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Antimicrobial Activity of Aztreonam-Avibactam Against Enterobacterales Causing Infection in United States Hospitals (2019–2021)

HS Sader, RE Mendes, LR Duncan, V Kantro, M Castanheira

JMI Laboratories, North Liberty, Iowa, USA

CONCLUSIONS

Aztreonam-avibactam demonstrated potent and consistent activity against Enterobacterales across infection types and over time.

Aztreonam-avibactam retained activity against MDR, XDR, and CRE-producing isolates, including MBL and OXA-48–like producers.

Meropenem-vaborbactam activity decreased slightly during the study period due to the increase of CRE isolates that produced MBL and/or OXA-48–like carbapenemases.

SCAN ME

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Contact Information

Helio S. Sader, MD, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

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INTRODUCTION

- The frequency of metallo-β-lactamase (MBL)-producing Enterobacterales is increasing in the United States (US) and effective antibiotics to treat infections caused by these organisms are urgently needed.
- We evaluated the activity of aztreonam-avibactam and comparators against a large collection of clinical Enterobacterales isolates from US hospitals.

METHODS

- 27,834 Enterobacterales isolates were consecutively collected from 74 US medical centers in 2019–2021.
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the investigation.
- Isolates were collected from patients with bloodstream infection (BSI; 5,159 isolates; 18.5%), pneumonia (4,013; 14.4%), skin and skin structure infection (SSSI; 3,418; 12.3%), urinary tract infection (UTI; 13,177; 47.3%), or other infections (2,067; 7.4%).
- Susceptibility testing was performed by CLSI broth microdilution method and aztreonam-avibactam was tested with avibactam at fixed concentration of 4 mg/L.
- A provisional aztreonam-avibactam PK/PD breakpoint of ≤8 mg/L was applied for comparison.
- The antimicrobial susceptibility and frequency of key resistance phenotypes were assessed and stratified by year and infection type.
- Carbapenem-resistant Enterobacterales (CRE) isolates were defined as displaying an imipenem and/or meropenem MIC ≥4 mg/L; imipenem was not applied to *Proteus mirabilis* and indole-positive Proteeae due to their intrinsically elevated MIC values.
- Multidrug resistance (MDR) was defined as nonsusceptible (CLSI breakpoints) to at least 3 antimicrobial classes and extensively drug-resistant (XDR) was defined as susceptible to ≤2 classes (Magiorakos et al., 2012).
- CRE were screened for carbapenemase (CPE) genes by whole genome sequencing (WGS).

RESULTS

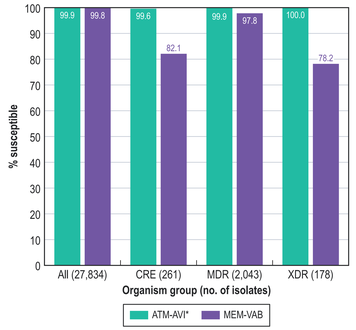
- Aztreonam-avibactam inhibited >99.9% of Enterobacterales at ≤8 mg/L (Tables 1 and 2; Figure 1).
- Only 3 isolates (0.01%) had an aztreonam-avibactam MIC >8 mg/L.
- The susceptibility of Enterobacterales to ceftriaxone varied from 84.0% in 2019 to 82.1% in 2021 (Table 2).
  - Susceptibility of ceftriaxone was lowest among isolates from patients with pneumonia (75.3%; Table 1).
- CRE rates were 0.8%, 0.9%, and 1.1% in 2019, 2020, and 2021, respectively (Figure 2).
- 99.6% (260/261) of CRE isolates were inhibited at an aztreonam-avibactam MIC of ≤8 mg/L (Table 2 and Figure 1).
- CRE susceptibility to meropenem-vaborbactam decreased from 91.7% in 2019 to 83.1% in 2020 and 76.5% in 2021 (82.1% overall; Figure 3).
- CRE and MDR phenotypes were markedly higher among isolates from pneumonia compared to other infections (Figure 4).
- The most common carbapenemase among CRE was KPC (65.5% of CRE), followed by NDM (11.1%), OXA-48–like (4.6%), SME (2.3%), and IMP (1.5%).
  - Four isolates (1.5% of CRE) had 2 carbapenemases.
- The percentages of CRE producing KPC carbapenemase decreased, whereas the percentages of CRE isolates producing MBLs and OXA-48–like increased markedly from 2019 to 2021 (Figure 5).
- Two *E. coli* (New York and Texas) and a *K. aerogenes* (Kentucky) displayed elevated aztreonam-avibactam MIC values (>8 mg/L).
  - The *E. coli* isolates were carbapenem susceptible, whereas the *K. aerogenes* exhibited MIC values of 2 mg/L for meropenem (intermediate) and 4 mg/L for imipenem.
  - Both *E. coli* isolates carried bla_{OXY} and $bla_{CTX\text{-}M\text{-}15}$ and exhibited a 4 amino acid insertion at residue 333 of PBP3.
  - The *K. aerogenes* isolate overexpressed AmpC and had a premature stop codon within OmpC.

