J Antimicrob Chemother 2026; **81**:
https://doi.org/10.1093/jac/dkaf496

Journal of Antimicrobial Chemotherapy 50 years

Pharmacokinetics of cefiderocol during prolonged intermittent kidney replacement therapy in two patients with septic shock

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Received 22 July 2025; accepted 16 December 2025

Objectives: Cefiderocol is a new siderophore cephalosporin for treating severe bacterial infections by Gram-negative pathogens in adults. Significant elimination of the drug will probably occur as a result of kidney replacement therapy, but there are currently insufficient pharmacokinetic data to guide dosing during prolonged intermittent kidney replacement therapy (PIKRT) or the use of the pathogen adsorber Seraph 100.

Materials and methods/case reports: Pharmacokinetic data were obtained from two critically ill patients undergoing PIKRT and hemoperfusion with the pathogen adsorber Seraph 100. Cefiderocol levels in plasma and dialysate samples were quantified using liquid chromatography with tandem mass spectrometry to evaluate the impact of extracorporeal therapy modalities on cefiderocol pharmacokinetics.

Results: The median cefiderocol dialyser clearance was 80.94 (38.7–87) mL/min, while the Seraph 100 showed no significant clearance [−1.8 (−7.9 to 3.6) mL/min]. The cefiderocol concentration in the total spent dialysate suggests a total elimination of 1350 and 400 mg of cefiderocol, or 68% and 40% of the administered dose.

Conclusion: Cefiderocol is substantially eliminated by PIKRT, but not during hemoperfusion with the Seraph 100. Consequently, dosage adjustments may be necessary depending on the intensity of the PIKRT procedure. Doses used for patients with normal renal function may be required to prevent underdosing during intensive PIKRT.

Introduction

Septic shock, caused by multi-resistant bacteria, is a life-threatening condition for critically ill patients.[1] Infections with MDR bacteria, immunosuppression and organ failure such as acute kidney injury (AKI) further increase the mortality of these patients. New drug and non-drug approaches are needed to improve sepsis outcomes.

Cefiderocol, is a siderophore cephalosporin approved by the EMA in 2020 for the treatment of severe bacterial infections in adults caused by Gram-negative pathogens, including MDR bacteria. The drug penetrates bacterial cell walls not only by diffusion via porins, but by active transport using iron transport mechanisms. Consequently, cefiderocol may circumvent bacterial resistance mechanisms based on porin alteration.[2]

The primary route of excretion is through the kidneys, with an elimination half-life of 2 to 3 hours. In patients with end-stage kidney disease, the half-life is increased to 9.6 hours. Due to its low molecular weight of 715 D, its moderate protein binding of 40%–60% and its low volume of distribution of 18 L it is easily removed by some kidney replacement therapies (KRT). This is relevant, as the PERSEUS study found that 27.2% of cefiderocol-treated patients needed KRT.[3] In eight patients undergoing intermittent haemodialysis for three to four hours with blood flow rates of 400 to 500 mL/min and dialysate flow rates of 600 to 700 mL/min using an OptiFlux F180NR, cefiderocol was significantly removed and 56.1% of the dose could be recovered from spot checks of the dialysate.[4] Data from nine patients were used in conjunction with *in vitro* data to develop dosing

Table 1. Main (PK)-characteristics of both cases.

