Potent activity of the novel combination Meropenem-Pilabactam (formerly ANT3310) against global *Acinetobacter baumannii* clinical isolates from 2019 to 2023

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INTRODUCTION

Antimicrobial resistance (AMR) is an urgent and increasing global threat with an estimated 1.3 million deaths attributable to bacterial AMR in 2019, 400,000 of which were due to lower respiratory tract infections (LRTI) [1]. Infections due to resistant pathogens lead to longer hospital stays, increased morbidity and mortality, and significantly higher healthcare costs [2]. Carbapenem-resistant Gram-negative bacteria, particularly Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are notoriously challenging. Treatment options for these pathogens, and particularly carbapenem-resistant *Acinetobacter baumannii* (CRAB), are limited and the current pharmaceutical development pipeline includes very few novel anti-infective agents which are effective against these organisms [3].

Pilabactam, formerly ANT3310, is a novel diazabicyclooctanone (DBO) serine β-lactamase inhibitor, in clinical development in combination with Meropenem (MEM) for the treatment of severe infections caused by Gram-negative pathogens in hospitalized patients. Meropenem-Pilabactam (MPI) has a broader spectrum of coverage than current marketed antibiotics, including carbapenem-resistant Enterobacterales (CRE) and *A. baumannii* (CRAB), as well as *P. aeruginosa*. The MPI combination is currently progressing through clinical development.

OBJECTIVES

The objectives of this study was to investigate the activity of MPI, and other antimicrobial agents, against 2,399 *A. baumannii* clinical isolates, including CRAB, collected worldwide from 2019 to 2023.

METHODS

Susceptibility testing:

- Clinical isolates from a widely distributed global collection (Figure 1) with diverse infection sources (Figure 2) were tested.
- MICs were determined by broth microdilution following CLSI methodology [4].
- Pilabactam was tested at a fixed concentration of 8 mg/L with MEM.
- Susceptibility and resistance breakpoints were determined following CLSI guidelines [5].
- A surrogate susceptibility breakpoint of 8 mg/L was used for MPI, as the MEM dosing regimen (2g, q8h, infused over 3h) used in clinical studies has >90% probability of target attainment for MICs ≤8 mg/L [6].

Characterization of resistant isolates:

- The presence of bla_{OXA-23}, bla_{OXA-24}, bla_{VIM}, bla_{IMP} and bla_{NDM} genes was assessed by PCR on all the isolates that showed MPI MICs >8 mg/L

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RESULTS

Figure 1. Distribution of clinical isolates by geographic location

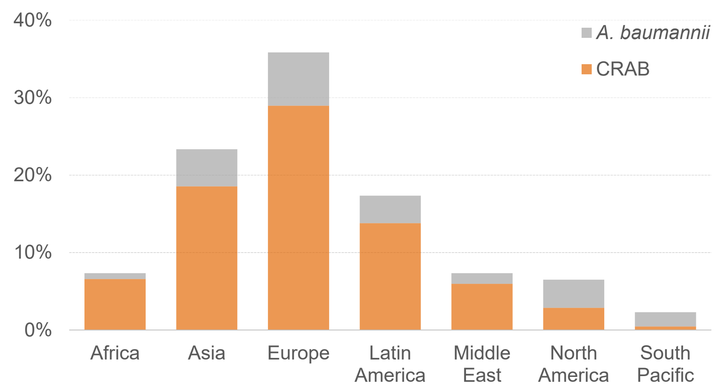
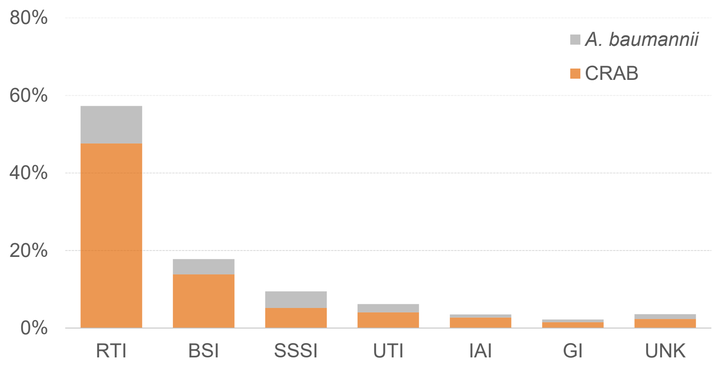


Figure 2. Distribution of clinical isolates by infection source



RTI, respiratory-tract infection; BSI, blood stream infection; SSSI, skin and skin structure infection; UTI, urinary-tract infection; IAI, intra-abdominal infection; GI, gastrointestinal infection; UNK, infection unknown

Susceptibility to MPI

Among the *A. baumannii* clinical isolates included in this study, 77.2% were CRAB. The prevalence of CRAB isolates varies worldwide, from as low as 20% in the South Pacific region, to as high as 90% in Africa (Figure 1). Most isolates were collected from RTI, followed by BSI (Figure 2)

Pilabactam restored the activity of MEM against 96% and 94.9% of the *A. baumannii* and CRAB clinical isolates, respectively (Table 1, Figure 3), reducing the MIC_{90} from >32 mg/L to 4 mg/L in both groups.

