Renal Replacement Therapy

CASE REPORT Open Access

Successful treatment of direct hemoperfusion with polymyxin B-immobilized fiber for septic shock and severe acute kidney injury due to ceftriaxone-resistant *Escherichia coli*: a case report with literature review

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Abstract

Background: Septic shock is a life-threatening condition and one of the most common causes of acute kidney injury. Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) is used to reduce endotoxin levels in blood. Here, we report a rare but important case of sepsis-induced acute kidney injury and septic shock, which was successfully treated with PMX-DHP in spite of inappropriate initial antibiotic therapy.

Case presentation: An 84-year-old man was hospitalized for septic shock and acute kidney injury. Although he was treated with ceftriaxone, he did not recover from hypotension and had reduced urine output. After initiating PMX-DHP on days 3 and 4, his blood pressure was immediately elevated and his white blood cell count and C-reactive protein levels improved. Because ceftriaxone-resistant *Escherichia coli* was identified in blood culture, we changed his antibiotics to levofloxacin on day 7. He successfully recovered from the septic shock and dialysis was withdrawn.

Conclusions: Considering the use of inappropriate initial antibiotics, the early induction of PMX-DHP might have been a key determinant of his outcome. PMX-DHP therapy should be considered in septic shock in addition to antibiotic treatment.

Keywords: Polymyxin B-immobilized fiber, Septic shock, Acute kidney injury

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Background

Septic shock is a life-threatening condition caused by infection [1]. Its pathogenesis is complex and involves various inflammatory cytokines such as tumor necrosis factor-α, interleukin-1, and interleukin-6 [1, 2]. The survival rate of patients with sepsis declines by 7.6% for every hour of delayed appropriate antibiotic treatment [3]. Septic shock is one of the most common causes of acute kidney injury (AKI) [2]. The mortality rate of sepsis is increased with AKI to up to 50–60% [4]. Therefore, an approach to promptly identify the source of infection in order to provide early treatment is needed [5].

Endotoxins, which are composed of the outer membrane of gram-negative bacteria, are also reported to play an important role in septic shock [2]. Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) is used to adsorb endotoxin in the treatment of septic shock [6]. It has been reported that PMX-DHP should be performed as soon as possible in septic shock [7]. However, the efficacy of PMX-DHP in septic shock is still controversial [8–10].

Here, we report a rare but important case of AKI and septic shock due to ceftriaxone-resistant *Escherichia coli*, which was successfully treated with PMX-DHP in spite of inappropriate initial antibiotic therapy.

