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Activity of aztreonam-avibactam against Enterobacterales isolated from patients with intra-abdominal infection from Europe, Asia, and Latin America (2020–2024)

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Introduction

- Aztreonam-avibactam (ATM-AVI) was recently approved by the US FDA for treatment of complicated intra-abdominal infection (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 against Enterobacterales isolated from patients with IAI.

Methods

- A total of 3,565 isolates (1/patient) were consecutively collected in 2020–2024 from patients with IAI in 52 medical centers from 28 countries as follows:
 - Western Europe (W-EU): 2,059 isolates from 25 centers in 10 countries
 - Eastern Europe (E-EU): 524 isolates from 7 centers in 5 countries
 - The Asia-Pacific region (APAC): 645 isolates from 12 centers in 7 countries
 - Latin America (LATAM): 337 isolates from 8 centers in 6 countries.
- Only bacterial isolates determined to be significant by local criteria as the reported probable cause of pneumonia 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.
- Carbapenem-resistant Enterobacterales (CRE) were screened for carbapenemases (CBase) by whole genome sequencing.

Results

- The most common Enterobacterales species were *E. coli* (50.4%), *K. pneumoniae* (18.0%), and *E. cloacae* species complex (8.0%).
- Susceptibility of Enterobacterales stratified by species is shown in Table 1.
- Only 2 Enterobacterales exhibited ATM-AVI MIC >4 mg/L ($MIC_{50/90}$, ≤0.03/0.12 mg/L), 2 *E. coli* with ATM-AVI MIC of 8 mg/L.
- A multidrug-resistant (MDR) phenotype (not susceptible [S] to ≥3 classes per EUCAST) was observed in 14.6% of Enterobacterales (*n*=522).
- The most active β-lactamase inhibitor combination (BLIC) against MDR isolates were ATM-AVI (99.6% S), ceftazidime-avibactam (CAZ-AVI; 91.9% S), meropenem-vaborbactam (MEM-VAB; 91.6% S), and imipenem-relebactam (IMI-REL; 87.9% S; Table 1).
- Piperacillin-tazobactam (PIP-TAZ) was active against 82.2% of Enterobacterales and 38.1% of MDR, and meropenem was active against 97.4% of Enterobacterales and 82.2% of MDR.
- A CBase was identified in 92 isolates (89.3% of CREs), and included KPCs (44.7% of CREs), MBLs (40.8%), and OXA-48 type (15.5%); 11.7% of CRE had 2 CBase types and a CBase was not identified in 10.7% of CREs (Figure 1).
- Only ATM-AVI showed good activity against CRE ($MIC_{50/90}$, 0.25/1 mg/L, 100.0% S); CAZ-AVI, MEM-VAB, and IMI-REL were active against 59.2%, 57.3%, and 43.4% of CRE, respectively (Figure 2).
- All CBase producers were susceptible to ATM-AVI whereas susceptibility to CAZ-AVI, MEM-VAB, and IMI-REL were 55.4%, 54.3%, and 42.9%, respectively (Figure 2).
- The frequencies of CBases varied markedly by region (Figure 3).

Conclusions

- ATM-AVI exhibited almost complete activity against Enterobacterales causing IAI in Europe, the Asia-Pacific region, and Latin America.
- The activities of CAZ-AVI, MEM-VAB, and IMI-REL against CRE were compromised by the high occurrence of MBL and OXA-48-like producers.

Acknowledgments

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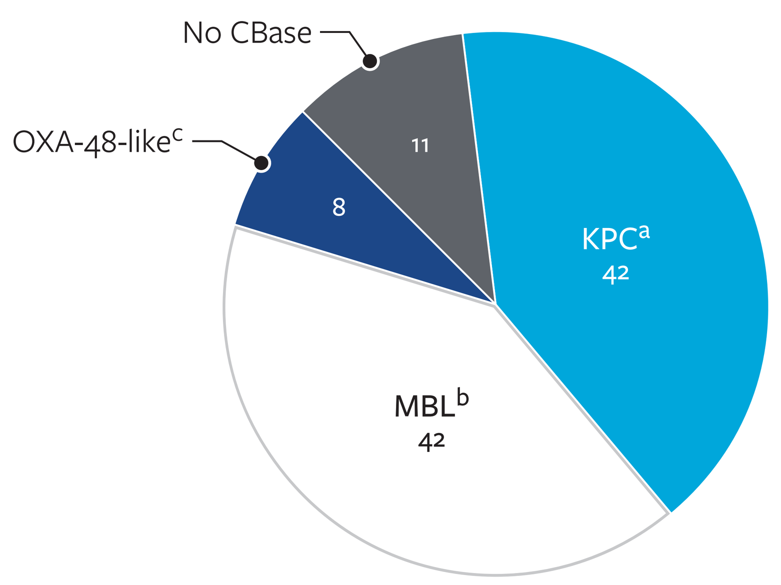
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Figure 1. Carbapenemase distribution (no. of isolates)


