Antimicrobial Activity of Aztreonam-avibactam and Comparator Agents against Ceftazidime-avibactam-resistant Enterobacterales (2019-2021)

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Objective

To evaluate aztreonam-avibactam activity against a global (ex-USA) collection of contemporary ceftazidime-avibactam-resistant (CAZ-AVI-R) Enterobacterales

Methods

- 20,750 unique isolates were consecutively collected in 2019-2021.
- Among these isolates, 285 (1.4%) were CAZ-AVI-R and were isolated from 38 medical centres in 24 countries.
- Isolates were tested by reference broth microdilution (CLSI).
- Aztreonam-avibactam was tested with avibactam at fixed 4 mg/L.
- EUCAST interpretive criteria were applied to comparators.
- CAZ-AVI-R isolates collected in 2019-2020 (*n* = 232) were submitted to whole genome sequencing (WGS).

Results

Table 1. Antimicrobial susceptibility of 285 CAZ-AVI-R Enterobacterales collected worldwide (2019-2021)

Antimicrobial agent	MIC (mg/L)		% Susceptible	
	MIC_{50}	MIC_{90}	CLSI	EUCAST
Aztreonam-avibactam	0.12	0.5	[98.9][a]	
Ceftazidime-avibactam	>32	>32	0.0	0.0
Meropenem-vaborbactam	32	>32	21.1	29.5
Ceftolozane-tazobactam	>16	>16	0.0	0.0
Piperacillin-tazobactam	>128	>128	2.5	1.4
Aztreonam	>16	>16	16.1	13.0
Cefepime	>32	>32	0.4	0.4
Ceftazidime	>32	>32	0.0	0.0
Ceftriaxone	>8	>8	0.0	0.0
Ertapenem	>2	>2	6.9	6.9
Imipenem	>8	>8	2.4	2.5
Meropenem	32	>32	9.1	11.9
Levofloxacin	16	>32	12.7	12.7
Gentamicin	>16	>16	37.5	34.0
Amikacin	16	>32	62.5	46.7
Tigecycline	0.5	2		[58.2][b]
Colistin	0.25	>8		77.1

[a] Percentage inhibited at ≤8 mg/L.
[b] EUCAST breakpoints for *E. coli* and *C. koseri* (≤0.5 mg/L) were applied.

- Aztreonam-avibactam inhibited 98.9% of CAZ-AVI-R isolates at ≤8 mg/L ($MIC_{50/90}$, 0.12/0.5 mg/L).
- Aztreonam-avibactam retained potent activity against MBL producers, independent of MBL type or geography.
- The most active comparator agents were:
  - Colistin: 77.1% S
  - Tigecycline: 58.2% inhibited at ≤0.5 mg/L
  - Amikacin: 46.7%S
  - Gentamicin: 34.0%S
  - Meropenem-vaborbactam: 29.5%S

