Special Article

Roles of Extracorporeal Blood Purification in Sepsis

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Severe sepsis represents the leading cause of mortality and morbidity in critically ill patients. Although the authors' understanding of the complex pathophysiological alterations that occur in severe sepsis and septic shock has increased greatly, mortality associated with the disorder remains unacceptably high. Recent treatment guidelines have reinforced the importance of early goal directed therapy. Recently, moderate doses of corticosteroid replacement and activated protein C (drotrecogin alfa[activated]) are the therapies demonstrating efficacy. Extra-corporeal blood purification techniques offer a variety of techniques that can efficiently eliminate septic mediators. The rationale for its use in sepsis is sound. Animal and human studies show promise with improvements in hemodynamics and mortality, but are limited by number and design. These techniques require large-scale well-conducted studies to demonstrate the validity in sepsis.

Keywords: *Sepsis, Blood purification, Adjunctive therapy, Hemofiltration, Sorbent, Plasmapheresis*

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The concept of removal of suspected toxic substances from the body has gained more popularity in the last three decades. This is due to the introduction of hemodialysis for the treatment of chronic renal failure, and later the development of new system namely continuous renal replacement therapy (CRRT) for the treatment of acute renal failure (ARF) in critically ill patients. The use of new devices and novel blood purification techniques, together with a better understanding of the underlying mechanisms of solute and water removal have permitted the physicians to achieve higher levels of efficiency and adopt such techniques for broader clinical indications. As an example, a beneficial effect from the hemodynamic point of view can be obtained by CRRT in patients with multiple organ failure and septic shock. Since some effects induced by CRRT could be related to the removal of inflammatory mediators, this hypothesis has spurred new interest in the application of therapies as extracorporeal blood purification techniques and immunomodulation[1]. The various techniques include hemodialysis (diffusive), hemofiltration (convective), hemodiafiltration (mixed), adsorbents, and plasmafiltration. Convective modalities have the advantage of removing higher molecular weight substances, which include many inflammatory mediators[2]. The removal of the broad spectrum of pathogenetic molecules identified in sepsis may be clinically beneficial. This is the biological rationale and theoretical basis of extracorporeal blood treatment (EBT) in sepsis.

In this chapter, the authors highlight some of the basic principles and rationale of such new horizons in blood purification, review animal experiments, and finally discuss the results of recent human studies and their implication.

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The humoral theory of sepsis

Sepsis is a complex process that involves many interactions between pleiotropic mediators with strong bioactivity at low concentrations, which can be broadly categorized as having pro- and anti-inflammatory characteristics. Microbial products are responsible for the induction of inflammation, which in turn propagates a deleterious inflammatory cascade mediated by cytokines and toxic molecules. This leads to local microvascular injury with potential dissemination and malignant sequelae at different organ levels. These effects are described as multiple organ failure (MOF)[3].

Initially, the pathogenesis of sepsis was described as an overproduction of locally released pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8, which amplify and orchestrate the inflammatory response. This was based on evidence that:

• Cytokines have pathogenic effects.

• Endotoxin injection induces cytokine production in a consistent and reproducible manner[4].

• Injection of purified cytokine preparations (TNF-α and IL-1) evokes the sepsis syndrome[5].

Inhibitory monoclonal antibodies to TNF-α and IL-1 were found to prevent or reverse septic shock in animals injected with endotoxin, but had disappointing results in human clinical trials[6].

Anti-inflammatory mediators also contribute to the pathology of sepsis by exaggerating the physiological feedback and producing a state of immunoparalysis or cell re-programming created by the compensatory anti-inflammatory response syndrome (CARS)[7,8]. Adding to the complexity, individual cytokines can function as both pro- and anti-inflammatory effectors[9]. Furthermore, cytokine plasma levels have been altogether discounted by some researchers, who have suggested that neither their presence nor their absence can reflect the complex interplay at tissue level[10]. Recently, evidence that elevated levels of both pro and anti-inflammatory cytokines have been shown to correlate with increased mortality[11].

