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Treatment of Pyonephritis Complicated by Septic Shock Using Extracorporeal Device Polymyxin B-Hemoperfusion

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Abstract
Direct hemoperfusion using polymyxin B-immobilized fiber (PMX-DHP) is an established treatment method for septic shock caused by Gram-negative infections. We report one instance in which PMX-DHP therapy has been used successfully in a 33-year-old woman with septic shock from urosepsis. Although there is lack of recommendations in latest Surviving Sepsis Campaign Guidelines, evidence of PMX-DHP efficacy in this subset of patients is growing.

Introduction

Urosepsis is caused by obstructive illness of the urinary tract secondary to ureteral stone, tumor, anomalies, urinary retention, by neurogenic bladder, and by urinary tract infection (UTI). Uroseptic source is identified in approximately 10–30% of all patients with septic shock. Mortality rates for patients with urosepsis range from 25 to 60% [1].

As the pathogen involved in urosepsis is frequently Gram-negative bacteria [2], endotoxin removal therapy is a logical therapeutic approach; however, few reports describe the clinical experience and efficacy of polymyxin (PMX)-DHP for septic shock focused on UTI [3]. We report the effect of direct hemoperfusion using polymyxin B-immobilized fiber in a patient with septic shock from urosepsis.

Case Report

A 33-year-old woman presented to the emergency department with a GCS of 15. She referred intense abdominal-lumbar pain and anuria. On physical examination, she presented tachypnea and desaturation in high-flow oxygen therapy, cold skin, peripheral cyanosis, and systemic hypotension refractory to volume replacement with crystalloids. Comorbidities of the patient were hypertension and psychiatric disorder on regular treatment since 5 years.

Blood gas analysis showed metabolic acidosis, lactate 6.2 mmol/L, BE-5.4 mmol/L. We decided to perform an abdomen chest computed tomography (CT). CT-chest highlighted multiple areas of bilateral parenchymal consolidation with pleural effusion in both right and left lungs; CT-abdomen and pelvis revealed acute

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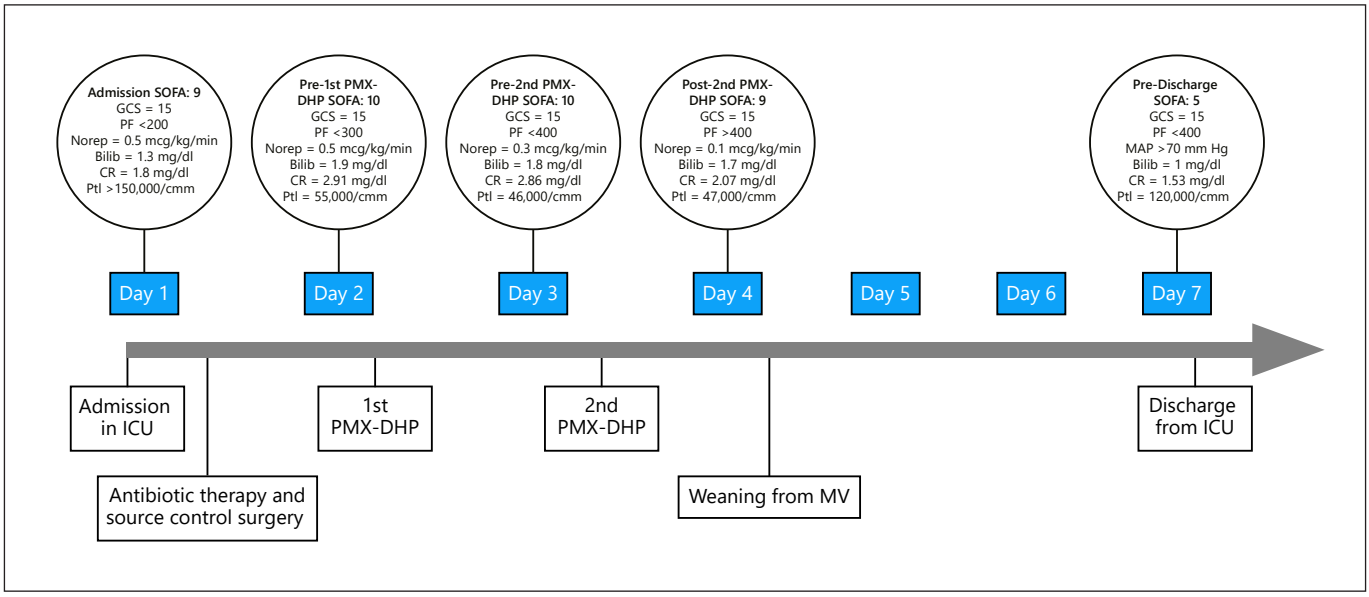

