

Extracorporeal blood purification for sepsis

HP Shum *, WW Yan, TM Chan

ABSTRACT

It has been speculated that extracorporeal blood purification therapies might improve the clinical outcome for patients with severe sepsis, with or without acute kidney injury, since the removal of inflammatory mediators and/or bacterial toxins from circulation could modulate the inflammatory responses that result in organ damage. Despite initial enthusiasm based on promising preliminary results, subsequent investigations did not show sustainable survival benefit. We review the principles and development of blood purification techniques for sepsis and septic acute kidney injury.

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¹ HP Shum *, FRCP, FHKAM (Medicine)

¹ WW Yan, FRCP, FHKAM (Medicine)

² TM Chan, MD, FHKAM (Medicine)

¹ Department of Intensive Care, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong

² Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong

* Corresponding author: shumhp@ha.org.hk

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Introduction

The concepts underlying the pathogenesis of septic acute kidney injury (AKI) are complex. It is characterised by renal macro- and micro-circulatory disturbance, surge of inflammatory markers, and de-regulation of oxidative stress, followed by a bioenergetic adaptive response and controlled cell cycle arrest aimed at preventing cell death.¹ Continuous renal replacement therapy is commonly performed in the critical care setting for patients with septic AKI. The use of low- or normal-volume continuous venovenous haemodialysis or haemofiltration, however, has failed to demonstrate any improvement of patient outcome in severe sepsis.^{2,3} Extracorporeal blood purification therapies have been proposed to improve the outcome for patients with severe sepsis with and without AKI. The underlying principle is the removal of excessive inflammatory mediators and/or bacterial toxins from the blood compartment in order to modulate the inflammatory response. This involves various techniques including haemoperfusion/haemoadsorption, high-adsorption haemofiltration, high-volume haemofiltration (HVHF), high cut-off (HCO) membrane haemofiltration/haemodialysis, plasma exchange, and coupled plasma filtration adsorption (CPFA) [Table 1]. These techniques are gaining popularity in Europe and Japan. This overview discusses the concept and latest advances in blood purification for sepsis and septic AKI.

Therapeutic concept of extracorporeal blood purification

During sepsis, triacylated peptides, diacylated peptides, or lipopolysaccharides (LPS) are released

by pathogens, and are recognised by the Toll-like receptors located on the surface of antigen-presenting cells.^{4,5} Toll-like receptors also recognise locally produced damage-associated molecular patterns (DAMPs) from ischaemic renal tissue and circulating DAMPs released from extensive extrarenal tissue damage in sepsis.⁶ This triggers the activation of leukocytes, endothelial cells, and epithelial cells that release more inflammatory mediators such as tumour necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, IL-8 and IL-10, causing cellular and tissue damage.^{7,8} This is called a 'cytokine storm', and can also occur in non-infectious conditions such as severe trauma, extensive burns, acute necrotising pancreatitis, and post-cardiac arrest. A cytokine storm per se, in the absence of life-threatening triggering factors, can induce haemodynamic instability and multi-organ failure as illustrated by Suntharalingam et al.⁹ Moreover, immunoparalysis might occur after a cytokine storm and contribute to severe secondary nosocomial infections.¹⁰ As demonstrated in a postmortem by Boomer et al,¹¹ patients who die of severe sepsis have biochemical and immunohistochemical findings consistent with immunosuppression. This gives rise to the concept of immunomodulation in sepsis. Low-dose steroid administration has been shown to improve septic shock reversal but is not associated with any survival benefits and is currently out of favour.^{12,13} The clinical benefit of intravenous immunoglobulins and anti-TNF- α in the treatment of severe sepsis is controversial and inconclusive.^{14,15} Blood purification may offer non-specific clearance of inflammatory mediators and/or microbial toxins and thus help to restore immune homeostasis. Five theories have been proposed to explain the potential

