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In Vitro Activity of Meropenem-Vaborbactam Against Isolates of KPC-producing *Enterobacteriaceae* Collected Worldwide in 2014-2015

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Revised Abstract

Background: Vaborbactam (formerly RPX7009) is a novel β-lactamase inhibitor with potent activity against class A carbapenemases such as KPC. The meropenem-vaborbactam (MEM-VAB) combination is in Phase 3 clinical trials. The activity of MEM-VAB and comparator agents was evaluated against a recent global collection of KPC-producing *Enterobacteriaceae*.
Methods: MICs of MEM alone or with VAB at fixed 8 µg/ml, tigecycline (TCG), polymyxin B (PMB), and gentamicin (GEN) were determined against 991 KPC-producing, OXA-48- and MBL-negative isolates following CLSI guidelines. The study collection was comprised of 11 species and six KPC variants collected in 2014-2015 in Europe, North and Latin Americas, and Asia/South Pacific.
Results: Cumulative % inhibited by MEM alone and with VAB are shown in the table below, with MIC_{90} values boxed and shaded.

		MIC (µg/ml)										
Organism (n)		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Enterobacteriaceae	MEM	0	0	0	0	0	0	4.1	11.9	24.5	39.6	53.7	100
(991)	MEM-VAB	46.3	51.9	57.7	71.3	85.4	93.4	97.4	98.9	99.5	99.7	99.7	100
Klebsiella spp.	MEM	0	0	0	0	0	0	2.3	8.1	20.3	35.0	49.6	100
(897)	MEM-VAB	43.3	48.5	54.0	68.8	84.2	92.9	97.1	98.8	99.4	99.7	100	100
E. coli	MEM	0	0	0	0	0	0	25.7	65.7	85.7	94.3	100	100
(35)	MEM-VAB	97.1	97.1	100	100	100	100	100	100	100	100	100	100
Enterobacter spp.	MEM	0	0	0	0	0	0	27.6	44.8	55.2	86.2	89.7	100
(29)	MEM-VAB	75.9	86.2	100	100	100	100	100	100	100	100	100	100

$MIC_{50}/_{90}$ for all strains for TGC, PMB, and GEN were 1/2, 0.5/16 and 1/>64 ug/ml, respectively.

Conclusions: MEM-VAB showed excellent *in vitro* activity against KPC-producing *Enterobacteriaceae*, lowering the meropenem MIC_{50} and MIC_{90} from 32 to 0.06 µg/ml, and >32 to 1 µg/ml, respectively. There were no significant differences in activity between species or KPC variant type. VAB restores the *in vitro* activity of MEM against this large collection of recent clinical isolates of KPC-producing *Enterobacteriaceae*.

Introduction

Vaborbactam (formerly RPX7009) is a novel β-lactamase inhibitor that is being developed in combination with meropenem for the treatment of gram-negative infections, including those due to carbapenem-resistant *Enterobacteriaceae,* and is currently in Phase 3 clinical trials. Vaborbactam exhibits potent activity against class A carbapenemases such as KPC, as well as class C enzymes [1]. The activity of meropenem-vaborbactam and comparator agents was evaluated against a recent collection of clinical isolates of KPC-producing, OXA-48- and MBL-negative *Enterobacteriaceae*.

Materials & Methods

Minimum inhibitory concentration (MIC) values were determined by broth microdilution using frozen panels prepared at International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA) following CLSI guidelines [2, 3]. Vaborbactam was tested at a fixed concentration of 8 µg/mL. Interpretive criteria followed CLSI 2016 guidelines for gentamicin and meropenem, [3], and FDA guidelines for tigecycline [4]. Meropenem breakpoints (1/2/4) were used for meropenem + vaborbactam for purposes of comparison. A total of 991 KPC-producing, OXA-48- and MBL-negative isolates from 2014 (n=580) and 2015 (n=411) were randomly chosen from the IHMA culture collection based on enzyme content and year of isolation. The presence of genes encoding KPC, metallo-β-lactamase (GES, NDM, IMP, VIM, SPM, and GIM) carbapenemases, and OXA-48 was assessed via multiplex PCR, followed by amplification of the full-length genes and sequencing.

