



# Use a Novel Hemoperfusion Cartridge Efferon LPS for Simultaneous Adsorption of Cytokines and Endotoxin in Septic Shock: A Case Report

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**Abstract:** A patient (age 75, male) with diffuse peritonitis (cecum rupture resulted from tumor obturation) was hospitalized and underwent emergency surgery. He was hypotensive (norepinephrine 0.56 mg/kg\*min) and exhibited multiple organ failure syndrome (SOFA=10), so a septic shock diagnosis was concluded. Standard of care treatment didn't result in improvement of his condition and so he was subjected to extracorporeal hemoperfusion with Efferon LPS adsorber. Efferon LPS is single-use therapeutic device, certified in Russia, a cartridge with selective adsorbent polymeric beads, which provide simultaneous lipopolysaccharide (LPS) and cytokines adsorption ("multimodal" action). Two conclusive hemoperfusions led to quick improvements in hemodynamic parameters and improvement of patient's condition. IL-6 serum level dropped from 1640 to 480 pG/mL, followed by subsequent decrease down to 350 pG/mL within next few days. Procalcitonin levels dropped from 98 nG/mL down to 5 nG/mL. Significant decrease in CD14<sup>+</sup> blood monocytes also was noted during each hemoperfusion session. The patient stayed in ICU for 8 days. He has survived and was discharged on day 24 in satisfactory condition. Extracorporeal sequestration of LPS, cytokines and which is extremely important CD14<sup>+</sup> monocytes from the bloodstream can dampen the systemic inflammation's crippling action in patients with sepsis. Efferon LPS hemoperfusion is prominent option for extracorporeal treatment of septic shock.

**Keywords:** LPS-selective Hemoperfusion, Anti-cytokine Hemoperfusion, Sepsis, Septic Shock, CD14<sup>+</sup> Monocytes, Procalcitonin, IL-6

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## 1. Introduction

Novel therapeutic methods to treat septic shock are a fundamental priority, as mortality rate of standard of care remains disturbingly high. Extracorporeal sequestration of inflammatory molecules is a prominent component in complex therapy of septic shock. Bacterial endotoxins (lipopolysaccharides, LPS) and endogenous inflammatory mediators (cytokines) are important therapeutic targets in extracorporeal treatment of septic shock. Corresponding

extracorporeal sequestration techniques (LPS-selective and anti-cytokine hemoperfusion) can dampen the damaging action of systemic inflammation [1, 2]. There are specific single-use therapeutic devices tailored for elimination of each type of these factors which are used for severe sepsis and septic shock treatment, however, their reported efficacy remains limited. Toraymyxin PMX-20R (Japan) devices for LPS-selective hemoperfusion are among the most well-studied extracorporeal adsorbers applied for septic shock management. Meta-analysis performed over 20-year period has shown its effectiveness in decrease of mortality rate of

the patients with septic shock [3]. The devices for anti-cytokine hemoperfusion are designated mainly for semi-selective elimination of various proteins, cytokines and other factors responsible for multi-organ failure syndrome development. They are used not only for sepsis treatment, but frequently also to prevent mono- or multiple-organ failure [4, 5]. In particular, they are used after major surgeries with cardiopulmonary bypass [6, 7]. Extracorporeal treatment devices (Efferon LPS, Russia) for simultaneous cytokines and LPS adsorption can effectively eliminate LPS, cytokines, other inflammatory mediators from bloodstream, have been recently introduced for the clinical use [8, 9]. Such novel therapeutic option provokes big interest and this case describes its clinical usage in treatment of septic shock.

