Ceftolozane-Tazobactam (C/T) for Severe Infections Caused by Carbapenem-Resistant *Pseudomonas aeruginosa*

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Abstract

Background: Ceftolozane/tazobactam (C/T) was recently approved to treat urinary tract and abdominal infections. Ceftolozane is a novel cephalosporin with potent activity against multidrug-resistant *P. aeruginosa*. We describe a case series of patients from 5 US centers that received C/T to treat carbapenem-resistant *P. aeruginosa* (CR-PAE) infections.

Methods: We reviewed all patients treated for ≥ 72 h with C/T for a CR-PAE infection. All relevant clinical and demographic data were extracted. Isolate identification and susceptibility testing were performed by standard methods at each participating center. Susceptibility to C/T was determined by Etest.

Results: C/T was used to treat CR-PAE infections in 35 patients (median age 55 years; 23% female). Eighteen (51%) cases had hospital-associated pneumonia (3 complicated with empyema). Overall, 6 patients had secondary bacteremia. A summary of the infection types is depicted in Fig. 1. Antipseudomonal antibiotics were given prior to C/T in 30 (86%) patients. Most isolates were resistant to ciprofloxacin and β-lactams while remaining susceptible to colistin (Fig. 2A).Despite the absence of previous exposure to C/T, 4 isolates were non-susceptible to the antibiotic (Fig. 2A). C/T was used as monotherapy in 27 (77%) patients and combined with an inhaled (n=5) or systemic (n=3) anti-pseudomonal agent in the remaining 8 cases. The approved C/T dose (1.5g Q8h) was used in 11/18 patients with normal renal function (≥ 70 mL/min), while the remaining 7 received 3g Q8h. C/T dosing among 7 patients with a creatinine clearance of 30-50 mL/min ranged from 0.375g to 3g Q8h. Patients on intermittent hemodialysis (HD, n=3) received 0.375g Q8h and subjects undergoing continuous HD (n=7) were dosed from 0.375g to 1.5g Q8h. Clinical success was achieved in 26 (74%) cases. A total of 9 patients were considered to have failed therapy (Fig. 3). All patients infected with C/T non-susceptible P. aeruginosa (n=4) failed therapy (Fig. 2B). Major adverse effects were not reported.

Conclusion: C/T may become an important alternative for the treatment of CR-PAE infections. Resistance resulting in poor clinical outcomes was observed. Hence, routine C/T susceptibility testing should be required.

Background and Methods

- Infections due to carbapenem-resistant *P. aeruginosa* (CR-PAE) infections are a major concern
- Ceftolozane/tazobactam (C/T) was recently approved to treat urinary tract and abdominal infections.
- Ceftolozane is a novel cephalosporin with potent activity against multidrug-resistant *P. aeruginosa*, including CR-PAE strains
- We reviewed all patients treated for ≥ 72 h with C/T for a CR-PAE infection in 5 large US academic institutions.
- All relevant clinical and demographic data were extracted.
- Isolate identification and susceptibility testing were performed by standard methods at each participating center
- Susceptibility to C/T was determined by Etest.

Results

- C/T was used to treat CR-PAE infections in 35 patients (median age 55 years; 23% female).
- Eighteen (51%) cases had hospital-associated pneumonia (3 complicated with empyema). Overall, 6 patients had secondary bacteremia. A summary of the infection types is depicted in Fig. 1
- Antipseudomonal antibiotics were given prior to C/T in 30 (86%) patients
- Most isolates were resistant to ciprofloxacin and β-lactams while remaining susceptible to colistin (Fig. 2).
- Despite the absence of previous exposure to C/T, 4 isolates were non-susceptible to the antibiotic (Fig. 2).

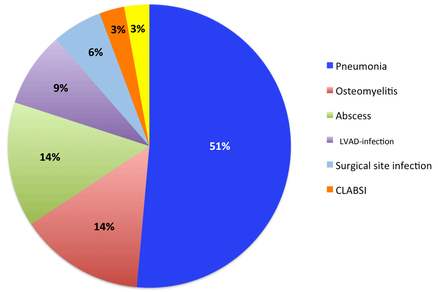

Fig. 1. Types of infections managed with ceftolozane/tazobactam. LVAD, left ventricular assist device; CLABSI, central line associated bloodstream infection