Bacterial lipopolysaccharide (LPS) or endotoxin, the major component of the outer membrane of all naturally occurring gram-negative bacteria, is also pivotal in the initiation and propagation of sepsis and has been extensively targeted as the 'magic bullet' cure for sepsis. Most patients with endotoxemia and septic shock have low concentrations of LPS. Higher concentrations are seen in severe shock and subjects with higher mortality[12]. The correlation between circulating endotoxin levels in septic patients with clinical outcome measures remains undefined. Strategies of neutralizing or removing LPS thus far have proven disappointing; however, it continues to be pursued as a potential route to treat sepsis[13].

The current available information makes it difficult to solve the puzzle of sepsis. It is likely that the sepsis syndrome reflects an imbalance of pro- and anti-inflammatory mediators-immunodysregulation rather than physiological immunohomeostasis. Either group of mediators could be present in excess contemporaneously in the same pool, at different times (sequential peak hypothesis), or in different compartments (parallel peak hypothesis) (Fig. 1). In this "peak concentration hypothesis", it is the abnormal peak levels of such substances that cause pathogenesis[14]. This has important implications as it suggests that different therapies are indicated for excessive pro-and anti-inflammatory states. As identifying and treating the appropriate state is unfeasible at present, therapies that target both states indiscriminately may be the best solution and help to restore immunohomeostasis.

Extra-corporeal blood purification therapy: from renal support to the adjunctive treatment of sepsis

While intermittent hemodialysis (IHD) is commonly used when renal supportive therapy is indicated in critically ill patients, continuous renal replacement therapy (CRRT) and sustained low-efficiency daily dialysis (SLEDD) are now increasingly performed in the intensive care unit (ICU) because they offer better practical advantages such as cardiovascular tolerance, stricter fluid balance, optimization of nutritional support to prevent fluid overload, and control of electrolyte and acid-base homeostasis[15]. SLEDD is a technical hybrid of CRRT and IHD that is proving to be a formidable alternative (Fig. 2)[16,17]. It provides comparable clearances to CRRT with good clinical tolerance at low cost and low labor-intensity. There has been no convincing evidence to date that CRRT confers mortality benefits over IHD and SLEDD techniques when used as the standard RRT in critically ill patients[18,19], but evidence exists on its potential efficacy in human sepsis.

The purification potential of CRRT in sepsis was demonstrated in animals 20 years ago[20]. The technique was so potent that the ultrafiltrate extracted by CRRT could induce the systemic changes seen in sepsis when it was re-infused[21]. Human studies have confirmed the therapeutic potential of removing inflammatory mediators[22]. One of the major criticisms attributed to continuous blood purification treatments in sepsis - its lack of specificity - could turn out to be a major strength. Non-specific and continuous removal of soluble mediators, be they pro- or anti-inflammatory, without completely eliminating their effect may be the most logical and adequate approach to a complex and long-running process like sepsis.

The application of a "renal dose" hemofiltration rate of 2000 mL/h has generally been adopted for CRRT[23]. This dose suffices for RRT and can remove inflammatory mediators; however, it does not alter plasma levels, suggesting its role in mediator clearance is insufficient[24]. This was reflected by the failure to

