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Evaluation of polymyxin B (PB)-based and dual-carbapenem combinations against carbapenem-resistant Enterobacteriaceae co-harbouring mcr-1 and KPC-2

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Background: In light of limited treatment options against carbapenemase-producing carbapenem resistant Enterobacteriaceae (CP-CRE), clinicians are now turning to PB for the treatment of CP-CRE infections. Unfortunately, the emergence of CP-CRE harbouring the polymyxin resistance gene *mcr-1* have threatened the utility of PB monotherapy. Hence, we evaluated the *in vitro* activity of multiple antibiotics in combination against *mcr-1* harbouring CP-CRE through time-kill studies (TKS) to identify the most promising combinations.

Material/methods: Three well-characterised CP-CRE isolates harbouring *mcr-1* [2 *Escherichia coli* (EC249, EC250), 1 *Enterobacter aerogenes* (EC702)] were tested. In addition to *mcr-1*, all 3 isolates harboured bla_{KPC-2}. MICs to various antibiotics were determined using the reference broth-dilution method. 24h TKS were conducted with 5 $\log_{10}$CFU/mL at baseline with maximum, clinical achievable concentrations of aztreonam (AZ) (28mg/L), levofloxacin (L) (8mg/L), cefepime (C) (50mg/L), rifampicin (R) (4mg/L), tigecycline (T) (2mg/L), imipenem (I) (12.5mg/L), meropenem (M) (20mg/L), doripenem (D) (26mg/L), piperacillin-tazobactam (PT) (35/7mg/L) singly and in combination with PB (2mg/L). 24h TKS were also conducted with ertapenem (E) (15mg/L) in combination with I, M, and D, to evaluate the utility of the “double-carbapenem strategy” against these isolates.

Results: All three isolates were extensively drug-resistant, but retained susceptibility to tigecycline (T MIC EC249: ≤0.25mg/L; EC250: ≤0.25mg/L, EC702: 0.5mg/L). EC702 was also susceptible to L (L MIC: 1mg/L). PB MIC was 4mg/L, 4mg/L and 8mg/L for EC249, EC250 and EC702 respectively. M and I MIC were ≥16mg/L for all isolates, while D MIC was 8mg/L for all isolates. In single drug TKS, none of the antibiotics were bactericidal (≥ 3 $\log_{10}$CFU/mL reduction from baseline) at 24h. M and D alone resulted in initial bactericidal killing at 2 – 4h followed by regrowth at 24h for all 3 isolates, while

PB alone resulted in initial bactericidal killing at 2 – 4h for only one isolate (EC249). In combination TKS, PB+R and PB+M were bactericidal against all 3 isolates at 24h, while PB+L was bactericidal against 2 isolates (EC250, EC702). Interestingly, despite susceptibility of the isolates to T, PB+T did not exhibit bactericidal activity against any isolates at 24h. In dual carbapenem TKS, E+I and E+M were each bactericidal against 2 out of 3 isolates, while E+D was bactericidal against all 3 isolates at 24h.

Conclusions: Despite the presence of the polymyxin resistance gene *mcr-1*, we found that PB-based combination, in particularly PB+M and PB+R, may still have utility in the treatment of local CP-CRE co-harbouring *mcr-1* and bla_{KPC-2}. In addition, dual carbapenem therapy may be a promising alternative. Further investigation of the clinical utility of these combinations against these isolates is warranted.

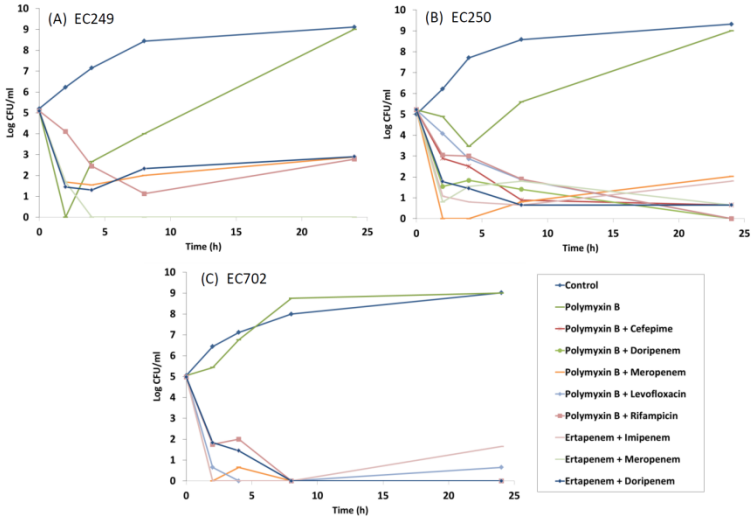

Figure 1. Time-kill curves depicting bactericidal combinations against (A)EC249, (B) EC250 and (C) EC702.