

# Strain-Specific Concentration-Resistance Relationships with Ciprofloxacin-Exposed *Pseudomonas aeruginosa*: Is It Possible to Predict the Enrichment of Resistant Mutants of the Same Bacterial Species?

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## Introduction

- The ratio of the 24-hour area under the antibiotic concentration-time curve ( $AUC_{24}$ ) to the mutant prevention concentration (MPC) is hypothesized to be a better predictor of bacterial resistance than  $AUC_{24}/MIC$ . However, the small number of attempts to compare these parameters has yielded conflicting results.
- To further compare the predictive potentials of  $AUC_{24}/MPC$  and  $AUC_{24}/MIC$ , the pharmacodynamics of ciprofloxacin against *P. aeruginosa* were studied in an *in vitro* model that simulates human pharmacokinetics.

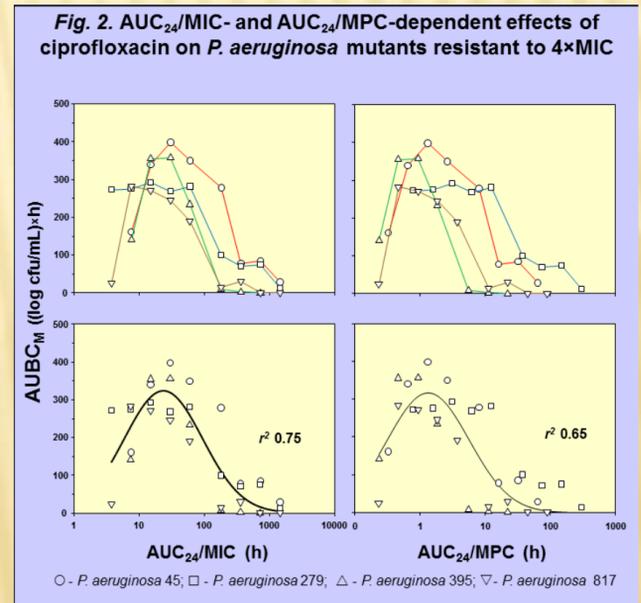
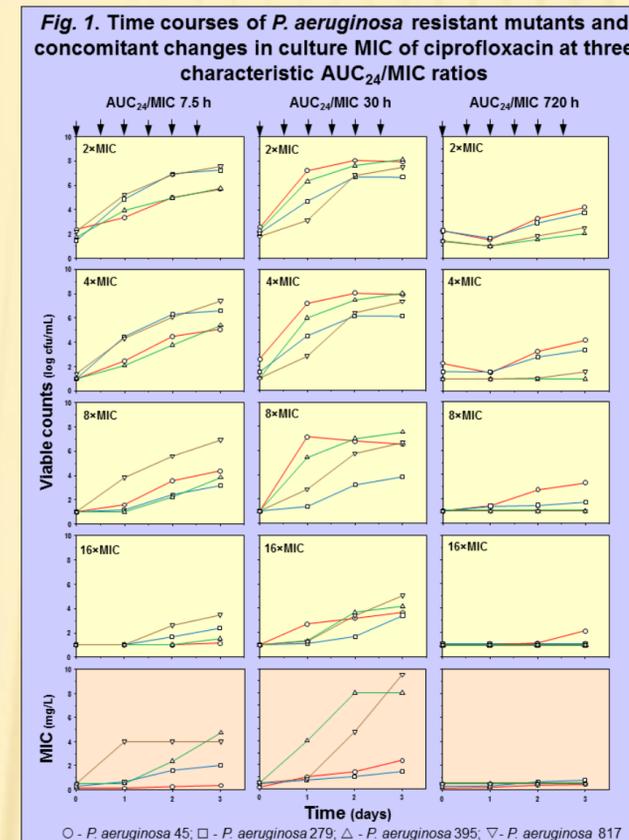
## Methods

- Four clinical isolates, *P. aeruginosa* 45, *P. aeruginosa* 279, *P. aeruginosa* 395 and *P. aeruginosa* 817 were selected for the study. The MIC of ciprofloxacin for *P. aeruginosa* 45 was 0.125 mg/L, the MICs for *P. aeruginosa* 279, 395 and 817 were 0.5 mg/L. The MPCs determined as described elsewhere [1] were 2.4, 2.8, 16 and 8 mg/L, respectively. MPC/MIC ratios varied from 11.2 to 32.
- A series of mono-exponential profiles that mimic twice-daily administration of ciprofloxacin (half-life 4 h) was simulated for three consecutive days in an *in vitro* dynamic model [1].
- To provide antibiotic concentrations within and out of the mutant selection window, the simulated treatments of each of four strains of *P. aeruginosa* were designed over a 100-200-fold range of the  $AUC_{24}/MIC$  ratio.
- The amplification of resistant mutants was monitored by plating on media with  $2 \times$ ,  $4 \times$ ,  $8 \times$  and  $16 \times$  MIC of ciprofloxacin.

- Time courses of resistant mutants were characterized by the 72-hour area under the bacterial mutant concentration – time curve ( $AUBC_M$ ) [1] corrected for the area under the lower limit of detection.
- To relate  $AUBC_M$  with simulated  $AUC_{24}/MIC$ s or  $AUC_{24}/MPC$ s, a modified Gaussian type function was used.
- Changes in *P. aeruginosa* susceptibility were examined by daily MIC determinations.

## Results

- Time courses of ciprofloxacin-resistant *P. aeruginosa* mutants grown on antibiotic-containing media are shown in Fig. 1.
- With each organism, mutants of *P. aeruginosa* resistant to  $2 \times$  -  $16 \times$  MIC of ciprofloxacin were enriched in an  $AUC_{24}/MIC$ -dependent pattern: weak or little mutant enrichment at the relatively low and high  $AUC_{24}/MIC$ s in contrast to pronounced mutant enrichment at the intermediate  $AUC_{24}/MIC$  ratio.
- The amplification of resistant mutants observed at the low and especially the intermediate  $AUC_{24}/MIC$ s was accompanied by concomitant loss in susceptibility.
- Regardless of the level of resistance, both  $AUC_{24}/MIC$  and  $AUC_{24}/MPC$  relationships with the  $AUBC_M$  were bell-shaped; data obtained with mutants resistant for example to  $4 \times$  MIC are shown in the upper portion of Fig. 2. The respective curves were stratified, more with  $AUC_{24}/MPC$  than with  $AUC_{24}/MIC$ .
- Using combined data obtained with all four organisms, correlations between  $AUBC_M$  and  $AUC_{24}/MPC$  or  $AUC_{24}/MIC$  were similar ( $r^2$  0.65 and 0.75, respectively) – see bottom portion of Fig. 2.



## Conclusion

This study suggests more pronounced strain specificity of the "anti-mutant"  $AUC_{24}/MPC$  ratio for *P. aeruginosa* compared with  $AUC_{24}/MIC$  ratios.

## Reference:

[1] Firsov AA, Smirnova MV, Strukova EN, Vostrov SN, Portnoy YA, Zinner SH. 2008. Enrichment of resistant *Staphylococcus aureus* at ciprofloxacin concentrations simulated within the mutant selection window: bolus versus continuous infusion. *Int. J. Antimicrob. Agents.* 32:488-493.

Fig. 3. Descending portions of the  $AUBC_M$ - $AUC_{24}/MIC$  curves and estimated anti-mutant  $AUC_{24}/MIC$  ratios with *P. aeruginosa* resistant to  $4 \times$  MIC of ciprofloxacin