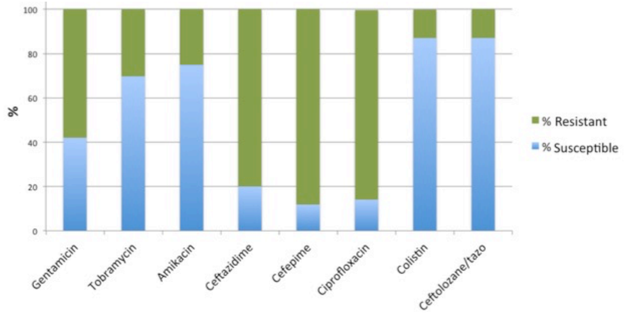

Fig. 2. Susceptibility profile of *P. aeruginosa* isolates included in the study

Results

- C/T was used as monotherapy in 27 (77%) patients and combined in 8 cases (5 inhaled and 3 systemic)
- The approved C/T dose (1.5g Q8h) was used in 11/18 patients with normal renal function, while the remaining 7 received 3g Q8h. Dosing among 7 patients with a creatinine clearance of 30-50 mL/min ranged from 0.375g to 3g Q8h.
- Patients on intermittent hemodialysis (HD, n=3) received 0.375g Q8h and subjects undergoing continuous HD (n=7) were dosed from 0.375g to 1.5g Q8h.
- Clinical success was achieved in 26 (74%) cases. A total of 9 patients were considered to have failed therapy (Table 1).
- All 4 patients infected with C/T non-susceptible *P. aeruginosa* failed therapy (Fig. 3)
- Major adverse effects were not reported

Results

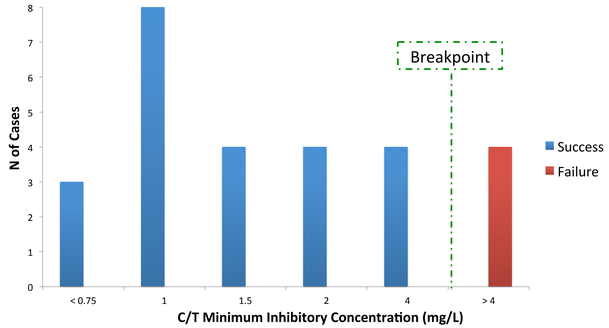

Fig. 3. Distribution of minimum inhibitory concentrations to ceftolozane/tazobactam and its relation with clinical failure

N	Age	Sex	Infection	Type of Culture	C/T MIC	Creatinine Clearence (mL/min)	Dose	Duration (days)	Comments
1	71	F	Pelvic abscess	Fluid aspirate	2	30-50	0.75g Q8h	7	Patient had a recurrent uterine malignancy and devloped and enterocutaneous fistula after hysterectomy. The cause of death was an acute massive gastric hemorrhage. Infection was felt to be under control.
2	55	M	Pneumonia	BAL	1.5	CVVHD	0.375g Q8h	12	Patient with a history of end-stage liver disease secondary to alcoholism. Care was withdrawn as per family request
3	39	M	Pneumonia	Blood	48	CVVHD	1.5g Q8h	7	Patient had a history of end-stage renal disease s/p renal transplant that failed to engraft. Admitted with severe renal impairment, respiratory failure and septic shock
4	32	M	Pneumonia	Tracheal aspirate	8	> 70	1.5g Q8h	18	Patient with a history of tetraplegia. Initial clinical improvement, but had recurrent episodes of pneumonia due to *P. aeruginosa*
5	61	M	Pneumonia	Pleural fluid	NR	HD	1.5g once, then 0.375g Q8h	6	Patient had a history of interstitial lung disease s/p bilateral orthotopic lung transplant complicated with an active bronchopleural fistula. Admitted with pneumonia, died due to progressive respiratory failure
6	31	M	Pneumonia	Sputum	8	> 70	1.5g Q8h	14	Patient had history of advanced cystic fibrosis s/p bilateral orthotopic lung transplant. Died of progressive respiratory failure
7	71	M	Pneumonia	Blood	16	> 50	3g Q8h	5	History of myelodisplastic syndrome with leukemic conversion s/p chemotherapy. Rapid worsening with progressive respiratory compromise, septic shock and multi organ failure
8	75	M	Osteomyelitis	Bone	2	> 70	3g Q8h	19	Patient had refractory cutaneous T-cell lymphoma and developed osteomyelitis of the left radius. He died due to septic shock secondary to a pneumonia 22 days after the initial C/T dose. BAL cultures yielded MDR *K. pneumoniae* and *A. baumanii.* No further *P. aeruginosa* was recovered after C/T therapy
9	26	M	Pneumonia	BAL	NR	30-50	1.5g Q8h	27	History of advanced cystic fibrosis and chronic kidney disease. Pneumonia initially improved after C/T, but had a new episode of pneumonia within a week of finishing the antimicrobials and died of respiratory failure

Table 1. Summary of the cases considered as therapeutic failures. BAL, bronchoalveolar lavage; C/T, ceftolozane/tazobactam; MIC, minimum inhibitory concentration; NR, not reported; CVVHD, continuous veno-venous hemodialysis; MDR, multidrug-resistant.

Conclusions

- C/T may become an important alternative for the treatment of CR-PAE infections
- Resistance resulting in poor clinical outcomes was observed and resulted in therapeutic failures
- Routine C/T susceptibility testing is probably warranted

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Acknowledgements

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