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CASE REPORT

Continuous infusion of cefiderocol in a critically ill patient with continuous venovenous haemofiltration

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Cefiderocol is a broad-spectrum cephalosporin antibiotic and is indicated in patients with difficult-to-treat Gram-negative bacterial infections. Cefiderocol is applied as a 2–4-times daily prolonged 3-h infusion. The therapeutic target of cefiderocol suggests that continuous infusion (CI) may be advantageous, since it is more likely to achieve 100% of time of the unbound concentration above the minimal inhibitory concentration (MIC). However, limited information on cefiderocol as CI has been assessed. We present a case of a critically ill 37-year-old woman with continuous venovenous haemofiltration (CVVH) treated with a CI of cefiderocol for multidrug-resistant *Pseudomonas aeruginosa*. She received 4 g per 24 h, in accordance with the recommendations for the total daily dose during CVVH with an effluent flow rate of 2.1–3 L/h. We evaluated intraperitoneal, plasma arterial pre- and postfilter and ultrafiltrate (urine) total cefiderocol concentrations and discussed the pharmacokinetics in respect to the CVVH settings. The predicted unbound plasma concentrations during CI resulted in 6.8–9.5-fold higher concentrations than the adopted MIC of 2 mg/L for cefiderocol against *P. aeruginosa*. The optimal time of the unbound concentration >MIC target of cefiderocol was met during the sampling period, suggesting adequate exposure during the total treatment period. The obtained intraperitoneal concentration indicated adequate cefiderocol exposure at the site of infection. Continuous infusion of 4 g cefiderocol per 24 h led to sufficient plasma concentrations in our anuric critically ill patient treated with CVVH. This case is supportive to the use of cefiderocol as continuous infusion.

KEYWORDS
cefiderocol, continuous infusion, continuous venovenous haemofiltration, critically ill, CRRT, CVVH, difficult-to-treat infections

1 | INTRODUCTION

Cefiderocol is a broad-spectrum siderophore cephalosporin and is indicated in patients with severe infections with difficult-to-treat Gram-negative bacteria, including carbapenem-resistant strains, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Cephalosporins act by binding to and inhibiting penicillin-binding proteins, preventing cell wall synthesis and initiating bacterial cell death. The unique mechanism of cefiderocol penetrating into bacterial cells is based on binding to ferric iron and active transport through iron

channels. After dissociation of iron from the siderophore, the cephalosporin core of cefiderocol subsequently binds to these penicillin-binding proteins.[1,2]

Cefiderocol is almost completely excreted unchanged by the kidneys and dose adjustments should be made in patients with renal dysfunction.[3,4] The molecular characteristics of cefiderocol support dialysability, including its low molecular weight, small volume of distribution, protein binding of 58% and being an uncharged molecule.[5] It was found that approximately 60% of the cefiderocol dose was eliminated from the body after a 3–4-h haemodialysis session.[6] In addition, the effluent flow (EF) rate during continuous renal replacement therapy (CRRT) proved to be the most important determinant of the clearance and, hence, the dosage during dialysis.[7–10] Besides, cefiderocol showed only low (approximately 10%) filter adsorption to the CRRT system.[7]

The therapeutic target of cefiderocol adopted in pivotal trials is 75% of time of the unbound concentration above the minimal inhibitory concentration (fT > MIC).[11] For additional suppression of resistance development, the suggested optimal target is 100% fT > MIC with concentrations at least 4–5 times the MIC.[11–13] Note that this is equivalent to an unbound minimum or steady state concentration over MIC ratio of at least 4–5 times.[12,13] To achieve these aggressive targets, intensified dosages and/or prolonged (extended or continuous) infusions are needed.[12,13] So far, cefiderocol is applied as a prolonged 3-h infusion, in accordance with the present dosing recommendations.[7] However, the therapeutic target of cefiderocol suggests that continuous intravenous administration may be advantageous, as fluctuations in systemic concentrations will be reduced and it is more likely to achieve the optimal target of 100% of fT > MIC.[14] Moreover, these extended infusions are favourable as treatment of severe infections due to a decrease in mortality without a rise in adverse events.[15] This may be the most relevant for critically ill patients undergoing CRRT, due to the continuous clearance of cefiderocol and changes in pharmacokinetic and pharmacodynamic parameters. In critically ill patients treated with continuous infusion of β-lactams, an unbound concentration of >5 times the MIC is suggested.[16] However, limited information on cefiderocol as continuous infusion (CI) and its true therapeutic target has been assessed.[17,18]

Here, we present a case of a critically ill patient with continuous venovenous haemofiltration (CVVH) treated with cefiderocol as CI. We evaluated plasma, pre- and postfilter and effluent total plasma cefiderocol concentrations and discussed the pharmacokinetics in respect to the CRRT settings.

