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Aztreonam-Avibactam Activity against Gram-negative Bacteria Isolated from Patients with Pneumonia from Europe, Asia, and Latin America (2021–2023)

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Introduction

- Aztreonam-avibactam has been recently approved by the European Medicine Agency (EMA) to treat adults who have complicated intra-abdominal infections (IAI), hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated urinary tract infections (UTI; including pyelonephritis), and infections caused by aerobic Gram-negative organisms in patients who have limited treatment options.
- Aztreonam-avibactam is under development in the United States (US) to treat infections caused by Gram-negative bacteria, including metallo-β-lactamase (MBL) producers.
- Phase 3 clinical trials REVISIT (NCT03329092) and ASSEMBLE (NCT03580044) evaluated the efficacy, safety, and tolerability of aztreonam-avibactam in treating serious bacterial infections due to Gram-negative bacteria, including MBL-producing multidrug-resistant pathogens for which there are limited or no treatment options.
- Results from these trials indicated that aztreonam-avibactam is effective and well-tolerated, with no new safety findings and a similar safety profile to aztreonam alone.
- We evaluated the *in vitro* activities of aztreonam-avibactam and comparators against Gram-negative bacilli isolated from patients with pneumonia.

Materials and Methods

- A total of 7,560 organisms were consecutively collected (1/patient) from patients with pneumonia in 59 medical centers located in:
  - Western Europe (W-EU): 3,977 isolates from 24 centers in 10 countries
  - Eastern Europe and Mediterranean region (E-EU): 1,617 isolates from 15 centers in 9 countries
  - Asia-Pacific region (APAC): 1,238 isolates from 12 centers in 7 countries
  - Latin America (LATAM): 728 isolates from 8 centers in 6 countries
- Only bacterial isolates from lower respiratory tract specimens determined to be significant by local criteria as the reported probable cause of pneumonia were included in the study.
- Isolates were susceptibility tested by CLSI M07 broth microdilution methods at a central laboratory and aztreonam-avibactam was tested with avibactam at fixed 4 mg/L.
- Aztreonam-avibactam susceptible breakpoint published by EUCAST (≤4 mg/L) was applied for Enterobacterales and the provisional pharmacodynamic/pharmacokinetic susceptible breakpoint of ≤8 mg/L was applied for *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* for comparison.
- Cefiderocol was only tested against carbapenem-resistant Enterobacterales (CRE).
- CRE isolates were screened for carbapenemase-encoding genes by whole genome sequencing.

Results

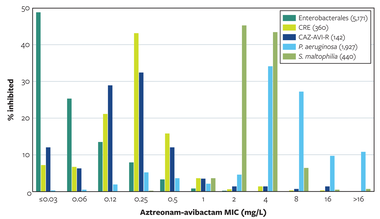
- Aztreonam-avibactam inhibited 99.9% of Enterobacterales at ≤4 mg/L ($MIC_{50/90}$, 0.06/0.25 mg/L) and showed consistent activity across regions (Table 1 and Figures 1 and 2).
- Only 4 Enterobacterales had an aztreonam-avibactam MIC >4 mg/L, 2 at 8 mg/L and 2 at 16 mg/L.
- Ceftazidime-avibactam was the most active comparator agent, with susceptibility ranging from 99.4% in W-EU to 93.9% in E-EU (97.3% overall; Figure 2).
- CRE rates varied from 1.3% in W-EU to 20.5% in LATAM (Figure 3).
- Aztreonam-avibactam retained potent activity against CRE ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.4% susceptible per EUCAST) and ceftazidime-avibactam-resistant isolates ($MIC_{50/90}$, 0.25/0.5 mg/L; 97.9% susceptible per EUCAST; Table 1 and Figures 1 and 4).
- Ceftazidime-avibactam (61.7% susceptible [S]), meropenem-vaborbactam (52.8% S), and imipenem-relebactam (44.5% S) showed limited activity against CRE and susceptibility to these agents varied greatly among regions (Table 1 and Figure 4).
- Cefiderocol was active against 95.1% of CRE, with susceptibility ranging from 100.0% in LATAM to 90.5% in APAC (Table 1 and Figure 4).
- An MBL was identified in 35.8% of CREs, varying from 23.8% in LATAM to 60.3% in APAC (Figure 5).
- KPC was the most common carbapenemase among CRE isolates in W-EU (46.2% of CREs) and LATAM (69.0%) and MBL predominated in E-EU (34.1%) and APAC (60.3%; Figure 5).
- Imipenem-relebactam (95.3% S), ceftazidime-avibactam (94.7% S), and ceftolozane-tazobactam (93.3% S) were the most active agents against *P. aeruginosa* (Table 1 and Figure 6).
- The percentage of *P. aeruginosa* isolates inhibited at ≤8 mg/L of aztreonam-avibactam (79.5%) was comparable to the susceptibility rates for piperacillin-tazobactam (76.1%), meropenem (76.6%), and ceftazidime (80.6%; Table 1 and Figure 6).
- Aztreonam-avibactam inhibited 98.9% of *S. maltophilia* isolates (n=440) at ≤8 mg/L (Figure 1).

