RES-342

In Vitro Activity of Aztreonam-avibactam against Carbapenemase-producing Enterobacterales Isolates Collected in China as a part of the ATLAS Global Surveillance Study, 2020-2022

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Introduction

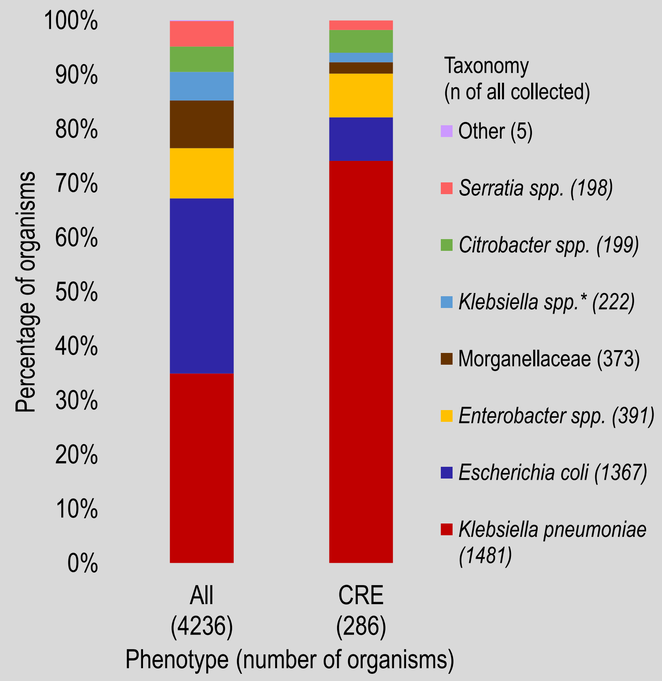
Aztreonam-avibactam (ATM-AVI) is an approved therapeutic in the United States, Europe, and China. Aztreonam is stable to hydrolysis by metallo-β-lactamases (MBLs), while avibactam inhibits class A, C, and some Class D β-lactamases, often co-carried by MBL-positive isolates, that inactivate aztreonam. This study examines the *in vitro* activity of aztreonam-avibactam against carbapenem-resistant Enterobacterales (CRE) isolates collected in China, 2020-2022, as a part of the ATLAS program [1].

Methods

- 4,236 Enterobacterales isolates were collected from 20 sites in mainland China and tested for susceptibility using the broth microdilution method according to CLSI guidelines [2] and analyzed using CLSI 2025 breakpoints [3]. EUCAST 2025 breakpoints were used for ATM-AVI [4], and FDA 2025 breakpoints were used for tigecycline [5].
- Meropenem-nonsusceptible isolates (defined as having MIC values above the CLSI breakpoint of 1 µg/mL) were characterized by short-read whole genome sequencing as previously described [6].

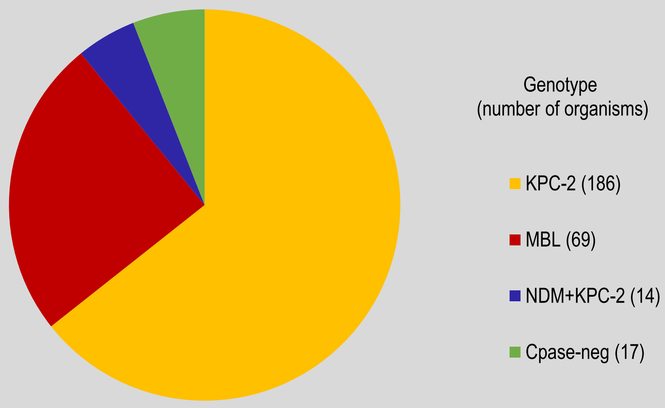
Results

Figure 1: Isolates in this study by taxonomy



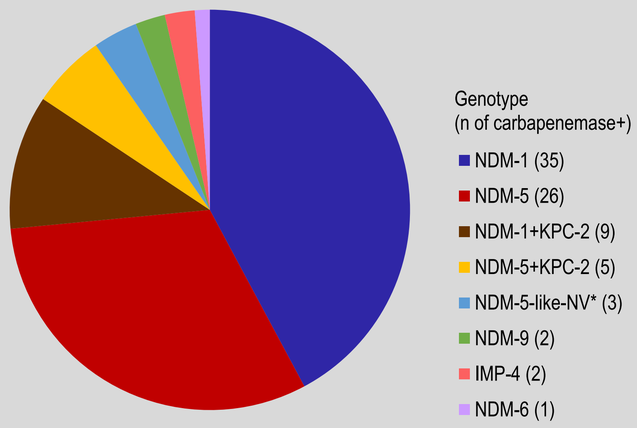
* Species other than *Klebsiella pneumoniae*

