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Activity of Meropenem-Vaborbactam and Comparators Against Enterobacterales Isolates from Patients in Hematology/Oncology and Transplant Units in the United States

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Introduction

- Patients undergoing treatment for cancer or receiving an organ transplant are often immunosuppressed and particularly susceptible to infections caused by Gram-negative pathogens, including carbapenem-resistant organisms.
- Meropenem-vaborbactam is a combination of a carbapenem and a β-lactamase inhibitor that is effective against Class A and C serine-β-lactamases, including KPC carbapenemase, and non-carbapenemase OXA class D enzymes.
- We evaluated the activity of meropenem-vaborbactam and comparators against Enterobacterales isolates collected in the US during 2014–2021 from patients in hematology, oncology, or transplant units of US medical centers as part of the SENTRY Antimicrobial Surveillance Program.

Methods

- A total of 2,185 clinical isolates were consecutively collected from patients in hematology/oncology or transplant units in 33 hospitals in all 9 US Census Divisions (shown below).
- Isolates were susceptibility tested using CLSI M11 (2018) broth microdilution methodology. Results were interpreted using CLSI M100 (2022) breakpoints.
- Carbapenem-resistant Enterobacterales (CRE) were characterized as having MIC values ≥4 mg/L to imipenem and/or meropenem.
- CREs were genotypically characterized for carbapenemase genes by PCR (prior to 2016) or whole genome sequencing (2016–2021), as previously described (Castanheira, 2017).
- States in US Census division
  - New England Division: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont
  - Middle Atlantic Division: New Jersey, New York and Pennsylvania
  - East North Central Division: Illinois, Indiana, Michigan, Ohio and Wisconsin
  - West North Central Division: Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota and South Dakota
  - South Atlantic Division: Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia and West Virginia
  - East South Central Division: Alabama, Kentucky, Mississippi and Tennessee
  - West South Central Division: Arkansas, Louisiana, Oklahoma and Texas
  - Mountain Division: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah and Wyoming
  - Pacific Division: Alaska, California, Hawaii, Oregon and Washington

Results

- 2,185 isolates were included in the study.
  - The most common species isolated were *Escherichia coli* (*n*=863), *Klebsiella pneumoniae* (*n*=518), and *Enterobacter cloacae* complex (*n*=284; Figure 1).
  - The most common infection type was bloodstream infection (*n*=1,057), followed by urinary tract infection (*n*=347; Figure 2).
  - Susceptibility was 99.6% to meropenem-vaborbactam, 98.5% to meropenem, and 83.4% to piperacillin-tazobactam (Table 1).
- 28 isolates (1.3%) were CRE.
  - Susceptibility of these isolates to meropenem-vaborbactam was 71.4%.
  - Susceptibility of these isolates to levofloxacin and piperacillin-tazobactam was 25.0% and 0.0%, respectively (Table 1).
- 25 CRE were genotypically characterized.
  - 13 isolates produced KPC.
    - 6 isolates were from the Mid-Atlantic Census Divsion, 4 were from West South Central Divsion, and 1 each from New England, South Atlantic and Pacific Divsions.
  - 5 isolates produced OXA-48/-232, 4 from West South Central and 1 from Mid-Atlantic Divsions
  - 2 isolates produced NDM-1/-5, both from the Mid-Atlantic Divsion
  - 2 produced IMP-4, both from the Mid-Atlantic Divsion
  - 3 were negative for known carbapenemase genes, 2 from South Atlantic and 1 from West South Central Divsions.
- Of the 25 genotypically characterized CRE isolates:
  - All 13 KPC–producing isolates were susceptible to meropenem-vaborbactam.
  - All 5 OXA-48/232–producing were resistant to meropenem-vaborbactam.
  - All 2 NDM–producing isolates were resistant to meropenem-vaborbactam.
  - 1 IMP-4–producing isolate was susceptible and 1 was intermediate to meropenem-vaborbactam.
  - All 3 CRE without a known carbapenemase were meropenem-vaborbactam susceptible.

