AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Multidrug-Resistant *Pseudomonas aeruginosa* Infection in a Child with Cystic Fibrosis

Jocelyn Y. Ang,[a,b] Nahed Abdel-Haq,[a,b] Frank Zhu,[a,b] Abrar K. Thabit,[c,d] David P. Nicolau[c,e]

Michael J. Satlin (Commentator),[f,g] David van Duin (Commentator)[h]

Division of Infectious Diseases, Children's Hospital of Michigan, Detroit, Michigan, USA[a]; Department of Pediatrics, Wayne State University School of Medicine, Detroit, Michigan, USA[b]; Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, USA[c]; Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia[d]; Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut, USA[e]; Division of Infectious Diseases, Weill Cornell Medicine, New York, New York, USA[f]; Transplantation-Oncology Infectious Diseases Program, Weill Cornell Medicine, New York, New York, USA[g]; Division of Infectious Diseases, University of North Carolina, Chapel Hill, North Carolina, USA[h]

This Journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. Two expert clinicians then provide a commentary on the case.

We describe a pediatric cystic fibrosis patient who developed a pulmonary exacerbation due to two multidrug-resistant (MDR) *Pseudomonas aeruginosa* isolates. In addition to these MDR organisms, the case was further complicated by β-lactam allergy. Despite the MDR phenotype, both isolates were susceptible to an antimicrobial combination.

CASE PRESENTATION

A 14-year-old female with a history of cystic fibrosis (CF) and β-lactam allergy presented with acute onset of difficulty of breathing, fever, and productive cough. Initial respiratory culture grew 2 strains of *Pseudomonas aeruginosa*. The nonmucoid *Pseudomonas* isolate was resistant to meropenem (MIC, 8 μg/ml) and tobramycin and gentamicin (for both, MIC of >8 μg/ml) but sensitive to ceftazidime (MIC, 8 μg/ml), cefepime (MIC, 4 μg/ml), piperacillin-tazobactam (TZP; MIC, ≤2/4 μg/ml), ciprofloxacin (MIC, < 0.5 μg/ml), and amikacin (MIC, 16 μg/ml). The mucoid *Pseudomonas* isolate was resistant to tobramycin (MIC, >1,024 μg/ml) and intermediate to cefepime (MIC, 16 μg/ml) but sensitive to meropenem (MIC, 0.125 μg/ml), amikacin (MIC, <8 μg/ml), TZP (MIC, ≤2/4 μg/ml), and ciprofloxacin (MIC, <0.5 μg/ml).

The patient was initially started on intravenous (i.v.) ciprofloxacin and amikacin treatment. Due to persistent fevers and increasing oxygen requirement, she underwent desensitization to TZP on day 6 of hospitalization because of history of cefepime allergy (rash). Because it was not clear whether this was an immediate-type sensitivity reaction and because of her critical respiratory status, desensitization to TZP was executed. Piperacillin-tazobactam at 2,400 mg was infused (over 1 h) every 6 h. Ciprofloxacin was continued. Because of lack of clinical improvement, extended infusion (over 3 h) of TZP was initiated on day 14 of hospitalization. However, minimal clinical improvement was noted over the next several days, and repeat respiratory culture obtained on day 15 of hospitalization revealed the development of multidrug resistance (MDR) in the mucoid strain, which was now resistant to cefepime (MIC, 32 μg/ml) and intermediate to TZP (MIC, 32/4 μg/ml) and ciprofloxacin (MIC, 2 μg/ml) (see Table S1 in the supplemental material).

CHALLENGE QUESTION

What would be the best treatment option for this patient at this time?

A. Ceftazidime-avibactam (C/A)
B. Ceftolozane-tazobactam (C/T)
C. Continuous piperacillin-tazobactam infusion
D. Combination treatment with ceftazidime and ciprofloxacin