Table 1. Activity of β-lactamase inhibitor combinations

Organism / resistant subset (no. tested)	% Susceptible per CLSI and US FDA						
	ATM-AVI[a]	CAZ-AVI	MEM-VAB	IMI-REL	Cefiderocol	TOL-TAZ	PIP-TAZ
Enterobacterales (5,171)	99.9	97.3	96.7	91.7		86.3	76.3
W-EU (2,896)	99.9	99.4	99.6	94.0		92.7	82.4
E-EU (1,139)	100.0	93.9	90.3	85.1		77.9	67.8
APAC (727)	99.9	95.0	95.6	92.8		80.7	71.9
LATAM (409)	100.0	95.1	95.8	92.8		74.8	63.8
CRE (360)	99.4	61.7	52.8	44.5	95.1		
W-EU (39)	97.4	66.7	71.8	56.5	95.2		
E-EU (179)	100.0	61.5	38.5	33.1	95.1		
APAC (58)	98.3	37.9	44.8	30.8	90.5		
LATAM (84)	100.0	76.2	79.8	75.0	100.0		
P. aeruginosa (1,927)	79.5	94.7	88.5[b]	95.3		93.3	76.1
W-EU (810)	83.2	97.7	92.8[b]	98.4		97.2	80.6
E-EU (381)	74.3	92.9	85.5[b]	92.7		90.6	69.3
APAC (451)	81.2	96.5	92.5[b]	95.9		95.3	78.7
LATAM (285)	73.3	85.6	74.4[b]	89.1		82.5	68.1

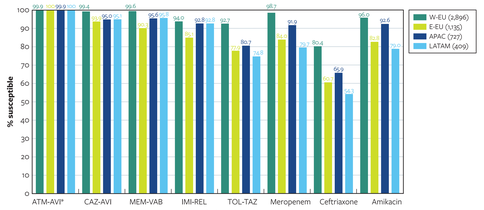
[a] % susceptible per EUCAST criteria for Enterobacterales and % inhibited at ≤8 mg/L for *P. aeruginosa*.
[b] MEM-VAB is not approved to treat *P. aeruginosa* in the United States; EUCAST breakpoint was applied.
Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; TOL-TAZ, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America; CRE, carbapenem-resistant Enterobacterales.

Figure 1. Aztreonam-avibactam MIC distributions against selected organism groups



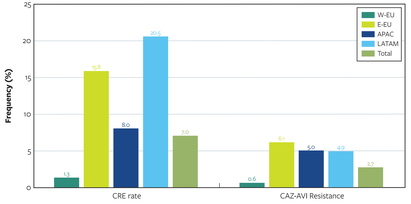
Abbreviations: CRE, carbapenem-resistant Enterobacterales; CAZ-AVI-R, ceftazidime-avibactam-resistant.

Figure 2. Antimicrobial susceptibility of Enterobacterales stratified by region



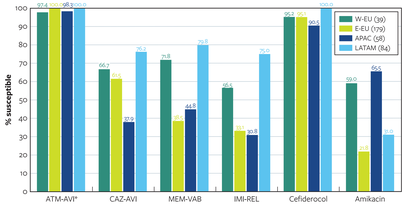
Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; TOL-TAZ, ceftolozane-tazobactam; W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America.
* Percentage susceptible per EUCAST criteria.

Figure 3. Frequencies of carbapenem-resistant Enterobacterales (CRE) and ceftazidime-avibactam resistance among Enterobacterales



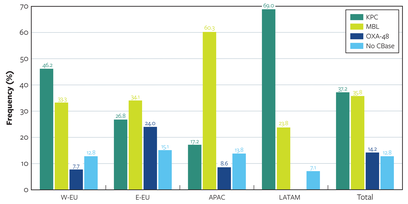
Abbreviations: CRE, carbapenem-resistant Enterobacterales; CAZ-AVI, ceftazidime-avibactam; W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region, APAC, Asia-Pacific region; LATAM, Latin America.

Figure 4. Antimicrobial susceptibility of carbapenem-resistant Enterobacterales (CRE) stratified by region



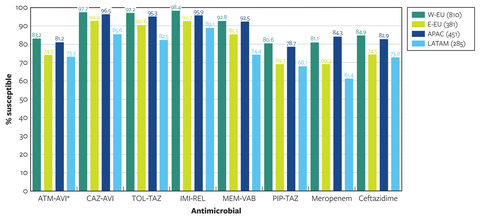
Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America.
* Percentage susceptible per EUCAST criteria.

Figure 5. Frequencies of carbapenemases among CRE isolates stratified by region



Abbreviations: W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region, APAC, Asia-Pacific region; LATAM, Latin America; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; CBase, carbapenemase.

Figure 6. Antimicrobial susceptibility of *P. aeruginosa*



Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; TOL-TAZ, ceftolozane-tazobactam; IMI-REL, imipenem-relebactam; MEM-VAB, meropenem-vaborbactam; PIP-TAZ, piperacillin-tazobactam; W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America.
* Percentage inhibited at ≤8 mg/L.

Conclusions

- Aztreonam-avibactam demonstrated potent activity against Enterobacterales, including CRE, MBL producers, and ceftazidime-avibactam-resistant isolates from patients with pneumonia collected worldwide (ex-US).
- Aztreonam-avibactam was the most active antibiotic against *S. maltophilia* and showed *in vitro* activity comparable to piperacillin-tazobactam, meropenem, and ceftazidime against *P. aeruginosa*.
- Aztreonam-avibactam has been recently approved by EMA in Europe, and our results support clinical development of aztreonam-avibactam to treat pneumonia caused by Enterobacterales (including MBL, OXA-48, and KPC producers), *P. aeruginosa*, and *S. maltophilia* in Asia and Latin America as well.

Acknowledgements

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