

Pharmacodynamics of Antimicrobials in Animal Models

William A. Craig, M.D.

University of Wisconsin-Madison

Patterns of Antimicrobial Activity

- Concentration-dependent killing and prolonged persistent effects
- Seen with aminoglycosides, quinolones, daptomycin, ketolides and amphotericin B
- Goal of dosing regimen: maximize concentrations
- AUC/MIC and Peak/MIC major parameters correlating with efficacy

Patterns of Antimicrobial Activity

- Time-dependent killing and minimal to moderate persistent effects
- Seen with all beta-lactams and flucytosine
- Goal of dosing regimen: optimize duration of exposure
- Time above MIC major parameter correlating with efficacy

Patterns of Antimicrobial Activity

- Time-dependent killing and prolonged persistent effects (duration related to AUC)
- Seen with glycopeptides, glycylicycline, macrolides, clindamycin, oxazolidinones tetracyclines, azithromycin, streptogramins and fluconazole
- Goal of dosing regimen: optimize amount of drug
- AUC/MIC major parameter correlating with efficacy

Neutropenic Murine Thigh and Lung Infection Models

- Cyclophosphamide 150 and 100 mg/kg at 4 and 1 day before infection
- Thigh infection produced by injection of 0.1 ml of 10^7 CFU/ml 2 hrs before treatment
- Lung infection produced by 45 min aerosol of 10^9 CFU/ml 14 hrs before treatment
- 10^{7-8} CFU/g in thigh or lung at start of therapy

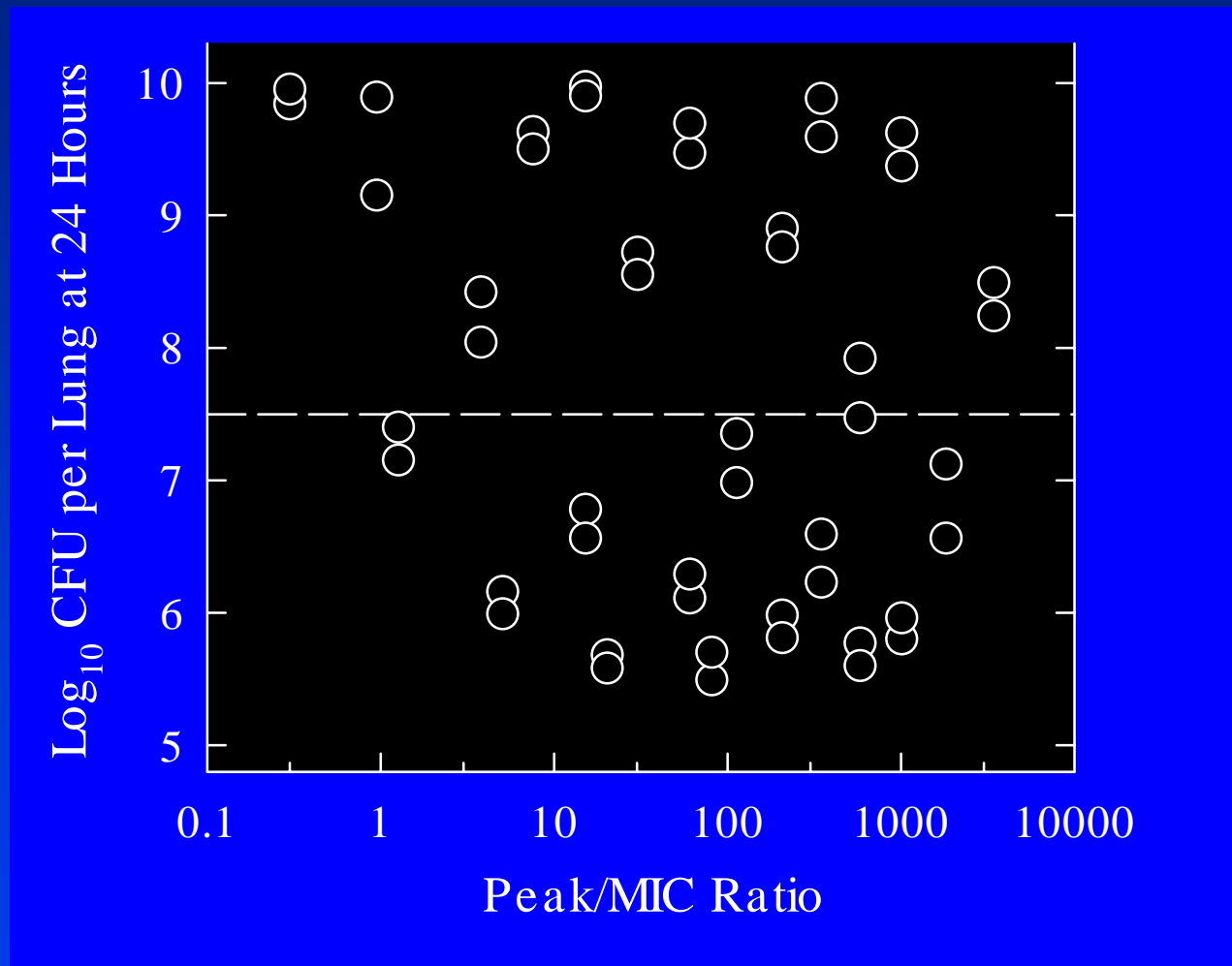
Correlation of Pharmacodynamic Parameters with Efficacy

- Use neutropenic murine thigh-and lung-infection models
- Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)
- Measure efficacy from change in Log_{10} CFU per thigh or lung at the end of 24 hours of therapy
- Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)

