Activity of Meropenem Combined with the β-Lactamase Inhibitor Xeruborbactam and Comparator Agents Tested Against Challenging Gram-negative Organisms

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Objective

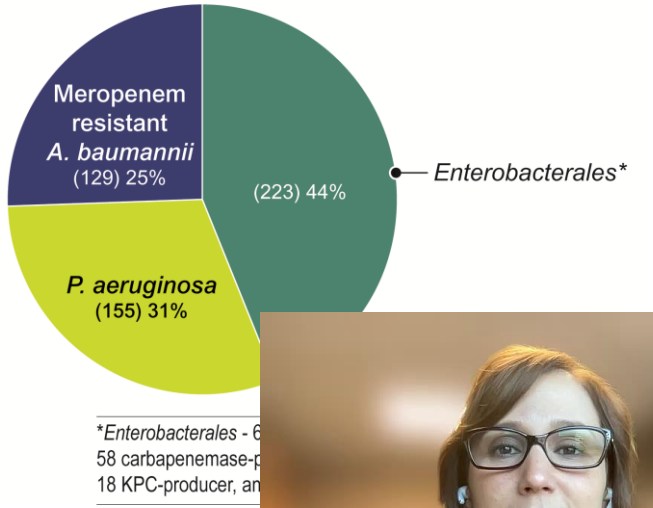
We evaluated the activity of meropenem combined with the novel β-lactamase inhibitor (BLI) xeruborbactam, previously QPX7728, against *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

Isolates included metallo-β-lactamase (MBL)-producers, multidrug-resistant (MDR; resistant to ≥3 antimicrobial classes), and meropenem-resistant isolates

Methods

- A total of 507 Gram-negative clinical isolates were tested (Figure 1).
- Isolates were susceptibility tested by reference broth microdilution against comparator agents and meropenem-xeruborbactam at fixed 4 and 8 mg/L. EUCAST breakpoints were applied for all comparators except tigecycline (FDA).
- Genes encoding β-lactamases were identified by whole genome sequencing.

Figure 1.



Results

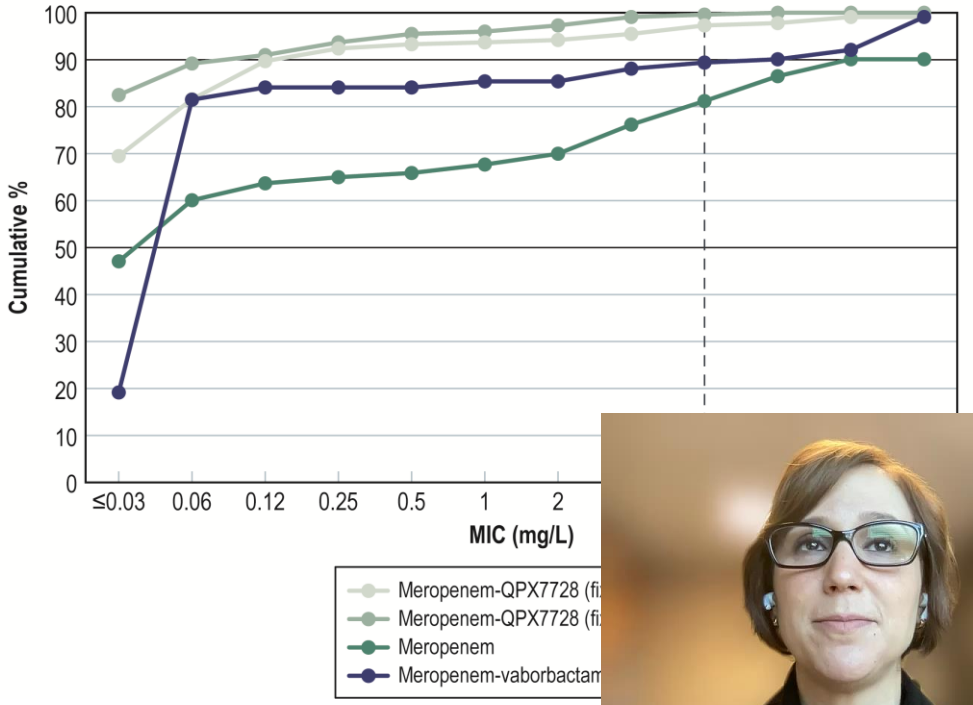
- Meropenem-xeruborbactam ($MIC_{50/90}$, ≤0.03/0.25 mg/L for BLI at fixed 4 mg/L and ≤0.03/0.12 mg/L for fixed 8 mg/L) was very active against 223 *Enterobacterales* isolates inhibiting 97.3% to 99.6% of the isolates at ≤8 mg/L (Table 1 and Figure 2).
- Meropenem-xeruborbactam at fixed 8 mg/L inhibited 98.5% of the CREs and 97.0% of the MBL producers.
- Among the comparator agents, amikacin, ceftazidime-avibactam, and tigecycline exhibited greater activity against the *Enterobacterales* isolates by inhibiting 83.9%, 85.2%, and 91.9% of these isolates, respectively.

