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NOVEL ID CASES

Cefiderocol Pharmacokinetics in a Patient Receiving Continuous Venovenous Hemodiafiltration

Emir Kobic,[1] Christian M. Gill,[2] A. Brian Mochon,[3,4] Nelson P. Nicolasora,[5] and David P. Nicolau[2,6]

[1]Department of Pharmacy, Banner University Medical Center, Phoenix, Arizona, USA, [2]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, USA, [3]Department of Pathology, University of Arizona College of Medicine, Phoenix, Arizona, USA, [4]Labratory Sciences Arizona/Sonora Quest Laboratories, Phoenix, Arizona, USA, [5]Division of Infectious Diseases, Banner University Medical Center, Phoenix, Arizona, USA, and [6]Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut, USA

Antimicrobial dosing in patients receiving continuous renal replacement therapy is a continued clinical challenge. We describe a case of a patient receiving cefiderocol 2 g intravenously every 8 hours as a 3-hour infusion for a multidrug-resistant *Pseudomonas aeruginosa* pneumonia and bacteremia while undergoing continuous venovenous hemodiafiltration. The clinical course and cefiderocol pharmacokinetics are described.

Keywords. antimicrobial dosing; cefiderocol; continuous renal replacement therapy; CRRT; CVVHDF; pharmacodynamics; pharmacokinetics.

Cefiderocol (brand name: Fetroja) is currently approved by the US Food and Drug Administration (FDA) for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) as well as complicated urinary tract infections (cUTIs), including pyelonephritis [1]. Cefiderocol has activity against many gram-negative bacteria including multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [2]. Pharmacokinetic data are available for patients with normal and impaired renal function, including those with end-stage renal disease (ESRD) requiring intermittent hemodialysis [3, 4]. The package insert provides recommendations for continuous renal replacement therapy (CRRT) dosing but states that regimens may need to be tailored based on residual renal function and the patient's clinical status. No pharmacokinetic studies in critically ill patients receiving cefiderocol and concomitant CRRT have been published. Previous reports with ceftazidime/avibactam (CZA) and ceftolozane/tazobactam (C/T) have suggested higher risk of clinical failure in critically ill patients receiving CRRT due to lower exposures [5, 6]. Additionally, recent data spanning the continuum of kidney function in critically ill patients including acute kidney injury, CRRT, and augmented renal clearance have suggested that for agents with wide toxicity thresholds (ie, most β-lactams), the maximum tolerated doses should be considered to account for other pharmacokinetic changes in acute illness (ie, elevated volume of distribution and residual renal function) and elevated MICs seen in high-risk populations [7]. Therefore, we set out to evaluate the cefiderocol plasma profile in a critically ill patient undergoing CRRT.

CASE REPORT

A 64-year-old woman with a medical history significant for diabetes mellitus type 2, breast cancer, end-stage liver disease due to alcohol use disorder and hemochromatosis, and ESRD was admitted in June 2020 for a combined kidney and liver transplant. Her postoperative course was complicated by acute respiratory distress syndrome requiring extracorporeal membrane oxygenation. Prolonged vasopressor requirements resulted in acute tubular necrosis of her renal graft and the initiation of continuous venovenous hemodiafiltration (CVVHDF). On day 14, her hospital course was complicated by *Candida krusei* fungemia, an MDR *Pseudomonas* pneumonia, and a vancomycin-resistant *Enterococcus faecium* (VRE) bacteremia on day 27. Furthermore, persistent *P. aeruginosa* pneumonia and multiple abdominal abscesses grew VRE and *P. aeruginosa*. The antibacterial profiles of novel β-lactams against *P. aeruginosa* isolates and Clinical and Laboratory Standards Institute (CLSI) interpretative criteria are listed in Table 1 [8].

