Xeruborbactam (QPX) Potentiates the Activity of β-Lactam Antibiotics Against a Diverse Group of Highly Drug-Resistant Enterobacterales

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BACKGROUND

Antibiotic resistant Enterobacterales (ENT) are a growing threat worldwide. QPX is an ultra-broad-spectrum β-lactamase inhibitor (BLI) with potent inhibition of classes A and D, and many metallo-β-lactamases, which has potential to fill the void of currently available BL-BLIs.

METHODS

- We evaluated QPX (fixed concentration of 8 µg/mL) in combination with meropenem (MEM), cefepime (FEP) and aztreonam (ATM) against a diverse group of ENT clinical isolates selected from a worldwide repository.
- Antibiotic resistance determinants were assessed by mining whole-genome sequencing data generated using Illumina MiSeq.

RESULTS

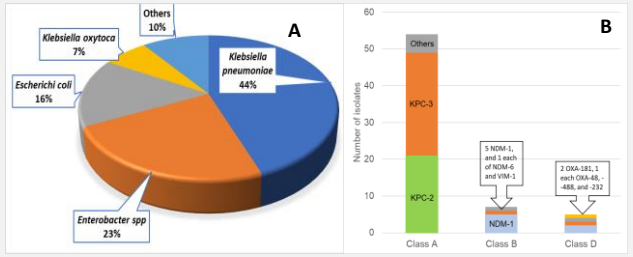

Figure 1. (A) Enterobacterales species; **(B)** Number of isolates producing carbapenemases

- *Klebsiella* spp, *Enterobacter* spp, and *Escherichia coli* were most common among the 90 isolates tested (**Figure 1A)**
- 72% (65) produced carbapenemases, 3 isolates produced both class A and B carbapenemases. (**Figure 1B)**
- 57% (51) were resistant to MEM, 31% to imipenem-relebactam, 17% (15) to ceftazidime-avibactam (CZA), and 9% to MEM-vaborbactam (MVB) **(Figure 2)**
- Addition of QPX to MEM, FEP and ATM reduced MIC_{50}s and MIC_{90}s of these agents ($p<0.0001$).
- Addition of QPX reduced MEM MICs more than did vaborbactam (median 533- versus 24-fold; $p=0.0006$).

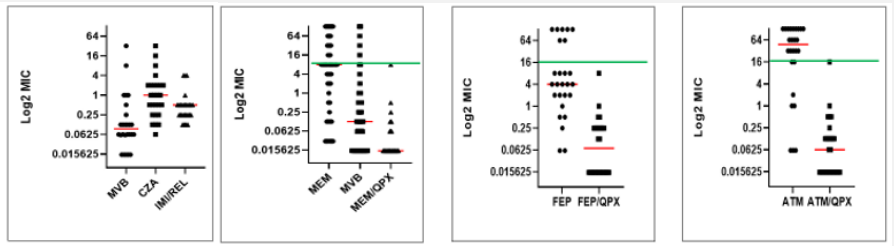

Figure 2. MIC distribution of 90 ENT isolates to selected BL agents +/- QPX agents. MIC distribution of these isolates to currently available BL-BLI are given in the first panel.. Red lines represent MIC50. Green lines represents resistant breakpoints (bp) for respective BL agents. Resistance to BL was defined according to CLSI bp, except for MEM and MVB, for which >8 µg/ml was used based on PK/PD of 2g MEM by IV infusion over 3h every 8h. Bp for BL+QPX were based on bp of companion BL.

