For Endotoxin Removal in Patients with Severe Sepsis and Septic Shock

Extracorporeal Hemoperfusion Cartridge

TORAYMYXIN

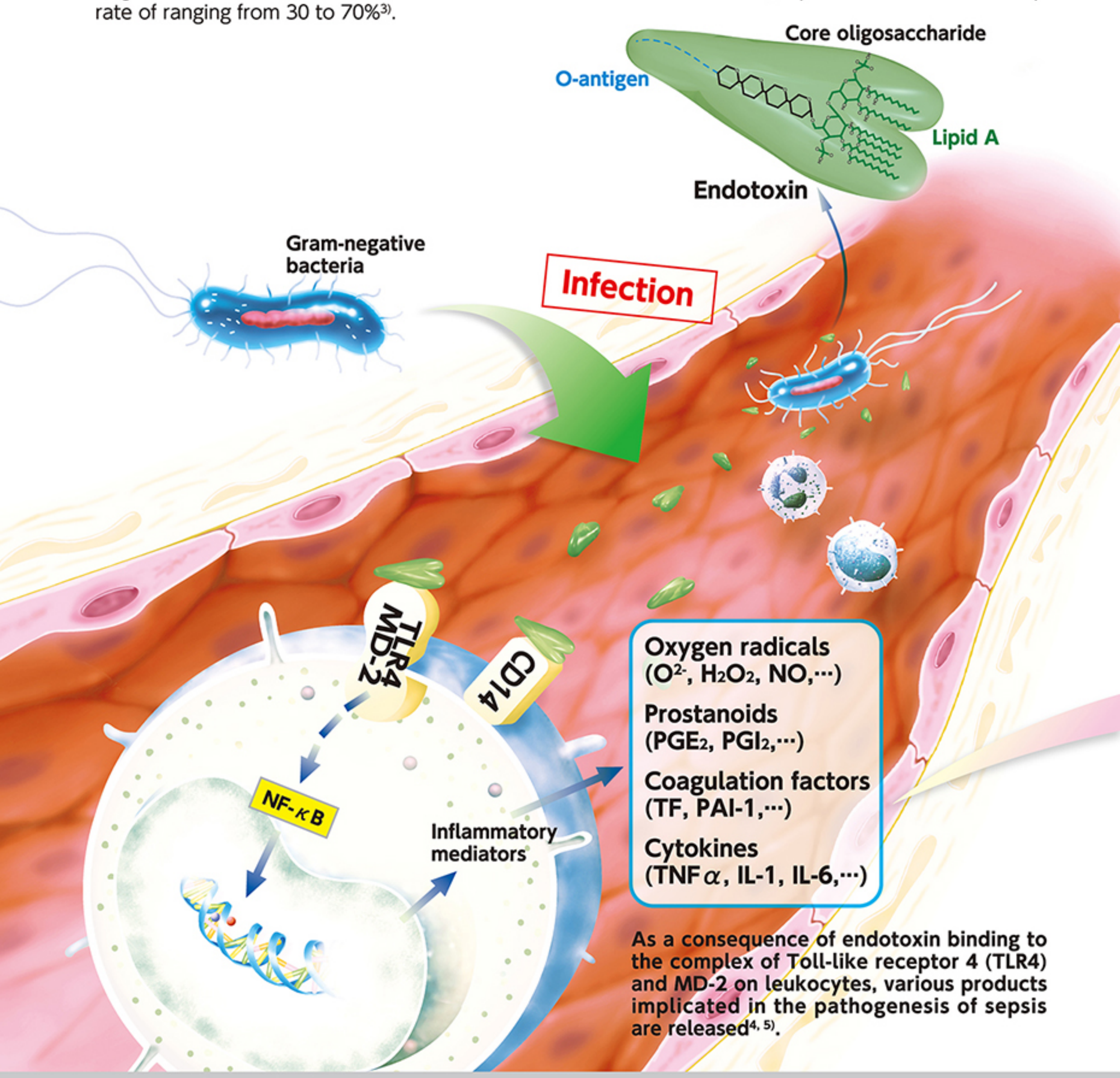
PMX-20R

"TORAY"

Innovation by Chemistry

Sepsis is a life-threatening complication.

