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In-vitro activity of aztreonam-avibactam against metallo-beta-lactamase producing Enterobacteriaceae isolates collected during a global surveillance program, 2012-2015

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Background: Aztreonam-avibactam is in development for use against infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE), especially isolates carrying metallo-β-lactamases (MBLs). Aztreonam is refractory to hydrolysis by MBLs but is inactivated by Class A (KPC, extended-spectrum β-lactamases) and plasmid-mediated or stably-derepressed chromosomally-encoded Class C serine β-lactamases. Avibactam inhibits the activities of Class A, C, and some Class D β-lactamases that are frequently co-carried with MBLs. MBL-positive isolates often carry mechanisms conferring resistance against other antimicrobial classes such as aminoglycosides and fluoroquinolones, and are increasingly found among species naturally resistant to colistin and tigecycline, further reducing available therapeutic options. This study evaluated the *in vitro* activity of aztreonam-avibactam and comparators against MBL-positive isolates of *Enterobacteriaceae* collected globally in 2012–2015.
Material/methods: 51,352 non-duplicate isolates of *Enterobacteriaceae* were collected from 208 medical centres in 40 countries. Susceptibility testing was performed by CLSI broth microdilution. Aztreonam-avibactam was tested at a fixed concentration of 4 mg/L avibactam. PCR and sequencing of β-lactamase genes was performed on isolates with meropenem, doripenem, or imipenem MIC >1 mg/L or ertapenem MIC >0.5 mg/L.

Results: 3343 isolates of *Enterobacteriaceae* were molecularly characterized. Genes encoding IMP, VIM or NDM were detected in 267 isolates (149 *Klebsiella* spp., 65 *Enterobacter* spp., 18 *Citrobacter freundii*, 18 Proteeae, 12 *Escherichia coli*, and 5 *Serratia marcescens*). 45% of MBL-positive isolates were collected in 3 countries (Greece, n=55; the Philippines, n=35; Romania, n=31), with the remaining 55% collected in 25 countries each contributing 1–15 MBL-positive isolates. 86.9% of

isolates co-carried MBLs and one or more Class A or Class C β-lactamase able to hydrolyze aztreonam, resulting in MIC_{90} values of ≥128 mg/L for this agent (Table). In contrast, aztreonam-avibactam demonstrated potent *in vitro* activity against these MBL-positive isolates of *Enterobacteriaceae*, with MIC_{90} values of 0.5–1 mg/L against NDM-, IMP- and VIM-positive isolates (Table). All 267 MBL-positive isolates were inhibited by ≤8 mg/L of aztreonam-avibactam.

Organism (n)[a]	**Drug**	**Cumulative percentage of isolates inhibited at each MIC (mg/L) (%):**													
		≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
MBL-positive, All (267)	ATM	4.9	6.0	9.0	19.5	23.2	26.2	28.5	29.2	30.3	33.7	42.3	59.6	84.3	**100**
	ATM-AVI	16.9	27.7	54.7	82.0	89.5	**95.9**	98.1	99.3	100					
IMP-positive (29)	ATM		6.9	6.9	20.7	24.1	27.6	27.6	31.0	34.5	34.5	51.7	65.5	89.7	**100**
	ATM-AVI	20.7	34.5	51.7	82.8	89.7	**93.1**	93.1	100						
VIM-positive (96)	ATM	7.3	9.4	15.6	29.2	34.4	39.6	42.7	42.7	44.8	49.0	60.4	79.2	**90.6**	100
	ATM-AVI	25.0	29.2	49.0	76.0	85.4	**96.9**	100							
NDM-positive (142)	ATM	4.2	3.5	4.9	12.7	15.5	16.9	19.0	19.7	19.7	23.2	28.2	45.1	78.9	**100**
	ATM-AVI	10.6	25.4	59.2	85.9	**92.3**	95.8	97.9	98.6	100					

MBL-positive, gene encoding a metallo-β-lactamase (MBL) was detected by PCR; ATM, aztreonam; ATM-AVI, aztreonam-avibactam; MIC_{90} is indicated in bold font.
[a] Includes isolates co-carrying class A, C, and D β-lactamases.

Conclusions: Aztreonam-avibactam was highly active *in vitro* against all genotypically identified MBL-containing *Enterobacteriaceae*, regardless of serine β-lactamase co-carriage, species or country of isolation. The emergence and increasingly widespread dissemination of MBLs among *Enterobacteriaceae*, including ESKAPE pathogens and species that are intrinsically resistant to last-in-line therapies such as colistin and/or tigecycline, warrants further development of aztreonam-avibactam to explore therapy against infections caused by CRE.