#05271 *In vitro* activity of meropenem-ANT3310 and comparators against carbapenem-resistant *Acinetobacter* clinical isolates: implications for low- and middle-income countries (LMIC).

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

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Background

Carbapenem-resistant *Acinetobacter* (CRA) continues to surge globally and is endemic in Latin America and other LMICs. In Argentina, CRA exceeds 90%. CRA is largely driven by class D carbapenemases, mainly bla_{OXA-23}, $bla_{OXA-24/40}$ and bla_{OXA-58}. ANT3310 is a next-generation diazabicyclooctane β-lactamase inhibitor being developed in combination with meropenem (MEM) to treat infections caused by carbapenem-resistant Gram-negatives, including OXA-producing CRA. Aim: to evaluate the in vitro antibacterial activity of MEM-ANT3310 and comparators against a contemporary CRA collection.

Methods

We studied contemporary clinical CRA isolates referred to the National Reference Laboratory for confirmation of extreme/pan-drug resistance and therapeutic guidance. MBL producers and outbreak-related strains were excluded. The final set comprised 102 isolates from 62 hospitals across 13 jurisdictions, recovered mainly from lower-respiratory tract (42 %) and blood (30 %). Isolate identification was performed using MALDI-TOF and β-lactamase background genotype was determined using PCR/sequencing and/or WGS. Reference susceptibility tests followed CLSI. ANT3310 was tested at a fixed concentration of 8 mg/L; durlobactam at 4 mg/L. Cefiderocol and rifabutin (BV-100) were tested in iron-depleted cation-adjusted Mueller-Hinton broth. A provisional susceptible breakpoint of ≤ 8 mg/L was applied for MEM-ANT3310 and rifabutin; other agents were interpreted per CLSI, EUCAST and/or FDA. Fisher's exact test (two-tailed) was used for comparisons.

Results

MEM alone showed MIC50 and MIC90 of 128 and 512 mg/L; with ANT3310 the MIC50/90 decreased to 1 and 4 mg/L, respectively (Figure 1 and Figure 2). MEM-ANT3310 was the most active agent (99% susceptible) and did not differ significantly from sulbactam-durlobactam (92%) or rifabutin (91%) ($p > 0.05$). MEM-ANT3310 outperformed tigecycline (78%), colistin (76%), cefiderocol (74%-83% by EUCAST/CLSI, respectively), amikacin (39%) and sulbactam (17%) ($p < 0.05$) (Figure 3).

Conclusions

ANT3310 restored MEM activity against a difficult, referral-based CRA panel, dominated by OXA-23 endemic background and representing isolates harder to treat than routine clinical populations. Activity was comparable to sulbactam-durlobactam and superior to cefiderocol. These results position MEM-ANT3310 as a reliable option for LMICs, restoring MEM utility against OXA-mediated CRA in settings with constrained access to new antibiotics.

MIC summary for novel agents against carbapenem-resistant Acinetobacter*

Figure 1. MIC summary for novel agents against carbapenem-resistant *Acinetobacter

Antimicrobial agent	MIC50 (mg/L)	MIC90 (mg/L)	Range (mg/L)
MEM	128	512	0.5** - 512
MEM-ANT3310	1	4	<=0.03 - 256
SUL	8	32	1 - 256
SUL-DURLO	1	4	<=0.12 - 256
RIFABUTIN	0.25	4	<=0.008 - >16
CEFIDEROCOL	1	16	0.12 - >64

MEM: meropenem. SUL: sulbactam. DURLO: durlobactam. Fixed inhibitor concentrations: ANT3310 8 mg/L; durlobactam 4 mg/L. Cefiderocol and rifabutin were tested in iron-depleted cation-adjusted Mueller–Hinton broth.

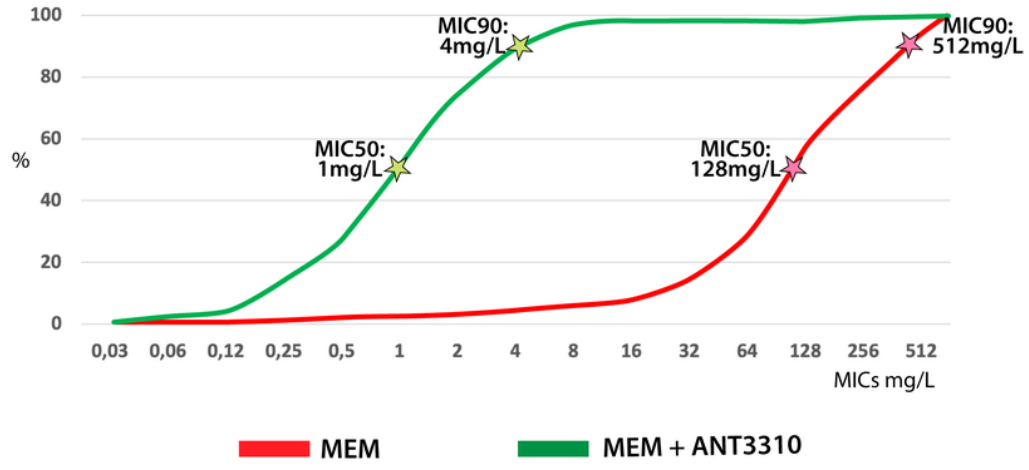
*Species: *A. baumannii* (n 97), *A. junii* (1), *A. johnsonii* (1), *A. pittii* (1), *A. ursingii* (1) and *A. bereziniae* (1). Genotypes: OXA-23 (n 82); OXA-58 (4); OXA-23 plus PBP3 (*ftsI*) A515V (4); OXA-23 plus PER-2 (3); OXA-23 plus CTX-M (1); OXA-24/40 (1); hyper-expressed OXA-51 (1); OXA-280+PER-2 (1); OXA-281+PER-2 (1); OXA-272+PER-2 (1); OXA-23+OXA-24/40 (1) and SHV-5(1).