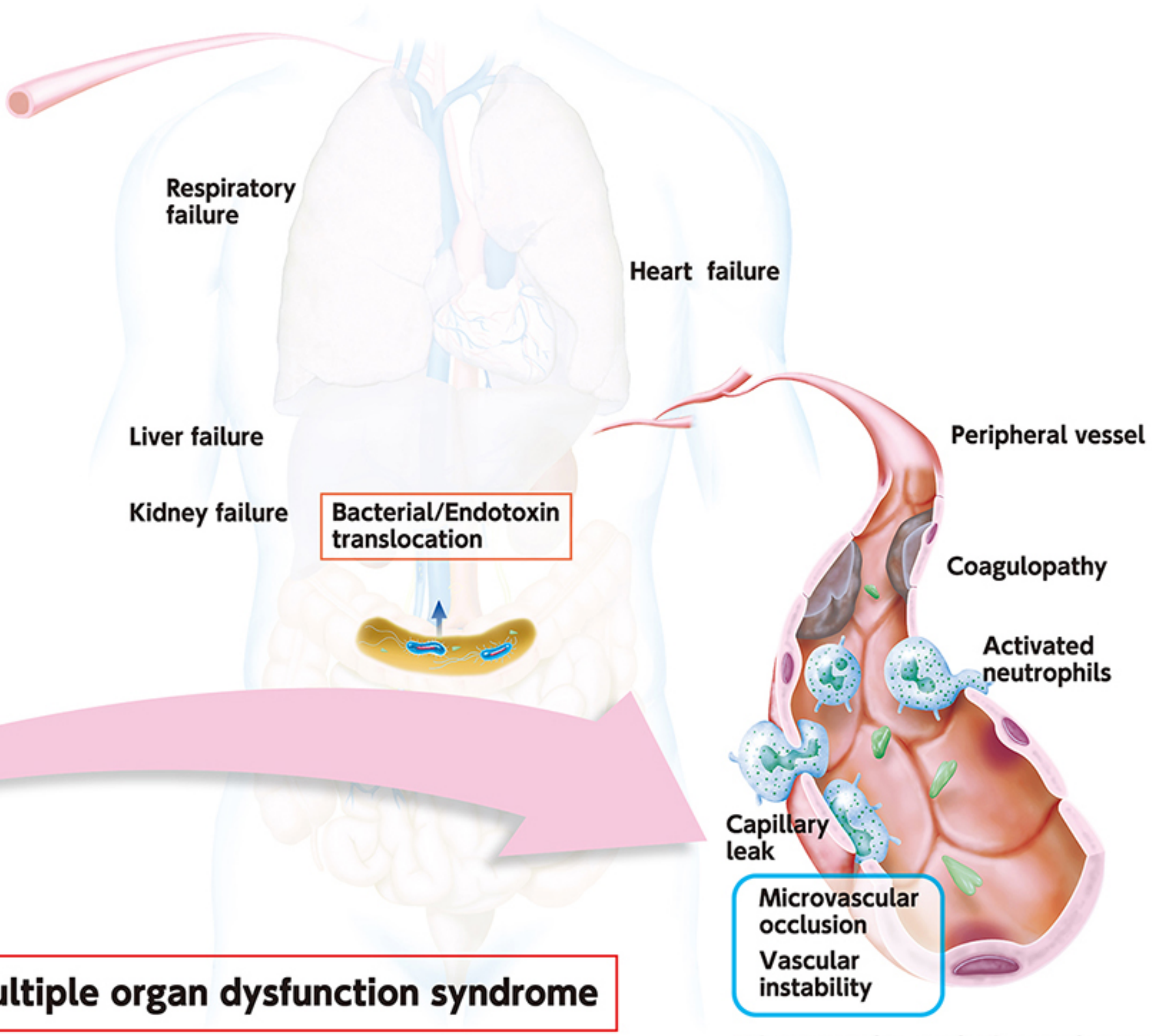
Sepsis causes a major clinical problem in the management of patients in the intensive care unit (ICU). Sepsis is a serious medical condition characterized by systemic inflammatory response caused by bacterial infection. Uncontrolled inflammatory responses to bacterial infection result in the collapse of the cardiovascular function, leading to multiple organ dysfunction syndrome (MODS) and death[1, 2]. Huge amount of efforts have been made these several decades. However, sepsis still carries a mortality rate of ranging from 30 to 70%[3].



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[4, 5].

Endotoxin is an important pathogenic trigger of sepsis.

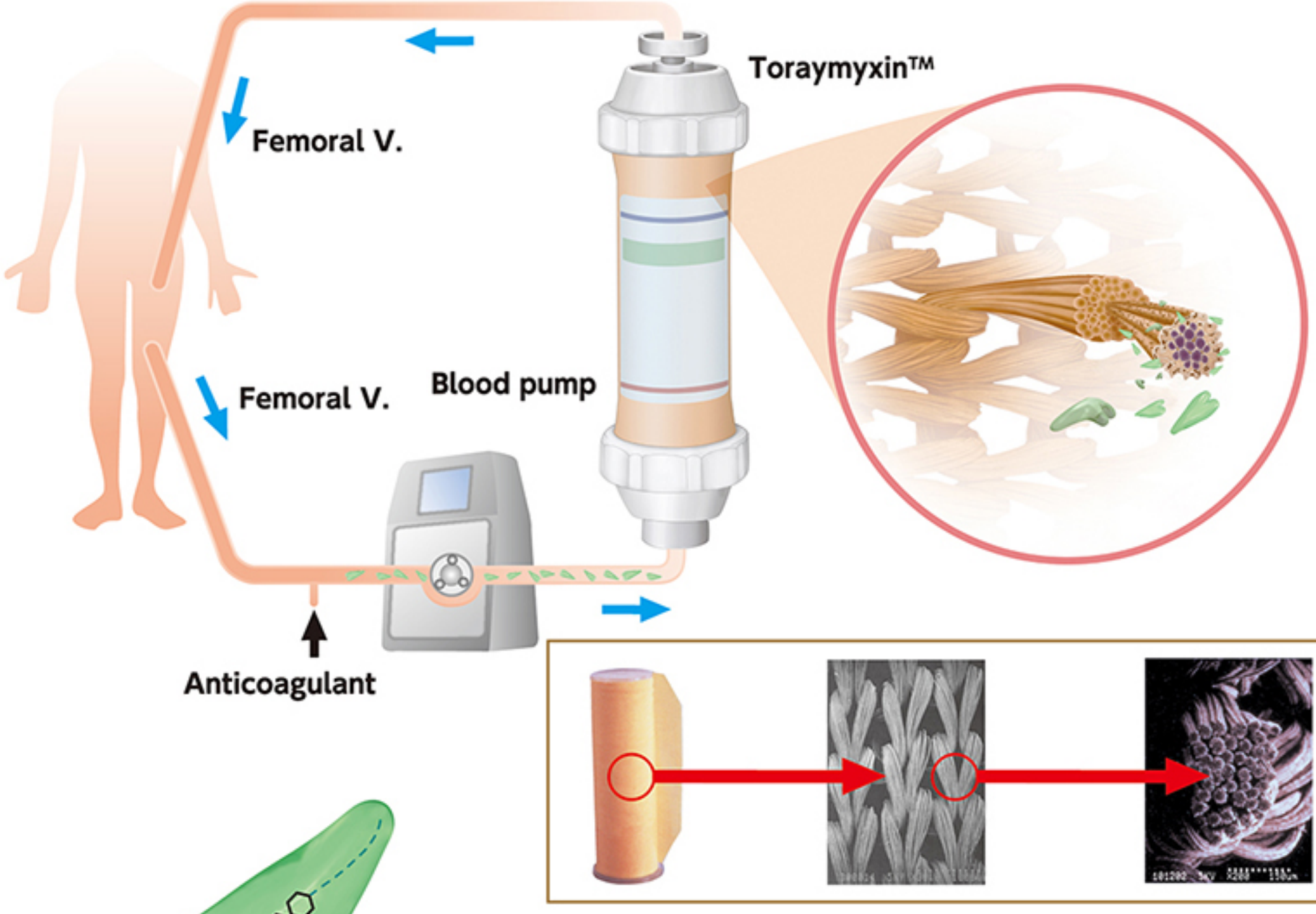
Endotoxin is one of the principal components of the outer membrane of Gram-negative bacteria[6]. It induces systemic inflammatory response characterized by induction of pro-inflammatory cytokines, fever, hypotension, intravascular coagulation and nitric oxide that lead to "endotoxin shock"[4, 7]. Higher level of endotoxin is associated with worse clinical outcomes[8]. Endotoxin invades into the blood stream from the infectious focus or by the bacterial or endotoxin translocation from the gut[9].