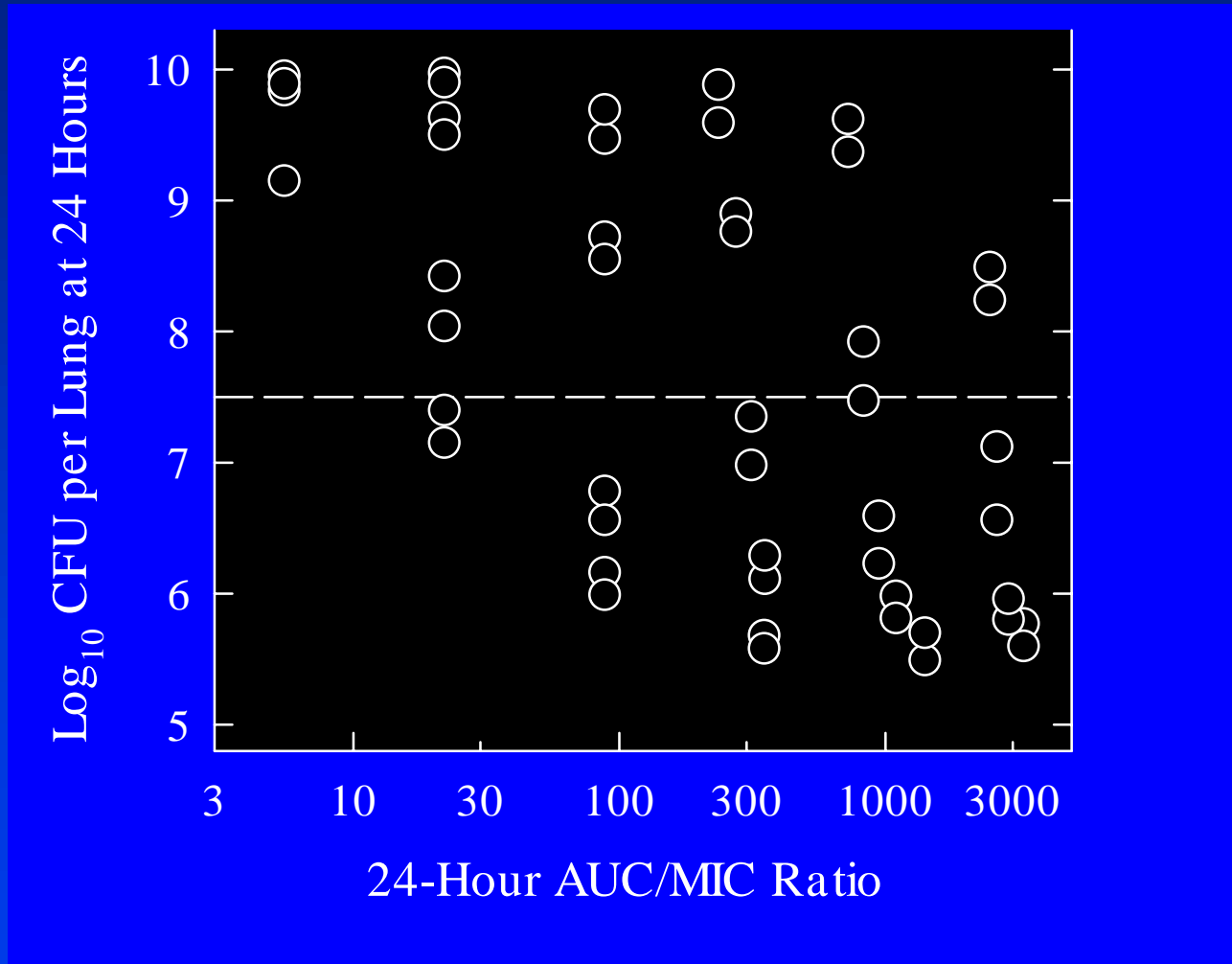
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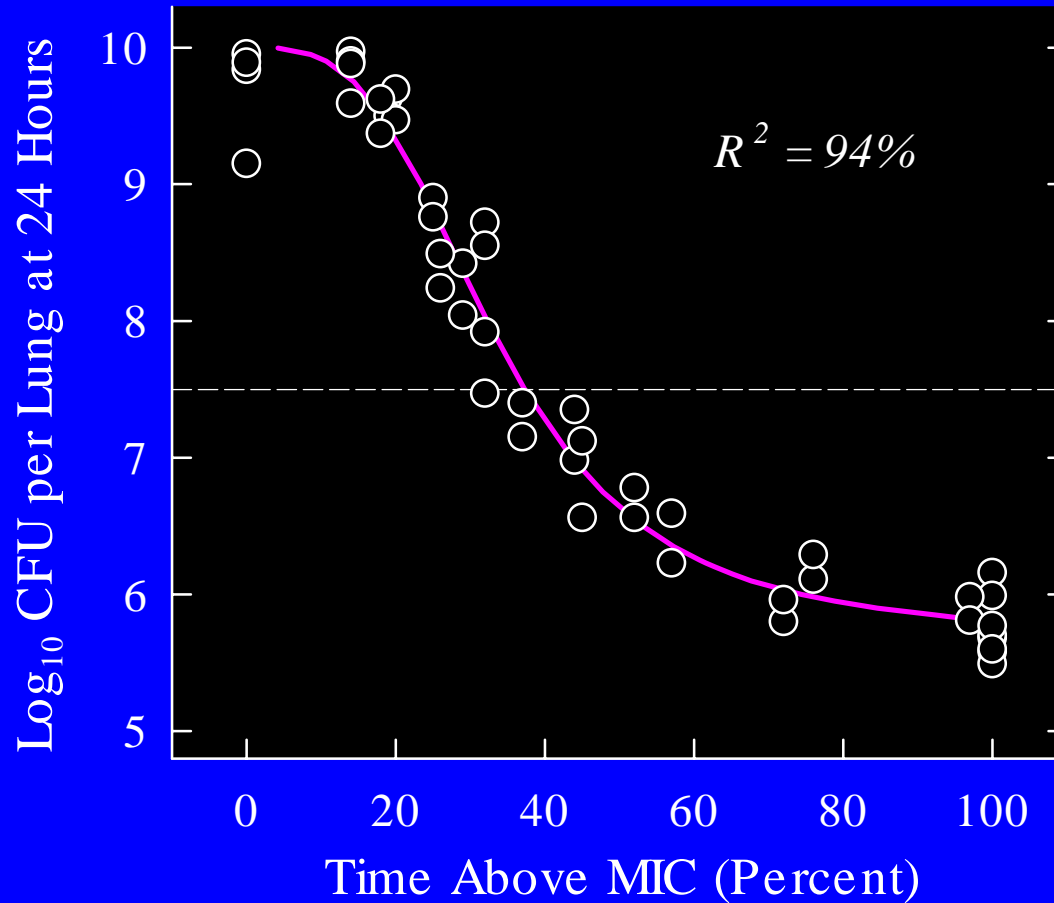
Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against Klebsiella pneumoniae in a Murine Pneumonia Model



Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against Klebsiella pneumoniae in a Murine Pneumonia Model



Relationship Between Time Above MIC and Efficacy for Cefotaxime against Klebsiella pneumoniae in a Murine Pneumonia Model



PK/PD Parameters Correlating with Efficacy in Murine Thigh and Lung Infections

Time Above MIC

Penicillins

Cephalosporins

Carbapenems

Monobactams

Tribactams

AUC (Peak)

Aminoglycosides

Fluoroquinolones

Metronidazole

Daptomycin

Ketolides

Azithromycin

Streptogramins

Glycopeptides

Tetracyclines

Macrolides

PK/PD Parameters Correlating with Efficacy in Murine Thigh and Lung Infections

Time Above MIC

Flucytosine

AUC (Peak)

Amphotericin B

Fluconazole

PK/PD Parameters

- Is the magnitude of the parameter required for efficacy the same in different animal species?
- Does the magnitude of the parameter vary markedly with:
 1. the dosing regimen?
 2. different drugs within the same class?
 3. different organisms ?
 4. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)?

