Role of Pharmacodynamics in Antimicrobial Therapy

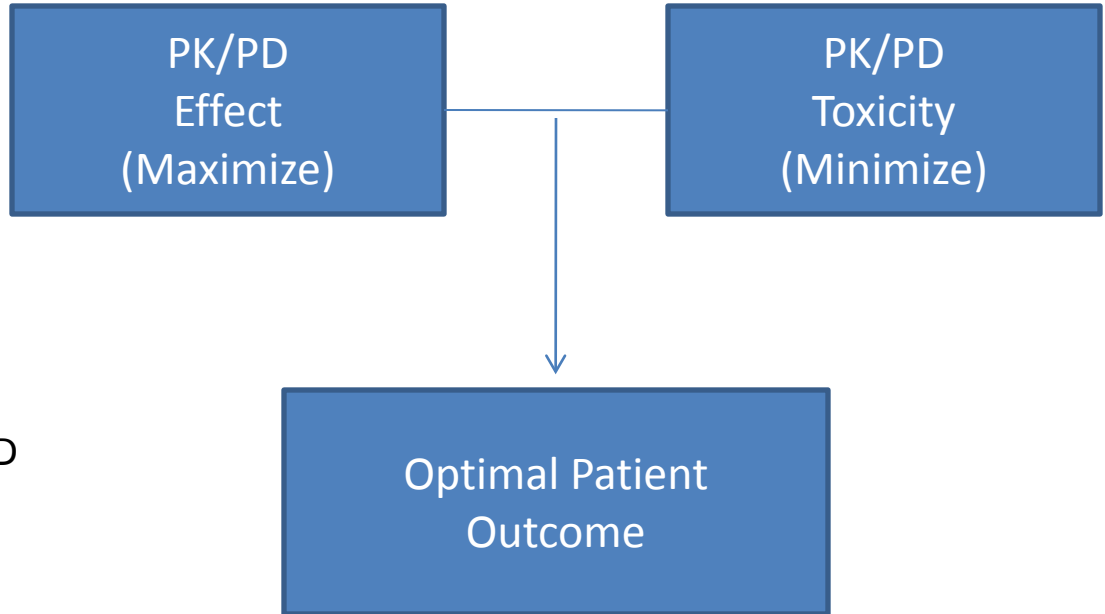## G.L. Drusano, M.D.

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What Do We Want?

Consequently, it is clear that there are two separate issues:
PK/PD for effect (organism kill – clinical outcome/resistance suppression and PK/PD for toxicity

Obviously we wish to maximize effect and minimize toxicity

The endpoint for toxicity is straightforward: the absence of an event

The endpoint for effect is quite different – which endpoint is desired?

1. **Clinical outcome**
2. **Microbiological outcome**
3. **Resistance suppression**

PK/PD
Effect
(Maximize)

PK/PD
Toxicity
(Minimize)

