#05356Targeting metallo-β-lactamase endemicity: activity of novel meropenem-ANT3310 in combination with aztreonam against contemporary Enterobacterales

03. Bacterial susceptibility & resistance
03c. Susceptibility testing methods (incl assay validation, phenotypic assays and comparative studies, excl TB)

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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. ANT3310, a next generation diazabicyclooctane SBL inhibitor, is being developed with meropenem to treat severe infections caused by Gram-negative pathogens in hospitalized patients. Our working hypothesis is that pairing ATM with meropenem-ANT3310 will neutralize accompanying SBLs and restore ATM's activity against MBLs. AIM: to evaluate the in vitro activity of ATM-ANT3310 against contemporary MBL-producing Enterobacterales.

Methods

We included 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. All except 5 isolates produced NDM; among the others: 4 VIM and 1 IMP. SβL co-produced are depicted in Figure 1. Species identification was with MALDI-TOF. MICs were determined by CLSI reference methods. SBL inhibitor were used at a fix concentration: ANT3310 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-ANT3310, ATM-RELE and ATM-CLAV; other agents were interpreted per CLSI, EUCAST or FDA.

Results

ATM alone showed high resistance (MIC50/90 >128 mg/L). Adding AVI or ANT3310 markedly reduced MIC50/90 to 0.12/0.25 mg/L (Figure 1-2). No isolates had ATM-ANT3310 MIC >0.5 mg/L (Figure 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-ANT3310 (<=0.06-0.25 mg/L). By categorical analysis, ATM-ANT3310 was the most active regimen (100 % susceptible) and did not differ significantly from ATM-AVI (97.2 %, p>0.05). ATM-ANT3310 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).

Conclusions

ANT3310 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-ANT3310 as a compelling option for MBL-endemic settings, pending clinical PK/PD confirmation and dose-ranging studies.

MIC summary for novel agents against MBL producer Enterobacterales*

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

Antimicrobial agent	MIC50 (mg/L)	MIC90 (mg/L)	Range (mg/L)
ATM	>128	>128	1** - >128
ATM-AVI	0.12	0.25	<=0.06 - 32
ATM-ANT3310	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

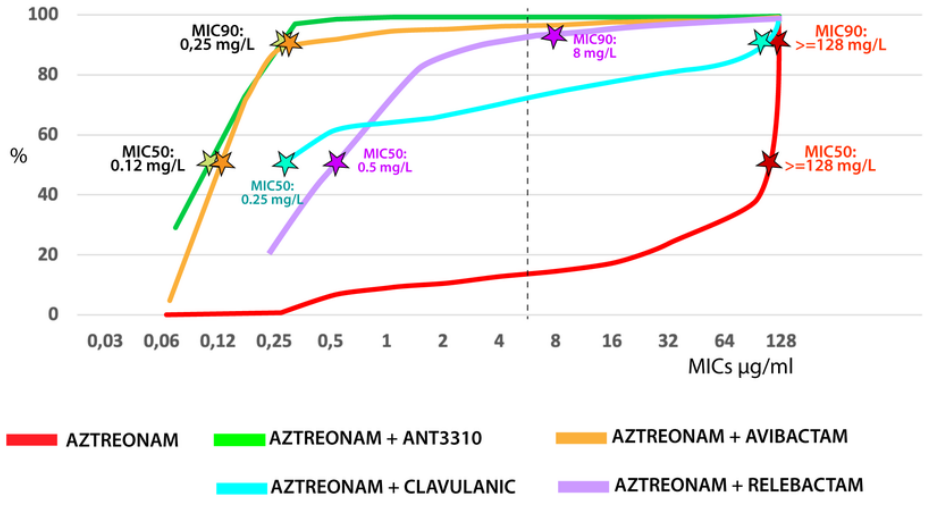
ATM: aztreonam. AVI: avibactam. RELE: relebactam. CLAV: clavulanic acid. Fixed inhibitor concentrations: ANT3310 8 mg/L; AVI, RELE, CLAV 4 mg/L. Cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton broth.

*Species included: *K. pneumoniae* (n 267), *E. coli* (13), *Enterobacter cloacae complex* (12) and other spp. (25). SβL co-produced were: CTX-M (n 204), CMY (32), OXA-163 (14), KPC (6), CTXM+CMY (3) and CTXM+PER (1).

** Some Protteae isolates carrying acquired bla_{CMY} or *bla*OXA-163 were phenotypically susceptible to ATM (MICs 1-4 mg/L).

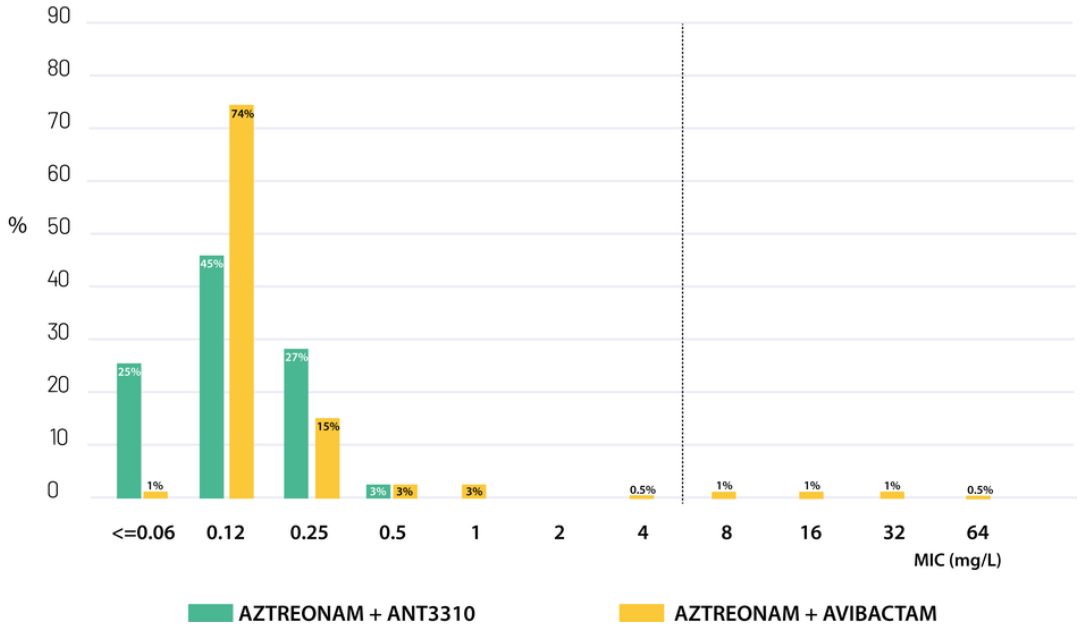
Cumulative MIC distributions for Aztreonam (ATM) alone and combined with different serine β-lactamase inhibitors against MBL-producing Enterobacterales

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



MIC distributions for aztreonam-avibactam and aztreonam-ANT3310 against MBL-producing Enterobacterales

Figure 3. MIC distributions for aztreonam-avibactam and aztreonam-ANT3310 against MBL-producing Enterobacterales



Keyword 1
Antimicrobial resistance (AMR)
Keyword 2
Antimicrobial susceptibility testing (AST)