	Case no. 1	Case no. 2
Age (y)	21	71
Weight (kg)	69.5	74
Height (cm)	201	166
Sex	Male	Male
Ethnicity	Caucasian	Caucasian
Comorbidities	DM Typ I	AML, CKD G3A1, HFpEF
SOFA score	13	13
End-organ failures	Kidney, Liver, Cardiovascular system, Coagulation	Kidney, Liver, Cardiovascular system, Coagulation
Cefiderocol dosing (mg/d)	6000	3000
ICU stay day no.	8	1
Albumin (g/L)	15.1	24
Creatinine at baseline (µmol/L)/estimated glomerular filtration rate acc. CKD EPI (mL/min/1.73 m^2)	106/>60	212/26
Plasma cefiderocol peak level (µg/mL)	82	29.7
Volume of distribution[a] (L)	24.4	33.7
Urine excretion (mL/d)	<100	<100
Haematocrit (%)	22	25
ECTR characteristics		
Modality of ECTR	PIKRT	PIKRT
Indication for ECTR	AKI III	AKI III
ECTR start after ICU admission (h)	120	5
ECTR device	GENIUS® system	GENIUS® system
ECTR time (min)	660	388
Blood flow (mL/min)	300/150	220
Dialysate flow (mL/min)	150/75	220
Ultrafiltration rate (mL/h)	50	50
Anticoagulation	heparin	none
Full body cefiderocol reduction ratio during ECTR (%)	>58%	>63%
Cefiderocol dialyser clearance (mL/min)	26.2 (22.3–51.1)	87.4 (86.6–93.7)
Cefiderocol adsorber clearance (mL/min)	−4.9 (−6.9 to −1.8)	4.4 (−5.0 to 5.3)
Total amount of cefiderocol in the collected dialysate (mg)	1350	400
Terminal half-life of cefiderocol during ECTR (h)	4.5	4.1

Results given as median (IQR).
AML, acute myeloid leukaemia; CKD, chronic kidney disease; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction.
[a]Volume of distribution calculated ($V_d = D/C0$).

recommendations in patients undergoing continuous kidney replacement therapy using the Prismaflex system with an AN69 filter. The treatment removed a substantial amount of cefiderocol that increased with the effluent flow rate of the treatment.[5]

The Seraph® 100 Microbind® Affinity Blood Filter (Seraph 100, ExtheraMedical, CA, USA) is the first CE certified device in the European union that uses immobilized heparin to mimic glycocalyx properties for unspecific pathogen adsorption. The Seraph 100 is licenced for the removal of several pathogens, including bacteria, viruses and fungi.[6]

AKI, septic shock and various extracorporeal treatment methods may jeopardize effective drug levels of anti-infective drugs, while pharmacokinetic (PK) data for the use of cefiderocol in patients undergoing prolonged intermittent kidney replacement therapy (PIKRT) and Seraph 100 therapy is limited. We report PK data from two patients with septic shock and simultaneous treatment with PIKRT and the Seraph 100.

Materials and methods/case reports

Informed consent was given by the patient or the legal guardian, which is in line with policy of our IRB. General patient characteristics as well as PK and extracorporeal treatment data are given in Table 1.

Case number 1

A 21-year-old student with type 1 diabetes mellitus presented with an initially severe diabetic ketoacidotic coma that was followed by a complicated course in intensive care unit. Severe aspiration pneumonia required prolonged mechanical ventilation, despite repeated intensification and broad antibiotic therapy, increasing pulmonary infiltrates, including the development of ARDS and ultimately multi-organ failure in septic shock, became apparent.

Microbiologically, multi-sensitive *Staphylococcus aureus* bacteraemia and candidemia were detected. As an MDR Gram-negative infection was expected the patient was treated with 2 g of cefiderocol three times a day.

