Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: May 31, 2024

Citation: Sertaridou E. and Papaioannou V., 2024. Sepsis pathophysiology and blood purification therapies: a literature review. Medical Research Archives, [online] 12(5). https://doi.org/10.18103/mra.v12i5.5034

DOI: https://doi.org/10.18103/mra.v12i5.5034

ISSN: 2375-1924

REVIEW ARTICLE

Sepsis pathophysiology and blood purification therapies: a literature review.

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ABSTRACT

Sepsis represents a lethal dysregulated host response to infection leading to organ dysfunction. Extracorporeal blood purification is proposed as an adjuvant therapy for sepsis, aiming at controlling the associated dysregulation of the immune system, preventing multiorgan failure. Even in the absence of strong indications deriving from large clinical studies, the removal of mediators is increasingly used in septic shock and in other clinical conditions characterized by a hyperinflammatory response. Different therapies have been developed to address certain steps of the immune dysregulation besides classical renal replacement therapy, such us High Volume Hemofiltration, High-cut-off membrane hemofiltration, hemoadsorption treatments and coupled plasma filtration and adsorption. Despite the different underlying mechanisms of action, most of such available devices focus on a single target, such as endotoxins, cytokines, or both, that triggers the inflammatory cascade. The attention in this review is focused on presenting Blood Purification Techniques and the evidence of their clinical effectiveness, clarifying the indications, ideal patient selection, timing, dosing and biomonitoring, important issues that should be solved in the future, to enable usage of these therapies in the best possible and most targeted manner.

Keywords: Sepsis pathophysiology, blood purification, hemoadsorption, hemofiltration.

Introduction

The definition of sepsis has evolved over time[1]. Most recently, the term "sepsis" has been defined as a lethal dysregulated host response to infection that leads to life-threatening organ dysfunction[2,3]. It can be triggered by a wide range of organisms, including bacterial, viral, fungal, parasitic or atypical, and presents in many different guises[1].

Sepsis is one of the commonest causes of death worldwide, affects millions of individuals per year, and carries a high risk of death even when care is provided promptly[4]. It is a clinical and biochemical syndrome which is characterized by heterogeneity and complexity and despite best efforts at guidelines-based care pathways, mortality among septic critically ill patients persists to be high at nearly 35% to 50%[1,5]. Sepsis continues to consider as the leading cause of extended length of Intensive Care Unit (ICU) stay and increased mortality[1].

The basis of septic shock treatment, that remains inconvertible the last decades, includes: early administration of antibiotics, monitoring guided intravenous fluid resuscitation, oxygenation and mechanical ventilation, vasopressors and inotropes to targeted specific hemodynamic goals[4]. Antibiotic therapy and supportive care have significantly improved survival following sepsis in the twentieth century, but further progress has been challenging[4]. Immunotherapy, mainly aimed at suppressing the immune response, have also failed, in part due to patient heterogeneity in the underlying immune disbalance[6]. Although Extracorporeal Blood Purification (EBP) techniques have become increasingly popular in the last few years, leading to their application in several fields of critical care, such as sepsis, cardiovascular surgery, autoimmune diseases, drug toxicity and organ transplantation[7], the recent Surviving Sepsis Campaign guidelines did not make any recommendation (either in favor or against) regarding EBP techniques, because of too low quality of evidence[4,5]. We present a narrative review describing the highlights of sepsis pathophysiology dealing with the mechanism of action of different Blood Purification (BP) techniques.

Pathophysiology of sepsis

The underlying pathophysiology is complex and remains to be fully elucidated. The innate immune response is the first line of defense against external triggers, e.g. pathogens[5,7]. To be more specific, in sepsis, pathogen-associated molecular patterns (PAMPS), such as microorganisms or their constituents, like Gram-negative bacterial lipopolysaccharide and fungal beta-D-glucan, can cause direct cellular damage, triggering an immune response in the host, as soon as they are identified as alien by extracellular and intracellular pattern recognition receptors (PRRs). When host cells are damaged, they release endogenous molecules known as DAMPs (damage-associated molecular patterns), such as adenosine triphosphate (ATP), mitochondrial deoxyribonucleic acid (DNA) and high-mobility group box 1 (HMGB-1). Both PAMPs and DAMPs, responsible for cellular signaling, are recognized by PRRs on the surface of immune cells, stimulating the release of inflammatory mediators into the blood, triggering the initial sepsis cascade, evoking both innate and cell-mediated immune responses. These mediators (such as

the Toll-like receptor or nucleotide-binding oligomerization domain-like receptor system) are key signaling molecules that regulate the inflammatory response, including pro- and anti-inflammatory cytokines e.g., interleukin (IL-6, IL-8, IL-10), tumor necrosis factor (TNF-α) and activated complement. They are released into the blood as part of the normal innate immune response to the recognition of a pathogen[7,8].

Overactivation of PRRs in sepsis leads to either excessive production or suppression of cytokines, hormones, and other mediators that often have contrasting effects. For example, these molecules can either boost or suppress inflammation, be pro- or anticoagulant, or cause microvascular vasodilation or vasoconstriction, which may lead to a series of reactions resulting in cellular and tissue injury[9]. When cytokines, DAMPs and PAMPs bind to injured cells, can activate their respective injured cell receptors. These activated cells may induce cell cycle arrest and apoptosis, resulting in renal tubular cells damage and early acute kidney injury (AKI), or lung endothelial cell apoptosis, which may also contribute to acute respiratory distress syndrome (ARDS)[10].

The sustained elevated release of inflammatory mediators, may initiate a hypermetabolic response known as hyperdynamic circulation, characterized by increased cardiac output and hypotension with decreased peripheral vascular resistance, which further cause tissue hypoperfusion and hypoxia, contributing to multiorgan dysfunction[11]. Moreover, these raised inflammatory mediators may result in increased vascular permeability and protein- and cell-rich fluid loss in third space and alveoli, worsening hypovolemia and ARDS[12]. This cytokine and mediators' overspill into the circulation via blood or lymph draining from the affected locus of infection, and thence in unaffected organs, such as liver or the lugs[3].

