ECCMID 2019 | Poster #L0041

Activity of Meropenem-Vaborbactam and Single-Agent Comparators against KPC-Producing *Enterobacterales* Isolates from European Countries (2016–2018) Stratified by Infection Type

Mariana Castanheira, Timothy B. Doyle, Caitlin J. Smith, Ross Donatelli, Dee Shortridge
JMI Laboratories, North Liberty, Iowa, USA

Introduction

- Carbapenem-resistant *Enterobacterales* (CRE) isolates are a growing issue worldwide
- Among carbapenemases detected in *Enterobacterales* species, *Klebsiella pneumoniae* carbapenemases (KPCs) have the most extensive global distribution
- KPC isolates are usually *K. pneumoniae* that are multidrug resistant and have limited options available for treatment
- Among the treatment options for KPC-producing isolates, colistin and tigecycline are widely used
  - Both compounds have limitations regarding toxicity or low plasma concentrations that may concern some about their use
  - Resistance to colistin and less often to tigecycline have 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 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 has been approved by the European Medicines Agency (EMA) for the treatment of complicated infections of the urinary tract, complicated abdominal infections, and hospital-acquired pneumonia, including ventilator-associated pneumonia and bacteremia
- We evaluated the activity of meropenem-vaborbactam and single-agent comparators against 246 KPC-producing *Enterobacterales* isolates collected in European hospitals from 2016–2018

Materials and Methods

- A total of 17,248 *Enterobacterales* clinical isolates, limited to 1 per patient episode and identified as causative of infection, were included in the study
  - These isolates were collected in 39 European hospitals located in 19 countries
  - The isolates were collected from bloodstream infection (BSI; n=5,967), pneumonia in hospitalized patients (pneumonia; n=3,464), urinary tract infection (UTI; n=3,369), skin and skin structure infection (SSSI; n=2,881), intra-abdominal infection (IAI; n=1,551), and other sites (n=16)
- Species identification was confirmed, when necessary, by matrix-assisted laser desorption ionization-time of flight mass spectrometry
- Isolates were susceptibility tested against meropenem-vaborbactam and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI; M07, 2018)
  - Vaborbactam was tested at a fixed concentration of 8 mg/L
  - Quality control (QC) was performed according to CLSI guidelines, and all QC MIC results were within acceptable ranges, as published in CLSI documents (M100, 2019)
  - Categorical interpretations for all comparator agents were those found in European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 9.0, January 2019), the CLSI criteria in M100 (2019), or the US Food and Drug Administration (FDA) website
- CRE was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L (*Proteus mirabilis* and indole-positive Proteeae used only meropenem due to intrinsically elevated imipenem MIC values)
  - CRE isolates were submitted to whole genome sequencing on a MiSeq (Illumina, San Diego, California, USA) 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
  - Isolates carrying bla_{KPC} were included in the study

Results

- Among 246 isolates carrying bla_{KPC}, 187 isolates harboured bla_{KPC-3}, 58 carried bla_{KPC-2}, and 1 isolate harboured bla_{KPC-12}
- *Klebsiella pneumoniae* was the most common organism carrying bla_{KPC} that was detected among 232 isolates of this species (94.3%, Figure 1)
  - Four other *Enterobacterales* species were noted to harbour bla_{KPC}: *Escherichia coli* (8 isolates), *Klebsiella oxytoca* (3), *Enterobacter cloacae* species complex (2), and *Pluralibacter gergoviae* (1)
- Isolates carrying bla_{KPC} were noted among 14 hospitals and 9 countries
  - bla_{KPC-2}-harbouring isolates were detected in 7 countries, but were only detected in all 3 years in Greece (21/58 isolates) and Italy (28/58 isolates; Figure 2)
  - Isolates harbouring the gene encoding KPC-3 were detected mainly in Italy (166/187), but also in 5 other countries
  - The single isolate carrying bla_{KPC-12} was detected in Greece
- Meropenem-vaborbactam inhibited 99.6% of the isolates carrying bla_{KPC} when applying EUCAST breakpoints while meropenem alone inhibited only 1.2% of these isolates (Figure 3)
  - Only 1 isolate had a meropenem-vaborbactam MIC >8 mg/L and this isolate from Italy had disruptions in *ompK35* and alterations in *ompK36* in addition to bla_{KPC-3}
  - OmpK36 alterations included the insertion of a glycine and aspartate in position 134 of the PEFDG motif in the L3 region of OmpK36 that is known to confer elevated MIC values against meropenem, among other β-lactams
- Meropenem-vaborbactam inhibited 100.0% of the isolates from IAI (n=17), pneumonia (n=58), UTI (n=16), and SSSI (n=20)
  - This combination inhibited 131 of the 132 isolates from BSI (99.2% susceptible; Figure 4)
- Meropenem alone inhibited 12.5% of the urinary tract infection isolates and 0.7% of the BSI isolates, but none of the isolates from other infection sources
- Among comparator agents, gentamicin, colistin, and tigecycline were the most active
  - Overall, gentamicin inhibited 65.4% of the isolates at the EUCAST breakpoints; however, this aminoglycoside displayed activity against 81.2% of the UTI isolates and 88.2% of the IAI isolates
  - Colistin inhibited 62.5% to 80.0% of the isolates, showing less activity against UTI isolates and more activity against SSSI isolates
  - Tigecycline was active against ≥87.5% of the isolates using US FDA breakpoints
  - Other selected comparators had limited activity against isolates carrying bla_{KPC}

