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REVIEW

New membranes for extracorporeal blood purification in septic conditions

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ABSTRACT

Severe sepsis and septic shock are still the leading cause of mortality and morbidity in the intensive care unit. The inflammatory response to infection is associated with an impressive, systemic release of pro- and anti-inflammatory mediators, which results in generalized endothelial damage, multiple organ failure and altered cellular immunological responsiveness. Over the last years, the substantial advances in the understanding of sepsis have led to the development of a large number of new approaches and technologies in the management of septic patients. Extracorporeal blood purification techniques using various membrane materials have been proposed to modulate multiple inflammatory mediators, and seem to be a potential adjuvant in the treatment of sepsis. However, the use of extracorporeal blood purification techniques during sepsis still remains controversial, thus precluding any definitive recommendations on the benefit of these methods. More data are needed to better recognize septic patients who are most likely to benefit from blood purification treatments, and clarify the optimal timing, duration, and number of applications of these techniques in the daily clinical practice. *(Minerva Anestesiol 2012;78:1265-81)*

Key words: Sepsis - Inflammation mediators - Renal replacement therapy - Membranes, artificial.

Severe sepsis and septic shock are major healthcare problems and are still the leading cause of mortality and morbidity in the intensive care unit (ICU).[1, 2] Over the last years, the substantial advances in the understanding of sepsis and inflammatory response have led to the development of a large number of new approaches and technologies in the management of septic patients. Extracorporeal treatments have been designed to obtain a non-selective removal of both pro- and anti-inflammatory mediators involved in the sepsis. Blood purification may be obtained by means of different mechanisms including diffusion, convection and adsorption, or a combination of these modalities. In turn, extracorporeal depurative techniques that use these mechanisms include hemodialysis, hemofiltration, hemoadsorption, plasma filtration or the simultaneous application of these techniques.

This overview will report on the latest advances in blood purification for septic conditions, focusing on the new membranes used for extracorporeal immunomodulation.

Rationale for blood purification in septic conditions

During sepsis, several cell-associated and soluble molecules including cytokines, nitric oxide, reactive oxygen species, and lysosomal enzymes are released into the circulation by the activation of leukocytes, macrophages, and endothelial cells. These molecules are thought to play a central role in the pathophysiology of septic shock

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and multiple organ failure (MOF).[3, 4] Blood purification as a treatment for severe sepsis or septic shock finds its rationale in containing the profuse systemic expression of pro- and anti-inflammatory substances during septic conditions. Several therapies proposed to block the synthesis or toxicity of a particular component of the cytokine storm during systemic inflammatory response syndrome (SIRS) have failed to show clear benefits.[5] This has led to the idea of performing a non-specific elimination of circulating cytokines and other inflammatory mediators by using continuous renal replacement therapies (CRRT).

CRRT modalities to treat sepsis

In recent years, various extracorporeal removal mechanisms have been developed. Continuous arterio-venous hemofiltration (CAVHF) and continuous veno-venous hemofiltration (CVVHF) use convection (fluid movement across a semi-permeable membrane with solute transport following a pressure gradient) as the main clearance mechanism, whereas continuous arterio-venous hemodialysis (CAVHD) and continuous veno-venous hemodialysis (CVVHD) also use diffusion (solute transport across a semi-permeable membrane following a concentration gradient) to remove solutes. Continuous venovenous hemodiafiltration (CVVHDF) combines the clearance mechanisms of both CVVHF and CVVHD. High-volume hemofiltration (HVHF) allows to increase plasma water exchanges compared with conventional hemofiltration used for acute kidney injury (25 to 35 mL/kg/h),[6, 7] thus enhancing the clearance of inflammatory mediators from the plasma. HVHF has been defined as continuous high-volume treatment of 70 mL/kg/h 24 hours a day,[8] whereas intermittent HVHF also known as "pulse" HVHF (PHVHF) is the brief, very-high-volume treatment at 100 to 120 mL/kg/h for a short period of 4 to 8 hours, followed by conventional CVVHF.[6] According to some experts, continuous high-volume treatment at more than 35 mL/kg per hour may be already considered HVHF.[9] The extent of convective clearance is determined by a series of parameters including the cut-off value of the membrane, the molecular weight, physic-chemical characteristics and structure of the solute. Molecules in the middle molecular weight range, such as many inflammatory mediators (Figure 1), are more efficiently removed by convection than by diffusion.[10] The currently available membranes used for hemofiltration are mainly synthetic: polysulfone (PS), polyamide (PA), polyacrylonitrile (PAN), polymethylmethacrylate (PMMA) and a copolymer of acrylonitrile and sodium methallylsulphonate (AN69).

Even though convection is more effective than diffusion in eliminating middle-molecular-weight substances such those implicated in sepsis and MOF, there is no strong evidence to suggest which is the most effective clearance treatment in septic conditions. In a study of 13 patients with systemic inflammatory response syndrome and acute renal failure receiving CRRT using AN69 hemofilters, Kellum *et al.*[11] showed that, although convective clearance (CVVHF) was better than diffusion (CVVHD) in reducing plasma TNF-a levels, the type of transport mechanism did not influence plasma levels of IL-6, IL-10, soluble L-selectin, or endotoxin. In addition, in this study differences in clearance for IL-6 between CVVHF and CVVHD did not translate into significant differences in cytokine plasma concentrations. Cole *et al.*[12] randomized 24 ICU septic patients to receive 48 hours of isovolemic CVVHF at 2 L/h of fluid exchange or no hemofiltration to study the effect of early CVVHF on plasma levels of several humoral mediators of inflammation (complement fractions C3a and C5a, interleukins 6, 8, and 10, and TNF-α) and subsequent organ dysfunction. In this study, CVVHF did not reduce circulating concentrations of inflammatory mediators or the organ dysfunction that followed severe sepsis, as well as it did not improve oxygenation or reduce the duration of vasopressor support and mechanical ventilation. Again, in a pig model of endotoxin-induced sepsis, Toft *et al.*[13] investigated the effect of a 24 hours CVVHF treatment at 35 mL/kg/h of ultrafiltration rate on the cell-mediated immunity, showing that CVVHF could decrease the oxidative burst activity of neutrophils after 2 hours of treatment, but it was unable to decrease the activated cell-mediated immunity or cytokine levels in the long term. In a study carried out by De Vriese *et al.*[14] on cy-

