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Activity of aztreonam-avibactam tested against genetically characterized non-carbapenemase-producing carbapenem-resistant Enterobacterales

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CONCLUSIONS

Carbapenem resistance among non-CPE CRE isolates seems to involve β-lactamase production with reduced access to the bacterial target due to changes in OMP and regulators that might increase drug efflux.

Despite the combinations of resistance mechanisms, aztreonam-avibactam and ceftazidime-avibactam were the most active agents tested, followed by meropenem-vaborbactam, imipenem-relebactam, and cefiderocol.

New β-lactam/β-lactamase inhibitors and cefiderocol are recommended for treatment of serious infections caused by CRE isolates and these agents display good activity against CRE isolates; however, the activity of these agents varies depending on the enzymes present.

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INTRODUCTION

- Carbapenem-resistant Enterobacterales (CRE) isolates are considered a threat to human health.
- Most of the CRE isolates produce carbapenemases, but a portion of them do not carry these enzymes and instead have combinations of resistance mechanisms that elevate the carbapenem MIC values along with those of other β-lactams.
- Aztreonam-avibactam was recently approved by the United States Food and Drug Administration (US FDA) for the treatment of complicated intra-abdominal infections in adults with limited or no alternative treatment options.
 – This combination agent displays activity against CRE isolates producing class A enzymes, some class D and also class B metallo-β-lactamases but limited data is available for its activity against non-carbapenemase-producing (non-CPE) CRE isolates.
- We evaluated the activity of aztreonam-avibactam and comparator agents against 111 non-CPE CRE isolates collected over a 7-year period in US hospitals (2016–2023).

Figure 1. Summary of β-lactam resistance mechanisms among 111 non-CPE CRE isolates

				Amino acid alteration					
Organism	**US State**	**MLST**	**Beta-lactamase**	**PBP3**	**ACRR**	**OMPC**	**OMPF**	**RAMR**	**SOXR**
Citrobacter freundii	TX	402	TEM-1						
	FL	519							
Citrobacter youngae	KY	30							
Enterobacter asburiae	MO	484	OXA-17						
	KY	162-like							
Enterobacter cloacae	WI	50							
Enterobacter hormaechei	WI	108							
	WI	198							
	IL	254							
	WA	550							
	IL	742							
	CO	782							
	WI	108-like							
	NY	120-like							
	NY	636-like							
	MA	93-like							
Enterobacter kobei	MN	54							
	FL	855-like							
Enterobacter ludwigii	CO	853-like							
Enterobacter spp.	LA	483	CTX-M-15, OXA-1, TEM-1						
Escherichia coli	FL	131	CTX-M-15						
	KS	131	CTX-M-15, OXA-1						
	LA	131	CMY-2, TEM-1						
	LA	131	CTX-M-15						
	MI	131	CTX-M-15-like, TEM-1						
	TX	131	CTX-M-15, TEM-1						
	VA	131	CMY-2						
	VA	131	CTX-M-15, OXA-1						
	CA	405	CTX-M-15, OXA-1						
	IN	405	CTX-M-15, CTX-M-33	YRIK					
	TX	744	TEM-1						
	TX	12468	CTX-M-14						
	MN	617-like	CTX-M-15, OXA-1						
Hafnia paralvei	CO	—							
Klebsiella aerogenes	CO	4							
	NY	4							
	TX	4							
	CA	92							
	CA	93							
	CA	93							
	CA	93							
	CA	93							
	CA	93							
	CO	93							
	CO	93							
	NJ	93							
	TX	93							
	TX	93							
	MA	116							
	MN	128							
	NY	135							
	CO	151							
	KY	176							
	TX	240							
	TX	246							
	IN	385							
	NJ	477							
	CO	484							
	CA	517							
	CA	613							
	MI	441-like							
	NY	73-like							
	NJ	93-like							
	PA	93-like							
	PA	99-like							
Klebsiella michiganensis	TX	107	CTX-M-15, OXA-1, TEM-1						
	CA	194							

