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Activity of Aztreonam-Avibactam and Other β-Lactamase Inhibitor Combinations against Gram-negative Bacteria Isolated from Patients Hospitalized with Pneumonia in US Medical Centers (2020–2022)

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CONCLUSIONS

Increasing resistance to recently approved BLIs, such as CAZ-AVI, MEM-VAB, and IMI-REL, among the CRE isolates causing pneumonia in US hospitals is of great concern and it appears to be due to increased occurrence of MBL producers.

ATM-AVI demonstrated potent *in vitro* activity against the GNB most commonly isolated from patients with pneumonia in US hospitals.

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INTRODUCTION

- Resistance to recently approved β-lactamase inhibitor combinations (BLIs), such as ceftazidime-avibactam (CAZ-AVI) and meropenem-vaborbactam (MEM-VAB), appears to be increasing among carbapenem-resistant Enterobacterales (CRE) in some US hospitals.
- Aztreonam is a monobactam stable to hydrolysis by metallo-β-lactamases (MBLs); avibactam is a non–β-lactam β-lactamase inhibitor that inhibits serine β-lactamases such as ESBLs, KPCs, AmpCs, and some OXAs.
- Aztreonam-avibactam (ATM-AVI) is under clinical development for the treatment of infections caused by Gram-negative bacteria (GNB), including MBL producers.
- We evaluated the frequency and antimicrobial susceptibility of Gram-negative bacteria (GNB) causing pneumonia in US hospitals.

METHODS

- A total of 3,911 Enterobacterales and 2,753 non-fermenters were consecutively collected (1/patient) from patients hospitalized with pneumonia.
- Isolates were collected in 69 medical centers in 2020–2022.
- Susceptibility testing was performed by CLSI broth microdilution in a monitoring laboratory.
- ATM-AVI was tested with AVI at fixed 4 mg/L and a pharmacokinetic/pharmacodynamic susceptible (S) breakpoint of ≤8 mg/L was applied for comparison.
- CRE isolates were screened for carbapenemases (CPE) by whole genome sequencing.

RESULTS

- GNB represented 71.2% of bacteria isolated from patients with pneumonia (Figure 1).
- The most common GNB species were *P. aeruginosa* (22.4% of organisms), *K. pneumoniae* (8.8%), *E. coli* (6.6%), *S. marcescens* (6.2%), *S. maltophilia* (4.9%), and *E. cloacae* complex (4.8%; Figure 1).
- ATM-AVI inhibited 100.0% of Enterobacterales at ≤8 mg/L and 99.9% at ≤4 mg/L and showed potent activity against CRE ($MIC_{50/90}$, 0.25/1 mg/L; Table 1 and Figure 2).
- CAZ-AVI and MEM-VAB were active against 89.4% and 88.5% of CREs, respectively (Figure 2).
- ATM-AVI inhibited all (100.0%) Enterobacterales non-susceptible to CAZ-AVI and/or MEM-VAB at ≤8 mg/L (n=19; $MIC_{50/90}$, 0.25/4 mg/L).
- The most common CPEs were KPC (69.2% of CREs), NDM (9.6%), and SME (4.8%; Figure 3).
- A CPE gene was not observed in 16.3% of CREs (Figure 3).
- CAZ-AVI and MEM-VAB were highly active against KPC and SME producers but showed limited activity against MBL producers.
- Among *P. aeruginosa*, 79.1% were inhibited at ≤8 mg/L of ATM-AVI, 77.2% were meropenem-susceptible, and 77.2% were piperacillin-tazobactam-susceptible (Figure 2).
- The most active compounds against *P. aeruginosa* were CAZ-AVI (96.1% susceptible [S]), imipenem-relebactam (IMI-REL; 97.1%S), and ceftolozane-tazobactam (TOL-TAZ; 96.9%S).
- ATM-AVI was highly active against *S. maltophilia*, inhibiting 99.5% of isolates at ≤8 mg/L (Figure 2).