Fig. 1. Timeline of treatment from admission in ICU.

pyelonephritis with perirenal effusion more evident on the left kidney, liver with homogeneous densitometry, and multiple lymphnodes of about 1 mm in the para-aortic area.

The patient was subsequently intubated, continuous infusion noradrenaline base (0.5 μg/kg/min) was initiated, and the patient was transferred to the ICU. Under suspicion of septic shock, routine exams (total blood count, coagulation, and hepato-renal function) of blood and urine culture, endotoxin activity assay (EAA™), and procalcitonin were obtained.

The patients had no risk factors for multidrug-resistant pathogen and intravenous piperacillin/tazobactam (16 g/day as continuous infusion), and amikacin (20 mg/kg) were initiated as empirical antibiotics therapy in 1 h after diagnosis of septic shock. The patient was transferred to the operating room (OR) for an urgent ureteral stent insertion and subsequently transferred to the ICU to continue antibiotic and intensive care treatment.

Laboratory investigation results were as follows: hemoglobin 9.1 g/dL, total leukocyte count 30,100/cmm, platelet count 592,000/cmm, BUN 65 mg/dL, Cr 1.8 mg/dL, sodium 139 mEq/L, potassium 4.3 mEq/L, chloride 95.3 mEq/L, bicarbonate 13.8 mEq/L, total bilirubin 1.3 mg/dL, direct bilirubin 0.3 mg/dL, SGOT 32 IU/L, SGPT 25 IU/L, ALP 210 IU/L, total proteins 7.7 g/dL, albumin 3.1 g/dL, C-reactive protein 142 mg/dL, amylase 71 IU/L, lipase 82 UI/L, procalcitonin 50 ng/mL, and lactate 6.12 mmol/L. On admission, the Acute Physiology and Chronic Health Evaluation II score was 21 and the Sequential Failure Assessment (SOFA) score was 9 (GCS 15, PF < 200 under mechanical ventilation, norepinephrine 0.5 μg/kg/min, bilirubin 1.3 mg/dL, platelet count 592,000/cmm, and Cr 1.8 mg/dL).

Although rapid treatment (antibiotic therapy and source control) was given, the clinical conditions worsened: hypothermia continued to be present, high level of inotropic support (0.5 μg/kg/min), high level of endotoxin activity assay (0.7 EU), and procalcitonin (101.88 ng/mL). The SOFA score on day 2 was 10 (GCS 15, PF < 300 under mechanical ventilation, norepinephrine 0.5 μg/kg/min, bilirubin 1.9 mg/dL, platelet count 55,000/cmm, and Cr 2.91 mg/dL).

Twelve hours from intervention, in view of ongoing septic shock and unstable hemodynamics, after obtaining written parental informed consent, collegial decision was taken to start the direct hemoperfusion using PMX-DHP (TORAYMYXIN®) (Fig. 1). After cannulation of right femoral vein with a 14 French bi-lumen dialysis catheter and priming the cartridge and blood lines with heparin sodium 2,000 IU, we connected the patient to the hemoperfusion machine.

We performed 2 h of direct hemoperfusion using a blood flow rate of 100 mL/min and heparin anticoagulation (20 IU/kg/h). After the first treatment, the SOFA score on day 3 was 10 (GCS 15, PF < 400 under mechanical ventilation, norepinephrine 0.3 μg/kg/min, bilirubin 1.8 mg/dL, platelet count 46,000/cmm, and Cr 2.86 mg/dL).

Subsequently, although the SOFA score did not change, vasopressor support was gradually reduced and oxygenation improved. For this reason, a 2nd cycle of PMX-B-hemoperfusion was administered to the patient.

