Real-World Outpatient Utilization of Ceftolozane/Tazobactam in Physician Office Infusion Centers (OICs)

IDWeek™ 2020
#1625

Lucinda J. Van Anglen, BS, PharmD[1]; Ramesh V. Nathan MD[2]; Brian S. Metzger, MPH, MD[3]; Quyen Luu, MD[4]; Claudia P. Schroeder, PharmD, PhD[1]

[1]Healix Infusion Therapy, Sugar Land, TX; [2]Mazur. Statner, Dutta, Nathan, PC, Thousand Oaks, CA; [3]Austin Infectious Disease Consultants, Austin, TX; [4]Central Georgia Infectious Diseases, Macon, GA

Abstract

Background: Ceftolozane/tazobactam (C/T) is indicated for the treatment (tx) of complicated Gram-negative infections including urinary tract infection (cUTI), intra-abdominal infection (cIAI), and hospital-acquired/ventilator-associated bacterial pneumonias caused by susceptible bacteria [1]. Real-world data on the use of C/T are limited. We present a multicenter observational review of C/T outpatient utilization in Infectious Disease OICs.

Methods: Medical records of patients (pts) who received C/T for ≥3 doses from May 2015 to Sept 2019 were reviewed. Data included demographics, diagnosis, disease history, pathogens, C/T tx, hospitalizations, emergency department (ED) visits and clinical outcomes. Clinical success was defined as complete or partial symptom resolution at completion of C/T with oral antibiotics as needed. Persistent infection and early discontinuation (D/C) of C/T were deemed non-successful. Indeterminant outcomes were deemed non-evaluable. Chi-Square, Fisher's exact, and t-tests were used to identify characteristics associated with clinical outcome.

Results: 120 pts (mean age: 59±15 years, 60% male) from 33 OICs were identified. Median Charlson score was 5 (IQR, 3-7), with 37% immunocompromised and 77% refractory/recurrent disease. Primary infections were bone and joint (25%), cUTI, (24%), respiratory tract (18%), cIAI (18%), complicated skin and skin-structure (12%), and bacteremia/endocarditis (3%). Most pts had multi-drug resistant Gram-negative pathogens (79/108; 73%), predominantly *Pseudomonas aeruginosa*. Polymicrobial infections were reported in 44%. Median duration of C/T therapy was 21 days (IQR, 14-34). C/T was initiated in the OIC in 59% of pts. Overall clinical success was 86% (100/117), with rates by infection type in Fig 1. Non-success was reported in 17, 10 due to persistent infection and 7 due to adverse events. The adverse events led to early D/C of C/T, all with resolution. Statistically, the infection type did not impact success rate. Hospitalizations and ED visits during tx occurred in 5% of pts with successful outcomes and 35% of pts with non-successful outcomes (p<0.002).

Conclusion: These real-world results support the effectiveness of C/T in a wide variety of complicated Gram-negative infections treated in the outpatient setting.

Background and Objectives

Real-world data describing the use of C/T in the outpatient setting are limited, including the treatment of Gram-negative infections other than the approved indications.[2-6] This study aimed to:

- characterize the pt cohort who received C/T between May 2015 and Sep 2019 and describe C/T utilization in OICs
- determine the clinical outcome of C/T therapy in these pts
- identify healthcare resources utilization including hospitalizations and emergency department (ED) visits during outpatient therapy

Methods

Study design: Observational, retrospective multicenter study

Study cohort: Pts (≥18 yrs of age) who received C/T for at least 3 doses for any diagnosis in an OIC

Data source: Pharmacy database and electronic healthcare records of pts treated with C/T from May 2015 to Sep 2019

Data collection: Demographics, comorbidities, disease history, diagnosis, microbiology, outpatient administration, C/T therapy regimen, clinical outcome at end of C/T therapy including hospitalizations or ED visits.

Outcome: Clinical success was defined as complete or partial symptom resolution of infection at end of C/T therapy with oral antibiotics allowed. Persistent infection and early discontinuation of C/T were deemed non-successful. Indeterminant outcomes were deemed non-evaluable.

Statistical analysis: Continuous data are reported as mean±SD or medians (range) and IQR, categorical data as counts and percentages. Chi-Square, Fisher's exact, and *t*-tests were used to identify variables associated with clinical success. A *P*-value less than 0.05 was considered significant.

Study Population

- 120 pts from 33 Infectious Disease physician OICs received C/T as outpatient therapy either following hospitalization or through initiation in the OIC.