No CBase
OXA-48-like[c]
11
8
KPC[a]
42
MBL[b]
42

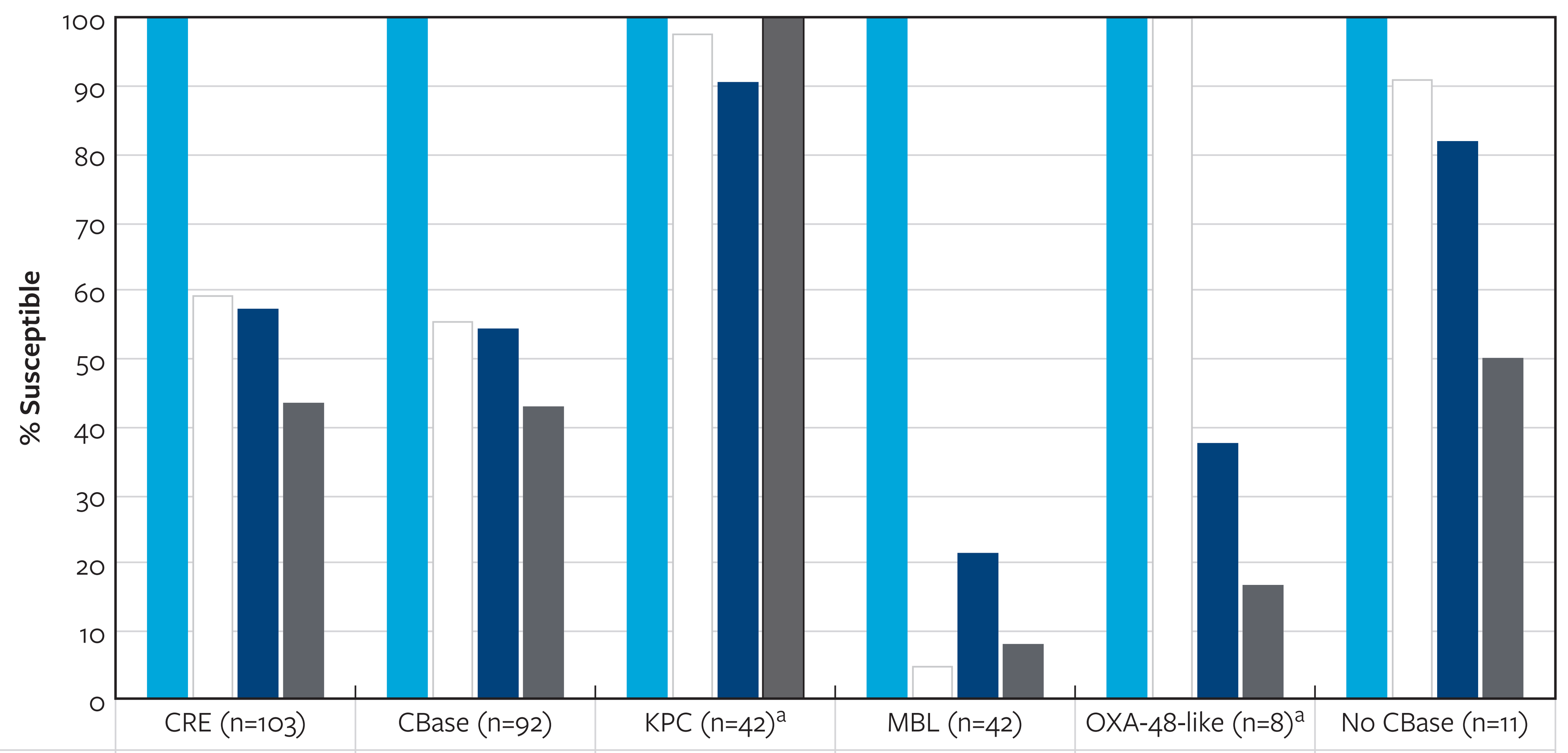
[a] Includes KPC-2 (22), KPC-3 (19), and KPC-4 (1); and excludes 4 MBL co-producers (KPC-2 plus NDM-1 [2], KPC-2 plus VIM-1 [1], and KPC-3 plus VIM-1 [1])
[b] Includes NDM-1 (23), NDM-5 (11), and VIM-1 (8). The MBL co-producers are included in this group.
[c] Includes OXA-48 (6), OXA-181 (1), and OXA-232 (1); and excludes 8 MBL co-producers (OXA-48 plus NDM-1 [2], OXA-48 plus NDM-5 [2], OXA-181 plus NDM-5 [1], OXA-232 plus NDM-1 [1], and OXA-232 plus NDM-5 (2).

