Adsorption in sepsis

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Adsorption in sepsis. The pathophysiology of sepsis offers a highly complicated scenario. In sepsis, endotoxin or other gram-positive-derived products induce a complex and dynamic cellular response, giving rise to several mediators known to be relevant in the pathogenesis of septic shock such as specific mediators, substances responsible for up- or down-regulation of cytokine receptors and cytokine antagonists, inactivators of transnational or transductional pathways, and precursor molecules. In this review, we delve into some new concepts stemming up from the use of sorbents in continuous plasma filtration. Nonspecific simultaneous removal of several mediators of the inflammatory cascade have led to improved outcomes in animal models of septic shock and to improved hemodynamics in a pilot clinical study. It seems of great importance to explore all possible treatment techniques that may have a direct impact on circulating mediators of sepsis and that also may interfere with the imbalance between proinflammatory and anti-inflammatory substances in the critically ill patient with multiple organ failure. In this view, the application of sorbents appears to open new and interesting therapeutic options. The search for innovative treatments specifically targeted to the special needs of the critically ill patients seems therefore more important than the attempt to adjust concepts and technologies that are normally applied to patients with chronic renal failure.

Sepsis is the leading cause of acute renal failure (ARF) and mortality in intensive care units [1–3]. It generally develops as a result of the host response to infection [4]. The pathogenesis of sepsis represents a complex mosaic of interconnected events in respect to which therapeutic strategies remain elusive. Sepsis may be considered a form of severe systemic inflammation caused by local and systemic effects of circulating proinflammatory mediators [5]. Although several therapeutic attempts have targeted specific components in the proinflammatory septic cascade, no improvement in survival has been obtained in large-scale clinical trials focusing on specific molecules [6]. Components of gram-negative bacteria cell wall, such as the lipid A-containing lipopolysaccha-

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of anti-inflammatory cytokines (Fig. 1) [7, 11–13]. All therapies specifically devoted to sepsis have so far obtained frustrating results [6]. Liano et al prospectively observed that ARF in the intensive care unit occurs predominantly as part of a multiple organ failure, while isolated ARF is the usual presentation in non-intensive care unit patients [14]. Their study implied a higher mortality in critically patients who developed ARF, supporting the concept of a direct effect of the ARF itself on the mortality. Nevertheless, not only should therapeutic strategies be applied to treat ARF itself, but any available technique should be involved in the possible prevention of such derangement. This global approach probably would help in modifying the course of the septic syndrome, and it may have an impact on mortality of the critically ill patients.

CONTINUOUS RENAL REPLACEMENT THERAPIES

Critically ill patients with ARF are preferably treated with continuous renal replacement therapies (CRRTs) [15, 16]. Conventional CRRTs such as hemofiltration (CVVH) or hemodiafiltration (CVVHDF) have allowed treatment of patients who could not be treated otherwise, because of the remarkable hemodynamic instability and the severe catabolic status [17]. Because of slow and gentle ultrafiltration, CRRTs make it possible to control fluid and electrolyte balance maintaining the patient in steady hemodynamic conditions. Continuous fluid removal allows infusion of large amounts of fluids and ensures adequate caloric intake. In spite of these definite advantages, the role of CRRTs in the framework of “blood purification” has been challenged, and it is sometimes considered of minimal or no clinical relevance [18, 19]. Nevertheless, the use of CRRTs is expanding, and new potential advantages have been proposed. The use of high permeability membranes in CRRTs allows the removal of measurable quantities of cytokines, although plasma levels seem to not be affected [19]. The mechanism of cytokine removal from the circulation seems to rely on filtration and membrane adsorption. Transport of sepsis-associated mediators across highly permeable membranes may be largely unpredictable because of variable effects of filtration rates, molecular interactions, presence of electric charges, hydrophilic or hydrophobic sites on the membrane, and finally binding to plasma proteins and/or acute phase reactants, as well as to cell receptors. The possible elimination of cytokine-inducing compounds rather than the cytokines should also be considered when dealing with highly permeable membranes. Hoffmann et al reported that hemofiltration may remove cardiotoxic compounds [20] and TNF-α−,
but not IL-6– or IL-1β–inducing compounds [21]. Figure 2 summarizes the list of different mediators that are known to be associated with sepsis. As can be seen, a large part of these mediators has molecular weights above the cutoff of highly permeable synthetic membranes used in CRRTs. Therefore, considering all of the previously mentioned factors, it seems that highly permeable membranes may have a limited capacity of removal for molecules involved in the pathogenesis of sepsis. Because of the limited capacity of filtration and...
Table 1. The use of sorbents in clinical practice

