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Meropenem-Vaborbactam Activity against *Enterobacteriaceae* Isolates, Including Carbapenem-Resistant and Carbapenemase-Producing Isolates, Collected in United States (US) Hospitals During 2016

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Amended Abstract

Background: Vaborbactam (VAB) is a cyclic boronic acid β-lactamase (BL) inhibitor that has activity against Ambler class A (including KPC) and C enzymes. This inhibitor has been combined with meropenem (MER), enhancing the activity of this carbapenem against KPC-producers. We evaluated the activity of MER-VAB against *Enterobacteriaceae* (ENT) clinical isolates collected in the US during 2016.

Methods: A total of 4,942 ENT isolates collected from 30 US hospitals were susceptibility (S) tested by reference broth microdilution methods for MER ± VAB (at fixed 8 µg/mL) and comparators. CLSI and EUCAST interpretative criteria were applied. Carbapenem-resistant *Enterobacteriaceae* (CRE; CLSI criteria) were submitted to whole genome sequencing and *de novo* assembly and screening for carbapenemase genes using an in-house-developed pipeline.

Results: MER-VAB inhibited all 4,942 ENT isolates at ≤4 µg/mL, whereas MER alone inhibited 4,899 (99.1%) of the isolates at the same concentration. MER ± VAB ($MIC_{50/90}$, 0.03/0.06 µg/mL for both) were the most active agents among comparators tested (Table). All 1,937 *E. coli* isolates were inhibited by MER-VAB at ≤1 µg/mL, including 2 MER nonsusceptible (NS) isolates. MER-VAB inhibited all *K. pneumoniae* isolates at ≤2 µg/mL, including 35 MER NS isolates. Among comparators, MER-VAB ($MIC_{50/90}$, 0.03/1 µg/mL) was the most active agent against CRE isolates (8 species), and all isolates were inhibited by this combination at ≤4 µg/mL. CRE isolates were most susceptible to colistin (COL; 88.5%S, EUCAST criteria) and tigecycline (TIG; 96.7%S, US FDA/90.2%S, EUCAST criteria). Carbapenemase genes were detected among 56 CRE isolates and included 31 bla_{KPC-2}, 22 bla_{KPC-3}, 2 bla_{SME-4} and 1 bla_{KPC-4}. MER-VAB inhibited all isolates carrying bla_{KPC} at ≤4 µg/mL, and these isolates displayed low S rates for several comparators.

Conclusions: MER-VAB was very active against ENT. VAB enhanced MER activity against CRE isolates that included isolates producing KPC and SME. MER-VAB is an important addition to the armamentarium of antimicrobial agents to treat CRE infections in the US.

Organism/group (no. tested)	Antimicrobial agent MIC_{50} /MIC_{90} (µg/mL): MER-VAB	MER	Piperacillin-tazobactam	Amikacin	COL	TIG
Enterobacteriaceae (4,942)	0.03/0.06	0.03/0.06	2/16	2/4	0.25/>8	0.25/1
E. coli (1,937)	≤0.015/0.03	≤0.015/0.03	2/8	2/4	0.12/0.25	0.12/0.25
K. pneumoniae (1,068)	0.03/0.03	0.03/0.03	2/16	1/2	0.12/0.25	0.25/1
CRE (61)	0.03/1	16/>32	>64/>64	8/32	0.25/>8	0.5/1
KPC-producers (45)	0.03/1	16/>32	>64/>64	8/32	0.0.25/2	0.5/2

Introduction

- Carbapenems were considered the last resource to treat serious infections caused by multidrug-resistant organisms producing β-lactamases
  - These agents are hydrolyzed by carbapenemases, which include KPC serine-carbapenemases, OXA-48, and class B metallo-β-lactamases (MBLs)
- In the United States (US), isolates producing KPC enzymes have been detected in most states
  - Isolates producing these enzymes are commonly detected in the New York City area and Texas
- Outside the US, KPC-producing isolates have been reported in Germany, Poland, Belgium, Hungary, Croatia, United Kingdom, Israel, China, and Brazil; KPC-producing organisms are considered endemic in Greece and Italy
- Vaborbactam (formerly RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A (including KPC) and C enzymes
  - Vaborbactam has been combined with meropenem and enhances the activity of this carbapenem against KPC-producing isolates when compared to meropenem tested alone
- We evaluated the activity of meropenem-vaborbactam against 4,942 *Enterobacteriaceae* clinical isolates collected in the 30 US hospitals during 2016

