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Activity of Meropenem-Vaborbactam against Bacterial Isolates Causing Pneumonia in Patients in U.S. Hospitals during 2014 to 2018

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ABSTRACT Meropenem-vaborbactam is approved to treat hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), in Europe. Meropenem-vaborbactam activity was evaluated against 3,193 *Pseudomonas aeruginosa* and 4,790 *Enterobacterales* isolates causing pneumonia, including VAP, in hospitalized patients in the United States. Susceptibility testing was performed by using the broth microdilution method, and all carbapenem-resistant isolates were submitted for whole-genome sequencing. Meropenem-vaborbactam exhibited almost complete activity against *Enterobacterales* (>99.9% susceptible), including carbapenem-resistant *Enterobacterales* (CRE), and was also very active against *P. aeruginosa* isolates (89.5% susceptible).

KEYWORDS CPE, CRE, *Enterobacterales*, *Enterobacteriaceae*, HAP, *Pseudomonas aeruginosa*, VAP, carbapenemase, hospital-acquired pneumonia, ventilator-acquired pneumonia

Hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP) represent major causes of mortality and resource utilization in hospitalized patients (1, 2). Although *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterobacterales* remain important causes of pneumonia in hospitalized patients (PHP), their susceptibility patterns have varied markedly over time and among geographical regions, and choosing an empirical therapy based on whether the patient is at a high or low risk for multidrug-resistant (MDR) infections is challenging (3–5).

Meropenem-vaborbactam was recently approved by the European Medicines Agency (EMA) for the treatment of HAP, including VAP, in addition to the treatment of complicated intra-abdominal and urinary tract infections and acute pyelonephritis. Meropenem-vaborbactam was also approved for bacteremia that occurs in association with any of these infections and infections due to aerobic Gram-negative organisms where treatment options are limited (24). In the United States, meropenem-vaborbactam is approved for the treatment of complicated urinary tract infections, including pyelonephritis (7).

This study evaluated the *in vitro* activity of meropenem-vaborbactam against 4,790 *Enterobacterales* and 3,193 *P. aeruginosa* isolates causing pneumonia in hospitalized patients (PHP) from 31 U.S. hospitals distributed among 22 states from all 9 census divisions during 2014 to 2018.

Isolates were tested for susceptibility to meropenem-vaborbactam (inhibitor at a fixed concentration of 8 mg/liter) and comparator agents at JMI Laboratories (North Liberty, IA) by reference broth microdilution (6). Quality control and results interpretation were performed in accordance with CLSI, EUCAST (meropenem-vaborbactam against *P. aeruginosa*; colistin against *Enterobacterales*), or the U.S. FDA antibacterial susceptibility test interpretative criteria (tigecycline against *Enterobacterales*) (8–10).

Meropenem-vaborbactam was very potent against the entire collection of *Entero-*

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bacterales ($MIC_{50/90}$, 0.03/0.06 mg/liter) isolates and inhibited >99.9% (4,788/4,790) of those isolates. Amikacin (98.7%), carbapenems (meropenem, 97.2%; imipenem, 92.8%), and tigecycline (96.6%) (Table 1) also showed susceptibility rates of >90%. Ceftriaxone, levofloxacin, piperacillin-tazobactam, and cefepime inhibited 77.7%, 80.7%, 87.3%, and 87.8% of *Enterobacterales* isolates, respectively, when applying CLSI breakpoints. Meropenem-vaborbactam MIC_{90} values were 32- to 256-fold lower than the established susceptibility breakpoints (CLSI, ≤4/8 mg/liter; EUCAST, ≤8/8 mg/liter), regardless of the *Enterobacterales* species: *K. pneumoniae* ($n = 1,219$; MIC_{90}, 0.03 mg/liter), *Escherichia coli* ($n = 919$; MIC_{90}, 0.03 mg/liter), *Serratia marcescens* ($n = 665$, MIC_{90}, 0.06 mg/liter), *Enterobacter cloacae* species complex ($n = 649$, MIC_{90}, 0.03 mg/liter), *Klebsiella aerogenes* ($n = 347$, MIC_{90}, 0.03/0.03 mg/liter), and *Proteus mirabilis* ($n = 211$, MIC_{90}, 0.12 mg/liter).