Furthermore, overproduction of IL-6 and other cytokines will excessively boost production of acute-phase proteins by the liver, such as C-reactive protein and procalcitonin[13]. The first one promotes hypotension and changes in intracellular calcium signaling, cytokine production, phagocytosis, and complement activation[14,15] whereas procalcitonin induces cytokine production and decreases neutrophil migration[16]. An imbalance between sympathetic and parasympathetic pathways can compromise neural control of inflammation and immunity[17]. Hormonal changes modify immune, metabolic, cardiovascular response[18]. The net effect of all the above changes is widespread stimulation or suppression of multiple pathways leading to dysfunction affecting multiple organs within the body.

The heart can be directly affected, resulting in myocardial depression affecting, to varying degrees, left and right ventricles and systolic and diastolic dysfunction. Mechanisms underlying this known as 'septic cardiomyopathy' include coronary microvascular changes, adrenergic pathway downregulation, oxidative and nitrosative stress, abnormalities in calcium handling and myofilament sensitivity, downregulation of sarcomeric and mitochondrial genes, and mitochondrial dysfunction. Myocardial depression can be severe enough, resulting in organ hypoperfusion[19,20].

In the early phases of sepsis, increased vascular permeability can result in excessive

leak of circulating fluid and proteins into interstitial extravascular spaces, resulting in tissue edema and hypovolemia[3]. Blood flow is also affected by alterations in vascular tone and responsiveness to catecholamines ("vascular hyporeactivity" or "vasoplegia"). This loss of vascular tone, over and above co-existing myocardial depression and hypovolemia, may result in persistent and irreversible hypotension and organ hypoperfusion, constitutes an independent prognostic factor of mortality in severe sepsis[21-23]. Furthermore, there are downstream irregularities in the microvasculature with patchy areas of constriction and dilatation. Blood flow to different microcirculatory areas within the same organ may be varied. This increase shunting of oxygenated blood, bypassing the cells and inducing a local tissue hypoxia in addition to concurrent microcirculatory deficiencies that compromises regional blood flow[3].

Meanwhile, clotting pathways are activated and are frequently identified in abnormal rages, potentially aggravating the prognosis[24]. In the early stages of sepsis, patients tend to exhibit a prothrombotic state through extrinsic pathway activation, cytokine-induced coagulation amplification, anticoagulant pathways suppression, and fibrinolysis impairment. In late sepsis stages, with the establishment of disseminated intravascular coagulation (DIC), hypocoagulability ensues. Furthermore, neutrophils migrate from the circulating blood to infected tissues, mediate the formation of neutrophil extracellular traps (NETs) and kill pathogens. The interaction of overactivated NETs with platelets, complement, and endothelium promotes immunothrombosis, causing DIC and damaging microcirculation[25-27].

Hyperlactatemia and lactic acidosis seen in sepsis are also common and are associated with significant mortality. They wrongly ascribed to be entirely related to anaerobic glycolysis consequent to inadequate oxygen delivery and tissue hypoxia. Although tissue hypoxia may exist mainly in the early unresuscitated period, multiple other causes for hyperlactatemia exist, such as liver and mitochondrial dysfunction, and catecholamine driven aerobic glycolysis with activation of muscle sodium pumps that allow supply of lactate to other organs as an energy substrate[28,29].

Hormonal production during sepsis is markedly affected and influences multiple systems including cardiovascular, immune, bioenergetic and metabolic, reflecting either the severity of disease or possibly as a direct consequence. The changes are complicated further by alterations in hormone receptor activity and density, or downstream pathways, resulting in either decreased or increased responsiveness to their specific hormones[3]. For example, catecholamine levels are markedly prolonged elevated, especially in nonsurvivors[30], while cortisol after an initially raised its production is decreased leading to corticosteroid insufficiency[31]. Thyroid hormone production is reduced both centrally and peripherally, with bioenergetic and metabolic consequents[32]. After a transient early rise, vasopressin levels are not further elevated in septic shock, due to decreased hypothalamic production[33].

The central nervous system (CNS) plays a major part in the dampening of the immune response after inflammation and infection, by controlling inflammation through sympathetic (or adrenergic), parasympathetic (or cholinergic) pathways, and the hypothalamic–pituitary–

adrenal axis[34]. An additional complexity in evaluating these mechanisms in patients with sepsis is that chemical agonists of these separate pathways are frequently used as therapies; for example, steroids, vasopressin and noradrenaline[35].

Organ dysfunction in sepsis seems to be more than cell apoptosis, tissue death and organ structural damage. Bioenergetic alteration and metabolic shutdown due to mitochondrial dysfunction, leading to an insufficiency of energy substrate, seem to have a key role to organ dysfunction[36,37].

Immunosuppression

After the initial pro-inflammatory mediator excess there is a shift toward an overall anti-inflammatory milieu. The main mechanisms sustaining this process have been discovered incrementally and are still regularly reinvestigated. Firstly, increased apoptosis of T-, B- lymphocytes and dendritic cells leads to a marked reduction in their abundance in the circulation of patients, reducing phagocytic capacity, neutrophil chemotaxis and immunoglobulin production[38]. Furthermore, lipopolysaccharide (LPS) and endotoxin tolerance caused by reduction of TNF production, increases phagocytic ability coupled with a conserved capacity to kill internalized pathogens, albeit with impaired antigen-presentation and chemotaxis capacities[39]. On the other hand, metabolic and epigenetic reprogramming leading to dramatic shifts in transcriptional profiles have emerged as central players in the induction and maintenance of sepsis-induced immune alterations[40].

Sepsis induced immunosuppression is characterized by the release of anti-inflammatory cytokines, abnormal death of immune effector cells, hyperproliferation of immune suppressor cells, and expression of immune checkpoints[41]. The net effect is to place the septic patient at risk of secondary infection, often with opportunistic organisms. Sustained immunosuppression can last for months after the septic event and may be an important factor underlying late deaths[42]. In conclusion, the pathophysiology of sepsis is considered as an initial hyperinflammatory phase that lasts hours to a few days (< 7-10 days), followed by a more protracted immunosuppressive phase. The current death distribution indicates peaks during the early phase, although at a lower magnitude, and another peak after 2-3 months that continues to increase over the next 2-3 years[43].

Blood Purification Techniques

Extracorporeal BP is proposed as an adjuvant therapy for sepsis, aiming to reduce the potential damage caused by dysregulation of the host response to infection, intending to nonspecific modulation of the uncontrolled immunoinflammatory process and immune homeostasis. The removal of substances which are involved in immune cascade, through such BP techniques, may attenuate the response particularly in the early phase of sepsis. Different therapies have been developed to address certain steps of the immune dysregulation. They could interfere with proinflammatory and anti-inflammatory mediators, with the infectious agent itself or its components, or both[44].