Figure 1 Bacterial species carrying bla_{KPC}

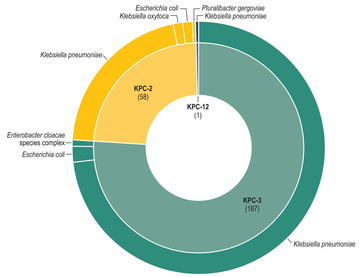


Figure 2 Distribution of isolates carrying bla_{KPC} among European countries and study years

Figure 3 Comparative activity of meropenem-vaborbactam and meropenem against 246 isolates carrying bla_{KPC} from European hospitals

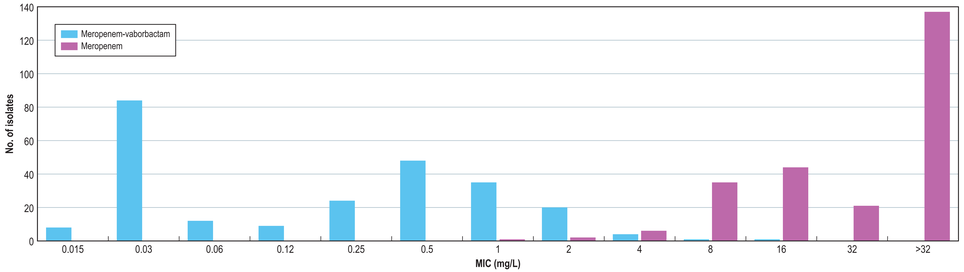
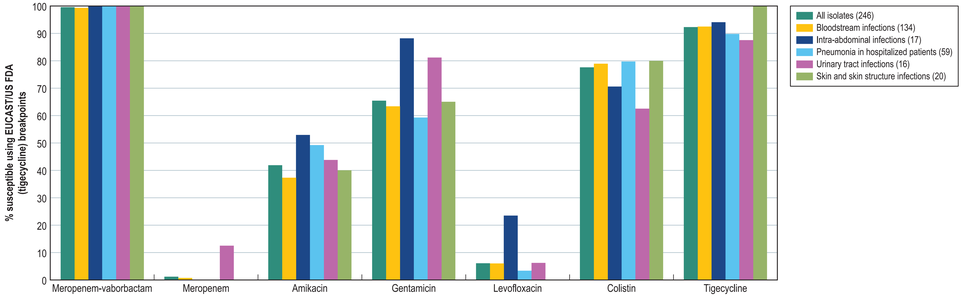


Figure 4 Activity of meropenem-vaborbactam and comparator agents 246 isolates carrying bla_{KPC} from European hospitals stratified by infection type



Conclusions

- Isolates carrying bla_{KPC} were mostly *K. pneumoniae*
  - These isolates were common in Greece and Italy, but also sporadically detected in 7 other European countries
- As demonstrated by these results, meropenem-vaborbactam has potent activity against *Enterobacterales* isolates carrying bla_{KPC} regardless of the infection source
  - Comparator agent activity varied some according to the infection sources
- In recent clinical experiences, meropenem-vaborbactam has demonstrated good pharmacodynamics and a safety profile recognized for other β-lactam agents
  - These characteristics are not observed in some comparators active against KPC-producers

Acknowledgements

This research was funded by Melinta Therapeutics.

References

Castanheira M, Rhomberg PR, Flamm RK, et al. (2016). Effect of the beta-Lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother* 60: 5454-5458.

Castanheira M, Huband MD, Mendes RE, et al. (2017). Meropenem-vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. *Antimicrob Agents Chemother* 61: e00567.

Clinical and Laboratory Standards Institute (2015). *M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-tenth edition*. Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2019). *M100Ed29E. Performance standards for antimicrobial susceptibility testing: 29th informational supplement*. Wayne, PA: CLSI.

EUCAST (2019). Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, January 2019. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf.

Kaye KS, Bhowmick T, Metallidis S, et al. (2018). Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: The TANGO I Randomized Clinical Trial. *JAMA* 319: 788-799.

Pfaller MA, Huband MD, Mendes RE, et al. (2018). In vitro activity of meropenem-vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem/vaborbactam surveillance programme. *Int J Antimicrob Agents* 52: 144-150.

Sun D, Rubio-Aparicio D, Nelson K, et al. (2017). Meropenem-vaborbactam resistance selection, resistance prevention, and molecular mechanisms in mutants of KPC-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 61: e01694.

Contact

Mariana Castanheira, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: mariana-castanheira@jmilabs.com

To obtain a PDF of this poster:

Scan the QR code or visit https://www.jmilabs.com/data/posters/ECCMID19-meropenem-vaborbactam-KPC-Enterobacterales.pdf

Charges may apply. No personal information is stored.