Pharmacodynamic Data from Mice and Men: Use and Calibration of Animal Models for BP Analysis

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Major Goal of PK/PD Metrics

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

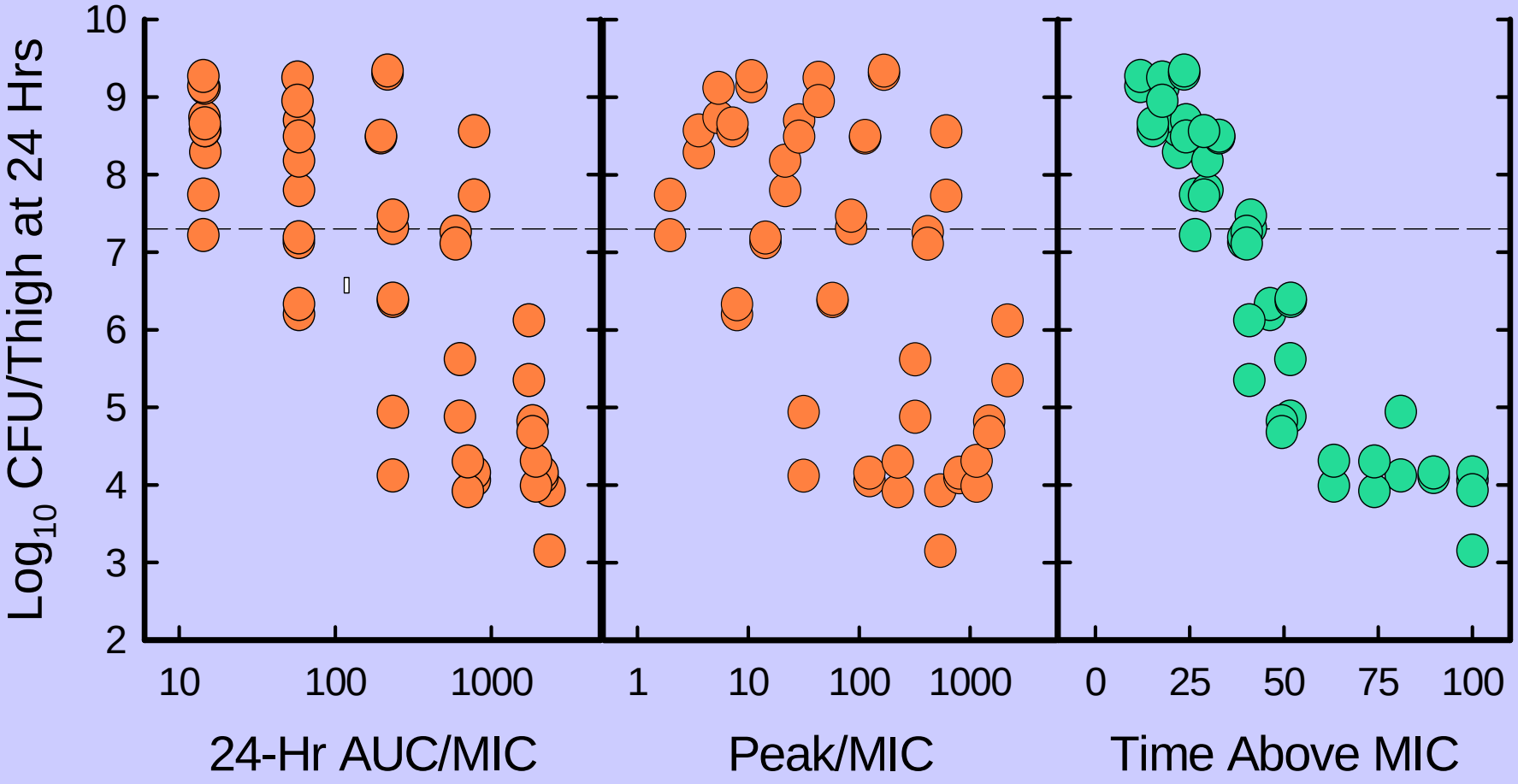
- determine the **magnitude** of the PK/PD indice required for in vivo efficacy (changes in cfu or survival in animals and clinical/microbiological cure in humans)

Use of Animal Models in PK/PD Evaluation of Anti-Infective Agents

Identifying PK/PD indices correlating with efficacy (Peak/MIC, AUC/MIC, Time>MIC)

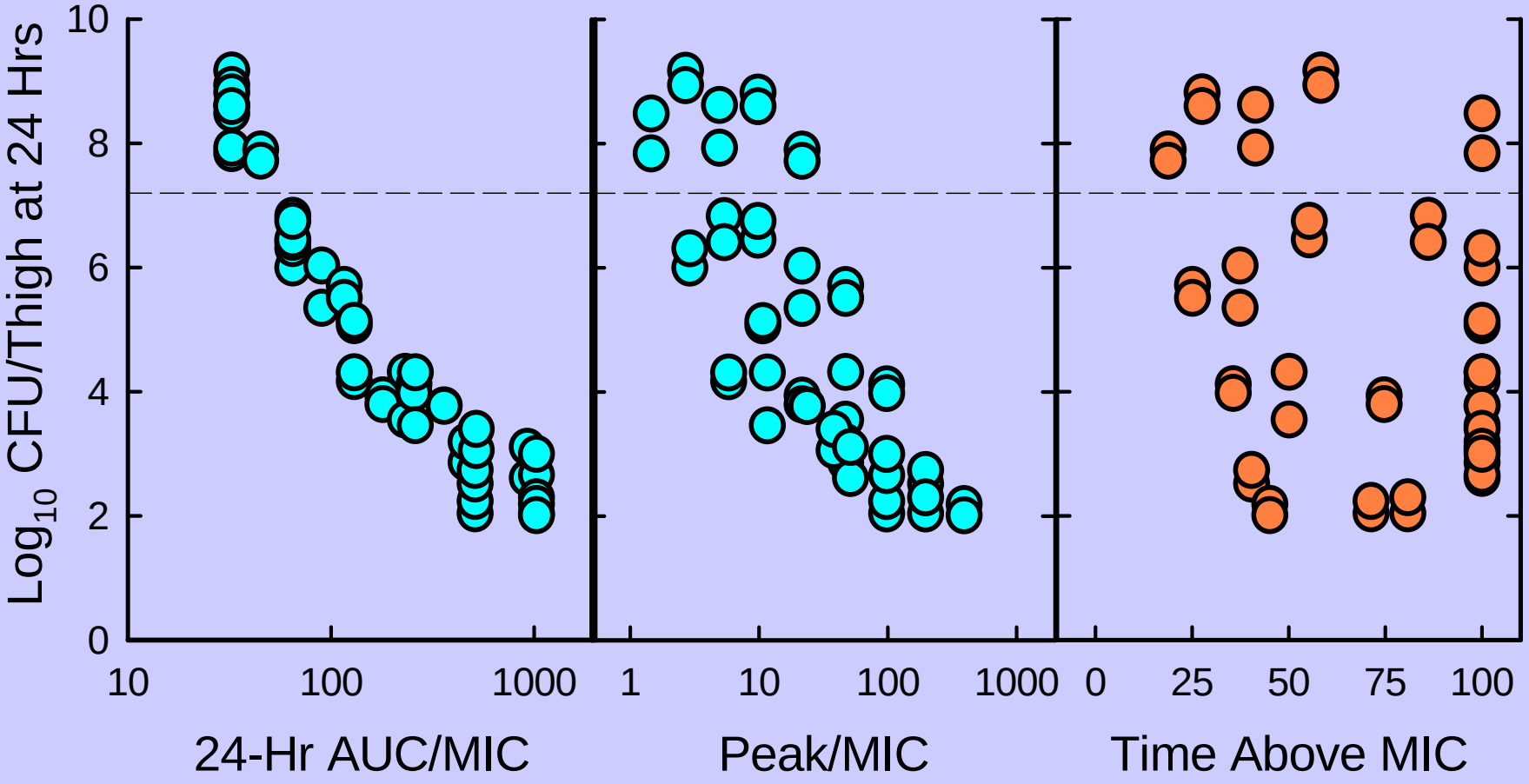
- dose-fractionation studies to reduce inter-dependence among the various indices
- usually use 3, 6, 12 and 24 hr intervals
- with long half-life drugs have used 12, 24, 36, and 72 hr intervals

