The role of apheresis treatment in severe sepsis - the Hannover experience

Jan T. Kielstein
Klinik für Nieren-und Hochdruckerkrankungen
Medizinische Hochschule Hannover
The role of apheresis treatment in severe sepsis - the Hannover experience

1) The unmet medical need
2) Therapeutic plasma exchange
3) Adsorbant technologies
   - Cytosorb ®
   - Seraph® Microbind®
4) EXCHANGE trial
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

FDA Drug Safety Communication: Voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] due to failure to show a survival benefit

Safety Announcement

[10-25-2011] The U.S. Food and Drug Administration (FDA) is informing healthcare professionals and the public that on October 25, 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of Xigris [drotrecogin alfa (activated)]. In a recent study, Xigris failed to show a survival benefit for patients with severe sepsis and septic shock.

Xigris treatment should not be started in new patients. Xigris treatment should be stopped in patients being treated with Xigris.

All remaining Xigris product should be returned to the supplier from whom it was purchased.

In a recently completed clinical trial (PROWESS-SHOCK trial), Xigris failed to show a survival benefit. In this trial of 1696 patients, 851 patients were enrolled in the Xigris arm and 845 patients were enrolled in the placebo arm. Results based on preliminary analyses done by Eli Lilly and Company, that were submitted to the FDA, showed a 28-day all cause mortality rate of 26.4% (223/846) in Xigris-treated patients compared to 24.2% (202/834) in placebo-treated patients, for a relative risk of 1.09; 95% CI (0.92, 1.28), and P-value = 0.31 (not statistically significant).

FDA previously issued an early communication about the ongoing safety review of Xigris in February 2009.
Extracorporeal therapies in non-renal disease: treatment of sepsis and the peak concentration hypothesis

Excess pro- and anti-inflammatory mediators removed by continuous combined therapies

Unselective high efficiency extracorporeal therapies might remove excess of pro- and anti-inflammatory mediators diminishing the amplified inflammatory response and the immunoparalysis induced by cell hyporesponsiveness.
Indications for therapeutic plasma exchange at the Hannover Medical School in 2012
(n=185 patients)
Vascular access gone bad- Air embolism after large bore catheter removal requiring ECMO therapy
EINECKE et al. submitted

- 20 yo Caucasian patient w bx proven IgA nephropathy
- refuses steroids
- insertion of a 15.5 F x 15 cm double lumen dialysis catheter in right internal jugular vein for 4 IA sessions | cytoxan
- after catheter removal “slurping noise” rapid deterioration
Vascular access gone bad- Air embolism after large bore catheter removal requiring ECMO therapy

EINECKE et al. submitted

Leucocytes: **69.4*/nl  (with 85% granulocytes)
C-reactive protein: 5.3 mg/L
Procalcitonin: 2.43 ng/mL
Vascular access gone bad - Air embolism after large bore catheter removal requiring ECMO therapy

EINECKE et al. submitted
Vascular access gone bad - Air embolism after large bore catheter removal requiring ECMO therapy

EINECKE et al. submitted
The role of apheresis treatment in severe sepsis - the Hannover experience

1) The unmet medical need

2) Therapeutic plasma exchange

3) Adsorbant technologies
   - Cytosorb ®
   - Seraph® Microbind®

4) EXCHANGE trial
## Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Apheresis Applications Committee of the ASFA

Szczepiorkowski  *Journal of Clinical Apheresis* 25:83–177, 2010

### TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| I        | Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.  
[Example: plasma exchange in Guillain-Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition]. |
| II       | Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.  
[Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease] |
| III      | Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure]. |
| IV       | Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.  
[Example: plasma exchange for active rheumatoid arthritis]. |
SEPSIS WITH MULTIORGAN FAILURE

Incidence: 300 per 100,000/year in the US

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPE</td>
<td>Grade 2B</td>
<td>III</td>
</tr>
</tbody>
</table>

# of reported patients*: >300

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>3 (146)</td>
<td>3 (90)</td>
<td>8 (149)</td>
<td>3</td>
<td>Type I</td>
</tr>
</tbody>
</table>

