CHAPTER 94

Blood Purification for Sepsis

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OBJECTIVES

This chapter will:
1. Introduce the concept of blood purification.
2. Explain the mechanisms of blood purification in sepsis.
3. Evaluate the commonly used blood purification technologies.
4. Discuss the limitations and future directions of blood purification technologies.

Extracorporeal blood purification (EBP) is a treatment in which a patient's blood is passed through a device (e.g., membrane, sorbent) in which solute (waste products, toxins) and possibly also water are removed. When fluid is removed, replacement fluid is added. EBP is used primarily in patients with renal failure (a procedure called *renal replacement therapy*). More than two decades ago,[1] it was observed that renal replacement therapy could remove inflammatory mediators from the plasma of septic patients. Subsequently, clinical improvements (e.g., hemodynamics, gas exchange) with hemofiltration were reported in animal studies.[2] A short time later, cytokine removal from the circulation of humans with sepsis also was demonstrated. Furthermore, a survival benefit associated with hemofiltration was reported.[3] With these advances, blood purification as a treatment for human septic shock was born. Since that time many technologic advances have occurred, along with substantial changes in medical professionals' basic understanding of sepsis and the inflammatory response. Modifications of existing technologies and new approaches have created a vast array of possible therapies to use or investigate.

MECHANISMS OF BLOOD PURIFICATION IN SEPSIS

Removal of Inflammatory Mediators

The pathophysiology of sepsis is complex and not yet completely understood. Sepsis includes the concomitant presence of an invasive infection and the host systemic inflammatory response syndrome (SIRS), which is characterized by an overinflammatory state resulting from a massive and deregulated activation of innate and adaptive immunity, usually followed by an equally massive and deleterious counterregulatory response leading to the so-called "immune paralysis." Therefore in septic patients there is a first early phase resulting from SIRS and a second late phase caused by immunosuppression and lymphocyte exhaustion.[4]

Septic AKI currently is considered to be the consequence of several concomitant factors: a dysfunction of the renal microvascular system, direct interaction of pathogen fragments with renal resident cells, the cytotoxic effect of the so-called "cytokine storm," and the deleterious cross-talk between failing organs. However, it generally is accepted that circulating inflammatory mediators directly may affect the renal parenchyma and are associated with an increased risk of mortality in AKI patients.[5] These soluble mediators include eicosanoids, leukotrienes, complement components, cytokines, chemokines, coagulation factors, and other potentially important small peptides and vasogenic substances.

Multiple attempts have been made to block the inflammatory response. Early efforts to block specifically the proinflammatory mediators failed. Thus the goal of EBP is

TABLE 94.1

Comparison of Commonly Used Technologies in Sepsis

TECHNOLOGIES	PRINCIPLES	FLUID BALANCE	PARAMETERS	COMMENTS
CVVH	Convection	Ultrafiltrate replaced by replacement solution	Q_B: 50–200 mL/min Q_{UF}: 20–35 mL/min K: 12–36 L/24 hr	High Q_{UF} needed to achieve meaningful cytokine removal
CHFD	Diffusion and convection	Replacement not required	Q_B: 50–200 mL/min P_F: 2–8 mL/min Q_D: 50–200 mL/min K: 40–60 L/24 hr	Limited data in sepsis
CPFA	Plasma filtration (convection) and hemadsorption	Maintained	Q_B: 50–200 mL/min P_F: 20–30 mL/min	Requires plasma separation
TPE	Plasma filtration/ exchange	Replaced with donor plasma	Q_B: 100–180 mL/min P_F: 39–82 mL/min	Sepsis with hematologic and other plasma-borne humoral diseases

CHFD, Continuous high-flux dialysis; *CPFA,* coupled plasma filtration adsorption; *CVVH,* continuous venovenous hemofiltration; *K,* clearance (urea); P_F, flow of plasma filtration; Q_B, blood flow; Q_D, flow of dialysate; Q_{UF}, flow of ultrafiltrate; *TPE,* therapeutic plasma exchange.

to restore homeostasis rather than to selectively inhibit pro- or antiinflammatory mediators.

