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Endotoxin and Cytokines Removal with Adsorption Device in a Child with Sepsis After Transplantectomy (Case Report)

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Summary

Sepsis is one of the leading causes of death in kidney transplant recipients.

We present our experience of effective removal of bacterial endotoxins and endogenous inflammatory mediators using a multimodal hemosorbent in sepsis, caused by gram-negative polyresistant *Klebsiella* spp. including *K. pneumoniae.* The device was used in a 15 y.o. patient after treatment failure of graft-bed abscess and removal of kidney transplant.

Results. Two 24-hour sorption procedures on Days 3 and 5 post- transplantectomy in combination with renal replacement therapy resulted in consistent decrease of pro-inflammatory markers concentrations (procalcitonin — 15.1→11.4→7.2 ng/ml; C-reactive protein — 234→199→90 mg/l), preventing therefore further progression of multiple organ dysfunctions.

Conclusion. Inclusion of selective adsorption of cytokines and/or lipopolysaccharides into multimodal intensive therapy in an immunosuppressed pediatric patient with sepsis caused by resistant microorganisms improved treatment outcomes.

Keywords: sepsis; endotoxins; extracorporeal therapy; cytokine sorption; Efferon

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Sepsis in children is a high-risk condition that requires timely diagnosis and treatment. Delayed initiation of treatment is associated with increased mortality [1, 2]. According to Weiss et al, refractory shock is the major cause of death in one-third of children with sepsis who die within the first 72 hours, while multiple organ dysfunction syndrome, respiratory failure, and neurologic complications are the major causes of death after 72 hours [3].

In kidney transplant recipients, sepsis is the main indication for intensive care unit (ICU) admission and a major cause of high in-hospital mortality, which can reach up to 30% [4–6].

Extracorporeal blood purification can be used in the management of patients with sepsis. Devices for the removal of endotoxins and cytokines have great potential, and their use in sepsis caused by Gram-negative pathogens can improve treatment outcomes [7].

Case Report

A 15-year-old patient was admitted to the renal transplant unit with a body temperature of 38°C and discharge from the fistulous tract in the postoperative wound area.

The patient was diagnosed with autosomal recessive polycystic kidney disease at the age of 4 years. Ten months ago, long-term hemodialysis was started due to progression of chronic kidney disease. Three months ago, he underwent right-sided nephrectomy with ABO-incompatible related kidney transplantation with placement of the graft in the retroperitoneal space of the right iliac fossa. In the post-transplant period, the child received immunosuppressive therapy, including tacrolimus 8 mg per day (under control of drug concentration in blood), prednisolone according to the scheme with reduction to 7.5 mg per day, mycophenolate mofetil 500 mg every 12 hours. Prevention of CMV infection (valganciclovir 450 mg per day), Pneumocystis pneumonia and bacterial infection (cefazolin 1 g every 8 hours) was also provided. Graft function was evident immediately, with a decrease in creatinine from the first postoperative day.

In the postoperative period, reconstruction of the arterial anastomosis was performed on day 9 due to the presence of signs of renal artery stenosis of the graft. Six days later, a surgical procedure in-

cluding stopping bleeding and performing prosthetic anastomosis with a xenograft was done. Based on the results of the microbiological examination of the wound discharge (*Klebsiella* spp., including *Klebsiella pneumoniae*, carbapenemase class B (MBL) producing strain), antibacterial therapy was prescribed with meropenem 500 mg every 8 hours, cefotaxime/sulbactam 3 g every 8 hours. Immunosuppressive therapy was continued with solumedrol 100 mg daily, tacrolimus 9 mg daily, while mycophenolate mofetil was suspended. The patient's condition improved, and 51 days after kidney transplantation, with satisfactory graft function (blood creatinine 120–130 μmol/L, GFR 83.7–77.2 mL/min/1.73 m²), the child was discharged from the hospital on immunosuppressive and antihypertensive therapy. The patient was instructed to continue prevention of Pneumocystis pneumonia and CMV infection.

After discharge, the patient developed fever, and ultrasound revealed a fluid collection under the transplanted kidney; the aspirate contained pus.

