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Potent activity of the novel combination Meropenem-Pilabactam (formerly ANT3310) against global OXA- and KPC-carbapenem-resistant Enterobacterales (CRE) 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 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 538 OXA-CRE and 537 KPC-CRE randomly selected clinical isolates, 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].

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RESULTS

Figure 1. Distribution of clinical isolates by geographic location

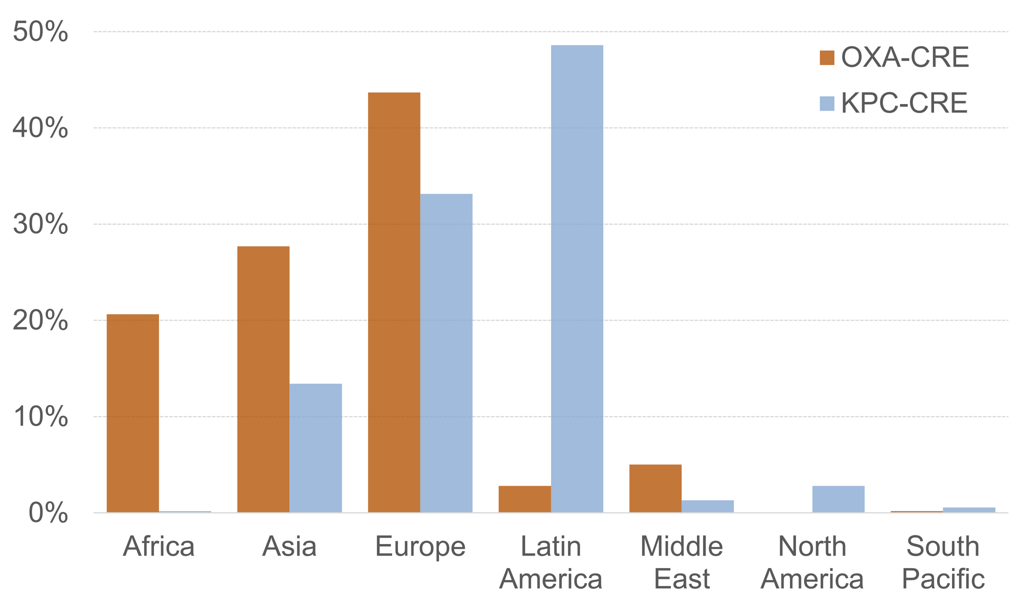
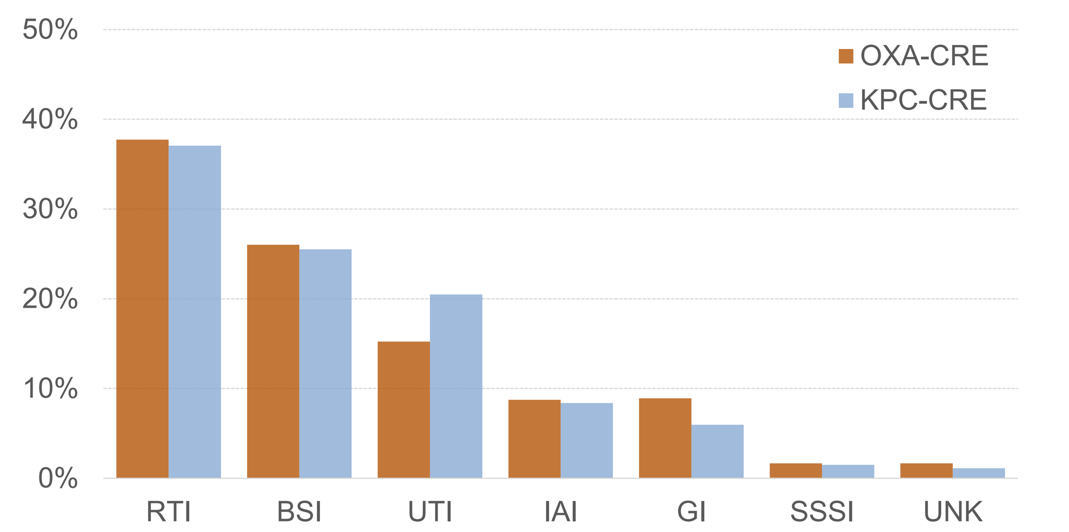