Determination of “Static Dose” in Murine Thigh and Lung Infections

- Determine cfu/thing in untreated controls and mice treated with 4-5 different total doses
- Use nonlinear regression and modified Hill equation to estimate E_{max} (difference from untreated control), P₅₀ (dose giving 50% of E_{max}) and slope (N) of dose-response relationship

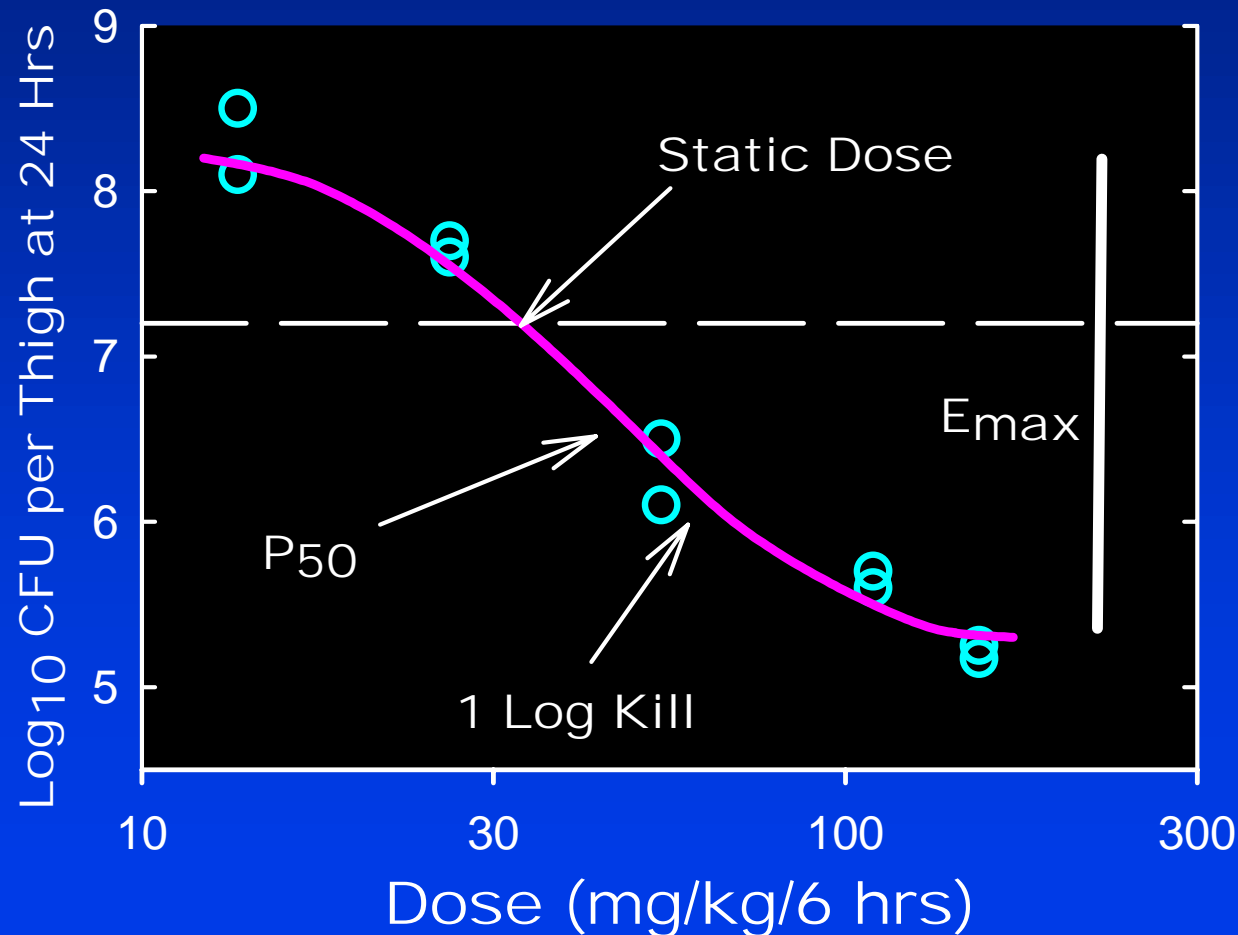
$$\Delta\text{CFU} = (\text{E}_{\text{max}}) \text{Dose}^N / \text{Dose}^N + P_{50}^N$$

- Calculate “static dose”

$$\text{Log “static dose”} = [\log (E/E - \text{E}_{\text{max}})]f/N + \log P_{50},$$

where E = control growth

Relationship Between 6-Hour Dose and Number of *Klebsiella pneumoniae* in Thighs of Neutropenic Mice



Time Above MIC Required for a Static Effect After 24-hours of Therapy with Four Cephalosporins

Drug	Time Above MIC (Percent of Dosing Interval)	
	Enterobacteriaceae	<i>S. pneumoniae</i>
Ceftriaxone (T)	72 (66-79)	74 (69-78)
Ceftriaxone (F)	38 (34-42)	39 (37-41)
Cefotaxime	38 (36-40)	38 (36-40)
Ceftazidime	36 (27-42)	39 (35-42)
Cefpirome	35 (29-40)	37 (33-39)

