Activity of Meropenem-Vaborbactam and Comparator Agents Tested against *Enterobacterales* Isolates from the United States Analyzed by Site of Infection

Dee Shortridge, Lalitagauri Deshpande, Rodrigo E. Mendes, Mariana Castanheira
JMI Laboratories, North Liberty, IA, USA

Introduction

- Carbapenem-resistant *Enterobacterales* (CRE) isolates are a growing global concern.
- Among carbapenemases detected in *Enterobacterales* (ENT) species, *Klebsiella pneumoniae* carbapenemases (KPCs) have disseminated worldwide and are considered endemic in various countries and several hospitals.
- *K. pneumoniae* containing KPC often are multidrug resistant and have limited treatment options.
- Colistin and tigecycline are widely used as treatment options for KPC-producing isolates.
  - Both compounds have limitations such as toxicity or low plasma concentrations that concern clinicians.
  - Resistance to colistin, and less often to tigecycline, has been reported among KPC-producing *K. pneumoniae*.
- Vaborbactam is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A, including KPC, and AmpC enzymes.
  - Vaborbactam combined with meropenem enhanced the activity of this carbapenem against KPC-producing isolates in comparison to meropenem tested alone.
  - Vaborbactam does not inhibit metallo-beta-lactamases (class D).
- Meropenem-vaborbactam has been approved for the treatment of adults with complicated urinary tract infections (UTI), including pyelonephritis in the US.
- Meropenem-vaborbactam was recently approved in Europe for the treatment of complicated UTIs, including acute pyelonephritis, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia, ventilator-associated pneumonia (VAP), and bacteremia.
- In this study, we evaluated the activity of meropenem-vaborbactam and comparators against ENT isolates stratified by infection site, including isolates producing KPC.

Materials and Methods

- A total of 23,114 ENT isolates were consecutively collected in 32 US hospitals between 2014 and 2018.
  - Each hospital collected one isolate per patient per infection type that was considered the probable cause for the infection by local criteria.
  - Infection types were bloodstream infections, pneumonia in hospitalized patients, intra-abdominal infections, skin and skin structure infections, and urinary tract infections.
  - Isolates were identified by the submitting laboratory and confirmed using biochemical and/or molecular methods by JMI Laboratories.
- Isolates were susceptibility (S) tested by broth microdilution methods CLSI M07 (2018) and the results were interpreted using CLSI (2020) breakpoints.
  - CLSI breakpoints for colistin were updated to categorize as intermediate all ENT isolates with colistin MIC values of ≤2 mg/L.
- Carbapenem-resistant ENT isolates were screened for carbapenemases using PCR/sequencing or whole genome sequencing.
- Isolates with an extended-spectrum β-lactamase (ESBL) phenotype were characterized according to CLSI criteria.

Results

- The most common ENT pathogens for the 5 infection types are shown in Figure 1.
  - *Escherichia coli* was the most common ENT pathogen in 4 of 5 infection types.
  - *Klebsiella pneumoniae* was the most common pathogen isolated from pneumonia.
- The MIC distributions of meropenem-vaborbactam and meropenem for all isolates are shown in Table 1.
- Meropenem-vaborbactam inhibited 99.9% of ENT isolates, regardless of infection type (Figure 2).
  - The activity of meropenem alone ranged from 97.2%–99.1%, with higher susceptible rates noted for UTI and lower for pneumonia.
  - Amikacin and tigecycline were the most active comparators across most infection types, inhibiting >99% and >94% of isolates, respectively.
- A total of 2,756 *E. coli*, *Klebsiella* spp., and *Proteus mirabilis* isolates were resistant to extended-spectrum cephalosporins and/or aztreonam (ESBL-phenotype; CLSI), susceptible to carbapenems, and inhibited by meropenem-vaborbactam, as shown in Figure 3.

