Chapter 50. Extracorporeal Blood Purification Therapy for Sepsis

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INTRODUCTION

Extracorporeal blood purification (ECBP) has been widely used during the past 30 years, initiating from the treatment of patients with end-stage renal disease (ESRD) with hemodialysis technique. The advancement in terms of the equipment and techniques related to blood purification as well as a better understanding and an increased body of knowledge about the mechanism of the solute clearance and fluid removal have led to an adaptation of the new techniques based on the principles of acute dialysis. Apart from being used in renal replacement therapy (RRT), this knowledge can be applied and used in the treatment of other organs such as in liver support therapy, respiratory support, and cardiac support. Moreover, the techniques employed in continuous renal replacement therapy (CRRT) can also be used to remove inflammatory mediators in patients with septic shock and multiple organ dysfunction syndrome (MODS).

The main objective of this chapter is to compile the body of knowledge related to the techniques used in ECBP in sepsis.

EXTRACORPOREAL BLOOD PURIFICATION FOR SEPSIS

Sepsis is frequently found and is the major cause of death in an intensive care unit. The average mortality rate is 30% and can be increased to 50% if septic shock is involved. For sepsis, the use of bactericidal antibiotics and fluid administration are considered as a standard medical therapy (SMT). With sepsis, however, not only is there bacteria that can negatively affect the body, but inflammatory mediators or bacterial toxins can also have a direct effect on the function of the major organs, such as the heart, lung, kidneys and the livers, causing circulatory failure, and hemodynamic instability.

The principle of an ECBP therapy is that it is an adjunctive therapy that helps remove inflammatory mediators or bacterial toxins from blood circulation. It is an adjunctive therapy to SMT at present. There are several techniques to remove these inflammatory mediators including high-volume hemofiltration (HVHF), cascade hemofiltration, hemoadsorption (hemoperfusion), plasmapheresis, coupled plasma filtration adsorption (CPFA), and high cutoff (HCO) hemodialysis.

This chapter will discuss the principles and theories related to the use of ECBP in sepsis, following by current techniques in use and clinical evidences.
Principles of Blood Purification

It is commonly known that a systemic inflammatory response occurring during sepsis and septic shock can cause immunologic instability. When this becomes uncontrollable, it can lead to a multiorgan failure syndrome (Fig. 50.1 and Table 50.1). Currently, there are four main theories trying to describe the mechanism of how ECBP can help with sepsis as follows:

FIGURE 50.1. Illustrating the role of extracorporeal blood purification in the treatment of multiple organ dysfunction syndrome namely performing isolated ultrafiltration for congestive heart failure, CO₂ removal blood purification for the treatment of acute respiratory distress syndrome, liver dialysis for liver failure, and continuous renal replacement therapy (CRRT) for the treatment of acute kidney injury.

1. Peak concentration hypothesis or “Ronco concept”: The mechanism of sepsis involves the production of proinflammatory cytokines and anti-inflammatory cytokines (shortly called a compensated anti-inflammatory response syndrome or CARS). This can occur in a serial manner, that is, proinflammatory cytokines are generated first, following by anti-inflammatory cytokines. This is called the serial sepsis theory. It can also occur in a parallel manner, that is, both pro- and anti-inflammatory cytokines are generated simultaneously. At present, there is still no consensus on which is the principle theory.

Ronco and Bellomo postulated the “peak concentration hypothesis” suggesting that both proinflammatory and anti-inflammatory mediators should be removed by any methods so as to cut the “peak” of these mediators in blood circulation in order to restore the situation of immunohomeostasis, that is, an immune-modulatory effect in the tissue level.  

2. Threshold immunomodulation hypothesis or “Honore’ concept”: This theory proposes that when the removal of cytokines in blood circulation occurs, other cytokines in the tissue level will be released into the circulation in...
order to create the balance point between the cytokines in blood circulation and tissues. This theory can explain the phenomenon why blood purification therapy in sepsis patients, possibly decrease the mortality rate in the patients without any reduction of inflammatory cytokines detected.