Table 1. Activity of meropenem-xeruborbactam and comparator agents against Enterobacterales

Antimicrobial agent	% Susceptibility applying EUCAST criteria [a]					
	All (*n*=223)	CRE (*n*=67)	CPE (*n*=58)	MBL (*n*=33)	KPC (*n*=18)	MDR (*n*=91)
Meropenem-xeruborbactam (fixed 4 mg/L)	[97.3]	[91.0]	[91.4]	[84.8]	[100.0]	[94.5]
Meropenem-xeruborbactam (fixed 8 mg/L)	[99.6]	[98.5]	[98.3]	[97.0]	[100.0]	[98.9]
Meropenem [b]	70.0	0	6.9	6.1	11.1	31.9
Aztreonam	52.5	11.9	15.5	27.3	0	9.9
Cefepime	51.1	1.5	1.7	0	0	2.2
Ceftazidime	49.3	1.5	1.7	0	0	0
Ceftazidime-avibactam	85.2	55.2	46.6	6.1	88.9	64.8
Ceftolozane-tazobactam	66.4	6	3.4	0	5.6	23.1
Piperacillin-tazobactam	61.7	4.5	3.4	3	0	14.3
Colistin	74.2	77.3	73.7	78.8	64.7	76.7
Amikacin	83.9	61.2	55.2	39.4	83.3	60.4
Gentamicin	71.7	37.3	31.0	24.2	33.3	34.1
Levofloxacin	58.7	16.4	15.5	18.2	16.7	8.8
Tigecycline	91.9 [d]	88.1 [d]	89.7 [d]	90.9 [d]	88.9 [d]	84.6 [d]

[a] A susceptibility meropenem-xeruborcatam of ≤8 mg/L was applied for comparison purposes and displayed in brackets.
[b] Using meningitis breakpoints.
[c] Susceptible, increased dosage.
[d] US FDA breakpoints were applied.

Figure 2. *Enterobacterales* (n=223)



Results

- Meropenem-xeruborbactam combinations ($MIC_{50/90}$, 4/64 or 2/32 mg/L for 4 or 8 mg/L of the BLI) inhibited 76.6% to 78.6% of the *P. aeruginosa* isolates at ≤8 mg/L (Figure 3).
- Against 129 meropenem-resistant *Acinetobacter* spp., meropenem-xeruborbactam displayed $MIC_{50/90}$ at 1/4 mg/L for the BLI at fixed 4 mg/L and 0.5/2 mg/L for the BLI at fixed 8 mg/L (Figure 4).

