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Evaluation of Aztreonam-Avibactam *In Vitro* Activity Against VIM and GES β-lactamase Producing, Carbapenem-Resistant *Pseudomonas aeruginosa* Collected From Contaminated Artificial Tear Products

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CONCLUSIONS

ATM-AVI demonstrated in vitro activity against all three XDR *P. aeruginosa* clinical isolates from infections caused by contaminated artificial tear products

The *in vitro* susceptibility evaluated using Disk diffusion, Etest and BMD methods demonstrated good correlation where tentative ATM-AVI PK/PD MIC breakpoints of ≤8/>8 mg/L (S/R) for BMD and E-test; or ≥23/18-22/≤17 mm (S/I/R) for disk diffusion were applied. All three XDR *P. aeruginosa* clinical isolates were susceptible to ATM-AVI

Treatment options for MBL-based infections are very limited. ATM-AVI has the potential to address emerging unmet medical needs to effectively combat MBL-producing pathogens co-expressing multiple resistance mechanisms attributed to XDR

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Clinical isolates were provided by CDC AR Bank.

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INTRODUCTION

- A rare strain of extensively drug-resistant (XDR) *Pseudomonas aeruginosa* was identified from contaminated artificial tear products that caused outbreak across 18 US states by May 2023 with 81 patients infected including 4 deaths, 8 reports of vision loss, and 4 reports of enucleation surgeries.[1]
- The strain carries Verona integron-encoded metallo-β-lactamase (VIM) and Guiana-Extended Spectrum-β-Lactamase (GES), a combination not previously identified in the US.[2]
- Aztreonam (ATM) is a monobactam that is stable against hydrolysis by metallo-β-lactamases (MBLs), and avibactam (AVI) is a non-β-lactam, β-lactamase inhibitor of a broad spectrum of enzymes, including Ambler Class A extended spectrum β-lactamases (ESBLs), Class A *Klebsiella pneumoniae* carbapenemase (KPC), Class C ampicillin (Amp) C enzymes, and some Class D enzymes.[3]
- ATM-AVI is currently in development for treatment of infections caused by drug-resistant Gram-negative pathogens, especially those co-producing MBLs and other problematic β-lactamases that contribute to multidrug resistance.
- The in vitro activities of ATM-AVI evaluated against 51,352 Enterobacterales clinical isolates collected in years 2012-2015, showed that > 99% of isolates were inhibited by aztreonam-avibactam at ≤4 mg/L, including isolates that produced IMP-, VIM-, and NDM-type MBLs in combination with other β-lactamases, such as ESBL, AmpC, and OXA-48. Against 11,842 *P. aeruginosa*, 73.4% of all isolates and 38.1% of MBL-producing isolates were inhibited at ATM-AVI MIC of ≤ 8 mg/L.[4]
- This study is to evaluate *in vitro* activities of ATM-AVI against VIM and GES producing carbapenem-resistant *P. aeruginosa* (VIM-GES-CRPA) isolates acquired from CDC AR Bank

METHODS

Bacterial Isolates

- Three VIM-GES-CRPA clinical isolates AR#1268, AR#1269 and AR#1270 were acquired from CDC AR Bank where the isolates were collected from urine, sputum, and cornea samples, respectively

Susceptibility Testing

- *In vitro* susceptibility to ATM, ATM-AVI (fixed concentration of 4 mg/L AVI), other β-lactam/β-lactamase inhibitors (BL/BLI), and comparators were tested by broth microdilution (BMD).
- The isolates were tested concurrently by disk diffusion method using ATM-AVI 30-20 µg disks manufactured by Becton Dickinson Biosciences (BD) and Mast Group (Mast); cefiderocol and ATM disks by Hardy diagnostics (Hardy); ATM-AVI E-test strips by Liofilchem, Inc.
- CLSI test methods were followed and CLSI 2023 breakpoints were applied for susceptibility interpretations.
- Tentative ATM-AVI pharmacokinetic/pharmacodynamic (PK/PD) MIC breakpoints of ≤8/>8 mg/L (Susceptible/Resistant) for BMD and E-test; or ≥23/18-22/≤17 mm (Susceptible/Intermediate/Resistant) for disk diffusion were applied for comparison purposes.

RESULTS

- The MIC values of ATM-AVI by BMD were in the range of 4-8 mg/L and correlated with the values measured by ATM-AVI Etest (2-6 mg/L) demonstrating *in vitro* activity against VIM-GES-CRPA (**Table 1, Table 3, Figure 1**)
- ATM-AVI inhibition zone diameters measured by both BD and Mast discs were in the range of 25-27 mm indicating the activity of ATM-AVI against VIM-GES-CRPA (**Table 3, Figure 2**)
- Out of 17 FDA approved antibiotics in the susceptibility test panel, only cefiderocol showed *in vitro* susceptibility (MIC 0.5mg/L) against VIM-GES-CRPA indicating limited treatment options for MBL-producing pathogens. (**Table 1**)
- Molecular characterization revealed almost identical resistance mechanisms harbored in three VIM-GES-CRPA isolates collected from urine, sputum, and cornea. VIM-80 and GES-9 combination was noted as the most critical factor attributing to XDR in the presence of other mechanisms co-expressed, such as porin mutation, etc. (**Table 2**)

Table 1. *In vitro* Susceptibility of Aztreonam/avibactam and Comparators Tested Against VIM and GES β-lactamase Producing, Carbapenem-Resistant *Pseudomonas aeruginosa* Collected From Contaminated Artificial Tear Products

