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BRIEF REPORT

Plasma and Cerebrospinal Fluid Therapeutic Drug Monitoring of Ceftolozane and Tazobactam During Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Meningitis

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We report a case of multidrug-resistant *Pseudomonas aeruginosa* meningitis treated with ceftolozane-tazobactam with concomitant therapeutic drug monitoring of plasma and cerebral spinal fluid. The data suggest that ceftolozane-tazobactam may be an option for select central nervous system infections; however, treatment decisions should be interpreted on a case-by-case basis.

Keywords. beta-lactamase inhibitor; central nervous system; difficult-to-treat; gram-negative.

Multidrug-resistant (MDR) gram-negative bacteria associated with difficult-to-treat phenotypes are a major challenge in clinical practice and are associated with high mortality [1, 2]. Central nervous system (CNS) infections pose an additional layer of complexity for clinicians due to low and possibly inadequate antimicrobial concentrations obtained in cerebral spinal fluid (CSF) at standard dosing as well as the poorly described distribution of drug into other spaces within the CNS [3]. While recently developed β-lactam/β-lactamase inhibitors (BLBLIs) including ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam have demonstrated promise in the treatment of pneumonia, urinary tract infections, intraabdominal infections, and bloodstream infections due to carbapenem-resistant *Enterobacteriaceae* [4, 5] and *Pseudomonas aeruginosa* [6–8], the real-world experience for use of these agents in CNS infections is limited [9–19]. Here, we describe a case of MDR *P. aeruginosa* meningitis treated with ceftolozane-tazobactam with concomitant therapeutic drug monitoring (TDM).

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CASE

A 39-year-old male presented to a referring facility as a level 1 trauma following an unhelmeted motorcycle crash resulting in a right frontotemporal contusion with subarachnoid hemorrhage and subdural hematoma. The patient was emergently taken to the operating room (OR) for a right subdural hematoma evacuation and frontotemporal decompressive hemicraniectomy. Upon arrival to our facility the next day, repeat imaging demonstrated stable multiple compartment intracranial hemorrhage. On hospital day 10, the patient became tachycardic and had new-onset leukocytosis. He was subsequently taken to the OR for right frontotemporoparietal wound washout and revision. Operative cultures grew *Escherichia coli, Serratia marcescens,* methicillin-susceptible *Staphylococcus aureus, P. aeruginosa,* and *Bacteroides* spp., which were treated with meropenem 2 g intravenously (IV) every 8 hours infused over 30 minutes.

The patient had subsequent wound debridement on hospital day 19 and wound closure with tensor fascia dural graft placement on hospital day 21. On hospital day 37, while on continued meropenem treatment, the patient developed new fevers, worsening leukocytosis, and tachycardia. Corresponding blood cultures were negative; however, CSF cultures grew MDR *P. aeruginosa* (Table 1). In response, meropenem was discontinued in favor of ceftolozane-tazobactam 3 g (2 g ceftolozane, 1 g tazobactam) IV every 8 hours infused over 1 hour (minimum inhibitory concentration [MIC] = 1 μg/mL), ciprofloxacin 400 mg IV every 8 hours (MIC ≤ 1 μg/mL), and metronidazole 500 mg IV every 8 hours. In addition, tobramycin 10 mg (MIC ≤ 1 μg/mL) was administered intraventricularly once on hospital day 38, followed by 5 mg every 24 hours on days 40–43. The patient demonstrated rapid clinical improvement with resolution of fever, leukocytosis, and hemodynamic stability and was subsequently discharged to an inpatient rehabilitation unit on hospital day 55. He completed a 6-week course of ceftolozane-tazobactam, ciprofloxacin, and metronidazole with complete wound and flap healing and resolution of meningitis. The patient remained infection-free through 1 year after treatment completion.

PHARMACOKINETIC ANALYSIS

Steady-state plasma and CSF ceftolozane and tazobactam concentrations were measured on hospital days 42 and 44 (Table 1). CSF was drawn from an external ventricular drain (EVD).