TREATMENT AND OUTCOME

Additional susceptibility testing of the *Pseudomonas* isolates revealed sensitivity to C/T in both mucoid and nonmucoid *Pseudomonas* strains (mucoid strain MIC, 0.5 μg/ml; nonmucoid strain MIC, 1 μg/ml). On day 20 of hospitalization, the patient underwent C/T desensitization (see Table S2 in the supplemental material) to a cumulative dose of 1.5 g and then C/T was given at 1.5 g every 8 h (q8h) (equivalent to 93 mg/kg of body weight/day of ceftolozane component) based on approved dosing for adults (1). Ciprofloxacin i.v. (30 mg/kg/day) was continued for double coverage of MDR *Pseudomonas*. A validated high-performance liquid chromatography (HPLC) method was utilized to determine the plasma concentrations of ceftolozane and tazobactam at the Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT. Blood samples ($n = 4$) were collected after administration of the fourth dose of C/T 1.5 g q8h given as a 1-h intravenous infusion. Pharmacokinetic (PK) parameters of C/T were modeled from their total concentrations in the plasma using one-compartment first-order input and elimination, by nonlinear least-squares techniques (Phoenix version 6.3; Pharsight Corp., Mountain View, CA). Compartment model selection was based on visual inspection of the pharmacokinetic profile and use of the correlation between the observed and calculated con-

Citation Ang JY, Abdel-Haq N, Zhu F, Thabit AK, Nicolau DP, Satlin MJ (Commentator), van Duin D (Commentator). 2016. Multidrug-resistant *Pseudomonas aeruginosa* infection in a child with cystic fibrosis. Antimicrob Agents Chemother 60:5627–5630. doi:10.1128/AAC.00705-16.

Address correspondence to Jocelyn Y. Ang (case author), jang@dmc.org, or David van Duin (commentator), david_vanduin@med.unc.edu.

Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.00705-16.

TABLE 1 Modeled pharmacokinetic parameters of ceftolozane and tazobactam at steady state based on total plasma concentrations (one-compartment model)[a]

Drug	C_{max} (μg/ml)	C_{min} (μg/ml)	AUC_{0-8} (μg · h/ml)	V (liters)	k_{el} (h^{-1})	$t_{1/2}$ (h)	CL (liters/h)
Ceftolozane	94.1	1.2	201.1	7.9	0.6	1.1	5.0
Tazobactam	12.1	0.04	21.4	28.1	0.8	0.8	23.3

[a] V, volume of distribution; k_{el}, elimination rate constant; $t_{1/2}$, half-life; C_{max}, peak plasma concentration; C_{min}, trough plasma concentration; AUC_{0-8}, area under drug concentration-time curve for the dosing interval; CL, clearance.

centrations. Since the percentage of the dosing interval in which free drug concentrations remain above the MIC (%*f*T>MIC) is the pharmacodynamic parameter that correlates with the antimicrobial efficacy of β-lactams (2), the pharmacokinetic parameters derived from the patient's C/T concentration-time profile were used to simulate a variety of C/T dosing regimens (1.5 g q8h given as 1-h infusion, 1.5 g q8h as 3-h infusion, 1.5 g q6h as 1-h infusion, 1.5 g q6h as 3-h infusion, 3 g q8h as 1-h infusion, and 3 g q8h as 3-h infusion) to highlight the impact of altering the dose and/or duration of infusion on drug exposures (i.e., %*f*T>MIC). Free ceftolozane concentrations were calculated based on mean percentage of plasma protein binding of 19% (range, 16 to 21%) (1). The %*f*T>MIC of ceftolozane was calculated using MIC values of 0.5, 1, 2, 4, and 8 μg/ml. These ceftolozane MIC values were selected to encompass the MICs observed in the current case as well as the MIC_{50} (2 μg/ml) and MIC_{90} (8 μg/ml) previously reported for *P. aeruginosa* derived from a CF population (3).

Modeled pharmacokinetic estimates of ceftolozane and tazobactam based on total plasma concentrations of the two compounds are shown in Table 1. Calculations of %*f*T>MIC values of ceftolozane for each of the simulated doses against the tested MIC range are shown in Table 2. All regimens exceeded the target *f*T>MIC of 40% (4) against the tested MICs where the lowest value was 56.3% and seen with the first regimen of 1.5 g q8h as 1-h infusion against MIC of 8 μg/ml.