On day 224, a new-onset fever, worsening hypoxemia, and increasing pressor requirement were noted while the patient was receiving tobramycin and polymyxin B. She had breakthrough bacteremia with *P. aeruginosa* due to cholangitis in the setting of ischemic cholangiopathy. Susceptibilities were requested for cefiderocol and the blood isolate was sent out to Laboratory Specialists, Inc, in Westlake, Ohio. The isolate was reported as resistant based on FDA breakpoints, having an MIC of 4 μg/mL to cefiderocol based on broth microdilution method. Indeed, the MIC was interpreted as susceptible per the newly adopted CLSI interpretive criteria for cefiderocol and *P. aeruginosa* (susceptible ≤4 μg/mL) [8]. The patient managed to clear the repeat blood cultures on intravenous (IV) polymyxin B and tobramycin. On day 228, endoscopic retrograde cholangiopancreatography, biliary sphincterotomy, stone extraction, and stent placement were done. On day 235, the

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Correspondence: David P. Nicolau, PharmD, FCCP, FIDSA, Center for Anti-Infective Research and Development, Hartford Hospital, 80 Seymour St, Hartford, CT 06102, USA (david.nicolau@hhchealth.org).

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Table 1. Susceptibility Profile of Novel β-Lactam Agents Against Pseudomonas aeruginosa Isolated From the Patient and Interpretation per Clinical and Laboratory Standards Institute Interpretive Criteria

			Novel β-Lactams and CLSI Interpretive Criteria		
Day of Hospitalization	Source	Isolates	Ceftazidime/Avibactam[a]	Ceftolozane/Tazobactam[a]	Cefiderocol[b]
Day 167	BAL	*P. aeruginosa* #1	16/4 (R)	2/4 (S)	0.12 (S)
		P. aeruginosa #2	>256 (R)	>256 (R)	8 (I)
Day 224	Blood	*P. aeruginosa*	>256 (R)	8 (I)	4 (S)
Day 235	BAL	*P. aeruginosa*	32/4 (R)	4/4 (S)	NA

Abbreviations: BAL, bronchoalveolar lavage; CLSI, Clinical and Standards Institute; I, intermediate; NA, not available; R, resistant; S, susceptible.

[a]Testing performed using Etest method (bioMérieux, Durham, North Carolina).

[b]Testing performed using broth microdilution.

patient became septic with high vasopressor requirements. The blood cultures remained negative, but a repeat bronchoalveolar lavage specimen revealed an MDR *P. aeruginosa* isolate that eventually showed CZA resistance (MIC = 32/4 μg/mL) and C/T susceptibility (MIC = 4/4 μg/mL), albeit this agent was not available due to a manufacturer recall. Given the elevated cefiderocol MIC from the previous blood culture in the setting of a compromised host, full-dose cefiderocol, 2 g every 8 hours over 3 hours, was added to polymyxin B and tobramycin while the patient was receiving CVHHDF. The patient clinically improved after cefiderocol was added to the polymyxin B and tobramycin regimen. Polymyxin B and tobramycin were subsequently discontinued after 3 and 10 days of combination therapy, respectively. On day 242, additional MDR *P. aeruginosa* were isolated, one from a drain and the second from an endotracheal aspirate (ETA). The drain and ETA isolates had cefiderocol MICs of 4 μg/mL and 8 μg/mL, respectively, values similar to the index isolate prior to cefiderocol exposure. The patient's clinical course continued to improve, cefiderocol was stopped after 2 weeks of therapy, and no adverse events were attributed to the compound. The patient remains on CVVHDF, is slowly weaning from the vent, and has been off antimicrobials for about a month at the time of this report. Written informed consent was obtained from the patient's legally authorized representative prior to obtaining the blood samples.

PHARMACOKINETIC ANALYSIS

On the 22nd dose of cefiderocol 2 g IV every 8 hours as a 3-hour infusion during CVVHDF, plasma samples were collected at 1, 3, 4, 6, and 8 hours during the dosing interval. Two post-hemodialysis filter plasma samples were collected at 4 and 8 hours concurrently with the prefilter plasma samples to assess CVVHDF clearance (CL_{CVVHDF}). Blood samples were stored frozen at –80°C and shipped on dry ice to Keystone Bioanalytical (North Wales, Pennsylvania) for cefiderocol concentration determination using modified methodology of a validated liquid chromatography–tandem mass spectrometry assay [4].