Carbapenem resistance was observed in a total of 131 (2.7%) PHP and 13 (1.6%) VAP *Enterobacterales* isolates, and these rates were similar to data published previously (11, 12). Among all antimicrobial agents tested, only meropenem-vaborbactam (MIC_{50}/MIC_{90}, 0.03/0.5 mg/liter; 98.5% susceptible) and tigecycline (MIC_{50}/MIC_{90}, 0.5/2 mg/liter; 96.9% susceptible) (Table 1) were active against >90% of carbapenem-resistant *Enterobacterales* (CRE) isolates. Colistin, amikacin, and gentamicin showed activity against 76.9%, 73.3%, and 52.7% of these isolates, respectively (Table 1). All other antimicrobials tested had limited activity against CRE isolates (<20%). All CRE isolates recovered from patients with VAP were susceptible to meropenem-vaborbactam (100%) (Table 1), and 84.6% displayed colistin and amikacin susceptible profiles. Levofloxacin was active against 53.8% of the CRE isolates causing VAP but had very limited activity against PHP isolates (16.8%) (Table 1).

Isolates that met the CRE criteria were submitted for whole-genome sequencing and analysis as previously described (13). Carbapenemase-encoding genes were detected in 53.4% (70/131) of CRE isolates, and this finding corroborates those from previous national studies (11, 12). *Klebsiella pneumoniae* carbapenemase (KPC; 94.2% [66/70]) remained the most frequent carbapenemase detected among carbapenemase-producing *Enterobacterales* (CPE) isolates causing PHP (Table 2). Unlike other carbapenemase enzymes that have been infrequently reported in U.S. hospitals, KPC-producing isolates have been reported in every U.S. state, though the endemicity of KPC-producing bacteria within the United States remains focused in regional hot spots (4, 12, 14). In this study, approximately two-thirds of the KPC-producing *Enterobacterales* isolates detected were from the Middle Atlantic region, although these isolates were also observed in most U.S. census divisions. Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.5 mg/liter) was 512-fold more active than meropenem ($MIC_{50/90}$, 16/>32 mg/liter) against KPC-producing isolates based on MIC_{50} values. These findings are in agreement with previous results where the combination of vaborbactam reduces meropenem MIC values >64-fold for CPE isolates (15–17).

All KPC-producing isolates were inhibited by meropenem-vaborbactam regardless of the KPC variant produced. KPC-3 ($n = 42$; 60.9% of all CPE) was more common than KPC-2 ($n = 24$; 34.8%) and was disseminated among 6 *Enterobacterales* species from all U.S. census divisions except West North Central, East South Central, and West South Central (Table 2). In contrast, KPC-2 was detected mainly in *K. pneumoniae* isolates and from 4 U.S. census divisions: Middle Atlantic (17 isolates), West South Central (5 isolates), East North Central (1 isolate), and Mountain (1 isolate). Of note, meropenem-vaborbactam showed similar activity against *K. pneumoniae* isolates carrying KPC-3 (MIC_{50}/MIC_{90}, 0.03/0.5 mg/liter) or KPC-2 (MIC_{50}/MIC_{90}, 0.03/1 mg/liter), in contrast to data published by Satlin and colleagues that showed higher ceftazidime-avibactam MIC values against KPC-3 producers (18).

Meropenem-vaborbactam (97.1% susceptible) displayed activity against all CRE isolates except 1 NDM-1-producing *S. marcescens* (MIC, 8 mg/liter) from Middle Atlantic and 1 IMP-64-producing *P. mirabilis* (MIC, 16 mg/liter) (Table 1) from Mountain divisions. Vaborbactam is a potent inhibitor of serine β-lactamases, but the agent lacks activity against metallo-β-lactamases (MBLs) and class D carbapenemase (19). In addition to

TABLE 1 Antimicrobial susceptibility of *Enterobacterales*, *P. aeruginosa* and resistant subsets collected in 2014–2018 from patients hospitalized with pneumonia and VAP

