Efficacy of Ceftolozane/Tazobactam for Multidrug-Resistant Gram-Negative Infections in Multiple Urban Hospitals

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ABSTRACT

Background: Ceftolozane/tazobactam (C/T) is a novel cephalosporin/beta-lactamase inhibitor combination developed for use against multidrug-resistant (MDR) Gram-negative infections, particularly *Pseudomonas aeruginosa* (PA). C/T is approved for complicated urinary tract and intraabdominal infections as well as hospital-acquired/ventilator-associated bacterial pneumonias. However, comprehensive clinical characterization of patients treated with C/T in non-FDA-approved indications is limited.

Materials/methods: Patients ≥18 years who received C/T for ≥48 hours while hospitalized in 9 acute care centers in Houston, TX from January 2016 through September 2018 were included. Demographic, microbiologic, treatment and clinical outcome data were retrospectively collected by chart review. In patients who received multiple inpatient courses of C/T, only the first course with C/T was assessed.

Results: 210 patients met inclusion criteria: 58% were non-white, 35% were female and 13% were immunocompromised. Median age was 61 years (IQR, 48 to 69). Median Charlson comorbidity index was 5 (IQR, 2 to 6). At the onset of the index episode, a significant proportion of patients required intensive care unit admission (44%), mechanical ventilation (37%) and pressor support (22%). Respiratory sources were the most common (50%) followed by urine (15%). Positive cultures were documented in 93% of the cases and PA was found in 86%. Majority (95%) of PA isolates were MDR. C/T use was guided by susceptibility testing of the index isolate in ~52%. In 5.7% of cases, C/T was used to escalate therapy without any documented C/T-susceptible organism. Half (51%) of the cohort received initial dosing appropriate for renal function while 36% receiving a lower than recommended dose. Clinical success (i.e., recovery from infection-related signs and symptoms) occurred in 77%. The in-hospital mortality rate in our cohort was 15% with 26 of 31 deaths deemed infection-related.

Conclusions: We report a large multicenter observational cohort that received C/T. A 77% clinical success with the use of C/T was documented. These data support the use of C/T in critically ill patients infected with MDR PA.

BACKGROUND

- *Pseudomonas* spp. exhibit some of the highest antimicrobial resistance rates among human pathogens due to multiple mechanisms of resistance including outer membrane porin changes, drug efflux pump upregulation, drug target alterations, drug-inactivating or modifying activity [1].
- C/T is a novel cephalosporin combined with an established β-lactamase inhibitor. Ceftolozane possesses high penicillin-binding protein affinity and enhanced *Pseudomonas* activity [2]. Data suggests MICs to ceftolozane or C/T are not affected by hyperexpression of drug efflux pumps or downregulation of the OprD membrane protein [3-5].
- C/T is FDA approved for complicated intraabdominal infections, and-urinary tract infections and hospital acquired bacterial and ventilator-associated pneumonia [2,6].

AIMS

- To describe patient characteristics and infectious indications among patients treated with ceftolozane/tazobactam
- To determine outcomes associated with ceftolozane/tazobactam use

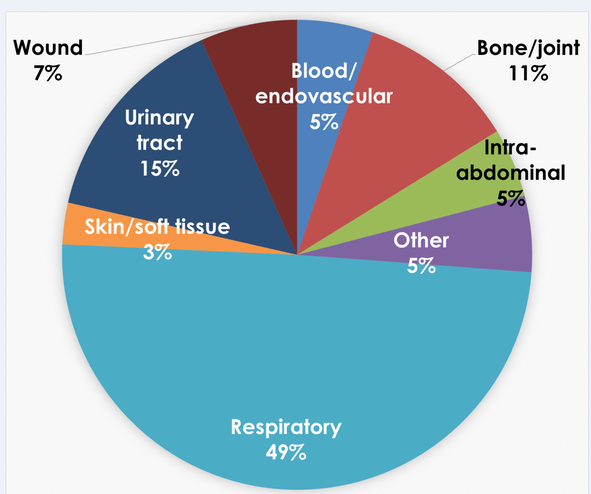
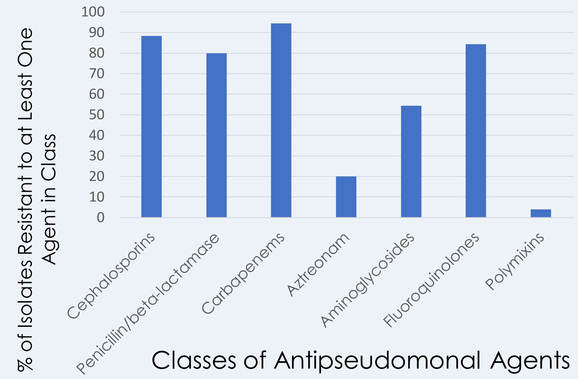