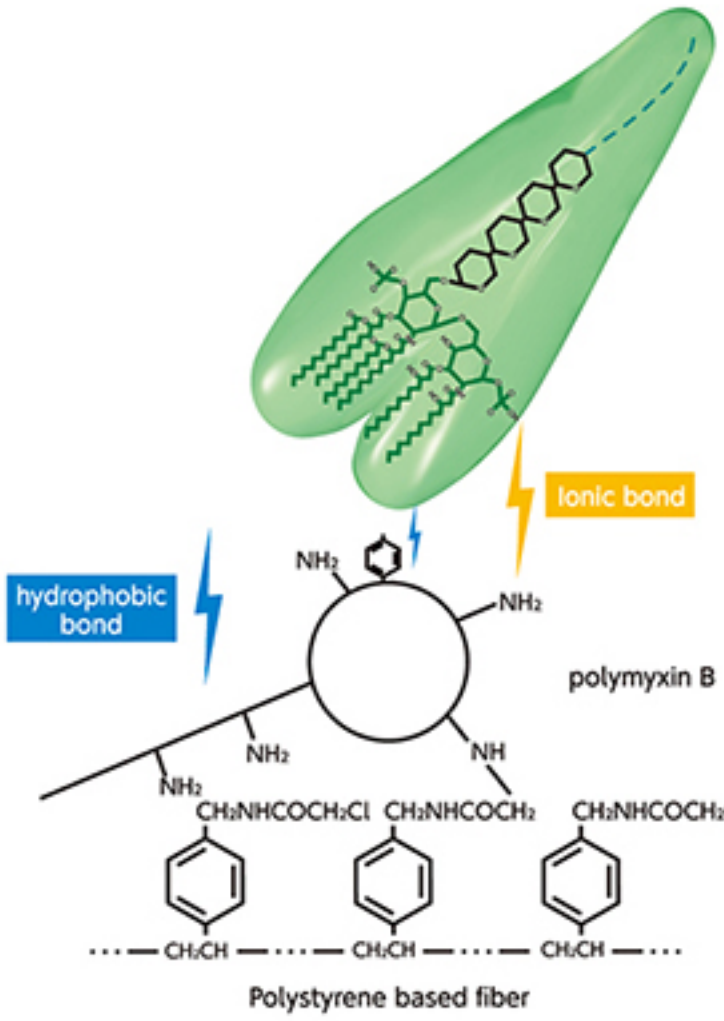


Microvascular occlusion and vascular instability leads to tissue hypoperfusion and hypoxia, and thus organ dysfunction[4].

Toraymyxin™ removes blood endotoxin.

Toraymyxin™ is an extracorporeal hemoperfusion device which is composed of polymyxin B covalently immobilized polystyrene derived fibers[10]. Polymyxin B antibiotics, is well known to bind endotoxin selectively and neutralize its toxicity[11]. Toraymyxin™ removes endotoxin in the blood[12].