- The %S of comparators ranged from 31.5% (cefepime) to 99.2% (meropenem).
- Against 262 KPC-producing isolates, meropenem-vaborbactam was the most active agent (99.2% S), followed by tigecycline (98.5%), as shown in Figure 3.
  - Other agents inhibited ≤80% of the isolates producing KPCs.
- The MIC distributions of meropenem-vaborbactam and meropenem against CRE isolates from the 5 infection types are shown in Table 2.
- Of the 12 meropenem-vaborbactam nonsusceptible isolates, 8 were NDM, 1 VIM, 1 OXA-17, 1 OXA-232, and 1 lacked a carbapenemase.

Conclusions

- Meropenem-vaborbactam was the most active agent against 23,114 ENT isolates collected in US hospitals over a 4-year period, regardless of infection type.
- Meropenem-vaborbactam also was the most active agent against ESBL-phenotype and KPC-producing organisms, the latter resistant to many comparators.
- This combination may be useful in cases of difficult-to-treat ENT isolates resistant to other agents.

Acknowledgements

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References

Clinical and Laboratory Standards Institute (2018). *M07 Eleventh edition. Methods for Dilution Antimicrobial Susceptibility Testing for Bacteria That Grow Aerobically*. Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2020). *M100 Ed30. Performance standards for antimicrobial susceptibility testing: 30th informational supplement*. Wayne, PA: CLSI.

Contact

Dee Shortridge, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: dee-shortridge@jmilabs.com

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Table 1 MIC distribution by infection type of meropenem-vaborbactam and meropenem when tested against *Enterobacterales* isolates collected from US medical centers (2014–2018; CLSI, 2020)

Antimicrobial agent	MIC (mg/L) ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	Total	MIC_{50}	MIC_{90}
All isolates																
Meropenem-vaborbactam	8,840	10,960	2,598	521	67	58	25	22	11	4	2	2	4	23,114	0.03	0.06
	38.2%	85.7%	96.9%	99.2%	99.4%	99.7%	99.8%	99.9%	99.9%	>99.9%	>99.9%	>99.9%	100.0%			
Meropenem	9,805	9,094	3,062	621	115	46	37	54	68	56	60	41	55	23,114	0.03	0.06
	42.4%	81.8%	95.0%	97.7%	98.2%	98.4%	98.6%	98.8%	99.1%	99.3%	99.6%	99.8%	100.0%			
Bloodstream infection																
Meropenem-vaborbactam	2,478	2,841	508	91	18	9	7	7	3	0	1	1	2	5,966	0.03	0.06
	41.5%	89.2%	97.7%	99.2%	99.5%	99.6%	99.8%	99.9%	99.9%	99.9%	99.9%	>99.9%	100.0%			
Meropenem	2,825	2,299	617	120	37	5	5	11	8	10	7	7	15	5,966	0.03	0.06
	47.4%	85.9%	96.2%	98.2%	98.9%	98.9%	99.0%	99.2%	99.3%	99.5%	99.6%	99.7%	100.0%			
Intra-abdominal infection																
Meropenem-vaborbactam	938	1,006	141	28	3	6	4	3	4	1	0	1		2,135	0.03	0.03
	43.9%	91.1%	97.7%	99.0%	99.1%	99.4%	99.6%	99.7%	99.9%	>99.9%	>99.9%	100.0%				
Meropenem	988	857	205	42	5	4	4	5	8	5	5	3	4	2,135	0.03	0.06
	46.3%	86.4%	96.0%	98.0%	98.2%	98.4%	98.6%	98.8%	99.2%	99.4%	99.7%	99.8%	100.0%			
Pneumonia in hospitalized patients																
Meropenem-vaborbactam	1,302	2,588	716	128	20	20	8	5	1	1	1			4,790	0.03	0.06
	27.2%	81.2%	96.2%	98.8%	99.2%	99.7%	99.8%	99.9%	>99.9%	>99.9%	100.0%					
Meropenem	1,316	2,286	842	159	26	16	9	24	29	17	28	18	20	4,790	0.03	0.06
	27.5%	75.2%	92.8%	96.1%	96.6%	97.0%	97.2%	97.7%	98.3%	98.6%	99.2%	99.6%	100.0%			
Skin and skin structure infection																
Meropenem-vaborbactam	1,031	1,500	669	129	13	11	2	6	2	1	0	0	1	3,365	0.03	0.06
	30.6%	75.2%	95.1%	98.9%	99.3%	99.6%	99.7%	99.9%	99.9%	>99.9%	>99.9%	>99.9%	100.0%			
Meropenem	1,076	1,343	728	128	23	11	10	5	9	12	7	6	7	3,365	0.03	0.06
	32.0%	71.9%	93.5%	97.3%	98.0%	98.3%	98.6%	98.8%	99.0%	99.4%	99.6%	99.8%	100.0%			
Urinary tract infection																
Meropenem-vaborbactam	3,038	2,938	543	140	13	11	3	1	1	1	0	0	1	6,690	0.03	0.06
	45.4%	89.3%	97.4%	99.5%	99.7%	99.9%	99.9%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%	100.0%			
Meropenem	3,542	2,238	640	167	24	8	9	9	12	12	13	7	9	6,690	≤0.015	0.06
	52.9%	86.4%	96.0%	98.5%	98.8%	98.9%	99.1%	99.2%	99.4%	99.6%	99.8%	99.9%	100.0%			
Other infection sites																
Meropenem-vaborbactam	53	87	21	5	0	1	1							168	0.03	0.06
	31.5%	83.3%	95.8%	98.8%	98.8%	99.4%	100.0%									
Meropenem	58	71	30	5	0	2	0	0	2					168	0.03	0.06
	34.5%	76.8%	94.6%	97.6%	97.6%	98.8%	98.8%	98.8%	100.0%							