Case presentation

An 84-year-old man was admitted to our hospital because of a feeling of sickness and nausea. The patient had a medical history of pacemaker implantation due to complete atrioventricular block, hypertension, and hypothyroidism. His baseline serum creatinine (sCr) level was 1.89 mg/dL (normal, < 1.09 mg/dL) at least 2 weeks before admission. On admission, his body temperature was 36.5 °C, blood pressure was 97/54 mmHg, heart rate was 64/min, and respiratory rate was 22 bpm. He also had severe watery diarrhea with no abdominal pain. He had no crackles in both lung fields and had no flank pain with costovertebral angle tenderness. Laboratory findings on admission are summarized in Table 1. Blood tests revealed the following: white blood cell count (WBC), 11,200/μL; hemoglobin, 10.9 g/dL; platelet count, 100,000/μL; C-reactive protein (CRP), 17.8 mg/dL; aspartate aminotransferase, 382 U/L; alanine aminotransferase, 156 U/L; γ-glutamyl transpeptidase, 258 U/L; lactate dehydrogenase, 390 U/L; and sCr, 5.16 mg/dL. The serum procalcitonin level was also elevated (7.09 ng/mL). Arterial blood gas analysis revealed the following: pH, 7.29; pCO_2, 34.5 mmHg; HCO_3^-, 16.2 mmol; BE, − 9.4 mmol. Urinalysis showed proteinuria (2+) without hematuria and pyuria. Urinary excretion of beta-2-microglobulin and *N*-acetyl-beta-D-glucosaminidase were elevated (5051 μg/L and 82.1 U/L, respectively). Test results for p-anti-neutrophil cytoplasmic antibody, c-anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, and antinuclear antibody were all negative. Protein electrophoresis of the urine and serum detected no monoclonal protein. Laboratory test was negative for CD toxin. Echocardiography revealed no collapse of the inferior vena cava. Renal ultrasound showed that the kidneys were of normal size (right, 9.8 × 6.2 mm; left, 9.6 × 5.7 mm) with no dilation of the urinary tract, renal pelvis, or calyces. The corticomedullary junction was obscure. The renal arterial resistive index (RI) was elevated (right, 0.83; left, 0.81). Computed tomography (CT) scan of the chest and abdomen did not reveal obvious infections except for perirenal fat stranding (PFS). Considering the clinical findings suggestive of infection, he was treated with antibiotics (ceftriaxone). The clinical course of the patient is shown in Figs. 1 and 2. CT scan detected no collapsed inferior vena cava. The Swan-Ganz catheter monitoring showed a mean pulmonary artery pressure of 28 mmHg, a pulmonary capillary wedge pressure of 26 mmHg and cardiac index of 2.3 L/min/m^2. Because his blood pressure decreased, vasopressors, including dopamine and noradrenaline, were continuously administered (day 2). However, he did not recover from the hypotension and reduced urine output. Therefore, we introduced hemodialysis. WBC count and CRP levels were further elevated (14,700/μL and 27.4 mg/dL, respectively) (Fig. 2). Because septic shock and sepsis-induced AKI were strongly suspected, we performed PMX-DHP (day 3 and day 4). The serum endotoxin was not elevated before PMX-DHP treatment. After the PMX-DHP treatment, his blood pressure was immediately elevated and the vasopressor dose was decreased. WBC count, CRP, and liver dysfunction were all improved. Because blood culture revealed ceftriaxone-resistant non-Extended-spectrum β-lactamase (ESBL)-producing *E. coli* (day 7), we changed his antibiotics to levofloxacin. Table 2 shows the results of antimicrobial susceptibility testing against *E. coli*. WBC, platelet count, CRP, and sCr all then improved, with an increase of urine output (Figs. 1 and 2). He successfully recovered from the septic shock and dialysis was withdrawn.

Discussion and conclusions

The present case highlights an important clinical issue. We were unable to specify the source of infection and treated the patient with ceftriaxone until sepsis due to ceftriaxone-resistant non-ESBL-producing *E. coli* was identified on day 7. Longer delays before the administration of appropriate antibiotics are associated with higher mortality [11]. It is indeed possible that partial treatment was achieved with ceftriaxone in this case, but the antibiotic treatment may have been ineffective during the

Table 1 Laboratory data on admission

Blood	
WBC	11,200/μL
RBC	3.84×10^6/μL
Hemoglobin	10.9 g/dL
Hematocrit	35%
Platelet count	100×10^3/μL
Total protein	6.3 g/dL
Albumin	3.3 g/dL
Total bilirubin	3.7 mg/dL
Direct bilirubin	2.9 mg/dL
BUN	65.2 mg/dL
Creatinine	5.16 mg/dL
Uric acid	6.2 mg/dL
AST	382 IU/L
ALT	156 IU/L
LDH	390 IU/L
ALP	77 IU/L
γGTP	258 IU/L
Sodium	138 mEq/L
Potassium	5.4 mEq/L
Chloride	104 mEq/L
Calcium	8.3 mg/dL
Phosphorus	4.6 mg/dL
Triglyceride	210 mg/dL
Total-cholesterol	128 mg/dL
LDL-cholesterol	60 mg/dL
HDL-cholesterol	26 mg/dL
Glucose	77 mg/dL
HbA1c	6.1%
C-reactive protein	17.8 mg/dL
Procalcitonin	7.09 ng/mL
BNP	1280.7 pg/mL
IgG	1402 mg/dL
IgA	218 mg/dL
IgM	89 mg/dL
IgE	550 IU/mL
C3	128 mg/dL
C4	25 mg/dL
CH50	41 mg/dL
ANA	< 40
MPO-ANCA	–
RP3-ANCA	–
Anti-GBM Ab	–
Cryoglobulin	–
Direct Coombs test	–
Haptoglobin	96 mg/dL
Arterial blood gasses	
pH	7.290
pCO_2	34.5 mmHg
pO_2	77.9 mmHg
HCO_3^-	16.2 mmol
BE	– 9.4 mmol
Urine	
Protein	4.52 g/gCr
RBC	3–5/HPF
WBC	0–2/HPF
Bacteria	–
β2 MG	5051 μg/L
NAG	82.1 IU/L

