Real-world Experience with Ceftazidime-avibactam Compared with Ceftolozane-tazobactam on Clinical Outcomes in *Pseudomonas aeruginosa* Infections

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Background

- Novel beta-lactam/beta-lactamase inhibitors including ceftolozane-tazobactam (C/T) and ceftazidime-avibactam (C/A) are first-line treatments for resistant *Pseudomonas aeruginosa* infections[1]
- C/T may often be preferred due to narrower spectrum and lower cost for *P. aeruginosa*
- A global shortage of C/T from December 2020 to January 2022 resulted in adoption of C/A as an alternative to C/T for *P. aeruginosa* infections at Montefiore Medical Center (MMC)[2]
- Real-world experience evaluating C/A for *P. aeruginosa* infections is limited and no evidence is available directly comparing C/A and C/T for *P. aeruginosa* infections[3]

Objective

- To compare outcomes between patients administered C/A versus C/T for treatment of *P. aeruginosa* infections

Methods

- **Study Design**: retrospective, single hospital system, comparative cohort
- **Inclusion Criteria:** Adults admitted between January 1st, 2018 and December 31st, 2021, who received C/A or C/T for >48 hours for culture-proven *P. aeruginosa* infection
- **Exclusion Criteria:** (1) suboptimal dosing of C/T for respiratory tract infections, (2) polymicrobial infections without appropriate therapy (3) administration of C/A or C/T for non-pseudomonal infections, (4) administration of both C/A and C/T within same course, (5) *In vitro* resistance to study drug, (6) missing follow-up information
- **Primary Outcome:** Clinical success (provider-documented symptomatic improvement, including resolution of fever and/or leukocytosis by end of therapy) in patients surviving to day 30
- **Secondary Outcomes:**

• Mortality by day 30	• Infection recurrence treated by day 90
• Resistance to study drug within 90 days	• Readmitted within 30 days
• Modification of therapy	• Overall length of stay of survivors
• Microbiological failure by day 14	• ICU length of stay of survivors

- **Statistical Analysis:**
  - Primary outcome: chi-square test
  - Secondary outcomes: chi-square test/Fisher's exact test for categorical variables and Student's t-test/Wilcoxon rank sum test for continuous variables
  - Two-tailed p-value of <0.05 considered statistically significant
  - Multivariate regression analysis included variables with a P-value <0.2 on univariate analysis
  - Sensitivity analyses excluded (1) C/A recipients before the C/T shortage occurred and (2) patients with non-multi-drug resistant *P. aeruginosa* isolates

Results

Table 1. Baseline Characteristics

	C/A (n=46)	C/T (n=56)	p-value
Median age (years) (IQR)	65 (56-74)	64 (53-73)	0.532
Male (%)	27 (58.7)	33 (58.9)	0.981
Median BMI (kg/m^2) (IQR)	28 (22-33)	25 (22-30)	0.191
BMI ≥30 kg/m^2 (%)	19 (41.3)	14 (25)	0.08
Median Charlson Comorbidity Index (IQR)	4 (3-7)	5 (3-8)	0.345
Immunocompromised* (%)	8 (17.4)	8 (14.3)	0.668
Median CrCl (mL/min) (IQR)	58.7 (42.1-86.4)	59.5 (41.2-94.5)	0.719
In intensive care unit on BLBLI initiation (%)	21 (45.7)	15 (26.8)	0.047
≥2 SIRS criteria met on BLBLI initiation (%)	30 (65.2)	33 (58.9)	0.515
On IHD at BLBLI initiation (%)	12 (26.1)	12 (21.4)	0.581
On CRRT at BLBLI initiation (%)	1 (2.2)	0	0.451
On invasive ventilation at BLBLI initiation (%)	35 (76.1)	31 (55.4)	0.029
On vasopressors at BLBLI initiation (%)	14 (30.4)	10 (17.9)	0.136
History of *P. aeruginosa* in culture within previous six months (%)	20 (43.5)	39 (69.6)	0.008
History of multi-drug resistant *P. aeruginosa* (%)	5 (10.9)	13 (23.2)	0.055
SARS-CoV-2 (+) test within 30 days of BLBLI administration	7 (15.2)	7 (12.5)	0.691

*Immunocompromised: history of organ transplantation, disease suppressing immunity (AIDS, lymphoma, leukemia), receipt of chemotherapy or stem cell transplant, or immunosuppressive treatment (prednisone ≥20mg/day for ≥7 days or equivalent)
Abbreviations: AIDS = acquired immunodeficiency syndrome; BLBLI = beta-lactam/beta-lactamase inhibitor; CRRT = continuous renal replacement therapy; IHD = intermittent hemodialysis; SIRS = systemic inflammatory response syndrome

