSorb, since this is currently commercially available for use in Europe. A case series of 16 patients undergoing cardiopulmonary bypass with CytoSorb therapy and CRRT demonstrated decreased serum levels of circulating cytokines, improved organ function and improved hemodynamic stability with these therapies [105]. Kogelmann et al. [83] also reported a retrospective case series of 26 septic patients having two-system organ failure who

were exposed to CytoSorb therapy and described increased hemodynamic stability, decreased serum lactic acid levels, and decreased vasopressor demands with this therapy. They posited that use of this therapy within 24 h of diagnosis could lead to decreased mortality in both medical and post-surgical patients [83]. The findings of improved serum lactate levels and decreased vasopressor requirements were replicated in a single-center prospective cohort of 20 patients with refractory septic shock, although this study's conclusions were limited by the lack of a control group with which to compare clinical outcomes [104]. None of these case series reported any device-associated adverse effects [83, 104, 105]. Table 1 presents a summary of peer-reviewed articles examining the benefits of CytoSorb therapy.

While CytoSorb has been approved for use by the International Organization of Standardization (ISO, Geneva, Switzerland) since 2010, the impetus provided by pre-clinical trials and case series is just now starting to translate to randomized controlled human trials. The 2 major, current, clinical indications for CytoSorb therapy are septic shock and post-cardiopulmonary bypass systemic inflammatory response syndrome. The first randomized controlled clinical trial was reported in the latter group of patients in 2016. Cytokine levels were measured prior to and following CytoSorb treatment of 37 patients undergoing elective cardiopulmonary bypass. There were no significant differences in cytokine removal, vasopressor dependence or 30-day mortality with hemoabsorption therapy [106]. A more recent randomized, controlled trial investigated clinical outcomes in 97 mechanically ventilated patients with sepsis who underwent hemoabsorption therapy for 6 h per day for 7 consecutive days [107]. Serum IL-6 levels were compared to those patients receiving the standard of care therapy and, following treatment, there were no significant differences in serum IL-6 levels between the 2 groups. The study also reported an increased 60-day mortality, in patients receiving hemoabsorption therapy, prior to adjustment for patient severity of illness. This finding disappeared after adjusting for patient comorbidities. The study's conclusions were that cytokine hemoabsorption with CytoSorb did not decrease mortality, organ dysfunction, or time on the ventilator.

The Future of Cytokine Adsorption Therapy

As described above, some animal and human studies have shown that hemoabsorption devices may effectively remove cytokines from the bloodstream, although this

has not translated to high-quality data demonstrating improved clinical outcomes [41]. This may be due to the broad clinical spectrum encompassed by a diagnosis of sepsis, to timing of therapy or patient-specific differences in the innate immune responses to infection [3]. Several genetic factors affect the course of sepsis [108, 109], and single nucleotide polymorphisms can greatly affect the serum levels of cytokines such as TNF- α in individuals [110, 111]. It is hardly surprising, therefore, that clinical outcomes following hemoabsorption therapy may vary greatly between patients. Indeed, almost 70 years of immunomodulation research in sepsis (starting with the use of corticosteroids in 1951) have thus far had disappointing results [3, 112].

While promising preclinical results may not ultimately translate to significant benefits in humans, given the infancy of hemoabsorption therapy, a more appropriate approach may be careful parameter- or biomarker-directed patient selection for clinical trials. Indeed, as our understanding of the immune dysregulation and cytokine storm in sepsis increases, the different *in vitro* adsorption properties of oXiris, Toraymyxin, and CytoSorb could enable treatment to be more tailored to patients [84]. CytoSorb and other hemoabsorption devices work in a concentration-dependent manner and only patients with high serum cytokine loads may benefit from this therapy [107]. Early initiation of therapy (preferably within 24 h) also appears to be important, improving hemodynamic stability and lowering the predicted rate of mortality [83]. However, due to the clinical heterogeneity of sepsis and hospital presentation of patients at different stages in the evolution of this disease, it may be difficult to treat patients early enough to derive significant benefit [3].

A concern that, we feel, has thus far been incompletely addressed relates to the long-term implications of system-wide cytokine neutralization. Sepsis has increasingly been described as an immunosuppressed state [113–116] causing long-term alterations in cellular immune function for sustained periods of time following clinical recovery [115]. The compromised host immune system is believed to result from leukocyte dysfunction and an inability to fight off opportunistic infections [98, 116–118]. Removal of pro- and anti-inflammatory cytokines in this setting may incrementally disrupt the body's ability to eradicate infections and restore physiologic homeostasis.

One must remain cognizant of the physiologic roles that cytokines play in the course of health and disease. They are absolutely necessary for the proper functioning of the localized and systemic host immune response. Re-

Table 1. Literature summary of clinical reports relating to CytoSorb therapy in peer-reviewed and indexed medical journals

