Plasma concentrations of Colistin sulfate in a patient with septic shock on extracorporeal membrane oxygenation and continuous renal replacement therapy: a case report

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Background: Polymyxins antibiotics have become the first-line clinical drugs in the treatment of refractory gram-negative bacterial infections. Currently, there is a lack of clinical studies on the effect of extracorporeal membrane oxygenation (ECMO) combined with continuous renal replacement therapy (CRRT) on polymyxin concentrations. The purpose of this report was to investigate the changes in the plasma concentrations of Colistin sulfate during ECMO and CRRT and to provide drug administration programs for critically ill patients receiving ECMO and CRRT.

Case Description: In this case report, a patient with septic shock caused by severe acute pancreatitis, with abdominal pain and dyspnea as the main manifestations, was treated with ECMO combined with CRRT for life support and multiple anti-infective drugs. However, the symptoms of infection had not got improved, the inflammatory indicators remain high and the body temperature fluctuates repeatedly 36.7–38.5 ℃, was considered as carbapenem-resistant organisms (CROs) infection, and was empirically given Colistin sulfate for anti-infection treatment. Finally, the patient's condition improved and ECMO and CRRT were gradually withdrawn. At the same time, the plasma concentrations of Colistin sulfate before and after ECMO combined with CRRT, was monitored to determine the changes in the plasma concentrations of Colistin sulfate during ECMO and CRRT. Trough and peak concentrations on the 4th day of venovenous ECMO (VV-ECMO) combined with CRRT were 0.36 and 0.98 mg/L, respectively. After withdrawal of ECMO and CRRT, the concentrations were, respectively, 0.27 and 0.34 mg/L for trough concentrations, and 0.82 and 0.98 mg/L for peak concentrations. The data showed that there were no significant differences in the trough and peak concentrations of Colistin sulfate before and after ECMO and CRRT. No adverse effects occurred during follow-up.

Conclusions: There were no significant differences in the trough and peak concentrations of Colistin sulfate before and after ECMO and CRRT. Therefore, no dose modification is required for Colistin sulfate in patients receiving ECMO with CRRT.

Keywords: Colistin sulfate; extracorporeal membrane oxygenation (ECMO); continuous renal replacement therapy (CRRT); plasma concentration monitoring; case report

Submitted Apr 06, 2022. Accepted for publication May 19, 2022.

doi: 10.21037/atm-22-2081

View this article at: https://dx.doi.org/10.21037/atm-22-2081

Introduction

Polymyxins are a class of polypeptide antibiotics isolated from the culture fluid of Bacillus polymyxa. They have a narrow antimicrobial spectrum and mainly act on Gram-negative bacteria, though have gradually been withdrawn from clinical use due to nephrotoxicity and neurotoxicity (1,2). In the past decade or so, the rate of severe infections caused by multidrug-resistant Gram-negative bacteria (MDR-GNB) (especially *Pseudomonas aeruginosa*, *Actinobacillus baumannii*, and *Enterobacteriaceae*, among others) has increased, the efficacy of existing antimicrobials is limited, and new antimicrobials are lacking. Polymyxins have become an important treatment option for MDR-GNB infections (3,4). Polymyxins include polymyxin B (PMB), Colistin sulfate and colistimethate sodium (CMS) in clinical use. CMS is an inactive prodrug and conversion into the active antibacterial colistin, however, PMB and Colistin sulfate (polymyxin E) directly acts in an active form in the body, the relevant pharmacokinetic profiles are not well-established at present.