Only Colistin (EUCAST) and Sulbactam/Durlobactam (CLSI) showed similar susceptibility levels.

Figure 3. Cumulative MIC distribution for MEM and MPI against CRAB clinical isolates (n=1852)

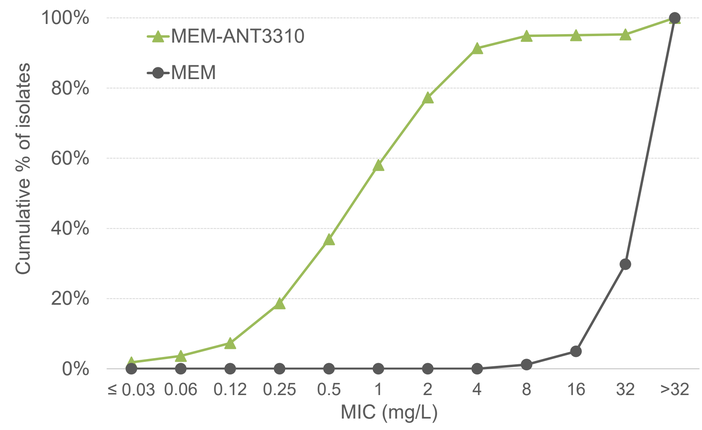


Table 1. Summary MIC and susceptibility data for MPI and comparator agents against *A. baumannii* and CRAB clinical isolates

Antimicrobial agent	*A. baumannii*					CRAB				
	N	MIC (mg/L)		% S (CLSI BP)	% S (EUCAST BP)	N	MIC (mg/L)		% S (CLSI BP)	% S (EUCAST BP)
		MIC_{50}	MIC_{90}				MIC_{50}	MIC_{90}		
MEM-Pilabactam [8 mg/L]	**2399**	**0.5**	**4**	**96.0%**	**96.0%**	**1852**	**1**	**4**	**94.9%**	**94.9%**
MEM	2399	>32	>32	22.3%	22.3%	1852	>32	>32	0.0%	0.0%
Ampicillin-Sulbactam [4 mg/L]*	404	32	>64	15.8%	NA	339	64	>64	1.5%	NA
Ceftazidime-Avibactam [4 mg/L]*	1995	32	>32	NA	NA	1513	>32	>32	NA	NA
Colistin	2399	0.5	1	NA	96.3%	1852	0.5	1	NA	95.5%
Cefepime-Taniborbactam [4 mg/L]*	1995	32	>32	27.9%	NA	1513	>32	>32	7.0%	NA
Cefiderocol	2399	0.25	2	87.3%†	NA	1852	0.25	2	84.6%†	NA
Imipenem-Relebactam [mg/L]*	1496	>32	>32	24.7%	NA	1131	>32	>32	0.4%	NA
Levofloxacin*	404	8	>16	NA	15.3%	339	16	>16	NA	2.7%
Sulbactam-Durlobactam [4 mg/L]*	2399	1	4	93.9%	NA	1852	2	4	92.1%	NA

*Comparator not tested every year
† For Cefiderocol, the FDA susceptibility breakpoint, 1 mg/L, has been used.
BP: breakpoint, NA: Not approved
For cefepime-taniborbactam, the CLSI cefepime BP, 8 mg/L, has been used; Cefepime not approved by EUCAST.

Characterization of isolates with MPI MIC >8 mg/L

Among the 1,852 CRAB clinical isolates included in this study, 93 (5%) had an MPI MIC >8 mg/L and were further investigated.

PCR analysis of these isolates showed that none carried bla_{VIM} or bla_{IMP} genes, while 92 of them (98.9%) carry the NDM encoding gene. Furthermore, 56 of these isolates (60.2%) were also positive for the gene encoding OXA (Table 2).

The remaining isolate, which had an MPI MIC of 16 mg/L, was negative for the OXA and MBL genes, and is currently being investigated through whole genome sequencing.

Table 2. PCR analysis of 93 isolates with high MPI MIC

	bla_{OXA-23} (+)	bla_{OXA-24} (+)	bla_{OXA} (-)	Total
bla_{NDM} (+)	45	11	36	92
bla_{NDM} (-)	0	0	1	1
Total	45	11	37	93

CONCLUSIONS

A randomly selected collection of global *A. baumannii* clinical isolates (2019-2023) shows that 77.2% were carbapenem-resistant.

MPI showed outstanding potency against CRAB, with 94.9% of isolates showing MICs ≤ 8 mg/L.

Of the comparators tested, only colistin and Sulbactam/Durlobactam, a drug approved only for *A. baumannii-calcoaceticus* complex treatment, showed similar susceptibility levels.

As expected, most of the isolates with MPI MIC >8 mg/L carried the bla_{NDM} gene.

These results support the further clinical development of MEM-Pilabactam for the treatment of life-threatening CRAB infections.

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