On readmission to the hospital on day 27 after discharge, the graft function was satisfactory. Computed tomography showed a limited collection of fluid from the L4 level behind the right iliac muscle, pushing it anteriorly and compressing the right common iliac vein, pushing the bladder to the left and extending to the renal graft hilum and the right inguinal region, with a volume of approximately 230 cm³, of non-homogeneous structure with gas bubbles. Microbiological examination of the wound discharge revealed *Klebsiella* spp., including *Klebsiella pneumoniae*, MBL-producing strain. Considering the clinical and laboratory data and the development of infection in a patient on immunosuppressive therapy, antibacterial therapy was prescribed with imipenem/cilastatin 1000/1000 mg every 8 hours, fosfomycin 4 g every 6 hours.

Due to the severity of the disease, persistent subfebrile temperature, increase in the volume of accumulated fluid, compression of iliac blood vessels, increase in inflammatory markers, three days after admission, revision of the retroperitoneal abscess and draining of its cavity were performed.

In the postoperative period, tacrolimus was discontinued, prednisolone dose was reduced, valganciclovir administration was interrupted, leukopoiesis stimulation (filgrastim 300 mcg) and antifungal prophylaxis (fluconazole 600 mg initially, then 300 mg daily) were started. Antimicrobial therapy was adjusted based on the preliminary data from the blood microbiological study (growth of Gram-negative and Gram-positive microorganisms) and included biapenem 600 mg every 12 hours, fosfomycin 4 g every 8 hours.

On the 7th day after the revision and drainage of the retroperitoneal space, the patient had a rise in body temperature to 39.7°C, an increase in proinflammatory markers (C-reactive protein 95.1 mg/L; procalcitonin 0.22 ng/mL). Taking into account: a) the presence of a fluid collection of up to 15 mL (pus) in the graft hilum on CT scan and a high risk of arterial bleeding, b) the polycystic left kidney as a probable source of infection, and c) the ineffectiveness of conservative therapy, transplantectomy and left-sided nephrectomy were performed. Due to sepsis manifestations, a session of renal replacement therapy (RRT) using the Prismaflex RRT device (Baxter, USA) and the oXiris set was started on the first day after surgery. The parameters of the procedure were as follows: blood flow rate 3–5 mL/kg/min (150–180 mL per minute), dialysate flow rate and renal replacement dose 30 mL/kg/hour (1400 mL per hour). Heparin at a dose of 10–18 U/kg/hour was used for anticoagulation during the procedure, and activated clotting time was maintained at 140–160 seconds (reference values 90-120 seconds). Taking into account the results of blood microbiology (*Klebsiella* spp., including *Klebsiella pneumoniae*) and ongoing renal replacement therapy, meropenem 1 g every 12 hours and fosfomycin 2 g every 8 hours were administered. An ultrasound scan revealed right iliac vein thrombosis, so the dose of heparin was increased and the activated clotting time was maintained at approximately 200 seconds.

Over the next three days, the patient's condition did not change significantly: fever up to 38.6°C and tachycardia up to 115 beats/min persisted despite RRT. Laboratory tests showed high levels of proinflammatory markers (procalcitonin increased from 6.58 to 15.13 ng/mL, C-reactive protein increased from 163.6 to 234 mg/L) (see Figure), while endotoxin activity (EAA) was 0.57. Blood pressure was within 120–150/60–90 mmHg without vasopressors, and SpO_2 was 98–99% on air-oxygen mixture (up to 4 L O_2/min).

Considering the lack of treatment effectiveness and negative laboratory changes, Efferon LPS (Efferon, Russia), a device for the adsorption of cytokines and lipopolysaccharide (LPS), was connected to the extracorporeal circuit before the hemofilter. Renal replacement therapy parameters were identical. After 24 h of adsorption, body temperature returned to normal. Based on blood and wound discharge microbiology (*Klebsiella pneumoniae* MDR+ (multidrug resistant), MBL+), the antibiotic therapy was changed to meropenem 2 g every 12 hours, polymyxin B 50 mg every 12 hours, 2, 3-bis (hydroxymethyl) quinoxaline 1, 4-di-N-oxide 300 mg every 8 hours, and Klebsiella polyvalent bacteriophage topical 20 mL every 12 hours.