Studies on the effect of continuous renal replacement therapy (CRRT) on colistimethate sodium (CMS) have shown that CMS is passively diffused in the dialysate through the CRRT device, resulting in a large fraction of the drug being eliminated. Therefore, the daily dose of CMS should be increased in critically ill patients treated with CRRT (5-7). Polymyxin B is mainly metabolized by non-renal routes. One study of CRRT in 2 patients resulted in a 12.2% and 5.62% total clearance of polymyxin B, suggesting that continuous hemodialysis does not significantly eliminate polymyxin B and no daily dose modification is required in CRRT patients (8,9). In view of the lack of clinical studies on the effect of extracorporeal membrane oxygenation (ECMO) combined with CRRT on plasma concentrations at present, and taking into account the special pathophysiological changes in critically ill patients (10), plasma concentrations of Colistin sulfate were monitored in this case report. PMB and Colistin sulfate are both active forms of drugs, which directly exerts its efficacy after entering the body and is mainly metabolized by non-renal routes. They differ only in the 6th amino acid on the molecular structure of the peptide ring (PMB is phenylalanine, Colistin sulfate is leucine).Therefore, we considered that maybe there were no significant differences in the concentrations of Colistin sulfate before and after ECMO and CRRT. This report pioneers the analysis on the changes of plasma polymyxin concentration in ECMO combined with CRRT in China. In this paper, the effectiveness of Colistin sulfate for anti-infection was observed in a patient with severe acute pancreatitis and intra-abdominal infection leading to severe septic shock and the plasma concentration during ECMO combined with CRRT was monitored. The valuable research data provided by the patient will help for the treatment of similar patients in the future. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2081/rc).

Case presentation

The case was a 36-year-old male, with height 175 cm, weight 100 kg, body mass index (BMI) 32.7 kg/m^2, Han nationality, and his occupation was farmer. He had a previous history of hepatitis B for more than 20 years which was untreated, a history of alcohol consumption for 12 years, and occasional current alcohol consumption. There was no special family history and personal history. The patient was admitted on 19 February 2021 due to "upper abdominal pain with dyspnea for more than 1 day". One day before admission, the patient developed upper abdominal pain without obvious inducement, with abdominal distension, nausea, and vomiting. Computed tomography (CT) in a municipal hospital revealed severe pancreatitis. The patient was given oxygen inhalation and fluid resuscitation. The effect was poor, and the patient gradually developed dyspnea, which became progressively aggravated, with hypotension and anuria. The patient was given invasive mechanical ventilation with endotracheal intubation and CRRT for symptomatic treatment. Symptoms such as hypotension did not be improved and he was transferred to our hospital. Diagnosis and treatment process after admission as follows (*Figure 1*): physical examination showed the following results: body temperature: 39.4 ℃, pulse: 144 bpm, respiration: 15 bpm [ventilator-assisted, mode: pressure control, FiO_2: 100%, frequency(f): 15 bmp, positive end-expiratory pressure (PEEP): 12 cmH_2O], blood pressure: 98/60 mmHg (norepinephrine injection 0.3 μg/kg/min), bilateral pupil diameter of about 2.5 mm, sluggish light reflex, tachypnea, coarse breath sounds in both lungs, and moist rales were heard; no precordial prominence, normal apical pulse, and no murmur in the auscultatory valve areas; abdominal bulge, abdominal wall tension, decreased bowel sounds, 2 times/min. The blood test results were as follows (*Figure 2*): white blood cell (WBC): 20.4×10^9/L, C-reactive protein (CRP): 347.45 mg/L, procalcitonin (PCT):

