THE EUPHRATES TRIAL

R. Phillip Dellinger MD, MSc, MCCM
Professor and Chair of Medicine
Cooper Medical School of Rowan University
Medical Director Adult Health Institute
Senior Critical Care Attending
Cooper University Hospital
Camden NJ USA
INTRINSIC COMPONENT OF THE OUTER MEMBRANE OF GRAM NEGATIVE BACTERIA

LPS

LIPID A
LIPOPOLYSACCHARIDE

POLYSACCHARIDE
CORE OLIGOSACCHARIDE
Endotoxemia

Endotoxin shed from local bacterial infection

Endotoxin translocation from GI Tract

- Every human has 25-30 grams of Endotoxin in their GI tract
- Less than 0.001 grams of Endotoxin is enough to kill a person

- Every human has 25-30 grams of Endotoxin in their GI tract
- Less than 0.001 grams of Endotoxin is enough to kill a person
Sepsis and Endotoxin


P<0.05
INTERVENTION

DIRECT HEMOPERFUSION WITH ADSORBENT COLUMN USING POLYMIXIN B IMMOBILIZED FIBER

Duration: 2 hours

BLOOD TUBE

FEMORAL or IJ VEIN

BLOOD PUMP
Perfusion rate 80-120 ml/min

ANTICOAGULANT
Heparin (3000 U in bolus followed by a continuous infusion of 20 U/kg/h)
Meta-analysis - Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PMX Events</th>
<th>PMX Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura 1999</td>
<td>12</td>
<td>30</td>
<td>14</td>
<td>20</td>
<td>13.1%</td>
<td>0.57 [0.34, 0.96]</td>
<td>1999</td>
</tr>
<tr>
<td>Nemoto 2001</td>
<td>32</td>
<td>54</td>
<td>39</td>
<td>44</td>
<td>17.9%</td>
<td>0.67 [0.52, 0.85]</td>
<td>2001</td>
</tr>
<tr>
<td>Suzuki 2002</td>
<td>6</td>
<td>24</td>
<td>18</td>
<td>24</td>
<td>9.9%</td>
<td>0.33 [0.16, 0.69]</td>
<td>2002</td>
</tr>
<tr>
<td>Nakamura 2002</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>4.9%</td>
<td>0.29 [0.08, 1.02]</td>
<td>2002</td>
</tr>
<tr>
<td>Nakamura 2003-II</td>
<td>2</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>4.8%</td>
<td>0.25 [0.07, 0.90]</td>
<td>2003</td>
</tr>
<tr>
<td>Nakamura 2003-I</td>
<td>9</td>
<td>35</td>
<td>16</td>
<td>25</td>
<td>11.3%</td>
<td>0.40 [0.21, 0.76]</td>
<td>2003</td>
</tr>
<tr>
<td>Nakamura 2004</td>
<td>3</td>
<td>15</td>
<td>6</td>
<td>10</td>
<td>5.8%</td>
<td>0.33 [0.11, 1.03]</td>
<td>2004</td>
</tr>
<tr>
<td>Vincent 2005</td>
<td>5</td>
<td>17</td>
<td>5</td>
<td>18</td>
<td>6.4%</td>
<td>1.06 [0.37, 3.02]</td>
<td>2005</td>
</tr>
<tr>
<td>Cruz 2009</td>
<td>11</td>
<td>34</td>
<td>16</td>
<td>30</td>
<td>12.0%</td>
<td>0.61 [0.34, 1.09]</td>
<td>2009</td>
</tr>
<tr>
<td>Payen 2015</td>
<td>33</td>
<td>119</td>
<td>22</td>
<td>113</td>
<td>14.0%</td>
<td>1.42 [0.89, 2.29]</td>
<td>2015</td>
</tr>
</tbody>
</table>

Total (95% CI) 347 303 100.0% 0.57 [0.42, 0.79]

Total events 115 151

Heterogeneity: Tau² = 0.14; Chi² = 22.19, df = 9 (P = 0.008); I² = 59%

Test for overall effect: Z = 3.37 (P = 0.0007)
## Meta-Analysis - Hemodynamics

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Change in MAP (random)</th>
<th>Weight %</th>
<th>Change in MAP (random)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial MAP &lt;70</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ono 2004</td>
<td>6.74</td>
<td>25.00</td>
<td>[16.45, 33.55]</td>
<td>D</td>
</tr>
<tr>
<td>Tojimbara 2004</td>
<td>10.26</td>
<td>26.00</td>
<td>[20.98, 31.02]</td>
<td>D</td>
</tr>
<tr>
<td>Tsujimoto 2004</td>
<td>6.43</td>
<td>28.40</td>
<td>[19.46, 37.34]</td>
<td>D</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>23.43</strong></td>
<td><strong>26.25</strong></td>
<td><strong>[22.35, 30.14]</strong></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 0.31, df = 2 (P = 0.85), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 13.21 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial MAP &gt;=70</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincent 2005</td>
<td>8.68</td>
<td>10.80</td>
<td>[4.33, 17.27]</td>
<td>A</td>
</tr>
<tr>
<td>Casella 2006</td>
<td>8.48</td>
<td>16.00</td>
<td>[9.34, 22.66]</td>
<td>D</td>
</tr>
<tr>
<td>Ikeda 2004</td>
<td>11.49</td>
<td>11.50</td>
<td>[7.58, 15.42]</td>
<td>D</td>
</tr>
<tr>
<td>Kojica 2006</td>
<td>5.40</td>
<td>23.80</td>
<td>[13.41, 34.19]</td>
<td>D</td>
</tr>
<tr>
<td>Nakamura 2004/B</td>
<td>5.89</td>
<td>16.00</td>
<td>[6.34, 25.66]</td>
<td>D</td>
</tr>
<tr>
<td>Tani 1998</td>
<td>8.32</td>
<td>15.00</td>
<td>[8.19, 21.82]</td>
<td>D</td>
</tr>
<tr>
<td>Ueno 2005</td>
<td>3.86</td>
<td>22.10</td>
<td>[8.77, 35.43]</td>
<td>D</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>76.57</strong></td>
<td><strong>15.89</strong></td>
<td><strong>[13.45, 18.33]</strong></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 14.71, df = 8 (P = 0.07), I² = 45.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 12.77 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.00</strong></td>
<td><strong>18.55</strong></td>
<td><strong>[15.48, 21.62]</strong></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 40.10, df = 11 (P &lt; 0.0001), I² = 72.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 11.85 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No survival benefit
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