Relationship Between PK/PD Indices and Efficacy for Ceftazidime against *Klebsiella pneumoniae* in a Murine Pneumonia Model



Craig WA: Pharmacodynamics of antimicrobials: General concepts and applications. In: Antimicrobial Pharmacodynamics in Theory and Clinical Practice, 2002:1-22.

Correlation of PK/PD Indices with Efficacy of Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice



Andes & Craig Int J Antimicrob Agents 2002;19:261-268

Use of Animal Models in PK/PD Evaluation of Anti-Infective Agents

- Determining magnitudes of the PK/PD indice required for efficacy and identifying factors that affect the magnitude
- - cfu changes (short durations of therapy) vs survival (longer courses)
- - clinical/microbiological efficacy in humans

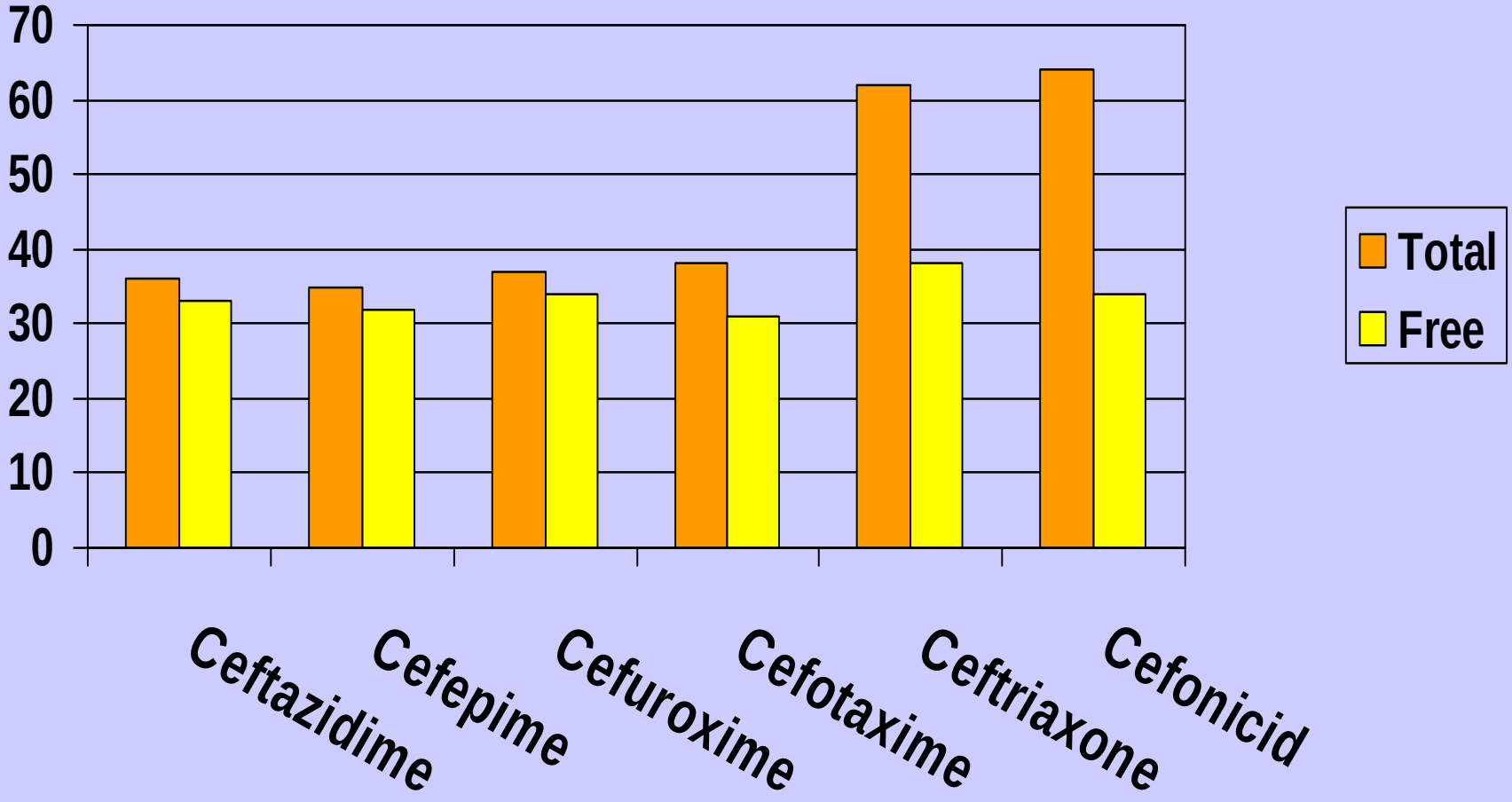
PK/PD Magnitude Variables

- Protein binding
- Antibiotic class (e.g. less T>MIC for carbapenems – faster killing)
- Organism (e.g. less T>MIC for Staphylococci)
- Immune status (normal vs neutropenic)
- Time survival is determined

