Activity of a Novel Polymyxin Analog, QPX9003, Tested against Resistant Gram-Negative Pathogens, Including Carbapenem-Resistant *Acinetobacter*, *Enterobacterales*, and *Pseudomonas*

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Introduction

- Polymyxins are cationic peptides that bind to lipopolysaccharide on the bacterial cell damaging the membrane and leading to cell death
  - Polymyxins have good activity against gram-negative organisms, including *Pseudomonas aeruginosa*, *Acinetobacter* spp., and most *Enterobacterales* species
- Due to high rates of multidrug resistance (MDR) among these species, polymyxins are often used as a last resource for the treatment of serious infections caused by MDR gram-negative bacteria due to the limited active therapeutic options against these pathogens
- Polymyxins have been associated with reports of adverse renal effects and less commonly with neurological effects
  - Although dosing strategies have been used to reduce the nephrotoxicity issues with polymyxins, an analog molecule with a better safety profile would be highly beneficial
- We evaluated the activity of QPX9003 against a large collection of gram-negative isolates collected worldwide that include MDR isolates

Materials and Methods

- A total of 1,015 *Enterobacterales*, 503 *Acinetobacter baumannii* isolates displaying elevated meropenem MIC values (≥8 mg/L), and 1,000 *P. aeruginosa* isolates were tested
  - *Enterobacterales* isolates included 507 isolates displaying ceftazidime and/or ceftriaxone resistance and 508 carbapenem-resistant *Enterobacterales* (CRE) isolates screened for the presence of carbapenemases
  - *P. aeruginosa* isolates included 400 isolates representing the normal distribution for meropenem and 600 challenge isolates displaying elevated MIC values for anti-pseudomonal β-lactam/β-lactamase inhibitor combinations
- Isolates were susceptibility tested by reference broth microdilution against QPX9003, colistin, levofloxacin, tigecycline, gentamicin, amikacin, meropenem, cefepime, meropenem-vaborbactam, piperacillin-tazobactam, ceftolozane-tazobactam, and ceftazidime-avibactam
  - Agents except meropenem and cefepime were provided by Qpex Biopharma
  - Quality control (QC) was performed according to Clinical and Laboratory Standards Institute (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

- QPX9003 ($MIC_{50/90}$, 0.25/0.25 mg/L) had potent activity against *P. aeruginosa* isolates and this new agent was 4-fold more potent than colistin ($MIC_{50/90}$ of 1/1 mg/L; Figure 1a)
  - These results were similar to the results for these compounds tested against a subset of 600 *P. aeruginosa* isolates enriched for resistance against β-lactam/β-lactamase inhibitor combinations ($MIC_{50/90}$, 0.25/0.25 mg/L for QPX9003 versus $MIC_{50/90}$ of 1/1 mg/L for colistin)
- QPX9003 ($MIC_{50/90}$, 0.12/1 mg/L) was 4-fold more potent than colistin ($MIC_{50/90}$, 0.5/4 mg/L) when tested against 503 carbapenem-resistant *Acinetobacter* spp. (Figure 1b)
- QPX9003 ($MIC_{50/90}$, 0.06/16 mg/L) had a modal MIC of 0.06 mg/L against 1,015 *Enterobacterales* isolates (Figure 1c)
  - Overall, the activities of QPX9003 and colistin ($MIC_{50/90}$, 0.12/>8 mg/L) were similar against *Enterobacterales* isolates regardless of the resistance group (CRE or cephalosporin resistant) or main species (*Klebsiella pneumoniae* and *Escherichia coli*)
- The activity of QPX9003 against 358 CRE isolates that did not carry a metallo-β-lactamase ($MIC_{50/90}$, 0.06/16 mg/L) was similar to the activity of this compound against isolates that produced these enzymes ($MIC_{50/90}$, 0.06/8 mg/L)
- QPX9003 ($MIC_{50/90}$, 0.06/16 mg/L) displayed potent activity against cephalosporin-resistant *Enterobacterales* isolates
- QPX9003 ($MIC_{50/90}$, 0.06/16 mg/L) had potent activity against 511 *K. pneumoniae* isolates included in this collection (data not shown)
  - *E. coli* isolates had considerably lower MIC results for QPX9003 ($MIC_{50/90}$, 0.06/0.12 mg/L) than *K. pneumoniae* isolates
- Isolates evaluated in this study were highly resistant to comparator agents (Figure 2)