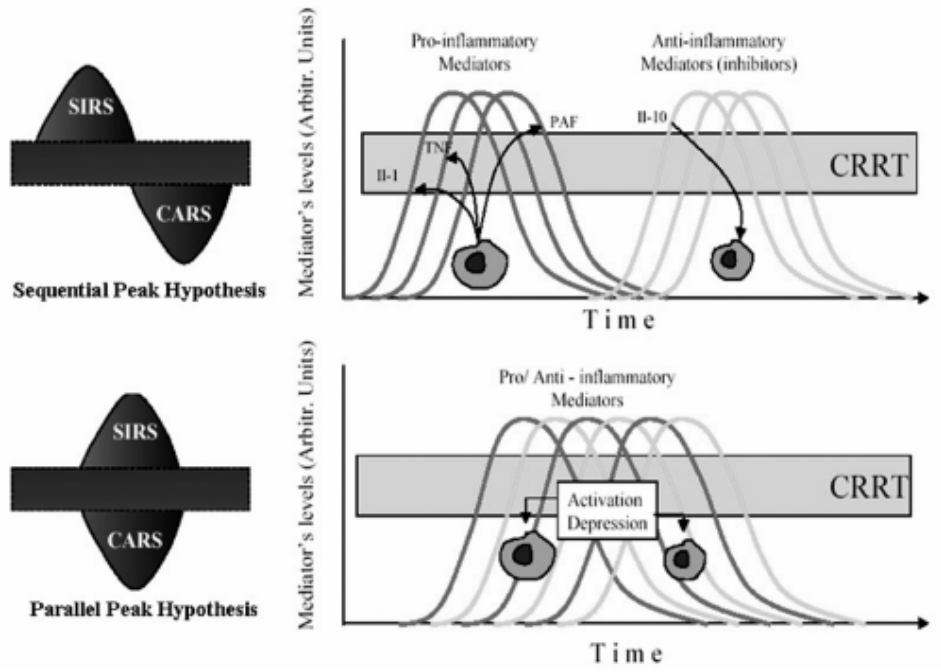

Fig. 1 A: The sequential theory of sepsis, a stimulus, such as endotoxin, creates a systemic inflammatory response with dissemination of proinflamatory mediators. Subsequent inhibition of the inflammatory process and consequent cell hyporesponsiveness occurs

B: In the parallel theory, both processes occur simultaneously, with synthesis of pro-and anti-inflammatory mediators contemporaneously but in different locations

The peak concentration hypothesis suggests that a nonselective control of the peaks of inflammation and immunoparalysis may help restore immunohomeostasis

The shaded area represents the effect of CRRT in terms of mediator clearance range. [Reprinted with permission from Ronco C, Bonello M, Bordoni V et al Extracorporeal therapies in non-renal disease: Treatment of sepsis and the peak concentration hypothesis. Blood Purif 2004; 22: 164-74]

demonstrate an improvement in organ dysfunction and survival[25]. From several animal and human investigations, the authors also know that our ability to remove middle molecules (especially those > 5,000 in molecular weight such as cytokines and complement components) is limited when using current CRRT technology.

For this reason, the authors present a brief classification of novel extracorporeal blood purification techniques using as adjunctive treatment of sepsis including the biological rationales, the operational characteristics, and potential results.

Continuous high-flux hemodialysis (HFHD)

Continuous high-flux hemodialysis (HFHD) uses standard counter-current dialysate flow and a highly permeable (high flux) membrane (Fig. 2). Liberal ultrafiltrate production in the proximal filter achieves optimal clearance of mid-sized molecules and is balanced by backfiltration. This obviates the need for fluid replacement. This technique provides optimal removal of inflammatory molecules. Furthermore, it has been shown to have plasma immunomodulatory effects[26,27]. However, there has been no evidence suggesting its benefits on clinical parameters and outcome.

High-volume hemofiltration

The absence of clinical benefit with renal dose hemofiltration in sepsis did not discourage the pursuit of a more efficient blood purification technique. The theory of increasing plasma water exchange or higher dose hemofiltration seems reasonable. Ronco et al demonstrated survival benefits by increasing the hemofiltration dose (35 mL/kg/h) beyond the conventional renal dose (20 mL/kg/h), but no further benefit was achieved even at a higher dose (45 mL/kg/h) in 425