Figure 2A: Carbapenemases identified in 286 CRE organisms in this study



Abbreviations: MBL, metallo-β-lactamase; Cpase neg, carbapenemase-negative

Figure 2B: Variants of carbapenemase(s) detected in organisms carrying metallo-β-lactamases



*NV, Novel Variant (all three of which are the same variant).

Table 1: *In vitro* activity of aztreonam-avibactam against carbapenem-resistant Enterobacterales in this study, by carbapenemase variant

Carbapenemase genotype	n	Aztreonam-avibactam MIC (µg/mL) and cumulative percent inhibited at concentration													
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Characterized CRE	286	3	4	9	39	40	79	66	**31**	12	1			1	1*
		1	2.4	5.6	19.2	33.2	60.8	83.9	**94.8**	99.0	99.3			99.7	100
KPC-2	186			1	9	25	65	52	**26**	6	1			1	
				0.5	5.4	18.8	53.8	81.7	**95.7**	98.9	99.5			100	
MBL±others	83	3	4	7	28	10	8	14	**3**	6					
		3.6	8.4	16.9	50.6	62.7	72.3	89.2	**92.8**	100					
NDM-1	35	2	2	5	15	5	**5**			1					
		5.7	11.4	25.7	68.6	82.9	**97.1**			100					
NDM-5	26		2	1	8	4	1	3	3	**4**					
			7.7	11.5	42.3	57.7	61.5	73.1	84.6	**100**					
NDM-1+KPC-2	9					1		8							
						11.1		100							
NDM-5+KPC-2	5						2	3							
							40	100							
NDM-5-like-NV	3				3										
					100										
NDM-9	2			1	1										
				50	100										
NDM-6	1									1					
										100					
IMP-4	2	1			1										
		50			100										

Abbreviations: CRE, carbapenem-resistant Enterobacterales; MIC, minimum inhibitory concentration; MBL, metallo-β-lactamase; NDM-5-like-NV, NDM-5-like-novel variant (all three of which were the same variant)
MIC_{90} values are bold for categories with ≥10 isolates.
Dotted line indicates EUCAST breakpoint of 4 µg/mL aztreonam with 4 µg/mL avibactam.
Characterized CRE include: *Klebsiella pneumonia* (n=212), *Enterobacter* spp. (n=23), *Escherichia coli* (n=23), *Citrobacter* spp. (n=12), *Morganellaceae* (n=6), other *Klebsiella* spp. (n=5), and *Serratia* spp. (n=5) (Figure 1, series 2).
*No β-lactamases were identified in one isolate of *P. mirabilis* testing with ATM-AVI MIC >64 µg/mL.

Table 2: Activity of aztreonam-avibactam and comparators against 286 carbapenem-resistant organisms

		Agent [MIC_{90}(µg/mL), percentage susceptible*]																			
		ATM-AVI		ATM		FEP		CAZ-AVI		MEM		LVX		CST		TZP		AMK		TGC	
Carbapenemase genotype	n	MIC_{90}	%S*	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%I*	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S*
Characterized CRE	286	2	**99.0**	>64	10.5	>32	0.3	>64	68.5	>16	0.0	>8	7.0	1	**93.4**	>64	1.7	>64	41.6	4	77.3
KPC-2	186	2	**98.9**	>64	0.0	>32	0.0	8	**98.4**	>16	0.0	>8	3.8	2	**91.9**	>64	0.0	>64	28.5	4	71.0
MBL±others**	83	2	**100**	>64	33.7	>32	0.0	>64	0.0	>16	0.0	>8	14.5	0.5	**97.6**	>64	1.2	>64	68.7	2	**92.8**
NDM-1	35	0.5	**100**	>64	42.9	>32	0.0	>64	0.0	>16	0.0	>8	28.6	0.5	**97.1**	>64	0.0	16	80.0	2	**94.3**
NDM-5	26	4	**100**	>64	38.5	>32	0.0	>64	0.0	>16	0.0	>8	7.7	0.5	**100**	>64	0.0	>64	84.6	4	88.5

Abbreviations: CRE, carbapenem-resistant Enterobacterales; ATM-AVI, aztreonam-avibactam; ATM, aztreonam; FEP, cefepime; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; LVX, levofloxacin; CST, colistin; TZP, piperacillin-tazobactam; AMK, amikacin; TGC, tigecycline; %S, percentage susceptible; %I, percentage intermediate.
Values in bold: >90% susceptible.
* Percentage susceptible using CLSI 2025 breakpoints except for ATM-AVI (EUCAST 2025 breakpoints) and tigecycline (FDA 2025 breakpoints).
** Categories with less than 10 isolates were excluded from further description.

