

Pharmacodynamics and the Dosing of Antibacterials

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PRESENTATION OUTLINE

- History of pharmacodynamics
- Different patterns of antimicrobial activity
- Pharmacodynamic target setting in animal models
- Identify major factors that alter the pharmacodynamic target
- Correlation between animal and human studies
- Uses of pharmacodynamic modeling
- Application to susceptibility breakpoints for gram-negative bacilli

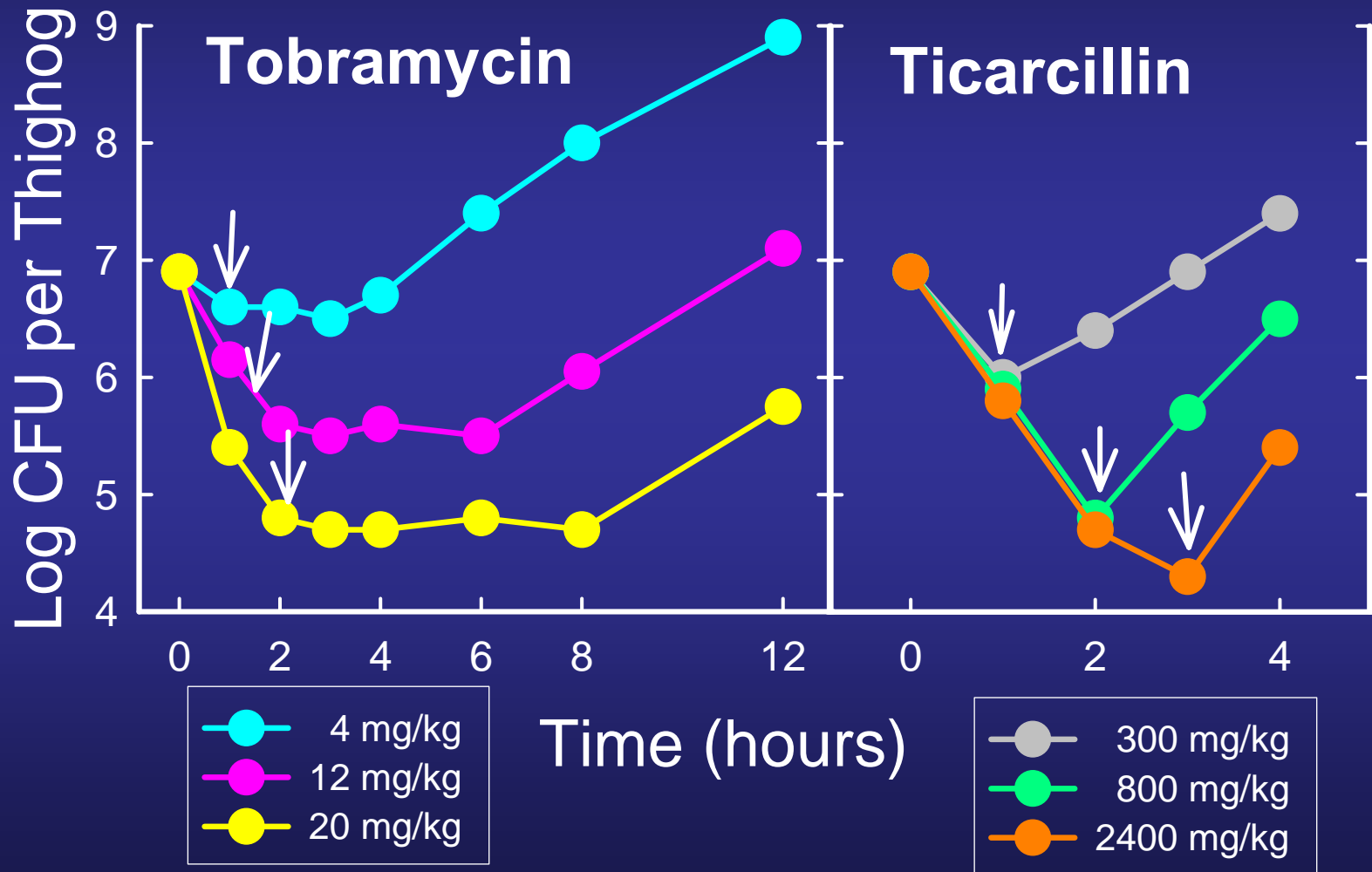
What is Pharmacodynamics ?

- **Relationship between concentration and pharmacologic and toxicologic effects of a drug**
- **Relationship between measures of in vivo drug exposure and microbiologic (and clinical) efficacy**

Why Interest in Pharmacodynamics?

- Always occurs when there is narrow difference between MICs and obtainable drug concentrations
 - early days of penicillin in 1940s (low doses used)
 - appearance of pseudomonas infections in 1960s and 1970s (high MICs)
 - appearance of resistant *Streptococcus pneumoniae* and other bacteria in 1990s

Bactericidal Activity of Tobramycin and Ticarcillin against *Pseudomonas aeruginosa*



1st Pattern of Antimicrobial Activity

- Concentration-dependent killing and prolonged persistent effects
- Seen with quinolones, aminoglycosides, ketolides, and daptomycin
- Goal of dosing regimen: maximize concentrations

2nd Pattern of Antimicrobial Activity

- Time-dependent killing and minimal or no persistent effects (except with staphylococci)
- Seen with all beta-lactams
- Goal of dosing regimen: optimize duration of exposure; maximum killing when levels constantly above 4-5 times MIC

3rd Pattern of Antimicrobial Activity

- Time-dependent killing and moderate to prolonged persistent effects
- Seen with macrolides, azithromycin, clindamycin, tetracyclines, glycylicyclines, streptogramins, glycopeptides, oxazolidinones, deformylase inhibitors
- Goal of dosing regimen: optimize amount of drug; maximum killing when $T > MIC$
100%

Major Goal of Pharmacodynamics

Establish the **PK/PD TARGET** required for effective antimicrobial therapy

- identify which **PK/PD indice** (T>MIC, AUC/MIC, peak/MIC) best predicts in vivo antimicrobial activity
- determine the **magnitude** of the PK/PD parameter required for in vivo efficacy (static effect, 1 or 2 log kill)

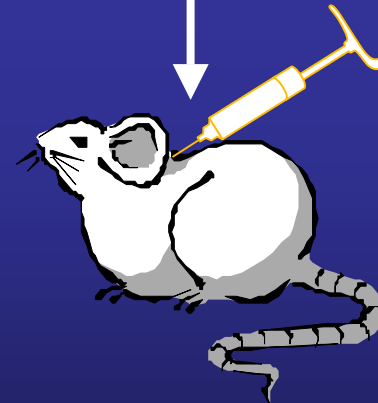
Neutropenic Mouse Thigh-Infection Model



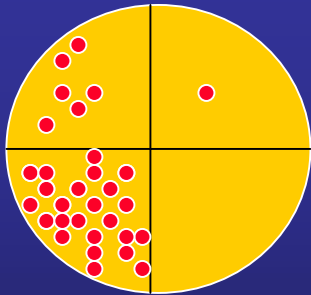
1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1