2 | CASE REPORT

A 37-year-old woman had given birth via caesarean section 1 week before intensive care unit (ICU) admission. She was readmitted because of abdominal sepsis with respiratory insufficiency due to intestinal perforation as a complication of the caesarean section. A laparotomy was performed with ileocaecal resection and no reconstitution of continuity. Postoperatively, she was admitted to the ICU with a Sequential Organ Failure Assessment (SOFA) score of 6. The initial antibiotic treatment consisted of ceftriaxone and metronidazole as empirical therapy in abdominal sepsis. The regimen was switched to meropenem, vancomycin and fluconazole when abdominal cultures showed *Candida albicans*, *Escherichia coli*, *Streptococcus oralis*, *Klebsiella oxytoca*, *Enterococcus faecium* and multidrug-resistant *P. aeruginosa*. In the following days, multiple relaparotomies were performed, with ileostomy and drainage of 2 abscesses as she experienced ongoing shock, sepsis with fever and respiratory insufficiency due to extensive faecal spillage and luxation of 1 of the abdominal drains. Subsequently, acute respiratory distress syndrome developed for which she was treated in prone position. Cultures from the vacuum-assisted closure system showed *P. aeruginosa* resistant to β-lactams and treatment with ceftazidime/avibactam as CI together with colistin was started.[11] As her clinical status was further complicated with acute kidney injury without residual diuresis, CVVH was started (Prismaflex; filter HF150, blood flow 200 mL/min, EF rate 2 L/h with 100% postdilution, coagulation citrate 70 mL/min). In the next weeks, several ultrasound guided drainages of abdominal abscesses were conducted with moderate effect. Recurrent gastro- and colonoscopies showed gastrointestinal bleeding and ischaemic colon, duodenum and jejunum due to ongoing shock. Inflammation parameters kept increasing, with a C-reactive protein (CRP) of 216 mg/L (SOFA score 16) and ceftazidime/avibactam was therefore switched to cefiderocol 2 g trice daily. Six and a half hours after the third dose, cefiderocol was converted to a CI of 4 g per 24 h in accordance with the recommendations for the total daily dose during CVVH with an EF rate of 2.1–3 L/h.[7] Regarding stability, the daily dose of cefiderocol was divided into 4 6-h infusions of 1 g (concentration 20 mg/mL, infusion rate 8.4 mL/h). On the second and third day of treatment, 1 fluid sample from an intraperitoneal drain and multiple plasma samples, pre- and postfilter, and ultrafiltrate (urine) samples were analysed for total cefiderocol plasma concentrations with a liquid chromatography–tandem mass spectrometry method.[19] The patient has consented to the anonymous publication of her case.

After 1 week of treatment with cefiderocol, CRP had decreased to 78 mg/L (SOFA score 13). However, colistin and ceftazidime/avibactam had to be restarted, because cefiderocol was no longer available in the Netherlands at that time. Nonetheless, ceftazidime/avibactam was switched because of ongoing sepsis with an elevation in CRP to 185 mg/L, to ceftazolane/tazobactam as CI.[11,20] All along, the patient was additionally treated with a large variety of antibacterial, -viral and -mycotic drugs for recurrent (line) infections, invasive candida species, cytomegalovirus enteritis and suspicion of invasive aspergillosis. Despite all efforts, the patient died after 3 months from ongoing multiple organ failure.

In Table 1, the total cefiderocol concentrations are presented, along with the corresponding CRRT settings, total cefiderocol clearances and sieving coefficients (SCs). Considering a protein binding of 58%, the predicted unbound cefiderocol concentrations ranged from 13.7 to 19.0 mg/L during CI in the arterial samples, reflecting jugular vein concentrations. The patients' exposure to total cefiderocol during CI was approximately 915 mg h/L. Postfilter concentrations were

TABLE 1 Cefiderocol concentrations in the intra-abdominal, arterial, pre- and postfilter and ultrafiltrate samples.

