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Frequency of Carbapenemases in United States Hospitals (2016–2020) and Activity of Meropenem-Vaborbactam and Comparator Agents Tested Against These Isolates

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Introduction

- The global dissemination of carbapenemase-producing Enterobacterales (CPE) poses a threat to human health and has been highlighted as an urgent threat pathogen by the Centers for Disease Control and Prevention (CDC).
- In a recent study, only 148 of 256 (57.8%) patients with CRE infections received empiric therapy containing at least one antimicrobial agent active against these organisms (Alexander et al.).
  - Only 83 subjects (32.4%) received empiric coverage with agents that had *in vitro* activity against the index CRE isolate.
  - Across all cases, 69 different regimens were used that were comprised of single or combination therapy with up to 4 agents.
- We used SENTRY Antimicrobial Surveillance Program data to evaluate the prevalence of carbapenemase enzymes among carbapenem-resistant Enterobacterales (CRE) isolates collected in US hospitals.
  - Additionally, we analyzed the activity of meropenem-vaborbactam and comparators against these isolates.

Materials and Methods

- A total of 22,725 Enterobacterales isolates were consecutively collected in 34 US hospitals located in 9 Census Divisions from 2016 to 2020.
  - Only 1 isolate per patient episode was included.
- Isolates were susceptibility tested against meropenem-vaborbactam, ceftazidime-avibactam, and other comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) and M100 (2022) documents.
  - Vaborbactam was tested at a fixed concentration of 8 mg/L.
  - Avibactam was tested at a fixed concentration of 4 mg/L.
- Quality control (QC) was performed according to the CLSI M100 (2022) criteria.
  - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all agents were those criteria found in the CLSI M100 (2022) or the US Food and Drug Administration (FDA) website.
- CRE isolates resistant to imipenem or meropenem were submitted to whole genome sequencing and data analysis for the detection of β-lactamases.
  - Only meropenem was used for indole-positive Proteaee due to intrinsically elevated imipenem MIC values.
- Whole genome sequencing was performed on a MiSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage.
  - Sequences were *de novo* assembled.
  - Analysis of β-lactam resistance mechanisms was performed *in silico*.
  - Genes encoding resistance were searched using a curated library with a criterion of >94% sequencing identity.
  - A 40% minimum length coverage was applied.

Results

- Among 22,725 Enterobacterales isolates tested, 1.0% (221) were CRE.
  - Most CRE isolates were collected from pneumonia in hospitalized patients (105 isolates), but also from urinary tract (41), bloodstream (34), skin/soft tissue (25), and intra-abdominal (16) infections.
  - CRE prevalence decreased in 2020 (0.8%) compared to 2016 (1.2%; Figure 1).
- Carbapenemases were detected among 193 (87.3%) of the CRE.
- Cumulatively, serine-carbapenemases—including KPC, SME (Class A), and OXA-48-like enzymes (Class D)—were observed among 181 (81.9%) of the CRE.
  - Most CRE isolates carried bla_{KPC} variants (174; 78.7%).
  - bla_{KPC} variants included 95 bla_{KPC-3}, 75 bla_{KPC-2}, and 1 each of bla_{KPC-4}, bla_{KPC-6}, bla_{KPC-58}, and the Ω-loop variant bla_{KPC-59}.
  - bla_{SME} was detected among 7 (3.6% of the CRE) *Serratia marcescens*.
  - Two isolates carried $bla_{OXA-232}$ and 1 harbored bla_{OXA-48} (1.8%).
- MBLs were detected among 9 (4.0%) of the CRE.
  - 5 isolates harbored bla_{NDM-1} (including 1 co-harboring $bla_{OXA-232}$), 2 bla_{NDM-5}, and 2 bla_{VIM-1}.
- No carbapenemase genes were carried by 28 (12.7%) of the CRE.
- CRE and carbapenemase-producing isolates prevalence varied among US Census Divisions (Figure 2).
- Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/2 mg/L) inhibited 93.2% of the CRE isolates.
  - Meropenem-vaborbactam was the most potent agent tested against all isolates (Figure 3).
- Comparator β-lactam agents had limited activity against CRE isolates (0.5%–9.5% susceptible).
  - Amikacin and tigecycline were the most active comparators, inhibiting 79.2% and 95.5% of the CREs, respectively.
  - Ceftazidime-avibactam ($MIC_{50/90}$, 1/4 mg/L) was tested against 168 (2017–2020) CRE isolates, inhibiting 93.5% (Figure 4).
- Against 181 isolates producing class A serine-carbapenemases, meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.5 mg/L) inhibited 98.9% of all isolates (Figure 3).
  - Ceftazidime-avibactam inhibited 99.2% of 129 isolates collected in 2017–2020.
- The activity of all agents was limited against MBL producers (Figure 3).

