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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics, Pharmacodynamics, and Dose Optimization of Cefiderocol during Continuous Renal Replacement Therapy

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Abstract

Background The need for continuous renal replacement therapy (CRRT) in critically ill patients with serious infections is associated with clinical failure, emergence of resistance, and excess mortality. These poor outcomes are attributable in large part to subtherapeutic antimicrobial exposure and failure to achieve target pharmacokinetic/pharmacodynamic (PK/PD) thresholds during CRRT. Cefiderocol is a novel siderophore cephalosporin with broad in vitro activity against resistant pathogens and is often used to treat critically ill patients, including those receiving CRRT, despite the lack of data to guide dosing in this population.

Objective The aim of this study was to evaluate the PK and PD of cefiderocol during in vitro and in vivo CRRT and provide optimal dosing recommendations.

Methods The PK and dialytic clearance of cefiderocol was evaluated via an established in vitro CRRT model across various modes, filter types, and effluent flow rates. These data were combined with in vivo PK data from nine patients receiving cefiderocol while receiving CRRT from phase III clinical trials. Optimal dosing regimens and their respective probability of target attainment (PTA) were assessed via an established population PK model with Bayesian estimation and 1000-subject Monte Carlo simulations at each effluent flow rate.

Results The overall mean sieving/saturation coefficient during in vitro CRRT was 0.90 across all modes, filter types, effluent flow rates, and points of replacement fluid dilution tested. Adsorption was negligible at 10.9%. Three-way analysis of variance (ANOVA) and multiple linear regression analyses demonstrated that effluent flow rate is the primary driver of clearance during CRRT and can be used to calculate optimal cefiderocol doses required to match the systemic exposure observed in patients with normal renal function. Bayesian estimation of these effluent flow rate-based optimal doses in nine patients receiving CRRT from the phase III clinical trials of cefiderocol revealed comparable mean (± standard deviation) area under the concentration-time curve values as patients with normal renal function (1709 ± 539 mg·h/L vs. 1494 ± 58.4 mg·h/L; $p = 0.26$). Monte Carlo simulations confirmed these doses achieved >90% PTA against minimum inhibitory concentrations ≤4 mg/L at effluent flow rates from 0.5 to 5 L/h.

Conclusion The optimal dosing regimens developed from this work have been incorporated into the prescribing information for cefiderocol, making it the first and only antimicrobial with labeled dosing for CRRT. Future clinical studies are warranted to confirm the efficacy and safety of these regimens.

1 Introduction

Serious infections due to difficult-to-treat (DTR) Gram-negative pathogens are responsible for significant morbidity, mortality, and excess healthcare costs [1–4]. Risk factors for infection due to these pathogens, specifically those that are carbapenem-resistant (CR), are well described and almost always include intensive care unit (ICU) admission, sepsis, renal dysfunction, and/or renal replacement therapy (RRT) [5–7]. In addition to acquisition risk, these same factors are also frequently associated with poor clinical outcomes. Recent studies of extended-spectrum β-lactamase

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Key Points

This is the first study to evaluate the pharmacokinetics (PK) of cefiderocol during continuous renal replacement therapy (CRRT) and to provide optimal dosing recommendations for these patients through integration of in vitro modeling, clinical PK, and in silico probability of target attainment (PTA) analyses. The results of this work have been incorporated into the revised prescribing information for cefiderocol, making it the first and only antimicrobial agent with US FDA labeled dosing for CRRT.

Thorough statistical analysis of in vitro CRRT data supported optimal dosing regimens of cefiderocol based only on effluent flow rate and simplified into four dosage levels. When applied to nine patients undergoing CRRT during phase III trials, these optimal effluent flow rate-based doses resulted in free plasma concentrations ≥8 mg/L in all patients during the dosing interval.

Monte Carlo simulation at each effluent flow rate demonstrated that the proposed optimal dosing regimens achieved >90% PTA at minimum inhibitory concentration (MIC) values ≤4 mg/L across effluent flow rates from 0.5 to 5 L/h. Therefore, the optimal CRRT dosing regimens developed herein should provide adequate cefiderocol exposure against cefiderocol susceptible, meropenem non-susceptible Enterobacterales, *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Stenotrophomonas maltophilia.*

(ESBL)-producing and CR Enterobacterales demonstrate that approximately 20% of patients require RRT at baseline and that the need for RRT is independently associated with clinical failure, development of resistance, and mortality [8–12]. Although mortality in this population is likely multifactorial in etiology, pharmacokinetic (PK) alterations in patients receiving continuous RRT (CRRT) have been shown to lead to suboptimal antimicrobial exposures and worse clinical outcomes, especially for highly renally eliminated agents with time-dependent pharmacodynamic (PD) properties such as the β-lactams [13]. Unfortunately, robust PK data in patients receiving CRRT are scarce and often include few critically ill patients on many different modes of CRRT with heterogeneous flow rates, filter types, dosing, and sampling schemes, making it difficult to draw meaningful conclusions [14–18]. As such, in vitro CRRT models are useful for generating precise assessments of sieving/saturation coefficients (SC/SA) across different modes, flow rates, filter types, and points of dilution while eliminating the variability introduced by the patient. These models can be used to guide dosing in the absence of, or when combined with, in vivo data, and have been shown to approximate in vivo total body clearance (CL_T) [19], allowing for data derived from in vitro investigations to be utilized in estimating clinical dosing regimens [20].

Cefiderocol is a novel catechol-substituted siderophore cephalosporin antibiotic with potent in vitro activity against clinically relevant DTR Gram-negative bacteria, including CR strains and those producing Ambler class A–D β-lactamases, porin channel alterations, and efflux pump overproduction [21]. Given this broad spectrum of activity, cefiderocol is often used for the treatment of critically ill patients with complex infections due to DTR pathogens, including those receiving CRRT [22]. This is evidenced by the 74 cases treated via the compassionate use program [23], and supported by the Infectious Diseases Society of America Antimicrobial Resistant Treatment Guidance for Gram-Negative Bacterial Infections as an alternative treatment agent [24]. Unfortunately, there are currently no PK data to inform dosing of cefiderocol during CRRT despite that its physiochemical properties (752.2 Da, 40–60% protein binding, apparent volume of distribution [V_d] 18 ± 3.4 L, 98.6% renal excretion) suggest it is likely to be readily dialyzable [25]. As such, the objective of this study was to evaluate the PK of cefiderocol during in vitro and in vivo CRRT in patients treated with cefiderocol while receiving CRRT during the phase III clinical program to provide guidance on optimal dosing in this population.