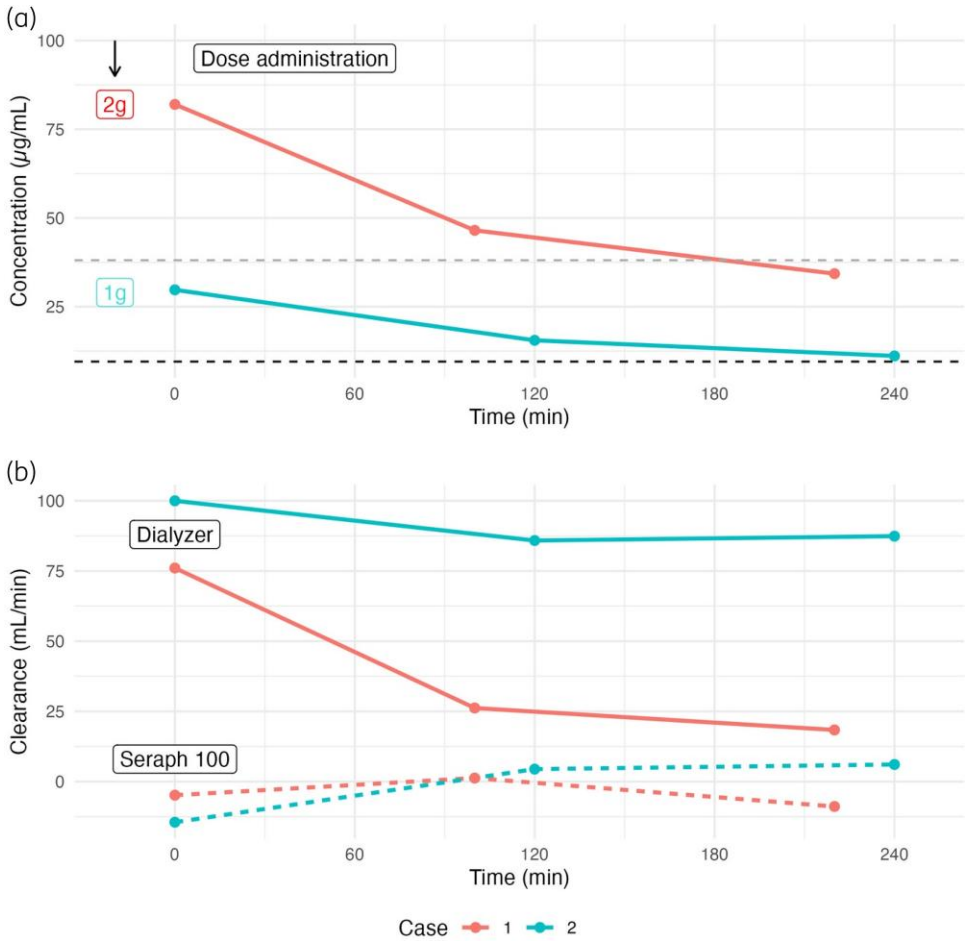

Figure 1. Course of the cefiderocol plasma concentrations (a) and extracorporeal clearance of the used dialyser and adsorber (b). Timepoint 0 represents the start of the extracorporeal treatment. (a) The dashed lines indicate required trough concentrations to attain the PK/PD target of $fC_{min}/MIC \geq 4$ (grey) and $fC_{min}/MIC \geq 1$ (black), given a 58% drug protein binding and a clinical breakpoint of 4 mg/L according to the CLSI susceptibility breakpoints for Gram-negatives.[7] (b) Solid lines represent dialyser clearance and dashed lines represent adsorber clearance (Seraph 100) over time.

Multi-organ failure with anuric AKI and lactic acidosis led to the initiation of PIKRT (660 min duration, initial blood flow of 300 mL/min and subsequent reduction to 150 mL/min after acidosis resolution) and the incorporation of the Seraph 100.

Plasma samples were taken at three different time points (0, 100 and 220 minutes) before and after the Seraph 100 and dialyser to calculate extracorporeal cefiderocol clearance. The total amount of cefiderocol removed was measured using a sample of the spent dialysate.

Time to positivity increased by 23 minutes when comparing pre- and post-Seraph 100 cultures for *Candida albicans* taken at the same time, which indicates that the Seraph 100 removes this pathogen.

Despite a single therapeutic plasma exchange treatment afterwards, the patient subsequently died in septic multi-organ failure.