3. **Mediator delivery hypothesis or “Alexander concept”**: According to this theory, not only HVHF is used to remove various mediators, but it also involves a large input of incoming fluids (3–5 L/h) into the body, causing the lymphatic flow to increase 20–40 times. This results in an increase of mediators and cytokines lymphatic drag from the tissue level to blood circulation.³

4. **Cytokinetic hypothesis**: Peng and colleagues believes that blood purification has an effect on inflammatory cells as it enhances the performances of monocytes, neutrophils, and lymphocytes after removal pro- and anti-inflammatory cytokines. There has been evidence in animal study which showed more inflammatory cells infiltrating around the infectious sites. This result in a better clearance of bacteria.

## Extracorporeal Blood Purification Technique in Sepsis

### High-volume Hemofiltration

High-volume hemofiltration is a modality of blood purification therapy that is most easily adapted and was widespread in the past. HVHF is in fact an increase of dose of CRRT (the UF rate of more than 35 mL/kg/h or 60 L/day in a patient of 70 kg) in order to increase the convection. The findings from an animal experiment pointed out that the use of HVHF to treat sepsis could yield the best result for the survival rate if used from the initial stage of sepsis. The HVHF of 100 mL/kg/h was used in experimental animals while that of averagely 40 mL/kg/h was used in patients with septic shock/severe sepsis. It was found that HVHF helped improve the hemodynamics, decreased the need of vasopressor,⁴–⁷ and tended to increase the survival rate of the patients.⁵⁻⁹

*Clinical evidence*: The latest data was derived from the IVOIRE study (High VOlume in Intensive caRE), a multicenter randomized controlled study in France targeting the treatment of septic patients with AKI based on the Risk, Injury, and Failure and Loss and End-stage Kidney (RIFLE) criteria. In this study, the 480 patients were randomized to treat with CVVH at the dose of 35 mL/kg/h compare with the dose of 70 mL/kg/h for 96 hours, and evaluate the survival rate on the 28th, 60th, and 90th day after ICU admission.

### Table 50.1. A summary of the studies on the use of high-volume hemofiltration in patients with septic shock.¹

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Clinical setting</th>
<th>Dose mL/kg/h</th>
<th>Improved hemodynamics with HVHF</th>
<th>Improved survival with HVHF</th>
<th>P value (survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honore’ et al. 2000</td>
<td>Prospective Cohort, uncontrolled</td>
<td>20</td>
<td>Refractory septic shock</td>
<td>115</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28-day survival:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(expected) uncontrolled</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>to 45% (observed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cole et al. 2001</td>
<td>Randomized, cross over</td>
<td>11</td>
<td>Septic shock with multiple organ failure</td>
<td>6,000 mL/h</td>
<td>Yes</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td>Joannes-Boyau et al. 2004</td>
<td>Prospective Cohort, uncontrolled</td>
<td>24</td>
<td>Septic shock</td>
<td>40–60</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;0.075</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28-day survival:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Extracorporeal Blood Purification Therapy for Sepsis