Description of the disease

Sepsis, a systemic inflammatory response to infection, is the most common cause of death in non-coronary intensive care units and the 10th most common cause of death in the United States. It accounts for 2–3% of all hospital admissions. The incidence of sepsis has increased over the last two decades with an unchanged mortality rate of 28–50%.
Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial


*Fig. 1* Cumulative survival in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis (*solid line*) or not (*dotted line*) in addition to standard sepsis treatment
Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 years)*</td>
<td>1.48</td>
<td>1.03–2.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female genital</td>
<td>0.54</td>
<td>0.07–4.00</td>
<td></td>
</tr>
<tr>
<td>Urological</td>
<td>0.15</td>
<td>0.02–0.93</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>4.04</td>
<td>0.74–22.2</td>
<td></td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>0.41</td>
<td>0.07–2.53</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1.60</td>
<td>0.30–8.62</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.71</td>
<td>0.33–8.88</td>
<td></td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>0.41</td>
<td>0.15–1.09</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Therapeutic plasma exchange as rescue therapy in severe sepsis and septic shock: retrospective observational single-centre study of 23 patients

Johannes Hadem¹*, Carsten Hafer², Andrea S Schneider¹, Olaf Wiesner³, Gernot Beutel⁴, Thomas Fuehner³, Tobias Welte³, Marius M Hoeper³ and Jan T Kielstein²

Abstract

Background: Several case series and small randomized controlled trials suggest that therapeutic plasma exchange (TPE) improves coagulation, hemodynamics and possibly survival in severe sepsis. However, the exact role of TPE in modern sepsis therapy remains unclear.

Methods: We performed a retrospective observational single-centre study on the use of TPE as rescue therapy in 23 consecutive patients with severe sepsis or septic shock from 2005 to 2012. Main surrogate markers of multiple organ failure (MOF) before, during and after TPE as well as survival rates are reported.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Septic focus and associated pathogen(s)</th>
<th>Risk factors for infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Septic shock (pneumonia, <em>Staphylococcus aureus</em>)</td>
<td>Microscopic polyangiitis, cryoglobulinemia, chronic renal disease</td>
</tr>
<tr>
<td>2</td>
<td>Severe sepsis (soft tissue infection, <em>Streptococcus pyogenes</em>)</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Septic shock</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Septic shock (perianal soft tissue infection, <em>Streptococcus group A</em>)</td>
<td>Excision of an anal tag</td>
</tr>
<tr>
<td>5</td>
<td>Septic shock (pneumonia, <em>Pseudomonas aeruginosa</em>)</td>
<td>UIP, Sjögren's syndrome, alveolitis, immune complex vasculitis</td>
</tr>
<tr>
<td>6</td>
<td>Septic shock (parastomal abscess, <em>Peptostreptococcus, Candida</em>) with septic or Infliximab-associated cardiomyopathy</td>
<td>Crohn's disease with anal and parastomal fistulas</td>
</tr>
<tr>
<td>7</td>
<td>Septic shock (pneumonia, <em>Streptococcus pneumoniae</em>)</td>
<td>Post splenectomy</td>
</tr>
<tr>
<td>8</td>
<td>Septic shock (pneumonia, <em>Escherichia coli</em>)</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Septic shock</td>
<td>Crohn's disease, short bowel syndrome</td>
</tr>
<tr>
<td>10</td>
<td>Severe sepsis (rhabdomyolysis and pneumonia, <em>Adenovirus, Streptococcus pneumoniae, Staphylococcus aureus</em>)</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>Severe sepsis (pneumonia, H1N1) with VAHS</td>
<td>Type 2 Diabetes, obesity hypoventilation syndrome</td>
</tr>
<tr>
<td>12</td>
<td>Septic shock (pneumonia, <em>Staphylococcus haemolyticus, Candida krusei</em>)</td>
<td>MDS with pancytopenia</td>
</tr>
<tr>
<td>13</td>
<td>Severe sepsis (pneumonia, H1N1, <em>Streptococcus mitis, Serratia marcescens</em>) with VAHS</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>Severe sepsis (pneumonia)</td>
<td>MDS, secondary AML, PBSCTx</td>
</tr>
<tr>
<td>15</td>
<td>Septic shock, OPSI (sinusitis, <em>Streptococcus pneumoniae</em>)</td>
<td>Post splenectomy</td>
</tr>
<tr>
<td>16</td>
<td>Septic shock (pneumonia, <em>Staphylococcus aureus</em>)</td>
<td>Cystic fibrosis, re-double-lung transplantation, diabetes, liver cirrhosis</td>
</tr>
<tr>
<td>17</td>
<td>Septic shock (pneumonia, <em>Streptococcus pneumoniae</em>)</td>
<td>Multiple myeloma, AL amyloidosis (cardiac, renal), autologous SCTx 4 months ago,</td>
</tr>
<tr>
<td>18</td>
<td>Septic shock (pneumonia)</td>
<td>Septic granulomatosis</td>
</tr>
<tr>
<td>19</td>
<td>Septic shock, OPSI (chronic otitis, <em>Streptococcus pneumoniae</em>)</td>
<td>Kidney transplantation, rapidly progressive GN, s/p acute rejection 3 weeks prior with subsequent rituximab treatment</td>
</tr>
<tr>
<td>20</td>
<td>Septic shock (colon perforation, <em>Pseudomonas aeruginosa, Acinetobacter baumanii, Klebsiella pneumonia</em>)</td>
<td>Crohn's disease, cachexia</td>
</tr>
<tr>
<td>21</td>
<td>Septic shock (pneumonia, <em>Streptococcus pneumoniae</em>)</td>
<td>COPD</td>
</tr>
<tr>
<td>22</td>
<td>Septic shock (acute liver failure due to HSV)</td>
<td>Hysterectomy because of uterine myomas</td>
</tr>
<tr>
<td>23</td>
<td>Septic shock (MOF due to VZV)</td>
<td>Type 2 Diabetes</td>
</tr>
</tbody>
</table>
Therapeutic plasma exchange as rescue therapy in severe sepsis and septic shock: retrospective observational single-centre study of 23 patients

