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Aztreonam-Avibactam Activity against Gram-negative Bacteria Isolated from Patients with Bloodstream Infections from Europe, Asia, and Latin America (2020–2021)

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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 serine β-lactamases such as ESBLs, KPCs, AmpCs, and some OXAs.
- Aztreonam-avibactam is under development to treat serious infections caused by Gram-negative bacteria (GNB), including metallo-β-lactamase (MBL) producers.
- We evaluated the activity of aztreonam-avibactam and recently approved β-lactamase inhibitor combinations against GNB recovered from patients with bloodstream infection (BSI) in Europe, Asia, and Latin America.

Materials and Methods

- A total of 5,592 organisms were consecutively collected (1/patient) from patients with BSI in 56 medical centres located in Western Europe (W-EU; 10 countries; 25 centres; 3,166 isolates), Eastern Europe and the Mediterranean region (E-EU; 8 countries; 11 centres; 968 isolates), the Asia-Pacific region (APAC; 7 countries; 12 centres; 820 isolates), and Latin America (LATAM; 6 countries; 8 centres; 638 isolates).
- Organisms were susceptibility tested at a monitoring laboratory by reference broth microdilution.
- MIC results were interpreted per EUCAST breakpoint criteria.
- A provisional pharmacokinetic/pharmacodynamic susceptible (S) breakpoint of ≤8 mg/L was applied for aztreonam-avibactam for comparison.
- Carbapenem-resistant Enterobacterales (CRE) isolates were subjected to whole genome sequencing (WGS).

Results

- The GNB represented 62.8% of organisms from BSI; the highest frequency was identified in LATAM (73.5%), followed by APAC (66.2%), E-EU (65.3%), and W-EU (59.5%).
- *E. coli* (42.7%), *Klebsiella pneumoniae* (19.4%), *Pseudomonas aeruginosa* (9.3%), and *Enterobacter cloacae* complex (5.5%) were the most common GNBs overall, but their frequencies and rank order varied by region (Figures 1A-D).
- *Stenotrophomonas maltophilia* ranked eighth in E-EU, APAC, and LATAM and 11th W-EU (Figure 1).
- Aztreonam-avibactam inhibited >99.9% of all Enterobacterales at ≤8 mg/L ($MIC_{50/90}$, ≤0.03/0.12 mg/L) and showed consistent activity across regions (Table 1).
- Only 1 Enterobacterales had an aztreonam-avibactam MIC >8 mg/L, an *E. coli* from Poland.
- CRE rates ranged from 2.2% (W-EU) to 11.9% (LATAM; Figure 2).
- Multidrug-resistance (MDR) rates among Enterobacterales varied from 11.2% (W-EU) to 33.7% (LATAM; Figure 2).
- Aztreonam-avibactam retained potent activity against CRE ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.5% inhibited at ≤8 mg/L) and MDR Enterobacterales ($MIC_{50/90}$, 0.06/0.5 mg/L; 99.9% inhibited at ≤8 mg/L; Table 1 and Figure 3).
- Ceftazidime-avibactam (77.9% susceptible [S]) and meropenem-vaborbactam (73.7%S) were the most active comparators against CRE, but susceptibility rates varied greatly among regions (Table 1 and Figure 3).
- Aztreonam-avibactam activity against *P. aeruginosa* (64.1% [E-EU] to 85.1% [APAC] inhibited at ≤8 mg/L) was similar to piperacillin-tazobactam (64.1% [E-EU] to 88.1% [APAC] inhibited at ≤16 mg/L; Figure 4).
- The most active agents against *P. aeruginosa* were ceftazidime-avibactam (94.9%S overall) and ceftolozane-tazobactam (93.6%S overall; Figure 4).
- All agents, except colistin (95.7%S), showed limited activity against *A. baumannii-calcoaceticus* complex.
- Aztreonam-avibactam inhibited 100.0% of *S. maltophilia* isolates at ≤8 mg/L (Table 1). The resistance rates of *S. maltophilia* (*n* = 75) to cotrimoxazole ranged from 0.0% in W-EU and LATAM to 13.3% in APAC (4.0% overall).
- Aztreonam-avibactam also was active against *Burkholderia cepacia* (*n*=15; 80.0% inhibited at ≤8 mg/L).
- KPC was the predominant carbapenemase (CPE) in W-EU (83.6% of CRE) and LATAM (72.4%), whereas MBL predominated in APAC (63.2%). KPC (35.2%) and OXA-48–like (32.4%) were common in E-EU (Figure 5).