Isolate	AR#1268		AR#1269		AR#1270	
Drug	MIC (mg/L)	INT	MIC (mg/L)	INT	MIC (mg/L)	INT
Amikacin	>64	R	>64	R	>64	R
Aztreonam	>32	R	>32	R	>32	R
Aztreonam/avibactam	8	NA	4	NA	4	NA
Cefepime	>32	R	>32	R	>32	R
Cefiderocol	0.5	S	0.5	S	0.5	S
Ceftazidime	>128	R	>128	R	>128	R
Ceftazidime/avibactam	>16	R	>16	R	>16	R
Ceftolozane/tazobactam	>16	R	>16	R	>16	R
Ciprofloxacin	>8	R	>8	R	>8	R
Colistin	1	I	0.5	I	1	I
Delafloxacin	NA	NA	>4	R	NA	NA
Imipenem	64	R	16	R	16	R
Imipenem/relebactam	64	R	8	R	8	R
Imipenem+chelators	8	---	2	---	2	---
Levofloxacin	>8	R	>8	R	>8	R
Meropenem	>8	R	>8	R	>8	R
Piperacillin/tazobactam	>128	R	64	R	64	R
Tobramycin	>16	R	>16	R	>16	R

Compiled MIC results from Abbvie data file and CDC AR Bank
I = intermediate; R = resistant; S = sensitive; S – I – R Interpretation (INT) derived from CLSI 2023 M100 S33
NA = not available

Table 2. Molecular Resistance Mechanisms Detected in VIM and GES β-lactamase Producing Carbapenem-Resistant *P. aeruginosa*

Resistance Category	AR#1268	AR#1269	AR#1270
Aminoglycoside	aac(6')-Ib-G, aadA1, aph(3")-Ib, aph(3')-IIb, rmtF2	aac(6')-Ib-G, aadA1, aph(3")-Ib, aph(3')-IIb, rmtF2	aac(6')-Ib-G, aadA1, aph(3")-Ib, aph(3')-IIb, rmtF2
Beta-lactam	**GES-9**, OXA-10, OXA-395, PDC-19A, **VIM-80**	**GES-9**, OXA-10, OXA-395, PDC-19A, **VIM-80**	**GES-9**, OXA-10, OXA-395, PDC-19A, **VIM-80**
Efflux pumps/Other	mexA, mexE, qacEdelta1	mexA, mexE, qacEdelta1	mexA, mexE, qacEdelta1
Fosfomycin	fosA	fosA	fosA
Macrolide-Lincosamide-Streptogramin	ere(A)	ere(A)	ere(A)
Phenicols/Bicyclomycins	bcr1, catB, floR, floR2	bcr1, catB, floR, floR2	bcr1, catB, floR, floR2
Sulfonamides	sul1	sul1	sul1
Tetracyclines	tet(G)	tet(G)	tet(G)
Trimethoprim	dfrA5	dfrA5	dfrA5

CDC AR Isolate Bank https://wwwn.cdc.gov/ARIsolateBank/Panel/PanelDetail?ID=10

Table 3. *In vitro* Susceptibility of Aztreonam-Avibactam Against VIM and GES β-lactamase Producing Carbapenem-Resistant *P. aeruginosa* Evaluated by Etest and Diffusion Disks

	ATM-AVI Etest	Disk (mm)			
	MIC mg/L	Aztreonam	Cefiderocol	ATM-AVI (Mast)	ATM-AVI (BD)
CDC AR#1268	6	14	26	25	27
CDC AR#1269	2	15	26	26	26
CDC AR#1270	3	16	26	26	27

BD = BD Biosciences, Mast = Mast Group

Figure 1. *In vitro* Susceptibility of Aztreonam/avibactam Tested Against VIM and GES β-lactamase Producing, Carbapenem-Resistant *P. aeruginosa* Collected From Contaminated Artificial Tear Products by E-test

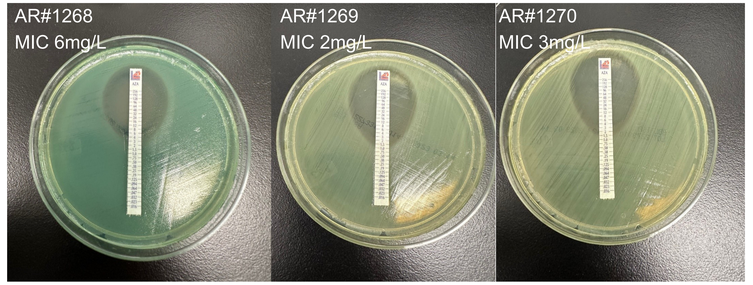
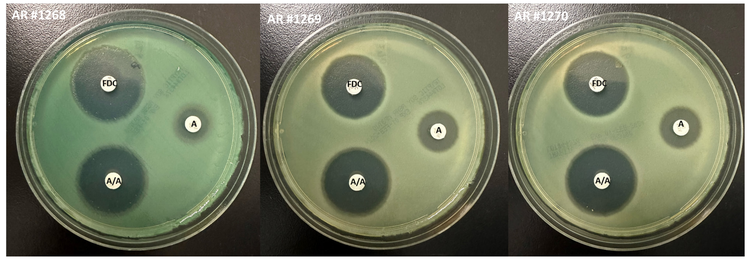


Figure 2. *In vitro* Susceptibility of Aztreonam/avibactam Tested Against VIM and GES β-lactamase Producing, Carbapenem-Resistant *P. aeruginosa* Collected From Contaminated Artificial Tear Products by Diffusion Disks



A = Aztreonam, A/A = Aztreonam-Avibactam, FDC = cifiderocol