Blood Purification

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Extracorporeal Blood Purification Therapies for Sepsis

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Keywords

Acute kidney injury · Adsorption · Blood purification therapy · Precision medicine · Renal replacement therapy · Sepsis

Abstract

Extracorporeal blood purification is proposed as an adjuvant therapy for sepsis, aiming at controlling the associated dysregulation of the immune system, which is known to induce organ dysfunctions. Different therapies have been developed to address certain steps of the immune dysregulation. Most of the available blood purification devices focus on a single target, such as the endotoxin that triggers the immune cascade, or the cytokine storm that causes organ damages. However, the highly adsorptive membrane named oXiris® is a unique 4-in-1 device that combines cytokine and endotoxin removal properties, renal replacement function, and antithrombogenic properties. More recently, promising treatments that focus on the pathogen itself or the immune cells have been developed and are currently under investigation. In this review, we aim to summarize, according to their target, the different extracorporeal blood purification techniques that are already available for use. We will also briefly introduce the most recent techniques that are still under development. Because of its unique ability to remove both endotoxins and cytokines, we will particularly discuss the highly adsorptive preheparinized oXiris® membrane. We will present its properties, advantages, pitfalls, as well as therapeutic perspectives based on experimental and clinical data. Video Journal Club "Cappuccino with Claudio Ronco" at https://www.karger.com/Journal/ArticleNews/223997?sponsor=52

Introduction

As proposed by the third international consensus definition for sepsis and septic shock (Sepsis-3), sepsis should now be defined as "*a life-threatening organ dysfunction caused by a dysregulated host response to infection*" [1]. This new definition arises from an improvement in the understanding of sepsis pathophysiology. It also highlights the crucial role of the excessive or unbalanced host immune response during sepsis [2]. Along with antibiot-

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ics, management of organ dysfunctions, and surgical treatment if required, various extracorporeal blood purification therapies may be proposed as adjunctive treatments designed to modulate the inflammatory response. However, this panel of techniques remains a subject of controversy due to the lack of positive multicenter randomized controlled trials (RCTs) confirming their clinical relevance [3].

The aim of this review is to discuss the currently available extracorporeal blood purification techniques. We will specifically focus on the highly adsorptive oXiris® membrane as it offers a unique combination of properties, allowing for extracorporeal kidney support as well as the removal of both endotoxins and cytokines. We will also introduce new therapies targeting the removal of cells (pathogens or immune cells) that are currently under development. Importantly, the list of blood purification devices reported in this review is not exhaustive but is meant to illustrate the technological progress and the different therapeutic targets.

Pathophysiology of Immune Response in Sepsis: From Pathophysiology to Treatment

The first step of the infectious process is the recognition of the pathogen by the immune system. All pathogens exhibit on their surface specific components, known as pathogen-associated molecular patterns (PAMPs), such as the endotoxins expressed by Gram-negative bacteria. During infection, PAMPs are recognized by the pattern recognition receptor expressed at the surface of immune cells [4]. This signal activates the leukocytes and induces the synthesis of pro- and anti-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 (IL-1), IL-6, IL-8, and IL-10. The massive release of cytokines in the blood has been described as a "cytokine storm" and is believed to be responsible for major organ dysfunctions [5, 6].

Injured host cells express on their surface damage-associated molecular patterns (DAMPs), such as the high-mobility-group-box-1 protein (HMGB1). DAMPs may be released in the circulation and are recognized by the pattern recognition receptor, thus enhancing leukocyte activation and cytokine synthesis, fuelling the vicious circle of uncontrolled immunoinflammatory process (Fig. 1) [7]. After the initial cytokine storm, an immunoparalysis state occurs, contributing to most of the sepsis-associated deaths because of health-care-associated infections and viral reactivations [8].

Addressing the unbalanced immune answer to infection has been a therapeutic challenge for many years. However, a better understanding of the mechanisms underlying sepsis has permitted to develop new immune therapies to modulate the inflammatory process. Promising results have been obtained with new molecules such as recombinant human IL-7 [9]. Another approach consists of removing a nonspecific broad spectrum of inflammatory mediators. This is now possible, thanks to the industrial advances and the development of extracorporeal blood purification devices [10]. Most of these extracorporeal techniques interfere at one particular step of the complex immune process, but some of them may have 2 or more targets. Various hypotheses have been developed to explain their effects. First, they may decrease cytokine concentrations under a "toxic threshold" in order to limit the local deleterious effects of cytokines [5]. Other authors have hypothesized that because of a restored concentration gradient, the decrease in cytokine blood concentrations could promote leukocyte chemotaxis toward infected tissue where cytokine concentrations are higher [11]. Another target of the blood purification techniques is the inhibition of the immunoinflammatory cascade trigger. The objective is therefore to remove pathogens or PAMPs such as endotoxins before they activate leukocytes [12]. Finally, the modulation of the immune process may directly involve the leukocytes, either through their direct removal or through an immune cell reprograming (modulation of surface markers expression, improvement of antigen-presenting capability, or adjustment of apoptosis) [13, 14].