Although C/A was a possible option, C/T was thought to be better than ceftazidime-avibactam because C/T has been shown *in vitro* to have enhanced potency against MDR *P. aeruginosa* isolates that have chromosomal AmpC enzymes, upregulation of efflux pumps, or loss of outer membrane porin, including carbapenem-resistant strains, for which C/A is less active. In addition, C/T was well tolerated when given in high doses to CF patients who may present with rapid drug clearance (5, 6). A recent study by Kuti and colleagues showed that C/T was associated with potent *in vitro* activity against *P. aeruginosa* isolates collected from children with CF, as bacterial susceptibility to the compound was 86% compared with 46%, 58%, and 50% for meropenem, ceftazidime, and piperacillin-tazobactam, respectively (3). Similarly, another study by Zamorano et al. showed superior *in vitro* potency of C/T to comparator antibiotics against *P. aeruginosa* isolates, including MDR isolates, from CF patients chronically infected with the organism (7). Although the *P. aeruginosa* isolate was susceptible to ceftazidime, it was not used in the setting of cefepime resistance. Since our patient was already receiving the maximum dose of TZP with extended infusion, continuous TZP infusion was not felt to be beneficial.

TABLE 2 Calculations of %*f*T>MIC values of simulated ceftolozane-tazobactam dosing regimens

Dose (duration of intravenous infusion)	%*f*T>MIC against MIC (μg/ml):				
	0.5	1	2	4	8
1.5 g q8h (1 h)	100	97.50	83.75	70	56.3
1.5 g q8h (3 h)	100	100	98.75	84.6	69.6
1.5 g q6h (1 h)	100	100	100	94.6	76.3
1.5 g q6h (3 h)	100	100	100	99.6	95.4
3 g q8h (1 h)	100	100	100	92.5	78.8
3 g q8h (3 h)	100	100	100	100	93.8

When the modeled pharmacokinetics of ceftolozane in our patient were compared with the parameters observed in healthy adult volunteers following a dose of 1.5 g q8h over 1 h (1), a higher peak plasma concentration (94.1 versus 74.4 μg/ml), a shorter half-life (1.1 versus 3.1 h), and a smaller volume of distribution (7.9 versus 13.5 liters) were seen in our pediatric patient. The short half-life indicates a faster clearance profile of ceftolozane, which can be attributed to her pediatric status as well as her underlying CF, a disease state which is generally associated with faster body clearance of drugs (6).

The reported target *f*T>MIC of ceftolozane against *P. aeruginosa* for 1-log killing is 40% (4). In this study, we showed that C/T administered at a dose of 1.5 g q8h over 1 h in this 32-kg CF patient was associated with pharmacodynamic target achievement of >40% *f*T>MIC against the two *P. aeruginosa* isolates with MICs of 0.5 and 1 μg/ml. Moreover, we demonstrated that the utilization of a higher dose, more frequent administration, and/or prolonged infusion of C/T in this pediatric patient offers the opportunity for pharmacodynamic optimization with organisms displaying a MIC value up to 8 μg/ml.

There was rapid improvement in her respiratory status, with successful wean of supplemental oxygen from 6 liters to room air over the following 5 days after C/T was initiated. On day 6 of C/T therapy, she was noted to have mild transaminitis (alanine aminotransferase [ALT] level increased from 51 to 106 units/liter over the last week). Additionally, she was also concomitantly receiving i.v. daptomycin treatment for *Staphylococcus aureus*-associated catheter-related bloodstream infection and completed a 14-day course 1 day earlier. Thus, the etiology of this mild transaminitis was not clear. Nevertheless, a 50% dose reduction of C/T was initiated (new dose, 750 mg q8h; 46.5-mg/kg/day ceftolozane component) with subsequent improvement in transaminitis noted 5 days later (ALT level, 77 units/liter). No other adverse events were attributed to C/T in this β-lactam-allergic pediatric patient. Upon completion of a 14-day i.v. antibiotic course of C/T and ciprofloxacin, she was discharged in stable condition (see Fig. S1 in the supplemental material). At the 2-week-postdischarge follow-up, she had returned to baseline respiratory status, remained afebrile, was tolerating her home g-tube feeds, and remained well at her next follow-up 3 months later.

