

## P0253 **Alternative predictors of staphylococcal resistance to linezolid**

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**Background:** The ratio of 24-hour area under the concentration-time curve (AUC) to the MIC is a common predictor of the emergence of bacterial resistance. More closely linked with the mutant selection window (MSW) hypothesis, time inside the mutant selection window ( $T_{MSW}$ ) and the time above the mutant prevention concentration (MPC;  $T_{>MPC}$ ) are used infrequently. To explore if  $T_{MSW}$  and  $T_{>MPC}$  can predict *Staphylococcus aureus* resistance, the enrichment of resistant *S. aureus* mutants was studied by simulating linezolid pharmacokinetics in an *in vitro* dynamic model.

**Materials/methods:** Three methicillin-resistant *S. aureus* strains including clinical isolates 479 and 688 and a well-characterized strain Mu50 (ATCC 700699) susceptible to linezolid (MIC 2 µg/ml) with MPCs of 5, 6 and 10 µg/ml, respectively, were studied. Mixed inocula of each of these strains and their previously selected resistant mutants with MIC of 8 µg/ml were exposed to twice-daily linezolid for five days. The simulated 32-fold range of the AUC/MIC ratio provided antibiotic concentrations below the MIC, between the MIC and MPC and above the MPC. The amplification of resistant mutants was monitored by plating on media with 4×MIC of linezolid.

**Results:** With each *S. aureus* strain, mutants resistant to 4×MIC of linezolid were enriched in a  $T_{MSW}$ -dependent manner.  $T_{MSW}$  plots of the area under the resistant mutant concentration – time curve (AUBC<sub>M</sub>) were qualitatively similar with all studied *S. aureus* strains. With each strain,  $T_{MSW}$  plots with the AUBC<sub>M</sub> split into two portions forming a hysteresis loop, with the upper plot meeting the condition of  $T_{>MPC} = 0$ , and the lower plot –  $T_{>MPC} > 0$ . Using AUBC<sub>M</sub> related to the maximal value observed with a given strain (normalized AUBC<sub>M</sub>), a strain-independent sigmoid relationship was established between AUBC<sub>M</sub> and  $T_{MSW}$  at  $T_{>MPC} > 0$ , as well as  $T_{>MPC}$  ( $r^2$  0.99 for both).

**Conclusions:** These findings suggest that  $T_{MSW}$  at  $T_{>MPC} > 0$  and  $T_{>MPC}$  are reliable bacterial strain-independent predictors of the enrichment of *S. aureus* mutants resistant to linezolid. Both indices can be alternatives to the AUC/MIC ratio as predictors of the emergence of staphylococcal resistance.