Detecting and Removing Endotoxin in sepsis

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HYPERINFLAMMATION IN SEPSIS

(Hotchkiss, Monneret and Payen, 2013)
IMMUNOSUPPRESSION IN SEPSIS

Intensity of response depends on:
- Pathogen load/virulence
- Patient’s comorbidities
- Host genetic factors

Early deaths due to overwhelming inflammation

Late deaths due to persistent immunosuppression and recurrent infections

(Hotchkiss, Monneret and Payen, 2013)
IMMUNODYSREGULATION IN SEPSIS

Pro-inflammatory Mediators
- TNF
- PAF
- IL-1

Anti-inflammatory Mediators (inhibitors)
- IL-10

CRRT

Immunohomeostasis

T i m e

Pro/ Anti - inflammatory Mediators

CRRT

Immunohomeostasis

T i m e

Ronco et Al Artif Organs 2003
LPS is recognised by monocytes through CD14 and may lead to endothelial cell activation (Pugin et al. 1993)

3714 genes are altered in response to LPS (Calvano et al. 2005)

Can modulation of one or more elements of the systemic response affect immunoresponse (Pro-Anti) without causing deleterious effects? (Cohen et al. 2002)
HOW TO INTERVENE?

Surviving Sepsis Guidelines

Resuscitation, antibiotic prophylaxis, source control and organ support

Modulation of immune response

Drugs have shown disappointing results in clinical trials
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mediators</th>
<th>Treatment</th>
<th>Results of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immunity</td>
<td>Lipopolysaccharide (endotoxin)</td>
<td>Antilipopolysaccharide⁹</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>TLR-2, TLR-4</td>
<td>TLR agonists¹⁰ and antagonists</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Monocytes, macrophages</td>
<td>GM-CSF, interferon gamma¹¹</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>G-CSF†</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Adaptive immunity</td>
<td>B cells (plasma cells and immunoglobulins)</td>
<td>IgG</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Proinflammatory pathway</td>
<td>TNF-α</td>
<td>Anti–TNF-α¹³,¹⁴</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Interleukin-1β</td>
<td>Interleukin-1–receptor antagonist¹⁵</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Interleukin-6</td>
<td>Interleukin-6 antagonist</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins, leukotrienes</td>
<td>Ibuprofen,¹⁶ high-dose corticosteroids¹⁷</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Bradykinin</td>
<td>Bradykinin antagonist¹⁸</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Platelet-activating factor</td>
<td>Platelet-activating factor acetyl hydrolase¹⁹</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Proteases (e.g., elastase)</td>
<td>Elastase inhibitor</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Oxidants</td>
<td>Antioxidants (e.g., N-acetylcysteine)²⁰</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
<td>Nitric oxide synthase inhibitor²¹</td>
<td>Negative</td>
</tr>
<tr>
<td>Pathway</td>
<td>Mediators</td>
<td>Treatment</td>
<td>Results of RCTs</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Procoagulant pathway</td>
<td>Decreased protein C</td>
<td>Activated protein C$^5$</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Decreased protein S</td>
<td>Protein S$^{22}$</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Decreased antithrombin III</td>
<td>Antithrombin III$^{23}$</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Decreased tissue factor–pathway inhibitor</td>
<td>Tissue factor–pathway inhibitor$^{24}$</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Increased tissue factor</td>
<td>Tissue factor antagonist$^{25}$</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Increased plasminogen-activator inhibitor 1</td>
<td>Tissue plasminogen activator</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Antiinflammatory</td>
<td>Interleukin-10</td>
<td>Interleukin-10$^7$</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>TNF-α receptors</td>
<td>TNF-α receptors$^{13}$</td>
<td>Negative</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Hypoxia-inducing factor 1α, vascular endothelial growth factor</td>
<td>Early, goal-directed therapy$^2$</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supernormal oxygen delivery</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythropoietin$^{26}$</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Immunosuppression or apoptosis</td>
<td>Lymphocyte apoptosis</td>
<td>Anticaspases$^{27}$</td>
<td>Not evaluated</td>
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<tr>
<td></td>
<td>Apoptosis of intestinal epithelial cells</td>
<td>Anticaspases$^{27}$</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Adrenal insufficiency</td>
<td>Corticosteroids$^{28}$</td>
<td>Mixed results$^9$</td>
</tr>
<tr>
<td></td>
<td>Vasopressin deficiency</td>
<td>Vasopressin$^{29}$</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>Intensive insulin therapy$^{30,31}$</td>
<td>Not evaluated</td>
</tr>
</tbody>
</table>
HOW TO INTERVENE?

