Endotoxin Removal in Gram Negative Sepsis

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Conflict of interest

Research Grant:
- Starmed
- Orion
- Pfizer
- Toray

Honoraria:
- Pfizer
- Covidien

Scientific Board:
- Cubist
- Covidien
- Drager
- Toray
• Mortality 30-70%
• Leads to Multiple Organ Failure
• Endotoxin from Gram-negative bacteria is an important trigger in the pathogenesis of sepsis
# Experimental Studies In Vivo

## DIRECT MEDIATOR REMOVAL

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<th>Author</th>
<th>Model</th>
<th>Results</th>
<th>Reference</th>
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<td>human sepsis</td>
<td>IL-1, TNF</td>
<td>Crit Care Med 21:522-6</td>
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<td>Crit Care Med 26:1995-2000</td>
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<td>C₃a</td>
<td>Kidney Int 53:S182-5</td>
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<td>pig endotoxemia</td>
<td>TNF, PGF, TxB</td>
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<td>Hoffman 99</td>
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<td>Lonnemann 99</td>
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<td>TNF</td>
<td>Kidney Int 56:S84-87</td>
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</table>
High levels of endotoxin activity are associated with worse clinical outcomes.

Marshall JID, 2004:190
Interaction between PMB and LPS is governed by

1. Ionic Binding Forces
2. Hydrophobic Binding Forces

Lipid A

PMB

1. Ionic Binding Forces
2. Hydrophobic Binding Forces
LPS Removal by PMX-DHP

Extracorporeal hemoperfusion using Toraymyxin device composed of PMX-B covalently immobilized polystyrene derived fibers removes circulating endotoxin
Hemoperfusion with Polymyxin B Column: Extracorporeal Removal of Endotoxin

- Blood pump 80-120 ml/min
- Femoral vein
- Anticoagulant Infusion

Hemoperfusion is performed for 2 hrs.

Double lumen CVC (12 Fr)
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: The EUPHAS Randomized Controlled Trial

Dinna N. Cruz; Massimo Antonelli; Roberto Fumagalli; et al.


http://jama.ama-assn.org/cgi/content/full/301/23/2445
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

JAMA, June 17, 2009—Vol 301, No. 23
The EUPHAS2 project

www.euphas2.eu

- Collaborative Multi-centre registry to record the clinical experience with Toraymyxin
- Observational, 1st phase retrospective / 2nd phase prospective

**Objectives:**
- To describe the use PMXB in clinical practice
- Reproducibility of the Euphas trial results
- To identify subgroups for potential benefit
16 RCTs on the efficacy of hemoperfusion, hemofiltration and plasma exchanges

Extracorporeal purification reduces the sepsis related mortality
Among Extracorporeal techniques, Polymyxin-B hemoperfusion significantly changes the global mortality.
55 Hospitals have registered as users

32 Hospitals have added 307 patients to this database
Where is EUPHAS2 Recruiting?

Countries Involved:

Europe
- Italy
- Switzerland
- Spain

Asia
- India
- Japan
28 D Mortality

42.0

Is that high?
28 D mortality

Does the geographical distribution influence the outcome?
An European Comparison: France

- 1495 patients with septic shock
- Treated in French ICUs

The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study

Critical Care 2013, 17:R65
An European Comparison: Italy

Epidemiology and outcome of sepsis syndromes in Italian ICUs: a multicentre, observational cohort study in the region of Piedmont

Sakr Y., Elia C., Mascia L., Barberis B., Cardellino S., Livigni S., Fiore G., Filippini C., Ranieri V. M.

Minerva Anestesiologica 2013;79(9):993-1002

• 305 patients with severe sepsis and septic shock
Does the EUPHAS2 confirm the results from EUPHAS?

EUPAHS2 Main Diagnosis

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: The EUPHAS Randomized Controlled Trial

Dinna N. Cruz; Massimo Antonelli; Roberto Fumagalli; et al.


http://jama.ama-assn.org/cgi/content/full/301/23/2445

128 patients with abdominal sepsis
28-Day Mortality in Abdominal Sepsis

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<th>Group</th>
<th>Mortality Percentage</th>
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<tr>
<td>EUPHAS Conv</td>
<td>53.0</td>
</tr>
<tr>
<td>EUPHAS PMX</td>
<td>32.0</td>
</tr>
<tr>
<td>EPISS</td>
<td>41.8</td>
</tr>
<tr>
<td>EUPHAS2 Europe</td>
<td>30.3</td>
</tr>
</tbody>
</table>
APACHE II Score at enrollment

- EUPHAS Conv.
- EUPHAS PMX
- EUPHAS2 Abdominal (European)
Does the EUPHAS2 confirm the results from EUPHAS?

EUPHAS2 Main Diagnosis

ABDOMINAL SS is a proxy of ENDOTOXIC SS
EA >0.6 as the main enrollment criterion?

40 patients monitored with EA

14 Abdominal
8 Respiratory
7 Cardio+ Bacteremia
4 Trauma
2 UTI
3 Other
2 Unknown

SAPSII : 50
SOFA T0 : 11.8
EA >0.6 as the main enrollment criterion

28 Days Mortality (%)

- Abdominal (128 pts.): 30%
- Non abdominal (178 pts.): 41%
- EAA >0.6 (40 pts.): 33%
EA as main enrollment criterion

Attività endotossinica

T0 T24 T48 T72
Conclusions

- EUPHAS 2 confirms an overall mortality reduction when compared to the population conventionally treated (epidemiological studies).

- Patients with abdominal SS are effectively treated with results identical to those of the original EUPHAS trial.

- Non-abdominal patients do not show a similar benefit, however data suggests that EAA could help in patient selection.