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Pharmacokinetics/pharmacodynamics of cefiderocol administered by continuous infusion in a case series of critically ill patients with carbapenem-resistant *Acinetobacter baumannii* infections undergoing continuous venovenous haemodiafiltration (CVVHDF)

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Abstract

Objectives: To assess the pharmacokinetics/pharmacodynamics (PK/PD) of cefiderocol administered by continuous infusion (CI) in a case series of critically ill patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections undergoing continuous venovenous haemodiafiltration (CVVHDF).

Methods: Critically ill patients receiving CI cefiderocol during CVVHDF for documented bloodstream infections (BSIs), ventilator-associated pneumonia (VAP), and/or complicated intrabdominal infections (cIAIs) caused by CRAB and undergoing therapeutic drug monitoring (TDM) from February 2022 to January 2023 were retrospectively assessed. Cefiderocol concentrations were determined at steady-state, and the free fraction (fC_{ss}) was calculated. Cefiderocol total clearance (CL_{tot}) was determined at each TDM assessment. fC_{ss}/MIC ratio was selected as PD determinant of cefiderocol efficacy and defined as optimal if >4, quasi-optimal if between 1 and 4, and suboptimal if <1.

Results: Five patients with documented CRAB infections (two BSI+VAP, two VAP, and one BSI+cIAI) were included. The maintenance dose of cefiderocol was always of 2g q8h over 8h by CI. Median average fC_{ss} was 26.5 mg/L (21.7-33.6 mg/L). Median CL_{tot} was 4.84 L/h (2.04-5.22 L/h). Median CVVHDF dose was 41.1 mL/kg/h (35.5-44.9 mL/kg/h), and residual diuresis was reported in 4/5 cases. Optimal PK/PD target was attained in all cases with a median cefiderocol fC_{ss}/MIC ratio of 14.9 (6.6-33.6).

Conclusion: CI administration of full doses could be a useful strategy for attaining aggressive PK/PD targets with cefiderocol for the treatment of severe CRAB infections among critically ill patients undergoing high-intensity CVVHDF and having residual diuresis.

Keywords: cefiderocol; continuous infusion; continuous renal replacement therapy; continuous venovenous haemodiafiltration; PK/PD target attainment; carbapenem-resistant *Acinetobacter baumannii*

Background

Acinetobacter baumannii represents a major cause of healthcare-associated infections in critically ill patients [1]. Nowadays, the widespread emergence of carbapenem-resistance among *A. baumannii* clinical isolates makes the treatment of carbapenem-resistant *A. baumannii* (CRAB)-related infections extremely challenging, causing high rates of clinical failure and mortality [1].

Cefiderocol is a recently licensed novel beta-lactam highly active against CRAB [2]. Recent real-world studies showed that cefiderocol could be a promising option in the management of severe CRAB infections [3,4]. According to recent findings, attaining aggressive pharmacokinetic/pharmacodynamic (PK/PD) targets defined as $100\%T_{>4\text{-}8xMIC}$ could not only maximize clinical efficacy of treatment with beta-lactams but also grant microbiological eradication with minimization of the likelihood of resistance development [5].

Renal replacement therapy (RRT) is a procedure that may replace the normal blood-filtering function of the kidney in patients with renal dysfunction. It may be applied by means of several different modalities, which may impact to a various extent on the pharmacokinetic behavior of renally cleared antibiotics, such as the beta-lactams [6]. Continuous veno-venous hemodiafiltration (CVVHDF) is one of the continuous renal replacement therapy (CRRT) modalities potentially applicable for managing acute kidney injury in critically ill patients with hemodynamic instability [6]. CVVHDF may make the attainment of aggressive PK/PD target with beta-lactams extremely challenging [7], and the PK/PD profile of cefiderocol under CVVHDF was assessed only in few single cases during standard administration by extended infusion (EI) over 3h [8–10].

The aim of this study was to assess the PK/PD of cefiderocol administered by continuous infusion (CI) in a case series of critically ill patients with CRAB infections undergoing therapeutic drug monitoring (TDM) while being on CVVHDF.

