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Activity of meropenem-vaborbactam and single-agent comparators against *Enterobacterales* isolates, including KPC-producing isolates, from European patients hospitalized with pneumonia including ventilator-associated pneumonia (2014–2019)

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Introduction

- Carbapenem-resistant *Enterobacterales* (CRE) isolates are a growing global concern.
- Among carbapenemases detected in *Enterobacterales* species, *Klebsiella pneumoniae* carbapenemases (KPCs) have disseminated worldwide and are endemic in many hospitals in various countries.
- *K. pneumoniae* containing KPC are often multidrug resistant and have limited treatment options.
- Colistin and tigecycline are often used as treatments for infections caused by KPC-producing isolates.
  - Both compounds have limitations that concern clinicians, such as toxicity or low plasma concentrations. In addition, tigecycline is not indicated by EMA to treat pneumonia.
  - Resistance to colistin, and less often to tigecycline, have been reported among KPC-producing *K. pneumoniae* (Sader, Castanheira et al. 2015).
- Vaborbactam is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A, including KPC, and C enzymes.
  - Vaborbactam combined with meropenem enhanced the activity of this carbapenem against KPC-producing isolates in comparison to meropenem tested alone.
  - Vaborbactam does not inhibit class B metallo-β-lactamases (MBL) or class D carbapenemases (Lomovskaya, Sun et al. 2017).
- Meropenem-vaborbactam (MVB) recently was approved in Europe for the treatment of complicated urinary tract infections (cUTIs), including acute pyelonephritis, complicated intra-abdominal infections (cIAI), hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and bacteremia that occurs with any of the infections listed above.
- We evaluated the activity of MVB and single-agent comparators against 6,846 *Enterobacterales* isolates from patients hospitalized with pneumonia (PHP) in European hospitals from 2014–2019.

Materials and Methods

- 6,846 *Enterobacterales* PHP clinical isolates collected in 40 European hospitals across 20 countries were susceptibility tested using reference broth microdilution methods (CLSI 2018).
  - EUCAST and CLSI interpretive criteria were used (CLSI 2020, EUCAST 2020)
- *Enterobacterales* isolates also were screened for the extended spectrum beta-lactamase (ESBL) phenotype (CLSI 2020). Isolates that were ESBL screen-positive isolates included both carbapenem-susceptible and carbapenem-nonsusceptible isolates; a subset of carbapenem-susceptible ESBL- phenotype isolates (ESBL non-CR) were also analyzed.
- Carbapenem-resistant isolates were subjected to whole genome sequencing and analyzed for the presence of carbapenemases (Castanheira, Huband et al. 2017).
- The susceptibilities of isolates from intensive care unit (ICU) and non-ICU patients were compared.
  - 3,218 isolates were from patients in the ICU and 2,627 were non-ICU. ICU vs. non-ICU designations were made by the submitting hospital.
  - A subset of 1,890 isolates from ICU patients with VABP were included.
  - The VABP designation was made by the submitting site. Only isolates from patients with VABP in ICU were included in the analysis.
  - A total of 1,001 isolates did not have an ICU or non-ICU designation from the submitting site. These 1,001 isolates were not included in the ICU/non-ICU analysis but were included in the total.

Results

- The top 5 species isolated from PHP caused by *Enterobacterales* are shown in Figure 1.
  - The most common *Enterobacterales* species isolated from patients hospitalized with pneumonia (PHP) were *Klebsiella pneumoniae* (n=1,877) and *Escherichia coli* (n=1,646).
- The susceptibilities of MVB and comparators tested against *Enterobacterales* for ICU and non-ICU patients, ICU patients with VABP and resistance groups are shown in Table 1.
- Overall, MVB had the highest percent susceptibility of the drugs tested, with 97.7/98.0% using CLSI or EUCAST breakpoints (CLSI, ≤4/8/≥16; EUCAST, ≤8/-/≥16 mg/L). MVB MIC distributions for all isolates and subgroups from patients in the ICU, ICU with VABP, and non-ICU are shown in Figure 2.
  - Amikacin was the most active comparator against all *Enterobacterales* (96.2/94.2% susceptible CLSI/EUCAST).
- For *Enterobacterales* isolates from ICU patients, MVB susceptibility was 96.6/97.1%. For non-ICU isolates, MVB susceptibility was 98.2/98.5% (CLSI/EUCAST) as shown in Table 1.
  - The susceptibilities of comparators for ICU vs non-ICU isolates were similar, except for levofloxacin (76.0/76.0%S ICU and 70.3/70.3%S non-ICU, CLSI/EUCAST).
  - Susceptibilities were similar between ICU PHP and VABP subsets.
- Overall, 20% of isolates had an ESBL-phenotype, 76.4% of these were carbapenem-susceptible.
  - Against isolates with an ESBL-phenotype, MVB inhibited 85.8/87.5% (CLSI/EUCAST). All ESBL-phenotype isolates that were non-CRE were susceptible to meropenem-vaborbactam.
- 5.3% of all isolates were CRE.
  - Meropenem-vaborbactam nonsusceptible CRE isolates contained Class B (NDM, VIM) or Class D (OXA-48-like group) carbapenamases. These isolates were also resistant to other comparators including amikacin, gentamicin, and levofloxacin.
- MVB inhibited 100% of CRE KPC-producing isolates as shown in Figure 3.
  - Colistin was the most active comparator against KPC-producing isolates (81.3% susceptible, EUCAST).
- Figure 4 shows the distribution of KPC, Class B MBL, and Class D OXA-48-like producing isolates in different European Countries. Striking differences were present in the carbapenemase distribution.
  - Russia and Turkey, had primarily OXA-48-producing isolates.
  - Belarus had primarily MBL-producing isolates, and Greece had both MBL and KPC-producing isolates.
  - Western European countries had primarily KPC-producing isolates.
- There were 75 KPC-producing isolates from 7 countries.
  - KPC-producing isolates were mainly *K. pneumoniae* (n=71), which included 58 bla_{KPC-3}, 16 bla_{KPC-2}, and 1 bla_{KPC-12}. Four *E. coli* had bla_{KPC-3}
  - Italy had the highest number of KPC-producing isolates at 42 (56%).
  - 29 KPC-producing isolates were from ICU patients, 36 from non-ICU.