HADEM et al. BMC Anesthesiol 7;14(1):24, 2014

Figure 1 Norepinephrine dose before, during and after first therapeutic plasma exchange (TPE) in non-survivors and survivors.
Norepinephrine doses as surrogate marker of hemodynamic instability are presented relating to the time of first TPE: 3 hours before initiation of TPE (h-3), initiation of TPE (h0), 3 hours after TPE (h+3), 6 hours after TPE (h+6), 9 hours after TPE (h+9), 12 hours after TPE (h+12), and 24 hours after TPE (h+24).
Therapeutic plasma exchange as rescue therapy in severe sepsis and septic shock: retrospective observational single-centre study of 23 patients

HADEM et al. BMC Anesthesiol 7;14(1):24, 2014

$\text{Net fluid balance (mL/12h)}$

- $p = 0.002$

12 hours before TPE

Hours 0 to 12 after TPE

Hours 12 to 24 after TPE
Therapeutic Plasma Exchange Decreases Levels of Routinely Used Cardiac and Inflammatory Biomarkers

Elimination des erhöhten Ang-2 bei vascular leakage durch Plasmapherese
The role of apheresis treatment in severe sepsis - the Hannover experience

1) The unmet medical need

2) Therapeutic plasma exchange

3) Adsorbant technologies
   - Cytosorb ®
   - Seraph® Microbind®

4) EXCHANGE trial
A powerful new weapon in the fight against Cytokine Storm

biocompatible, highly porous polymer bead designed to capture and adsorb cytokines (~10-50 kDa)

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Molecular weight</th>
<th>% removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>8 kDa</td>
<td>100%</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>17 kDa</td>
<td>100%</td>
</tr>
<tr>
<td>IL-1α</td>
<td>17 kDa</td>
<td>100%</td>
</tr>
<tr>
<td>IL-10</td>
<td>18 kDa</td>
<td>85%</td>
</tr>
<tr>
<td>IL-6</td>
<td>26 kDa</td>
<td>87%</td>
</tr>
<tr>
<td>HMGB1</td>
<td>30 kDa</td>
<td>80%</td>
</tr>
<tr>
<td>TNF-α trimer</td>
<td>51 kDa</td>
<td>55%</td>
</tr>
</tbody>
</table>
Extracorporeal cytokine removal in a septic shock patient undergoing ECMO therapy

