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BRIEF REPORT

Multicenter Evaluation of Ceftolozane/Tazobactam for Serious Infections Caused by Carbapenem-Resistant *Pseudomonas aeruginosa*

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A multicenter, retrospective study of patients infected with carbapenem-resistant *Pseudomonas aeruginosa* who were treated with ceftolozane/tazobactam was performed. Among 35 patients, pneumonia was the most common indication and treatment was successful in 26 (74%). Treatment failure was observed in all cases where isolates demonstrated ceftolozane-tazobactam minimum inhibitory concentrations ≥8 μg/mL.

Keywords. ceftolozane; carbapenem resistant; *P. aeruginosa*; multidrug resistant.

Ceftolozane/tazobactam (C/T) is a novel combination of an oxyimino-aminothiazolyl cephalosporin (ceftolozane) and a β-lactamase inhibitor (tazobactam) [1]. C/T was recently approved for the treatment of complicated intra-abdominal and urinary tract infections (UTIs) [2]. Notably, C/T demonstrates activity against many multidrug-resistant (MDR) isolates of *Pseudomonas aeruginosa*, including carbapenem-resistant strains that do not produce a carbapenemase (eg, OprD loss or modification) [3–5]. Few clinical studies support the use of C/T to treat carbapenem-resistant *P. aeruginosa* infections. Here, we report a multicenter evaluation of patients with serious infections caused by carbapenem-resistant *P. aeruginosa* from different hospitals in the United States treated with C/T.

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MATERIALS AND METHODS

We retrospectively reviewed the clinical records of all patients diagnosed with an infection due to a carbapenem-resistant *P. aeruginosa* who received at least 72 hours of C/T while admitted to 6 hospitals located in Houston, Texas (n = 2), Seattle, Washington (n = 1), Cleveland, Ohio (n = 2), and Miami, Florida (n = 1). Eligible patients were identified using ongoing pharmacy registries available at each of the participating centers. The different types of infections were defined and classified following National Healthcare Safety Network criteria [6]. All relevant clinical and demographic data were extracted from the electronic medical records. The identification of the isolate and susceptibility profile was performed according to routine microbiologic methods at each participating center. Etest was performed following the manufacturer's recommendations to determine the minimum inhibitory concentration (MIC) to C/T. An MIC ≤4 μg/mL was considered susceptible, 8 μg/mL intermediate, and ≥16 μg/mL resistant according to the US Food and Drug Administration–approved labeling [7].

The decision to use C/T as well as the dose and duration prescribed were at the discretion of the treating physicians. We extracted information regarding demographic and medical history, renal function, source of the infection (based on culture type and medical record documentation), and clinical outcomes. Clinical success was defined as a composite of in-hospital survival, resolution of signs and symptoms of the infection (as reported by treating physicians), and absence of recurrence of the infection within the admission. Microbiologic failure was defined as persistence of clinical cultures yielding *P. aeruginosa* after 72 hours of therapy when repeated cultures were available. The institutional review board at each participating institution approved the study.

RESULTS

C/T was used in 35 patients with carbapenem-resistant *P. aeruginosa* infections (Supplementary Table 1). Pneumonia was the most common diagnosis (n = 18 [51%]) including 3 episodes in patients with cystic fibrosis and recurrent *P. aeruginosa* infections. Importantly, 6 patients were also reported to have a secondary bloodstream infection. Susceptibility profiles are summarized in Supplementary Table 2. Resistance to quinolones and β-lactams was commonly observed and most isolates were susceptible to colistin (87%) and to at least 1 aminoglycoside (88%) (Supplementary Figure 1; Supplementary Table 2). Susceptibility testing for C/T was not performed in 5 cases. Among the remaining 30 isolates, 26 (87%) were susceptible, 2 were intermediate, and 2 were fully resistant (with MICs of

16 μg/mL and 48 μg/mL). Among 23 isolates resistant to all other β-lactams tested, C/T remained active against 19 (83%) (Supplementary Table 2).

