Activity of Aztreonam-avibactam and Carbapenem-resistant Enterobacterales Isolates Collected in a Six-year Period (2017–2022)

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CONCLUSIONS

KPC enzymes are still the most common carbapenemase among Enterobacterales isolates collected in US hospitals but isolates harboring MBLs and OXA-48–like enzymes were also detected in this collection.

New BL/BLIs and FDC displayed good activity against a large collection of CRE isolates.

ATM-AVI followed by FDC was the most active agent against isolates producing MBLs.

New BL/BLIs and FDC are recommended for the treatment of serious infections caused by CRE isolates, as these agents display good activity. However, the activity of these agents varies depending on the enzymes present.

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References

1. CLSI. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Wayne, PA. Clinical and Laboratory Standards Institute, 2018.
2. CLSI. M100Ed33. Performance standards for antimicrobial susceptibility testing. Wayne, PA, Clinical and Laboratory Standards Institute, 2023.
3. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations. Clin Infect Dis. 2019 Jan 18;68(3):519-524. doi: 10.1093/cid/ciy576
4. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M, Lagacé-Wiens PRS, Walkty A, Denisuik A, Golden A, Gin AS, Hoban DJ, Lynch JP 3rd, Karlowsky JA. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-β-Lactamase Inhibitor Combinations. Drugs. 2018 Jan;78(1):65-98. doi: 10.1007/s40265-017-0851-9. Erratum in: Drugs. 2018 May 10.
5. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2022 Apr 19:ciac268. doi: 10.1093/cid/ciac268. Epub ahead of print.

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INTRODUCTION

- Treatment options for carbapenem-resistant Enterobacterales (CRE) were limited until new β-lactam/β-lactamase inhibitor combinations (BL/BLIs), such as ceftazidime-avibactam (CAZ-AVI), meropenem-vaborbactam (MEV), and imipenem-relebactam (IR) were introduced in clinical practice.
- Despite being active against isolates producing KPC enzymes and other class A carbapenemases, these agents displayed variations in their activity against isolates producing class D oxacillinases and limited activity against class B metallo-β-lactamases (MBLs).
- Aztreonam-avibactam (ATM-AVI) and cefiderocol (FDC) display activity against CRE isolates producing class A enzymes, some class D, and also class B MBLs.
- In this study, we tested the activity of ATM-AVI, CAZ-AVI, MEV, IR, and FDC against >500 CRE isolates collected in US hospitals during a 6-year period (2017–2022).

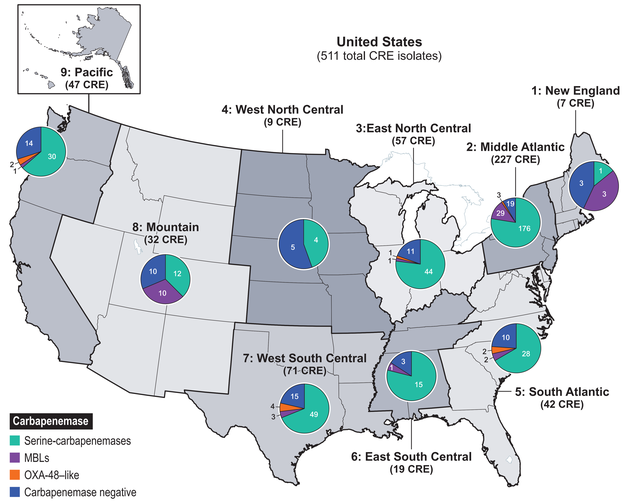
MATERIALS AND METHODS

- A total of 54,576 Enterobacterales isolates were collected during 2017–2022 in 62 US hospitals that participated in the surveillance for all 6 years.
  - Isolates were identified as the cause of infection.
  - Isolates were limited to 1 per patient.
- Isolates were susceptibility tested using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) and M100 (2022) documents.
  - Avibactam and relebactam were tested at a fixed concentration of 4 mg/L.
  - Vaborbactam was tested at a fixed concentration of 8 mg/L.
- Cefiderocol powder was acquired from MedChem Express (Monmouth Junction, NJ) and tested using iron-depleted media.
- Quality control (QC) was performed according to the CLSI M100 (2022) criteria.
  - All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator 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.
- WGS was performed on a MiSeq (Illumina, San Diego, CA) instrument targeting a 30X coverage.
  - Sequences were *de novo* assembled.
  - Analysis of β-lactam resistance mechanisms was performed *in silico.*
  - Genes encoding resistances were searched using a curated library. A criteria of >94% sequencing identity and 40% minimum length coverage was applied.