- Surviving Sepsis Guidelines
- Modulation of immune response
- Removal of endotoxin

- Resuscitation, antibiotic prophylaxis, source control and organ support
- Drugs have shown disappointing results in clinical trials
- Extracorporeal removal of endotoxin has shown promising results
History of PMX

- 2003: Start Utilization
- 2006: Meta-Analysis & Euphas Trial Design
- 2009: Euphas publication
- 2010: Euphas2 Design
- 2012: 300 pts on file
- 2013: Euphrates North America

Flags:
- Japan
- European Union
- United States
- Canada
• Sometimes less complex tx is successful
• Not always blood endotoxin level is high
• Not all sepsis are by *Gram negative* bacteria
• Studies: underpowered, single center/country mixed populations studied.
• More evidence needed for PMX-B HP
## RR FOR DEATH WITH PMX-F TREATMENT

### Study or sub-category

<table>
<thead>
<tr>
<th>Study</th>
<th>PMX n/N</th>
<th>Conventional n/N</th>
<th>RR (random)</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>01 Randomized Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamura (c) 2003</td>
<td>9/35</td>
<td>16/25</td>
<td>0.40 [0.21, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Vincent 2005</td>
<td>5/17</td>
<td>5/18</td>
<td>1.06 [0.37, 3.02]</td>
<td></td>
</tr>
<tr>
<td>Nakamura 1999</td>
<td>12/30</td>
<td>14/20</td>
<td>0.57 [0.34, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Nakamura (a) 2002</td>
<td>2/9</td>
<td>7/9</td>
<td>0.29 [0.08, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Nakamura(b) 2003</td>
<td>2/10</td>
<td>8/10</td>
<td>0.25 [0.07, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Nakamura (e) 2004</td>
<td>3/15</td>
<td>6/10</td>
<td>0.33 [0.11, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Nemoto 2001</td>
<td>32/54</td>
<td>39/44</td>
<td>0.67 [0.52, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Suzuki 2002</td>
<td>6/24</td>
<td>18/24</td>
<td>0.33 [0.16, 0.69]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>194</td>
<td>160</td>
<td>0.50 [0.37, 0.68]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>71 (PMX), 113 (Conventional)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> Ch² = 10.97, df = 7 (P = 0.14), I² = 36.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 4.43 (P &lt; 0.00001)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>02 Nonrandomized Studies</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nakamura (d) 2003</td>
<td>66/206</td>
<td>73/108</td>
<td>0.47 [0.37, 0.60]</td>
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<tr>
<td>Nakamura 2005</td>
<td>4/14</td>
<td>7/12</td>
<td>0.49 [0.19, 1.27]</td>
<td></td>
</tr>
<tr>
<td>Ono 2004</td>
<td>3/10</td>
<td>0/13</td>
<td>8.91 [0.51, 154.95]</td>
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</tr>
<tr>
<td>Tani 1998</td>
<td>17/37</td>
<td>21/33</td>
<td>0.72 [0.47, 1.11]</td>
<td></td>
</tr>
<tr>
<td>Tsugawa 2002</td>
<td>9/31</td>
<td>21/51</td>
<td>0.71 [0.37, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Tsujimoto 2004</td>
<td>1/7</td>
<td>1/10</td>
<td>1.43 [0.11, 19.20]</td>
<td></td>
</tr>
<tr>
<td>Tsushima 2002</td>
<td>4/24</td>
<td>8/10</td>
<td>0.21 [0.08, 0.54]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>329</td>
<td>237</td>
<td>0.55 [0.38, 0.81]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>104 (PMX), 131 (Conventional)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> Ch² = 11.76, df = 6 (P = 0.07), I² = 49.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 3.10 (P = 0.0002)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>PMX n/N</th>
<th>Conventional n/N</th>
<th>RR (random)</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>523</td>
<td>397</td>
<td>0.53 [0.43, 0.65]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>175 (PMX), 244 (Conventional)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong> Ch² = 21.98, df = 14 (P = 0.08), I² = 36.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 5.98 (P &lt; 0.00001)</td>
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</tr>
</tbody>
</table>

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**RR 0.53 (0.43, 0.65)**

Favors PMX-F

Favors conventional
Research

Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review

Dinna N Cruz¹,², Mark A Perazella³, Rinaldo Bellomo⁴, Massimo de Cal¹, Natalia Polanco¹, Valentina Corradi¹, Paolo Lentini¹, Federico Naless⁰¹, Takuya Ueno⁵, V Marco Ranieri⁶ and Claudio Ronco¹

Mortality risk of Toraymyxin™ therapy was reduced by 0.53. 95% CI (0.43, 0.65) p<0.001.