We next examined how clinicians used C/T. C/T was prescribed as monotherapy in 27 (77%) patients. Among the 8 subjects who received a concomitant antipseudomonal antibiotic, an inhaled drug was used in 5 patients (colistin and tobramycin), and systemic antimicrobials were administered on 4 occasions (ciprofloxacin in 2 and colistin and tobramycin in 1 each). A total of 31 (88%) patients received antimicrobials with expected activity against *P. aeruginosa* before the diagnosis of a carbapenem-resistant infection and initiation of C/T therapy. A wide variation of the dosing of C/T (Supplementary Table 1) was observed. Among subjects with a creatinine clearance >50 mL/minute (n = 20 [57%]), the approved dose of 1.5 g every 8 hours was used in 11 cases and the remaining 9 patients received 3 g every 8 hours. C/T dosing among 4 patients with a calculated creatinine clearance of 30–50 mL/minute ranged from 0.75 g to 1.5 g every 8 hours. Patients on intermittent hemodialysis (n = 3) received 0.375 g every 8 hours, and among 7 subjects undergoing continuous hemodialysis, the dose scheme ranged from 1.5 g to 0.375 g every 8 hours.

Treatment was considered successful using clinical standards in 26 (74%) of the 35 cases and follow-up cultures were available in 25 patients, none of whom was found to have a microbiological failure. A summary of 9 patients considered to have failed C/T therapy is provided in Table 1. Among them, the cause of death in 3 patients was not directly attributed to failure of C/T. Care was withdrawn in 1 case, another case developed polymicrobial pneumonia with carbapenem-resistant *Klebsiella pneumoniae* and MDR *Acinetobacter baumannii*, and death was secondary to a massive gastrointestinal hemorrhage in the third case. Considering the remaining 6 cases of clinical failure, 4 patients were infected with C/T nonsusceptible isolates and susceptibility testing results were not available in the other 2.

Two cases of adverse effects attributed to C/T were reported. One patient developed self-limited diarrhea with a negative *Clostridium difficile* molecular assay; the other was found to have peripheral eosinophilia and eosinophiluria and was thought to have possible interstitial nephritis. Renal injury did not develop and the eosinophilia resolved after stopping C/T (total duration of therapy was 14 days).

DISCUSSION

Although C/T is approved for complicated UTI and intraabdominal infections, clinicians have prescribed C/T to treat other infections due to the lack of options with reliable antipseudomonal activity [8]. Here, we analyzed the use of C/T in patients with serious infections caused by carbapenem-resistant *P. aeruginosa*. Our findings provide important insights into the "real world" performance of C/T in infections with limited therapies and add clinical context to the in vitro activity of this novel antibiotic.

Among clinical isolates from diverse geographic locations within the United States, C/T was active against 83% of *P. aeruginosa* isolates resistant to all other antipseudomonal β-lactams (Supplementary Figure 1), in agreement with previously reported data [4, 9]. In addition, resistance to C/T did not correlate with resistance to colistin, the current "drug of last resort" for MDR *P. aeruginosa*, as all isolates were susceptible to at least 1 of these 2 agents. It is important to highlight these properties as *P. aeruginosa* manifests a cadre of resistance strategies that could contribute to the MDR phenotype [10].

In our study, the use of C/T against these highly resistant strains was associated with successful clinical outcomes in 70% when used as monotherapy and in 87% of those who received C/T plus any other potentially active agent. These results compare favorably with most series evaluating different therapeutic approaches for the management of infections caused by MDR gram-negative organisms, including carbapenem-resistant *P. aeruginosa* strains. In particular, several retrospective studies have assessed the use of colistin in such clinical setting, reporting clinical success rates ranging between 40% and 60% [11–15]. Similarly, in terms of mortality, the all-cause in-hospital mortality rate in our series was 22.8%. Although the time points in which mortality was assessed varies (14-day, 30-day, in-hospital), several retrospective reports have found that the mortality of subjects infected with MDR *P. aeruginosa* and treated with colistin fluctuates between approximately 45% and 65%, which is certainly higher than what we observed in our study. Moreover, similar results in terms of mortality were recently found in a recently published prospective study that included 529 patients infected with a carbapenem-resistant gram-negative organism (only 89 *P. aeruginosa*), with a 28-day, all-cause mortality rate of 48% [16].

