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Optimized combination therapy: the future to eradicate hypermutable bacteria

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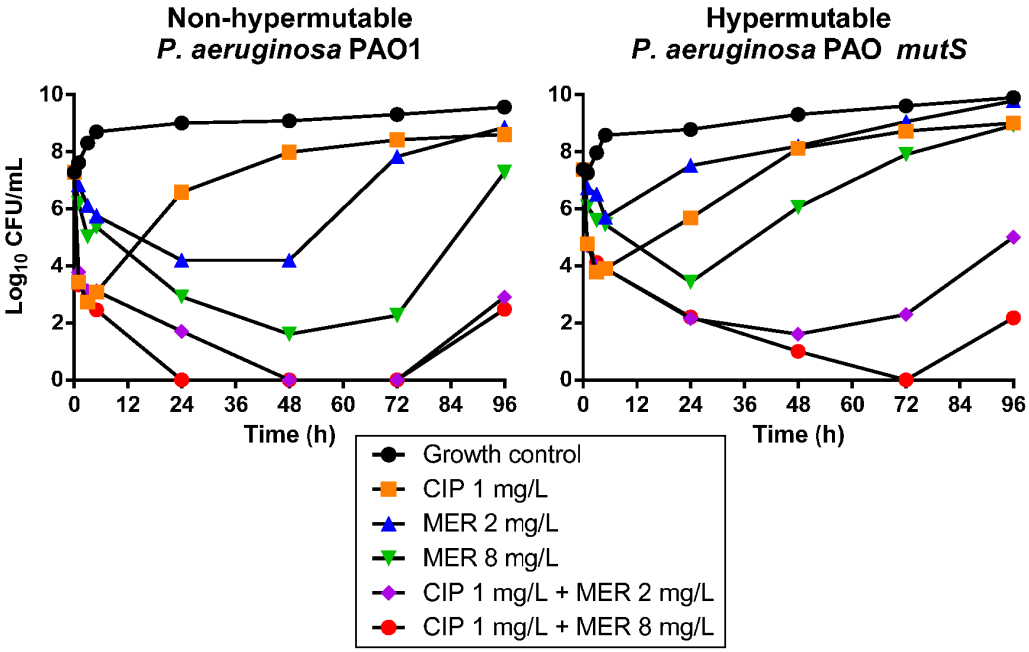
Background: Hypermutable *Pseudomonas aeruginosa* (Pa) have a greatly increased mutation rate resulting more frequently in antibiotic resistance than non-hypermutable Pa. Hypermutable Pa has been associated with reduced lung function in cystic fibrosis (CF). Monotherapy of available antibiotics is becoming ineffective due to the rapid rise of antibiotic resistance in serious respiratory infections. This study aimed to evaluate the time-course of bacterial killing and resistance of ciprofloxacin (CIP) and meropenem (MER) in combination against hypermutable and non-hypermutable Pa.

Material/methods: The combination of CIP and MER was assessed against non-hypermutable PAO1 and hypermutable PAOΔ*mutS* (in duplicate), along with hypermutable CW08 and CW44 isolates from CF patients, in static concentration time-kill studies (112 profiles) over 72 or 96 h. The initial inoculum of $10^{7.5}$ colony forming units (CFU) / mL was targeted to represent serious respiratory infections. Front-loading, short-term (1-2 h) and continuous CIP exposures were compared in monotherapy and combinations with MER at clinically achievable concentrations. Serial viable counts of total and

resistant (at 5x MIC_{MER} and 10x MIC_{CIP}) populations were determined at 0, 0.5, 1.5, 3, 6, 24, 48, 72 and 96 h to evaluate bacterial killing and emergence of resistance.

Results: Both MER and CIP in monotherapy provided limited bacterial killing followed by rapid emergence of resistance for all isolates (Figure). The combinations were synergistic and demonstrated better initial bacterial killing with all Pa strains (Figure) although the emergence of MER and CIP resistant populations was not entirely suppressed. The hypermutable PAOΔ*mutS* (MIC_{CIP} 0.25 mg/L, MIC_{MER} 1.0 mg/L) had less bacterial killing and enhanced emergence of resistance in comparison to non-hypermutable PAO1 (MIC_{CIP} 0.125 mg/L, MIC_{MER} 1.0 mg/L; Figure). Therefore, further CIP optimisation was carried out against the difficult-to-treat hypermutable strains. In PAOΔ*mutS*, the front-load, short-duration and continuous CIP (*f*AUC_{24h} 26.3 mg*h/L for all treatments) in combination with 8 mg/L meropenem revealed ~5.0, ~3.5 and ~6.0 log_{10} CFU/mL bacterial killing, respectively. Limited regrowth and suppression of resistance was observed at 72 h except for the short-duration CIP combination that showed substantial regrowth with CIP and MER resistant populations. CW08 (MIC_{CIP} 1.5 mg/L, MIC_{MER} 4.0 mg/L) revealed less bacterial killing and comparable resistance to PAOΔ*mutS*. CW44 (MIC_{CIP} 0.19 mg/L, MIC_{MER} 2.0 mg/L) showed comparable bacterial killing to PAOΔ*mutS*, but regrowth by 72 h was observed with complete replacement of susceptible populations by MER and CIP resistant populations.



Conclusions: Hypermutable Pa revealed more emergence of resistance compared to non-hypermutable Pa. CIP with MER was demonstrated to be a promising synergistic combination for all isolates. Therefore this combination should be optimised and evaluated in dynamic models to aid the translation to CF patients; enabling better therapies to combat difficult-to-treat hypermutable respiratory Pa infections.