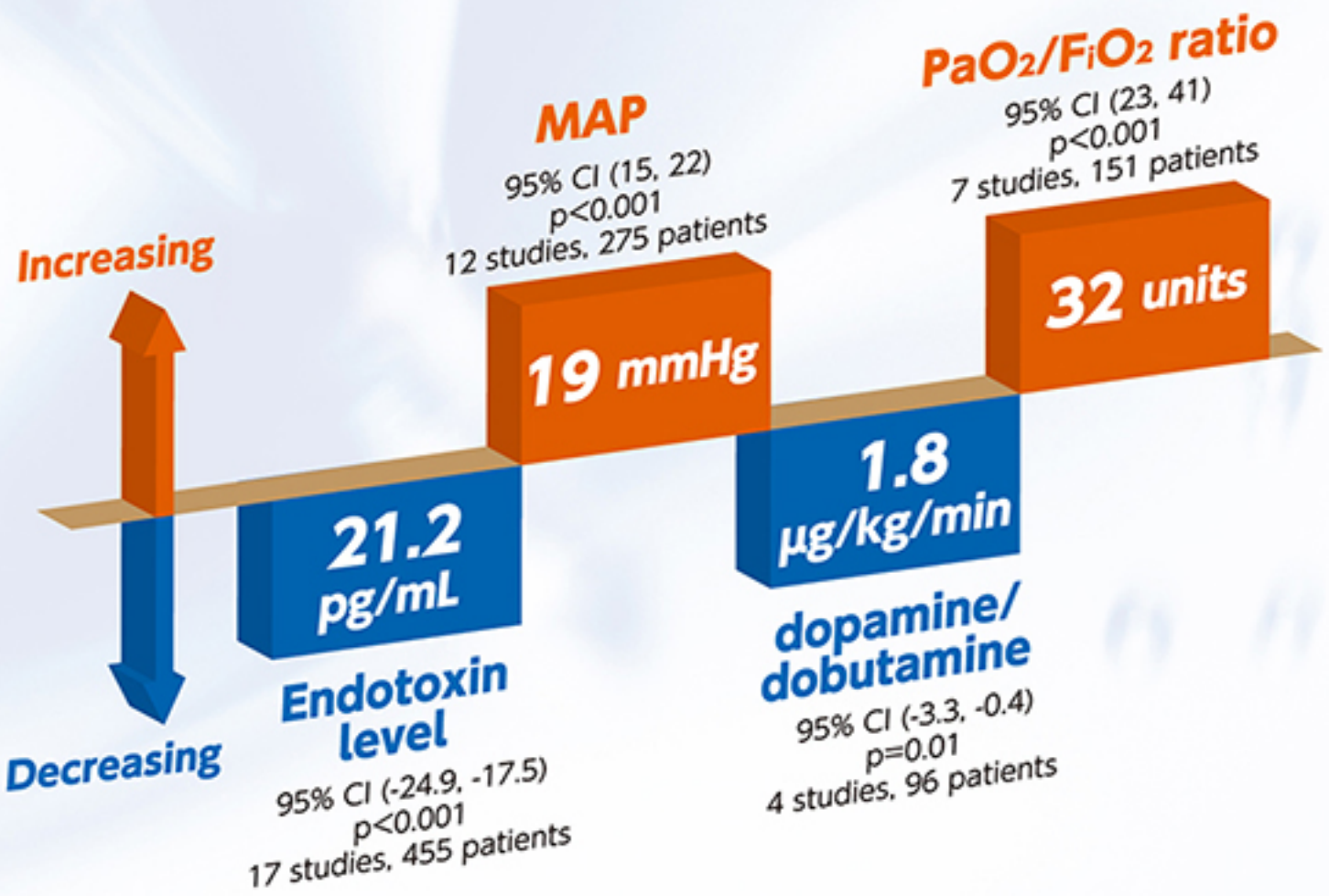
Polymyxin B interacts with the lipid A moiety of endotoxin through hydrophobic and ionic interactions.

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[13]. 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[14].

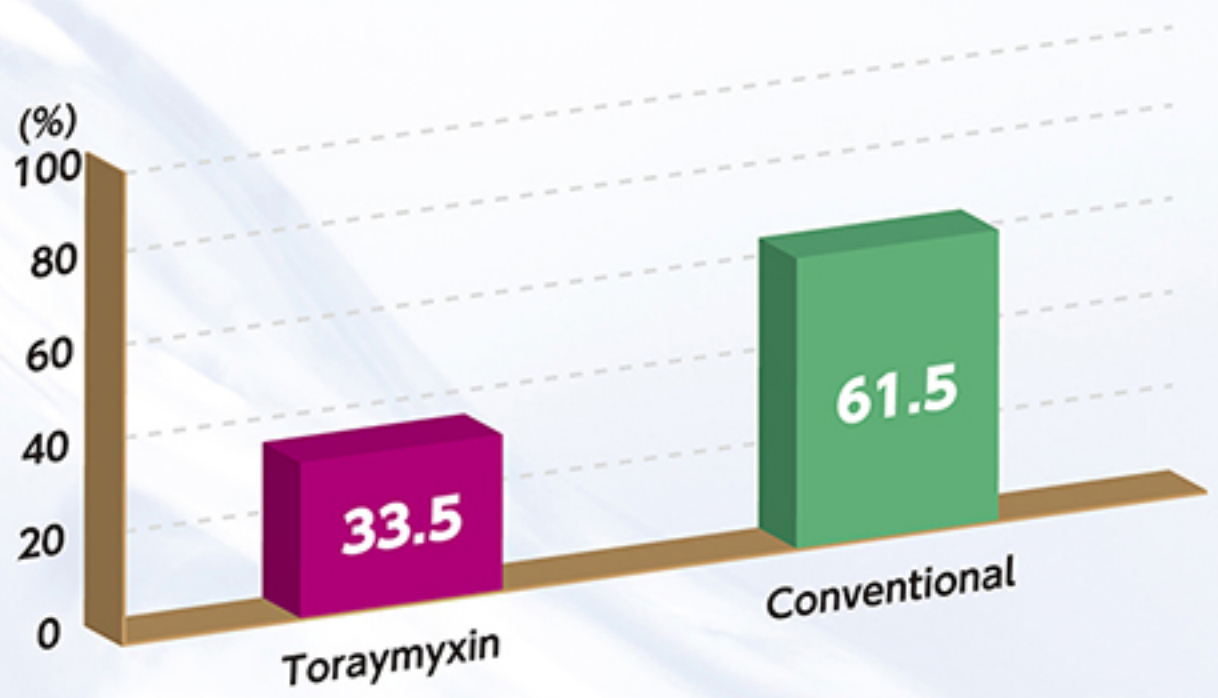
Toraymyxin™ reduces blood endotoxin level and improves hemodynamics in patients with sepsis.

Twenty eight publications about clinical studies with Toraymyxin™ were identified and systematically reviewed[15]. 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 PaO_2/FiO_2 ratio increased after hemoperfusion with Toraymyxin™.