Figure 1. Occurrence of CRE isolates (221/22,725; 1.0%) in US hospitals from 2016 to 2020

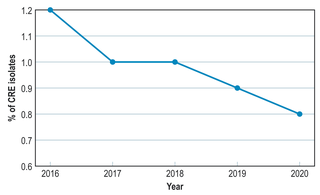


Figure 2. CRE isolates prevalence by US Census Divisions

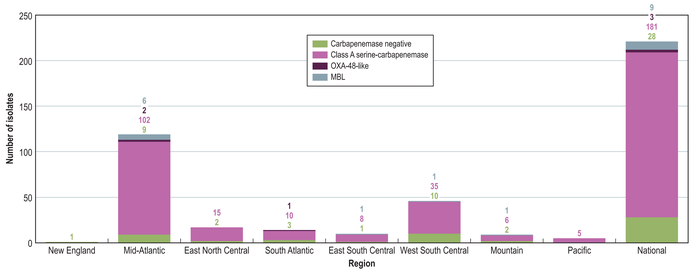
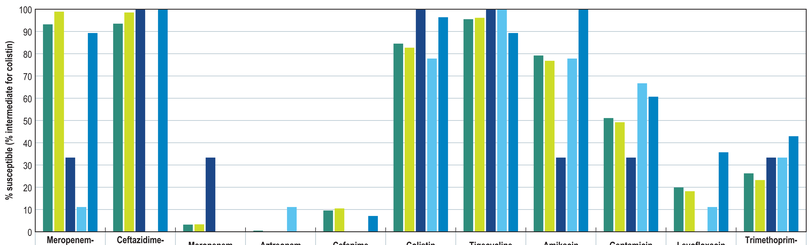
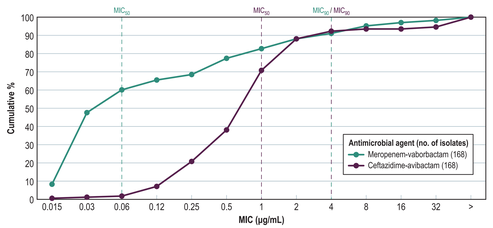


Figure 3. Activity of antimicrobial agents against CRE isolates



	Meropenem-vaborbactam	Ceftazidime-avibactam	Meropenem	Aztreonam	Cefepime	Colistin	Tigecycline	Amikacin	Gentamicin	Levofloxacin	Trimethoprim-sulfamethoxazole
CRE (n=221)	93.2	93.5	3.2	0.5	9.5	84.5	95.5	79.2	51.1	19.9	26.2
Class A serine-carbapenemase (n=181)	98.9	98.5	3.3	0.0	10.5	82.7	96.1	76.8	49.2	18.2	23.2
OXA-48-like producers (n=3)	33.3	100.0	33.3	0.0	0.0	100.0	100.0	33.3	33.3	0.0	33.3
MBL producers (n=9)	11.1	0.0	0.0	11.1	0.0	77.8	100.0	77.8	66.7	11.1	33.3
Carbapenemase negative (n=28)	89.3	100.0	0.0	0.0	7.1	96.4	89.3	100.0	60.7	35.7	42.9

Figure 4. Activity of meropenem-vaborbactam compared to ceftazidime-avibactam tested against 168 CRE isolates from 2017–2020



Conclusions

- The occurrence of carbapenemases declined from 1.2% to 0.8% during the study period.
- KPC-producing isolates are dominant among CRE from US hospitals.
- Isolates carrying MBLs and/or OXA-48-like enzymes were observed in small numbers (<0.1% overall).
- Meropenem-vaborbactam and ceftazidime-avibactam were very active against isolates producing class A serine-carbapenemases.

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