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Antimicrobial Activity of Aztreonam-Avibactam against Gram-negative Bacteria Isolated from Patients Hospitalised with Pneumonia in European Medical Centres (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 clinical development for the treatment of serious infections caused by Gram-negative bacteria (GNB), including MBL producers.
- We evaluated the activity of aztreonam-avibactam and recently approved β-lactamase inhibitor combinations against GNB recovered from patients with pneumonia in European hospitals.

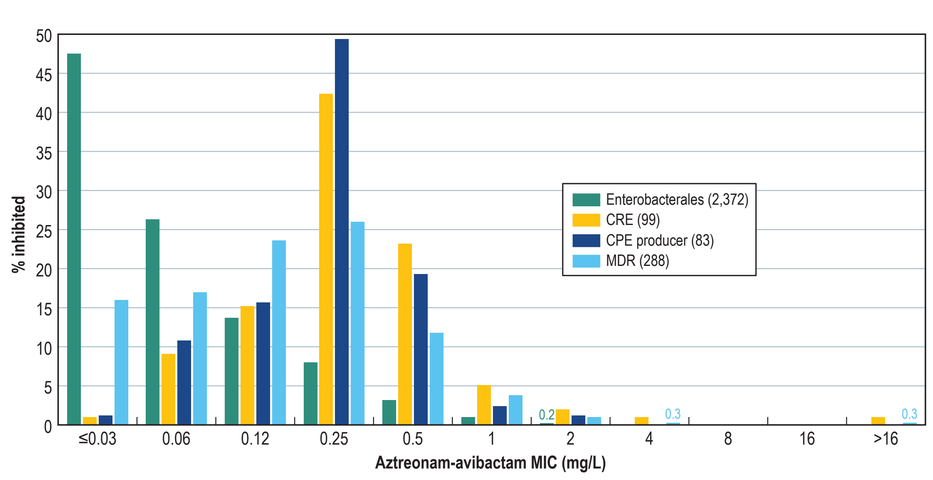
Materials and Methods

- A total of 3,304 bacterial isolates were consecutively collected (1/patient) in 2020–2021 from 33 medical centres located in Western Europe (W-EU; *n*=2,411; 22 centres; 10 countries) and Eastern Europe and the Mediterranean region (E-EU; *n*=893; 11 centres; 8 countries).
- 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

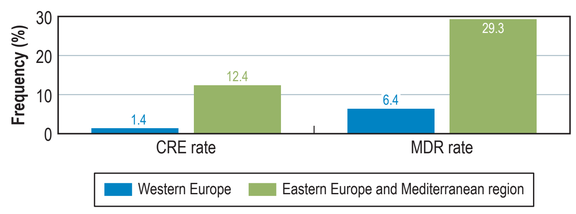
- Among Enterobacterales ($MIC_{50/90}$, 0.06/0.25 mg/L), 100.0%/99.8% of isolates from W-EU/E-EU were inhibited at ≤8 mg/L of aztreonam-avibactam (>99.9% overall; Figure 1).
- Aztreonam-avibactam retained potent activity against CRE (99.0% inhibited at ≤8 mg/L) and multidrug-resistant (MDR) Enterobacterales (99.7% inhibited at ≤8 mg/L; Figure 1).
- CRE rates were 1.4%/12.4% and MDR rates were 6.4%/29.3% in W-EU/E-EU (Figure 2).
- A carbapenemase (CPE) was identified in 83 (83.8%) CRE isolates, 23 (92.0% of CREs) from W-EU and 60 (81.1% of CREs) from E-EU.
- KPC was the most common CPE; it was identified in 60.0%/37.8% of CREs from W-EU/E-EU (51.8% overall; Figure 3).
- An MBL gene was detected in 16.0%/28.4% of CREs from W-EU/E-EU (25.3% overall) and OXA-48–like was identified in 28.0%/20.3% of CREs from W-EU/E-EU (Figure 3).
- The highest aztreonam-avibactam MIC among CPE producers was only 2 mg/L (Figure 1).
- Enterobacterales susceptibility rates for comparator agents were lower in E-EU compared to W-EU (Figure 4).
- Against CRE, ceftazidime-avibactam was active against 84.0%/70.3% and meropenem-vaborbactam was active against 84.0%/51.4% of isolates from W-EU/E-EU (Figure 5).
- Aztreonam-avibactam activity against *P. aeruginosa* (82.0%/72.9% from W-EU/E-EU inhibited at ≤8 mg/L) was comparable to ceftazidime (80.5%/76.2%S inhibited at ≤8 mg/L in W-EU/E-EU) and slightly better than piperacillin-tazobactam (77.3%/69.6% inhibited at ≤16 mg/L) and meropenem (76.4/66.7%S; Figure 6).
- Ceftazidime-avibactam (97.3%/92.5%S in W-EU/E-EU) and ceftolozane-tazobactam (95.1%/90.8%S), were the most active β-lactams against *P. aeruginosa*.
- Aztreonam-avibactam inhibited 99.2%/94.5% of *S. maltophilia* isolates from W-EU/E-EU at ≤8 mg/L (97.8% overall; Figure 6).