Table 1. Ceftolozane and Tazobactam Plasma and CSF Levels Measured During Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Meningitis[a]

Hospital Day	Time	Action	Total Ceftolozane Concentration, μg/mL	Total Tazobactam Concentration, μg/mL
41	2344	2 g ceftolozane, 1 g tazobactam (dose #7) administered (1-h infusion)	NA	NA
42	0750	Plasma sample drawn	8.46	1.4
42	0801	2 g ceftolozane, 1 g tazobactam (dose #8) (1-h infusion)	NA	NA
42	1000	Plasma sample drawn	54.81	12.58
42	1210	Plasma sample drawn	29.45	3.34
42	1546	Plasma sample drawn	8.76	0.59
42	1625	2 g ceftolozane, 1 g tazobactam (dose #9) (1-h infusion)	NA	NA
42	1830	Plasma sample drawn	55.75	11.44
42	1830	CSF sample drawn	4.13	BDL
44	0755	2 g ceftolozane, 1 g tazobactam (dose #15) (1-h infusion)	NA	NA
44	0905	Plasma sample drawn	81.61	24.30
44	0905	CSF sample drawn	6.98	0.82

Abbreviations: BDL, below detectable limit of 0.4 μg/mL; CSF, cerebral spinal fluid; MIC, minimum inhibitory concentration; NA, no sample collected.

[a]*P. aeruginosa* isolate was resistant to aztreonam (MIC > 16 μg/mL), ceftazidime (MIC > 16 μg/mL), cefepime (MIC > 16 μg/mL), piperacillin/tazobactam (MIC > 64 μg/mL), and meropenem (MIC > 8 μg/mL) and susceptible to ciprofloxacin (MIC ≤ 1 μg/mL), gentamicin (MIC ≤ 1 μg/mL), tobramycin (MIC ≤ 1 μg/mL), ceftolozane/tazobactam (MIC = 1 μg/mL), and ceftazidime/avibactam (MIC = 3 μg/mL).

Whole-blood samples were immediately centrifuged; plasma and CSF were stored at −80°C until analysis by validated high-performance liquid chromatography (HPLC) as described previously [20]. At the time of sampling, the patient weighed 70 kg and had an estimated glomerular filtration rate of 119 mL/min/1.73 m^2. The patient was in the neurosurgical intensive care unit (ICU) but was not intubated or sedated at the time of sampling.

After the patient's eighth dose of ceftolozane-tazobactam, the calculated maximum (C_{max}) and minimum (C_{min}) plasma concentrations of ceftolozane were 72.7 μg/mL and 9.8 μg/mL, respectively. Ceftolozane half-life, Vd, and total body clearance from plasma were 2.42 hours, 35.9 L, and 10.28 L/h, respectively. Corresponding values for tazobactam were 23 μg/mL (C_{max}), 0.3 μg/mL (C_{min}), 1.13 hours ($t_{1/2}$), 32.6 L (Vd), and 19.9 L/h (CL). Two hours after the start of the next dose of ceftolozane-tazobactam, simultaneous samples from plasma and CSF showed ceftolozane concentrations of 55.75 μg/mL and 4.13 μg/mL, respectively. Total and free drug (assuming 20% plasma protein binding) penetration ratios were 0.074 and 0.093, respectively. Corresponding tazobactam concentrations from plasma and CSF were 11.44 μg/mL and <0.4 μg/mL, respectively. Repeat plasma and CSF samples drawn 1 hour after the start of 15th dose showed ceftolozane concentrations of 81.61 μg/mL and 6.98 μg/mL, respectively; calculated penetration ratios using total and free drug concentrations were 0.085 and 0.107. At the same time point, the tazobactam concentration in plasma was 24.30 μg/mL, and in CSF it was 0.82 μg/mL.

DISCUSSION

We present a case of MDR *P. aeruginosa* meningitis treated with ceftolozane-tazobactam where concomitant TDM was performed in both plasma and CSF. The confluence of drug-resistant bacteria causing a life-threatening infection at a body site impermeable to many antibiotics represents a serious challenge to clinicians. For these reasons, we opted to use combination therapy for this patient, which confounds the interpretation of any specific therapy on the patient outcome. It is unclear if a shorter duration of therapy or treatment with monotherapy would have resulted in a similar outcome. Nevertheless, we have shown that therapeutic concentrations of ceftolozane were achieved in the CSF with standard doses that may have contributed to clinical cure for the patient.