benefit of blood purification in sepsis. First, Ronco et al¹⁶ proposed the “cytokine peak concentration hypothesis” and suggested that eliminating the peaks in cytokine blood concentration during the early phase of sepsis could stop the inflammatory cascade, limit organ damage, and consequently decrease the incidence of multi-organ failure syndrome. Second, Honoré and Matson¹⁷ proposed the “threshold immunomodulation hypothesis” that indicated cytokines will equilibrate between the blood and tissue compartments. This provided an explanation for the clinical benefit of blood purification techniques even without any significant changes in cytokine level within the blood compartment. Third, Di Carlo and Alexander¹⁸ proposed the “mediator delivery hypothesis” and suggested that high-volume fluid replacement during haemofiltration might promote lymphatic flow and displace inflammatory mediators to the blood compartment, making them available for removal. Fourth, Peng et al¹⁹ suggested that blood purification therapies could act directly at the cellular level to restore immune function. Finally, Rimmelé and Kellum²⁰ proposed the “cytokinetic model” which indicated that blood purification techniques remove cytokines from the blood compartment and widen the cytokine/chemokine concentration gradient between blood and infected tissue. This improves leukocyte trafficking towards

the infective foci, and thus promotes bacterial killing.

Haemoperfusion/haemoadsorption

This technique binds toxins and other mediators in the extracorporeal circuit and removes them from the blood compartment.²⁰ The sorbents, which consist of microfibres or resin-covered beads, are normally contained in cartridges that are placed in series within the extracorporeal circuit. They have a selective or non-selective binding capacity for cytokines, chemokines, super-antigens, or endotoxins by means of hydrophobic interaction, van der Waals forces, or ionic interactions.²⁰ Initial clinical applications were complicated by severe thrombocytopenia and leukopenia but these were

體外血液淨化療法治療膿毒症

沈海平、殷榮華、陳德茂

體外血液淨化療法能去除血液中過多炎症介質和/或細菌毒素以達至調節炎症反應效果，因此被推測在有或沒有急性腎損傷情況下能改善嚴重膿毒症的治療效果。初期研究的結果令人鼓舞，可惜及後的研究未能證實可延長病人的存活。本文回顧體外血液淨化療法對於膿毒症及膿毒性急性腎損傷的原理和發展。

TABLE 1. Comparison between major blood purification techniques

Therapy	Mode of action	Comments
Polymyxin B-immobilised fibre column (Toraymyxin; Toray Industries, Tokyo, Japan)	Endotoxin haemoadsorption	<ul style="list-style-type: none"> • Potential mortality benefit based on RCTs • Well-studied treatment modality • Not available locally
MATISSE-Fresenius system (Fresenius SE, Bad Homburg, Germany)	Endotoxin haemoadsorption	<ul style="list-style-type: none"> • Multicentre RCT showed no significant clinical benefit
Alteco LPS Adsorber (Alteco Medical AB, Lund, Sweden)	Endotoxin haemoadsorption	<ul style="list-style-type: none"> • Limited clinical experience • Ex-vivo study showed unacceptable LPS clearance
Cytokines haemoadsorptive device	Cytokine haemoadsorption	<ul style="list-style-type: none"> • Good cytokine clearance • Limited clinical experience
oXiris haemofilter (Gambro Hospal, Stockholm, Sweden)	Endotoxin and cytokine haemoadsorption plus renal support	<ul style="list-style-type: none"> • Simple and familiar technique • Limited clinical experience
PMMA haemofilter	Cytokine haemoadsorption plus renal support	<ul style="list-style-type: none"> • Simple and familiar technique • No RCT available • Low cost
HVHF	Haemofiltration	<ul style="list-style-type: none"> • Well-studied treatment modality • No survival or haemodynamic benefit
High cut-off haemofiltration/haemodialysis	Cytokine removal by haemofiltration/haemodialysis	<ul style="list-style-type: none"> • Simple and familiar technique • One unpublished RCT showed no mortality or other clinical benefit
Plasmapheresis	Cytokine removal by haemofiltration	<ul style="list-style-type: none"> • Conflicting results from RCTs • Loss of vital component during prolonged treatment
CPFA	Cytokine removal by haemofiltration and haemoadsorption	<ul style="list-style-type: none"> • One RCT showed no mortality benefit • More complicated setup when compared with other blood purification techniques