In conclusion, C/T provided a potent *in vitro* option despite the MDR phenotypic profile displayed by the *P. aeruginosa* isolates

infecting our pediatric patient. As such, this new compound was a viable option for our patient and thus may be considered a potent alternative agent to treat patients with CF infected with *P. aeruginosa*. Despite the β-lactam allergy of our patient and a milligram-per-kilogram dose that was 2 to 3 times that observed in adults, C/T was well tolerated. Moreover, this case also provides pharmacokinetic data in support of the currently utilized 1.5-g q8h dose administered over 1 h in this pediatric patient and further reveals that manipulations of the dose, dosing interval, and/or infusion duration may provide opportunities to optimize the exposures of C/T up to a MIC of 8 μg/ml. Since the pharmacokinetics of drugs may be altered in patients with CF, additional studies assessing the pharmacokinetics of C/T in this patient population are warranted.

COMMENTARY

Respiratory infections caused by *Pseudomonas aeruginosa* are common in patients with CF and are associated with decreased lung function and survival (8). In particular, patients with CF are prone to becoming colonized and infected with mucoid phenotypes of *P. aeruginosa*. This case describes treatment-emergent resistance in mucoid *P. aeruginosa* in an adolescent with CF.

This case highlights the remarkable ability of *P. aeruginosa* to develop resistance during antimicrobial therapy, particularly in the setting of pneumonia. In a randomized clinical trial that compared doripenem to imipenem for ventilator-associated pneumonia (VAP), carbapenem resistance developed while on therapy in approximately one-third of cases caused by *P. aeruginosa* (9). This high rate of developing resistance on therapy is due to the multiple mechanisms of resistance that *P. aeruginosa* can upregulate in the presence of β-lactam agents, such as increased production of efflux pumps and AmpC β-lactamases (10). Combination therapy with a β-lactam and a fluoroquinolone, as used in this patient, has demonstrated the ability to suppress the emergence of resistance to either agent in a murine model of *P. aeruginosa* pneumonia (11). However, the ability of combination therapy to prevent the emergence of resistance has not been properly evaluated in clinical studies and prevention was not successful in this case. Furthermore, various hypermutable *P. aeruginosa* clones with different resistance phenotypes may coexist, and MDR clones may become dominant under antibiotic pressure (12).

An additional strategy that was used in this patient was extended-infusion TZP. The rationale for this extended infusion is to maximize the time that the free concentration of TZP is greater than the MIC, which is correlated with optimal bactericidal killing in preclinical models. Observational studies have demonstrated improved clinical outcomes in critically ill patients with *P. aeruginosa* infection who receive a prolonged infusion of TZP compared with a 30-min infusion (13). Unfortunately, by the time that extended-infusion TZP was initiated in this patient, the MIC against the mucoid strain of *P. aeruginosa* had increased to 32/4 μg/ml (intermediate). At this MIC, even an extended-infusion regimen of TZP may not yield adequate exposures that are required for maximal bactericidal activity.

C/T therapy was then initiated and resulted in a good clinical response in this patient. C/T is a newly available antimicrobial agent with enhanced *in vitro* activity against *P. aeruginosa* compared to other cephalosporins (14). Approximately 70% of *P. aeruginosa* strains that are not susceptible to ceftazidime, meropenem, and TZP are susceptible to C/T based on CLSI breakpoints (14). The enhanced antipseudomonal activity of this combination is due to ceftolozane, as tazobactam does not inhibit AmpC β-lactamases produced by this organism. To date, the efficacy of C/T has been evaluated only in clinical trials of complicated urinary tract and intra-abdominal infections (14). Furthermore, these trials enrolled very few patients with MDR *P. aeruginosa* infections. A randomized clinical trial is under way (ClinicalTrials.gov registration no. NCT02070757) to evaluate the safety and efficacy of C/T for VAP.

An additional important component of this case was the assessment of C/T bloodstream concentrations to establish a pharmacokinetic (PK) model for this agent in adolescent patients with CF. The PK parameters identified in this patient were different from those observed in healthy adult volunteers, highlighting the importance of studies that assess PK parameters in critically ill patients, including pediatric patients. Using PK modeling, the authors found that the U.S. FDA-approved adult dosage of 1.5 g q8h in this 32-kg adolescent would reliably achieve the optimal pharmacodynamic target for *P. aeruginosa* strains with C/T MICs of 0.5 or 1 μg/ml. This dosage, in milligrams per kilogram, is similar to the 3-g q8h dosage that is being evaluated in the clinical trial of C/T for VAP in adults. The authors' PK modeling also suggests that prolonged infusions of C/T or q6h dosing may be necessary to reliably achieve target exposures when the C/T MIC is 4 to 8 μg/ml.

