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Ceftolozane/Tazobactam: Outpatient Treatment of Gram-Negative Infections at Physician Office Infusion Centers (POICs)

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Abstract

Background: Ceftolozane/tazobactam (C/T) is a novel cephalosporin and beta-lactamase inhibitor combination with enhanced activity against multidrug-resistant (MDR) *Pseudomonas aeruginosa* and extended-spectrum β-lactamase (ESBL)-producing strains. With increasing bacterial resistance coupled with recurrent drug shortages and toxicities with other agents, C/T may be an option in outpatient management of these infections. We report the first outpatient clinical experience of C/T in POICs.

Methods: A retrospective review was conducted of all patients (pts) receiving C/T in 12 POICs from March 2015 to May 2016. Demographics, therapy characteristics, pathogens, adverse events (AEs), and clinical outcomes were evaluated. Clinical success at end of therapy was defined as cured (complete resolution of infection) or improved (partial resolution of infection and/or continued oral antibiotics).

Results: A total of 28 pts were identified with a mean age of 57 years and 43% female. Infections included 8 respiratory infections (RI), 7 complicated intra-abdominal infections (cIAI), 7 complicated urinary tract infections (cUTI) and 6 complicated skin and soft tissue infections (cSSTI). Multidrug-resistant (MDR) pathogens (n=19, 68%) were predominant including MDR *Pseudomonas aeruginosa* (n=12), ESBL positive (ESBL+) *Escherichia coli* (n=5), ESBL+ *Klebsiella oxytoca* (n=1) and MDR *Achromobacter xylosoxidans* (n=1). Half of pts (n=14) had mixed infections. Median length of therapy was 17 days (range 7-58). Rationale for C/T included lack of alternatives due to MDR organism (n=15) and treatment failure on prior antibiotics (n=13). Therapy was initiated in the POIC in 43%. The majority of pts (n=21, 75%) self-administered C/T at home using elastomeric devices. AEs occurred in 11 pts, most commonly diarrhea (n=3), nausea/vomiting (n=2), and fatigue (n=2). Clinical success was achieved in 89% (24 of 27) evaluable pts, with 100% success in the 11 pts who had treatment initiated in POIC.

Conclusion: C/T outpatient use for a variety of MDR pathogens causing challenging infections was highly effective. AEs were tolerable, suggesting a valuable outpatient treatment option for MDR gram-negative pathogens. Additional studies are warranted.

Introduction

The continuous rise of bacterial resistances to available antimicrobials support the need for novel, safe, and effective agents [1]. C/T (Zerbaxa™), a cephalosporin/β-lactamase inhibitor combination, was approved in December 2014 to treat adults with cIAI and cUTI [2]. It exhibits enhanced activity against MDR gram-negative organisms including ESBL+ bacteria and *Pseudomonas aeruginosa* [3]. Clinical trial data for the treatment of cIAI and cUTI are available [4, 5]. However, little is known about the use of C/T for gram-negative infections in an outpatient setting. This study evaluated diagnosis, microbiology, safety and outcomes of C/T used in a POIC.

Methods

A multi-center retrospective chart review was conducted to identify pts who received C/T at 12 POICs nationwide. Data collected included demographics, prior antimicrobial use, diagnosis, therapy characteristics, baseline microbiology, safety and clinical outcomes.

- Inclusion criteria: pts ≥18 yrs old receiving C/T at a POIC from approval date to May 2016, available culture data, concomitant IV antimicrobials
- Exclusion criteria: none
- Descriptive statistics (median, range) was used for length of therapy, percentages were used for diagnosis, microbiology, safety, and outcome data
- Clinical outcomes evaluated at the end of OPAT were defined as:
  - Cured: resolution of signs/symptoms and no further treatment needed
  - Improved: partial resolution of signs/symptoms or continued oral antibiotics
  - Non-success: new or worsening signs/symptoms of infection

