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Methods of Extracorporeal Hemocorrection in Sepsis (Review)

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Summary

Sepsis and septic shock remain a major problem in critical care medicine being the most common causes of death in the intensive care unit. Currently, such methods of extracorporeal blood purification as hemodiafiltration, high-volume hemofiltration, high cut-off (HCO) membrane hemofiltration are among preferable options for treatment of severe systemic disorders and pathological conditions including sepsis.

The purpose of the review is to show the potentialities and prospects of the use of various extracorporeal hemocorrection methods, including those that are commonly employed in medical practice, and novel ones, either recently developed, or still under the development in experimental settings according to sepsis pathophysiology. The selected 82 papers represent comprehensible clinical and experimental data from the literature of the last five years and several earlier publications remained of current interest in a medical practice.

The review presents current methods of extracorporeal hemocorrection (EHC) in patients with sepsis. The clinical pathophysiology of sepsis is described in relation to treatment options that target endotoxemia and «cytokine storm». We consider commonly used EHC methods (hemodiafiltration, high-volume hemofiltration, high cut-off membrane hemofiltration and others) and novel promising technologies that include extracorporeal kidney support device, immune support system, leukocyte inhibition module, and artificial spleen, which have been recently developed and are still under investigation in the intensive care.

Conclusion. Currently, EHC methods are increasingly used not only to support renal function, but also as pathogenetic therapy option for multiple organ support and immunomodulation by reducing the level of circulating inflammatory mediators. Exploration of novel extracorporeal blood purification techniques for the pathogenetic treatment of patients with sepsis seems encouraging and promising.

Keywords: sepsis; extracorporeal hemocorrection; endotoxin

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Introduction

Currently, extracorporeal blood purification (EBP) plays an important role in the management of sepsis. EBP is defined as the targeted quantitative and qualitative modification of the cellular, protein, water-electrolyte, enzyme, and gas composition of blood by processing it outside the body's vascular system [1].

Modern methods of EBP are based on centrifugation, precipitation, membrane, adsorption, electrochemical, photochemical, electromagnetic and immunomagnetic technologies. Centrifugation, membrane and adsorption EBP methods are the most widely used in sepsis [1]. It should be noted that centrifugation technology and apheresis are separation-type methods based on blood fractionation and removal of one or another component.

Centrifugation technology uses the principle of weight fractionation of whole blood components. This principle is implemented as follows: the centrifugal force generated by the centrifuge separates the blood cells according to their mass, forming fractions. This technology makes it possible to separate plasma and the main cellular components from the blood, which is the core of plasmapheresis and various types of cytapheresis.

Membrane technology, in which diffusion, ultrafiltration (filtration), convection and osmosis play a leading role, allowing the transfer of proteins, electrolytes and gases, is based on transmembrane mass transfer, depending on the type of membrane, the size and number of pores and the surface area. A semipermeable membrane is a selectively permeable barrier between two phases. Mass transfer across a membrane is also called permeability because it occurs only when there is a driving force or potential gradient of some effect on the system on either side of the membrane [2].

Adsorption technology is based on the absorption of substances from biological fluids by forming bonds with active centers on the surface of the adsorbent. It is based on specific and non-

specific mechanisms (adsorption, absorption, chemisorption, ion exchange and complexation). The technology is implemented through a series of processing steps of both whole blood and its components, using activated carbon, ion exchange resins, and selective (immune, affinity, and receptor) compounds as sorbents [2–4].

Exchange transfusion, hemoadsorption, plasmapheresis, non-selective plasma adsorption are the least selective technologies. The most specific in the removal of certain substances are methods of immunoadsorption, affinity adsorption and biospecific adsorption of blood and its components [2]. In the efferent therapy of sepsis, in addition to all the above technologies, membrane and adsorption methods are used. Further discussion will focus on these methods of EBP.

According to the international multicenter study Sepsis Occurrence In Acutely Ill Patients (SOAP) (results from 198 European medical centers), the average in-hospital mortality from hospital-acquired sepsis was 24.1% (ranging from 14% in Switzerland to 41% in Portugal) [5]. Results from another multicenter study, Promoting Global Research Excellence in Severe Sepsis (PROGRESS), showed a nosocomial mortality rate of 49.6% [6]. The prognosis in sepsis is often unpredictable: mortality in leading clinics in developed countries reaches 40%, while in septic shock it can be as high as 80–90% [7]. Therefore, sepsis and septic shock remain a major challenge in clinical medicine, as they are the leading causes of death in the intensive care unit (ICU). Sepsis and the resulting inflammatory response can lead to multiple organ dysfunction [8].

