ECCMID 2021 | Poster #01047

Activity of Meropenem-Vaborbactam and Comparators against European Carbapenem-Resistant *Enterobacterales* Isolates without a Carbapenemase

Dee Shortridge, Lalitagauri M. Deshpande, Jennifer M. Streit, Mariana Castanheira
JMI Laboratories, North Liberty, Iowa, USA

ECCMID 2021 TOP RATED POSTER

Introduction

- Meropenem-vaborbactam is a combination of a carbapenem and a β-lactamase inhibitor that is active against serine β-lactamases including carbapenemases.
  - Meropenem-vaborbactam has been approved in Europe for the treatment of the following infections in adults: complicated urinary tract infection (cUTI), including acute pyelonephritis, complicated intra-abdominal infection (cIAI), hospital-acquired bacterial pneumonia (HAP), ventilator-associated pneumonia (VAP), and bacteremia (BSI) that occurs in association with or is suspected to be associated with any of the infections listed above.
  - Meropenem-vaborbactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.
- Carbapenem-resistant *Enterobacterales* (CRE) isolates have disseminated worldwide.
  - These isolates typically produce a carbapenemase.
  - However, some CRE isolates are negative for known carbapenemases.
- In this study, we evaluated the activity of meropenem-vaborbactam and comparators against CREs without a carbapenemase (non-CP CREs) collected from European hospitals from 2016 to 2019.

Materials and Methods

- 23,043 *Enterobacterales* clinical isolates were consecutively collected from 41 European hospitals in 20 countries over the 4-year period.
  - Participating laboratories submitted 1 isolate per patient per infection episode.
- Susceptibility (S) testing was performed using the broth microdilution method.
- EUCAST (2021) interpretive criteria were used.
- 978 CREs were identified under the criteria of having a MIC >2 mg/L to doripenem, imipenem and/or meropenem. Imipenem was not used for *Proteus, Providencia,* or *Morganella* spp.
- Whole genome sequencing was performed on each CRE isolate.
- 125 CRE isolates were negative for known carbapenemase genes, including bla_{KPC}, bla_{NDM}, bla_{IMP}, bla_{VIM}, and $bla_{OXA-48-like}$.
- NonCP CRE isolates were analysed for the presence of other beta-lactamases, multilocus sequence typing (ST), increased expression of AmpC or efflux pumps, and disruptions in or increased expression of outer membrane protein (OMP) sequences.

Results

- The most common infections were pneumonia (n=37), UTI (n=26), cIAI (n=23), and BSI (n=22).
- The rate of CREs during this period was 4.2%.
  - 12.8% of the CREs lacked a known carbapenemase gene.
- The most common species of nonCP CRE were *Klebsiella pneumoniae* (n=97, 77.6%), *Enterobacter cloacae* species complex (n=11, 8.8%) and 10 *K. aerogenes* (8.0%; Figure 1).
- 84.0% of nonCP CRE (n=105) were from Poland, including 90.7% of nonCP CRE *K. pneumoniae* (n=88; Figure 1).
- Among the 92 *K. pneumoniae* isolates with an ST identified, 30 belonged to ST11, 18 to ST152, and 17 to ST147, but at least 13 other STs were observed (Figure 2).
  - The *K. pneumoniae* isolates from Poland were primarily ST11 (n=29), ST152 (n=18), and ST147 (n=17; Figure 2).
- Most (n=91, 72.8%) isolates carried $bla_{CTX-M-15}$, including 86 of 97 *K. pneumoniae* isolates.
  - Other acquired β-lactamases included bla_{SHV}, bla_{OXA-1}, bla_{TEM}, bla_{DHA-1}.
  - 96.8% of the isolates had two or more acquired β-lactamases.
- OMP disruptions were noted among the *Klebsiella pneumoniae*: 23 isolates had disruptions of both OmpK35 and OmpK36, 7 had only OmpK35 disrupted, and 43 had only OmpK36 disrupted.
- Meropenem-vaborbactam susceptibility was 97.6% while meropenem was 8.0% (Table 1 and Figure 3).
  - The MIC distribution of all isolates and *K. pneumoniae* with OMP disruptions or alterations is shown in Figure 3.
  - Two of the 3 meropenem-vaborbactam resistant isolates were *K. pneumoniae* and had alterations or disruptions in both OmpK35 and 36. These isolates also contained $bla_{CTX-M-15}$, bla_{SHV-12}, $bla_{OXA-1, OXA-10}$, and bla_{TEM-57}.
  - The third meropenem-vaborbactam resistant isolate was a *K. aerogenes* with elevated AmpC expression and an OmpC disruption.
- NonCP CRE isolates were resistant to many comparator agents. The most active agents were colistin and amikacin (susceptibility was 74.8% and 65.6%).