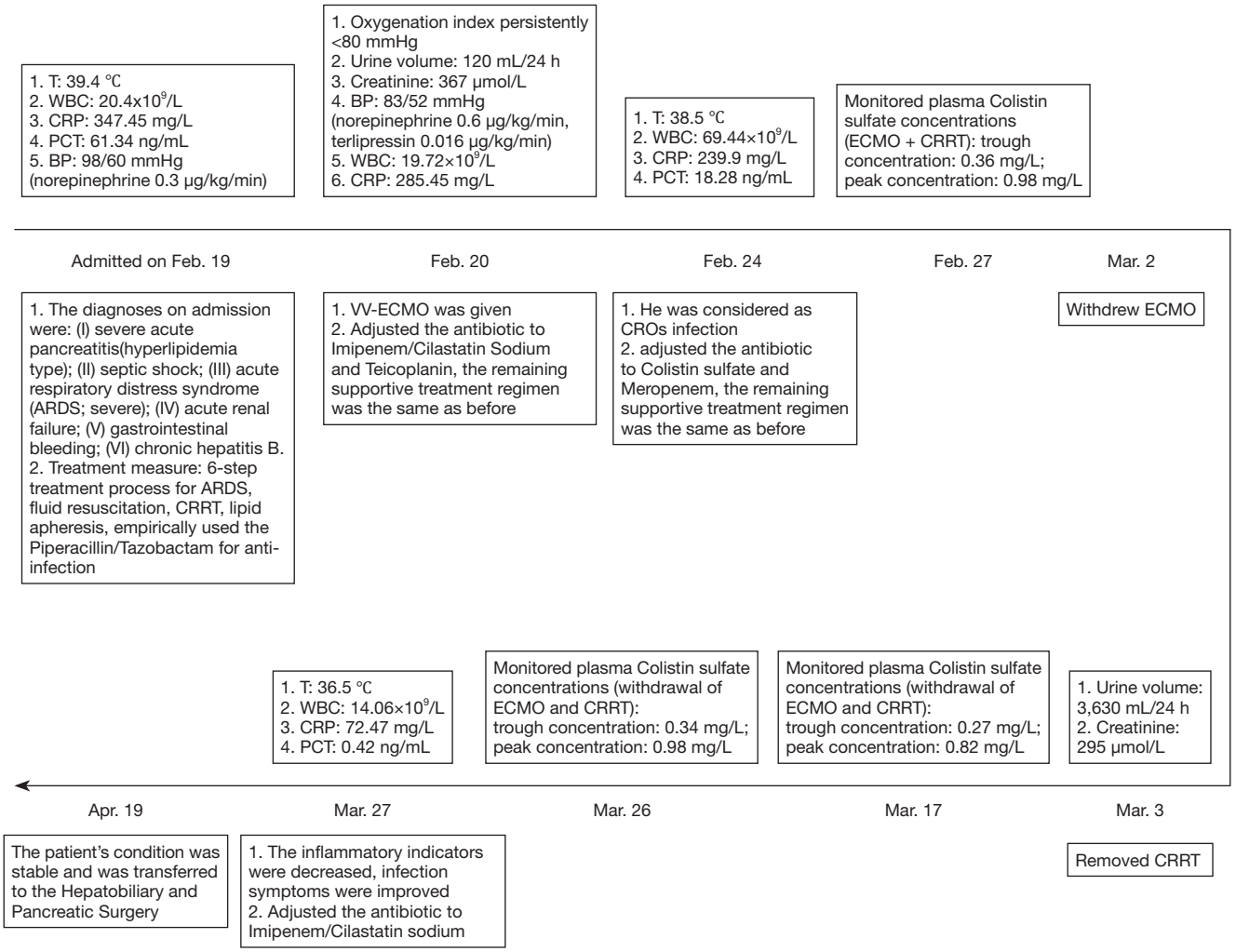

Figure 1 Diagnosis and treatment process. T, temperature; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; BP, blood pressure; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; VV, venovenous; CROs, carbapenem-resistant organisms.