Plasma concentrations were modeled using Phoenix WinNonLin (Certara, Princeton, New Jersey). The CL_{CVVHDF} was calculated using $\frac{[Cpre \bullet Qplasma]-[Cpost \bullet (Qplasma-QUF)]}{Cpre}$ as previously described, where C_{pre} is the prefilter concentration, C_{post} is the postfilter concentration, Q_{plasma} is the blood flow corrected for hematocrit, and Q_{UF} is the ultrafiltration flow rate [9]. CVVHDF was conducted using Prismaflex filter AN69 high-flux, M100 membrane set (Gambro, Meyzieu, France). The derived pharmacokinetic parameters were then used to simulate the plasma time profile of different cefiderocol dosing regimens. The pharmacodynamic adequacy of the pharmacokinetic simulations was evaluated using a more conservative pharmacodynamic target of 82% $fT >$ MIC derived from an in vivo infection model specific to *P. aeruginosa* [10].

The patient's CVVHDF settings were as follows: blood flow, dialysate, replacement fluid (continuous pre- and postfilter replacement), and prepump blood flow rates were 200 mL/minute, 1000 mL/hour, 250 mL/hour, and 500 mL/hour, respectively. The patient had no urine output during the dosing and sampling time periods, indicating that no residual renal function was present. Based on the prescribed effluent rate for the CVVHDV, the cefiderocol dose from the package insert was 1.5 g IV every 12 hours as a 3-hour infusion; however, it states that residual renal function and patient clinical status should be considered when selecting a dosing regimen [1]. Considering the cefiderocol MICs were on the higher end of the susceptible range, previous data with similar agents (ie, cefepime) requiring full doses during CRRT [11], the patient's high severity of illness, and overall safety of β-lactam antibiotics, a dose of cefiderocol 2 g IV every 8 hours as a 3-hour infusion was administered.

The cefiderocol half–life, clearance, and volume of distribution derived from a 1-compartment model of the patient's observed plasma concentrations were 6.2 hours, 2.33 L/hour, and 20.9 L, respectively. The patient's observed fC_{max} (maximum free plasma concentration of drug) and fC_{min} (minimum free plasma concentration of drug) were 55 mg/L and 31.6 mg/L, respectively. The calculated CL_{CVVHDF} based on the pre- and postfilter concentrations was 2.2 (2–2.39) L/hour, suggesting that nearly

all of the patient's total clearance was due to CL_{CVVHDF}. Free plasma concentrations were corrected using the average protein binding from clinical pharmacokinetic studies (protein binding 58%) [12]. Table 2 compares the *fT* > MIC, free drug area under the concentration-time curve from 0 to 24 hours ($fAUC_{0-24}$), and total AUC_{0-24} when the pharmacokinetic parameters from this patient were used to simulate the profile of 2 g IV every 8 hours as a 3-hour infusion compared with the labeled dose based on CVVHDF effluent rate of 1.5 g IV every 12 hours as a 3-hour infusion. Indeed, the cefiderocol total AUC_{0-24} in our patient receiving cefiderocol 2 g IV every 8 hours was comparable to the mean exposure observed in the clinical trials for cUTI and HABP/VABP of 1920, 1944, and 1773 mg × hour/L, respectively [1]. Both dosing regimens produced a high *fT* > MIC 8 µg/mL exceeding 82% of the dosing interval using the patient-derived pharmacokinetic parameters. Using the same threshold, the pharmacodynamic target was met for an MIC of 16 µg/mL using the dose of 2 g every 8 hours.