Sepsis is a life-threatening acute organ dysfunction resulting from an impaired host response to infection. In essence, it is an impaired inflammatory homeostasis triggered by infection with a multifactorial progression. Hyperreactive pro- and anti-inflammatory mechanisms can interfere with each other, creating a destructive immunological dissociation that increases the risk of death. Inflammatory signals inhibit homeostatic signals, which have a higher priority for organism survival, whereas pro- and anti-inflammatory cytokines act simultaneously in sepsis. Such redundant and multifaceted simultaneous signaling, with multiple effects on effector tissues, ultimately leads to immune imbalance.

After infection, the pathogen encounters the body's innate immune system, including leukocytes, epithelial and endothelial cells. The innate immune cells «recognize» pathogens through PAMPs (pathogen-associated molecular patterns), such as lipopolysaccharide (LPS) activating intracellular cascades of inflammatory mediator production. Proinflammatory cytokines involved in the pathogenesis of sepsis include tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-12, and IL-18 [9]. Blocking or eliminating these cytokines was found to be protective in animal models of acute fulminant infection [10]. Importantly, the anti-inflammatory response can also lead to critical multi-organ failure through a diminished immune response, also referred to as «immune paralysis». Thus, the other side of the immune response imbalance in sepsis is immune suppression, affecting both the innate and adaptive immune systems. The understanding that LPS and other PAMPs can induce the production of cytokines, which in turn, when released into the systemic circulation, exert their deleterious effects on effector cells and tissues (primarily on the endothelium of organ capillaries and other immune defense participants, leading to a state of septic multiple organ failure or immunological anergy, respectively) provides a rationale for the routine use of various EGC methods in sepsis. The aim of this paper is to expand the knowledge of a broad medical audience about the role of current extracorporeal blood purification in sepsis.

Extracorporeal Blood Purification in Sepsis

The basic technologies used in EBP include separation, diffusion, convection, and adsorption, with the possibility of using any combination of these, depending on the clinical context and the specific needs of the patient. Table 1 shows the main modern methods of EBP used in sepsis and summarizes their principles.

Earlier EBP methods were used in patients with sepsis primarily to replace renal clearance and reduce uremic complications. In recent years, there has been a paradigm shift from renal replacement alone to more comprehensive multiple organ support therapy (MOST). Extracorporeal blood purification (EBP) methods are theoretically well suited for the MOST concept. EBP methods only have access to the intravascular compartment and can therefore partially influence its composition by removing unwanted components from the blood, such as inflammatory mediators and LPS, or by adding necessary components, such as bicarbonate, which replenishes the buffering capacity of the blood [11]. Support in cardiovascular failure can be achieved by controlling fluid balance, optimizing preload and afterload (using transmembrane fluid transfer along a hydrostatic gradient). Removal of extravascular pulmonary fluid is also possible [12, 13]. Elimination of uremic toxins and correction of blood acid-base balance (ABB) can potentially alleviate septic encephalopathy (ABB and water-electrolyte disturbances can be effectively addressed with dialysis technologies). Moreover, continuous renal replacement therapy (RRT) offers the added benefit of minimizing both osmotic shifts and hemodynamic

Table 1. Extracorporeal blood purification methods used in sepsis.

Method	Aim	Principle
Separation — plasmapheresis — plasma exchange	Separation of plasma and blood cells, control of hemostasis (in case of freshly frozen plasma replacement)	Centrifugal separation of blood components based on differences in their specific gravity
hemodialysis/filtration (CVVHDF) Continuous veno-venous	Multiple organ support therapy (MOST) + non-selective elimination of inflammatory mediators	Combination of diffusion and convection mass transfer
High volume hemofiltration (HVHF) гемофильтрация (HVHF)		Convective elimination of toxins
ГHigh cut-off membrane (HCOM) hemofiltration	Non-selective elimination of inflammatory mediators	Convective elimination of toxins
Coupled plasma filtration-adsorption (CPFA)	Non-selective elimination of inflammatory mediators	Adsorption of toxins from plasma
Molecular Adsorbent Recirculating System (MARS)	Elimination of water, low- and medium molecular weight substances, hydrophobic albumin-bound components of blood plasma	Low flux hemodialysis and semiselective adsorption with albumin regeneration
Fractionated Plasma Separation and Adsorption (FPSA)	Elimination of water, low- and medium molecular weight substances, hydrophobic albumin-bound components of blood plasma	High flux hemodialysis and selective plasma filtration
Endotoxin adsorption	Selective elimination of endotoxins	Endotoxin adsorption
Cytokin adsorption	Selective elimination of inflammatory mediators	Adsorption of inflammatory mediators
oXiris membrane	Non-selective adsorption of endotoxins and inflammatory mediators	By modifying the positively charged polyimine-ethylene layer, the AN69 membrane adsorbs negatively charged endotoxins and cytokine molecules

disturbances that can potentially impair brain perfusion [14]. In liver failure, the albumin-regenerative dialysis system promotes the elimination of albumin-related toxins, such as bilirubin, to provide partial liver support [15]. The extracorporeal circuit can control body temperature by changing the line length, i.e., the heat exchange area, and the temperature of the dialysis and/or replacement solution, which is used in hyperthermia or severe hypothermia. Thus, it is possible to beneficially affect multiple target organs in sepsis using EBP methods.

