IDWeek 2022 | Poster #P1688

Aztreonam-Avibactam Activity against a Large Collection of Carbapenem-Resistant Enterobacterales (CRE) Collected in Hospitals from Europe, Asia, and Latin America (2019–2021)

Helio S. Sader, Cecilia G. Carvalhaes, John H. Kimbrough, Valerie Kantro, Mariana Castanheira, Rodrigo E. Mendes
JMI Laboratories, North Liberty, IA, USA

Introduction

- Aztreonam-avibactam is under development to treat infections caused by Gram-negative bacteria.
- Some β-lactamase inhibitor combinations have shown potent *in vitro* activity and clinical efficacy against carbapenem-resistant Enterobacterales (CRE) that produce serine carbapenemases, but current clinically available combinations are not active against metallo-β-lactamase (MBL)–producing Enterobacterales.
- Aztreonam is stable to hydrolysis by MBLs, but it is hydrolyzed by most clinically important serine β-lactamases.
- Avibactam is a non-β-lactam β-lactamase inhibitor that inhibits the activities of most clinically relevant serine β-lactamases, such as ESBLs, AmpC enzymes, and KPC producers.
- We evaluated the *in vitro* activities of aztreonam-avibactam and comparators against a global (ex-US) collection of CRE, including ceftazidime-avibactam–resistant isolates.

Methods

- A total of 24,924 Enterobacterales isolates were consecutively collected (1/patient) from 69 medical centers in 36 countries in 2019–2021.
- Isolates were susceptibility tested by CLSI broth microdilution; CRE isolates (n = 1,098; 4.4%) were further evaluated.
- CRE isolates were from Western Europe (W-EU; n = 227), Eastern Europe (E-EU; n = 454), Latin America (LATAM; n = 240) and the Asia-Pacific region (APAC; n = 177).
- An aztreonam-avibactam PK/PD breakpoint of ≤8 mg/L was applied for comparison.
- All CRE isolates were screened for carbapenemase genes by whole genome sequencing (WGS).
- Susceptibility results were stratified by geography and carbapenemase gene.

Table 1. Activity of aztreonam-avibactam and comparator antimicrobial agents tested against 1,098 CRE isolates collected worldwide (ex-US) in 2019–2021

Antimicrobial agent	MIC in mg/L		CLSI and US FDA[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R
Aztreonam-avibactam[b]	0.25	0.5	[99.6][b]		
Ceftazidime-avibactam	2	>32	68.2		31.8
Meropenem-vaborbactam	2	>32	60.5	3.8	35.7
Ceftolozane-tazobactam	>16	>16	2.6	1.5	95.9
Aztreonam	>16	>16	7.9	0.5	91.5
Ciprofloxacin	>4	>4	7.7	2.0	90.3
Levofloxacin	16	>32	10.4	6.7	82.9
Gentamicin	16	>16	44.1	3.7	52.1
Amikacin	8	>32	64.0	9.8	26.1
Minocycline	4	>32	57.8	16.0	26.2
Tigecycline	0.5	2	93.4	5.5	1.1
TMP-SMX[c]	>4	>4	16.5		83.5
Colistin	0.25	>8		73.3	26.7

[a] Criteria as published by CLSI (M100, 2022) and/or US FDA.
[b] The value in brackets indicates the percentage of isolates inhibited at ≤8 mg/L of aztreonam-avibactam.
[c] Trimethoprim-sulfamethoxazole.

Results

- Aztreonam-avibactam inhibited 99.6% of CREs at ≤8 mg/L ($MIC_{50/90}$, 0.25/0.5 mg/L), including 98.9% (345/349) of ceftazidime-avibactam–resistant isolates (Table 1 and Figure 1).
- Susceptibility rates for aztreonam-avibactam, ceftazidime-avibactam, and meropenem-vaborbactam stratified by geographic region are shown in Figure 2.
- Aztreonam-avibactam activity was consistent across geographic regions (98.9%–100.0% inhibited at ≤8 mg/L), but susceptibility to its comparators varied markedly (Figure 2).
- The most active comparator was tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 93.4% susceptible [S] per US FDA criteria; Table 1).
- Aztreonam-avibactam retained activity against isolates nonsusceptible (NS) to colistin (99.7% inhibited at ≤8 mg/L) or tigecycline (99.6% inhibited at ≤8 mg/L; Figure 1).
- A carbapenemase gene was identified in 972 isolates (88.5%) submitted to WGS (Table 2).
- The most common carbapenemases overall were KPC (43.1% of CREs), NDM (26.6%), and OXA-48-like (18.7%), but carbapenemase type varied substantially by region (Table 2).
- Fifty-seven isolates (5.2%) carried more than one carbapenemase gene (Table 2) and 97.6% of isolates were inhibited at aztreonam-avibactam MIC of ≤8 mg/L ($MIC_{50/90}$, 0.5/2 mg/L).
- Aztreonam-avibactam inhibited 99.9% of carbapenemase producers at ≤8 mg/L independent of carbapenemase type or geography, whereas currently available β-lactamase inhibitor combinations exhibited limited activity against isolates producing MBL or OXA-48–like enzymes (Figures 2 and 3).
- Characterization results for the isolates that exhibited aztreonam-avibactam MIC results >8 mg/L are displayed in Table 3.