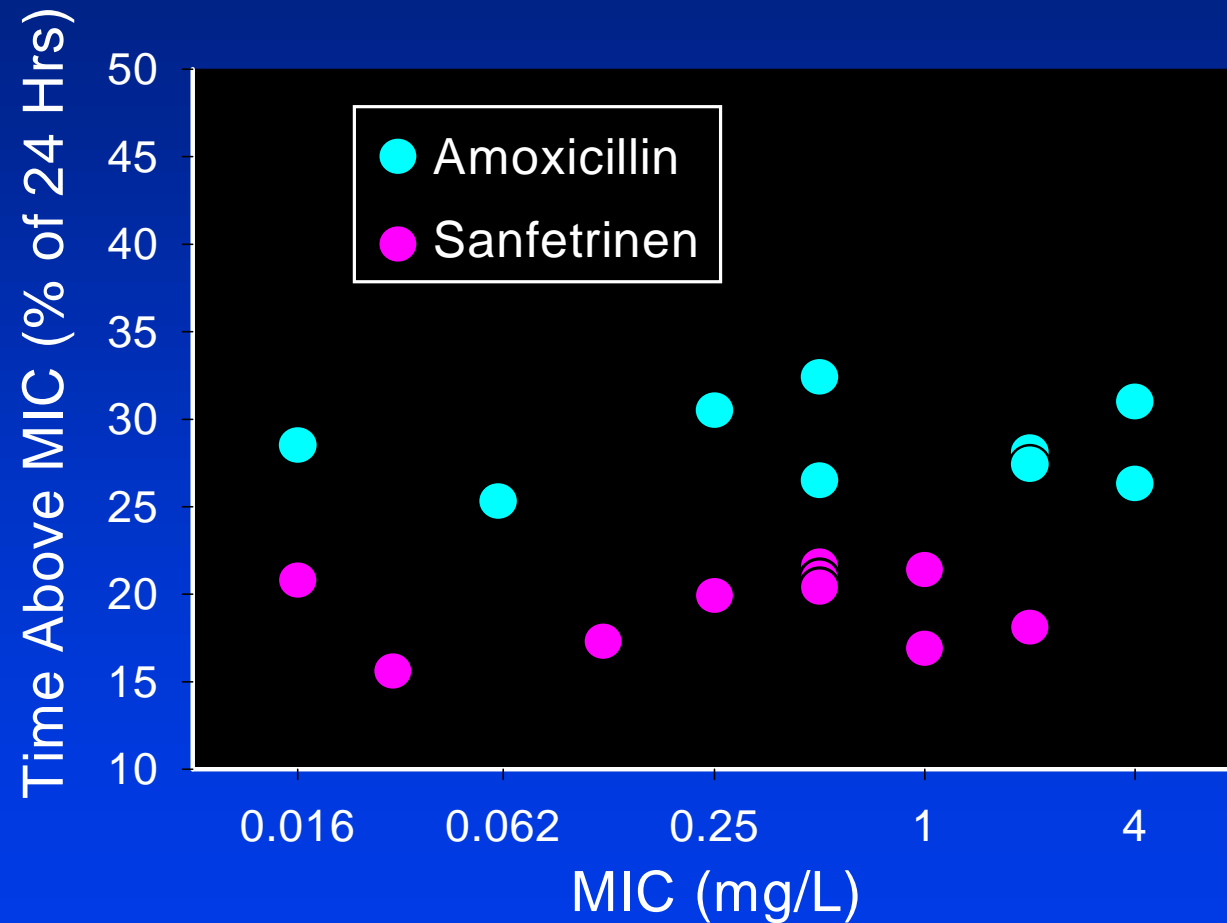
Pharmacokinetic/Pharmacodynamic Parameters

- Studies suggest that the magnitude of the PK/PD parameter required for efficacy is relatively similar in different animal species and in human infections
- Thus, results from animal studies could be predictive of antimicrobial activity in humans. This would be useful for dosage regimen design in situations where it is difficult to collect sufficient clinical data (e.g. new emerging resistance)