Conclusions

- QPX9003 had excellent activity against this collection of highly resistant gram-negative isolates for which non-polymyxin comparator agents had limited activity
- QPX9003 was more active than colistin against *P. aeruginosa* and carbapenem-resistant *Acinetobacter* spp., and its activity was similar to that of colistin against *Enterobacterales* isolates
- QPX9003 is a promising next-generation polymyxin agent that has improved safety features compared to colistin and polymyxin B

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Figure 1 Activity of QPX9003 and colistin against *P. aeruginosa*, carbapenem-resistant *Acinetobacter* spp., and *Enterobacterales*

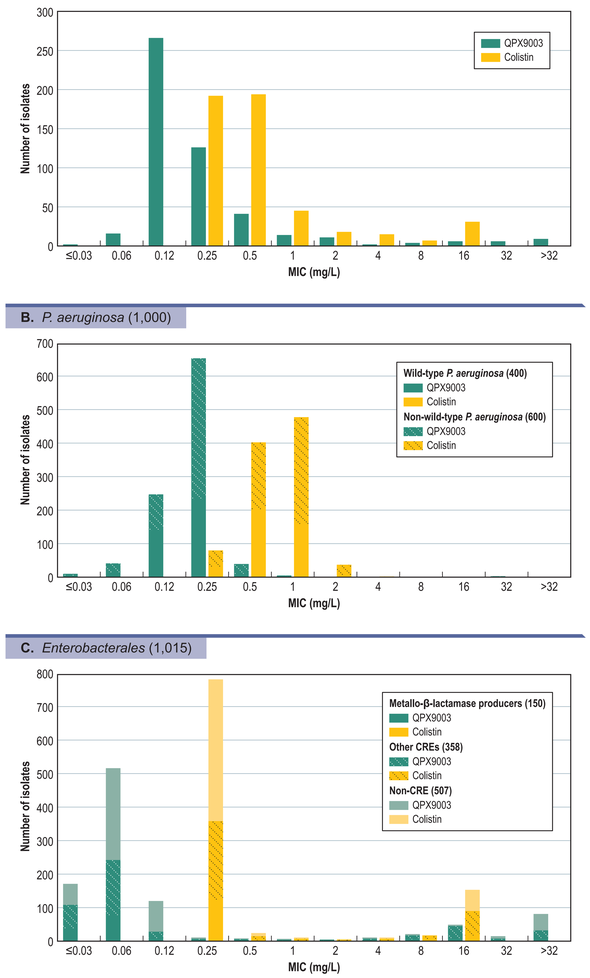
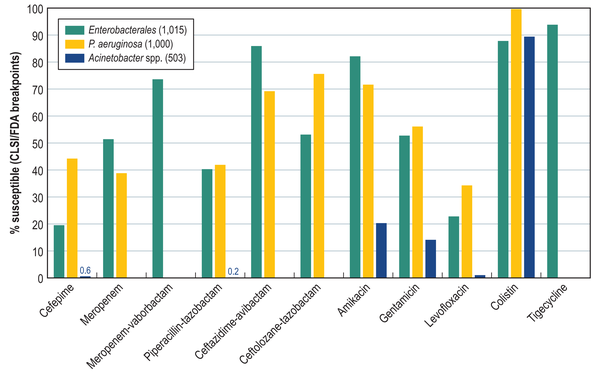


Figure 2 Activity of comparator agents against main organism groups tested



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