Our experience builds upon limited clinical data describing the use of ceftolozane-tazobactam for the treatment of meningitis and is similar to a previously published case report of MDR *P. aeruginosa* otogenous meningitis treated with ceftolozane-tazobactam in combination with IV fosfomycin, rifampin, and appropriate source control [14]. Another case report of ceftolozane-tazobactam for MDR *P. aeruginosa* meningitis is a 22-year-old male who received monotherapy for 11 days with initial microbiological cure and a favorable clinical outcome, but had recurrence of infection by day 28 [16]. Winans and colleagues described a 36-year-old male who received ceftolozane-tazobactam 9 g via continuous infusion for treatment of carbapenem-resistant *P. aeruginosa* meningitis; they measured ceftolozane concentrations in the CSF, which were 83% of those in the serum [19]. There are also limited data to suggest that ceftazidime-avibactam may be a viable option for treatment of meningitis. In our case, ceftolozane-tazobactam was chosen based on our local susceptibility rates, which demonstrate a higher likelihood of activity in the empiric setting, and was continued after susceptibility testing confirmed a lower MIC than ceftazidime-avibactam against the MDR *P. aeruginosa* isolate.

While the pharmacokinetics of antibiotics in the CSF are poorly defined, the half-life of cephalosporins may be prolonged and vary based on rates of CSF production, EVD drainage pressure scale and alternations, volume of CSF space including ventricle size, and integrity of the blood–brain barrier [3]. As drug entry into the CSF is delayed compared with other body fluids and compartments through a phenomenon known as system hysteresis, it is likely that the ratio of drug in CSF to plasma increases from the time of initiation of the drug infusion [18, 21]. Therefore, the ratio of the AUC of CSF to serum at steady state (AUC_{CSF}/AUC_{SS}) is the most accurate means of characterizing drug penetration into the CSF [3, 18]. The AUC_{CSF}/AUC_{Ss} for traditional cephalosporins ranges from 0.007 to 0.17 and is dependent upon the degree of meningeal inflammation and other patient-specific factors [3, 22]. Recently, Sime and colleagues evaluated 10 critically ill patients with an indwelling EVD and found a mean free AUC_{CSF}/AUC_{plasma} ratio of 0.2 after a single 3-g dose of ceftolozane/tazobactam [18]. Notably *f*AUC ratios were highly variable (SD of 0.2) and lower among patients without CNS infections (mean penetration ratio of 0.0685 ± 0.0156). We were unable to define the AUC_{CSF} for our patient due to limited EVD drainage; however, our point estimates are similar to those described for cephalosporins used commonly in the treatment of meningitis, even in patients with uninflamed meninges [3]. It should be noted that at the time of sampling, our patient had been hospitalized for 6 weeks and demonstrated stable encephalomalacia on imaging. We anticipate that ceftolozane penetration ratios may be even higher in the setting of acute meningeal inflammation compared with those observed here, which are consistent with the findings of Sime and colleagues [18].

The ceftolozane-tazobactam MIC was 1 μg/mL against the *P. aeruginosa* strain in this case, and thus pharmacodynamic targets of 100% *f*T > MIC and 100% *f*T > 4× MIC were achieved in the plasma. These targets are useful predictors of clinical efficacy and suppression of resistance, respectively [23]. A plasma level drawn 4 hours after the start of the ceftolozane infusion in our patient was 29.45 μg/mL; if 9%–11% of unbound ceftolozane penetrated into the CNS as suggested by our sampling, then at least 50% *f*T > MIC was achieved in the CNS. The efficacy target for ceftolozane and *P. aeruginosa* meningitis has not been described. In a nonmeningitis murine model, an *f*T > MIC of 31.5% ± 3.9% achieved 1-$\log_{10}$ bacterial kill against wild-type *P. aeruginosa,* a threshold lower than other cephalosporins that is associated with more rapid killing of *P. aeruginosa* [24].

