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 C/A vs M/V comparison is lacking.2
- 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.3

Objective

To compare clinical outcomes in patients who received C/A vs 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.
- Exclusion: Patients with CRE organisms that were not included in the study.
- Primary outcome: Clinical success defined as survival at 30 days, resolution of signs and symptoms of infection, sterilization of radiological 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) length of stay (LOS)
  - Recurrence of CRE infection within 90 days of index infection

- Statistical analysis: Student’s t test and Chi-square 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

- Clinical success was similar between C/A and M/V despite C/A being
- 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.3

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>C/A</th>
<th>M/V</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>58 (52.3%)</td>
<td>68 (61.3%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Age, years, median [IQR]</td>
<td>64 (31.05)</td>
<td>63 (31.05)</td>
<td>0.92</td>
</tr>
<tr>
<td>Weight, kg, median [IQR]</td>
<td>72.0 (21.0)</td>
<td>72.0 (21.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Community-acquired, n (%)</td>
<td>44 (40.9%)</td>
<td>44 (40.9%)</td>
<td>0.72</td>
</tr>
<tr>
<td>APACHE II score, median [IQR]</td>
<td>27.0 (9.3)</td>
<td>27.0 (9.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Primary bacteremia, n (%)</td>
<td>7 (6.3%)</td>
<td>7 (6.3%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Secondary bacteremia, n (%)</td>
<td>30 (27.2%)</td>
<td>12 (10.9%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Intrabdominal</td>
<td>7 (7.5%)</td>
<td>7 (7.5%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>17 (15.5%)</td>
<td>17 (15.5%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>8 (7.4%)</td>
<td>8 (7.4%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
<td>0.92</td>
</tr>
<tr>
<td>CRE organism, n (%)</td>
<td>83 (75.1%)</td>
<td>83 (75.1%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>81 (73.6%)</td>
<td>81 (73.6%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>35 (31.8%)</td>
<td>35 (31.8%)</td>
<td>0.92</td>
</tr>
<tr>
<td>E. coli</td>
<td>9 (8.1%)</td>
<td>9 (8.1%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>7 (6.3%)</td>
<td>7 (6.3%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>3 (2.7%)</td>
<td>3 (2.7%)</td>
<td>0.92</td>
</tr>
<tr>
<td>CRE infection, n (%)</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

- Clinical success defined as survival at 30 days, resolution of signs and symptoms of infection, sterilization of radiological cultures within 7 days of treatment initiation in patients with bacteremia, and absence of recurrent infections.
- Other limitations include the retrospective design and lack of study drug directed laboratory testing.

Table 2. Outcomes

- Clinical success, n (%) | 70 (63.1%) | 70 (63.1%) | 0.08 |
- 30-day mortality, n (%) | 21 (18.9%) | 21 (18.9%) | 0.22 |
- 30-day mortality, n (%) | 31 (27.9%) | 31 (27.9%) | 0.55 |
- ICU LOS, days, median [IQR] | 26.0 (36.0) | 30.0 (45.0) | 0.31 |
- Recurrence of CRE infection, n (%) | 15 (13.5) | 15 (13.5) | 0.40 |

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

- Primary outcome: Clinical success defined as survival at 30 days, resolution of signs and symptoms of infection, sterilization of radiological 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) length of stay (LOS)
- Recurrence of CRE infection within 90 days of index infection

- Statistical analysis: Student’s t test and Chi-square 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.

Figure 2. Adverse Events (n = 48)

- Clinical success defined as survival at 30 days, resolution of signs and symptoms of infection, sterilization of radiological cultures within 7 days of treatment initiation in patients with bacteremia, and absence of recurrent infections.
- Other limitations include the retrospective design and lack of study drug directed laboratory testing.

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; however, the small sample size remains a limitation of the study.
- Our study 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


Disclosures

- The authors of this poster received a research grant from Merck for microbiology support.
- Danya Rosdy and Jacqueline Lopez served as consultants to Paralek Pharmaceuticals and received compensation for these services.
- Christopher Polk has current research funding from Gilead Sciences and VIV healthcare, and serves as an advisory board member for VIV Healthcare.