2 Materials and Methods

2.1 In Vitro CRRT

In vitro CRRT was simulated using a Prismaflex 7.2 control unit (Baxter Healthcare Corporation, Deerfield, IL, USA) in continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodialysis (CVVHD) modes using fresh 1.4 m^2 polyarylethersulfone (PAES; Prismaflex HF1400) and 1.5 m^2 acrylonitrile (AN69; Prismaflex M150) hemofilter sets for each experiment. One liter of heparinized (20 units/mL; West-Ward Pharmaceutical Corp., Eatontown, NJ, USA) bovine plasma containing a potassium oxalate/sodium-fluoride stabilizer (Lampire Biological Labs, Pipersville, PA, USA) was heated to 37 °C in a water bath and stirred continuously. The measured albumin content of the potassium oxalate/sodium-fluoride bovine plasma was 3.74 g/dL (Biologic Resources Laboratory, University of Illinois at Chicago, Chicago, IL, USA), within range of previous in vivo studies of patients undergoing CRRT [26]. The Prismaflex circuit was initially primed with 186 mL (HF1400) or 189 mL (M150) of 0.9% sodium chloride per the manufacturer's operating instructions [27, 28]. Prior to

the start of each experiment, plasma was then allowed to circulate throughout the system for at least 10 min to permit adequate exposure of the hemofilter to proteins. The plasma flow rate was fixed at 200 mL/min for all experiments, while CVVH replacement fluid (PrismaSOL® BGK 2/0; Baxter Healthcare Corporation) and CVVHD dialysate (PrismaSATE® BGK 2/0; Baxter Healthcare Corporation) rates of 2 and 4 L/h were tested with each filter type. During CVVH at 2 L/h, replacement fluid was added at 100% pre-filter, 100% post-filter, and at 50% pre-/50% post-filter. During CVVH at 4 L/h, replacement fluid was added at 50% pre-/50% post-filter. All experiments were performed in at least duplicate in each mode, at each rate, and with each filter for a total of 24 experiments (excluding adsorption experiments).

Cefiderocol (Fetroja®, S-649266, GSK2696266 sodium drug product, Shionogi & Co., Ltd, Osaka, Japan) was reconstituted from vials with sterile water for injection per manufacturer's instructions. Once reconstituted, cefiderocol was added as a bolus to the central plasma reservoir at a concentration approximately equal to the mean peak serum concentration (C_{max}) observed in adults after a 2 g dose infused over 3 h (approximately 90 mg/L) [29] and allowed to equilibrate for at least 1 min prior to sampling. Bovine plasma was also supplemented with urea (Sigma-Aldrich, St Louis, MO, USA) at a concentration of 75 mg/dL and allowed to equilibrate to serve as a control solute.

After equilibration, serial pre-filter plasma samples were collected in K_2 EDTA vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) immediately (0 min) and at 10, 20, 30, 60, and 90 min, with simultaneous post-filter plasma and effluent samples also collected at 10 and 30 min. Plasma and effluent samples were frozen at −80 °C within 30 min of collection until analysis. To ensure sample stability, prior to freezing, plasma and effluent samples were diluted 1:1 with a 0.2 mol/L ammonium acetate buffer (pH 5 ± 0.2) made in-house.

2.2 Adsorption

To evaluate potential adsorption of cefiderocol to the hemofilters, the initial CRRT model was modified to create a closed-circuit system. Effluent was rerouted to the central plasma reservoir and 0.9% normal saline was exogenously pumped into the effluent bag via a Masterflex® Peristaltic pump (Cole-Parmer, Vernon Hills, IL, USA) at the same rate to prevent the Prismaflex system from aborting due to the patient blood loss/gain alarm. Serial plasma samples were drawn from the central reservoir at 0, 10, 20, 30, 45, 60, 90, 105, 120, 150, and 180 min and frozen at −80 °C within 30 min of collection until analysis. A total of six adsorption experiments were performed incorporating various CRRT modes, filters, and flow rates.

2.3 Protein Binding

To assess cefiderocol protein binding in bovine plasma, pre-filter samples taken at 0, 10, 30, and/or 60 min after drug equilibration from four in vitro CRRT experiments along with four contrived samples were immediately centrifuged in a fixed-angle rotor at 1800 × *g*, 37 °C, 15 min using a Centrifree® Ultrafiltration Device (Merck Millipore Ltd, Tullagreen, Carrigtwohill, County Cork, Ireland). An equal volume of 0.2 mol/L ammonium acetate buffer (pH 5 ± 0.2) was added into an aliquot of the filtrate and the mixture was frozen at −80 °C within 30 min until analysis.

2.4 In Vivo Continuous Renal Replacement Therapy (CRRT)

Nine of the 12 patients from the phase III nosocomial pneumonia (APEKS-NP; $n = 3$) and CR Gram-negative infection (CREDIBLE-CR; $n = 6$) studies undergoing CRRT during cefiderocol administration were included in this analysis. Three patients were excluded due to a lack of information on the CRRT effluent flow rate that was necessary to determine the optimal dosing regimen. Full study details have been published previously [30, 31]. The administered dose of cefiderocol was 1 g every 12 h as a 3-h infusion for patients undergoing CVVH and 1.5 g every 12 h as a 3-h infusion for patients undergoing CVVHD or continuous veno-venous hemodiafiltration (CVVHDF). As no data were available at the time of study design, the cefiderocol dosing regimens used for patients receiving CRRT were developed based on the clearance of cefepime during CRRT, given its structural similarity to cefiderocol (accounting for differences in protein binding) and the clearance of cefiderocol during intermittent hemodialysis [32, 33]. Blood samples for PK analysis were obtained pre-filter at a site contralateral to the cefiderocol infusion at steady-state on day 3 prior to the infusion (0 h) and at 1, 3, and 4 h after the start of infusion.

2.5 Bioanalytical Procedures

Concentrations of cefiderocol and urea in bovine plasma and dialysis solutions were measured via validated liquid chromatography-tandem mass spectrometry (Keystone Bioanalytical, North Wales, PA, USA) [34]. The calibration range of the cefiderocol assay was linear from 0.2 to 200 mg/L ($r \geq 0.999$). The precision and accuracy acceptance criteria for the quality control samples and calibration standards were ≤15% CV and ±15% relative error determined at each concentration level. The mean percentage recovery of cefiderocol from bovine plasma was 95.7% and all precision and acceptance criteria were met, while the mean percentage recovery of cefiderocol from dialysis solutions was 96.2% and all precision and acceptance criteria were met.

Concentrations of cefiderocol in human plasma were quantified via validated liquid chromatography-tandem mass spectrometry as previously described [35].

