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# *In Vitro* Activity of Meropenem-Vaborbactam Against KPC-producing *Enterobacteriaceae* from Europe Collected in 2014-2015

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## Abstract

**Background**: Vaborbactam (formerly RPX7009) is a novel β-lactamase inhibitor with potent activity against class A carbapenemases such as KPC. The meropenem-vaborbactam combination has completed Phase 3 clinical trial for the treatment of complicated urinary tract infections and is being investigated in patients with suspected or documented carbapenem-resistant Enterobacteriaceae (CRE) infections in comparison to best available therapy. The activity of meropenem-vaborbactam and comparator agents was evaluated against a recent European collection of KPC-producing *Enterobacteriaceae*.

**Methods**: MICs of meropenem alone or with vaborbactam at a fixed concentration of 8 mg/L, tigecycline, polymyxin B, and gentamicin were determined against 496 KPC-producing, OXA-48- and MBL-negative isolates following CLSI guidelines. The study collection was comprised of 6 species (n): *Klebsiella pneumoniae* (475), *Escherichia coli* (12), *K. oxytoca* (3), *Enterobacter cloacae* (3), *E. aerogenes* (2) and *Citrobacter freundii* (1) and three major KPC variants (n), KPC-2 (242), KPC-3 (252) and KPC-9 (2), collected in 2014-2015 in 12 European countries.

**Results:** Cumulative % inhibited by meropenem (MEM) alone or with vaborbactam (VAB) is shown in the table below, with $MIC_{50}$ values boxed and shaded. $MIC_{50}/_{90}$ values for all strains for meropenem-vaborbactam, tigecycline, polymyxin B, and gentamicin were 0.25/1, 1/2, 0.5/16 and 1/64 mg/L.

| Genotype | | MIC (mg/L) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (n) | | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | >32 |
| All | MEM | | | | | | | 0.8 | 4.0 | 15.3 | 27.0 | 39.1 | **100** |
| (496) | MEM-VAB | 36.3 | 41.7 | 47.4 | 64.3 | 83.7 | **93.1** | 97.2 | 98.8 | 99.2 | 99.6 | | 100 |
| KPC-2 | MEM | | | | | | | | 3.3 | 14.9 | 27.7 | 42.6 | **100** |
| (242) | MEM-VAB | 37.2 | 45.9 | 50.4 | 62.4 | 82.2 | **92.1** | 97.5 | 99.2 | 99.6 | 99.6 | | 100 |
| KPC-3 | MEM | | | | | | | 1.6 | 4.8 | 15.9 | 26.6 | 36.1 | **100** |
| (252) | MEM-VAB | 35.7 | 38.1 | 44.8 | 66.7 | 84.9 | **94.0** | 96.8 | 98.4 | 98.8 | 99.6 | | 100 |
| KPC-9 | MEM | | | | | | | | | | | | **100** |
| (2) | MEM-VAB | | | | | **100** | | | | | | | |
| KPC; ESBL pos | MEM | | | | | | | 0.6 | 3.8 | 13.3 | 22.2 | 34.0 | **100** |
| (158) | MEM-VAB | 43.0 | 53.8 | 56.3 | 66.5 | 86.7 | **95.6** | 98.7 | 99.4 | | | | 100 |
| KPC; ESBL neg | MEM | | | | | | | 1.3 | 4.4 | 19.6 | 37.3 | 50.0 | **100** |
| (338) | MEM-VAB | 33.1 | 36.1 | 43.2 | 63.3 | 82.2 | **92.0** | 96.4 | 98.5 | 99.1 | 99.7 | | 100 |

**Conclusions** Meropenem-vaborbactam showed excellent *in vitro* activity against KPC-producing *Enterobacteriaceae* from Europe, lowering the meropenem $MIC_{50}$ and $MIC_{90}$ from >32 to 0.25 mg/L, and >32 to 1 mg/L, respectively. KPC-type or additional ESBLs do not have impact on the activity of meropenem-vaborbactam. Vaborbactam restores the *in vitro* activity of meropenem 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 collection of recent clinical isolates of KPC-producing *Enterobacteriaceae* from Europe.

## 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]. Vaborbactam was tested at a fixed concentration of 8 µg/mL. Interpretive criteria followed EUCAST 2017 guidelines where available [3]. A total of 496 European KPC-producing, OXA-48- and MBL-negative isolates from 2014 (n=309) and 2015 (n=187) 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**

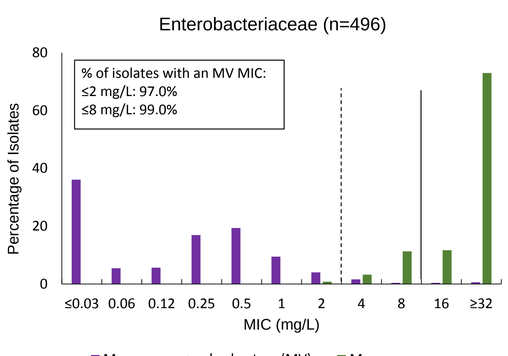
| Organism | N | KPC-2 | KPC-3 | KPC-9 |
|---|---|---|---|---|
| ***Citrobacter freundii*** | **1** | | **1** | |
| ***Enterobacter aerogenes*** | **2** | **1** | **1** | |
| ***Enterobacter cloacae*** | **3** | **2** | **1** | |
| ***Escherichia coli*** | **12** | **1** | **11** | |
| ***Klebsiella oxytoca*** | **3** | **1** | **2** | |
| ***Klebsiella pneumoniae*** | **475** | **237** | **236** | **2** |
| **Total** | **496** | **242** | **252** | **2** |