Abbreviations: CPFA = coupled plasma filtration adsorption; HVHF = high-volume haemofiltration; LPS = lipopolysaccharides; PMMA = polymethylmethacrylate; RCT = randomised controlled trial

subsequently managed using a biocompatible coating.

Polymyxin B-immobilised fibre column

Polymyxin B (PMX)-immobilised fibre column haemoperfusion (Toraymyxin, Toray Industries, Tokyo, Japan) is the most commonly used approach, and has been used for the treatment of septic shock since 1994 in Japan and since 2002 in Europe. It has gained popularity worldwide in recent years, especially after the landmark EUPHAS (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis) study.²¹ The PMX is a group of cyclic cationic polypeptide antibiotics derived from *Bacillus polymyxa*. Endotoxins are heat and pH stable, and thus can be difficult to remove from protein-rich solutions such as blood. The PMX is capable of binding and neutralising endotoxins. Nephrotoxicity and neurotoxicity, however, are very common and thus limit their clinical use.²² To overcome this problem, PMX is immobilised onto polystyrene fibres that effectively remove endotoxin without leaching. The blood is perfused at a rate of 80 to 100 mL/min through a PMX-immobilised fibre column. Anticoagulation is achieved using unfractionated heparin, low-molecular-weight heparin, or the protease inhibitor nafamostat mesylate. Treatment usually lasts for 2 to 27 hours once or in some patients up to 4 times, depending on the clinical response. Three meta-analyses (approximately 1000 patients) were published before 2015: Studies by Mitaka and Tomita²³ (17 studies, 975 patients) and Cruz et al²⁴ (28 studies, 1425 patients) included both randomised controlled trials (RCTs) and observational studies. When reported, Gram-negative infections were identified in approximately 70% of patients (range, 37.9%-100% in individual studies). In general, PMX treatment led to significant haemodynamic improvement with a reduction in the use of inotropic agents/vasopressors in patients with sepsis. Moreover, it was associated with a decreased endotoxin level, modulation of inflammatory markers, and improvement of the PaO₂/FiO₂ ratio (ratio of the partial pressure of oxygen in arterial blood to the inspired oxygen fraction) in most included studies.^{23,24} Treatment by PMX significantly reduced 28-day mortality compared with conventional therapy. The meta-analysis by Zhou et al²⁵ (8 studies, 370 patients) included RCTs only and focused on mortality, and showed significant survival benefit compared with conventional treatment. Only a few clinically important adverse effects were reported during PMX haemoperfusion, including cartridge clotting, hypotension, and hypersensitivity. Nonetheless, the largest multicentre RCT (232 patients) testing the performance of PMX haemoperfusion in peritonitis-induced septic shock was published in

April 2015, and reported contrasting findings.²⁶ No significant differences in 28-day mortality (27.7% in PMX-treated group vs 19.5% in controls; P=0.14), haemodynamic patterns, or organ failure evolution were observed. This negative result was similar to a large retrospective study (642 patients) by Iwagami et al²⁷ who examined the effect of postoperative PMX haemoperfusion on peritonitis-induced septic shock. Patients treated with one or two PMX haemoperfusion sessions showed similar mortality at day 28 (17%) to propensity-matched patients without PMX treatment (16.3%). EUPHRATES (safety and efficacy of PMX haemoperfusion for septic shock study), a very large multicentre US-based phase III trial in patients with confirmed endotoxaemia, is currently underway and results should be available after July 2017.²⁸ Based on current evidence, the clinical benefit of PMX haemoperfusion in Gram-negative sepsis is unclear. Moreover, the cost of individual haemoperfusion cartridges is very high (approximately HK\$40 000 per cartridge) and limits its clinical use in local settings. Currently, PMX-immobilised fibre column haemoperfusion is not available in Hong Kong.