<table>
<thead>
<tr>
<th>Sorbent Type</th>
<th>Modality</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonselective Charcoal</td>
<td>Hemoperfusion</td>
<td>Poisoning, Chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>uncoated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>coated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncharged resins (Amberlite XAD-7)</td>
<td>Hemodialfiltration, Chronic renal failure</td>
</tr>
<tr>
<td>Selective Hydrophobic resins</td>
<td>Coupled plasma filtration adsorption (CPFA)</td>
<td>Rabdomiolysis, hepatic failure</td>
</tr>
<tr>
<td>Powdered sorbent</td>
<td>Hemodialfiltration and regenerative push-pull pheresis</td>
<td>HIV; drug overdose; hepatic failure</td>
</tr>
<tr>
<td>Microsphere-based detoxification system</td>
<td>Regenerative push-pull pheresis</td>
<td>Poisoning, LDL apheresis</td>
</tr>
<tr>
<td>Engineered matrices: Polymyxin-B</td>
<td>polystyrene-derivative fibers; macroporous cellulotic beads;</td>
<td></td>
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<tr>
<td>Engineered matrices: polyethylenimine</td>
<td>macroporous cellulotic beads</td>
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the possible early saturation of the sites for adsorption, it is very unlikely to obtain significant variations in plasma circulating levels of the substances involved in the systemic inflammatory syndrome.

INNOVATIVE TECHNIQUES IN CRRTS

Conventional CRRTs have gained increased popularity because of their ability to remove the excess fluid and sodium in septic patients. The efficiency in terms of urea and other toxin removal is not questioned today. Limitations seem to become evident for protein-bound compounds or for solutes in the molecular range beyond the membrane cutoff. In order to enhance the removal of septic-associated mediators, two approaches have been taken under consideration. In their original proposal, Grootendorst et al suggested that high-volume (100 L/day) hemofiltration could remove myocardial depressant factors and other sepsis mediators [22]. Some of these mediators could be found in the ultrafiltrate extracted from a pig model of septic shock. In a subsequent clinical study, Bellomo et al confirmed this possibility, as evidenced by a significant reduction in norepinephrine administration in animals with septic shock [23].

A different approach has been to use membranes with larger pores and permeability characteristics superior to those currently used in hemofiltration. Lee et al suggested an increased survival in a porcine model of septic shock and related it to a general effect of enhanced blood purification [24]. Other authors have reported either in animal [25] or human [26] studies improved survival when using plasmapheresis. In vitro studies show that plasma filtration allows the removal of higher amounts of proinflammatory cytokines such as TNF-α, IL-1β, and IL-8. Clearance and sieving coefficients of these cytokines are significantly increased with “open” plasma filtration membranes in comparison to high-flux hemofiltration membranes [27]. Based on these considerations, it would appear of great interest to expand the use of plasmapheresis in septic patient and to study its impact on survival on a larger scale. However, plasmapheresis is hardly considerable as a CRRT. Large amounts of plasma substitutes and the evident cost implications may, in fact, limit the application of these techniques in the clinical stage. Furthermore, plasma filtration techniques may lead to unwanted losses of plasma constituents that cannot be adequately replaced by substitution fluids.

The combined requirements of a CRRT with high sieving capacity and possible selective removal of sepsis-associated mediators seem to find an answer in the application of sorbents.

