Novel Beta-lactam Beta-lactamase Inhibitors Against Alternative Antibiotics for the Treatment of Complicated Urinary Tract Infections and Pyelonephritis Caused by Carbapenem-resistant *Enterobacterales*

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Introduction

- Carbapenem-resistant *Enterobacterales* (CRE) is an urgent public health threat[1]
- Urinary tract infections (UTIs), which include complicated UTIs (cUTIs) and acute pyelonephritis (AP), are the most common type of CRE infection encountered[1]
- Limited treatment options exist:
  - Historic agents: high-dose carbapenems, aminoglycosides (AGs), polymyxins, and tigecycline
  - Novel beta-lactam beta-lactamase inhibitors (BL-BLIs): ceftazidime/avibactam (CZA) and meropenem/vaborbactam (MVB)
- Little data exists on the comparative efficacy or safety of CRE-targeted BL-BLIs versus alternative antibiotics for the treatment of CRE cUTI/AP[2,3]
- It would be ideal to preserve CZA/MVB for more invasive infections in order to reduce utilization and subsequent development of resistance[4]

Objective

To evaluate clinical failure and tolerability in patients with CRE cUTI/AP treated with CRE-targeted BL-BLIs (MVB or CZA) vs. alternative antibiotic regimens, as monotherapy or combination therapy.

Methods

This was a multicenter, retrospective cohort study of adults admitted with a CRE cUTI/AP treated with CRE-active antibiotic(s), including combination therapy, for at least 48 hours between January 2012 and June 2019.

Exclusion Criteria:
- Non-urinary source co-infection
- Non-*Enterobacterales* UTI
- CRE colonization of the urine
- Nitrofurantoin or fosfomycin as primary therapy
- Mortality within 48 hours of index culture

Primary Outcome:
- Clinical failure

Secondary Outcomes:
- 30- and 90-day recurrence
- 30-day hospital readmission
- 30-day mortality
- Length of hospital stay (LOS)
- Treatment-limiting adverse effects
- Non-treatment limiting acute kidney injury (AKI)
- *C. difficile* infection 90-days of index culture

Statistics:
- Categorical variables: Chi-square & Fishers exact tests
- Continuous variables: Student's t-test & Wilcoxon rank-sum tests
- Estimated clinical failure rate in the alternative group ~16%[6]
- Only 20% power to detect a difference in the rate of clinical failure between groups, with an equivalence margin of ±10% and a significance level of 0.05

Definitions

CRE: defined in accordance with the Centers for Disease Control and Prevention (CDC) definition[1]

cUTI and AP: defined based on the US Food and Drug Administration (FDA) guidance[5]

Clinical failure: persistence, worsening or reappearance of clinical signs and symptoms of cUTI/AP or recurrence at 30 days from index culture

Recurrence: presence of a repeat urine culture with the original CRE isolate accompanied by signs and symptoms of cUTI/AP

Urologic complications: chronic indwelling urinary catheter, ureteral stent(s), nephrostomy tube(s), neurogenic bladder, obstructive uropathy, ileal conduit

Results

Figure 1: Patient Selection

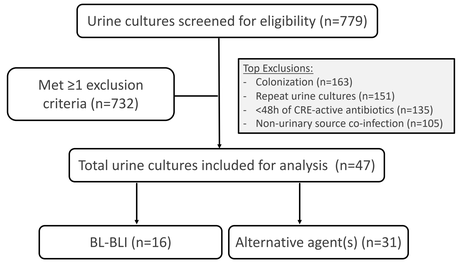


Table 1: Baseline Characteristics

	BL-BLI (n=16)	Alternative (n=31)
Male sex [n (%)]	4 (25.0)	12 (38.7)
Age (years) (median [IQR])	64.0 [50.0,74.0]	67.0 [52.0,76.0]
Past CRE infection/colonization [n (%)]	6 (37.5)	11 (35.5)
Urologic complications [n (%)]	9 (56.3)	18 (58.1)
ICU admission during treatment [n (%)]	5 (31.3)	6 (19.4)
Comorbidities		
Charlson Comorbidity Index (median [IQR])	4.0 [3.0,5.0]	4.0 [2.0,6.0]
Chronic kidney disease [n (%)]	3 (18.8)	11 (35.5)
Cirrhosis [n (%)]	4 (25.0)	3 (9.7)
Malignancy [n (%)]	2 (12.5)	4 (12.9)
Diabetes mellitus [n (%)]	6 (37.5)	11 (35.5)
CRE urine isolates		
Klebsiella pneumoniae	13 (81.3)	27 (87.1)