WBC white blood cell, *RBC* red blood cell, *BUN* blood urea nitrogen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *γGTP* γ-glutamyl transpeptidase, *HbA1c* hemoglobin A1c, *BNP* brain natriuretic peptide, *Ig* immunoglobulin, *C3* complement component 3, *C4* complement component 4, *CH50* 50% hemolytic complement, *ANA* antinuclear antibody, *MPO-ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibody, *PR3-ANCA* proteinase-3 anti-neutrophil cytoplasmic antibody, *GBM* glomerular basement membrane, *BE* base excess, *HPF* high power field, *β2 MG* beta2-microglobulin, *NAG N*-acetyl-beta-D-glucosaminidase

first 7 days. Considering inappropriate initial antibiotics, the early introduction of PMX-DHP might have been a key determinant of his outcome after the initiation of septic shock.

Suspecting sepsis is the first step towards early diagnosis. The quick Sepsis-related Organ Failure Assessment (qSOFA) score has been recommended for identifying patients at risk of sepsis [12]. It consists of three elements, respiratory rate ≥ 22 bpm, systolic blood pressure ≤ 100 mmHg, and altered mentation [12]. The present case fulfilled two criteria of the qSOFA score—an early indicator of sepsis [12]. The identification of the source of sepsis and treatment with appropriate antibiotics is important in the early phase of sepsis. In this case, CT revealed PFS, which is a common finding in acute pyelonephritis [13]. However, a previous report suggested that PFS was not useful in the diagnosis of acute pyelonephritis [14]. Because the patient did not present with hematuria and pyuria, the possibility of acute pyelonephritis was considered less likely. Empirical antibiotic treatment should be considered for suspected sepsis induced by enteritis. In this case, we chose ceftriaxone as the initial treatment [15]. Considering severe diarrhea and bacteremia caused by *E. coli*, we believe enteritis due to *E. coli* caused sepsis due to bacterial translocation [16]. Ceftriaxone is a third-generation cephalosporin