The reduction of blood cytokines is believed to result in decreased mortality in sepsis [16]. Over the years, several extracorporeal methods have been developed to target circulating blood substances such as LPS, inflammatory mediators, and coagulation factors. In addition, new experimental systems using phagocytic cells, immobilized antibodies for targeted immunomodulation, and magnetic nanoparticles coated with artificial human opsonin have emerged. A brief review of the main methods currently used in clinical practice for the purpose of extracorporeal blood purification in sepsis is given below.

Hemodiafiltration (HDF, CVVHF) and High-Volume Hemofiltration (HVHF) in Sepsis

Hemodiafiltration is a combination of diffusive and convective mass transfer that efficiently removes both small and medium-sized molecules. This method transports toxins dissolved in a hydrostatic pressure gradient filtered fluid through a semipermeable membrane. In the ICU, continuous veno-venous hemodiafiltration (CVVHDF) is preferred [17, 18]. Replacement of the removed fluid is performed in the pre- or postdilution mode, i. e., before or after the filter.

Several factors influence the choice of HDF and dilution method [19].

- The clearance of low molecular weight substances in hemodiafiltration is identical to that in hemodialysis.
- The clearance of medium molecular weight substances in hemodiafiltration is significantly higher than in hemodialysis and increases with increasing ultrafiltration rate.
- Predilution is preferable for elimination of medium molecular weight substances with insignificant reduction in urea and creatinine clearance.
- Postdilution provides adequate (compared to hemodialysis) elimination of low-molecular-weight substances with a slight reduction in clearance of medium-molecular-weight substances compared to predilution.

It has long been thought that decreased blood cytokine levels during EBP may result in reduced mortality in patients with sepsis. Three theories have been proposed to explain the potential benefit of high-volume hemofiltration (HVHF) in sepsis.

Ronco et al. proposed the «peak concentration hypothesis», suggesting that reducing both pro- and anti-inflammatory mediators («cutting off»

peak concentrations) may limit the associated target organ damage. Nevertheless, some studies have demonstrated clinical improvement and improved survival in septic patients with HVHF without significant reduction in blood levels of mediators [16].

Honore et al. proposed a more dynamic view to potentially explain these results, which they called the «immunomodulation threshold hypothesis». It is suggested that after removal of inflammatory mediators from the bloodstream in HVHF, these mediators are subsequently removed at the tissue level. Removal of inflammatory mediators at the tissue level leads to a clinical effect even without a significant change in their blood levels [20, 21].

Di Carlo and Alexander, with the «mediator delivery hypothesis» [22], suggested that HVHF not only removes solutes, but also increases lymphatic transport between the interstitial and intravascular compartments. This increase in lymphatic transport has been demonstrated in several studies showing a 20–40-fold increase in lymphatic flow with HVHF [23, 24]. According to the authors, this lymphatic mechanism enhances endogenous clearance of inflammatory mediators, particularly at the tissue level.

Ratanarat et al. also showed that HVHF reduced the levels of endotoxin and apoptosis mediators [25]. Regarding the recovery of renal function, the study by Boussekey et al. showed a significant increase in urine output with HVHF [26]. In addition, other studies in severe sepsis and septic shock have shown a reduced need for vasopressors with HVHF [27–29].

Potential side effects of HVHF include loss of vitamins, micronutrients, and some medications. An important issue in HVHF is appropriate antibiotic dosing. There are guidelines for antimicrobial dosing in critically ill patients undergoing renal replacement therapy. Therefore, monitoring of antibiotic concentrations and adequate dose adjustments are critical to prevent inappropriate dosing [30]. Due to the high clearance of small molecules in HVHF, strict electrolyte monitoring is also necessary to avoid hypokalemia and hypophosphatemia observed in some studies [31, 32].

In a prospective, randomized, multicenter IVOIRE trial [33] comparing «standard dose» hemofiltration (35 mL/kg per hour) with HVHF (70 mL/kg per hour), the authors found no reduction in 28-day mortality and no improvement in hemodynamic and organ function parameters in patients with sepsis.