Authors	Disease or surgery	Number of Patients	Study type	Outcome		Control group (yes/no)	Comments
				primary	secondary		
Kogelmann et al. [83]	Sepsis with need for renal replacement therapy	26	Case series	Vasopressor requirement	Hospital mortality and blood lactate levels	No	Decreased catecholamine demand, predicted mortality (APACHE II), and lactate levels. No increased adverse effects
Friesecke et al. [104]	Refractory septic shock	20	Prospective single-center cohort	NE requirement after 6 and 12 h of CytoSorb	SOFA score, resolution of shock, and lactate clearance	No	Decrease in NE requirement and serum lactate. Improved mortality compared to predicted
Schadler et al. [107]	Sepsis or septic shock with ARDS	97	Randomized, controlled multicenter trial	Plasma IL-6 levels	Multiple organ dysfunction score, entilation time, time course of oxygenation	Yes	No significant difference in primary and secondary outcomes
Nemeth et al. [134]	Orthotopic heart transplant	84	Prospective, observational	Hemodynamic stability, vasopressor demand (48 h post-operatively), and post-operative inflammatory response (CRP and PCT)	Volume of postoperative bleeding, rate of reoperation, need for blood products (first 24 h post-operatively), need for postoperative RRT	Yes	Significantly decreased vasopressor demand and less frequent RRT with CytoSorb. No difference in inflammatory response. No increased adverse events
Bernardi et al. [106]	CPB surgery	37	Randomized, single-center controlled trial	Serum IL-1 β , IL-6, IL-18, TNF- α , and IL-10 levels during first 5 days post-operatively	Measurement of other inflammatory markers, 30-day mortality	Yes	No reduction in proinflammatory response or mortality following treatment. Strong inter-individual response to CytoSorb, suggesting some patients may have exaggerated inflammatory responses
Träger et al. [136]	CPB surgery complicated by infective endocarditis	39	Case series	Serum IL-6 and IL-8, vasopressor dose, MAP, lactate levels, and need for post-operative support	Postoperative and 24-h post-operative APACHE II score, and intensive care and hospital length of stay	Yes	Reduction in serum IL-6, IL-8, and lactate levels. Improvement in hemodynamic stability following CytoSorb compared to control.
Träger et al. [105]	CPB surgery complicated by SIRS	16	Case series	Not applicable	Not applicable	No	Overall reduction in cytokine levels and improvement in hemodynamic stability and organ function. No increased adverse effects
MAP, mean arterial pressure; NE, norepinephrine; PCT, procalcitonin; CPB, cardiopulmonary bypass.							

removal of IL-6 and TNF- α may, for example, alter cell signaling and attenuate the innate immune response to PAMPs and DAMPs [119]. Both cytokines are evolutionarily conserved and are part of a bundle of “common responses” to infectious stimuli [3, 119–121]. IL-6 binds to the IL-6 receptor (IL-6R), which exists both in membrane-bound and soluble forms (sIL-6R). IL-6 binding involves both gp130 and sIL-6R, and the IL-6/sIL-6R/gp130 complex mediates downstream signaling and activation of the JAK-STAT pathway [119]. Studies have demonstrated that the deleterious effects of IL-6 almost exclusively involve sIL-6R, whereas the membrane-bound form protects against infections and is involved in tissue regeneration [119, 122]. Treatment with exogenous IL-6 has also been shown to improve viral clearance in patients with human immunodeficiency virus [123]. Similarly, TNF exists both in secreted and membrane-bound forms. Most of the proinflammatory actions of TNF are believed to be mediated by TNF receptor-1. The roles of the TNF receptor-2, while incompletely understood [119], may include the resolution of inflammation [124, 125], tissue regeneration, neuroprotection [126], and suppression of cytotoxic T-cell populations that cause type 1 diabetes mellitus [127]. Removal of serum TNF may compromise signaling through this receptor, thus abrogating these physiologic functions.

Removal of anti-inflammatory cytokines may similarly lead to adverse effects in the setting of sepsis and critical illness. IL-10 and IL-1RA are crucial for the maintenance of epithelial structural integrity and for reducing the inflammatory responses through NF- κ B signaling [8, 128]. Additionally, IL-1RA diminishes the expression of the intracellular adhesion molecule (ICAM)-1, decreasing the risk of excessive cellular adhesion and aggregation [128]. Removal of these anti-inflammatory cytokines may perpetuate a continued proinflammatory state contributing to the increased expression of cellular adhesion molecules and promoting thrombogenicity, microvascular occlusion, and end-organ damage. Furthermore, the carcinogenic risks of prolonged and chronic inflammation have been well established in the medical literature [129].

We believe that the broad proposed indications for nonspecific cytokine adsorption therapy, combined with the paucity of listed contraindications and randomized clinical trials, should make clinicians wary of the risks of indiscriminate use of this technology. As of April 2018, the Food and Drug Administration approved the REFRESH II-AKI trial, the first randomized, controlled multicenter trial in the United States investigating the ef-

fect of CytoSorb during cardiac surgery on postoperative acute kidney injury, hospital length-of-stay, and mortality [130]. The study is currently ongoing, and these authors are hopeful that it will reveal promising and clinically significant outcome benefits. We also believe that data evaluating the effects of CytoSorb on the incidence of secondary opportunistic infections or malignancy are direly needed to establish its long-term safety profile. A recent *in vitro* study, however, indicates that the new sorbent cartridges for hemoperfusion are not associated with leukocyte cytotoxicity [131].

The International CytoSorb Registry [132] has been established to collect and analyze treatment data from all over the world, and is being independently managed by the Center of Clinical Studies at the University of Jena, Germany. Its goal is to track patient mortality (primary endpoint) and secondary outcomes such as hospital- and intensive care unit-length of stay, vasopressor use, renal replacement therapy, and end-organ function. Multi-center data from 198 patients (68% of whom had sepsis with a mean APACHE II score of 33.1) were analyzed in the registry's third interim analysis and reported in 2017 [133]. Serum IL-6 levels following CytoSorb therapy were markedly decreased and the reported mortality with this therapy was 65% (compared to 78% predicted by their APACHE II score). The authors reported that none of the patients were affected by any device-associated side effects. Given the widespread reported use of this technology thus far, we are hopeful that the rate of clinician self-reporting increases in the future.

Conclusion

The normal host immune response to infection involves a well-orchestrated temporal and spatial response, coordinated by proinflammatory and anti-inflammatory cytokines. Extracorporeal blood purification using cytokine hemoadsorption therapy has been shown to normalize serum cytokine levels in patients with sepsis and septic shock, although this has not consistently translated to improved patient outcomes. The jury is still out until larger, RCTs are performed to validate the safety and efficacy of this emerging technology.

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