Several theories have been proposed to explain the potential positive effects of blood purification techniques. First, Ronco et al in 2003 proposed the "The peak concentration

hypothesis"[45]. They suggest that continues renal replacement therapies (CRRT) decrease indiscreetly proinflammatory and anti-inflammatory mediators, with a rate depending on the type of membrane and dosage of the treatment, avoiding a "toxic threshold" to be reached, and thus minimizing organ dysfunctions. Later, Honoré and Matson suggested the "threshold immunomodulation hypothesis"[46]. According to this theory, cytokine removal from the blood compartment would mobilize cytokines from the tissues via concentration equalization, limiting their local deleterious effects. Afterwards, Rimmelé and Kellum propounded "The Cytokinetic theory"[47]. According to this hypothesis, decreasing cytokine blood concentration would restore an appropriate cytokine gradient between blood and infected tissues, promoting leukocyte chemotaxis.

Moreover, the "cellular theory" suggested that complex interactions could occur between the adsorbing material or the hemofilter and immune cells. The interaction between the membrane and the immune cells, as demonstrated by the modulation of surface molecules during different BP procedures. For example, expression of surface molecules, involved in leukocyte adhesion and migration, antigen presentation, and apoptosis, may be modulated by various BP techniques. Some immune cells (such as monocytes and neutrophils) also can be adsorbed on the blood purification device, thus participating in the immune modulation[48,49]. However, none of these theories explain adequately the pathophysiologic mechanism under BP treatment. More likely, different BP techniques act with more than one mechanism, in different timepoints of immune response[50].

Different BP techniques are used to clear the mediators produced during sepsis. Their removal is related to the characteristic of the mediators, including their molecular weight and the chemico-physical properties; and of the device used, such as the cut off value of the membrane, its surface of contact with the substrate to be processed, and the affinity for the substance to be cleared[50]. Thus, EBP can be considered a general term including different techniques that can be primarily subdivided into blood- and plasma-processing procedures, which can run in a stand-alone mode or, more commonly, in association with a RRT (Table 1).

Table 1: Blood Purification Techniques – mechanism of action

	Type	Mechanism of action	Target molecules	Proposed in
Convection therapies	conventional Renal Replacement Therapy (RRT)	Convection ± diffusion	Water soluble small molecules (urea, ammonia, creatinine, electrolytes)	AKI, drug toxicity
	High-volume hemodialysis (HVHD)	Diffusion	Water soluble small to medium molecules (50-60 kDalton) (urea, ammonia, creatinine, electrolytes, cytokines)	AKI, septic shock, drug toxicity

	Type	Mechanism of action	Target molecules	Proposed in
	High-volume hemofiltration (HVHF)	Convection	50-60 kDalton (cytokines)	AKI, septic shock, drug toxicity
	High-Cut-Off membranes (HCO)	Convection	>60 kDalton (cytokines and alboumin)	AKI, septic shock, drug toxicity
Hemoadsorption	Polymyxin B-immobilised fiber column - Toraymyxin®; Toray, Tokyo, Japan	adsorbing column containing multiple polymixin-immobilized fibers	endotoxin molecules	septic shock caused by Gram-negative bacteria
	Alteco LPS Adsorber; (Alteco Medical AB, Lund, Sweden)	cartridge filled with porous plates of polyethylene	endotoxin molecules	septic shock caused by Gram-negative bacteria
	Cytosorb®, (Cytosorbents Corporation, Monmouth Junction, NJ, USA; Afereticas.r.l., Bologna, Italy)	polystyrene and divinylbenzene microbeads	5-60 kDaltons hydrophobic pro- and anti- inflammatory mediators	hyperinflammatory conditions, septic shock
	Seraph 100® (ExThera Medical Corp, Martinez, CA, USA)	polymer beads covered with covalent end-point heparin ultra-high-MW polyethylene.	toxins, bacteria, and Antithrombin III, mainly SARS-CoV-2	treatment of COVID-19 patients
Blood combination therapies	oXiris® (Baxter, Meyzieu, France)	modified AN69 membrane associated with a positively charged polyethyleneimine polymer	endotoxin and several different septic mediators plus local anticoagulation	AKI, septic shock
Plasma combination therapies	Coupled Plasma Filtration Adsorption (CPFA)		bilirubin, tryptophan, phenols, bile acids, and cytokines	liver indications, liver transplantation
	Plasmapheresis		Selectively remove the immunoglobulin fraction from the serum	autoimmune diseases
	Plasma exchange			autoimmune diseases

Convection therapies

During conventional RRT, high-volume hemodialysis (HVHD) or hemofiltration (HVHF) molecules diffuse across a semipermeable membrane along the solute concentration gradient, supported by a pressure gradient, controlled by the effluent pump, in the case of the convective therapies. The basis of this method is convective clearance, when solutes and fluids, both in the blood and in the dialysate, are transported through the pores of a semipermeable membrane by the processes of convection and diffusion. During convection, both middle and large solutes (50-60 kDalton) together with the flow of water are displaced through the membrane (dragging of solutes by the solvent), while upon diffusion only small solutes, such as urea, creatinine, electrolytes and some smaller mediators from the bloodstream, are displaced from an area of high concentration to an area of lower[50].

Particularly, HVHF is a modification of CRRT in hemofiltration mode, where ultrafiltration flow is set to a much higher value (>50 mL/kg/h) than that recommended for standard renal support for AKI[50]. High ultrafiltration flow enhances middle molecular weight (500 Dalton to 60 kDalton) hydrophilic molecule clearance[51]. Solutes can also be eliminated from the blood by their adhesion to membranes. More recently, high-cut-off (HCO) membranes may also be utilized since they let through higher molecular weight molecules (up to 60 kDalton). Although, their possible beneficial clinical effect, their use is associated with massive albumin and nutrients losses into the effluent, while cost and nursing workload are increased owing to the frequent change of substitution fluid containers[50]. These membranes have shown promising properties on inflammation mediator removal, although the level of evidence remains low[44].