Optimal Patient
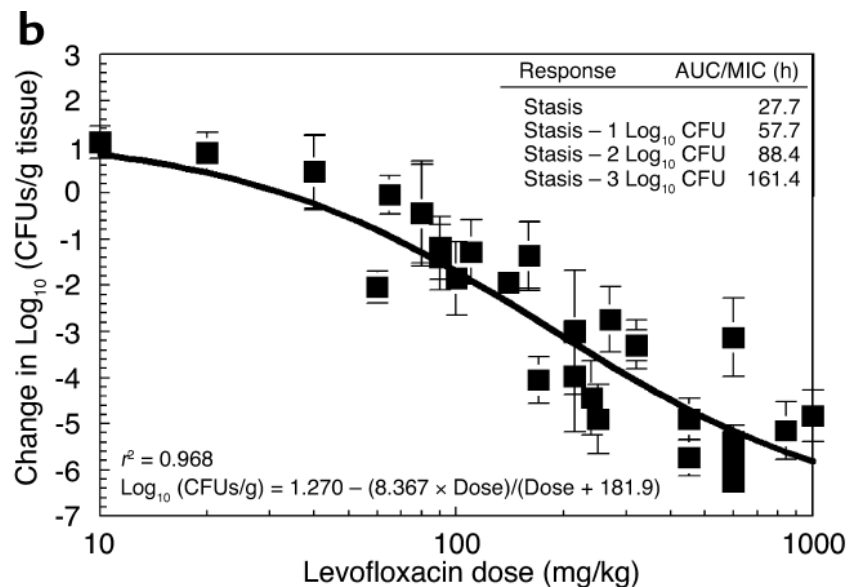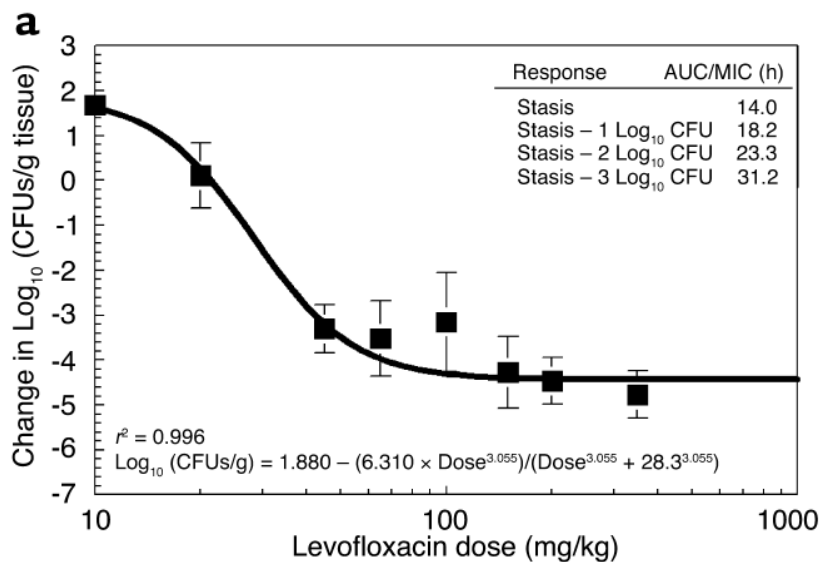Outcome

Role of PK/PD

- The Hierarchy of Endpoints (more therapeutic intensity required to achieve endpoint)
  1. Clinical/Microbiological Outcome
  2. Resistance Suppression

- Let us first look at Microbiological Outcome (cell kill in animals) versus Resistance Suppression in an animal model system and, finally, (Micro Outcome) in a clinical trial

Role of PK/PD

Inoculum of *P. aeruginosa* 10^6   **Inoculum of *P. aeruginosa* 10^7**
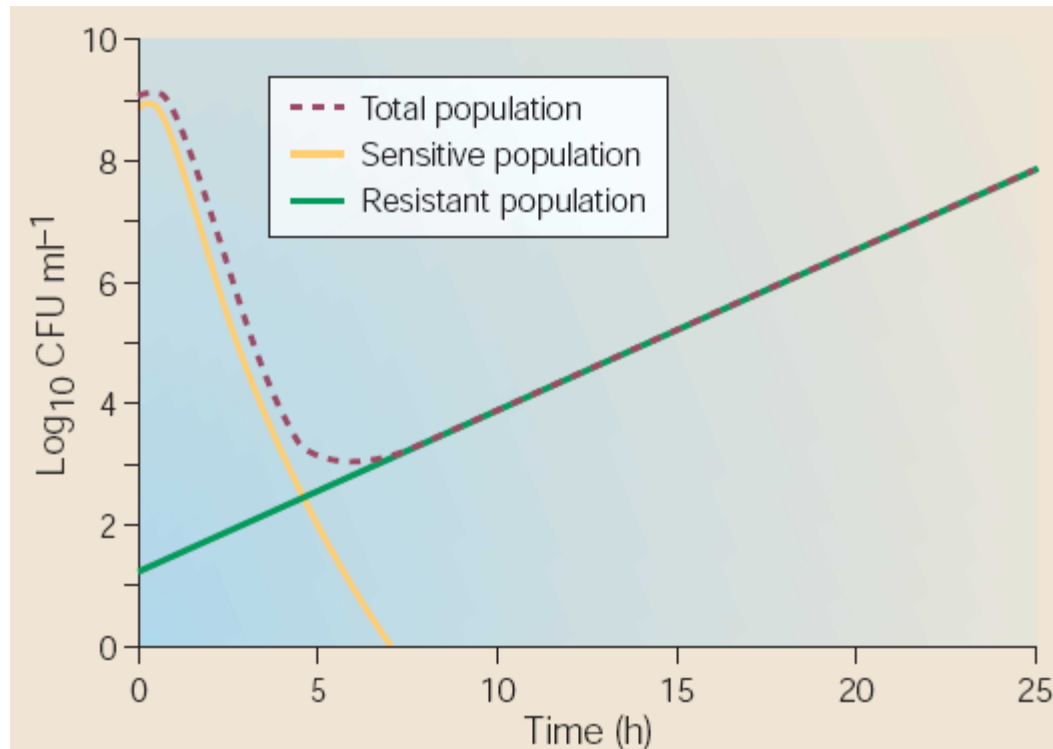
Non-Neutropenic Mouse Thigh Infection Model