Removing Endotoxins

One of the most widely used endotoxin removal therapies is adsorption with polymyxin B-immobilised fiber column (Toraymyxin®; Toray, Tokyo, Japan). This blood purification device is routinely used in Japan for patients with a Gram-negative bacteria infection, but the results of recent clinical trials remain inconclusive regarding the impact of Toraymyxin® on mortality [15]. Numerous RCTs comparing polymyxin B adsorption to a standard treatment found conflicting results, suggesting that the positive effect of Toraymyxin® could be greater in particular subgroups of patients such as severe patients, patients with endotoxin activity levels (as evaluated by the endotoxin activity assay) between 0.6 and 0.9, or those presenting a particular genetic profile [16, 17].

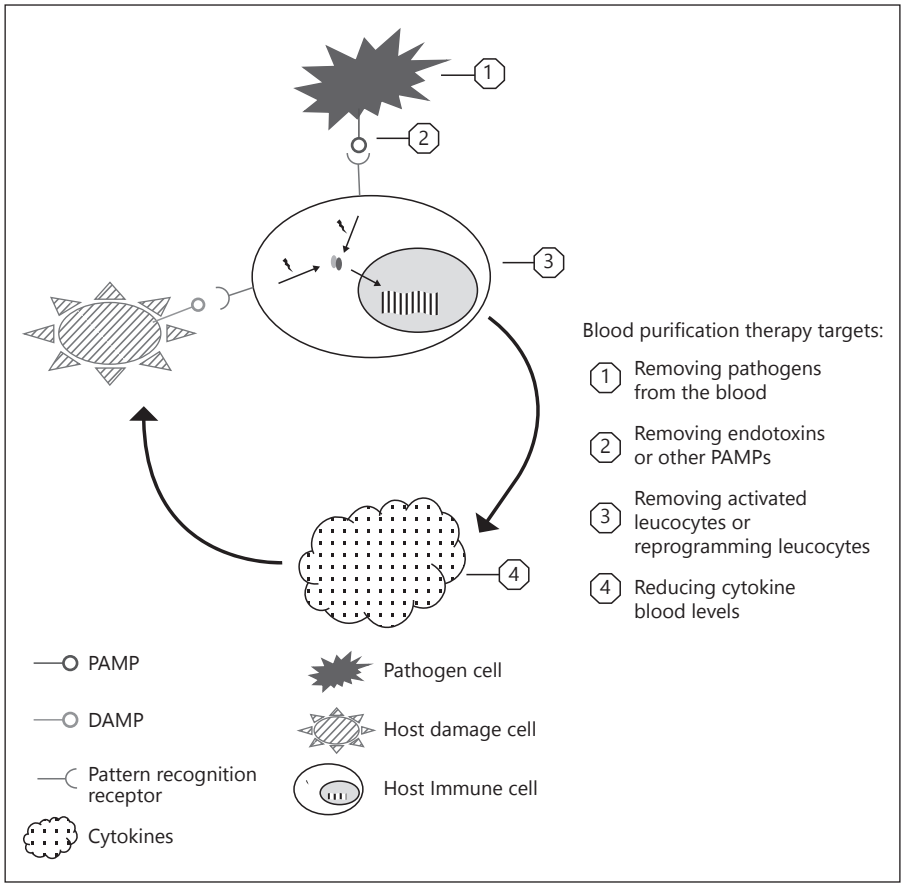

Fig. 1. Immunoinflammatory cascade and extracorporeal blood purification targets. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern.

The Alteco® LPS adsorber (Alteco Medical AB; Lund, Sweden) contains a synthetic peptide developed for endotoxin adsorption. The peptide covers the surface of a porous polyethylene matrix designed to provide an optimal binding surface. A few case series in critically ill adults have reported a decrease in endotoxin levels and a hemodynamic improvement [18–20]. However, the ASSET (abdominal septic shock – endotoxin adsorption treatment) multicenter RCT evaluating the feasibility of Alteco® LPS adsorber was terminated early because of patient recruitment issues [21].

Removing Cytokines

High-volume hemofiltration (HVHF) is a continuous renal replacement therapy (CRRT) with a high ultrafiltration rate (>50 $mL \cdot kg^{-1} \cdot h^{-1}$) offering an enhanced removal of hydrophilic middle molecular weight molecules [22]. After encouraging results in animals, human studies showed conflicting results. Whereas some studies found an improvement of hemodynamic parameters and a lower than expected mortality [23–26], the IVOIRE (high volume in intensive care) RCT failed to find a significant difference in mortality between the high-volume group (70 $mL \cdot kg^{-1} \cdot h^{-1}$) and the standard volume group (35 $mL \cdot kg^{-1} \cdot h^{-1}$), but also it could not find an improvement in secondary outcomes such as hemodynamic parameters, severity scores and length of stay [27]. This absence of beneficial effects was confirmed by 2 recent meta-analyses [28, 29].

To address the significant drawbacks of HVHF such as the loss of small active molecules (nutrients, vitamins, trace elements), cascade hemofiltration was developed. Two hemofilters with different cutoffs are combined in a single extracorporeal circuit, allowing the exclusive removal of middle weight molecules [30]. However, a study conducted in humans failed to find any beneficial effect of cascade hemofiltration as compared to standard care [31].

