

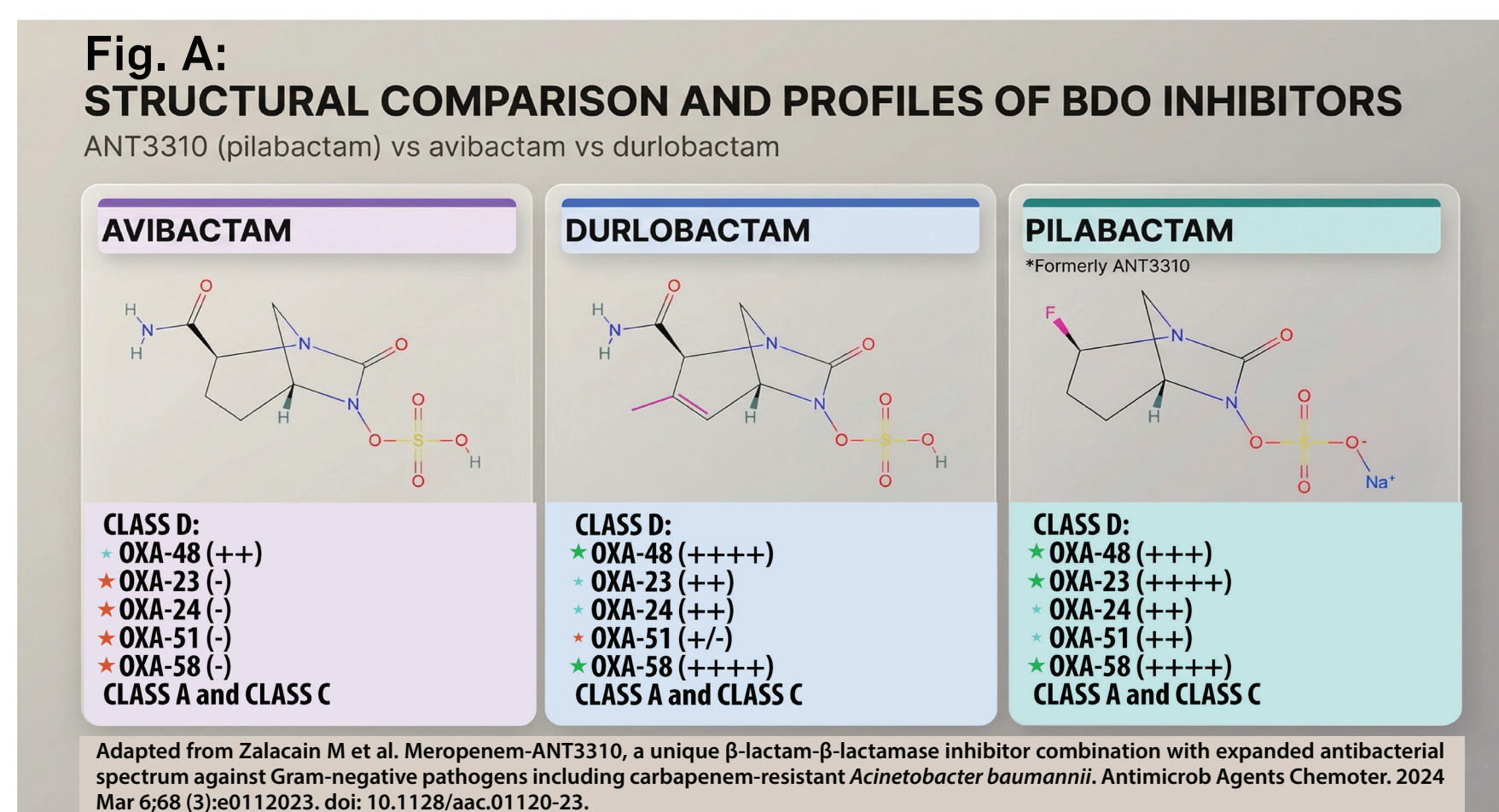
Targeting Metallo- β -lactamase Endemicity: Activity of Novel Meropenem-Pilabactam in Combination with Aztreonam against Contemporary Enterobacterales

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Background

Metallo- β -lactamase (MBL)-producing Enterobacterales are globally increasing and are associated with substantial mortality. Aztreonam (ATM) is intrinsically stable to MBL hydrolysis; however, its activity is often nullified by co-produced serine β -lactamases-SBL- (ESBLs, AmpC, and/or KPC). A rational strategy is to pair ATM with a potent SBL inhibitor. Pilabactam (formerly, Pilabactam), a next generation diazabicyclooctane SBL inhibitor, is being developed in combination with meropenem for the treatment of severe infections caused by Gram-negative pathogens in hospitalized patients (Figure A). Our working hypothesis is that pairing ATM with meropenem-Pilabactam will neutralize accompanying SBLs and restore ATM's intrinsic activity against MBLs.



Objective

To evaluate the in vitro activity of ATM-Pilabactam against contemporary MBL-producing Enterobacterales.