Not major factors

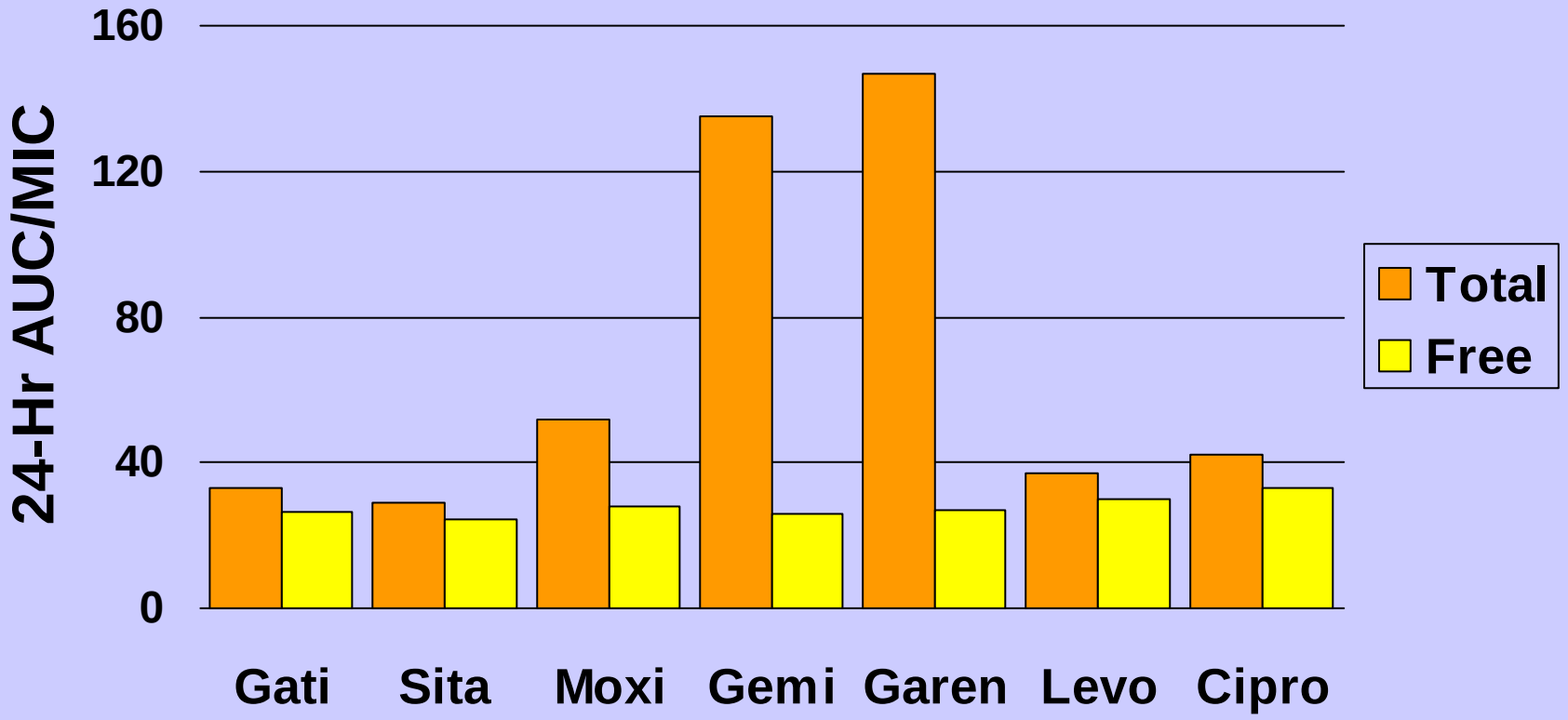
- Presence of resistance mechanism(s)
- Dosing regimen

Time Above MIC for Total and Free Drug for the Static Dose of Different Cephalosporins *Klebsiella pneumoniae* ATCC 43615



Craig DMID 22: 89, 1995

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



Ambrose et al Inf Dis Clinics of N Amer

Impact of Neutrophils

Gram-Negative Bacilli (GNB):

Minimal effect with ß-Lactams

Slight effect with fluoroquinones and aminoglycosides (less than 2-fold enhancement)

Streptococcus pneumoniae:

Slight effect with ß-Lactams (less than 2-fold)

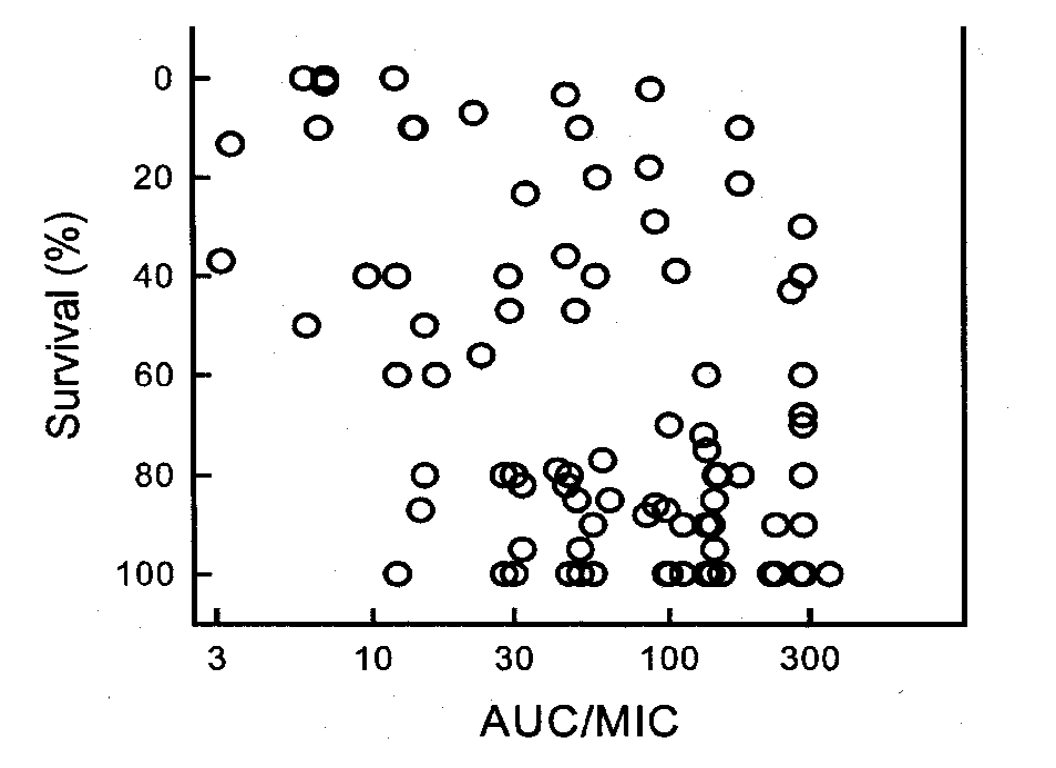
Moderate effect with macrolides and clindamycin (3- to 4-fold enhancement)

Marked effect with fluoroquinolones (5- to 6-fold enhancement)

Survival Endpoints – When Should Survival/Mortality be Assessed?