High cutoff membranes with continuous venovenous hemofiltration (CVVH) have been shown to improve cardiovascular parameters in septic patients but at the cost of massive albumin leakage [32, 33]. These positive

results on hemodynamic parameters were not confirmed in a recent RCT that did not find any reduction in the norepinephrine requirements when critically ill patients with acute kidney injury (AKI) were treated with CVVH and high cutoff membrane versus CVVH and standard membrane [34]. However, these membranes are currently used with diffusive methods or after optimization of their architecture to limit albumin losses while preserving their capacity to remove middle molecular weight molecules [35, 36]. Observational studies including patients with septic shock treated with high cutoff membranes and diffusive CRRT found an effective removal of cytokines and a reduction of intensive care unit length of stay and mortality [37–39].

Coupled plasma filtration and adsorption (CPFA) is a blood purification technique in which a first high cutoff filter is included at the beginning of the circuit and separates the plasma from the blood. The plasma slowly flows through an adsorbing material before being returned to the circuit where all the blood will undergo conventional hemofiltration. Interesting results were obtained in the combining plasma filtration and adsorption clinical trial 1 (COMPACT 1) RCT, mainly in the group who received the highest dose of treatment [40]. Unfortunately, it seems that the combining plasma filtration and adsorption clinical trial 2 (COMPACT 2), evaluating the effect of high doses, was recently terminated earlier because of adverse events associated with CPFA (NCT01639664). A letter was sent to all CPFA users around the world mentioning that CPFA is no longer indicated for treatment of septic shock.

The CytoSorb® technology (CytoSorbents, Monmouth Junction, NJ, USA) is an hemoperfusion cartridge filled with polymer beads that can adsorb pro- and anti-inflammatory mediators, but not endotoxins [41]. In vitro experiments have shown removal rates of cytokines >90–95% [42]. It is able to remove not only broad-spectrum cytokines but also myoglobin, bilirubin, bile acids, PAMPs and DAMPs [43]. However to date, clinical studies remain scarce and often limited to case series that report encouraging results on hemodynamic parameters and blood lactate levels [44, 45]. A recent RCT compared standard treatment to hemoperfusion with CytoSorb® (6 h per day for 7 days) and failed to find any decrease of IL-6 plasma levels over time, despite significant removal during sessions [46]. Some concerns were raised regarding the dose of hemoperfusion and the initial immune profile of the enrolled patients (initial low IL-6 plasma levels).

Cytokine-adsorbing hemofilters are primarily designed for RRT, but the material used to build the membrane may also offer adsorbing properties that can be used for blood purification. The polymethylmethacrylate (PMMA) membrane is a synthetic polymeric membrane with a symmetric microporous structure. This membrane is able to adsorb small and middle molecular weight molecules such as cytokines and beta-2-microglobulin but also immunoglobulin light chains [47]. Regarding its very high adsorption properties, the PMMA membrane was proposed for blood purification in sepsis. Continuous venovenous hemodiafiltration with PMMA hemofilter has been reported to improve 28-day survival rate in patients with septic shock [48]. However, the PMMA membrane presents a high rate of clogging due to a nonselective protein adsorption into the membrane pores, as assessed by a time-dependent increase of transmembrane pressure [49]. High thrombogenicity has also been attributed to structural changes of the adsorbed proteins, which induces platelets activation and adhesion on the membrane surface. To address these issues, a new PMMA-based membrane that limits structural changes of adsorbed proteins was recently engineered, allowing for improved permeability and preserved adsorptive properties [50]. This should encourage the conduct of large RCTs to confirm the feasibility and the efficacy of this membrane.

Removing Cytokines and Endotoxins: The oXiris® Membrane

The improvement of industrial processes led to the development of the oXiris® membrane, a heparin-grafted membrane specifically designed for cytokine and endotoxin adsorption, alongside RRT.

From AN69 to oXiris®

AN69 Membrane

The AN69 membrane was developed in France and was first marketed in 1969. It is composed of a copolymer combining acrylonitrile and sodium methallylsulfonate molecules. Due to the sulfonate groups, the membrane is highly negatively charged and able to adsorb the cytokines via their cationic residues. This membrane exhibits a symmetric microporous architecture with a hydrogel structure. The latter allows cytokine adsorption within the entire bulk of the membrane, enhancing the overall adsorption capacity. In a canine model of endotoxic shock, CVVH with a polyacrylonitrile membrane improved cardiac performance compared with a polysulfone (PS) membrane that do not have adsorptive proper-

ties [51]. This positive effect was attributed to a more effective adsorption of inflammatory mediators. A previous study reported by Kellum et al. [52] supported this hypothesis as they reported the suppression of the expected increase of IL-6 blood level after induction of peritonitis in rodents treated with an AN69 membrane. Importantly, contact between blood and the surface of the membrane can induce bradykinin generation, which may be responsible for severe hypotension, particularly in patients treated with angiotensin-converting enzyme inhibitors [53, 54].

AN69-Surface Treated

To address this biocompatibility pitfall, a particular surface treatment was added to the native AN69 membrane. The surface treatment consists of a coating with polyethyleneimine (PEI), a positively charged molecule that allows for a better biocompatibility by reducing the zeta potential of the membrane and thus the bradykinin production. The PEI coating also offers antithrombogenic opportunities as the hemofilter may be primed with a heparinized solution (the free positive charges of the cationic PEI polymer are able to adsorb the negatively charged heparin molecules); the adsorbed heparin is fixed on the membrane surface but remains active. Prospective studies reported successful reduction of systemic heparin dose for chronic intermittent hemodialysis in patients at high risk of bleeding when using a heparin-primed AN69-surface-treated (AN69ST) membrane [55, 56].