Hemoadsorption

Hemoadsorption (HA) is a technique in which blood is circulated extracorporeally through an adsorbent. The direct contact between the blood and the sorbent permits the adhesion of the circulating mediators on the surface of a membrane able to capture them. There are many adsorption mechanisms (Figure 1), such as bipolar or polar where positively charged region of the semipermeable membranes interacts with negative region of water molecules[52], hydrophobic between the hydrophobic sites of the membrane surface and the hydrophobic region of a solute[53] and ionic where negatively charged sulfonate group of the membrane electrostatically interacts with positively charged amimo-group of cytokines[52]. Ionic interaction between solute and membrane is the strongest type.

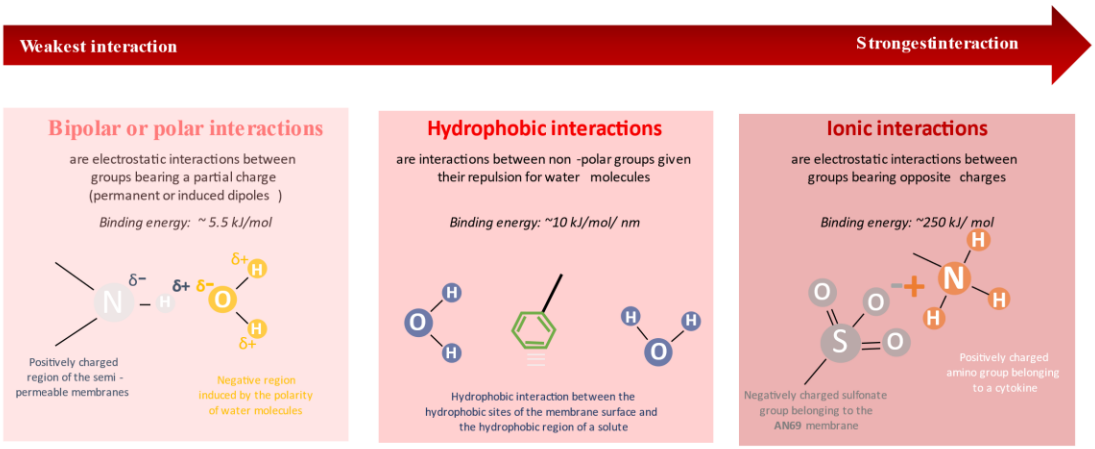

Figure 1: Adsorption mechanisms

Five basic devices have been developed so far:

The first takes advantage of an adsorbing column containing multiple polymyxin-B-immobilized fibers (Toraymixin®, Toray Industries, Tokyo, Japan) arrayed into a cartridge to remove the endotoxin molecules. Due to this characteristic, its use has been advocated in the treatment of septic shock caused by Gram-negative bacteria only[54]. After that, a new alternative for extracorporeal endotoxin removal was developed consisting of a cartridge filled with porous plates of polyethylene (Alteco LPS Adsorber; Alteco Medical AB, Lund, Sweden). This is a tailormade nontoxic, nondrug peptide with high affinity for endotoxin. During hemoperfusion with this absorber, the cationic part of the peptides captures the negatively charged endotoxin molecules[55,56].

The third technique consists of a cartridge containing a synthetic resin constituted by polystyrene and divinylbenzene microbeads (Cytosorb®, Cytosorbents Corporation, Monmouth Junction, NJ, USA; Afereticas.r.l., Bologna, Italy). The wide adsorptive surface (~40.000m^2) can adsorb hydrophobic pro- and anti- inflammatory mediators with molecular weight ranging from 5-60 kDalton. The efficacy of Cytosorb® is concentration-dependent, as substances present in large concentrations are removed more efficiently than those with lower blood levels. Cytosorb® can run in a stand-alone mode or can be associated with a CRRT or with an extra corporeal membrane oxygenation (ECMO) apparatus[9].

The fourth technique is based on a filter containing a modified AN69 membrane associated with a positively charged polyethyleneimine polymer able to absorb both endotoxin and several different septic mediators (oXiris®, Baxter, Meyzieu, France) from the bloodstream, covered by a heparin grafting for local anticoagulation, while

simultaneously providing CRRT[50]. The final technique consists in an HA device (Seraph100®, Ex Thera Medical Corp, Martinez, CA, USA) packed with polymer beads covered with covalent end-point heparin ultra-high-MW polyethylene. This design mimics the heparan sulfate attached on the cell surface, allowing the in vitro binding of toxins, bacteria, and Antithrombin III, thus clearing them from the bloodstream[57].

Due to these properties, the US Food and Drug Administration (FDA) recently approved its use for the treatment of COVID-19 patients (Figure 2).

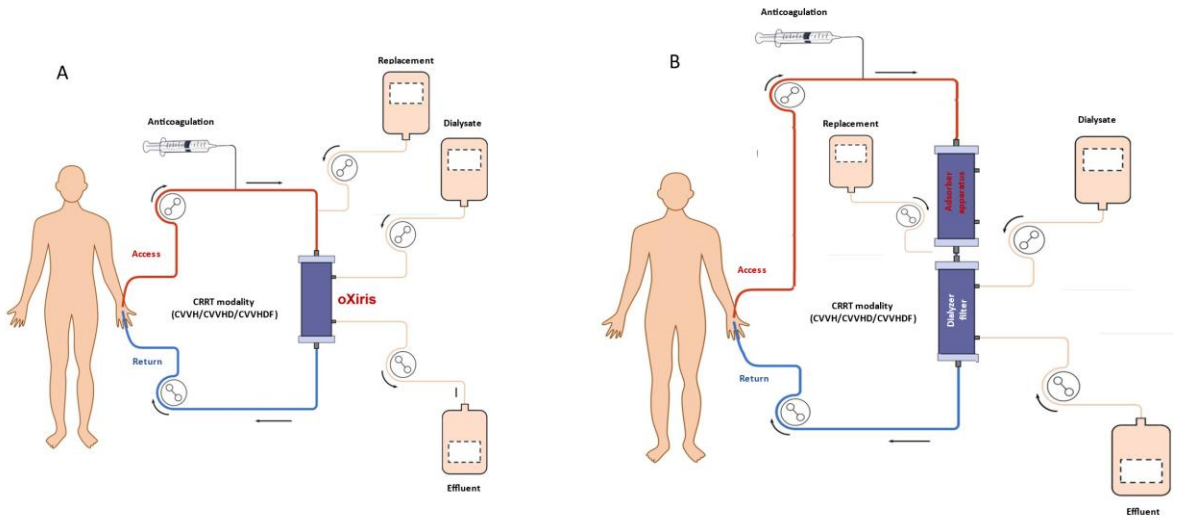

Figure 2: Adsorption technics. A: OXiris filter, B: Adsorber apparatus associated with dialyzer filter.