Studies with Multiple Fluoroquinolones

Survival 7-12 days after therapy

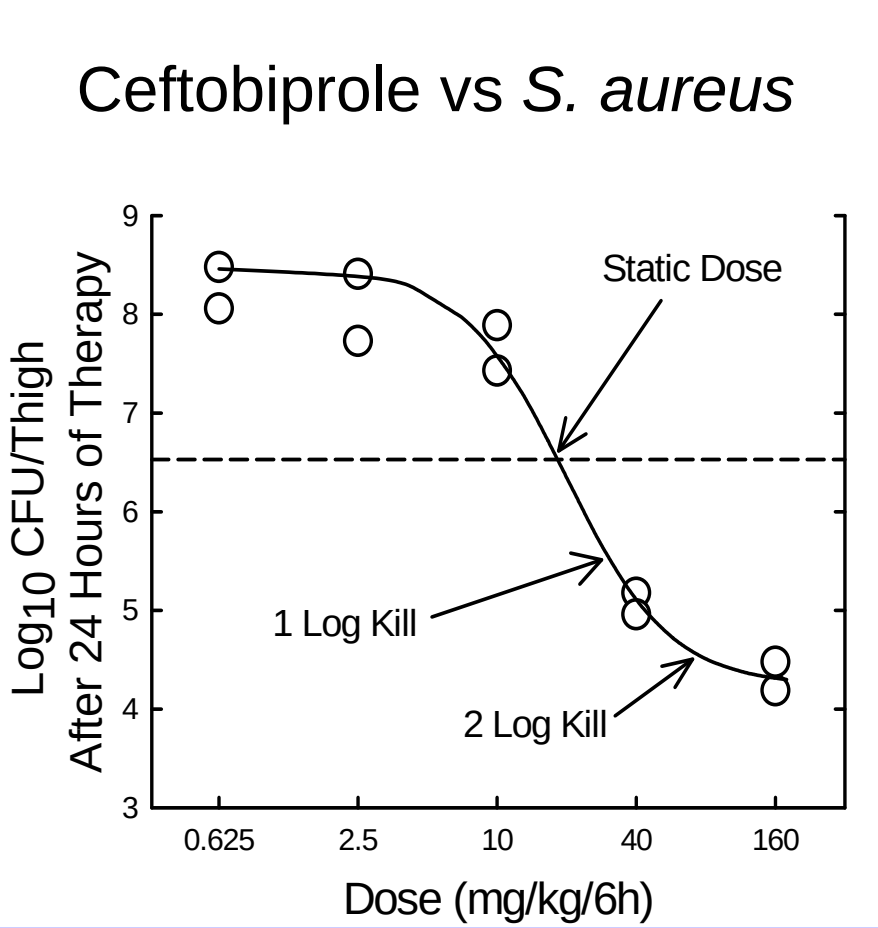


Andes & Craig Int J Antimicrob Agents 2002;19:261-268

Survival/Mortality Studies

- Mortality in control animals 80-100% by end of therapy
- Animals treated for at least 48 hrs
- Mortality assessed within 24 hrs of end of therapy
- Pharmacokinetics included so PK/PD magnitudes for important indices could be estimated

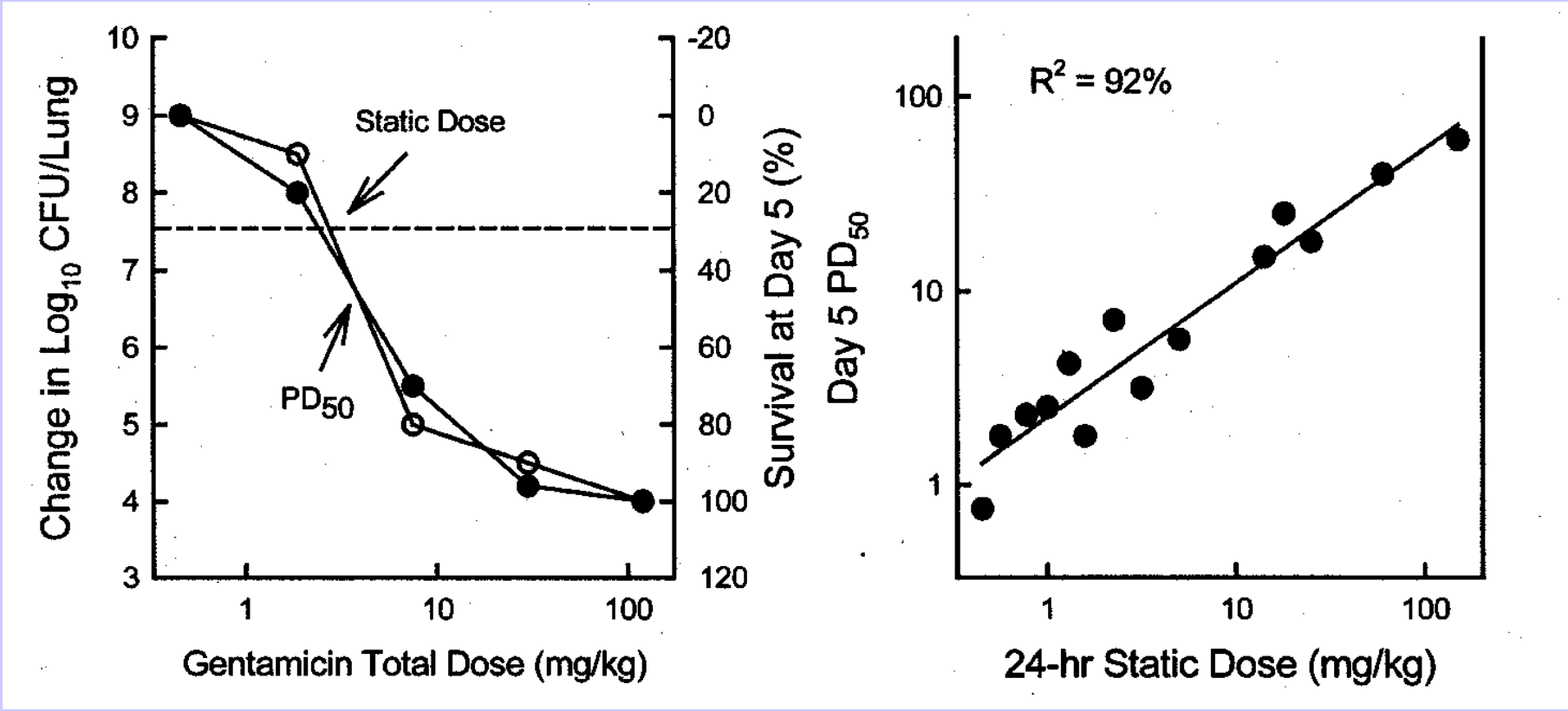
Mathematical Analysis of Dose-Response Data from Animal Models after 24 Hours of Therapy



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

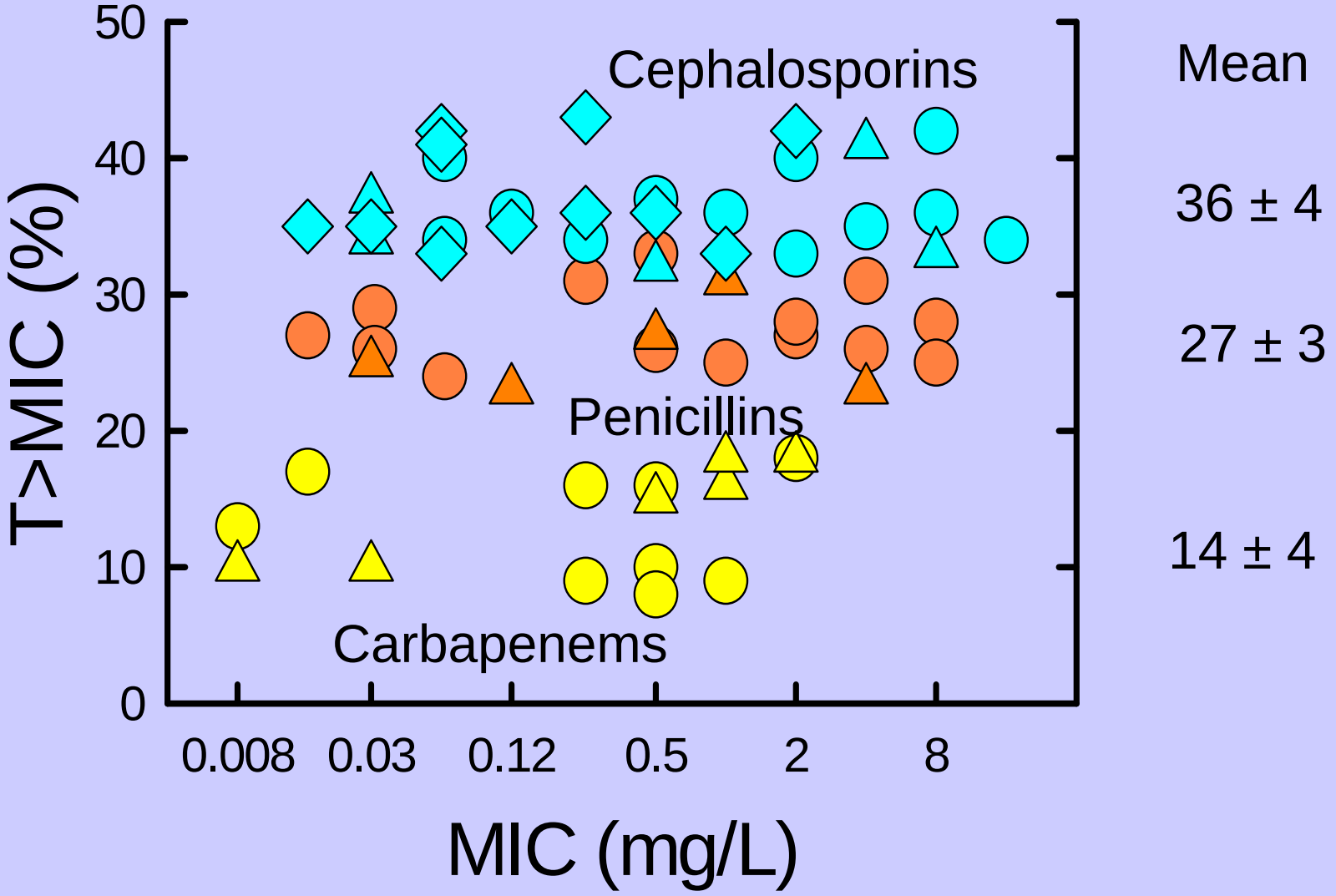
$$\Delta CFU = \frac{(Emax)\ Dose^{N}}{Dose^{N} + P_{50}{}^{N}}$$