Methods

- 317 eligible isolates from a National Prevalence Survey (RECAPT-AR; 181 hospitals) with confirmed MBL production (PCR/WGS) and phenotypic ATM resistance or SBL co-production.
- Resistance mechanisms: 312 NDM producers, 4 VIM and 1 IMP. S β L co-produced are depicted in Figure 1.
- Species identification was performed using MALDI-TOF. MICs were determined by CLSI reference methods. SBL inhibitor were used at a fix concentration: Pilabactam 8 mg/L; avibactam (AVI), relebactam (RELE) or clavulanic acid (CLAV) 4 mg/L. A provisional breakpoint of ≤ 4 mg/L defined susceptibility for ATM-Pilabactam, ATM-RELE and ATM-CLAV; other agents were interpreted per CLSI, EUCAST or FDA.

Results

ATM alone showed high resistance (MIC_{50/90} >128 mg/L). Adding AVI or Pilabactam markedly reduced MIC_{50/90} to 0.12/0.25 mg/L (Figure 1-2). No isolates had ATM-Pilabactam MIC >0.5 mg/L (Figures 3). Eleven NDM producers with elevated ATM-AVI MICs (8-32 mg/L) were mostly cross-resistant to cefiderocol (9/11, 82%) and yet remained susceptible to ATM- Pilabactam (≤ 0.06 -0.25 mg/L). By categorical analysis, ATM-Pilabactam was the most active regimen (100 % susceptible) and did not differ significantly from ATM-AVI (97.2 %, $p > 0.05$). ATM- Pilabactam outperformed other ATM combinations (84.5% ATM-RELE, 71.1% ATM-CLAV), colistin (78.3%), fosfomycin (71.5%), cefiderocol (68.7%-51.3% by EUCAST/CLSI) and amikacin (19%) ($p < 0.05$).

Figure 1. MIC summary for novel agents against MBL producer Enterobacterales*

Antimicrobial agent	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	Range (mg/L)
ATM	>128	>128	1** - >128
ATM-AVI	0.12	0.25	≤ 0.06 - 32
ATM-Pilabactam	0.12	0.25	≤ 0.06 - 0.5
ATM-RELE	1	8	≤ 0.25 - 64
ATM-CLAV	0.25	>128	≤ 0.25 - >128
CEFIDEROCOL	2	>8	≤ 0.06 - >8

ATM: aztreonam. AVI: avibactam. RELE: relebactam. CLAV: clavulanic acid. Fixed inhibitor concentrations: Pilabactam 8 mg/L; AVI, RELE, CLAV 4 mg/L. Cefiderocol was tested in iron-depleted cation-adjusted Mueller-Hinton broth.
*Species included: *K. pneumoniae* (n 267), *E. coli* (13), *Enterobacter cloacae complex* (12) and other spp. (25).
S β L co-produced were: CTX-M (n 204), CMY (32), OXA-163 (14), KPC (6), CTXM+CMY (3) and CTXM+PER (1).
** Some Protease isolates carrying acquired *bla*_{CMY} or *bla*_{OXA-163} were phenotypically susceptible to ATM (MICs 1-4 mg/L).

Figure 2. Cumulative MIC distributions for aztreonam (ATM) alone and combined with different serine β -lactamase inhibitors against MBL-producing Enterobacterales

