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Antimicrobial Activity of Aztreonam-avibactam, Ceftazidime-avibactam, and Meropenem-vaborbactam against Enterobacterales causing Bloodstream Infection in US Medical Centers (2020–2022)

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CONCLUSIONS

ATM-AVI demonstrated potent activity against a large collection of Enterobacterales isolated from patients with BSI in US hospitals, including CREs and isolates resistant to recently approved β-lactamase inhibitor combinations.

ATM-AVI may represent valuable treatment options for infections caused by MBL-producing Enterobacterales.

The results of this investigation support further clinical development of ATM-AVI.

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INTRODUCTION

- As the frequency of Enterobacterales producing metallo-β-lactamase (MBL) and/or OXA-48 is increasing in some US medical centers, effective antimicrobials to treat the infections caused by these organisms are urgently needed.
- Aztreonam-avibactam (ATM-AVI) is under clinical development for treatment of infections caused by Gram-negative bacteria, including MBL producers.
- We evaluated the activities of ATM-AVI, ceftazidime-avibactam (CAZ-AVI), meropenem-vaborbactam (MEM-VAB), and comparators against Enterobacterales isolated from patients with bloodstream infections (BSIs).

Figure 1. ATM-AVI MIC distributions for Enterobacterales and CRE isolates

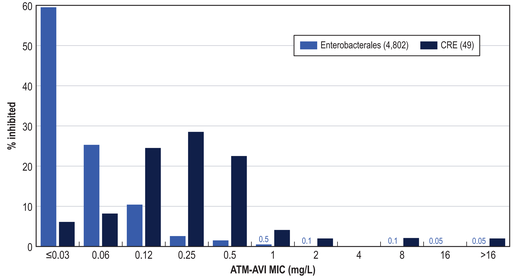
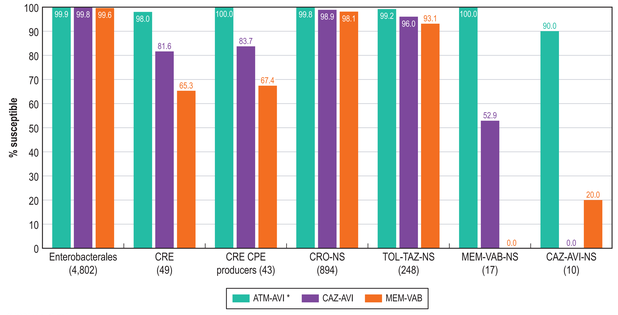
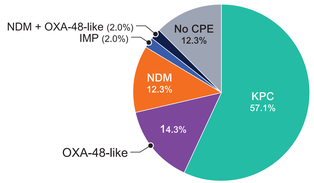


Figure 2. Aztreonam-avibactam (ATM-AVI), ceftazidime-avibactam (CAZ-AVI), and meropenem-vaborbactam (MEM-VAB) against Enterobacterales and selected resistant subsets



% inhibited at ≤8 mg/L.
Abbreviations: CRE, carbapenem-resistant Enterobacterales; CPE, carbapenemase; CRO, ceftriaxone; NS, nonsusceptible; and TOL-TAZ, ceftolozane-tazobactam.

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



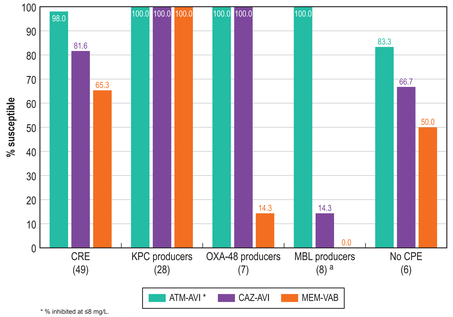
METHODS

- 4,802 Enterobacterales were consecutively collected (1/patient) from 72 US medical centers in 2020–2022 and susceptibility tested by CLSI broth microdilution method.
- ATM-AVI was tested with AVI at a fixed 4 mg/L.
- A pharmacokinetic/pharmacodynamic susceptible breakpoint of ≤8 mg/L was applied to ATM-AVI for comparison.
- Carbapenem-resistant Enterobacterales (CRE) isolates were screened for carbapenemase (CPE) by whole genome sequencing.

RESULTS

- ATM-AVI was highly active against Enterobacterales (Figure 1); only 2 isolates showed ATM-AVI MICs >8 mg/L: 1 *E. coli* (meropenem-susceptible) and 1 *K. aerogenes* (CRE).
- All CPE producers and 98.0% of CREs were inhibited at an ATM-AVI MIC of ≤8 mg/L (Figures 1 and 2).
- CAZ-AVI and MEM-VAB were active against 81.6% and 65.3% of CREs, respectively (Table 1 and Figure 2).
- Ceftolozane-tazobactam (TOL-TAZ) was active against only 72.6% of ceftriaxone (CRO)-nonsusceptible (NS) isolates (Table 1).
- ATM-AVI retained activity (MIC, ≤8 mg/L) against all MEM-VAB-NS and 90.0% of CAZ-AVI-NS isolates (Figure 2).
- The most common CPEs were KPC-2/3 (57.1% of CREs), OXA-48–like (16.3%), and NDM (14.3%; Figure 3).
- A CPE gene was not observed in 12.3% of CREs (Figure 3).
- CAZ-AVI and MEM-VAB were active against 100.0% of KPC producers, but CAZ-AVI showed limited activity against MBL producers and MEM-VAB showed limited activity against OXA-48–like and MBL producers (Figure 4).

Figure 4. Aztreonam-avibactam (ATM-AVI), ceftazidime-avibactam (CAZ-AVI), and meropenem-vaborbactam (MEM-VAB) against CRE isolates stratified by carbapenemase (CPE) type



* % inhibited at ≤8 mg/L.
a Include isolate with NDM + OXA-48-like.

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

	% Susceptible per CLSI and or FDA criteria (no. of isolates)				
Antimicrobial agent	ENT (4,802)	CRE (49)	CPE (43)	CRO-NS (894)	MDR (437)
Aztreonam-avibactam	>99.9 [a]	98.0 [a]	100.0 [a]	99.8 [a]	99.5 [a]
Ceftazidime-avibactam	99.8	81.6	83.7	98.9	97.9
Meropenem-vaborbactam	99.6	65.3	67.4	98.1	96.3
Imipenem-relebactam	95.0 [b]	61.2 [b]	62.8	94.2 [b]	93.7 [b]
Ceftolozane-tazobactam	94.8	2.0	2.3	72.6	70.0
Piperacillin-tazobactam	88.7	2.0	2.3	53.4	40.4
Ceftriaxone	81.4	0.0	0.0	0.0	3.2
Ceftazidime	84.7	2.0	2.3	20.1	12.4
Cefepime	86.9	2.0	2.3	30.8	12.6
Meropenem	98.9	2.0	2.3	94.1	88.1
Imipenem	92.9 [b]	4.1 [b]	0.0 [b]	89.1 [b]	85.1 [b]
Levofloxacin	79.5	16.3	14.0	42.9	13.3
Gentamicin	90.2	49.0	44.2	66.5	34.0
Amikacin	93.4	44.9	41.9	82.3	63.8
Tigecycline	96.7	95.9	95.3	96.3	95.2

a % inhibited at ≤8 mg/L.
b All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species.