Table 1. Activity of β-lactamase inhibitor combinations and ceftriaxone against Enterobacterales from intra-abdominal infections

Organism / group (no.)	% Susceptible per EUCAST (MIC_{90} in mg/L)					
	ATM-AVI	CAZ-AVI	MEM-VAB	IMI-REL	PIP-TAZ	CRO
Enterobacterales (3,565)	99.9 (0.12)	98.8 (0.5)	98.8 (0.06)	97.6 (0.5)	82.2 (64)	75.2 (>8)
MDR (522)	99.6 (0.5)	91.9 (2)	91.6 (4)	87.9 (8)	38.1 (>128)	11.1 (>8)
E. coli (1,798)	99.9 (0.06)	99.7 (0.25)	99.7 (0.03)	99.8 (0.12)	90.7 (8)	79.0 (>8)
K. pneumoniae (641)	100.0 (0.25)	95.6 (1)	94.5 (0.5)	93.3 (0.5)	69.6 (>128)	67.9 (>8)
E. cloacae complex (285)	100.0 (1)	98.2 (1)	98.9 (0.06)	98.0 (0.25)	60.7 (128)	57.9 (>8)
K. oxytoca (157)	100.0 (0.12)	98.7 (0.25)	100.0 (0.03)	98.9 (0.25)	81.4 (>128)	87.3 (4)
P. mirabilis (124)	100.0 (≤0.03)	99.2 (0.06)	100.0 (0.12)	77.0 (4)	99.2 (1)	91.9 (≤0.06)
C. freundii complex (117)	100.0 (0.5)	100.0 (0.5)	100.0 (0.03)	100.0 (0.12)	61.5 (128)	60.7 (>8)
Other species (443)	100.0 (0.25)	100.0 (0.5)	100.0 (0.06)	99.3 (1)	81.3 (64)	76.7 (>8)

Abbreviations: ATM-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam; PIP-TAZ, piperacillin-tazobactam; CRO, ceftriaxone; MDR, multidrug-resistant.