Plasma Processing Techniques

Plasmapheresis (PF) is based on the selective removal of one or more plasma components (lipoproteins, paraproteins, etc.), and is not currently used in the treatment of septic shock[50]. Total Plasma Exchange (PEX) consists in the removal of one or more volumes of plasma, which is replaced with donors' plasma or albumin. It involves the non-selective removal of plasma from the blood and replacement with fresh plasma and/or blood products, indicated mainly in autoimmune diseases such as thrombotic thrombocytopenic purpura[52].

Coupled Plasma Filtration and Adsorption (CPFA) (Figure 3) is an extracorporeal therapy which uses a plasma filter to separate plasma from blood, allowing the separated plasma to pass slowly through an adsorbing cartridge for nonspecific removal of several mediators. After purification, plasma is returned to blood, which can then pass through a hemofilter for

further purification by means of conventional haemodialysis, hemofiltration, or hemodiafiltration in case of acute renal failure. The adsorptive capabilities of the resin are exhausted after 10 h, but the CRRT can continue beyond this limit by excluding the plasma processing unit. The main therapeutic goal of CPFA is to hit the excess of pro- and anti-inflammatory mediators, in order to reestablish a normal immune function[7,52]

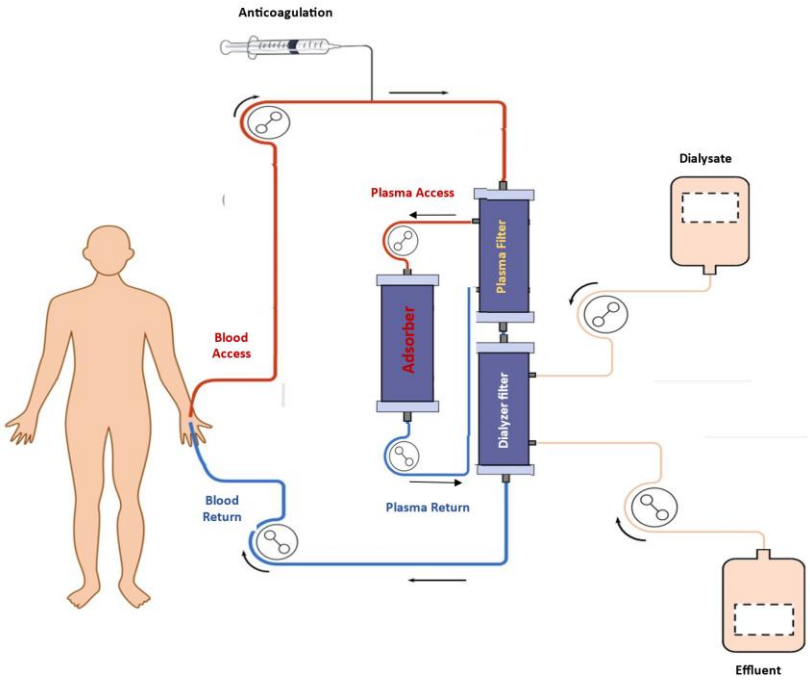

Figure 3: Coupled Plasma Filtration and Adsorption

Blood Purification clinical efficacy

Regarding convection therapies numerous clinical studies (Table 2) have shown hemodynamic[60-62,64,66] and respiratory improvement[63,64], as well as improved outcome[58,63,65]. However, the hIgh VOlume in Intensive care randomized controlled (IVOIRE) trial compared ultrafiltration flow rates of 35 and 70 mL/kg/h during a 96-hour period in 140 early septic shock patients with AKI and failed to show any difference on outcome[67]. The following RESCUE trial which included 37 burned, septic patients was terminated earlier due to slow patients' enrollment. They compared HVHF (dose: 70ml/kg/h) to standard therapy and they show hemodynamic improvement and a reduction in SOFA score, although survival rate and cytokines level remain unaffected[68].

Table 2: Clinical efficacy of Blood Purification – Clinical studies referred to sepsis and convection therapies

Technique	Study	Method	Material	Intervention	Results
CRRT	Ronco C et al. Lancet 2000;356(9223):26-30[58]	randomized, control	425 ICU patients with AKI	HF 20 vs 35 vs 45 ml/kg/h	Improved 15-days mortality when treated with HF (45 ml/kg/h)
	Tolwani AJ et al. J Am Soc Nephrol 2008;19(6):1233-8[59]	randomized, control	200 ICU patients with AKI	CVVHDF 20 vs 35 ml/kg/h	- Worst survival in 30 days (49 vs 56%, p=0,32) - rarer renal recovery (69 vs 80%, p=0,29)
High Volume Hemofiltration (HVHF)	Honore PM et al. Crit Care Med 2000;28(11):3581-7[60]	Unicentric, randomized	20 patients with septic shock and AKI	**No control group** 35 lit/4 h HVHF and then standard CVVHF	- hemodynamic improvement
	Cole L et al. Int Care Med 2001;27(6):978-86[61]	Unicentric, randomized, control	11 patients with septic shock and AKI	6 lit/h HVHF vs 1 lit/h standard HF for 8 hours	- hemodynamic improvement in HVHF group
	Ratanarat R et al. Crit Care 2005;9(4):R294-302[62]	Unicentric, randomized	15 patients with septic shock and AKI	**No control group** 85 ml/kg/h HVHF for 6-8 hours and then 35 ml/kg/h	- hemodynamic improvement
	Ghani RA et al. Nephrology (Carlton) 2006;11(5):386-93[63]	Unicentric, randomized, control	33 patients with septic shock and AKI	100 ml/kg/h HVHF vs 35 ml/kg/h standard HF for 6 hours	- better SOFA in 7 days - reduce IL-6 in HVHF group - same SOFA in 20th day
	Boussekey N et al. Int Care Med 2008;34(9):1646-53[64]	Unicentric, randomized, control	20 patients with septic shock and AKI	65 ml/kg/h HVHF vs 35 ml/kg/h standard HF	- no difference in 28days mortality, - mechanical ventilation duration - and ICU length of stay - hemodynamic improvement and - increased diuresis in HVHF group
	Zhang P et al. Nephrol Dial Transplant 2012;27:967-73[65]	Unicentric, randomized, control	280 patients with septic shock and AKI	50 ml/kg/h HVHF vs 85 ml/kg/h EHVHF	- same mortality in 28, 60 and 90 days
	Tapia P et al. J Trauma Acute Care Surg 2012;72(5):1228-32[66]	Unicentric, randomized	31 patients with septic shock and AKI	**No control group** 40 ml/kg/h HVHF for 6 hours and then <35ml/kg/h	- hemodynamic improvement