The second advantage of the AN69ST is that its capacity to remove cytokines is preserved despite the surface treatment. For instance, Yumoto et al. [49] reported the results of an in vitro comparison between 4 different hemofilters for the removal of HMGB1, a key mediator of sepsis-induced inflammation. In this study, the AN69ST membrane exhibited better HMGB1 removal as compared to PMMA membrane and much better removal than polyarylethersulfone and PS membranes [49]. The adsorptive capacities of the AN69ST were also clinically confirmed in acute patients treated with CRRT and an AN69ST membrane [57, 58].

oXiris® Membrane

The oXiris® hemofilter (Baxter, Meyzieu, France) was subsequently developed to enhance the adsorptive properties of the AN69ST membrane. Compared with the AN69ST, the oXiris® membrane is pregrafted with an average of 4,500 UI/m^2 heparin during manufacturing while the AN69ST needs a priming with a heparinized solution to gain its antithrombotic properties. The second major improvement stands with the PEI grafting. With a much higher amount of free amino groups that are positively charged, this particular linear PEI grafting confers the possibility to adsorb large negatively charged molecules, such as endotoxins. The oXiris® membrane is therefore made of 3 different layers, and this unique design allows for the combination of 4 properties in 1 device: renal support, cytokine removal, endotoxin removal, and local anticoagulant treatment (Fig. 2).

Cytokine and Endotoxin Removal

Similarly to the native AN69 membrane, cytokine adsorption remains possible in the bulk of the membrane between the cationic amino acid group of the cytokine and the negatively charged sulfonate group of the membrane copolymer. Moreover, the PEI treatment is able to adsorb the endotoxins that are known to trigger the immune cascade. Two experimental studies confirmed these properties.

In a porcine model of septic shock, HVHF with the oXiris® membrane was compared to HVHF with an AN69 M100® (Gambro, Meyzieu, France) membrane. Six hours after the initiation of HVHF, nonsignificantly lower cytokine levels were observed in the oXiris® group, associated with an improvement of hemodynamic parameters, a reduction of infused fluid volume, and a reduction of blood lactate levels. The endotoxin levels were significantly lower in the oXiris® group 1 h after HVHF initiation [59].

More recently, Malard et al. [42] conducted an in vitro experiment, comparing endotoxin and cytokine adsorption with 3 different devices: oXiris®, CytoSorb®, and Toraymyxin®; oXiris® was found to combine high endotoxin adsorption capacity, similar to Toraymyxin®, with a removal rate of inflammatory mediators comparable to CytoSorb®.

Antithrombogenic Treatment

The pregrafting with a large amount of heparin confers a major advantage for patients at high risk of bleeding or those with a risk of citrate accumulation. The use of heparin pregrafted membranes increases the rate of successful heparin-free intermittent hemodialysis sessions in high bleeding risk patients [60] and allows for a reduction of systemic heparin dosing, without compromising the dialysis session [61]. However, none of the published studies assessing the oXiris® membrane has specifically evaluated its antithrombogenic properties in the setting of acute septic patients and CRRT. Use of circuit anticoagulation is therefore mandatory.