Figure 3. *P. aeruginosa* (n=155)

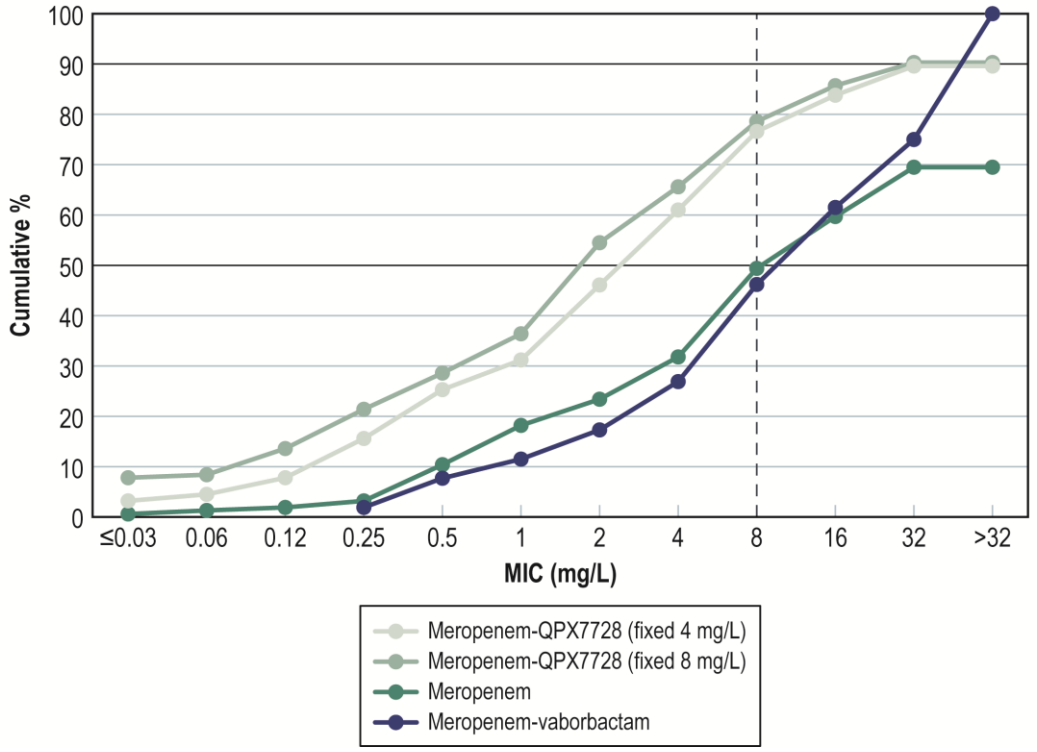
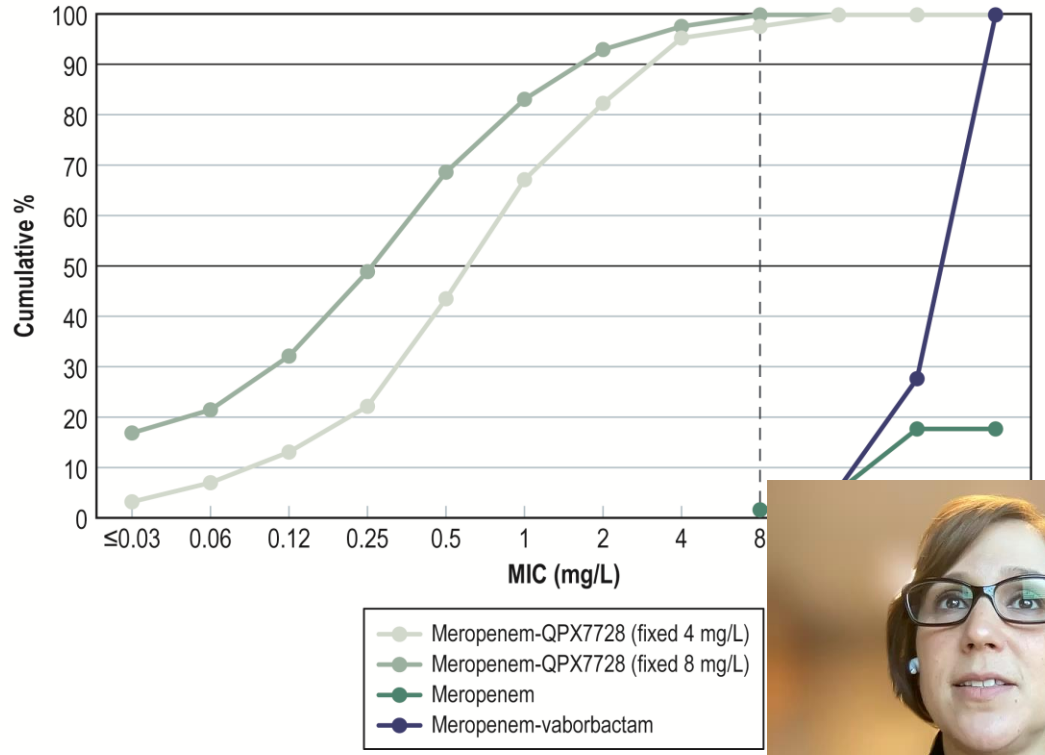
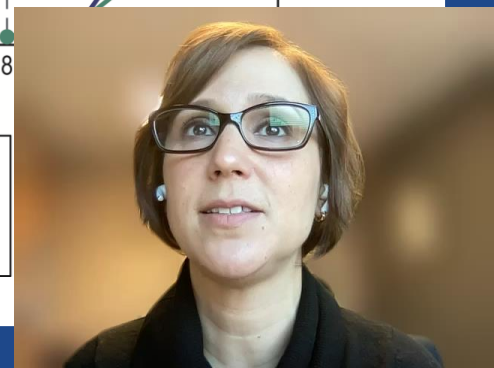