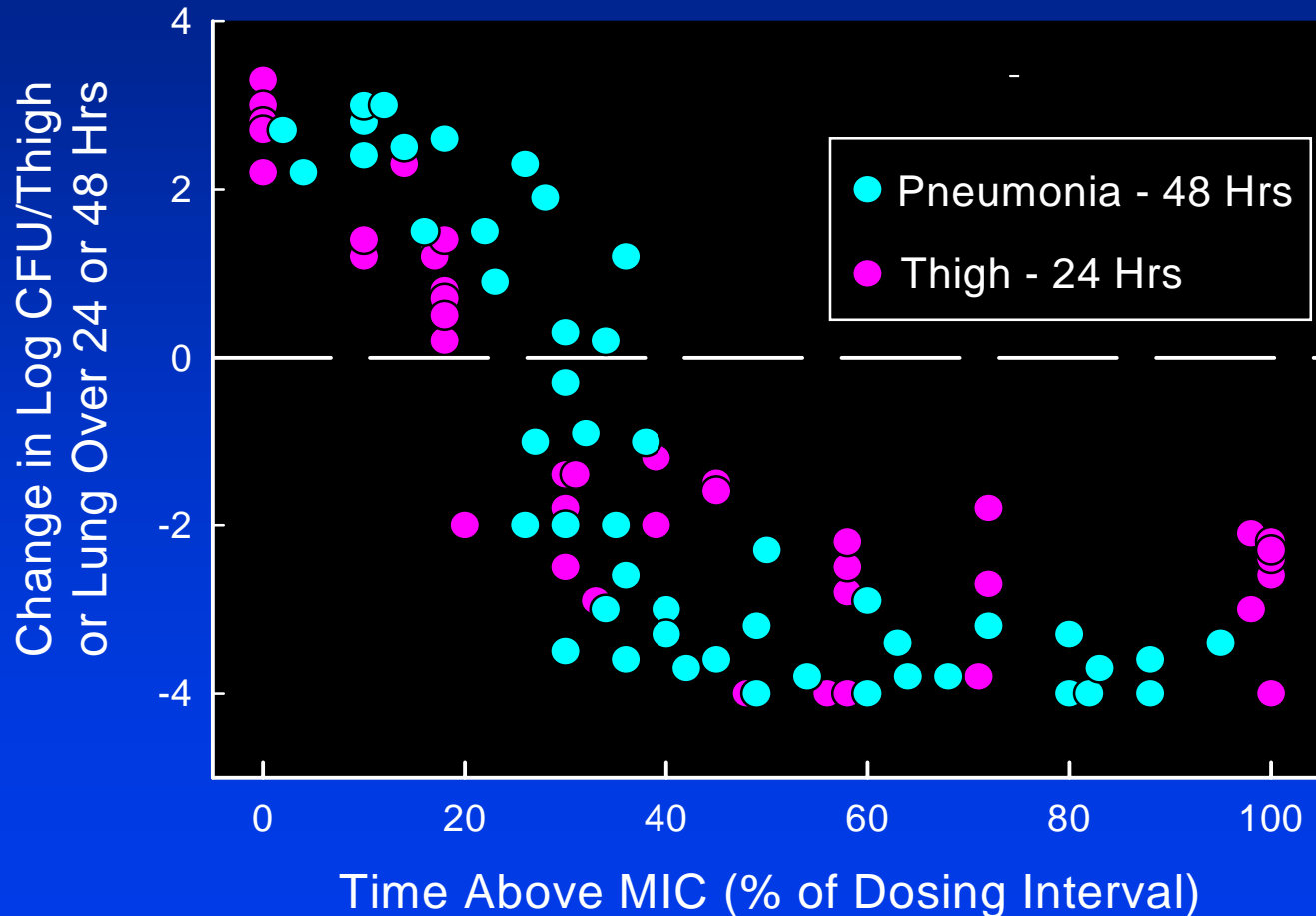
PK/PD Parameters: β -Lactams

- Time above MIC is the important parameter determining efficacy of the β -Lactams
- $T > MIC$ required for static dose vary from 25-40% of dosing interval for penicillins and cephalosporins to 10-25% for carbapenems and tribactams
- Free drug levels of penicillins and cephalosporins need to exceed the MIC for 40-50% of the dosing interval to produce maximum survival

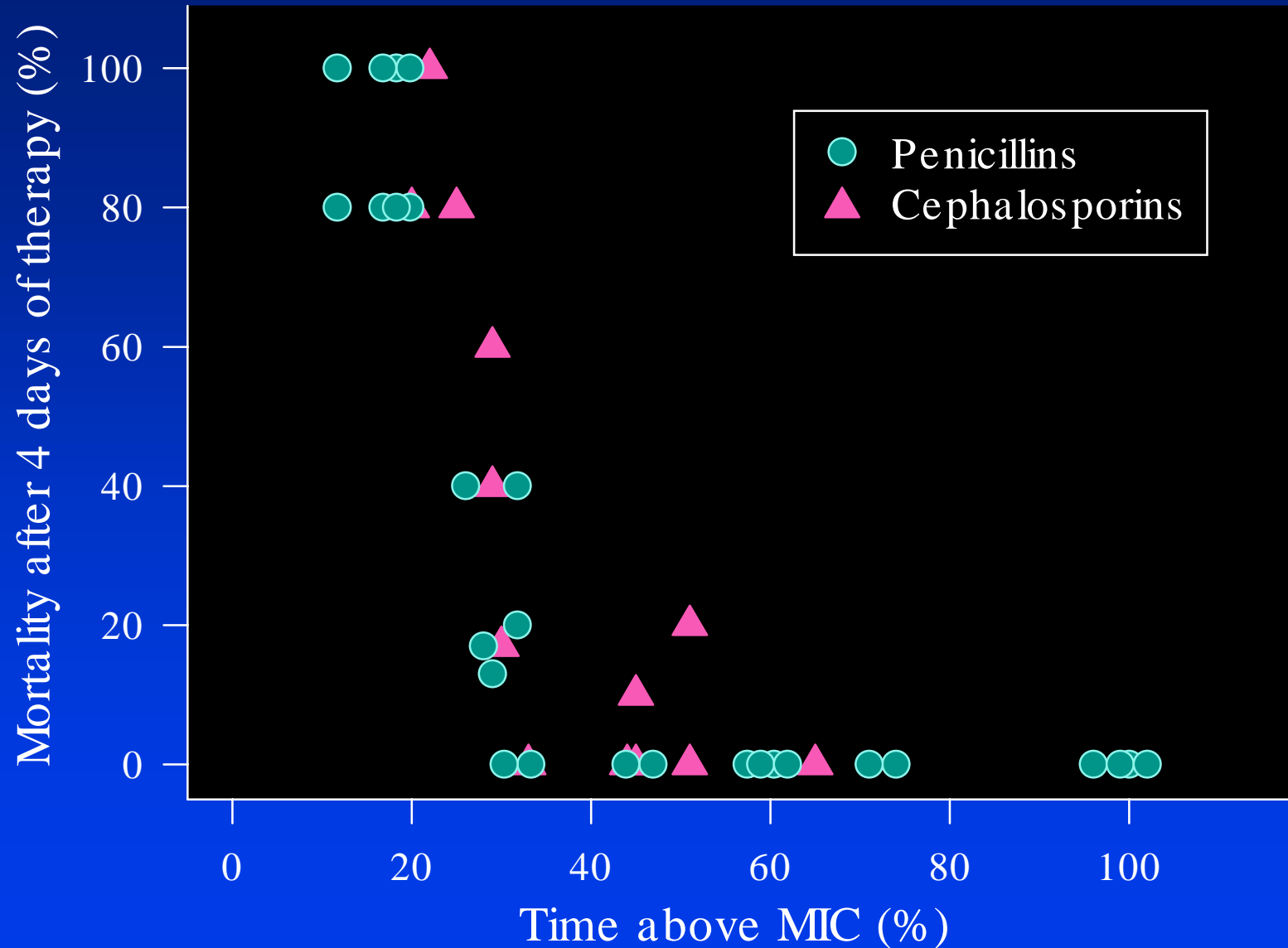
Relationship Between MIC and T>MIC for Amoxicillin & Sanfetrinen with *S. pneumoniae*



Relationship Between T>MIC and Efficacy for Amoxicillin against *Streptococcus pneumoniae* in Rat Pneumonia and Murine Thigh-Infection Models