Success rate (%) =(cured + improved)/(no. of evaluable pts) x 100%

Results

Demographics

- 28 pts across 12 POICs received C/T for the following gram-negative infections: complicated intra-abdominal infection (**cIAI**); complicated urinary tract infection (**cUTI**); respiratory tract infection (**RI**); and complicated skin and soft tissue infection (**cSSTI**)

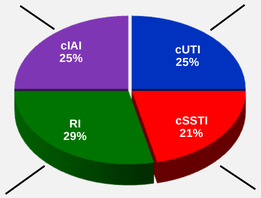
Characteristics	No. of Pts per Diagnosis (%)				
	cIAI (n=7)	cUTI (n=7)	RI* (n=8)	cSSTI* (n=6)	Total
Age, years					
18 - 64	6 (86)	5 (72)	5 (62)	6 (100)	**22 (79)**
≥65	1 (14)	2 (28)	3 (38)	-	**6 (21)**
Gender, female	4 (57)	3 (43)	4 (50)	1 (17)	**12 (43)**
Co-morbidities					
Hypertension	3 (43)	3 (43)	6 (75)	4 (67)	**16 (57)**
Cancer	1 (14)	3 (43)	5 (62)	2 (33)	**11 (39)**
Cardiovascular disease	2 (28)	3 (43)	3 (38)	3 (50)	**11 (39)**
Diabetes mellitus	1 (14)	2 (28)	2 (25)	3 (50)	**8 (29)**
Genitourinary disorder	-	5 (72)	3 (38)	-	**8 (29)**
Gastrointestinal disease	1 (14)	3 (43)	2 (25)	1 (17)	**7 (25)**
Obesity	3 (43)	1 (14)	1 (12)	1 (17)	**6 (21)**
Pulmonary disorder	1 (14)	1 (14)	4 (50)	-	**6 (21)**
Baseline Creatinine Clearance					
>50 mL/min	7 (100)	6 (86)	8 (100)	6 (100)	**27 (96)**
30-50 mL/min	-	1 (14)	-	-	**1 (3)**
Prior IV Antimicrobial Use	6 (86)	6 (86)	8 (100)	5 (83)	**25 (89)**
Known Drug Allergy	1 (14)	5 (72)	5 (62)	2 (33)	**13 (46)**
Location Prior to OPAT					
Hospital	7 (100)	1 (14)	3 (38)	5 (83)	**16 (57)**
Home/Physican office	-	6 (86)	5 (62)	1 (17)	**12 (43)**

* Off-label indications for C/T

Diagnosis

Diverticulitis (n=3)
Intra-abdominal abscess (n=2)
Appendiceal abscess (n=1)
Acute cholecystitis (n=1)

Pyelonephritis (n=3)
Indwelling catheter (n=2)
Urosepsis (n=1)
Neurogenic bladder (n=1)



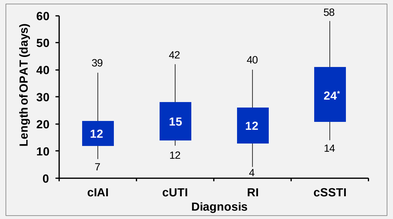
Pneumonia (n=5)
Bronchiectasis (n=2)
Chronic pansinusitis (n=1)

Diabetic foot infection (n=3)
Surgical wound (n=3)

Therapy Characteristics

- Renal dosing was required for one cUTI pt (4%)
- C/T was used in combination with other IV antimicrobials in 4 pts (14%), all with vancomycin (1 cIAI, 2 RI, 1 cSSTI)
- Reasons for C/T usage were lack of alternatives due to MDR organisms (54%) and failure of prior drug therapy (46%)

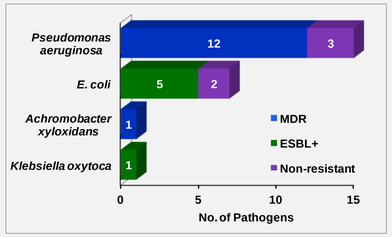
Median Length of Therapy



*; Length of OPAT for 3 non-healing surgical wound infections (21, 21, 14 days) and 3 persistent diabetic foot infections (41, 27, 58 days)