[a] Susceptible isolates are indicated in green (CLSI, 2020).

Table 2 MIC distribution by infection type of meropenem-vaborbactam and meropenem when tested against carbapenem-resistant enteric isolates collected in the US 2014–2018 (CLSI, 2020)

Infection type/ Antimicrobial agent	MIC (mg/L) ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>	Total	MIC_{50}	MIC_{90}
All infection types																
Meropenem-vaborbactam	52	107	44	14	11	30	17	17	11	4	2	2	4	315	0.03	2
	16.5%	50.5%	64.4%	68.9%	72.4%	81.9%	87.3%	92.7%	96.2%	97.5%	98.1%	98.7%	100.0%			
Meropenem					0	1	7	27	68	56	60	41	55	315	8	>32
					0.0%	0.3%	2.5%	11.1%	32.7%	50.5%	69.5%	82.5%	100.0%			
Bloodstream infection																
Meropenem-vaborbactam	5	15	7	1	1	5	5	5	3	0	1	1	2	51	0.06	4
	9.8%	39.2%	52.9%	54.9%	56.9%	66.7%	76.5%	86.3%	92.2%	92.2%	94.1%	96.1%	100.0%			
Meropenem							0	4	8	10	7	7	15	51	16	>32
							0.0%	7.8%	23.5%	43.1%	56.9%	70.6%	100.0%			
Intra-abdominal infection																
Meropenem-vaborbactam	4	2	4	0	0	4	4	3	4	1	0	1		27	0.5	4
	14.8%	22.2%	37.0%	37.0%	37.0%	51.9%	66.7%	77.8%	92.6%	96.3%	96.3%	100.0%				
Meropenem							0	2	8	5	5	3	4	27	8	>32
							0.0%	7.4%	37.0%	55.6%	74.1%	85.2%	100.0%			
Pneumonia in hospitalized patients																
Meropenem-vaborbactam	20	56	17	10	7	10	5	3	1	1	1			131	0.03	0.5
	15.3%	58.0%	71.0%	78.6%	84.0%	91.6%	95.4%	97.7%	98.5%	99.2%	100.0%					
Meropenem					0	1	4	14	29	17	28	18	20	131	16	>32
					0.0%	0.8%	3.8%	14.5%	36.6%	49.6%	71.0%	84.7%	100.0%			
Skin and skin structure infection																
Meropenem-vaborbactam	8	14	9	1	0	6	1	5	2	1	0	0	1	48	0.06	2
	16.7%	45.8%	64.6%	66.7%	66.7%	79.2%	81.2%	91.7%	95.8%	97.9%	97.9%	97.9%	100.0%			
Meropenem						0	3	4	9	12	7	6	7	48	8	>32
						0.0%	6.2%	14.6%	33.3%	58.3%	72.9%	85.4%	100.0%			
Urinary tract infection																
Meropenem-vaborbactam	15	20	6	2	3	4	2	1	1	1	0	0	1	56	0.03	1
	26.8%	62.5%	73.2%	76.8%	82.1%	89.3%	92.9%	94.6%	96.4%	98.2%	98.2%	98.2%	100.0%			
Meropenem							0	3	12	12	13	7	9	56	16	>32
							0.0%	5.4%	26.8%	48.2%	71.4%	83.9%	100.0%			

