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In Vitro Activity of Aztreonam-Avibactam and Comparator Agents Against Enterobacterales from Patients with Urinary Tract Infections Collected During the ATLAS Global Surveillance Program, 2017-2020

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Introduction

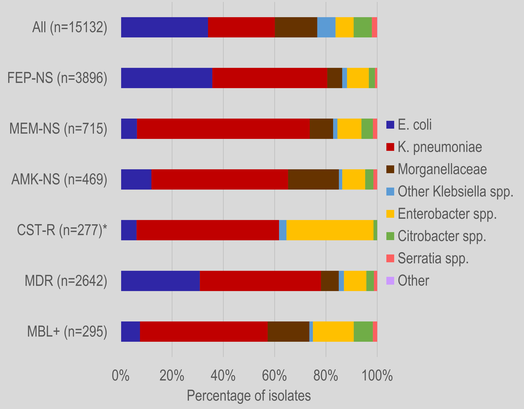
β-lactamase-producing Enterobacterales frequently carry resistance mechanisms for multiple drug classes, limiting treatment options. Avibactam (AVI) inhibits class A, class C, and some class D serine β-lactamases, while aztreonam (ATM) is refractory to hydrolysis by class B metallo-β-lactamases (MBLs). Aztreonam-avibactam is being developed for use against drug-resistant isolates of Enterobacterales, especially those co-producing MBLs and serine β-lactamases. This study evaluated the *in vitro* activity of aztreonam-avibactam and comparators against Enterobacterales collected in 2017-2020 from patients with urinary tract infections (UTI) as part of the ATLAS global surveillance program.

Methods

- 15,132 non-duplicate clinical isolates were collected from patients with UTI in 239 sites in 55 countries in Europe, Latin America, Asia/Pacific (excluding mainland China and India), and Middle East/Africa.
- Susceptibility testing was performed by CLSI broth microdilution and interpreted using CLSI 2022 and FDA (tigecycline) breakpoints (1,2). Multidrug-resistant (MDR) is defined here as resistant to at least three of seven sentinel agents: amikacin, aztreonam, colistin, cefepime, levofloxacin, meropenem and piperacillin-tazobactam.
- PCR and Sanger sequencing were used to identify β-lactamase genes in isolates testing with meropenem MIC >1 µg/ml, and *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* with ATM or ceftazidime MIC >1 µg/ml as described previously (3).

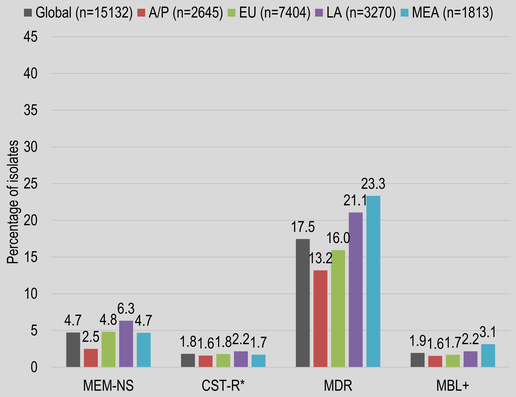
Results

Figure 1: Distribution of species among isolates collected in this study



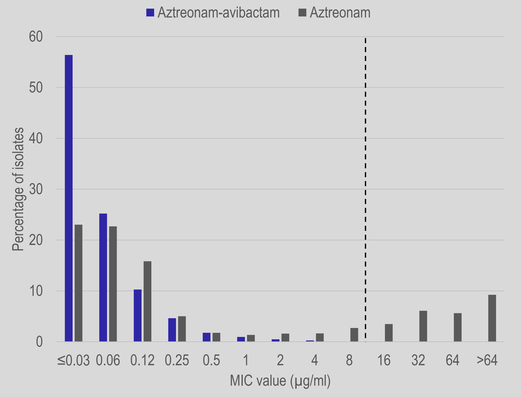
NS, nonsusceptible; FEP, cefepime; MEM, meropenem; AMK, amikacin; CST, colistin; MDR, multidrug-resistant; MBL+, metallo-β-lactamase positive.

Figure 2: Percentages of meropenem-nonsusceptible, colistin-resistant, multidrug-resistant, and MBL-producing Enterobacterales, by region



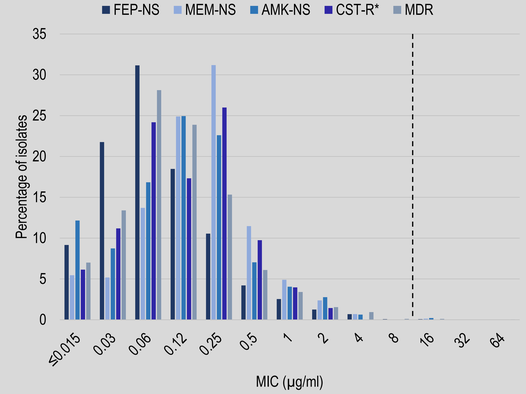
*Excludes *Morganellaceae* and *Serratia* spp. that have intrinsic resistance to colistin.
A/P, Asia/Pacific; EU, Europe; LA, Latin America; MEA, Middle East/Africa; MEM, meropenem; NS, nonsusceptible; CST, colistin; R, resistant; MDR, multidrug-resistant; MBL, metallo-β-lactamase.