2.6 Pharmacokinetic Analysis

2.6.1 In Vitro CRRT

PK parameters for cefiderocol were estimated from observed pre-filter plasma concentrations via non-compartmental analysis in Phoenix WinNonlin version 8.2 (Certara USA Inc., Princeton, NJ, USA). Reported parameters included C_{max}, half-life ($t_{½}$), V_d, clearance (designated CL_{CRRT}), area under the concentration-time curve (AUC) from time zero to infinity (AUC_{∞}) and AUC from time zero to the last measurable concentration (AUC_{last}) as determined via the linear up/log down method. As in vitro experiments were run for 1.5 h, AUC_{last} was multiplied by 16 to demonstrate proportional AUC from time zero to 24 h (AUC_{24}) values. The SC and SA of cefiderocol and urea were calculated as follows [36]:

- sieving coefficient (SC) = (2 * C_{uf}) / (C_{pre} + C_{post})
- saturation coefficient (SA) = (2 * $C_{dialysate}$) / (C_{pre} + C_{post})

where C_{uf} is the concentration in the ultrafiltrate, C_{pre} is the concentration from the pre-filter sampling port, $C_{dialysate}$ is the concentration in the dialysate, and C_{post} is the concentration from the post-filter sampling port [36–38].

Adsorption was calculated as the difference between the total amount of cefiderocol added to the system and the total amount recovered in the dialysate and plasma after 180 min using the following equation at each sampling time point:

- Adsorption (%) = Σ1 − [(dose of cefiderocol added at time zero) / (concentration of cefiderocol * measured volume in central reservoir)] [39].

2.7 Dose Optimization

Optimal dosing was calculated to provide a mean AUC value equivalent to that achieved by the 139 cUTI/AP patients administered 2 g every 8 h during the phase III APEKS-cUTI trial (1184 mg·h/L) [40] via the equation AUC = Total Daily Dose/CL_T. Clearance by CRRT in vitro (CL_{CRRT}) was substituted for renal CL (CL_R) and added to non-renal CL (CL_{NR}) to estimate CL_T. CL_{NR} was imputed as the average CL_{NR} from subjects included in the phase I renal impairment study (1.298 L/h), excluding the value from end-stage renal disease subjects receiving dialysis [41], and was assumed to be constant. Calculations were performed for CRRT effluent flow rates from 0.5 to 5 L/h, in 0.5 L/h increments, to generate total daily dose estimations, which were converted to optimal dosing regimens by rounding to the nearest 500 mg and diving into two to three daily doses to align with the labeled dosing of cefiderocol (including the recommended 3-h infusion) [42].

These optimal dosing regimens were then used to calculate the post hoc C_{max}, AUC, and plasma trough concentration (C_{trough}) for each of the nine CRRT patients. An established population PK model with Bayesian estimation was applied to their individual plasma cefiderocol concentration data to predict CL_T [35]. Dosing regimens were then assessed for their probability of target attainment (PTA) based on a $\%fT_{>MIC}$ target of ≥75% against minimum inhibitory concentration (MIC) values of 0.25–16 mg/L in log_2 dilutions using 1000-subject Monte Carlo simulations at each effluent flow rate. The target 75% $fT_{>MIC}$ was selected from animal infection models, as analysis of phase III data failed to identify a clear PK/PD clinical outcome relationship [35, 43]. For PTA analyses, CL_T was again obtained by adding in vitro CL_{CRRT} and CL_{NR} (CL_{NR} was simulated according to uniform distribution from 1.1 to 1.5 L/h [41]) given the minimal variability in CL_T observed in vivo secondary to the narrow range of doses and effluent flow rates employed. Steady-state PK were assumed and interindividual variability was set to that of the established population PK model. As body weight and albumin were significant covariates in the population PK model, they were assumed to be log-normally distributed, with a covariance of 30% each and set to the original population mean values of 72.6 kg and 2.8 g/dL, respectively. Free concentrations were estimated using an unbound fraction of 0.422 [44]. Monte Carlo simulations were performed using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD, USA) and R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria), as previously described [35].

2.8 Statistical Analysis

Data are presented as mean (± standard deviation [SD]) or with 95% confidence intervals (CIs), or as geometric mean and (CV%) unless otherwise specified. Continuous data were compared via Student's *t*-test or Mann–Whitney *U* test as appropriate. For in vitro data, one- and two-way analysis of variance (ANOVA) models with Tukey's post hoc test were built to evaluate significant differences in mean CL_{CRRT} according to CVVH point of dilution within and between each filter type. Three-way ANOVA models were then fit using CL_{CRRT} as the outcome to evaluate the interaction between CRRT mode, filter type, and effluent flow rate. ANOVA-generated means of CL_{CRRT} were then used to estimate optimal total daily doses of cefiderocol during CRRT. Finally, multiple linear regression via backwards stepwise analysis was used to correlate effluent flow rate with mean CL_{CRRT} while adjusting for covariates (CRRT

mode, filter type, point of dilution, and effluent flow rate) and predict optimal dosing regimens across effluent flow rates from 0.5 to 5 L/h. Model performance was assessed via the adjusted R^2 value, and collinearity was assessed via tolerance and variance inflation factors. A p-value ≤ 0.05 was considered statistically significant in the final model. All statistical analyses were performed using SPSS® version 26 (IBM Corporation, Armonk, NY, USA).

3 Results

3.1 In Vitro CRRT

Mean (±SD) pre-filter PK parameters of cefiderocol in bovine plasma during CRRT, as estimated via non-compartmental analyses, are summarized in Table 1, and respective concentration-time profiles are shown in Fig. 1. The mean (±SD) C_{max} value observed across the 24 experiments was 92.8 ± 7.24 mg/L, which was ≤3% different from the target value of 90 mg/L. Notably, CL_{CRRT} did not consistently scale exactly proportionally with effluent flow rate and increased 1.4- to 1.8-fold as effluent flow rate increased from 2 to 4 L/h. Overall, the PK were comparable between CRRT modes at the same flow rate. The mean (±SD) AUC_{24} during CVVH and CVVHD, respectively, at 2 L/h was 914.3 ± 97.3 mg·h/L and 906.7 ± 76.1 mg·h/L ($p = 0.89$) and at 4 L/h was 597.7 ± 53.8 mg·h/L and 626.5 ± 96.7 mg·h/L ($p = 0.62$).

Table 2 displays mean (±SD) SC and SA values for cefiderocol stratified by CRRT mode, filter type, effluent flow rate, and point of replacement fluid dilution. The mean cefiderocol SC during CVVH with the M150 filter was 0.855, and 0.984 with the HF1400 ($p = 0.019$), while mean SA during CVVHD was 0.781 with M150 and 0.940 with HF1400 ($p = 0.009$). The average SC across CVVH was 0.919, and SA across CVVHD was 0.860 ($p = 0.204$). The overall mean SC/SA for cefiderocol was 0.90 across all CRRT modes, filter types, effluent flow rates, and points of replacement fluid dilution tested. Mean (±SD) urea SC and SA values across all experiments were 1.06 ± 0.14 and 1.20 ± 0.07, respectively, and were comparable with previously established parameters obtained in analogous experimental conditions [45].