Emergency surgery was performed on the 4th day after transplantation due to continued bleeding from the site of the removed graft (volume of blood loss was 500 mL). Relaparotomy, revision, lavage and drainage of the abdominal cavity and retroperi-

toneal space were performed. The next day, due to high levels of proinflammatory markers and endotoxin (EAA 0.87), the second session of cytokine and LPS adsorption for 24 hours with Efferon LPS was performed. Antibacterial therapy was again changed to ceftazidime/avibactam 1250 mg every 8 hours, aztreonam 1 g every 8 hours. The patient's condition improved and the levels of inflammatory markers decreased (see Figure).

Later, the patient underwent two surgical procedures for bleeding from the retroperitoneal space on day 8 post-transplantation and from the abdominal cavity on day 13. During the latter surgery, there was a diapedetic hemorrhage from the wound, so renal replacement therapy was continued from day 14 with the use of the oXiris kit and citrate anticoagulation.

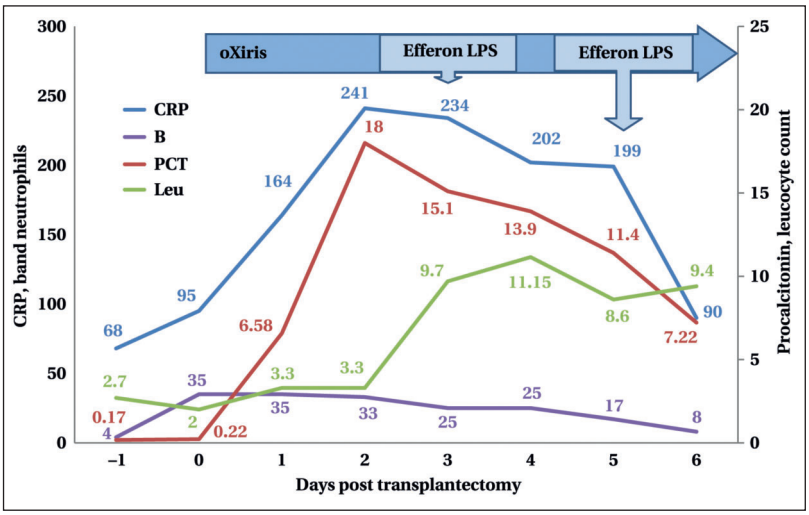

Fig. Changes in laboratory parameters (CRP — C-reactive protein, mg/l; Leu — leukocytes, ×10⁹/l; B — bands, %; PCT — procalcitonin, ng/mL) after transplantectomy.

In total, continuous renal replacement therapy was administered for 21 days. Thereafter, treatment was continued with daily hemodiafiltration procedures with a switch to a long-term regimen of 4 times per week for 4 hours.

Discussion

In 2005, the International Pediatric Sepsis Consensus Conference (IPSCC) proposed age-adjusted definitions of sepsis and its stages in pediatrics, which relied on the presence of systemic inflammatory response syndrome (SIRS) as the main criterion. However, because SIRS is not specific for sepsis, the IPSCC criteria for diagnosing sepsis have low specificity and sensitivity. As a result, the proposed definitions of sepsis and septic shock for adult patients (Sepsis-3) have been adapted for pediatric use.

Sepsis is the response of the body to an infection. It can be uncontrolled and «exaggerated» with severe clinical manifestations or mild due to immunosuppression [8]. Piskin et al. showed that in the first two months after kidney transplantation, when immunosuppression was most intense, infection was the only primary cause of mortality [9].

Gram-negative bacteremia is a common complication of renal transplantation [10]. LPS is the main mediator of sepsis under these conditions. LPS itself is not considered toxic, and its endotoxic effects are mediated by activation of the immune system. Sensitivity to LPS depends primarily on factors that influence the susceptibility of the body rather than the actual mechanisms of action of LPS [11]. It triggers the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukins (IL), by the cells of the body. The imbalance between pro- and anti-inflammatory mediators serves as a factor in the development of sepsis [12]. To suppress redundant systemic effects in sepsis, it is necessary, among other things, to eliminate cytokines below an individual critical threshold. Cytokines are considered as prime targets for modulation to improve the condition of patients with severe inflammation, sepsis, and septic shock [13].

Currently, there are three methods of treatment for end-stage chronic kidney disease, including in children, which are peritoneal dialysis, hemodialysis and kidney transplantation.