Table 1. Occurrence of carbapenemases detected among 511 CRE isolates collected during 2017–2022 in US hospitals

Carbapenemases	No. of isolates	% of CRE
Serine-carbapenemases	359	70.3
KPC-10, KPC-6	1	0.2
KPC-18	1	0.2
KPC-2	144	28.2
KPC-58	1	0.2
KPC-59	1	0.2
KPC-2–like (E286D)	1	0.2
KPC-3	193	37.8
KPC-4	3	0.6
KPC-6	2	0.4
NMC-A	2	0.4
SME-2	5	1.0
SME-4	5	1.0
MBLs	50	9.8
IMP-27	1	0.2
IMP-4	2	0.4
IMP-4, KPC-3	1	0.2
NDM-1, KPC-3	1	0.2
NDM-5, KPC-3	1	0.2
NDM-1	24	4.7
NDM-1, OXA-181	1	0.2
NDM-1, OXA-232	1	0.2
NDM-5	14	2.7
NDM-5, OXA-181	2	0.4
VIM-1	2	0.4
OXA-48–like	12	2.3
OXA-181	2	0.4
OXA-232	3	0.6
OXA-48	7	1.4
Carbapenemase negative	90	17.6
Total	511	

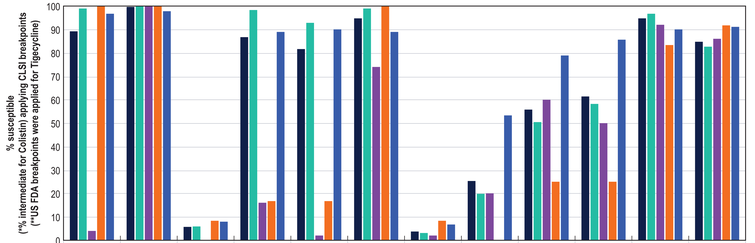
Figure 1. Distribution of the carbapenemases in the US Census Divisions



RESULTS

- Among 511 (0.9% of the isolates) CRE isolates, 347 (67.9% of the CRE) were KPC producers that did not carry MBLs (Table 1).
  - KPC producers were predominantly KPC-3 and KPC-2 (193 and 144 isolates, respectively), but other 5 variants were detected.
  - One isolate carried the genes encoding KPC-6 and KPC-10.
- Another 12 isolates carried genes encoding NMC-A and SME (Table 1) that are also class A serine-carbapenemases. These isolates were grouped with KPC for further analysis.
- OXA-48–like enzymes alone were noted among 12 isolates (Table 1).
- Genes encoding MBLs were detected among 50 isolates and 44 of these isolates carried genes encoding NDM-1 or NDM-5 alone or with other carbapenemases (Table 1).
  - Another 6 isolates carried IMP or VIM-encoding genes.
- Most CRE isolates were observed in the Middle Atlantic Census Division (227 isolates) followed by West South Central (71 isolates), East North Central (57), Pacific (47), and South Atlantic (42; Figure 1).
- ATM-AVI inhibited 99.6% of the CRE isolates when applying a PK/PD breakpoint of 8 mg/L (Figure 2).
  - FDC, CAZ-AVI, MEV, and IR inhibited 94.7%, 89.2%, 86.7%, and 81.6% of the CRE isolates, respectively.
  - Ceftolozane-tazobactam had limited activity against CREs.
- Against class A serine-carbapenemase–producing isolates (KPC, SME, NMC-A) without MBLs, ATM-AVI, CAZ-AVI, FDC, and MEV demonstrated activity >98.3% (Figure 2).
  - IR inhibited 92.8% of these isolates.
- Except for ATM-AVI and FDC, other BL/BLIs had limited activity against MBLs, ranging from 2.0% S for IR to 16% S for MEV against MBL isolates.
  - ATM-AVI inhibited 100.0% of the MBL isolates while FDC inhibited 74.0%.
- ATM-AVI, CAZ-AVI, IR, FDC, and MEV inhibited 97.8%, 96.7%, 90.0%, 88.9%, and 88.9% of the carbapenemase-negative isolates (n=90), respectively.
- MEV and IR had limited activity against 12 OXA-48–like producing isolates (only 16.7% susceptible), but ATM-AVI, CAZ-AVI and FDC were active against all isolates.
- Among comparators, tigecycline was the most active, inhibiting 94.7% of the CRE isolates; 84.7% of these isolates displayed a colistin intermediate MIC value of ≤2 mg/L (Figure 2).

Figure 2. Susceptibility patterns of antimicrobial agents against 511 CRE isolates collected during 2017–2022 in US hospitals



	Ceftazidime-avibactam	Aztreonam-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam	Imipenem-relebactam	Cefiderocol	Meropenem	Levofloxacin	Gentamicin	Amikacin	Tigecycline**	Colistin*
CRE (511)	89.2	99.6	5.7	86.7	81.6	94.7	3.7	25.3	55.8	61.4	94.7	84.7
Serine-carbapenemase (359)	98.9	100.0	5.9	98.3	92.8	98.9	3.1	19.8	50.4	58.2	96.7	82.6
MBL (50)	4.0	100.0	0.0	16.0	2.0	74.0	2.0	20.0	60.0	50.0	92.0	86.0
OXA-48–like (12)	100.0	100.0	8.3	16.7	16.7	100.0	8.3	0.0	25.0	25.0	83.3	91.7
Carbapenemase negative (90)	96.7	97.8	7.9	88.9	90.0	88.9	6.7	53.3	78.9	85.6	90.0	91.1