#01344 Reassessing β-lactamase inhibition strategies for carbapenem-resistant *Acinetobacter*: a comparative analysis of *in vitro* activities of sulbactam/durlobactam vs sulbactam/avibactam

03. Bacterial susceptibility & resistance
03b. Resistance surveillance & epidemiology: Healthcare-associated bacteria

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Background

Carbapenem-resistant *Acinetobacter* (CRA) continues to surge globally. Sulbactam (SUL) retains intrinsic activity against *Acinetobacter* but is frequently compromised by β-lactamases. IDSA recommends SUL-durlobactam (SUL-DUR), with a carbapenem, as preferred therapy for CRA. DUR and avibactam (AVI) are diazabicyclooctane β-lactamase inhibitors, but head-to-head data against CRA are scarce. We compared the *in vitro* activity of SUL-DUR versus SUL-AVI against CRA and explored pharmacodynamic and mechanistic correlates.

Methods

We studied 116 *Acinetobacter* isolates (112 CRA) from the NRL repository and the US CDC AR Isolate Bank. Carbapenemases (OXA, MBL) were characterized by PCR/WGS. MICs were determined by BMD for SUL alone and in fixed combinations with DUR or AVI (4mg/L); a subset was tested with meropenem (MEM; 1:1). Essential (EA) and categorical agreement (CA) between SUL-DUR and SUL-AVI were calculated. Time-kill assays (0–24h) assessed bactericidal activity of SUL ± DUR or AVI, with/without MEM. An *A. baumannii* mutant panel was used to probe genetic determinants of DUR vs AVI potentiation.

Results

Both SUL-DUR and SUL-AVI restored SUL activity against OXA-producers, with high EA (88.2%) and CA (95.6%) (Figure 1). In NDM producers, DUR frequently induced a paradoxical SUL MIC increase (“MIC shift”) (Fig.2A). Adding MEM had divergent effects: SUL-DUR MICs were largely unchanged, whereas SUL-AVI MICs often increased, especially in NDM producers, attenuating the AVI advantage (Fig.2B). In TKA, both combinations were bactericidal against an OXA-23 *A. baumannii* model; MEM enhanced SUL-DUR but impaired SUL-AVI, mirroring MIC shifts (Fig.3). Against an OXA-58 *A. junii*, both combinations were bactericidal and MEM added no benefit. AVI potentiation mapped to multiple targets, whereas DUR potentiation depended on *recA*and *mrdB*.

Conclusions

SUL-DUR and SUL-AVI were broadly comparable and highly active against OXA-CRA, supporting use of SUL-DUR MICs as a surrogate to infer likely SUL-AVI activity when MBLs are excluded. Pharmacodynamic data suggest SUL-DUR may benefit from MEM co-administration, whereas SUL-AVI may be blunted by MEM under some conditions. These findings refine the comparative roles of SUL-DUR and SUL-AVI and offer a testable framework for therapeutic selection in settings lacking SUL-DUR.

MIC summary

Figure 1. MIC summary for sulbactam alone and in combinations with durlobactam and avibactam against carbapenem-resistant *Acinetobacter*

