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Activity of Aztreonam-Avibactam and Comparators against Difficult-to-Treat Resistant (DTR) Enterobacterales from United States Medical Centers (2020–2024)

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CONCLUSIONS

ATM-AVI retained potent activity against DTR Enterobacterales from US medical centers and its activity was not adversely affected by clinically relevant CBases or resistance to agents used to treat multidrug-resistant Enterobacterales.

The activities of CAZ-AVI, MEM-VAB, and IMI-REL were compromised by the increased occurrence of MBL producers among DTR and CRE isolates.

INTRODUCTION

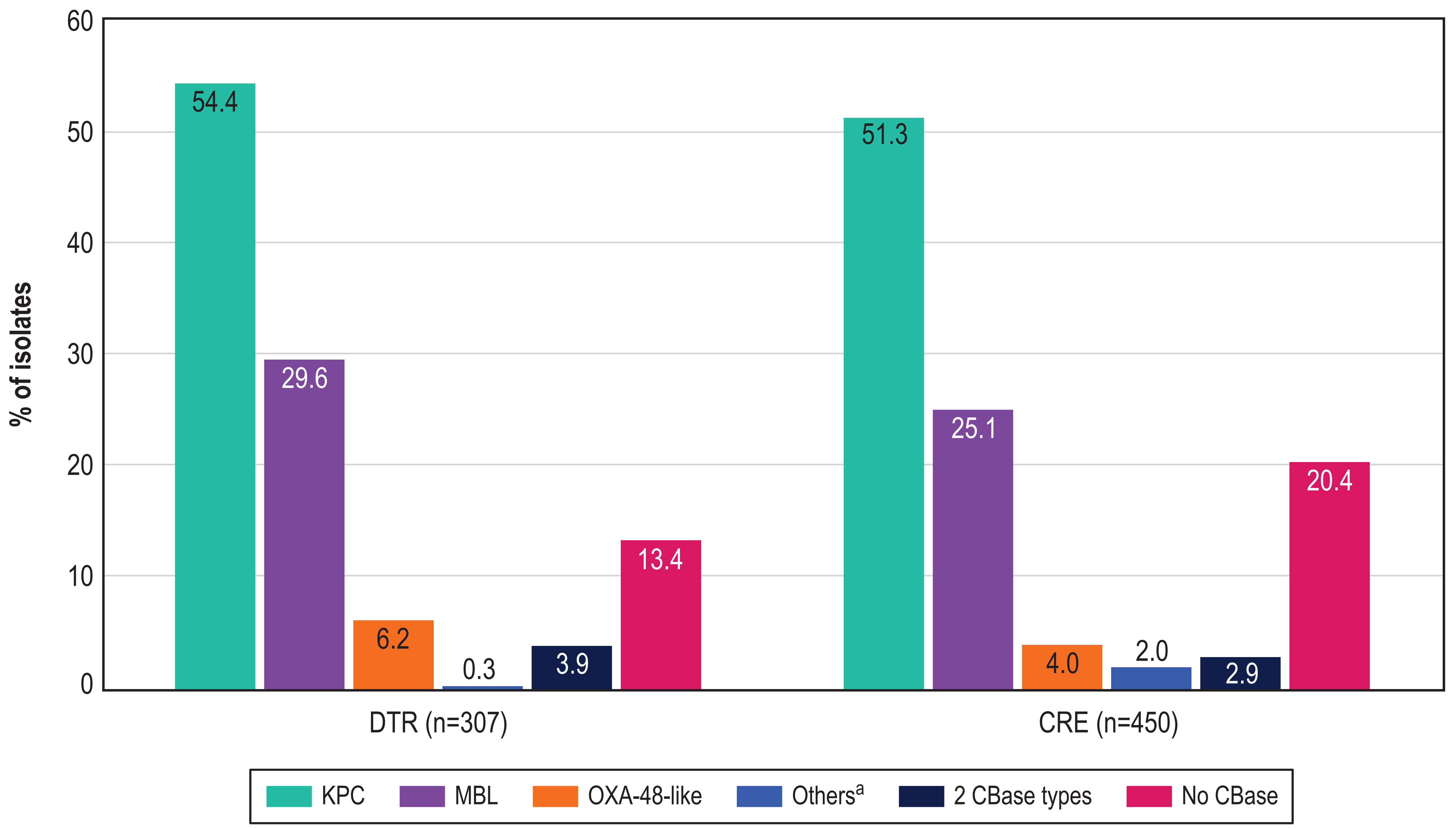
- Aztreonam-avibactam (ATM-AVI) was recently approved by the US FDA for treatment of complicated IAI and by the EMA in the European Union for treatment of adults with complicated IAI, complicated urinary tract infection (cUTI), hospital-acquired pneumonia, including ventilator-associated pneumonia, and infections due to aerobic Gram-negative bacteria in adults with limited treatment options.
- Aztreonam-avibactam (ATM-AVI) has demonstrated potent activity against multidrug-resistant (MDR) Enterobacterales worldwide, including metallo-β-lactamase (MBL) producers.
- We evaluated the activity of ATM-AVI and comparators against DTR Enterobacterales from US medical centers.

