Activity of Novel β-Lactamase Inhibitor QPX7728 Combined with β-Lactam Agents When Tested against Carbapenem-Resistant *Enterobacterales* (CRE) Isolates

Mariana Castanheira[1], Jill Lindley[1], Holly Huynh[1], Rodrigo E. Mendes[1], Olga Lomovskaya[2]

[1]JMI Laboratories, North Liberty, Iowa; [2]Qpex Biopharma, San Diego, California

Introduction

- Carbapenem-resistant *Enterobacterales* (CRE) isolates have emerged worldwide with areas of endemic dissemination of these isolates
- Serious infections caused by CRE organisms have a higher attributable mortality rate when compared to isolates susceptible to carbapenems
  - Higher mortality rates have been associated with delayed administration of appropriate antimicrobial therapy
- Recently approved β-lactam/β-lactamase inhibitor combinations that include ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam are active against KPC and some OXA-48 producers, but not against isolates producing metallo-β-lactamases (MBLs)
- QPX7728 is a new ultra-broad-spectrum boronic β-lactamase inhibitor that has activity against both serine carbapenemases, including class D, and MBLs
- We tested QPX7728 paired with various β-lactams against a collection of CRE isolates characterized for the presence of carbapenemases

Materials and Methods

- The 508 CRE isolates selected exhibited doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L (*Proteus mirabilis* and indole-positive Proteeae used only meropenem or doripenem due to intrinsically elevated imipenem MIC values)
  - These isolates were screened for the presence of carbapenemase-encoding genes using PCR/Sanger sequencing or whole genome sequencing (WGS) analysis
    - PCR/Sanger sequencing was performed as described elsewhere
    - WGS was performed on a MiSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage
    - For WGS, 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
- Isolates were susceptibility tested against meropenem, tebipenem, cefepime, ceftolozane, and ertapenem combined with QPX7728 at fixed 2, 4, and/or 8 mg/L using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI; M07, 2018)
  - Agents were provided by Qpex Biopharma except for meropenem, cefepime, and ertapenem
  - Quality control (QC) was performed according to CLSI guidelines, and all QC MIC results were within acceptable ranges, as published in CLSI documents (M100, 2019)
  - Categorical interpretations for β-lactams alone were those found in European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 9.0, January 2019), the CLSI criteria in M100 (2019), or the US Food and Drug Administration (FDA) website