Most immune mediators are water soluble and fall into the middle-molecular-weight category (roughly 5–50 kD) and therefore can be removed theoretically by EBP using standard techniques. EBP technologies can remove these inflammatory mediators via convection, diffusion, or adsorption. The effects are broad spectrum, autoregulating, and limited to the circulating pool of inflammatory mediators rather than influencing local tissue concentrations. These advantages provide a powerful rationale for blood purification used in sepsis.

Organ Support

The use of renal replacement therapy (RRT) in septic patients has been evaluated for renal support and immunomodulation. Although the modulation of inflammatory mediators appears to be the major objective of blood purification in sepsis, this therapy also may offer additional physiologic benefits, including temperature control, acid-base control, fluid balance control, cardiac support, protective lung support, brain protection, bone marrow protection, and blood detoxification and liver support. The extracorporeal circulation can be a potent modulator of body temperature and overall thermal balance. Negative thermal balance can be obtained depending on the length of blood lines, room temperature, and the replacement fluid temperature. Cardiac support can be achieved by optimizing fluid balance, reducing organ edema, and restoring preload and afterload to desirable levels. Optimizing the patient's volume state and removing interstitial fluid through the use of extracorporeal therapy may provide additional support to the failing lung. Blood purification may improve the encephalopathy of sepsis by removing uremic toxins and amino acid derivatives and correcting acidemia. Through the removal of uremic toxins, blood purification also offers bone marrow support. Through the combination of membrane separation processes and adsorption mechanisms, the blood purification system is available for detoxification and potentially has some role in liver support.

PURIFICATION TECHNOLOGIES AND THEIR EVALUATION IN SEPSIS

Several clinical trials in patients with severe sepsis and septic shock did not show outcome improvement. Septic patients still have an unacceptably high mortality rate, and the management is almost exclusively based on supportive therapies not able to interfere with the mechanisms of tissue injury and loss of immune homeostasis.

Blood purification therapies designed to remove substances from the circulation include diffusion-based hemodialysis, convection-based hemofiltration (including high-volume hemofiltration), mixed diffusive-convective strategies (hemodiafiltration), plasma therapy, hemoperfusion, or some combination thereof (Table 94.1). Despite considerable advances in knowledge and technical capability in recent years, there still is no consensus regarding the optimal method and optimal conditions under which to use these therapies.

High-Flux Conventional Hemodialysis

Solutes are transported across a semipermeable membrane generated by a concentration gradient. The extent of clearance is determined by the molecular weight of the solute, the concentration gradient across the membrane, temperature, and the membrane surface area, thickness, and pore size. Small solutes such as urea, creatinine, and electrolytes are cleared efficiently by diffusion. Therefore conventional hemodialysis is suitable for renal replacement therapy in renal failure. The addition of countercurrent dialysate flow accomplishes diffusive clearance by maximizing the concentration gradient between blood and dialysate through the length of membrane. Ultrafiltrate production is controlled by a blood pump whereby there is a balance of filtration and backfiltration, with ultrafiltrate produced in the proximal portion of the fibers and reinfused by backfiltration in the distal portion of the fibers so that replacement fluid is not always required. Dialysis membranes are classified further based on their ultrafiltration coefficients into high-flux and

low-flux membranes. For a given transmembrane pressure gradient, high-flux membranes have a higher filtration rate than do low-flux membranes.

