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Activity of Meropenem-Vaborbactam and Comparator Agents against Multidrug-Resistant *Enterobacteriaceae* Isolates from the United States Analyzed by Site of Infection

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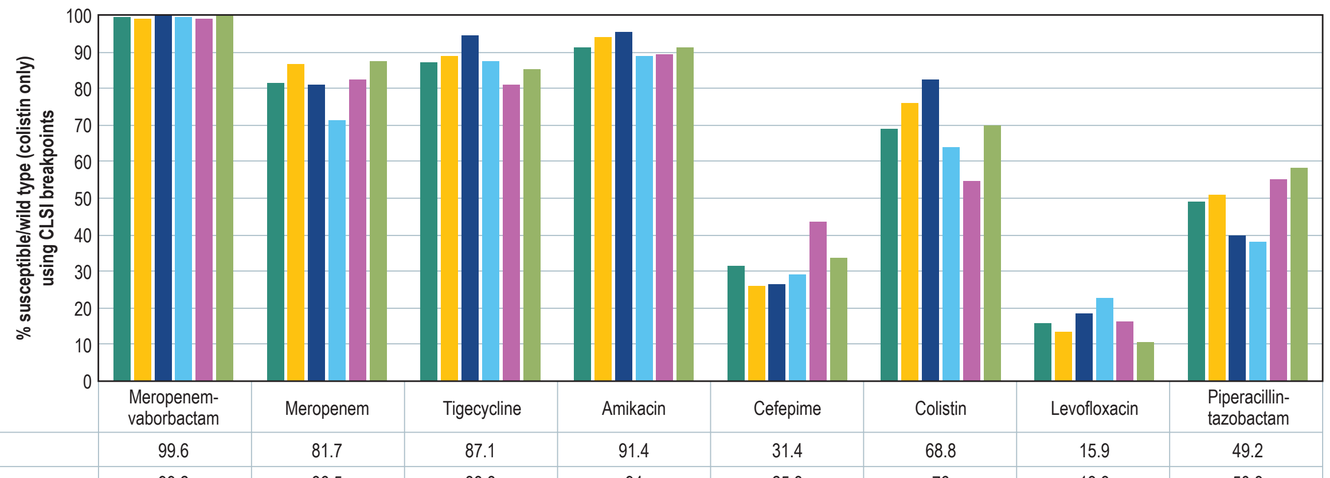
Introduction

- Therapy of invasive infections due to multidrug-resistant *Enterobacteriaceae* (MDR-E) is challenging
  - Carbapenems are the drugs of choice for extended-spectrum β-lactamase and AmpC producers, but alternatives are needed because the rate of carbapenem resistance is rising
  - Initiating appropriate empirical therapy is very important for the successful outcome of serious infections caused by MDR organisms
- Vaborbactam (formerly RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A, including *Klebsiella pneumoniae* carbapenemase (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
  - Meropenem-vaborbactam has been approved by the United States Food and Drug Administration (US FDA) for the treatment of complicated urinary tract infections
- We evaluated the activity of meropenem-vaborbactam and comparator agents against 1,506 multidrug-resistant *Enterobacteriaceae* collected during 4 years in US hospitals stratified by infection site

Materials and Methods

- Among 18,480 *Enterobacteriaceae* clinical isolates consecutively collected in 31 US hospitals from 2014 to 2017, 1,506 were categorized as MDR and further analyzed
  - MDR *Enterobacteriaceae* was defined as any isolate nonsusceptible (Clinical and Laboratory Standards Institute [CLSI] criteria) to ≥1 agent in ≥3 of the following antimicrobial classes: broad-spectrum cephalosporins, carbapenems, broad-spectrum penicillin combined with a β-lactamase-inhibitor, fluoroquinolones, aminoglycosides, glycylcyclines, and the polymyxins (European Committee on Antimicrobial Susceptibility Testing [EUCAST] breakpoint)
  - Isolates were collected consecutively from bloodstream, skin and skin structure, pneumonia from hospitalized patients, urinary tract, and intra-abdominal tract specimens determined to be significant by local criteria as the reported cause of infection
- Isolates were tested for susceptibility against meropenem-vaborbactam (inhibitor at fixed 8 mg/L) and comparator agents using the reference broth microdilution method as described by CLSI (M07, 2018)
  - Quality control (QC) was performed according to CLSI guidelines, and all QC MIC results were within acceptable ranges, as published in the CLSI M100 (2018)
  - Categorical interpretations for all comparator agents were those found in CLSI M100 (2018) criteria, EUCAST breakpoint tables (version 8.1, May 2018), and/or the US FDA website
- Extensively drug-resistant (XDR) *Enterobacteriaceae* was defined as any isolate nonsusceptible (CLSI criteria) to ≥1 agent in ≥5 of the following antimicrobial classes: broad-spectrum cephalosporins, carbapenems, broad-spectrum penicillin combined with a β-lactamase-inhibitor, fluoroquinolones, aminoglycosides, glycylcyclines, and the polymyxins
- Carbapenem-resistant *Enterobacteriaceae* (CRE) was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L (*Proteus mirabilis* and indole-positive Proteeae used only meropenem and doripenem due to intrinsically elevated imipenem MIC values)