** Two *non-baumannii* isolates carrying acquired bla_{OXAs} were phenotypically susceptible to MEM.

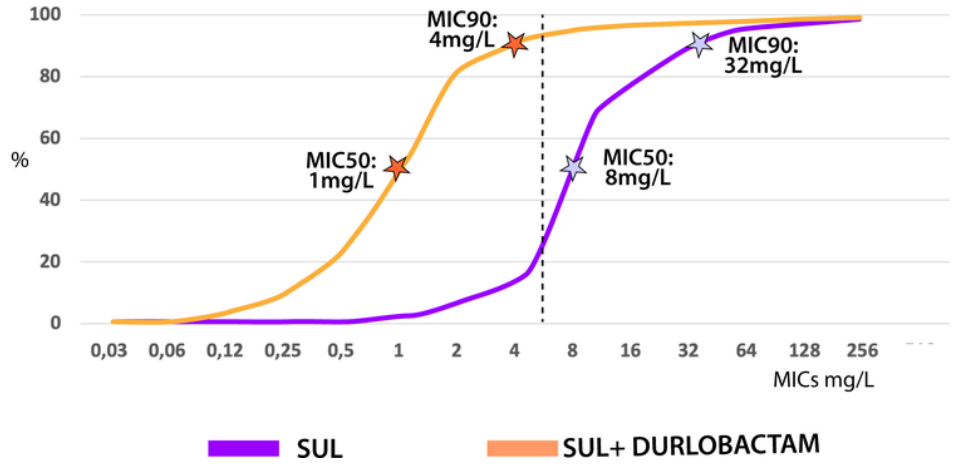
Cumulative MIC distribution against carbapenem-resistant Acinetobacter

Figure 2. Cumulative MIC distributions against carbapenem-resistant *Acinetobacter*

A) meropenem (MEM) and MEM-ANT3310

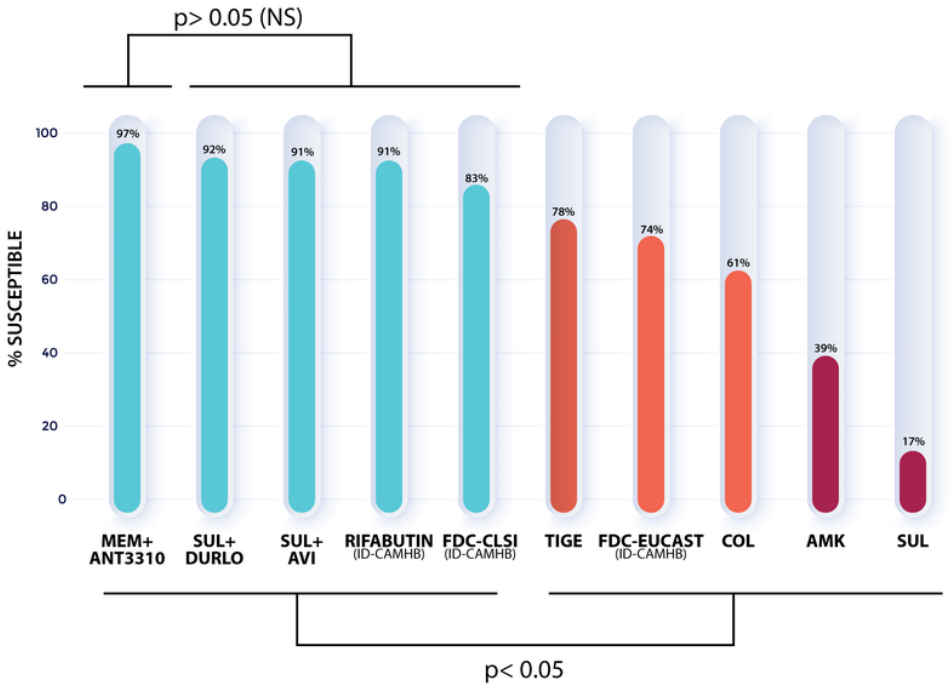


B) sulbactam (SUL) and SUL-durlobactam



Susceptibility of carbapenem-resistant Acinetobacter to MEM-ANT3310 and comparators

Figure 3. Susceptibility of carbapenem-resistant *Acinetobacter* to MEM–ANT3310 and comparators.



MEM: meropenem. SUL: sulbactam. DURLO: durlobactam. AVI: avibactam. FDC: cefiderocol. TIGE: tigecycline.
COL: colistin. AMK: amikacin. ID-CAMHB: iron-depleted cation adjusted Mueller Hinton broth. NS: non-significant difference

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