Table 1. Antimicrobial susceptibility of selected resistant subsets

Antimicrobial agent	% Susceptible per CLSI or US FDA criteria (no. of isolates)					
	DTR (307)	CAZ-AVI-NS DTR (89)	MEM-VAB-NS DTR (106)	Cefiderocol-NS DTR (20)	MBL-producer DTR (91)	CRE (450)
ATM-AVI	98.0	95.5	96.2	90.0	97.8	97.1
CAZ-AVI	71.0	0.0	21.7	20.0	5.5	74.4
MEM-VAB	65.5	6.7	0.0	20.0	8.8	70.9
IMI-REL	63.2	3.4	5.7	15.0	2.2	66.4
Cefiderocol	93.5	82.0	84.9	0.0	84.6	94.0
Gentamicin	54.4	59.6	53.8	65.0	59.3	61.6
Amikacin	57.0	56.2	51.9	65.0	54.9	66.2

Abbreviations: DTR, difficult-to-treat resistant; CAZ-AVI, ceftazidime-avibactam; NS, nonsusceptible; MEM-VAB, meropenem-vaborbactam; MBL, metallo-β-lactamase; CRE, carbapenem-resistant Enterobacterales; ATM-AVI, aztreonam-avibactam; IMI-REL, imipenem-relebactam.

Figure 1. Distribution of carbapenemase types among DTR and CRE isolates


% of isolates
0
10
20
30
40
50
60
54.4
29.6
6.2
0.3
3.9
13.4
51.3
25.1
4.0
2.0
2.9
20.4
DTR (n=307)
CRE (n=450)
KPC
MBL
OXA-48-like
Others[a]
2 CBase types
No CBase

[a] Includes GES-6 (1 isolate) for DTR and SME-2 (5), SME-4 (2), GES-6 (1), and IMI-4 (1) for CRE.
Abbreviations: DTR, difficult-to-treat resistant; CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases; OXA, oxacillinase; CBase, carbapenemase.

