**Note**

*In vitro* evaluation of meropenem-vaborbactam against clinical CRE isolates at a tertiary care center with low KPC-mediated carbapenem resistance

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**ABSTRACT**

The *in vitro* activity of meropenem-vaborbactam was examined against clinical carbapenem-resistant Enterobacteriaceae isolates collected over 3 years at our medical center. Only 3 KPC-producers were identified. Susceptibility to meropenem-vaborbactam was noted in 15/16 (94%) isolates (MIC<sub>90</sub> 2 mg/L) that were nonsusceptible to meropenem. Meropenem-vaborbactam may have utility at centers where non-KPC-producers are more frequent.

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Carbapenem-resistant *Enterobacteriaceae* (CRE) are a significant global threat with substantially poorer outcomes and limited treatment options (Bassetti et al., 2016; Doi et al., 2017; Duin and Doi, 2017; Logan and Weinstein, 2017). Meropenem-vaborbactam was FDA-approved in 2017 for use in adult patients with complicated urinary tract infections (Drugs@FDA). Vaborbactam is a cyclic boronic acid derivative with potent activity against Ambler class A and class C β-lactamases (Lomovskaya et al., 2017). Its major utility has been demonstrable potency in *in vitro* and efficacy in clinical trials against Ambler class A carbapenemase-producing *Enterobacteriaceae*, specifically isolates with KPC-mediated resistance (Castanheira et al., 2016, 2017; Hackel et al., 2018; Kaye et al., 2017; Lomovskaya et al., 2017; Pfaffer et al., 2018). While these results were particularly encouraging, there is still considerable variation in KPC prevalence between medical centers even in similar geographical locations. At the University of Wisconsin Hospitals and Clinics, we have had approximately 1 KPC-producing clinical isolate per year (0.3 per 100 000 patient days and 0.007% of all *Enterobacteriaceae* isolates processed annually at our clinical laboratory). In contrast, non-KPC-producing CRE isolates are much more common, numbering 15–20 per year. Given the very low incidence of KPC-producing isolates, we sought to answer whether meropenem-vaborbactam could have potential benefit in our patient population by evaluating its *in vitro* potency against CRE clinical isolates from our institution.

Retrospective review of the clinical microbiology database at the University of Wisconsin Hospitals and Clinics from 1/1/2015 to 12/30/2017 was performed. Over this period, it was standard practice to test and report ertapenem and meropenem susceptibility results on all *Enterobacteriaceae* isolates. A clinical isolate had to be resistant by CLSI interpretive criteria to at least 1 carbapenem to be included in analysis. Forty-six CRE isolates were identified from unique clinical encounters; 44 were able to be recovered from frozen stocks and included in the analysis. These isolates included *E. cloacae* complex (*n* = 19), *E. coli* (*n* = 10), *K. pneumoniae* (*n* = 8), *S. marcescens* (*n* = 5), *Klebsiella* (formerly *Enterobacter*) aerogenes (*n* = 1), and *K. oxytoca* (*n* = 1). Isolates were most commonly recovered from urine (*n* = 21), followed by intraabdominal source (*n* = 9), lung (*n* = 6), blood (*n* = 3), skin and soft tissue (*n* = 3), bone (*n* = 1), and sinus (*n* = 1). Antimicrobial susceptibility testing performed by CLSI broth microdilution techniques (MicroScan, Beckman Coulter, Indianapolis, IN) at the time of isolation (CLSI, 2018a, 2018b) from the clinical specimen revealed 2 distinct groups of isolates: 1) resistant to ertapenem but susceptible to meropenem (*n* = 28, 64%) and 2) resistant to ertapenem and nonsusceptible (intermediate *n* = 2, resistant *n* = 14) to meropenem.
(total n = 16, 36%). Each isolate was sent to the Wisconsin State Laboratory of Hygiene for molecular detection of carbapenemase genes for KPC, NDM-1, and OXA-48-like via real-time PCR. Only 3 were positive, and all were KPC-producing K. pneumoniae isolates.