Table 1. Activity of aztreonam-avibactam and comparators against US Enterobacterales isolates stratified by infection type (2019–2021)

Antimicrobial agent	MIC in mg/L		% Susceptible[a] by infection type (no. of isolates)					
	MIC_{50}	MIC_{90}	BSI (5,159)	Pneumonia (4,013)	SSSI (3,418)	UTI (13,177)	Others (2,067)	All (27,834)
Aztreonam-avibactam[b]	≤0.03	0.12	[>99.9][b]	[100.0][b]	[>99.9][b]	[100.0][b]	[100.0][b]	[>99.9][b]
Meropenem-vaborbactam	0.03	0.06	99.7	99.8	99.9	99.9	99.8	99.8
Ceftolozane-tazobactam	0.25	1	95.1	88.9	94.1	96.4	92.7	94.5
Piperacillin-tazobactam	2	16	88.3	79.1	89.7	92.0	87.7	88.8
Ceftriaxone	≤0.06	>8	82.3	75.3	82.3	85.7	82.8	82.9
Meropenem	0.03	0.06	98.9	97.3	99.1	99.5	99.3	99.0
Levofloxacin	0.06	8	79.4	83.3	84.8	82.2	85.4	82.4
Gentamicin[c]	0.5	2	87.7	88.6	89.0	89.0	90.8	88.8[c]
Amikacin[c]	2	4	92.7	94.2	94.9	94.7	95.2	94.4[c]

[a] Criteria as published by CLSI (2022).
[b] Percentage inhibited at ≤8 mg/L for comparison.
[c] The susceptible breakpoints recently approved by CLSI for gentamicin (≤1 mg/L) and amikacin (≤4 mg/L) were applied.
Abbreviations: BSI, bloodstream infection; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Figure 1. Antimicrobial activities of aztreonam-avibactam (ATM-AVI) and meropenem-vaborbactam (MEM-VAB) against US Enterobacterales isolates and resistant subsets (2019–2021)



Abbreviations: CRE, carbapenem-resistant Enterobacterales; MDR, multidrug-resistant; XDR, extensively drug-resistant.
* Percentage inhibited at ≤8 mg/L

Table 2. Activity of aztreonam-avibactam and comparators against US Enterobacterales and resistant subsets stratified by year (2019–2021)

