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Aztreonam-avibactam susceptibility testing for carbapenemase-producing Enterobacterales (CPE) in the National Reference Laboratory (NRL): 2019-2021 surveillance results.

03. Bacterial susceptibility & resistance

3b. Resistance surveillance & epidemiology: Gram-negatives

Fernando Pasteran [1], Paola Ceriana [1], Celeste Lucero [1], Alejandra Menocal [1], Ezequiel Albornoz [1], Magali Chavez [1], Mariano Echegorry [1], Alejandra Corso [1]

Antimicrobianos INEI ANLIS Malbrán - Caba (Argentina)

Please add any third party affiliations (research group, study group etc.) for your abstract ATM-AVI Susceptibility Group

Background Aztreonam-avibactam (ATM-AVI) is a drug combination pending phase 3 clinical trials and is suggested for treatment of severe infections caused by metallo-beta-lactamase (MBL)-producing Enterobacterales. It also retains activity against KPC and several OXA-48-like variants. This study describes in vitro ATM-AVI susceptibility of CPE clinical isolates received at the NRL from January 2019 through October 2021.

Methods In 2019, the NRL started of ATM-AVI surveillance testing by agar dilution, using fixed 4 µg/ml AVI (CLSI/EUCAST). Enterobacterales that met the following criteria were eligible: 1) PCR-positive for ≥1 carbapenemase gene: blaNDM, blaVIM, blaIMP, blaKPC, blaOXA-48-like (L) and 2) exhibited not susceptible MICs (>1.0 mg/L) or halos (<21 mm) for ATM (EUCAST). Due to lack of interpretive criteria for ATM-AVI, MICs were interpreted with EUCAST (S<1-R>1mg/L) or CLSI (S<4-R>16mg/L) breakpoints for ATM alone.

Results 926 CPEs met the inclusion criteria: Citrobacter spp. (n=15), Enterobacter cloacae (n=107), Escherichia coli(n=55), Klebsiella aerogenes (n=9), K. oxytoca (n=25), K. pneumoniae (n=636), Proteae (n=39), Salmonella(n=2) and Serratia marcescens (n=38). Carbapenemase genes distribution (n) was: 331 (35.9%) blaNDM, 229 (24.6%) blaKPC, 174 (18.8%) blaOXA-48L, 13 (1.4%) blaIMP, 3 (0.3%) blaVIM, 124 (13.4%) blaKPC + blaNDM, 24 (2.6%) blaNDM + blaOXA-48L, 22 (2.4%) blaKPC + blaOXA-48L, 3 (0.3%) blaKPC + blaNDM + blaOXA-48L, 1 (0.1%) blaIMP + blaOXA-48L, 1 (0.1%) blaVIM + blaOXA-48L and 1 (0.1%) blaNDM + blaVIM. ESBL/plAmpC co-production: 232 blaCTXM, 65 blaPER, 24 blaCMY. 85% of MBLs had acquired an ESBL/plAmpC gene. ATM-AVI MIC50 and MIC90 were 0.12/4 mg/L and 1/4 mg/L. About 92.2% and 98.4% were categorized as susceptible using EUCAST and CLSI ATM criteria, respectively. MICs distribution by resistance mechanisms and bacterial species is shown in Figure 1.

Conclusions ATM-AVI demonstrated potent in vitro activity against CPEs, specifically NDMs. ATM-AVI retained activity against CPEs co-harboring several carbapenemases. Isolates with MICs >1.0/4 mg/L were mainly associated to PER coproduction (50/72, 69%), a ceftazidimase poorly inhibited by AVI, mainly found in E. cloacae (a specie that carried significantly more serine enzymes than MBLs, 88% vs 12%, respectively). ATM-AVI in vitro activity is uniform high, but differences can be found associated with species, type of carbapenemases and coproduction of ESBL PER.

Isolate categories	No. of isolates tested	No of isolates at each ATM-AVI MIC (mg/L)												MIC50	MIC90	% of susceptible according to	
		<=0,03	0,06	0,12	0,25	0,5	1	2	4	8	16	32	>=64			EUCAST	CLSI
ALL	926	121	111	271	182	93	76	35	22	7	2	4	2	0.12	1	92.2	98.4
Resistance mechanism																	
MBL	347	78	34	102	69	22	24	11	6	1				0.12	1	94.8	99.7
NDM	331	74	32	100	67	19	24	11	4					0.12	1	95.4	100
VIM	3			1	1	1											
IMP	13	4	2	1	1	2			2	1				0.12	4	76.9	92.3
KPC	229	13	26	76	45	15	19	13	9	5	2	4	2	0.12	2	84.7	94.3
OXA	174	22	10	31	35	37	23	9	6	1				0.25	1	90.1	99.4
Carbapenemase combinations	176	8	41	62	33	19	10	2	1					0.12	0.5	98.3	100
KPC+NDM	124	5	33	49	24	10	3							0.12	0.5	100	100
NDM+OXA	24	2	4	9	2	4	2	1						0.12	1	95.8	100
KPC+OXA	22	1	3	3	4	4	5	1	1					0.25	1	90.1	100
KPC+NDM+OXA	3		1	1		1											
IMP+OXA, VIM+OXA and VIM+NDM	3				3												
Main bacterial species																	
E. coli	55	19	15	13	5	1	1	1						0.06	0.25	98.2	100
E. cloacae	107	9	10	17	17	11	16	7	10	6	2	2		0.5	4	74.5	90.1
K. pneumoniae	636	64	41	181	166	93	59	19	9	1		1	2	0.25	1	94.9	97.9

MIC50, MIC90 and susceptible rates were calculated only for groups with >10 isolates. Colour shading indicates the not susceptible MICs according to ATM alone breakpoints by EUCAST (MIC >1 mg/L) or CLSI (MIC >= 8 mg/L)