There were no significant differences in CL_{CRRT} during CVVH across any of the three points of dilution (100% pre-filter, 100% post-filter, or 50%/50% pre-/post-filter) regardless of the effluent flow rate tested or filter type used. Ignoring point of dilution, the three-way ANOVA for the effect of CRRT mode, filter type, and effluent flow rate on CL_{CRRT} demonstrated no significant two-way interactions between CRRT mode and filter ($p = 0.059$), filter and effluent flow rate ($p = 0.182$), or CRRT mode and effluent flow rate ($p = 0.340$). The three-way interaction between CRRT mode, filter, and effluent flow rate was also non-significant ($p = 0.051$), with an adjusted R^2 of 0.872. The estimated marginal means and 95% CI for CL_{CRRT} generated from

Table 1 Mean (±SD) bovine plasma pharmacokinetic parameters of cefiderocol during in vitro CRRT, determined via non-compartmental analyses

CRRT modality	C_{max} (mg/L)	$t_{½}$ (h)	V_d (L)	CL_{CRRT} (L/h)	$AUC_{∞}$ (mg·h/L)	AUC_{last} (mg·h/L)	AUC_{24} (mg·h/L)
CVVH				*HF1400*			
2 L/h, 50/50%	87.7 ± 5.59	0.54 ± 0.04	1.54 ± 0.06	1.98 ± 0.07	61.70 ± 0.56	52.90 ± 0.84	846.44 ± 13.52
2 L/h, 100/0%	97.2 ± 1.40	0.56 ± 0.01	1.35 ± 0.05	1.67 ± 0.08	70.19 ± 2.81	59.11 ± 2.60	945.84 ± 41.61
2 L/h, 0/100%	96.8 ± 5.94	0.48 ± 0.02	1.35 ± 0.15	1.97 ± 0.14	59.48 ± 1.09	53.13 ± 0.38	850.01 ± 6.00
4 L/h, 50/50%	96.7 ± 4.87	0.31 ± 0.01	1.38 ± 0.10	3.11 ± 0.34	37.78 ± 0.74	36.47 ± 0.45	583.57 ± 7.15
CVVHD							
2 L/h	88.0 ± 4.53	0.48 ± 0.03	1.30 ± 0.02	1.88 ± 0.16	63.89 ± 5.49	56.41 ± 3.81	902.61 ± 60.90
4 L/h	86.9 ± 3.04	0.29 ± 0.02	1.39 ± 0.18	3.36 ± 0.21	34.92 ± 0.95	34.04 ± 0.69	544.70 ± 11.01
CVVH				*M150*			
2 L/h, 50/50%	93.2 ± 18.20	0.49 ± 0.02	1.19 ± 0.39	1.68 ± 0.48	71.71 ± 14.13	62.25 ± 12.43	995.97 ± 198.89
2 L/h, 100/0%	99.8 ± 1.24	0.55 ± 0.05	1.27 ± 0.05	1.61 ± 0.07	72.96 ± 3.44	62.15 ± 4.34	994.41 ± 69.38
2 L/h, 0/100%	94.0 ± 9.90	0.49 ± 0.01	1.37 ± 0.01	1.94 ± 0.03	60.50 ± 4.43	53.32 ± 4.31	853.12 ± 68.98
4 L/h, 50/50%	90.6 ± 6.68	0.30 ± 0.02	1.35 ± 0.24	3.13 ± 0.34	39.36 ± 5.38	38.24 ± 5.53	611.86 ± 88.55
CVVHD							
2 L/h	85.8 ± 4.52	0.52 ± 0.04	1.32 ± 0.00	1.77 ± 0.15	65.32 ± 9.64	56.93 ± 7.29	910.87 ± 116.69
4 L/h	97.2 ± 8.27	0.36 ± 0.03	1.29 ± 0.14	2.50 ± 0.09	46.81 ± 2.63	44.27 ± 2.11	708.35 ± 33.77

SD standard deviation, *CRRT* continuous renal replacement therapy, C_{max} maximum concentration, $t_{½}$ half-life, V_d apparent volume of distribution, CL_{CRRT} clearance by CRRT, *AUC* area under the concentration-time curve, $AUC_{∞}$ AUC from time zero to infinity, AUC_{last} AUC from time zero to the last measurable concentration, AUC_{24} AUC from time zero to 24 h, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis

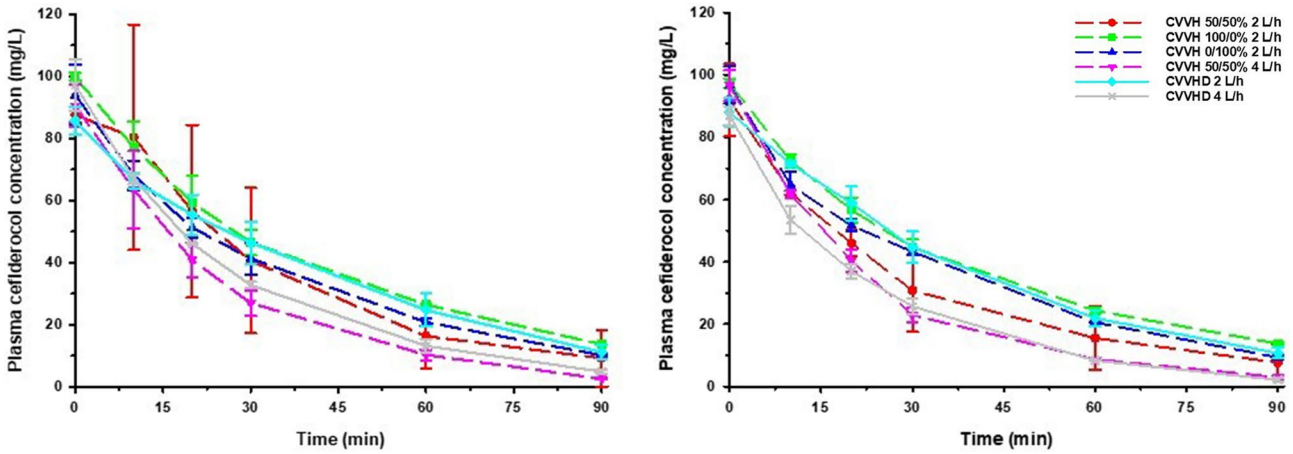

Fig. 1 Pre-filter plasma concentration-time profiles of cefiderocol during in vitro CVVH and CVVHD at each rate and point of dilution with the HF1400 filter (left) and M150 filter (right). Mean values are displayed with error bars representing standard deviations. *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis

Table 2 Mean (±SD) sieving and saturation coefficient values of cefiderocol during in vitro CRRT

CRRT modality	HF1400
CVVH	*SC*
2 L/h, 50/50%	1.01 ± 0.20
2 L/h, 100/0%	0.81 ± 0.09
2 L/h, 0/100%	1.01 ± 0.07
4 L/h, 50/50%	1.11 ± 0.13
CVVHD	*SA*
2 L/h	0.93 ± 0.02
4 L/h	0.94 ± 0.05
	M150
CVVH	*SC*
2 L/h, 50/50%	0.82 ± 0.17
2 L/h, 100/0%	0.74 ± 0.06
2 L/h, 0/100%	0.94 ± 0.07
4 L/h, 50/50%	0.92 ± 0.11
CVVHD	*SA*
2 L/h	0.90 ± 0.05
4 L/h	0.67 ± 0.11

SD standard deviation, *CRRT* continuous renal replacement therapy, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis, *SC* sieving coefficient, *SA* saturation coefficient

these ANOVAs as a function of CRRT mode, filter type, and effluent flow rate are displayed in electronic supplementary Table 1. Despite consistently higher mean SC and SA values observed for the HF1400 filter compared with the M150 filter, the only significant difference in marginal mean CL_{CRRT} values was observed between CVVHD at 4 L/h with the HF1400 filter (3.355 L/h) and the M150 filter (2.503 L/h) [$p = 0.034$].

3.2 Adsorption

The overall mean (±SD) percentage adsorption was 10.93 ± 6.28% across CRRT modes, filter types, effluent flow rates, points of dilution, and time. Adsorption peaked at 10–20 min for both filter types. although the percentage adsorbed to the HF1400 filter was significantly higher than to the M150 filter (14.87 ± 0.13% vs. 8.96 ± 4.97%, $p = 0.004$).

3.3 Protein Binding

Overall, mean (±SD) percentage protein binding in bovine plasma across 16 samples was 36.1 ± 0.04%. No differences were observed between the experimental and contrived samples or between CRRT modes, filter types, or effluent flow rates (data not shown). Protein binding also did not appear to be concentration-dependent as mean percentage bound was approximately constant over time at 0 min (33.9%), 10 min (36.6%), 30 min (36.2%), and 60 min (42.4%).

3.4 In Vivo CRRT

Available characteristics and CRRT settings for each of the nine patients undergoing CRRT from the phase III nosocomial pneumonia ($n = 3$) and CR Gram-negative infection ($n = 6$) studies are shown in Table 3. Importantly, the CRRT modalities employed in vivo matched well with our in vitro CRRT model and were representative of the machines, filter types, and settings most commonly utilized in clinical practice worldwide [46, 47]. All but two patients received CRRT via the Prismaflex system with an AN69 filter. The most commonly employed CRRT mode was CVVHDF in seven (78%) patients, with replacement fluid added either

100% pre-filter ($n = 2$) or 100% post-filter ($n = 3$) most often. All patients with available data reported a blood flow rate of between 100 and 200 mL/min and a median (interquartile range) effluent flow rate of 1.25 L/h (1.15–2.2 L/h), with 78% of effluent flow rates set between 1 and 3 L/h. Individual observed plasma concentration-time profiles from each of the nine CRRT patients are displayed in Fig. 2.

3.5 Dose Optimization

All four applicable covariates (CRRT mode, filter type, effluent flow rate, and point of dilution) were entered into the multiple linear regression model. Effluent flow rate was the only significant covariate retained in the final model, demonstrating an increase of 0.655 L/h (95% CI 0.508–0.803; $p < 0.001$) in CL_{CRRT} for every 1 L/h increase in effluent flow rate with excellent correlation (adjusted $R^2 = 0.856$). The regression equation $CL_{CRRT} = 0.497$ L/h + (effluent flow rate * 0.655) was then used to make predictions for CL_{CRRT} and suggest optimal dosing regimens for cefiderocol during CRRT across effluent flow rates from 0.5 to 5 L/h (Table 4). Four optimal dosing regimens (each infused over 3 h) were proposed over the 10 effluent flow rates simulated, which allowed for simplification into the following recommendations:

- 1.5 g every 12 h for effluent flow rate ≤2 L/h
- 2 g every 12 h for effluent flow rate 2.1–3 L/h
- 1.5 g every 8 h for effluent flow rate 3.1–4 L/h
- 2 g every 8 h for effluent flow rate ≥4.1 L/h

Estimated post hoc plasma cefiderocol PK parameters derived from the population PK model using these optimal effluent flow rate-based dosing regimens for each of the nine CRRT patients individually and in aggregate are shown in Table 5. Electronic supplementary Fig. 1 illustrates the satisfactory individual observed versus predicted fits ($R^2 = 0.795$) for the nine CRRT patients. Additionally, individual predicted plasma concentration-time profiles from the nine CRRT patients receiving optimal effluent flow rate-based dosing regimens are overlayed on the 95% prediction interval of plasma concentrations from patients not undergoing CRRT receiving cefiderocol 2 g every 8 h in phase III studies in Fig. 3. Optimal dosing regimens based on effluent flow rate were equivalent to the dose actually received in the phase III studies for five patients and were higher than the actual dose received in the remaining four patients. The estimated geometric mean (±SD) C_{max} and AUC, respectively, for the nine CRRT patients receiving optimal dosing regimens versus those patients from phase III trials with normal renal function receiving 2 g every 8 h were similar at 108 ± 35.7 mg/L versus 101 ± 51.6 mg/L ($p = 0.68$) and

Table 3 Characteristics and CRRT settings for the nine patients undergoing CRRT while receiving cefiderocol in phase III clinical trials

