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P1156 *In vitro* activities of aztreonam-avibactam and comparator agents against carbapenemase-producing *Enterobacteriaceae* collected during the ATLAS Global surveillance program 2015-2017

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Background: Carbapenemase-producing *Enterobacteriaceae* (CPE) are often multidrug-resistant and cause significant morbidity and mortality. Aztreonam-avibactam is a β-lactam/β-lactamase inhibitor combination with activity against both serine carbapenemases and metallo-β-lactamases (MBL) in development for treatment of infections caused by CPE. We evaluated the *in vitro* activity of aztreonam-avibactam against CPE collected in 2015-2017 through the ATLAS global surveillance program.

Materials/methods: Non-duplicate, clinically significant *Enterobacteriaceae* isolates were collected from 145 medical centers in 34 countries in Europe, Latin America, Asia/Pacific, and the Middle East/Africa region. Susceptibility testing was performed by CLSI broth microdilution and results were interpreted using EUCAST 2018 breakpoints. Avibactam was tested at a fixed concentration of 4 mg/L in combination with aztreonam. All *Enterobacteriaceae* with meropenem MIC > 1 mg/L and all *Escherichia coli*, *Klebsiella* spp. and *Proteus mirabilis* phenotypically positive for ESBL activity (2015) or with aztreonam or ceftazidime MIC > 1 mg/L (2016-2017) were screened for the presence of β-lactamase genes by PCR and sequencing.

Results: 3.9% of collected isolates (1,199 *Klebsiella pneumoniae*, 104 *Enterobacter cloacae*, 88 *E. coli*, and 174 isolates of 16 other species) were CPE. Of these, 73.5% (n=1150) carried serine carbapenemases (KPC, OXA-48-like, GES), 23.3% (n=365) carried MBLs (NDM, VIM, IMP), and 3.2% (n=50) carried both serine- and metallo-carbapenemases (Table). Aztreonam-avibactam tested with MIC_{90}s of 0.12 mg/L against all collected *Enterobacteriaceae* and 0.5 mg/L against the overall collection of CPE and subsets of KPC-positive, OXA-48-like-positive and MBL-positive isolates. 99.94% (1564/1565) of CPE were inhibited by ≤8 mg/L of aztreonam-avibactam. The tested comparators showed reduced activity (<84% susceptible) against all subsets of CPE except GES-positive isolates, which were 100% susceptible to all agents but aztreonam.

Phenotype/Enzyme content (n)	MIC_{90} [mg/L]/% Susceptible[a]									
	ATM		ATM-AVI		MEM		CST		TGC	
	MIC_{90}	% S	MIC_{90}	% S	MIC_{90}	% S	MIC_{90}	% S	MIC_{90}	% S
All *Enterobacteriaceae* (40,320)	64	72.0	0.12	NA[b]	8	95.3	>8	83.3	1	90.3
All CPE (1,565)	>128	7.0	0.5	NA	>8	18.4	>8	75.8	2	79.0
KPC+, MBL- (713)[c]	>128	0.1	0.5	NA	>8	6.2	>8	71.4	2	80.1
GES+, MBL- (4)	0.5-128	25.0	0.03-0.25	NA	0.03-2	100	0.25-2	100	0.25-1	100
OXA-48-like+, MBL- (433)	>128	8.8	0.5	NA	>8	44.3	>8	75.3	2	82.4
MBL+ (415)[d]	>128	16.9	0.5	NA	>8	11.6	>8	83.9	4	73.5

CPE, carbapenemase-producing *Enterobacteriaceae*; MBL, metallo-β-lactamase; ATM, aztreonam; ATM-AVI, aztreonam-avibactam; MEM, meropenem; CST, colistin; TGC, tigecycline; n, number of isolates.
[a] % Susceptible was defined using EUCAST 2018 breakpoints. MIC_{90} was not determined for n <10 isolates, but the MIC range was provided instead.
[b] NA, no breakpoints available.
[c] Included 2 isolates co-carrying KPC and OXA-48-like carbapenemases.
[d] Included 45 isolates co-carrying MBL and OXA-48-like and 5 isolates co-carrying MBL and KPC carbapenemases.

Conclusions: Based on MIC_{90} values, aztreonam-avibactam was the most potent agent tested against CPE, including MBL-positive isolates and those carrying multiple carbapenemases, and retained activity against isolates resistant to the last-resort agents tigecycline and colistin. The promising *in vitro* activity of aztreonam-avibactam warrants further development of this combination for future use against infections caused by CPE.