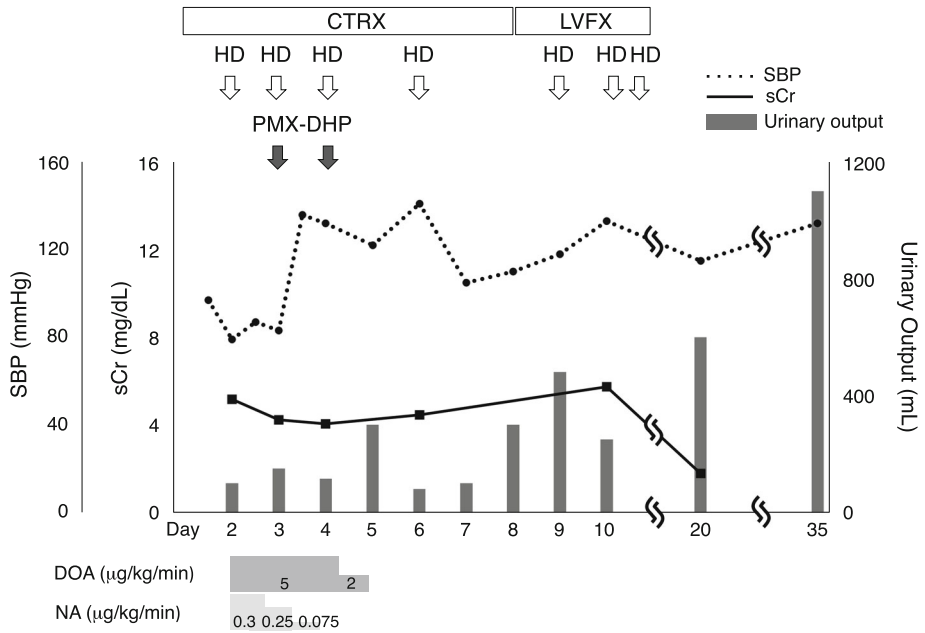

Fig. 1 Time course of SBP, serum creatinine, and urinary output before and after treatment. SBP, systolic blood pressure; sCr, serum creatinine; PMX-DHP, polymyxin B-immobilized fiber column direct hemoperfusion; HD, hemodialysis; CTRX, ceftriaxone; LVFX, levofloxacin; DOA, dopamine; NA, noradrenaline

antibiotic used to treat invasive infections due to Enterobacteriaceae such as *E. coli*. Ceftriaxone-resistant Enterobacteriaceae is recognized as an important global health problem [17]. The main mechanisms underlying ceftriaxone resistance are ESBL and AmpC β-lactamase [18]. Because AmpC β-lactamase was not investigated in this case, ceftriaxone-resistant *E. coli* possibly resulted from the production of AmpC β-lactamase.

Arterial blood gas analysis revealed mixed respiratory and metabolic acidosis in sepsis. Disseminated intravascular coagulation (DIC) is a common complication in sepsis [19]. A decrease in platelet count from day 2 to day 6 might have been caused by DIC. Though blood coagulation tests were not performed, improvement in platelet count with antibiotic treatment might be due to sepsis-induced DIC.

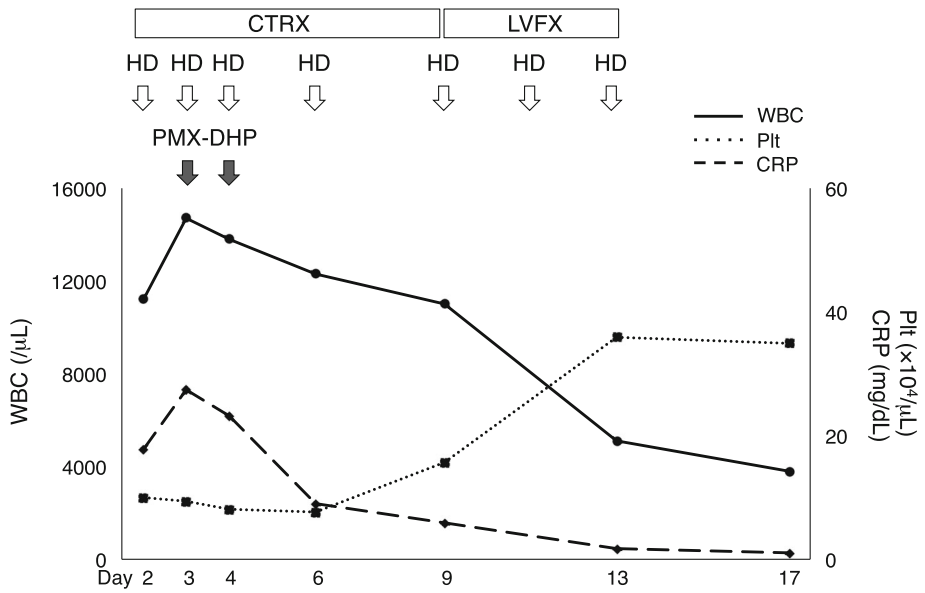

Fig. 2 Time course of the laboratory data. WBC, white blood cell; Plt, platelet; CRP, C-reactive protein

Table 2 Susceptibilities of antibiotics against *E. coli* isolated from the blood