Figure 1. Summary of aztreonam-avibactam activity against Enterobacterales isolated from patients hospitalised with pneumonia (2020–2021)



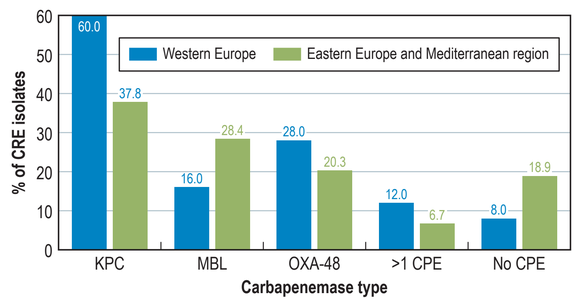
Abbreviations: CRE, carbapenem-resistant Enterobacterales; CPE, carbapenemase; MDR, multidrug-resistant

Figure 2. Carbapenem resistance and multidrug–resistance rates among Enterobacterales stratified by region



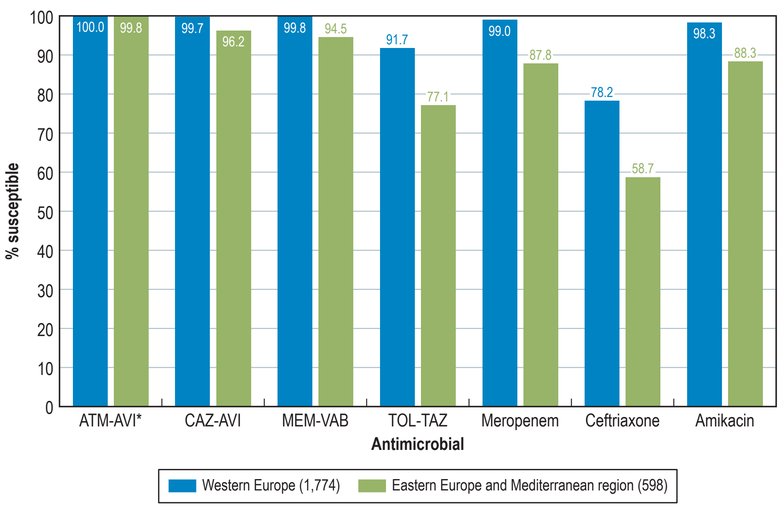
Abbreviations: CRE, carbapenem resistant; MDR, multidrug resistant

Figure 3. Frequencies of carbapenemases among CRE isolates stratified by region



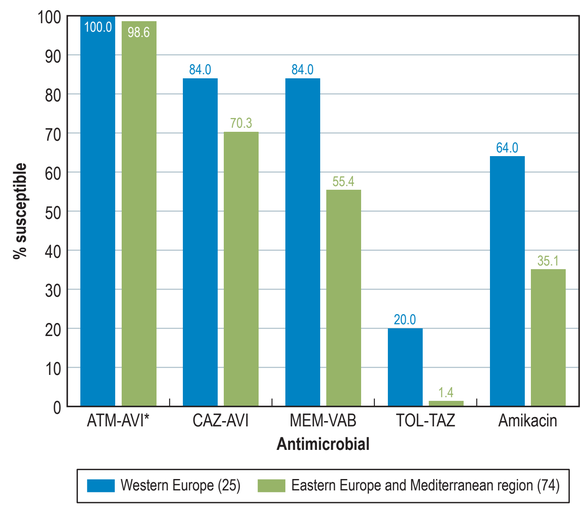
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; CPE, carbapenemase

Figure 4. Antimicrobial susceptibility of Enterobacterales stratified by region



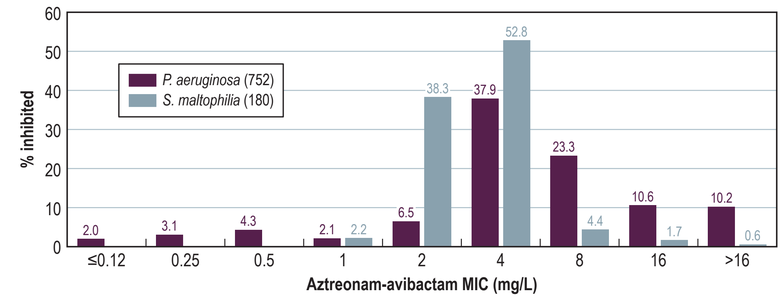
Abbreviation: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; TOL-TAZ, ceftolozane-tazobactam
* Percentage inhibited at ≤8 mg/L.

Figure 5. Antimicrobial susceptibility of carbapenem-resistant Enterobacterales stratified by region



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

Figure 6. Summary of aztreonam-avibactam activity against *P. aeruginosa* and *S. maltophilia* isolated from patients hospitalised with pneumonia (2020–2021)



Conclusions

- Aztreonam-avibactam demonstrated potent activity against Enterobacterales, *P. aeruginosa*, and *S. maltophilia* isolates collected from patients with pneumonia in European medical centres.
- 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*.

Acknowledgements

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