Table 2. Infection Source and Microbiology Characteristics

	C/A (n=46)	C/T (n=56)	p-value
Infection source (%)			
• Primary bacteremia only	1 (2.2)	2 (3.6)	1.000
• Urinary only	4 (8.7)	9 (16.1)	0.266
• Respiratory only	29 (63)	29 (51.8)	0.253
• Intra-abdominal only	2 (4.3)	4 (7.1)	0.688
• Soft tissue or wound only	6 (13)	12 (21.4)	0.269
• Bone and joint only	1 (2.2)	0	0.451
• Multiple sources	3 (6.6)	0	0.088
Concomitant *P. aeruginosa* bacteremia (%)	3 (6.5)	3 (5.4)	0.84
Source control achieved (%)	11 (23.9)	12 (21.4)	0.765
MDR index *P. aeruginosa* organism (%)*	35 (76.1)	54 (96.4)	0.002
Polymicrobial infections (%)	27 (58.7)	30 (53.6)	0.604
• CRE	10	0	
• Non-CRE	13	9	
• Other[#]	16	29	

*Multi-drug resistance defined in accordance with CDC definitions as intermediate or resistant susceptibility to at least one drug in at least 3 of the following five categories: 1) extended-spectrum cephalosporins (cefepime, ceftazidime/avibactam, ceftolozane/tazobactam), 2) fluoroquinolones, 3) aminoglycosides, 4) carbapenems, 5) piperacillin/tazobactam

[#]Other includes: *Acinetobacter* spp. (C/T n=3), MRSA (C/A n=2; C/T n=5), MSSA (C/A n=1; C/T n=4), *Enterococcus* spp. (C/A n=5; C/T n=9), *Streptococcus* spp. (C/T n=3), *Candida* spp. (C/A n=3; C/T n=2), "Other", unspecified (C/A n=5; C/T n=3)
Abbreviations: CRE = carbapenem-resistant Enterobacterales; MDR = multi-drug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*

Table 3. Antimicrobial Therapy Characteristics

	C/A (n=46)	C/T (n=56)	p-value
Median time from culture to active therapy (hours) (IQR)	73.8 (50.3-119.6)	71.6 (39.9-105.9)	0.882
Received concomitant systemic antimicrobial therapy with antipseudomonal activity (%)*	3 (6.5)	4 (7.1)	1.000
Study drug renally adjusted at initiation (%)	22 (47.8)	35 (62.5)	0.735
Appropriately dosed after renal adjustment (%)	20 (90.9)	31 (88.6)	1.000
Median treatment duration (days) (IQR)	7 (5-12)	7 (6-10)	0.837

*Concomitant drugs: ciprofloxacin (C/A n=2), gentamicin (C/A n=1; C/T n=2), meropenem (C/T n=1), polymyxin B (C/T n=1)

Table 4. Outcomes

	C/A (n=46)	C/T (n=56)	p-value
Clinical success by end of treatment (%)	33 (71.7)	35 (62.5)	0.325
Mortality by day 30 (%)	7 (15.2)	15 (26.8)	0.158
Resistance within 90 days (%)	14 (30.4)	9 (16.1)	0.084
Modification of therapy (%)	3 (6.5)	2 (3.6)	0.656
Microbiological failure by day 14 (%)	14 (30.4)	15 (26.8)	0.684
Infection recurrence treated by day 90 (%)	22 (47.8)	23 (41.1)	0.494
Readmitted within 30 days (%)	13 (28.3)	17 (30.4)	0.817
Median overall length of stay of survivors (days) (IQR)	39 (20-72)	43 (17-62)	0.734
Median ICU length of stay of survivors (days) (IQR)	17 (14-29)	13 (8-21)	0.283

Discussion

- No differences observed in primary or secondary outcomes comparing C/A to C/T, despite greater proportion of patients on mechanical ventilation or in ICU in C/A group
- No characteristics on multivariate regression analyses associated with clinical failure
- Similar findings to primary analysis for both sensitivity analyses
- Limitations: single hospital system, retrospective, reliance on physician documentation of infection and improvement, small and heterogeneous sample, baseline groups imbalanced by ventilation and ICU status, repeat cultures not routinely obtained

Conclusions

- No difference in outcomes was found in this small, heterogeneous sample comparing C/A vs. C/T for treatment of *P. aeruginosa* infections of various infectious sources
- Larger, well-designed comparative studies are necessary to confirm these findings

References

1. Tamma PD, et al. *Clin Infect Dis*. 2021 Apr 8;72(7):e169-e183.
2. U.S. Food & Drug Administration. FDA Drug Shortages. January 4, 2021.
3. Jorgensen SCJ, et al. *Open Forum Infect Dis*. 2019 Dec 6;6(12):ofz522