a

Response	AUC/MIC (h)
Stasis	14.0
Stasis – 1 Log$_{10}$ CFU	18.2
Stasis – 2 Log$_{10}$ CFU	23.3
Stasis – 3 Log$_{10}$ CFU	31.2

$r^2 = 0.996$

$$\text{Log}_{10}\,(\text{CFUs/g}) = 1.880 - (6.310 \times \text{Dose}^{3.055})/(\text{Dose}^{3.055} + 28.3^{3.055})$$

b

Response	AUC/MIC (h)
Stasis	27.7
Stasis – 1 Log$_{10}$ CFU	57.7
Stasis – 2 Log$_{10}$ CFU	88.4
Stasis – 3 Log$_{10}$ CFU	161.4

$r^2 = 0.968$

$$\text{Log}_{10}\,(\text{CFUs/g}) = 1.270 - (8.367 \times \text{Dose})/(\text{Dose} + 181.9)$$

One needs more drug exposure to obtain a greater kill AND the bacterial burden is important!

J Clin Invest 2003;112:275-285

Role of PK/PD

- It is important to ask and answer the question of **"Why does a minor increase in bacterial burden lead to such discordant drug intensities required for specific amounts of cell kill?"**
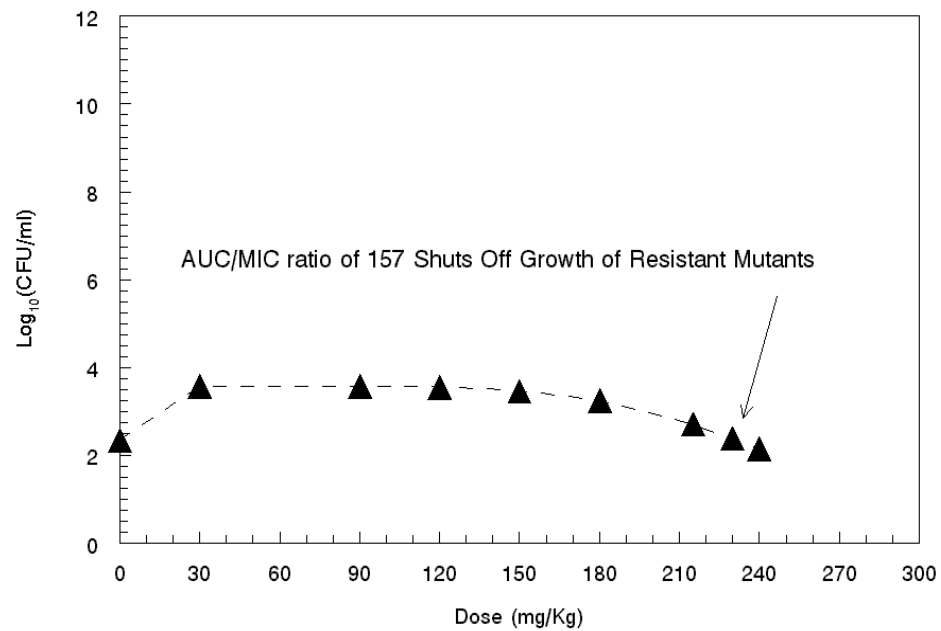
Role of PK/PD