Although our patient lacked residual renal function, an exploratory analysis was conducted by simulating both dosing regimens when administered to this patient as if there were residual renal function in addition to the CVVHDF to depict what the pharmacokinetic profile may be in patients on CRRT who have regained or begin to regain residual renal function [7]. Cefiderocol clearance was estimated using the previously described population pharmacokinetic model to calculate clearances that corresponded to 11 and 27 mL/minute of renal function, which were to the geometric mean creatinine clearance from participants in the renal dysfunction study with ESRD without hemodialysis and the upper end of the range in the same population [4, 13]. Calculated clearance was then added to the 2.2 L/hour of CL_{CVVHDF} to estimate the contribution of both methods of clearance seen in some patients on CRRT. The pharmacodynamic indices of these simulations are presented in Table 2. When either estimate of residual renal function is added, the *fT* > MIC 8 µg/mL for the labeled dosing regimen (1.5 g IV every 12 hours) decreased to 81% and 65% *fT* < MIC, respectively. Conversely, the 2 g IV every 8 hours dose continued to provide >90% *f*TMIC 8 µg/mL in both scenarios.

Table 2. Pharmacodynamic Indices of the Pharmacokinetic Simulations Using Parameters Derived From Modeling the Patient's Cefiderocol Plasma Concentrations

		Pharmacodynamic Indices of Pharmacokinetic Simulations									
		% *fT* > MIC, µg/mL									
PK Parameters	Cefiderocol Regimen	0.25	0.5	1	2	4	8	16	32	$fAUC_{0-24}$ (mg × h/L)	Total AUC_{0-24} (mg × h/L)
Patient-specific PK parameters	2 g IV every 8 h, 3-h inf	**100**	**100**	**100**	**100**	**99**	**98**	**95**	*57*	806	1920
	1.5 g IV every 12 h, 3-h inf	**100**	**100**	**100**	**99**	**98**	**97**	*59*	*1*	435	1037
Patient PK parameters with simulated residual renal function (11 mL/min)	2 g IV every 8 h, 3-h inf	**100**	**100**	**100**	**100**	**99**	**98**	**91**	*25*	632	1504
	1.5 g IV every 12 h, 3-h inf	**100**	**100**	**100**	**99**	**98**	*81*	*37*	*0*	336	800
Patient PK parameters with simulated residual renal function (27 mL/min)	2 g IV every 8 h, 3-h inf	**100**	**100**	**100**	**100**	**99**	**98**	*77*	*12*	534	1270
	1.5 g IV every 12 h, 3-h inf	**100**	**100**	**100**	**99**	**97**	*65*	*27*	*0*	281	669

Additional assessments were conducted to simulate the effect of residual renal function added to the continuous venovenous hemodiafiltration clearance. Bolded values represent attainment of the in vivo pharmacodynamic target of 82% *fT* > MIC while italicized values represent failure to meet this threshold.

Abbreviations: $fAUC_{0-24}$, free drug area under the concentration-time curve from 0 to 24 hours; inf, infusion; IV, intravenous; MIC, minimum inhibitory concentration; PK, pharmacokinetic.

DISCUSSION

To our knowledge, this is the first study to assess the pharmacokinetics of cefiderocol in a patient receiving CVVHDF. It is well described that obtaining optimal antibiotic concentrations in critically ill patients undergoing CRRT is a noted clinical challenge and insufficient dosing may predispose to clinical failure [5–7]. Considering the patient's severity of illness, isolation of an organism with a relatively high cefiderocol MIC, and high burden of infection, a higher dose of cefiderocol 2 g IV every 8 hours as a 3-hour infusion was selected for this patient. The pharmacokinetic data revealed that this cefiderocol dose

produced sufficiently high exposures (ie, 98% *fT* > MIC 8 μg/mL) and a positive clinical response was observed. Similarly, the selected cefiderocol dose was well tolerated, which is reinforced as the total cefiderocol exposure seen in this patient was similar to those in the clinical trials of infected patients [1]. Indeed, the pharmacokinetics of cefiderocol have been compared to that of cefepime [11]. The pharmacokinetic changes in our patient on CVVHDF were similar to that reported for cefepime in the setting of CRRT with half-life increases from 2–3 hours in healthy volunteers to 5–6 hours in setting of CRRT for both agents [10, 11]. It is also notable that extended infusions of cefepime at maximum doses (2 g IV every 8 hours) have been found to produce high pharmacodynamic target attainment in the setting of CRRT [11].

