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Antimicrobial Activity of Aztreonam-Avibactam and Comparator Agents against Gram-Negative Bacteria Isolated from Bloodstream and Complicated Urinary Tract Infections in Europe, Asia, and Latin America (2019–2020)

Helio S. Sader, Rodrigo E. Mendes, Cecilia Carvalhaes, Timothy Doyle, Mariana Castanheira
JMI Laboratories, North Liberty, Iowa, USA

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 serine β-lactamases such as ESBLs, KPCs, AmpCs, and some OXAs.
- 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 for treatment of Gram-negative infections.
- We assessed the *in vitro* activity of aztreonam-avibactam against a large collection of contemporary (2019–2020) clinical isolates recovered from patients hospitalized with bloodstream (BSI) or complicated urinary tract infections (cUTI) in medical centers located in Western Europe (W-EU), Eastern Europe and the Mediterranean region (E-EU), the Asia-Pacific region (APAC), and Latin America (LATAM).

Materials and Methods

Bacterial isolates

- A total of 10,103 isolates were consecutively collected from 66 medical centers: 25 from W-EU (n=5,238; 10 countries), 13 from E-EU (n=1,729; 10 countries), 17 from APAC (n=1,817; 9 countries), and 11 from LATAM (n=1,319; 7 countries).
- These isolates were collected from patients with BSI (5,314 isolates) or cUTI (4,789 isolates).
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.

Resistant subsets

- Carbapenem-resistant *Enterobacterales* (CRE) isolates were defined as displaying imipenem and/or meropenem MIC values at ≥4 mg/L (CLSI, 2021).
  - Imipenem was not applied to *Proteus mirabilis* and indole-positive Proteeae due to their intrinsically elevated MIC values.
- MDR and extensively drug-resistant (XDR) *Enterobacterales* isolates were classified according to recommended guidelines (Magiorakos et al., 2012).
- Classifications were based on the following parameters:
  - MDR = nonsusceptible (CLSI breakpoints) to at least 3 antimicrobial classes.
  - XDR = susceptible to 2 or fewer antimicrobial classes.

Susceptibility testing

- The broth microdilution test method was conducted according to CLSI.
- Aztreonam-avibactam was tested with avibactam at fixed concentration of 4 mg/L.
- CLSI/US FDA and EUCAST susceptibility interpretive criteria were applied to comparator agents.
- A tentative susceptible breakpoint of ≤8 mg/L was applied for aztreonam-avibactam.

Results

- Overall, 99.9% of *Enterobacterales* ($MIC_{50/90}$, ≤0.03/0.12 mg/L), including 99.7% of CRE ($MIC_{50/90}$, 0.25/0.5 mg/L), were inhibited at an aztreonam-avibactam MIC of ≤8 mg/L (Tables 1 and 2 and Figures 1 and 2).
- CRE rates among BSI/cUTI isolates were 2.1%/0.6% in W-EU, 8.4%/5.7% in E-EU, 2.8%/2.5% in APAC, and 7.1%/4.9% in LATAM (3.8%/2.6% overall; Figure 3).
- Aztreonam-avibactam was very active against MDR ($MIC_{50/90}$, 0.06/0.5 mg/L; 99.6% inhibited at ≤8 mg/L) and XDR ($MIC_{50/90}$, 0.25/0.5 mg/L; highest MIC, 2 mg/L) *Enterobacterales* (Table 1).
- Among *P. aeruginosa*, the percentage of isolates inhibited at ≤8 mg/L of aztreonam-avibactam (78.3%) was similar to the susceptibility rates for piperacillin-tazobactam (78.8%), meropenem (79.1%), and ceftazidime (80.6%; Table 2).
- *Enterobacterales* and *P. aeruginosa* susceptibility to comparator agents was generally lower in E-EU and LATAM than W-EU and APAC (Table 2).
- Among *S. maltophilia* isolates, 100.0% were inhibited at ≤8 mg/L of aztreonam-avibactam and 95.4% were susceptible to trimethoprim-sulfamethoxazole (Table 3).
- Aztreonam-avibactam was highly active against *Aeromonas* spp. (highest MIC, 0.25 mg/L) and showed good activity against *B. cepacia* ($MIC_{50/90}$, 4/16 mg/L; Table 3).

Conclusions

- Aztreonam-avibactam demonstrated potent and consistent activity against a large collection of *Enterobacterales* isolated from patients with BSI and cUTI from Europe, the Asia-Pacific region, and Latin America.
- Aztreonam-avibactam retained potent activity against carbapenem-resistant, MDR, and XDR *Enterobacterales* from all geographic regions evaluated.
- Aztreonam-avibactam activity against *P. aeruginosa* was comparable to piperacillin-tazobactam and meropenem.
- Our results support clinical development of aztreonam-avibactam to treat BSI and cUTI caused by *Enterobacterales*, *P. aeruginosa*, *S. maltophilia*, *B. cepacia*, and *Aeromonas* spp.

