Activities of Daptomycin (DAP), Vancomycin (VAN) and Linezolid (LZD) alone or in combination with Fusidic acid (FUS) in an *in vitro* dynamic model of *Staphylococcus aureus* Biofilm

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Background: FUS is currently evaluated as an oral drug for the treatment of cSSSTI in which biofilms play a major role. We evaluated the activity of FUS alone or combined with other antistaphylococcal antibiotics (DAP, VAN, LZD in an in vitro pharmacodynamic model of staphylococcal biofilm using the CDC reactor system, exposing biofilms to shear forces and mimicking antibiotic pharmacokinetics.

Methods: Biofilms of S. aureus ATCC25923 were grown at 37°C on polycarbonate coupons inserted into rods contained in the CDC biofilm reactor using a starting inoculum of 105 CFU/ml. Preconditioning was achieved in TSB + 1% glucose and 2%NaCl by 6h batch incubation followed by 14h of continuous flow (11.6 mL/min). Antibiotics were then injected at concentrations corresponding to their human fCmax, with flow rates adapted to simulate their respective half-lives. Coupons were collected over time and washed in PBS. Bacteria were recovered by 3 alternating 60-s cycles of vortexing and sonication, and plated for CFU counting.

Results: FUS alone had no activity while VAN, LZD and DAP alone caused a minimal decrease in CFU (0.5-0.7 log). Combinations of FUS with DAP or LZD were highly synergistic, reaching 2.45 and 3.97 log10 CFU decrease compared to control, respectively. In contrast, combining FUS with VAN did not markedly improve activity on biofilms.

Conclusion: Combinations of FUS with DAP or LZD were the most effective against S. aureus biofilm in this pharmacodynamic model, warranting testing in vivo.