Each isolate recovered from stock underwent additional antimicrobial susceptibility testing against meropenem-vaborbactam by antimicrobial gradient diffusion (Liofilchem Inc., Waltham, MA) and disk diffusion (Mast Group Ltd., Bootle, UK) per manufacturer instructions with a fixed vaborbactam concentration of 8 mg/L per manufacturer instructions. Quality control testing was performed with ATCC reference strains (University of Wisconsin Hospitals and Clinics, 2015–2017). As expected, the combination of meropenem-vaborbactam against isolates that were resistant to ertapenem but susceptible to meropenem was efficacious with all 28 isolates demonstrating susceptibility to the combination with an MIC\(_{50}\) of 0.125 mg/L and MIC\(_{90}\) of 0.5 mg/L (Table 1). In the group resistant to ertapenem and nonsusceptible to meropenem, meropenem-vaborbactam continued to demonstrate efficacy with an MIC\(_{50}\) of 0.125 mg/L and MIC\(_{90}\) of 2 mg/L (Table 1). Susceptibility to meropenem-vaborbactam was noted in 15 of 16 (94%) isolates in this group (Table 2). Notably, 11 of 16 isolates had a 24-fold decrease and 9 of 16 had a ≥16-fold decrease in MIC for meropenem-vaborbactam compared to meropenem alone. On average, the meropenem-vaborbactam MIC decreased by almost 128-fold compared with meropenem alone. There were no discrepancies between susceptibility interpretation using gradient diffusion and disk diffusion.

This study demonstrates a number of important findings. First, we found that a majority (94%) of the CRE isolates at our center are resistant to ertapenem but are susceptible to other carbapenems such as meropenem. This has been reported as due to the combination of ESBL β-lactamase production with contribution of active efflux pumps and/or porin loss (Woodford et al., 2007), and other carbapenems usually maintain activity against these isolates. Second, for CRE isolates that were resistant to ertapenem and nonsusceptible to meropenem, non-KPC-producers are much more frequently encountered at our center than KPC-producing isolates (81% vs. 19%). Nonetheless, we found that vaborbactam significantly decreased the meropenem MIC in most isolates compared to meropenem alone for this group. Previously published large in vitro studies have demonstrated a relative decrease in potency for meropenem-vaborbactam against non-KPC-producing CRE (Castanheira et al., 2017; Lomovskaya et al., 2017; Pfaffer et al., 2018). For example, Pfaffer et al. (2018)...

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**Table 1**


<table>
<thead>
<tr>
<th>CRE phenotype</th>
<th>N (%)</th>
<th>Meropenem-vaborbactam MIC(_{50}) (mg/L)</th>
<th>Meropenem-vaborbactam MIC(_{90}) (mg/L)</th>
<th>Number (%) susceptible to meropenem-vaborbactamb</th>
<th>Number (%) susceptible to ciprofloxacin(^b)</th>
<th>Number (%) susceptible to piperacillin/tazobactampa</th>
<th>Number (%) susceptible to tobramycin(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem resistant, meropenem susceptible(^d)</td>
<td>28 (64)</td>
<td>0.125</td>
<td>0.5</td>
<td>28 (100)</td>
<td>18 (64)</td>
<td>5 (18)</td>
<td>23 (82)</td>
</tr>
<tr>
<td>Ertapenem resistant, meropenem nonsusceptible(^d)</td>
<td>16 (36)</td>
<td>0.125</td>
<td>2</td>
<td>15 (94)</td>
<td>8 (50)</td>
<td>7 (44)</td>
<td>10 (63)</td>
</tr>
</tbody>
</table>

\(^a\) 2018 US FDA MIC interpretative criteria for meropenem-vaborbactam as follows: susceptible ≤4/8 mg/L, intermediate 8/8 mg/L, and resistant ≥16/8 mg/L.

\(^b\) 2018 US FDA MIC interpretative criteria for meropenem-vaborbactam as follows: susceptible ≤4/8 mg/L, intermediate 8/8 mg/L, and resistant ≥16/8 mg/L.

\(^c\) Approved CLSI breakpoints at the time of testing were used for determining susceptibility to ciprofloxacin, piperacillin/tazobactam, and tobramycin.

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**Table 2**

*In vitro* susceptibility results for meropenem-vaborbactam by gradient diffusion and disk diffusion for CRE clinical isolates that were resistant to ertapenem and nonsusceptible to meropenem (University of Wisconsin Hospitals and Clinics, 2015–2017).

