Activity of meropenem-vaborbactam and singleagent 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), hospitalacquired 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

- in Figure 1
- 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, $\leq 4/8/\geq 16$; EUCAST, $\leq 8/-216$ 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-48like 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.
- 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.

The top 5 species isolated from PHP caused by *Enterobacterales* are shown

- The most common *Enterobacterales* species isolated from patients hospitalized with pneumonia (PHP) were Klebsiella pneumoniae
- (n=1,877) and *Escherichia coli* (n=1,646).

There were 75 KPC-producing isolates from 7 countries.

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

	% susceptible using CLSI/ EUCAST ^a breakpoints						
Organisms and organism groups (n)	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 CI SI M100 30th Ed., EUCAST v10.0 (2020) No CLSI susceptible category for colistin

CR carbapenem resistant



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



KPC, carbapenemase

^d Metallo-β-lactamase (MBL) included NDM (n=50) or VIM (n=14); OXA-48 included OXA-48-like carbapenemases

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



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

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

32	>32	
32 42	>32 29	
32 42 34	> 32 29 17	
32 42 34 15	> 32 29 17 16	

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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