Hemofiltration Through a High Cut-off Membrane

Most commercially available hemofilters do not provide effective removal of cytokines and endotoxins due to the relatively low cutoff of the membranes. High cut-off membranes (HCOM) have a larger pore diameter. This technical feature allows to increase the permeability up to a cut-off of 100 kDa [34]. HCOMs used in RRT have demonstrated higher clearance rates of some inflammatory mediators compared to standard membranes [35]. In a pilot RCT, 30 patients were assigned to HCOM-CVVHF or standard continuous venovenous hemofiltration (CVVHF) with an average continuous RRT rate of 31 ml/min. Compared to standard CVVHF, HCOM-CVVHF reduced the need for norepinephrine infusion and demonstrated better clearance of IL-6 and IL-1 [36]. HCOM improves peripheral blood monocyte proliferation and polymorphonuclear cell phagocytosis and decreases lymphocyte proliferative activity, but, as with HVHF, is associated with loss of vitamins, micronutrients, and antibiotics, making accurate dosing of the latter difficult. Protein and albumin losses were higher with convection (compared to diffusion) and at higher flow rates [37].

Combination EBP Methods

Combined EBP methods, such as CPFA, MARS, and FPSA, have been developed to overcome the disadvantages and enhance the advantages of membrane and adsorption extracorporeal methods. However, these methods have not been widely used in routine sepsis care, and few studies of these methods in the context of multi-organ support in septic shock speak more about the benefit of abandoning these methods in the treatment of sepsis. In particular, a second clinical trial (COMPACT 2) investigating the effect of high-dose CPFA was stopped early due to higher mortality in the CPFA group compared to the control group, especially in the first days of treatment, as observed in the interim analysis. It was also mentioned that CPFA is no longer indicated for the treatment of septic shock [38].

LPS Adsorption

Endotoxin is incorporated into the outer membrane of gram-negative bacteria and is considered one of the major biological agents causing sepsis. Lipopolysaccharide (LPS)-circulating endotoxin (ET) activates the coagulation system, complement, blood cells (monocytes, macrophages, neutrophils, eosinophils), and endothelial cells with initiation of multiple mediator release, which clinically manifests as a severe systemic inflammatory response with development of multiple organ failure [39, 40].

Removal of endotoxins from the blood of patients with sepsis and septic shock can reduce the severity of multiple organ failure and associated mortality. To implement this idea, specific methods of endotoxin adsorption have been developed.

Among the adsorbents currently used in clinical practice are immobilized polymyxin B (PMX-B) cartridges (Toraymyxin-20R, Japan), LPS adsorber (Alteco Medical AB, Sweden), MATISSE-Fresenius sys-

tem (Fresenius SE, Germany), Toxipac (NPF «Pokard», Russia), Efferon-LPS (OOO «Efferon», Russia).

The most studied and widely used in patients with sepsis and septic shock is the PMX-B immobilized cartridge. PMX-B is a cationic polypeptide antibiotic with high activity against Gram-negative bacteria and affinity for endotoxins. Intravenous use of PMX-B is limited due to its high nephro- and neurotoxicity. The ability to fix PMX-B to the polystyrene fiber of the cartridge allows the removal of ET without the risk of side effects. The PMX-B (Toraymyxin-20R) cartridge was developed and approved for clinical use in Japan in 1993. The results of one of the largest open-label, controlled studies conducted in Japan were published in 2003. 314 patients with sepsis were followed, of which 206 (the main group) were treated with Toraymyxin-20R. The study showed that the 28-day mortality rate in the main group was reduced to 32% [41]. It should be noted that Toraymyxin-20R is currently the most studied of all endotoxin adsorber cartridges [42–44].

The LPS adsorber consists of a series of porous polyethylene plates coated with an ET-specific peptide. This adsorbent is designed to adsorb endotoxins from blood. Currently, there are few publications in the world literature on the use of LPS Adsorber in patients with sepsis. Russian authors reported the results of using LPS Adsorber in the treatment of patients with sepsis and septic shock [45]. They have shown that the addition of the adsorbent to the treatment leads to a decrease in the levels of ET and inflammatory mediators and clinical improvement manifested by restoration of respiratory and hemodynamic parameters. A comparative analysis of the efficacy of Toraymyxin 20R and LPS Adsorber in patients with Gram-negative sepsis showed no significant differences in disease outcome [46, 47].

The MATISSE-Fresenius system is an ET sorption system based on the ability of serum albumin to covalently bind to macroporous acrylic polymer beads. The results of a randomized trial showed no significant effect compared to standard therapy in patients with sepsis [48].

Toxipack sorption column (NPF «PCARD», Russia) is designed for selective adsorption of ET. It consists of an adsorbent containing a polysaccharide granular matrix and a chemical ligand specific for gram-negative bacteria. Clinical experience with this adsorbent is limited. Sokolov A. A. and Handel L. L. reported improvement of clinical and laboratory parameters and reduction of organ dysfunction in patients with sepsis and septic shock using the Toxipack column [49, 50].