Figure 2. Distribution of clinical isolates by infection source



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

Figure 3. Cumulative MIC distribution for MEM and MPI against OXA-CRE clinical isolates (n=538)

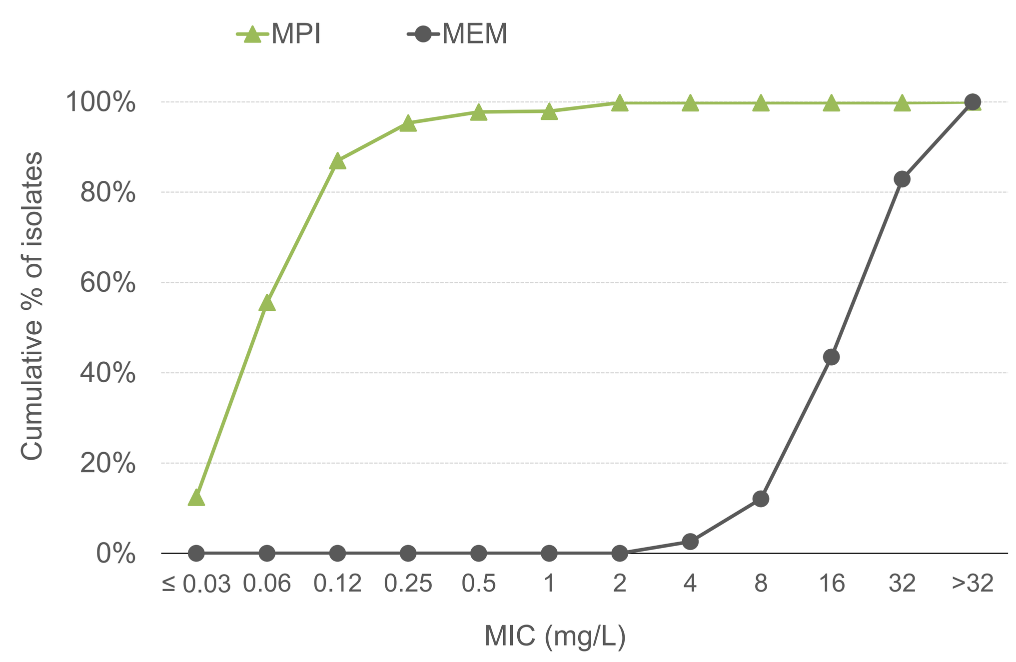


Figure 4. Cumulative MIC distribution for MEM and MPI against KPC-CRE clinical isolates (n=537)