Table 2. Frequency of carbapenemase genes stratified by geographic region

β-Lactamase	No. of isolates (% of CREs for the region)				
	W-EU	E-EU	APAC	LATAM	All regions
KPC type	151 (66.5)	116 (25.6)	38 (21.5)	168 (70.0)	473 (43.1)
KPC-2	20 (8.8)	81 (17.8)	37 (20.9)	158 (**65.8**)	296 (27.0)
KPC-3	131 (**57.7**)	35 (7.7)	—	10 (4.2)	176 (16.0)
KPC-4	—	—	1 (0.6)	—	1 (0.1)
MBL	44 (19.4)	134[a](29.5)	109 (61.6)	60 (25.0)	347 (31.6)
NDM type	26 (11.5)	109[a](24.0)	101 (**57.1**)	56[c](23.3)	292 (26.6)
VIM type	18 (7.9)	25[a](5.5)	3 (1.7)	3 (1.3)	49 (4.5)
IMP type	—	1 (0.2)	5 (2.8)	1 (0.4)	7 (0.6)
OXA-48 type	31 (13.7)	144 (**31.7**)	29 (16.4)	1 (0.4)	205 (18.7)
≥2 Carbapenemases	12 (5.3)	22 (4.8)	21 (11.9)	2 (0.8)	57 (5.2)
Total	**214 (94.3)**	**374 (82.4)**[c]	**155 (87.6)**	**229 (95.4)**	**972 (88.5)**
No carbapenemase	13 (5.7)	80 (17.6)	22 (12.4)	11 (4.6)	126 (11.5)

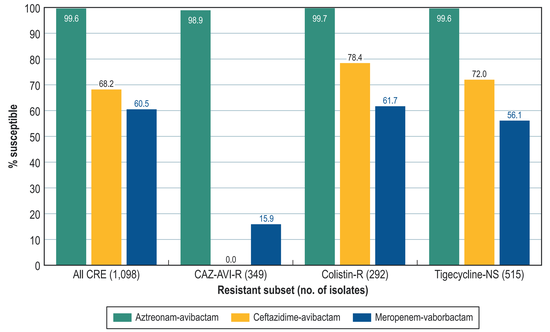
[a] One isolate had an NDM-1 and a VIM-1.
[b] One isolate had an NDM-1 and an NDM-5.
[c] 86.3% (69/80) of carbapenemase-negative CRE were from Poland.

Table 3. Summary of the results on the characterization of isolates exhibiting aztreonam-avibactam MIC results >8 mg/L

Collection number	Organism	Country	MIC[a] (mg/L)				MLST	β-lactamase genes	mRNA expression[b]		Amino acid alterations		
			ATM-AVI	CAZ-AVI	MEM-VAB	ATM			*acrA*	*ampC*	OmpF/OmpK35	OmpC/OmpK36	PBP3
1183154	*E. coli*	Poland	>16	>32	>8	>16	410	CMY-141, TEM-190	2.6	1.1E[7]	Y316X	N147X	R333insYRIK
1183311	*E. cloacae* complex[c]	Poland	>16	>32	>8	>16	89	CTX-M-15, OXA-1, TEM-1, ACT-17	2.0	85.6	D226X	Various mutations	Various mutations
1116221	*K. pneumoniae*	Thailand	>16	16	2	>16	273	DHA-1, LAP-2, SHV-11, TEM-1	8.3	N/A	Various mutations	Y43X	WT
1215485	*K. pneumoniae*	Taiwan	16	>32	0.03	>16	15	KPC-2, VEB-31, SHV-28, OXA-10, TEM-1	2.8	N/A	Various mutations	Various mutations	WT

