

A Novel Dosing Strategy of Ceftolozane/Tazobactam in a Patient Receiving Intermittent Hemodialysis

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We describe the case of a 54-year-old male receiving intermittent hemodialysis (iHD) who was found to have *Pseudomonas aeruginosa* bacteremia secondary to osteomyelitis of the calcaneus bone. The patient was clinically cured without recurrence using a ceftolozane/tazobactam (CTZ) dosing strategy of 100/50 mg every 8 hours (standard dosing) and 1000/500 mg thrice weekly following iHD. Utilizing a susceptibility breakpoint of ≤ 4 $\mu\text{g/mL}$ for *P. aeruginosa*, the $T > \text{MIC}$ for standard dosing and the 1000/500-mg thrice-weekly following iHD regimen were calculated to be 92.7% and 94.1%, respectively. Ceftolozane total body clearance for the standard q 8 h dosing and the 1000/500-mg thrice-weekly following iHD regimen were calculated to be 0.196 L/h and 0.199 L/h, respectively. To our knowledge, this is the first report to illustrate the administration of CTZ at a dose of 1000/500 mg thrice weekly following iHD.

Keywords. ceftolozane; hemodialysis; *Pseudomonas*; thrice weekly.

Ceftolozane/tazobactam (CTZ) has demonstrated potent in vitro activity and clinical efficacy against *Pseudomonas aeruginosa*, including multidrug-resistant (MDR) strains. Unfortunately, this difficult pathogen is increasingly common among intermittent hemodialysis (iHD) patients in whom infection is a leading cause of death [1,2]. Moreover, optimized dosing of renally cleared antimicrobials in patients with impaired renal function is challenging especially in the setting of dialytic support [3–5]. Although CTZ administered as a 1-time 500/250-mg intravenous loading dose followed by 100/50 mg every 8 hours is recommended by the package insert in patients

receiving iHD (standard dosing), utilizing this renally dose-adjusted regimen has been associated with clinical failure [5,6]. On the other hand, a prior real-world study was unable to show an association between clinical success and administration of higher doses of CTZ [7]. Although CTZ is generally well tolerated, adverse effects may be more likely to occur in the setting of renal disease. Thus, for the nearly half a million patients requiring iHD in the United States, optimal dosing of antimicrobials to account for PK alterations is paramount to ensure good clinical outcomes [8].

The utilization of thrice-weekly administration of ceftazidime and cefazolin post-iHD has been demonstrated to achieve therapeutic exposures [9,10]. Implementation of this convenient dosing strategy can often spare the need for placement of a central line, prevent continued hospitalization, and/or avoid unnecessary transfer to a skilled nursing facility for multiple daily dose regimens. While increasingly utilized in the setting of iHD, current prescribing guidance for CTZ does not recommend this strategy [6]. Therefore, we describe the clinical outcome and PK analysis of a patient with MDR *P. aeruginosa* bacteremia who was treated using CTZ thrice-weekly dosing following iHD.

CASE

The patient was a 54-year-old male (101 kg, 170.2 cm, 40.64 kg/m², albumin of 3.9 g/dL) with a medical history significant for end-stage renal disease (ESRD) secondary to type II diabetes mellitus who required thrice-weekly iHD. His medical history was also significant for a recent admission for left ankle pain in which he was found to have extensive liquefactive necrosis and ulceration of the plantar lateral aspect of the left heel. He was managed with wound debridement. Following identification of *Citrobacter Koseri* from wound culture, the patient was started on ertapenem therapy.

After 7 days of ertapenem, the patient developed a fever of 101.5°F. Blood cultures were obtained, which subsequently isolated *P. aeruginosa* that was nonsusceptible to piperacillin/tazobactam, meropenem, ciprofloxacin, and ceftazidime. Fortunately, the blood isolate of *P. aeruginosa* was susceptible to CTZ with a Kirby-Bauer zone size of 26 mm. Therefore, CTZ was administered as a 1-time 500/250-mg intravenous loading dose followed by 100/50 mg every 8 hours [6]. The presumed source was osteomyelitis of the calcaneus bone based on a recent magnetic resonance image of the left foot that revealed signal abnormalities of the marrow.