	PHP					VAP				
	MIC (mg/liter)			CLSI (%)[a]		MIC (mg/liter)			CLSI (%)[a]	
Antimicrobial agent	50%	90%	*N*	S	R	50%	90%	*N*	S	R
Enterobacterales			4,790					814		
Meropenem-vaborbactam	0.03	0.06		>99.9	<0.1	0.03	0.06		100.0	0.0
Meropenem	0.03	0.06		97.2	2.3	0.03	0.06		98.3	1.5
Imipenem	0.25	1		92.8	3.6	0.25	1		94.3	2.2
Cefepime	≤0.5	8		87.8[b]	9.2	≤0.5	2		92.4	5.5
Ceftazidime	0.25	32		82.8	15.6	0.25	32		85.3	13.4
Ceftriaxone	0.12	>8		77.7	20.6	0.12	>8		80.6	17.2
Piperacillin-tazobactam	2	64		87.3	7.1	2	64		87.0	7.5
Aztreonam	≤0.12	>16		82.3	16.4	≤0.12	>16		84.0	14.6
Amikacin	2	4		98.7	0.3	2	4		99.1	0.1
Gentamicin	≤1	2		91.3	7.5	≤1	≤1		95.3	3.6
Tigecycline[c]	0.25	1		96.6	0.3	0.25	1		97.1	0.2
Levofloxacin	≤0.12	>4		80.7	16.8	≤0.12	>4		84.3	12.8
Colistin[d]	≤0.5	>8		76.1	23.9	≤0.5	>8		77.8	22.2
CRE[e]			131					13		
Meropenem-vaborbactam	0.03	0.5		98.5	0.8	0.06	1		100.0	0.0
Meropenem	16	>32		3.8	85.5	4	32		0.0	92.3
Imipenem	>8	>8		0.0	98.5	8	>8		0.0	84.6
Cefepime	>16	>16		8.4[c]	77.9	16	>16		30.8	53.8
Ceftazidime	>32	>32		4.6	93.1	>32	>32		15.4	76.9
Ceftriaxone	>8	>8		2.3	96.9	>8	>8		0.0	92.3
Piperacillin-tazobactam	>64	>64		3.8	89.3	>64	>64		7.7	61.5
Aztreonam	>16	>16		1.5	96.9	>16	>16		7.7	84.6
Amikacin	8	32		73.3	6.1	2	32		84.6	7.7
Gentamicin	4	>8		52.7	26.7	≤1	>8		76.9	15.4
Tigecycline[c]	0.5	2		96.9	1.5	0.5	1		100.0	0.0
Levofloxacin	>4	>4		16.8	79.4	0.5	>4		53.8	38.5
Colistin[d]	≤0.5	>8		76.9	23.1	≤0.5	>8		84.6	15.4
Pseudomonas aeruginosa			3,193					545		
Meropenem-vaborbactam[d]	0.5	16		89.5	10.5	0.5	16		88.8	11.2
Meropenem	0.5	16		76.4	16.9	0.5	16		73.8	10.3
Imipenem	1	>8		74.5	21.4	1	>8		77.2	22.8
Cefepime	4	16		82.4	6.1	4	16		82.5	5.1
Ceftazidime	2	32		81.7	13.2	2	32		82.4	12.7
Piperacillin-tazobactam	4	>64		77.5	11.7	8	>64		74.3	11.9
Aztreonam	8	>16		66.5	21.9	8	>16		63.7	23.5
Amikacin	4	16		94.2	3.3	4	8		96.9	1.3
Gentamicin	2	>8		82.5	10.3	2	8		85.0	9.0
Levofloxacin	1	>4		62.0	26.7	0.5	>4		67.7	23.9
Colistin	1	2		99.7	0.3	1	2		99.8	0.2
MDR[f] *P. aeruginosa*			697					124		
Meropenem-vaborbactam[d]	8	32		59.0	41.0	8	32		59.7	40.3
Meropenem	8	32		22.1	63.1	8	32		21.0	38.7
Imipenem	8	>8		22.8	69.6	8	>8		23.4	70.2
Cefepime	16	>16		32.9	24.7	16	>16		34.7	20.2
Ceftazidime	16	>32		35.3	48.5	16	>32		46.8	41.9
Piperacillin-tazobactam	64	>64		23.0	43.6	64	>64		19.4	41.1
Aztreonam	>16	>16		16.8	66.7	>16	>16		15.3	67.7
Amikacin	8	>32		80.8	12.1	8	16		90.3	3.2
Gentamicin	8	>16		44.9	35.7	8	16		49.2	33.1
Levofloxacin	>4	>4		9.2	74.5	>4	>4		14.5	69.4
Colistin	0.5	2		99.1	0.9	1	2		100.0	0.0
XDR[g] *P. aeruginosa*			440					70		
Meropenem-vaborbactam[d]	16	32		48.6	51.4	16	32		47.1	52.9
Meropenem	16	32		10.0	76.6	16	32		10.0	72.9
Imipenem	>8	>8		13.2	79.5	8	>8		15.7	77.1
Cefepime	16	>16		18.2	34.1	16	>16		20.0	24.3

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TABLE 1 (Continued)