Changes in parameters before and after Toraymyxin™ treatment



Mortality

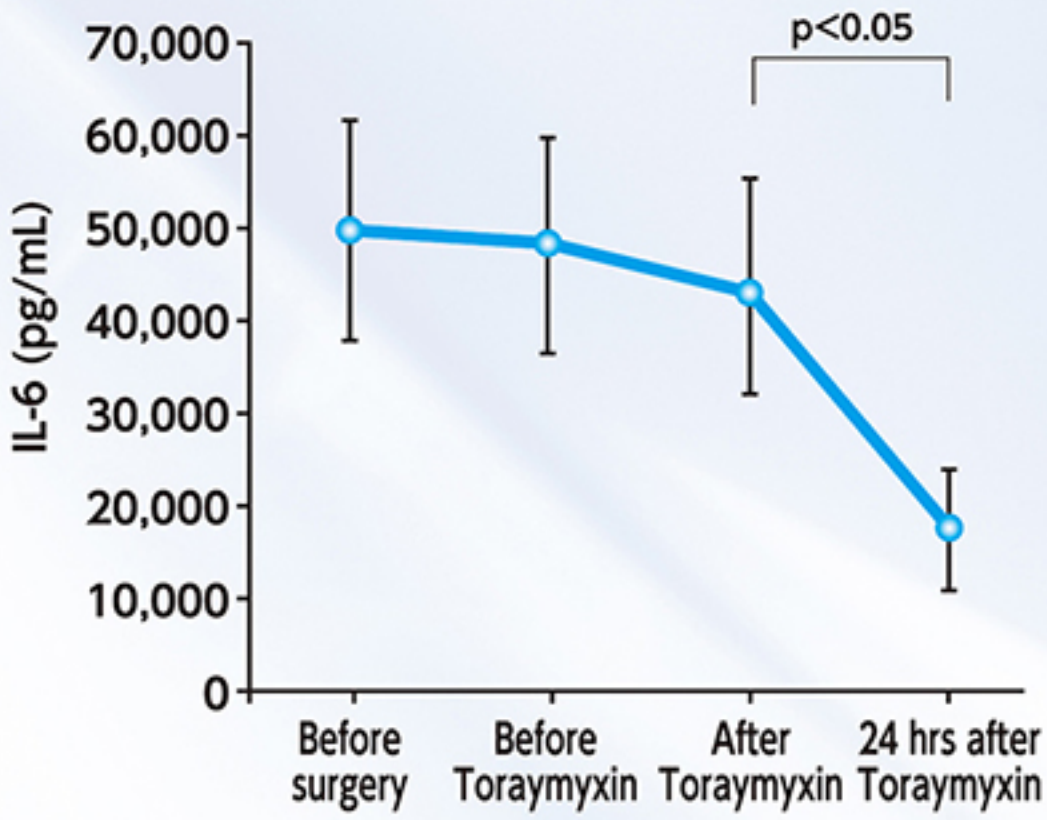


Mortality risk of Toraymyxin™ therapy was reduced by 0.53.
95% CI (0.43, 0.65) p<0.001.
15 studies, 920 patients.

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[7]. 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[16] and PAI-1[17] level are decreased.

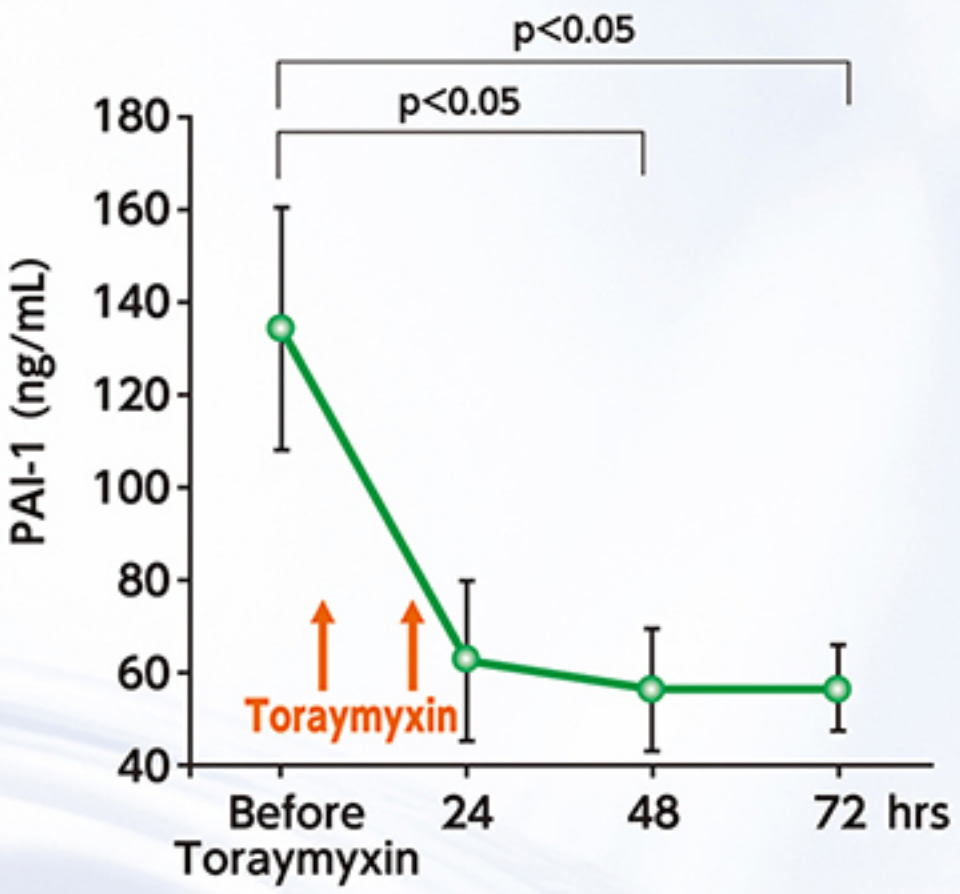
Plasma IL-6 level



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[16]]