Case number 2

A 71-year-old male patient was admitted to our intensive care unit due to vasopressor dependent septic shock in neutropenia after stem cell transplantation. During admission to our ICU the patient was awake but haemodynamic unstable with a noradrenaline dose of 0.49 µg/kg/min. The patient had a known history of Gram-negative bacteraemia with carbapenem-resistant *Pseudomonas aeruginosa* that tested susceptible to colistin and cefiderocol, with pathogen positivity after 5 days of colistin treatment. Cefiderocol with a dose of 1 g three times daily according to the dosage recommendations at the time for patients with a creatinine clearance <30 mL/min was given. However, the patient developed anuric AKI with lactic acidosis requiring KRT right before the first cefiderocol dose was administered. We initiated PIKRT in addition with haemoperfusion with the Seraph 100 device. A single PIKRT treatment (373 min duration, blood and dialysate flow of 220 mL/min, ultrafiltration rate 50 mL/h) after the infusion of 1 g of cefiderocol was performed. Plasma samples were drawn right after the initiation of PIKRT, 120 and 240 minutes into the treatment. The treatment was stopped after 388 minutes and a total of 82 L of spent dialysate, due to system clotting. Although a single therapeutic plasma exchange treatment was initiated after the first PIKRT session, vasopressor resistant vasoplegia could not be resolved and the patient died due to septic shock 18 hours after ICU transferral.

Extracorporeal treatment (ECTR) specifics

In both cases, PIKRT was initiated with the GENIUS® dialysis system (Fresenius Medical Care, Bad Homburg) using a FX60 (1.4 m^2 high-flux membrane) and Polyflux 170H (1.7 m^2 high-flux membrane) dialyser. In addition, the Seraph® 100 Microbind® Affinity Blood Filter (Seraph

100, ExtheraMedical, CA, USA) was connected in series upstream of the dialyser.

Cefiderocol measurement and PK analysis

All plasma samples were immediately centrifuged at 1300**g** for 10 min at 4°C and frozen to −80°C until analysis. A sample from the dialysis tank of the GENIUS dialysis machine was drawn after mixing the whole spent dialysate by air insufflation.

Cefiderocol concentrations in human plasma and dialysate were quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) using an API 5500 triple quadrupole mass spectrometer (SCIEX, Concord, Ontario, Canada). The turnaround time was <2 h. To 25 µL of human EDTA plasma or dialysate samples, 25 µL of sample preparation buffer (0.2 M ammonium acetate, pH 5) was added. Samples were deproteinized by 150 µL of 0.2% trifluoroacetic acid (TFA) in methanol containing cefiderocol-d12 sodium as internal standard. The mixture was subsequently vortex-shaken and centrifuged for 3 minutes at 4°C at 11.000 rpm. Then 25 µL of the supernatant was further diluted with 475 µL of 0.1% TFA in water. Ten microlitres were injected into the LC-MS/MS system. Quantification of cefiderocol was performed by peak area ratio of analyte to internal standard. The linearity of the calibration curve for cefiderocol was proved from 0.534 to 100 µg/mL. The lower limit of quantification in human plasma and dialysate was set to 0.100 µg/mL. No interferences were observed for cefiderocol and the internal standards in human plasma or dialysate. The intra-and inter-day precision of the spiked quality control samples was below 5% with an intra- and inter-day accuracy between 90% and 110%.

Extracorporeal clearance was calculated from concentrations before (C_{in}) and after (C_{out}) the dialyser and Seraph 100 as $Cl_{Extracorp} = \frac{Fl_{in}*C_{in}-Fl_{out}*C_{out}}{C_{in}}$ with plasma flow in (Fl_{in}) and out (Fl_{out}) of the device estimated by blood flow, haematocrit and ultrafiltration rate. Volume of distribution was calculated using $V_d = \frac{D}{C_0}$. Terminal drug half-life during extracorporeal therapy was calculated as $t_{\frac{1}{2}} = \frac{\ln 2}{k}$ and $k = \frac{\ln C_1 - \ln C_2}{\Delta t}$ using the second and third measured plasma levels. Results given as median (IQR). Non-compartmental statistical analysis was performed using R (version 4.5.1).