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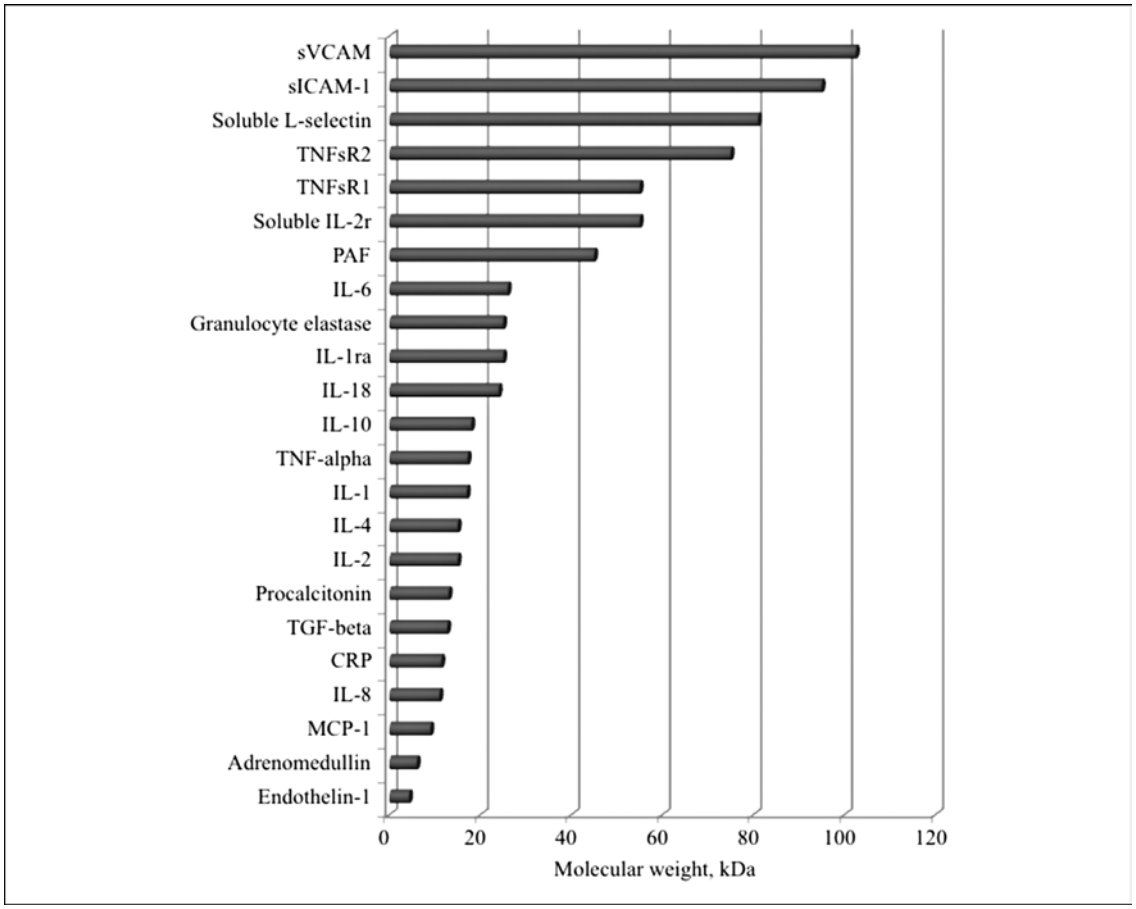

Figure 1.—Inflammatory mediators and their molecular weight. CRP: C-reactive protein; IL: interleukin; IL-1ra: interleukin-1 receptor antagonist; IL-2R: interleukin-2 receptor; MCP: monocyte chemoattractant protein-1; PAF: platelet-activating factor; sICAM: soluble intercellular adhesion molecule-1; sVCAM: soluble vascular cell adhesion molecule-1; TGF: transforming growth factor; TNF-sR: tumour necrosis factor soluble receptor.

tokine removal mechanisms in 15 patients with septic shock and acute renal failure undergoing CVVHF with an AN69 membrane, adsorption appeared to be the main mode of clearance, being most noticeable soon after change of hemofilter and decreasing gradually thereafter, indicating rapid saturation of the membrane. Additionally, a blood flow rate of 200 mL/min was associated with a 75% increase of the ultrafiltration rate and a significantly higher cytokine removal than at a blood flow rate of 100 mL/min. The investigators concluded that optimal cytokine clearance could be achieved with a combination of a high ultrafiltration rate and frequent membrane changes.

In addition to diffusion and convection, adsorption has been found to be an essential clearance mechanism.[15] Molecule adsorption onto membranes is mainly obtained by hydrophobic interactions, by electrostatic interactions between zones with different polarities, and by ionic bindings between dissociated chemical groups with opposite charges. Adsorption allows to clear substances with a molecular weight higher than the membrane cutoff, thus allowing the removal of molecules that cannot be removed by means of ultrafiltration. Of note, most hemofiltration membranes also have some adsorptive properties, thus improving effectiveness of blood purification treatments. Except for AN69, membranes used for the treatment of sepsis have been mainly evaluated in Japan.