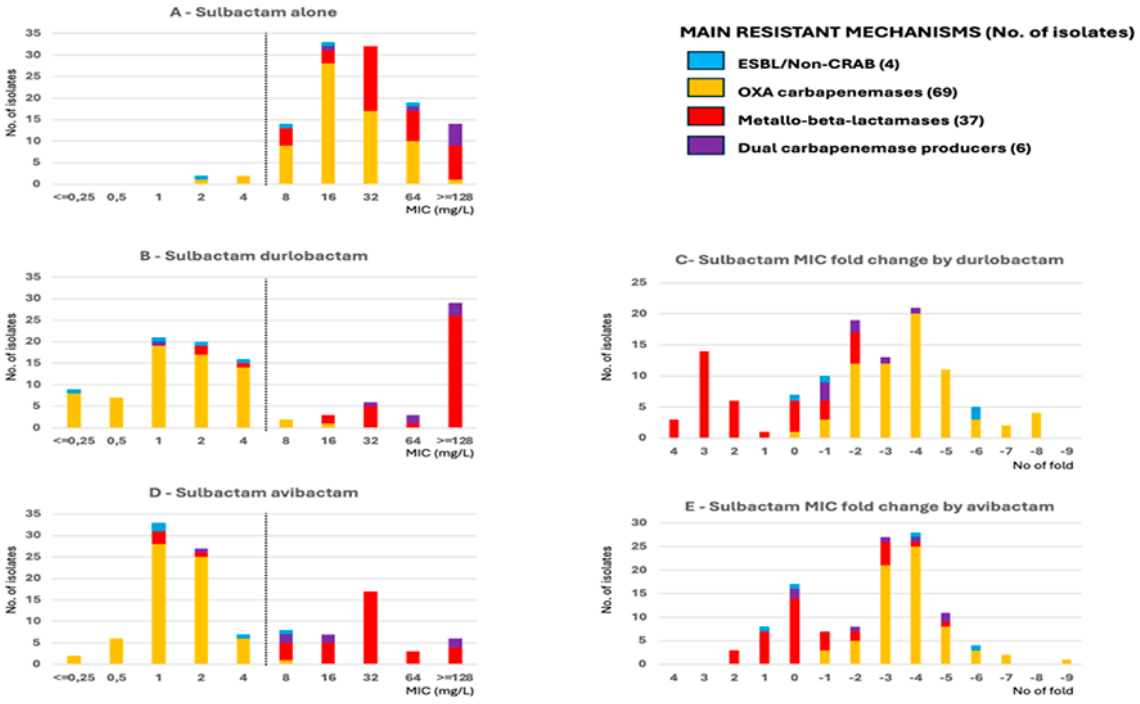
Carbapenemase Class (n)	SUL				SUL-DUR				SUL-AVI			
	Range	MIC_{50}	MIC_{90}	% <= 4 mg/L	Range	MIC_{50}	MIC_{90}	% <= 4 mg/L	Range	MIC_{50}	MIC_{90}	% <= 4 mg/L
Class D (69)	2->128	16	64	4.8%	<=0.25-16	1	4	96.8%	<=0.25-16	1	4	96.8%
Class B (37)	8->128	32	>128	0%	2->128	>128	>128	3%	1->128	32	>128	3%
Class B plus D (6)	64->128	>128	>128	0%	32->128	>128	>128	0%	8->128	16	>128	0%

MIC values in mg/L. SUL: sulbactam. DUR: durlobactam. AVI: avibactam

MIC distributions

Figure 2

A) MIC frequency distribution of sulbactam alone, sulbactam-durlobactam and sulbactam-avibactan according to the main resistance mechanism



B) Effect of Meropenem on SUL-DUR and SUL-AVI MICs by Resistance Profile.

Number of isolates showing the indicated fold-change in sulbactam MIC following the addition of meropenem (MEM) (1:1 ratio)