It is important to note that while CSF concentration is the closest approximation of drug concentration in the extracellular space of the CNS and is therefore used in clinical practice as a surrogate of total drug exposure in the CNS, it has been demonstrated that antibiotic levels in the CSF vary significantly and do not predict clinical cure [25]. Moreover, it is unknown how drug concentrations in various compartments of the nervous tissue (eg, interstitial space, meningeal layers) are related to CSF concentrations at any point in time. Indeed, biopsied animal brain tissue has demonstrated antimicrobial concentrations in brain parenchyma that are 10%–20% of those in serum despite undetectable CSF levels [26].

Our data should be interpreted cautiously when considering ceftolozane-tazobactam for non–*P. aeruginosa* CNS infections. The concentration threshold of free tazobactam when combined with ceftolozane for efficacy in CTX-15-producing *Escherichia coli* and *Klebsiella pneumoniae* infections has been described as half the value of the ceftolozane-tazobactam MIC (ie, a tazobactam concentration threshold of 0.5 μg/mL for an isolate with an MIC of 1 μg/mL) for 77% of the dosing interval to achieve a change in $\log_{10}$ CFU from baseline [27]. Based on our patient's peak tazobactam concentration in CSF and previously published pharmacokinetic data regarding tazobactam and CSF, ceftolozane-tazobactam is unlikely to achieve the tazobactam pharmacodynamic target necessary for 1-$\log_{10}$ bacterial kill against extended-spectrum β-lactamase (ESBL)–producing *Enterobacterales* in the CSF [28].

CONCLUSIONS

This is the first described case of steady-state plasma and CSF ceftolozane and tazobactam concentrations measured during the treatment of MDR *P. aeruginosa* bacterial meningitis. The data suggest that ceftolozane pharmacodynamic targets in both the CSF and plasma can be achieved using a regimen of 3g IV q 8h; however, these data should be interpreted on a case-by-case basis. Further investigations are needed to make any distinction between specific β-lactam/β-lactamase inhibitor combinations for meningitis, for monotherapy vs combination therapy considerations, and to determine the optimal duration of treatment for MDR *P. aeruginosa* meningitis.

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Patient consent. The patient's written consent was confirmed before collection of plasma and CSF samples. All procedures followed were

