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The combination of polymyxin B and minocycline is synergistic against carbapenem-resistant Klebsiella pneumoniae and Pseudomonas aeruginosa in 24-h time-kill experiments

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Background: Combination therapy is used for severe infections caused by multidrug-resistant Gram-negative bacteria to enhance the efficacy of available antibiotics. In this study we evaluated the activity of polymyxin B combined with six other antibiotics, representing different antibiotic classes, against carbapenem-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The antibacterial effects of single drugs and combinations were assessed with automated time-lapse microscopy and in static 24-h time-kill experiments.

Material/methods: Five clinical isolates each of carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* were provided by the Public Health Agency of Sweden. Nine strains were susceptible to polymyxin B (MICs 0.5-2 mg/L), and one *K. pneumoniae* was resistant (MIC 64 mg/L). An initial screening was performed using automated microscopy (oCelloScope, Philips BioCell) to assess the effects of polymyxin B (0.25, 0.5, 1 and 2 mg/L) in combination with amikacin, chloramphenicol, ciprofloxacin, meropenem, minocycline and rifampicin at three clinically achievable concentrations, yielding at total of 72 combinations. Bacterial starting inocula were ~$5x10^6$ cfu/mL. Growth curves were generated using the background corrected absorption (BCA) algorithm. Combinations were considered of interest if the 24 h BCA value was ≤8 with the combination and >8 with both single drugs. Static 24-h time-kill experiments were performed using antibiotic concentrations selected based on the screening results. Samples were taken at 0, 3 and 24 h for viable counts. Synergistic and

additive effects were defined as ≥2 $\log_{10}$ and 1-2 $\log_{10}$ cfu/mL reduction, respectively, with the combination as compared to its most active constituent at 24 h.

Results: Based on the 24 h BCA values, polymyxin B combinations with amikacin, chloramphenicol, meropenem, minocycline and rifampicin were considered of interest against 2, 2, 4, 4 and 4 of the 5 *K. pneumoniae* strains, respectively, while no interaction was seen with ciprofloxacin. Twelve of these 16 combinations were synergistic and 2 showed additive effects in time-kill experiments. For *P. aeruginosa*, polymyxin B combinations with amikacin, chloramphenicol, ciprofloxacin, meropenem, minocycline and rifampicin were considered of interest against 1, 0, 2, 2, 4 and 2 strains, respectively. In the time-kill experiments, 9 of these 11 combinations showed synergy and one an additive effect. Overall, polymyxin B and minocycline was the most promising combination resulting in synergy against 7 of the 10 strains used.

Conclusions: Our results suggest that the combination of polymyxin B and minocycline could be useful against carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* and should be further explored. Automated time-lapse microscopy was efficient for screening purposes and the obtained data correlated well with the results of static time-kill experiments.