Clinical and Safety Evaluation of Continuously Infused Ceftolozane/Tazobactam in the Outpatient Setting

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**Background.** Ceftolozane/tazobactam (C/T) is a novel cephalosporin/β-lactamase inhibitor currently dosed by 8-hour intervals to treat complicated and multidrug-resistant *Pseudomonas aeruginosa* infections in inpatients. This dosing strategy limits the ability to transition patients to outpatient antimicrobial therapy. There are limited data in the literature to support continuous infusion (CI) dosing.

**Methods.** This study is a retrospective chart review of patients who received CI C/T at an infusion center part of a community health system. Patients were evaluated from August 2016 through January 2018. Patients were included in the study if they were ≥ 18 years old and received their entire course of C/T as a CI in the outpatient setting. Patients were excluded if they received any part of their therapy as an inpatient.

**Results.** The primary outcome evaluated was symptom resolution. Secondary outcomes evaluated were microbiologic resolution as well as patient satisfaction. Seven patients received either 4.5 or 9 grams of continuous infusion C/T every 24 hours in the outpatient setting over the study period. For the primary outcome, 6 of 7 patients had symptom resolution. For the secondary outcomes, 3 of 3 patients had microbiologic resolution, and patient satisfaction scores were overall positive among respondents.

**Conclusions.** Ceftolozane/tazobactam delivered as a continuous infusion may be a safe, effective, and convenient way to treat infections caused by *P aeruginosa*. This novel treatment regimen can be an option for patients to avoid hospital admission or discharge to complete therapy as an outpatient.

**Keywords.** ceftolozane/tazobactam; OPAT.
RESULTS

Baseline Demographics

Seven patients received CI C/T therapy as outpatients and were included in the study. Median age was 71 years (range, 59–86 years), median creatinine clearance was 55 mL/minute (range, 41–130 mL/minute), and 5 of the 7 patients were female. All patients were afebrile at baseline and had baseline white blood cell counts within normal range, with the exception of 1 value of 14.43 k/mm$^3$.

Primary and Secondary Outcomes

Table 1 summarizes the patients' infectious diagnosis, antibiotic allergies, C/T therapy, susceptibility, and average satisfaction survey score, if applicable. All patients received C/T therapy as an outpatient, but 3 patients received different antimicrobial treatment as inpatients before being transitioned to C/T as outpatients. Patient 3 received 8 days of cefepime and tobramycin before completing therapy as an outpatient with 6 days of CI C/T. Patient 6 received 5 days of cefepime as an inpatient before transitioning to outpatient CI C/T to complete 14 days. Patient 5 received 3 days of tobramycin before receiving 7 days of CI C/T for her cUTI. The labeled dosing of 1.5 grams every 8 hours was converted to a 24-hour dose of 4.5 grams/day for all but 1 patient. Patient 3, who received a total of 9 grams/day, was dosed based on pharmacokinetic modeling data needed for target attainment in pneumonia available at the time (3 grams every 8 hours) [5]. For the primary outcome, 6 of 7 patients (85.7%) had symptom resolution at the end of therapy. One patient (patient 4) reported unresolved back pain at the completion of a 6-week treatment course for discitis. For the secondary outcome of microbiologic resolution, 3 patients (patients 1, 5, and 6) had a clinically evaluable repeat culture demonstrating microbiologic resolution. Three patients completed the patient satisfaction survey, and 4 did not respond (2 were deceased, 2 did not return investigator calls). Patients who completed the survey responded with either agree (4 points) or strongly agree (5 points) to all statements. Their average survey score is reflected in the table. Of note, 4 patients were not tested for susceptibility. Two of the 4 had pan-susceptible isolates, and 1 had been previously tested and shown to be susceptible to C/T. No adverse effects were reported from patients receiving CI. It is important to note that 3 patients had a listed penicillin allergy. Two patients had previously tolerated cefalosporins, with listed allergies of itching and swelling, respectively. The third patient had a listed allergy of rash and had never previously been documented as having tolerated cefalosporins. None of the 3 patients had a documented reaction to C/T. From the patient satisfaction questionnaire, it was noted that 2 patients are now deceased. From review of chart, both patients completed therapy and were in the clinical cure group, but they later succumbed to comorbid conditions.

