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In-vitro activity of aztreonam-avibactam against isolates of Enterobacteriaceae collected in Europe as part of a global surveillance program, 2015

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Background: Aztreonam-avibactam is a β-lactam/β-lactamase inhibitor combination being developed for use against carbapenem-resistant *Enterobacteriaceae*, especially isolates producing metallo-β-lactamases (MBL). Aztreonam is stable to hydrolysis by MBL but inactivated by many serine β-lactamases. Avibactam is active against serine β-lactamases often co-carried with MBLs, including extended-spectrum β-lactamases (ESBL), AmpC β-lactamases, and serine carbapenemases. This study evaluated the *in vitro* activity of aztreonam-avibactam and comparators against *Enterobacteriaceae* collected in 2015 in Europe.

Material/methods: Non-duplicate clinical isolates of *Enterobacteriaceae* were collected from 67 centres in 17 European countries. Susceptibility testing was performed using CLSI broth microdilution and interpreted using EUCAST breakpoints. Aztreonam-avibactam was tested at a fixed concentration of 4 mg/L avibactam. Multidrug resistant (MDR) was defined as resistant by EUCAST breakpoints to sentinel agents from three or more drug classes (cephalosporins, monobactams, β-lactam/β-lactamase inhibitor combinations, carbapenems, fluoroquinolones, aminoglycosides, glycylcyclines, and polymyxins). PCR and sequencing were used to determine the β-lactamase genes present in isolates with meropenem MIC >1 mg/L, ceftazidime MIC >8 mg/L, and those phenotypically positive for ESBL activity.

Results: Aztreonam-avibactam demonstrated good activity against *Enterobacteriaceae*, with an MIC_{90} of 0.12 mg/L against the overall population and MIC_{90}s of 0.5–1 mg/L against aztreonam non-

susceptible, meropenem non-susceptible, colistin-resistant, MDR, and MBL-positive subsets (Table). >99.9% of isolates (6445 of 6449), including those that produced MBLs, were inhibited by ≤8 mg/L of aztreonam-avibactam. In comparison, 83.0–96.2% of overall isolates were susceptible to meropenem, tigecycline, and colistin. Activity of these comparator agents was greatly reduced against resistant subsets with the exception of colistin, which was active against MBL-positive isolates (MIC_{90} 1 mg/L, 96.7% susceptible). VIM- and NDM-type MBLs were found in 60 isolates of 5 species of *Enterobacteriaceae* collected in 10 European countries. 95.0% (n=57) of MBL-producing isolates co-carried one or more plasmid- or chromosomally-mediated ESBL, AmpC, or serine carbapenemase, including CTX-M-15, KPC-2 and OXA-48. No IMP-type MBLs were found in *Enterobacteriaceae* from Europe.

	Drug (MIC_{90} /% Susceptible)									
Species/Phenotype (n)	**ATM-AVI**		**ATM**		**MER**		**CST**		**TGC**	
Enterobacteriaceae , All (6449)	0.12	NA[a]	64	75.4%	0.12	96.2%	>8	83.0%	2	88.3%
ATM-NS (1590)	0.5	NA	>128	0.0%	>8	85.6%	4	89.8%	2	87.8%
MER-NS (248)	1	NA	>128	7.7%	>8	0.0%	>8	75.4%	2	76.2%
CST-R (125)[b]	1	NA	>128	24.0%	>8	51.2%	>8	0.0%	2	84.0%
MDR (1029)[c]	0.5	NA	>128	6.4%	>8	77.2%	>8	82.1%	4	80.0%
MBL-negative (6389)	0.12	NA	64	75.9%	0.12	97.0%	>8	82.9%	2	88.4%
MBL-positive (60)	1	NA	>128	21.7%	>8	10.0%	1	96.7%	2	70.0%

ATM-AVI, aztreonam-avibactam; ATM, aztreonam; MER, meropenem; CST, colistin; TGC, tigecycline; MDR, multidrug resistant; MBL, metallo-β-lactamase. EUCAST breakpoints were used to determine % susceptible and to define non-susceptible (NS) and resistant (R) subsets.
[a] NA, no breakpoints available
[b] Excludes isolates of Proteeae and *Serratia* spp.
[c] MDR, resistant by EUCAST breakpoints to sentinel agents from 3 or more drug classes.

Conclusions: Aztreonam-avibactam was highly potent *in vitro* against *Enterobacteriaceae* collected in Europe in 2015, including difficult-to-treat meropenem non-susceptible isolates (of which 21.8% carried MBLs), MDR, and colistin-resistant isolates. The promising activity of aztreonam-avibactam against MBL-producing isolates that often carry resistance mechanisms to multiple drug classes warrants further development of this combination for use against these pathogens.