This illustrative case highlights the remarkable capacity for *P. aeruginosa* to develop resistance on therapy and the potential role of C/T for MDR *P. aeruginosa* pneumonia. Additional studies are needed to identify the optimal dosing of C/T for this indication, particularly in pediatric patients with CF who are highly vulnerable to these infections.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. **Merck & Co., Inc.** 2015. Product information: Zerbaxa intravenous injection, ceftolozane/tazobactam intravenous injection. Merck & Co., Inc., Whitehouse Station, NJ.
2. **Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, Drusano GL.** 2007. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis **44:**79–86. http://dx.doi.org/10.1086/510079.
3. **Kuti JL, Pettit RS, Neu N, Cies JJ, Lapin C, Muhlebach MS, Novak KJ, Nguyen ST, Saiman L, Nicolau DP.** 2015. Microbiological activity of ceftolozane/tazobactam, ceftazidime, meropenem, and piperacillin/tazobactam against *Pseudomonas aeruginosa* isolated from children with cystic fibrosis. Diagn Microbiol Infect Dis **83:**53–55. http://dx.doi.org/10.1016/j.diagmicrobio.2015.04.012.
4. **Lepak AJ, Reda A, Marchillo K, Van Hecker J, Craig WA, Andes D.** 2014. Impact of MIC range for *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* on the ceftolozane *in vivo* pharmacokinetic/pharmacodynamic target. Antimicrob Agents Chemother **58:**6311–6314. http://dx.doi.org/10.1128/AAC.03572-14.
5. **Hong MC, Hsu DI, Bounthavong M.** 2013. Ceftolozane/tazobactam: a novel antipseudomonal cephalosporin and beta-lactamase-inhibitor combination. Infect Drug Resist **6:**215–223. http://dx.doi.org/10.2147/IDR.S36140.
6. **Touw DJ.** 1998. Clinical pharmacokinetics of antimicrobial drugs in cystic fibrosis. Pharm World Sci **20:**149–160. http://dx.doi.org/10.1023/A:1008634911114.
7. **Zamorano L, Juan C, Fernandez-Olmos A, Ge Y, Canton R, Oliver A.** 2010. Activity of the new cephalosporin CXA-101 (FR264205) against *Pseudomonas aeruginosa* isolates from chronically-infected cystic fibrosis patients. Clin Microbiol Infect **16:**1482–1487. http://dx.doi.org/10.1111/j.1469-0691.2010.03130.x.
8. **Pritt B, O'Brien L, Winn W.** 2007. Mucoid Pseudomonas in cystic

fibrosis. Am J Clin Pathol **128:**32–34. http://dx.doi.org/10.1309/KJRPC7DD5TR9NTDM.

9. **Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I.** 2008. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. Crit Care Med **36:**1089–1096. http://dx.doi.org/10.1097/CCM.0b013e3181691b99.
10. **Breidenstein EB, de la Fuente-Nunez C, Hancock RE.** 2011. Pseudomonas aeruginosa: all roads lead to resistance. Trends Microbiol **19:**419–426. http://dx.doi.org/10.1016/j.tim.2011.04.005.
11. **Louie A, Liu W, VanGuilder M, Neely MN, Schumitzky A, Jelliffe R, Fikes S, Kurhanewicz S, Robbins N, Brown D, Baluya D, Drusano GL.** 2015. Combination treatment with meropenem plus levofloxacin is synergistic against Pseudomonas aeruginosa infection in a murine model of pneumonia. J Infect Dis **211:**1326–1333. http://dx.doi.org/10.1093/infdis/jiu603.
12. **Oliver A, Canton R, Campo P, Baquero F, Blazquez J.** 2000. High frequency of hypermutable Pseudomonas aeruginosa in cystic fibrosis lung infection. Science **288:**1251–1254. http://dx.doi.org/10.1126/science.288.5469.1251.
13. **Lodise TP, Jr, Lomaestro B, Drusano GL.** 2007. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis **44:**357–363. http://dx.doi.org/10.1086/510590.
14. **van Duin D, Bonomo RA.** 2016. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation beta-lactam/beta-lactamase inhibitor combinations. Clin Infect Dis **63:**234–241. http://dx.doi.org/10.1093/cid/ciw243.