Antimicrobial agent	% Susceptible[a] by year (no. of isolates)			
	2019 (9,686)	2020 (9,262)	2021 (8,916)	All (27,834)
All isolates				
Aztreonam-avibactam[b]	[>99.9][a]	[>99.9][a]	[>99.9][a]	[>99.9][b]
Meropenem-vaborbactam	99.9	99.8	99.7	99.8
Ceftolozane-tazobactam	95.0	94.6	94.1	94.5
Piperacillin-tazobactam	89.2	89.1	88.2	88.8
Ceftriaxone	84.0	82.7	82.1	82.9
Meropenem	99.1	99.0	98.8	99.0
Levofloxacin	82.2	82.1	82.9	82.4
Gentamicin[c]	89.8	88.2	88.5	88.8[c]
Amikacin[c]	95.2	94.1	93.7	94.4[c]
CRE	(80)	(83)	(98)	(261)
Aztreonam-avibactam[b]	[100.0][b]	[100.0][b]	[99.0][b]	[99.6]
Meropenem-vaborbactam	91.7	83.1	76.5	82.1
Levofloxacin	20.3	25.3	28.6	25.0
Gentamicin[c]	42.5	49.4	51.0	47.9
Amikacin[c]	62.5	55.4	59.2	59.0
MDR	(660)	(711)	(672)	(2,043)
Aztreonam-avibactam[b]	[99.8]	[99.9]	[99.9]	[99.9]
Meropenem-vaborbactam	99.1	98.0	96.7	97.8
Ceftolozane-tazobactam	68.2	67.8	66.4	67.4
Piperacillin-tazobactam	33.9	39.0	33.9	35.7
Ceftriaxone	5.3	4.4	4.2	4.6
Meropenem	87.9	88.0	84.8	86.9
Levofloxacin	16.2	17.9	19.9	18.0
Gentamicin[c]	37.3	34.2	35.1	35.5
Amikacin[c]	68.8	66.7	67.9	67.7
XDR	(52)	(65)	(61)	(178)
Aztreonam-avibactam[b]	[100.0]	[100.0]	[100.0]	[100.0]
Meropenem-vaborbactam	90.0	81.5	68.9	78.2
Ceftolozane-tazobactam	0.0	3.1	0.0	1.1
Piperacillin-tazobactam	0.0	0.0	0.0	0.0
Ceftriaxone	0.0	0.0	0.0	0.0
Meropenem	3.8	7.7	1.6	4.5
Levofloxacin	3.8	4.6	6.6	5.1
Gentamicin[c]	19.2	32.3	23.0	25.3
Amikacin[c]	44.2	33.8	32.8	36.5

[a] Criteria as published by CLSI (2022).
[b] Percentage inhibited at ≤8 mg/L for comparison.
[c] The susceptible breakpoints recently approved by CLSI for gentamicin (≤1 mg/L) and amikacin (≤4 mg/L) were applied.
Abbreviations: CRE, carbapenem-resistant Enterobacterales; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Figure 2. Frequencies of carbapenem-resistant Enterobacterales (CRE) and multidrug-resistant (CRE) Enterobacterales stratified by year (2019–2021)

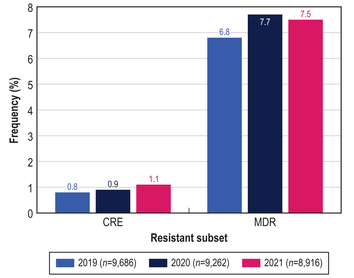
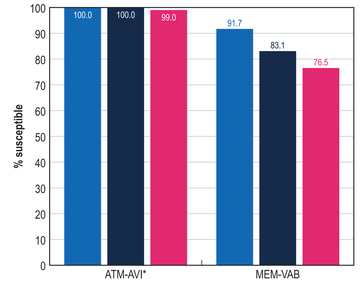
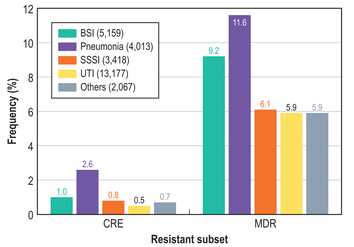


Figure 3. Antimicrobial activities of aztreonam-avibactam (ATM-AVI) and meropenem-vaborbactam (MEM-VAB) against US carbapenem-resistant Enterobacterales (CRE) stratified by year (2019–2021)



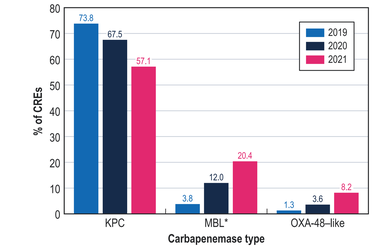
* Percentage inhibited at ≤8 mg/L.

Figure 4. Frequencies of carbapenem-resistant Enterobacterales (CRE) and multidrug-resistant (MDR) Enterobacterales stratified by infection type (2019–2021)



Abbreviations: BSI, bloodstream infections; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Figure 5. Frequencies of isolates producing KPC, MBL, and OXA-48–like carbapenemases among US carbapenem-resistant Enterobacterales (CRE) stratified by year (2019–2021)



* Includes NDM (87.9%) and IMP (12.1%) carbapenemase types.