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Contact

Helio S. Sader, MD, PhD
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

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Table 1. Antimicrobial activity of aztreonam-avibactam and comparator agents tested against *Stenotrophomonas maltophilia*, *Burkholderia cepacia* species complex, and *Aeromonas* spp. isolates from patients with bloodstream or urinary tract infections in hospitals located in W-EU, E-EU, APAC, and LATAM (2019–2020)

Organism (no. tested)	No. of isolates and cumulative % inhibited at aztreonam-avibactam MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	MIC_{50}	MIC_{90}
Enterobacterales (9,288)	5,199 56.0%	2,505 82.9%	960 93.3%	372 97.3%	152 98.9%	57 99.5%	23 99.8%	9 99.9%	6 99.9%	4 >99.9%	1 100.0%	≤0.03	0.12
CRE (324)	21 6.5%	30 15.7%	71 38.0%	123 75.6%	63 95.1%	10 98.1%	4 99.4%	0 99.4%	1 99.7%	0 99.7%	1 100.0%	0.25	0.5
XDR (240)	17 7.1%	20 15.4%	53 37.5%	86 73.3%	53 95.4%	7 98.3%	4 100.0%					0.25	0.5
P. aeruginosa (718)				6 0.8%	4 1.4%	6 2.2%	35 7.1%	280 46.1%	231 78.3%	74 88.6%	82 100.0%	8	>16
S. maltophilia (65)						4 6.2%	27 47.7%	31 95.4%	3 100.0%			4	4
Burkholderia cepacia (21)							9 42.9%	6 71.4%	3 85.7%	2 95.2%	1 100.0%	4	16
Aeromonas spp. (11)	8 72.7%	1 81.8%	1 90.9%	1 100.0%								≤0.03	0.12

Abbreviations: CRE, carbapenem-resistant *Enterobacterales*; XDR, extensively drug-resistant.

Table 2. Antimicrobial activity of aztreonam-avibactam and comparator agents tested against *Enterobacterales* isolates stratified by geographic region and infection type

Organism/ Antimicrobial agent	% Susceptible per EUCAST criteria (no. tested) BSI W-EU	E-EU	APAC	LATAM	UTI W-EU	E-EU	APAC	LATAM
Enterobacterales	**(2,825)**	**(761)**	**(670)**	**(545)**	**(2,077)**	**(820)**	**(933)**	**(657)**
Aztreonam-avibactam	[100.0][a]	[99.9][a]	[99.9][a]	[100.0][a]	[>99.9][a]	[99.9][a]	[100.0][a]	[100.0][a]
Meropenem	97.8	91.2	96.9	91.9	99.4	92.7	97.2	94.7
Ceftriaxone	77.9	58.1	73.0	54.7	84.3	62.0	74.6	65.6
Ceftolozane-tazobactam	94.0	81.7	91.8	82.9	96.2	85.2	94.0	88.6
Piperacillin-tazobactam	89.0	74.6	89.2	79.6	93.4	81.1	91.1	83.8
Levofloxacin	77.8	58.4	74.7	59.8	81.1	57.0	71.2	59.7
Gentamicin	88.5	79.1	86.0	72.8	91.6	80.2	84.7	75.6
Amikacin	98.3	93.6	98.7	91.7	99.4	93.8	99.0	96.8
CRE	**(64)**	**(72)**	**(22)**	**(44)**	**(13)**	**(50)**	**(26)**	**(34)**
Aztreonam-avibactam	[100.0][a]	[98.6][a]	[100.0][a]	[100.0][a]	[100.0][a]	[100.0][a]	[100.0][a]	[100.0][a]
Levofloxacin	6.2	13.9	18.2	22.7	23.1	2.0	11.5	11.8
Gentamicin	50.0	54.2	50.0	43.2	38.5	26.0	26.9	38.2
Amikacin	62.5	61.1	81.8	75.0	69.2	42.0	76.9	70.6
P. aeruginosa	**(198)**	**(82)**	**(76)**	**(67)**	**(97)**	**(49)**	**(109)**	**(40)**
Aztreonam-avibactam	[83.3][a]	[64.6][a]	[77.6][a]	[73.1][a]	[91.8][a]	[69.4][a]	[75.2][a]	[77.5][a]
Meropenem	84.3	62.2	85.5	67.2	91.8	61.2	83.5	75.0
Ceftazidime	83.8	73.2	89.5	76.1	80.4	69.4	82.6	80.0
Ceftolozane-tazobactam	97.0	82.9	94.7	83.6	97.9	79.6	86.2	87.5
Piperacillin-tazobactam	81.3	64.6	89.5	80.6	80.4	63.3	81.7	80.0
Levofloxacin	73.2	62.2	67.1	70.1	83.5	44.9	67.0	67.5
Tobramycin	94.4	79.3	93.4	76.1	96.9	69.4	81.7	80.0