Drusano GL. Nat Rev Microbiol 2004;2:289-300

Role of PK/PD

Levofloxacin Effect: Mouse Thigh Infection Model
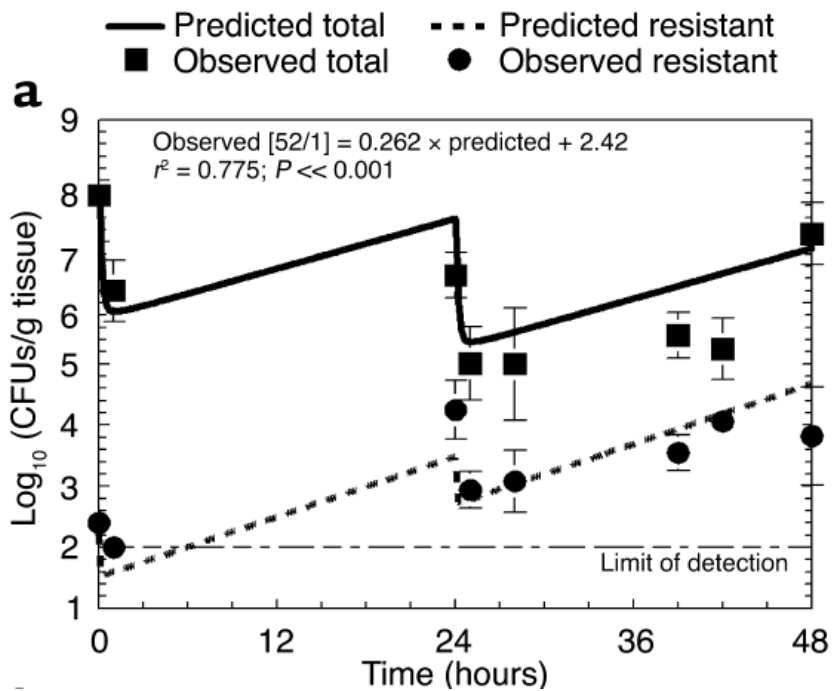Preventing Emergence of the Resistant Mutant Population

AUC/MIC ratio of 157 Shuts Off Growth of Resistant Mutants
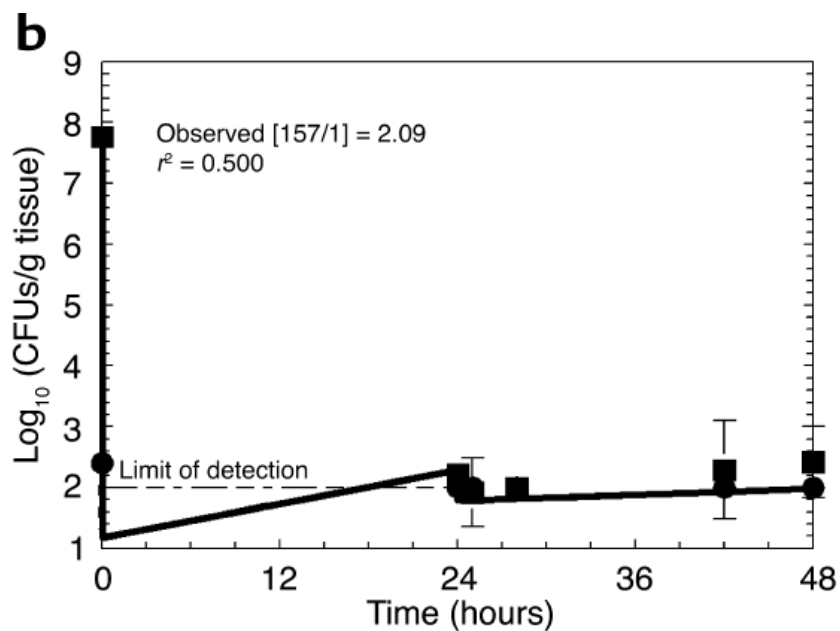
Jumbe et al J Clin Invest 2003;112:275-285
Drusano GL. Nat Rev Microbiol 2004;2:289-300