61.34 ng/mL. The blood lipid results were as follows: total cholesterol: 9.88 mmol/L, triglyceride: 10.51 mmol/L, high-density lipoprotein cholesterol: 0.42 mmol/L, low-density lipoprotein cholesterol: 3.22 mmol/L. Arterial blood gas analysis showed: pH: 7.225, PaO_2: 57 mmHg, $PaCO_2$: 56.1 mmHg, HCO_3^-: 19.5 mmol, Lac: 3.24 mmol/L. The diagnoses on admission were as follows: (I) severe acute pancreatitis (hyperlipidemia type); (II) septic shock; (III) acute respiratory distress syndrome (ARDS; severe); (IV) acute renal failure; (V) gastrointestinal bleeding; (VI) chronic hepatitis B. According to the 6-step treatment process for ARDS, treatment measures including small tidal volume, high PEEP, deep sedation and analgesia [Richmond Agitation-Sedation Scale (RASS) score –4 to –5], and muscle relaxants were given. The patient was in a state of shock, which was considered to be distributive shock, and was given fluid resuscitation, CRRT [continuous venovenous hemofiltration (CVVH) mode], and lipid apheresis. Meanwhile, piperacillin and tazobactam were empirically used for anti-infection. After drug treatment and ventilator adjustment, the patient's oxygen index was still less than 80 mmHg, so venovenous ECMO (VV-ECMO) advanced life support was given. The ECMO mode was as follows: V-V, blood flow 4.0 L/min, rotation speed 2,880/min, oxygen concentration 100%, air flow 3.5 L/min. The anticoagulant regimen consisted of heparin sodium injection