MATISSE-Fresenius system

The MATISSE-Fresenius system (Fresenius SE, Bad Homburg, Germany) binds endotoxins to human albumin. The extracorporeal circuit is maintained by the Fresenius haemoadsorption machine using the MATISSE haemoadsorber that contains human serum albumin immobilised on polymethacrylate beads. Trends in the improvement of morbidity and organ dysfunction were reported in initial non-randomised studies,^{29,30} although a subsequent multicentre RCT could not identify any significant clinical benefit, which then limited its clinical use.³¹ Currently, the MATISSE-Fresenius system is not available in Hong Kong.

Alteco Lipopolysaccharide Adsorber

The Alteco LPS Adsorber (Alteco Medical AB, Lund, Sweden) captures endotoxins using specially designed synthetic peptides. This device was launched in 2006. Tailor-made synthetic peptides with a high affinity for endotoxins are attached to the surface of the polyethylene plates using a covalent bonding technique. Clinical experience with this device is scarce, and is limited mainly to case reports and case series.³²⁻³⁴ In general, these case series report a shorter vasopressor infusion duration in adsorber-treated patients compared with controls. Only one underpowered RCT has been published by local investigators.³⁵ The study was terminated early and showed no significant clinical benefit (disease severity score, vasopressor use, length of study, and 28-day mortality) following the addition of the Alteco LPS Adsorber to conventional therapy

in patients who had intra-abdominal sepsis with shock.³⁵ The side-effect profile of this novel device was acceptable but a recent ex-vivo experimental study showed that the Alteco LPS Adsorber could not achieve acceptable LPS clearance in serum, heparinised plasma, or whole blood.³⁶ Therefore, the potential benefit of the Alteco LPS Adsorber in sepsis is not clear.

Cytokines haemoadsorptive device

Several cytokine-absorbing columns have been tested in animal studies, showing excellent adsorption rates for inflammatory cytokines such as TNF- α , IL-1 β , IL-6, and IL-8.³⁷ Human data are limited to case reports and case series.³⁸⁻⁴⁰ CytoSorb (CytoSorbents Corporation; Monmouth Junction [NJ], US) is a novel synthetic haemabsorption column that targets inflammatory mediators.⁴¹ It is currently the only European-approved extracorporeal device for cytokine haemoadsorption. Case reports show good cytokine clearance and haemodynamic improvement with this device.⁴¹⁻⁴⁴ Further studies focused on clinically relevant endpoints are highly recommended. CytoSorb is not available in Hong Kong.

High-adsorption haemofiltration

The AN69 and polymethylmethacrylate (PMMA) membrane haemofilters are the currently available options for performing high-adsorption haemofiltration in septic patients. Both have a high cytokine adsorption capacity but surface treatment can further modify their haemoadsorptive properties.⁴⁵⁻⁴⁷

oXiris haemofilter

oXiris (Gambro Hospal, Stockholm, Sweden) is an AN69-based membrane haemofilter that is surface-treated with a polyethyleneimine and grafted with heparin (Table 2). The AN69 core membrane has superior cytokine-binding capacity compared with

the traditional polysulphone membrane. Surface treatment with polyethyleneimine enhances endotoxin capture,⁴⁸ while heparin coating reduces membrane thrombogenicity, and prolongs the filter life and improves efficiency. A case-control study by Shum et al⁴⁹ involving Gram-negative septicaemic patients (n=6) showed that oXiris continuous venovenous haemofiltration (CVVH) was associated with a greater reduction in Sequential Organ Failure Assessment score compared with conventional polysulphone-based CVVH (n=24). Subsequent large case series (n=40) suggested that oXiris treatment had a positive effect on haemodynamics with a reduction in cytokine levels (IL-6).⁵⁰ Treatment usually lasts for 72 hours (manufacturer's recommendation) and costs approximately HK\$8000 per haemofilter. As of mid 2015, at least five public hospitals in Hong Kong have clinical experience with oXiris haemofilters in the treatment of septic shock. A large-scale RCT will be necessary to determine the potential benefit of this device, however.