SORBENTS IN EXTRACORPOREAL THERAPIES

The use of sorbents in extracorporeal therapies has been applied to the management of both acute and chronic renal failure (Fig. 3 and Table 1) [28]. Classically, hemoperfusion (HP) has been described as a technique in which the sorbent was placed in direct contact with blood in an extracorporeal circulation. More recently, this technique and other techniques like apheresis have witnessed intensive research. Sorbents may be of natural origin such as charcoal (mineral or vegetal) or synthetic (different resins with covalently bound groups reactive with specific ligands). Sorbents have been applied in different treatment modalities such as HP, HP coupled with hemodialysis (HPHD), double-chamber hemodialfiltration (PFDsorb), or coupled plasma filtration-adsorption (CPFA; Fig. 4). HP has the advantage of a much simpler circuit, but it requires a very biocompatible sorbent because of the direct contact with blood and with blood cells in particular. Charcoal has a high adsorbing capacity, especially for low molecular weight waste products that accumulate during kidney or liver failure. Its use in HP, however, requires a coating of the sorbent surface to make it biocompatible. Coated charcoal, although biocompatible, has a remarkably reduced adsorptive capacity because of the cutoff of the coating material. More recently, synthetic polymers have been introduced with remarkable capacity for adsorption. The size selectivity is only offered by the size of the pores on the surface of the granular elements and not by the material
Fig. 4. Possible modes of application of sorbents. (Top) The sorbent unit is placed in series before the hemodiafilter. Blood comes in direct contact with the sorbent, and high biocompatibility is required. The system is defined HPHD. (Middle) The sorbent unit is placed online in the ultrafiltrate produced from an hemofilter. The hemofilter is placed in series with the hemodiafilter. The system is used for online hemodiafiltration in chronic patients, and it is defined as paired filtration dialysis with sorbent (PFDsorb). (Bottom) The sorbent unit is placed online in the plasma filtrate produced from a plasma filter. The plasma filter is placed in series with the hemodiafilter. The system is used for critically ill patients with septic shock, and it is defined as coupled plasma filtration adsorption (CPFA).

Table 2. Plasma treatment in sepsis: Criteria to assess safety.

<table>
<thead>
<tr>
<th>In vitro</th>
<th>In vivo</th>
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</thead>
<tbody>
<tr>
<td>• Absorption of proteins (e.g., coagulation factors)</td>
<td>• Mortality in control animals</td>
</tr>
<tr>
<td>• Adsorption of antibiotics</td>
<td></td>
</tr>
<tr>
<td>• Activation of fluid phase systems (e.g., complement, coagulation, fibrinolysis, kinins)</td>
<td></td>
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<tr>
<td>• Toxicology tests</td>
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<tr>
<td>• Endotoxin content</td>
<td></td>
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<tr>
<td>• Particulate release</td>
<td></td>
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<tr>
<td>• Pressure drop</td>
<td></td>
</tr>
<tr>
<td>• Biocompatibility tests (ISO 9000)</td>
<td></td>
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<tr>
<td>• Risk analysis of the circuit</td>
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</tbody>
</table>

In another technique using uncoated sorbents [detoxification plasma filtration (DTPF); HemoCleanse, Inc., West Lafayette, IN, USA], a hemodiabsorption mechanism is associated with a push-pull plasma filtration system (a suspension of powdered sorbents surrounding 0.5 microns plasma filter membranes). Bidirectional plasma flow (at 80 to 100 mL/min) across the plasma filtration membrane provides direct contact between plasma proteins and powdered sorbents, as well as clearance of cytokines (TNF-α, IL-1β, and IL-6) [29].

There has been a widespread tendency to remove “bad factors” rather than to attempt to bring about a restoration of balance of physiological factors. Often, too much emphasis has been placed on individual markers. We suggest that treatments should focus more carefully on a “balancing hypothesis” trying to restore a correct equilibrium between immunologic suppression and activation.

This is particularly true when the converging concepts of plasma filtration coupled with adsorption are to be applied to the very complex scenario of severe sepsis evolving in septic shock.
CONTINUOUS PLASMA FILTRATION ADSORPTION

Continuous plasma filtration adsorption (CPFA) is a modality of blood purification in which plasma is separated from whole blood and circulated in a sorbent cartridge. After the sorbent unit, plasma is returned to the blood circuit, and the whole blood undergoes hemofiltration or hemodialysis.