Sample type	Sampling time (h)	Total concentration (mg/L)	BF (mL/min)	SF (mL/h)	EF (mL/h)	Total clearance (L/h)	SC
Arterial	2 h after ending third prolonged 3-h infusion/1.5 h before start CI[a]	49.8	150	1750	1850	-	1.1
Prefilter		51.6					
Postfilter		62					
Ultrafiltrate		56.8					
Abdominal drain fluid	3 h after ending third prolonged 3-h infusion/0.5 h before start CI	15.3	-	-	-	-	-
Arterial	3.5 h after start CI	43	200	2000	2100	3.9	0.9
Prefilter		53.9					
Postfilter		52.6					
Ultrafiltrate		48.9					
Arterial	18.5 h after start CI	32.6	200	2000	2150	5.1	-
Prefilter		37.5					
Postfilter		46.3					
Arterial	24.5 h after start CI[b]	45.3	200	2000	2200	3.7	-
Prefilter		45.7					
Postfilter		50.5					

Note: Arterial: catheter position right jugular vein. The patients' exposure to cefiderocol was estimated with the trapezoidal rule using the concentrations in the arterial samples during CI and extrapolated to the 24-h area under the concentration–time curve; total clearance was calculated by the infusion rate (mg/h) divided by the arterial plasma concentration.

Abbreviations: BF, blood flow; CI, continuous infusion; EF, effluent flow; SC, sieving coefficient, calculated by the concentration of drug in the ultrafiltrate divided by the concentration in prefilter blood; SF, substitution flow; -, unknown or not applicable.

[a]Filter age: 15 h.

[b]Filter age: 1 h.

mostly 10–20% higher than prefilter concentrations, due to volume extraction during CRRT before substitution with the replacement fluid. The total cefiderocol concentration in the intraperitoneal drain fluid was 15.3 mg/L.

3 | DISCUSSION

Cefiderocol as continuous infusion with 4 g per 24 h led to sufficient plasma concentrations for treatment of multidrug-resistant *P. aeruginosa* in our critically ill patient with CVVH. Cefiderocol clearance and SCs were in accordance with earlier observations.[7–10,17] However, we could not differentiate between EF rates. The intraperitoneal concentration seemed to be sufficient for abdominal sepsis. Although these observations were in 1 patient, the data support the use of cefiderocol as CI, meeting current practices on the use of (novel) β-lactam antibiotics in critically ill patients with multidrug-resistant Gram-negative bacterial infections.[11]

The adopted MIC of cefiderocol against *P. aeruginosa* is ≤2 mg/L according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.[21] In a case series of Pinna *et al*., 3 critically ill patients with CVVH and difficult-to-treat *A. baumannii* received cefiderocol 2 g every 8 h as prolonged 3-h infusions.[10] This resulted in unbound trough concentrations ranging from 3.0 to 15.0-fold the adopted EUCAST clinical breakpoint of cefiderocol against *A. baumannii* of 2 mg/L (MIC similar to *P. aeruginosa*), meeting 100% fT > MIC target. This cefiderocol dosage was therefore deemed sufficient in critically ill patients for difficult-to-treat *A. baumannii*. No severe adverse events were observed. Kobic *et al*. had similar findings for a patient colonized with *P. aeruginosa* while treated with cefiderocol 2 g every 8 h as prolonged 3-h infusion during continuous venovenous haemodiafiltration (CVVHDF).[8] It should be noted that this dosing regimen was recommended for CRRT with EF rates of ≥4.1 L/h.[7] The EF rates in the described cases were lower, suggesting that a less intensified dosing regimen may also have been sufficient for these patients. However, the patients' residual kidney functions were taken into account when selecting the dosing regimen.

In a recent case series of Gatti *et al*., 5 critically ill patients with CVVHDF were treated with 6000 mg cefiderocol as CI for carbapenem-resistant *A. baumannii*.[17] Median predicted unbound cefiderocol concentrations were 26.5 mg/L (interquartile range 21.7–33.6) with a 14.9-fold (interquartile range 6.6–33.6) higher concentration than the MIC (ranging 0.125–4 mg/L). A regimen of 6000 mg cefiderocol per 24 h as CI was deemed suitable for ICU patients with CVVHDF and residual diuresis for target attainment of resistant strains with a MIC value up to 4 mg/L. Despite these excessive

concentrations, none of the patients had adverse events related to cefiderocol. In our patient, the predicted unbound plasma concentrations during CI resulted in a mean 8-fold (range 6.8–9.5) higher concentration than the adopted EUCAST clinical breakpoint of 2 mg/L. This means that the optimal 100% fT > MIC target of cefiderocol with concentrations at least 5 times the MIC was met during the sampling period, suggesting adequate exposure during the total treatment period. Moreover, cefiderocol has been shown an antibiotic with excellent tolerability in highly comorbid patients with a diversity of multidrug-resistant infections. No adverse effects on renal, hepatic or bone marrow function were seen during cefiderocol treatment, confirming its wide margin of safety.[22]