2. Bacteria injected into thighs on day 0 (10^{6-7})

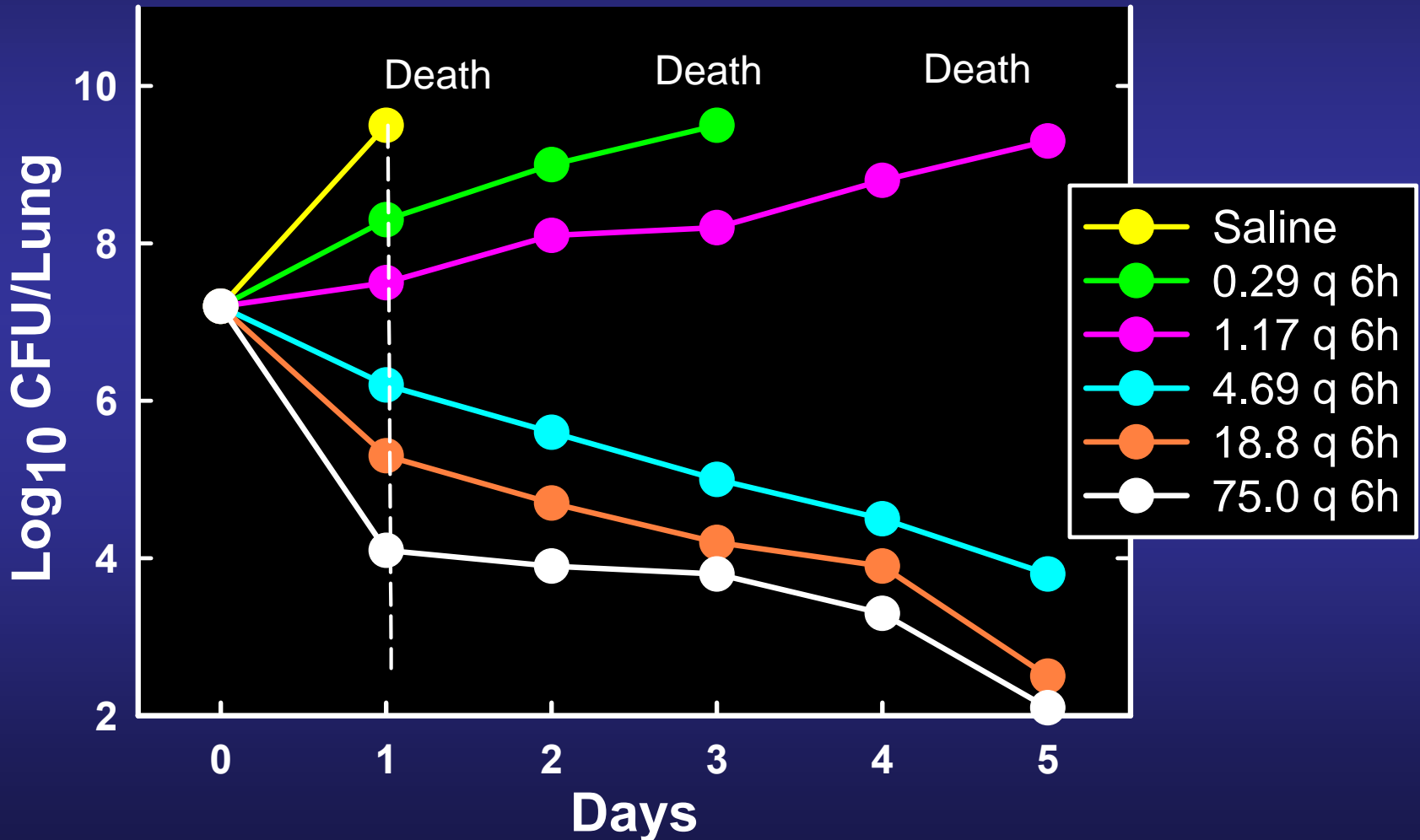


3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days



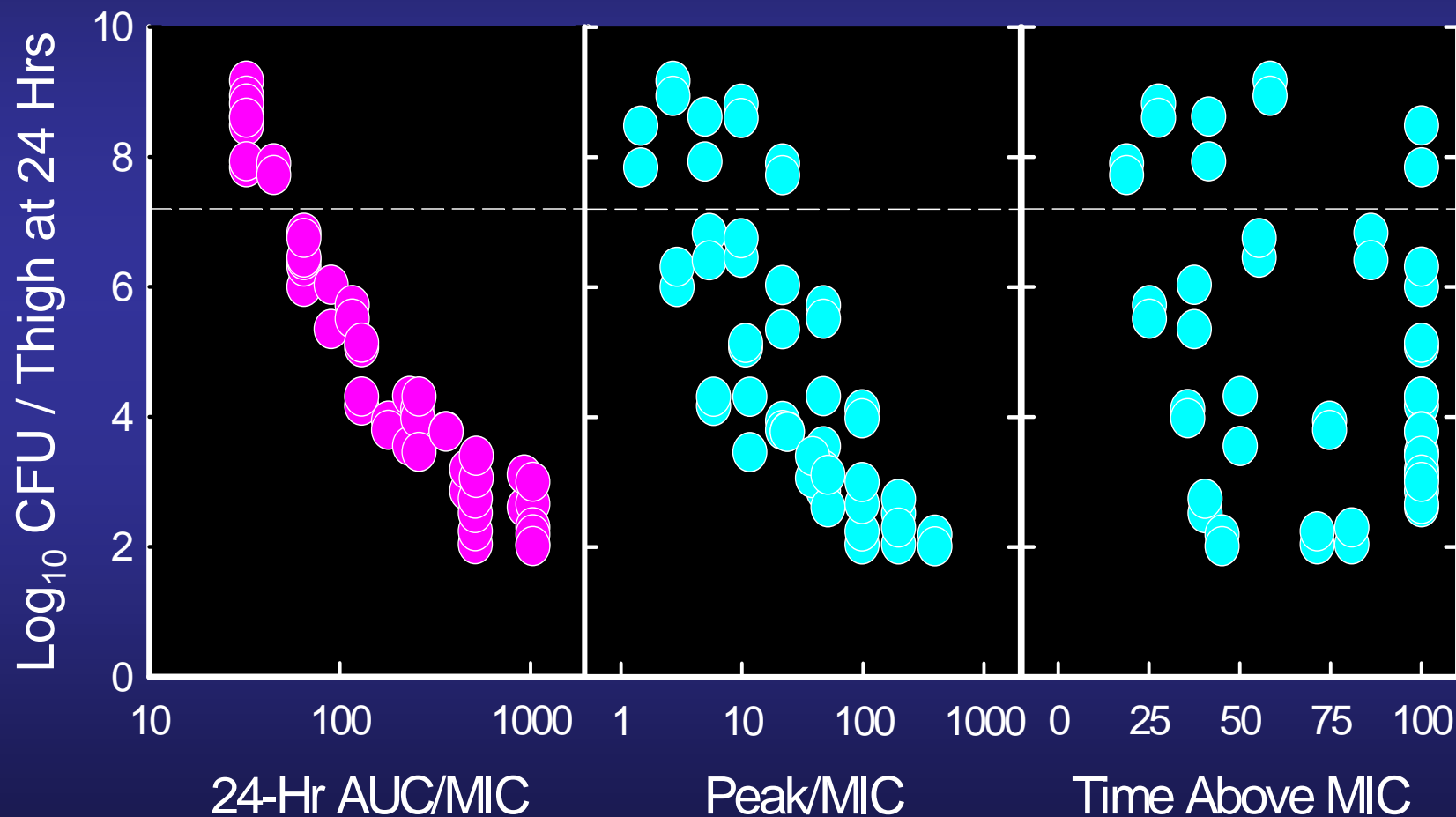
4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