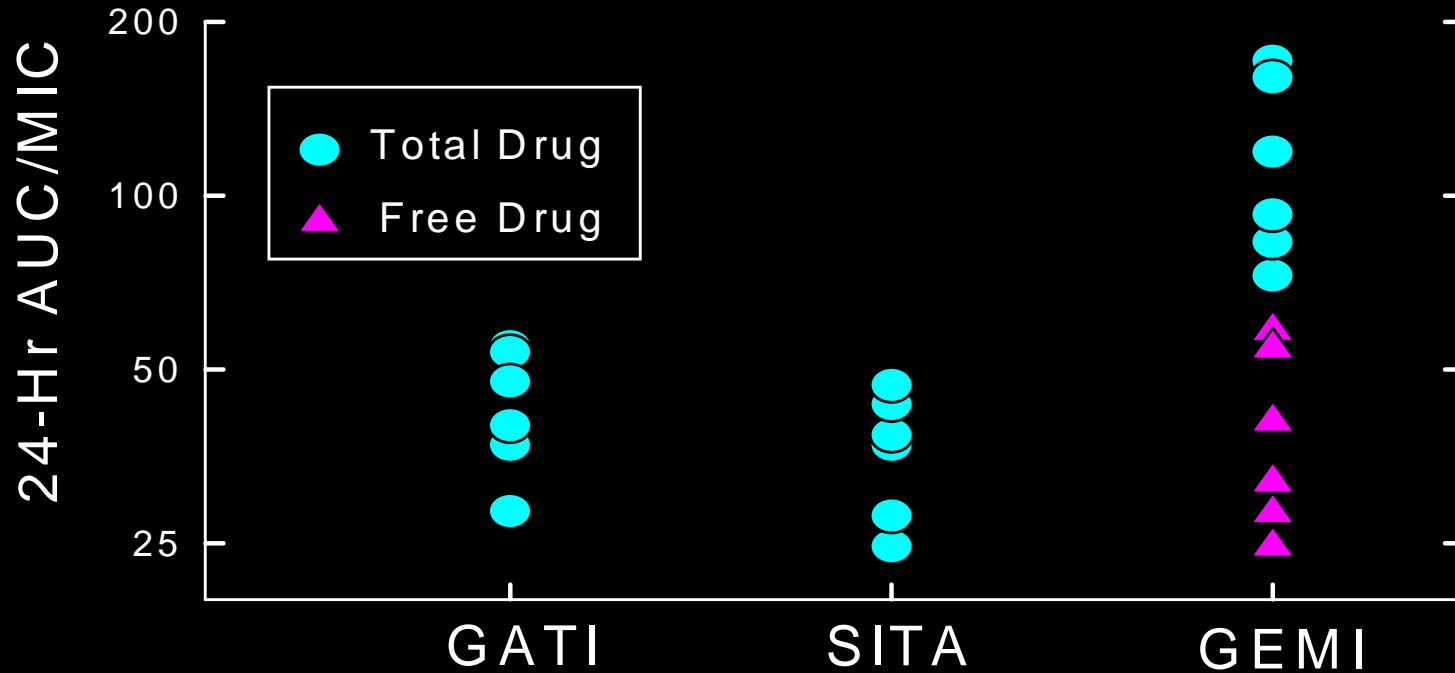
Relationship Between Time Above MIC and Efficacy in Animal Infection Models for *S. pneumoniae*



PK/PD Parameters with Fluoroquinolones

- 24-hr AUC/MIC (incorrectly referred to as AUIC) is the parameter that best predicts activity of fluoroquinolones.
- 24-hr AUC/MIC (using free drug levels) for static dose range from 25-50 for most organisms in neutropenic mice

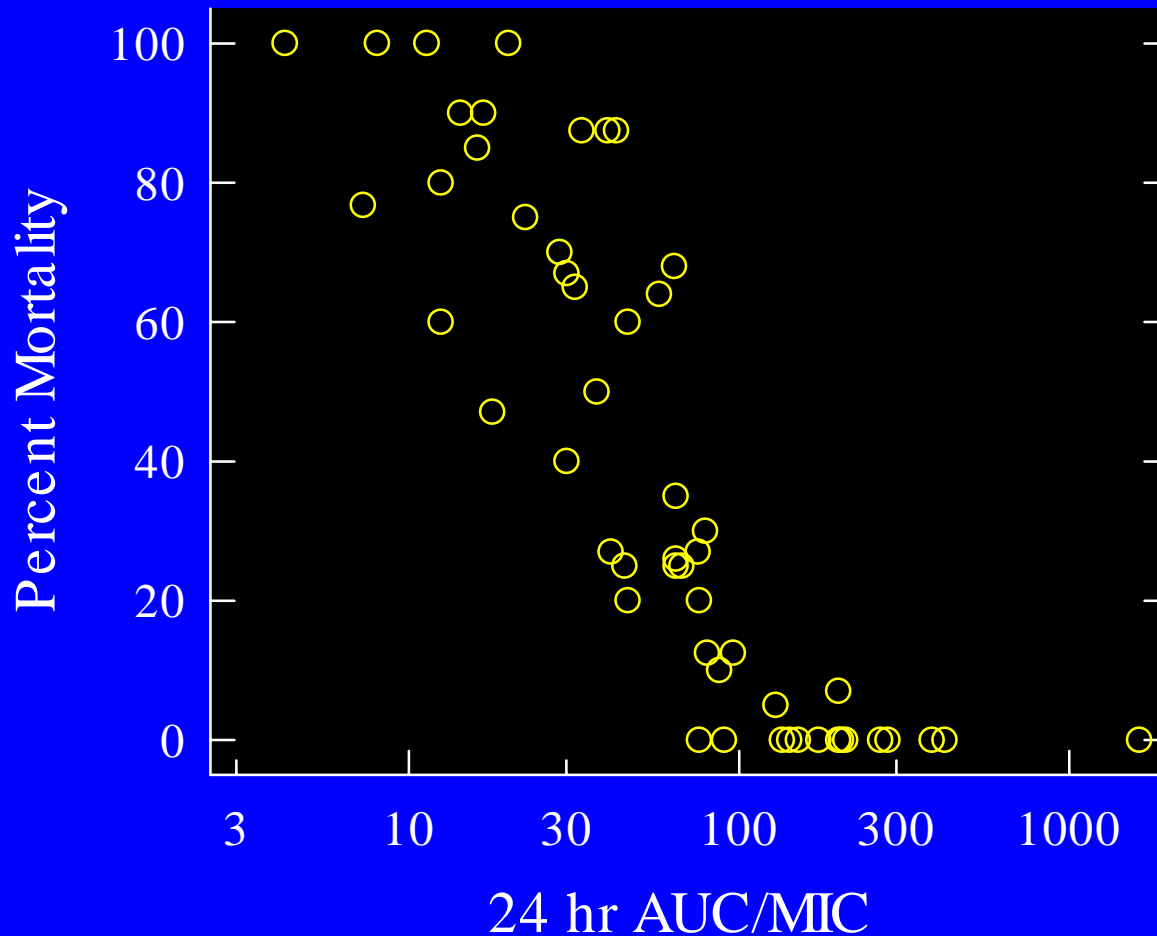
24-Hr AUC/MIC for Static Doses of Gatifloxacin, Sitafloxacin and Gemifloxacin Against 6 Strains of *Streptococcus pneumoniae*