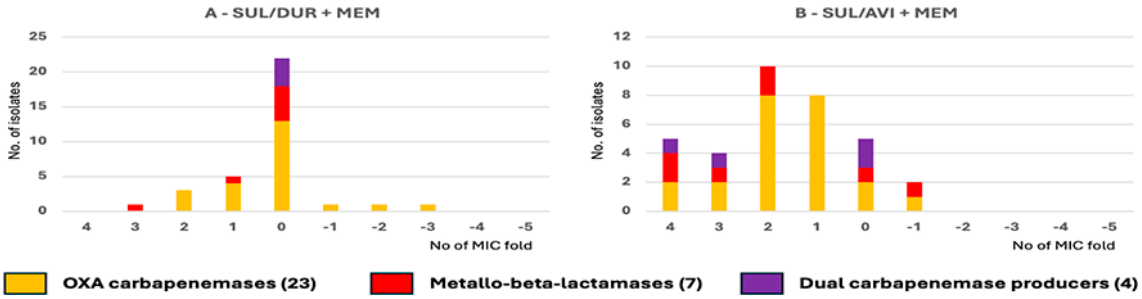
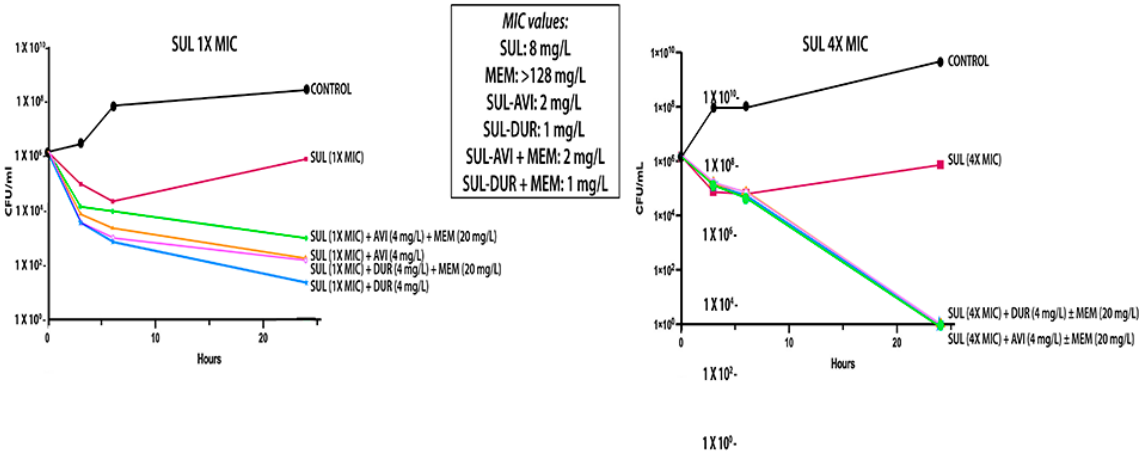
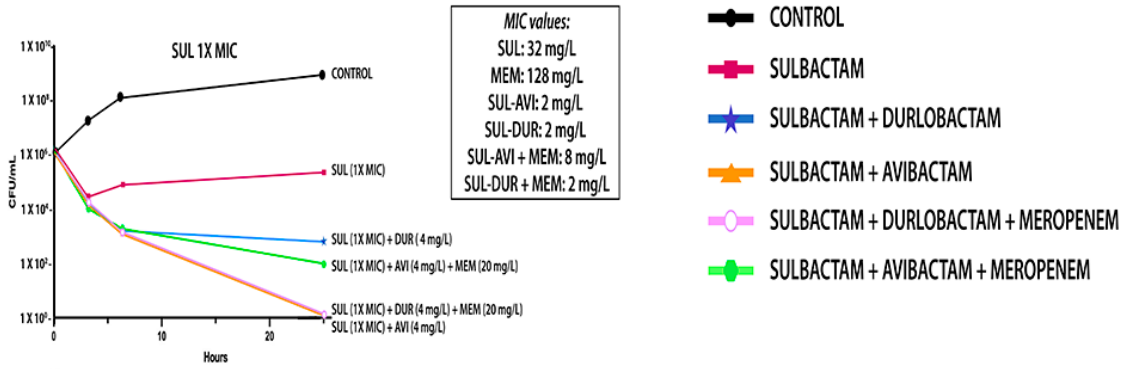


Fig. 3 - Time kill assays

A. junii AMA204: OXA-58



A. baumannii 27872: OXA-23 + OXA-66 (AR Bank #0056)



Keyword 1
Antimicrobial resistance (AMR)
Keyword 2
Antimicrobial susceptibility testing (AST)
Keyword 3 (Please provide your suggestion)
Acinetobacter