15 studies, 920 patients.
A targeted extracorporeal therapy for endotoxemia: the time has come.

Kellum JA.
The CRISMA Laboratory, Critical Care Medicine, University of Pittsburgh, Terrace Street, Pittsburgh, PA 15261, USA. kellumja@ccm.upmc.edu

Abstract
Endotoxemia, whether primary (due to Gram-negative infection) or secondary (due to epithelial barrier dysfunction), appears to be extremely common in the critically ill and injured. High levels of endotoxin activity are associated with worse clinical outcomes. In Japan, polymyxin B hemoperfusion has been available to treat endotoxemia for more than ten years. Multiple small trials, often limited by methodological quality, show that polymyxin B hemo-perfusion may have favorable effects on survival and hemodynamics. Further study of this therapy would seem justified.

Comment on
Crit Care. 2007;11(2):R47.
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: The EUPHAS Randomized Controlled Trial

<table>
<thead>
<tr>
<th>Physiological End Points</th>
<th>Polymyxin B Hemoperfusion Mean (95% CI)</th>
<th>P Value</th>
<th>Conventional Therapy Mean (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>Baseline (n = 34)</td>
<td>76 (72-80)</td>
<td>.001</td>
<td>74 (70-78)</td>
</tr>
<tr>
<td></td>
<td>72 Hours (n = 34)</td>
<td>84 (80-88)</td>
<td></td>
<td>77 (72-82)</td>
</tr>
<tr>
<td>Inotropic score</td>
<td>Baseline (n = 30)</td>
<td>29.9 (20.4-39.4)</td>
<td>&lt;.001</td>
<td>28.6 (16.6-40.7)</td>
</tr>
<tr>
<td></td>
<td>72 Hours (n = 27)</td>
<td>6.8 (2.9-10.7)</td>
<td></td>
<td>22.4 (9.3-35.5)</td>
</tr>
<tr>
<td>Vasopressor dependency index, mm Hg (^{-1})</td>
<td>Baseline (n = 30)</td>
<td>4.3 (2.7-5.9)</td>
<td>&lt;.001</td>
<td>4.1 (2.3-6.0)</td>
</tr>
<tr>
<td></td>
<td>72 Hours (n = 27)</td>
<td>0.9 (0.3-1.5)</td>
<td></td>
<td>3.3 (1.3-5.3)</td>
</tr>
<tr>
<td>PaO(_2)/FiO(_2)</td>
<td>Baseline (n = 34)</td>
<td>235 (206-265)</td>
<td>.049</td>
<td>217 (188-247)</td>
</tr>
<tr>
<td></td>
<td>72 Hours (n = 34)</td>
<td>264 (236-292)</td>
<td></td>
<td>228 (199-258)</td>
</tr>
<tr>
<td>Renal replacement therapy, No. (%)</td>
<td>Baseline (n = 34)</td>
<td>13 (38)</td>
<td>.50</td>
<td>6 (20)</td>
</tr>
<tr>
<td></td>
<td>72 Hours (n = 34)</td>
<td>15 (44)</td>
<td></td>
<td>8 (30)</td>
</tr>
</tbody>
</table>

Change in SOFA scores at 72 h

28-day Survival

Log-rank P = .03
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

Table 3. Physiological Data

<table>
<thead>
<tr>
<th>Physiological Data</th>
<th>PMX (n=28)</th>
<th>Conv (n=27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>82</td>
<td>83</td>
<td>.37</td>
</tr>
<tr>
<td>Inotropic score</td>
<td>35.5</td>
<td>36.5</td>
<td>.14</td>
</tr>
<tr>
<td>Vasopressor dependent</td>
<td>6.3</td>
<td>7.0</td>
<td>.26</td>
</tr>
<tr>
<td>( \text{Pao}_2/\text{FiO}_2 )</td>
<td>258</td>
<td>258</td>
<td>.79</td>
</tr>
<tr>
<td>Renal replacement No. (%)</td>
<td>50</td>
<td>50</td>
<td>.50</td>
</tr>
</tbody>
</table>

Abbreviations: Cl, continuous; \( \text{Pao}_2 \), partial pressure of arterial oxygen; \( \text{FiO}_2 \), fraction of inspired oxygen.