Study	CRRT machine	Filter set (type)	CRRT mode	Point of dilution	Blood flow rate (Qb, mL/min)	Ultrafiltration rate (Quf, L/h)	Dialysate flow rate (Qd, L/h)	Replacement fluid flow rate (Qr, L/h)	Effluent flow rate (Qe, L/h)	Cefiderocol dosing regimen[a]
APEKS-NP	Prismaflex	ST150 (AN69)	CVVHDF	100% pre-filter	120	–	–	1.80	3.85	1.5 g q12h
APEKS-NP	Prismaflex	M150 (AN69)	CVVHD	N/A	–	NA	1.25	NA	1.25	1.5 g q12h
APEKS-NP	Prismaflex	M150 (AN69)	CVVHDF	50% pre-filter, 50% post-filter	180	0.20	2.00	1.00	2.20	1.5 g q12h
CREDIBLE-CR	Prismaflex	M100 (AN69)	CVVHDF	100% post-filter	120	0.70	2.00	NA	2.70	1.5 g q12h
CREDIBLE-CR	Fresenius	PS	CVVHDF	100% post-filter	200	0.15	1.50	1.50	1.65	1.5 g q12h
CREDIBLE-CR	Prismaflex	–	CVVH	100% post-filter	130	1.12	NA	0.25	1.12	1 g q12h
CREDIBLE-CR	Prismaflex	ST150 (AN69)	CVVHDF	–	120	0.15	1.00	1.00	1.15	1.5 g q12h
CREDIBLE-CR	Prismaflex	ST150 (AN69)	CVVHDF	–	120	0.15	1.00	1.00	1.15	1.5 g q12h
CREDIBLE-CR	Fresenius	Ultraflux AV 600S (PS)	CVVHDF	100% pre-filter	100	0.04	0.70	0.70	0.74	1.5 g q12h

CRRT continuous renal replacement therapy, *NA* not applicable, *q12h* every 12 h, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis, *CVVHDF* continuous veno-venous hemodiafiltration, – indicates data not available

[a]Per the study protocol, cefiderocol was administered as a 3-h infusion at a dose of 1 g q12h for CVVH and 1.5 g q12h for CVVHD and CVVHDF

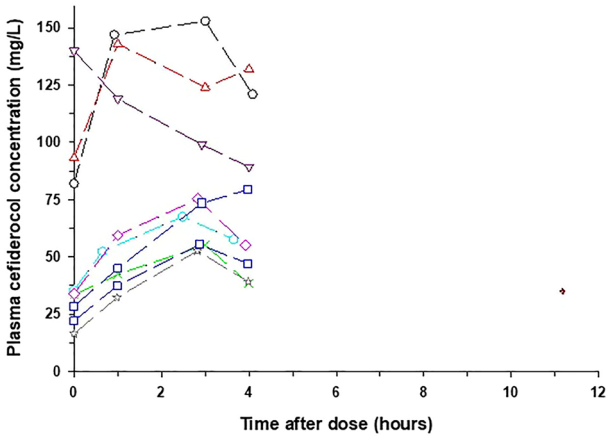

Fig. 2 Individual observed plasma cefiderocol concentration-time profiles for the nine patients receiving CRRT in phase III trials. Each color and symbol combination represents a unique patient (one patient was sampled on days 3 and 9). *CRRT* continuous renal replacement therapy

1709 ± 539 mg·h/L versus 1494 ± 58.4 mg·h/L ($p = 0.26$). Assuming protein binding of 58%, the predicted geometric mean (range) fC_{trough} for patients undergoing CRRT receiving optimal dosing regimens was 17.9 mg/L (12.2–39.3 mg/L), with four patients <16 mg/L and no patients <8 mg/L (Table 5). At 75% of the dosing interval (6 or 9 h post-dose), all nine patients had a free plasma concentration ≥8 mg/L (Fig. 3). Similar geometric mean (range) fC_{trough} values of 12.7 mg/L (0.856–89.5 mg/L) and 16.3 mg/L (2.91–84.8 mg/L) were estimated from the nosocomial pneumonia and CR Gram-negative pathogen studies, respectively.

Figure 4 illustrates the PTA for cefiderocol by effluent flow rate and associated optimal dosing regimen according to MIC, with the actual percentage PTA shown in electronic supplementary Table 2. Across 1000 simulated patients undergoing CRRT at various effluent flow rates, the proposed optimal dosing regimens of cefiderocol conferred >94% PTA against MIC values ≤4 mg/L at all flow rates. Against an MIC of 8 mg/L, PTA was >75% at all 10 effluent flow rates and >80% for all but two flow rates. All PTAs dropped below 60% at an MIC of 16 mg/L.

4 Discussion

Non-clinical and clinical PK/PD models play a critical role in designing human dosage regimens and are essential tools for dose optimization in special patient populations, such as those undergoing CRRT [20, 48]. Critically ill patients with CR infections on concomitant CRRT are at risk for worse outcomes due in large part to suboptimal antimicrobial exposure secondary to inadequate dosing stemming from a lack of reliable PK/PD data [49]. This is the first study to evaluate the PK of cefiderocol during CRRT and to provide optimal dosing recommendations for these patients through integration of in vitro modeling, clinical PK, and in silico PTA analyses. It is also the largest and most comprehensive CRRT study of the modern anti-CR agents to date [39, 50–54]. The results of this work have been incorporated into the revised prescribing information for cefiderocol, making it the first and only antimicrobial agent with US FDA labeled dosing for CRRT [25, 55]. Encouragingly, these optimized CRRT dosing regimens have already begun to demonstrate the ability to achieve target PK/PD thresholds and lead to clinical and microbiological cure against MDR pathogens as predicted herein [56].

Table 4 Optimal dosing recommendations of cefiderocol according to the CRRT effluent flow rate

CRRT effluent flow rate (L/h)	CL_{CRRT} (L/h)[a]	CL_{NR} (L/h)	CL_T (L/h)	Goal AUC (mg·h/L)	Optimal total daily dose (mg)	Optimal dosing regimen (3-h infusion)
0.5	0.825	1.298	2.123	1184	2513.0	1.5 g q12h
1	1.152	1.298	2.450	1184	2900.8	1.5 g q12h
1.5	1.480	1.298	2.778	1184	3288.6	1.5 g q12h
2	1.807	1.298	3.105	1184	3676.3	2 g q12h
2.5	2.135	1.298	3.433	1184	4064.1	2 g q12h
3	2.462	1.298	3.760	1184	4451.8	1.5 g q8h
3.5	2.790	1.298	4.088	1184	4839.6	1.5 g q8h
4	3.117	1.298	4.415	1184	5227.4	2 g q8h
4.5	3.445	1.298	4.743	1184	5615.1	2 g q8h
5	3.772	1.298	5.070	1184	6002.9	2 g q8h

CRRT continuous renal replacement therapy, CL_{CRRT} clearance by CRRT, CL_{NR} non-renal clearance, CL_T total body clearance, *AUC* area under the concentration-time curve

[a]Predicted via the regression equation: CLTM = 0.497 L/h + (flow rate (L/h) * 0.655

Table 5 Post hoc plasma pharmacokinetic parameters assessed by Bayesian estimation via an established population pharmacokinetic model according to the optimal effluent flow rate-based dosing regimens in nine CRRT patients from phase III trials