Time Course of Antimicrobial Activity of Ciprofloxacin Against *Klebsiella* ATCC 43816 in Lungs of Neutropenic Mice

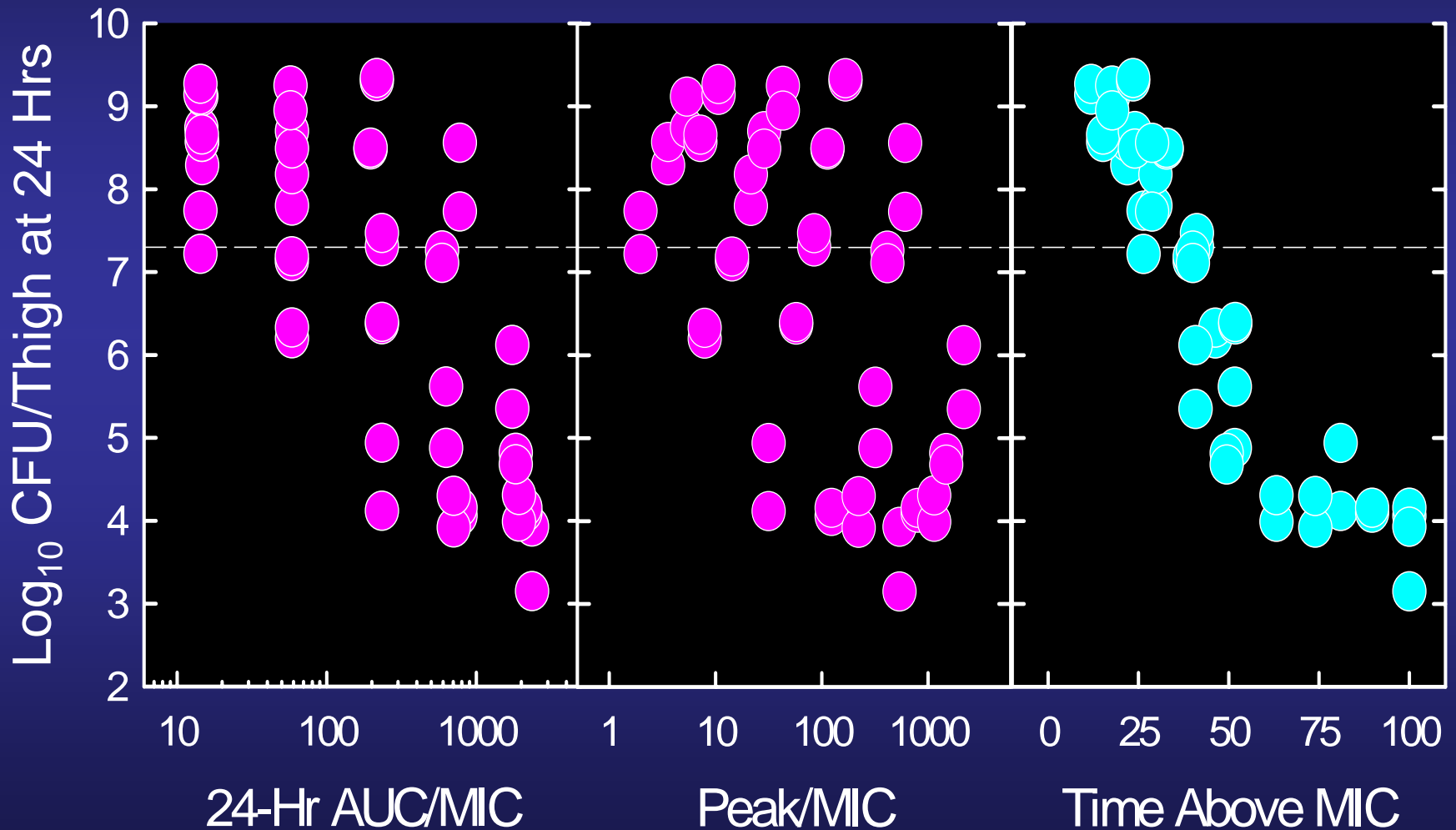


Correlation of PK/PD Parameters with Efficacy

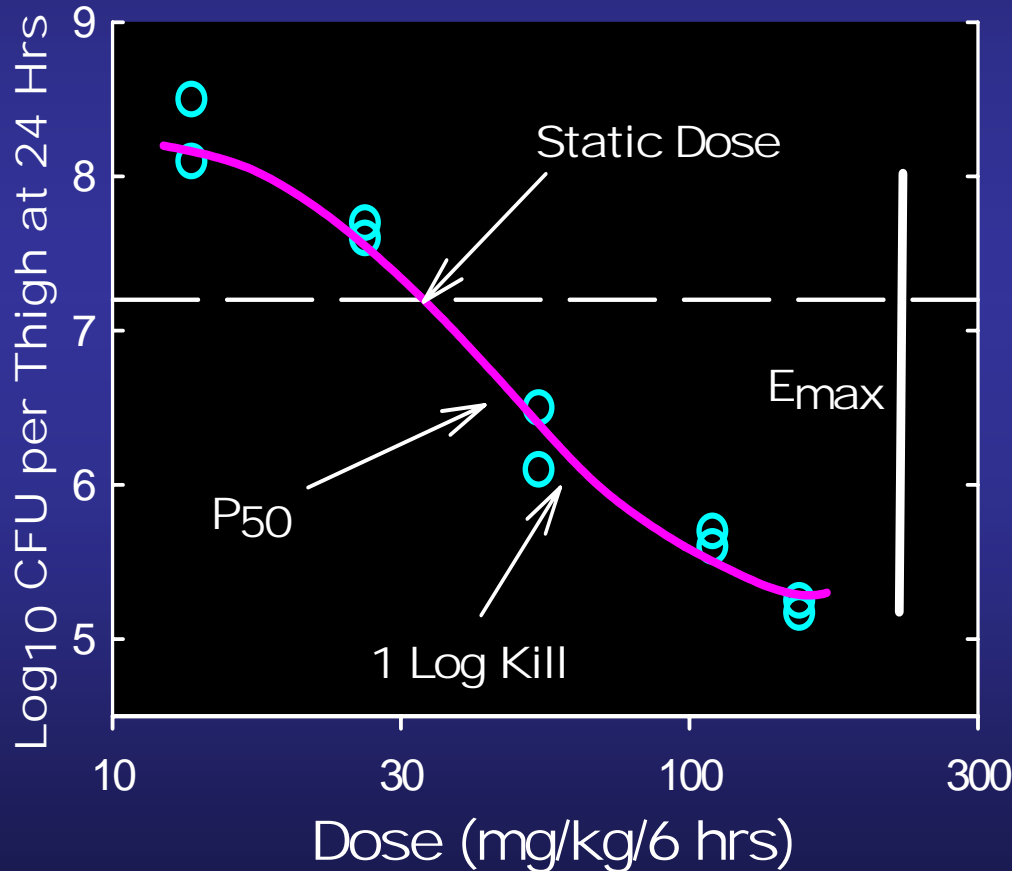
Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice



Relationship Between PK/PD Parameters and Efficacy for Cefpirome against *Klebsiella pneumoniae* in Lungs of Neutropenic Mice



Mathematical Analysis of Dose-Response Data from Animal Models after 24 Hours of Therapy



Nonlinear regression and Hill equation to estimate E_{max} (difference from untreated control), P₅₀ (dose giving 50% of E_{max}) and slope (N) of the dose-response relationship

