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The β-Lactamase Inhibitor QPX7728 Restores the Activity of β-Lactam Agents against Contemporary ESBL-Producing and CRE Isolates, Including Isolates Producing Metallo-β-Lactamases

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Introduction

- Extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant *Enterobacterales* (CRE) isolates continue to cause difficult to treat infections worldwide.
- New β-lactam/β-lactamase inhibitor combinations, including ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam, are active against ESBLs and some CREs, but they have limited activity against isolates producing metallo-β-lactamases (MBLs).
- A new boronic β-lactamase inhibitor in Phase 1 development, QPX7728, has a broader range of activity than its comparators as it inhibits isolates carrying the most common β-lactamases as well as serine carbapenemases and MBLs.
- We tested QPX7728 paired with various oral and intravenous β-lactams, including carbapenems, against a large collection of *Enterobacterales* isolates characterized for the presence of ESBLs and carbapenemases.

Materials and Methods

- A total of 1,027 *Enterobacterales* isolates genetically characterized for the presence of extended-spectrum β-lactamases and/or carbapenemases were tested.
- The 507 CRE isolates were identified by elevated MIC values of ≥2 mg/L to doripenem, imipenem, and/or meropenem. *Proteus mirabilis* and indole-positive Proteeae used only meropenem due to intrinsically elevated imipenem MIC values.
  - The CRE subset included 195 isolates carrying class A serine carbapenemases, 168 producing MBLs, 97 OXA-48-like-carrying isolates, and an additional 47 CRE with no detectable carbapenemase.
- The 520 ESBL isolates had elevated MIC values of ≥2 mg/L to ceftazidime, ceftriaxone, aztreonam, or cefepime.
- These isolates were subjected to whole genome sequencing (WGS) on a MiSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage.
  - The sequences were *de novo* assembled and searched for the presence of acquired carbapenemases using a curated library and applying criteria of >94% sequencing identity and 40% minimum length coverage.
- Susceptibility testing was performed by reference broth microdilution against aztreonam, cefepime, cefdinir, ceftibuten, ceftolozane-tazobactam, piperacillin-tazobactam, meropenem, and tebipenem combined with QPX7728 at a fixed 4 and 8 mg/L (CLSI; M07, 2018).
  - QPX7728 and tebipenem were provided by Qpex Biopharma, while the remaining agents were supplied by Sigma-Aldrich (St. Louis, MO, United States) or United States Pharmacopeia (Rockville, MD, United States).
  - Quality control (QC) was performed according to CLSI guidelines and results were evaluated against acceptable published ranges (CLSI; M100, 2021).

Results

- Most β-lactam agents tested alone had limited activity against 520 ESBL-producing isolates.
  - Cefdinir, aztreonam, cefepime, and ceftibuten all displayed MIC_{50} values of >64 and had low susceptibility rates using current CLSI breakpoints (0.2%, 16.9%, 21.0%, and 61.0% S, respectively).
  - Piperacillin-tazobactam and ceftolozane-tazobactam were slightly more active, with 80.4% and 85.6% of ESBL isolates susceptible at CLSI breakpoints, respectively. Meropenem and tebipenem displayed $MIC_{50/90}$ values of ≤0.03/0.06-0.12 mg/L, respectively, and inhibited 99.0% of ESBL-producing isolates by ≤2 mg/L (Figure 1A and 1C).
- When combined with a fixed concentration of 4 or 8 mg/L QPX7728, all tested β-lactams displayed MIC_{90} values of ≤0.5 mg/L against the ESBL isolates (Figure 1B and 1D).
- The oral agents cefdinir, ceftibuten, and tebipenem displayed MIC_{90} values of ≤0.12 mg/L against ESBL isolates when combined with a fixed concentration of 4 mg/L QPX7728.
- Aztreonam, cefepime, and meropenem with QPX7728 at a fixed concentration of 8 mg/L and tebipenem with QPX7728 at a fixed concentration of 4 mg/L were the most active combinations against ESBL isolates with MIC_{90} values of ≤0.03 mg/L.
- The β-lactam agents tested alone displayed limited activity against the 507 CRE isolates ($MIC_{50/90}$ values, ≥32/>64 mg/L; Figure 2A and D).
  - At current CLSI breakpoints, the CRE isolates were ≤6.7% S to all β-lactam agents tested alone, except for ceftibuten (21.9% S).
- Amongst the CRE isolates, >90% were inhibited by aztreonam, cefepime, and meropenem at ≤0.5 mg/L with the addition of 8 mg/L QPX7728.
  - Meropenem tested with 8 mg/L of QPX7728 was the most active combination ($MIC_{50/90}$, ≤0.03/0.12 mg/L); however, cefepime with a fixed concentration of 8 mg/L QPX7728 inhibited all CRE isolates at 4 mg/L.
- Against the 339 CRE isolates that did not carry MBLs, aztreonam, cefepime, ceftibuten, ceftolozane-tazobactam, tebipenem, and meropenem tested with a fixed concentration of 4 or 8 mg/L QPX7728 inhibited ≥96.2% of isolates at ≤2 mg/L (Figure 2B and E).
  - Cefdinir and piperacillin-tazobactam tested with a fixed concentration of 4 and 8 mg/L QPX7728, respectively, were less active against the non-MBL CRE subset than ESBL subset; however, these combinations still inhibited ≥96% of isolates at ≤8 mg/L.
- Most β-lactam and QPX7728 combinations were less active against MBL-producing CREs, but aztreonam, cefepime, and meropenem all exhibited good activity against MBL-producing isolates when tested with a fixed concentration of 8 mg/L QPX7728 with MIC_{90} values of 0.12, 0.5, and 1 mg/L, respectively (Figure 2C and F).
  - Both aztreonam and cefepime tested with a fixed concentration of 8 mg/L QPX7728 inhibited all isolates producing MBLs at ≤4 mg/L.

