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A descriptive pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime-avibactam for treating DTR gram-negative infections in a case series of critically ill patients undergoing continuous veno-venous haemodiafiltration (CVVHDF)

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ABSTRACT

Purpose: To explore pharmacokinetic/pharmacodynamic (PK/PD) profile of continuous infusion (CI) ceftazidime-avibactam for treating difficult-to-treat resistant Gram-negative (DTR-GN) infections in critical patients undergoing continuous venovenous haemodiafiltration (CVVHDF).

Materials and methods: Patients treated with CI ceftazidime-avibactam for DTR-GN infections during CVVHDF were retrospectively assessed. Ceftazidime and avibactam concentrations were measured at steady-state and the free fraction (fC_{ss}) was calculated. Total clearance (CL_{tot}) of both agents were calculated and the impact of CVVHDF intensity was assessed by linear regression. The joint PK/PD target of ceftazidime-avibactam was defined as optimal when both fC_{ss}/MIC≥4 for ceftazidime and $fC_{ss}/C_T > 1$ for avibactam were achieved. Relationship between ceftazidime-avibactam PK/PD targets and microbiological outcome was assessed.

Results: Eight patients with DTR-GN infections were retrieved. Median fC_{ss} were 84.5 (73.7–87.7 mg/L) for ceftazidime and 24.8 mg/L (20.7–25.8 mg/L) for avibactam. Median CL_{tot} was 2.39 L/h (2.05–2.96 L/h) for ceftazidime and 2.56 L/h (2.12–2.98 L/h) for avibactam. Median CVVHDF dose was 38.6 mL/h/kg (35.9–40.0 mL/kg/h). CL_{tot} were linearly correlated with CVVHDF dose ($r = 0.53$;$p = 0.03$, and $r = 0.64$;$p = 0.006$, respectively). The joint PK/PD targets were optimal granting microbiological eradication in all the assessable cases.

Conclusion: CI administration of 1.25–2.5 g q8h ceftazidime-avibactam may allow prompt attainment and maintenance of optimal joint PK/PD targets during high-intensity CVVHDF.

1. Introduction

The widespread diffusion of difficult-to-treat resistant (DTR) Gram-negative pathogens is a health concern, representing one of the main causes of hospital morbidity and mortality [1]. Ceftazidime-avibactam is a recently licensed beta-lactam/beta-lactamase inhibitor (BL/BLI) combination that is used to treat DTR Gram-negative infections caused by either *Klebsiella pneumoniae* carbapenemase (KPC)-producing or OXA-48-producing *Enterobacterales* and by carbapenem-resistant *Pseudomonas aeruginosa* [2].

Based on recent findings, aggressive pharmacokinetic/pharmacodynamic (PK/PD) targets up to 100%$T_{>4\text{-}8xMIC}$ should be pursued with beta-lactams for maximizing clinical efficacy and microbiological eradication, and minimizing the risk of resistance development [3,4]. Unfortunately, the application of continuous renal replacement therapy (CRRT) could make the PK/PD target attainment extremely challenging.

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Some real-world studies showed that critically ill renal patients receiving renal dosing adjustments of ceftazidime-avibactam while undergoing CRRT may have an increased risk of clinical and microbiological failure [5-7]. Indeed, renal dosing adjustments of ceftazidime-avibactam during CRRT might cause underexposure, since the magnitude of drug clearance (CL) may be extremely changeable depending on both patient-related and CRRT-related factors [8]. Unfortunately, which could be the most appropriate dosing regimen of ceftazidime-avibactam under different CRRT conditions has still to be defined. Up to date, the PK/PD profile of ceftazidime-avibactam during CRRT was assessed only in few cases under heterogeneous operative conditions and while receiving the drug over 2 h infusion [9-12]. Indeed, continuous infusion (CI) administration was shown to represent a valuable strategy for increasing the likelihood of attaining aggressive PK/PD targets with ceftazidime-avibactam [13-15].