CRRT mode	Effluent flow rate (L/h)	Optimal dosing regimen (3-h infusion)	C_{max} (mg/L)	AUC (mg·h/L)	fC_{trough} (mg/L)[a]
CVVHDF	3.85	1.5 g q8h	90.3	1577	18.8
CVVHD	1.25	1.5 g q12h	76.6	1185	12.2
CVVHDF	2.20	2 g q12h	179	2419	19.8
CVVHDF	2.70	2 g q12h	113	1618	14.7
CVVHDF	1.65	1.5 g q12h	138	1813	13.9
CVVH	1.12	1.5 g q12h	105	1692	18.4
CVVHDF	1.15	1.5 g q12h	72.2	1197	13.8
CVVHDF	1.15	1.5 g q12h	92	1627	20.4
CVVHDF	0.74	1.5 g q12h	148	2840	39.3
Geometric mean (CV%)			108 (31.4)	1709 (29.2)	17.9 (35.8)

CRRT continuous renal replacement therapy, C_{max} maximum concentration, *AUC* area under the concentration-time curve, *CVVHDF* continuous veno-venous hemodiafiltration, *CVVHD* continuous veno-venous hemodialysis, *CVVH* continuous veno-venous hemofiltration, *qxh* every *x* hours, *CV%* percentage coefficient of variation

[a]Estimated from total concentrations using an unbound fraction of 0.422

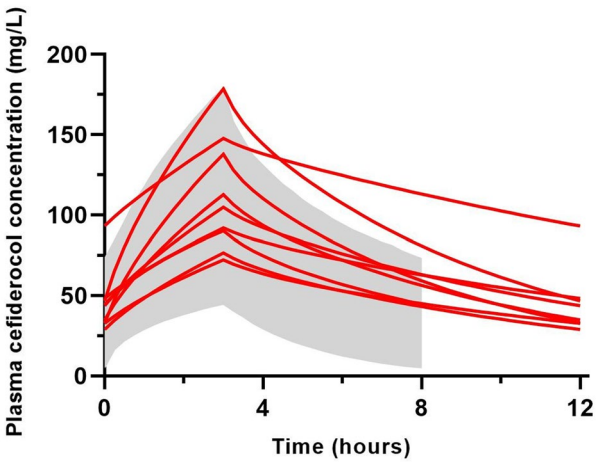

Fig. 3 Individual predicted plasma concentration-time profiles for the nine patients receiving CRRT at optimal effluent flow rate-based dosing regimens (red lines) and the 95% prediction interval of plasma concentrations for patients not undergoing CRRT receiving cefiderocol 2 g every 8 h in phase III trials (gray shaded area). *CRRT* continuous renal replacement therapy

Importantly, thorough statistical evaluation provided confidence that the proposed dosing strategies could be simplified to be based only on effluent flow rate while ignoring CRRT mode, filter type, and point of dilution, and thereby easing translation into clinical practice. The predominant influence of effluent flow rate observed in the current study is supported by previous large-scale studies demonstrating clear and consistent associations between CRRT effluent flow rate and clearance of β-lactams such as piperacillin and meropenem [57]. When applied to patients undergoing CRRT during phase III trials, these optimized dosing regimens resulted in comparable exposure to patients with normal renal function receiving the labeled dose of cefiderocol. Furthermore, these optimal effluent flow rate-based dosing regimens were predicted to achieve >90% PTA against MIC values ≤4 mg/L. Given that the MIC_{90} against meropenem non-susceptible Enterobacterales, *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* is ≤4 mg/L [58], the proposed effluent flow rate-based doses recommended herein should provide adequate cefiderocol exposure against all of these pathogens and cover all organisms considered susceptible based on Clinical and Laboratory Standards Institute (CLSI), FDA, and European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria. Finally, as the predicted geometric mean total C_{trough} for patients receiving CRRT was 42.4 mg/L, the proposed optimal dosing regimens may also be sufficient to prevent the emergence of resistance to cefiderocol at MICs ≤4 mg/L [59].

In addition to providing clinicians with the first set of dosing recommendations for cefiderocol during CRRT, our study has several other notable strengths. Primarily, our methodology for assessing CL_{CRRT} employed a rich sampling scheme and non-compartmental PK analyses, which significantly improved our ability to accurately estimate drug removal during in vitro CRRT. The majority of previous studies attempt to estimate CL_{CRRT} by multiplying SC or SA derived from a single time point by the flow rate [60–63]. These methods falsely assume SC and SA are static over time and that CL_{CRRT} is directly proportional to flow rate across the continuum of CRRT settings. Moreover, the methods used for calculating SC, SA, and CL_{CRRT} have varied dramatically throughout the literature, even among the same authors/groups across different studies [36, 64–70],

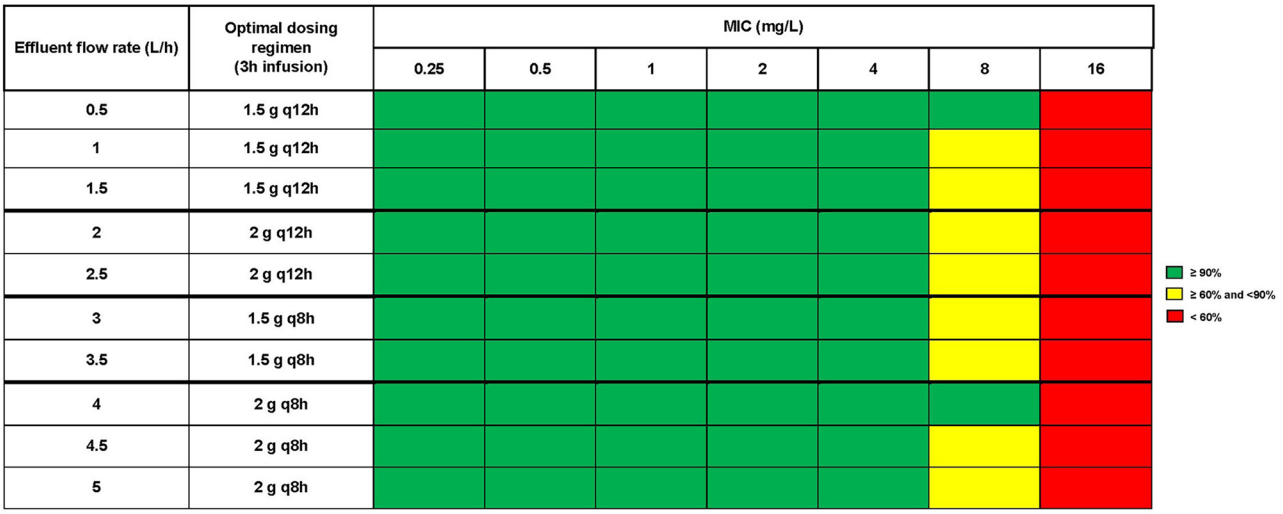

Fig. 4 Probability of attaining 75% $fT_{>MIC}$ for patients receiving CRRT and optimal effluent flow rate-based dosing regimens. $fT_{>MIC}$ free time above the minimum inhibitory concentration, *CRRT* continuous renal replacement therapy, *MIC* minimum inhibitory concentration, *qxh* every *x* hours