Methods

This was a retrospective case series of critically ill renal patients who, while undergoing CVVHDF at the general intensive care unit (ICU) or at the transplant ICU of the IRCCS Azienda Ospedaliero-Universitaria of Bologna in the period between 01st February 2022 and 31st January 2023, received cefiderocol administered by CI for the treatment of documented CRAB infections and underwent TDM. Demographic and clinical/laboratory data were collected for each patient. Data on isolated pathogens with punctual MIC values for cefiderocol, type/site of infection, dosage, and treatment duration with cefiderocol, use of monotherapy or combination therapy with other antibiotics active against CRAB isolates were retrieved. CVVHDF operative conditions (i.e., type of filter, blood flow rate [Q_b], pre-blood pump [PBP] fluid rate, dialysate flow rate [Q_d], percentage of pre-/post-dilution, replacement fluid rate, net removal rate per hour) and status of renal function were retrieved at each TDM assessment. The total effluent flow rate was defined based on the following equation: pre-filter replacement fluid rate + post-filter replacement fluid rate + net removal rate + PBP fluid rate + Q_d. CVVHDF dose intensity was calculated by normalizing the total effluent flow rate for body weight. At each TDM assessment, cefiderocol total CL (CL_{tot}) was calculated based on the following formula: CL_{tot} (L/h) = infusion rate (mg/h) / C_{ss} (mg/L). Area under concentration-time curve (AUC) was calculated by means of the following formula: AUC (mg·h/L) = dose (mg/24h) / CL (L/h).

The types of infection were defined according to the following standard criteria: documented bloodstream infection (BSI) was defined by means of CRAB isolation from blood cultures. Documented ventilator-associated pneumonia (VAP) was defined by means of CRAB isolation with a bacterial load $\geq 10^4$ CFU/mL in the bronchoalveolar lavage (BAL) fluid culture after >48 hours from endotracheal intubation and starting mechanical ventilation in patients with a new or progressive lung infiltrate [11]. Complicated intrabdominal infection (cIAI) was defined by means of CRAB isolation from peritoneal fluid patients with infection extended beyond a single organ into the peritoneal space [12].

Antimicrobial susceptibility testing for cefiderocol was performed by means of broth microdilution method with iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB), as previously described [13]. The MIC of cefiderocol against CRAB isolates was determined according to the EUCAST guidelines by evaluating the relative growth reduction (button of <1 mm) in comparison to the ID-CAMHB growth control

well. CRAB strains showing an MIC value > 2 mg/L were deemed resistant according to the EUCAST PK/PD non-species related breakpoints [14].

Cefiderocol was prescribed as first-line or rescue therapy at the discretion of the infectious disease consultant in accordance with current clinical practice guidelines implemented at the IRCCS Azienda Ospedaliero-Universitaria of Bologna. Treatment was always started with a loading dose (LD) of 2g over 2h infusion followed by a maintenance dose (MD) of 2g q8h administered over 8h (namely by CI). For this purpose, aqueous solutions were reconstituted every 8h [15].

Blood samples for measuring cefiderocol steady-state concentrations (C_{ss}) were collected firstly after at least 24 hours from CVVHDF initiation and then reassessed whenever feasible. Total serum cefiderocol concentrations were determined by means of a validated liquid chromatography-tandem mass spectrometry method [16].

As only total cefiderocol concentrations were measured, the free fraction (*f*) was calculated by considering a plasma protein binding of 58%, as reported in the literature [2]. The time with serum cefiderocol fC_{ss} above the MIC was selected as PD parameter of efficacy and expressed as fC_{ss}/MIC ratio. The fC_{ss}/MIC ratio was defined as optimal if ≥ 4, quasi-optimal if between 1 and 4, and suboptimal if < 1, as previously reported [13,17].

Continuous data were presented as median and interquartile range (IQR), whereas categorial variables were expressed as count and percentage. The study was approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n. 442/2021/Oss/AOUBo approved on 28th June 2021).

Results

Overall, a total of five critically ill patients with CRAB infections receiving treatment with CI cefiderocol while undergoing CVVHDF were included (**Table 1**). Median (IQR) age was 64 years (43-71 years). All patients were male, underwent invasive mechanical ventilation and required haemodynamic support with vasopressors.

CVVHDF was always performed by means of Prisma Flex System equipped with an AN69 high-flux ST-150 filter membrane. The operative conditions are summarized in **Table 2**. Median (IQR) Q_b and total effluent flow rate were 150 mL/min (150-150 mL/min) and 2,900 mL/h (2,840-3,590 mL/h), respectively. Median (IQR) CVVHDF dose was 41.1 mL/kg/h (35.5-44.9 mL/kg/h). Four out of the five patients (80%) had residual diuresis with a median (IQR) 24-h urinary output of 297.5 mL (283.8-337.5 mL).

Types of infections were BSI plus VAP and VAP in two cases each, and BSI plus cIAI in one case patient. Overall, three out of the five CRAB isolates had an MIC of 4 mg/L, and were considered resistant to cefiderocol. The MD of cefiderocol was always of 2 g q8h over 8h by CI. The median (IQR) duration of treatment was 11 days (10-14 days), and the median (IQR) CVVHDF duration was 10 days (7-11 days). TDM of cefiderocol was assessed more than once during CVVHDF in 2 out of 5 cases. Cefiderocol was administered as monotherapy in two cases, and as combination therapy in the other three (with fosfomycin in two patients and with ampicillin-sulbactam in the other).

