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Recurrence of infection and emergence of drug resistance after treatment with meropenem/vaborbactam compared to ceftazidime/avibactam in carbapenem-resistant *Enterobacteriaceae* infections

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Background

- Prior to 2015, optimal treatment for carbapenem-resistant *Enterobacteriaceae* (CRE) infections consisted of high dose combination therapy to optimize pharmacokinetic/pharmacodynamic parameters, resulting in increased toxicities[1]
- Ceftazidime/avibactam (CA) and meropenem/vaborbactam (MV) are superior in both safety and efficacy outcomes vs. historical regimens for treatment of CRE, but direct comparison between these beta-lactam beta-lactamase inhibitors is lacking[2,3]
- At both Atrium Health and AdventHealth, MV replaced CA as initial therapy for CRE infections given the increasing evidence of the development of CA resistance[4]

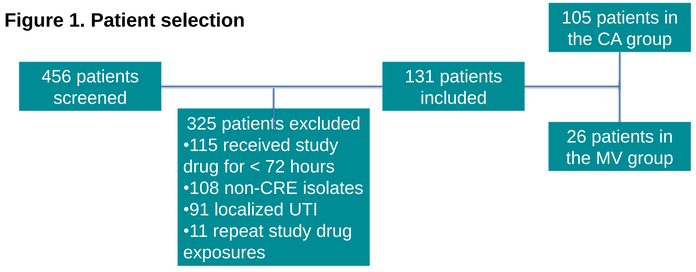
Objective

To compare clinical outcomes, including recurrence of infection and emergence of drug resistance, in patients who received CA vs. MV for CRE infections

Methods

- Multicenter, retrospective, IRB-approved cohort study at Atrium Health and AdventHealth
- Inclusion criteria:
  - ≥ 18 years old
  - Received either CA or MV for ≥ 72 hours
  - Polymicrobial infections
- Exclusion criteria:
  - Localized urinary tract infections (UTI)
  - Repeat study drug exposures
- Primary outcome: Clinical success defined as survival at 30 days, resolution of signs and symptoms of infection, sterilization of blood cultures within 7 days of treatment initiation in patients with bacteremia, and absence of recurrent infections within 90 days
- Secondary outcomes:
  - 30- and 90-day mortality
  - Adverse events (nephrotoxicity, leukopenia, rash, hepatotoxicity, neurotoxicity)
  - Hospital and intensive care unit (ICU) lengths of stay (LOS)
  - Recurrence of infection and development of study drug resistance within 90 days
- Statistical analysis: Student's t-test, Wilcoxon rank sum, and Chi-square test were used to compare continuous, ordinal, and categorical variables, respectively. A post-hoc subgroup analysis was performed

Figure 1. Patient selection



Results

Table 1. Baseline characteristics

	CA (N=105)	MV (N=26)	P-value
Male sex, n (%)	58 (55.2)	12 (46.2)	0.41
Age, years, median [IQR]	62 [51-69]	57.5 [50-70]	0.68
APACHE II score, median [IQR]	26 [22-30]	27 [24-34]	0.19
Primary bacteremia, n (%)	7 (6.7)	1 (3.8)	0.75
Secondary bacteremia, n (%)	37 (35.2)	8 (30.8)	0.75
Urinary tract	13 (35.1)	1 (12.5)	0.43
Intra-abdominal	6 (16.2)	3 (37.5)	
Respiratory	7 (18.9)	2 (25.0)	
Catheter-associated	5 (13.5)	0	
Soft tissue	2 (5.4)	1 (12.5)	
Other	4 (10.8)	1 (12.5)	
Non-bloodstream infection, n (%)	61 (58.1)	17 (65.4)	0.75
Respiratory	30 (49.2)	10 (58.8)	0.47
Soft tissue	18 (29.5)	2 (11.8)	
Intra-abdominal	12 (19.7)	5 (29.4)	
Other	1 (1.6)	0	
CRE organism, n (%)			
Klebsiella spp.	76 (72.4)	15 (57.7)	0.15
Enterobacter spp.	20 (19.1)	8 (30.8)	0.19
Escherichia coli	9 (8.6)	3 (11.5)	0.70
Citrobacter spp.	2 (1.9)	2 (7.7)	0.18
Serratia spp.	0	1 (3.9)	0.20
Presence of Bla_{KPC} gene, n/N (%)	23/32 (71.9)	10/13 (76.9)	1.0
Study drug susceptibility, n/N (%)	90/90 (100.0)	13/14 (92.9)	0.13
Combination therapy, n (%)	64 (61.0)	4 (15.4)	<0.01