Conclusions

- Aztreonam-avibactam demonstrated potent activity against Enterobacterales, *P. aeruginosa*, and *S. maltophilia* isolates collected from patients with BSI in Europe, the Asia-Pacific region, and Latin America.
- Our results support the clinical development of aztreonam-avibactam to treat BSI caused by GNB.

Table 1. Activity of aztreonam-avibactam (ATM-AVI) and ceftazidime-avibactam (CAZ-AVI) against selected Gram-negative organisms from patients with bloodstream infection stratified by region

Organism (n) Antimicrobial	ATM-AVI: % Inhibited at ≤8 mg/L CAZ-AVI: % Susceptible			
	W-EU	E-EU	APAC	LATAM
Enterobacterales (4,656)	(2,721)	(766)	(680)	(489)
ATM-AVI	100.0	99.9	100.0	100.0
CAZ-AVI	99.7	97.8	98.4	96.9
CRE (209)	(61)	(71)	(19)	(58)
ATM-AVI	100.0	98.6	100.0	100.0
CAZ-AVI	91.8	78.9	42.1	73.7
MDR (748)	(306)	(190)	(87)	(165)
ATM-AVI	100.0	99.5	100.0	100.0
CAZ-AVI	97.7	91.1	87.4	90.9
P. aeruginosa (374)	(169)	(78)	(67)	(60)
ATM-AVI	84.6	64.1	85.1	80.0
CAZ-AVI	97.6	88.5	95.5	95.0
S. maltophilia (75)	(32)	(20)	(15)	(8)
ATM-AVI	100.0	100.0	100.0	100.0
CAZ-AVI*	25.0	35.0	33.3	25.0

Abbreviations: W-EU, Western Europe; E-EU, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; Latin America; ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; CRE, carbapenem-resistant Enterobacterales; MDR, multidrug-resistant.
* Percentage inhibited at ≤8 mg/L.

Figure 1. Frequency of Gram-negative organisms isolated from patients with bloodstream infection stratified by region

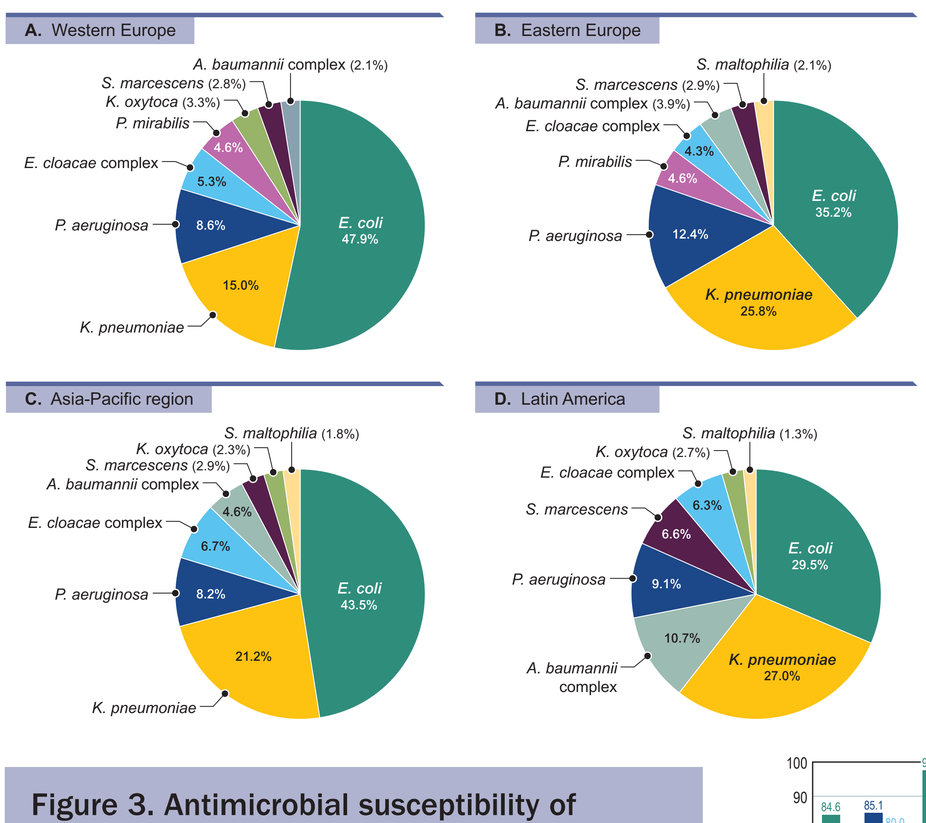


Figure 2. Carbapenem resistance (CRE) rates among Enterobacterales and multidrug-resistance (MDR) rates among Enterobacterales and *P. aeruginosa* stratified by geographic region