Materials and Methods

- A total of 4,942 *Enterobacteriaceae* clinical isolates collected during 2016 from 30 hospitals located in the US were included in the study
- Isolates were limited to 1 per patient episode and were collected from bloodstream infections (n=1,319), intra-abdominal infections (n=380), pneumonia in hospitalized patients (n=1,011), skin and skin structure infections (n=730), urinary tract infections (n=1,427), and other sources (n=75)
- Species identification was confirmed, when necessary, by matrix-assisted laser desorption ionization-time of flight mass spectrometry
- Isolates were susceptibility tested against meropenem-vaborbactam (inhibitor at fixed 8 µg/mL) and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI)
  - Quality control (QC) was performed according to CLSI guidelines (M100-S27), and all QC MIC results were within acceptable ranges, as published in CLSI documents
  - Categorical interpretations for all comparator agents were those found in CLSI criteria in M100-S27 (2017), EUCAST breakpoint tables (version 7.0, January 2017), and/or United States Food and Drug Administration (US FDA) package inserts
- ESBL-phenotype criterion was applied for *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, and *P. mirabilis* displaying an MIC value ≥2 µg/mL for ceftriaxone, ceftazidime, and/or aztreonam (M100-S27)
- Carbapenem-resistant *Enterobacteriaceae* (CRE) was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 µg/mL (*Proteus mirabilis* and indole-positive Proteeae used only meropenem due to intrinsically elevated imipenem MIC values)
  - CRE isolates were submitted to whole genome sequencing on a MiSeq (Illumina, San Diego, California, US) instrument targeting a 30X coverage
  - Sequences were de novo assembled and searched for the presence of acquired carbapenemases using a curated library and applying criteria of >94% sequencing identity and 40% minimum length coverage

Results

- Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 µg/mL) was active against *Enterobacteriaceae* isolates, and the activity of this combination was identical to the activity of meropenem alone ($MIC_{50/90}$, 0.03/0.06 µg/mL) against these isolates (Table 1)
  - Meropenem-vaborbactam and meropenem were equally active against the 2 most common *Enterobacteriaceae* species, *E. coli* (1,937 isolates; $MIC_{50/90}$, ≤0.015/0.03 µg/mL) and *K. pneumoniae* (1,068 isolates; $MIC_{50/90}$, 0.03/0.03 µg/mL; Table 1)
- A total of 61 (1.2% of the *Enterobacteriaceae*) CRE were observed among US *Enterobacteriaceae* isolates
  - CRE isolates belonged to 8 bacterial species/species complex, and *K. pneumoniae* accounted for 52.5% of the isolates
  - CRE rates varied among US Census divisions and were higher in the Mid-Atlantic (4.2%) when compared to the remaining regions (0.0 to 1.6%; Figure 1)
- Against CRE isolates, the highest meropenem-vaborbactam MIC was 4 µg/mL ($MIC_{50/90}$, 0.03/1 µg/mL; Table 1)
  - Meropenem alone ($MIC_{50/90}$, 16/>32 µg/mL) displayed limited activity against CRE isolates
- CRE isolates displayed considerably higher MIC results for piperacillin-tazobactam ($MIC_{50/90}$, >64/>64 µg/mL) and amikacin ($MIC_{50/90}$, 8/32 µg/mL; Table 2)
  - Colistin had reduced activity against some CRE isolates (MIC_{90}, >8 µg/mL)
- Among 61 CRE isolates, 56 (91.8% of the CRE) carried genes encoding serine-carbapenemases that included: 22 bla_{KPC-2}, 31 bla_{KPC-3}, 1 bla_{KPC-4}, 2 bla_{SME-4}
  - Isolates carrying metallo-β-lactamases or oxacilinases with carbapenemase spectrum were not observed in this collection
  - Five isolates had negative results for the presence of carbapenemases
- Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/1 µg/mL) displayed activity against 56 *Enterobacteriaceae* isolates producing carbapenemases that included 54 isolates carrying bla_{KPC} and 2 *S. marcescens* carrying bla_{SME-4}
  - As expected, meropenem activity was limited against carbapenemase-producing ($MIC_{50/90}$, >32/>32 µg/mL) or KPC-producing ($MIC_{50/90}$, >32/>32 µg/mL) *Enterobacteriaceae*

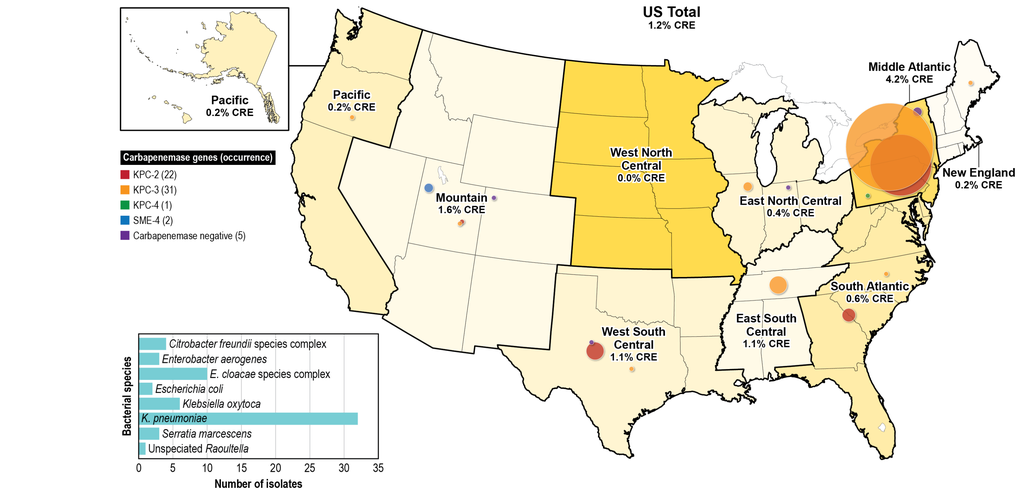
Results

Table 1. Distributions of the main organisms and organism groups when susceptibility tested against meropenem-vaborbactam and meropenem