especially with regard to the influence of point of dilution during CVVH. Therefore, our optimal dosing regimens were generated exclusively via non-compartmental analyses given its increased precision and lack of influence by CRRT mode, filter type, or point of dilution. Notably, our optimized dosing recommendations resulted in the same or higher, but never lower, total daily doses of cefiderocol compared with the dosing regimens used in the phase III trials. This finding highlights the shortcomings of extrapolating data from other agents (even if physiochemically similar), the inability to use CL during intermittent hemodialysis to accurately predict CRRT clearance, and the importance of avoiding unnecessary and detrimental dose reductions in these vulnerable patients [55].

We also directly assessed the effect of protein binding and adsorption on the clearance of cefiderocol during CRRT. Although protein binding is known to be one of the most important factors affecting drug removal during CRRT [49], exceedingly few agents have available data regarding binding to bovine plasma as these animals are not typically utilized in the drug development process [71]. The mean protein binding of 36.1% observed in this study (despite a measured bovine albumin concentration of 3.7 g/dL) was slightly lower than the range previously reported in humans (40–60%) [72]. In the population PK model utilized for this study, a negative correlation between albumin concentration and volume of distribution (V_1) was observed, although C_{max}, AUC, and CL_T were similar regardless of albumin concentration, suggesting hypoalbuminemia may not have a significant effect on cefiderocol exposure. Even if the slightly higher free fraction of cefiderocol in bovine plasma resulted in higher CL_{CRRT} values, and therefore higher than necessary dosing recommendations, the estimated C_{max} and AUC of cefiderocol in patients undergoing CRRT receiving optimized effluent flow rate-based dosing regimens were similar to those of patients with normal renal function from the phase III studies and well below the exposure level that has been previously well tolerated after supratherapeutic doses of 3 and 4 g [29].

Although we observed negligible degrees of filter adsorption comparable with those reported for other similar β-lactam agents [39, 73–75], which aided in our ability to recommend dosing regimens based strictly on CRRT effluent flow rate, adsorption was significantly higher with the HF1400 filter compared with the M150 filter. This is consistent with our previous investigations [76] and is likely due to known differences in filter composition [77–79]. While the interaction between CRRT mode and filter was not statistically significant ($p = 0.051$), ANOVA-generated marginal mean CL_{CRRT} was significantly higher during CVVHD at 4 L/h with the HF1400 filter versus the M150 filter, suggesting higher doses may need to be considered in this specific situation. As only one CRRT patient had an effluent flow rate >3.5 L/h (fC_{trough} = 18.8 mg/L), this requires confirmation in future investigations.

Despite these strengths, our study is not without limitations. First, although as many different CRRT modes, filter types, dilution points, and flow rates as possible were included, the results may not be representative of all modalities of CRRT. Second, we assumed non-renal drug clearance to be stable when providing dosing recommendations. Although there are some data to suggest acute kidney injury (AKI) may affect CL_{NR} [80], there are currently no practical methods or useful biomarkers to assess changes in CL_{NR}. We

also assumed residual renal function to be negligible as is common in critically ill patients with AKI receiving CRRT [81]. Although this could possibly have underestimated clearance and impacted dosing recommendations, the optimal effluent flow rate-based doses of cefiderocol established in vitro demonstrated adequate in vivo exposure comparable with that observed in patients with normal renal function therefore this is unlikely. Third, the use of a new hemofilter and circuit for each experiment may have limited our ability to fully assess the effect of filter life on adsorption and CL_{CRRT} as well as the impact of repeated cefiderocol dosing. Due to the complicated logistics of in vitro adsorption experiments, caution should be taken when interpreting these data [82]. Fourth, as the PK of cefiderocol have already been extensively described, our 1.5-h sampling scheme in this study was designed solely to evaluate the CL_{CRRT} of cefiderocol during in vitro CRRT, and therefore the half-lives reported should be interpreted with care. Finally, post-filter and effluent samples were not collected in vivo and some patient information was unavailable, including the type of filter used and any interruptions in CRRT therapy that may have impacted the PK results.

5 Conclusion

The thorough exploration of cefiderocol PK during in vitro and in vivo CRRT in this study resulted in optimal dosing recommendations based only on effluent flow rates that provide >90% PTA against pathogens with an MIC ≤4 mg/L. These effluent flow rate-based dosing recommendations have been incorporated into the labeled dosing for cefiderocol and offer a simple dosing algorithm for adoption in the clinical arena. Further confirmation of the efficacy of these doses in clinical studies is warranted.

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Declarations

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Conflicts of Interest/Competing Interests Eric Wenzler serves on the speaker's bureau for Melinta Therapeutics, Astellas Pharma, and Allergan Plc., and on the advisory board for GenMark Diagnostics and Shionogi & Co., Ltd. Takayuki Katsube is currently an employee of Shionogi & Co., Ltd, and Toshihiro Wajima was an employee of Shionogi & Co., Ltd at the time of this work. David Butler and Xing Tan certify no potential conflicts of interest.

Ethics Approval The study design of phase III trials followed US regulatory considerations that were valid in 2016 and were approved by the EMA Committee for Medicinal Products for Human Use (CHMP). Study protocols were approved by relevant national authorities and Institutional Review Boards or independent Ethics Committees. No additional ethical approvals were required for the current study.

Consent to Participate Written informed consent was obtained from all participants during phase III trials. Informed consent was not necessary for the current work.

Consent for Publication Not applicable.

Availability of Data and Material Protocols for the phase III clinical studies are available on ClinicalTrials.gov as NCT03032380, NCT02714595, and NCT02321800. Data generated from this study are not publicly available due to confidentiality agreements with the sponsor, although they may be provided upon reasonable requests by healthcare providers, investigators, and researchers to address specific scientific or clinical objectives.

Code Availability May be made available upon reasonable request.

Author Contributions EW was responsible for conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing/reviewing/editing the manuscript. DB contributed to the conceptualization, formal analysis, investigation, and writing/reviewing/editing the manuscript. XT contributed to the formal analysis, investigation, and writing/reviewing/editing the manuscript. TK and TW contributed to the formal analysis, investigation, and reviewing and editing the manuscript. All authors read and approved the final manuscript.

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