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An in-vitro evaluation of biofilm dispersal as a therapeutic strategy to restore antimicrobial efficacy

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Background: The use of systemic or topical antibiotics administrated in combinations at high dosages is recommended for efficient eradication of bacterial biofilms. Novel anti-biofilm strategies have recently highlighted the potential therapeutic interest of biofilm dispersal agents to enhance killing efficiency of combined antibiotic treatments. As a proof-of-concept study, we evaluated the impact of biofilm dispersal on the *in-vitro* and *in-vivo* efficacy of imipenem (IMI) and tobramycin (TOB) against 3-day-old biofilms of *Pseudomonas aeruginosa*.

Material/methods: Two *P. aeruginosa* strains: PAO1/pJN105 (vector control) and PAO1/p_{BAD}-*yhjH* which contains the pJN105 plasmid carrying the *yhjH* phosphodiesterase (PDE) gene under the arabinose-inducible p_{BAD} promoter. Minimum biofilm eradication concentration (MBEC) values were determined for TOB and IMI using 3-day-old biofilms for both strains with and without biofilm dispersal induced by arabinose addition. Potential for synergy of the combination of TOB+IMI as well as impact of biofilm dispersal on the antimicrobial efficacy were further assessed using *in-vitro* (checkerboard, time-kill and flow cells) and *in-vivo* (corneal infection mice models) biofilm models. All experiments were performed in triplicate using Mueller Hinton II (MHII) as recommended by CLSI guidelines.

Results: The MBEC values of IMI and TOB against 3-day-old biofilms without dispersal were >2048 mg/L and >32 mg/L, respectively. In checkerboard assay, combination of IMI+TOB demonstrated a strong synergistic effect against biofilms of PAO1/p_{BAD}-*yhjH* following dispersal (∑FBEC = 0.016). In contrast, in absence of dispersal, the combination demonstrated same efficiency as compared to the control strain (∑FBEC = 0.125). Using time kill assays, IMI+TOB (4 mg/L) only demonstrated synergistic effect against PAO1/p_{BAD}-*yhjH* biofilms following dispersal (-2.03 log10 CFU/ml). Using flow cells and independent of the induction of biofilm dispersal, IMI+TOB demonstrated little effect against biofilms of the control strain PAO1/pJN105 (Dead/Live biovolume ratio of 0.4 +/- 0.1). In contrast, IMI+TOB demonstrated strong killing potential against biofilms of PAO1/p_{BAD}-*yhjH* following induction

of biofilm dispersal (Dead/Live biovolume ratio of 0.7 +/- 0.2 compared to 0.3 +/- 0.1 in absence of dispersal).

Conclusions: Results of this proof-of-concept study support the idea that inducing biofilm dispersal may improve antimicrobial killing efficiency of IMI and TOB against mature biofilms of *P. aeruginosa*. This strategy might also lead to substantial reductions in the required antibiotic concentrations for efficient biofilm eradication both *in-vitro* and *in-vivo*. Further investigations using clinical strains and dispersal agents are now warranted to confirm the therapeutic interest.