Xeruborbactam (QPX) potentiates the activity of multiple β-lactams against highly resistant *Pseudomonas aeruginosa* to a greater degree than other beta-lactamase inhibitors

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Background

Pseudomonas aeruginosa (PA) is an important pathogen notorious for antibiotic resistance. Xeruborbactam (QPX) is a potent ultra-broad-spectrum boronic acid β-lactam (BL) inhibitor that, in combination with selected BL antibiotics, has excellent *in vitro* activity against carbapenem-resistant Enterobacterales-(CRE), and *Acinetobacter baumanii* or PA producing class A/B or C carbapenemases. We evaluated QPX in combination with anti-pseudomonal BLs against clinical PA isolates from tertiary care US hospitals.

Materials and Methods

- We tested PA clinical isolates resistant to ≥1 BL (imipenem (IMP), meropenem (MEM), cefepime (FEP), piperacillin-tazobactam (PIP-TAZ), ceftolozane-tazobactam (TOL-TZP), ceftazidime-avibactam (CZA), IMI-relebactam (IMI-REL), MEM-vaborbactam (MVB)) against QPX (in fixed concentration of 8 µg/mL) combined with IMP, MEM, FEP, PIP and TOL.
- We performed short-read whole-genome sequencing on isolates using the MiSeq platform (Illumina).

Results

Antibiograms and resistance determinants of 77 isolates tested to date are summarized in Figs 1, 2. 91% of isolates were CR; 43%, 58% and 61% were resistant to CZA, IMI-REL and MVB, respectively.

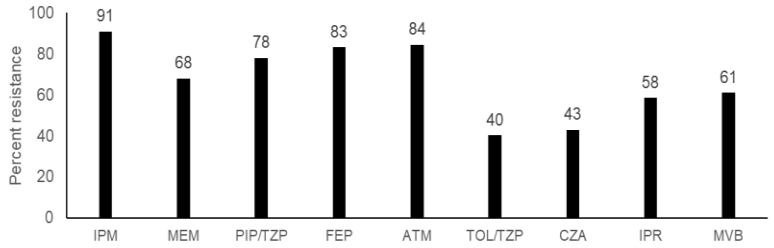

Figure 1. Antibiogram of *P. aeruginosa* clinical isolates. Resistant breakpoints (BPs) were defined according to CLSI BPs, except for MEM when BP of >8 µg/mL is used, which was based on PK/PD BP for 2g MEM as a 3-h IV infusion every 8h.

No isolates produced class A/B/D carbapemases. All except 2 isolates carried PDC variants. 92% either had *oprD* porin single nucleotide polymorphism (SNP) or deletions. *mutS* mutations (present in 23% of isolates) was associated with resistance to IPM/QPX (p=.04), but not TOL-QPX or PIP-QPX.

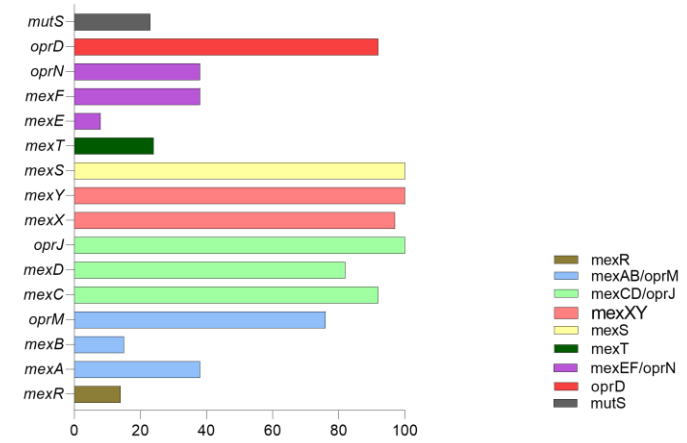

Figure 2. Rate (%) of non synonymous variants observed within genes encoding for efflux pumps or porins.

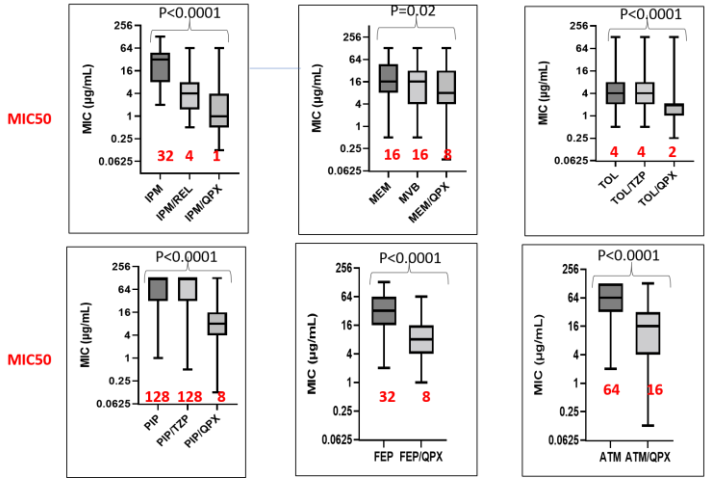

Figure 3. Impact of QPX in combination with BL on median MICs of clinical PA isolates.

- Addition of QPX significantly reduced MIC_{50} of IPM (32-fold), PIP (16-fold), FEP and ATM (4-fold) (all p<.0001, Fig 3). Addition of QPX to MEM or TOL reduced MIC_{50} by 2-fold (p=.02, p<.0001). QPX reduced IMP and PIP MICs more than did REL (32 vs 8-fold, p<.0001) or TZP (16 vs nil, p=.0007), respectively.

- Addition of QPX reduced BL resistance, especially for TOL, PIP and IMP (Fig 4).
- Factors associated with BL/QPX resistance by logistic regression:
  - MP/QPX: IMP resistance (p=.001), SNP in *mexB* (p=.01)
  - TOL/QPX: TOL resistance (p=.02);
  - PIP/QPX (SNP in *mexR* and *mexB* (p=.03).

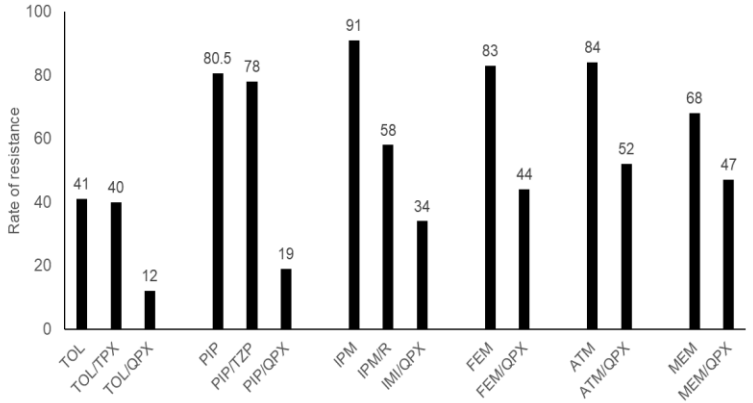

Figure 4. Impact of QPX addition to β-lactams on the rate of resistance. Breakpoints (BPs) for resistance of BL antibiotic combined with QPX were defined according to BP of the companion antibiotic

CONCLUSION

QPX enhanced the activity of BLs, especially TOL and PIP, against PA with baseline resistance to BL, more so than other BLIs. TOL/QPX and PIP/QPX are less impacted by PA efflux and porin mutations than IMP/QPX.

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