Relationship Between Static Dose after 24 Hrs and Protective Dose-50 after 5 Days of Therapy in Neutropenic Mice

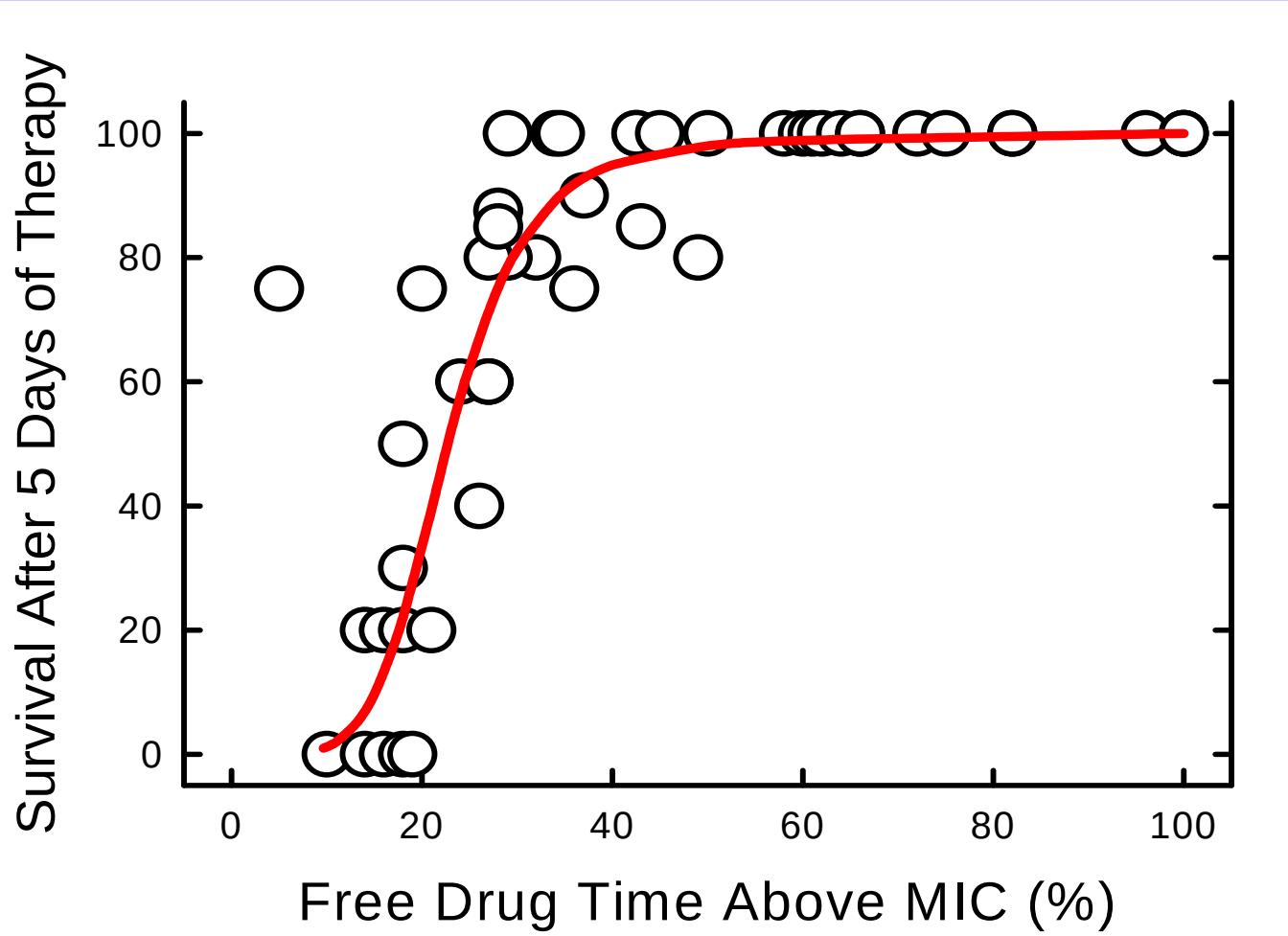


Andes & Craig, Int J Antimicrob Agents 2002;19:261-268

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



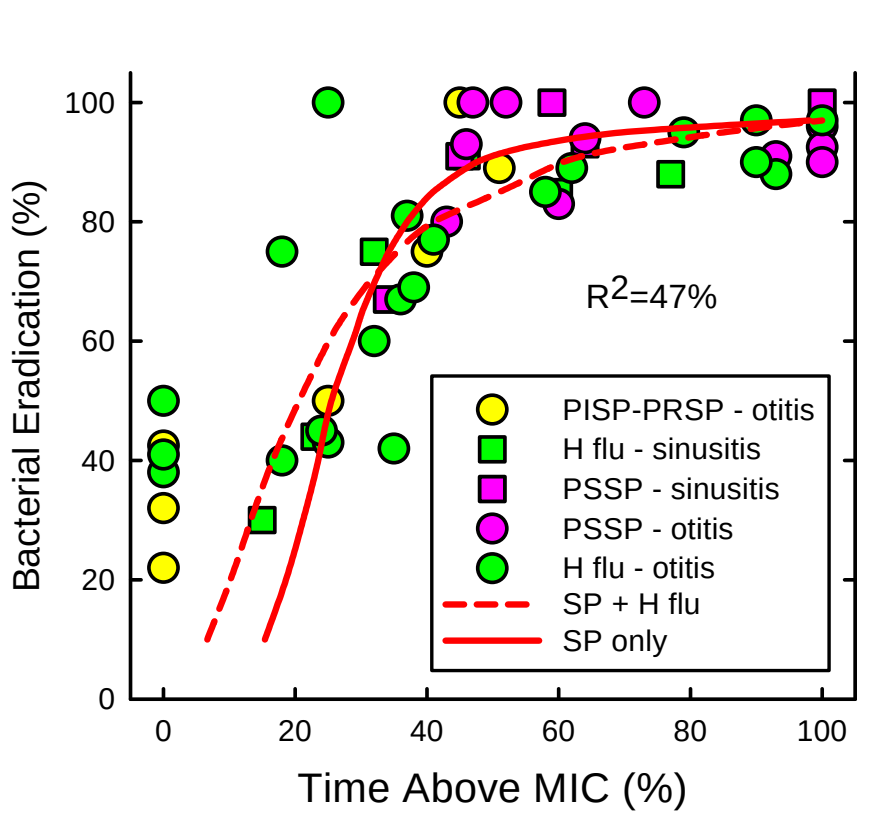
Survival in Neutropenic Mice Infected with *S. pneumoniae* After 5 Days of Therapy with Penicillins and Cephalosporins



Craig WA: Pharmacodynamics of antimicrobials: General concepts and applications. In: Antimicrobial Pharmacodynamics in Theory and Clinical Practice, 2007:1-35.

