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P2113 Optimising combination dosage regimens of piperacillin/tazobactam plus tobramycin against a clinical *Pseudomonas aeruginosa* isolate in a dynamic *in vitro* infection model

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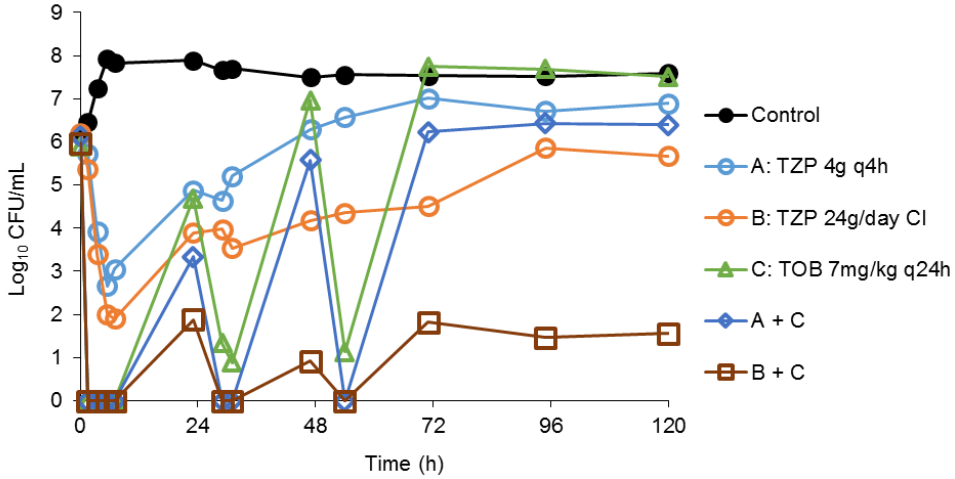
Background: *Pseudomonas aeruginosa* (Pa) is a common cause of nosocomial infections in various patient groups including the critically-ill. Critically-ill patients are particularly vulnerable to treatment failures, which may be due to sub-optimal antibiotic exposures. We evaluated piperacillin-tazobactam (TZP) plus tobramycin (TOB) regimens simulating the pharmacokinetics of critically-ill patients with normal renal function.

Materials/methods: Static time-kill studies (STK, inocula 10^6 and $10^{7.5}$ CFU/mL, 32 experimental arms total) assessed TZP and TOB in monotherapies and combinations over 72h. A clinical isolate (MICTZP 4mg/L, MICTOB 0.5mg/L) from a critically-ill patient was evaluated in STK and subsequently studied in 120h dynamic one-compartment *in vitro* infection models (IVM, inoculum 10^6 CFU/mL, performed in n=2 replicates). The IVM simulated the pharmacokinetics of TZP ($t_{1/2}$=1.5h) and TOB ($t_{1/2}$=3.1h), based on published population pharmacokinetic models. Regimens were: A. TZP 4g q4h as 0.5h infusions; B. TZP 24g/day as continuous infusion (CI); C. TOB 7mg/kg q24h as 0.5h infusions; A+C; and B+C. Total viable counts were determined at 13 time points and resistant bacteria quantified at 24h intervals. Mechanism-based modelling was performed.

Results: STK demonstrated initial killing and suppression of regrowth by TZP+TOB at both inocula over 72h. As a monotherapy TOB 8 mg/L suppressed regrowth at the lower inoculum (10^6), however regrowth occurred at the higher inoculum ($10^{7.5}$). In the IVM (Figure), A provided <4 $\log_{10}$ CFU/mL initial killing, followed by regrowth close to control values by 72h. B provided 4.0-4.5 $\log_{10}$ initial killing, followed by regrowth close to initial inoculum by 96h. C and A+C provided extensive killing (up to 6 $\log_{10}$) after each dosing interval up to 54h, with regrowth to control values and starting inoculum, respectively, and resistance emergence by 72h. B+C provided extensive initial killing and supressed regrowth (to <2 $\log_{10}$) and resistance emergence over 120h.



Conclusions: Only TZP 24g/day CI + TOB suppressed regrowth and the emergence of resistance of Pa over 120h.

As an intermittent regimen, the same daily dose of TZP with TOB resulted in sustained regrowth by 72h. Thus, the shape of the concentration-time curve was an important factor for achieving synergistic antibiotic effects with the combination treatment.