IL-6: Interleukin-6

Plasma PAI-1 level



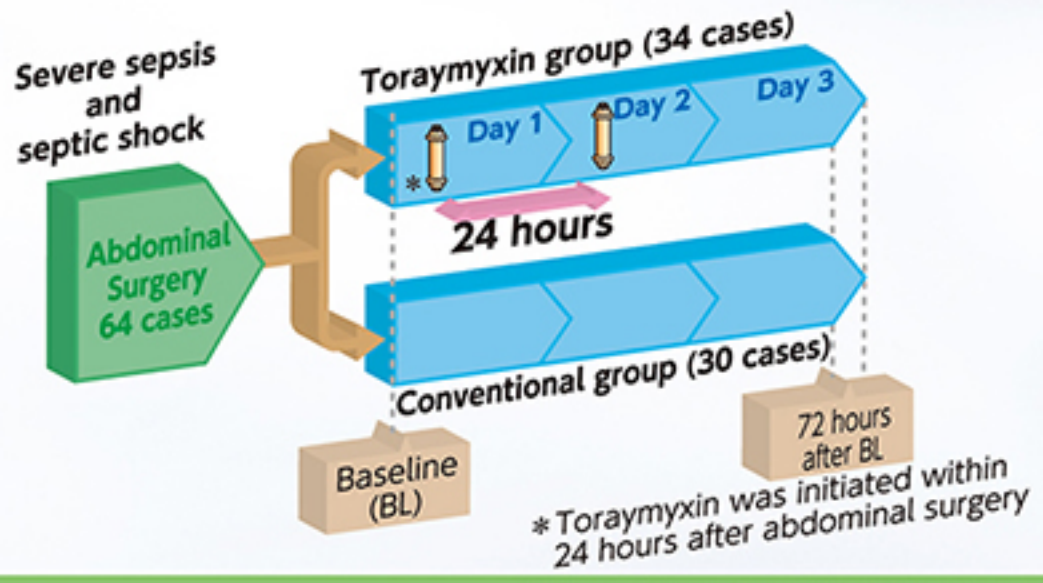
Thirty-six patients with sepsis after acute lung injury or acute respiratory distress syndrome were subjected to hemoperfusion with Toraymyxin™. [Cited from the open-access journal[17]]

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 cavity infection requiring emergency abdominal surgery were included in a randomized controlled study, the EUPHAS trial[18].

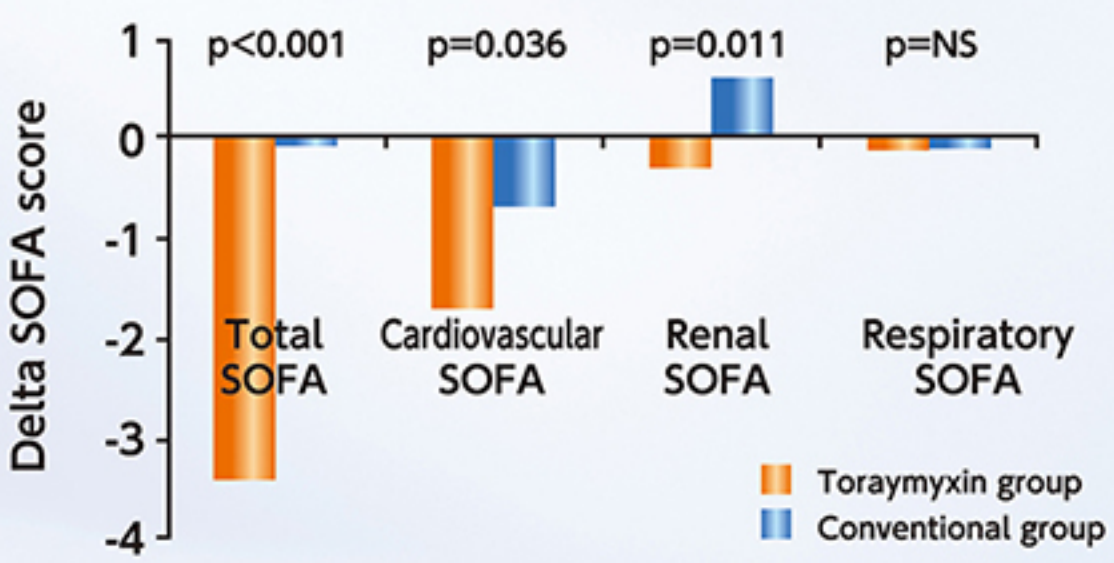
Study Procedures



Patients were randomized to two groups and one group received conventional therapy alone according to the Surviving Sepsis Campaign guidelines (Conventional group: 30 patients) and the other group was subjected to hemoperfusion with Toraymyxin™ (Toraymyxin™ group: 34 patients) in addition to standard therapy. The duration of hemoperfusion was 2 hours and the second session of hemoperfusion was performed 24 hours later.