Microbiology

Drug-Resistant Pathogens



- A total of 33 gram-negative isolates were reported in 23 pts including 13 pts with MDR (47%) and 6 pts with ESBL positive (21%) organisms for a total of 19 pts (68%) with drug-resistant pathogens
- Other pathogens identified include *Bacteroides fragilis* (n=2), *Klebsiella pneumoniae* (n=2), *Acinetobacter* sp (n=1), *Citrobacter* sp (n=1), *Enterobacter cloaceae* (n=1), *Pseudomonas putida* (n=1), and *Proteus mirabilis* (n=1)

Safety

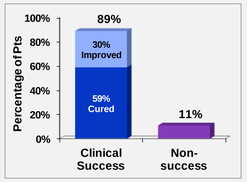
- A total of 16 AEs occurred in 11 pts (39%)
- Discontinuation of C/T was required in one pt (cIAI), who developed maculopapular rash on day 7 of C/T therapy

Adverse Event	No. of Pts (%)
Diarrhea	3 (11%)
Yeast infection	3 (11%)
Nausea/vomiting	2 (7%)
Fatigue	2 (7%)
Hyperkalemia	2 (7%)
Anemia	1 (3%)
Constipation	1 (3%)
Headache	1 (3%)
Maculopapular rash*	1 (3%)

*; pt had prior drug allergy to piperacillin/tazobactam

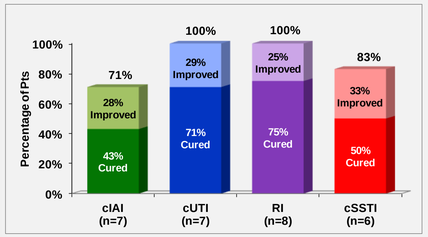
Clinical Outcomes

Overall Outcomes



- Overall success was 89% including 59% cured (n=16) and 30% improved (n=8)
- 3/8 improved pts continued oral antimicrobials at discharge
- Non-success was 11% (n=3) due to 2 inadequate responses to therapy (cIAI, cSSTI) and 1 drug-related AE (cIAI)

Outcomes by Diagnosis



- Clinical success rates by diagnosis were 71% for cIAI (43% cured, 28% improved), 100% for cUTI (71% cured, 29% improved), 100% for RI (75% cured, 25% improved) and 83% for cSSTI (50% cured, 33% improved)
- Cure rate of pts with monomicrobial MDR or ESBL+ pathogens (n=12) was 100%

Discussion

This study describes a nationwide outpatient experience of C/T used for various gram-negative infections.

- A total of 28 pts (mean age 57 yrs, 43% female) received C/T for cIAI (n=7), cUTI (n=7), RI (n=8), and cSSTI (n=6)
- 43% (12/28) of pts initiated C/T in POICs
- 89% (25/28) of pts received IV antimicrobials prior to C/T
- Median length of OPAT for cIAI, cUTI, RI, and cSSTI was 12, 15, 12, and 24 days, respectively
- Infections were frequently polymicrobial (50%). Most prevalent organisms were *Pseudomonas aeruginosa* (65%, n=15) and *E. coli* (30%, n=7)
- Resistant pathogens were present in 19 pts (68%) including 13 pts with MDR (43%) and 6 pts with ESBL+ (18%) organisms on culture
- AEs were reported in 39% (11/28) of pts, most commonly diarrhea (11%), yeast infections (11%), nausea/vomiting (7%), fatigue (7%), and hyperkalemia (7%). Discontinuation of C/T due to AEs occurred in one pt. Overall incidence of AEs was similar to those reported in the ASPECT-cUTI (34.4%) and ASPECT-cIAI (44%) trials [4, 5]
- Overall clinical success of C/T was 89% (24/27) with 59% of patient infections cured and 30% improved

Conclusion

C/T appears to be a safe and effective option for outpatient management of serious gram-negative infections, when required, particularly with resistant organisms. Clinical success was high with manageable AEs.

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