DISCUSSION

There are limited data published on the use of CI C/T. Nateson et al [6] have previously reported Monte Carlo simulations demonstrating possible use of C/T as a 24-hour infusion. We have previously detailed the first successful use of CI C/T in the outpatient treatment of a UTI caused by MDR $P$ aeruginosa using 4.5 grams of C/T infused over 24 hours daily in a patient

| Patient | Infectious Diagnosis | Pathogen | Susceptible to C/T? | Antibiotic Allergies | Dose/Day (Grams) | Duration (Days) | Satisfaction Score (avg) |
|---------|---------------------|----------|---------------------|----------------------|-----------------|-----------------|-------------------------|
| 1       | cUTI                | MDRI Pseudomonas aeruginosa | Susceptible (25-mm zone diameter) | PCN | 4.5 | 14 | N/A |
| 2       | Pneumonia           | $P$ aeruginosa | Not tested | None | 4.5 | 17 | N/A |
| 3       | Pneumonia           | $P$ aeruginosa | Not tested | None | 9   | 6   | N/A |
| 4       | Discitis            | $P$ aeruginosa | Not tested | PCN | 4.5 | 42 | N/A |
| 5       | cUTI                | MDRI $P$ aeruginosa | Intermediate (Etest MIC = 8/4 mcg/mL) | Erythromycin | 4.5 | 7   | 4   |
| 6       | Bacteremia          | $P$ aeruginosa | Not tested | PCN, Sulfa | 4.5 | 10 | 4.2 |

Table 1. Patients Receiving CI C/T Outpatient Therapy

Abbreviations: avg, average; CI, continuous infusion; C/T, ceftolozane/tazobactam; cUTI, complicated urinary tract infection; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; N/A, not applicable; PCN, penicillin.

*Clinical cure (6 of 7 patients).

*Microbiological cure (3 of 3 patients).
with documented intolerance of CI P/T. The patient experienced microbiologic resolution without side effects [7]. Two other cases have been reported: one detailed the treatment of a lung abscess caused by a carbapenem-resistant \textit{P. aeruginosa} treated for 42 days as an outpatient in an immunocompromised patient with renal insufficiency, and the detailed other a pulmonary exacerbation in a cystic fibrosis patient with augmented renal clearance that received 6 grams of C/T CI daily for 10 days [8, 9].

In this case series from a retrospective chart review, CI C/T was shown to be efficacious and safe in a limited patient population with various infectious diagnoses. Treatment was focused against \textit{P. aeruginosa} and varied in length for each diagnosis, with some patients receiving treatment with other antimicrobials as inpatients before transitioning to C/T for outpatient parenteral antimicrobial therapy. Although safety was not formally evaluated, no patients reported any adverse events during therapy, and all patients completed their prescribed course.

Patient satisfaction was evaluated due to the lack of oral treatment options in many of these infections (primarily \textit{P. aeruginosa}, including several MDR strains) and the ability to receive treatment as an outpatient for an antimicrobial that is normally given 3 times per day. Even though delivery of the medication required placement of a central line and daily visits to the infusion center, patients included from the survey agreed or strongly agreed that this was a better alternative to hospitalization to treat the infection. Increased importance has been given to patient satisfaction recently from the Hospital Consumer Assessment of Healthcare Providers and Systems program. Hospitals must now report these data on patient experiences for value-based incentive payments [10].

CONCLUSIONS

There is currently a need for safe and effective treatments that can be given to outpatients for difficult-to-treat infections or convenience. Overall, the use of CI C/T was a safe, well tolerated, and convenient way to treat infections caused by \textit{P. aeruginosa}. Although CI from a pharmacokinetic/pharmacodynamic standpoint is unnecessary in isolates reported susceptible to C/T, logistically it may be a feasible option for convenience in the outpatient setting to avoid admission or decrease length of stay. Patients that have a MDR \textit{P. aeruginosa} infection with limited treatment options may specifically benefit having transitions of care to outpatient infusion. More data are needed to demonstrate safety and efficacy of CI and specific use in the outpatient setting.

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