Dinna N. Cruz, MD, MPH
Massimo Antonelli, MD
Roberto Fumagalli, MD
Francesca Foltran, MD
Nicola Brienza, MD, PhD
Abele Donati, MD
Vincenzo Malcangi, MD
Flavia Petrini, MD
Giada Volta, MD
Franco M. Bobbio Pallavicini, MD
Federica Rottoli, MD
Francesco Giunta, MD
Claudio Ronco, MD

Context  Polymyxin B fiber column is a medical device designed to reduce blood endotoxin levels in sepsis. Gram-negative-induced abdominal sepsis is likely associated with high circulating endotoxin. Reducing circulating endotoxin levels with polymyxin B hemoperfusion could potentially improve patient clinical outcomes.

Objective  To determine whether polymyxin B hemoperfusion added to conventional medical therapy improves clinical outcomes (mean arterial pressure [MAP], vasopressor requirement, oxygenation, organ dysfunction) and mortality compared with conventional therapy alone.

Design, Setting, and Patients  A prospective, multicenter, randomized controlled trial (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]) conducted at 10 Italian tertiary care intensive care units between December 2004 and December 2007. Sixty-four patients were enrolled with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection.

Intervention  Patients were randomized to either conventional therapy (n=30) or conventional therapy plus 2 sessions of polymyxin B hemoperfusion (n=34).

Main Outcome Measures  Primary outcome was change in MAP and vasopressor requirement, and secondary outcomes were PaO₂/FiO₂ (fraction of inspired oxygen) ratio, change in organ dysfunction measured using Sequential Organ Failure Assessment (SOFA) scores, and 28-day mortality.
Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial

Didier M. Payen
Joelle Guilhot
Yoann Launey
Anne Claire Lukaszewicz
Mahmoud Kaaki
Benoît Veber
Julien Pottecher
Olivier Joannes-Boyau
Laurent Martin-Lefèvre
Matthieu Jabaudon
Olivier Mimoz
Rémi Coudroy
Martine Ferrandière
Eric Kipnis
Carlos Vela
Stéphanie Chevallier
Jihad Mallat
René Robert
The ABDOMIX Group
Versus EUPHRATES

- 19.5% mortality in control group
- Incomplete PMX sessions
- Enrollment not based on EAA

ENDOTOXIN ACTIVITY ASSAY
EAA™

THERAGNOSTICS
Rapid: 30 minutes
Minimal laboratory footprint
Highly sensitive
Highly specific
Result unique to each patient
cutoffs for low, intermediate and high levels

0.6-1.0 high EAA

Intermediate zone

0-0.39 low EAA

Endotoxin Activity Assay

LPS pg/ml (standard e. coli E55:B5)
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
5. The patient must have received intravenous fluid resuscitation of ≥ 30mL/kg administered within 24hours of eligibility

1. EAA ≥ 0.6
• The PMX cartridge will be administered using two cartridges, approximately 24 hours apart. Each treatment will last for 2 hours, at a flow rate of approximately 100 ml/minute, but will be used within the range of 80 to 120 ml/minute.
Interim Analysis
Amendment – MODS$_{\geq 10}$
• 446 Subjects

• >1000 – will have met all entry criteria and had EAA measured and followed to 28 day mortality

• Post amendment
  • MODS 12
  • Composite mortality 48%
The Lives of a Cell
Notes of a Biology Watcher
Lewis Thomas
1974
Houston we have a problem!
The microorganisms that seem to have it in for us . . . turn out to be rather more like bystanders, strays, strangers in from the cold.

Lewis Thomas, 1974
When we sense lipopolysaccharide (endotoxin), we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all the tissues in the area.
Our arsenals for fighting off bacteria are so powerful . . . That we are in more danger from them than from the invaders. We live in the midst of explosive devices; we are mined.
We are, in effect, at the mercy of our own pentagons . . .
Is the cat out of the bag?
Important question to be answered by this study

- Is persistent endotoxemia in established septic shock driving organ dysfunction or just a bystander?
Predator

If it bleeds, we can kill it!
If endotoxin is driving this, we can remove it!
And will it make a difference?

0 - 377 - 446

85%
Thank you