## 2. Case Presentation

Patient S. (aged 75 years old) was urgently hospitalized with the signs of acute abdomen and shock. After 2-hour examinations and conducted surgery, the following diagnosis was established: colon tumor in rectosigmoid region with stenosis; acute intestinal obstruction; diastatic rupture and perforation of the dome of the cecum; diffuse peritonitis; septic shock. Emergency surgery was performed: right-sided hemicolectomy, sigmoid colon exteriorization, resection of deserosed part of small intestine followed by suturing the ends of it, abdominal cavity lavage and drainage. Through surgery lasted 2.5 hours, crystalloids infusion was associated with sympathomimetics introduction (norepinephrine 0.56 mg/kg\*min). 8 hours after the operation is over and infusion therapy and sympathomimetics introduction is continued, the first hemoperfusion with Efferon LPS was carried out that lasted 120 minutes. The blood circulation was provided by a pump of AK-10 machine (Gambro, Sweden) with the speed

100 mL/min using dual-lumen catheter placed into the internal jugular vein.

Non-fractionated heparin was used for anticoagulation: intravenous bolus injections of 5,000 U before hemoperfusion and then by 1,000 U/hour continuously into the bloodstream during the hemoperfusion.

Hypotension was present throughout the first hemoperfusion and upon its completion. Blood pressure normalization was managed on the beginning of the next day by adding  $\beta$  adrenergic agonists epinephrine.

The laboratory tests were taken on the day 1 after surgery (2 points — at the beginning of hemoperfusion and at the moment of its completion), day 2 (before relaparotomy), day 3 (2 points — at the beginning of hemoperfusion procedure and at the moment of its completion), and days 4 and 6. Blood cell counts were assessed (with a hematological analyzer Sysmex XT4000, Japan). Phenotypic and activation markers of blood cells such as relative and absolute counts of CD14<sup>+</sup> monocytes and CD14<sup>+</sup> neutrophilic granulocytes (NCL-CD14), HLA-DR<sup>+</sup> mononuclear cells (NCL-LN3, Leica Biosystems). IL-6 (ELISA, Vector-Best, Russia) and procalcitonin (immunofluorescence method, Brahms AG, "Lumat LB 9507", Germany) blood levels were also determined.

The severity of multiorgan disorders was assessed using the SOFA scale [10].

On the day 2 under normal blood pressure stabilization process and epinephrine support cessation, an elective surgery of small intestine patency restoration was performed. The second hemoperfusion with similar parameters was carried out in the morning of the day 3.

The table 1 data summarizes significant biomarkers change that occur during 6-day patient monitoring.

**Table 1.** Time changes in patient's condition and test results.

Indicators / control level healthy adults	Days after the surgery						
	Day 1, before hemoperfusio n 1	Day 1, after hemoperfusio n 1	Day 2, re-lapatomy	Day 3, before hemoperfusio n 2	Day 3, after hemoperfusio n 2	Day 4	Day 6
SOFA, points	10	10	7	5	5	5	1
Blood pressure, mm Hg	74/51	79/43	80/50- 105/65	119/73	126/78	122/78	127/86
Norepinephrin i.v. mG/kG*min	0,56	0,69	0,80-0,05	0	0	0	0
Epinephrin i.v. mG/kG*min	0	0	0,03-0	0	0	0	0
IL-6, 2,11±2,84 pG/mL	1686	1388	1281	692	411	395	395
Procalcitonin, 0,1±0,1 nG/mL	98	80	67	28	37	21	5
CD14 <sup>+</sup> monocytes, 0,03±0,01*10 <sup>9</sup> /L	0,13	0,03	0,27	0,30	0,18	0,28	0,20
Lymphocytes, 1,88±0,39 *10 <sup>9</sup> /L	0,8	0,4	0,8	1,7	1,0	0,9	1,6
Granulocytes, 3,1±0,8 *10 <sup>9</sup> /L	3,0	3,5	7,5	11,8	12,4	10,1	8,3
Trombocytes, 244±45 *10 <sup>9</sup> /L	177	177	164	119	106	85	188

The patient's general condition has been gradually improving during the monitoring period. The arterial blood pressure was normalized on day 2. The sympathomimetic support was discontinued on day 3. On the day 6, the lymphocytopenia has been resolved and the level of multiple organ disorders has declined down to point 1 according to SOFA score. The patient stayed in ICU for 8 days. He has

survived and was discharged on day 24 in satisfactory condition.