Results

An MBL gene was identified in 214 of 232 (92.2%) isolates submitted to WGS

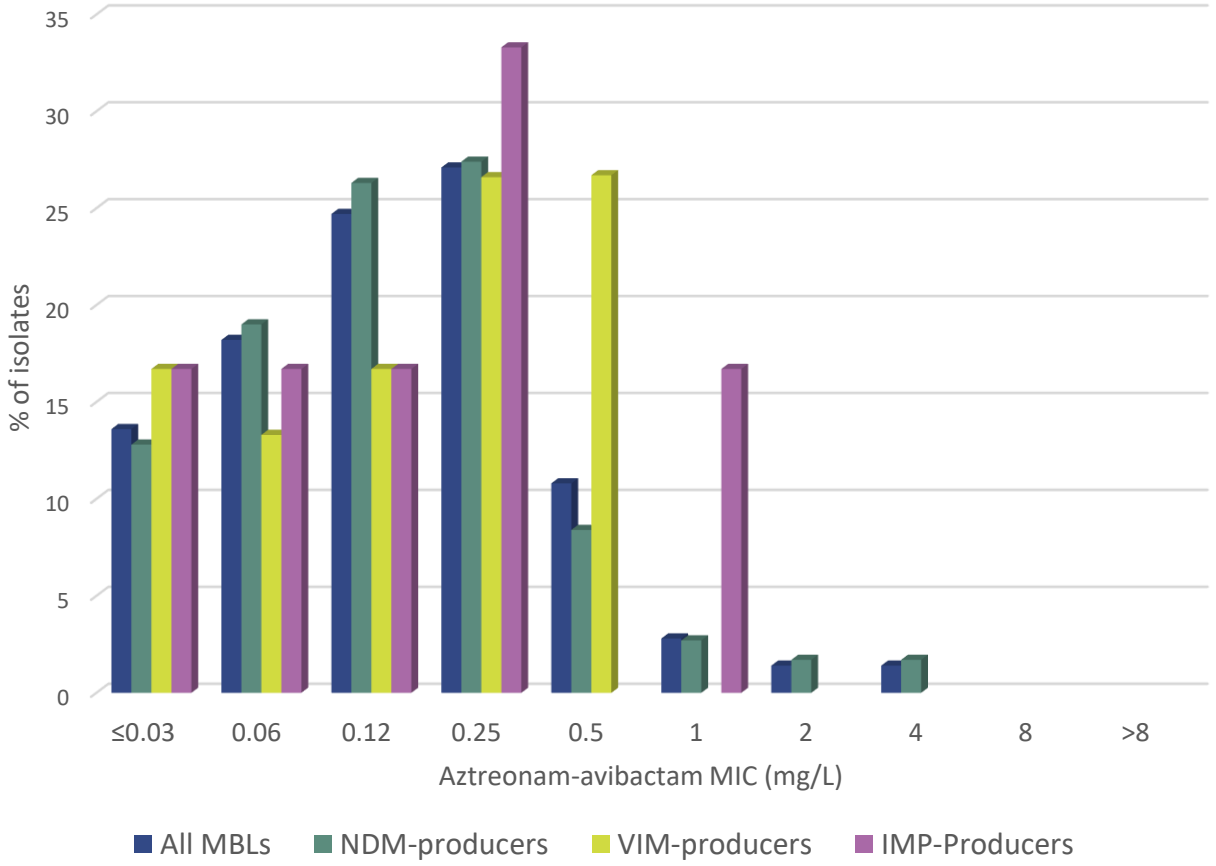
Table 2. Metallo-β-lactamases (MBLs) identified among ceftazidime-avibactam-resistant isolates

MBL[a]	No. of isolates	%
IMP	**6**	**2.8**
IMP-1	1	0.5
IMP-4	1	0.5
IMP-8	4	1.9
NDM[a]	**179**	**83.6**
NDM-1	129	60.3
NDM-4	9	4.2
NDM-5	26	12.1
NDM-7	15	7.0
VIM[a]	**30**	**14.0**
VIM-1	26	12.1
VIM-19	3	1.4
VIM-23	1	0.5

[a] One isolate had an NDM-1 and a VIM-1.

Aztreonam-avibactam inhibited all MBL producers at ≤4 mg/L ($MIC_{50/90}$, 0.12/0.5 mg/L)

Figure 1. Aztreonam-avibactam MIC distributions by MBL type



Results

- Isolates with aztreonam-avibactam MICs >8 mg/L (*n* = 3) were from:
  - Poland: 1 *E. coli* and 1 *E. cloacae*
  - Thailand: 1 *K. pneumoniae*
- These isolates exhibited alterations on the PBP3 and/or membrane porins.

Conclusions

- MBL production was the most common mechanism of resistance to CAZ-AVI.
- Aztreonam-avibactam exhibited potent and consistent activity against CAZ-AVI-R Enterobacterales from APAC, Europe, and Latin America.
- Aztreonam-avibactam was highly active against MBL producers.

Acknowledgements

This study at JMI Laboratories was supported by Pfizer Inc. (New York, NY). JMI Laboratories received compensation fees for services in relation to preparing the poster, which was funded by Pfizer Inc.

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