Antimicrobial agent	PHP					VAP				
	MIC (mg/liter)			CLSI (%)[a]		MIC (mg/liter)			CLSI (%)[a]	
	50%	90%	*N*	S	R	50%	90%	*N*	S	R
Ceftazidime	32	>32		23.9	58.4	16	>32		44.3	44.3
Piperacillin-tazobactam	>64	>64		8.9	53.2	64	>64		2.9	48.6
Aztreonam	>16	>16		9.5	77.3	>16	>16		10.0	78.6
Amikacin	8	>32		76.8	23.2	8	32		87.1	5.7
Gentamicin	8	>16		37.0	41.8	8	>16		40.0	40.0
Levofloxacin	>4	>4		2.5	83.6	>4	>4		1.4	81.4
Colistin	0.5	1		99.1	0.9	1	2		100.0	0.0

[a]Criteria as published by CLSI (38).
[b]Intermediate interpreted as susceptible-dose dependent.
[c]FDA breakpoints (39).
[d] Criteria as published by EUCAST (37).
[e]CRE, carbapenem-resistant *Enterobacterales*.
[f]MDR, multidrug resistant.
[g]XDR, extensively drug resistant.

KPC enzymes, SME-4-encoding genes ($n = 2$) were also detected in *S. marcescens* isolates from Middle Atlantic and Mountain divisions, and meropenem-vaborbactam inhibited both isolates at an MIC of ≤0.06 mg/liter (Table 2). No class D carbapenemase genes were detected among CRE isolates.

No carbapenemase genes were observed in 61 CRE isolates (46.6%), and meropenem-vaborbactam was the only agent tested to inhibit 100% of these isolates. Tigecycline, colistin, and amikacin were active against 98.4%, 75.4%, and 68.9%, respectively. Limited activity was observed for all β-lactams agents, including meropenem ($MIC_{50/90}$, 8/>32 mg/liter; 4.9% susceptible). Resistance mechanisms other than carbapenemase production, such as lack of major porins and overexpression of AcrAB-TolC efflux pumps combined with extended spectrum cephalosporinases or AmpC production, are well known causes of meropenem resistance. Some of those, in addition to an increase in the bla_{KPC} gene copy number, were described to possibly affect meropenem-vaborbactam activity (19, 20). However, these mechanisms can be overcome by targeting *in vivo* exposures that maximize the efficacy of the meropenem-vaborbactam combination. Recently completed clinical trials demonstrated that these target exposures appear to be achievable due to the excellent safety profiles of both meropenem and vaborbactam (21–23).

TABLE 2 Distribution of carbapenemase genes detected among *Enterobacterales* isolates causing pneumonia in hospitalized patients in U.S. medical centers (2014 to 2018)

Organism	Carbapenemase detected	No. of isolates	US census division(s)	MIC range (mg/liter)	
				Meropenem	Meropenem-vaborbactam
Citrobacter freundii species complex	KPC-2	1	Middle Atlantic	2	<0.015
	KPC-3	2	Middle Atlantic	8 to 16	0.03
Klebsiella oxytoca	KPC-2	2	Mountain, East North Central	2 to 32	0.03
	KPC-3	4	Middle Atlantic, South Atlantic	1 to 32	0.03
Klebsiella pneumoniae	KPC-2	21	Middle Atlantic, West South Central	1 to >32	<0.015 to 2
	KPC-3	19	Middle Atlantic, East North Central, Pacific	2 to >32	<0.015 to 1
Enterobacter cloacae species complex	KPC-3	10	New England, Middle Atlantic, Mountain	2 to >32	0.03 to 0.25
Escherichia coli	KPC-3	1	Middle Atlantic	16	0.03
Serratia marcescens	KPC-3	6	Middle Atlantic, East North Central	2 to >32	0.06 to 1
	SME-4	2	Mountain, Middle Atlantic	>32	0.03 to 0.06
	NDM-1	1	Middle Atlantic	4	8
Proteus mirabilis	IMP-64	1	Mountain	16	16

Results of the phase 3 clinical trial (Tango II) to evaluate the safety, efficacy, and tolerability of meropenem-vaborbactam monotherapy in treating patients with serious CRE infections versus best available therapy (BAT) were very encouraging (23). Patients randomized to the meropenem-vaborbactam arm received 7 to 14 days of treatment as monotherapy (2 g-2 g) via intravenous infusion over 3 h every 8 h, and BAT therapy included polymyxins, carbapenems, aminoglycosides, or tigecycline as monotherapy or in combination and ceftazidime-avibactam monotherapy. Day 28 all-cause mortality was 15.6% (5/32) and 33.3% (5/15) for meropenem-vaborbactam and BAT, respectively. Although only 5 patients with HAP/VAP were included, meropenem-vaborbactam is a promising β-lactam/β-lactam-inhibitor combination for treating pathogens causing HAP and VAP, including CRE infections, and this combination compound gained EMA approval for these indications (24).