Blood samples were drawn at the Efferon LPS device inlet and outlet to assess the direct removal of certain cells and factors (Table 2). The samples were drawn in two points: at the beginning of hemoperfusion procedure (1st minute) and at its end (120th minute), average values were obtained.

Ratio of these two averages summarizes the adsorption capacity towards these cells.

**Table 2.** Average adsorption capacity of Efferon LPS (n=4).

Values of blood	(Input-output)/input*100
CD14 <sup>+</sup> granulocytes	37%
HLA-DR <sup>+</sup> mononuclear cells	27%
CD14 <sup>+</sup> monocytes	25%
Monocytes	19%
Granulocytes	16%
Leukocytes	14%
Procalcitonin	12%
Trombocytes	10%
Lymphocytes	2%
Erythrocytes	2%

According to Table 2 data, Efferon LPS hemoperfusion directly adsorbs activated leukocytes, especially the ones with LPS attached (CD14<sup>+</sup> cells), as well as moderate-to low amounts of platelets, erythrocytes and lymphocytes. This is the first mention of selective action of Efferon LPS hemoperfusion towards the functionally active leukocytes, which are playing an important role in systemic inflammation, multiple organ dysfunctions and septic shock.

There were no technical difficulties or adverse effects noted during the hemoperfusion or after it. Anticoagulation protocol haven't yielded any blood pressure increase in the extracorporeal circuit.

### 3. Discussion

Abruption of inflammatory cascade at early stage of sepsis can be achieved by elimination of the soluble factors from the bloodstream: either the initial trigger (LPS), or the downstream proteins, such as inflammatory cytokines and polypeptides leading vascular thrombosis. These downstream proteins are expressed by the immune cells, which play an essential role in the septic cascade development. Some of them are located in the tissues and endothelium (Kupffer cells of the liver, endothelium dendritic cells and so on), and are not accessible for direct extracorporeal elimination, while the other cells are circulating in the bloodstream and are exposed to hemoperfusion. The serum monocytes and granulocytes have specific receptors for binding LPS presented by a complex with LPS-binding protein. After being bond to this complex, the receptors can be identified as CD14. The CD14<sup>+</sup> monocytes are getting activated and start expressing a broad range of various cytokines responsible for proinflammatory (mainly) and anti-inflammatory reactions [11]. The monocytes migrate from the bloodstream into the tissues where they transform into the macrophages and continue their regulating action. For example, mainly monocytes possessing CD16 receptors can migrate into lungs. LPS-activated CD14<sup>+</sup>CD16<sup>+</sup> pulmonary macrophages will support release of inflammatory cytokines into surrounding tissues [11, 12].

It was shown for PMX-20R that about 30% of all monocytes are adsorbed on the polymeric surface, where mostly the activated CD14<sup>+</sup>CD16<sup>+</sup>TLR4<sup>high</sup> monocytes are

getting eliminated [13]. Another study by M. Nichiboria et al. [14], concluded that the monocytes amount to ~80% of all adsorbed leukocytes. It was shown in another study that the serum levels of inflammatory cytokines IL-6 and IL-8 increase after PMX-20R hemoperfusion session is carried out [15].

Efferon LPS polymeric adsorbent is the first case of multimodal polymeric adsorbents for hemoperfusion [16, 17]. Its original structure (mesoporous hypercrosslinked styrene-divinylbenzene copolymer with surface-immobilized LPS-selective ligand) provides simultaneous sequestration of two dissimilar therapeutic targets (LPS and cytokines). First component of its structure is meso- and macropores. Adsorption of cytokines and inflammatory mediators undergoes in mesopores via non-specific (hydrophobic, van der Waals) interactions. Second component of the adsorbent's structure is a synthetic ligand to Lipid A domain of lipopolysaccharide (LPS) which is covalently immobilized on the styrene-divinylbenzene copolymer scaffolds's surface. Synthetic ligand's interaction with LPS molecule via two glycosamine phosphates and acyl chains mimics its well-studied interaction with lysine-rich Polymyxin B [18]. This novel approach provides elimination the broader range of pathogenic substances which are responsible for the development of septic cascade and multiple organ dysfunctions/failure [2].