				Amino acid alteration					
Organism	**US State**	**MLST**	**Beta-lactamase**	**PBP3**	**ACRR**	**OMPC**	**OMPF**	**RAMR**	**SOXR**
Klebsiella oxytoca	NY	176							
	CA	287							
Klebsiella pneumoniae	FL	11	CTX-M-15, OXA-1, SHV-11						
	NY	15	SHV-1						
	WA	15	CTX-M-15, SHV-28, TEM-1						
	CA	16	CTX-M-15, SHV-1						
	CA	16	CTX-M-15, SHV-1						
	TX	25	CTX-M-71, SHV-11, TEM-1						
	TX	29	CTX-M-15, OXA-1, SHV-187, TEM-1						
	OH	37	CTX-M-15, OXA-1, SHV-11, TEM-1						
	CO	45	CTX-M-15, OXA-1, SHV-1, TEM-1						
	MI	45	SHV-1						
	NY	45	CTX-M-2, OXA-2, SHV-1, TEM-1						
	WA	45	SHV-1						
	KS	147	CTX-M-15, SHV-11						
	LA	147	CTX-M-15, OXA-1, SHV-11						
	NY	147	CTX-M-15, SHV-11, TEM-1						
	NY	152	CTX-M-15, OXA-1, SHV-1, TEM-1						
	PA	258	SHV-12-like						
	AZ	307	CTX-M-33, SHV-205						
	CA	307	CTX-M-15, OXA-1, SHV-28, TEM-1						
	FL	307	CTX-M-15, OXA-1, SHV-28, TEM-1						
	NC	307	CTX-M-15, OXA-1, SHV-28, TEM-1						
	NJ	307	CTX-M-15, OXA-1, SHV-28						
	NY	307	CTX-M-15, OXA-1, SHV-28, TEM-1						
	CA	348	CMY-2, CTX-M-14, SHV-11, TEM-1						
	MN	392	CTX-M-15, SHV-11, TEM-1						
	MA	1229	CTX-M-15, SHV-11						
	CO	1774	CTX-M-15, OXA-2, SHV-11						
	VA	1818	CTX-M-15, OXA-1, SHV-11, TEM-1						
	NY	1835	CTX-M-15, OXA-1, SHV-11, TEM-1						
	NY	2004	CTX-M-15, OXA-1, SHV-168, TEM-1						
	TX	3576	CTX-M-15, OXA-1-like, SHV-1, TEM-1						
	UT	3846	SHV-11						
	TX	4961	CTX-M-220, SHV-52-like, TEM-1						
	OR	5437	SHV-11						
Klebsiella quasipneumoniae	FL	1455	CTX-M-15, OXA-1						
Raoultella ornithinolytica	TX	105	CTX-M-14						
	NY	NT	CARB-2, FOX-5						
Serratia marcescens	OH	365							
	OH	491	CTX-M-15, OXA-1, TEM-1						
	NY	622							
	FL	381-like							
	NJ	386-like							
	FL	NT							

