# Can Clinical Dosing Regimens Provide "Anti-mutant" Fluoroquinolone Concentrations? Predictions Using *In Vitro* Dynamic Models

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## Introduction

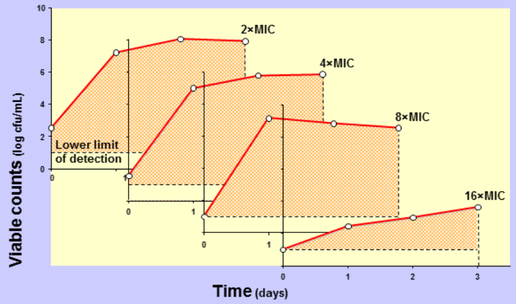
- *In vitro* studies performed mostly with fluoroquinolone-exposed *Staphylococcus aureus* allowed delineation of bell-shaped relationships between the enrichment of resistant mutants and the ratio of the 24-hour area under the curve ($AUC_{24}$) to the MIC [1-4].
- To explore if similar relationships apply to Gram-negative bacteria, the pharmaco-dynamics of ciprofloxacin were studied against *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* over a wide range of antibiotic exposures.

## Methods

- Four strains of *E. coli*, ATCC 25922, 4300, 4454 (MICs 0.008 mg/L) and GM 2995 (MIC 0.016 mg/L), three strains of *K. pneumoniae*, 185 (MIC 0.125 mg/L), 1145 (MIC 0.5 mg/L) and 1885 (MIC 2 mg/L) and four strains of *P. aeruginosa*, 45 (MIC 0.125 mg/L), 279, 395 and 817 (MICs 0.5 mg/L) were selected for the study.
- A series of mono-exponential profiles that mimic twice-daily administration of ciprofloxacin (half-life 4 h) was simulated for 3 consecutive days in an *in vitro* dynamic model [5] over a >100-fold range of the $AUC_{24}$/MIC ratio.
- The enrichment of resistant mutants was monitored by plating on media with 2×, 4×, 8× and 16×MIC of ciprofloxacin. Time courses of resistant mutants were characterized by the area under the bacterial mutant concentration – time curve ($AUBC_M$) [5] corrected for the area under the lower limit of detection (Fig. 1).
- To relate $AUBC_M$ to the simulated $AUC_{24}$/MICs, a modified Gaussian type function was used. Using a descending portion of the $AUBC_M$–$AUC_{24}$/MIC curve for each bacterial species strain, the "anti-mutant" $AUC_{24}$/MIC ratio was taken as the point where the Gaussian curve reaches the level of $AUBC_M$ = 30 log (cfu/mL) × h.

***Fig. 1.* Determination of $AUBC_M$**

(*P. aeruginosa* 45 exposed to ciprofloxacin at $AUC_{24}$/MIC of 30 h)

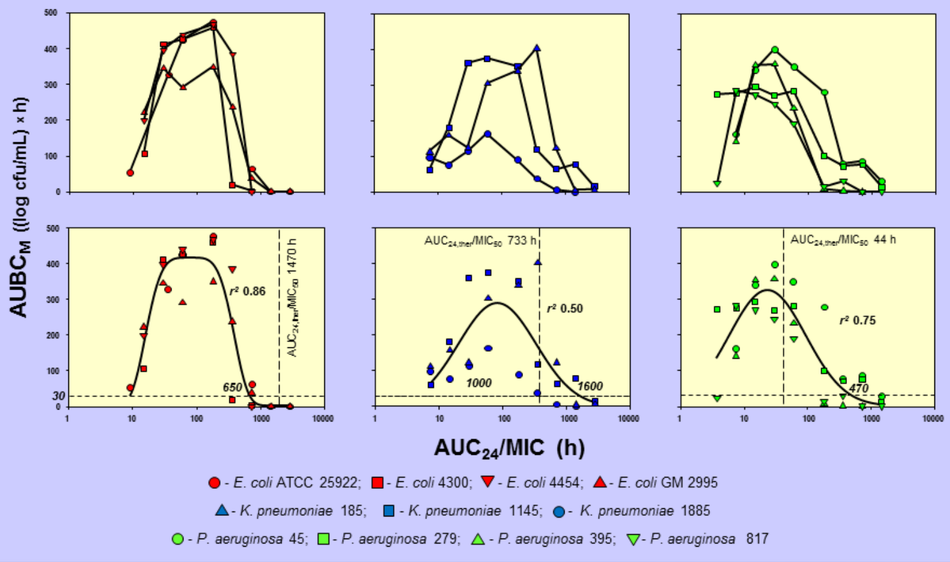



Shaded areas reflect $AUBC_M$

## Results

- $AUC_{24}$/MIC relationships with $AUBC_M$ were bell-shaped with each organism (upper portion of Fig. 2,). Gaussian functions fit combined data on all strains of *E. coli*, *K. pneumoniae* or *P. aeruginosa* ($r^2$ 0.86, 0.50 and 0.75, respectively) – see bottom portion of Fig. 2. The respective "anti-mutant" $AUC_{24}$/MICs were 650, 1600 and 470 h.
- The "anti-mutant" $AUC_{24}$/MIC was less than clinically achievable $AUC_{24,ther}/MIC_{50}$ ratio only for *E. coli* {1470 h (22 mg×h/L [6]/0.016 mg/L[7])} but not *K. pneumoniae* {730 h (22/0.03 [7])} and *P. aeruginosa* {44 h (22/0.5 [8-10])}.

***Fig. 2.* $AUC_{24}$/MIC- dependent effects of ciprofloxacin on *E. coli*, *K. pneumoniae* and *P. aeruginosa* resistant to 4×MIC**




## Conclusions

- Like *S. aureus*, $AUC_{24}$/MIC-resistance relationships with *E. coli*, *K. pneumoniae* and *P. aeruginosa* are bell-shaped.
- Based on these relationships, "anti-mutant" $AUC_{24}$/MIC ratios can be achieved at clinically attainable $AUC_{24,ther}/MIC_{50}$s for *E. coli*, but not *K. pneumoniae* and *P. aeruginosa*.

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