The aim of this study was to describe the PK/PD analysis of CI ceftazidime-avibactam for treating DTR Gram-negative infections in a case series of critically ill renal patients undergoing homogeneous conditions of continuous veno-venous haemodiafiltration (CVVHDF).

2. Materials and methods

This was a retrospective case series of critically ill renal patients undergoing CVVHDF who were treated with CI ceftazidime-avibactam for documented DTR Gram-negative infections and underwent real-time therapeutic drug monitoring (TDM) of both ceftazidime and avibactam. Included patients were admitted at the general- or at the post-transplant- intensive care unit (ICU) of the IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy, in the period between 01st July 2022 and 31st January 2023. Demographic and clinical/laboratory data were retrieved for each case. Isolated pathogens with MIC values for ceftazidime-avibactam, type/site of infection, ceftazidime-avibactam dosage, treatment duration, and eventual combination therapy with other antibiotics active against DTR Gram-negatives were collected. CVVHDF settings (namely 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 residual renal function were collected at each TDM assessment. Total effluent flow rate was defined according to the following equation: pre-filter replacement fluid rate + post-filter replacement fluid rate + net removal rate + PBP fluid rate + Q_d. CVVHDF dose was calculated by normalizing the total effluent flow rate per body weight. At each TDM assessment, total CL (CL_{tot}) of both ceftazidime and avibactam were calculated according to the following formula: CL_{tot} (L/h) = infusion rate (mg/h) / C_{ss} (mg/L).

The types of infection were defined according to the following standard criteria: documented bloodstream infection (BSI) was defined as the isolation of a DTR Gram-negative pathogen from blood cultures; documented ventilator-associated pneumonia (VAP) was defined as the isolation of a DTR Gram-negative pathogen with a bacterial load $\geq 10^4$ CFU/mL in the bronchoalveolar lavage (BAL) fluid culture after >48 h from endotracheal intubation and start of mechanical ventilation; documented intrabdominal infection (IAI) was defined as the isolation of a DTR Gram-negative pathogen from the peritoneal fluid [16,17].

Antimicrobial susceptibility of ceftazidime-avibactam was tested by broth microdilution (panel provided by Merlin Diagnostika GMBH, Bornheim-Hersel, Germany). The tested MIC values for ceftazidime ranged from 1 to 64 mg/L in presence of a fixed target avibactam concentration (C_T) of 4 mg/L. Molecular analysis of DTR Gram-negative isolates was performed. Identification of the specific carbapenemase type (IMP, VIM, NDM, KPC, OXA-48) was detected by means of multiplex immunochromatographic assay NG test CARBA 5 (NG Biotech, Guipry-Messac, France). MIC values of ceftazidime-avibactam were interpreted according to the EUCAST guidelines [18], and resistance was defined as >8 mg/L.

Ceftazidime-avibactam was prescribed at the discretion of the treating physician or infectious disease consultant according to the current clinical practice guidelines implemented at the IRCCS Azienda Ospedaliero-Universitaria of Bologna. Treatment was started with a loading dose (LD) of 2.5 g over 2 h infusion followed by an initial maintenance dose (MD) of 2.5 g q8h administered by CI then optimized by means of TDM. For granting properly CI, aqueous solutions were reconstituted every 8 h and infused over 8 h due to stability restrictions [19].

Blood samples for measuring ceftazidime and avibactam steady-state concentrations (C_{ss}) were collected firstly after at least 24 h from starting CVVHDF, and then reassessed whenever feasible. Total ceftazidime and avibactam serum concentrations were determined by means of a validated liquid chromatography-tandem mass spectrometry method [20].