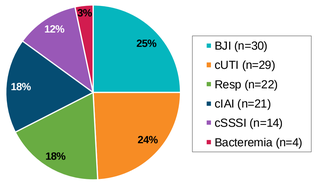
Table 1. Demographics and Clinical Characteristics

Parameter	Results (N=120)
Age in years, mean±SD	59±15
Male gender, n (%)	72 (60)
Charlson comorbidity index, median (IQR)	5 (3-7)
Body mass index ≥30 mg/kg², n (%)	49 (41)
Comorbidities, n (%)	
cardiovascular disease	81 (68)
diabetes mellitus	44 (37)
immunocompromised*	44 (37)
malignancy	31 (26)
chronic kidney disease	12 (10)
paraplegia	7 (6)
Recurrent or refractory disease**	92 (77)
Immediate prior intravenous therapy, n (%)	59 (49)
Location prior to POIC, n (%)	
hospital	49 (41)
community	71 (59)
Primary payor, n (%)	
federally-funded	56 (47)
commercial	64 (53)

*; pts with immune deficiency (cancer, HIV, genetic disorder, autoimmune disease, organ transplant, CKD), use of steroids, methotrexate, biologics, chemotherapy, or radiation.
**; recurrence or exacerbation of the same diagnosis previously treated.

Diagnosis

Figure 1. C/T Utilization by Infection Type



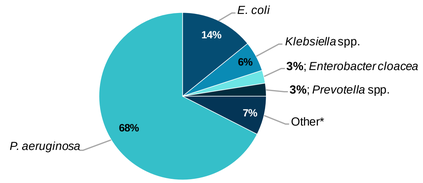
Abbreviations: BJI: bone and joint infection; Resp: respiratory infection; cSSSI: compl. skin and skin structure infection.

Diagnostic sub-groups included:

- BJI: 27 osteomyelitis, 1 discitis, 1 PJI, 1 septic arthritis;
- Resp: 15 pneumonia, 7 others
- Bacteremia: 2 device infections, 2 endocarditis

Microbiology

Figure 2. Distribution of Gram-Negative Pathogens



*; *Proteus mirabilis* (n=2), *Achromobacter dinitrificans* (n=1), *Bacteroides fragilis* (n=1), *Bacteroides vulgatus* (n=1), *Citrobacter koseri* (n=1), *Providencia stuartii* (n=1), and *Stenotrophomonas maltophilia* (n=1).

- Overall, 120 Gram-negative pathogens were identified in 108 pts, 47 pts (44%) had ≥2 Gram-negative pathogens.
- 53 pts had polymicrobial infections. Of these, 33 pts had mixed Gram-negative/Gram-positive pathogens including methicillin-sensitive *S. aureus* (n=6) and *Streptococcus* spp. (n=8).

Table 2. Incidence of Resistant Gram-Negative Pathogens

Gram-Negative Pathogen	Total No.	Resistant Isolates* (n, %)	Resistance Type
P. aeruginosa	81	61 (75)	51 MDR, 10 CR
E. coli	17	12 (65)	12 ESBL
Klebsiella spp.	7	4 (57)	4 ESBL
Enterobacter cloacae	3	1 (33)	1 ESBL
Prevotella spp.	3	2 (67)	2 ESBL
Achromobacter spp.	1	1 (100)	1 CR
Other	8	-	-
Total	**120**	**81 (68)**	**51 MDR, 19 ESBL, 11 CR**

* Pathogen resistance as noted by the laboratory.
Abbreviations. CR: Carbapenem-resistant; ESBL: extended beta-lactamase; MDR: multidrug-resistant.

- 81 resistant Gram-negative pathogens were isolated in 79/108 pts (73%)
- Resistant pathogens were identified in cUTI (83%) Resp (77%), BJI (63%), cSSSI (57%), cIAI (48%) and bacteremia (25%)

Outpatient Administration

- C/T was dispensed in elastomeric devices or PVC bags for various methods of administration, allowing for optimal drug stability.[7]

Table 3. Infusion Devices and Methods of C/T Administration

Infusion Device	No. of pts (%)	Description of Use
Elastomeric pump	77 (64)	self-administration at home of all doses via elastomeric pump with intermittent frequency
Ambulatory pump	39 (33)	ambulatory pump administration of total daily dose in a 24-hr PVC bag programmed for intermittent frequency
Ambulatory pump	3 (2)	ambulatory pump administration of total daily dose in a 24-hr PVC bag programmed for continuous infusion
Stationary pump	1 (1)	office administration of total daily dose (pt with renal dosing)

C/T Therapy Regimen

Table 4. Duration of C/T Therapy by Diagnosis

Diagnosis	Duration of C/T Therapy				
	Inpatient days		Outpatient days		Total days
	No. of pts	median (range)	No. of pts	median (range)	median (range)
BJI	6	3 (1-5)	30	34 (11-181)	34 (14-181)
cUTI	3	4 (2-6)	29	14 (6-43)	14 (6-43)
Resp inf	3	4 (3-5)	22	21 (7-50)	21 (7-50)
cIAI	3	2 (2-6)	21	21 (4-39)	21 (4-39)
cSSSI	1	3	14	31 (13-83)	31 (13-86)
Bacteremia	1	2	4	28 (11-77)	28 (11-78)
Total	**17**	**3 (1-6)**	**120**	**21 (4-181)**	**21 (4-181)**