Polymethylmethacrylate haemofilter

The PMMA membrane has a higher cytokine adsorption capacity than the traditional polyacrylonitrile and polysulphone membrane.⁵¹ Membrane binding site saturation is one of the main concerns during treatment involving highly adsorptive haemofiltration. The PMMA haemofilter can maintain its cytokine adsorption capacity for at least 24 hours after being changed.⁵² The initial clinical experience of PMMA continuous haemodiafiltration in the treatment of sepsis is encouraging, with significant haemodynamic improvement and potential survival benefit.^{53,54} A local RCT (Australian New Zealand Clinical Trial Registry ACTRN12611000652976) that is aimed at investigating the clinical benefit of PMMA-based CVVH in patients with septic shock and AKI is currently underway. Treatment usually lasts for 24 to 48 hours and costs approximately HK\$300 per haemofilter.

TABLE 2. Characteristics of locally available filters used in high cut-off haemodialysis, highly adsorptive haemofiltration, and plasmapheresis

Company	Filter name	Material	Therapy mode	Effective surface area (m ²)	Cut-off (kDa)	Machine	Blood flow (mL/min)	Treatment time (hours)
FMC	EMiC 2	Polysulphone	CVVHD	1.8	40	Multifiltrate AK200US	100-350	72 (maximum)
Gambro/Baxter	septeX	PAES	CVVHD	1.1	45	Prismaflex	80-400	24 (maximum)
Gambro/Baxter	oXiris	AN69 ST	CVVH/CVVHDF	1.0	~20	Prismaflex	100-250	72 (maximum)
Toray	BG2.1U	PMMA	CVVH/CVVHD/ CVVHDF	2.1	~20	Multifiltrate AK200US 5008	150-350	24-48
FMC	PlasmaFlux	Polysulphone	Plasmapheresis	0.6	400-800	Multifiltrate	80-250	2-4

Abbreviations: CVVH = continuous venovenous haemofiltration; CVVHD = continuous venovenous haemodialysis; CVVHDF = continuous venovenous haemodiafiltration; FMC = Fresenius Medical Care; PAES = polyarylethersulphone; PMMA = polymethylmethacrylate

High-volume haemofiltration

In 2002, HVHF was defined as >35 mL/kg/h, based on recommendations from the Acute Dialysis Quality Initiative Workgroup.⁵⁵ Nonetheless in clinical practice, 35 mL/kg/h is not that high and can be achieved with ease, especially in those with low body weight. To clarify this issue, Honore et al⁵⁶ defined continuous HVHF as 50 to 70 mL/kg/h, and 100 to 120 mL/kg/h for 4 to 8 hours followed by conventional CVVH as pulse HVHF. In addition, HVHF is regarded as effective blood purification therapy because circulating inflammatory mediators are mostly water-soluble and range between 5 kDa and 60 kDa. They are more effectively removed by convective means than by diffusion techniques. Moreover, haemofilter membranes have some adsorptive properties that allow the removal of mediators with a molecular weight higher than the membrane cut-off point. It is clear that conventional haemofiltration with low ultrafiltration rates is ineffective for cytokine removal.^{2,3} Increasing the ultrafiltration flow rate can increase the adsorption capacity of the haemofilter because of its effect on transmembrane pressure (greater membrane site recruitment) and the exposure of more available adsorptive surface area.⁵⁷ Only two RCTs that investigated the potential benefit of HVHF over conventional CVVH in septic patients were available before the publication of the landmark trial (high-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury study) in 2013.^{57,58} Cole et al⁵⁷ performed the first randomised crossover clinical trial that involved 11 patients with septic shock and multi-organ failure. Patients were assigned to either 8 hours of HVHF (6 L/h) or 8 hours of standard CVVH (1 L/h) in a random order. The results showed that HVHF was associated with a greater reduction in vasopressor use. A study by Boussekey et al⁵⁸ (HVHF 65 mL/kg/h vs control 35 mL/kg/h; n=20) yielded similar findings and showed no survival benefit of HVHF over conventional CVVH. Multiple non-randomised studies showed decreased mortality with HVHF for septic shock patients but most of the studies were relatively small.⁵⁹⁻⁶¹ Despite the initially encouraging results, HVHF has not gained in popularity because the use of a large volume of ultrapure replacement solution equates to significant increases in treatment cost, risk of severe electrolyte disturbance, and nursing workload. The landmark IVORIE study was published in 2013.⁶² This multicentre RCT involved 140 critically ill septic shock patients who were randomised to receive either HVHF at 70 mL/kg/h or standard CVVH treatment at 35 mL/kg/h. It showed neither significant survival benefit nor haemodynamic improvement for HVHF compared with standard treatment. Subsequently two meta-analyses (4 studies with approximately 500 patients)