Only total ceftazidime and avibactam concentrations were measured. Considering that the plasma protein binding of ceftazidime and avibactam reported in the literature was 10% and 7%, respectively [21], the free fraction (f) was calculated by multiplying total ceftazidime and avibactam C_{ss} by 0.90 and 0.93, respectively. The percentage of time with concentrations above the MIC was selected as PD parameter of ceftazidime efficacy and expressed as fC_{ss}/MIC ratio. The percentage of time with avibactam concentrations above the C_T was selected as PD parameter of avibactam efficacy and expressed as fC_{ss}/C_T ratio. The primary goal was the attainment of a joint PK/PD target of ceftazidime-avibactam. This was defined as optimal when both fC_{ss}/MIC ratio of ceftazidime was ≥4 (equivalent to 100% $fT_{>4 \times MIC}$) and fC_{ss}/C_T ratio of avibactam was >1 (equivalent to 100% $fT > C_T$ of 4.0 mg/L), quasi-optimal if only one of the two thresholds was achieved, and suboptimal if none of the two thresholds was achieved [15]. Ceftazidime-avibactam dosing adjustments were provided on the basis of our current clinical practice, as previously reported [3,22].

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 ceftazidime-avibactam treatment, as previously reported [5]. Resistance development was defined as an increase of the ceftazidime-avibactam MIC against the clinical isolate beyond the EUCAST clinical breakpoint of susceptibility. Primary outcome was microbiological eradication, defined as the absence of the index pathogens from the primary site of infection (documented in blood, BAL, and/or peritoneal fluid cultures depending on case-by-case) in at least two subsequent assessments. Secondary outcomes included 30-day mortality rate and occurrence of adverse events (AEs).

Continuous data were presented as median and interquartile range (IQR), whereas categorial variables were expressed as count and percentage. The impact of CVVHDF dose intensity on CL_{tot} of both ceftazidime and avibactam was assessed by linear regression, and the Pearson's r value was calculated. P values <0.05 were considered statistically significant. 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).

3. Results

Overall, a total of 8 critically ill patients undergoing CVVHDF received CI ceftazidime-avibactam for the treatment of documented DTR Gram-negative infections during the study period (Table 1). Median (IQR) age was 47.5 (41–59) years with a male preponderance (75%). Three out of 8 patients were solid organ transplant recipients, and all underwent invasive mechanical ventilation and required haemodynamic support with vasopressors. All but one patient had normal renal function at baseline and developed sepsis-associated AKI requiring CVVHDF support. Patient #5 had a history of chronic kidney disease, and needed CVVHDF support in the early post-renal transplant period because of renal graft dysfunction.

CVVHDF was always performed by means of Prisma Flex System equipped with an AN69 high-flux ST-150 filter membrane. Operative

Table 1
Demographics and clinical features of critically ill patients undergoing continuous renal replacement therapy treated with continuous infusion ceftazidime-avibactam.

ID case	Age /Sex	Underlying disease	Pathogen	MIC (mg/L)	Type of Infection	CFZ/AVI Initial Dose	Dosing adjustment while on CVVHDF	Average CFZ *f*Css (mg/L)	Average AVI *f*Css (mg/L)	CFZ *f*Css/MIC ratio	AVI *f*Css/C_T ratio	Joint PK/PD target	CFZ/AVI treatment duration	CVVHDF treatment duration while on CAZ-AVI	Combo therapy	ME BSI	ME VAP/IAI	30-day mortality
#1	62/ M	Septic shock	OXA-48-producing Kp	1	VAP	2.5g q8h CI	1.25 g q8h CI°	85.5	24.8	85.5	6.2	Optimal	13	12	Fosfomycin	//	Yes (VAP)	No
#2	41/ M	OLT	OXA-48-producing Kp	2	BSI + IAI	2.5g q8h CI	1.25 g q8h CI	58.5	14.2	29.3	3.5	Optimal	21	14	No	Yes	Yes (IAI)	No
#3	75/ M	Septic shock	DTR-PA	2	BSI + VAP	2.5g q8h CI	No*	94.3	25.7	47.2	6.4	Optimal	10	5	No	Yes	Yes (VAP)	No
#4	41/ F	Acute-on-chronic liver failure	KPC-producing Kp	2	BSI + VAP	2.5g q8h CI	No**	74.3	28.7	37.1	7.2	Optimal	3	3	No	Yes	NA**	Yes
#5	58/ M	Renal transplant recipient	KPC-producing Kp	8	BSI	2.5g q8h CI	No	85.5	24.8	10.7	6.2	Optimal	6	5	Tigecycline	Yes	//	No
#6	54/ M	Acute-on-chronic liver failure	OXA-48-prdocuing *E. coli*	2	BSI + VAP	2.5g q8h CI	No**	83.5	22.7	41.8	5.7	Optimal	5	4	No	Yes	NA**	Yes
#7	27/ F	Acute myocarditis	DTR-PA + Carbapenem-resistant *E. cloacae*	2	BSI + VAP	2.5g q8h CI	No*	99.6	26.1	49.8	6.5	Optimal	15	5	No	Yes	Yes (VAP)	No
#8	41/ M	Bowel perforation in OLT	OXA-48-producing Kp	2	IAI	2.5g q8h CI	1.25 g q8h CI	71.9	14.9	36.0	3.7	Optimal	13	10	No	//	Yes (IAI)	No