Table I summarizes the main studies on the use of membrane materials in sepsis.[11, 12, 14-47]

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TABLE I.—*Summary of the main studies on the use of membrane materials in sepsis.*

	First author	Ref.	Year	Population	Design	Sample size
AN69	Bellomo	16	1993	Septic, ARF pts	Prospective, controlled	18
	Bellomo	17	1995	Septic, ARF, MOF pts	Prospective, controlled	10
	Sander	18	1997	SIRS pts	RCT	28
	Kellum	11	1998	SIRS, ARF pts	Randomized, crossover	13
	De Vriese	14	1999	Septic, ARF pts	Prospective	15
	Cole	19	2001	Septic, MOF pts	Randomized, crossover	11
	Cole	12	2002	Septic pts	RCT	24
	Klouche	20	2002	Septic, ARF pts	Prospective	11
	Rogiers	21	2003	Endotoxemic dogs (mean, 30.2 kg)	Prospective	15
	Jiang	22	2005	Acute pancreatitis pts	Prospective, randomized	37
	Rimmelé	23	2009	Septic pigs (mean, 35kg)	*In vivo* prospective, randomized + *in vitro*	20
CTR	Taniguchi	24	2006	Endotoxemic rats (mean, 380g)	*In vivo* prospective + *in vitro*	42
	Taniguchi	25	2007	Endotoxemic rats (mean, 382g)	Prospective, randomized	48
CytosorbTM	Kellum	26	2004	Endotoxemic rats (mean, 536g)	Randomized, controlled, experiment, *in vivo* + *ex vivo*	66
	Peng	27	2008	CPL rats (400-600g)	Randomized, controlled, experiment	33
	Peng	28	2012	CPL rats (450-550g)	Randomized, controlled, experiment	90
HCO	Morgera	29	2003	Septic, ARF pts	Prospective, randomized	28
	Morgera	30	2003	Septic, ARF pts	Prospective, randomized	28
	Morgera	31	2003	Septic, MOF pts	Prospective	16
PMMA	Nakada	32	2008	Septic pts	Cohort	43
	Nishida	33	2011	Septic pts	Prospective	55

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Intervention	Q_B (mL/min)	UFR	Mediators removed	Main results/clinical outcomes
CVVHDF	150	NR	TNF-α, IL-1 β (found in UF)	See previous column
CVVHDF	150	NR	IL-6, IL-8 (found in UF)	See previous column
CVVHF vs CT	150	1 L/h	IL-6 (found in UF); TNF-α not found in UF; both cytokines not decreased in plasma	See previous column
CVVHF vs CVVHD	150-200	2 L/h	IL-6 (found in UF), TNF-α (decreased in plasma only with CVVHF)	See previous column
CVVHF	100-200	1.5-2.7 L/h	TNF-α, IL-1 β, IL-6, IL-1ra, sTNFR-I/II (IL-10 not found in UF)	See previous column
8h-CVVHF vs 8h-HVHF	200 vs 300	1 L/h vs 6 L/h	C3a, C5a, IL-10, temporary reduction in both group	HVHF decreased vasopressors requirements
48h-CVVHF vs CT	200	2 L/h	No reduction in plasma levels of C3a, C5a, IL-6, IL-8, IL-10, TNFα	No improvement in hemodynamics/organ dysfunction
CVVHF	240	1.65 L/h	IL-6 (plasma IL-6 and TNF-α not affected)	Improved hemodynamics
AN69 vs PS-CVVHF vs no treatment	NR	3 L/h	TNF-α (very low levels in UF with both membranes)	Improved hemodynamics, more with AN69
Low-volume CVVHF vs high-volume CVVHF	250-300	1 vs 4 L/h	TNF-α, IL-6, IL-1b (more with high-volume CVVHF)	Both modalities improved hemodynamics and survival
6h-HVHF using AN69 vs treated polyacrylonitrile membrane with enhanced adsorption	150	50 mL/kg/h	With treated membrane: in vitro, greater adsorption for endotoxin, TNF-α, IL-1β, IL-6, IL-1ra; in vivo, lower endotoxin after 1h, and lower IL-1β after 6h	Improved hemodynamics with treated membrane
No hemoadsorption vs hemoadsorption without CTR or with CTR. In vitro, human/bovine serum and human blood	1.5	NA	TNF-α, IL-1β, IL-6, IL-10	Improved survival
Hemoadsorption without CTR vs 3 different doses of CTR	1.5	NA	TNF-α, IL-6 (dose-dependently decreased)	CTR dose-dependently decreased mortality
Hemoadsorption vs sham	0.2–2.2	NA	TNF, IL-6, IL-10, NF-kB, no effect on endotoxin	Improved survival
Hemoadsorption vs sham	1	NA	TNF, IL-1β, IL-6, IL-10	Improved hemodynamics and survival
4h-low-intensity hemoadsorption (with no acute change in cytokine levels) vs sham vs control	0.8-1	NA	48h after treatment, TNF, IL-1β, IL-6, IL-10	Improved 1-week survival and organ function
High-flux polyamide membrane CVVHF; nominal cut-off point, 60 vs 30 kDa	150	1 L/h	NR	Restoration of peripheral blood mononuclear cell proliferation
High-flux polyamide membrane CVVHF; nominal cut-off point, 60 (intermittent) vs 30 kDa	150	1 L/h	NR	Decreased phagocytosis rate
High-flux polyamide membrane (nominal cut-off point, 60 kDa) intermittent CVVHF	150	1 L/h	IL-6, poor filtration capacity for TNF-α	See previous column
CVVHDF	80-120	0.3-0.5 L/h	IL-6	Improved survival
Sustained high-efficiency daily diafiltration	150	1.5 L/h	IL-6	Improved hemodynamics

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Table I.—*Continues from previous page.*