[a] Values in brackets indicate percentages inhibited at ≤8 mg/L.
Abbreviations: BSI, bloodstream infection; cUTI, complicated urinary tract infection; W-EU, Western Europe; E-EU, Eastern Europe and the Mediterranean; APAC, Asia-Pacific region; LATAM, Latin America; CRE, carbapenem-resistant *Enterobacterales*; MDR, multidrug-resistant; XDR, extensively drug-resistant

Table 3. Antimicrobial activity of aztreonam-avibactam and comparator agents tested against *Stenotrophomonas maltophilia*, *Burkholderia cepacia* species complex, and *Aeromonas* spp. isolates from patients with bloodstream or urinary tract infections in hospitals located in Western Europe, Eastern Europe, the Asia-Pacific region, and Latin America (2019–2020)

Antimicrobial agent	mg/L MIC_{50}	MIC_{90}	MIC range	CLSI[a] %S	%R	EUCAST[a] %S	%R
S. maltophilia (65)							
Aztreonam-avibactam	4	4	1 to 8	[100.0][b]			
Ceftazidime	>32	>32	1 to >32	18.5	66.2		
Levofloxacin	1	4	0.25 to 16	80.0	4.6		
Minocycline	0.5	1	0.12 to 4	100.0	0.0		
Trimethoprim-sulfamethoxazole	0.25	1	≤0.12 to >4	95.4	4.6	[c]	3.1
Tigecycline	1	4	0.25 to 8				
B. cepacia (21)							
Aztreonam-avibactam	4	16	2 to >16	[85.7][b]			
Ceftazidime	4	32	2 to 32	76.2	14.3		
Meropenem	4	4	2 to 4	100.0	0.0		
Levofloxacin	2	8	0.5 to 16	57.1	23.8		
Minocycline	4	32	2 to >16	52.4	33.3		
Tigecycline	4	>8	0.5 to >8				
Aeromonas spp. (11)							
Aztreonam-avibactam	≤0.03	0.12	≤0.03 to 0.25	[100.0][b]			
Aztreonam	≤0.03	1	≤0.03 to >16	90.9	9.1	90.9	9.1
Ceftazidime	0.25	2	0.06 to >32	90.9	9.1	81.8	9.1
Piperacillin-tazobactam	4	8	0.5 to >128	90.9	9.1		
Meropenem	0.12	0.5	≤0.015 to >32	90.9	9.1		
Levofloxacin	≤0.015	0.25	≤0.015 to 0.5	100.0	0.0	100.0	0.0
Amikacin	2	4	1 to 8	100.0	0.0		
Minocycline	0.5	2	0.25 to 2				
Tigecycline	0.25	0.5	0.12 to 0.5				

[a] Criteria as published by CLSI (2021) and EUCAST (2021).
[b] Values in brackets indicate percentages inhibited at ≤8 mg/L.
[c] An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure.

Figure 1. Antimicrobial activity of aztreonam-avibactam tested against *Enterobacterales* isolates from patients with BSI or cUTI stratified by geographic region (2019–2020)

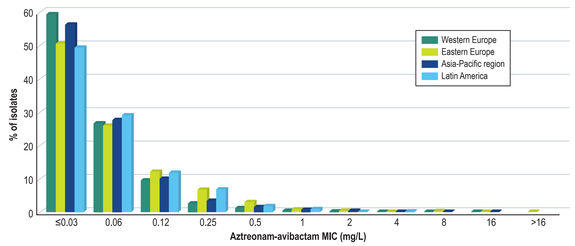


Figure 2. Antimicrobial activity of aztreonam-avibactam tested against carbapenem-resistant *Enterobacterales* (CRE) isolates from patients with BSI or cUTI stratified by geographic region (2019–2020)

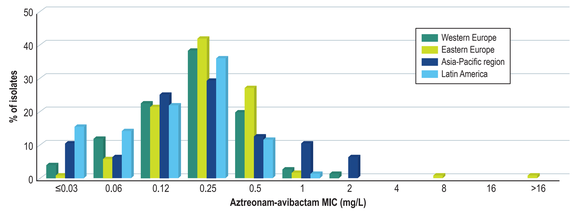
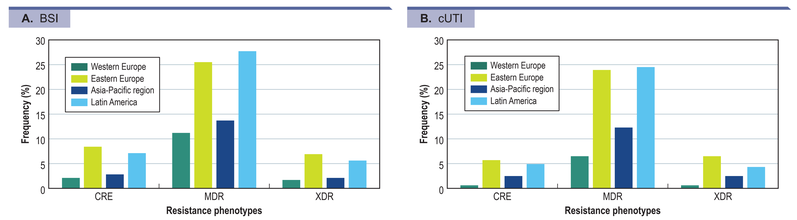


Figure 3. Frequency of carbapenem-resistant (CRE), multidrug-resistant (MDR), and extensively drug-resistant (XDR) *Enterobacterales* among isolates from BSI and cUTI



Abbreviations: CRE, carbapenem-resistant *Enterobacterales*; MDR, multidrug-resistant; XDR, extensively drug-resistant