Therapeutic failure was reported in all cases in which the C/T MIC was above the Clinical and Laboratory Standards Institute susceptibility breakpoint of 4 mg/L (Supplementary Figure 2), and the 3 cases of treatment failure in patients whose isolates had MICs in the susceptible range were not directly attributed to an active *P. aeruginosa* infection (of note, C/T MICs were not available in the 2 remaining cases of failure). These results suggest that C/T susceptibility testing of confirmed *P. aeruginosa* infections should be strongly considered before initiating therapy with this antibiotic.

The limitations of this study include the retrospective nature of the data and reliance on documentation for assessing clinical outcomes via medical records review. Moreover, the decision to use C/T was at the discretion of the treating clinicians rather than prespecified in a protocol, and the use of previous therapy may have contributed to clinical success. Ideally, a prospective comparative trial of C/T vs polymyxin or aminoglycoside-based

Table 1. Summary of the Cases Considered as Therapeutic Failures

No.	Age	Sex	Infection	Type of Culture	C/T MIC	Creatinine Clearance, mL/min	Dose	Duration, d	Comments
10	71	F	Pelvic abscess	Fluid aspirate	2	30–50	0.75 g q8h	7	Patient had a recurrent uterine malignancy and developed and enterocutaneous fistula after hysterectomy. The cause of death was an acute massive gastric hemorrhage. Infection was thought to be under control with negative follow-up cultures
12	55	M	Pneumonia	BAL	1.5	CVVHD	0.375 g q8h	12	Patient with a history of end-stage liver disease secondary to alcoholism. Care was withdrawn as per family request.
15	39	M	Pneumonia	Blood	48	CVVHD	1.5 g q8h	7	Patient had a history of end-stage renal disease s/p renal transplant that failed to engraft. Admitted with septic shock and respiratory failure, died due to progressive multiorgan failure. No follow-up cultures yielded *Pseudomonas aeruginosa*
18	32	M	Pneumonia	Tracheal aspirate	8	>70	1.5 g q8h	18	Patient with a history of tetraplegia. Initial clinical improvement, but had a recurrent episode of pneumonia due to *P. aeruginosa*
20	61	M	Pneumonia	Pleural fluid	NR	HD	1.5 g once, then 0.375 g q8h	6	Patient had a history of interstitial lung disease s/p bilateral orthotopic lung transplant complicated with an active bronchopleural fistula. Admitted with pneumonia, died due to progressive respiratory failure
21	31	M	Pneumonia	Sputum	8	>70	1.5 g q8h	14	Patient had history of advanced cystic fibrosis s/p bilateral orthotopic lung transplant. Died of progressive respiratory failure
24	71	M	Pneumonia	Blood	16	>50	3 g q8h	5	History of myelodysplastic syndrome with leukemic conversion s/p chemotherapy. Rapid worsening, died with progressive respiratory compromise, septic shock, and multiorgan failure
30	75	M	Osteomyelitis	Bone	2	>70	3 g q8h	19	Patient had refractory cutaneous T-cell lymphoma and developed osteomyelitis of the left radius. He died due to septic shock secondary to pneumonia 22 days after the initial C/T dose. BAL cultures yielded MDR *Klebsiella pneumoniae* and *Acinetobacter baumannii*. No further *P. aeruginosa* was recovered after C/T therapy
34	26	M	Pneumonia	BAL	NR	30–50	1.5 g q8h	27	History of advanced cystic fibrosis and chronic kidney disease. Pneumonia initially improved after C/T, but had a new episode of pneumonia with *P. aeruginosa* within a week of finishing the antimicrobials and died of respiratory failure

Abbreviations: BAL, bronchoalveolar lavage; C/T, ceftolozane/tazobactam; CVVHD, continuous venovenous hemodialysis; HD, hemodialysis; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; NR, not reported; q8h, every 8 hours; s/p, status post.

therapy would need to be performed to definitively assess the comparative effectiveness of therapies for MDR *P. aeruginosa*. Until such a study is performed, the data collected in this multicenter study provide "real world" emerging clinical information about the use of C/T in challenging cases for which there is an urgent need for evidence to guide clinicians facing MDR *P. aeruginosa* without reliable therapeutic options. Our results suggest that C/T may be a useful option for severe infections caused by carbapenem-resistant *P. aeruginosa* that are confirmed to be susceptible to this novel β-lactam β-lactamase inhibitor combination.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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