	First author	Ref.	Year	Population	Design	Sample size
Polymyxin B	Tani	34	2001	Septic, ARF, MOF pts	Prospective	88
	Suzuki	35	2002	Septic, ARF pts	Prospective, randomized	48
	Nakamura	36	2003	Septic (MRSA) pts	Prospective	60
	Vincent	37	2005	Septic (abdominal) pts	Pilot-RCT	36
	Kushi	38	2005	Septic, ALI/ARDS pts	Prospective	36
	Cruz	39	2009	Septic (abdominal) pts	RCT	64
PS	Heering	40	1997	Septic, ARF pts	Prospective, controlled, subgroup	33
	Rogiers	41	1999	Endotoxemic dogs (mean, 28.7kg)	Prospective	30
	Honoré	42	2000	Septic pts	Prospective	20
	Cornejo	43	2006	Septic pts	Prospective	20
	Piccinni	44	2006	Septic pts	Retrospective	80
	Boussekey	45	2008	Septic, ARF pts	Prospective, randomized	20
	Zhu	46	2009	Acute pancreatitis pts	Retrospective	63
	Zhu	47	2011	Acute pancreatitis pts	Prospective	75

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; ARF: acute renal failure; CAVHF: continous arteriovenous hemofiltration; CLP: cecal ligation and puncture; CT: conventional treatment; CVVH: continuous venovenous hemofiltration; CVVHD: continuous venovenous hemodialysis; CVVHDF: continous venovenous hemodiafiltration; HCO: high-cutoff membranes; HVHF: high volume hemofiltration; IL: interleukin; MOF: multiple organ failure; MRSA: methicillin-resistant Staphylococcus aureus; NA: not applicable; NE: neutrophil elastase; NR: not reported; PAI-1: plasminogen activator inhibitor-1; PMMA: polymethylmethacrylate; PS: polysulfone; Q_B: blood flow rate; RCT: randomized controlled trial; SIRS: systemic inflammatory response syndrome; TNF: tumor necrosis factor; UF: ultrafiltration; UFR: ultrafiltration rate.

The studies reported in the table were selected according to their scientific relevance in terms of study design, sample size, and provision of information about clearance properties of the membrane materials studied.

Hypotheses

Over the past years, various theories on the mechanism of blood purification in attenuating the inflammatory response during infec-

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Intervention	Q_B (mL/min)	UFR	Mediators removed	Main results/clinical outcomes
Polymyxin B	80-100	NA	In survivors, decreased endotoxin, TNF-α, IL-6, IL-10, and PAI-1 activities after treatment	See previous column
CVVHDF + Polymyxin B vs CVVHDF	100	NA	Decreased endotoxin and IL-6 after combined treatment	Improved survival with combined treatment
Polymyxin B vs teicoplanin vs combined treatment vs CT	80-100	NA	Decreased endotoxin after either Polymixin B or combined treatment	Improved survival with combined treatment
Polymyxin B vs CT	80-120	NA	No differences in the change of endotoxin or IL-6 levels between groups	Improved hemodynamics
Polymyxin B	80-100	NA	Decreased PAI-1, NE and IL-8 after treatment	Oxygenation improvement related to the decreases in NE and IL-6
Polymyxin B vs CT	NR	NA	NR	Improved hemodynamics and survival
CVVHF	150-200	1 L/h	TNF-α, TNF-α-RII, IL-1β, IL-1RA, IL-6, IL-6R, IL-8 (all found in UF, not decreased in plasma)	Improved hemodynamics
CVVHF, reinfusion of UF from endotoxemic or non endotoxemic dogs	NR	3-6 L/h	TNF-α (very low levels in UF)	Improved hemodynamics
4h-HVHF + 1 L/h AN69 CVVHF	450	35 L / 4h	NR	HVHF may improve hemodynamics and survival
12h-HVHF	200	60-120 mL/kg/h	NR	Improved hemodynamics; survival higher than expected
20 mL/kg/h CVVHF vs 6h/day 45 mL/kg/h CVVHF + 20 mL/kg/h CVVHF	150 vs 250	20 vs 45 mL/kg/h	NR	Pulse HVHF improved hemodynamics and survival
CVVHF, 65 vs 35 mL/kg/h	200-300 vs 180-250	65 vs 35 mL/kg/h	NR	HVHF improved hemodynamics, not survival
CT vs CVVHF	250-300	60-80 mL/kg/h	NR	HVHF improved survival, not hemodynamics
CT vs CVVHF	250-300	75 mL/kg/h	NR	HVHF improved survival, not hemodynamics

tion have been developed. According to the "peak concentration hypothesis" described by Ronco *et al.*,[48] continuous hemofiltration may provide a non-selective removal of inflammatory mediators from the blood compartment by cutting their sequentially appearing peaks in the pro-inflammatory phase of sepsis. In this setting, the optimal timing for applying a blood purification treatment would be in the early phase of sepsis. Honoré and Matson [49]

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suggested that circulating inflammatory mediators rapidly traffic between circulation and tissues, with cytokines of pathologic significance being active at the tissue level. Consequently, depletion of plasma pools of inflammatory mediators through extracorporeal removal techniques may result in kinetic reduction of inflammatory mediator concentrations in the various tissues. With the "mediator delivery hypothesis" introduced by Di Carlo and Alexander,[50] high-volume hemofiltration may exert its effect by reinvigorating lymphatic flow and function, due to the high amounts of crystalloid solution infused to restore intravascular volume lost through production of ultrafiltrate. Partial redistribution into interstitium and lymph mobilizes inflammatory mediators together with other proteins, cellular byproducts, excessive ground matrix, fragments of apoptotic cells and free DNA, that are then metabolized, scavenged or cleared at multiple sites. Finally, Peng *et al*.[51] suggested that blood purification, apart from removing a wide array of inflammatory mediators, may restore immune function through improving antigen-presenting capability, adjusting leukocyte recruitment, oxidative burst and phagocytosis, and improving leukocyte responsiveness. This theory is supported by the observations of Ono *et al*.[52] who showed that some surface antigens, HLA-DR on monocytes and CD16 on granulocytes, are extremely decreased in septic patients after polymyxin B hemoadsorption, and that polymyxin treatment is effective for beneficially increasing the surface antigen expression on leukocytes. On the basis of these findings, hemoadsorption has been deemed as a new strategy for helping patients recover from immunoparalysis in septic conditions.