Figure 1. Sites of clinical infectious diagnosis (%)

METHODS

- Using a pharmacy database we identified all patients who received for ≥48 hours while hospitalized in 9 acute care centers in Houston, TX from January 2016 through September 2018.
- Demographic, microbiologic, treatment and clinical outcome data were retrospectively collected by chart review.
- For patients who received multiple inpatient courses of C/T, only the first course with C/T was assessed.

Figure 2. Resistance profile of *P. aeruginosa* isolates in index culture (n=180)



RESULTS

- 210 patients were included: 58% were non-white, 35% were female. Median age was 61 years (IQR, 48 to 69).
- Median Charlson comorbidity index was 5 (IQR, 2 to 6).
- 180 patients (86%) had a culture-proven *P. aeruginosa* infection, 95% of which were classified as multidrug-resistant.

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Table 1. Clinical, microbiologic and treatment characteristics, n (%)

Immunocompromised[a]		29 (13.8)
HIV	2	
Prednisone 10 mg daily or greater	13	
Neutropenic	3	
Recent cancer chemotherapy (past 6 months)	2	
Monoclonal antibody therapy	3	
History of transplant	17	
Heart recipient	7	
Kidney recipient	2	
Liver recipient	2	
	6	
ICU within 24 hours of infection onset		92 (43.8)
Vasopressor-requiring within 24 hours of infection onset		46 (21.9)
Invasive mechanical ventilatory support-requiring within 24 hours of infection onset		78 (37.1)
Index culture[a,b]		
Positive cultures		195 (92.9)
No cultures obtained		8 (3.81)
Pseudomonas aeruginosa isolated		180 (85.7)
Polymicrobial growth		76 (36.2)
C/T use		
Duration, median number of days (IQR)		7 (4 to 13)
Initial dosing lower than indicated for CrCl[c]/ indication		75 (41.7)
Culture-guided use		109 (51.9)
Empiric use[d]		83 (39.5)
Therapeutic escalation for clinical non-response		12 (5.7)
Concurrent Gram-negative-active systemic therapy[a]		48 (22.9)
Aminoglycoside	18	
Carbapenem	5	
Cephalosporin	2	
Polymyxin	11	
Tetracycline	4	
Trimethoprim/sulfamethoxazole	1	
	11	
Adverse events associated with C/T therapy		8 (3.8)
C. difficile infection	4	
Non-*C. difficile* diarrhea	1	
Eosinophilia	2	
Drug fever	1	

[a]Categories were not mutually exclusive. [b]Index culture refers to initial culture sent to identify etiology of the clinical infectious diagnosis treated with C/T ≥48 hours. [c]CrCl was creatinine clearance by Cockcroft-Gault equation. [d]Use was deemed empiric if C/T use was not guided by isolation of an organism shown to be susceptible to C/T by *in vitro* testing.

Table 2. In-hospital treatment outcomes, n (%)

Recovery from infection-related signs/symptoms	161 (76.7)
In-hospital mortality	31 (14.8)
Infection-related in-hospital mortality	26 (12.4)

Table 3. 14- and 30-day clinical outcomes, n (%)

Outcome Parameter	14-day	30-day
Discharged (to home, skilled nursing/long-term care facility)	105 (50.0)	124 (59.1)
Rehospitalized after discharge	11 (5.2)	27 (12.7)
Transitioned to hospice/comfort care	5 (2.4)	5 (2.4)
Death	18 (8.5)	22 (10.5)

DISCUSSION & CONCLUSION

- A significant proportion of this cohort were seriously ill patients requiring intensive care and suffered MDR *Pseudomonas* infections.
- The 76.7% success rate is similar to that reported in other case series in the literature (54%-100%) [7-14].
- C/T is an important therapeutic option for MDR isolates for which few options are available or desirable.