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

Factors That Affect the Magnitude of PK/PD Parameters

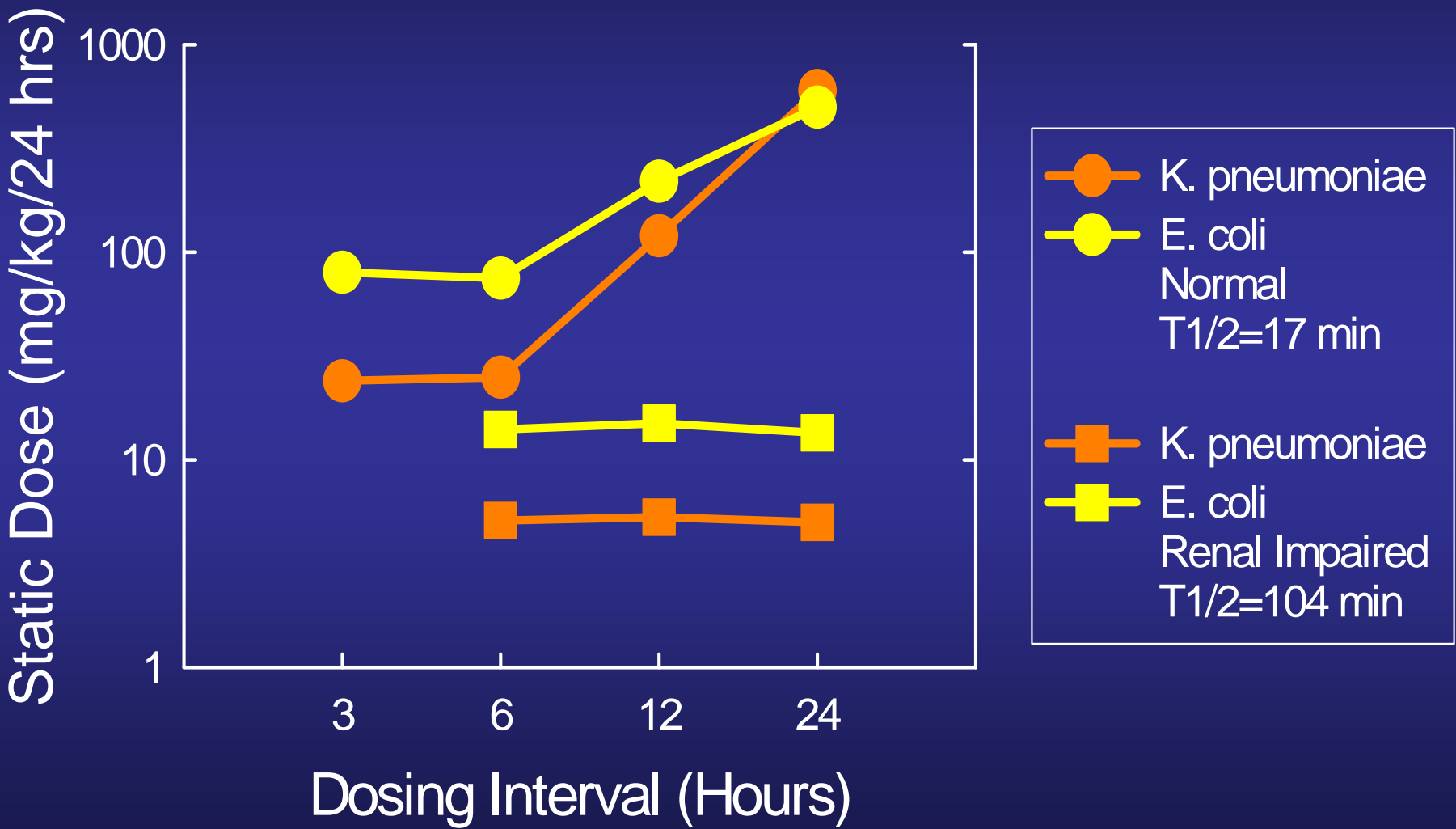
- dosing regimen
- drug class
- protein binding
- infecting pathogen
- presence or absence of neutrophils
- site of infection

Magnitude of PK/PD Parameters

Does the magnitude of the parameter vary with:

1. different dosing regimens? **NO, unless the clearance is too rapid in the animal model**

Impact of Dosing Interval on Static Dose for Amikacin against *K. pneumoniae* and *E. coli* in Mice with Normal and Impaired Renal Function



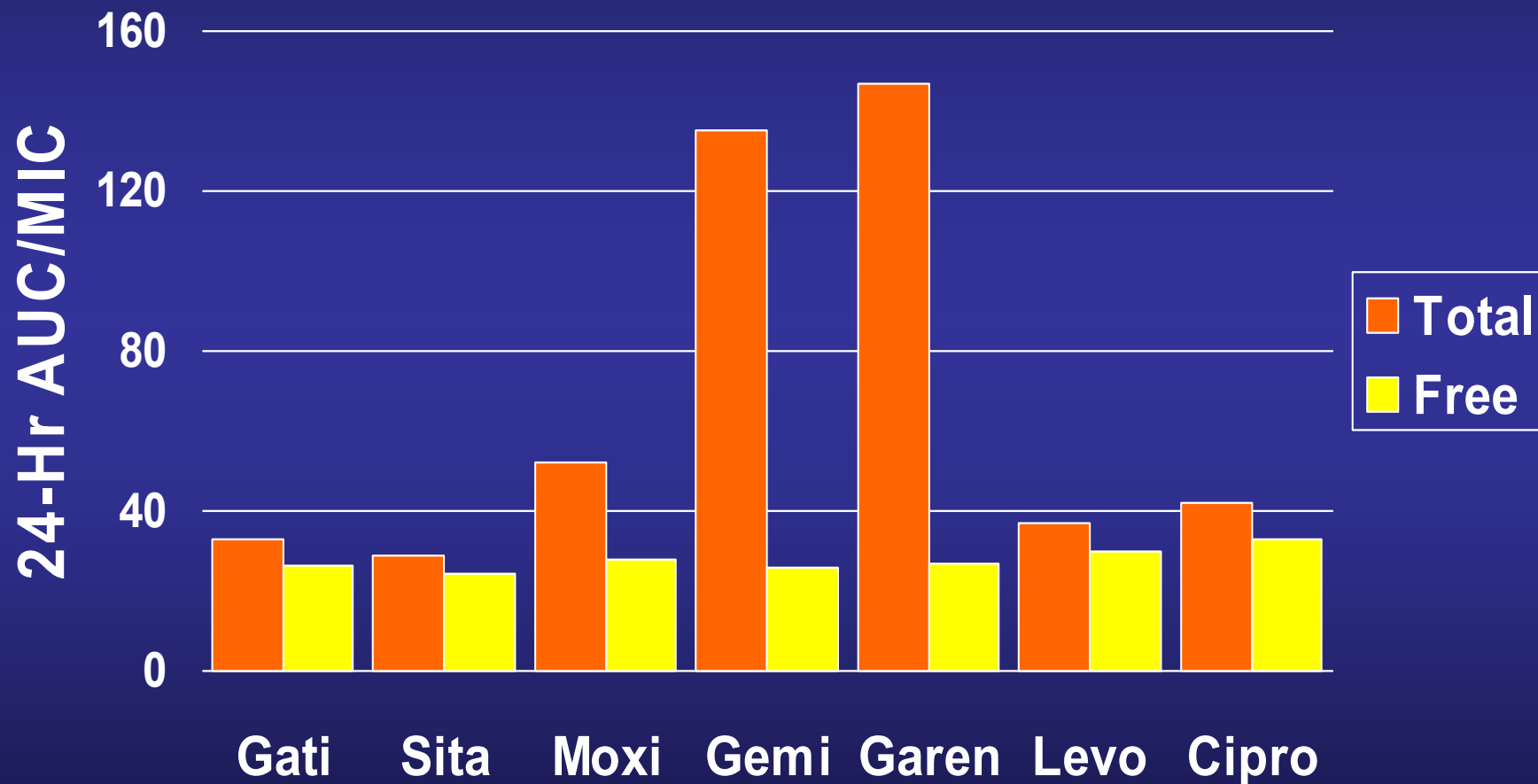
Magnitude of PK/PD Parameters

Does the magnitude of the parameter vary with:

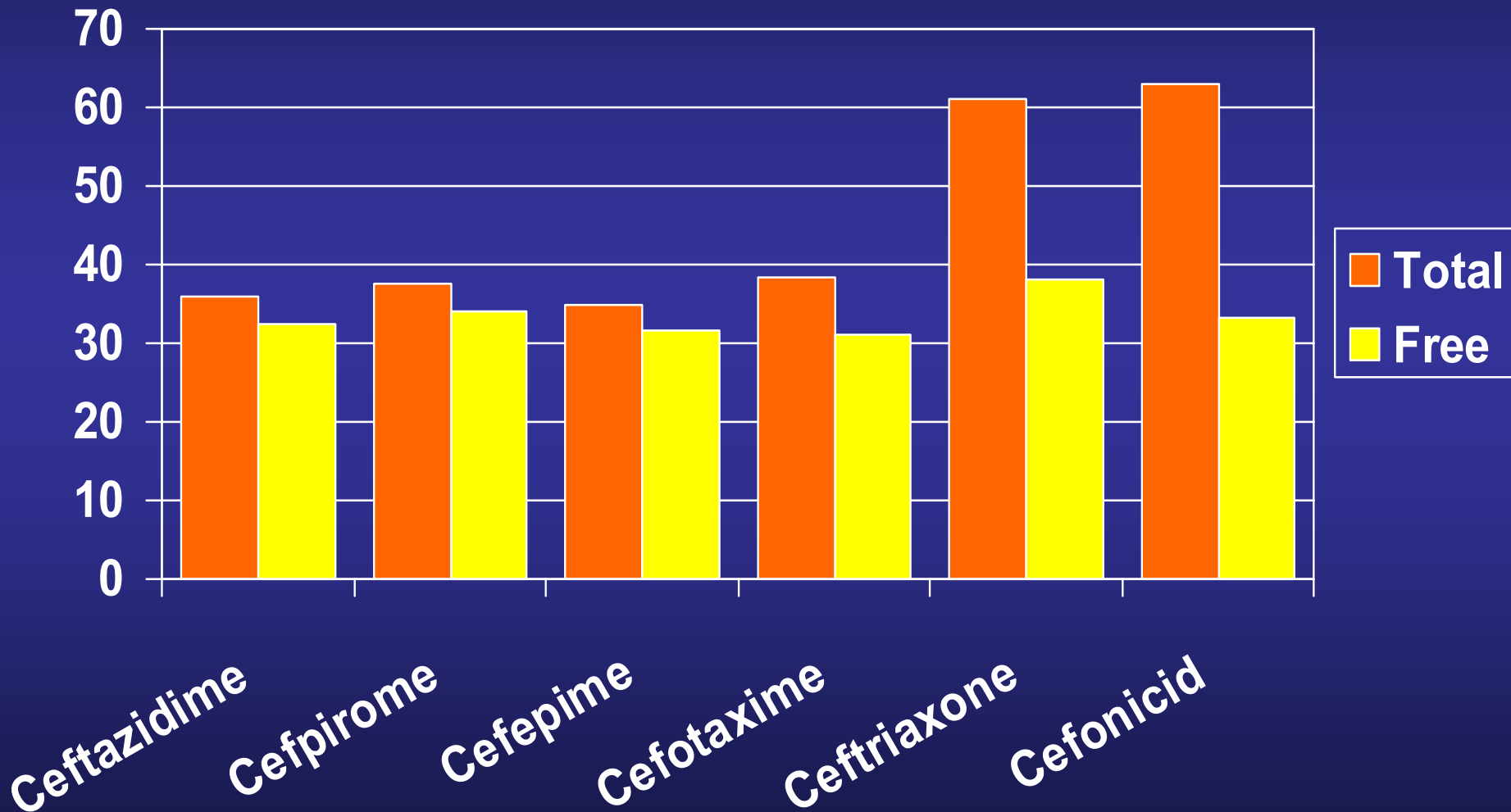
1. different dosing regimens? **NO**
2. different drugs within the same class?
NO, if free drug levels are used

Protein binding is important !!

24-Hr AUC/MIC with Total and Free Drug for the Static Dose of Different Fluoroquinolones with *S. pneumoniae* ATCC 10813



Time Above MIC for Total and Free Drug for the Static Dose of Different Cephalosporins with *Klebsiella pneumoniae* ATCC 43816



Magnitude of PK/PD Parameters

Does the magnitude of the parameter vary with:

1. different dosing regimens? **NO**
2. different drugs within the same class?
NO, if free drug levels are used
3. different organisms ?

Similar for most organisms in neutropenic mice; less $T > MIC$ with staphylococci with β -lactams

Time Above MIC Required for a Static Effect with 4 Cephalosporins

Time Above MIC (% of Dosing Interval)

Drug	GNB	S. pneumoniae	S.aureus
Ceftazidime	36 (27-42)	39 (35-42)	22 (19-24)
Cefpirome	35 (29-40)	37 (33-39)	22 (20-25)
Cefotaxime	38 (36-40)	38 (36-40)	24 (20-28)
Ceftriaxone	38 (34-42)	39 (37-41)	24 (21-27)

