1234

Activity of Meropenem-Vaborbactam (VABOMERE™) against *Enterobacteriaceae* Isolates Carrying *bla*$_{KPC}$ Collected Worldwide

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Introduction

- Vaborbactam (formerly RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A, including *Klebsiella pneumoniae* carbapenemase, 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 **(VABOMERE™)** was recently approved by the United States Food and Drug Administration (US FDA) for the treatment of urinary tract infections caused by *Enterobacteriaceae*
- Isolates producing KPC enzymes have been detected in most states of the United States (US)
  - Isolates producing these enzymes are commonly detected in the New York City area and Texas
- Outside the US, KPC-producing isolates have been reported in Germany, Poland, Belgium, Hungary, Croatia, United Kingdom, Israel, China, and Brazil; KPC-producing organisms are considered endemic in Greece and Italy
- We evaluated the activity of meropenem-vaborbactam against 517 *Enterobacteriaceae* clinical isolates carrying *bla*$_{KPC}$ collected in 34 countries as part of the SENTRY Antimicrobial Surveillance Program during 2014-2016

Materials and Methods

- 34,069 *Enterobacteriaceae* clinical isolates collected in 2014 to 2016 from hospitals located in 34 countries were susceptibility tested
- Species identification was confirmed, when necessary, by matrix-assisted laser desorption ionization-time of flight mass spectrometry
- Isolates were susceptibility tested against meropenem-vaborbactam (inhibitor at fixed 8 µg/mL) and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI)
  - Quality control (QC) was performed according to CLSI guidelines (M100-S27), and all QC MIC results were within acceptable ranges, as published in CLSI documents
  - Categorical interpretations for all comparator agents were those found in CLSI document M100-S27 (2017), EUCAST breakpoint tables (version 7.1, March 2017), and/or US FDA package inserts
  - For meropenem-vaborbactam, recently approved US FDA breakpoints of 4/8/16 µg/mL were applied for susceptible/intermediate/resistant
- Carbapenem-resistant *Enterobacteriaceae* (CRE) was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at >2 µg/mL (*Proteus mirabilis* and indole-positive Proteeae used only meropenem due to intrinsically elevated imipenem MIC values)
  - CRE isolates were subjected to PCR to detect carbapenemase-encoding genes followed by Sanger sequencing, as previously described, or whole genome sequencing (WGS)
  - WGS was performed on a MiSeq (Illumina, San Diego, California, US) instrument targeting a 30X coverage

Sequences were *de novo* assembled and searched for the presence of acquired carbapenemases using a curated library and applying criteria of >94% sequencing identity and 40% minimum length coverage

Results

- Among 34,069 *Enterobacteriaceae* isolates, 942 (2.8%) were CRE and among those 517 (1.5% overall) isolates carried *bla*$_{KPC}$
  - 6 *bla*$_{KPC}$ variants were observed: 293 *bla*$_{KPC-3}$, 218 *bla*$_{KPC-2}$, 2 *bla*$_{KPC-4}$, 2 *bla*$_{KPC-17}$, and 1 each of *bla*$_{KPC-2}$-like and *bla*$_{KPC-12}$ (Figure 1)
- Isolates harboring *bla*$_{KPC}$ were mainly *K. pneumoniae* (437), but also 32 *E. cloacae species complex* (herein *E. cloacae*), 13 *K. oxytoca*, 12 *E. coli*, 12 *S. marcescens*, and 4 other species (Figure 2)
- *bla*$_{KPC}$-carrying isolates were detected in 17 countries and its occurrence ranged from <0.1% to 11.3%, being highest in Brazil, Italy (9.3%), Poland (5.6%), and Argentina (5.2%; Figure 3)
- Meropenem-vaborbactam inhibited 511/517 (98.8%) isolates carrying *bla*$_{KPC}$ at ≤4 µg/mL and were categorized as susceptible using US FDA breakpoints (Figure 4)
  - 3 isolates displaying elevated meropenem-vaborbactam MIC values (>8 µg/mL) co-harbored *bla*$_{NDM-1}$ or *bla*$_{OXA-48}$-like in addition to *bla*$_{KPC,}$ or had a nonsense mutation in *ompK35*
- Meropenem alone (MIC$_{50/90}$, 32/>32 µg/mL; Figure 1), imipenem (MIC$_{50/90}$, >8/>8 µg/mL; data not shown), and doripenem (MIC$_{50/90}$, >4/>4 µg/mL; data not shown) were not active against isolates harboring *bla*$_{KPC}$
  - Isolates carrying *bla*$_{KPC}$ were mostly resistant to cephalosporins and piperacillin-tazobactam (92.2– 99.6% resistant; CLSI criteria; data not shown)
- Meropenem-vaborbactam (MIC$_{50/90}$, 0.12/1 µg/mL) was the most active agent tested against isolates carrying *K. pneumoniae bla*$_{KPC}$ inhibiting 98.6% of the isolates at approved US FDA breakpoints (Figure 5)
  - Amikacin (MIC$_{50/90}$, 16/>32 µg/mL) and gentamicin (MIC$_{50/90}$, 2/>8 µg/mL) inhibited only 48.3% and 60.4% of the isolates, respectively (CLSI breakpoint; Figure 5)
  - Colistin (MIC$_{50/90}$, ≤0.5/>8 µg/mL; 68.2% S/EUCAST breakpoint) and tigecycline (MIC$_{50/90}$, 0.5/1 µg/mL; 99.8% S/US FDA criteria) were the most active comparators (Figure 5)