Technique	Study	Method	Material	Intervention	Results
	Joannes-Boyau O et al. (**IVOIRE** trial). Intens Care Med. 2013; 39(9): 1535–46[67]	Multicentre, randomized, control	140 patients with septic shock and **AKI**	70 ml/kg/h HVHF vs 35 ml/kg/h standard HF	- same 28 days mortality - no hemodynamic improvement - same SOFA
	Chung KK et al. (**RESCUE** trial) Crit Care 2017;21(1):289[68]	Multicentre, randomized, control	37 burned patients with septic shock and **AKI**	70 ml/kg/h HVHF vs standard dose according to local practices for 48 hours	The study was terminated earlier. - Hemodynamic improvement in 48 hours - better SOFA in 14 days - same survival - same cytokines level after 48 hours
High-Cut-Off membranes (HCO)	Atan R et al. Int J Artif Organs 2016;39(9):479-86[69]	Unicentric, randomized, control	26 patients with septic shock and **AKI**	CVVH-HCO vs CVVH-standard	same cytokines level
	Kade G et al. Med Sci Monit 2016;22:4338-44[70]	Unicentric, retrospective	28 patients with septic shock and **AKI**	**No control group** 24 hours CVVH-HCO	Reduce level of IFN-α, IL-1β, IL-2, IL-6, IL-10 and IL-12

Abbreviations: AKI: Acute Kidney Injury, CVVHF: Continuous Veno-Venous Hemofiltration, CVVHDF: Continuous Veno-Venous HemoDiaFiltration, HF: Hemofiltration, HVHF: High Volume Hemofiltration, ICU: Intensive Care Unit, SOFA: Sequential Organ Failure Assesment.

Table 3: Clinical efficacy of Blood Purification – Clinical studies referred to sepsis and Adsorption therapies

Technique	Study	Method	Material	Intervention	Results
Polymyxin-B	Vincent JL et al. Shock 2005;23(5):400-5[71]	Multicentre, randomized, control	36 postsurgical patients with intraabdominal sepsis	17 patients: 2 hours polymyxin-B vs 19 patients: standard therapy	- same level of IL-6 - hemodynamic improvement - less CRRT days - same SOFA
	Cruz DN et al. (**EUPHAS** trial) JAMA 2009;301(23):2445-52[72]	Multicentre, randomized, control	64 septic patients with Gram (-) peritonitis	2 sessions of polymyxin-B vs standard therapy	- hemodynamic improvement - better SOFA - better 28 days survival
	Coudroy R et al. (**ABDOMIX** trial). Shock 2017;47(1):93-99[73]	Multicentre, randomized, control	213 septic patients with peritonitis	2 sessions of polymyxin-B vs standard therapy	- same survival - same level of cytokines - reduce level of IL-17A
	Dellinger RP et al. (**EUPHRATES** trial). JAMA 2018;320(14):1455-63[74]	Multicentre, randomized, control	450 patients with septic shock and **AKI** (eaa >0,6)	2 sessions of polymyxin-B (90-120 sec) vs HF	- same 28 days mortality

Technique	Study	Method	Material	Intervention	Results
Alteco® LPS adsorber	Yaroustovsky M et al. Blood Purif 2009;28(3):227-33[75]	Unicentric, randomized	13 Gram (-) septic, cardiosurgical patients	6 patients with Selective LPS adsorption (group I) vs 7 with Toraymyxin (group II)	- reduce endotoxin level (76% in group I vs 88% in II) - reduce procalcitonin level (86% in group I vs 76% in II) - reduce white blood cells and temperature in both
	Ala-Kokko TI et al. Blood Purif 2011;32(4):303-9[55]	Unicentric, randomized, control	9 septic patients vs 15 controls	2 hours HA	- hemodynamic improvement - better SOFA - reduce endotoxin level
	Adamik B et al. Arch Immunol Ther Exp (Warsz) 2015;63(6):475-83[56]	Observational study	18 septic patients	LPS adsorption and standard therapy	- reduce endotoxin level - hemodynamic improvement - better SOFA - same outcome
	Lipcsey M et al.(**ASSET** trial) Shock 2020;54(2):224-31[76]	Multicentre, randomized, control phase **IIα**	Aim to allocate 32 patients with intraabdominal sepsis and MOD	LPS adsorption vs HF	The study was terminated early. - no difference in endotoxin level - no difference in inflammatory mediators' level - same adverse event
CytoSorb®	Kogelmann K et al.Crit Care 2017;21(1):74[77]	Unicentric, randomized	26 septic patients treated with RRT	**No control group**	- hemodynamic stabilization - reduce serum lactate level - better survival
	Schädler D et al. PLoS One 2017;12(10):e0187015[78]	Multicentre, randomized, control	97 septic patients	CytoSord for 6 hours for 7 days vs standard therapy	- same IL-6 level - worse 60 days mortality (44,7% vs 26%) - same SOFA
	Hawchar F et al. J Crit Care 2019;49:172-8[79]	Unicentric, randomized, control	20 septic patients without **AKI**	10 patients CytoSord for 24 hours vs 10 standerd therapy	- hemodynamic improvement - reduce procalcitonin level - reduce Big-endothelin-1 level - same SOFA
	Singh YP et al. Int J Artif Organs 2020;43(6):372-8[80]	Unicentric, retrospective	36 septic patients	**No control group**	- reduce procalcitonin level - reduce white blood cells - better SOFA - better survival according to APACHE II score