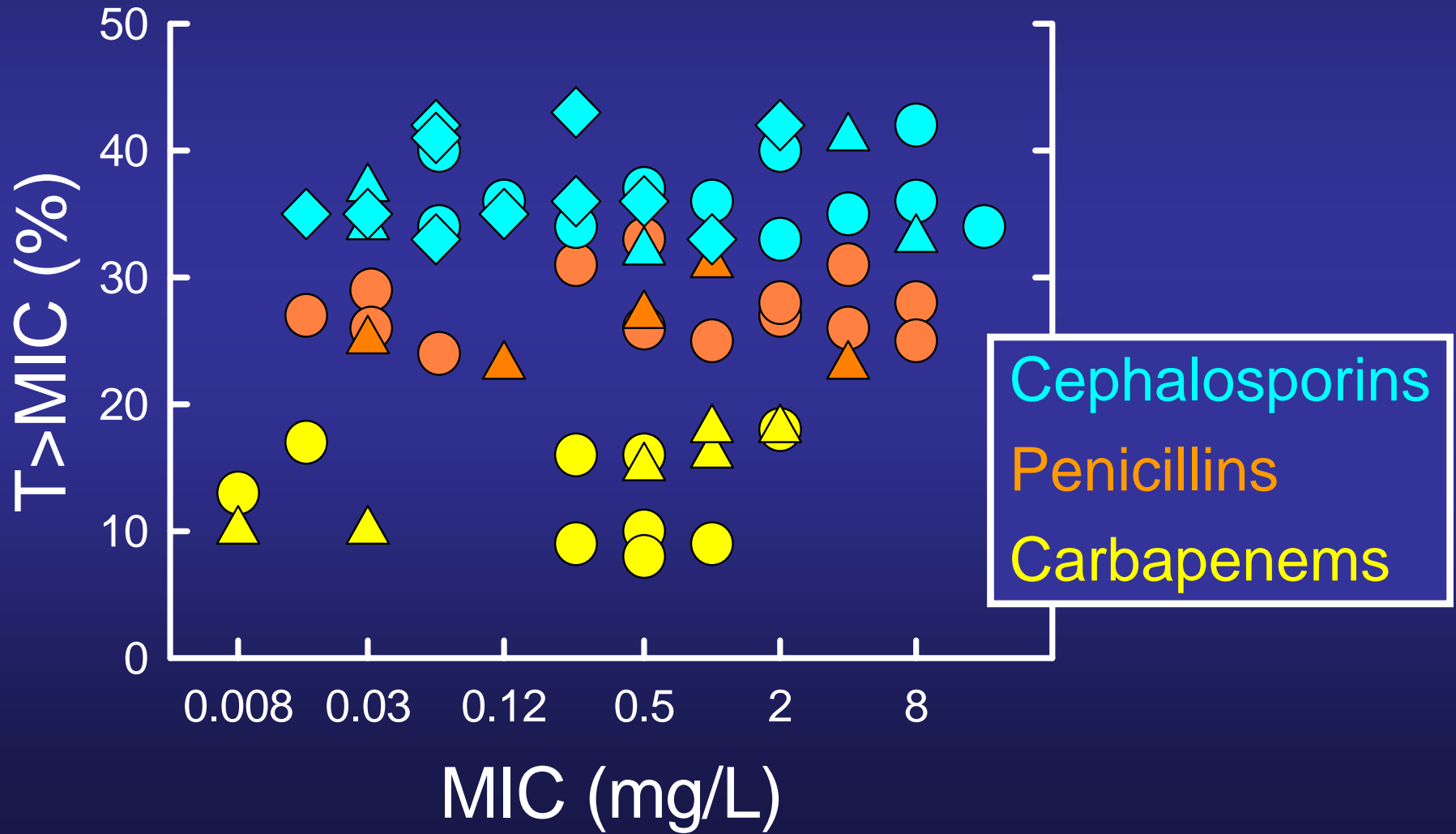
Magnitude of PK/PD Parameters

Does the magnitude of the parameter vary with:

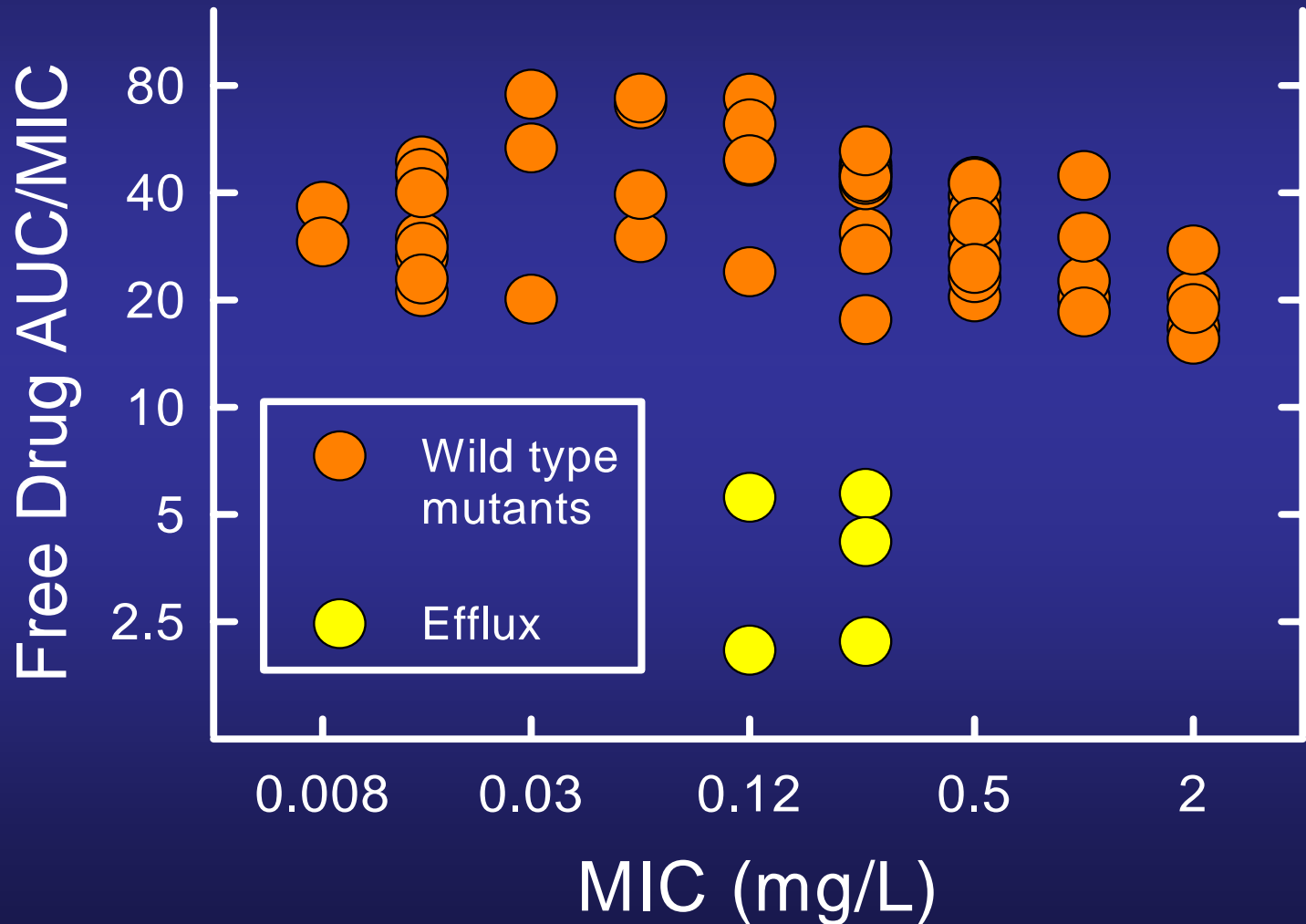
4. resistant organisms

No

T>MIC for Free Drug for Static Doses with Cephalosporins, Penicillins and Carbapenems against Multiple Strains of *S. pneumoniae* with Various Penicillin MICs



24-Hr AUC/MIC of Gemifloxacin (Free Drug) for the Static Doses with 61 Strains of *S. pneumoniae* in Thighs of Neutropenic Mice



Magnitude of PK/PD Parameters

Does the magnitude of the parameter vary with:

4. resistant organisms

NO

5. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)?