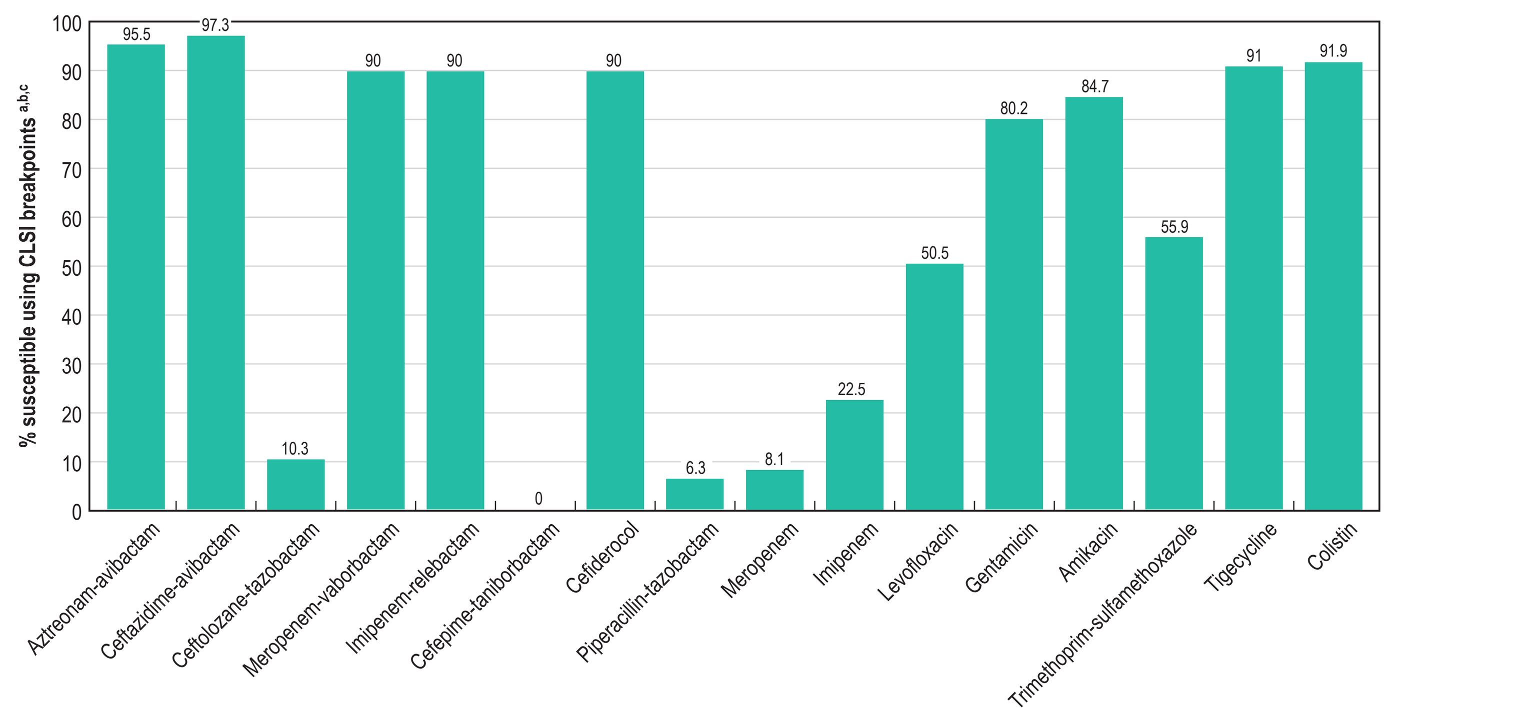
MATERIALS AND METHODS

- A total of 72,265 Enterobacterales isolates were collected during 2016–2023 in 62 US hospitals.
 – Isolates were identified as the cause of infection.
 – Isolates were limited to 1 per patient.
- Isolates were susceptibility tested against aztreonam-avibactam and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2022) and M100 (2025) 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 cation adjusted Mueller-Hinton broth.
- Quality control (QC) was performed according to the CLSI M100 (2025) criteria.
 – All QC MIC results were within acceptable ranges.
- Categorical interpretations for all comparator agents were those criteria found in the CLSI M100 (2025), or the US FDA website.
- Aztreonam-avibactam breakpoints were those approved by the US FDA.
- CRE isolates resistant to imipenem or meropenem were submitted to whole genome sequencing and data analysis for the detection of β-lactam resistance mechanisms.
- WGS was performed on MiSeq or NextSeq (Illumina, San Diego, California, USA) instruments targeting a 30X coverage.
 – Sequences were *de novo* assembled.
 – Analysis of β-lactam resistance mechanisms was performed *in silico.*

RESULTS

- Among 694 CREs collected during 2016–2023, 111 (16.0% of the CRE, 0.2% overall) were non-CPE.
- Non-CPE CRE isolates belonged to 6 genera, but *K. pneumoniae* (n=34) and *K. aerogenes* (n=30) were the dominant species (Figure 1).
- Non-CPE CRE isolates were observed in 49 hospitals distributed in all US Census divisions.
 – Notably, 10 isolates were collected in one hospital in Colorado.
- Multilocus sequence typing (MLST) analysis showed that some *E. coli* and *K. pneumoniae* non-CPE CRE isolates belonged to successful clones such as ST131 and ST307, but genetic diversity was noted for other species (Figure 1).
- A total of 47 isolates carried acquired β-lactamase genes, including all 13 *E. coli* and 28/34 *K. pneumoniae* (Figure 1).
 – 29/34 *K. pneumoniae* and 10/13 *E. coli* isolates carried CTX-M-encoding genes with most being CTX-M-15.
 – Acquired enzymes were not common among *K. aerogenes*, *Enterobacter*, *Citrobacter*, and *Serratia* species.
- Early terminations/lost start or stop codons in outer membrane protein (OMP) genes were noted in 64 isolates for a single gene (Figure 1).
 – 36 isolates displayed these disruptions for both *ompC/ompK36* and *ompF/ompK35*, including 10 *E. coli* and 10 *K. pneumoniae.*
- Disruptions in the genes encoding the efflux regulators RamR were noted among 6/30 *K. aerogenes*, 1/3 *C. freundii*, and 5/17 *E. cloacae* species complex.
- Aztreonam-avibactam and ceftazidime-avibactam were active against 95.5% and 97.3% of the isolates and had the highest susceptibility rates among the agents tested (Figure 2).
- Meropenem-vaborbactam, imipenem-relebactam, and cefiderocol inhibited 90.0%, 90.0%, and 90.1% of the non-CPE CRE isolates.
 – Other agents displaying activity against >80% of the isolates were gentamicin (80.2% susceptible), amikacin (84.7%), and tigecycline (91.0%).
 – 91.9% of the isolates were intermediate to colistin.
- The two isolates were resistant to aztreonam-avibactam: one *E. coli* producing CTX-M-15 and CTX-M-33 with disruptions in the genes encoding AcrA, OmpC, OmpF, and a PBP3 alteration YRIK and one *K. aerogenes* with OMP and RamR disruptions.
 – These isolates had cefiderocol MIC values >64 mg/L but were susceptible to meropenem-vaborbactam and imipenem-relebactam.

Figure 2. Susceptibility patterns of antimicrobial agents tested against 111 non-CPE CRE isolates collected during 2016–2023 in US hospitals


% susceptible using CLSI breakpoints a,b,c
0
10
20
30
40
50
60
70
80
90
100
95.5
97.3
10.3
90
90
0
90
6.3
8.1
22.5
50.5
80.2
84.7
55.9
91
91.9
Aztreonam-avibactam
Ceftazidime-avibactam
Ceftolozane-tazobactam
Meropenem-vaborbactam
Imipenem-relebactam
Cefepime-taniborbactam
Cefiderocol
Piperacillin-tazobactam
Meropenem
Imipenem
Levofloxacin
Gentamicin
Amikacin
Trimethoprim-sulfamethoxazole
Tigecycline
Colistin

[a] Aztreonam-avibactam and tigecycline using FDA breakpoints
[b] Cefepime alone breakpoints were applied for cefepime-taniborbactam for comparison purposes only
[c] Percentage intermediate for colistin