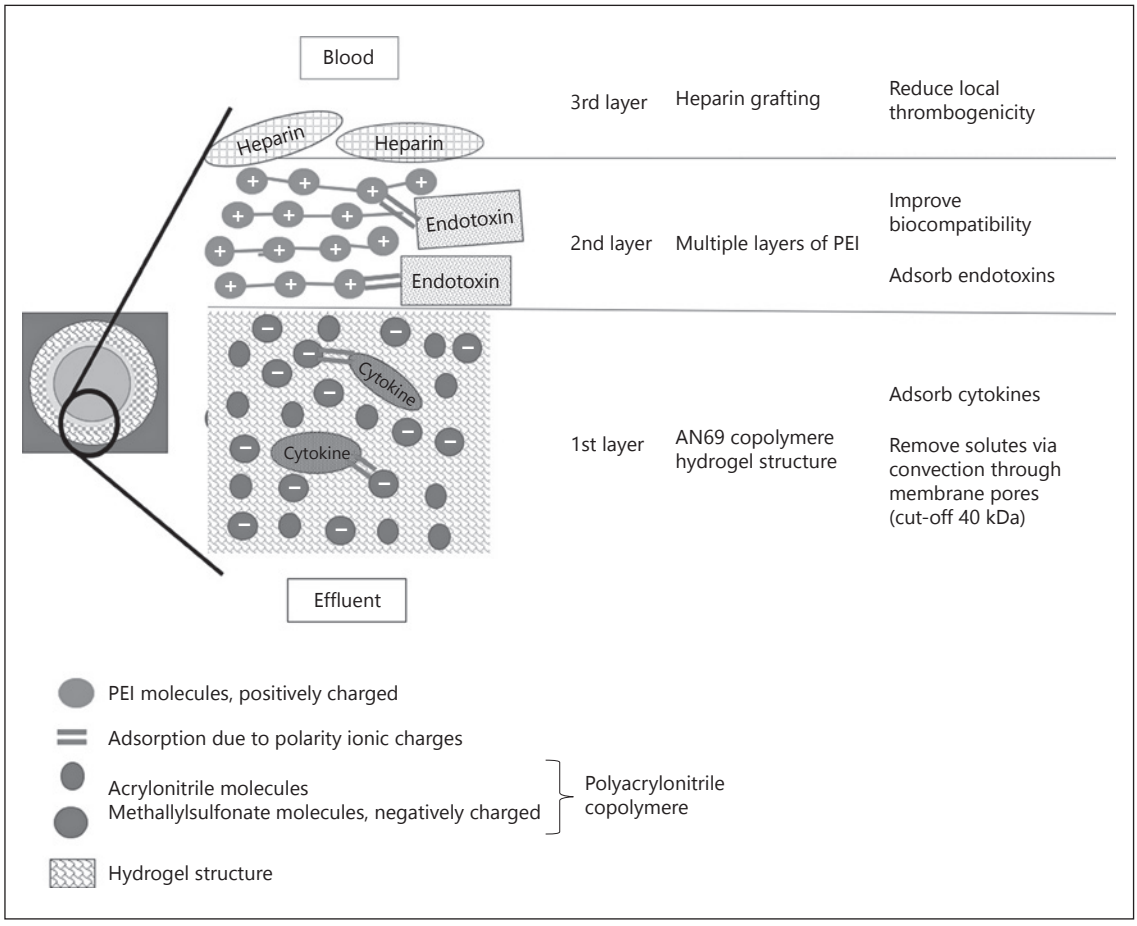

Fig. 2. The 3 layers of the oXiris® membrane. PEI, polyethyleneimine.

In vivo Evaluations

Although the oXiris® membrane can already be used in septic patients with AKI in several European and Asian countries, clinical studies involving critically ill patients remain scarce and are mostly reported in oral communications or congress abstracts (Table 1). Shum et al. [62] reported the outcomes of 6 patients with sepsis-induced AKI due to Gram-negative bacteria treated with oXiris® and continuous venovenous hemofiltration (CVVH). These patients were matched to 24 historical controls treated with CVVH and a PS high-flux hemofilter. The SOFA score was significantly reduced by 37% at 48 h after initiation in the oXiris® group versus 3% in the control group [62].

Taken together with the previously reported experimental findings, these clinical studies suggest a positive role of the oXiris® hemofilter during sepsis management, possibly due to the removal of inflammatory mediators. However, RCTs are needed to further confirm these results. Several studies have therefore recently been launched and are currently in progress. The results from a prospective RCT conducted in Sweden should be available soon. This crossover trial included patients with Gram-negative bacteria infections treated either with oXiris® or a standard ST-150 hemofilter. Endpoints are change in endotoxin levels, change in cytokine levels, and change in hemodynamic parameters (NCT 02600312). The enrolment phase of a second trial, the multicenter endotoxins and cytokines removal during continuous hemofiltration with oXiris® (ECRO) trial, has just started. This study randomizes patients with a peritonitis-induced sepsis and AKI KDIGO stage 2 to receive CVVH either with an oXiris® hemofilter or a HF-1400 standard filter (NCT03426943). A third trial, the ENDoX study (NCT 01948778) will compare the oXiris® membrane versus a polymyxin B-immobilized fiber column (Toramyxin®) on endotoxin activity 72 h after treatment initiation in patients with septic shock and endotoxin activity level ≥0.6.

Table 1. Studies evaluating the oXiris® haemofilter in adult patients admitted to intensive care units (congress abstracts)