Significance of removing inflammatory mediators in sepsis

Cytokine extraction through extracorporeal blood purification techniques is assumed to attenuate the progression of multiple organ dysfunction in patients with sepsis. Over the last years, this concept has represented a driving force in the development of new filtration membrane designs in order to specifically augment the clearance of inflammatory cytokines in septic conditions. However, the role of acute removal of inflammatory mediators by means of blood purification methods during sepsis still remains unclear.

In 11 septic ICU patients with acute renal failure, Klouche *et al*.[20] showed that CVVHF using AN69 hemofilters at a blood flow rate of 240 mL/min and mean ultrafiltration rate of 1.65 L/h for a 24-hour period could improve mean arterial pressure and systemic vascular resistance, though plasma levels of interleukin (IL)-6 or tumor necrosis factor (TNF)-α were unaffected throughout the study. In a recent experimental study in septic rats undergoing a low dose of extracorporeal blood purification treatment using Cytosorb™ that did not result in any acute changes in plasma concentrations of common sepsis mediators (TNF-α, IL-1β, IL-6, and IL-10), Peng *et al*.[28] observed that the overall survival to 7 days was significantly higher in those rats that received extracorporeal blood purification compared to those that received a sham procedure of extracorporeal circulation without blood purifying sorbent. In this study, plasma levels of cytokines as well as creatinine and alanine aminotransferase were significantly lower 72 hours following extracorporeal blood purification compared to the sham-treated group. Based on these findings, the authors suggested that the effects of blood purification on clinical outcomes in sepsis could not be related exclusively to an acute modulation of plasma cytokine levels.

Also the role of inflammatory mediator-directed therapies in sepsis does remain unclear. In the early 1990s, a study undertaken by Ziegler *et al*.[53] in 200 patients with sepsis and gram-negative bacteremia randomized to receive HA-1A - a human monoclonal antibody against endotoxin - or placebo, showed that HA-1A treatment was associated with a significantly higher rate of survival and more rapid resolution of the major complications of sepsis than was placebo. However, in spite of the initial excitement resulting from these promising results, subsequent studies on immunomodulating approaches in sepsis were disappointing.[54, 55]

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Hemoadsorption

Hemoadsorption or hemoperfusion was introduced by Yatzidis in early 1960s.[56] According to this technique a sorbent is placed in direct contact with blood in an extracorporeal circuit to remove toxic substances. Hemoadsorption is dependent on membrane material and filtration operating parameters. Non-specific adsorbents, typically charcoal and resins, attract solutes through a variety of forces, including hydrophobic interactions, ionic attraction, hydrogen bonding, and electrostatic interactions between zones with different polarities. Sorbents have been applied in different treatment modalities, including hemoadsorption and hemoadsorption coupled with hemodialysis or plasma filtration. The choice of modality is based on different factors including the properties of the sorbent, the technique used, and the clinical purposes. The porous structure of an adsorbent and the kinetic adsorption rate can be manipulated, thus improving the size specificity for particular solutes. In this way, solute molecules are sieved according to their size by their ability to penetrate the porous system of the sorbent. The addition of a hemocompatible coating to the newer resin adsorbents has improved the poor biocompatibility of the first materials which often caused thrombocytopenia and neutropenia. Engineering a large population of pores and modificating the surface polarity have significantly increased the affinity of resin sorbents for substances of various molecular weight, including uremic toxins, bilirubin, and also inflammatory mediators. This encouraged research on various applications of CRRT methods for treatment of sepsis.

The following sections will describe the various membrane materials recently used to perform hemoadsorption in septic conditions.

CytoSorb™

CytoSorb™ cartridge (RenalTech International, New York, NY, USA) contains 10 grams of polystyrene divinyl benzene copolymer beads with a biocompatible polyvinylpyrrolidone coating. In a randomized controlled laboratory experiment on 66 rats, CytoSorb™ provided a dramatic and sustained decrease in the three cytokines measured (TNF, IL-6, and IL-10), even though it did not eliminate endotoxin.[26] Also, CytoSorb™ hemoadsorption reduced nuclear factor (NF)-kB DNA binding that is involved in the gene expression of several inflammatory cytokines, including TNF and IL-6.[26] In another laboratory experiment on 33 rats rendered septic by cecal ligation and puncture randomized to receive either hemoadsorption using Cytosorb™ beads or sham treatment using an arterial-venous circuit for 3 hours, hemoadsorption could remove circulating plasma cytokine concentration (TNF, IL-1, IL-6, IL-10), improving mean arterial pressure and overall survival rate at 12 hours after randomization.[27]

CTR adsorbent

CTR (Kaneda Corporation, Osaka, Japan) is a resin composed of porous cellulose beads to which a hydrophobic organic compound with a hexadecyl alkyl chain has been covalently bound to the surface as a ligand. Lixelle, the predecessor of CTR, was originally used as a β2-microglobulin adsorption column for the treatment of patients with dialysis-related amyloidosis and, later on, it was shown to remove various inflammatory cytokines as well.[57] In a laboratory investigation, Taniguchi *et al.*[24] found that CTR effectively adsorbed small- to middle-sized proteins such as enterotoxins and cytokines in vitro. Moreover, *in vivo*, extracorporeal treatment with CTR column that was carried out for 2 hours after endotoxin injection drastically reduced the high mortality rate and inhibited inflammatory responses in endotoxin-induced shock in rats.[24] Subsequently, the same investigators reported that CTR treatment dose-dependently decreased the mortality rate and inhibited inflammatory responses in a rat model for endotoxic shock, suggesting that CTR treatment may be effective against sepsis and septic shock.[25]