Antibiotics	Susceptibility (μg/mL)	
Piperacillin	64	I
Piperacillin/tazobactam	< 16	S
Sultamicillin		I
Cefazolin	> 32	R
Sulbactam/cefoperazone	< 16	S
Ceftazidime	8	I
Ceftriaxone	> 4	R
Cefepime	< 2	S
Meropenem	< 1	S
Amikacin	< 4	S
Isepamicin		S
Clindamycin		R
Minocycline	< 2	S
Fosfomycin	< 4	S
Levofloxacin	< 0.5	S
Pazufloxacin		S
Sulfamethoxazole/trimethoprim	< 38	S

I intermediate, *R* resistant, *S* susceptible

AKI is diagnosed by serum creatinine elevation or oliguria [1]. The precise mechanisms and specific treatments for sepsis-induced AKI are still unknown. Sepsis-induced AKI is not only associated with hypoperfusion but with increased or maintained renal blood flow [20, 21]. In the present case, the possibilities of pre-renal and post-renal AKI were unlikely based on ultrasound, CT, and Swan-Ganz catheter. Urinalysis and urine biochemistry are usually not suitable for diagnosing AKI due to oliguria. Although various new biomarkers for rapid AKI diagnosis have been reported [2], the early recognition of sepsis-induced AKI is still difficult. The renal arterial RI is a useful tool for earlier AKI diagnosis [22]. Higher RI may be predictive of sepsis-induced AKI [22], and this applies to our case. Early initiation of renal replacement therapy (RRT) in sepsis-induced AKI is not associated with favorable mortality [23, 24]. RRT can be applied intermittently (IRRT) or continuously (CRRT). CRRT was reported to be suitable for patients with hemodynamic instability [25]. However, no difference in mortality has been reported between CRRT and IRRT for AKI [25, 26]. Therefore, we initiated HD on day 2 in this case.

PMX was performed for 2 h in two treatment sessions. However, it remains unclear how many times should PMX be performed and when should the second PMX be performed. In this case, the second PMX was performed the next day because the hemodynamics of the patient did not fully improve after the first treatment. PMX reduces all-cause hospital mortality and length of ICU stay in patients with septic shock [10]. Contrary to this, the risk ratio of a 28-day mortality associated with PMX was 1.03 [27]. Therefore, there is insufficient evidence supporting the routine use of PMX in patients with septic shock. The review of the literature on PubMed for septic shock caused by *E. coli* treated with PMX since 2013 is summarized in Table 3 [28, 29]. Urosepsis is the most common. In the present case, endotoxin levels were below the detectable limit in blood. PMX was also found useful in cases where endotoxin levels did not elevate [30]. Though the reason why the serum endotoxin was not elevated in this case is ambiguous, the positive rate of blood endotoxin is generally low [31]. Because of various reasons such as pretreatment, measurement method, contamination, and endotoxin concentration, there are no standard methods for endotoxin measurement [31, 32]. Our endotoxin measurement method might be different from other cases

Table 3 Case reports of septic shock caused by *E. coli* treated with PMX since 2013

No.	Author	Age/sex	Diagnosis	Bacteria	Endotoxin (pg/mL)	Outcome
1	Suzuki [28]	79F	Urinary tract infection	*ESBL+ E. coli*	4.2	Survival
2	Suzuki [28]	65F	Urinary tract infection	*E. coli*	18.4	Survival
3	Suzuki [28]	74F	Urinary tract infection	*E. coli*, *Klebsiella pneumoniae*	5.4	Survival
4	Suzuki [28]	83F	Urinary tract infection	*E. coli*	48.8	Survival
5	Suzuki [28]	48F	Urinary tract infection	*E. coli*	6.1	Survival
6	Suzuki [28]	44F	Urinary tract infection	*E. coli*, *P. aeruginosa*	28.7	Survival
7	Suzuki [28]	86M	Urinary tract infection	*E. coli*	98.5	Survival
8	Suzuki [28]	79F	Urinary tract infection	*ESBL+ E. coli*	38.3	Survival
9	Kohno [29]	62M	Urinary tract infection	*ESBL+ E. coli*	(-)	Survival
10	Our case	84M	Enteritis	*E. coli*	(-)	Survival