The continuous high-flux dialysis technology uses a high molecular flow membrane (HFM), which has an average cutoff value of approximately 30 to 40 kDa and is capable of eliminating significant amounts of inflammatory mediators, including chemokines and cytokines in the middle-molecular weight category, without compromising the clearance of urea, and it is available for use in sepsis. Early studies have shown cytokine removal, and therefore the potential exists to exploit this therapy for sepsis.[6] However, these inflammatory mediators have a very high generation rate: for this reason, studies using CRRT failed to show any significant modulation of plasma levels of different cytokines.[7]

These continuous dialysis techniques also may use high cutoff membranes (HCO), which are porous enough to achieve the removal of larger molecules (30–60 kDa). Several studies showed benefits of using HCO therapy, such as an improved immune cell function, removal of inflammatory cytokines, and a reduction of catecholamine dosage. An undesired effect is albumin loss, which can be attenuated by albumin replacement or by using HCO membranes in a diffusive and not convective modality.[8]

High-Volume Hemofiltration and Convective Therapies

Hemofiltration is achieved by convective clearance, in which solutes are transported across a semipermeable membrane, along with movement of solvent (ultrafiltration) that occurs in response to a positive transmembrane pressure gradient. Here, the clearance depends on the ultrafiltration rate and sieving characteristics of the membrane and solute and, to a lesser extent, on the molecular size of the solute. Studies comparing convective clearance and diffusive clearance have shown that middle-molecular-weight substances and large molecules are better removed by convection. Although most of the inflammatory molecules fall in the middle-molecular-weight category and theoretically can be removed by hemofiltration, they have very high generation rates relative to uremic toxins. Thus the intensity of blood purification and the beneficial effects have been relatively modest with the traditionally used effluent flow rates of 1 to 2 L/hr. It generally is agreed that conventional hemofiltration is not effective for treatment of sepsis. Subsequently, investigators seeking to achieve "adequate blood purification" in sepsis hypothesized that higher ultrafiltration rates would be necessary. Defined by an ultrafiltration flow rate in excess of 35 mL/kg/hr and often as high as 75 to 120 mL/kg/hr, high-volume hemofiltration (HVHF) may be necessary to achieve clinically meaningful convective removal of inflammatory mediators. To achieve HVHF, it is necessary to use a high permeability membrane with a large surface area and sieving coefficient close to 1 for a wide spectrum of molecules.

Numerous studies have shown that synthetic filters used in hemofiltration can extract a wide array of substances involved in sepsis, at least to a certain degree.[6] HVHF has been shown to improve hemodynamics and survival either in endotoxic animal models or in septic patients. Use of HVHF was the subject of a recent Cochrane review[9]: selected trials comparing HVHF with a standard dialysis dose did not show any improvement of patients' outcome. As also suggested by the results of the recent clinical trial IVOIRE study,[10] despite a reported increase of hemodynamic stability and the absence of relevant adverse effects, these studies did not evidence a strong recommendation for the use of HVHF in critically ill patients with severe sepsis and septic shock. Furthermore, the application of HVHF potentially may cause an increased clearance of antibiotics and other drugs, electrolyte disturbances, and depletion of micronutrients, which may lead to a less favorable outcome.

Hemadsorption

Hemadsorption is a technique in which a sorbent is placed in direct contact with blood in an extracorporeal circuit. Nonspecific adsorbents, typically charcoal and resins, attract solutes through a variety of forces, including hydrophobic interactions, ionic (or electrostatic) attraction, hydrogen bonding, and van der Waals interactions. Manipulating the porous structure of solid-phase sorbents makes it possible to increase the selectivity of nonspecific adsorbents for particular solutes. In this case, solute molecules are separated according to their size and by their ability to penetrate the porous network of the sorbent materials. The adsorptive capacity for resins and charcoals is often high, in excess of 500 m^2 per gram of sorbent. Until recently, poor biocompatibility has been the major clinical limitation of these materials. Newer resin sorbents appear to have solved this issue with the addition of a biocompatible outer layer. In view of the high-molecular-weight adsorption characteristics of sorbents, it is possible to target larger molecules, exceeding the molecular weight cutoff of synthetic high-flux dialysis membranes. This makes sorbents potentially ideal for intervention in sepsis. Sorbents have been applied in combination with different treatment modalities, including being coupled with hemodialysis or coupled with plasma filtration.[11] The choice of modality is based on the properties of the sorbent and the technique used.[12,13]

The biocompatibility of these devices is the main limitation for their use and thrombocytopenia and bleeding risk are the potential most relevant side effects.[14]