Figure 3: MIC distribution for aztreonam and aztreonam-avibactam against Enterobacterales collected from urinary tract infections (n=15,132)



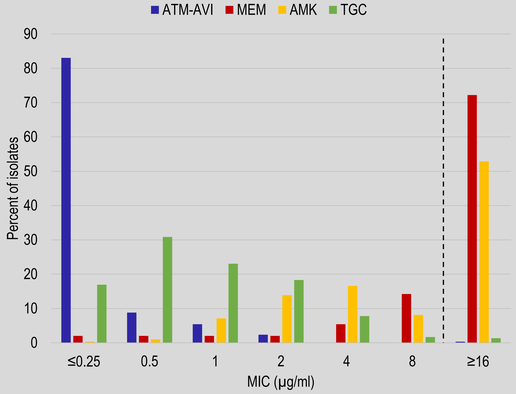
The dashed line represents the preliminary PK/PD cutoff of ≤8 µg/ml for aztreonam-avibactam.
Difficult to visualize due to scale of graph and low number of isolates: isolates testing with aztreonam-avibactam MIC values of 16 µg/ml (n=3), 32 µg/ml (n=1), and 64 µg/ml (n=1). All five of these isolates were *E. coli*.

Figure 4: Distribution of aztreonam-avibactam MIC values against isolates, by phenotype



The dashed line represents the preliminary PK/PD cutoff of ≤8 µg/ml for aztreonam-avibactam.
*Excludes *Morganellaceae* and *Serratia* spp. that have intrinsic resistance to colistin.

Figure 5: Distribution of MIC values for aztreonam-avibactam and select comparators against isolates harboring a metallo-β-lactamase (n=295)



The dashed line represents the preliminary PK/PD cutoff of ≤8 µg/ml for aztreonam-avibactam.
ATM-AVI, aztreonam-avibactam; MEM, meropenem; AMK, amikacin; CST, colistin; TGC, tigecycline.

Table 1: *In vitro* activity of aztreonam-avibactam and comparator agents against isolates, by resistance phenotypes or presence of a metallo-β-lactamase

Phenotype (n)	MIC$_{90}$ [µg/mL] / % Susceptible											
	ATM-AVI		ATM		FEP		MEM		AMK		TGC	
	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S
All UTI (n=15,132)	0.12	NA	64	72.9	>16	74.3	0.12	95.3	8	96.9	2	96.2
FEP-NS (n=3,896)	0.25	NA	>64	9.6	>16	0.0	>8	82.5	32	89.8	2	95.5
MEM-NS (n=715)	0.5	NA	>64	18.2	>16	4.6	>8	0.0	>64	64.6	2	93.0
AMK-NS (n=469)	0.5	NA	>64	26.9	>16	15.6	>8	46.1	>64	0.0	2	90.8
CST-R (n=277)[a]	0.5	NA	>64	40.1	>16	40.8	>8	59.9	>32	80.5	2	93.5
MDR (n=2,642)	0.5	NA	>64	6.7	>16	4.4	>8	74.3	>32	84.5	2	94.4
MBL-positive (n=295)	0.5	NA	>64	31.5	>16	2.0	>8	6.1	>32	56.6	4	89.2

ATM-AVI, aztreonam-avibactam; ATM, aztreonam; FEP, cefepime; MEM, meropenem; AMK, amikacin; TGC, tigecycline; CST, colistin; S, susceptible; NS, susceptible; NA, no breakpoint available; MBL, metallo-β-lactamase; MDR, multidrug-resistant.
[a]Excludes *Morganellaceae* and *Serratia* spp. with intrinsic resistance to colistin.

Results

- While only 25% of the urinary tract isolates collected were *K. pneumoniae*, this species accounted for ≥45% of isolates with the resistant phenotypes observed in this study, including 47% of the multidrug-resistant (MDR) and 50% of the MBL-positive isolates (Figure 1).
- Isolates with resistant phenotypes were present in each of the regions included in this study, with proportions of MDR isolates ranging from 13.2% (Asia/Pacific) to 23.3% (Middle East/Africa) (Figure 2).
- Of all UTI isolates, 15,127/15,132 (99.97%) tested with MIC values ≤8 µg/ml for aztreonam-avibactam (Figure 3). Five isolates of *E. coli* tested with aztreonam-avibactam MIC values of 16-64 µg/ml.
- The MIC$_{90}$ for ATM-AVI was lower than for all tested comparators against UTI isolates (0.12 µg/ml) as well as all resistant subsets (0.25-5 µg/ml) and MBL-positive isolates (0.5 µg/ml) (Figures 3-5, Table 1).

Conclusions

- Based on MIC$_{90}$ values, aztreonam-avibactam demonstrated potent *in vitro* activity against this collection of 15,132 isolates collected from patients with a urinary tract infection from 2017-2020.
- Further, aztreonam-avibactam MIC$_{90}$ values were lower than for comparators tested against resistant subsets of isolates, including MDR isolates and those carrying metallo-β-lactamases.

References

1. Clinical and Laboratory Standards Institute (CLSI) 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standards-Eleventh Edition*. CLSI Document M07-A11 (ISBN 1-56238-836-3). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
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3. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm, DF. 2015. *Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013*. Antimicrob Agents Chemother 59:3606-3610.

Disclosures

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