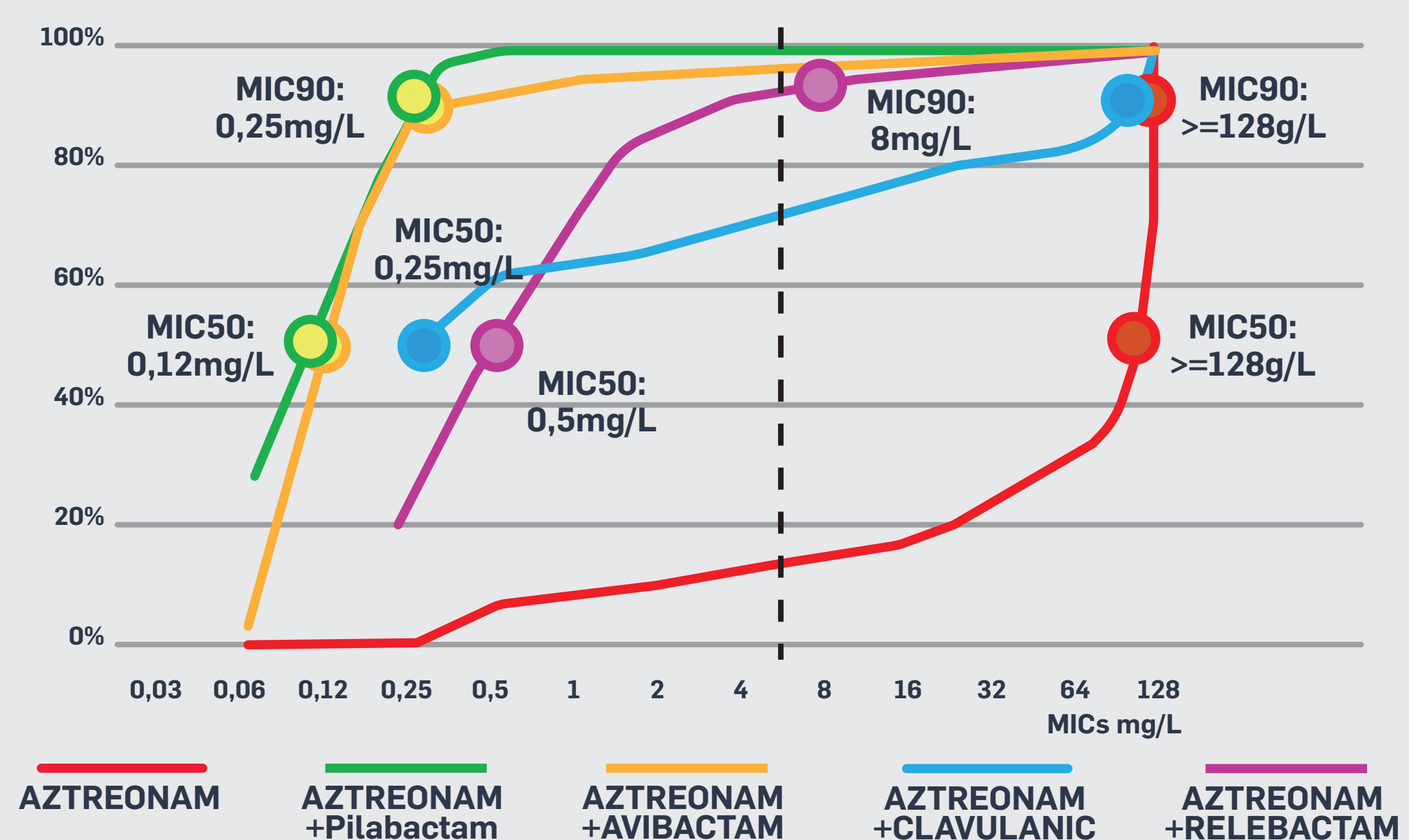
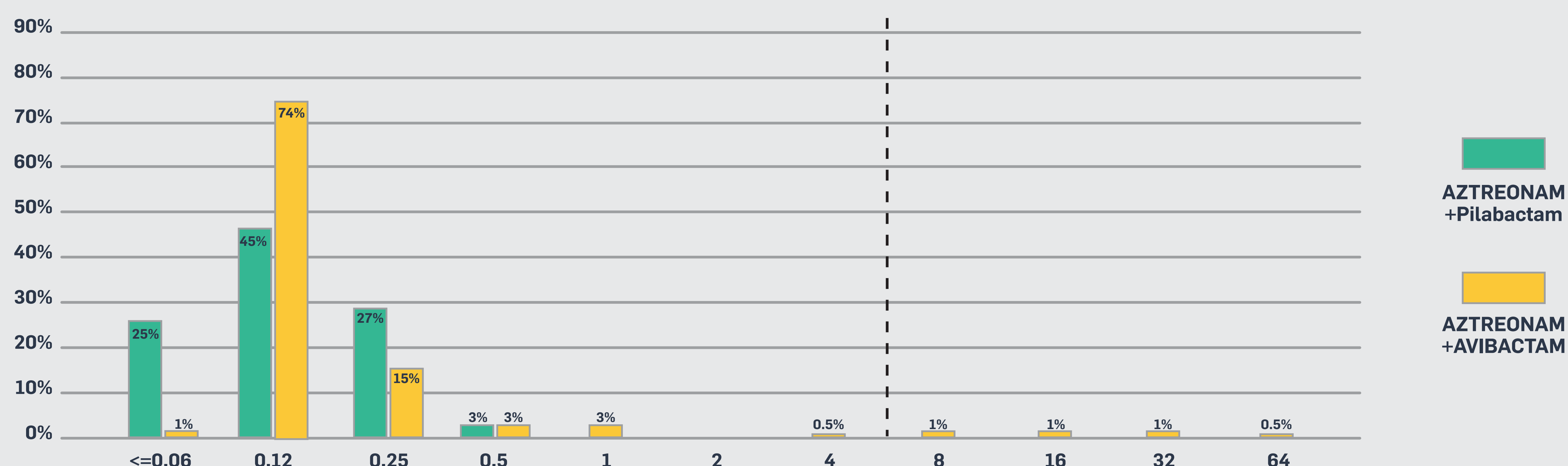


Figure 3. MIC distributions for aztreonam-avibactam and aztreonam-Pilabactam against MBL-producing Enterobacterales



Conclusions

Pilabactam restored ATM activity across a large, molecularly diverse MBL-producing Enterobacterales collection, even in isolates non-susceptible to ATM-AVI and cefiderocol. These findings support ATM in combination with MEM-Pilabactam as a compelling option for MBL-endemic settings, pending clinical PK/PD confirmation and dose-ranging studies.