\(^a\) See “Methods” section.
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

Mortality rate %

Euphas

- Toraymyxin: 32.0%
- Convenzionale: 53.0%

Metanalysis

- Toraymyxin: 33.5%
- Convenzionale: 61.5%

Cruz D et al, JAMA 2009, 301:2445-52
CONCLUSION: In this preliminary study, polymyxin B hemoperfusion added to conventional therapy significantly improved hemodynamics and organ dysfunction and reduced 28-day mortality in a targeted population with severe sepsis and/or septic shock from intra-abdominal gram-negative infections.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00629382.
Facts

• Sepsis: deadly condition, still very high mortality
• Pharmacological approaches: unsatisfactory
• Often high endotoxin levels in blood
• Endotoxin levels correlate with outcomes
• Rationale: remove circulating endotoxin
• Endotoxin removal technique is available
• PMX-B HP decreased mortality and improved organ function in a RCT of abdominal sepsis
EUPHAS trial was not designed as a mortality study. Instead it was designed to determine whether PMX-B HP would result in improved MAP and less requirement for vasopressors in patients with septic shock due to presumed abdominal infections. Given the modest differences in these end points it was therefore surprising that 28-day mortality was so drastically different between groups 32% vs 53%. This results open new avenues for the treatment of sepsis/ septic shock for the future. A larger RCT will probably be required as a confirmatory proof.
EUPHAS2

- Multi-center collaborative data collection reporting clinical experience with Toraymyxin device

- Phase 1 (closed): Observational, retrospective

- Phase 2 (now open): Observational, prospective

**Aim:**
- To describe clinical efficacy of Polymyxin-B based hemoperfusion in current clinical practice
- To verify the reproducibility of published data
- To identify subgroup of patients which could potentially benefit of the treatment
PHASE 1: RETROSPECTIVE DATA COLLECTION

PRO:
• Description of every day practice
• Description of adherence to published published evidence
• New trends in application of the treatment

CONS:
• No control group
• No enrolment/exclusion criteria (eterogeneity of patients)
• Possible lack of data due to retrospective nature
• Possible underpower in statistical analyses
### EUPHAS2: PATIENTS AT ADMISSION

<table>
<thead>
<tr>
<th>Characteristics at admission</th>
<th>N = 357</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.4 ± 15.3</td>
</tr>
<tr>
<td>Gender, male, N(%)</td>
<td>240 (67)</td>
</tr>
<tr>
<td>SAPSII at admission</td>
<td>50.3 ± 19.2</td>
</tr>
<tr>
<td>APACHEII at admission</td>
<td>21.8 ± 7.2</td>
</tr>
<tr>
<td>SOFA at admission</td>
<td>10.9 ± 3.5</td>
</tr>
<tr>
<td>Incidence of shock (%)</td>
<td>85</td>
</tr>
<tr>
<td>Septic source, (%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>44%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>18%</td>
</tr>
<tr>
<td>Urinary</td>
<td>4.5%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6.4%</td>
</tr>
<tr>
<td>Trauma</td>
<td>5.3%</td>
</tr>
<tr>
<td>Other</td>
<td>22%</td>
</tr>
</tbody>
</table>
EUPHAS2 vs. EUPHAS: SURVIVAL

EUPHAS2 vs. EUPHAS control $p=0.46$
The prospective RCT EUPHAS, in a targeted population showed:

- Improved hemodynamics and organ dysfunction
- Reduced 28-day mortality

EUPHAS 2 Retrospective phase (357 patients) showed a reduction in mortality compared to EUPHAS controls.