- 17 pts (14%) started C/T in the hospital before transition of care to an OIC

Table 5. Dosing Regimen of C/T Therapy

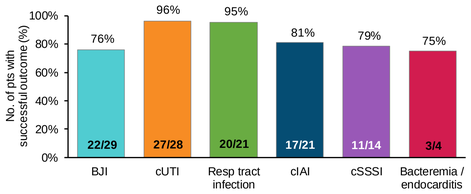
Dosing Regimen	No. of Pts (%)	Daily Dose (g)	Dosing Frequency
Standard	91 (76)	4.5	q8h
Renally-adjusted*	24 (20)	≤ 3	q8h - q24h
High-dose**	5 (4)	9	q8h, continuous

*; includes q8h (n=22), q12h (n=1), q24 (n=1).
**; high-dose includes 3g q8h or 9g daily; q8h (n=3), continuous (n=2).

- High-dose C/T included: 2 pneumonia, 2 BJI and 1 bacteremia/endocarditis
- All pneumonia pts except one treated received high dose therapy after FDA approval with revised dosing for pneumonia[1]
- 18 pts (15%) received concomitant antibiotics for Gram-positive coverage

Clinical Outcome

Figure 3. Clinical Success with C/T Therapy by Infection Type



- Overall clinical success was 86% (100 of 117), of which 25% continued oral antibiotics. No outcomes were available for 3 pts.
- 70 of 86 pts (81%) with a single Gram-negative pathogen had clinical success including 81% with *P. aeruginosa*, 73% with *E. coli*, 100% with *E. cloacae*, 100% with *Klebsiella* spp, 100% with *A. nitrificans*, and 100% with *C. koseri*.
- Of 17 pts with non-successful outcomes (14%), 10 had persistent or recurrent infection and 7 discontinued C/T early due to an adverse event (3 rash, 1 increased serum creatinine, 1 *C. difficile* infection, 1 dyspnea, 1 catheter event).

Clinical Outcome, cont.

Table 6. Baseline Variables Associated with Clinical Outcome

Variable	Success (n=100)	Non-success (n=17)	P-value*
Age in years, mean ± SD	59.7±16	58.1±12	0.68
Male gender, n (%)	**56 (56.0)**	**14 (82.4)**	**0.04**
Charlson index, mean ± SD	4.9±2.6	4.5±2.2	0.54
Refractory or recurrent infection	77 (77.0)	12 (70.6)	0.57
Hospital or ED visit during C/T therapy, n (%)	**5 (5.0)**	**6 (35.3)**	**0.002**

*; Chi square Fisher's exact tests for categorical variables and *t*-test for continuous data.

- Significant variables identified for C/T non-success were male gender (p=0.04) and hospital or ED visit (p=0.002) during C/T therapy.
- Hospitalization and/or ED visits occurred in 11 of 117 (9.4%) pts including 5 infection exacerbations, 1 adverse event, and 5 unrelated to C/T. Of these, 5 returned to OIC for successful completion of C/T therapy.

Discussion and Conclusion

This multicenter study reviewed real-world utilization of C/T in the outpatient setting.

- 120 patients were treated through 33 Infectious Disease physician office infusion centers nationally.
- Patients were highly comorbid (mean Charlson index: 5) and 77% had refractory or recurrent infections.
- BJI and cUTI were the most prevalent diagnoses treated
- Nearly three fourth of patients had resistant Gram-negative pathogens. Of the resistant pathogens, 86% were MDR or ESBL and 9% were carbapenem-resistant strains. The most frequent resistant pathogens were *P. aeruginosa* and *E. coli*.
- In the outpatient setting, C/T can be provided in an elastomeric device, which allows for optimal patient ease of use for intermittent dosing. The majority of patients received C/T through the OIC using this device.
- Overall clinical success of C/T was 86%, with the highest success observed in cUTI and respiratory tract infections. Male gender and healthcare resource utilization were associated with poor clinical outcome.

Ceftolozane/tazobactam provided in office infusion centers was safe and effective for the treatment of multiple diagnoses in a patient population with mostly refractory diseases and a high incidence of resistant Gram-negative pathogens.

References

1. ZERBAXA® (ceftolozane/tazobactam). Whitehouse Station, NJ, Merck & Co, Inc. Revised 09/2020.
2. Wagenlehner FM, Umeh O, Steenbergen J, et al. *Lancet* 2015; 385:1949-56.
3. Solomkin J, Hershberger E, Miller B, et al. *Clin Infect Dis* 2015; 60:1462-71.
4. Dietl B, Sanchez I, Arcenillas P, et al. *Int J Antimicrob Agents* 2018; 51:498-502.
5. Xipell M, Paredes S, Fresco L, et al. *Int J Antimicrob Resistance* 2018; 13: 165-170.
6. Nathan RV, Alvarado FS, Prokesch RC, et al. *OFID* 2016; 3 (1):2055.
7. Terracciano J, Rhee EG, Walsh J. *Current Ther Res* 2017; 84:22-25.