Relationship Between T>MIC and Bacterial Eradication with ß-Lactams in Otitis Media (Circles) and Maxillary Sinusitis (Squares)

- Bacteriologic cure for ß-lactam antibiotics with *S. pneumoniae* and *H. influenzae* from double-tap studies in acute otitis media and acute maxillary sinusitis
- Time above MIC calculated from serum levels and MICs

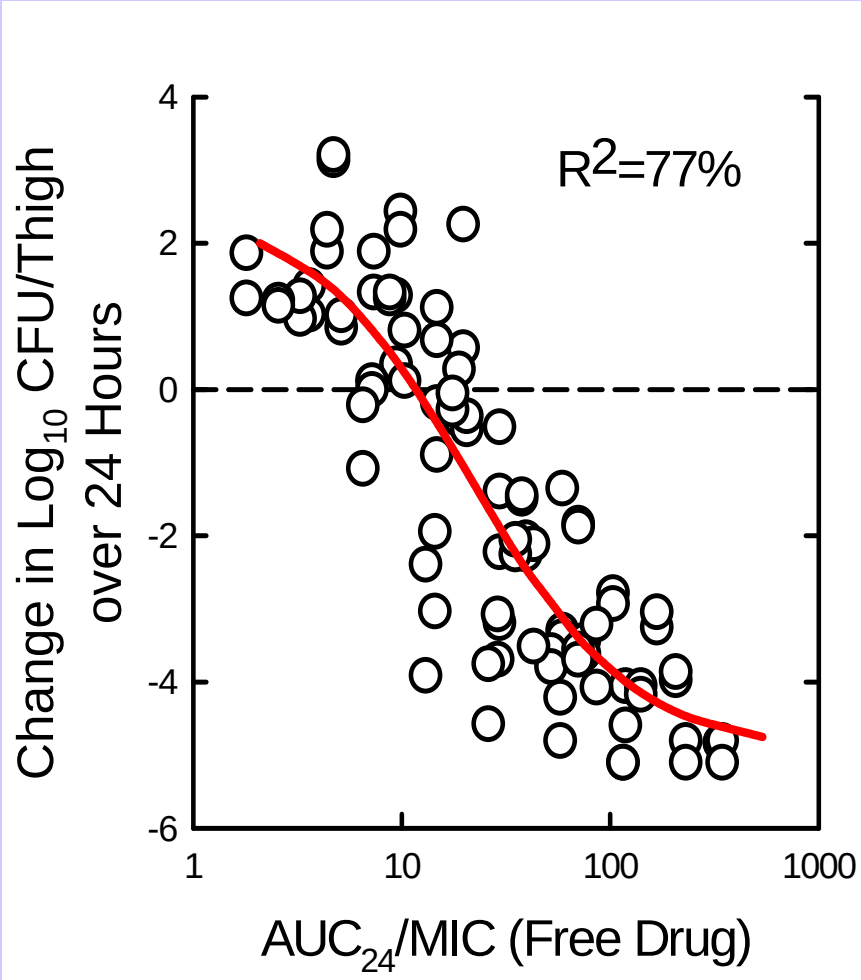


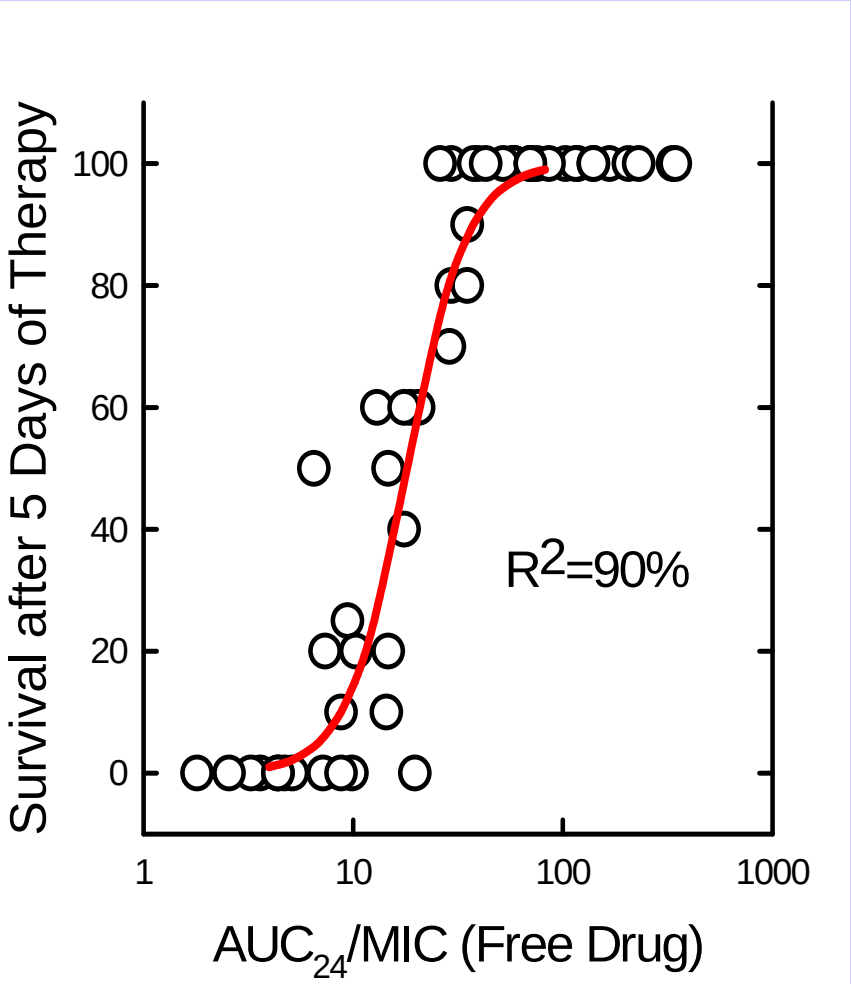
Craig Infect Dis Clinics N Am 17:479-501, 2003

Efficacy of Penicillins/Cephalosporins against *Streptococcus pneumoniae* in Animals and Humans

Source	Parameter	Drug T>MIC (%)
Animal Neutro-penic	Stasis - Penicillins	27 ± 3
	Cephalosporins	36 ± 4
	50% Survival	23 ± 1
	90% Survival	35 ± 2
Human	85% Microbiological Cure	40%

Free Drug AUC_{24}/MIC versus Change in CFUs over 24 Hours and Survival after 5 days of Therapy with Fluoroquinolones in Non-Neutropenic Mice