The Efferon LPS adsorption column (ZAO Efferon, Russia), which contains a multimodal hemoadsorbent based on a super cross-linked styrene-divinyl-benzene copolymer with immobilized LPS-selective ligand, is also intended for endotoxin adsorption and is currently one of the most studied columns for lipopolysaccharide adsorption. In an in vitro and ex vivo experimental study, data were obtained demonstrating the efficacy and safety of this device for LPS adsorption [51]. In a clinical trial, patients (*N*=9) with confirmed Gram-negative bacterial infection and septic shock (SEPSIS-3, 2016) underwent LPS-selective hemoperfusion. LPS adsorption using the Efferon-LPS column was found to result in a rapid reduction in endotoxin activity (EAA test), a more than twofold reduction in plasma interleukin-1 levels (immunoassay), as well as a significant clinical improvement in seven out of nine patients with septic shock, suggesting the need for further expanded clinical studies to evaluate the efficacy of this adsorbent and its contribution to reducing mortality in patients with septic shock [52].

In recent years, publications have appeared indicating the ineffectiveness of standard regimens for the use of LPS adsorption cartridges with PMX-B. A prospective, randomized, multicenter, controlled trial of 243 patients with septic shock found a non-significant increase in mortality in the treatment group [53]. In addition, the use of PMX-B had no effect on the severity of multiple organ failure. The inefficacy of PMX-B can be explained by possible adsorption of antibiotics during the EBP procedure, therefore studies adjusting the dose of antibiotics according to their concentration during hemoperfusion could influence the final results [54].

Cytokine Adsorption

Another option for non-selective adsorption is the use of cytokine adsorbing columns (cartridges) such as CytoSorb, PMMA, CYT-860-DHP, Lixelle, CTR-001, HA330, and MPCF-X [55]. Binding to various cytokines and mediators results from specific hydrophobic interactions, electrostatic attraction, hydrogen bonding, and van der Waals forces. In this regard, the structures of these columns vary considerably.

One of the most widely used and studied cytokine adsorption cartridges, Cytosorb, and a relatively novel, well-studied polymethyl methacrylate (PMMA) membrane were selected for a detailed review of this EBP method.

Animal models of sepsis have demonstrated the ability of CytoSorb to remove pro- and anti-inflammatory cytokines, other inflammatory mediators, and metabolites from the blood and to improve survival in sepsis [56, 57]. However, only one multicenter RCT has evaluated its efficacy in human sepsis [58]. In this study, 97 patients with septic shock and acute lung injury or acute respiratory distress syndrome were randomized to receive standard therapy or hemoadsorption with CytoSorb for

6 hours per day for up to 7 consecutive days. The authors found no differences in IL-6 levels (primary endpoint) or plasma levels of other key cytokines between the two groups. There was no evidence of improvement in multiple organ dysfunction in the CytoSorb group.

In addition to the small sample size, this study has several limitations. For example, according to the study design, therapy was administered in short (6-hour) daily sessions. This strategy may be inappropriate, as 24 hours of exposure is thought to be necessary for complete saturation of the adsorbent, and treatment-free intervals may lead to recovery of cytokine levels [56]. In addition, the mean baseline IL-6 levels were 552 (162 to 874) pg/mL (in the CytoSorb group) and 590 (125 to 2147) pg/mL (in the control group), which is considered low in sepsis. Since cytokine removal with CytoSorb is dependent on the level of inflammatory mediators, the combination of short duration of therapy and low IL-6 levels likely prevented the detection of potential adsorption efficacy. All other studies have been observational. The largest cohort is based on data from an international registry of 198 patients (68% with sepsis) [59]. In these patients, CytoSorb use was associated with lower IL-6 levels and lower than expected hospital mortality. Two case series reported reduced norepinephrine requirements and lactate levels in 20 and 26 patients with sepsis, respectively, who received efferent therapy with CytoSorb in combination with prolonged RRT [60–62]. The validity of these observational studies is largely limited by the lack of a control group.

Thus, experimental models and observational studies have shown significant clinical improvement, while RCTs have not yet demonstrated clinical benefit. However, their limited number and size, as well as the relatively low severity of the patients included, do not allow a definitive conclusion. Therefore, further studies should focus on populations with high blood cytokine levels, including pre-cytokine adsorption assays. Adequate definition of the target population is essential for future evaluation of cartridges and devices (not only Cytosorb) to prevent both misuse and unwarranted abandonment of this method.