Table 1 Susceptibility of meropenem-vaborbactam and comparators against *Enterobacterales* isolates from patients hospitalized with pneumonia

Organisms and organism groups (n)	% susceptible using CLSI/ EUCAST[a] breakpoints					
	Meropenem-vaborbactam	Meropenem	Amikacin	Gentamicin	Levofloxacin	Colistin[b]
Enterobacterales (6,846)	97.7/98.0	94.6/95.1	96.2/94.2	86.0/85.3	75.0/75.0	-/76.8
ESBL-phenotype (1,368)	89.5/90.6	75.7/77.4	83.0/75.1	49.9/48.8	22.6/22.6	-/88.3
ESBL nonCR[c] (1045)	100.0/100.0	98.6/100.0	94.0/87.0	53.4/52.4	28.4/28.4	-/92.5
CRE (362)	56.6/63.0	3.6/7.7	51.9/41.4	42.5/39.8	8.9/8.9	-/74.2
KPC-producing (75)	100.0/100.0	0.0/0.0	56.0/48.0	61.3/60.0	6.7/6.7	-/81.3
MBL or OXA-48[d] (157)	21.0/29.9	6.4/12.1	40.8/32.5	27.4/26.1	8.3/8.3	-/85.3
ICU isolates (3,218)	96.6/97.1	93.4/94.2	95.0/93.0	85.2/84.6	76.0/76.0	-/76.4
ESBL-phenotype (705)	85.8/87.5	72.6/75.3	79.1/71.2	47.1/45.7	22.8/22.8	-/86.1
ESBL nonCR (519)	100.0/100.0	97.7/100.0	92.1/85.0	49.9/48.7	29.4/29.4	-/90.5
CRE (206)	47.6/55.3	3.9/9.2	47.1/37.9	42.2/39.8	9.3/9.3	-/73.3
KPC-producing (29)	100.0/100.0	0.0/0.0	48.3/37.9	79.3/75.9	6.9/6.9	-/62.1
MBL or OXA-48 (113)	19.5/30.1	6.2/10.6	37.2/29.2	28.3/26.5	7.1/7.1	-/89.4
ICU-VAP isolates (1,890)	95.9/96.7	92.1/93.2	93.7/91.5	83.3/82.6	74.3/74.3	-/76.8
ESBL-phenotype (455)	84.2/86.8	69.9/73.8	75.6/67.3	46.2/44.6	20.7/20.7	-/86.5
ESBL nonCR (324)	100.0/100.0	96.6/100.0	89.2/82.4	49.1/47.8	27.5/27.5	-/90.4
CRE (144)	45.8/56.2	4.9/11.1	45.8/34.7	41.7/38.9	7.7/7.7	-/77.1
KPC-producing (11)	100.0/100.0	0.0/0.0	27.3/18.2	81.8/81.8	0.0/0.0	-/72.7
MBL or OXA-48 (89)	21.3/34.8	6.7/11.2	39.3/30.3	31.5/29.2	8.0/8.0	-/92.1
non-ICU isolates (2,627)	98.2/98.5	94.2/94.5	96.4/94.0	84.5/83.7	70.3/70.3	-/78.2
ESBL-phenotype (530)	92.3/92.8	74.3/75.1	84.9/76.6	49.8/48.9	19.2/19.2	-/89.4
ESBL nonCR (396)	100.0/100.0	99.2/100.0	94.9/88.1	53.5/52.8	24.7/24.7	-/93.7
CRE (153)	69.9/74.5	3.3/5.9	59.5/47.1	43.8/40.5	8.5/8.5	-/75.7
KPC-producing (46)	100.0/100.0	0.0/0.0	60.9/54.3	50.0/50.0	6.5/6.5	-/93.5
MBL or OXA-48 (41)	26.8/31.7	7.3/17.1	53.7/43.9	26.8/26.8	12.2/12.2	-/75.0