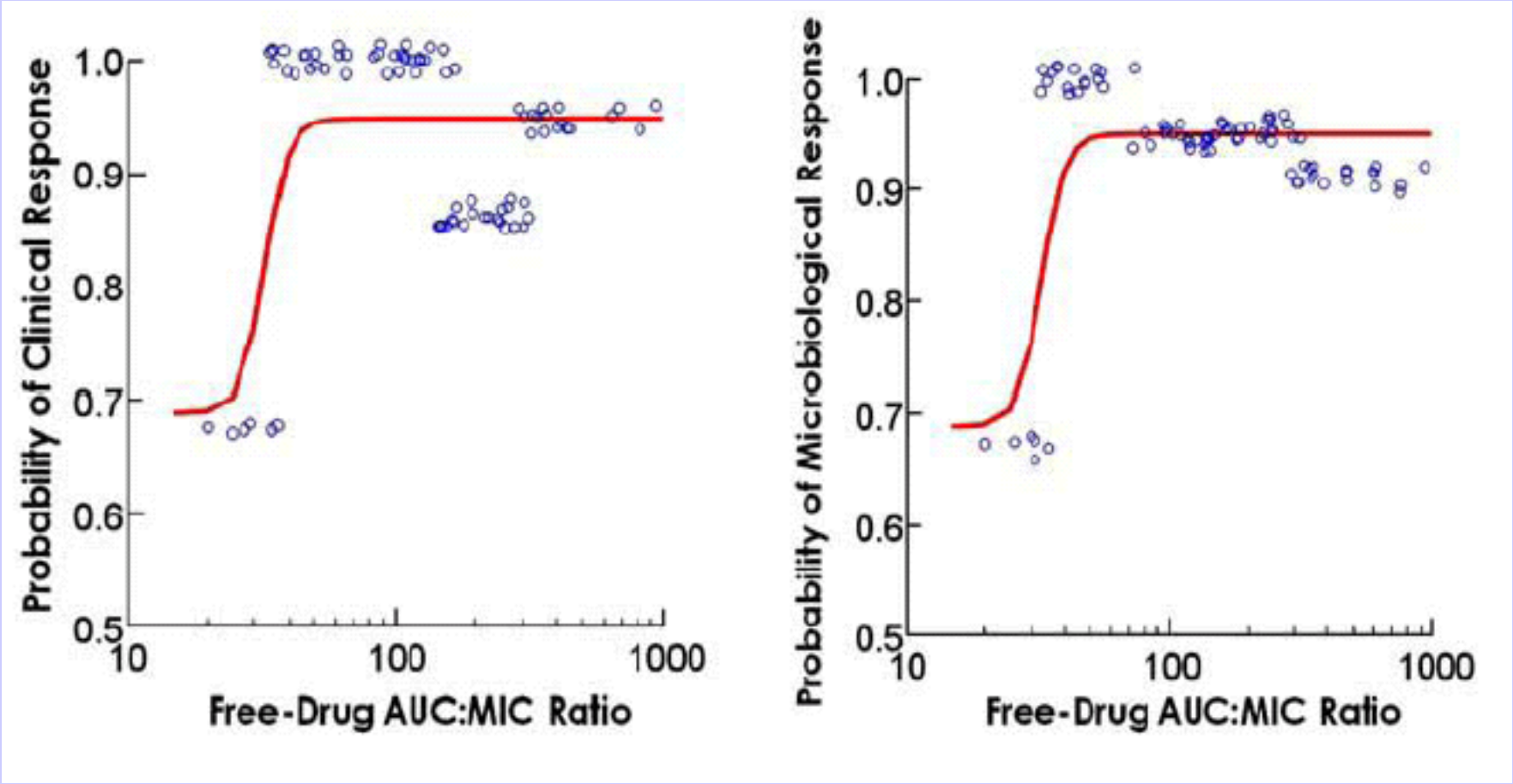




Craig WA, Andes DR 40th ICAAC, September 2000.

FLUOROQUINOLONES

Pneumococcal Pneumonia

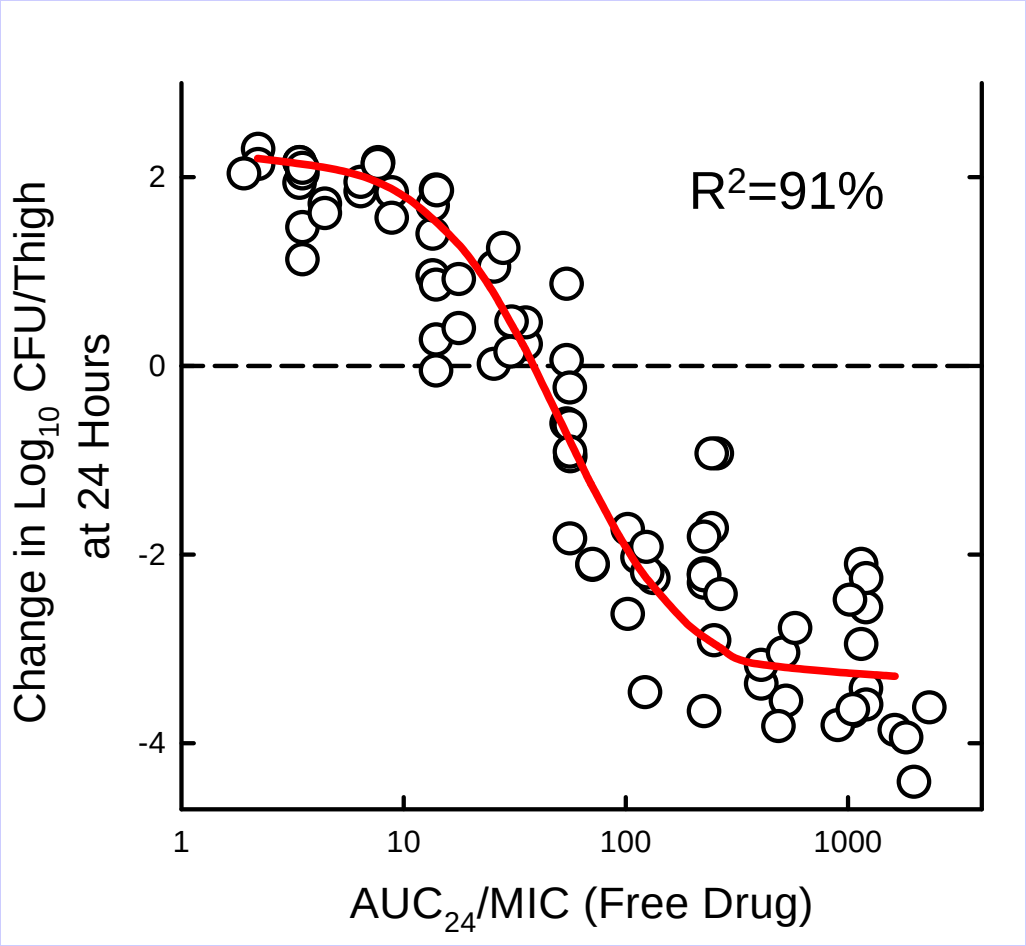


Bhavnani SM, Forrest A, Hammel JP, Drusano GL, Rubino CM, Ambrose PG. *Diagnos. Microbio Infect Dis.* 2008;62:99-101.