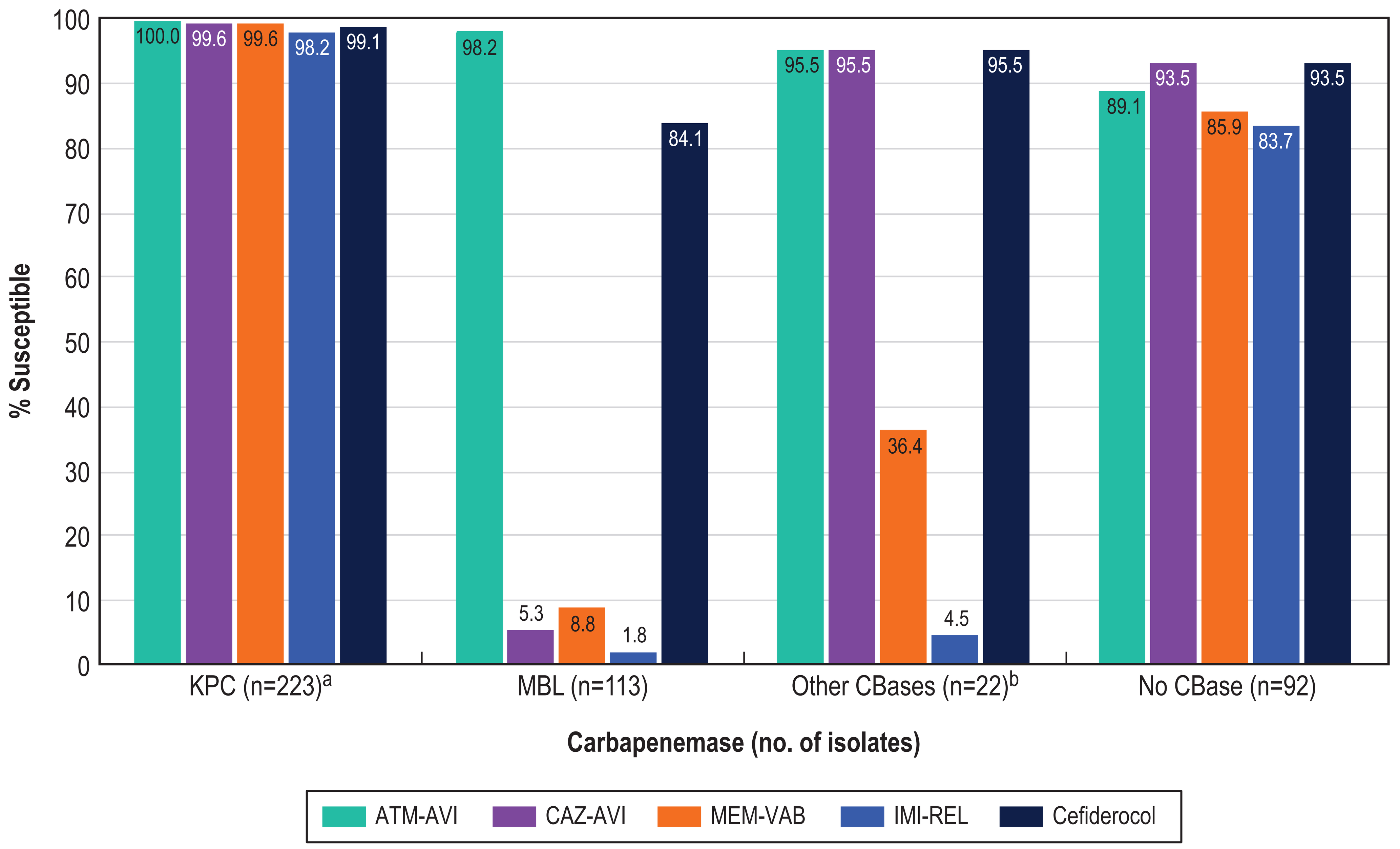
METHODS

- A total of 42,295 Enterobacterales isolates were consecutively collected (1/patient) from 85 US medical centers in 2020–2024.
- The collection included 450 carbapenem-resistant (CRE) and 307 difficult-to-treat resistant (DTR) Enterobacterales.
 - CRE was defined as resistant to meropenem and/or imipenem.
 - DTR was defined as a CRE isolate resistant to fluoroquinolones (levofloxacin and/or ciprofloxacin).
- Only bacterial isolates determined to be significant by local criteria as the reported probable cause of infection were included in the study.
- Isolates were susceptibility tested by CLSI M07 broth microdilution method.
- The ATM-AVI susceptible breakpoint of ≤4 mg/L, which was established by the US FDA and EMA for Enterobacterales, was applied.
- All CRE isolates were screened for β-lactamase genes by whole genome sequencing.

RESULTS

- ATM-AVI was active (MIC ≤4 mg/L) against 98.0% of DTR ($MIC_{50/90}$, 0.25/1 mg/L) and 97.1% of CRE ($MIC_{50/90}$, 0.25/1 mg/L) isolates (Table 1).
- ATM-AVI retained potent activity against DTR isolates nonsusceptible to ceftazidime-avibactam (CAZ-AVI; 95.5% susceptible [S]; $MIC_{50/90}$, 0.25/1 mg/L), meropenem-vaborbactam (MEM-VAB; 96.2% S; $MIC_{50/90}$, 0.25/1 mg/L), and/or cefiderocol (90.0% S; $MIC_{50/90}$, 0.5/4 mg/L; Table 1).
- Cefiderocol was active against 93.5% of DTR isolates, whereas CAZ-AVI, MEM-VAB, IMI-REL, and the aminoglycosides exhibited limited activity against these organisms (Table 1).
- The most common carbapenemase (CBase) genes identified among DTR (n=307) isolates were bla_{KPC} (54.4% of isolates) and bla_{NDM} (28.0%).
- DTR and CRE isolates exhibited similar frequencies of CBase types (Figure 1).
- An MBL gene was observed in 29.6% of DTR and 25.1% of CRE isolates (Figure 1).
- ATM-AVI ($MIC_{50/90}$, 0.12/0.5 mg/L) and cefiderocol ($MIC_{50/90}$, 2/8 mg/L) were active against 98.2% and 84.1% of MBL producers, respectively, whereas MEM-VAB and IMI-REL exhibited poor activity against these organisms (Figure 2).

Figure 2. Susceptibility stratified by β-lactamase type


% Susceptible
0
10
20
30
40
50
60
70
80
90
100
100.0
99.6
99.6
98.2
99.1
98.2
5.3
8.8
1.8
84.1
95.5
95.5
36.4
4.5
95.5
89.1
93.5
85.9
83.7
93.5
KPC (n=223)[a]
MBL (n=113)
Other CBases (n=22)[b]
No CBase (n=92)
Carbapenemase (no. of isolates)
ATM-AVI
CAZ-AVI
MEM-VAB
IMI-REL
Cefiderocol

[a] Excludes MBL co-producers.
[b] Includes OXA-48-like (14), SME type (7), and IMI-4 (1); and excludes MBL co-producers.
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases; CBase, carbapenemase; ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam.

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