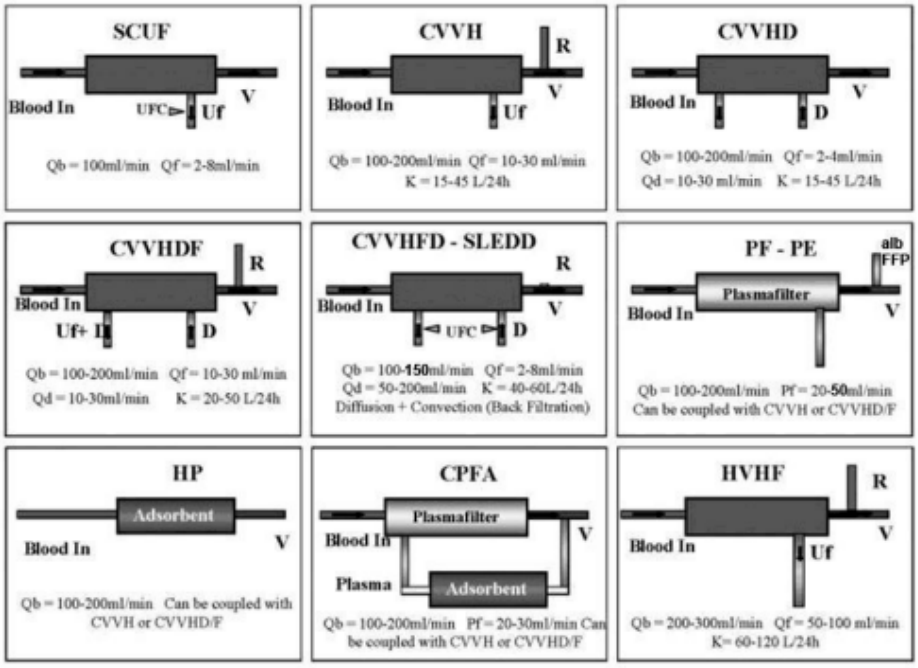

Fig. 2 Different extracorporeal therapy techniques
Blood In: blood inlet; SCUF: slow continuous ultrafiltration; CVVH: continuous venovenous hemofiltration; CVVHD: continuous venovenous hemodialysis; CVVHDF: continuous venovenous hemodiafiltration; CVVHFD-SLEDD: continuous venovenous high-flux dialysis-sustained low efficiency daily dialysis (6-10 h duration); PF-PE: continuous plasmapheresis-plasma exchange; HP: continuous hemoperfusion; CPFA: coupled plasmafiltration adsorption; HVHF: high-volume hemofiltration (applied continuously or as short pulses); Qb: blood flow rate; Qd: dialy sate flow rate; Qf: ultrafiltration rate; K: urea clearance; R: replacement solution; Uf: ultrafiltrate; D: dialysate; UFC: ultrafiltration control; V: venous return; alb: albumin; FFP: fresh frozen plasma

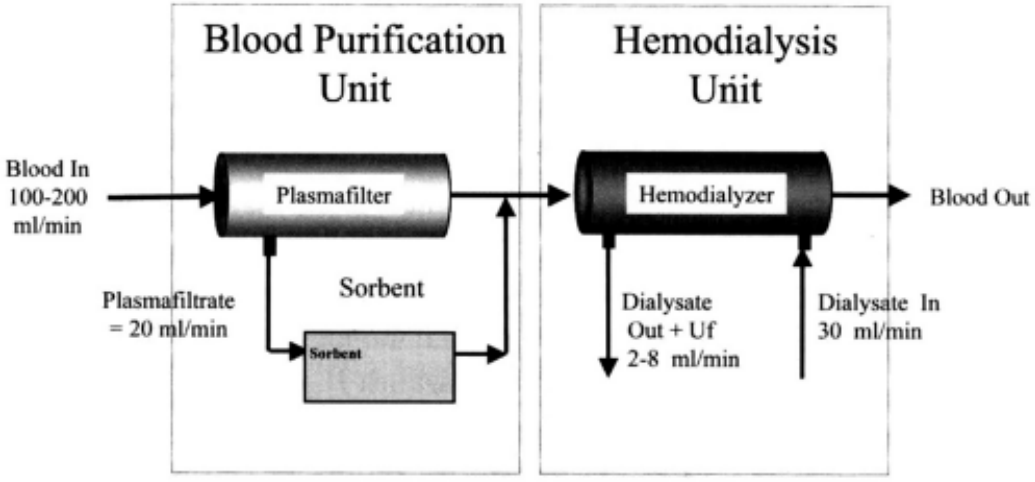

Fig. 3 Blood purification and hemodialysis units in CPFA [Modified from reference 58]