Polymyxin B hemoperfusion

The PMX cartridge (Toraymyxin, Toray Industries, Tokyo, Japan) (Figure 2) is an extracorporeal hemoperfusion device that uses

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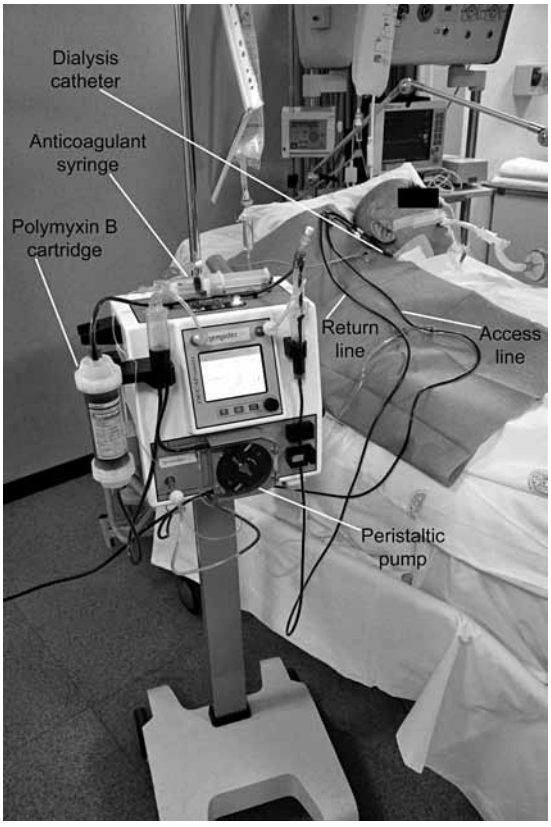

Figure 2.—Polymyxin B hemoperfusion in a critically ill patient.

polymyxin-B chemically immobilized to polystyrene derived fibers that are packed in the cartridge. Polymyxin-B perturbs cell membrane permeability of gram-negative bacteria after binding to endotoxin, a component of the outer bacterial membrane that plays an important role in causing initial cytokines release in sepsis. Polymyxin B was initially used as a conventional antibiotic for its endotoxin-binding properties, but its significant nephrotoxic and neurotoxic effects have discouraged its intravenous administration.

Several studies on animal models of endotoxic shock reported that hemoperfusion over immobilized polymyxin-B could remove endotoxin from the circulation.[58, 59] Subsequently, a Japanese clinical study on 37 endotoxemic patients with multiple organ failure who underwent direct hemoperfusion for 2 hours using a PMX column showed a decrease in the plasma endotoxin concentration associated with an improvement of cardiovascular parameters.[60]

In a multicenter European study on 36 postsurgical ICU patients with severe sepsis or septic shock secondary to intra-abdominal infection who were randomized to receive a single session of polymyxin B treatment or standard therapy, those patients treated with polymyxin B hemoperfusion demonstrated significant improvement in cardiac and renal dysfunction, even though no significant difference in mortality between the two groups was observed.[36] Interestingly, this pilot study failed to show significant differences in the change in endotoxin levels after hemoperfusion sessions between the two groups.

In a systematic review,[61] direct hemoperfusion with the polymyxin B device appeared to have favorable effects on mean arterial pressure, vasopressor use, gas exchange, and mortality. However, the conclusions were limited by the suboptimal methodological quality of the available studies and heterogeneous study populations.

A prospective, multicenter, randomized controlled trial (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]) conducted in 10 Italian ICUs randomized 64 patients with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection to either conventional therapy or conventional therapy plus two sessions of polymyxin B hemoperfusion.[39] This study was prematurely stopped because it was judged to be unethical to deprive a potentially beneficial therapy to a group of patients that carry high mortality. Polymyxin B hemoperfusion added to conventional therapy was effective in improving 28-day and hospital survival, blood pressure, vasopressor requirement, and degree of organ failure, as indicated by the delta SOFA (Sequential Organ Failure Assessment) score. Also, observed adverse effects associated with polymyxin B hemoperfusion were minimal and similar to those that would be encountered for any extracorporeal therapy in the ICU. While these findings were in agreement with those of other studies in diverse populations, the EUPHAS study possessed some important limitations, including a slow accrual rate, enrolling only 64 patients between 2004 and 2007, inability to blind treating physicians,

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and a premature study termination based on the results of the scheduled interim analysis. These limitations resulted in a modest patient sample size, which may have overestimated the true magnitude of the clinical effect. Moreover, in their editorial, Kellum and Uchino [62] stated that the EUPHAS trial was not designed as a definitive trial with a patient-centered end point, but instead was to determine whether polymyxin B hemoperfusion would result in improved mean arterial pressure and less requirement for vasopressors in patients with septic shock due to presumed abdominal infections. In another Italian study [63] on 12 ICU patients with severe sepsis or septic shock due to intra-abdominal cavity infection, the application of two cycles of polymyxin B hemoperfusion in addition to standard therapy markedly reduced plasma levels of cytokines, such as IL-6, IL-10 and TNFα, and improved cardiovascular and respiratory dysfunctions.