Role of PK/PD
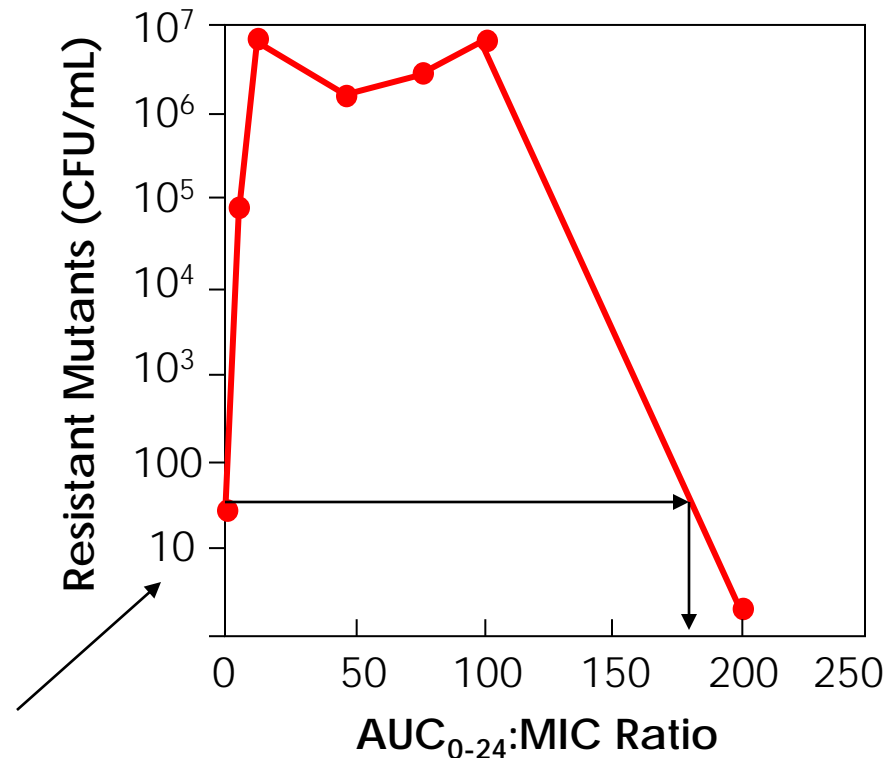
AUC/MIC = 52

AUC/MIC = 157

Role of PK/PD

P. aeruginosa - Prevention of Amplification of Resistant Subpopulation

- The amplification of the resistant sub-population is a function of the AUC/MIC ratio

- The response curve is an inverted "U".

- The AUC/MIC ratio for resistant organism stasis is circa 185/1

Graph: y-axis "Resistant Mutants (CFU/mL)" with values 10, 100, 10^3, 10^4, 10^5, 10^6, 10^7; x-axis "AUC$_{0-24}$:MIC Ratio" with values 0, 50, 100, 150, 200, 250.

Resistant organisms at baseline

All other data points represent resistant organism counts at 48 hours of therapy

Role of PK/PD

- These data indicate that:

  1. To kill more organisms, more drug exposure is required

  2. To suppress resistance, more drug exposure is required than to kill wild-type cells

* Can we identify relationships in the clinic?

Clinical PK/PD

- Our group has identified the relationship between drug exposure and response, drug exposure and toxicity as well as (once) drug exposure and resistance suppression 15-20 times

- We approach this in a standard fashion:
  1. Identify a small number of blood sampling times using a Stochastic Optimal Design approach (D-optimality; determinant of the inverse Fisher Information Matrix)
  2. Perform population PK modeling
  3. Perform Bayesian estimation to obtain individual patient exposures to the drug; normalize to patient pathogen MIC
  4. Linking exposure to response (logistic regression; time-to-event modeling)

Clinical PK/PD

- Following, we will display data that were generated with a relatively small number of patients

- The data were drawn from patients in a Phase III trial of Hospital-Acquired Bacterial Pneumonia

- As above, we have done this many times for many drugs of different classes

- We also have relationships for exposure-toxicity, so outcomes can be truly optimized

Clinical Trial of Levofloxacin 750 mg Daily for Patients with HAP

Population pharmacokinetic parameter values derived from 58 Patients with Nosocomial Pneumonia Receiving 750 mg of Levofloxacin as a 1.5 Hour Constant Rate, Intravenous Infusion

	Vol	Kcp	Kpc	CL
Units	L	hr^{-1}	hr^{-1}	L/hr
Means	34.4	7.65	6.07	7.24
Medians	23.3	2.66	0.924	6.24
S.D.	33.5	9.59	12.0	4.36

Vol = Volume of the central compartment; Kcp and Kpc are first order ntercompartmental transfer rate constants connecting the central and peripheral compartments; CL = Total clearance of Levofloxacin

Drusano GL, SL Preston, C Fowler, M Corrado, B Weisinger, J Kahn
J Infect Dis. 2004;189:1590-1597.