Organism / organism group (no. of isolates)	No. of isolates at MIC (µg/mL; cumulative %): ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>	MIC_{50}	MIC_{90}
Enterobacteriaceae															
Meropenem-vaborbactam (4,942)	1,716 34.7	2,481 84.9	558 96.2	141 99.1	19 99.5	13 99.7	8 99.9	5 >99.9	1 100.0					0.03	0.06
Meropenem (4,942)	2,218 44.9	1,789 81.1	640 94.0	176 97.6	35 98.3	8 98.5	10 98.7	10 98.8	13 99.1	12 99.4	9 99.6	11 99.8	11 100.0	0.03	0.06
Escherichia coli															
Meropenem-vaborbactam (1,937)	1,246 64.3	658 98.3	26 99.6	4 99.8	1 99.9	1 99.9	1 100.0							≤0.015	0.03
Meropenem (1,937)	1,576 81.4	311 97.4	34 99.2	10 99.7	1 99.7	1 99.8	2 99.9	0 99.9	1 99.9	1 100.0				≤0.015	0.03
Klebsiella pneumoniae															
Meropenem-vaborbactam (1,068)	137 12.8	878 95.0	34 98.2	6 98.8	2 99.0	3 99.3	4 99.6	4 100.0						0.03	0.03
Meropenem (1,068)	302 28.3	687 92.6	32 95.6	8 96.3	3 96.6	0 96.6	1 96.7	5 97.2	1 97.3	3 97.6	9 98.4	10 99.3	7 100.0	0.03	0.03
CRE *Enterobacteriaceae*															
Meropenem-vaborbactam (61)	9 14.8	25 55.7	12 75.4	1 77.0	1 78.7	2 82.0	6 91.8	4 98.4	1 100.0					0.03	1
Meropenem (61)						0 0.0	1 1.6	4 8.2	13 29.5	12 49.2	9 63.9	11 82.0	11 100.0	16	>32
Carbapenemase-producing *Enterobacteriaceae*															
Meropenem-vaborbactam (56)	9 16.1	25 60.7	12 82.1	1 83.9	1 85.7	1 87.5	4 94.6	3 100.0						0.03	1
Meropenem (56)						0 0.0	1 1.8	4 8.9	12 30.4	8 44.6	9 60.7	11 80.4	11 100.0	16	>32
KPC-producing *Enterobacteriaceae*															
Meropenem-vaborbactam (54)	9 16.7	25 63.0	10 81.5	1 83.3	1 85.2	1 87.0	4 94.4	3 100.0						0.03	1
Meropenem (54)						0 0.0	1 1.9	4 9.3	12 31.5	8 46.3	9 63.0	11 83.3	9 100.0	16	>32

Table 2. Activity of meropenem-vaborbactam and meropenem against the main organisms and organism groups

Organism/group (no. tested)	MIC_{50} /MIC_{90} (µg/mL): Meropenem-vaborbactam	Meropenem	Piperacillin-tazobactam	Amikacin	Colistin	Tigecycline
Enterobacteriaceae (4,942)	0.03 / 0.06	0.03 / 0.06	2 / 16	2 / 4	0.25 / >8	0.25 / 1
Escherichia coli (1,937)	≤0.015 / 0.03	≤0.015 / 0.03	2 / 8	2 / 4	0.12 / 0.25	0.12 / 0.25
Klebsiella pneumoniae (1,068)	0.03 / 0.03	0.03 / 0.03	2 / 16	1 / 2	0.12 / 0.25	0.25 / 1
CRE *Enterobacteriaceae* (61)	0.03 / 1	16 / >32	>64 / >64	8 / 32	0.25 / >8	0.5 / 1
Carbapenemase-producing *Enterobacteriaceae* (56)	0.03 / 1	16 / >32	>64 / >64	8 / 32	0.25 / >8	0.5 / 2
KPC-producing Enterobacteriaceae (54)	0.03 /1	16 / >32	>64 / >64	8 / 32	0.0.25 / 2	0.5 / 2



Conclusions

- Meropenem-vaborbactam displayed activity against *Enterobacteriaceae* isolates collected from US hospitals during 2016
  - The highest meropenem-vaborbactam MIC result was 4 µg/mL, and this collection included 61 CRE isolates displaying meropenem MIC values ranging from 1 to >32 µg/mL
- The activity of meropenem-vaborbactam against CRE isolates that are usually associated to multidrug-resistant phenotypes highlights the importance of this compound in the armamentarium against infections caused by resistant organisms

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