The SOFA score, after the second treatment with PMX-DHP, was 9 (GCS 15, PF > 400 under mechanical ventilation, norepinephrine 0.1 μg/kg/min, bilirubin 1.7 mg/dL, platelet count 47,000/cmm, and Cr 2.07 mg/dL). Blood culture was positive for *Escherichia coli* with no pattern of resistance shown, and urine culture was negative.

Lactic acid level, biomarker of tissue perfusion gradually decreased and returned to a normal value within 48 h, WBC count decreased, and endotoxin activity assay was 0.3 EU (Table 1). SOFA scores improved following 2 treatment with PMX-DHP; delta-SOFA score (differences between worse and pre-discharge score) 72 h after the last cycle of PMX was 5.

Prothrombin time and activated partial prothrombin time values decreased, and the fibrinogen level increased after PMX treatment. After improvement of clinical conditions, the patient was

Table 1. Evolution of clinical status during and after PMX-B-hemoperfusion

	Pretreatment	Post 1st PMX-DHP	Post 2nd PMX-DHP	48 h posttreatment
Heart rates, beats per min	125	120	115	95
Mean arterial pressure, mm Hg	60	78	83	85
Noradrenaline, μg/kg/min	0.5	0.3	0.1	Nil
Endotoxin activity assay, EU	0.7	Nil	Nil	0.45
WBC, 10^3/μL	30,000	20,000	15,000	9,500
Lactate, mmol/L	6.7	4	3	0.8
Urine output, mL/kg/h	Nil	0.3	0.5	0.8

PMX, polymyxin.

successfully weaned from mechanical ventilation on the 4th day of ICU stay.

The piperacillin/tazobactam therapy was maintained for a total of 14 days when procalcitonin was 2.03 ng/mL. Subsequent blood cultures were negative. The patient was transferred to a general ward after 7 days of stay in ICU and discharged home in good clinical condition.

Discussion

In this case report, we describe a case of pyonephritis due to Gram-negative bacteria complicated with septic shock. Septic shock is a life-threatening disorder, and it has been shown that endotoxin, a major cell-wall component of Gram-negative bacteria, is a central initiator of Gram-negative septic shock [4]. Current therapy is not effective once the cascade of septic shock is initiated.

PMX-B is a cyclic cationic polypeptide antibiotic derived from *Bacillus polymyxa* with the ability to bind and neutralize endotoxin. Developed in Japan, PMX-DHP is thought to reverse septic vasodilatation by removing circulating endotoxin [5]. A meta-analysis of 28 studies (978 patients) [6] using PMX-DHP in patients with severe sepsis and septic shock demonstrated improved MAP as well as PaO_2/FiO_2 ratio in addition to reduced mortality. In 2009, a randomized trial of 64 surgical patients with abdominal septic shock showed improvement of organ function and lower 28-day mortality risk along with improvements in hemodynamic outcome [7]. Recently, Suzuki et al. [3] analyzed severely ill patients with septic shock secondary to UTI receiving initial resuscitation and PMX-DHP. Treatment resulted in rapid hemodynamic stabilization and improved pulmonary oxygenation. Of the 15 included patients, 1 patient did not survive to 28 days. They concluded that direct hemoperfusion with PMX-B-immobilized fiber rapidly stabilizes hemodynamics in patients with septic shock secondary to UTI who do not respond to conventional therapy [3].

The efficacy of hemoadsorption treatment in this case could probably be due to multiple mechanism of immunomodulation, not only endotoxin removal. Notably PMX-DHP reduces the concentration of pro-inflammatory and anti-inflammatory cytokines [8], high mobility group box protein 1 (HMGB-1) [9], and the receptor for advanced glycation end-products [10] decreasing in the excessive systemic host inflammatory response to infection.

PMX-DHP increases surface antigen HLA-DR and CD16 expression on granulocytes, helping immune cells to recovery from immunoparalysis [11]. In this case report, we obtained the resolution of pathology by assembling rapidly conventional surgical therapy and hemoperfusion therapy with immobilized PMX-B cartridges, even though there was no recommendation for this treatment and there was a lack of literature.