According to the Russian Register of Renal Replacement Therapy for 2019, 81 children received hemodialysis, 130 peritoneal dialysis, and 434 children had a functioning kidney transplant [14]. Kidney transplantation is the optimal treatment for children with stage 5 chronic kidney disease, leading to significant improvements in survival, duration and quality of life compared to dialysis [15]. However, continuous immunosuppression makes patients more susceptible to viral and bacterial infections [16, 17].

Infectious complications after kidney transplantation may be associated with pre-transplant infection of the recipient, infection of the donor organ, presence of hospital (nosocomial) or community-acquired infection [18]. In addition, the clinical presentation of the infectious process may be altered in patients receiving immunosuppressive therapy, leading to diagnostic difficulties. And once the infection has developed, the decline in the body's immune response is critical to the outcome of the disease. Infectious and cardiovascular complications are the main causes of death in kidney transplant recipients [19]. The most dangerous period for the development of infectious and inflammatory complications is the first 1–2 months after transplantation [20].

Urinary tract infection (UTI) is a major cause of complications, including sepsis, in kidney recipients [21–23]. Typically, UTIs are caused by ascending Gram-negative bacteria [24]. Treatment of infections caused by multidrug-resistant ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*) pathogens can be especially challenging [25].

The emergence of multidrug-resistant bacteria has become a significant challenge in disease management, leading to increased mortality rates due to ineffective treatment. ESKAPE pathogens, through genetic mutation and acquisition of mobile genetic elements, have developed resistance mechanisms to a wide range of antibiotics including oxazolidinones, lipopeptides, macrolides, fluoroquinolones, tetracyclines, beta-lactams, combinations of beta-lactams and beta-lactamase inhibitors, as well as «last resort» antibiotics such as carbapenems, glycopeptides, and polymyxins. Infections caused by carbapenem-resistant Enterobacteriaceae have particularly high mortality rates, often surpassing 40% globally. Among these infections, carbapenem-resistant strains of *K. pneumoniae* (CRKP) are associated with the most severe cases [26].

After kidney transplantation, *K. pneumoniae* is found in blood cultures in approximately one-third of cases (as in this observation), and in more than half of cases, it is resistant to most antibacterial drugs [20]. The progression of infection to sepsis can be rapid and unpredictable, and antimicrobial therapy is not always effective because of the resistance of the recipient's microflora caused by multiple previous courses of antibiotics [20]. Septic complications are the major cause of mortality after parenchymal organ transplantation. In immunosuppressed patients, sepsis is associated with a 50% mortality [27].

Infectious complications such as acute graft pyelonephritis and sepsis are the most common indications for graft removal in the early postoperative period. Kidney recipients who develop Gram-negative bacteremia after transplantation have a higher risk of allograft loss and death [10].

In addition to appropriate antibiotic therapy and source control of sepsis in surgical cases, techniques for removing cytokines and/or lipopolysaccharides show great promise in managing infectious complications. Renal replacement therapy alone may not be sufficient.

Currently available devices for selective adsorption of cytokines (CytoSorb, CytoSorbents Corporation, USA; HA330, Jafron Biomedical Co., China; Efferon CT, «Efferon», Russia) and endotoxins (Alteco LPS Adsorber, Alteco Medical AB, Sweden; Toraymyxin, Toray Medical Co, Ltd, Japan; Toxipak, NPF «POCARD», Russia; Efferon LPS Adsorption Device «Efferon», Russia) for adsorption of LPS and excess of endogenous inflammatory mediators, can be used alone or in combination with renal replacement therapy. Often more than one session is required, and the duration of such treatment depends on the type of adsorption cartridge used [7, 28, 29].

The results of the use of such devices for the treatment of bacterial sepsis are currently controversial. The evidence of their effectiveness is insufficient. According to some authors, the results of treatment depend on the initial concentration of inflammatory mediators and the stage of the process at the beginning of adsorption. Therefore, the use of such methods should be personalized [28].

Our observation demonstrates that the use of multimodal hemosorbent for removal of bacterial endotoxins and endogenous inflammatory mediators allows to reduce the excessive inflammatory response of the organism against the infection and to prevent further progression of multiorgan dysfunction in Gram-negative sepsis caused by multidrug-resistant pathogens.

Conclusion

Inclusion of selective adsorption of cytokines and/or lipopolysaccharides into the intensive treatment of an immunosuppressed pediatric patient with sepsis caused by resistant microorganisms improved the treatment outcome.

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