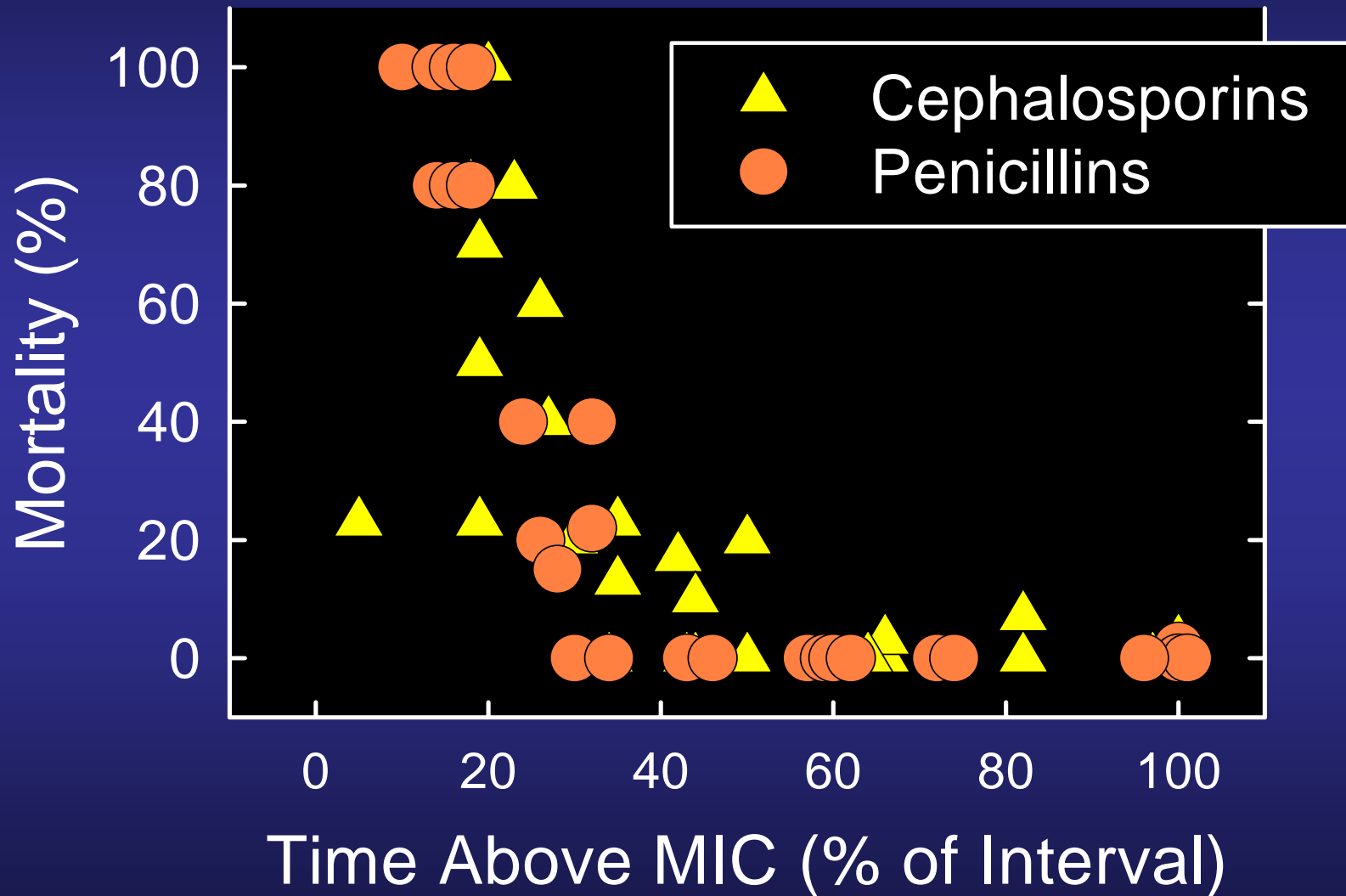
NO for most drugs; vancomycin less potent in lung infection than thigh

Factors That Do Not Affect the Magnitude of PK/PD Parameters

- resistant organisms
- animal species

Can values obtained in animals be predictive of efficacy in humans ?

T>MIC for β -Lactams Versus Mortality in Animal Models: Literature Review

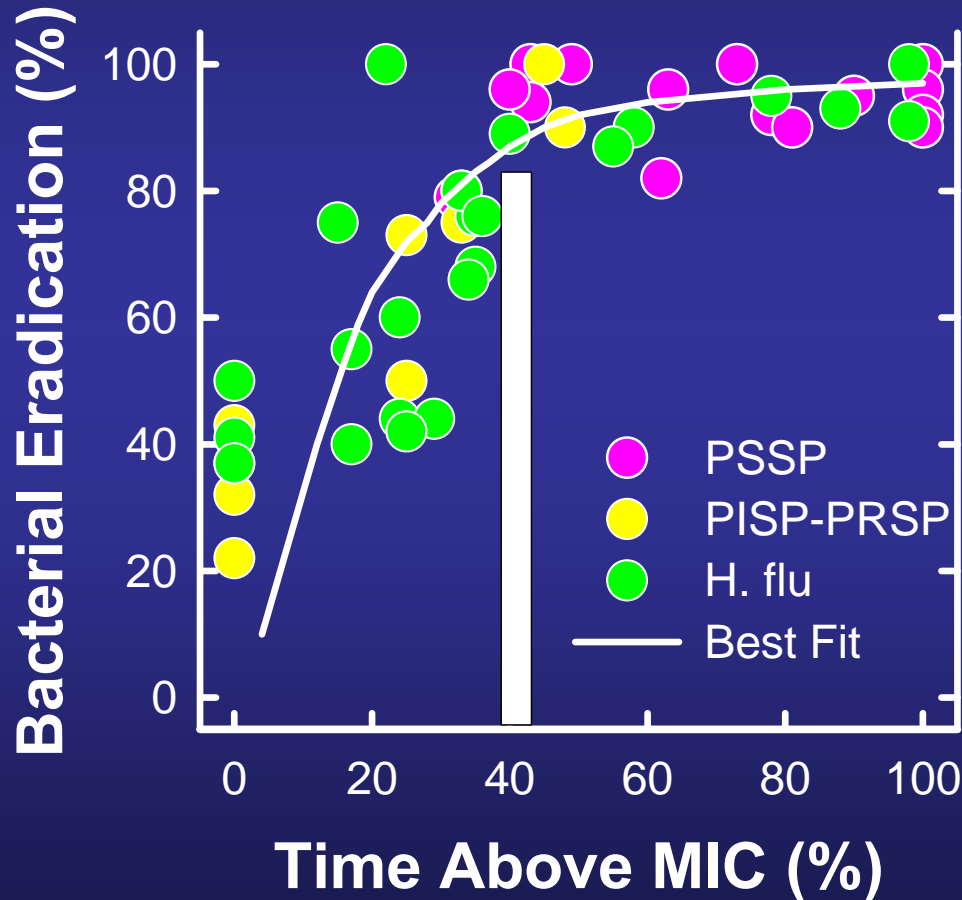


Double Typanocentesis Studies in Acute Otitis Media

- First tap to identify the causative pathogen
- Second tap at 3-5 days to determine if organisms had been eradicated
- Techniques first performed by Howie. Most recent studies with resistant organisms performed by Dagan.
- Time above MIC calculated from serum levels and MICs

Craig & Andes, *Pediatr Infect Dis J* 15:255, 1996;
Multiple studies by Dagan et al

Relationship Between T>MIC and Bacterial Eradication with β -Lactams in Acute Otitis Media



Uses of Pharmacodynamic Studies

- Drug development
 - new formulations active against organisms with high MICs (e.g. high dose amoxicillin/clavunate)
 - dosage regimens for phase II and III clinical trials
 - drug selection for clinical studies
- Optimize dosing regimens
 - longer infusions and continuous infusion of beta-lactams
 - once-daily dosing of aminoglycosides

