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O0826 Evaluation of synergistic meropenem-ciprofloxacin combination dosage regimens for critically ill patients with altered pharmacokinetics via mechanism-based modelling and the dynamic hollow fibre infection model

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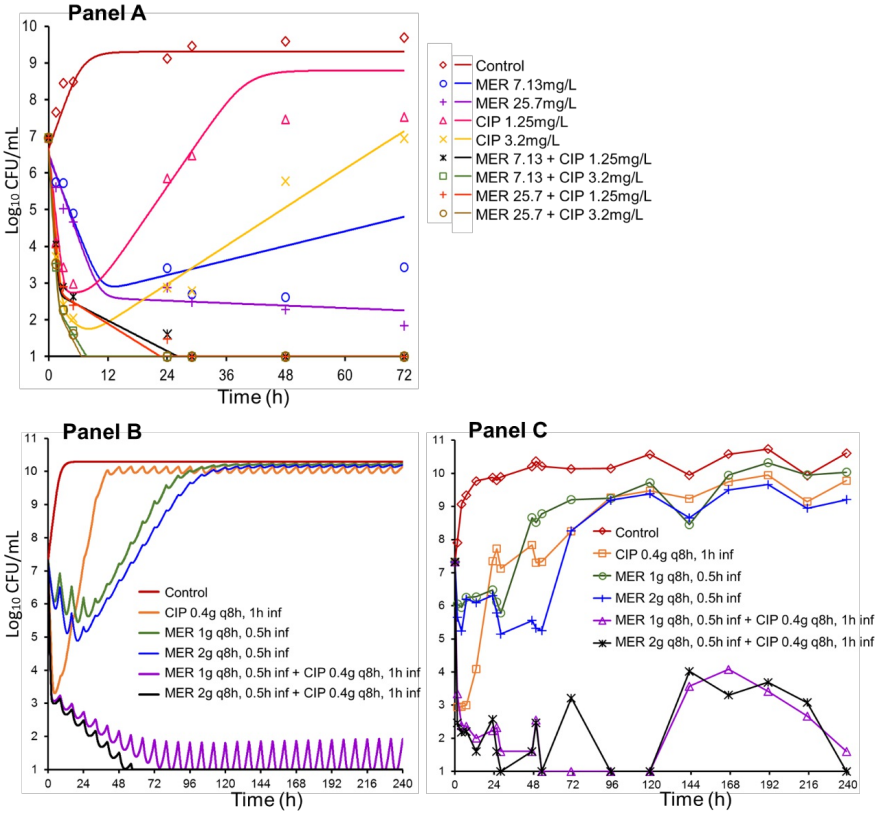
Background: Infections due to *Pseudomonas aeruginosa* (Pa) are associated with high morbidity and mortality in critically-ill patients. Alterations in antibiotic concentrations at the infection site are a major concern in this patient population due to augmented renal clearance (ARC) affecting renally excreted antibiotics. The impact of ARC on bacterial killing and resistance emergence has not been characterised *via* the hollow-fibre infection model (HFIM) for the combination of meropenem (MER) and ciprofloxacin (CIP).

Materials/methods: MER and CIP alone and in combinations were investigated against isolate Pa1280 (MIC_{MER} and MIC_{CIP} 0.25mg/L) from a critically-ill patient using static-concentration time-kill (SCTK) experiments (32 profiles in total). Mechanism-based modelling (MBM) of the SCTK data and *in silico* simulations for clinically relevant regimens were conducted. Promising combination regimens were evaluated in a 10-day HFIM study (inoculum ~10^7 CFU/mL) simulating ARC (CL_{CR} 250mL/min). Total and resistant bacterial counts were determined.

Results: All CIP concentrations evaluated in SCTK achieved >3log_{10} CFU/mL killing in the first 5h followed by regrowth almost similar to control counts by 72h. MER 7.13mg/L produced >4log_{10} killing at 48h followed by regrowth. MER 25.7mg/L suppressed regrowth to <2log_{10} at 72h. All combinations yielded >5log_{10} killing and suppressed regrowth to <1log_{10} (limit of counting) over 72h. MBM well described the viable count profiles for all treatments (A) and indicated substantial subpopulation synergy. *In silico* simulations (B) of clinically relevant dosage regimens predicted regrowth to control values for all monotherapies and ~4log_{10} killing with regrowth suppression for combinations. HFIM results (C) were in good agreement with *in silico* predictions. All monotherapies produced regrowth similar to control values with extensive resistance emergence (MIC_{MER} 16mg/L, MIC_{CIP} 32mg/L at 240h). Both combination regimens suppressed regrowth and resistance emergence with viable counts <2log_{10} at 240h.



Conclusions: MBM predictions based on SCTK data were successfully translated to the dynamic HFIM. For the pharmacokinetics of critically-ill patients with ARC, a combination of approved dosage regimens of MER and CIP was required to suppress regrowth and resistance emergence over 10 days. These combination regimens are highly promising for improved clinical effectiveness and suppression of resistance emergence, even in the near-worst-case scenario of ARC.