AVI: avibactam; BSI: bloodstream infection; CAZ-AVI: ceftazidime-avibactam CFZ: ceftazidime; CI: continuous infusion; C_{ss}: steady-state concentrations; C_T: threshold concentration; DTR: difficult-to-treat resistance; IAI: intrabdominal infection; Kp: *Klebsiella pneumoniae*; ME: microbiological eradication; NA: not assessable; OLT: orthotopic liver transplantation; PA: *Pseudomonas aeruginosa*; PK/PD: pharmacokinetic/pharmacodynamic; VAP: ventilator-associated pneumonia. Green box: microbiological eradication; red box: microbiological failure. ° At first TDM assessment, CAZ-AVI dosage was confirmed. Dosing reduction was recommended after the second TDM assessment; * CVVHDF discontinuation; ** Not assessable: in case #4 because of switch to meropenem-vaborbactam for treating KPC-related VAP, and in case #6 due to CFZ/AVI withdrawal because of clinical worsening and implementation of compassionate care. Dosing reduction to 1.25 g q8h CI was recommended but TDM reassessment was not performed due to CAZ-AVI discontinuation. // means not applicable.

conditions applied at time of each TDM assessment are summarized in Table 2. Median (IQR) Q_b and total effluent flow rate were 150 mL/min (130–150 mL/min) and 2200 mL/h (1,835–2955 mL/h), respectively. Median (IQR) CVVHDF dose was 38.6 mL/kg/h (35.9–40.0 mL/kg/h). Four patients (50%) had some residual diuresis with a median (IQR) 24-h urinary output of 200 mL (50–537.5 mL).

Types of infection were BSI plus VAP in four cases, BSI plus IAI, primary BSI, VAP, and IAI in one case each. Causative pathogens were carbapenemase-producing OXA-48-producing *Klebsiella pneumoniae* in three cases, KPC-producing *Klebsiella pneumoniae* in two cases, DTR—*P. aeruginosa* in two cases (with co-isolation of AmpC-producing *Enterobacter cloacae* in one case) and OXA-48-producing *Escherichia coli* in one case. All clinical isolates were fully susceptible to ceftazidime-avibactam, with MIC values ranging from 1 to 8 mg/L.

All patients were initially treated with full MD of 2.5 g q8h over 8 h CI ceftazidime-avibactam. The median (IQR) duration of treatment was 11.5 days (5.75–13.5 days), and the median (IQR) duration of CVVHDF treatment while on ceftazidime-avibactam was 5 days (4.75–10.5 days). Ceftazidime-avibactam monotherapy was administered in 6 out of 8 patients (75%), whereas in the other two it was co-administered with fosfomycin in one case and with tigecycline in the other one.