Median (IQR) average cefiderocol fC_{ss} was 26.5 mg/L (21.7-33.6 mg/L). Median (IQR) CL_{tot} of cefiderocol was 4.84 L/h (2.04-5.22 L/h). Optimal PK/PD targets were attained in all of the five patients, the median (IQR) fC_{ss}/MIC being 14.9 (6.6-33.6).

Discussion

Our study may add some knowledge about the changeable PK behaviour of cefiderocol under different CVVHDF conditions and may provide firstly evidence about the likelihood of attaining aggressive PK/PD targets with CI administration in the treatment of critically ill patients with severe CRAB infections while undergoing CVVHDF.

In our case series, the median CL_{tot} of cefiderocol (4.84 L/h) was 1.5- to 2- fold higher than observed previously in three separated cases [8–10]. Kobic *et al*. [8] found a CL_{tot} of 2.33 L/h in an anuric patient having a bacteraemic VAP due to DTR *Pseudomonas aeruginosa* and undergoing CVVHDF with a total effluent flow rate of 1,750 mL/h. Fratoni *et al*. [10] reported a cefiderocol CL_{tot} of 2.7 L/h in an anuric patient affected by bacteraemic pneumonia due to *Stenotrophomonas maltophilia* and undergoing CVVHDF with a total effluent flow rate of 2,200 mL/h. Finally, Kobic *et al*. [9] found a cefiderocol CL_{tot} of 3.4 L/h in an anuric patient with VAP due to CRAB undergoing CVVHDF with a total effluent flow rate of 3,500 mL/h.

Overall, our PK results may be explained by two rationales. First, the quite high effluent rates and CVVHDF dose intensities that were applied in our series [18], in agreement with the findings of an *ex vivo* model showing that cefiderocol CL_{tot} may increase proportionally to CRRT dose intensity [19]. Second, the presence of residual diuresis in most of our cases, in agreement with the estimation that a residual creatinine clearance of 15-30 mL/min could promote a theoretical increase in cefiderocol CL_{tot} of 1.36–2.18 L/h [8,10].

The finding of changeable CL_{tot} of cefiderocol under different CVVHDF operative conditions may support the contention that adopting a "patient-center" approach should be the way forward for optimizing antimicrobial treatment during CRRT [7].

The choice of administering full MD of cefiderocol by CI, namely 2g q8h over 8h, allowed us to attain aggressive PK/PD targets in all of the included patients, even in those having infections sustained by CRAB strains with an MIC of 4 mg/L, namely theoretically *in vitro* resistant to cefiderocol according to the EUCAST. This may be very valuable from the clinical standpoint, since attainment of aggressive PK/PD targets of $100\%fT_{>4\text{-}8\ x\ MIC}$ is actually considered mandatory with beta-lactams for granting microbiological eradication and minimizing the risk of resistance development [5,20]. Noteworthy, no patient suffered from cefiderocol-

related adverse event. Overall, these findings may support the contention that, among patients undergoing high-intensity CVVHDF and having residual diuresis, a dosing regimen of 2g q8h over 8h (namely by CI) could be appropriate for attaining aggressive PK/PD targets with cefiderocol against all CRAB strains with an MIC value up to or even higher than the EUCAST PK/PD non-species related breakpoint (namely 2 mg/L). Of course, larger prospective studies are warranted for confirming our hypothesis. Furthermore, it is noteworthy that our findings could be applicable only in ICUs in which high-intensity CVVHDF is usually implemented. Indeed, the adoption of different CRRT modalities and the variations in effluent flow rate may strongly impact on beta-lactam clearance, including cefiderocol [6,7]. CVVHDF, by combining convection and diffusion properties, usually represents the most efficient RRT modality in terms of drug removal [6]. Consequently, it could not be ruled out that our cefiderocol dosing regimen may be not appropriate in patients undergoing other CRRT modalities or in which lower effluent flow rate is delivered.

We recognize that our study has some limitations. The retrospective monocentric study design and the limited sample size should be acknowledged. Total cefiderocol concentrations were measured, and the free fraction were only estimated. We recognize that measuring 24-hour urinary creatinine clearance would have allowed a better estimate of residual renal function. Finally, we admit that our findings could not be reliable in addressing correctly the issue among patients undergoing low-intensity CVVHDF.

In conclusion, this study may provide evidence about the usefulness that CI administration of full doses may have in attaining aggressive PK/PD targets with cefiderocol for the treatment of severe CRAB infections among critically ill patients undergoing high-intensity CVVHDF and having residual diuresis. Large prospective confirmatory studies are warranted for assessing clinical and microbiological outcome.