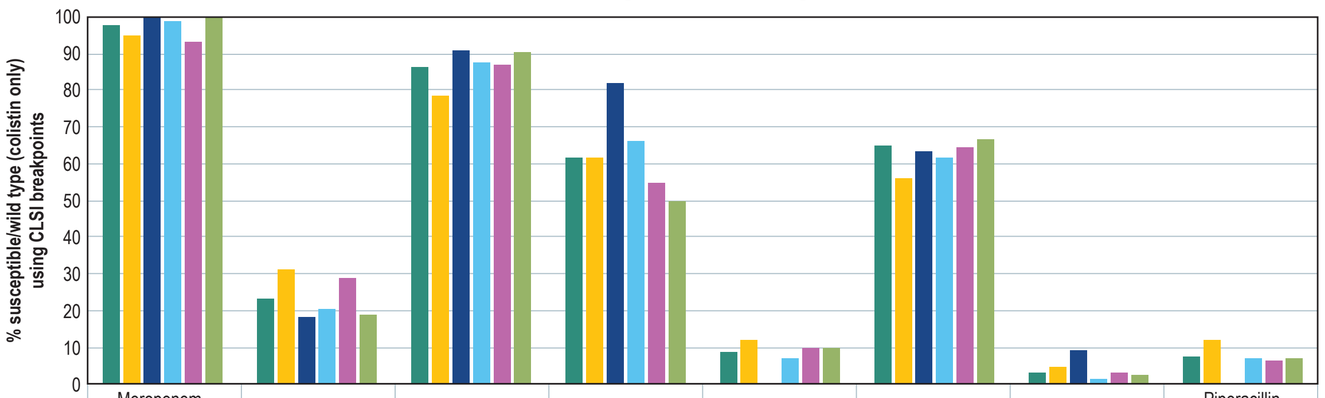
Figure 1 Activity of meropenem-vaborbactam and selected comparator agents tested against 1,506 MDR *Enterobacteriaceae* isolates



	Meropenem-vaborbactam	Meropenem	Tigecycline	Amikacin	Cefepime	Colistin	Levofloxacin	Piperacillin-tazobactam
All MDR (1,506)	99.6	81.7	87.1	91.4	31.4	68.8	15.9	49.2
Bloodstream infection (384)	99.2	86.5	88.8	94	25.8	76	13.3	50.8
Intra-abdominal infection (125)	100	80.8	94.4	95.2	26.4	82.4	18.4	40
Pneumonia in hospitalized patients (399)	99.7	71.4	87.7	88.7	29.3	63.9	22.6	38.2
Skin and skin structure infection (205)	99	82.4	81	89.3	43.6	54.7	16.1	55.1
Urinary tract infection (388)	100	87.6	85.3	91.2	34	70.1	10.8	58.5

Note: MDR, multidrug-resistant

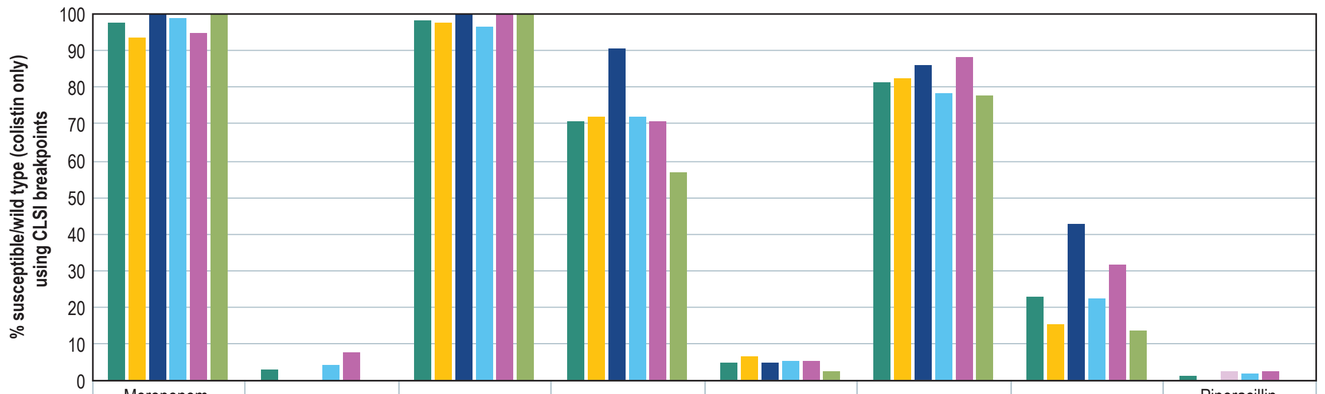
Figure 2 Activity of meropenem-vaborbactam and selected comparator agents tested against XDR *Enterobacteriaceae* isolates