Results

Key pharmacokinetic findings as well as patient and ECTR characteristics are presented in Table 1. Cefiderocol plasma levels as well as dialyser and adsorber clearance are presented in Figure 1. After a single-dose administration of cefiderocol we measured a peak concentration of 82 and 29.7 µg/mL at the start of the PIKRT. The median cefiderocol clearance was 80.94 (38.7–87) mL/min for the dialyser and −1.8 (−7.9 to 3.6) mL/min for the Seraph 100. Dialyser clearance was higher in case no. 2 and dropped in case no. 1 after blood and dialysate flow rate was reduced (Figure 1b). The cefiderocol concentration in the total spent dialysate was 15 and 4.44 µg/mL suggesting a total amount of 1350 and 400 mg of cefiderocol or 68% and 40% of the administered dose. Terminal plasma half-life was 4.5 and 4.1 hours during dialysis.

Discussion

Inadequate anti-infective treatment in septic patients is associated with the risk of high morbidity and mortality especially during infections with MDR bacteria.[8] Altered drug clearances, such as those seen in AKI or during kidney replacement therapy, are common in critically ill patients, who are particularly reliant on effective anti-infective therapy during sepsis.

Population PK studies in different cefiderocol patients showed a high PK/PD target attainment, defined as fT > MIC of 75%, in different groups of healthy and infected patients with different renal functions.[9] However, much higher PK/PD targets that exceed the MIC many times over the treatment period are being discussed to avoid bacterial resistance in beta-lactam antibiotics. Microbiological failure has been reported in critically ill patients with drug-resistant *Acinetobacter baumannii* infections who were treated with cefiderocol and had non-optimal PK/PD target attainment (target defined as fC_{min}/MIC ≥ 4).[10]

Although we have only measured plasma levels over 4 hours, extrapolating the cefiderocol curve shown here demonstrates the risk of underdosing in case no. 2. We observed a lower cefiderocol dialyser clearance after reducing blood and dialysate flow in case no. 1, which suggests that treatment intensity in PIKRT probably affects drug elimination, as seen in other KRT modalities. This emphasizes the importance of adjusting the antibiotic dose to the actual administered PIKRT dose, as already recommended for CKRT.[11] The use of the Seraph 100 adsorber seems not to eliminate a clinically relevant cefiderocol amount. This finding is in line with previous studies on other anti-infective drugs.[12]

Interestingly, we observed much lower plasma peak concentrations after the administration of 1 or 2 g of cefiderocol, compared with data in healthy people.[13] This may reflect an increase in the volume of distribution, commonly seen in critically ill patients receiving beta-lactam antibiotics.[14] This should be taken into account when considering whether to use a loading dose to achieve PK/PD targets. In general, the administration of a loading dose is recommended for beta-lactam antibiotics, according to the Surviving Sepsis Guidelines.[15] However, it is not recommended for cefiderocol in the product information.

On the basis of the limited data of the two presented cases, cefiderocol elimination by PIKRT is substantial. An adequate loading dose should be considered in all critically ill patients. Consecutive dose administration should be based on PIKRT intensity, residual kidney function and other potential influencing factors. Further prospective PK data are needed to give dose recommendations for the use of cefiderocol in critically ill patients undergoing PIKRT.

Funding

This study was supported by Shionogi.

Transparency declarations

J.J.S. and J.T.K. received research support from ExThera Medical and advisory fees from Shionogi. All other authors: none to declare.

Author contributions

Julius Schmidt (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing—original draft, Writing—review & editing), Julia Hagemann (Conceptualization, Data curation, Investigation, Writing—original draft, Writing—review & editing), Uta Hillebrand (Data curation,

Investigation, Writing—review & editing), Stephan Scherneck (Writing—review & editing), Fritz Sörgel (Investigation, Methodology, Writing—review & editing), Martina Kinzig (Investigation, Methodology, Writing—review & editing), and Jan Kielstein (Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing)

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