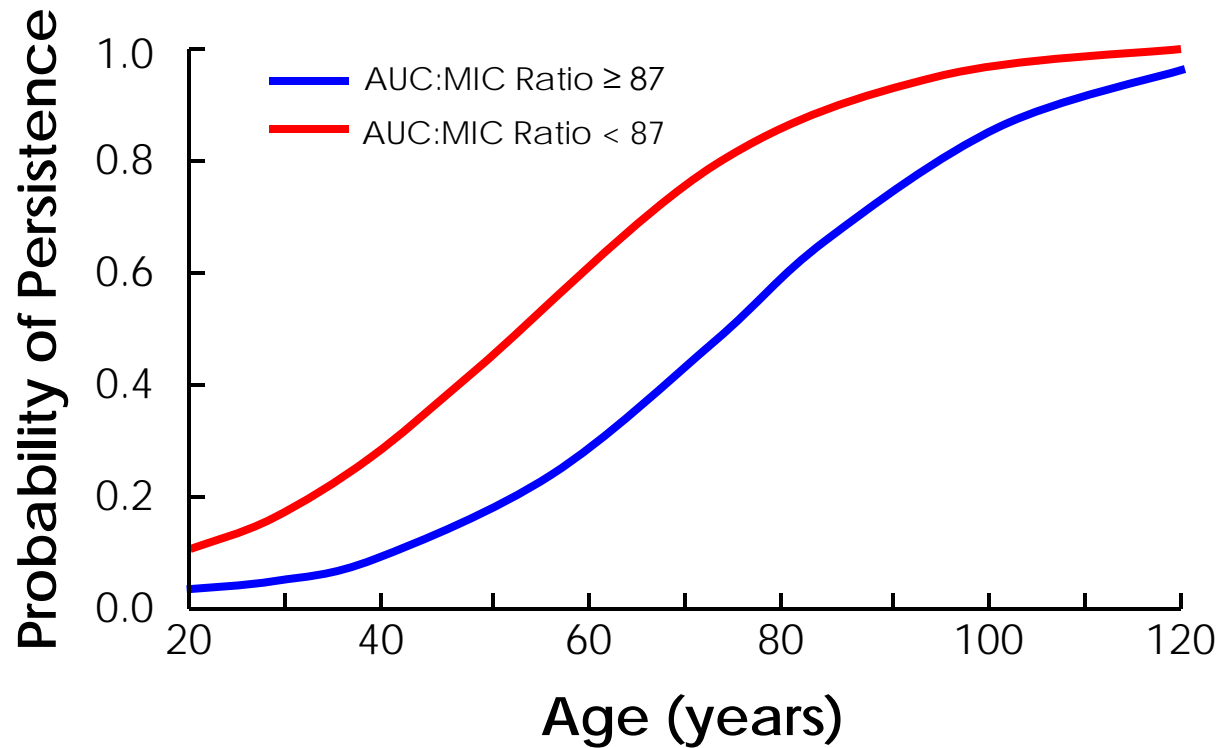# Final model for microbiological outcome for nosocomial pneumonia patients with receiving levofloxacin daily

Final Model for Microbiological Outcome

Constant	Parameter	Odds Ratio	95% Confidence Interval for Odds Ratio
	(AUC/MIC $\geq$ 87)		
-2.197			
	1.374	3.952	11.596 – 1.347
	(Age)		
	0.067	1.069	1.138 - 1.004

p = 0.001; McFadden's ρ^2 = 0.31

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Role of PK/PD
Levofloxacin and Hospital-Acquired Pneumonia