Figure 4. Meropenem-resistant *A. baumannii* (n=129)





Results

- Colistin was the only comparator displaying >51% susceptibility against *P. aeruginosa* and *Acinetobacter* spp. isolates.

Table 2. Activity of meropenem-xeruborbactam and comparator agents against Non-fermentors

Antimicrobial agent	% Susceptibility applying EUCAST criteria [a]		
	P. aeruginosa		Meropenem-resistant *A. baumannii* (*n*=129)
	All (*n*=155)	MDR (*n*=114)	
Meropenem-xeruborbactam (fixed 4 mg/L)	[76.6]	[71.9]	[97.7]
Meropenem-xeruborbactam (fixed 8 mg/L)	[78.6]	[74.6]	[100.0]
Meropenem [b]	22.1	20.2	0
Aztreonam	49.4 [c]	45.6 [c]	
Cefepime	23.4 [c]	13.2 [c]	
Ceftazidime	25.3 [c]	13.2 [c]	
Ceftazidime-avibactam	46.2	36.8	
Ceftolozane-tazobactam	49.4	38.6	
Piperacillin-tazobactam	21.4 [c]	8.8 [c]	
Colistin	96.1	94.7	89.8
Amikacin	50.6	37.7	23.4
Gentamicin			22.5
Levofloxacin	11.0	1.8	2.3
Tigecycline			

[a] A susceptibility meropenem-xeruborcatam of ≤8 mg/L was applied for comparison purposes and displayed in brackets.
[b] Using meningitis breakpoints.
[c] Susceptible, increased dosage.
[d] US FDA breakpoints were applied.

Conclusions

- Meropenem-xeruborbactam combinations were very active against *Enterobacterales* isolates, including isolates carrying MBLs and meropenem-resistant *Acinetobacter* spp.
- Against *P. aeruginosa* isolates, the combination displayed greater activity than all comparators except colistin.
- Further development of meropenem-xeruborbactam is warranted to add to the armamentarium against challenging Gram-negative isolates.

Acknowledgements

This study at JMI Laboratories was supported by Qpex Biopharma. JMI Laboratories received compensation fees for services in relation to conducting the study and preparing the poster.

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