Adsorptive membranes such as polymethyl methacrylate (PMMA) and AN69ST have also been used to enhance endotoxin and cytokine clearance and some clinical trials are underway in septic patients with AKI (mainly used in CVVHDF modality).[7]

Polymyxin B (PMX-B) is a cationic polypeptide antibiotic with activity against gram-negative bacteria and high affinity to endotoxin, but its intravenous use has been limited because of its nephrotoxicity and neurotoxicity. PMX-B has been fixed and immobilized onto polystyrene fiber in a hemoperfusion column cartridge that allows endotoxin removal without toxic effects.[15] The main mechanism of action is through removal of circulating endotoxin, although its effects are likely pleiotropic, including the entrapment of inflammatory cells such as monocytes and neutrophils and the clearance of cytokines TNF-α and IL-6 with a consequent reduction of the intracellular mechanisms of apoptosis.[16] Cruz et al.[15] published a meta-analysis showing that PMX-B hemoperfusion was used in patients with severe sepsis leading to an improvement of hemodynamics as measured by mean arterial pressure as well as by oxygenation. These results were observed in the EUPHAS trial in Europe that confirmed preliminary data coming from the Japanese experience.[17] However, the sample size of these studies was small and the confirmation of these clinical benefits in larger studies is still awaited. The first randomized, controlled, diagnostic-directed, and theragnostic trial named EUPHRATES (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults

Treated for Endotoxemia and Septic shock) is still ongoing in the United States and Canada.[18]

LPS Adsorber is a medical device designed for the extracorporeal use that contains a series of porous polyethylene plates coated with a peptide specific to endotoxin. Yaroustovsky et al. compared LPS adsorber and PMX-B hemoperfusion in patients with gram-negative sepsis without finding any significant difference in outcome (even with a small number of enrolled patients).[19]

CytoSorb is a highly adsorptive and biocompatible polymer able to remove multiple inflammatory mediators from the bloodstream. Animal studies have shown that the therapeutic apheresis using CytoSorb can restore chemokine gradients toward infected tissue and away from healthy organs through a sort of leukocyte trafficking control.[20]

Plasma Therapy

The term *plasma therapy* encompasses two therapies: plasmapheresis and plasma exchange.[13] Plasmapheresis is a two-step process in which blood first is separated into its components (cells and plasma) by means of a centrifugal pump or filter. Then the separated plasma is allowed to flow along column(s) containing different adsorbents, allowing the selective removal of components, and the processed plasma is reinfused in the patient. Therefore, in plasmapheresis, no (or minimal) replacement fluids are necessary. However, plasma exchange is a single-step process in which blood is separated into plasma and cells similarly through the use of centrifugation pumps or a filter, and the cells are returned to the patient, while the plasma is replaced with either donor plasma or albumin. Replacing volume lost with fresh frozen plasma is also done to replete any factor(s) (immunoglobulins) necessary to restore homeostasis and often to correct the underlying disorder for which the plasma therapy was prescribed. Simply put, plasma exchange is used to remove "bad" things and replace "good" things, whereas plasmapheresis simply removes harmful substances. It has been argued that plasma therapy is most likely to be effective in patients with sepsis-associated thrombotic microangiopathy.[21,22]

Plasma filtration is an imprecise term because it can be used to perform either plasmapheresis (if the treated plasma is reinfused) or plasma exchange (if donor plasma is used). Plasma exchange using filtration has advantages over centrifugal plasma exchange in that it is less expensive and can be performed with the same machines used for continuous renal replacement therapy. Past animal studies and clinical trials show plasma filtration and/or adsorption are promising blood purification technologies in sepsis.[23–30] To overcome the shortcomings of plasma filtration and improve the removal efficiency, a technology called *coupled plasma filtration adsorption* (CPFA) uses an activated charcoal sorbent cartridge placed in series with, but downstream of, the plasma filter.[11] CPFA improves the removal of nonspecific mediators. This system is coupled in series with a standard RRT circuit.