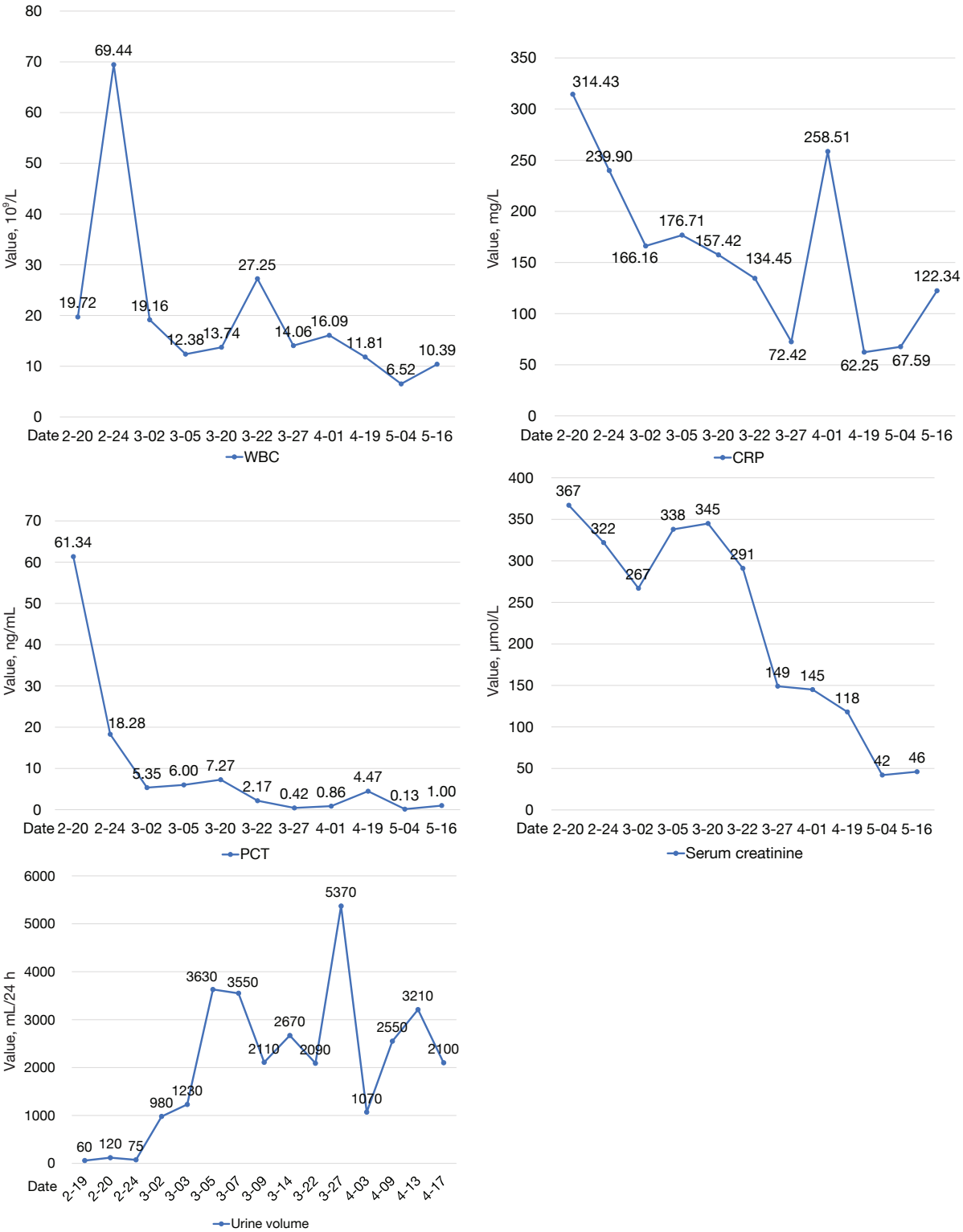

Figure 2 Changes in WBC, CRP, PCT, serum creatinine and urine volume over time. WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin.

Table 1 Plasma concentration monitoring of Colistin sulfate

Sampling time	Administration days	Collection time	Result (mg/L)	Reference interval (mg/L)
During ECMO + CRRT	Day 2 of administration (trough concentration)	2021/2/25 04:55	Not detected	<2.00
	Day 2 of administration (peak concentration)	2021/2/25 07:00	0.13	<2.00
	Day 4 of administration (trough concentration)	2021/2/27 16:55	0.36	<2.00
	Day 4 of administration (peak concentration)	2021/2/27 19:00	0.98	<2.00
After withdrawal of ECMO and CRRT	Day 22 of administration (trough concentration)	2021/3/17 08:55	0.27	<2.00
	Day 22 of administration (peak concentration)	2021/3/17 10:30	0.82	<2.00
	Day 31 of administration (trough concentration)	2021/3/26 21:25	0.34	<2.00
	Day 31 of administration (peak concentration)	2021/3/26 23:00	0.98	<2.00

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

12,500 IU continuous micro-pump pumping, and activated clotting time (ACT) was maintained at 127–196 seconds. During this period, the patient had recurrent high fever, no bacteria were detected in blood culture, ascites culture, and general bacterial culture, and inflammatory indicators such as WBCs were not significantly decreased (*Figure 2*). The antibiotic was adjusted to imipenem-cilastatin sodium combined with teicoplanin, the effect was still poor, and infection symptoms were further aggravated. On the 6th day after admission, the patient experienced chills and fever with a maximum body temperature of 38.5 ℃. His blood pressure progressively decreased. Multiple vasoactive drugs (norepinephrine 0.6 μg/kg/min, terlipressin 0.016 μg/kg/min) were used to maintain circulation, and probable septic shock, intra-abdominal infection, and infection with carbapenem-resistant organisms (CROs) were considered. The antibiotic was adjusted to Colistin sulfate (loading dose 1,000,000 IU, maintenance dose 500,000 IU, Q12h, IV drip for 1 h) combined with meropenem for anti-infection, and the remaining supportive treatment regimen was the same as before. ECMO support was discontinued on the 12th day of admission and CRRT was discontinued on the 13th day of admission based on changes in the patient's condition. After treatment with Colistin sulfate, the fever was gradually relieved, WBCs and other inflammatory indicators were gradually decreased, and the dose of vasoactive drugs was gradually reduced (*Figure 2*). On the 37th day after admission, reexamination showed that the inflammatory indicators were significantly decreased, infection symptoms were improved, anti-infective treatment was effective, and Colistin sulfate was discontinued and adjusted to imipenem-cilastatin sodium. The total course of Colistin sulfate was 32 days. Finally, the patient's condition was stable and he was transferred to the hepatobiliary and pancreatic surgery department for continued treatment. The patient's symptoms were significantly relieved, his body temperature was normal, and inflammatory parameters were roughly normal during follow-up after 28 days.

