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# Endpoints in bacterial resistance studies using in vitro dynamic models: an integral parameter versus a point parameter

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**Background:** Postexposure number of mutants ($N_M$) is a conventional endpoint in bacterial resistance studies using *in vitro* dynamic models that simulate antibiotic pharmacokinetics. To compare $N_M$ with a recently introduced integral parameter $AUBC_M$ (the area under time course of resistance mutants), the enrichment of resistant *Staphylococcus aureus* was studied *in vitro* by simulating single [daptomycin (DAP, doxycycline (DOX)] and combination treatments [DAP + rifampicin (RIF), linezolid (LZD) + RIF].

**Material/methods:** Two strains of *S. aureus*, ATCC 43300 (MICs of DAP and RIF 0.39 and 0.012 mg/L, respectively) and a clinical isolate *S. aureus* 10 (MICs of LZD, RIF and DOX 2.0, 0.016 and 0.1 mg/L, respectively) were exposed to 5-day treatments with the antibiotics. Pharmacokinetic profiles that mimic time courses of once-daily DAP, DOX and RIF and twice-daily LZD in humans were simulated with their respective half-lives (9, 15, 3 and 6 h). The designed ratios of 24-hour area under the concentration – time curve (AUC) to the MIC were 64, 90, 100-1850 and 60 h, respectively. The enrichment of mutants resistant to 2×MIC of DAP and 2×, 4×, 8× and 16×MIC of RIF and DOX was monitored by plating on media containing the respective antibiotic. Time courses of resistant mutants were characterized by $N_M$ at the end of each experiment (120 h) and $AUBC_M$ was calculated from time zero to 120 h.

**Results:** With DAP given alone, DAP-resistant mutants were enriched soon after the start of single treatment of *S. aureus* ATCC 43300, whereas with DAP + RIF the amplification of mutants occurred only on the third day of treatment. The enrichment of RIF-resistant mutants of *S. aureus* 10 was observed later at higher RIF AUC/MICs than at lower ratios when given in combination with LZD. Time courses of *S. aureus* ATCC 43300 mutants resistant to 2×, 4×, 8× and 16×MIC of RIF combined with LZD as well as time courses of *S. aureus* 10 mutants resistant to 2×, 4×, 8× and 16×MIC of DOX were distinctly stratified: the higher the resistance level, the lower the numbers of mutants. These differences were clearly reflected by $AUBC_M$ but not $N_M$, because in most cases postexposure numbers of resistant mutants were similar, masking the true effects of the AUC/MIC ratio and different levels of resistance.

**Conclusions:** These findings suggest that $AUBC_M$ is a more reliable endpoint of the amplification of resistant mutants than $N_M$.