critically ill patients with ARF[28]. Nevertheless, there was an improvement in survival at the highest dose (45 mL/kg/h) in the same study for the subset of patients with sepsis. Additionally, benefits have been demonstrated in several animal models of sepsis. Improvements in cardiac function and hemodynamics were replicated in these animal studies using ultrafiltration rates up to 120 mL/kg/h[29,30]. Technological problems initially limited the clinical application of the technique, but newer machines permit a full range of treatment modes with powerful heating systems for maintaining constant sufficiently high temperature for the high volumes of infused solution and higher pre- or post-dilution effluent flow rates, as well as being more user-friendly. Septic dose hemofiltration or high-volume hemofiltration (HVHF) was thus conceived and applied in human sepsis. Improvements in hemodyamics with decreased vasopressor requirements and trends to improved survival provide evidence that HVHF may be efficacious[31-34]. The major concerns with HVHF are not only substantially increased loss of beneficial substances such as electrolytes, vitamins, trace elements, and amino acids, but intensive labor and technical difficulty. Because of technical requirements of high blood flows, tight ultrafiltration control and increase use of infusion fluids, the technique is generally applied for short periods of up to 6-8 hours per day, providing intense plasma water exchange and aptly named 'Pulse HVHF'(PHVHF). *PHVHF is performed with the ultrafiltration (UF) rate 85 ml/kg/h for 6 hours/day followed by standard continuous venovenous hemofiltration (CVVH) (UF rate 35 ml/kg/h) for 18 hours leading to a cumulative dose of approximately 48 ml/kg/h*. Treatments were performed on a daily basis, and were terminated if 1) the patient was dead; or 2) the physician considered the septic process was ending and the patient's clinical parameters were better. Preliminary data in 14 severe sepsis patients with ARF demonstrated that hemodynamics were improved, allowing a significant reduction of noradrenaline dose already at mid-and end-PHVHF and this was maintained decreasing at 6 and 12 h after treatment. The observed 28-day mortality (47%) was much better than the expect ones predicted by severity scores (70%)[35]. The daily PHVHF regimen tailored according to clinical response seem sufficient in magnitude which answer the question whether how long it would take for a clinically relevant benefit to manifest.

Recently, a randomized study has shown that very high volume hemofiltration (200 ml/kg/h for 8 h) was associated with a lower risk of death by intractable shock and a higher 6-month survival rate in 61 patients with post-cardiac arrest, a sepsis-like syndrome[36]. Although a large, well-conducted multicenter trial in sepsis patients is necessary, the biological effects demonstrated in the small, nonrandomized, non-controlled studies carried out to date are promising. In addition, HVHF are likely to be able to eliminate apoptotic factors and may help restore homeostasis and diminish the pathological pro-apoptotic pattern observed in sepsis. A recent study has observed a significant reduction in apoptotic mediators in circulating blood in septic patients treated with HVHF compared with those randomized to receive conventional CRRT, demonstrating a positive biological effect on the "cellular environment"[37]. Recombinant activated protein C has strong anti-apoptotic properties[38], in addition to its other activities; it would be interesting to combine its use with HVHF in patients with severe sepsis.

High permeability hemofiltration (Super high-flux hemofiltration, High cut-off renal replacement therapy)

A further approach would be to increase the porosity of the hemofilter membrane to augment middle molecular clearance. The filter utilized in standard hemofiltration had a nominal molecular weight exclusion limit (cut-off point) of 50,000 daltons (50 kilodaltons [kD]). Moreover, In the presence of whole blood and/or blood proteins, the functional molecular weight limit can be much less due to polarization of the membrane and/or protein deposition (adsorption) on the membrane. In *ex vivo* studies the use of this technique with a cutoff point of 100 kD membrane has been effective in yielding higher cytokine clearances than that with a cutoff point of 50 kD both in hemofiltration and hemodialysis modes[39,40]. Such "high porosity" hemofiltration has been tested in an animal study with promising results in terms of survival[41]. For clinical trials, Morgera et al have performed the comparison between 72-hour duration of CVVH and continuous venovenous hemodialysis (CVVHD) with polyflux hemofilter with a nominal cutoff point of 60 kD in 24 septic shock patients with ARF. CVVH achieved significantly greater interleukin-1 receptor antagonist (IL-1ra) removal than CVVHD[42]. In addition, 12-hour high permeability hemofitration exhibits immunomodulatory effects on leukocytes of septic patients. This therapy could restore peripheral blood mononuclear cell proliferation[43], and attenuate polymorphonuclear neutrophil phagocytosis[44]. Compared to conventional CVVH, the treatment with high cutoff CVVH in 30 septic patients with ARF was associated with a significant