: Standard therapy according to Surviving Sepsis Campaign guideline

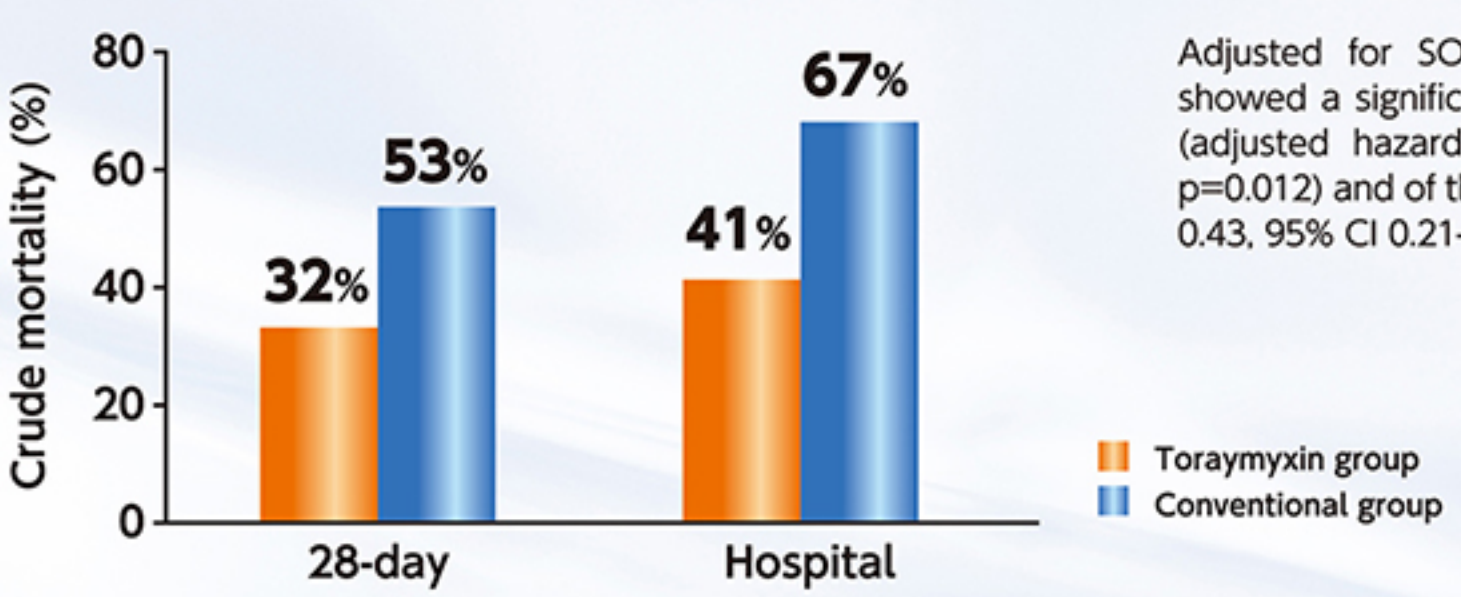
Change in SOFA scores at 72 hours



Sequential Organ Failure Assessment (SOFA) score expresses the severity of organ dysfunction or failure. Delta SOFA score, which is the change in the degree of organ dysfunction between baseline and 72 hours, showed significant improvement of organ failure in the Toraymyxin™ group. Compared to the Conventional group, at 72 hours the Toraymyxin™ group showed a greater reduction in terms of the total SOFA, cardiovascular SOFA, and renal SOFA.

◆Negative values for delta SOFA scores indicate improvement in organ function, while positive values indicate worsening.

Crude mortality after hemoperfusion with Toraymyxin™ and after Conventional therapy



Adjusted for SOFA score, the Toraymyxin™ group showed a significant reduction of the 28-day mortality (adjusted hazard ratio [HR] 0.36, 95% CI 0.16-0.80, p=0.012) and of the hospital mortality rate (adjusted HR 0.43, 95% CI 0.21-0.90, p=0.026).

Target patients and ideal timing for Toraymyxin™ treatment

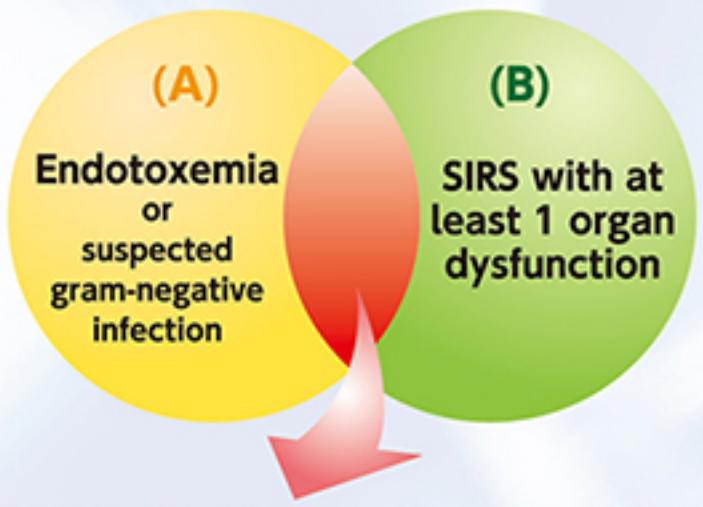
Target patients

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.

and

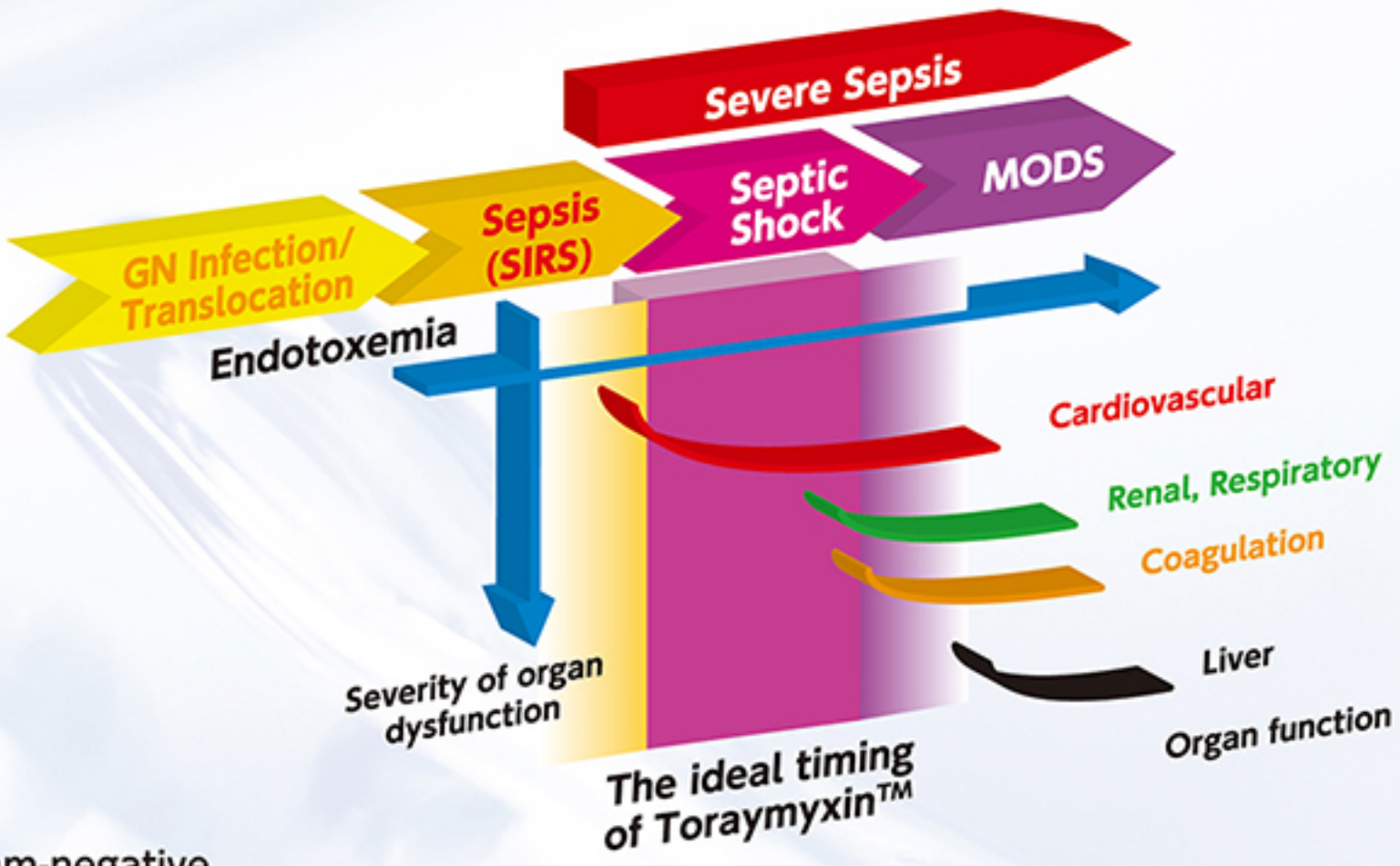
(B) Systemic Inflammatory Response Syndrome (SIRS*) with at least 1 organ dysfunction.