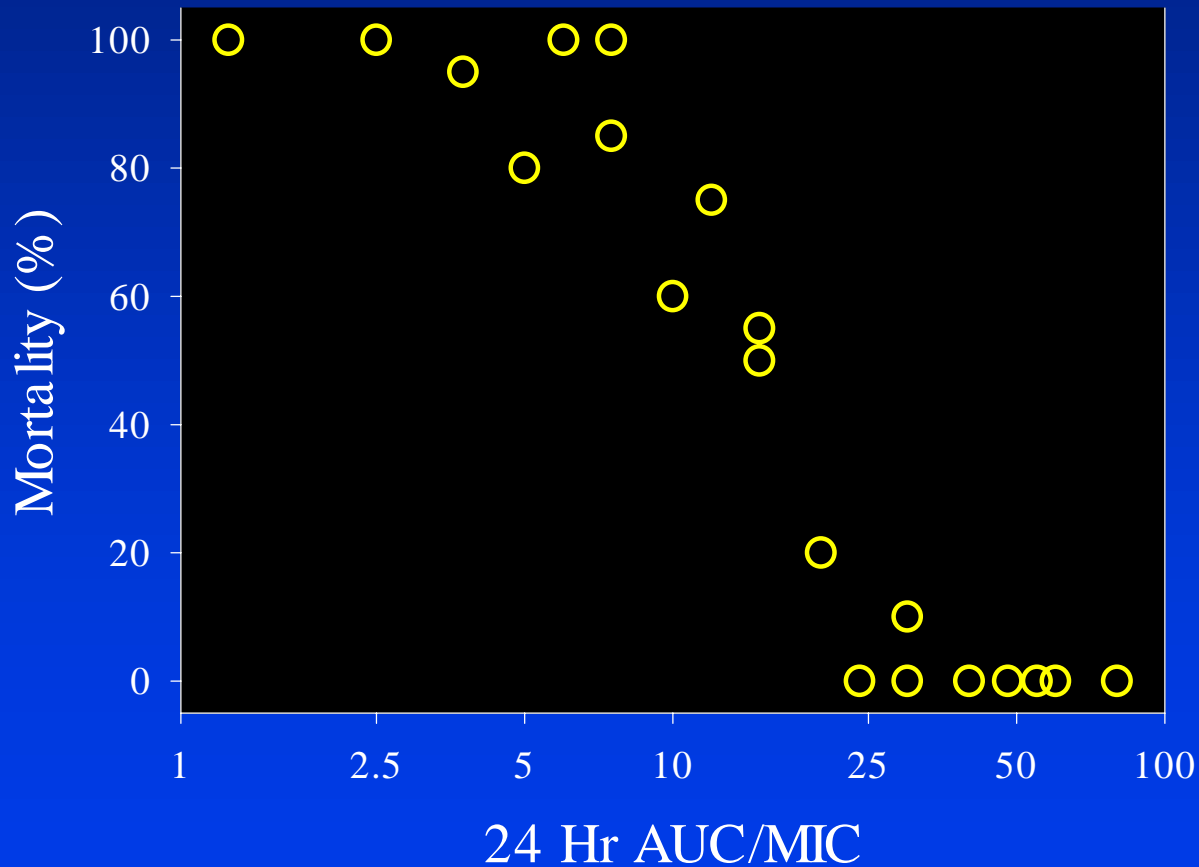
Pharmacodynamics of Fluoroquinolones

- Magnitude of 24-Hr AUC/MIC in serum required for 90-100% survival in animal infection models varies from about 25 in immunocompetent animals for *Streptococcus pneumoniae* to about 100 in immunocompromised animals for gram-negative bacilli
- 24-Hr AUC/MIC values of 25 and 100 are equivalent to averaging one and four times the MIC over a 24-hr period

Relationship Between 24 Hr AUC/MIC and Mortality for Fluoroquinolones in Immunocompromised Animal Models



Relationship Between 24 Hr AUC/MIC and Mortality for Fluoroquinolones against *Streptococcus pneumoniae* in Immunocompetent Animals



Magnitude of PK/PD Parameter Required for Effective Dose-50 Against *Candida albicans* in Kidneys of Neutropenic Mice

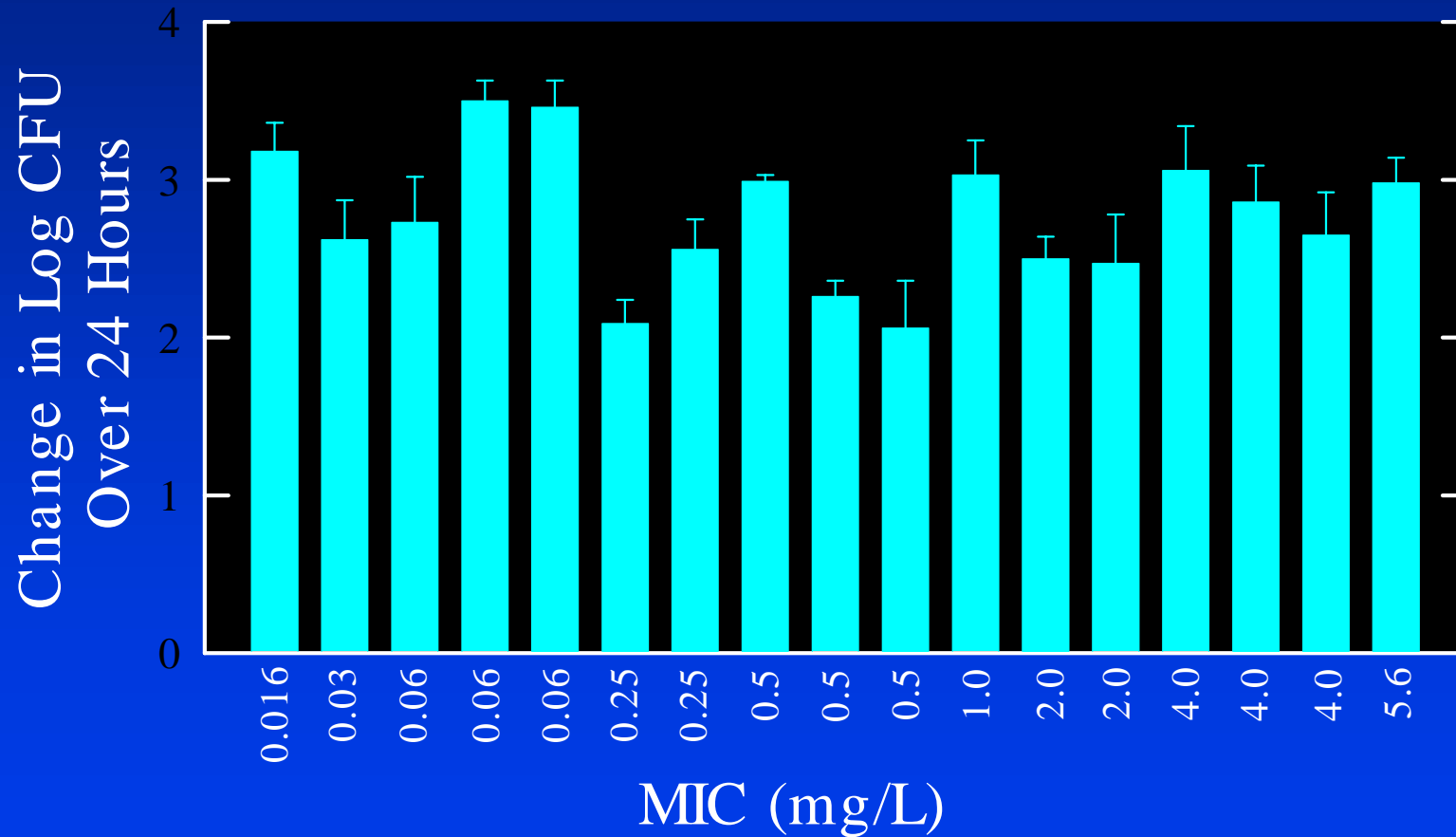
<u>Drug</u>	<u>MIC</u>	<u>ED-50</u>	<u>AUC/MIC</u>
Fluconazole	0.5	1.9	24
	16	61	15
	32	114	20