On day 24 of CTZ, the patient was transitioned to CTZ 1000/500 mg thrice weekly following iHD. On day 25 of CTZ, the patient underwent a left below-knee amputation. CTZ was continued to complete an additional week. The patient did not

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experience any adverse effects attributed to CTZ and received follow-up with a physician at least once every month. After 2 years of follow-up, the patient has not suffered a recurrent infection requiring antimicrobial therapy.

PHARMACOKINETIC ANALYSIS

In an effort to derive supportive evidence for this novel CTZ regimen relative to that of standard q 8 h dosing, serum concentrations were assessed during each of the regimens. CTZ concentrations were determined with a validated HPLC assay utilizing a reverse-phase column and cefepime as the internal standard [11]. Ceftolozane concentrations in relation to dosing administration, iHD sessions, and urine output are displayed in Table 1. Samples were immediately centrifuged and stored at -80°C . The CTZ standard dosing regimen was evaluated between day 22 and day 24 immediately before iHD. The CTZ thrice-weekly

following iHD regimen was evaluated between day 29 immediately following iHD and day 31 immediately before iHD. This time frame consisted of a 3-day period in between dialysis sessions. Total body clearance was calculated using a 2-compartment linear model with the software Insight-Rx [12].

Utilizing the Food and Drug Administration (FDA) susceptibility breakpoint of $\leq 4 \mu\text{g/mL}$ for *P. aeruginosa*, the ceftolozane $T > \text{MIC}$ for the standard q 8 h dosing and 1000/500-mg thrice-weekly following iHD regimen produced similarly high drug exposures, at 92.7% and 94.1%, respectively [6]. Ceftolozane total body clearance for the standard q 8 h dosing and 1000/500-mg thrice-weekly following iHD regimen was calculated to be 0.196 L/h and 0.199 L/h, respectively. Tazobactam determinations were hampered by interference. As a result, tazobactam could only be determined in a single sample with a concentration of $1.55 \mu\text{g/mL}$ relative to the corresponding ceftolozane concentration of $8.78 \mu\text{g/mL}$.

DISCUSSION

To our knowledge, this is the first report to illustrate the administration of CTZ at a dose of 1000/500 mg thrice weekly following iHD. A case series of 6 subjects with end-stage renal disease evaluated a dosing strategy of CTZ 500/250 mg before and after iHD [13]. Although clinical efficacy could not be assessed as none of these subjects had active infection, the authors found that this before-and-after iHD regimen yielded favorable PK and safety profiles [13]. Given that 66% of ceftolozane is removed from serum during a 3–4 iHD session, we anticipated that an exclusive post-iHD dosing strategy would produce sufficiently high, sustained drug exposures and be more convenient for the patient [13].

A neutropenic mouse model not only observed that ceftolozane required a mean $T > \text{MIC}\%$ of 31.5 ± 3.9 to achieve 1 log kill of *P. aeruginosa* but also found that the $T > \text{MIC}$ requirement for 1-log kill with ceftolozane for *P. aeruginosa* was demonstrated to be lower compared with ceftazidime [14]. Similarly, an in vivo fitness model found that a mean $T > \text{MIC}\%$ of 31.5 ± 3.9 was required to achieve 2 log kill of *P. aeruginosa* [15]. Therefore, the 40% $fT > \text{MIC}$ target required to drive good clinical outcomes for *P. aeruginosa* and other pathogens with an MIC of ≤ 8 has been considered standard for dose justification [16]. In our patient, not only were the overall pharmacodynamic profiles of the 2 dosing regimens similar, but when applying the FDA susceptibility breakpoint of $\leq 4 \mu\text{g/mL}$ for *P. aeruginosa*, each achieved a $T > \text{MIC}$ in excess of 90%, which may have been responsible for clinical cure [6].

Given the persistently elevated antimicrobial resistance rates to *P. aeruginosa* coupled with the inclining rate of hospitalization due to bacterial infection among patients on iHD, one can anticipate CTZ to be commonly used in the management of MDR *P. aeruginosa* in iHD patients in the years to come [17, 18].