Authors, years	Population	Number of patients	Study design	Objectives and endpoints	Intervention	Comparator	Results
Adamik et al. [20], 2013	Septic shock AKI requiring RRT Endotoxaemia Suspected GNB infection	7	POS	HDN improvement Changes in EA	CRRT-oXiris®	Before/after	↘EA levels* ↘NE requirements* ↘SOFA score* ↘PCT ↗MAP*
Broman et al. [86], 2018	Septic shock AKI requiring RRT EA >0.03 EU/mL GNB	16	RCT cross-over double-blind	Changes in EA Changes in cytokine levels (TNFα, interleukins, interferon-y and GM-CSF)	CRRT-oXiris® 24 h	CRRT-standard 24 h	↘EA levels in the first 8 h Similar removal of cytokines
Candidi et al. [87], 2012	Postoperative CPB sepsis Septic shock AKI requiring RRT EA >0.6 EU/mL	25	POS	Safety Cardiorespiratory response Changes in IL-6 and PCT	CVVHDF-oXiris® Effluent dose: 50 mL/kg/h	Before/after	↘NE requirements* ↘SOFA score* ↘PCT and IL-6* ↗MAP* ↗Urine output*
Caravetta et al. [88], 2013	Severe sepsis Septic shock AKI	34	POS	HDN improvement Changes in IL-6 and PCT	CVVHDF-oXiris® Effluent dose: 40 mL/kg/h	Before/after	↘SOFA score* ↗MAP* ↘NE requirements* ↘PCT and IL-6 * ↗Urine output*
Govil et al. [89] 2017	Sepsis AKI	10	ROS	Changes in cytokine levels	CRRT-oXiris®	Before/after	↘ IL-6, IL-10, NE in 6/10 patients ↗UO
Govil et al. [89] 2017	Sepsis AKI	15	ROS	Impact of the initiation timing	Early group (n = 10): start CRRT-oXiris® within 3 h after adequate fluid resuscitation	Late group (n = 5): start CRRT- oXiris® as last resort option	In early group: Higher ↘ of NE requirements and SOFA Higher ↗ of MAP and UO Survival: 7/10 vs. 1/5
Kelway et al. [90], 2017	CVVH	93	ROS	Duration, efficiency (URR), dysfunctions and cost between two filters with antithrombogenic properties	CRRT-oXiris®	CRRT-AN69ST	No difference in terms of duration, URR and dysfunctions. CVVH- oXiris® more expensive
Lumlertgul et al. [91] 2018	Septic shock AKI requiring RRT dysfunction of >2 organs	35	ROS	HDN improvement	CRRT-oXiris®	Before/after	↘NE requirements ↘Blood lactate* ↘Base excess* ↗MAP
Martin et al. [92], 2009	AKI requiring RRT ± systemic anticoagulation ± bleeding risk (PT <30%, platelets <50 G/L, fibrinogen <1g/L)	25	POS multicentre	Filter lifespan without anticoagulation	CVVHF-oXiris® Effluent dose: 35 mL/kg/h	2 subgroups: with/without bleeding risk with/without systemic anticoagulation	oXiris median lifetime: 19.8 h Prolonged filter lifetime in patients with systemic anticoagulation or high bleeding risk (NS for both)
Mikolasevic et al. [93], 2015	AKI requiring CRRT GNB infection	6	POS	Safety, efficacy	CVVHDF-oXiris® within 24–48 h of ICU admission Effluent dose: >25 mL/kg/h	Before/after	↘CRP ↘Leucocytes ↗MAP ↘NE requirements 3 patients survived
Plata-Menchaca et al. [94], 2016	CPB	20	Prospective controlled	Safety and feasibility	CPB + CRRT-oXiris®	CPB alone	↘IL-1 and IL-6 ↗IL-4 and IL-10 No adverse effects
Prato et al. [95], 2017	Septic shock AKI	17	ROS	HDN improvement Changes in inflammatory markers	CVVHDF-oXiris®	Before/after	↘in NE ↘PCT and CRP 7 patients survived

Table 1. (continued)

Authors, years	Population	Number of patients	Study design	Objectives and endpoints	Intervention	Comparator	Results
Tang et al. [96], 2018	Septic shock AKI GNB or GPB	12	ROS	Comparison of survivors versus non-survivors	CRRT-oXiris® Survivors (n = 4)	CRRT-oXiris® non-survivors (n = 8)	Survivors had a shorter initiation time (7.2 vs. 12.5 h) ↘ of vasopressors and lactate was earlier in GPB than GNB: 24 vs. 72 h
Tang et al. [97], 2016	Intra-abdominal sepsis Septic shock AKI requiring RRT	8	ROS	HDN improvement	CVVHDF-oXiris® (n = 3)	CVVHDF-standard (n = 5)	Mortality with oXiris® 33 vs. 60% ↘NE requirements* No difference in duration of MV and CRRT, ICU LOS
Tengattini et al. [98], 2018	Septic shock	10	ROS	HDN improvement Tissue perfusion	CVVHDF-oXiris® Within 24 h from ICU admission	Before/after	↘NE * ↘ blood lactate ↘CRP 6 patients survived
Turani et al. [99], 2013	Sepsis Septic shock EA >0.6 EU/mL	40	POS	Safety HDN improvement Changes in EA Changes in cytokine levels	CVVHDF-oXiris® Effluent dose: >50 mL/kg/h	Before/after	↗ UO ↘NE requirements* ↘IL-6* ↘PCT * ↘EA levels
Turani et al. [100], 2015	Severe sepsis	24	POS	(1) Evaluate whether thromboelastography detects hypercoagulation (2) Evaluate changes in coagulation with oXiris®	CPFA-heparin	CPFA-Citrate CRRT-oXiris®	oXiris® do not reverse sepsis-associated hypercoagulability but restores fibrinolysis
Turani et al. [101], 2016	Sepsis Septic shock AKI EA >0.6	53	POS	Changes in EA Changes in IL-6 and PCT	CRRT-oXiris®	3 groups: 1. EA >0.6 2. EA 0.4–0.59 3. EA <0.4	↘ EA levels, Il-6 and PCT in group 1 EA levels at 48 h were lower in survivors (n = 33) than non-survivors (n = 20)
Turani et al. [102], 2018	Septic shock AKI	73	Cohort propensity matched multi-center	(1) Changes in cytokine levels and PCT (2) Comparison to RRT (3) Cardio-renal improvement	RRT-oXiris® (n = 50)	RRT-standard (n = 23)	32 oXiris® patients matched to 22 standard patients In the oXiris® group: ↘IL-6, PCT, NE requirements* ↗MAP, UO, PaO2/Fi02, diuresis In the standard group: no improvement
Wong et al. [103], 2018	AKI or end-stage renal disease Bleeding risk and anticoagulation-free-CRRT	20	RCT sequential crossover	Filter life TMP, efficiency, coagulation parameters	CRRT-oXiris®	CRRT-M150 filter	Median oXiris® life 13 vs. 18 h (ns) TMP at 12 h 111 vs. 75 mm Hg No difference in small solutes sieving coefficient. Similar coagulation parameters

* $p < 0.05$.

