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Antimicrobial Activity of Aztreonam-Avibactam against Gram-Negative Bacteria Isolated from Patients Hospitalized with Pneumonia in Europe, Latin America, and Asia in 2019

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Introduction

- Aztreonam is a monobactam stable to hydrolysis by metallo-β-lactamases (MBL) and avibactam is a non-β-lactam β-lactamase inhibitor that inhibits Ambler class A, C, and some class D enzymes (e.g., ESBL, KPC, and AmpC).
- Because *Enterobacterales* isolates that produce MBLs usually coproduce serine β-lactamases, aztreonam was combined with avibactam. This novel β-lactamase-inhibitor combination is under clinical development.
- We assessed the *in vitro* activity of aztreonam-avibactam against a large collection of contemporary (2019) clinical isolates recovered from patients hospitalized with pneumonia in medical centers located in Europe, Latin America, and the Asia-Pacific region.

Materials and Methods

- A total of 1,630 *Enterobacterales* and 952 nonfermentative Gram-negative bacilli (GNB) were collected consecutively from 56 medical centers located in Western Europe (W-EU; 22 centers in 10 nations), Eastern Europe (E-EU; 12 centers in 9 nations), Latin America (LATAM; 10 centers in 6 nations), and the Asia-Pacific region (APAC; 12 centers in 8 nations) in 2019.
- Only isolates determined to be significant by local criteria as the reported probable cause of pneumonia were included in the program.
- Carbapenem-resistant *Enterobacterales* (CRE) isolates were defined as displaying imipenem and/or meropenem MIC values at ≥4 mg/L (imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to their intrinsically elevated MIC values).
- Isolates were tested for susceptibility by reference broth microdilution methods in a central monitoring laboratory (JMI Laboratories).
- Avibactam was provided by Pfizer (New York, NY, USA) and combined with aztreonam at a fixed concentration of 4 mg/L for susceptibility testing.
- MIC results were interpreted per CLSI/US-FDA and EUCAST criteria.
- CRE isolates were tested for β-lactamase-encoding genes using next-generation sequencing.

Results

- Overall, 99.8% of *Enterobacterales* isolates were inhibited at aztreonam-avibactam of ≤4 mg/L ($MIC_{50/90}$, ≤0.03/0.12 mg/L), including 99.1% of CRE ($MIC_{50/90}$, 0.25/0.5 mg/L) and 100.0% of MBL-producers ($MIC_{50/90}$, 0.12/0.5 mg/L; Table 1 and Figures 1 and 2).
- Only 3 *Enterobacterales* isolates exhibited aztreonam-avibactam MIC >4 mg/L; these isolates were 1 *K. pneumoniae* from Argentina (MIC, 8 mg/L), 1 *E. cloacae* from Poland (MIC, 8 mg/L), and 1 *K. pneumoniae* from Thailand (MIC, >16 mg/L; data not shown).
- The highest aztreonam-avibactam MIC value for *Enterobacterales* was only 2 mg/L in W-EU (Figure 1).
- The most active comparators tested against *Enterobacterales* were amikacin (84.5-99.4% susceptible [S], 96.6% overall), tigecycline (95.3-97.3%S per US-FDA criteria; 95.9% overall), and meropenem (77.3-98.4%S, 93.0% overall; Table 1).
- Susceptibility rates for ceftriaxone, meropenem, levofloxacin, and gentamicin were highest in W-EU (78.4%, 98.4%, 82.8%, and 91.9%, respectively) and lowest in E-EU (45.0%, 77.3%, 52.2%, and 68.0%, respectively; Table 1).
- CRE rates were 1.4%, 23.7%, 9.6%, and 6.3% in W-EU, E-EU, APAC, and LATAM, respectively (6.9%).
- Aztreonam-avibactam exhibited potent and consistent activity against CRE from all geographic regions, inhibiting all (100.0%) isolates from W-EU, E-EU, and LATAM, and 96.0% of isolates from APAC at ≤4 mg/L (Table 1 and Figure 2).
- A carbapenemase (CPE) was identified in 95 of 113 CRE isolates (84.1%), including NDM-like (31.0% of CRE), KPC-like (26.5%), OXA-48-like (24.8%), and VIM-like (7.1%); 6 isolates produced 2 CPEs.
- Aztreonam-avibactam was highly active against MBL-producers (n=43; $MIC_{50/90}$, 0.12/0.5 mg/L), inhibiting all isolates at ≤4 mg/L (Figure 2).
- Overall, 75.1% of *P. aeruginosa* isolates were inhibited at ≤8 mg/L of aztreonam-avibactam, which is the CLSI susceptible breakpoint for aztreonam (Table 1). Only 14.4% had MICs >16 mg/L (CLSI and EUCAST resistant breakpoint for aztreonam). The percentage inhibited at ≤8 mg/L was highest in W-EU (82.0%) and lowest in E-EU (64.3%; Table 1).
- *P. aeruginosa* susceptibility rates to piperacillin-tazobactam, meropenem, and ceftazidime were substantially lower in E-EU (52.8%, 45.2%, and 58.3%, respectively) compared to W-EU, APAC, and LATAM (77.8-82.8%, 72.7-77.8%, and 80.7-82.8%, respectively; Table 1).
- Aztreonam-avibactam inhibited 96.4% of *S. maltophilia* (n=110; $MIC_{50/90}$, 2/4 mg/L) and all *B. cepacia* (n=10; $MIC_{50/90}$, 2/8 mg/L) isolates at ≤8 mg/L (Table 1).