decline in norepinephrine dose, and plasma cytokine levels (IL-1ra, and IL-6)[45]. However, these techniques especially with 100 kD filter are associated with the loss not only of albumin (66 kD) but also protein C and antithrombin III which have molecular weights approximately equal to that of albumin. The *in vivo* application of this therapy would require carefully monitoring of this protein loss. For the impact on clinical course and outcome, well-powered properly designed clinical studies are needed to prove its beneficence.

Plasmapheresis

The separation of plasma from cells allows the most efficient purification of blood. Additionally, it is an established treatment in plasma toxin-related diseases such as Goodpastures's syndrome and thrombotic micro-angiopathy. Plasmapheresis allows purification techniques to be applied to the plasma, before reuniting it with the cells. Plasma exchange involves removal of plasma and its replacement with a constituent, usually albumin and fresh frozen plasma, with clotting factors (Fig. 2). A plasma filter attached to a RRT machine is the most convenient and cost-efficient method for performing the separation.

Plasma exchange can effectively reduce the plasma concentration of an extensive range of inflammatory mediators in septic patients[46]. The technique has been demonstrated to improve hemodynamic parameters in several studies, but it has failed to modify the outcome in a consistent manner[47,48]. The only prospective randomized trial conducted in 106 sepsis patients showed that the 28-day, all-cause mortality rate was 33.3% in the plasmapheresis group and 53.8% in the control group[49]. The adverse events included transient hypotension and allergy to fresh frozen plasma. Like most of the work on extracorporeal techniques, the studies have produced encouraging results, but suffer from small numbers and design flaws. The duration of treatment necessary to affect outcome is a further issue. Plasmapheresis is hardly considerable as a continuous therapy. Interestingly, in the diseases where plasma exchange is effective, treatment duration can be directed by quantitative measures. The sepsis syndrome still lacks a sensitive marker that correlates with the state of disease[50]. Such a marker would be extremely useful for the early diagnosis of sepsis, monitoring the response to therapy, and verifying the efficacy of such a therapy.

Hemoperfusion (Hemoadsorption)

Sorbents have been in use since the 1850s when inorganic allumosilicates (zeolites) were first used in NH_4 and Ca^{2+} exchange. The sorbent is normally contained in cartridges that are placed in series with the extracorporeal circuit namely "hemoperfusion" or "hemoadsorption" (Fig. 2). Although clinical application was initially troubled by leukopenia and thrombocytopenia, recent improvements in design and biocompatible coatings have revived interest in this adjuvant blood purification technique. Both animal and clinical studies confirm the removal of a variety of inflammatory mediators[51,52]. Kellum et al have recently demonstrated the beneficial effect of additional use of hemoadsorption in an experimental sepsis. Interestingly, levels of IL-6, TNF-α, IL-10 and liver nuclear factor-κB were significantly reduced; however, endotoxin (LPS) levels were unchanged[53].

Specific sorbents designed for adsorbing inflammatory mediators are available. LPS remains an important mediator in the sepsis process. Polymyxin B-immobilized hemoperfusion (Toraymyxin) have been shown to bind endotoxin efficiently. These resins can significantly lower plasma LPS levels[54], plasminogen activator inhibitor-1, and IL-8[55], improve hemodynamics[56], improve oxygenation[55], and demonstrate insignificant trends to reducing mortality[54]. This therapy is widely utilized in septic shock patients with suspected gram-negative bacterial infection in Japan. The technique attempts to remove inducing mediators thus has specific indications based on timing and certain clinical characteristics, therefore it has had little acceptance elsewhere. The only multicenter randomized controlled study has been conducted in 36 surgical patients with severe sepsis secondary to intra-abdominal infection (suspected gram-negative infection)[57]. The patients treated with 2-hour Polymyxin B-immobilized hemoperfusion within 24-48 hrs of diagnosis of severe sepsis significantly increased cardiac index, left ventricular stroke work index, and oxygen delivery index compared with the controls.