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References

1. Kadri SS, Adjemian J, Lai YL, et al; National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI). Difficult-to-treat resistance in gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis **2018**; 67:1803–14.
2. Huh K, Chung DR, Ha YE, et al. Impact of difficult-to-treat resistance in gram-negative bacteremia on mortality: retrospective analysis of nationwide surveillance data. Clin Infect Dis **2020**; 71:e487–96.
3. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev **2010**; 23:858–83.
4. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother **2017**; 61:e00883–17.
5. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. Infect Dis Ther **2018**; 7:439–55.
6. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. Clin Infect Dis **2020**; 70:1799–808.
7. Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant pseudomonas aeruginosa. Clin Infect Dis **2020**; 71:304–10.
8. Jorgensen SCJ, Trinh TD, Zasowski EJ, et al. Real-world experience with ceftazidime-avibactam for multidrug-resistant gram-negative bacterial infections. Open Forum Infect Dis **2019**; 6:XXX–XX.
9. Iosifidis E, Chorafa E, Agakidou E, et al. Use of ceftazidime-avibactam for the treatment of extensively drug-resistant or pan drug-resistant *Klebsiella pneumoniae* in neonates and children <5 years of age. Pediatr Infect Dis J **2019**; 38:812–5.
10. Gofman N, To K, Whitman M, Garcia-Morales E. Successful treatment of ventriculitis caused by *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae* with i.v. ceftazidime-avibactam and intrathecal amikacin. Am J Health Syst Pharm **2018**; 75:953–7.
11. Rodríguez-Núñez O, Ripa M, Morata L, et al. Evaluation of ceftazidime/avibactam for serious infections due to multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa*. J Glob Antimicrob Resist **2018**; 15:136–9.
12. Holyk A, Belden V, Lee JJ, et al. Ceftazidime/avibactam use for carbapenem-resistant *Klebsiella pneumoniae* meningitis: a case report. J Antimicrob Chemother **2018**; 73:254–6.
13. Xipell M, Bodro M, Marco F, et al. Clinical experience with ceftazidime/avibactam in patients with severe infections, including meningitis and lung abscesses, caused by extensively drug-resistant *Pseudomonas aeruginosa*. Int J Antimicrob Agents **2017**; 49: 266–8.
14. Frattari A, Savini V, Polilli E, et al. Ceftolozane-tazobactam and fosfomycin for rescue treatment of otogenous meningitis caused by XDR *Pseudomonas aeruginosa*: case report and review of the literature. IDCases **2018**; 14:e00451.
15. Samuel S, Edwards NJ, Rojas JL, et al. Ceftazidime-avibactam for the treatment of post-neurosurgical meningitis caused by a *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*. Open Forum Infect Dis **2016**; 3:1182.
16. Dinh A, Wyplosz B, Kernéis S, et al. Use of ceftolozane/tazobactam as salvage therapy for infections due to extensively drug-resistant *Pseudomonas aeruginosa*. Int J Antimicrob Agents **2017**; 49:782–3.
17. Yasmin M HJ, Marshall S, et al. Using therapeutic drug monitoring to treat KPC-producing *Klebsiella pneumoniae* central nervous system infection with ceftazidime/avibactam. Open Forum Infect Dis **2020**; XXX:XXX–XX.
18. Sime FB, Lassig-Smith M, Starr T, et al. Cerebrospinal fluid penetration of ceftolozane/tazobactam in critically ill patients with an indwelling external ventricular drain [published online ahead of print October 19 2020]. Antimicrob Agents Chemother **2020**. doi: 10.1128/AAC.01698-20.
19. Winans SA, Guerrero-Wooley RL, Park SH, et al. Continuous infusion of ceftolozane-tazobactam resulted in high cerebrospinal fluid concentrations of ceftolozane in a patient with multidrug-resistant *Pseudomonas aeruginosa* meningitis [published online ahead of print August 29, 2020]. Infection **2020**. doi: 10.1007/s15010-020-01510-8.
20. Sutherland CA, Nicolau DP. Development of an HPLC method for the determination of ceftolozane/tazobactam in biological and aqueous matrixes. J Chromatogr Sci **2016**; 54:1037–40.
21. Nau R, Zysk G, Thiel A, Prange HW. Pharmacokinetic quantification of the exchange of drugs between blood and cerebrospinal fluid in man. Eur J Clin Pharmacol **1993**; 45:469–75.
22. Lodise TP Jr, Rhoney DH, Tam VH, et al. Pharmacodynamic profiling of cefepime in plasma and cerebrospinal fluid of hospitalized patients with external ventriculostomies. Diagn Microbiol Infect Dis **2006**; 54:223–30.
23. Tam VH, Chang KT, Zhou J, et al. Determining β-lactam exposure threshold to suppress resistance development in gram-negative bacteria. J Antimicrob Chemother **2017**; 72:1421–8.
24. Craig WA, Andes DR. In vivo activities of ceftolozane, a new cephalosporin, with and without tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae, including strains with extended-spectrum β-lactamases, in the thighs of neutropenic mice. Antimicrob Agents Chemother **2013**; 57:1577–82.
25. Beach JE, Perrott J, Turgeon RD, Ensom MHH. Penetration of vancomycin into the cerebrospinal fluid: a systematic review. Clin Pharmacokinet **2017**; 56:1479–90.
26. Kethireddy S, Andes D. CNS pharmacokinetics of antifungal agents. Expert Opin Drug Metab Toxicol **2007**; 3:573–81.
27. Vanscoy B, Mendes RE, McCauley J, et al. Pharmacological basis of β-lactamase inhibitor therapeutics: tazobactam in combination with ceftolozane. Antimicrob Agents Chemother **2013**; 57:5924–30.
28. Nau R, Kinzig-Schippers M, Sörgel F, et al. Kinetics of piperacillin and tazobactam in ventricular cerebrospinal fluid of hydrocephalic patients. Antimicrob Agents Chemother **1997**; 41:987–91.