**Study**  | **Design**  | **N**  | **Clinical setting**  | **Dose mL/kg/h**  | **Improved hemodynamics with HVHF**  | **Improved survival with HVHF**  | **P value (survival)**
--- | --- | --- | --- | --- | --- | --- | ---
Laurent et al. 2005  | RCT  | 61  | Resuscitated cardiac arrest  | 200  | Yes  | Yes  | 6-month survival: 21–45%  | 0.026
Jiang et al. 2005  | RCT  | 37  | Severe acute pancreatitis  | 4,000 mL/h  | Yes  | Yes  | 14-day survival: 68.4–94.4%  | <0.01
Ratanarat et al. 2005  | Prospective Cohort, uncontrolled  | 15  | Severe sepsis  | 85 (pulse HVHF)  | Yes  | Yes  | 28-day survival: 30% (expected) to 53% (observed)  | N/A
Piccinni et al. 2006  | Retrospective, uncontrolled  | 80  | Septic shock  | 45  | Yes  | Yes  | 28-day survival: 27.5–55%  | 0.005
Cornejo et al. 2006  | Prospective Cohort, uncontrolled  | 20  | Refractory septic shock  | 100  | Yes  | Yes  | Hospital survival: 37% (expected) to 60% (observed)  | <0.03
Boussekey et al. 2008  | RCT  | 20  | Septic shock  | 65  | Yes  | No  |  | 0.65
Zhu et al. 2009  | Retrospective  | 63  | Severe acute pancreatitis  | 60–80  | No  | Yes  | 28-day survival: 65.5–91.2%  | 0.014
IVOIRE study, 2013  | RCT  | 150  | Septic shock  | 70  | No  | No  | 28-day mortality  | 0.94
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Clinical setting</th>
<th>Dose mL/kg/h</th>
<th>Improved hemodynamic with HVHF</th>
<th>Improved survival with HVHF</th>
<th>P value (survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HVHF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(HVHF: high-volume hemofiltration; RCT: randomized controlled trial)

Table 50.2. A list of adsorbers, manufacturers, and the types of sorbents available at present.

<table>
<thead>
<tr>
<th>Names of adsorbers</th>
<th>manufacturers</th>
<th>Types of sorbents</th>
<th>Substances to be adsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMX</td>
<td>Toray, Japan</td>
<td>PMX covalently bound to polypropylene-polystyrene fiber</td>
<td>Endotoxin</td>
</tr>
<tr>
<td>oXiris</td>
<td>Baxter, USA</td>
<td>AN69, PEI, heparin grafting</td>
<td>Endotoxin, cytokines</td>
</tr>
<tr>
<td>HA330</td>
<td>Jafron, China</td>
<td>Neutral resin</td>
<td>Cytokines</td>
</tr>
<tr>
<td>MG350</td>
<td>Biosun, China</td>
<td>Neutral resin</td>
<td>Cytokines</td>
</tr>
<tr>
<td>CPFA</td>
<td>Bellco, Italy</td>
<td>PES plasma filter, hydrophobic resin cartridge, high-flux hemofilter</td>
<td>Cytokines</td>
</tr>
<tr>
<td>Cytosorb</td>
<td>Cytosorbents, USA</td>
<td>Polystyrene-divinyl benzene copolymer beads with biocompatible polyvinylpyrrolidone coating</td>
<td>Cytokines</td>
</tr>
<tr>
<td>LPS adsorber</td>
<td>Alteco, Sweden</td>
<td>Synthetic polypeptide bound to porous polyethylene disks</td>
<td>Endotoxin</td>
</tr>
</tbody>
</table>

(PMX: polymyxin; CPFA: coupled plasma filtration absorption; LPS: lipopolysaccharide; PEI: polyethylenimine; PES: polyethersulfone)

The findings, however, show that no significant differences in the mortality rate were found.\textsuperscript{10}

**Hemoadsorption**

Hemoadsorption is a technique utilizing a sorbent to adsorb undesirable substances using the quality of hydrophobic interactions, ionic attraction, hydrogen bonding, and the van der Waals forces.\textsuperscript{11} The interesting aspect of hemoadsorption is its ability to adsorb substances with high molecular weight that cannot generally be filtered through a common high-flux filter. At present, there are certain filters with the ability to adsorb endotoxin, proinflammatory cytokines, and anti-inflammatory cytokines as shown in Table 50.2. This chapter will mainly discuss the polymyxin hemoperfusion technique as it is the technique with abundant clinical data and the longest clinical use.

**Polymyxin B Hemoperfusion, PMX-HP (Toraymyxin®)**

Polymyxin B is a bactericidal antibiotic used against Gram-negative bacteria and it can neutralize endotoxin (lipopolysaccharide) by directly binding with endotoxin. This antibiotic cannot be administered through IV as it will
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become toxic for the kidneys and the nervous system. Polymyxin-B is bound with synthetic to form polymyxin B-immobilized fiber which possesses an ability to be a hemoperfusion column that can adsorb endotoxin, but without its bactericidal quality or its systemic effect until it becomes toxic for the kidneys and the nervous system (Fig. 50.2).