Some studies have shown interesting results concerning an improvement of hemodynamics, microvascular derangement, and respiratory parameters in the course of CPFA. In the COMPACT (COMbining Plasma-filtration and Adsorption Clinical Trial) study[31] Livigni et al. did not observe a reduction in mortality, or in other important clinical outcomes, in patients with septic shock treated with CPFA. However, in this study, a subgroup analysis suggested that CPFA could reduce mortality when a high volume of plasma is treated. The ongoing COMPACT2 study will clarify whether the application of high doses of CPFA in addition to the current clinical practice is able to reduce hospital mortality in septic shock patients in intensive care units.

INDICATION AND INTERVENTION OUTCOMES

Even though available blood purification technology has no proven value in sepsis, patients with refractory septic shock often benefit from the blood purification intervention, at least in terms of hemodynamic improvement. Furthermore, some humoral immunopathogenic diseases that can complicate sepsis, such as thrombotic thrombocytopenic purpura and thrombocytopenia-associated multiple-organ failure, respond to plasma therapy.

Possible physiologic and biologic outcomes for the blood purification therapy include improved organ dysfunction (in particular cardiopulmonary and renal function), decreased need for vasopressor drugs, improved vital signs, improved acid-base homeostasis, and decreased cell toxicity of plasma and blood levels of mediators. Among these mediators, interleukin-6 and procalcitonin appear to show the tightest correlation with clinical outcome and may be particularly useful markers in sepsis. For thrombotic thrombocytopenic purpura and thrombocytopenia-associated multiple-organ failure, removal of very large von Willebrand factors and possibly other mediators is essential.[25]

Of particular interest is the observation that some extracorporeal therapies may limit sepsis-associated AKI: this protective effect may be ascribed to the removal of endotoxin or other inflammatory mediators, thus limiting the mechanisms of microvascular alterations and tubular epithelial cell injury.[32]

CONCLUSION

Although this wider approach to blood purification in sepsis seems logical and promising and opens new perspectives, many questions still remain unanswered, including the timing, duration, and frequency of these therapies in the clinical settings. Current technologies still remain inadequate for the removal of middle-molecular-weight substances, and the current practice worldwide is extremely variable. Moreover, there is a lack of large-scale randomized clinical trials.

To address these limitations, several approaches are worthy of further investigation. One of them would be to increase the porosity of membranes to improve middle molecular clearance. Such high-porosity hemofiltration has been tested in animals with promising results.

Large multicenter trials evaluating the efficacy of these therapies to improve valid clinical outcomes (i.e., mortality or organ failure), rather than surrogate markers such as mediator clearance or transient improvement in physiologic variables, are required to define the precise role of these therapies in the management of sepsis.

New developing technologies may enhance the clinical results of current RRT strategies: a renal assist device (RAD) containing viable tubular epithelial cells has been evaluated in experimental studies and in clinical trials showing a significant reduction of mortality in comparison to standard RRT.[33] Other devices able to sequestrate activated leukocytes within dialysis filter limiting inflammation are currently

under investigation: the selective cytophoretic device (SCD) showed a reduction of mortality and dialysis dependence in septic patients.[34] Last, anticoagulation strategy may play a key role in the inflammatory mechanisms related to sepsis: recent studies that should be confirmed by observation in a larger number of patients suggested that in respect to heparin, regional citrate anticoagulation (RCA) may have antiinflammatory properties associated with a reduced mortality.[34]

Key Points

1. There is currently a clear biologic rationale for blood purification used in sepsis. Immunomodulation and organ support play important roles in the application of blood purification.
2. Conventional continuous venovenous hemofiltration and hemodialysis have been shown not to be effective in sepsis in the absence of concomitant acute renal failure.
3. Plasma therapies, high-volume hemofiltration, hemadsorption, or combinations of these therapies appear promising.
4. Multicenter randomized controlled trials are needed to test these promising blood purification technologies.

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A complete reference list can be found online at ExpertConsult.com.

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