Figure 2. CA combination therapy (n=64)

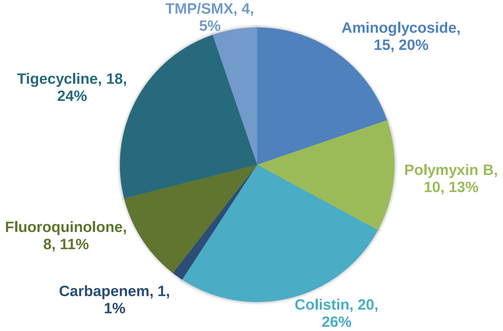


Table 2. Outcomes

	CA (N=105)	MV (N=26)	P-value
Clinical success, n (%)	65 (61.9)	18 (69.2)	0.49
30-day mortality, n (%)	20 (19.1)	3 (11.5)	0.57
90-day mortality, n (%)	30 (28.6)	7 (26.9)	0.48
Hospital LOS, days, median [IQR]	26 [15-53]	32.5 [15-56]	0.70
ICU LOS, days, median [IQR]	15 [5-32]	12 [5-22]	0.53
Recurrence of CRE infection, n (%)	15 (13.5)	6 (19.4)	1.0

Figure 3. Adverse events (N=131)

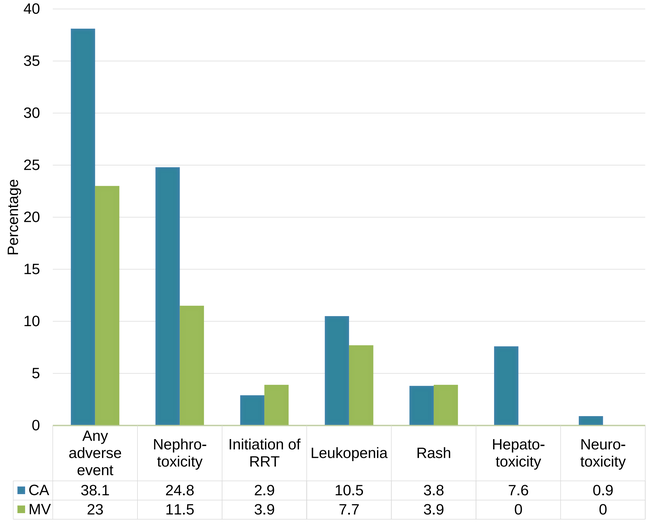


Table 3. Post-hoc subgroup analysis of patients with recurrent CRE infection

	CA monotherapy (N=41)	CA combination (N=64)	MV monotherapy (N=22)	P-value
Recurrent CRE infection, n (%)	9 (22.0)	6 (9.4)	3 (13.6)	0.20
MIC increase, n (%)	5 (12.2)	1 (1.6)	0	0.03
Development of resistance, n (%)	3 (7.3)	0	0*	0.07

*One case of MV resistance was observed in a patient who had received 4 prior courses of MV, but this episode was outside of the study period

Discussion/Conclusions

- Clinical success was similar between CA and MV despite CA being used more frequently as part of a combination regimen
- Patients in the CA group experienced higher rates of adverse events compared to those in the MV group, specifically nephrotoxicity and hepatotoxicity
  - Seen in both CA combination and monotherapy groups
- In patients with a recurrent CRE infection, development of resistance occurred most frequently in the CA monotherapy group
- Our study supports that MV monotherapy is a safe and effective option for treatment of CRE infections
- MV monotherapy may be preferred over CA combination therapy due to the potential for decreased adverse events
- Limitations of our study include the retrospective design, small sample size, and lack of study drug susceptibility and resistance mechanism testing for all CRE isolates
- Future prospective, randomized-controlled trials should compare CA and MV to confirm our results, as well as compare to newer agents with activity against CRE

References

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