The polymethylmethacrylate (PMMA) membrane is a synthetic polymeric membrane with a symmetrical microporous structure. This membrane, like CytoSorb, is capable of adsorbing low and medium molecular weight molecules such as cytokines, beta-2-microglobulin and immunoglobulin light chains [63]. Due to its extremely high adsorption properties, a PMMA membrane has been proposed for EBP in sepsis. Continuous veno-venous HDF with a PMMA blood filter has been reported to improve 28-day survival in patients with septic shock [64]. However, the PMMA membrane is characterized by a high degree of clogging due to non-selective adsorption of macromolecular substances, mainly proteins, on the membrane pores, as evidenced by the increase in transmembrane pressure in the filter over time [65]. The high thrombotic potential can also be explained by structural changes in the adsorbed proteins, causing activation and adhesion of platelets to the membrane surface. To solve these problems, a new PMMA-based membrane was developed to limit the structural changes of the adsorbed proteins, thereby improving permeability and preserving adsorption properties [66].

oXiris Membrane

The AN69-based oXiris membrane is modified with a positively charged polyimine ethylene layer capable of adsorbing negatively charged endotoxin molecules. In addition to its adsorption capacity, the oXiris filter is a conventional dialysis filter capable of full dialysis purification. In contrast to the 4 recent developments in extracorporeal blood purification described above, the oXiris membrane was evaluated in a RCT [67].

The aim of this study was to evaluate the ability of the oXiris dialysis filter membrane to reduce endotoxin and cytokine levels during a 24-hour treatment period in patients with septic shock and to compare the results with those obtained using a standard filter. Endotoxin levels were significantly reduced with the oXiris filter compared to the standard filter. In in vitro studies, the oXiris filter was the only hemoperfusion device tested that demonstrated removal of both endotoxins and cytokines [68]. Importantly, indiscriminate removal of all cytokines can disrupt immune regulation, but when one or more cytokines are in excess, as in sepsis, the proportion of the latter removed by adsorption will be greater than that of cytokines present at lower concentrations, theoretically helping to restore cytokine balance [69]. Circulating levels of TNF-α, IL-6, IL-8 and IFNγ were significantly reduced with both filters, but to a greater extent with oXiris than with the standard filter. The other cytokines analyzed (IL-1β, IL-2, IL-4, IL-10 and GM-CSF) were present at very low levels and were not compared between groups [67]. Blood lactate levels were significantly reduced in the oXiris group during the first 24 hours of treatment, and norepinephrine doses were also reduced after only 4 hours in the oXiris group. These observations suggest that the ability of the oXiris filter to remove endotoxins and cytokines may improve hemodynamic status. The main limitation of this study was the small cohort size of only 16 patients [67]. A recent study (2022) in a sample of 30 patients with septic shock clearly demonstrated that the use of oXiris-CVVH was associated with lower mortality, lower norepinephrine dose, lower lactate, procalcitonin

Table 2. The latest EBP methods.

Method	Aim	Principle
Renal assist device (RAD)	Replacement of filtration, transport, metabolic, endocrine and immunological function of the kidneys	Cell technology: hemofiltration through a membrane coated with renal cells
Extracorporeal immune support system (EISS)	Direct immunomodulation and phagocytosis	Cell technologies: plasma perfusion through a chamber with phagocytic mononuclear cells
Leukocyte inhibition module (LIM)	Direct immunomodulation and leukocyte apoptosis	Extracorporeal immunotherapy: blood perfusion through a polyurethane matrix with covalently bound Fas-stimulating antibodies
Magnetic opsonin and biospleen device (MOBD)	Removal of microorganisms and cellular debris from blood	Magnets remove opsonin-related toxins from the blood
Modified reduced graphene oxide pellets	Selective endotoxin removal	PMX-B applied to reduced graphene oxide pellets binds and removes endotoxins.

levels and leukocyte count compared to AN69-CVVH [70]. A pilot RCT showed that use of the oXiris filter may improve hemodynamics during initial continuous RRT in severe surgical septic shock with AKI [71]. Further large multicenter RCTs are needed to determine the effect of the oXiris filter on patient outcomes.

Promising Methods of Extracorporeal Blood Purification

New methods of EBP based on cell technologies are able to directly regulate the immune system and may become valuable tools in the armamentarium of future sepsis treatments (Table 2).

Renal Assist Device

The Renal Assist Device (RAD) is an extracorporeal device that uses a standard hemofiltration cartridge containing approximately 109 proximal renal tubular cells grown as a fusion monolayer along the inner surface of the fibers. The cells used in this device are isolated from donor kidneys for cadaveric transplants deemed unsuitable for transplantation. The non-biodegradability and pore size of the hollow fibers allow the membrane to act as a scaffold for the cells and a protective immune barrier. The RAD can be placed in series with the hemofilter in the extracorporeal circuit. In this scheme, the RAD is placed in series with the continuous venous hemofiltration (CVVH) circuit. The blood after the CVVH filter is pumped into the RAD cartridge and the processed blood is then returned to the patient. Ultrafiltrate (UF) from the CVVH is reabsorbed by the cell-coated hollow fibers of the RAD, and the treated UF exiting the RAD lumen is removed from the blood. The above scheme allows simultaneous replacement of filtration, transport, metabolic and endocrine functions of the kidney [72].