Results

Table 1. Distribution of Isolates by Species and KPC Variant

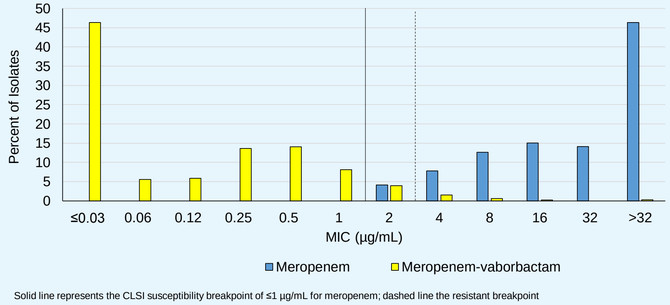
		KPC Variant					
Organism	**N**	**KPC-18**	**KPC-2**	**KPC-3**	**KPC-5**	**KPC-6**	**KPC-9**
Citrobacter freundii	11		7	4			
Citrobacter koseri	2		1	1			
Enterobacter aerogenes	8		7	1			
Enterobacter asburiae	3		3				
Enterobacter cloacae	17		13	3	1		
Enterobacter hormaechi	1		1				
Escherichia coli	35	3	20	12			
Klebsiella oxytoca	19		15	3		1	
Klebsiella pneumoniae	878		534	341	1		2
Raoultella ornithinolytica	1			1			
Serratia marcescens	16		11	5			
Total KPC variant	991	3	612	371	2	1	2

Table 2. *In Vitro* Activity of Meropenem + Vaborbactam and Comparators Against 911 KPC-producing *Enterobacteriaceae*.

Organism	Drug	%S	%I	%R	MIC_{50}	MIC_{90}	Range
All *Enterobacteriaceae* (991)	Meropenem + vaborbactam	na	na	na	0.06	1	≤ 0.03 - > 32
	Meropenem	0	4.1	95.9	32	> 32	2 - > 32
	Gentamicin	63.4	6.3	30.4	1	> 64	≤ 0.06 - > 64
	Polymyxin B	na	na	na	0.5	16	0.25 - > 16
	Tigecycline	95.8	3.6	0.6	1	2	≤ 0.06 - 8
Klebsiella spp. (897)	Meropenem + vaborbactam	na	na	na	0.12	1	≤ 0.03 - > 32
	Meropenem	0	2.3	97.7	> 32	> 32	2 - > 32
	Gentamicin	64.2	6.2	29.5	1	> 64	≤ 0.06 - > 64
	Polymyxin B	na	na	na	0.5	16	0.25 - > 16
	Tigecycline	96.0	3.3	0.7	1	2	0.12 - 8
E. coli (35)	Meropenem + vaborbactam	na	na	na	≤ 0.03	≤ 0.03	≤ 0.03 - 0.12
	Meropenem	0	25.7	74.3	4	16	2 - 32
	Gentamicin	57.1	5.7	37.1	1	> 64	0.25 - > 64
	Polymyxin B	na	na	na	0.5	0.5	0.25 - 1
	Tigecycline	100	0	0	0.25	0.5	≤ 0.06 - 1
Enterobacter spp. (29)	Meropenem + vaborbactam	na	na	na	≤ 0.03	0.12	≤ 0.03 - 0.12
	Meropenem	0	27.6	72.4	8	> 32	2 - > 32
	Gentamicin	51.7	13.8	34.5	4	> 64	0.25 - > 64
	Polymyxin B	na	na	na	0.5	1	0.25 - 16
	Tigecycline	93.1	6.9	0	1	2	0.25 - 4

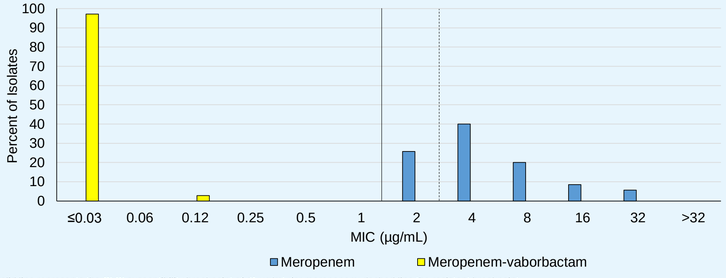
%S, I, R: percent susceptible, intermediate, resistant by CLSI 2016 (gentamicin, meropenem), FDA guidelines (tigecycline); MIC_{50}, MIC_{90}, and range in µg/mL; na; no established breakpoints

Figure 1. Effect of Vaborbactam on the MIC Frequency Distribution of Meropenem for 991 KPC-producing *Enterobacteriaceae*.