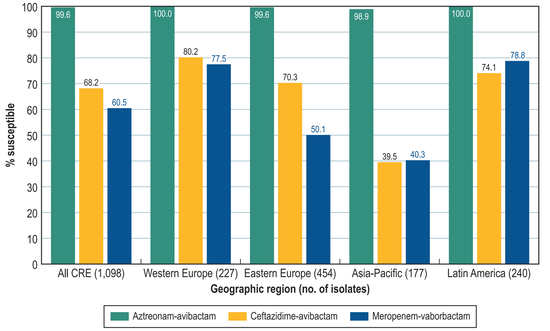
[a] Abbreviations: MIC, minimum inhibitory concentration; ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; MLST, multilocus sequence typing; PBP, penicillin-binding protein; WT, wildtype; N/A, not applicable.
[b] Expression results were reported as fold changes relative to a susceptible control isolate.
[c] Identified as *E. hormaechei* by whole genome sequencing.

Figure 1. Antimicrobial activities of aztreonam-avibactam, ceftazidime-avibactam, and meropenem-vaborbactam against CRE clinical isolates stratified by resistant subsets



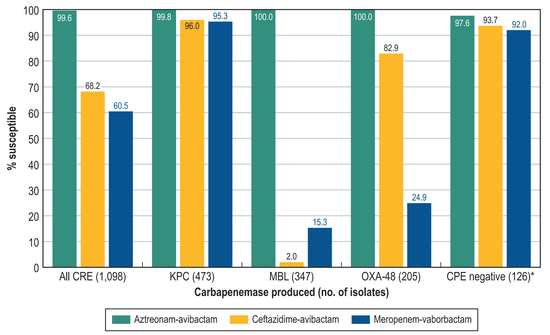
Abbreviations: CRE, carbapenem-resistant Enterobacterales; CAZ-AVI, ceftazidime-avibactam; R, resistant; NS, nonsusceptible.

Figure 2. Antimicrobial activities of aztreonam-avibactam, ceftazidime-avibactam, and meropenem-vaborbactam against CRE clinical isolates stratified by geographic region



Abbreviation: CRE, carbapenem-resistant Enterobacterales

Figure 3. Antimicrobial activities of aztreonam-avibactam, ceftazidime-avibactam, and meropenem-vaborbactam against CRE clinical isolates stratified by type of carbapenemase (CPE) produced



Abbreviations: CRE, carbapenem-resistant Enterobacterales; CPE, carbapenemase.
* A carbapenemase gene was not identified.

Conclusions

- Aztreonam-avibactam demonstrated potent activity against a large collection of contemporary CRE isolates, including MBL producers and ceftazidime-avibactam–resistant isolates.
- Aztreonam-avibactam activity was not adversely affected by clinically relevant carbapenemases.
- The results of this large international investigation support the clinical development of aztreonam-avibactam.

Funding

This study was supported by Pfizer Inc. All authors are employees of JMI Laboratories, which was a paid consultant to Pfizer in connection with the development of this poster.

Acknowledgments

The authors thank all participants of the SENTRY Antimicrobial Surveillance Program for their work in providing isolates. Editorial support was provided by Amy Chen at JMI Laboratories and funded by Pfizer.

References

CLSI. 2022. M100Ed32. Performance standards for antimicrobial susceptibility testing: 32nd informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.

Cornely OA, Cisneros JM, Torre-Cisneros J *et al.* 2020. Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: results from the REJUVENATE study. *J Antimicrob Chemother* 75: 618-27.

Sader HS, Carvalhaes CG, Arends SJR, Castanheira M, Mendes RE. 2021. Aztreonam/avibactam activity against clinical isolates of Enterobacterales collected in Europe, Asia and Latin America in 2019. *J Antimicrob Chemother* 76: 659-66.

Sader HS, Mendes RE, Arends SJR, Carvalhaes CG, Castanheira M. 2022. Antimicrobial activities of aztreonam-avibactam and comparator agents tested against Enterobacterales from European hospitals analysed by geographic region and infection type (2019-2020). *Eur J Clin Microbiol Infect Dis* 41: 477-87.

Contact

Helio S. Sader, MD, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

To obtain a PDF of this poster:
Scan the QR code or visit https://www.jmilabs.com/data/posters/IDWeek2022_AztAviVsGlobalCREs.pdf

SCAN ME

Charges may apply.
No personal information is stored.