Figure 1. KPC variants (no. of isolates)

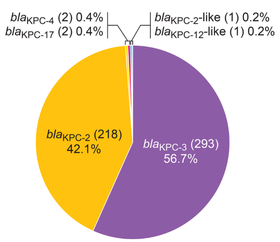


Figure 2. Bacterial species carrying *bla*$_{KPC}$ (no. of isolates)

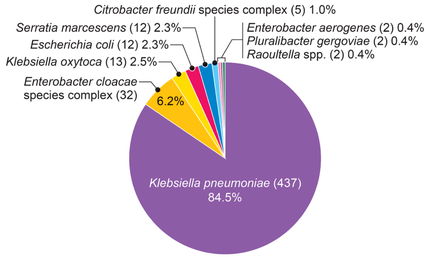
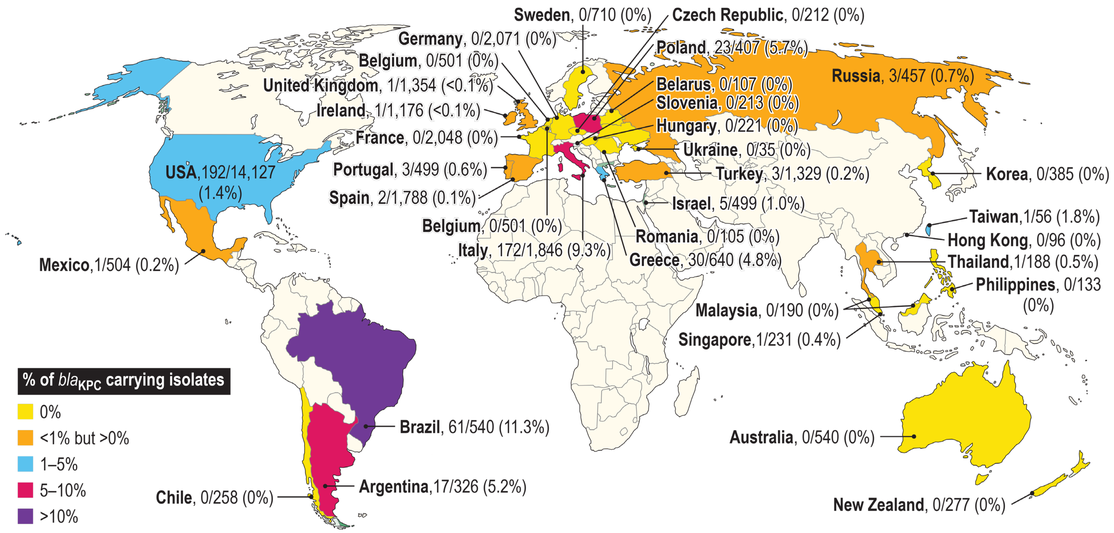


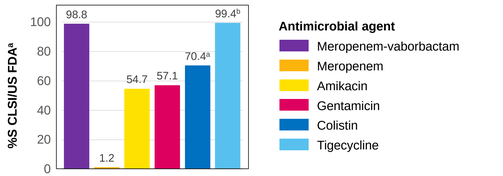
Figure 3. Countries participating in SENTRY Program and occurrence of isolates carrying blaKPC



No. of isolates carrying *bla*$_{KPC}$/no. *Enterobacteriaceae* tested

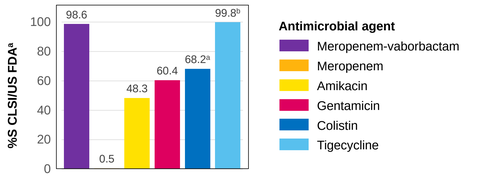
All participating countries, 517/34,069 (1.5%)

Figure 4. Activity of meropenem-vaborbactam and selected comparators tested against *Enterobacteriaceae* carrying *bla*$_{KPC}$ (517 isolates)



[a] Criteria as published by CLSI [2017] or breakpoints from FDA package insert/press release (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573955.html)
[b] Criteria as published by EUCAST [2017]

Figure 5. Activity of meropenem-vaborbactam and selected comparators tested against *K. pneumoniae* carrying *bla*$_{KPC}$ (437 isolates)



[a] Criteria as published by CLSI [2017] or breakpoints from FDA package insert/press release (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573955.html)
[b] Criteria as published by EUCAST [2017]

Conclusions

- The overall occurrence of *bla*$_{KPC}$ worldwide is low (1.5%); however, these rates were as high as 5-11% in a few countries
  - Although most isolates carrying *bla*$_{KPC}$ were *K. pneumoniae*, 8 other bacterial species harbored these genes
- Isolates carrying *bla*$_{KPC}$ were highly resistant to available antimicrobial agents, including cephalosporins, carbapenems, tetracyclines, and fluoroquinolones
- Meropenem-vaborbactam displayed activity against >98.0% of the isolates carrying *bla*$_{KPC}$ at ≥4 µg/mL
  - This combination agent will be a useful alternative to treat infections caused by these organisms

Acknowledgements

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