Three milliliters of blood specimens were drawn half an hour before administration (trough plasma concentration) and half an hour after administration (peak plasma concentration) on the 2nd and 4th day of intravenous Colistin sulfate, and after withdrawal of ECMO and CRRT. The peripheral blood specimens were immediately stored in a refrigerator at 4 ℃. Within 1 hour, the supernatant was collected after centrifugation at 3,000 rpm for 5 minutes and cryopreserved in a –80 ℃ freezer, and the specimens were uniformly shipped to a third-party, Medical Laboratory Company, to detect the concentrations using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). The monitoring results showed that (*Table 1*) trough concentrations on the 2nd and 4th day of VV-ECMO combined with CRRT were, respectively, not detected and 0.36 mg/L, and the peak concentrations were 0.13 and 0.98 mg/L. After withdrawal of ECMO and CRRT, the concentrations were, respectively, 0.27 and 0.34 mg/L for trough concentrations, and 0.82 and 0.98 mg/L for peak concentrations. No significant differences in plasma concentrations were observed after withdrawal of ECMO and CRRT, and no adverse effects occurred in the patient during the treatment period.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written

Table 2 Serum creatinine, urine volume, and plasma concentrations.

Date	Serum creatinine (μmol/L)	Urine volume (mL/24 h)	Plasma concentration trough/peak (mg/L)
2021/02/20	367	120	Not detected
2021/02/25	329	110	Not detected/0.13
2021/02/27	321	60	0.36/0.98
2021/03/03	295	1,230	Not monitored
2021/03/17	181	3,300	0.27/0.82
2021/03/26	149	5,370	0.34/0.98
2021/03/29	193	3,450	Not monitored
2021/04/01	145	3,600	Not monitored

informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The patient was admitted due to severe acute pancreatitis, had persistent fever and shock after admission, and was empirically given multiple antibiotics for combination therapy, but the efficacy was poor and symptoms were further aggravated. Considering the possibility of CRO infection, treatment was adjusted to Colistin sulfate combined with anti-infective treatment. Significant decreases in various inflammatory indicators were observed after the use of Colistin sulfate, and the vasoactive drug was gradually tapered, indicating that anti-infection treatment with Colistin sulfate was effective.

During ECMO combined with CRRT, the trough plasma concentration of Colistin sulfate was not detected on day 2, with a post-dose peak concentration of 0.13 mg/L. This concentration was significantly low according to the target plasma Colistin sulfate of 2 mg/L was suggested by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (9), the results showed that the target concentration of Colistin sulfate was not reached on the second day of administration. The dose regimen of 500,000 IU Q12h was continued, and the plasma concentration was measured again on day 4 of treatment, which showed a significant increase compared with day 2. The results of the 2 plasma concentrations measured after withdrawal of ECMO and CRRT showed subtle differences from those on day 4, indicating that the steady-state concentration of Colistin sulfate was reached on day 4 of treatment. After withdrawal of ECMO and CRRT, the trough and peak plasma concentrations were 0.27 and 0.82 mg/L on day 22 of treatment, respectively, which did not change significantly compared with those during ECMO combined with CRRT on day 4 of treatment, indicating that there were no significant differences in the concentrations of Colistin sulfate before and after ECMO and CRRT. The reasons for no significant differences in the concentrations before and after ECMO combined with CRRT in this study may be as follows: (I) CRRT mimics the principle of glomerular filtration and performs solute exchange and clearance by means of diffusion and convection (11), and non-renal cleared drugs are therefore less affected by CRRT. Colistin sulfate is mainly metabolized by non-renal routes, so it is minimally affected by CRRT. (II) It was found that the Protein-binding of colistin sulfate in severe patients was 59–74% (12), which was significantly higher than that in animals (13). The higher the Protein-binding, the lower the level of unbound fractions of colistin sulfate, so it is less likely to be cleared by CRRT. (III) Colistin sulfate is hydrophilic and lipophilic. Clinical studies of adult ECMO patients show that (14-16) the ECMO circuit has little adsorption and influence on most antibacterial drugs, which is consistent with the results of this case. In order to verify the results, we monitored plasma Colistin sulfate concentrations again on day 31 of treatment, and the results also showed no significant difference from concentrations on day 4. Therefore, no significant differences in plasma concentrations were observed after withdrawal of ECMO and CRRT. During the treatment, the patient's renal function was gradually improved, urine volume gradually returned to normal, and serum creatinine gradually decreased, but still did not decrease to normal (*Table 2*). Based on the 2 different