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Angelini, BeiGene, Gilead, MSD, Pfizer, Shionogi, outside the submitted work. The other authors report no potential conflicts of interest for this work.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n. 442/2021/Oss/AOUBo approved on 28th June 2021).

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Continuous-Infusion Ceftazidime-Avibactam in a Case Series of Difficult-to-Treat Resistant Pseudomonas aeruginosa Bloodstream Infections and/or Hospital-Acquired Pneumonia. Antibiotics 2022;11:1739. https://doi.org/10.3390/antibiotics11121739.

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Table 1 – Demographics and clinical features of critically ill patients undergoing continuous venovenous haemodiafiltration (CVVHDF) treated with CI cefiderocol

ID case	Age	Underlying disease	Pathogen	MIC	Infection	Dose	Average *f*Css	*f*Css/MIC	Cefiderocol PK/PD target	Treatment duration	CVVHDF treatment duration while on cefiderocol	Microbiological eradication BSI	Microbiological eradication VAP/IAI	Combination therapy
#1	64/M	ARDS in COVID-19	CRAB	4	BSI + VAP	2g LD 2g q8h CI	59.7	14.9	Optimal	14	14	Yes	Yes (VAP)	No
#2	29/M	Polytrauma	CRAB	0.125	VAP	2g LD 2g q8h CI	21.7	173.3	Optimal	14	10	//	Yes (VAP)	No
#3	43/M	Acute-on-chronic liver failure	CRAB	1	VAP	2g LD 2g q8h CI	33.6	33.6	Optimal	10	3	//	Yes (VAP)	Ampicillin/ sulbactam (6g/3g LD 6g/3g q8h CI)
#4	71/M	Abdominal perforation	CRAB	4	BSI + cIAI	2g LD 2g q8h CI	26.5	6.6	Optimal	11	11	Yes	No (cIAI)	Fosfomycin (6g LD 16g/day CI)
#5	74/M	Septic shock in COVID-19	CRAB	4	BSI + VAP	2g LD 2g q8h CI	17.6	4.4	Optimal	7	7	Yes	No (VAP)	Fosfomycin (6g LD 16g/day CI)

ARDS: acute respiratory distress syndrome; BSI: bloodstream infection; CI: continuous infusion; cIAI: complicated intrabdominal infection; CRAB: carbapenem-resistant *Acinetobacter baumannii*; C_{ss}: steady-state concentrations; LD: loading dose; MIC: minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamic; VAP: ventilator-associated pneumonia. //: not applicable. Green box: microbiological eradication; red box: microbiological failure. Microbiological failure was defined as the persistence of the same bacterial pathogen in the primary site of infection (documented in blood, BAL, and/or peritoneal fluid cultures depending on case-by-case) after ≥7 days from starting cefiderocol treatment.

Table 2 – CVVHDF (equipped with AN-69 ST150 filter membrane and application of citrate regional anticoagulation) operative conditions and cefiderocol CL and AUC at each TDM assessment

ID case	Sampling time after starting FDC therapy (day)	Weight (Kg)	Q_b rate (mL/min)	PBP rate (mL/h)	Q_d rate (mL/h)	Pre/Post-dilution	Replacement fluid rate (mL/h)	Net removal (mL/h)	CVVHDF dose intensity (mL/kg/h)	Residual diuresis (mL/24h)	Total effluent flow rate (mL/h)	FDC CL (L/h)	FDC AUC (mg*h/L)
#1	12	100	150	1250	800	0/100	800	80	29.3	280	2930	1.76	3409.1
#2	4	70	150	1250	1300	0/100	1000	140	52.7	300	3690	5.22	1149.4
#2	8	70	150	1250	500	0/100	1000	140	41.3	350	2890	2.04	2941.2
#2	11	70	150	1250	1300	0/100	1000	140	52.7	295	3690	4.99	1202.4
#3	10	80	180	500	2500	0/100	500	90	44.9	830	3590	1.97	3045.7
#4	2	80	150	1250	500	0/100	1000	150	36.3	0	2900	7.84	765.3
#4	5	80	150	1250	500	0/100	1000	90	35.5	0	2840	4.84	1239.7
#4	6	80	150	1250	500	0/100	1000	90	35.5	0	2840	3.97	1511.3
#5	6	65	150	1250	500	0/100	800	120	41.1	225	2670	5.95	1008.4

AUC: area under concentration-time curve; CL: clearance; CVVHDF: continuous venovenous haemodiafiltration; FDC: cefiderocol; PBP: pre-blood pump flow rate; Q_b: blood flow rate; Q_d: dialysate flow rate; TDM: therapeutic drug monitoring