RRT, renal replacement therapy; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous haemofiltration; CVVHDF, continuous venovenous haemodiafiltration; TMP, transmembrane pressure; AKI, acute kidney injury; GNB, Gram-negative bacilli; GPB, Gram-positive bacilli; CPB, cardiopulmonary bypass surgery; HDN, haemodynamic; MAP, mean arterial pressure; NE, norepinephrine; PCT, procalcitonin; EA, endotoxin activity; IL-6, interleukine-6; URR, urea reduction ratio; UO, urine output; POS, prospective observational study; ROS, retrospective observational study; ns, non-significant.

Advantages and Limits

Simplicity

Because the oXiris® membrane combines the blood purification and the kidney support functions in a single device, it is simple to use and does not require additional nurse education. Furthermore, the use of this membrane in clinical practice does not increase the nursing workload, as compared to a standard CRRT session.

Heparin Allergy

Due to the major heparin grafting, the main contraindication of the oXiris® hemofilter concerns patients with a history of heparin allergy or heparin-induced thrombocytopenia.

Unwanted Removal of Micronutrients and Active Substances

Major variability and inadequate antibiotic levels during CRRT have been previously described [63]. It is of importance to consider that the oXiris® membrane may adsorb not only cytokines and endotoxins but also therapeutic and active substances such as vancomycin and amikacin [64, 65]. To the best of our knowledge, no clinical study has focused on the loss of antibiotics and micronutrients with CRRT using a highly adsorptive hemofilter. A careful drug-monitoring strategy should be recommended to ensure appropriate antibiotic concentrations in this particular context [66].

Unanswered Questions

Filter Lifespan

The question concerning the optimal length of use remains unsolved. The adsorptive capacities probably decrease with time, due to a saturation phenomenon and hence diminish the removal of cytokines and endotoxins over time. To sustain the cytokine and endotoxin removal, De Vriese et al. [67] recommended a frequent change of the adsorption device. Nevertheless, this must be counterbalanced with the increase of nurse workload and the treatment interruption that are necessary to change the hemofilter. Also, Yumoto et al. [49] were not able to identify a saturation effect of HMGB-1 on the AN69ST, suggesting an extremely high adsorption capacity of the membrane, due to its particular microstructure which allows adsorption in the entire bulk. Instructions for use recommend changing the filter every 24 h, but it can be used for up to 72 h.

Initiation Timing

If timing of RRT initiation for AKI is an unanswered and largely debated question, it is also of utmost importance regarding blood purification therapies for sepsis. The oXiris® membrane, with its particular function on both endotoxins and cytokines, is probably more beneficial if introduced early in the sepsis time course, thus limiting the host immune response. In a clinical study including 15 critically septic patients who underwent CRRT with the oXiris® membrane, early application (within 3 h of adequate fluid resuscitation) of the treatment seemed to improve outcomes (reduction of vasopressor use, SOFA score, improved survival) compared to initiation in a last-resort option after organ damage had begun [68]. This issue has to be addressed by large RCTs.

Patients

It remains unanswered which patients will benefit the most from treatment with oXiris®. Most studies or reported clinical cases have included patients with sepsis due to Gram-negative bacteria because endotoxins are a key component of such microorganisms, unlike Gram-positive bacteria. However, this treatment could also be beneficial in case of septic shock due to Gram-positive bacteria, as gut hypoperfusion often leads to a translocation of Gram-negative bacteria from the digestive lumen to the blood. The severity of sepsis and the endotoxin level could also help the clinician to select the patients who will benefit the most from treatment with oXiris®. Similarly, it has been recently suggested that endotoxin adsorption with polymyxin B could be more beneficial in the group of patients with an endotoxin activity assay ≥0.6–0.89 [16]. As the oXiris® membrane also offers kidney support for AKI, it is currently mainly used in patients with AKI and indication for RRT. Whether it could be beneficial in patients without AKI remains unknown, but clinicians should be aware that some studies suggest a significant negative impact of a too early CRRT initiation in septic patients [69].

Some authors have suggested that its use during cardiopulmonary bypass surgery could reduce the inflammatory mediator blood levels and hence decrease the organ dysfunction and particularly reduce the incidence of post cardiac surgery AKI. These authors conducted a RCT addressing this hypothesis, but the results remain unpublished (NCT02398019).

Acting at the Cellular Level

During the past decade, scientists have developed new therapeutic approaches of the sepsis-associated immune dysregulation targeting the pathogens or the host im-

mune cells. The early and broad-spectrum removal of pathogens from the blood could avoid the trigger of the immune cascade, and, in the future, it could also offer a therapeutic opportunity in case of extensive drug-resistant pathogens. Different devices have been developed with this objective.

The Seraph® 100 Microbind® Affinity Blood Filter (ExThera Medical, Martinez, CA, USA) is an affinity apheresis treatment using heparin columns. It consists of columns packed with polyethylene beads on which heparin has been covalently immobilized beforehand. Many pathogens use glycosaminoglycans, such as heparan sulfate, on the surface of human cells as receptors. Because heparin has a similar structure to heparan sulfate, it is also able to bind these microorganisms. Preclinical studies have confirmed that the Seraph® is able to bind various pathogens such as viruses, both Gram-negative and Gram-positive bacteria, drug-resistant bacteria, but also cytokines [70, 71]. Recently, a first-in-human safety study was completed in Germany in patients undergoing RRT; the results are yet to be published (NCT02914132).