Uses of Pharmacodynamic Studies

- Guidelines for antimicrobial usage
- Reduction of emergence of resistance organisms
- Modifications of susceptibility and resistance breakpoints
 - oral β -lactams for *S. pneumoniae*
 - parenteral cephalosporins for *S. pneumoniae*
 - fluoroquinolones for *S. aureus*

ESBLs and Clinical Failures

- Emergence of Enterobacteriaceae with increased MICs due to novel β -lactamases (ESBLs)
- Associated with clinical failures and existing breakpoints fail to detect all these enzymes
- Development by NCCLS of reference methods for screening and confirmation of ESBLs in some Enterobacteriaceae; does not work for all Enterobacteriaceae.
- Elevated MICs in may also arise from mechanisms not targeted by the current ESBL test

Pharmacodynamic Studies of Extended-Spectrum Cephalosporins against Enterobacteriaceae with and without ESBLs in Thighs of Neutropenic Mice

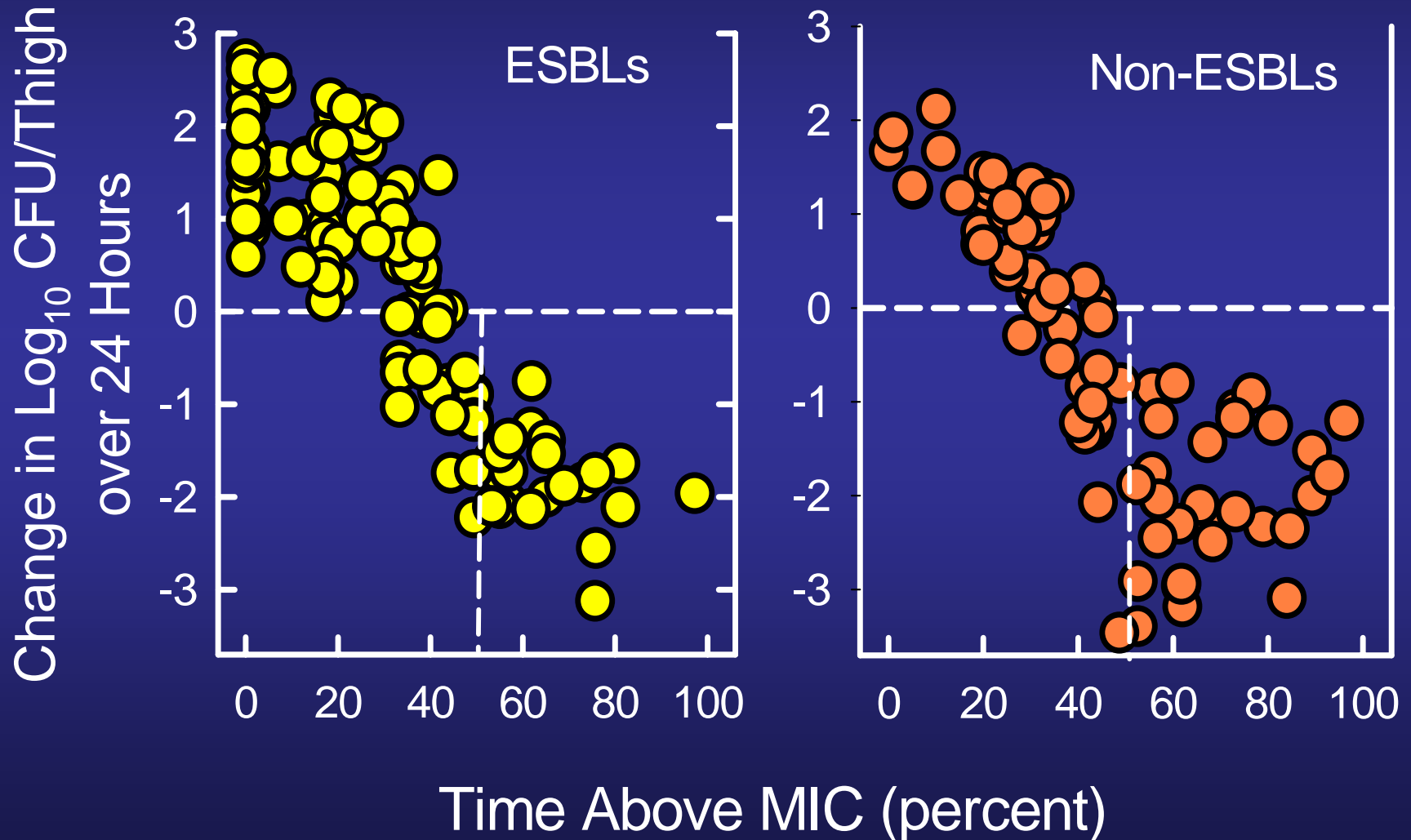
Drugs: Cefotaxime, Ceftriaxone, Ceftazidime and Cefepime

ESBLs: TEM-3, TEM-7, TEM-10, TEM-12, TEM-26, SHV-2, SHV-4, SHV-5, SHV-7, CTX-M2, CTX-M3 alone or in combination with OXA-1, OXA-2, TEM-1, and/or AMP-C

Non-ESBLs: TEM-1, TEM-1 and OXA-1, AMP-C, wild-type

High inocula – 10^{7-8}

Activity of 4 Cephalosporins against Various Enterobacteriaceae with and without ESBLs in Murine Thigh-Infection Model



Monte Carlo Simulation

PK Variation
In Normal
Volunteers
or Patients

Simulate



PK Variation in
10,000 Patients



Determine Percentage of Patients
that would meet the PK/PD Target
required for efficacy

Monte Carlo Simulation: Cefotaxime Percent of 10,000 Patients Attaining Indicated PK/PD Exposure Target

T>MIC with 2g every 8 hr

<u>MIC</u>	<u>30%</u>	<u>40%</u>	<u>50%</u>	<u>60%</u>	<u>70%</u>
0.5	100	100	99	96	88
1	100	99	97	89	73
2	99	98	89	71	49
4	98	91	67	41	22
8	92	62	29	11	4
16	65	15	3	0	0

Clinical Outcome in 42 Patients with ESBL-Producing Klebsiella/E. coli Bacteremia and Treated with Cephalosporin Monotherapy

Outcome	MIC ≤ 1 $\mu\text{g/L}$	MIC 2 $\mu\text{g/L}$	MIC 4 $\mu\text{g/L}$	MIC 8 $\mu\text{g/L}$
Success	13 (81%)	4 (67%)	3 (27%)	1 (11%)
Failure	3 (19%)	2 (33%)	8 (73%)	8 (89%)

Paterson et al J Clin Micro 39:2206, 2001; Kim et al AAC 46:1481, 2002; Wong-Beringer et al Clin Infect Dis 34:135, 2002; Kang et al AAC In press 2004; Bhavani et al 44rd ICAAC, Abstract K-1588, 2004

Distribution of Enterobacteriaceae with MICs of 4 and 8 mg/L

Total Of 11, 913 Isolates from ICU Patients

	Total Strains	E. coli	Kleb spp	Other
Ceftazidime	464	89 (19%)	158 (34%)	217 (47%)
Ceftriaxone	532	46 (9%)	169 (32%)	317 (59%)

2002-2003 Sentry Program

Acknowledgements

Pharmacodynamics

Andes DR

Bundtzen R

Ebert S

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Mouton J

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Totska K

Turnidge J

Van Ogtrop M

Vogelman B

Walker R

Watanabe Y

Otitis

Dagan R

ESBLs

Ambrose P

Dudley M

Jones R

It all started with a mouse.

-Walt Disney