Conclusions

- The activity of all non-carbapenem β-lactam agents increased ≥64-fold against ESBL-producing isolates when tested with a fixed concentration of 4 or 8 mg/L QPX7728.
- Most β-lactam-QPX7728 combinations showed greater activity against non-MBL CREs when compared to CREs producing MBLs, and all combinations except cefdinir and piperacillin-tazobactam inhibited >90% of non-MBL CRE isolates at ≤0.5 mg/L when tested with a fixed concentration of 4 or 8 mg/L QPX7728.
- Aztreonam, cefepime, and meropenem tested with 8 mg/L QPX7728 displayed better activity than all comparators against 168 MBL-producing isolates with MIC_{90} values of ≤1 mg/L.
- Further development of QPX7728 paired with various β-lactam agents for difficult to treat ESBL and CRE infections seems warranted.

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Figure 1. Antimicrobial activity of QPX7728 in combination with β-lactam agents tested against ESBL-carrying isolates

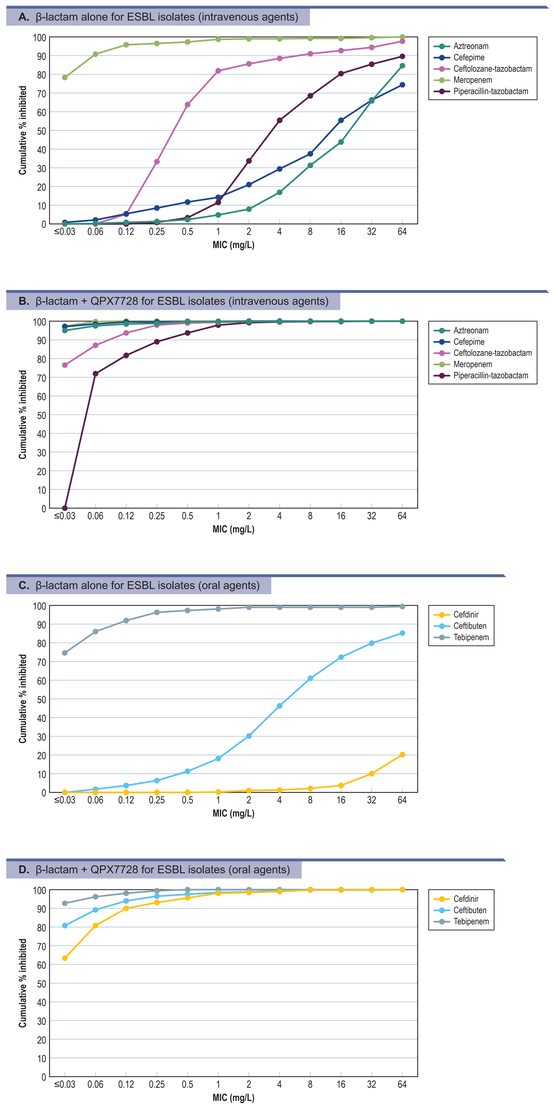

Figure 2. Antimicrobial activity of QPX7728 in combination with β-lactam agents tested against CRE isolates