<table>
<thead>
<tr>
<th>Organism (CRE phenotype)</th>
<th>Meropenem MIC (mg/L)(^a)</th>
<th>Meropenem-vaborbactam MIC (mg/L)(^c)</th>
<th>Meropenem-vaborbactam inhibition zone diameter (nearest whole mm)(^d)</th>
<th>Carbapenemase detected(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacter cloacae complex</td>
<td>2</td>
<td>2</td>
<td>21</td>
<td></td>
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<tr>
<td>Enterobacter cloacae complex</td>
<td>2</td>
<td>0.5</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Enterobacter cloacae complex</td>
<td>4</td>
<td>2</td>
<td>20</td>
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<tr>
<td>Escherichia coli ≥8</td>
<td>8</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli ≥8</td>
<td>4</td>
<td>0.06</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli ≥8</td>
<td>4</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Klebsiella (formerly Enterobacter) aerogenes</td>
<td>4</td>
<td>4</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Klebsiella oxytoca ≥8</td>
<td>4</td>
<td>0.03</td>
<td>29</td>
<td></td>
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<tr>
<td>Klebsiella pneumoniae ≥8</td>
<td>8</td>
<td>0.125</td>
<td>20</td>
<td>KPC</td>
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<tr>
<td>Klebsiella pneumoniae ≥8</td>
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<td>0.06</td>
<td>23</td>
<td>KPC</td>
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<tr>
<td>Serratia marcescens ≥8</td>
<td>4</td>
<td>0.06</td>
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<tr>
<td>Serratia marcescens ≥8</td>
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<td>0.06</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Meropenem-vaborbactam MIC testing was performed with fixed vaborbactam concentration of 8 mg/L per manufacturer instructions.

\(^b\) 2018 CLSI M100 interpretive criteria for meropenem-vaborbactam as follows: susceptible ≤1 mg/L, intermediate 2 mg/L, and resistant ≥4 mg/L.

\(^c\) 2018 US FDA MIC interpretative criteria for meropenem-vaborbactam as follows: susceptible ≤4/8 mg/L or ≥16 mm, intermediate 8/8 mg/L or 14–16 mm, and resistant ≥16/8 mg/L or ≥13 mm.

\(^d\) Isolates were tested for KPC, NDM-1, and OXA-48-like carbapenemases via real-time PCR.
recently published meropenem-vaborbactam activity against 330 CRE isolates from a worldwide collection during 2015 in this comprehensive study, meropenem-vaborbactam demonstrated an MIC_50 and MIC_90 against non-KPC-producers of 16 mg/L and 32 mg/L, respectively, due to the large number of MBL (52/121; 43%) and OXA-48 (40/121; 33%) producing isolates in this subset. Against the 16 isolates that were resistant to ertapenem and nonsusceptible to meropenem in our study, the MIC_50 was 0.125 mg/L and MIC_90 only 2 mg/L. Thus, we noted relatively preserved effectiveness despite the vast majority of our isolates in this group being non-KPC-producers. We believe this retained activity noted in our study can be explained by a relatively higher comparative incidence of other class A carbapenemase resistance mechanisms and lack of NDM and OXA-48–like isolates. The data presented in Table 2 demonstrate that most of the enhanced potency in our non-KPC-producing CRE was noted in 4 S. marcescens isolates, 2 E. coli, and a single K. oxytoca isolate. The S. marcescens isolates mimicked phenotypically a classic SME pattern, a class A carbapenemase. Based on the dramatic decrease in MIC in the presence of vaborbactam, it is possible that the E. coli and K. oxytoca isolates may have other less common class A carbapenemase genes present. Unfortunately, we were not able to assess for other serine Ambler class A carbapenemases (e.g., SME, IMI, GES, NMC, etc.) in these isolates. In general, these are considered relatively uncommon at many health care centers; however, our data suggest that these mechanisms may be as common as or more common than KPC-mediated resistance at some centers.

In conclusion, our study demonstrates that meropenem-vaborbactam activity is highly dependent on local epidemiology, may have retained in vitro potency against non-KPC-producers, and could be an important treatment option for patients with CRE at our institution despite a very low incidence of KPC-mediated resistance. Our in vitro evaluation serves as a template for other institutions to assess the activity of novel antimicrobial agents in the context of the local epidemiological distribution of resistance mechanisms circulating at their centers to best inform clinicians, guide antimicrobial stewardship efforts, and ensure their patients have access to optimized therapies.

Acknowledgments

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References


Drugs@FDA. FDA approved drug products. www.accessdata.fda.gov.