The FcMBL (Opsonix, Wakefield, MA, USA) is a genetically engineered recombinant protein derived from human opsonin mannose-binding lectin (MBL) and further linked to the Fc domain of a human immunoglobulin. The opsonin MBL is naturally able to bind the pathogen-carbohydrates patterns (PAMPs) found on the surface of all pathogens (bacteria, viruses, fungi, parasites, toxins) [72]. An extracorporeal hemoadsorption device made of a hemofilter containing hollow PS fibers coated with the FcMBL could consequently remove pathogens from the blood flowing through the extracorporeal circuit. The first animal study evaluating this new device has shown promising results, in synergy with antibiotics. Didar et al. [73] observed that treatment with bactericidal antibiotics in septic rats resulted in a major increase of PAMPs blood levels, but these PAMPs were actively removed from blood with the FcMBL-hemoadsorption device; clinically, they also observed more stable vital signs in the septic rats treated with antibiotics and FcMBL-hemoadsoprtion as compared to antibiotics alone.

The Hemopurifier® (Aethlon Medical, San Diego, CA, USA) is a lectin affinity plasmapheresis device able to remove viruses from blood. It combines a first step of plasma separation using a plasmafilter and a second step of virus capture via immobilized affinity agents fixed in the extra capillary spaces of the plasmafilter. The affinity agent used in the Hemopurifier® is a lectin protein from the common snowdrop (*Galanthus Nivalis Agglutinin*) that presents a high affinity for the ubiquitous glycoproteins on the surface of enveloped viruses. This therapy has already been successfully used to treat a patient with severe Ebola virus disease [74].

Finally, because activated leukocytes are key players of sepsis pathogenesis, another approach consists of removing the activated immunological cells from the blood [13, 75, 76]. Pino et al. [75] have developed a selective cytopheretic device (SCD) composed of a synthetic biomimetic membrane that binds activated leukocytes. This device must be included in an extracorporeal circuit with regional citrate anticoagulation. After flowing through the CRRT hemofilter, the blood is diverted through to the extracapillary space of the SCD where activated leukocytes (mainly neutrophils) are adsorbed [77]. In a preclinical study on septic pigs, the SCD with citrate significantly improved the cardiovascular parameters and decreased the sequestration of activated leukocytes in the lungs as compared to control groups (SCD with heparin or no SCD); it also improved renal function and survival time [78]. A prospective, single-center study was conducted to evaluate the safety and efficacy of SCD on patients with AKI requiring RRT. The mortality in the SCD treatment group was 22%, whereas it was 78% for the case-matched controls ($p = 0.027$) [79]. A multicenter RCT that included 134 ICU patients with AKI to receive CRRT alone or CRRT plus SCD confirmed the safety of the device but failed to find a change in mortality. However, a nonsignificant decrease in mortality was observed in the subgroup of SCD-treated patients with an ionized calcium in the circuit <0.4 mmol/L, suggesting an immunomodulatory effect of the low calcium levels. Further studies need to address the efficacy of the SCD device in combination with more regulated citrate-calcium objectives [80].

Interestingly, it has been suggested that hemoadsorption devices such as CytoSorb® could also adsorb leukocytes (mainly activated monocytes and neutrophils) in addition to their designated targets (cytokines and/or endotoxins), and thus modulate the immune response at a cellular level [14]. Furthermore, Srisawat et al. [81] have suggested that polymyxin B could also act at the cellular level of the immune modulation, by improving the expression of the monocyte human leukocyte antigen at the surface of leukocytes in septic ICU patients. These observations suggest that blood purification techniques remain not fully understood and may implicate different mechanisms of action.

Tailored Strategies in Precision Medicine

The use of extracorporeal blood purification techniques remains controversial because of the conflicting results observed in RCTs. We hypothesize that, as in other fields of intensive care, the "negative" results observed in some studies may be due the heterogeneity of the patients included and/or the unsuitable timing, dose, or duration of the therapies. It is therefore of major importance to carefully select the patients enrolled in future trials in order to offer each patient the best therapy in a more personalized manner. A tailored therapy should ideally be adapted to the time course of sepsis, patient severity, as well as genetic and immune profiles [82]. Importantly, immune biomarkers are not currently routinely available. Therefore, ongoing trials describing immune profiles of septic patients in the ICU will probably help clinicians to better select patients who may benefit the most from blood purification and to choose the best therapy according to their immune profile [83, 84].

Conclusion

Several extracorporeal blood purification therapies are now available. Most target endotoxins and/or the cytokines and aim at restoring a balanced immune response. To date, the highly adsorptive membrane oXiris® is the only therapy combining the removal of both endotoxins and cytokines, the replacement of renal function, and to offer antithrombogenic properties. Despite encouraging findings obtained from case series and experimental evaluation, current lack of clinical RCTs limits the clinical acceptance of this membrane by clinicians. Along with patient-tailored therapies, future research developments are also expected with therapies targeting the cellular level of the immune response. Thus, as mentioned in the 2016 surviving sepsis campaign, extracorporeal blood purification therapies could be of interest in the battle against sepsis, but further research is needed to clarify their mechanisms of action, indications, and clinical benefits [85].

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