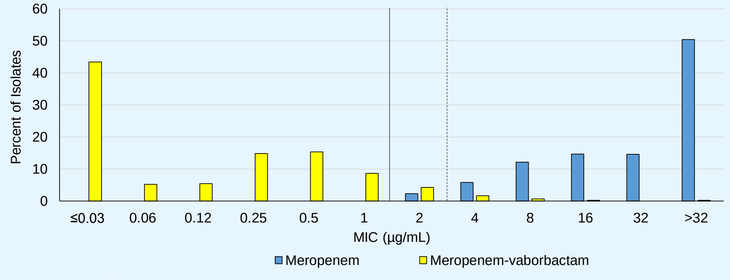
Solid line represents the CLSI susceptibility breakpoint of ≤1 µg/mL for meropenem; dashed line the resistant breakpoint

Figure 2. Effect of Vaborbactam on the MIC Frequency Distribution of Meropenem for 35 KPC-producing *E. coli*.



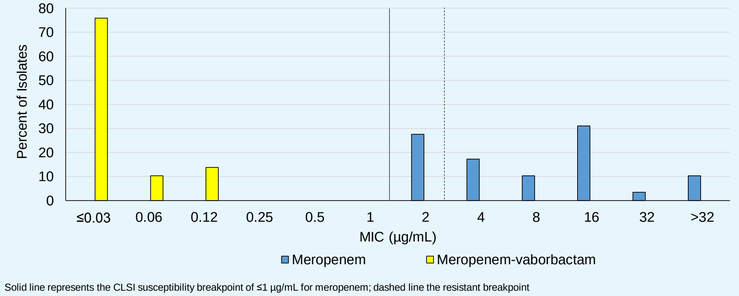
Solid line represents the CLSI susceptibility breakpoint of ≤1 µg/mL for meropenem; dashed line the resistant breakpoint

Figure 3. Effect of Vaborbactam on the MIC Frequency Distribution of Meropenem for 897 KPC-producing *Klebsiella* spp.



Solid line represents the CLSI susceptibility breakpoint of ≤1 µg/mL for meropenem; dashed line the resistant breakpoint

Figure 4. Effect of Vaborbactam on the MIC Frequency Distribution of Meropenem for 29 KPC-producing *Enterobacter* spp.



Solid line represents the CLSI susceptibility breakpoint of ≤1 µg/mL for meropenem; dashed line the resistant breakpoint

Results Summary

- **Among 991 KPC-producing, OXA-48- and MBL-negative, *Enterobacteriaceae*, the modal meropenem MIC dropped from >32 to ≤0.03 µg/mL in the presence of vaborbactam (Figure 1). The MIC_{90} dropped from 32 to 0.06 µg/mL (Table 1).**
- **The *in vitro* activity of meropenem + vaborbactam was equivalent to tigecycline (MIC_{90} 1 µg/mL; Table 1).**
- **There were no appreciable differences in activity between species.**

Conclusions

- **Meropenem + vaborbactam demonstrated excellent *in vitro* activity against KPC-producing *Enterobacteriaceae*, with 93.4% inhibited at ≤1 µg/mL.**
- **Vaborbactam exhibited strong potential for restoring the *in vitro* activity of meropenem against KPC-producing pathogens otherwise non-susceptible to carbapenems.**
- **Further development of this compound could provide a valuable therapeutic option for treating infections caused by resistant gram-negative bacilli.**

References:

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2. Clinical Laboratory Standards Institute (CLSI). 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Tenth Edition. CLSI document M07-A10 (ISBN 1-56238-988-2). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
3. Clinical and Laboratory Standards Institute (CLSI). 2016. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement. CLSI Document M100S (ISBN 1-56238-990-4). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
4. Tygacil®, 2016. Tigecycline FDA prescribing information. Pfizer, Inc., Collegeville, PA.