For Endotoxin Removal in Patients with Severe Sepsis and Septic Shock
Sepsis is a life-threatening complication.

Sepsis causes a major clinical problem in the management of patients in the intensive care unit (ICU). Sepsis is a serious medical condition characterized by systemic inflammatory response caused by bacterial infection. Uncontrolled inflammatory responses to bacterial infection result in the collapse of the cardiovascular function, leading to multiple organ dysfunction syndrome (MODS) and death. Huge amount of efforts have been made these several decades. However, sepsis still carries a mortality rate of ranging from 30 to 70%.

As a consequence of endotoxin binding to the complex of Toll-like receptor 4 (TLR4) and MD-2 on leukocytes, various products implicated in the pathogenesis of sepsis are released.
Endotoxin is an important pathogenic trigger of sepsis.

Endotoxin is one of the principal components of the outer membrane of Gram-negative bacteria. It induces systemic inflammatory response characterized by induction of pro-inflammatory cytokines, fever, hypotension, intravascular coagulation and nitric oxide that lead to “endotoxin shock.” Higher level of endotoxin is associated with worse clinical outcomes. Endotoxin invades into the blood stream from the infectious focus or by the bacterial or endotoxin translocation from the gut.

Multiple organ dysfunction syndrome
Toraymyxin™ removes blood endotoxin.

Toraymyxin™ is an extracorporeal hemoperfusion device which is composed of polymyxin B covalently immobilized polystyrene derived fibers. Polymyxin B antibiotics is well known to bind endotoxin selectively and neutralize its toxicity. Toraymyxin™ removes endotoxin in the blood.

Polymyxin B interacts with the lipid A moiety of endotoxin through hydrophobic and ionic interactions.

The hydrophobic amino acids (Phe, Leu) of polymyxin B interact with lipid A fatty acid of endotoxin via hydrophobic bonds, and the phosphate groups of lipid A with a negative charge interact with the amino groups of polymyxin B via ionic bonds to stabilize the complex. Because of this tight interaction, it is unlikely that endotoxin is dissociated from the polymyxin B immobilized fiber (Toraymyxin™) into the blood. The in vitro endotoxin adsorbing capacity of Toraymyxin™ was found to be 64,000 ng contained in bovine serum.
Toraymyxin™ reduces blood endotoxin level and improves hemodynamics in patients with sepsis.

Twenty eight publications about clinical studies with Toraymyxin™ were identified and systematically reviewed. After hemoperfusion using Toraymyxin™, the blood endotoxin level decreased, mean arterial pressure (MAP) increased, and thus the dopamine / dobutamine dose was reduced. In addition, the PaO₂/FiO₂ ratio increased after hemoperfusion with Toraymyxin™.

**Changes in parameters before and after Toraymyxin™ treatment**

- **MAP**: 19 mmHg (95% CI (15, 22), p<0.001, 12 studies, 275 patients)
- **Endotoxin level**: 21.2 pg/mL (95% CI (-24.9, -17.5), p<0.001, 17 studies, 455 patients)
- **PaO₂/FiO₂ ratio**: 32 units (95% CI (23.4, 41), p<0.001, 7 studies, 151 patients)
- **Dopamine/dobutamine**: 1.8 μg/kg/min (95% CI (-3.3, -0.4), p=0.01, 4 studies, 96 patients)

**Mortality**

Mortality risk of Toraymyxin™ therapy was reduced by 0.53. 95% CI (0.43, 0.65) p<0.001. 15 studies, 920 patients.
The levels of inflammatory mediators and coagulation factors decrease after hemoperfusion with Toraymyxin™

During sepsis, coagulation and inflammation interact each other, which leads to a prothrombic state and to organ dysfunction. It is well known that plasma levels of IL-6, a proinflammatory cytokine, and PAI-1, that prevents anti-coagulation, are high in patients with septic shock and severe sepsis. After endotoxin removal with Toraymyxin™, plasma IL-6 and PAI-1 level are decreased.

**Plasma IL-6 level**

Forty-five patients with severe sepsis or septic shock due to colorectal perforation were subjected to hemoperfusion with Toraymyxin™. (Reproduced with permission from the publisher)

IL-6: Interleukin-6

**Plasma PAI-1 level**

Thirty-six patients with sepsis after acute lung injury or acute respiratory distress syndrome were subjected to hemoperfusion with Toraymyxin™. (Cited from the open-access journal)

PAI-1: Plasminogen activator inhibitor-1
Toraymyxin™ reduces mortality due to severe sepsis and septic shock.

Sixty-four patients who developed severe sepsis or septic shock due to intra-abdominal infection requiring emergency abdominal surgery were included in a randomized controlled study, the EUHASS trial.
Target patients and ideal timing for Toraymyxin™ treatment

**Target patients**

Toraymyxin™ is used in the treatment of severe sepsis or septic shock patients, who fulfill the following conditions:

(A) **Endotoxemia**
- or suspected gram-negative infection.

(B) **Systemic Inflammatory Response Syndrome (SIRS*) with at least 1 organ dysfunction.**

*SIRS is defined by the presence of at least two of the following four conditions:
1. Fever or hypothermia (body temperature > 38°C or < 36°C)
2. Tachycardia (heart rate > 90 bpm)
3. Tachypnea (respiratory rate > 20 breaths /min, or PaCO₂ < 32 mmHg)
4. White blood cell count > 12,000 cells /mm³, < 4,000 cells /mm³ or > 10% immature (band) forms.

**Ideal timing**

After the onset of septic shock, earlier use of Toraymyxin™ is more effective. Toraymyxin™ was initiated within 24 hours after abdominal surgery in the EUPHAS trial.**
**Toraymyxin™ cartridge**

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>225 mm</td>
</tr>
<tr>
<td>Diameter (max)</td>
<td>63 mm</td>
</tr>
<tr>
<td>Priming volume</td>
<td>135 ± 5 mL</td>
</tr>
<tr>
<td>Fibers (dry weight)</td>
<td>56 ± 3 g</td>
</tr>
<tr>
<td>Inlet pressure</td>
<td>&lt; 250 mmHg</td>
</tr>
<tr>
<td>Maximum pressure</td>
<td>500 mmHg</td>
</tr>
<tr>
<td>Sterilization</td>
<td>High-pressure steam sterilization</td>
</tr>
<tr>
<td>Expiration</td>
<td>2 years after sterilization</td>
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</table>

**Operating procedure**

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Method</td>
<td>Direct Hemoperfusion (DHP)</td>
</tr>
<tr>
<td>Blood Flow Rate</td>
<td>100 (80-120) mL/min</td>
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<tr>
<td>Duration of DHP</td>
<td>2 hours</td>
</tr>
<tr>
<td>Washing</td>
<td>at least 4 L of physiological saline</td>
</tr>
<tr>
<td>Priming</td>
<td>500 mL of heparinized saline (4 U/mL)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Heparin 3,000 U as bolus, 20 U/kg body weight/hr as maintenance. The maximum maintenance dose allowed for any patient is 2,000 U/hr.</td>
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</tbody>
</table>

**Equipment needed**

- A blood pump for extracorporeal circulation at a blood flow rate of 20-200 mL/min, monitors for inlet (Pi) and outlet (Po) pressures and an infusion pump for the administration of anticoagulants

- Hemoperfusion blood tubing suitable for use with the hemoperfusion pump

- 12F or 14F double lumen catheter

  - Sterile
  - Single Use only
  - Do not re-use
  - Do not use if the packaging is damaged or open
  - Do not use if the sterilization indicator is whitish yellow
  - Read Instructions For Use carefully before use.

**Reference**