Table 1. Therapeutic Drug Monitoring Summary

CTZ Dose or iHD ^a	Time	Ceftolozane Serum [C], $\mu\text{g/mL}$
Day 22: urine output: 300 mL		
150-mg dose	06:00	–
Level	9:00	8.78
iHD	09:00–13:00	–
Level	13:00	3.17
150-mg dose	15:30	–
Level	17:30	5.94
Day 23: urine output: 1750 mL		
150-mg dose	00:45	–
Level	8:30	5.54
150-mg dose	09:30	–
Level	16:00	6.20
150-mg dose	17:00	–
Day 24: urine output: 200 mL		
150-mg dose	01:15	–
Level	8:00	6.27
iHD	08:00–12:00	–
Level	12:00	2.73
1.5-g dose	16:15	–
Day 25: urine output: 575 mL		
Day 26: urine output: 400 mL		
iHD	07:30–12:00	–
1.5-g dose	17:00	–
Day 27: urine output: 1275 mL		
Day 28: urine output: 850 mL		
Day 29: urine output: 0 mL		
Level	8:00	7.59
iHD	8:00–12:00	–
1.5-g dose	15:30	–
Day 30: urine output: 1350 mL		
Day 31: urine output: 200 mL		
Level	15:15	3.33
iHD	15:15–19:00	–

Abbreviations: CTZ, ceftolozane/tazobactam; iHD, intermittent hemodialysis.

^aCeftolozane/tazobactam was dosed with a 500/250-mg loading dose on day 1, followed by 100/50 mg every 8 hours on days 1 through 23. All CTZ infusions were over 1 hour.

Thrice-weekly antimicrobial dosing following iHD not only has the potential to shorten or avoid hospitalization, but this dosing strategy has the potential to improve quality of life, compliance with antimicrobial therapy, and can decrease health care contact and personal protective equipment in the setting of a pandemic [19]. Furthermore, these benefits are likely most pronounced in patients requiring long-term therapy, and real-world data suggest that ~25% of patients treated with CTZ require >14 days of treatment [7]. Thus, in an era of MDR pathogens, the administration of CTZ at a dose of 1000/500 mg thrice weekly following iHD may represent an important treatment consideration.

Limitations of this anecdotal report should be recognized. First, tazobactam concentration determinations were hampered by unknown interfering substances. While this will not impact the activity of CTZ against *P. aeruginosa* as tazobactam has limited activity against this organism, the tazobactam concentration–time profile is a consideration for Enterobacterales, notably for those producing extended-spectrum beta-lactamases [20]. Although limited inference can be made from the tazobactam data in our patient, concentrations resulting from this regimen are expected to be sufficiently high based on its previously defined PK profile in patients with reduced renal function inclusive of end-stage renal disease on iHD [13]. Of note, subjects requiring iHD demonstrated a 2.3-fold change in the tazobactam C_{max} with ceftolozane-tazobactam compared with a 1.6-fold change observed with piperacillin-tazobactam [13]. Second, our patient produced significant urine, and >95% of ceftolozane is excreted in the urine as unchanged drug [6]. While this would similarly impact any iHD dosing regimen, consideration of intrinsic clearance is warranted. Finally, in addition to antimicrobial therapy, source control with below-knee amputation is credited as a pivotal intervention in our patient's case, and the 1000/500-mg thrice-weekly iHD dosing of CTZ may warrant caution in more acutely ill patients and in patients in whom CTZ dose optimization is required for adequate antimicrobial penetration into the source of infection. For instance, in patients with normal renal function, CTZ is approved for pneumonia at a higher dose of 3 g every 8 hours given that the epithelial lining fluid to plasma concentration is only 50% [21]. Although a prior report describes a patient with ESRD on iHD who presented with pneumonia due to *P. aeruginosa* and was cured with CTZ at a dose of 300 mg every 8 hours, further research is required to conclude that CTZ at a dose of 2000/100 mg thrice weekly following iHD would be an acceptable dosing strategy for the treatment of pneumonia [22].

CONCLUSIONS

Our observations in the current patient who received this novel 1000/500-mg thrice-weekly CTZ regimen following iHD support the robustness of drug exposures and the well-tolerated

nature of the regimen. This dosing strategy may represent a convenient dosing regimen for patients requiring iHD who suffer from infections due to MDR *P. aeruginosa*. However, further investigation of this dosing strategy is warranted to better characterize the PK profile, clinical efficacy in more severe infections, and utility in infections due to Enterobacterales.

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Patient consent. The patient's written consent was confirmed before collection of serum samples. All procedures followed were in accordance with the ethical standards of the Helsinki Declaration. This work was approved by the Yale New Haven Institutional Review Board.

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