Figure 1 Aztreonam-avibactam MIC distributions for *Enterobacterales* stratified by geographic region

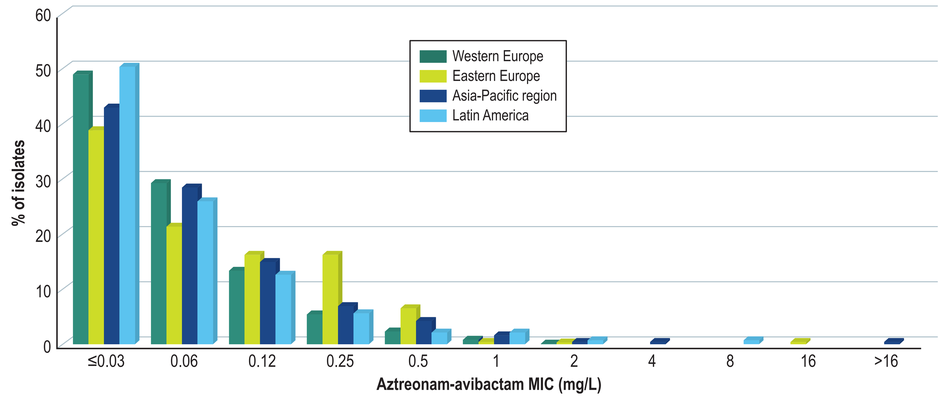

Figure 2 Aztreonam-avibactam MIC distribution for all carbapenem-resistant *Enterobacterales* (CRE) isolates combined and MBL-producers from all regions combined

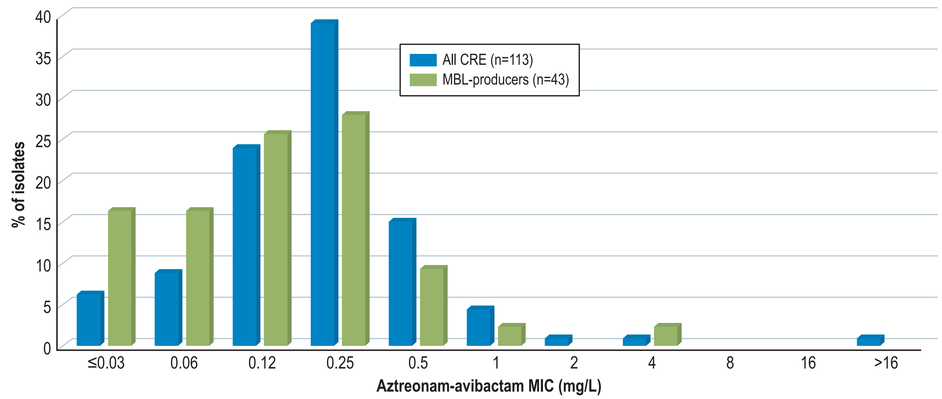

Table 1 Antimicrobial activity of aztreonam-avibactam and comparator agents tested against *Enterobacterales* isolates from Western Europe (W-EU), Eastern Europe (E-EU), the Asia-Pacific region (APAC), and Latin America (LATAM)

