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Poster Session VI
PK/PD of antifungals and miscellaneous antibacterials

PREDICTING BACTERIAL RESISTANCE USING THE TIME INSIDE THE MUTANT SELECTION WINDOW: PROS AND CONS

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Objective: Reports on the predictive power of the time inside the mutant selection window (MSW) - T_{MSW} are controversial. To elucidate reasons for these controversies, the enrichment of ciprofloxacin-resistant *Escherichia coli* was studied in an in vitro dynamic model at widely ranging T_{MSW}s.

Methods: Four strains of *E. coli* with different ratios of the mutant prevention concentration (MPC) to the MIC (MPC/MIC from 12 to 31) were exposed to twice-daily ciprofloxacin for three days. Peak antibiotic concentrations were simulated to be close to the MIC, between the MIC and the MPC and above the MPC, with T_{MSW} varying from 0 to 100% of the dosing interval. The amplification of resistant mutants was monitored by plating on media with 8×MIC of the antibiotic and was expressed by the area under the bacterial mutant concentration – time curve ($AUBC_M$) determined from the beginning of treatment to 72 h.

Results: With each organism, T_{MSW} plots of the $AUBC_M$ exhibited a hysteresis loop. At the relatively low antibiotic concentrations that do not reach the MPC ($T_{>MPC}$ = 0), the $AUBC_M$-T_{MSW} curves were above those observed at higher concentrations that exceed the MPC ($T_{>MPC}$ >0). Stratifying the points that meet the condition of either $T_{>MPC}$ = 0 (points corresponding to the ascending branch of the bell-shaped $AUBC_M$-AUC/MIC curve) or $T_{>MPC}$ >0 (points corresponding to the descending branch of the $AUBC_M$-AUC/MIC curve) revealed a more pronounced selection of resistant mutants associated with the shorter T_{MSW} at $T_{>MPC}$ = 0 than at $T_{>MPC}$ > 0. Given the similar pattern of the $AUBC_M$-T_{MSW} relationships observed with individual organisms, the respective combined data were fitted by a sigmoid function, separately for the points that meet the condition $T_{>MPC}$ = 0 (r^2 0.81) and those that meet the condition $T_{>MPC}$ >0 (r^2 0.92). In contrast to the separate data sets, fitting the whole data pool while ignoring the $T_{>MPC}$ factor was less successful (r^2 0.61).

Conclusion: This analysis suggests a rationale for the use of T_{MSW} as a predictor of bacterial resistance. The unjustified integration of data obtained at $T_{>MPC}$ = 0 and $T_{>MPC}$ >0 is probably the main reason for the conflicting results using T_{MSW} to predict resistance.