creatinine clearance rates, the calculated creatinine clearance rates on day 22 and 31 of treatment were 70.93 and 86.13 mL/min/1.73 m^2, respectively. The measured trough concentrations on day 22 and 31 of treatment were 0.27 and 0.34 mg/L, respectively. The peak concentrations on day 22 and 31 of treatment were 0.82 and 0.98 mg/L, respectively. This indicates that clearance of Colistin sulfate is essentially independent of creatinine clearance and no dose modification is required based on creatinine clearance. Overall, there were no significant differences in the concentrations of Colistin sulfate before and after ECMO and CRRT. The patient's steady-state trough concentration was 0.36 mg/L, therefore, there is a large adjustable space from the average steady-state concentration. Furthermore, if the treatment effect of Colistin sulfate is poor, the regimen of 750,000 IU Q12h or 500,000 IU Q8h can be used, while closely monitoring plasma concentration to ensure efficacy and avoid toxicity. In this case, Colistin sulfate is effective and no dose modification is made.

Colistin sulfate was developed in China. At present, there is a lack of clinical data. Clinicians lack confidence in the efficacy of Colistin sulfate in the treatment of CRO infection. In this case, Colistin sulfate had good efficacy in the treatment of CRO infection. Meanwhile, through the monitoring of plasma concentrations, it guides clinicians to use drugs rationally, avoids toxicities, and reduces hospitalization costs and length of hospital stay. However, the most notable limitation of this case is that changes in drug concentration were not monitored after withdrawal of ECMO and discontinuation of CRRT, respectively, which more visually indicates the changes of ECMO and CRRT on drug concentrations. Therefore, subsequent studies should monitor the changes of plasma concentration after withdrawal of ECMO and CRRT. Meanwhile, multiple drugs were used in this patient, and whether other drugs had an effect on the metabolism of Colistin sulfate has not been taken into consideration. The observation results should be further investigated, and more studies should focus on the changes of ECMO combined with CRRT on drug concentrations.

Colistin sulfate is effective in the treatment of CRO infections, and bacterial resistance has become more and more pronounced in recent years, especially to carbapenems, becoming one of the most important problems threatening global public health. Given that no new targeted antimicrobial agents have been developed, Colistin sulfate is recommended as an important first-line drug therapy. Meanwhile, there were no significant differences in the concentrations of Colistin sulfate before and after ECMO and CRRT. No dose modification is required for Colistin sulfate in patients receiving ECMO with CRRT.

Summary

Colistin sulfate are effective in the treatment of patients with multidrug-resistant Gram-negative organisms. In critically ill patients, in addition to inherent pathophysiological changes, the introduction of ECMO and CRRT may affect the pharmacokinetics of antimicrobial drugs in different ways. Therefore, critically ill patients need accurate drug therapy support, and there is an urgent need to deeply investigate the potential pharmacokinetic changes in critically ill patients on ECMO combined with CRRT. It is recommended to monitor the blood concentration whenever possible.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2081/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2081/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Peng D, Zhang F, Lv P, Chen Y, Yang J, Zhu W, Zhu S, Shao H. Plasma concentrations of Colistin sulfate in a patient with septic shock on extracorporeal membrane oxygenation and continuous renal replacement therapy: a case report. Ann Transl Med 2022;10(10):614. doi: 10.21037/atm-22-2081