[a] CLSI M100 30th Ed., EUCAST v10.0 (2020)
[b] No CLSI susceptible category for colistin
[c] CR carbapenem resistant
[d] Metallo-β-lactamase (MBL) included NDM (n=50) or VIM (n=14); OXA-48 included OXA-48-like carbapenemases.

Figure 1 Five most common *Enterobacterales* species isolated from pneumonia

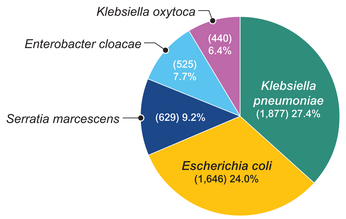
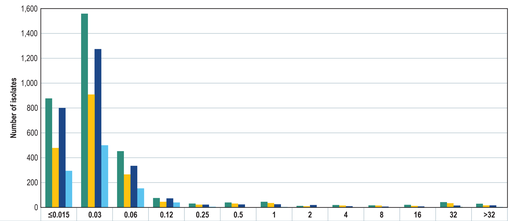


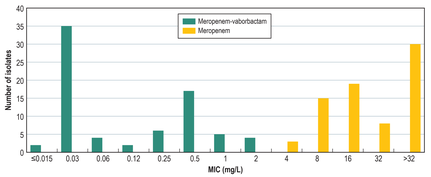
Figure 2 Meropenem-vaborbactam MIC (mg/L) distribution of *Enterobacterales* isolates from PHP* for ICU patients, ICU patients with VAP, non-ICU patients, and patients for which ICU status was not available



	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
ICU	877	1,559	452	76	31	39	45	12	19	16	21	42	29
ICU-VAP	479	908	265	46	23	31	35	10	15	15	12	34	17
non-ICU	800	1,274	335	73	22	24	25	19	9	7	8	15	16
No info	294	500	153	40	5	1	4	1					3

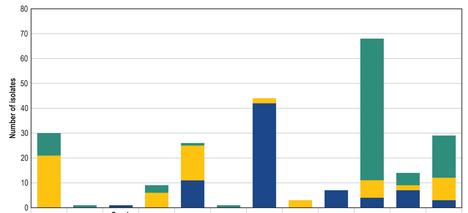
*PHP, patients hospitalized with pneumonia; ICU, intensive care unit; ICU-VAP ICU patients with ventilator-associated pneumonia; non-ICU, in hospital service other than ICU; no info, ICU status was not indicated by submitting laboratory

Figure 3 Activity of meropenem and meropenem-vaborbactam against KPC-producing isolates



KPC, carbapenemase

Figure 4 European countries with KPC, metallo-β-lactamases or OXA-48-like carbapenemases



	Belarus	Belgium	Czech Republic	Germany	Greece	Ireland	Italy	Poland	Portugal	Russia	Spain	Turkey
OXA-48-like	9	1	0	3	1	1	0	0	0	57	5	17
MBL	21	0	0	6	14	0	2	3	0	7	2	9
KPC	0	0	1	0	11	0	42	0	7	4	7	3

OXA-48-like carbapenemases
MBL- NDM (n=50) or VIM (n=14) metallo-β-lactamases;
KPC- *Klebsiella pneumoniae* carbapenemase, KPC 2, 3 and 12.

Conclusions

- Meropenem-vaborbactam had the highest susceptibility (97.7/98.2%) of tested agents against pathogens isolated from patients hospitalized with pneumonia, including VABP.
  - Isolates from ICU and non-ICU patients had similar susceptibilities for all antimicrobials except levofloxacin, which had a lower susceptibility rate in non-ICU isolates.
- The overall rate of CRE isolates was 5.3%, and the type of carbapenemase varied by country, with more KPC-producing isolates in Western European, and more OXA-48 and MBL-producing isolates in Eastern European countries.
- Meropenem-vaborbactam was very active against *Enterobacterales* isolates producing KPC enzymes inhibiting 100% of the studied isolates.
- These data suggest that meropenem-vaborbactam is a useful treatment option for both ICU and non-ICU patients hospitalized with pneumonia, including VABP, even when pneumonia is caused by carbapenem-resistant strains, in regions with a high prevalence of KPC.

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