Technique	Study	Method	Material	Intervention	Results
	Paul R et al. World J Crit Care Med 2021;10(1):22-34[81]	Multicentre, retrospective,	45 septic patients	No control group	- hemodynamic improvement - better SOFA and APACHE II - better survival according to APACHE II score
oXiris® filter	Shum HP et al. Hong Kong Med J 2013;19(6):491-7[82]	Unicentric, randomized,	6 patients with Gram (-) sepsis and AKI	6 patients: CVVH with oXiris vs standard therapy	- better SOFA in 48 hours - hemodynamic improvement - same mortality
	Turani F et al. Blood Purif 2019;47 Suppl 3:1-5[83]	Unicentric, retrospective	60 septic patients	CVVH with oXiris	- hemodynamic improvement - better oxygenation - better SOFA - reduce IL-6, IL-10, endotoxin and procalcitonin
	Broman ME et al. PLos One 2019;14(8):e0220444[84]	Unicentric, randomized, control	16 septic petients with AKI and endotoxin level >0,03 EU/ml	CRRT with oXiris vs AN69-ST	- hemodynamic improvement - reduce endotoxin, IL-6, IL-8, IFNγ, TNF-α and lactate level
	Zhai Y et al. Am J Transl Res 2021;13(4):3839-44[85]	Unicentric, randomized,	Septic patients	23 patients: CRRT with oXiris vs 30 with AN69-ST	- hemodynamic improvement - better SOFA - reduce IL-6, IL-10, lactate and procalcitonin - better outcome
	Zang S et al. Blood Purif 2022;51(7):617-29[86]	Unicentric, randomized, control	44 septic patients	22 patients: CVVH with oXiris vs 22 with AN69-ST	- hemodynamic improvement - reduce cytokine level - same outcome
Seraph 100®	Eden G et al. Crit Care 2022;26(1):181[57]	Multicentre, randomized, control	15 patients with (+) blood cultures and AKI	4 hours CRRT with Seraph	Faster resolution of blood infection
	Schmidt JJ et al. Nephrol Dial Transplant 2022;37(4):673-80[87]	Multicentre, retrospective	82 patients with Covid-19 and MOD	Seraph HA	- better SOFA - reduce mortality (50,7% vs 56,7%)
	Chitty SA et al. Crit Care Explor 2022;4(4):e0662[88]	Multicentre, randomized, control	106 patients with Covid-19	53 patients: Seraph vs standard therapy	same outcome

Abbreviations: AKI: Acute Kidney Injury, CRRT: Continuous Renal Replacement Therapy, CVVH: Continuous Veno-Venous Hemodialysis, CVVHF: Continuous Veno-Venous Hemofiltration, CVVHDF: Continuous Veno-Venous HemoDiaFiltration, eaa: endotoxin activity assay, HF: Hemofiltration, ICU: Intensive Care Unit, MOD: Multi Organ Dysfunction, MOF: Multi Organ Failure, SOFA: Sequential Organ Failure Assesment.

Table 4: Clinical efficacy of Blood Purification – Clinical studies referred to sepsis and Combination Adsorption therapies

Technique	Study	Method	Material	Intervention	Results
Coupled Plasma Filtration Adsorption - CPFA	Livigni S et al. (COMPACT-1) BMJ Open 2014;4(1):e003536[89]	Multicentre, randomized, control	192 septic patients	CPFA vs standard therapy	- same mortality (45,1% vs 47,3%) - same outcome
	Mariano F et al. Burns 2020;46(1):190-8[90]	Unicentric, retrospective	39 burn, septic patients with AKI under RRT	39 CPFA vs 87 standard RRT	reduce mortality (51,3% vs 77,1%)
	Garbero E et al. (COMPACT-2 trial) Intensive Care Med 2021;47(11):1303-11[91]	Multicentre, randomized, control	115 septic patients	CPFA vs standard therapy	- increased mortality (55,6% vs 46,2%) - increased mortality among patients without AKI treated with CPFA - earlier study termination
Plasmapheresis	Busund R et al. Intensive Care Med 2002;28(10):1434-9[92]	Multicentre, randomized, control	106 septic patients	plasmapheresis vs standard therapy	- reduce mortality (33,3% vs 53,8%)
	Knaup H et al. Crit Care 2018;22(1):285[93]	Unicentric, randomized	20 septic patients	plasmapheresis	- hemodynamic improvement - reduce cytokines and inflammatory mediators level
	Stahl K et al. Crit Care 2022;26(1):134[94]	Multicentre, randomized, control	40 septic patients	20 plasmapheresis vs 20 standard therapy	- hemodynamic improvement - reduce lactate and inflammatory mediators level
	David S et al. (EXCHANGE-2 trial) Trials 2023;24(1):277[95]	Multicentre, randomized, control, of 33 months duration	274 septic patients (with early sepsis, randomized in less than 24 hours)	plasmapheresis vs standard therapy	Primary endpoint - mortality - SOFA

Abbreviations: AKI: Acute Kidney Injury, CVVHF: Continuous Veno-Venous Hemofiltration, CVVHDF: Continuous Veno-Venous HemoDiaFiltration, HF: Hemofiltration, HVHF: High Volume Hemofiltration, MOD: Multi Organ Dysfunction, MOF: Multi Organ Failure, ICU: Intensive Care Unit, RRT: Renal Replacement Therapy, SOFA: Sequential Organ Failure Assesment.

Concerning endotoxin adsorption (Table 3), polymyxin B (Toraymyxin; Toray Industries, Tokyo, Japan) is the most commonly used adsorbing material worldwide, particularly in Japan, where it routinely is provided to patients with gram-negative bacilli (GNB)-induced severe septic conditions. In the Early Use of Polymixin-B Hemoperfusion in Abdominal Septic Shock (EUPHAS) study, patients treated with this technique demonstrated hemodynamic and respiratory improvements associated with a trend toward a better outcome [80]. However, a subsequent study performed in patients with septic shock due to peritonitis, the ABDOMIX trial, demonstrated a trend of increased mortality in the treatment group[73]. Finally, the EUPHRATES trial performed in septic shock patients with elevated Endotoxin Activity Assay (EAA) (>0,6) demonstrated a beneficial effect on different variables, including survival, only in patients with high EAA results[74]. According to the second device, approved for endotoxin adsorption, Alteco LPS Adsorber (Alteco Medical AB, Lund, Sweden), only limited results exist, from small, non-randomized trials, since the ASSET trial was terminated early due to lack of treatment benefit[76].