**Table 2. *In Vitro* Activity of Meropenem + Vaborbactam and Comparators Against 496 KPC-producing *Enterobacteriaceae*.**

| Organism (N) | Drug | %S | %I | %R | $MIC_{50}$ | $MIC_{90}$ | Range |
|---|---|---|---|---|---|---|---|
| **Enterobacteriaceae (496)** | **Meropenem + vaborbactam** | **na** | **na** | **na** | **0.25** | **1** | **≤0.03 - > 32** |
| | **Meropenem** | **0.8** | **14.5** | **84.7** | **> 32** | **> 32** | **2 - > 32** |
| | **Gentamicin** | **76.4** | **1.2** | **22.4** | **1** | **64** | **0.12 - > 64** |
| | **Polymyxin B** | **na** | **na** | **na** | **0.5** | **16** | **0.25 - > 16** |
| | **Tigecycline** | **76.8** | **19.6** | **3.6** | **1** | **2** | **0.12 - 8** |
| ***E. coli* (12)** | **Meropenem + vaborbactam** | **na** | **na** | **na** | **≤0.03** | **≤0.03** | **≤0.03 - ≤0.03** |
| | **Meropenem** | **25.0** | **66.7** | **8.3** | **4** | **8** | **2 - 16** |
| | **Gentamicin** | **66.7** | **0.0** | **33.3** | **0.5** | **> 64** | **0.25 - > 64** |
| | **Polymyxin B** | **na** | **na** | **na** | **0.5** | **1** | **0.25 - 1** |
| | **Tigecycline** | **100** | **0** | **0** | **0.25** | **0.5** | **0.12 - 1** |
| ***K. pneumoniae* (475)** | **Meropenem + vaborbactam** | **na** | **na** | **na** | **0.25** | **1** | **≤0.03 - > 32** |
| | **Meropenem** | **0.2** | **12.0** | **87.8** | **> 32** | **> 32** | **2 - > 32** |
| | **Gentamicin** | **77.5** | **1.1** | **21.5** | **1** | **64** | **0.12 - > 64** |
| | **Polymyxin B** | **na** | **na** | **na** | **0.5** | **16** | **0.25 - > 16** |
| | **Tigecycline** | **76.6** | **20.0** | **3.4** | **1** | **2** | **0.25 - 8** |

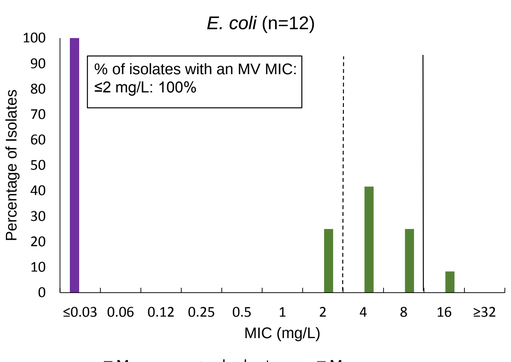
%S, I, R: percent susceptible, intermediate, resistant by EUCAST 2017 guidelines; meropenem + vaborbactam, meropenem + vaborbactam at a fixed concentration of 8 mg/L; $MIC_{50}$, $MIC_{90}$, and range in mg/L; na; no established breakpoints

**Figure 1. Effect of Vaborbactam on the MIC Frequency Distribution of Meropenem for 496 KPC-producing *Enterobacteriaceae* from Europe.**



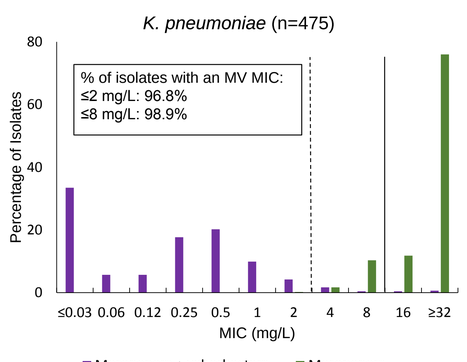

Dashed line represents the EUCAST susceptible breakpoint of ≤2 mg/L for meropenem; solid line the resistant breakpoint

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




Dashed line represents the EUCAST susceptible breakpoint of ≤2 mg/L for meropenem; solid line the resistant breakpoint

**Figure 3. Effect of Vaborbactam on the MIC Frequency Distribution of Meropenem for 475 KPC-producing *K. pneumoniae* from Europe.**




Dashed line represents the EUCAST susceptible breakpoint of ≤2 mg/L for meropenem; solid line the resistant breakpoint

## Results Summary

- Among 496 KPC-producing, OXA-48, MBL-negative, *Enterobacteriaceae* from Europe, the modal meropenem MIC dropped from ≥32 to ≤0.03 mg/L in the presence of vaborbactam (Figure 1), and the $MIC_{90}$ dropped from >32 to 1 mg/L, (Table 2).
- The combination of meropenem + vaborbactam inhibited 97.0% of KPC-producing Enterobacteriaceae at an MIC of ≤2 mg/L, and 99.0% at an MIC of ≤8 mg/L .
- There were no appreciable differences in activity between species.

## Conclusions

- Meropenem plus vaborbactam demonstrated excellent *in vitro* activity against KPC-producing *Enterobacteriaceae* from Europe, with 97.0% inhibited at ≤2 mg/L.
- 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 and Acknowledgments:**

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3. The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2017; http://www.eucast.org/clinical_breakpoints/