Procalcitonin level, showing severity of multiple organ disorders in sepsis, has declined from prognostically unfavorable level 98 nG/mL down to 5 nG/mL.

Two consequent hemoperfusions resulted in prominent decrease of the levels of basic inflammatory cytokine interleukin-6 to the end of both procedures — first from 1686 to 1388 pG/mL, and second from 692 to 411 pG/mL. These fast drops of serum IL-6 illustrates direct removal of this factor during hemoperfusion.

CD14<sup>+</sup> monocytes levels before and after hemoperfusion procedures were evaluated. These cells belong to main producers of proinflammatory cytokines of the inflammatory cascade. Profound decrease of serum levels of these cells was noted over the course of each hemoperfusion. First hemoperfusion yielded 0.13 to 0.03 \* 10<sup>9</sup>/L cell amount decrease, and second one yielded decrease from 0.30 to 0.18 \* 10<sup>9</sup>/L. It should be noted that the bone marrow restores (or even increases) their amount on the next day. However, these "naive" monocytes are incomparably less active and express inflammatory mediators to a lesser extent.

Serum leukocytes adsorption process is of great importance for regulation of inflammatory response in critical patients. Indeed, after the source of infection is surgically removed, activated serum leukocytes at 20–40\*10<sup>9</sup>/L levels still can lead to dramatic consequences. Reduction of the activated blood cells which possess cytotoxic and tissue-damaging properties may contribute to a clear clinical benefit.

Amount of granulocytes increased to the end of every hemoperfusion and within the entire monitoring period, whereas platelets level remained almost unchanged. Apart

from immediate elimination of certain cells and cytokines, we noted a prolonged beneficial effect of the Efferon LPS hemoperfusions on a systemic inflammation. Within 6 days, the lymphocytes count in the blood has increased gradually from the lymphocytopenia level up to a normal one (Table 1).

We did not directly assess the decrease of LPS molecule due to its weak prognostic value. However, Efferon LPS' high adsorption capacity towards LPS molecule exceeds its possible clinically relevant serum levels in multiple times.

Hemoperfusion with Efferon LPS in elderly septic shock patient with colon cancer has shown the device's high level adsorption activity towards extremely elevated initial serum levels of main proinflammatory cytokine IL-6, as well as CD14<sup>+</sup> monocytes and CD14<sup>+</sup> granulocytes. The positive laboratory effects are presented by lymphopenia compensation, decrease of IL-6 and CD14<sup>+</sup> monocytes, increase of granulocytes levels from normal (probably not adequate for inflammatory response) to optimal, and reduced levels of inflammation marker procalcitonin. The positive clinical effects include hemodynamic parameters stabilization and inotropic support reduction up to permanent discontinuation by the beginning of the second hemoperfusion that reversed the unfavorable course of septic shock and led to patient's convalescence.

## 4. Conclusion

As shown in the case of treatment of elderly patient with colon tumor complicated by peritonitis and septic shock, the use of Efferon LPS cartridge for LPS and cytokines adsorption provides beneficial clinical effect. This therapeutic device possesses high-level sorption characteristics towards bacterial endotoxin and cytokines (IL-6), while also showing decrease in levels of proinflammatory blood cells (CD14<sup>+</sup> monocytes and CD14<sup>+</sup> granulocytes). The patient's condition laboratory monitoring has revealed lowering of the concentration of the systemic inflammation marker PCT and normalization of the state of the cell-mediated immunity. No undesirable effects were registered during hemoperfusion procedures.

## Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

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