Based on this plasma profile, the recommended package insert dosing (1.5 g IV every 12 hours) would have achieved >82% *T* > MIC of unbound cefiderocol for an MIC up to 4 μg/mL (with or without residual renal clearance). Conversely, a dose of 2 g IV every 8 hours achieved the same threshold up to MICs of 8 μg/mL. Intuitively, more aggressive dosing is needed when the MICs of the infecting organism are higher, such as intermediate (ie, 8 μg/mL for cefiderocol) or into the resistant range (ie, 16 μg/mL for cefiderocol). However, reported MICs may vary a doubling dilution on either side of the value, necessitating coverage at least 1 dilution higher than reported [14]. Thus, more aggressive dosing regimens should be considered even for susceptible organisms, particularly if they are at the high end of the susceptibility range (ie, 4 μg/mL in this case). Additionally, the MIC of the organism may not be known at the time therapy is initiated and thus dosing regimens should be designed to cover organisms up to the highest MICs achievable within the safety index for the agent. Similarly, higher *fT* > MIC targets have been advocated for and should be considered with serious infections in critically ill patients [15]. Indeed, the calculated CL_{CVVHDF} exceeded the prescribed effluent rate in our case, which may be attributed to a number of factors including potential adsorption of cefiderocol to the filter/tubing, inability to assess effluent drug concentration, and/or the inherent variability in the assay. Nonetheless, the cefiderocol exposure observed in this patient was sufficient to meet pharmacodynamic targets with administered dose during CVVHDF therapy.

Another challenge in optimal dosing of antimicrobials during CRRT is residual renal function [7]. While residual renal clearance has been implicated in affecting drug clearance during CRRT, the pharmacokinetic and pharmacodynamic consequences of this intrinsic function are poorly categorized [16]. While our patient's urine output was used to determine that no residual renal function was present, pharmacokinetic simulations with added residual renal function were undertaken. With added residual renal function, the creatinine clearance 27 mL/minute simulation demonstrated that 1.5 g every 12 hours as a 3-hour infusion (package insert dose) had lower exposure with

Table 3. Considerations When Selecting Dosing Regimens of Antimicrobials During Continuous Renal Replacement Therapy and Practical Methods for Implementation

Considerations for Dosing During CRRT	Practical Implementation
Considerations for more aggressive dosing	
Agents with wide safety margins (ie, β-lactams)	• Use maximum tolerated doses
Presence of or increase in residual renal function	• Daily monitoring of urine output and other measures suggestive of presence or return of residual function • Increase or decrease of dose in response to changes
Changes in prescribed CRRT effluent rates	• Daily monitoring to increase doses in response to increases in effluent rates
Elevated or unknown MICs	• Use maximum tolerated doses • Use regimens that produce target attainment even with MICs outside of susceptible range
Considerations for more conservative dosing	• Practical implementation
Agents with narrow toxicity thresholds (ie, aminoglycosides)	• Utilize early TDM to optimize patient-specific PK within efficacy and safety thresholds

Abbreviations: CRRT, continuous renal replacement therapy; MIC, minimum inhibitory concentration; PK, pharmacokinetics; TDM, therapeutic drug monitoring.

65% fT > MIC 8 μg/mL, indicating suboptimal pharmacodynamic exposure. Keen daily assessments to changes in the effluent rate and residual renal function are needed, particularly if lower doses are administered. As one would expect, the overall exposure (total AUC) in our simulation was nearly half that of the simulation without residual renal function which, when the package insert dose (1.5 g IV every 12 hours) was simulated, falls below that which was seen in healthy volunteers receiving 2 g every 8 hours [1].

The present study is not without limitations. Although the analysis is limited to a single patient case and estimations for residual renal function, the discrepancy in overall exposure warrants a systematic investigation into cefiderocol dosing in patients with various degrees of residual clearance during CRRT. Additionally, this study provides a real-life scenario where cefiderocol was utilized for salvage therapy by optimizing pharmacokinetic/pharmacodynamic dosing principles for an infection caused by MDR *P. aeruginosa*. A single case report limits the generalizability of this study, particularly among different CRRT modalities. Pharmacokinetic data from larger patient populations receiving cefiderocol concomitantly with various CRRT modalities are needed.