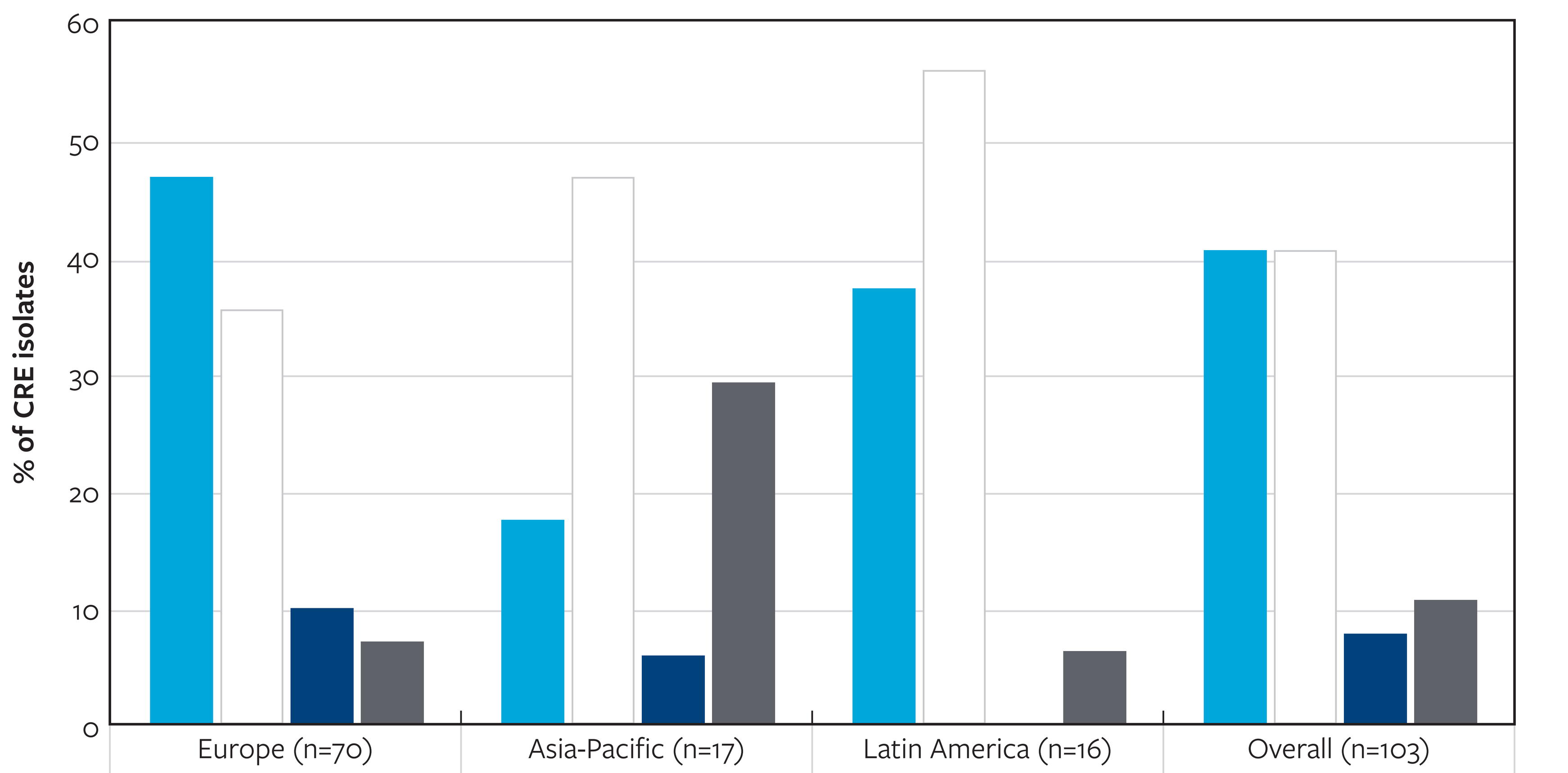
Figure 2. Activity of selected BLICs against CRE isolates stratified by carbapenemase type


% Susceptible
0
10
20
30
40
50
60
70
80
90
100

	CRE (n=103)	CBase (n=92)	KPC (n=42)[a]	MBL (n=42)	OXA-48-like (n=8)[a]	No CBase (n=11)
ATM-AVI	100.0	100.0	100.0	100.0	100.0	100.0
CAZ-AVI	59.2	55.4	97.6	4.8	100.0	90.9
MEM-VAB	57.2	54.3	90.5	21.4	37.5	81.8
IMI-REL	43.4	42.9	100.0	8.0	16.7	50.0

[a] Excludes MBL co-producers.
Abbreviations: BLICs, β-lactamase inhibitor combinations; CRE, carbapenem-resistant Enterobacterales; CBase, carbapenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; OXA, oxacillinase.

Figure 3. Distribution of carbapenemase types by region


% of CRE isolates
0
10
20
30
40
50
60

	Europe (n=70)	Asia-Pacific (n=17)	Latin America (n=16)	Overall (n=103)
KPC[a]	47.1	17.6	37.5	40.8
MBL	35.7	47.1	56.3	40.8
OXA-48-like[a]	10.0	5.9	0.0	7.8
No CBase	7.1	29.4	6.3	10.7

[a] Excludes MBL co-producers.
Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; OXA, oxacillinase; CBase, carbapenemase.

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