Table 1. Antimicrobial susceptibility of organisms from patients hospitalized with pneumonia in US medical centers (2020–2022)

	% Susceptible per CLSI and or FDA criteria (no. of isolates)					
Antimicrobial agent	ENT (3,911)	CRE (104)	KPN (961)	ECLC (515)	PSA (2,130)	XM (200)
Aztreonam-avibactam	100.0 [a]	100.0 [a]	100.0 [a]	100.0 [a]	79.1 [a]	99.5 [a]
Ceftazidime-avibactam	99.6	89.4	99.6	99.0	96.1	
Meropenem-vaborbactam	99.7	88.5	99.5	99.2		
Imipenem-relebactam	95.0 [b]	80.6 [b]	98.7	98.7	97.1	
Ceftolozane-tazobactam	88.6	11.5	91.6	67.5	96.9	
Piperacillin-tazobactam	79.4	6.7	78.4	62.2	77.2	
Ceftriaxone	74.8	5.8	77.9	58.3		
Ceftazidime	79.5	11.5	78.1	61.4	81.2	22.0
Cefepime	85.5	14.4	78.9	81.6	83.3	
Ertapenem	95.2		95.3	85.5		
Imipenem	92.0 [b]		95.6	96.3	76.5 [b]	
Meropenem	97.3	6.7	95.2	96.1	77.2	
Ciprofloxacin	81.7	30.5	77.4	91.1	79.3	
Levofloxacin	84.3	35.6	81.6	92.6	70.6	83.5
Gentamicin	91.0	60.6	88.6	95.3		
Amikacin	95.1	73.1	96.1	98.3		
Tobramycin					89.4	
Tigecycline	96.2	95.2	97.0	97.3	--	91.5 [c]
TMP-SMX						97.5

a % inhibited at ≤8 mg/L.
b All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species.
c at ≤2 mg/L.
Abbreviations: ENT, Enterobacterales; CRE, carbapenem-resistant Enterobacterales; KPN, *K. pneumoniae*; ECLC, *Enterobacter cloacae* species complex; PSA, *P. aeruginosa*; XM, *S. maltophilia*.

Figure 1. Frequency of organisms isolated from patients with pneumonia in US medical centers (2020–2022)

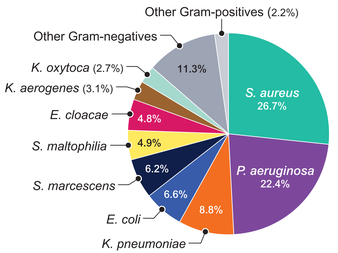
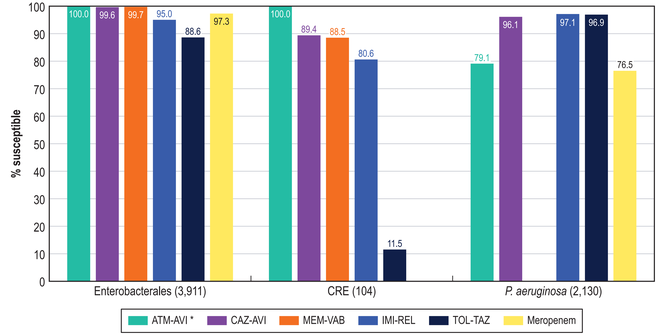
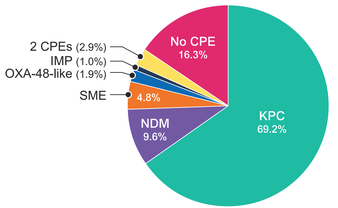


Figure 2. Antimicrobial activity of beta-lactamase inhibitors and meropenem against Enterobacterales, CRE, and *P. aeruginosa* isolated from patients hospitalized with pneumonia in US medical centers (2020–2022)



* % inhibited at ≤8 mg/L

Figure 3. Frequency of carbapenemases among CRE isolates from patients hospitalized with pneumonia



Abbreviation: CPE, carbapenemase.