Although source control surgery was performed, the patient failed to respond to antibiotic therapy resulting in extreme hemodynamic instability due to septic shock. Positivity to endotoxin assay and positivity to blood culture for *E. coli* led us to initiate a hemoperfusion treatment with PMX B.

The achievement of the therapeutic goal was probably due to optimal timing at which we decided to initiate our intervention according to latest Surviving Sepsis Campaign Guideline on septic shock [12] and the post hoc analysis of EUPHRATES trial that shows a 28-day lower mortality in a subgroup of patients with EAA™ (Endotoxin Activity Assay) of 0.6 but inferior to 0.89 EU. This subgroup of patients also showed an improvement in hemodynamics and ventilator-free days [13].

Catecholamines, particularly norepinephrine, are beneficial on macrocirculation in septic shock to restore vascular tone; nevertheless, high dose could be dangerous and cause direct organ injury via multiple effects on metabolism, immune system, and coagulation [14]. PMX-DHP could be useful in reduction of norepinephrine dose in very unstable patients. We want to underline the time dependency of treatment of urinary tract septic shock in which organ insufficiency caused by dysregulation of host response could be stabilized by PMX-DHP in an early phase of hyper-inflammation where standard therapy does not improve the clinical condition.

Statement of Ethics

The subject enrolled in this case report gave written informed consent to publication.

Conflict of Interest Statement

All authors declare that there is no conflict of interest regarding the publication of this case report.

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References

1 Shigemura K, Tanaka K, Adachi M, Yamashita M, Arakawa S, Fujisawa M, et al. Chronological change of antibiotic use and antibiotic resistance in Escherichia coli causing urinary tract infections. J Infect Chemother. 2011 Jan 1;17(5):646–51.

2 Jiang Y, Li J, Zhang Y, Hu X, Zhang X, Shang X, et al. Clinical situations of bacteriology and prognosis in patients with urosepsis. Biomed Res Int. 2019;2019:1–9.

3 Suzuki Y, Kojika M, Sato H, Inoue Y, Endo S. Clinical effects of polymyxin B hemoperfusion in patients with septic shock caused by urinary tract infection. Ther Apher Dial. 2019;23(1):80–5.

4 Weis S, Dickmann P, Pletz MW, Coldewey SM, Gerlach H, Bauer M. The third international consensus definitions for sepsis and septic shock (sepsis-3). Dtsch Arztebl Int. 2017;114(29–30):801–10.

5 Shimizu T, Miyake T, Tani M. History and current status of polymyxin B-immobilized fiber column for treatment of severe sepsis and septic shock. Ann Gastroenterol Surg. 2017;1(2):105–13.

6 Zhou F, Peng Z, Murugan R, Kellum JA. Blood purification and mortality in sepsis: a meta-analysis of randomized trials. Crit Care Med. 2013;41(9):2209–20.

7 Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA. 2009;301(23):2445–52.

8 Esteban E, Ferrer R, Alsina L, Artigas A. Immunomodulation in sepsis: the role of endotoxin removal by polymyxin B-immobilized cartridge. Mediat Inflamm. 2013;2013:1–12.

9 Nakamura T, Sato E, Fujiwara N, Kawagoe Y, Maeda S, Yamagishi S. Suppression of high-mobility group box-1 and receptor for advanced glycation end-product axis by polymyxin B-immobilized fiber hemoperfusion in septic shock patients. J Crit Care. 2011;26(6):546–9.

10 Takahashi G, Hoshikawa K, Matsumoto N, Shozushima T, Onodera C, Kan S, et al. Changes in serum S100A12 and sRAGE associated with improvement of the PaO2/FiO2 ratio following PMX-DHP therapy for postoperative septic shock. Eur Surg Res. 2011;47(3):135–40.

11 Srisawat N, Tungsanga S, Lumlertgul N, Komaenthammasophon C, Peerapornratana S, Thamrongsat N, et al. The effect of polymyxin B hemoperfusion on modulation of human leukocyte antigen DR in severe sepsis patients. Crit Care. 2018;22(1):279.

12 Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.

13 Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018;44(12):2205–12.

14 Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. Intensive Care Med. 2016;42(9):1387–97.