Rationale

The rationale consists in the attempt to achieve adequate removal of molecules that are not removed by other hemofiltration or hemodialysis techniques. The rationale for exposing the plasma to the sorbent in a plasma filtration system is to exclude the blood cells from the contact with the sorbent and to reinfuse endogenous plasma after nonselective simultaneous removal of different sepsis-associated mediators without the need of donor plasma. The main issue is concerning the sparing effect on endogenous plasma as compared with potential unwanted losses of autologous plasma compounds.

The interesting rationale for such application has stimulated a series of in vitro studies [27] and in animals, specifically on a model of rabbit endotoxic shock [30]. These studies also aimed at assessing safety (Table 2). Various types of sorbents have been tested for this application (Fig. 5).

In vitro studies

In vitro studies demonstrated that removal rates for different molecules may be very different according to the structure and nature of the used sorbent [27]. More importantly, when tested at different linear velocity of the cross flow, the efficiency in removing cytokines is maintained in a wide range of flow rates. Increased cross flow velocity may reduce the efficiency of the sorbent. In spite of that, the amount of cytokine removed in one passage is far above the overall amount of cytokine carried into the sorbent cartridge (calculated on the basis of the highest levels detected in the plasma and the blood flows utilized in CRRT) by the blood from septic patients [27]. These studies also showed that for hydrophobic resins of a given particle and pore size the binding of cytokines (TNF-α) occurs after prior adsorption of α2-macroglobulin, the carrier of cytokines in plasma.

A major criticism may be raised concerning the removal of beneficial substances or drugs by the mechanism of adsorption. By using the experimental conditions described in Tetta et al [27], we assessed the different adsorptive properties of a hydrophobic resin for the most commonly used antibiotics (Fig. 6). Except for Vancomycin, where a modest removal can be observed, the levels of other antibiotics such as Tobramycin or Amikacin tend to remain stable over time.

Animal studies

Animal studies were performed in a rabbit model of septic shock [30]. The model consisted of a single intravenous injection of LPS. The dose was experimentally adjusted to determine a mortality of 80% of the control animals at 72 hours. Coupled plasma filtration-adsorption resulted in a significant (P = 0.0041) survival (85%) at 72 hours with respect to untreated control rabbits injected with the same amount of LPS.

In the pathogenesis of gram-negative infections, the
complex and dynamic host interaction involves the inflammatory cascade, complement activation, coagulation cascade, and hemodynamic derangements. In the animal model, improved survival was negatively correlated with the severity score, which included plasma LPS concentration, bioactive TNF, as well as mean arterial pressure (MAP), base excess (BE), and white blood cell count (WBC). However, cumulative survival was not correlated with the levels of circulating TNF. It must be emphasized that the overall net effect on survival could be due to the removal not only of the measured mediators, but also to many other mediators not monitored in our study. The possibility that simultaneous removal of different mediators could be linked in a cause-effect relationship with improved survival in our experimental model was suggested. Furthermore, the study provided the rationale for the application of this new method of blood purification in septic patients undergoing CRRT [31, 32].

**Clinical trial**

A prospective randomized crossover trial aimed at comparing clinical and biological effects of CPFA versus CVVH in critically ill septic patients has recently been concluded. Preliminary results were presented in abstract form (abstract: Brendolan et al, *J Am Soc Nephrol* 9:A0655, 1998). The major findings can be summarized as follows: restoration of cell responsiveness to exogenous
LPS after five hours of treatment in all patients; increased systemic vascular resistances and significant reduction of the dose of norepinephrine required to maintain a stable hemodynamics in the patients (mean 30%). These data suggest the possibility that CPFA, as opposed to CVVH, may ensure an improved hemodynamic response in highly unstable patients. Since CPFA may be modular to conventional CVVH, the two modalities can be carried out in series. The system may ensure a fluid and salt balance together with enhanced blood purification for various molecules.

Efficiency and adequacy of treatment, known milestones in the extracorporeal treatment for chronic renal failure, are now reconsidered in critical care nephrology. The complex scenario of sepsis must not be underestimated. Notwithstanding, 20 years or so after the first descriptions, we all face a disease with an ever-increasing incidence and unacceptably high mortality.

Innovative techniques address the importance of dedicated extracorporeal systems for sepsis where ARF is just one of the pathologic complications. This wider approach to the concept of blood purification opens new perspectives in a revisited strategy for the application of extracorporeal treatments.

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REFERENCES