The findings of this study, where meropenem-vaborbactam, aminoglycosides, carbapenems, and tigecycline were the only agents displaying susceptibility rates >90% against 4,790 *Enterobacterales* isolates, reinforce the challenges to improve care for patients with HAP/VAP, for which delayed and inadequate treatments have been associated with increased rates of morbidity and mortality (25, 26). Similar results were observed when these agents were tested against a worldwide collection of *Enterobacterales* recovered from different infection sources (12). The emergence and widespread geography of CRE isolates have added considerable challenges to treating severe infections, and mortality rates are as high as 40% to 50% (27–29). Therapeutic options to treat CRE HAP/VAP infections are limited, and traditionally, agents from either the polymyxin or aminoglycoside classes have been recommended in combined therapy, usually with carbapenem-containing regimens (1, 26, 30, 31). However, studies have shown that colistin, tigecycline, and gentamicin have poor lung penetration, whereas carbapenems have good distribution in lungs, achieving clinically relevant concentrations (26, 32). In fact, herein, only meropenem-vaborbactam (98.5%) and tigecycline (96.9%) displayed >90% susceptibility rates against CRE isolates causing PHP.

P. aeruginosa isolates were recovered from 3,193 PHP, including 545 isolates deemed to cause VAP. Overall, 89.5% of *P. aeruginosa* isolates were inhibited at the meropenem-vaborbactam susceptible breakpoint established by EUCAST (≤8 mg/liter) compared to 76.4% susceptible to meropenem alone (at ≤2 mg/liter) (Tables 1 and 2). Colistin ($MIC_{50/90}$, 1/2 mg/liter; 99.7% susceptible), amikacin ($MIC_{50/90}$, 4/16 mg/liter; 94.2% susceptible), and meropenem-vaborbactam ($MIC_{50/90}$, 0.5/16 mg/liter) were the most active agents against those isolates, followed by gentamicin ($MIC_{50/90}$, 2/>8 mg/liter; 82.5% susceptible) and cephalosporins (cefepime: $MIC_{50/90}$, 4/16 mg/liter; 82.4% susceptible; and ceftazidime: $MIC_{50/90}$, 2/32 mg/liter; 81.7% susceptible). MDR and extensively drug-resistant (XDR) phenotypes (33, 34) were observed among 697 (21.8%) and 440 (13.8%) respective *P. aeruginosa* isolates, and meropenem-vaborbactam was the most active β-lactam agent tested, inhibiting 59.0% and 48.6% of these highly resistant pathogens, respectively (Table 1). Colistin was the only compound active against >90% of MDR ($MIC_{50/90}$, 0.5/2 mg/liter; 99.1% susceptible) and XDR ($MIC_{50/90}$, 0.5/1 mg/liter; 99.1% susceptible) subsets, followed by amikacin ($MIC_{50/90}$, 8/>32 mg/liter; 80.8 to 76.8% susceptible). However, colistin and aminoglycoside therapy raise concerns on ensuring that therapeutic and nontoxic levels will be delivered to the patient (23). Similar susceptibility rates were observed between *P. aeruginosa* isolates recovered from patients with PHP and VAP (Table 1).

Facing the epidemic of multidrug-resistant Gram-negative bacilli, carbapenems have become the most empirically prescribed β-lactams in intensive care units for HAP/VAP in many geographic regions (35, 36). However, the meropenem standard dosage (1 g every 8 h, 30-min infusion) used to treat *P. aeruginosa* infections showed lower coverage (76.4% susceptible) against these isolates than the coverage observed by meropenem-vaborbactam (89.5% susceptible) when the approved dosage (2 g-2 g via intravenous [i.v.] infusion over 3 h every 8 h) and current EUCAST breakpoints were applied (37).

In summary, meropenem-vaborbactam was very active against a large collection of

Enterobacterales isolates recovered from PHP and VAP in 31 U.S. hospitals over a 4-year period. This collection included CRE isolates that were resistant to many comparator agents but mostly (>99%) susceptible to meropenem-vaborbactam. Meropenem-vaborbactam was also active against *P. aeruginosa* isolates that were resistant to many antipseudomonal agents and had high MDR and XDR rates. This combination agent may be considered an effective alternative for the treatment of HAP/VAP infections in U.S. hospitals when the FDA approves that indication.

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