Table 3: *In vitro* activity of aztreonam-avibactam against carbapenem-resistant Enterobacterales carrying NDM-5, by organism type and PBP3 mutations

Organism; PBP3 genotype	N	Aztreonam-avibactam MIC (µg/mL)							
		0.03	0.06	0.12	0.25	0.5	1	2	4
E. coli; PBP3 insertion	8						3	2	3
E. coli; No PBP3 insertion	3	2				1			
Non-*E. coli*; No PBP3 insertion	15		1	8	4			1	1

Abbreviations: MIC, minimum inhibitory concentration; CRE, carbapenem-resistant Enterobacterales; PBP3 insertion, penicillin binding protein 3 insertion at amino acid 333 of YRIK (4) or YRIN (4).

Results Summary

- 351 of the 4,236 isolates in this study were CRE, of which 286 were available for molecular characterization. Although *Klebsiella pneumoniae* and *Escherichia coli* represented 35% and 32% of the 4,236 isolates in this study, *K. pneumoniae* represented 74% of the CRE isolates examined molecularly, while *E. coli* represented 8% (Figure 1).
- Of the 286 CRE that were characterized, 65% carried the carbapenemase KPC-2, 24% carried an MBL, or 5% carried a combination of NDM-1 or NDM-5 and KPC-2 (Figure 2A).
- Among the CRE that carried MBLs, the most common were NDM-1 (53%) and NDM-5 (37%). Other variants of NDM and IMP-4 accounted for the remaining 10% (Figure 2B).
- Of characterized CRE, 99.0% were aztreonam-avibactam-susceptible (MIC_{90} of 2 µg/mL) (Table 1). This was comprised of KPC-2-producing isolates and isolates that carried an MBL with or without other carbapenemases (98.9% and 100% susceptible, respectively, MIC_{90} of 2 µg/mL for both). The modal MIC value was 0.5 µg/mL for all characterized CRE isolates and for those carrying KPC-2, and the modal MIC value was 0.12 µg/mL for those carrying MBL with or without other carbapenemases. All isolates carrying NDM-1 or NDM-5 were susceptible to aztreonam-avibactam, with MIC_{90}s of 0.5 and 4 µg/mL, respectively.
- The *in vitro* activity of aztreonam-avibactam was as high or higher than those of all comparator agents (Table 2). The percent of isolates intermediate to colistin ranged from 0-7.0 percentage points lower in all CRE categories compared to those of aztreonam-avibactam. The percentages of isolates susceptible to tigecycline were ≥7.2 points lower compared to aztreonam-avibactam in all categories.
- While the MIC_{90} of aztreonam-avibactam was higher against NDM-5-positive isolates (4 µg/mL) than NDM-1-positive isolates (0.5 µg/mL), this can be attributed to 8 isolates of *E. coli* that carry insertions of YRIK (4) and YRIN (4) at position 333 in PBP3 and exhibited MIC values ranging from 1-4 µg/mL (Table 3).

Conclusions

- Carbapenem-resistant Enterobacterales continue to be a threat to public health. In this study, KPC-2, NDM-1, and NDM-5 were the dominant carbapenemases among clinical Enterobacterales in China. Aztreonam-avibactam demonstrated potent *in vitro* activity against these isolates, including *E. coli* isolates co-carrying PBP3 mutations which have been associated with higher MIC values for the combination [7].
- Aztreonam-avibactam presents a promising therapeutic option to treat infections caused by CRE.

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Disclosures

This study was sponsored by Pfizer. GS an KP are employees of Pfizer. ME, JD, and DS are employees of IHMA, which received fees from Pfizer for the conduct of the study and poster preparation.

Presented at APCCMI 2025 on November 2 - 4, 2025 in Bangkok, Thailand