In Japan, there is a widespread use of PMX-HP because since 1994, the Pharmaceuticals and Medical Devices Agency of Japan has approved the use of it in patients with all three conditions as follows:

1. With endotoxemia or having indication to be infected with Gram-negative bacteria.
3. Patients with septic shock who need to be treated with vasopressor.

PMX-HP Techniques

PMX-HP employs the same circuit as normal hemodialysis, with the use of a double lumen dialysis catheter like in hemodialysis. During the process, there is no need for any dialysate solution or replacement fluid. Two sessions of PMX-HP are needed, with the duration of 2 hours per session. During the PMX-HP process, it is advisable that 3,000 unit of heparin is employed as anticoagulant, with the rate of 20 unit/kg/h. However, even with contraindication against the use of anticoagulant, PMX-HP can still be performed. After the treatment, if the condition of the patient is still not better, it is possible to consider increasing the duration per session or increasing the number of session for PMX-HP process for particular patient. Figure 50.3 illustrates the PMX-HP circuit.

Clinical evidence: A meta-analysis examining the use of PMX-HP in the treatment of sepsis patients was conducted by compiling 16 comparative studies done on 1,040 patients (nine out of these studies were RCT), and 16 pre-post studies on 385 patients, 83 of which using hemoperfusion with PMX-F together with a SMT, with the blood flow rate of 50–150 mL/min through venovenous access for 2 hours/session, for 1–2 times. It was found that the patients receiving PMX-F had a lower rate of endotoxin, increased mean arterial pressure (MAP) (26%), could decrease the use of dopamine/dobutamine, and had a significant increase of oxygenation (PaO\textsubscript{2}/FiO\textsubscript{2}).

FIGURE 50.2. Illustrating an adsorber with polymyxin B coated on the surface, enabling it to have no systemic side effect as polymyxin B will directly bind with endotoxin.
FIGURE 50.3. Illustrating the PM-HP circuit in which the blood is directly passed through PMX filter without any fluid input or output from the patients’ body.

When including only the studies that reported the mortality rate on the 28th and 30th day done on 704 patients were compared, it was found that the treatment with PMX-F could decrease the mortality rate with statistical significance compared with SMT (relative risk 0.5; 95% confidence interval 0.43–0.68).

Two RCT studies done in Europe by Vincent and colleagues together with the EUPHAS study (Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock) done on postoperative patients with severe sepsis/septic shock from abdominal infection found that PMX-HP could increase cardiac output and oxygen delivery index, decrease the treatment using CRRT 80 MAP, decrease the use of vasopressor, increase oxygenation (PaO\textsubscript{2}/FiO\textsubscript{2} ratio), and decrease the mortality rate on the 28th day (32%) when compared with the use of standard medical therapy (SMT) (53%) [adjusted hazard ratio (HR) 0.36; 95% confidence interval 0.16–0.80]. Still, a concerning that the EUPHAS trial was terminated too early, and as a result, under power to conclude the benefit of decreasing of the mortality rate. The interesting point is that, in this study, PMX-HP was initiated quite early, that is, within 6 hours after operations. Moreover, the study was conducted on patients who tended to have a high level of endotoxin and with the sources of infection that could be well controlled. Because of this, if the findings from this study are to be applied to patients with severe sepsis/septic shock resulting from other causes, it is still very crucial to consider clinical context and its high cost.