Extracorporeal Immune Support

Neutrophils and monocyte-derived macrophages play an important role in phagocytosis and antibacterial defense. Immune phagocytosis results in the efficient removal of live and dead pathogens such as bacteria, cell debris, endotoxins and exotoxins. In the absence of this specific neutrophil function, immune paralysis can occur. The Extracorporeal Immune Support System (EISS) is a promising experimental immunomodulatory therapy for sepsis.

It is based on the hypothesis that temporary replacement of phagocytic mononuclear functions by an extracorporeal cellular reactor can help the patient overcome the critical phase of immunosuppression in sepsis. First, the blood passes through a hemofilter. Next, the patient's separated plasma is perfused through the cellular compartment of the extracorporeal bioreactor, where phagocytes remove antigenic and apoptotic material that has escaped the patient's own neutrophils and macrophages. The circuit then ensures that the purified plasma passes through the cell filter and is returned to the patient [73]. Using a model of Gram-positive sepsis in pigs, Sauer et al. observed lower lactate concentrations and higher arterial blood oxygen pressure (PaO_2) in the group of animals that underwent the EISS procedure, indicating significantly better oxygen delivery in these animals. No adverse effects on the lungs or other organs were observed [74]. The first human study was performed in 10 patients with septic shock [75]. All patients tolerated the treatment well. There was a significant reduction in bacterial endotoxin, C-reactive protein and procalcitonin levels. Vasopressor doses were also reduced. Thus, the first studies of EISS demonstrated the safety of the procedure and yielded interesting and promising results.

Leukocyte inhibition module. The leukocyte inhibition module (LIM) is an experimental extracorporeal therapy aimed at reducing leukocyte activity [76]. In sepsis, unwanted overactivation of leukocytes occurs. To prevent or interrupt the inflammatory cascade, activated leukocytes, especially neutrophils, should be immediately inactivated and/or removed from the bloodstream. Adequate cross-binding of the appropriate ligands to the Fas

receptors on the surface membrane of neutrophils is known to stimulate pro-apoptotic signaling pathways [77]. Systemic administration of immunomodulatory antibodies can reduce neutrophil hyperactivity; however, this approach is expensive and can be associated with serious side effects. LIM is a biofunctional medical device for extracorporeal circulation that contains a polyurethane matrix with covalently bound Fas-stimulating antibodies. When neutrophils in the circulating blood come into contact with immobilized Fas antibodies, they rapidly become inactive and begin to undergo apoptosis [76]. Inactivated neutrophils can then be removed from the blood by phagocytosis or sequestration in the spleen. In this case, antibodies against Fas remain in the cassette and are cleared from the blood.

In an animal study, IL-8-mediated leukocyte chemotactic migration activity was completely abolished in animals treated with LIM and increased in animals not treated with this method. In addition, serum levels of TNF-α remained stable in the LIM group but increased in the other groups. As for human studies, the authors of the Leukocyte Inhibition Module Frankfurt (LIMFRA) single-center RCT concluded that LIM is safe and effective in limiting neutrophil-mediated perioperative inflammation [76]. These initial results with the LIM device demonstrate the potential for immunomodulation primarily in the cardiopulmonary bypass setting. It has not yet been studied in specific sepsis conditions in either animals or humans. The LIM technology has been applied at a very early stage of the inflammatory cascade. In cardiac surgery practice, the LIM cartridge has been integrated into the circulatory circuit, i. e., LIM has been used simultaneously with the event that would be expected to cause neutrophil activation. The future of this method is unclear and requires further study.

Biospleen Device

In 2014, Nature Medicine published a technical letter by Kang et al. on the possibilities of a new device for extracorporeal blood purification [78]. The authors named this device the «Magnetic Opsonin and Biospleen Device» (MOBD). Blood flowing through the MOBD circuit is mixed with magnetic nanoparticles coated with an engineered human opsonin, mannan-binding lectin (MBL), which captures a wide range of pathogens and toxins without activating complement and coagulation factors. Magnets remove opsonin-related toxins from the blood, and the purified blood is then returned. MOBD effectively removes many gram-negative and gram-positive bacteria, fungi, and endotoxins from human whole blood flowing through a single MOBD unit at up to 1.25 L/h *in vitro* [78].