At first TDM assessment, full dosing regimen of ceftazidime-avibactam was confirmed in 2 out of 8 patients (25%), whereas a decrease to 1.25 g q8h over 8 h CI was recommended in the other 6 cases. In these latter, TDM reassessment after dosing reduction was feasible while on CVVHDF only in two cases, as in the others discontinuation of CVVHDF (2 cases; one maintained the 1.25 g q8h CI dose until end of treatment, and the other need a further dosing reduction to 0.625 g q8h because of persistence of severe renal dysfunction) or of ceftazidime-avibactam (switch to meropenem-vaborbactam in one patient, and implementation of compassionate care in the other) was applied. Median (IQR) average fC_{ss} were 84.5 mg/L (73.7–87.7 mg/L) for ceftazidime and 24.8 mg/L (20.7–25.8 mg/L) for avibactam. Median (IQR) CL_{tot} of ceftazidime and avibactam were 2.39 L/h (2.05–2.94 L/h) and 2.56 L/h (2.22–2.96 L/h), respectively. CVVHDF dose intensity was significantly associated with CL_{tot} of both ceftazidime ($r = 0.53$; $p = 0.03$) and avibactam ($r = 0.64$; $p = 0.006$) (Fig. 1).

The joint PK/PD targets of ceftazidime-avibactam were optimal in all of the cases. Microbiological eradication was documented from all the sites of infection in the six patients who had fulfilled the treatment course (2 with BSI plus VAP, and one case each with BSI plus IAI, BSI, VAP, and IAI). In the other two patients having BSI plus VAP, microbiological eradication was assessable and confirmed before ceftazidime-avibactam discontinuation only from blood. In no case resistance development to ceftazidime-avibactam emerged. No ceftazidime-avibactam-related adverse event emerged during treatment. The overall 30-day mortality rate was 25%.

4. Discussion

To the best of our knowledge, this is the first study that described the pharmacokinetics and the pharmacodynamics of ceftazidime-avibactam administered by CI for treating DTR Gram-negative infections in a cases series of critically ill renal patients undergoing CVVHDF.

Data on ceftazidime-avibactam PK during CRRT were just previously reported in some patients [9-12], only one of whom underwent CVVHDF [10]. Interestingly, the median CL_{tot} of both ceftazidime and avibactam were 1.5-fold higher in our case series compared to those reported in the previous case (2.39 vs. 1.54 L/h and 2.56 L/h vs. 1.45 L/h, respectively) [10]. These augmented CLs may be explained by two reasons, namely the quite high CVVHDF dose intensity applied in several cases and the presence of residual renal function in some cases. Notably, the median CVVHDF dose intensity implemented in our case series (38.6 mL/kg/h) was 1.3-fold higher than in the case reported previously by Soukup et al. (29.2 mL/kg/h) that had no residual renal function [10].

Ceftazidime–avibactam is extensively removed by CRRT, especially whenever high total effluent flow rates are applied and/or the patient has some degree of residual renal function [8]. The significant relationship found between the CVVHDF dose intensity and the CL_{tot} of both ceftazidime and avibactam may support this contention and is consistent with what just previously observed with other beta-lactams [23-25]. Consequently, implementing renal dosing adjustments of ceftazidime-avibactam during CRRT may cause suboptimal PK/PD target attainment, particularly when administered by intermittent infusion over 2-h, and CRRT was shown to be a risk factor for treatment failure and resistance among patients with carbapenem-resistant *Enterobacterales* infections [5-7].

Some studies showed that the adoption of alternative dosing strategies with beta-lactams, namely prolonged/continuous infusion, may be helpful for attaining aggressive PK/PD targets in patients undergoing CRRT and having residual renal function [26,27]. Our findings suggest that in this scenario administering ceftazidime-avibactam by CI may

Table 2
CVVHDF (equipped with AN-69 ST150 filter membrane) operative conditions and ceftazidime-avibactam CL at each TDM assessment.