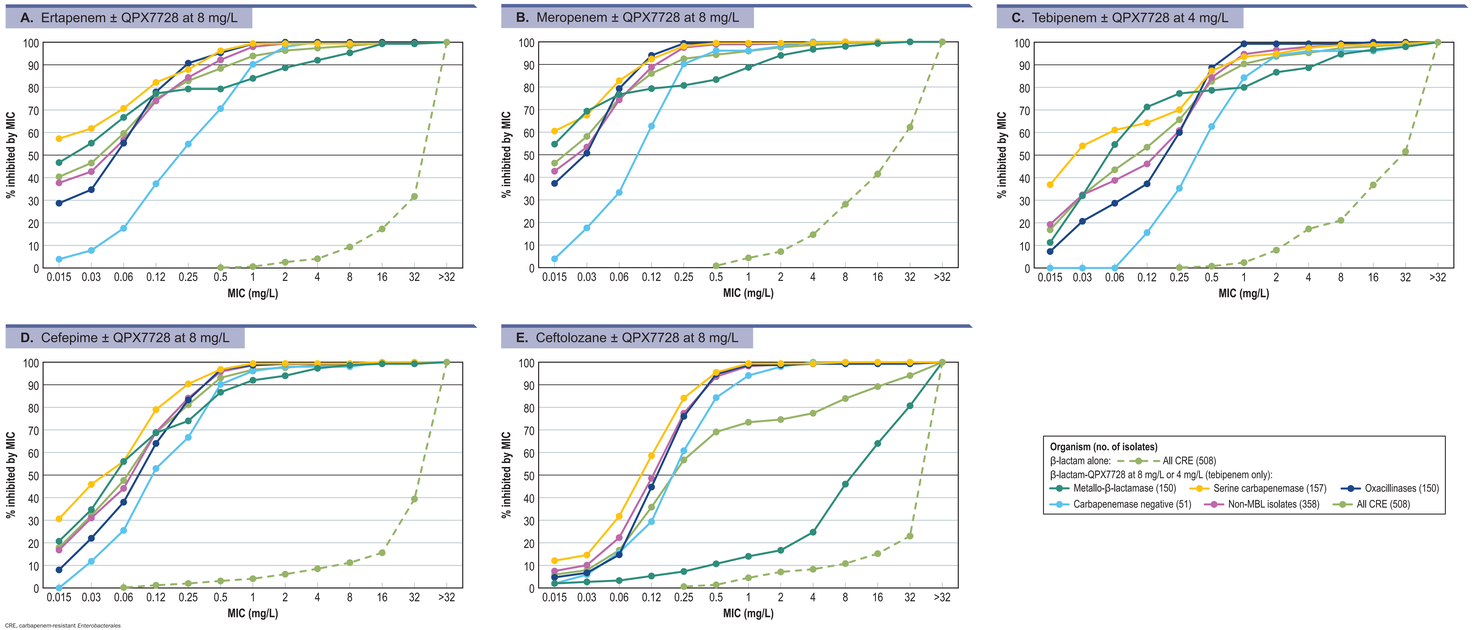
Results

- Overall, β-lactam agents tested alone had limited activity against the 508 CRE isolates tested, displaying $MIC_{50/90}$ values at ≥32 mg/L/≥32 mg/L (Figure 1)
- The combinations of cefepime, ceftolozane, tebipenem, meropenem, and ertapenem plus QPX7728 at fixed 4 mg/L or 8 mg/L inhibited 96.2% to 99.4% of the 157 isolates producing serine carbapenemases at ≤2 mg/L
  - Among all combinations, the lowest $MIC_{50/90}$ values were noted for meropenem-QPX7728 when the inhibitor was tested at fixed 8 mg/L ($MIC_{50/90}$, ≤0.015/0.12 mg/L)
- Ertapenem and meropenem combined with QPX7728 inhibited all isolates harboring OXA-48-like genes (n=150) at ≤2 mg/L or ≤8 mg/L, respectively, regardless of the inhibitor concentration
  - QPX7728 tested with cefepime, ceftolozane, and tebipenem inhibited all but 1 isolate producing OXA-48-like at ≤2 mg/L
- All 51 CRE isolates that did not carry carbapenemases were inhibited at ≤4 mg/L when using 8 mg/L of QPX7728 in combination with meropenem, ertapenem, and ceftolozane and meropenem plus QPX7728 using 4 mg/L of the inhibitor
  - Tebipenem-QPX7728 at fixed 4 mg/L and cefepime-QPX7728 regardless of the inhibitor concentration inhibited 96.1% and 98.0% of these isolates at ≤4 mg/L, respectively
- Against isolates harboring genes encoding MBLs, the combination of meropenem and ertapenem with QPX7728 at a fixed 8 mg/L inhibited 96.7% and 92.0% of the isolates at ≤4 mg/L, respectively
  - Using fixed 8 and 4 mg/L of inhibitor, cefepime and tebipenem combinations with QPX7728 inhibited 97.3% and 88.7% of the isolates at ≤4 mg/L, respectively
  - Ceftolozane plus QPX7728 had limited activity against MBL-producing isolates and <50% at ≤8 mg/L

Conclusions

- QPX7728 restored the activity of several β-lactams when tested against 508 CRE isolates that include 157 harboring serine carbapenemase, 150 isolates producing oxacillinases, and 150 MBL-producing isolates
- Combination results for β-lactams plus QPX7728 for MBL-producing isolates were slightly higher than the activity of these investigational combinations against other carbapenem-resistant groups
  - The combinations with meropenem, ertapenem, and cefepime displayed good activity inhibiting >90% of the isolates at ≤4 mg/L
- Further development of this β-lactam/lactamase inhibitor with activity against all carbapenemase types seems warranted

Figure 1 Antimicrobial activity of QPX7728 in combination with β-lactam agents tested against CRE isolates characterized for the presence of carbapenemase genes



CRE, carbapenem-resistant *Enterobacterales*

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Contact

Mariana Castanheira, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: mariana-castanheira@jmilabs.com

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