To develop a broad-spectrum opsonin that could be used to easily purify whole blood flowing through the extracorporeal circuit, a large (650 kDa) native mannan-binding lectin (MBL) protein was engineered and then the collagen helix was removed. The remaining MBL carbohydrate recognition domain (MBL-CRD) was fused to an Fc fragment of human IgG1, allowing for high expression and secretion, as well as efficient, rapid and inexpensive purification of the smaller (90 kDa, compared to the original 650 kDa) recombinant protein. The resulting FcMBL was then attached to nanoparticles.

MOBD also allows researchers and clinicians to overcome two important issues, according to the authors of the paper [78]. First, the use of broad-spectrum FcMBL opsonin allows rapid treatment of systemic blood infections and prevention of sepsis progression without prior identification of the causative agent. Second, it is possible to rapidly process the entire volume of a patient's blood and perform multiple cycles of blood purification without significant coagulation of the blood or significant changes in blood composition.

Since FcMBL binds to several clinical isolates of antibiotic-resistant microorganisms, MOBD may also provide an effective therapeutic strategy for patients who have failed previous drug treatments. This dialysis-like blood purification system allows the entire volume of blood to be passed through the device repeatedly during a single procedure. Thus, even if only a fraction of pathogens are removed in a single pass, the number of pathogens in the bloodstream can be significantly reduced by circulating the blood multiple times over a 24-hour period. Although this procedure does not remove pathogens present in organs or abscesses, the results of the present study show that it can significantly reduce the spread of infectious agents to distant sites and reduce circulating endotoxin and inflammatory cytokine levels, thereby extending the time for exposure to other treatments, including antibiotic therapy. In fact, broad-spectrum antibiotic therapy or targeted therapy can be used in conjunction with the procedure because FcMBL magnetic opsonins bind to both dead and live pathogens. The ability of the MOBD to effectively trap pathogens also provides a potential way to rapidly capture large numbers of live infectious agents, helping to expedite pathogen identification and antibiotic susceptibility testing. Finally, this blood purification device is a versatile technology because it can be used to remove proteins (such as cytokines or autoantibodies) as well as other cell types (such as circulating cancer cells, stem cells, fetal cells in the maternal bloodstream) from whole patient blood volumes by coating magnetic beads with appropriate ligands specific for particular cells or proteins [78].

Modified Reduced Graphene Oxide Pellets

Reduced graphene oxide (rGO) is a promising endotoxin adsorbent for hemoperfusion due to its excellent adsorption capacity, but has the side effect of non-specific adsorption and low blood compatibility. Polymyxin B (PMX-B) acts as an organic affinity ligand that can specifically bind endotoxins. As an anticoagulant, heparin (Hep) can reduce the risk of blood clotting and improve the blood compatibility of materials. In the study by Li et al., the adsorbent used was reduced graphene oxide (rGO) with PMX-B and Hep on pellets, with polydophamine (pDA) as the active coating to immobilize PMX-B and further bind to Hep. These features were expected to successfully immobilize PMX-B and Hep on the rGO pellets. PMX-B endowed rGO pellets with higher adsorption capacity (143.84±3.28 EU/mg) and good selectivity for endotoxin. Hep significantly improved the compatibility of rGO pellets with blood. These modified rGO pellets also achieved good adsorption capacity and endotoxin adsorption selectivity in plasma, serum, and blood. Thus, rGO/pDA/PMB/Hep pellets appear to be promising adsorbents for endotoxin removal during EBP [79].

Trends in the Use of Extracorporeal Blood Purification

In recent decades, there has been a paradigm shift in the use of EBP. Until recently, EBP was used exclusively as renal replacement therapy to correct complications associated with acute renal failure. Currently, these methods are increasingly being used not only to support renal function, but also as a pathogenetic therapy for multi-organ support and immunomodulation by reducing levels of circulating inflammatory mediators [80–82].

A particular area of research is the clearance of specific substances such as antibiotics and other drugs, components of parenteral nutrition formulas, micronutrients and albumin through new cartridges. There is limited data on this topic, and consensus guidelines for device-specific antibiotic dosing have not yet been developed. These issues have been addressed in the international Surviving Sepsis Campaign guidelines [83].

Conclusion

We have briefly reviewed some of the extracorporeal treatment methods, including hemodiafiltration and high-volume hemofiltration, high cut-off membrane hemofiltration, plasmosorption combined with hemofiltration, albumin dialysis with albumin regeneration, hemodialysis with selective plasma filtration and adsorption, various techniques for adsorption of endotoxin and cytokines. We have also highlighted new experimental systems using human phagocytes and immobilized antibodies for targeted immunomodulation, as well as magnetic nanoparticles in addition to conventional membranes and adsorbents.

Importantly, of all the EBP methods listed, only a few have evidence from randomized clinical trials for their use in specific diseases. The study of novel variants of EBP as a method of pathogenetic treatment in patients with sepsis seems both intriguing and promising.

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