According to the latest study referred to as ABDOMIX by Payen and colleagues conducted in 18 hospitals throughout France, no significant differences in the mortality rate on the 28th day were found in the patients treated with PMX-HP compared with the controlled group. Of note, there were only 81 of 119 patients (69.8%) who received 2 PMX-HP sessions in ABDOMIX study. Both EUPHAS study, and ABDOMIX study did not use EAA level to guide PMX-HP initiation. The latest meta-analysis by Fujii et al. included 6 trials, 857 participants, could not show the benefit of PMX-HP on 28-day mortality and organ dysfunction scores. Again, most of the included studies did not use endotoxin level to guide intervention (Table 50.3).

We conducted a randomized controlled trial in patients with EAA level more than or equal to 0.6 to explore the effect of PMX-HP on immune cell (monocyte and neutrophil). Patients in the PMX-HP group received a 2-hour PMX-HP treatment plus standard treatment for 2 consecutive days. Patients in the non-PMX-HP group received only standard treatment.
Table 50.3. A summary of current important clinical studies on polymyxin hemoperfusion.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Severe sepsis and septic shock after surgery due to abdominal cavity infection</td>
<td>Severe sepsis and septic shock requiring emergency surgery due to intra-abdominal cavity infection</td>
<td>Abdominal septic shock triggered by lower-gastrointestinal tract perforation</td>
<td>Septic shock requiring CRRT</td>
<td>Severe sepsis and septic shock requiring emergency surgery due to intra-abdominal cavity infection</td>
</tr>
<tr>
<td>Types of studies</td>
<td>RCT</td>
<td>RCT</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>RCT</td>
</tr>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>64</td>
<td>1,080</td>
<td>2,230</td>
<td>232</td>
</tr>
<tr>
<td>PMX initiation timing</td>
<td>Within 24 # 48 hours after surgery</td>
<td>Within 24 hours after surgery</td>
<td>Day 0 or day 1 after operation</td>
<td>At the timing of CRRT initiation</td>
<td>Within 12 hours after surgery</td>
</tr>
<tr>
<td>Number of PMX-HP Sessions</td>
<td>1</td>
<td>2</td>
<td>1 or 2</td>
<td>1 or 2</td>
<td>2</td>
</tr>
<tr>
<td>Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality (%)</td>
<td>P = NS</td>
<td>P = 0.01</td>
<td>P = NS</td>
<td>P = 0.003</td>
<td>P = NS</td>
</tr>
<tr>
<td>• PMX treated</td>
<td>29 (n = 17)</td>
<td>32 (n = 34)</td>
<td>17 (n = 590)</td>
<td>41 (n = 1,115)</td>
<td>40 (n = 119)</td>
</tr>
<tr>
<td>• Control</td>
<td>28 (n = 19)</td>
<td>53 (n = 30)</td>
<td>16 (n = 590)</td>
<td>47 (n = 1,115)</td>
<td>27 (n = 113)</td>
</tr>
</tbody>
</table>

(CRRT: continuous renal replacement therapy; NS: nonsignificant; PMX-HP: polymyxin hemoperfusion; RCT: randomized controlled trial)

The primary outcome compared the groups on median change in mHLA-DR expression between day 3 and baseline. 59 patients were randomized to PMX-HP (n = 29) and non-PMX-HP (n = 30) groups. At baseline, mHLA-DR expression, CD11b, neutrophil chemotaxis, and clinical parameters were comparable between groups. The median change in mHLA-DR expression between day 3 and baseline was higher in PMX-HP patients than in patients receiving standard therapy alone, P = 0.027. The mean change in CD11b between day 3 and baseline was significantly lower in PMX-HP than in non-PMX-HP, P = 0.002. There were no significant changes from baseline in neutrophil chemotaxis, presepsin, CVS SOFA scores, vasopressor doses, or EAA level between groups. On day 28 after enrollment, mortality, ICU-free days, ventilator-free days, dialysis dependence status, renal recovery, serum creatinine, vasopressor-free days, and MAKE 28 were comparable between groups.18

Currently, there is the largest multicenter randomized trial, Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES), which finished trial in 2017, but yet unpublished. This study aimed to prove the concept of using a biomarker, EAA, to identify the patients who will receive the most benefit form PMX-HP treatment.19

REFERENCES


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