Sascha David, Bernhard MW Schmidt, Johannes Hadem, Kristina Thamm, Christian Kühn, Christine Falk and Jan T Kielstein
Extracorporeal cytokine removal in a septic shock patient undergoing ECMO therapy

Sascha David, Bernhard MW Schmidt, Johannes Hadem, Kristina Thamm, Christian Kühn, Christine Falk and Jan T Kielstein
SIRS in der Herzchirurgie: Neue Therapiemöglichkeiten durch den Einsatz eines Cytokin-Adsorbers während EKZ?

BORN et al. KARDIOTECHNIK 2/2014

<table>
<thead>
<tr>
<th>Gruppen</th>
<th>HLM Zeit</th>
<th>Cross Clamp</th>
<th>Reperfusion</th>
<th>Stillstand</th>
<th>Hirnperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=20)</td>
<td>224,45</td>
<td>144,30</td>
<td>68,75</td>
<td>50,30</td>
<td>47,95</td>
</tr>
<tr>
<td>CS (n=20)</td>
<td>213,05</td>
<td>138,55</td>
<td>59,20</td>
<td>40,80</td>
<td>43,45</td>
</tr>
<tr>
<td>n.s. p = 0,463</td>
<td>n.s. p = 0,618</td>
<td>n.s. p = 0,223</td>
<td>n.s. p = 0,169</td>
<td>n.s. p = 0,568</td>
<td></td>
</tr>
</tbody>
</table>

Tab. 1: Charakterisierung der Patientenkollektive bezüglich Maschinenzeiten, Ischämie- und Reperfusionszeiten, Zeit des Herzstillstandes und der Hirnperfusion (Zeiten in Minuten)

Abb. 9: Postoperativer Verlauf von CRP in beiden Vergleichsgruppen
The role of apheresis treatment in severe sepsis - the Hannover experience

1) The unmet medical need
2) Therapeutic plasma exchange
3) Adsorbant technologies
   - Cytosorb ®
   - Seraph® Microbind®
4) EXCHANGE trial
Safety and Performance Evaluation of the Seraph® Microbind® Affinity Blood Filter for Reducing Bacteremia in Patients on Hemodialysis

How Seraph works
ExThera’s Seraph® Microbind® Affinity Blood Filter (Seraph) captures and removes a broad range of normal and drug-resistant bacteria, viruses, toxins and pro-inflammatory cytokines from human blood.

SINGLE-USE SERAPH® MICROBIND® AFFINITY BLOOD FILTER
Each cartridge is filled with proprietary ‘microspheres’ coated with molecular receptor sites that mimic the receptors on human cells used by pathogens when they invade the body.

As blood flows between the microspheres in the filter bed, the invaders and their toxins bind to the surface just as they would in blood vessels within the body.

NOTE: Drawing is for explanation only and is not to scale.
The role of apheresis treatment in severe sepsis - the Hannover experience

1) The unmet medical need

2) Therapeutic plasma exchange

3) Adsorbant technologies
   - Cytosorb ®
   - Seraph® Microbind®

4) EXCHANGE trial
Randomized, prospective, multicenter, open-label, controlled, parallel-group trial investigating the efficacy of add-on plasma-exchange as an adjunctive strategy against septic shock with multiple organ dysfunction (EXCHANGE trial)

Onset of septic shock <12h
NA >0.5 ug/kg/min, MODS

n= 173/group

TPE Group (FFP)
Standard Sepsis Guideline Treatment + TPE* 1st Treatment < 12h + pretreatment (anti-histamines)

Control group
Standard Sepsis Guideline Treatment + TPE pretreatment (anti-histamines)

* FFP exchange volume
1.0-1.4 x plasma-volume

2nd Treatment d2
3rd Treatment d3

PI: Dr. Sascha David
Hannover Medical School, GERMANY
I will survive
Role of Cytokine Hemoadsorption in Cardiopulmonary Bypass-Induced Ventricular Dysfunction in a Porcine Model
VOCELKA et al. JECT 45:220–227, 2013