An Efficacy and Safety Evaluation of Continuous Infusion of Ceftolozane/Tazobactam for Treatment of Multi-Drug Resistant Gram-Negative Infections in the Home Infusion Setting

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Background

Mortality and morbidity from unsuccessfully treated infections are on the rise.[1] This can be attributed to the emergence of multidrug resistant (MDR) bacteria, most commonly with isolates of MDR Pseudomonas aeruginosa. Ceftolozane/tazobactam, an antipseudomonal cephalosporin in combination with a β-lactamase inhibitor, has emerged as an option for the treatment of MDR pseudomonas unresponsive to the usual first line agents such as cefepime, piperacillin-tazobactam, ceftazidime, carbapenems (excluding ertapenem) and ciprofloxacin. Outside of its indication for serious infections due to MDR P. aeruginosa, it is also used for the treatment of resistant gram-negative bacterial infections including complicated urinary tract infection, intraabdominal infection, and hospital-acquired or ventilator associated pneumonia.

The recommended dosing regimen is either 1.5g or 3g infused over 60 mins every 8 hours. An extended infusion time of 3 grams over 3 hours is recommended for treating serious MDR gram-negative infections.[2] However, with ceftolozane/tazobactam exhibiting time-dependent bactericidal activity, recent data suggest that the standard intermittent infusion regimen concentrations fail to exceed four times the minimum inhibitory concentration (MIC) for more resistant strains of pseudomonas and are not as effective.[3]

As a result, maximizing the time that ceftolozane/tazobactam concentrations above the MIC through continuous infusion can be an effective way to optimize exposure against susceptible MDR gram negative bacteria. It is a more conducive method for aiding in transition of care compared to intermittent dosing due to once daily device change. Piperacillin/tazobactam exhibits a similar time-dependent bactericidal activity and has proven to be safe and effective when administered as a continuous infusion.[4]

Purpose

The purpose of this study is to determine the effectiveness of continuous infusion of ceftolozane/tazobactam through completion of prescribed therapy, defined as infection resolution without adverse drug effects.

Methods

This was a retrospective, multicenter study of patients discharged on continuous infusion of ceftolozane/tazobactam over an 11-month period. All patients received ceftolozane/tazobactam via an elastomeric device, delivered as 1.35, 4.5 or 9 grams in 240 mL normal saline IV every 24 hours infused at a rate of 10 mL/hour.

An electronic medical record was utilized for data collection which included age, sex, creatinine clearance, concomitant antibiotic use, diagnosis, culture results, dosage, and duration of therapy. This data was analyzed using descriptive statistics (mean, range, and frequency). Patients were included if they had a discharge assessment documented in the electronic medical record and had received at least 5 doses of the therapy at home. Patients < 18 years old were excluded.

Table 1: Baseline Characteristics, n=24

Sex	
Female	10 (41.6%)
Male	14 (58.3%)
Age Range	
20-39	4 (16.7%)
40-49	8 (33.3%)
60-79	10 (41.7%)
80-99	2 (8.3%)
Creatinine Clearance (ml/min)	
>50 - 130	15 (62.5%)
30 - 50	8 (33.3%)
Dialysis dependent	1 (4.2%)
Mean CrCl	69.27
Medication Side Effects	
No reaction	23 (95.8%)
Mild Nausea	1 (4.2%)
Duration of therapy	
< 1 week	1
1 week – 2 weeks	9
>2 weeks – 4 weeks	8
>4 weeks – 6 weeks	4
>6 weeks	2
Mean Average (weeks)	3.3*

Figure 1: Culture Results

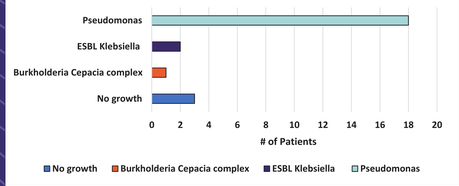


Figure 2: Categories of Diagnoses

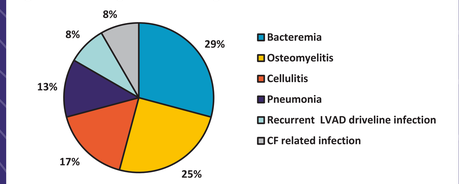
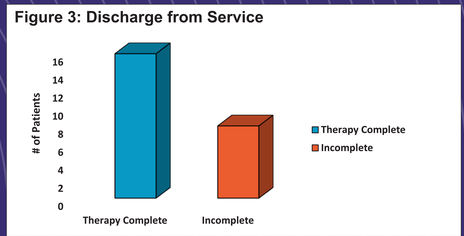


Figure 3: Discharge from Service



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Results

Twenty-four patients were included in the analysis. Baseline characteristics are depicted in *Table 1* which includes sex, age, duration of therapy, creatinine clearance, culture results and dose strength. The most commonly prescribed dose was 9 grams (n=13, 54.2%), followed by 4.5 gm (n=10, 41.6%). All doses were appropriate for renal function (mean CrCl = 69.27 ml/min) prior to admission on service. The mean duration of treatment was 3.3 weeks. The most common bacteria for all patients was pseudomonas (n=18, 75%) whereas 3 patients had cultures with no growth *(Figure 1)*.

The top 3 diagnoses as shown in *Figure 2* were bacteremia, osteomyelitis, and pneumonia. There were 16 therapy completions vs. 8 incomplete therapy courses *(Figure 3)*. Those that were incomplete were either hospitalized (4), admitted to skilled nursing facility (1), discharged against medical advice (1), or did not complete for unknown reasons (2) *(Figure 3)*. Two of the hospitalization cases were due to worsening of baseline symptoms including drainage, high fever, worsening redness, and pain. The other two rehospitalizations were unrelated to infection or antimicrobial therapy. The only documented adverse event was mild nausea, requiring no additional intervention.

Of the 6 patients who had concomitant antibiotic use, daptomycin (3) was the most common, followed by linezolid (2) and tobramycin (1). One of the four hospitalizations occurred in a patient on daptomycin while the other three were in patients on monotherapy of ceftolozane/tazobactam.

Discussion

This study focused on the primary outcome which was therapy completion of the regimen through resolution of symptoms. Figure 2 shows that 16 of the 24 patients (67%) were discharged from service with therapy completion with data showing resolution of symptoms of infection from baseline. Additionally, the regimen appeared safe with one minimal reported medication side effects and of the 4 rehospitalizations, none were due to a severe adverse reaction from the antimicrobial therapy. However, beyond the pharmacodynamic and pharmacokinetic profiles, a once-daily device change potentially offers a more convenient option for patients receiving intravenous medications at home.

Some noted limitations of the study are the small sample size and limited interoperability of inpatient EMRs with outpatient EMRs.

Conclusion

There is a need for more data related to continuous infusion antimicrobial therapy, including with ceftolozane/tazobactam. This study provides insight into patient characteristics, outcomes, and concomitant antimicrobial use in patients receiving continuous infusion of ceftolozane/tazobactam in the home infusion setting. Further studies will be needed to fully understand the efficacy and safety of the continuous infusion of ceftolozane/tazobactam regimen.

Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation: Rodney Kumi; Maria Giannakos; Christopher Roy; Olivia Hanley; Melissa Ostrander: Nothing to disclose.

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