Accordingly, data for Cytosorb® (Cytosorbents Corporation, Monmouth Junction, NJ, USA; Afereticas.r.l., Bologna, Italy) come from small cohorts and low quality trials[77,79-81], since interventional study groups are heterogenous, and the intensity of the treatment, the initiation indications and time vary. The only multicenter controlled trial[78], included 100 septic patients randomized to have either CytoSorb adsorption for 6 hours a day, for 7 days, or just the standard sepsis treatment, failed to show any benefit of the method.

OXiris membrane (oXiris®, Baxter, Meyzieu, France) experimentally, was demonstrated to have the same endotoxin-removing capabilities as Toraymixin® and was similar to Cytosorb® regarding the clearance of mediators[96]. Currently, the clinical experience is limited and basically consists in small case series of patients with septic shock and AKI, in whom improvements of the hemodynamic conditions, decreases in the blood concentrations of endotoxin and septic mediators, and the decrease of expected mortality was observed[82-86]. However, there is no large randomized clinical trial compares the three devises, like the experimental one[96]. Furthermore, in the absence of clinical trials, the role of Seraph100 (Seraph100®, Ex Thera Medical Corp, Martinez, CA, USA) is still uncertain. Recently, Eden et al.[57] demonstrated a rapid resolution of bacteremia in a group of AKI patients undergoing RRT.

If the role of the different HA techniques in sepsis is not yet clear, even less definite is that of PEX (Table 4). Besides the time-honored indications in critically ill patients, use of PEX in septic shock patients appears somewhat overshadowed by HA. Accordingly, different investigators reported either the improvement of hemodynamic conditions or better outcomes with CPFA in several relatively small case series of septic shock patients[90]. In the first multicentre, randomized, clinical trial (COMPACT)-1[89], patients who received the highest dose of CPFA seemed to have no survival benefit, compared with controls (45,1% vs 47,3%). A post hoc analysis demonstrated that survivors had a larger volume of plasma processed (≥0.20 L/kg/session) than controls[89]. Therefore, the COMPACT-2 trial (NCT

01639664) evaluated the effect of higher doses of CPFA in septic shock. This study was stopped prematurely because CPFA was associated with an increase mortality compared with the control group (55,6% vs 46,2%), especially among patients without AKI, treated with CPFA[91].

Although the lack of clinical trials, encouraging data come emerge from large international registries, that have been increasingly used to provide real-world evidence on the effectiveness, quality, and safety of EBP techiques. Hawchar et al.[97], evaluating 1434 patients, included in CytoSorb registry, with different clinical conditions containing 936 cases of septic shock treated with Cytosorb® demonstrated that, although the primary outcome of hospital mortality was higher than that reported in other studies (59% vs. 46.5%, respectively), it was lower than expected according to the APACHE II score (66%). The COSA registry includes Covid-19 patients treated with Seraph100[87] and shows that early initiation of Seraph100 treatment (within 60 hours of ICU admission) reduces the observed mortality (34,5% vs 51,7% the predicted mortality).

Data published come from existed clinical trials (Table 2, 3 and 4), characterized by heterogeneity and low quality, are too conflicting to firmly answer if EBP could be part of standard sepsis management. Although hemodynamic and respiratory improvements, along with inflammation mediator removal, have been observed when using such techniques, a clear clinical positive effect on patient survival has not been proven yet. The most recent guidelines of the Surviving Sepsis Campaign do not advise for or against leaving centers free to adopt their own policy of BP[5]. The uncertainties concerning the use of BP in septic shock patients are caused by factors other than infections, such as:

The indicated patient: According to the existed data, the best candidates are patients with septic shock whose source of sepsis has been identified and properly treated. Due to their costs and inherent risk of iatrogenic complications, the risk/benefit ratio should be considered in every BP candidate[7,50].

The initiation time: it appears that the early initiation of BP in the hyperinflammatory phase of septic shock is associated with a better outcome. However, there is a lack of clarity regarding their possible role in chronic critically ill patients in whom anti-inflammatory mediators prevail and set the stage for infections with opportunistic germs and viral reactivation[50].

The ideal type and dose of the treatment: The type of device and the treatment is determined by the characteristics of the inflammatory mediators should be removed. It appears that a dose- and time-effect relationship exists, especially for HA techniques, although the risk of drugs elimination and nutrients should not be overlooked[7,98].

The efficacy assessment: Survival by itself does not represent a reliable marker of the efficacy of BP; consequently, other biochemical and clinical variables, should be used as proxies of efficacy. Such biomarkers can be IL-6 or cytokine levels, procalcitonin kinetics, endotoxin activity, MR-pro ADM. The serious limitation of such biomonitoring is the high cost and its daily availability. In clinical

practice, the variation of the blood lactate, white blood cells and C-reactive protein levels and the changes of vasopressors dose and SOFA score could be handheld[98].

Undesired elements or drug removal: Repeated measurements of the blood concentrations of antibiotics and other drugs and drug monitoring are warranted, especially in the initiation of a BP procedure, when the clearance capabilities are maximal, for ensuring that drugs therapeutic targets are achieved[99].

Lack of precision: BP techniques efficiently remove from the bloodstream all substances with certain chemico-physical properties, independent from their role in that timeframe. In many cases, the rule of "one size fits all" is still the rule for BP. This is far removed from precision medicine approaches that aim to apply treatment tailored to the needs of the individual patient, on the basis of precise biomarkers and molecular mechanisms, defining specific immune endotypes. Although this approach is still experimental in critically ill septic patients, has the potential to lead to the establishment of immunomodulation through EBP as a successful pillar in the treatment of sepsis in the future[50].

Conclusions

A highly complex series of events occur in sepsis, likely involving each and every system within the body, and can swing wildly during the course of the illness. Pathways are either up- or downregulated. BP is proposed as the process of removing mediators and toxins, which may cause pathogenesis. Different such techniques have been developed to address the effects of an unbalanced immune system, with varying mechanisms and target molecules, since it is the only therapy that can effectively remove PAMPs, DAMPs and/or inflammatory mediators, helping mitigate progression to multiorgan failure. Despite the somewhat conflicting results of literature, BP techniques can be a valid adjunctive measure, provided that they are applied appropriately and considering their potential scavenging effects on antibiotics and other therapeutic agents.

Conflict of Interest:

The authors declare that they have no conflict of interest.

Funding:

Baxter Hellas.

Acknowledgements:

None.

Authorship

S.E. Reviewed the literature and wrote the manuscript.

P.V. Reviewed the manuscript and approved the final version.

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