Coupled plasmafiltration adsorption

Coupled plasma filtration adsorption (CPFA) is another technique that utilizes a sorbent placed in the plasma circuit in order to avoid bioincompatibility between blood cells and the sorbent. It uses a plasma filter that isolates plasma and redirects it through a synthetic resin cartridge before returning it to the blood (Fig. 2). A further filter can be coupled to provide standard RRT (Fig. 3). Animal studies have confirmed the efficacy of this technique, with the elimination of inflammatory mediators, immunomodulatory effects

(demonstrated by restored leukocyte responsiveness), and improved survival[52]. Human studies are limited but promising. Ronco et al have demonstrated that CPFA improves hemodynamics and leukocyte responsiveness compared with hemodiafiltration in 10 patients with hyperdynamic septic shock[58]. Not only was the capacity of monocytes to produce TNF in response to lipopolysaccharide restored, but phagocytosis was also returned to near-normal levels. In the second study, CPFA was applied in twelve septic patients with and without renal failure and showed improvements in hemodynamics and impressive survival rates (90% at day 28), despite high severity scores[59]. However, the size and design of the study prevented significant conclusions from being drawn.

Bioartificial kidney (BAK)

Cell therapy is the technique directed toward the expansion of specific cells to perform differentiated tasks and the introduction of these cells or cell products into a patient either within extracorporeal circuits or as implants in order to replace important differentiated processes damaged or lost in various disease states[60]. The concept of this therapeutic approach is based upon the growing appreciation that most disease processes are not due to the lack or excess of a single protein, but develop due to alterations in the complex interactions of a variety of cell products. Cells may provide a dynamic, interactive, and individualized therapy that responds to the pathophysiological condition of the patient.

As a result of a methodology to isolate and grow in tissue culture renal proximal tubular progenitor cells from adult mammalian kidneys, scientists could construct a combination of these living cells supported on synthetic polymeric hollow fibers[61]. Then a bio-artificial renal tubular assist device (RAD) was developed as a confluent monolayer along the inner surface of hollow fibers in a multi-fiber hollow fiber system[62]. This technique was proven *in vitro*[62] that it not only provided a clearance or filtration function of solutes, but also replaced the lost transport, metabolic, and endocrine properties of the kidney, which are predominately found in the tubular elements of the organ. Further studies have shown that the RAD, when incorporated in series with a hemofiltration cartridge in an extracorporeal blood perfusion circuit to formulate a bio-artificial kidney (BAK) (Fig. 4) replaces all of these functions in acutely uremic dogs[63]. Furthermore, BAK have been demonstrated to decrease

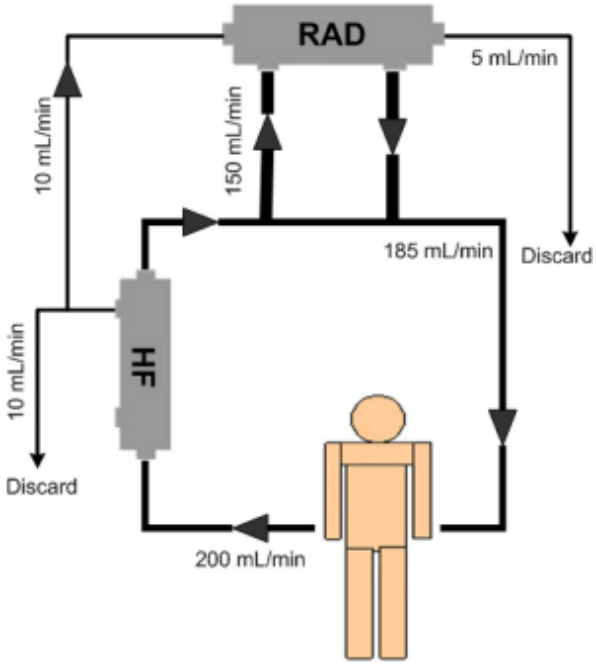

Fig. 4 Schematic of the extracorporeal circuit of the bioartificial kidney
RAD: renal tubular assist device; HF: hemofiltration cartridge [Modified from reference 66]

plasma cytokine levels, improve hemodynamics, and increase survival time in experimental septic animal models[64,65].