89 patients “EUPHAS-like by severity and timing” confirmed the results of EUPHAS.
STANDARD TREATMENT OF SEPSIS

Survival

Patients not responding to standard therapy

Hypotension, shock and tissue hypoperfusion cause organ failure and high mortality

Standard treatment

Complexity/severity
FOCUSING ON SEPTIC SHOCK

According to recent publications, shock patients are all hypotensive needing cardiovascular support but…

Survival ≈ 80%
370(18):1683-93

Survival ≈ 60%
N Engl J Med. 2014 Oct 1
ahead of print

Survival ≈ 40%
Critical Care 2013, 17:R65

HOW DO WE IMPROVE SURVIVAL?

Survival

Intervention

Standard treatment

Complexity/severity
HOW TO PLAN CLINICAL STUDIES?

Survival

Standard treatment

Complexity/severity

Intervention

Study 1

Study 2

Study 3
THE WINDOW OF OPPORTUNITY FOR IMPROVED SURVIVAL

Survival

Intervention

Standard treatment

Complexity/severity
All enrolled patients required vasopressor support at 24 hours from diagnosis.
## LESSONS FROM EUPHAS 2

<table>
<thead>
<tr>
<th>Treatments</th>
<th>576</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>26</td>
<td>4.5</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>1.7</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Clotting</td>
<td>13</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Data from 109 hospitals, 377 patients and 956 used cartridges.

Blood clotting in the cartridge is the most frequent event with a total of 36 events (3.8%).
EUPHRATES

Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock

Principal Investigator: Dr. Phil Dellinger
Steering Committee: Dr. M. Antonelli, Dr. J. Marshall, Dr. S. Trzeciak, C. Shorr, Dr. P. Walker (sponsor), Dr. P. Palevsky, D. Foster (sponsor)
**EUPHRATES**

**Design**: Blinded, randomized controlled trial of standard care versus PMX cartridge plus standard care

**Setting**: Intensive Care Units in approximately 60 centers – US and Canada

**Population**: Approximately 650 patients (325/arm) with septic shock
Inclusion criteria

1. Age ≥ 18 years old
2. Documented or suspected infection with definitive or empiric antibiotics
3. Evidence of at least 1 new onset organ dysfunction that is considered to be related to current sepsis illness:
   - Positive pressure ventilation and intubated (ET tube or trach)
   - Thrombocytopenia (<150,000 or 50% reduction from prior)
   - Acute oliguria (<0.5ml/kg/hr for 6 hours) despite adequate fluid
4. Hypotension requiring vasopressor support:
   requirement for at least one of the vasopressors below at the dose shown for at least 2 continuous hours & a maximum of 30h
   - Norepi ≥ 5 mcg/min
   - Dopamine ≥ 10 mcg/kg/min
   - Phenylephrine ≥ 25 mcg/min
   - Epinehrine ≥ 5 mcg/min
   - Vasopressin >0.03 units/min
   - Vasopressin (any dose) in combination with 1 vasopressor listed above
5. The patient must have received intravenous fluid resuscitation of ≥ 30mL/kg administered within 24 hours of eligibility
6. EAA ≥ 0.6
Exclusion criteria

• Inability to obtain an informed consent from the subject, family member or an authorized surrogate
• Lack of commitment for full medical support
• Inability to achieve or maintain a minimum mean arterial pressure (MAP) of ≥65mmHg despite vasopressor therapy and fluid resuscitation
• Subject has end stage renal disease and requires chronic dialysis
• There is clinical support for non-septic shock such as
  – Acute pulmonary embolus
  – Transfusion reaction
  – Severe congestive heart failure (e.g. NYHA Class IV, ejection fraction < 35%)
• Subject has had chest compressions as part of CPR this hospitalization without immediate return to communicative state
• Subject has had an acute myocardial infarction (AMI) within the past 4 weeks
• Subject has uncontrolled hemorrhage (acute blood loss requiring > 3 UPC in the past 24 hours)
• Major trauma within 36 hours of screening
• Subject has severe granulocytopenia (leukocyte count less than 500 cells/mm³) or severe thrombocytopenia (platelet count less than 30,000 cells/mm³)
Exclusion Criteria (continued)