Table 1. Activity of meropenem-vaborbactam and comparator antimicrobial agents tested against 125 CRE, nonCP European isolates (2016–2019)

Antimicrobial agent	No. of isolates	mg/L MIC$_{50}$	mg/L MIC$_{90}$	MIC range	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Meropenem-vaborbactam	125	1	4	0.03 to 16	97.6		2.4
Meropenem	125	8	16	0.12 to 32	8.0 [b] 8.0 [c]	80.0	92.0 12.0
Imipenem	125	4	>8	0.5 to >8	48.8	24.0	27.2
Amikacin	125	8	32	0.5 to >32	65.6 [d]		34.4
Aztreonam	125	>16	>16	2 to >16	0.0	3.2	96.8
Cefepime	125	>16	>16	0.5 to >16	0.8	8.8	90.4
Ceftazidime	125	>32	>32	2 to >32	0.0	2.4	97.6
Colistin	123	0.25	>8	≤0.06 to >8	74.8		25.2
Gentamicin	125	2	>8	≤0.12 to >8	56.0 [e]		44.0
Levofloxacin	125	>4	>4	≤0.03 to >4	11.2	5.6	83.2
Piperacillin-tazobactam	125	>64	>64	8 to >64	0.8		99.2

[a] Criteria as published by CLSI (2021) and EUCAST (2021).
[b] Using meningitis breakpoints.
[c] Using non-meningitis breakpoints.
[d] For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.
[e] Intermediate is interpreted as susceptible-dose dependent.
Organisms include: *Enterobacter cloacae* species complex (11), *Escherichia coli* (3), *Hafnia alvei* (2), *Klebsiella aerogenes* (10), *K. oxytoca* (1), *K. pneumoniae* (97), and *Serratia marcescens* (1).

Figure 1. Country and species distributions of nonCP CREs in Europe

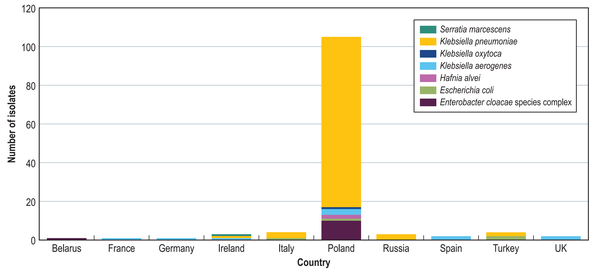


Figure 2. *K. pneumoniae* sequence type (ST) distribution of nonCP CRE isolates by country

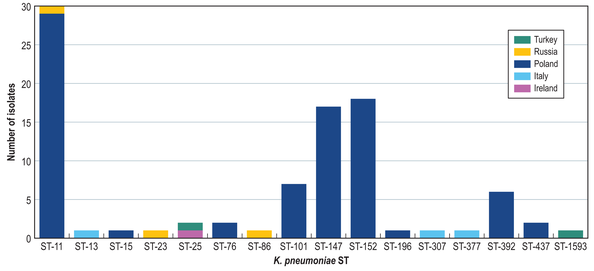
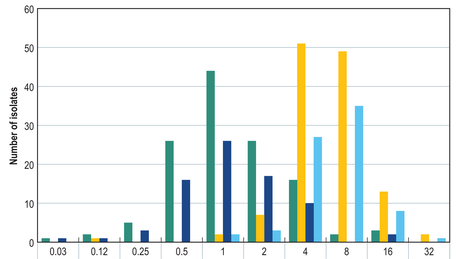


Figure 3. MIC distribution of meropenem-vaborbactam (MVB) and meropenem (MER) tested against all nonCP CRE isolates and against *K. pneumoniae* isolates with OmpK35 or OmpK36 disruptions



	0.03	0.12	0.25	0.5	1	2	4	8	16	32
MVB All isolates	1	2	5	26	44	26	16	2	3	0
MER All isolates	0	1	0	0	2	7	51	49	13	2
MVB *K. pneumoniae* OMP mutations	1	1	3	16	26	17	10		2	
MER *K. pneumoniae* OMP mutations	0	0	0	0	2	3	27	35	8	1

Conclusions

- These results demonstrate meropenem-vaborbactam was the most active drug tested against CRE isolates that lack known carbapenemases, with 97.6% of these isolates considered susceptible.
  - 8.0% were susceptible to meropenem.
  - The higher EUCAST breakpoint of meropenem-vaborbactam reflect the higher dose of the meropenem component and a maximal inhibitory effect of the vaborbactam component.
- *K. pneumoniae* was the most common nonCP CRE accounting for 77.6%.
  - 84% of the *K. pneumoniae* isolates were from Poland and represented 9 different ST types.
- Resistance mechanisms observed among the nonCP CRE isolates in this study included multiple acquired β-lactamases (CTX-M-15, OXA, SHV, and TEM) and/or disruption of OmpC (*K. aerogenes* and *E. cloacae*) or OmpK35 or K36 in *K. pneumoniae*.
- The increased activity of meropenem-vaborbactam against these isolates shows that inhbition of the non-carbapenemase β-lactamases by vaborbactam increases the activity of meropenem alone.
- These results suggest that meropenem-vaborbactam may be a useful treatment for infections caused by CREs that lack a carbapenemase.

Acknowledgements

This poster has been funded by A. Menarini Industrie Farmaceutiche Riunite SRL.

References

CLSI. *M07 Eleventh edition. Methods for Dilution Antimicrobial Susceptibility Testing for Bacteria That Grow Aerobically.* Clinical and Laboratory Standards Institute, Wayne, PA, 2018.

EUCAST. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, v 11.0, January 1, 2021. http://www.eucast.org (Access Date Jan 31, 2021).

Castanheira M, Rhomberg PR, Flamm RK and Jones RN. Effect of the β-lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 60:545-8. 2016.

Contact

Dee Shortridge
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: dee-shortridge@jmilabs.com

To obtain a PDF of this poster:
Scan the QR code or visit https://www.jmilabs.com/data/posters/ECCMID2021_MeroVaborVEuroCRE.pdf

Charges may apply. No personal information is stored.