ID case	Weight (Kg)	Q_b (mL/min)	PBP rate (mL/h)	Q_d (mL/h)	Pre/Post-dilution	Replacement fluid rate (mL/h)	Net removal rate (mL/h)	CVVHDF dose intensity (mL/kg/h)	Residual diuresis (mL/24 h)	Total effluent flow rate (mL/h)	CFZ CL (L/h)	AVI CL (L/h)
#1	85	150	1250	500	0/100	1000	200	34.8	0	2955	3.88	2.96
#1	85	150	1250	500	0/100	300	180	26.3	0	2235	1.99	1.94
#2	50	150	1250	400	0/100	200	150	40.0	1000	2000	2.97	2.73
#2*	50	180	1083	400	0/100	200	150	36.7	0	1835	2.77	3.00
#2*	50	180	500	1000	0/100	300	50	34.3	0	1850	1.94	2.02
#2*	50	150	1250	500	0/100	400	50	39.2	0	2200	1.89	2.58
#3	87	150	1250	700	0/100	400	80	27.9	0	2430	2.39	2.26
#4	55	150	1250	700	0/100	1000	80	54.2	610	3030	3.03	2.02
#5	68	150	1250	700	0/100	1000	50	44.1	0	3000	2.38	1.78
#5	68	150	1250	700	0/100	1000	50	44.1	0	3000	2.94	3.43
#6	75	130	1083	800	0/100	1000	80	39.5	40	2965	2.69	2.56
#7	53	150	1083	500	0/100	200	120	35.9	0	1905	2.26	2.22
#8	45	100	833	500	0/100	300	100	38.6	0	1735	2.27	2.51
#8	45	100	833	500	0/100	300	100	38.6	80	1735	2.77	3.14
#8*	45	100	833	500	0/100	300	0	36.3	0	1635	1.81	2.22
#8*	45	100	833	500	0/100	300	50	37.4	320	1685	2.05	2.89
#8*	45	150	1250	500	0/100	1000	80	62.3	40	2830	3.63	6.13

AVI: avibactam; CFZ: ceftazidime; CL: clearance; CVVHDF: continuous venovenous haemodiafiltration; PBP: pre-blood pump flow rate; Q_b: blood flow rate; Q_d: dialysate flow rate; TDM: therapeutic drug monitoring.

* TDM assessment performed at the reduced dosage of 1.25 g q8h administered by continuous infusion.

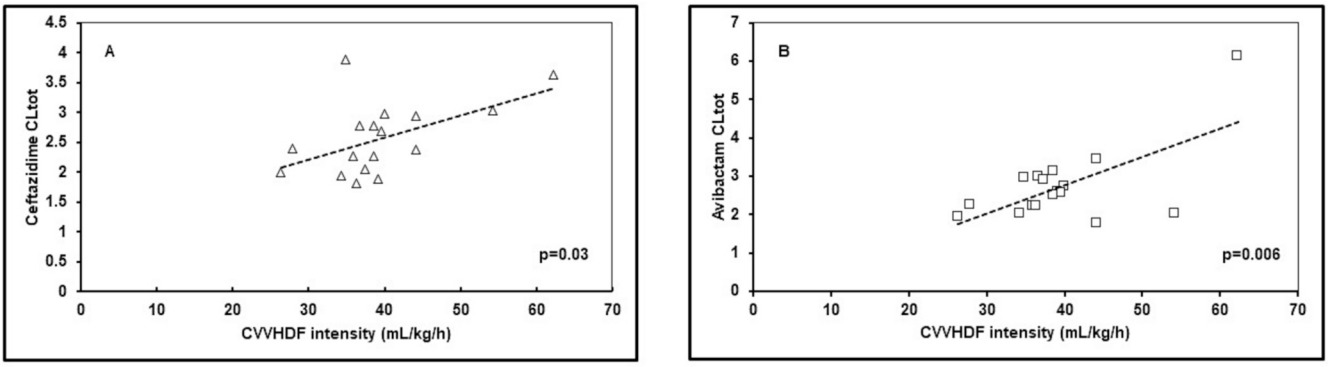

Fig. 1. Relationship between CVVHDF dose intensity and CL_{tot} of ceftazidime (panel A) and avibactam (panel B).