The patients' exposure to total cefiderocol was approximately 915 mg h/L based on the 3 arterial cefiderocol concentrations during CI. These 3 data points were measured over a time course of 21 h, calculating the area under the concentration–time curve (AUC) using the trapezoidal rule and extrapolated to the AUC over 24 h (AUC_{0-24}). The AUC_{0-24} could be used as a surrogate parameter to reflect an adequate through concentration for T > MIC target attainment with cefiderocol as prolonged 3-h infusion.[7,9] An AUC_{0-24} of 1560 mg h/L was used for achieving the therapeutic goal in pneumonia patients across a clinically relevant EF rate range of 0.5–5 L/h.[9] Wenzler *et al*. considered a target AUC_{0-24} of 1184 mg h/L, derived from the phase III APEKScUTI trial for the formulation of the dosage recommendations.[5,7] The exposure to total cefiderocol in our patient was lower than the therapeutic AUC_{0-24} considered in these studies. However, there are fewer fluctuations in cefiderocol concentrations during CI and no question of a minimum and maximum concentration. Therefore, a lower constant cefiderocol concentration during CI may still result in an adequate exposure with 100% fT > MIC target attainment. This was confirmed by the predicted unbound plasma concentrations in our patient, which exceeded >5 times the MIC during the sampling period, indicating optimal target attainment. This also implied that the current recommended cefiderocol dosing regimen for CVVH (EF rate 2.1–3 L/h) given as CI was sufficient for aggressive target attainment without the need for measurement of cefiderocol concentrations or AUC to guide decision making.

Further, the observed total cefiderocol clearances were in accordance with the findings of Gatti *et al*., even though the patients in that study had high EF rates of ≥2.7 L/h and residual kidney function.[17] Clearances were calculated by the infusion rate (mg/h) divided by the arterial plasma concentration.[17] For this calculation, it was assumed that cefiderocol concentrations were in steady state during CI, since the patient was already loaded with cefiderocol due to the prolonged 3-h infusions prior to the start of CI. However, true steady state may be questioned, since the total cefiderocol concentrations fluctuated over time, despite constant infusion and EF rates and no residual kidney function. This indicates the changeable pharmacokinetic behaviour of cefiderocol under different CRRT conditions, which was also supported by Gatti *et al*.[17] Also, our observed SCs were in accordance with earlier observations.[7,9]

A first limitation of our approach in this case was that total cefiderocol concentrations were measured, whereas concentrations of unbound cefiderocol were predicted based on a protein binding of 58%.[5,6] ICU patients may have variable protein binding, affecting the unbound cefiderocol concentration.[23] the current findings may only be applicable to critically ill patients with similar CRRT modalities and no residual diuresis, and cannot be extrapolated to other patients. Therefore, confirmatory studies with cefiderocol as CI in different conditions are needed.

A final interesting aspect was the relatively high cefiderocol concentration in the abdominal drain fluid. Cefiderocol is known for its small volume of distribution. However, it is conceivable that the volume of distribution was enlarged due to the ongoing sepsis with capillary leakage. This may have resulted in additional leakage of solutes into the peritoneal space. In favour of our patient, the intra-abdominal concentration may indicate adequate cefiderocol exposure at the site of infection.

4 | CONCLUSION

Continuous infusion of 4 g cefiderocol per 24 h in a critically ill patient treated with CVVH without residual kidney function led to adequate exposure for difficult-to-treat Gram-negative bacterial infections. The predicted unbound plasma concentrations exceeded the MIC target of cefiderocol. These real-time data support the use of continuous infusion of cefiderocol, meeting current practices on the use of (novel) β-lactam antibiotics and to obtain the right dosage for critically ill patients during CVVH. However, confirmatory studies with cefiderocol as CI in different conditions are needed.

AUTHOR CONTRIBUTIONS

All authors contributed to writing and/or revising the manuscript. Julia Möhlmann, Maaike Sikma and Esther Uijtendaal interpreted the pharmacokinetics of cefiderocol. Matthijs van Luin and Noël Zahr contributed to performance of the cefiderocol analysis. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available within the article.

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