published in 2014 concluded that neither HVHF nor pulse HVHF offered any added clinical benefit when compared with standard-volume haemofiltration.^{63,64} Therefore, the routine use of HVHF for treatment of sepsis is not recommended.

High cut-off haemodialysis/haemofiltration

Inflammatory mediators are relatively large (TNF- α : 17 kDa, IL-6: 26 kDa, and IL-8: 8 kDa), and are classified as middle molecules. The conventional high-flux haemofilter has a cut-off point at approximately 20 kDa and is unlikely to achieve good cytokine clearance.^{2,3} The nominal cut-off point for HCO membranes ranges from 60 to 150 kDa and the clinical cut-off point in blood ranges from 40 to 100 kDa.⁶⁵ This can greatly increase the sieving coefficients of various inflammatory mediators at the expense of loss of albumin (66 kDa), antithrombin-III (60 kDa), protein C (62 kDa), and many other vital proteins. Reducing the pore size slightly can limit vital protein loss but also decrease cytokine removal. Ex-vivo studies showed that HCO haemofiltration displayed the greatest consistency in cytokine removal when compared with standard haemofiltration.⁶⁶ The CPFA and haemoadsorption appeared to offer a similar level of cytokine clearance to the HCO technique. Albumin loss was comparable between HCO haemofiltration, HCO haemodialysis, and HCO haemodiafiltration.⁶⁶ Morgera et al⁶⁷ published the first study on the use of HCO haemofiltration among septic shock patients and showed good IL-6 (but not TNF- α) clearance. Subsequently, Morgera et al⁶⁸ conducted an RCT that involved 30 septic AKI patients who were randomised to HCO or conventional haemofiltration. The HCO group showed a significant decline in vasopressor use and cytokine level.⁶⁸ The largest RCT was the High Cut-Off Continuous Venovenous Hemodialysis (CVVHD) in Patients Treated for Acute Renal Failure After Systemic Inflammatory Response Syndrome (SIRS)/Septic Shock (HICOSS) study.⁶⁹ The estimated sample size was 120 patients but the study was terminated early because of a lack of difference between the groups after 81 patients had been recruited. There was no difference in 28-day mortality, vasopressor use, duration of mechanical ventilation, length of stay in intensive care unit, or albumin level between the groups.⁶⁹ This underpowered RCT (due to premature termination) cannot provide a clear answer about the potential benefit of HCO haemofiltration/haemodialysis in septic patients and a further large-scale prospective RCT is recommended. Only the septeX (Gambro Hospal, Stockholm, Sweden) and EMiC 2 (Fresenius SE, Bad Homburg, Germany) HCO haemofilters are available in Hong Kong (Table 2). Treatment usually lasts for 24 to 72 hours and costs approximately

HK\$8000 per HCO haemofilter.