Drusano GL, SL Preston, C Fowler, M Corrado, B Weisinger, J Kahn
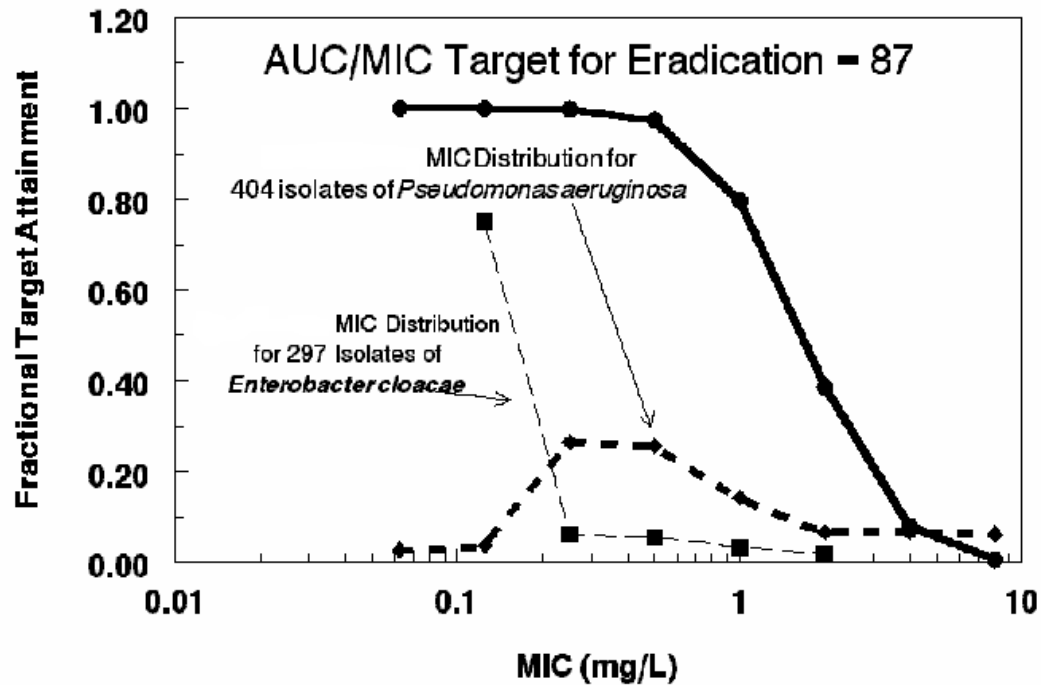**J Infect Dis. 2004;189:1590-1597.**

Role of PK/PD
Levofloxacin and Hospital-Acquired Pneumonia

- So, the exposure target (AUC/MIC ratio) that mediates a 2 $\log_{10}$ CFU/g drop in the mouse is identified as the exposure needed to drive a high probability of a good microbiological outcome in patients with nosocomial pneumonia

- How often does a fixed dose of drug achieve this target?

- We will examine this with Monte Carlo Simulation

Drusano GL, SL Preston, C Fowler, M Corrado, B Weisinger, J Kahn
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Table 6. Target-attainment rates for a 750 mg intravenous dose of levofloxacin, for distributions of *Pseudomonas aeruginosa* (n = 404) and *Enterobacter cloacae* (n = 297) isolates, by use of a 10,000 subject Monte Carlo simulation.

AUC:MIC ratio Breakpoint	*P. aeruginosa*, %	*E. cloacae*, %
87.0	72.4	91.7

PK-PD of Antibacterial Agents
Right Choice, *Right Time*, *Right Dose*

- So, Levofloxacin 750 mg daily is an "adequate" dose for *E. cloacae* (circa 92% target attainment), but is inadequate as a single agent for *P. aeruginosa* (72%)

- *The pharmacodynamics lessons learned from in vivo and in vitro models **DO** bridge to man*

- *We CAN perform smaller, focused trials using a pharmacodynamic approach that teach us how to use these agents optimally*

- What about resistance suppression? We have the data, but not the time. For those interested, please chat with me at the break