Recently, Hume et al have conducted a phase I/II clinical study to perform up to 24 hours of use of the BAK containing *human* proximal tubular cells as a RAD (Fig. 4) in ten ICU patients with ARF and multi-organ failure[66]. The results have suggested that, with the exception of one report of hypoglycemia, adverse events were limited to exacerbation of thrombocytopenia and hypotension, of which the latter responded to standard therapy. The RAD also demonstrated functional and metabolic performance in these patients. Therefore, a randomized, controlled phase II clinical trail is underway to assess the clinical safety and efficacy of this new approach.

Conclusion

A potent and convincingly efficacious treatment for sepsis remains elusive at present. Recent treatment guidelines are based on the established concept of early goal-directed therapy and essentially provides for supportive care. Drotrecogin alfa (activated) is one of the most promising of the options available, and its combination with other therapies is a further option.

A plethora of inflammatory mediators with pleiotropic characteristics propagates the sepsis syndrome when present in peak concentrations. Extracorporeal blood purification techniques can remove such mediators and may be the key to providing an efficacious treatment.

Renal dose hemofiltration is ineffective in sepsis. Higher dose hemofiltration or increasing plasma water exchange provides better quality blood purification of such mediators. This can be achieved by HVHF, high cutoff hemofiltration, plasmapheresis using a plasma filter and adjuvant modalities, such as sorbents. On the basis of cell therapy, the preliminary result of bio-artificial kidney is promising as a novel strategy in terms of renal replacement, even if its efficacy has not been proven as therapeutic option in sepsis.

All of these modalities demonstrate impressive results in animal and human studies in modifying hemodynamic variables and outcome. However, their true potential remains to be seen due to the lack of large, well-constructed studies. The timing of initiation of these therapies may be critical for their efficacy. A sensitive and specific marker for sepsis would greatly facilitate the recognition of a valid therapy, but none has yet been identified or at least been made available for a bedside test.

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บทบาทของ extracorporeal blood purification ในภาวะติดเชื้อในกระแสโลหิต

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ภาวะติดเชื้อในกระแสโลหิตชนิดรุนแรง เป็นสาเหตุลำดับต้น ๆ ของการเสียชีวิตและการเจ็บป่วยในผู้ป่วยวิกฤต ในปัจจุบันแม้ว่าจะมีความเข้าใจในพยาธิสรีรวิทยาของภาวะนี้เพิ่มขึ้น แต่อัตราการเสียชีวิตยังสูงมาก แนวทางการรักษาภาวะติดเชื้อในกระแสโลหิตที่สำคัญคือ การให้สารน้ำอย่างรวดเร็วในระยะแรกของโรค การให้คอร์ติโคสเตียรอยด์ขนาดปานกลางและการรักษาด้วย activated protein C สำหรับการใช้เทคนิคพิเศษต่าง ๆ เพื่อนำเลือดออกมาฟอกนอกร่างกาย สามารถกำจัดสารต่าง ๆ ที่เกิดขึ้นในภาวะติดเชื้อในกระแสโลหิตได้ การศึกษาในสัตว์ทดลองและในมนุษย์ที่มีภาวะการติดเชื้อในกระแสโลหิต พบว่าเทคนิคเหล่านี้ทำให้พลศาสตร์การไหลเวียนเลือดดีขึ้น และมีแนวโน้มที่จะใช้เป็นการรักษาเสริมในผู้ป่วยติดเชื้อในกระแสโลหิตชนิดรุนแรงหรือในผู้ป่วยที่มีภาวะช็อกจากการติดเชื้อได้ สำหรับผลทางคลินิกต่ออัตราการเสียชีวิตยังต้องรอการศึกษาที่มีขนาดใหญ่และเป็นการศึกษาแบบสุ่มต่อไป