Treatment and Outcomes of Cefoxitin-Non-Susceptible *Serratia marcescens, Klebsiella aerogenes, Citrobacter freundii, Enterobacter cloacae, and Morganella morganii* Bacteremia with Piperacillin/Tazobactam Versus Cefepime or Carbapenem in Immunocompromised Patients

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Background

- AmpC beta-lactamases produced by members of the *Enterobacterales* order induced by beta-lactam exposure can cause treatment failure[1]
- Cefepime/carbapenems are effective antibiotics for AmpC-producing organisms, but results are less clear for piperacillin-tazobactam [2-4]
- Data to describe treatment outcomes for serious infections due to AmpC-producing organisms specifically in immunocompromised patients are lacking

Objective

- To compare rates of clinical and microbiological failure between piperacillin-tazobactam and cefepime or a carbapenem in immunocompromised patients with bacteremia due to organisms with inducible AmpC

Methods

- **Study Design:** Retrospective, IRB-approved, cohort study comparing definitive treatment with either piperacillin/tazobactam versus a carbapenem or cefepime for bacteremia due to organisms with inducible AmpC in immunocompromised patients
  - Conducted January 1, 2016, to December 31, 2021, at Stanford Health Care

Inclusion Criteria	• Adult (≥18 years old) immunocompromised inpatients[a] • Blood culture growing cefoxitin-non-susceptible *Enterobacterales*
Exclusion Criteria	• Polymicrobial bacteremia • Death within 72 hours of index blood culture • Antibiotic treatment at outside facility for *Enterobacterales* • Pregnancy/incarceration
Primary Endpoint	• Composite of: - **Clinical failure** (30-day mortality, white blood cell >12k or maximum temperature ≥38°C on days 5-7) - **Microbiological failure** between days 3-5 (blood culture with index organism) - **Microbiological relapse** between days 5-30 (growth from sterile site with index organism)
Secondary Endpoints	• Hospital length of stay • Intensive care unit length of stay • *Clostridioides difficile* infection
Statistical Analysis	• Analyses included independent t-test for continuous data and chi square test for categorical data • Logistic regression using an a priori model was constructed • P-values <0.05 were considered statistically significant

[a]*See Table 1 for immunocompromised criteria*

Results

Table 1. Baseline Demographics

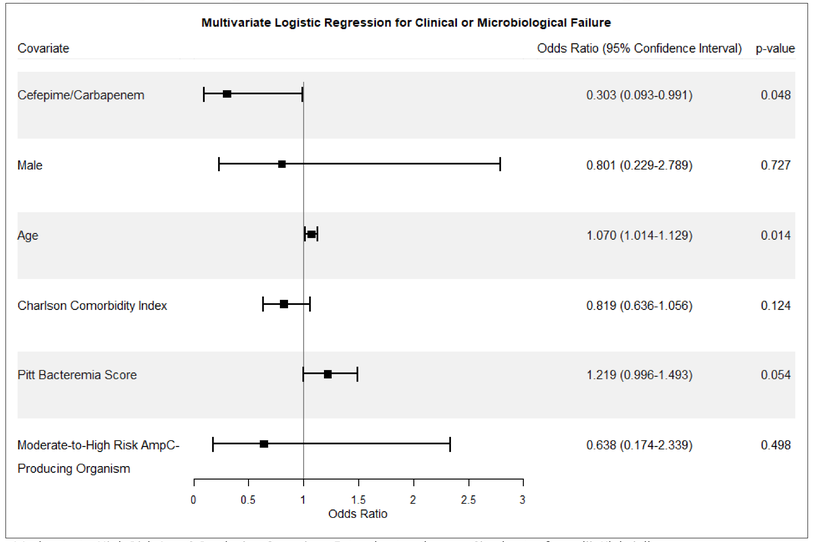
Characteristic	Piperacillin-Tazobactam (n=35)	Cefepime or Carbapenem (n=46)	p-value
Male, n (%)	24 (68.6)	35 (76.1)	0.451
Age (years), mean (SD)	61.7 (12.9)	64.9 (13.8)	0.277
β-lactam Allergy, n (%)	3 (8.6)	11 (23.9)	0.070
ICU Admission, n (%)	9 (25.7)	16 (34.8)	0.381
Renal Replacement Therapy[a], n (%)	2 (5.7)	1 (2.2)	0.403
Charlson Comorbidity Index, mean (SD)	6.4 (3.0)	5.7 (2.3)	0.304
Pitt Bacteremia Score, mean (SD)	0.9 (1.9)	2.2 (3.3)	**0.042**
Infectious Diseases Consult, n (%)	17 (48.6)	25 (54.4)	0.606
Immunocompromised Criteria, n (%)			
Chemotherapy	17 (48.6)	23 (50.0)	0.899
High-Dose Corticosteroids[b]	1 (2.9)	1 (2.2)	0.844
Immunosuppressive Drug	9 (22.9)	10 (22.2)	0.946
Severe Neutropenia[c]	3 (8.6)	15 (32.6)	**0.010**
Solid Organ Transplant	4 (11.4)	3 (6.5)	0.436
Bone Marrow Transplant	1 (2.9)	7 (15.2)	0.065
Leukemia/Lymphoma	7 (20.0)	17 (37.0)	0.098