AKI acute kidney injury, *M* male, *F* female, *ESBL* extended-spectrum b-lactamase

reported by Suzuki et al. as summarized in Table 3. PMX adsorbs not only endotoxin but also excessive inflammatory cytokines, including IL-6, IL-10, IL-18, and TNF-α [33, 34], which are responsible for establishing septic shock. Therefore, PMX might be effective against sepsis in endotoxin-negative cases. Moreover, PMX also adsorbs anandamide, which is a paracrine mediator of septic shock-induced hypotension [35]. The blood pressure rapidly elevated and stabilized hemodynamics after PMX-DHP, and the patient's baseline sCr level was already elevated before hospitalization, which meant having pre-existing CKD. AKI patients with pre-existing CKD are more likely to be dialysis-dependent [36]. In this case, early diagnosis and treatment of sepsis-induced AKI, including antibiotic treatment, PMX-DHP, and prevention of hypotension, were crucial for recovery from septic shock and withdrawal of dialysis.

Abbreviations

AKI: Acute kidney injury; PMX-DHP: Polymyxin B-immobilized fiber column direct hemoperfusion; *E. coli*: *Escherichia coli*; sCr: Serum creatinine; MG: Microglobulin; NAG: *N*-acetyl-beta-D-glucosaminidase; RI: Resistive index; CT: Computed tomography; PFS: Perirenal fat stranding; ESBL: Extended-spectrum β-lactamase; CTRX: Ceftriaxone; LVFX: Levofloxacin; DOA: Dopamine; NA: Noradrenaline; qSOFA: Quick Sepsis-related Organ Failure Assessment; DIC: Disseminated intravascular coagulation; RRT: Renal replacement therapy; IRRT: Intermittently renal replacement therapy; CRRT: Continuously renal replacement therapy

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Authors' contributions

HS drafted the first manuscript. HS, TK, TN, TI, SH, NT, and MN managed the patient. HS, TK, MH, YH, CM, TB, NN, AI, TI, MT, KK, KO, and JM performed the literature search. TK, TN, TI, SH, NT, MH, YH, CM, TB, NN, AI, TI, MT, MN, KK, and KO coordinated the data analysis and critically commented on the manuscript. CM, TB, NN, AI, TI, MT, MN, KK, and JM helped with writing the manuscript. All authors participated in discussions and read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not required because this is a case report

Consent for publication

Written consent was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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References

1. Keeley A, Hine P, Nsutebu E. The recognition and management of sepsis and septic shock: a guide for non-intensivists. Postgrad Med J. 2017;93:626–34.
2. Zarjou A, Agarwal A. Sepsis and acute kidney injury. J Am Soc Nephrol. 2011;22:999–1006.
3. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006; 34:1589–96.
4. Wang K, Xie S, Xiao K, Yan P, He W, Xie L. Biomarkers of sepsis-induced acute kidney injury. Biomed Res Int. 2018;2018:6937947.
5. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580–637.
6. Shimizu T, Endo Y, Tsuchihashi H, Akabori H, Yamamoto H, Tani T. Endotoxin apheresis for sepsis. Transfus Apher Sci. 2006;35:271–82.
7. Matsukuma S, Sakamoto K, Nishiyama M, Tamesa T, Yoshino S, Hazama S, et al. Prognostic factors in patients with septic shock in digestive surgery who have undergone direct hemoperfusion with polymyxin b-immobilized fibers: a retrospective observational study. J Intensive Care. 2015;3:13.
8. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, et al. Effect of targeted polymyxin b hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the euphrates randomized clinical trial. Jama. 2018;320:1455–63.
9. 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;44:2205–12.
10. Nakamura Y, Kitamura T, Kiyomi F, Hayakawa M, Hoshino K, Kawano Y, et al. Potential survival benefit of polymyxin b hemoperfusion in patients with septic shock: A propensity-matched cohort study. Crit Care. 2017;21:134.
11. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. The New England journal of medicine. 2017;376:2235–44.
12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). Jama. 2016;315:801–10.
13. Stunell H, Buckley O, Feeney J, Geoghegan T, Browne RF, Torreggiani WC. Imaging of acute pyelonephritis in the adult. European radiology. 2007;17: 1820–8.
14. Fukami H, Takeuchi Y, Kagaya S, Ojima Y, Saito A, Sato H, et al. Perirenal fat stranding is not a powerful diagnostic tool for acute pyelonephritis. Int J Gen Med. 2017;10:137–44.
15. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65: e45–80.
16. Vaishnavi C. Translocation of gut flora and its role in sepsis. Indian J Med Microbiol. 2013;31:334–42.
17. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World Health Organization; 2017.
18. Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications. BMJ. 2016;352:h6420.
19. Iba T, Watanabe E, Umemura Y, Wada T, Hayashida K, Kushimoto S, et al. Sepsis-associated disseminated intravascular coagulation and its differential diagnoses. J Intensive Care. 2019;7:32.
20. Garofalo AM, Lorente-Ros M, Goncalvez G, Carriedo D, Ballen-Barragan A, Villar-Fernandez A, et al. Histopathological changes of organ dysfunction in sepsis. Intensive Care Med Exp. 2019;7(Suppl 1):45.

21. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow in experimental septic acute renal failure. Kidney Int. 2006;69:1996–2002.
22. Lerolle N, Guerot E, Faisy C, Bornstain C, Diehl JL, Fagon JY. Renal failure in septic shock: predictive value of doppler-based renal arterial resistive index. Intensive Care Med. 2006;32:1553–9.
23. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyere R, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med. 2018;379:1431–42.
24. Xiao L, Jia L, Li R, Zhang Y, Ji H, Faramand A. Early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: a systematic review and meta-analysis. PLoS One. 2019;14:e0223493.
25. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentrerandomised trial. Lancet. 2006; 368:379–85.
26. Rabindranath K, Adams J, Macleod AM, Muirhead N. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev. 2007;3:CD003773.
27. Fujii T, Ganeko R, Kataoka Y, Furukawa TA, Featherstone R, Doi K, et al. Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med. 2018;44:167–78.
28. 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;23:80–5.
29. Kohno Y, Fukui N, Kageyama Y, Higashi Y. Case of septic shock caused by extended spectrum beta-lactamase producing *Escherichia coli* after transrectal prostate biopsy, successfully treated by endotoxin adsorption therapy. Hinyokika kiyo Acta urologica Japonica. 2013;59:593–6.
30. Endo S, Inada K, Inoue Y, Otsu T, Kasai T, Kuwata Y, et al. Endotoxin and cytokines in patients with gastrointestinal tract perforation. Mediators Inflamm. 1992;1:45–8.
31. Inada K. History and current state of endotoxin research in Japan. Jpn J Crit Care Endotoxemia. 2016;20:19–27.
32. Saito N, Sugiyama K, Ohnuma T, Kanemura T, Nasu M, Yoshidomi Y, et al. Efficacy of polymyxin B-immobilized fiber hemoperfusion for patients with septic shock caused by Gram-negative bacillus infection. PLoS One. 2017;12: e0173633.
33. Okabayashi H, Ichiyasu H, Hirooka S, Akaike K, Kojima K, Jodai T, et al. Clinical effects of direct hemoperfusion using a polymyxin B-immobilized fiber column in clinically amyopathic dermatomyositis-associated rapidly progressive interstitial pneumonias. BMC Pulm Med. 2017;17:134.
34. Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, et al. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. Crit Care. 2007;11:R47.
35. Wang Y, Liu Y, Sarker KP, Nakashima M, Serizawa T, Kishida A, et al. Polymyxin b binds to anandamide and inhibits its cytotoxic effect. FEBS letters. 2000;470:151–5.
36. Khosla N, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini E, et al. Preexisting chronic kidney disease: a potential for improved outcomes from acute kidney injury. Clin J Am Soc Nephrol. 2009;4:1914–9.

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