Figure 2: Antibiotic Regimens

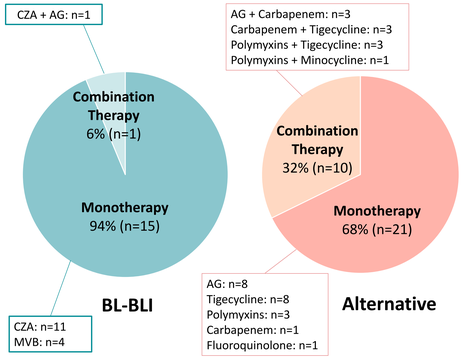


Table 2: Outcomes

Efficacy Outcomes	BL-BLI (n=16)	Alternative (n=31)	p-value
Clinical failure [n (%)]	2 (12.5)	12 (38.7)	0.063
30-day recurrence [n (%)]	1 (50)	3 (25)	
Persistent symptoms [n (%)]	1 (50)	9 (75)	
90-day recurrence [n (%)]	3 (18.8)	8 (25.8)	0.59
30-day readmission [n (%)]	5 (31.3)	16 (51.6)	0.18
Infection-related	0 (0.0)	8 (53.3)	0.055
30-day all-cause mortality [n (%)]	1 (6.3)	2 (6.5)	0.99
LOS (days) (median [IQR])	12.5 [7.5,17]	11.0 [7.0,19.0]	NS
Safety Outcomes			
Treatment-limiting adverse effect [n (%)]	**0 (0.0)**	**9 (29.0)**	**0.017**
Non-treatment limiting AKI [n (%)]	3 (18.8)	6 (19.4)	0.96
C. difficile infection [n (%)]	1 (6.3)	2 (6.5)	0.99

Figure 3: Efficacy Outcomes

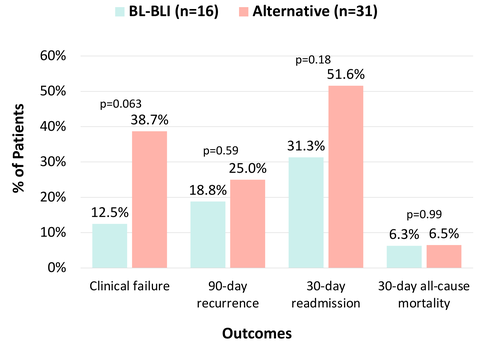
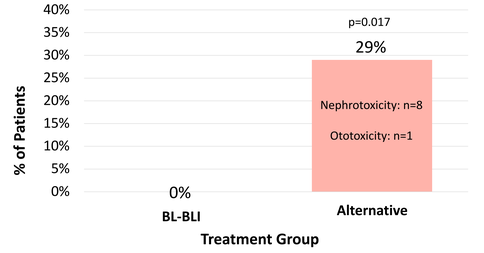


Figure 4: Treatment-Limiting Adverse Effects



Discussion

- No difference in efficacy outcomes resulted between treatment groups, but this study was underpowered
- Patients in the alternative group did numerically worse in all study outcomes
- High utilization of suboptimal monotherapy regimens likely contributed
  - 63% (n=5) treated with tigecycline monotherapy failed
  - 67% (n=2) treated with a polymyxin monotherapy failed
- Significant difference found in treatment-emergent adverse effects, largely driven by nephrotoxicity in the alternative group
  - Polymyxins accounted for ~63% (n=5) of all treatment-limiting nephrotoxicity
  - AGs accounted for 25% (n=2) of treatment-limiting nephrotoxicity
- BL-BLI group consisted of predominately CZA and performed similar to MVB in the TANGO II subgroup analysis[4]
- BL-BLIs resulted in zero treatment-limiting adverse effects and there were no cases of acquired resistance on repeat urine culture

Strengths	Limitations
- Multicenter design - Large sample size for a study on CRE cUTI/AP - First study of its kind in CRE cUTI/AP, comparing novel agents to historic regimens specifically	- Retrospective design - Not adequately powered - Did not assess antibiotic dosing or therapeutic-drug monitoring - Practice changes throughout study period: CRE definitions, breakpoint data, CRE mechanism testing

Conclusions & Future Directions

- In this retrospective study, no difference in clinical failure resulted among groups
- Significantly more treatment-limiting adverse effects occurred in the alternative group compared to the BL-BLI group, driven by nephrotoxicity
- Larger studies, including more aminoglycoside-based regimens, with or without high-dose carbapenems, would be of greater utility in making comparisons amongst agents and subsequent treatment recommendations

Resources

1) Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the US, 2013. Updated April 10, 2017.
2) Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. *Infect Dis Ther*. 2018;7(4):439-455.
3) Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. *Open Forum Infect Dis*. 2015;2(2):ofv050.
4) Shields RK, Chen L, Cheng S, et al. *Antimicrob Agents Chemother*. 2017;61:e02097-16.
5) U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Complicated Urinary Tract Infections: Developing Drugs for Treatment; Guidance for Industry. June 2018 .
6) Igbinosa O, Dogho P, Osadiaye N. *Am J Infect Control*. 2020;48(1):7-12.

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Acknowledgements

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