[a]Within 24 hours before to 24 hours after index culture
[b]20 mg daily prednisone or equivalent for > 14 days
[c]Absolute neutrophil count <500 cells/µL
Abbreviations: ICU, intensive care unit; SD, standard deviation

Table 2. Microbiological Data

Microbiologic Data, n (%)	Piperacillin-Tazobactam (n=35)	Cefepime or Carbapenem (n=46)	p-value
Organism			
Moderate-High Risk of AmpC	26 (74.3)	32 (69.6)	0.641
Enterobacter cloacae	19 (54.3)	27 (58.7)	
Citrobacter freundii	2 (5.7)	3 (6.5)	
Klebsiella aerogenes	5 (14.3)	2 (4.4)	
Low Risk of AmpC	9 (25.7)	14 (30.4)	
Serratia marcescens	9 (25.7)	13 (28.3)	
Morganella morganii	0 (0.0)	1 (2.2)	
Bacteremia Source			
Urinary Tract Infection	7 (20.0)	3 (6.5)	0.430
Intraabdominal	16 (45.7)	23 (50.0)	
Vascular Catheter-related	2 (5.7)	3 (6.5)	
Surgical Site	2 (5.7)	1 (2.2)	
Pneumonia	3 (8.6)	2 (4.4)	
Mucositis/Neutropenia	2 (5.7)	9 (19.6)	
Musculoskeletal	0 (0)	1 (2.2)	
Skin/Soft Tissue Infection	2 (5.7)	2 (4.4)	
Unknown	1 (2.9)	2 (4.4)	
Source Control Achieved	28 (80.0)	32 (69.6)	0.288
Appropriate Initial Antibiotic	33 (94.2)	44 (95.7)	0.779

Figure 1. Logistic Regression for Clinical or Microbiological Failure



Moderate-to-High Risk AmpC-Producing Organism: Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes

Results (cont.)

Table 3. Primary Endpoint

Primary Outcome, n (%)	Piperacillin-Tazobactam (n=35)	Cefepime or Carbapenem (n=46)	p-value
Clinical or microbiological failure	17 (48.6)	17 (37.0)	0.294
In-hospital 30-day mortality	2 (5.7)	3 (6.5)	0.881
WBC >12 x 10^9/L (days 5-7)	8 (22.9)	10 (21.7)	0.905
T_{max} ≥38°C (days 5-7)	6 (17.1)	10 (21.7)	0.607
Microbiological failure (days 3-5)	4 (11.4)	0 (0.0)	**0.019**
Microbiological relapse (days 5-30)	1 (2.9)	2 (4.4)	0.725

Abbreviations: WBC, white blood cell

Table 4. Secondary Endpoints

	Piperacillin-Tazobactam (n=35)	Cefepime or Carbapenem (n=46)	p-value
Hospital LoS (days), median (IQR)	12.4 (6.1-22.2)	13.2 (5.5-25.1)	0.260
ICU LoS (days), median (IQR)	2.4 (1.0-3.3)	10.1 (2.8-14.6)	0.855
***Clostridioides difficile* infection, n (%)**	0 (0.0)	2 (4.4)	0.212

Abbreviations: ICU, intensive care unit; LoS, length of stay

Discussion/Conclusion

- Treatment with cefepime/carbapenems was associated with a lower odds of clinical and microbiological failure versus piperacillin/tazobactam in immunocompromised patients with infections due to organisms with inducible AmpC (OR = 0.303 [95% CI 0.093-0.991])
- Piperacillin/tazobactam was associated with more frequent microbiological failure compared to cefepime or carbapenems
- No difference was observed in the secondary outcomes
- Despite higher Pitt bacteremia scores and rates of severe neutropenia, patients treated with cefepime and carbapenems did not have worse outcomes compared to piperacillin/tazobactam
- This was a single center, retrospective study and further, larger prospective trials are needed

Disclosures

- All authors have no potential conflicts of interest or disclosures

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