allow the attainment of optimal joint PK/PD targets even when applying high-intensity CVVHDF, thus overcoming the issue related to a CL_{tot} increase under these circumstances. In our experience, starting treatment with full-dose ceftazidime-avibactam by CI allowed prompt attainment of optimal joint PK/PD targets within the first 72 h. The real-time TDM-guided approach allowed to maintain the desired joint PK/PD targets even when reducing ceftazidime-avibactam dosing to 1.25 g q8h over 8-h. This approach granted microbiological eradication of DTR Gram-negative infections in all assessable patients undergoing CVVHDF, with much lower failure rate compared to previous studies [5,6].

Overall, the findings highlight once more the importance that strategies based on a "patient-center" approach and administration by CI may have in maximizing the attainment of aggressive PK/PD targets in patients undergoing CRRT [8,13]. This means that for optimizing antimicrobial treatment in patients undergoing CRRT it does not suffice to consider the intrinsic physicochemical properties of the drug, but it is needed to take into account also the specific CRRT settings, the eventual presence of the patient's residual renal function, the site of infection, and the MIC of the isolated pathogen [8]. In regard to ceftazidime-avibactam, a loading dose of 2.5 g over 2 h was shown to grant initial adequate concentrations but the subsequent maintenance doses by CI should depend on the RRT dose and on the residual renal function of the patient, and should be hopefully TDM-guided. In centers where real-time TDM is unfeasible, we believe that, by taking into account that in our case series the joint PK/PD targets were even more than optimal during the 2.5 q8h CI dosing regimen, a maintenance dosing regimen of 1.25 g q8h CI could be a valuable approach for ensuring optimal joint PK/PD targets against susceptible pathogens with an MIC value for ceftazidime-avibactam up to the EUCAST clinical breakpoint of 8 mg/L.

Our study has some limitations. The retrospective monocentric study design and the limited sample size should be acknowledged. Only total ceftazidime-avibactam concentrations were measured, and the free moieties were only estimated according to data retrieved in health volunteers, which potentially limits its extrapolation to critically ill patients affected by significant pathophysiologic alterations. Conversely, the real-life experience exploring firstly the PK/PD target attainment and microbiological outcome of CI ceftazidime-avibactam in the scenario of DTR Gram-negative infections under very homogeneous CVVHDF operative conditions is a point of strength.

5. Conclusions

In conclusion, our findings found a significant correlation between CVVHDF dose intensity and ceftazidime-avibactam CL_{tot}. Administering full-dose CI ceftazidime-avibactam and optimizing exposure by means of a real-time TDM-based approach may allow prompt attainment and maintenance of very aggressive joint PK/PD targets against DTR Gram-negative infections in critically ill patients undergoing CVVHDF, with microbiological eradication in all assessable cases. Large prospective clinical studies are warranted for confirming our findings.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethical committee [No. EM 232-2022_308/2021/Oss/AOUBo on 16 March 2022].

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CRediT authorship contribution statement

Milo Gatti: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Matteo Rinaldi:** Investigation. **Paolo Gaibani:** Investigation. **Antonio Siniscalchi:** Investigation, Writing – review & editing. **Tommaso Tonetti:** Investigation, Writing – review & editing. **Maddalena Giannella:** Writing – review & editing. **Pierluigi Viale:** Writing – review & editing, Funding acquisition. **Federico Pea:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

MG has received personal fees from Angelini and Shionogi, outside the submitted work. PV has served as a consultant for bioMérieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on the speaker's bureaus for Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma, and Pfizer, outside the submitted work. FP reports personal fees from Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis, Shionogi, Thermo Fisher, and Accelerate Diagnostics, outside the submitted work; has participated in speaker's bureau for Accelerate Diagnostics, Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis, Shionogi, Thermo Fisher, and as consultant for Angelini, Basilea Pharmaceutica, Gilead, MSD, Pfizer, Shionogi, outside the submitted work. The other authors report no potential conflicts of interest for this work.

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