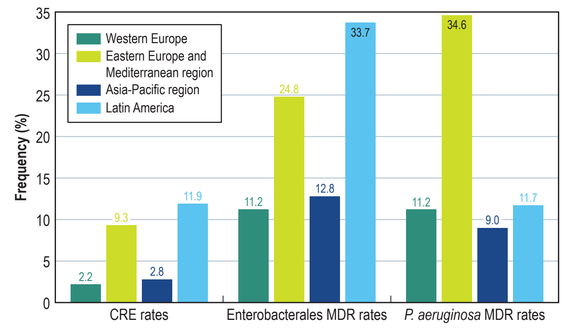
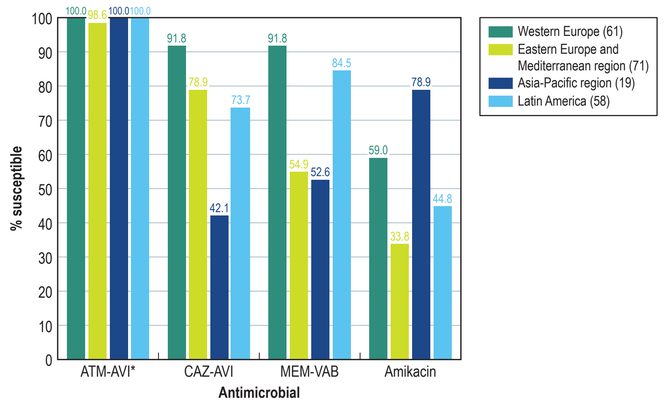
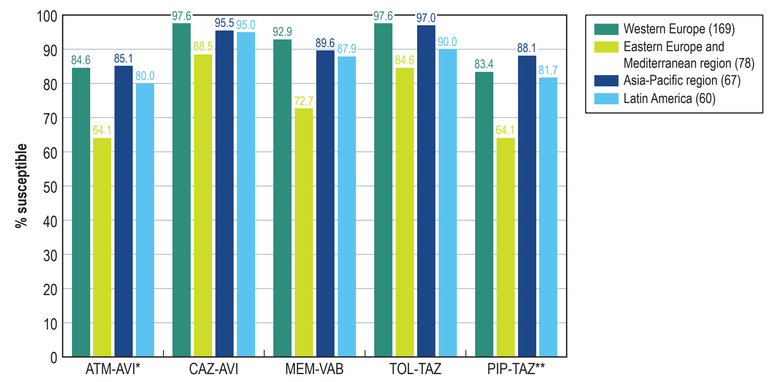


Figure 3. Antimicrobial susceptibility of carbapenem-resistant Enterobacterales (CRE) stratified by region



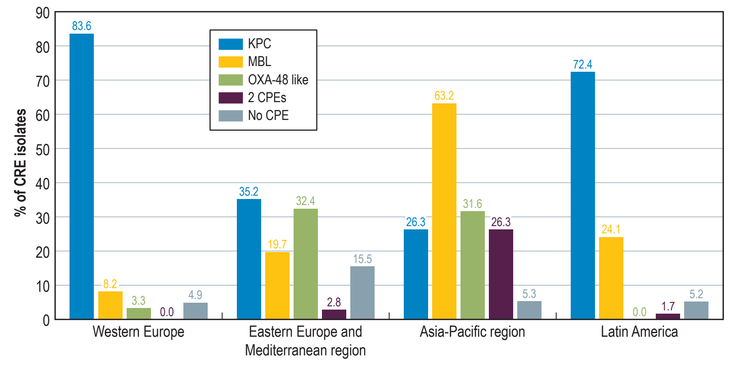
Abbreviation: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam
* Percentage inhibited at ≤8 mg/L.

Figure 4. Antimicrobial susceptibility of *P. aeruginosa* stratified by region



Abbreviation: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; TOL-TAZ, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam.
* Percentage inhibited at ≤8 mg/L.
** Susceptible, increased exposure (EUCAST 2023).

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



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