[a] Susceptible isolates are indicated in green (CLSI, 2020).

Figure 1 Top enteric species isolated by infection type

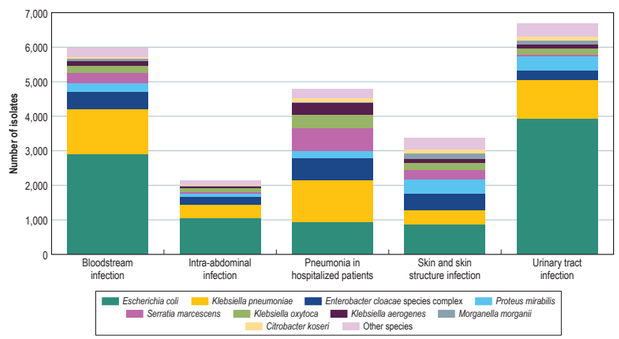
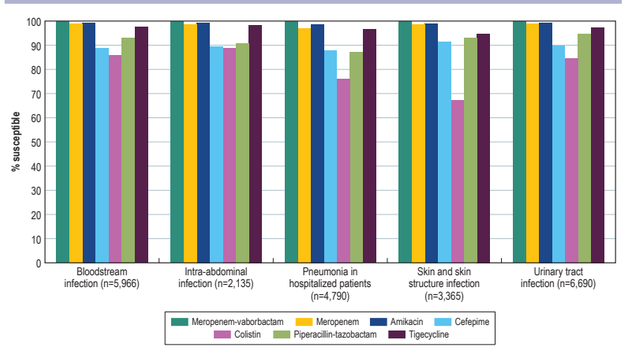
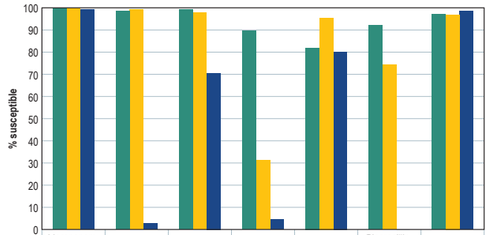


Figure 2 Percent susceptible of meropenem-vaborbactam and comparators by infection type [a]



[a] According to CLSI 2020 breakpoints. Isolates with colistin MIC ≤2 mg/L are now categorized as intermediate.

Figure 3 Susceptibility of meropenem-vaborbactam and comparators against all *Enterobacterales*, cephalosporin resistant, and KPC-producing isolates [a]



	Meropenem-vaborbactam	Meropenem	Amikacin	Cefepime	Colistin	Piperacillin-tazobactam	Tigecycline
All *Enterobacterales* (n=23,114)	99.9	98.6	99.3	89.5	82.0	92.1	97.0
Cephalosporin resistant (n=2,756)	100.0	99.2	97.9	31.2	95.5	74.2	96.9
KPC producers (n=262)	99.2	2.7	70.6	4.6	80.2	0.0	98.5

[a] According to CLSI 2020 breakpoints. Isolates with colistin MIC ≤2 mg/L are now categorized as intermediate.