***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 $PaCO_2$ < 32 mmHg)]
(4) White blood cell count > 12,000 cells /mm^3, < 4,000 cells/mm^3 or > 10% immature (band) forms.

Ideal timing



GN : Gram-negative
MODS : Multiple organ dysfunction syndrome

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[18].

Toraymyxin™ cartridge	
Length	225 mm
Diameter (max)	63 mm
Priming volume	135 ± 5 mL
Fibers (dry weight)	56 ± 3 g
Inlet pressure	< 250 mmHg
Maximum pressure	500 mmHg
Sterilization	High-pressure steam sterilization
Expiration	2 years after sterilization

Operating procedure	
Method	Direct Hemoperfusion (DHP)
Blood Flow Rate	100 (80-120) mL/min
Duration of DHP	2 hours
Washing	at least 4 L of physiological saline
Priming	500 mL of heparinized saline (4 U/mL)
Anticoagulant	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.

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

1. Vincent JL et al.: Microvascular dysfunction as a cause of organ dysfunction in severe sepsis, Crit Care 9: S9-S12, 2005
2. Abraham E et al.: Mechanisms of sepsis-induced organ dysfunction, Crit Care Med 35: 2408-2416, 2007
3. Riedermann NC et al.: Novel strategies for the treatment of sepsis, Nat Med 9: 517-524, 2003
4. Cohen J.: The immunopathogenesis of sepsis. Nature 420: 885-891, 2002
5. Jerala R.: Structural biology of the LPS recognition. Int J Med Microbiol 297: 353-363, 2007
6. Stewart I, et al.: Cyanobacterial lipopolysaccharides and human health - a review. Environ Health 5: 1-23, 2006
7. Kuhlen R. et al. eds.: 25 years of progress and innovation in intensive care medicine. (Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft, 2007), 163-176.
8. Marshall JC et al.: Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study, J Infect Dis 190: 527-534, 2004
9. MacFie J. et al.: Bacterial tranlocation studies in 927 patients over 13 years. Br J Surg 93 : 87-93, 2006
10. Shoji H et al.: Extracorporeal endotoxin removal by polymyxin B immobilized fiber cartridge: designing and antiendotoxin efficacy in the clinical application. Ther Apher 2: 3-12, 1998
11. Cardoso LS, et al.: Polymyxin B as inhibitor of LPS contamination of Schistosoma mansoni recombinant proteins in human cytokine analysis. Microb Cell Fact 6: 1-6, 2007
12. Aoki H et al.: Treatment of sepsis by extracorporeal elimination of endotoxin using polymyxin B-immobilized fiber. Am J Surg 167: 412-417, 1994
13. Vesentini S. et al.: Multi-scale analysis of the toraymyxin adsorption cartridge. Part I: molecular interaction of polymyxin B with endotoxins. Int J Artif Organs 29: 239-250, 2006
14. Sakai Y. et al.: New extracorporeal blood purification devices for critical care medicine under development. Therapeutic Plasmapheresis (XII): 837-842, 1993
15. Cruz DN, et al.: Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. Crit Care 11: 1-12, 2007
16. Shimizu T et al.: The clinical significance of serum procalcitonin levels following direct hemoperfusion with polymyxin B-immobilized fiber column in septic patients with colorectal perforation. Eur Surg Res 42: 109-117, 2009
17. Kushi H et al.: Early hemoperfusion with an immobilized polymyxin B fiber column eliminates humoral mediators and improves pulmonary oxygenation. Critical Care 9: R653-661, 2005
18. Cruz DN, Antonelli M, Fumagalli R. et al.: Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 301: 2445-2452, 2009

CE 0123

EC REP

Toray International Italy S.r.l.

Via Mecenate 86, 20138 Milan, ITALY
TEL: +39-02-580-39133 / FAX: +39-02-580-16317

Exporter:

Toray Medical Co., Ltd.

Global Marketing Department, Critical Care Section
4-1, Nihonbashi-Honcho 2-chome,
Chuo-ku, Tokyo 103-0023, JAPAN
TEL: +81-3-6262-3832
FAX: +81-3-6262-3840
http://www.Toray-medical.com/en/

Manufacturer:

Toray Industries, Inc.

1-1, Nihonbashi-Muromachi 2-chome,
Chuo-ku, Tokyo 103-8666, JAPAN

Printed in Japan (1407)