Figure 1. Species causing infections in hematology/oncology or transplant patients

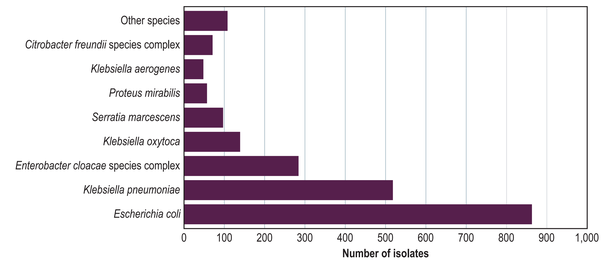


Figure 2. Types of infections in hematology/oncology/transplant patients

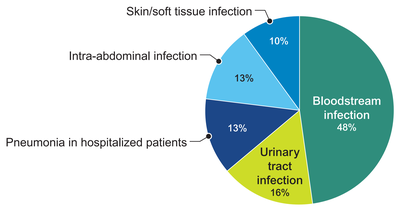
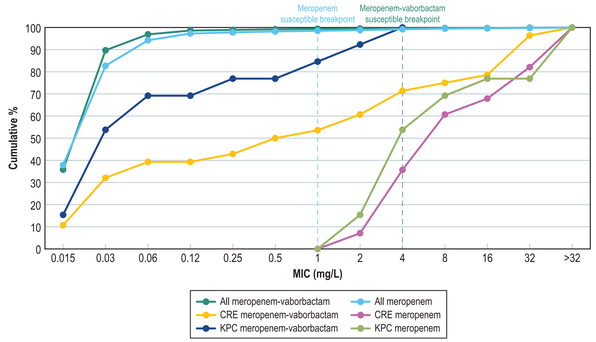


Table 1. Activity of meropenem-vaborbactam and comparator antimicrobial agents tested against Enterobacterales isolates and CRE subset collected from patients in the hematology/oncology or transplant units in US hospitals

Organism group/ Antimicrobial agent	mg/L MIC$_{50}$	mg/L MIC$_{90}$	MIC range	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R
All isolates (*n*=2,185)						
Meropenem-vaborbactam	0.03	0.06	≤0.015 to >32	99.6	<0.1	0.3
Meropenem	0.03	0.06	≤0.015 to >32	98.5	0.3	1.2
Ceftazidime	0.25	>32	0.03 to >32	80.5	1.9	17.5
Levofloxacin	≤0.12	>4	≤0.12 to >4	73.3	2.7	24.0
Piperacillin-tazobactam	2	32	≤0.5 to >64	83.4	4.8[b]	11.8
CRE[c] (*n*=28)						
Meropenem-vaborbactam	0.5	32	≤0.015 to >32	71.4	3.6	25.0
Meropenem	8	>32	2 to >32	0.0	7.1	92.9
Ceftazidime	>32	>32	8 to >32	0.0	3.6	96.4
Levofloxacin	>4	>4	0.06 to >4	25.0	3.6	71.4
Piperacillin-tazobactam	>64	>64	32 to >64	0.0	0.0	100.0
KPC (*n*=13)						
Meropenem-vaborbactam	0.03	2	≤0.015 to 4	100.0	0.0	0.0
Meropenem	4	>32	2 to >32	0.0	15.4	84.6
Ceftazidime	>32	>32	8 to >32	0.0	7.7	92.3
Levofloxacin	>4	>4	0.06 to >4	23.1	0.0	76.9
Piperacillin-tazobactam	>64	>64	64 to >64	0.0	0.0	100.0

[a] Criteria as published by CLSI M100 (2022).
[b] Susceptible-dose dependent is shown as I.
[c] CRE, carbapenem-resistant Enterobacterales. Organisms included: *Citrobacter freundii* species complex (1), *Enterobacter cloacae* (1), *E. cloacae* species complex (7), *Escherichia coli* (2), *Klebsiella oxytoca* (1), *K. pneumoniae* (14), *Serratia marcescens* (2).

Figure 3. Cumulative percent MIC distributions of meropenem-vaborbactam and meropenem for all Enterobacterales (*n*=2,185), CRE (*n*=28) and KPC (*n*=13). Susceptible breakpoints indicated in green (meropenem-vaborbactam) and blue (meropenem).



Conclusions

- Meropenem-vaborbactam was very active, with 99.6% susceptibility when tested against Enterobacterales isolates causing infections in hematology/oncology or transplant patients.
- 1.3% of these isolates were CRE.
  - KPC was the most common carbapenemase.
  - 100% of KPC–producing isolates and all 3 of the carbapenemase-negative CRE isolates were meropenem-vaborbactam susceptible.
- These *in vitro* data suggest that meropenem-vaborbactam would be an effective treatment option for hematology/oncology or transplant patients with infections caused by Gram-negative pathogens, including KPC–producing CRE, and CRE not producing metallo-beta-lactamases or OXA-carbapenemases.

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