Thank You for Your Attention!
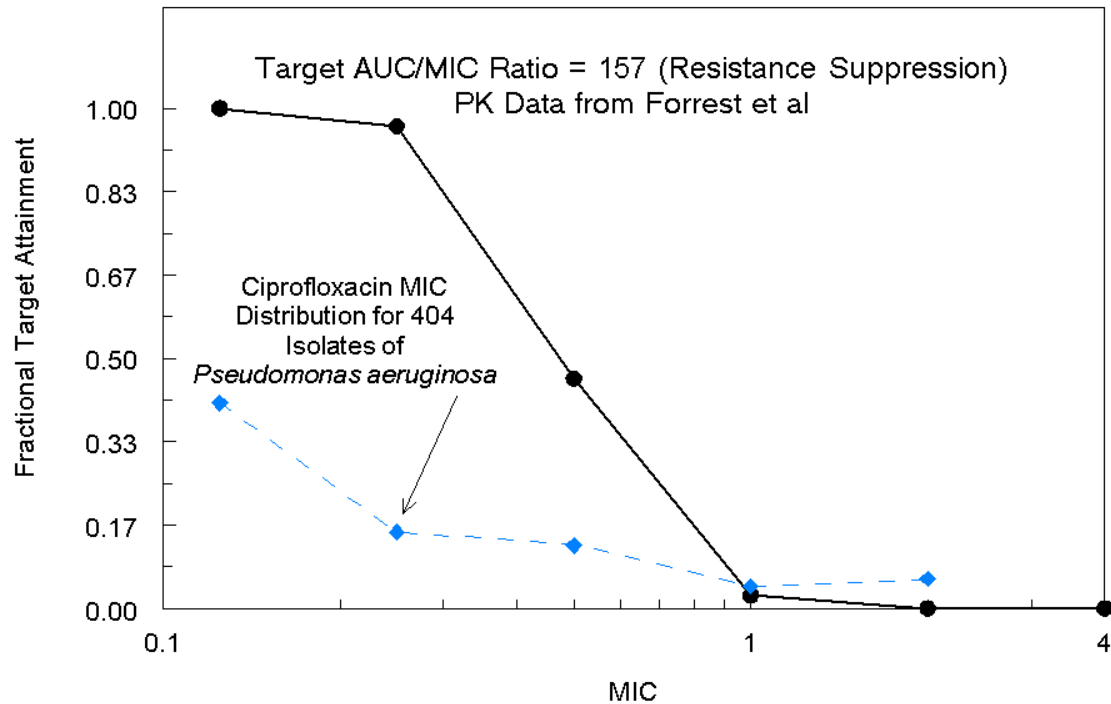
Resistance suppression

- We cannot use the levo HAP trial to evaluate resistance suppression, as, when *P. aeruginosa* was isolated, a second drug was added – BUT the Fink trial with ciprofloxacin (400 mg IV Q8 h) and the Peloquin Cipro trial (200 IV Q12h) were single agent trials

PK-PD TARTGET ATTAINMENT
Ciprofloxacin Against P. aeruginosa
Use of Monte Carlo Simulation

Target Attainment for Ciprofloxacin 400 mg
IV Q8h at Steady State for 10000 Simulated Subjects

Target AUC/MIC Ratio = 157 (Resistance Suppression)
PK Data from Forrest et al

Ciprofloxacin MIC Distribution for 404 Isolates of *Pseudomonas aeruginosa*

Taking the expectation demonstrates an overall target attainment of 62% and a predicted emergence of resistance rate of 38% for 400 Q8h.

For 200 Q12h, the expected results would be 25% target attainment and 75% resistance emergence

MONTE CARLO SIMUATION
Is It Predictive?

- Peloquin studied 200 mg IV Q 12 h of ciprofloxacin in nosocomial pneumonia - *P aeruginosa* resistance rate 70% (7/10 - pneumonia only) - 77% (10/13 - Pneumonia plus bronchiectasis [2] plus empyema [1])

- MCS (resistance suppression target) predicts emergence of resistance in 75%

- Fink et al studied ciprofloxacin in nosocomial pneumonia (400 mg IV Q 8 h) - *P aeruginosa* resistance rate 33% (12/36)

- MCS at this dose and schedule predicts suppression in 62% and emergence of resistance in 38%

Peloquin et al Arch Int Med 1989;1492269-73

Fink et al AAC 1994;38:547-57

Role of PK-PD
Lessons Learned

- **We have shown that the cell kill in the animal model of 2 logs is associated with an AUC/MIC ratio of 88; a ratio of 87 was demonstrated in a clinical trial to be linked to good microbiological outcome**

- ***In vitro* (not shown) and animal models demonstrated the ability to choose a dose to suppress resistance**

- **These predictions are validated in two different clinical trials with two different doses and schedules**

- **We have shown in an *in vitro* model that Resistance Suppression Requires More Drug Exposure than Cell Kill!**