Antimicrobial agent	% Susceptible by geographic region (no. of isolates)[a]				
	W-EU	E-EU	APAC	LATAM	All regions
All *Enterobacterales*	(948)	(278)	(261)	(143)	(1,630)
Aztreonam-avibactam[b]	[100.0][b]	[99.6][b]	[99.6][b]	[99.3][b]	[99.8][b]
Ceftriaxone	78.4	45.0	67.4	67.8	70.0
Piperacillin-tazobactam	84.6	58.6	77.4	80.4	78.6
Meropenem	98.4	77.3	89.7	93.7	93.0
Levofloxacin	82.8	52.2	69.6	69.7	74.3
Gentamicin	91.9	68.0	84.3	75.5	85.2
Amikacin	99.4	84.5	98.9	97.9	96.6
Tigecycline[c]	95.6	95.3	97.3	96.5	95.9
Colistin[d]	77.5	81.7	84.1	80.3	79.5
CRE	(13)	(66)	(25)	(9)	(113)
Aztreonam-avibactam	[100.0][b]	[100.0][b]	[96.0][b]	[100.0][b]	[99.1][b]
Levofloxacin	30.8	12.1	4.0	33.3	14.2
Gentamicin	53.8	40.9	56.0	55.6	46.9
Amikacin	76.9	47.0	92.0	88.9	63.7
Tigecycline[c]	92.3	98.5	96.0	77.8	95.6
Colistin[d]	92.3	77.3	84.0	77.8	80.5
P. aeruginosa	(405)	(199)	(129)	(99)	(832)
Aztreonam-avibactam	[82.0][b]	[64.3][b]	[69.8][b]	[75.8][b]	[75.1][b]
Piperacillin-tazobactam	77.8	52.8	78.3	82.8	72.5
Ceftazidime	80.7	58.3	81.4	82.8	75.7
Meropenem	77.8	45.2	77.5	72.7	69.4
Levofloxacin	72.3	35.7	58.1	53.5	59.1
Tobramycin	92.8	66.8	87.6	86.9	85.1
Colistin	99.5	99.5	100.0	99.0	99.5
S. maltophilia	(40)	(43)	(20)	(7)	(110)
Aztreonam-avibactam	[95.0][b]	[100.0][b]	[90.0][b]	[100.0][b]	[96.4][b]
Ceftazidime	15.0	20.9	10.0	14.3	16.4
Minocycline	100.0	100.0	100.0	100.0	100.0
Levofloxacin	77.5	83.7	90.0	100.0	83.6
TMP-SMX	90.0	97.7	100.0	85.7	94.5
B. cepacia	(3)	(3)	(4)	(0)	(10)
Aztreonam-avibactam	[100.0][b]	[100.0][b]	[100.0][b]	—	[100.0][b]
Ceftazidime	100.0	100.0	50.0	—	80.0
Meropenem	100.0	100.0	100.0	—	100.0
Minocycline	100.0	100.0	75.0	—	90.0
Levofloxacin	66.7	66.7	50.0	—	60.0
TMP-SMX	100.0	100.0	100.0	—	100.0

[a] Criteria as published by CLSI (2019), except for tigecycline (US-FDA) and colistin (EUCAST).
[b] Values in brackets indicate % inhibited at ≤4 mg/L (*Enterobacterales*) or at ≤8 mg/L (non-fermenters) for comparison purpose.
[c] US FDA susceptible breakpoint (≤2 mg/L) was applied for comparison purpose.
[d] EUCAST criteria was applied.
Abbreviations: W-EU, Western Europe; E-EU, Eastern Europe; APAC, Asia-Pacific region; LATAM, Latin America; CRE, carbapenem-resistant *Enterobacterales*; TMP-ZMX, trimethoprim-sulfamethoxazole.

Conclusions

- Aztreonam-avibactam demonstrated potent activity against a large collection of contemporary (2019) *Enterobacterales* isolates from Europe, LATAM, and APAC, including CRE and MBL-producers.
- Aztreonam-avibactam activity against *P. aeruginosa* was comparable to the activity of piperacillin-tazobactam, meropenem, and ceftazidime.
- Aztreonam-avibactam was very active against *S. maltophilia* and *B. cepacia*.
- Resistance rates for comparator agents were generally higher in E-EU compared to W-EU, APAC, and LATAM.
- The results of this large worldwide (ex-United States) investigation support the clinical development of aztreonam-avibactam for treatment of pneumonia caused by Gram-negative bacteria, including CRE and MBL-producing *Enterobacterales*.

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