Certainly, polymyxin B cannot be expected to be a definitive cure for sepsis, but it could potentially serve as an adjunct to conventional management of septic conditions. Further studies are needed to investigate the effect of polymyxin B hemoperfusion in the different ICU patient populations with sepsis, as well as provide definitive answers on the effects of dose, duration, and number of required polymyxin B treatments. In this context, the endotoxin activity assay may be a useful tool to either identify patients eligible for polymyxin B treatment or help in therapeutic dosing.[64]

There are ongoing clinical trials on the use of polymyxin B-hemoperfusion in septic patients. A group of Italian investigators and users of polymyxin B hemoperfusion have recently designed a prospective, multicentered, open, collaborative data collection study, entitled EUPHAS 2 which aims to collect a large database regarding polymyxin B-hemoperfusion treatments in order to better evaluate the efficacy and biological significance of endotoxin removal in clinical practice.[65] Additionally, the EUPHAS 2 study aims to verify the reproducibility of the data currently available in the literature, evaluate the patient population chosen for treatment, and identify subpopulations of patients who may benefit from this treatment more than others.

Another ongoing trial, the EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock), was designed to test the safety and efficacy of polymyxin B hemoperfusion in a randomized controlled fashion, again to address methodological criticisms of previous clinical trials, including the absence of blinding, the use of surrogate outcomes and lack of longer term mortality outcomes, the variability in the number of treatment cartridges used, the selection of subjects based on likelihood of endotoxin presence without endotoxin measurement, and small sample sizes in mainly single-center trials.[66]

Finally, an ongoing randomized, comparative, open, multicenter study aims to investigate whether two sessions of polymyxin B hemoperfusion performed after the surgery of a peritonitis due to hollow organ perforation can improve survival in patients with septic shock.[67]

Coupled plasma filtration adsorption

Coupled plasma filtration adsorption (CPFA) is a hybrid technique in which CRRT and another purification method are combined in series. With CPFA plasma is first separated from blood by means of a plasma filter and then, the plasma is passed through a sorbent for inflammatory mediator adsorption and returns to the blood. Subsequently, the blood circulates through a second blood filter using hemofiltration, hemodialysis, or hemodiafiltration for renal support. The resin used for CPFA has high homogeneity, good pressure-flow performance, and excellent mechanical and chemical stability, and shows effective adsorptive properties for inflammatory mediators, as well as low levels of extractable toxins/metals, and good pressure-flow performance. Applying hemoadsorption to plasma, rather than to blood, can limit coagulation changes, platelet aggregation and hemolysis. Also, it allows the use of a low flow rate, thus prolonging the time of contact between the inflammatory mediators and the sorbent, with a consequent enhancement of adsorption. The development of this hybrid technique was pro-

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ceeded by a number of publications on the use of therapeutic plasma exchange in rescue therapies. In this context, the first report dates back to the early 1990s, when Van Deuren *et al.*[68] showed that plasma exchange could improve mortality in a case series of 13 patients with meningococcal sepsis.

Few data are available in the current literature regarding CPFA. In a randomized, pilot, crossover clinical trial on 10 septic ICU patients, CPFA was more effective than CVVHDF in restoring immune cell homeostasis and improving hemodynamics.[69] In an *ex vivo* model, a closed hemofiltration/adsorption circuit, obtained with a combination of a large-pore hemofilter and charcoal cartridge, efficiently reduced serum levels of a wide set of cytokines.[70] In 12 ICU septic shock patients with or without concomitant acute renal failure, CPFA was demonstrated to be feasible and safe, exerting a remarkable improvement in the hemodynamics, pulmonary function, and outcome.[71] A more recent pilot study on septic shock patients with acute kidney injury already undergoing CRRT, failed to show any difference in hemodynamic effects between PHVHF and CPFA.[72] Another pilot study on 7 patients with severe infection and MOF who received both 10 hours of CPFA and 10 hours of HVHF with a 12-hour interval and in random order, found CPFA superior to HVHF in increasing the ratios of anti-inflammatory to proinflammatory mediators, improving antigen presentation ability and restoring leukocyte responsiveness.[73] In particular, in this study both HLA-DR expression by blood monocytes and TNF-α production increased with CPFA, but did not change with HVHF. Additionally, the suppression of TNF-α production of normal human monocytes incubated *in vitro* with the patients' plasma diminished after CPFA, but did not change after HVHF.[73] These findings suggested the potential role for CPFA in the treatment of MOF.

Extracorporeal immunoadsorption by Prosorba® column is referred to as protein immunoadsorption treatment using a highly purified protein A (isolated from *S. aureus*) which is bonded to a silica matrix. With this technique, circulating immune complexes and immunoglobulin G bind to the protein A and are thus selectively removed from plasma. The possible role of this approach in sepsis has not been clarified.

Hemofiltration membranes with enhanced adsorption properties

Manipulation of ultrafiltrate dose and membrane composition or structure has yielded promising findings in removing inflammatory mediators. In addition, associating standard hemofiltration with adsorption seems to be a quite interesting adjuvant strategy for blood purification. Rimmelé *et al.*[23] randomized 20 septic pigs to receive 6-h HVHF sessions with either a standard hemofiltration membrane or a treated membrane with *in vitro* enhanced adsorption properties with a particular surface treatment added to strongly adsorb high-molecular-weight molecules, such as endotoxins and cytokines. This treated membrane was a polyacrylonitrile hemofiltration membrane prototype with a modification of the surface polarity obtained by the addition of a polycation on the membrane surface. HVHF with this membrane could improve hemodynamics compared to the standard hemofiltration membrane.

The Oxiris® set, a novel modified AN69 membrane, is surface-treated with a permanent heparin grafting to improve hemocompatibility. For its capability in the adsorption of inflammatory mediators, such as endotoxins, anaphylatoxins and cytokines, this membrane might have a role in the treatment of sepsis.

Blood purification using membrane materials with enhanced adsorption properties is a potentially promising approach in treating septic conditions, but more pre-clinical and clinical research is still warranted.