Andes & vanOgtrop, AAC 44:943, 2000

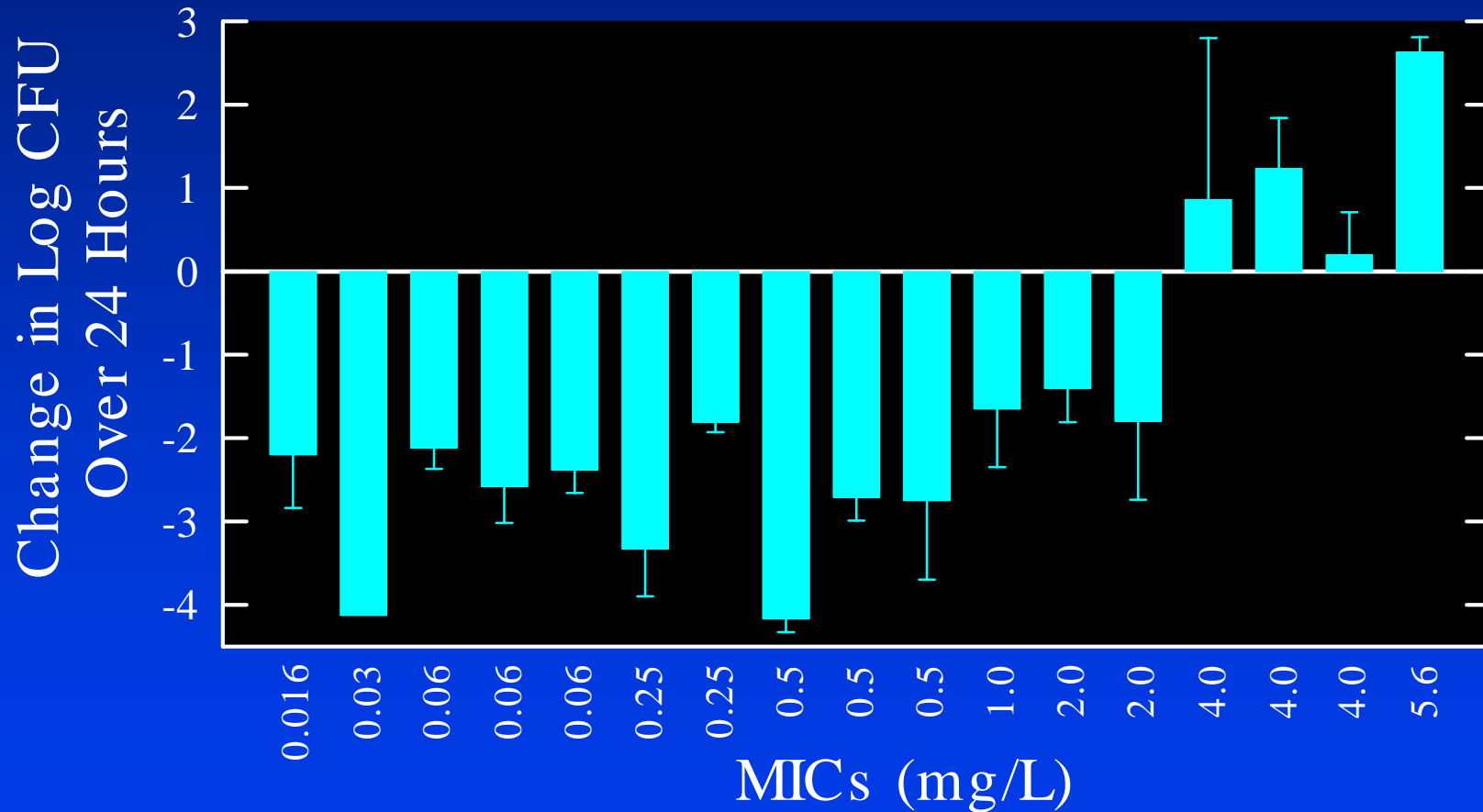
Animal Models for Susceptibility Breakpoint Determinations

- Simulate human pharmacokinetics in animals (induce renal impairment with uranyl nitrate)
- Infect groups of animals with organisms with varying MICs
- Treat the animals for at least 24 hours with dosage regimen used to treat human infections
- Find the MIC value that separates bacterial killing from bacterial growth

Growth of 17 Strains of *S. pneumoniae* in Thighs of Neutropenic Mice



Effect of Amoxicillin (7 mg/kg) on 17 Strains of *S. pneumoniae* in Thighs of Neutropenic Mice



PK/PD Parameters

- Is the magnitude of the parameter required for efficacy the same in different animal species?

YES

- Does the magnitude of the parameter vary with:
 1. the dosing regimen? NO
 2. different drugs within the same class? NO
 3. different organisms ? Minimal
 4. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)? NO