	Meropenem-vaborbactam	Meropenem	Tigecycline	Amikacin	Cefepime	Colistin	Levofloxacin	Piperacillin-tazobactam
All XDR (215)	97.7	23.3	86.5	61.4	8.4	65	2.8	7.4
Bloodstream infection (42)	95.2	31	78.6	61.9	11.9	56.1	4.8	11.9
Intra-abdominal infection (11)	100	18.2	90.9	81.8	0	63.6	9.1	0
Pneumonia in hospitalized patients (88)	98.9	20.5	87.5	65.9	6.8	61.4	1.1	6.8
Skin and skin structure infection (31)	93.5	29	87.1	54.8	9.7	64.5	3.2	6.5
Urinary tract infection (42)	100	19	90.5	50	9.5	66.7	2.4	7.1

Note: XDR, extensively drug-resistant

Figure 3 Activity of meropenem-vaborbactam and selected comparator agents tested against CRE isolates



	Meropenem-vaborbactam	Meropenem	Tigecycline	Amikacin	Cefepime	Colistin	Levofloxacin	Piperacillin-tazobactam
All CRE (262)	97.7	3.1	98.1	71	5	81.5	22.9	1.1
Bloodstream infection (46)	93.5	0	97.8	71.7	6.5	82.2	15.2	0
Intra-abdominal infection (21)	100	0	100	90.5	4.8	85.7	42.9	0
Pneumonia in hospitalized patients (111)	99.1	4.5	96.4	72.1	5.4	78.4	22.5	1.8
Skin and skin structure infection (38)	94.7	7.9	100	71.1	5.3	88.2	31.6	2.6
Urinary tract infection (44)	100	0	100	56.8	2.3	78	13.6	0

Note: CRE, carbapenem-resistant *Enterobacteriaceae*

Results

- MDR isolates corresponded to 8.1% (1,506/18,480) of the *Enterobacteriaceae* collected in the study period
  - The most common MDR species were *Escherichia coli* (n=545), *Klebsiella pneumoniae* (360), *Proteus mirabilis* (181), and *Enterobacter cloacae* (154)
- Meropenem-vaborbactam inhibited 99.6% of the MDR isolates overall and 99.0% to 100.0% of the isolates stratified by most common infection site (Figure 1)
  - Meropenem alone was active against 81.7% of the isolates overall and inhibited 71.4% to 87.6% of the isolates displaying higher susceptibility rates for urinary tract infections and lower rates for pneumonia in hospitalized patients
  - Amikacin and tigecycline were the most active comparators across the most common infection sites, inhibiting 88.7% to 95.2% and 81.0% to 94.4% of isolates, respectively
  - Other selected comparators had limited activity against MDR *Enterobacteriaceae* isolates
- Among MDR-E isolates, 215 (14.3% of the MDR-E and 1.2% overall) were XDR and these belonged to 9 species/species complex with *K. pneumoniae* the most common (128 isolates)
  - Meropenem-vaborbactam inhibited 93.5% to 100.0% of the XDR isolates from different infection sources (Figure 2)
  - Tigecycline and amikacin were active against 86.5% and 61.4%, respectively, of XDR isolates overall
- A total of 262 CRE isolates were noted among the MDR *Enterobacteriaceae*
  - Among CRE, 154 *K. pneumoniae* and an additional 9 bacterial species/species complex isolates were observed
  - Meropenem-vaborbactam inhibited 93.5% to 100.0% of the CRE isolates (Figure 3)
  - Among comparators, tigecycline was the most active agent, inhibiting 96.4% to 100.0% of the isolates

Conclusions

- Meropenem-vaborbactam displayed activity against >99.0% of the MDR *Enterobacteriaceae* isolates collected in US hospitals over a 4-year period
  - These isolates displayed resistance to comparator agents, and tigecycline was the only comparator with activity >95.0% for all the groups
- Meropenem-vaborbactam is likely to be a useful therapeutic alternative in cases of difficult-to-treat *Enterobacteriaceae* isolates displaying resistance to other available agents

Acknowledgements

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