High cut-off membranes

Increasing membrane pore size allows to widen the spectrum of substances sieved by the blood purification technique. Membranes with a high-molecular-weight cutoff (HCO, high-cutoff membranes) have a nominal cut-off of 60-150 kD which equals 40-100 kD in human

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blood. Preliminary clinical studies showed that HCO membranes may decrease plasma cytokine levels and the need for vasopressor therapy.[74] In a study on 28 septic patients, hemofiltration with high permeability membranes restored peripheral blood mononuclear cell proliferation, probably by eliminating immunomodulatory mediators.[75] In another study on 30 patients with sepsis-induced acute renal failure, HCO hemofiltration was shown to be superior to conventional hemofiltration in the cytokine removal rate, exerting a beneficial effect on the need for vasoactive agents.[76]

The preliminary results of the High Cut-Off Sepsis study (HICOSS) [77] on patients with septic shock and acute kidney injury who were randomized to receive CVVHD with either a conventional membrane or an HCO membrane showed no difference in the two treatments groups as regard to 28-day mortality. In addition, no difference was observed in vasopressor need, duration of mechanical ventilation, or length of stay in the ICU. Interestingly in this study, no difference in albumin serum concentrations was found between the two groups.

Indeed, conflicting results are reported on the risk for reduction in serum albumin concentrations after treatment with HCO membranes.[78, 79] Hence, further data are needed before definitive recommendations on the use HCO hemofiltration in septic patients can be made.

Blood purification in sepsis: non-positive results and adverse events of the technique

Several studies on blood purification methods in the treatment of septic conditions have not shown positive results. Furthermore, a large variety of harmful effects potentially associated with these methods have been reported.

A number of trials showing no or even negative effects of extracorporeal techniques in the treatment of sepsis are available in the literature. In a group of 280 patients with sepsis and acute kidney injury randomized to be given CRRT either by high-volume hemofiltration (50 mL/kg/h) or extra high-volume hemofiltration (85 mL/kg/h), increasing the intensity of CRRT had no effect on survival at 28 and 90 days.[80] In a trial on 1124 critically ill patients with acute kidney injury (septic patients, N.=579) randomized to receive intensive renal-replacement therapy (intermittent hemodialysis and sustained low-efficiency dialysis six times per week and CVVHDF at 35 mL/kg/h) or less intensive renal-replacement therapy (the corresponding treatments provided thrice weekly and at 20 mL/kg/h), the intensive renal support strategy did not decrease mortality, accelerate recovery of kidney function, or alter the rate of non-renal organ failure as compared with the less-intensive regimen.[81] A multicenter, controlled trial randomized 1508 critically ill patients with acute kidney injury (septic patients, N.=723) to undergo CRRT in the form of CVVHDF with an effluent flow of either 40 mL/kg/h for the higher intensity group or 25 mL/kg/h for the lower intensity group, showing that treatment with higher intensity CRRT did not reduce mortality at 90 days.[82] Additionally, hypophosphatemia was more common when CRRT was performed with higher effluent flows. Worse outcomes and prolongation of organ support have also been described with the use of CRRT techniques. A multicenter randomized trial in 80 septic patients, CVVHF with an ultrafiltration rate of 25 mL/kg/h failed to limit or improve organ failure, prolonging the requirement for organ support and even showing a trend to higher mortality at 14 days compared with a conventionally managed control group, irrespective of the presence of renal failure.[83] In addition, this study could not detect any modifications in cytokine plasma levels. A meta-analysis of 12 trials on patients with acute kidney injury treated with renal replacement therapy modalities including CRRT, intermittent hemodialysis, sustained low-efficiency dialysis, and a combination of all three found no effect of high-dose renal replacement therapy on mortality or dialysis dependence among survivors.[84] According to this analysis, the effect on mortality was similar in patients with sepsis *versus* without sepsis, and in patients treated exclusively with CRRT versus other modalities alone or in combination. The authors concluded that high-dose renal replacement therapy in acute kidney injury does not improve patient survival or recovery of renal function overall or in the subgroup of patients with sepsis.

Renal replacement treatments are not exempt

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from complications. A wide array of detrimental effects associated with these treatments have been described. In two large studies on the intensity of CRRT in critically ill patients with acute kidney injury, adverse events potentially related to blood purification techniques included catheter-related complications (insertion-related and late complications), arterial hypotension requiring vasopressor therapy, hypophosphatemia, hypokalemia, arrhythmias, disequilibrium syndrome, cerebral edema, bleeding, cardiac arrest, heparin-induced thrombocytopenia, hypoxiemia, cardiogenic shock, and a too rapid correction of hyponatremia.[81, 82]

Despite the favorable results obtained in some studies, the matter remains controversial about the use of extracorporeal blood purification methods in septic conditions, thus precluding any definitive recommendations on the benefit of these methods in septic patients.

Conclusions

The role of blood purification in sepsis does remain controversial. The currently available evidence encourages future research on the use of blood purification techniques through the new membrane materials in selected patients with septic conditions. More data would be useful to better recognize septic patients who are most likely to benefit from blood purification treatments, and clarify the optimal timing, duration, and number of applications of these techniques in the ICU clinical practice. Finally, interesting information could derive by further investigations on mixing different CRRT modalities and combining different membrane materials.

Key messages

— Extracorporeal blood purification techniques using various membrane materials have been proposed in the treatment of septic conditions.

— The use of extracorporeal blood purification techniques during sepsis still remains controversial, thus precluding any definitive recommendations on the benefit of these methods in septic conditions.

— More data would be useful to: better recognize septic patients who are most likely to benefit from blood purification treatment; clarify the optimal timing, duration, and number of applications of blood purification techniques; define the effectiveness of mixing different renal replacement modalities and combining different membrane materials.

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