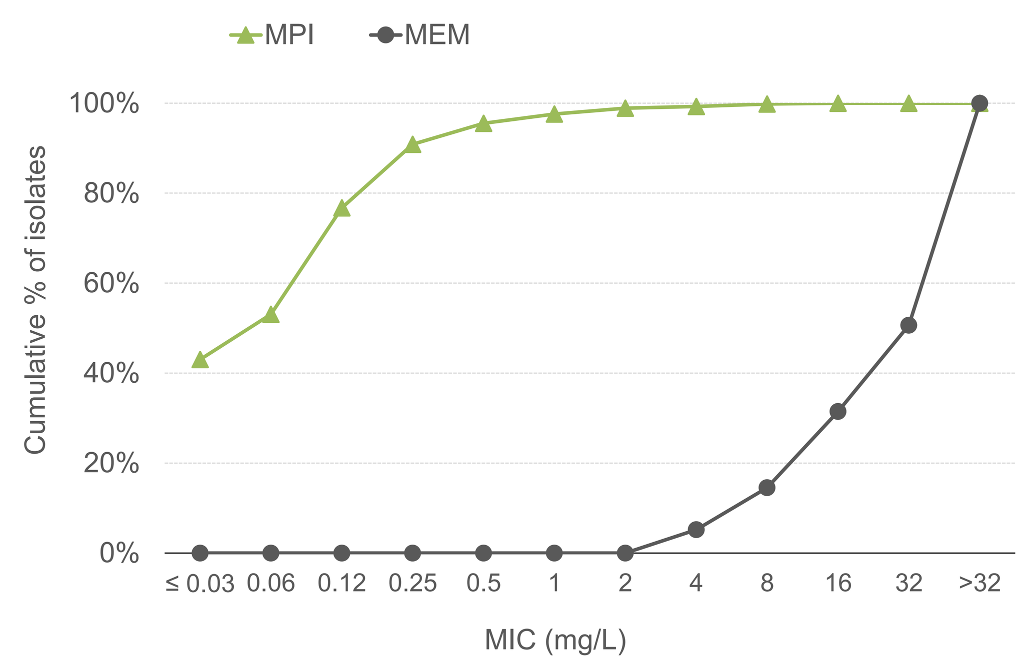


Table 1. Summary MIC and susceptibility data for MPI and comparator agents against OXA- and KPC-CRE clinical isolates

Antimicrobial agent	OXA-CRE					KPC-CRE				
	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]	**538**	**0.06**	**0.25**	**99.8%**	**99.8%**	**537**	**0.06**	**0.25**	**99.8%**	**99.8%**
MEM	538	32	>32	0.0%	0.0%	537	32	>32	0.0%	0.0%
Aztreonam-Avibactam [4 mg/L]*	391	0.25	0.5	99.7%	99.7%	385	0.25	0.5	100.0%	100.0%
Ceftazidime-Avibactam [4 mg/L]*	391	1	2	99.5%	99.5%	385	2	4	99.2%	99.2%
Colistin	538	0.5	>16	NA	66.9%	537	0.5	16	NA	76.4%
Cefepime-Taniborbactam [4 mg/L]	538	2	8	98.0%	26.4%	537	1	4	98.1%	66.3%
Cefiderocol	538	0.5	2	99.1%	92.4%	537	1	2	98.3%	93.5%
Imipenem-Relebactam [4 mg/L]*	147	8	32	1.4%	7.5%	152	0.25	1	92.8%	96.7%
MEM-Vaborbactam [8 mg/L]*	293	16	>32	3.1%	15.0%	288	0.25	2	97.9%	99.0%

*Comparator not tested every year
BP: breakpoint, NA: Not approved
For cefepime-taniborbactam, the CLSI or the EUCAST cefepime BP, 8 mg/L or 1 mg/L, respectively, have been used.

Susceptibility to MPI

OXA- and KPC-CREs displayed distinct geographic distributions (Figure 1). Most OXA-CREs were collected in Europe (43.7%), followed by Asia (27.7%) and Africa (20.6%), whereas KPC-CREs were found mainly in Latin America (48.6%), followed by Europe (33.2%). Most isolates were associated with RTI (~37%) and BSI (~26%) in both cases (Figure 2).

Pilabactam restored the activity of MEM against 99.8% of both OXA- and KPC-CRE clinical isolates (Table 1, Figure 3 and 4), reducing the MEM MIC_{90} from >32 mg/L to 0.25 mg/L in both groups. The susceptibility level achieved with MPI in these CRE subgroups were comparable to those observed with aztreonam-avibactam and ceftazidime-avibactam (Table 1).

CONCLUSIONS

The activity of MPI was evaluated against a randomly selected collection of global OXA- and KPC-CRE clinical isolates (2019-2023).

MPI demonstrated remarkable potency *in vitro* against both groups, with 99.8% of isolates showing MICs ≤ 8 mg/L.

Only two isolates, one KPC-2 *K. pneumoniae* and one OXA-48(c) *S. marcescens,* showed MPI MICs >8 mg/L, 16 and 32 mg/L, respectively. These isolates are currently being investigated through whole genome sequencing.

These results support the further clinical development of MEM-Pilabactam for the treatment of life-threatening OXA- and KPC-CRE infections.

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