- HIV infection in association with a last known or suspected CD4 count of <50/mm$^3$
- Subject’s baseline state is non-communicative
- Subject has sustained extensive third-degree burns within the past 7 days
- Body weight < 35 kg (77 pounds)
- Known hypersensitivity to polymyxin B
- Subject has known sensitivity or allergy to heparin or has a history of heparin associated thrombocytopenia (H.I.T.)
- Subject is currently enrolled in an investigational drug or device trial
- Subject has been previously enrolled in the current trial
- Any other condition, that in the opinion of the investigator, would preclude the subject from being a suitable candidate for enrollment, such as end stage chronic illness with no reasonable expectation of survival to hospital discharge
- MODS ≤ 9 **

** new for 2014 as recommended by DSMB
1. Use of a diagnostic test – the EAA
   ▪ Clinical criteria for septic shock + endotoxemia (EAA≥ 0.60 EAA units)
   ▪ NO SIRS criteria

2. Relatively smaller number of patients compared to other sepsis trials

3. Blinded device trial

4. Recruitment managed by special committee
EUPHRATES: impact of EAA

• Clinically eligible patients based on clinical criteria: 648
  • EAA ≥ 0.60 = 382 (60%)
  • EAA < 0.60 = 255*
  • No EAA = 11

* Low EAA septic shock and High EAA non-randomized followed for 28 day mortality [data from 21 Oct 2014]
Several Trials → Wrong Targets

Centoxin AB → Right target, wrong method

Euphas → Right target, Right method, Right population, Small size

Euphrates → Right target, Right method, Right population, Right size
The future of interventions?

• Endotoxin removal is the future but...

• Only for high risk (high mortality) populations (trials)

• Adopt dynamic prescription criteria

• Include biomarkers into the enrolment procedure
**Dynamic prescription**

**Azotemia**

- AKI
- Day 1
- Day 3
- Day 5
- Day 7

CRRT 30ml/Kg/h

CRRT 20ml/Kg/h

**E A**

- PMX-B HP
- Day 1
- Day 3
- Day 5
- Day 7

Sepsis
SHOULD WE CHANGE THE ENDPOINT?

Possible endpoint: Recovery/Prevention

Possible endpoint: Long-term effects

Survival

Complexity/severity
**Personalized medicine: tailored treatments**

**Medicine of the present: one treatment fits all**
- Patients with sepsis

**Medicine of the future: more personalized diagnostics**
- Blood, DNA, urine and tissue analysis
- Endotoxin Assay
- Targeted Therapy

**Therapy**
- PMX

**Effect**
- No effect
- Adverse effects
## Polymyxin-hemoperfusion during laparotomy for fecal peritonitis, a proof-of-concept study

<table>
<thead>
<tr>
<th></th>
<th>PMX group (n=15)</th>
<th>Controls (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>74 ± 11</td>
<td>70 ± 18</td>
<td>ns</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>6/9</td>
<td>9/4</td>
<td>ns</td>
</tr>
<tr>
<td>SAPS2 (points)</td>
<td>49 ± 21</td>
<td>53 ± 30</td>
<td>ns</td>
</tr>
<tr>
<td>IV volume perfused in OR (L)</td>
<td>4.7 ± 1.5</td>
<td>4.4 ± 2.7</td>
<td>ns</td>
</tr>
<tr>
<td>Admitted to the ICU, n (%)</td>
<td>3 (20%)</td>
<td>9 (69%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

PMX, continuous hemoperfusion with Toraymyxin® columns for 2 hours, started at the time of incision in the operating room

*Pavlovic and Pugin, submitted to ESA meeting 2015*
Hemodynamic and oxygenation effects of polymyxin-hemoperfusion during laparotomy for fecal peritonitis

**Norepinephrine dose (mg/hr)**

- PMX (n=15) vs. Controls (n=13)
  - PMX: 0.55 mg/hr, Controls: 0.40 mg/hr
  - Before operation: PMX: 0.55 mg/hr, Controls: 0.40 mg/hr
  - After operation: PMX: 0.40 mg/hr, Controls: 0.30 mg/hr

**PaO₂/FiO₂ (kPa)**

- PMX (n=15) vs. Controls (n=13)
  - PMX: 40 kPa, Controls: 35 kPa
  - Before operation: PMX: 35 kPa, Controls: 30 kPa
  - After operation: PMX: 30 kPa, Controls: 25 kPa

*p* = 0.022, ns

**Pavlovic and Pugin, submitted to ESA meeting 2015**
Vicenza Course on AKI & CRRT

June 7-10, 2016
Fiera di Vicenza Convention Center
Vicenza, Italy

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