Meropenem/Vaborbactam versus Ceftazidime/Avibactam for Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections

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Background

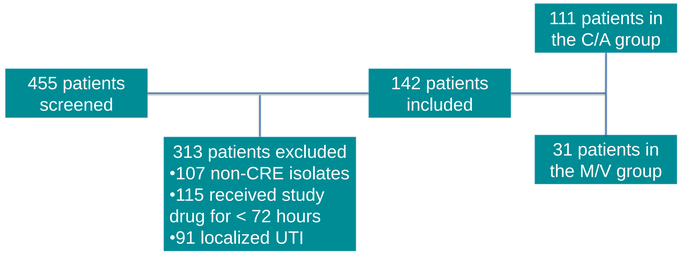
- Prior to 2015, optimal treatment for carbapenem-resistant *Enterobacteriaceae* (CRE) infections consisted of high dose combination therapy to optimize pharmacokinetic/pharmacodynamic parameters, resulting in increased toxicities.[1]
- Two new drugs have been approved with activity against KPC-producing CRE: ceftazidime/avibactam (C/A) and meropenem/vaborbactam (M/V).
- C/A and M/V are superior in both safety and efficacy outcomes vs. historical regimens for treatment of CRE, but direct comparison between agents is lacking.[2,3]
- At both Atrium Health and AdventHealth, M/V replaced C/A as initial therapy for CRE infections given the increasing evidence of the development of C/A resistance.[4]

Objective

To compare clinical outcomes in patients who received C/A versus M/V for CRE infections.

Methods

- Multicenter, retrospective, IRB-approved cohort study evaluating patients with a CRE infection who received either C/A or M/V between 2/25/15 – 10/31/18 at Atrium Health and AdventHealth facilities.
- Inclusion: Patients ≥ 18 years old who received either C/A or M/V for ≥ 72 hours. Polymicrobial infections and repeat study drug exposures were included.
- Exclusion: Localized urinary tract infections (UTI).
- Organisms were defined as CRE if resistant to any carbapenem per the Clinical Laboratory Standards Institute breakpoints or if detected by direct PCR testing.
- 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.
- 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 CRE infection within 90 days of index infection
- Statistical analysis: Student's t-test, the Wilcoxon rank sum test, and the Chi-square test were used to compare continuous, ordinal, and categorical variables, respectively. A multivariable logistic regression analysis was performed for binary outcomes.



Results

Table 1. Baseline Characteristics

	C/A N=111	M/V N=31	P-value
Male sex, n (%)	62 (55.9)	17 (54.8)	0.92
Age, years, median [IQR]	62.0 [18.0]	57.0 [21.0]	0.38
Weight, kg, median [IQR]	74.2 [32.2]	82.7 [18.0]	0.27
Hospital-acquired, n (%)	67 (60.4)	17 (54.8)	0.58
Community-acquired, n (%)	44 (39.6)	14 (45.2)	0.58
APACHE II score, median [IQR]	27.0 [9.5]	27.0 [8.0]	0.41
Primary bacteremia, n (%)	7 (6.3)	1 (3.2)	0.80
Secondary bacteremia, n (%)	40 (36.0)	12 (38.7)	0.80
Intra-abdominal	7 (17.5)	7 (58.3)	0.08
Urinary tract	13 (32.5)	1 (8.3)	
Respiratory	8 (20.0)	2 (16.7)	
Catheter-associated	6 (15.0)	0	
Soft tissue	2 (5.0)	1 (8.3)	
Other	4 (10.0)	1 (8.3)	
Non-bloodstream infection, n (%)	64 (57.7)	18 (58.1)	0.80
Soft tissue	18 (28.1)	2 (11.1)	0.48
Intra-abdominal	14 (21.9)	5 (27.8)	
Respiratory	3 (48.4)	11 (61.1)	
Other	1 (1.6)	0	
CRE organism, n (%)			
Klebsiella spp.	81 (73.0)	20 (64.5)	0.36
Enterobacter spp.	20 (18.0)	8 (25.8)	0.34
Escherichia coli	9 (8.1)	3 (9.7)	0.72
Citrobacter spp.	3 (2.7)	2 (6.5)	0.30
Serratia spp.	0	1 (3.2)	0.22
Combination therapy, n (%)	70 (63.1)	4 (12.9)	<0.01

Figure 1. C/A Combination Therapy (n = 70)

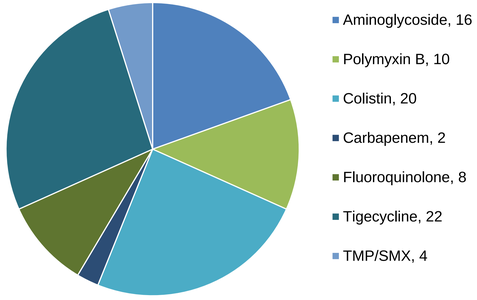
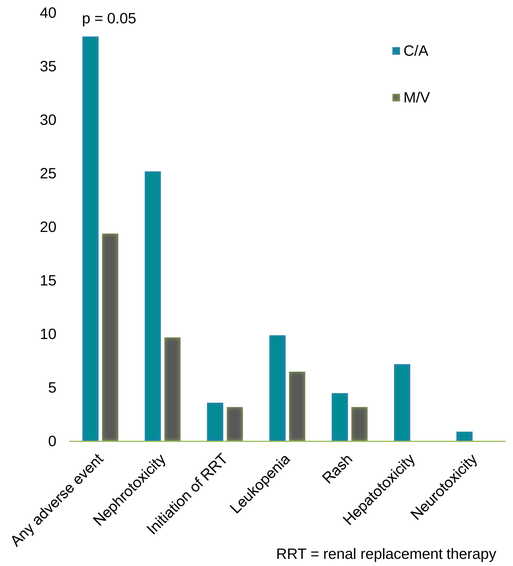


Figure 2. Adverse Events (n = 48)



RRT = renal replacement therapy

Table 2. Outcomes

	C/A N=111	M/V N=31	P-value
Clinical success, n (%)	70 (63.1)	19 (61.3)	0.86
30-day mortality, n (%)	21 (18.9)	3 (9.7)	0.22
90-day mortality, n (%)	31 (27.9)	7 (22.6)	0.55
Hospital LOS, days, median [IQR]	26.0 [38.0]	39.0 [45.0]	0.31
ICU LOS, days, median [IQR]	17.0 [27.0]	12.0 [17.0]	0.39
Recurrence of CRE infection, n (%)	15 (13.5)	6 (19.4)	0.40

Conclusions

- Clinical success was similar between C/A and M/V despite C/A being used more frequently as part of a combination regimen.
- Patients in the C/A group experienced higher rates of adverse events compared to those in the M/V group, specifically nephrotoxicity.
- Our study supports that M/V monotherapy is a safe and effective option for CRE infections.
- M/V monotherapy may be preferred over C/A combination therapy due to the potential for more adverse events, drug-drug interactions, drug monitoring, and costs.

Limitations / Future Directions

- Our study included twice as many patients in the M/V group than previous studies;[3] however, the small sample size remains a limitation of the study.
- Other limitations include the retrospective design and lack of study drug susceptibility and resistance mechanism testing for all CRE isolates.
- Future prospective, randomized-controlled trials should compare C/A and M/V to confirm our results, as well as comparison to newer agents with activity against CRE (e.g. plazomicin, eravacycline).
- Routine drug susceptibility and resistance mechanism testing should be performed.

References

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Disclosures

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