Plasmapheresis and coupled plasma filtration adsorption

The nominal cut-off point for the plasma filter ranges from 400 to 800 kDa and therefore can achieve good cytokine removal with significant albumin loss (Table 2). Only three RCTs have been published to date. Busund et al⁷⁰ published the largest RCT involving 106 adult septic patients randomised to receive either two sessions of plasmapheresis or standard therapy. Plasmapheresis offered better 28-day survival compared with the control group (67% vs 47%). Studies by Reeves et al⁷¹ and Long et al⁷² showed no survival benefit, however. Therefore, the debate regarding the benefit of plasmapheresis in sepsis continues. One important drawback of plasmapheresis is the significant loss of albumin, fibrinogen, antithrombin, and immunoglobulin that takes a long time to regenerate in the absence of post-treatment replacement.⁷³ This problem can be resolved with the use of CPFA (Lynda, Bellco, Mirandola, Italy). This CPFA therapy comprises a plasma filter, a non-selective hydrophobic resin cartridge with high affinity for inflammatory mediators, and a high-flux haemofilter for convective solute removal (Fig).⁷⁴ Only filtrated plasma has direct contact with the sorbents that have no biocompatibility problems when compared with direct haemoperfusion. Treatment lasts for approximately 10 hours and requires cartridge changes due to saturation problems. Livigni et al⁷⁵ published the only multicentre RCT focused on patients with septic shock. Patients were randomised to standard treatment with or without CPFA. The CPFA therapy was performed daily for 5 days and lasted at least 10 hours/day. The estimated sample size was 330 patients but the study was terminated early on the grounds of futility after 192 patients had been recruited. No significant benefits for mortality, organ dysfunction, or intensive care unit stay were observed. Therefore, based on the available evidence, the routine use of CPFA for treatment of septic shock is not recommended. The CPFA is currently not available in Hong Kong.

Conclusion

Building on the concept of excessive inflammatory mediator release, blood purification techniques have emerged as an adjunctive therapy for patients with severe sepsis and septic AKI. They are effective in clearing endotoxin or inflammatory mediators and are well tolerated. Despite initially promising results, most blood purification techniques have not provided any sustainable mortality benefits. In severe sepsis, source control, early appropriate antibiotics, and haemodynamic support are the three most

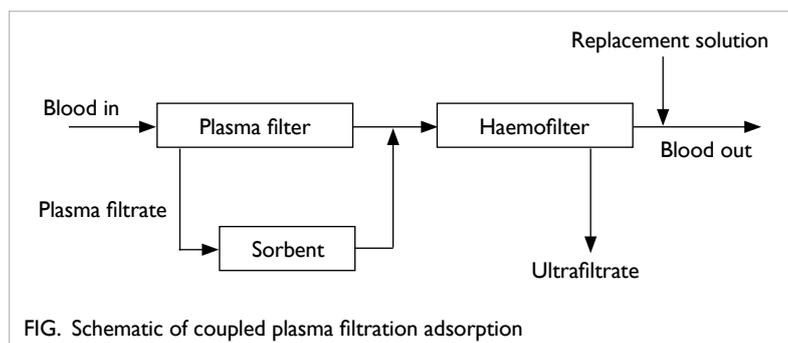


FIG. Schematic of coupled plasma filtration adsorption

important treatment components.⁷⁶ As a supportive treatment, blood purification techniques may not significantly affect patient mortality. Since the outcome for septic patients has improved over time, much larger sample sizes will be needed to detect the relatively small effects of these new therapies on sepsis.⁷⁷ Large-scale, well-designed, prospective RCTs are the way forward. The application of these novel techniques should be individualised but more specific recommendations must await further evidence.

Declaration of interests

All authors have disclosed no conflicts of interest.

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