In conclusion, using a single uniform dose based on CRRT settings may oversimplify many complex components associated with the pharmacokinetic exposure in critically ill patients. Several factors should be considered when selecting dosing regimens for any antibacterial agent for critically ill patients undergoing CRRT to suggest more aggressive dosing including elevated MICs (ie, high end of susceptible/intermediate range), the severity of patient illness, safety of the agent, and presence of residual renal function (Table 3). Considering these factors, in the absence of therapeutic drug monitoring, clinicians should place greater emphasis on consequences of underdosing rather than adverse effects of overdosing when administering agents with a wide margin of safety such as most β-lactams and cefiderocol during CRRT. Further data evaluating the pharmacokinetics of cefiderocol in patients undergoing CRRT are needed.

Notes

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References

1. Shionogi & Co. Cefiderocol: product information. Available at: www.fetroja.com. Accessed 27 February 2021.
2. Ito A, Kohira N, Bouchillon SK, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting gram-negative bacteria. J Antimicrob Chemother **2016**; 71:670–7.
3. Saisho Y, Katsube T, White S, et al. Pharmacokinetics, safety, and tolerability of cefiderocol, a novel siderophore cephalosporin for gram-negative bacteria, in healthy subjects. Antimicrob Agents Chemother **2018**; 62:e02163–17.
4. Katsube T, Echols R, Arjona Ferreira JC, et al. Cefiderocol, a siderophore cephalosporin for gram-negative bacterial infections: pharmacokinetics and safety in subjects with renal impairment. J Clin Pharmacol **2017**; 57:584–91.
5. Shields RK, Potoski BA, Haidar G, et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis **2016**; 63:1615–8.
6. Bassetti M, Castaldo N, Cattelan A, et al; CEFTABUSE Study Group. Ceftolozane/tazobactam for the treatment of serious *Pseudomonas aeruginosa* infections: a multicentre nationwide clinical experience. Int J Antimicrob Agents **2019**; 53:408–15.
7. Gill CM, Nicolau DP. Pharmacologic optimization of antibiotics for gram-negative infections. Curr Opin Infect Dis **2019**; 32:647–55.
8. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing, 30th ed. Wayne, PA: CLSI; **2020**.
9. Bremmer DN, Nicolau DP, Burcham P, et al. Ceftolozane/tazobactam pharmacokinetics in a critically ill adult receiving continuous renal replacement therapy. Pharmacotherapy **2016**; 36:e30–3.
10. Ghazi IM, Monogue ML, Tsuji M, Nicolau DP. Pharmacodynamics of cefiderocol, a novel siderophore cephalosporin, in a *Pseudomonas aeruginosa* neutropenic murine thigh model. Int J Antimicrob Agents **2018**; 51:206–12.
11. Philpott CD, Droege CA, Droege ME, et al. Pharmacokinetics and pharmacodynamics of extended-infusion cefepime in critically ill patients receiving continuous renal replacement therapy: a prospective, open-label study. Pharmacotherapy **2019**; 39:1066–76.
12. Katsube T, Echols R, Wajima T. Pharmacokinetic and pharmacodynamic profiles of cefiderocol, a novel siderophore cephalosporin. Clin Infect Dis **2019**; 69:552–8.
13. Kawaguchi N, Katsube T, Echols R, Wajima T. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection. Antimicrob Agents Chemother **2021**; 65:e01437–20.
14. Mouton JW, Muller AE, Canton R, et al. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother **2018**; 73:564–8.
15. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T > MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents **2008**; 31:345–51.
16. Vaara S, Pettila V, Kaukonen KM. Quality of pharmacokinetic studies in critically ill patients receiving continuous renal replacement therapy. Acta Anaesthesiol Scand **2012**; 56:147–57.