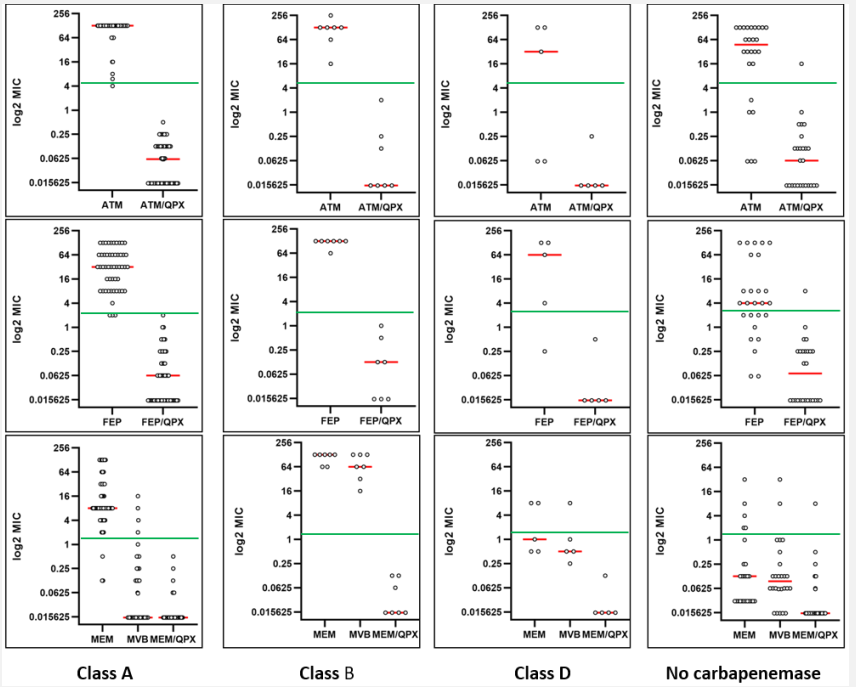

Figure 3. MIC distribution of ENT isolates to selected BL agents +/- QPX, stratifying by carbapenemases. Green lines represents MIC susceptible breakpoints for respective BL agents.

- QPX reduced MICs of MEM, FEP and ATM to levels below respective breakpoints for non-susceptibility (Fig. 2).
- QPX potentiated activity of MEM, FEP or ATM against ENT, regardless of whether they produced class A, B or D carbapenemases. (**Figure 3**)

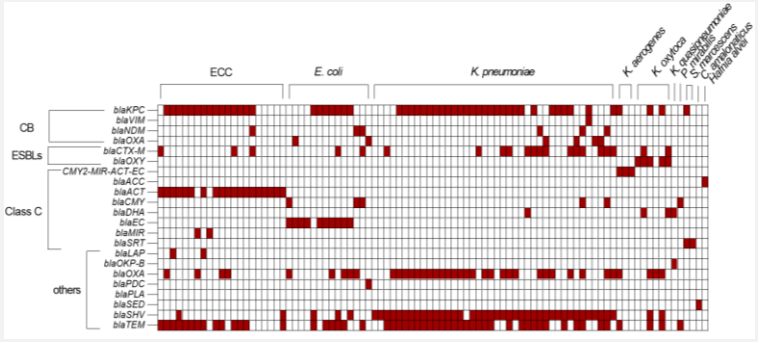

Figure 4. Heatmap showing the distribution of beta-lactam antibiotic resistance genes in ENT isolates .

- 72% (65) carried carbapenem-resistance genes, 27 % (24) carried extended-spectrum β-lactamase (ESBL) genes (**Figure 4**)
- 15% (6) of *K. pneumoniae* isolates harbored mutations in *ompK* 36: 3 p.AA135-136DT, 2 IS elements and 1 other mutation within ORF
- ENT-resistant to CZA were due to production of class B, D or KPC-3 variants, or *ompC* mutation in a *K. aerogenes* isolate.
- ENT-resistant to MVB were due to carbapenemase class B or D enzymes; class A carbapenemase or class C, with *ompK36* or *ompC* mutations.
- Addition of QPX reduced MICs of BLagents to below the susceptible breakpoints for all isolates tested except a *K. aerogenes* isolate which harbors ompC mutations. Over-expression of ampC and *ompC* mutations are likely the mechanism of resistance

CONCLUSION

QPX enhanced activity of MEM, FEP and ATM against carbapenemase-producing or other carbapenem-resistant ENT (CRE), regardless of species or other resistance determinants. Most remarkably, QPX rendered each BL equally active against CRE. The expanded spectrum of QPX against class B and D carbapenemases addresses a major unmet need against CRE.

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