Efficacy of Fluoroquinones against *S. pneumonia* in Animals and Humans

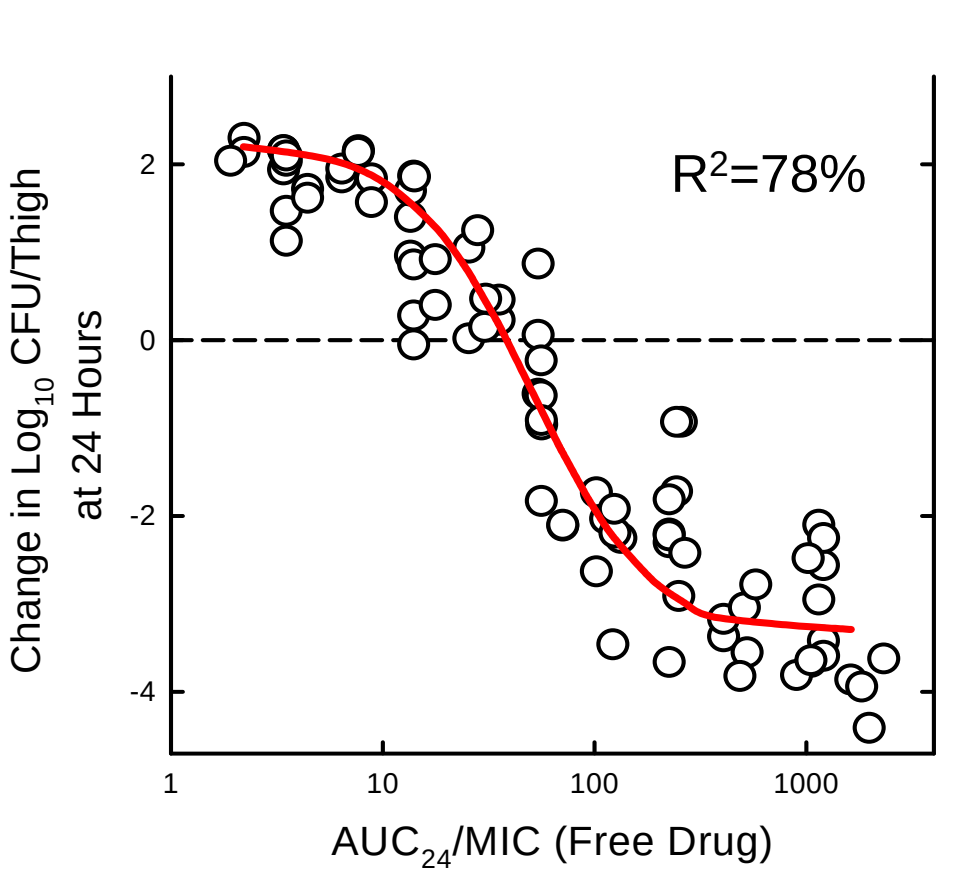
Source	Parameter	Free Drug AUC_{24}/MIC
Animal Non-neutro-penic	Stasis	12 ± 2
	50% Survival	18 ± 1
	1 Log Kill	19 ± 4
	2 Log Kill	31 ± 6
	90% Survival	35 ± 2
Human	90% Clinical Cure	34
	90% Microbiological Cure	29

Change in Free Drug AUC_{24}/MIC over 24 Hours for Multiple Fluoroquinolones in Neutropenic Mice



Craig & Andes – unpublished data

Survival in Animal Models Infected with Gram-Negative Bacilli Treated with Multiple Fluoroquinolones



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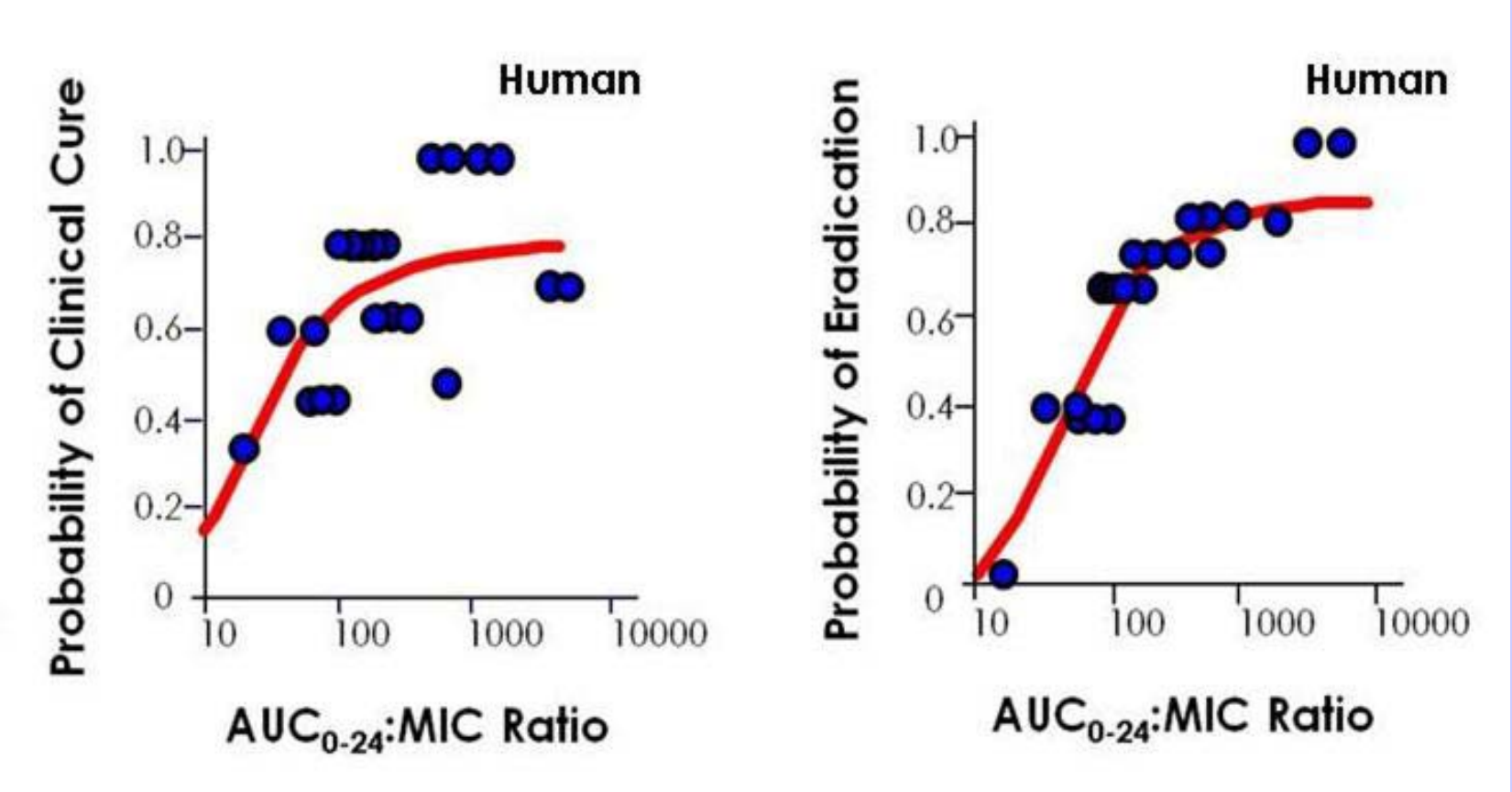
CIPROFLOXACIN

Hospital-Acquired Pneumonia

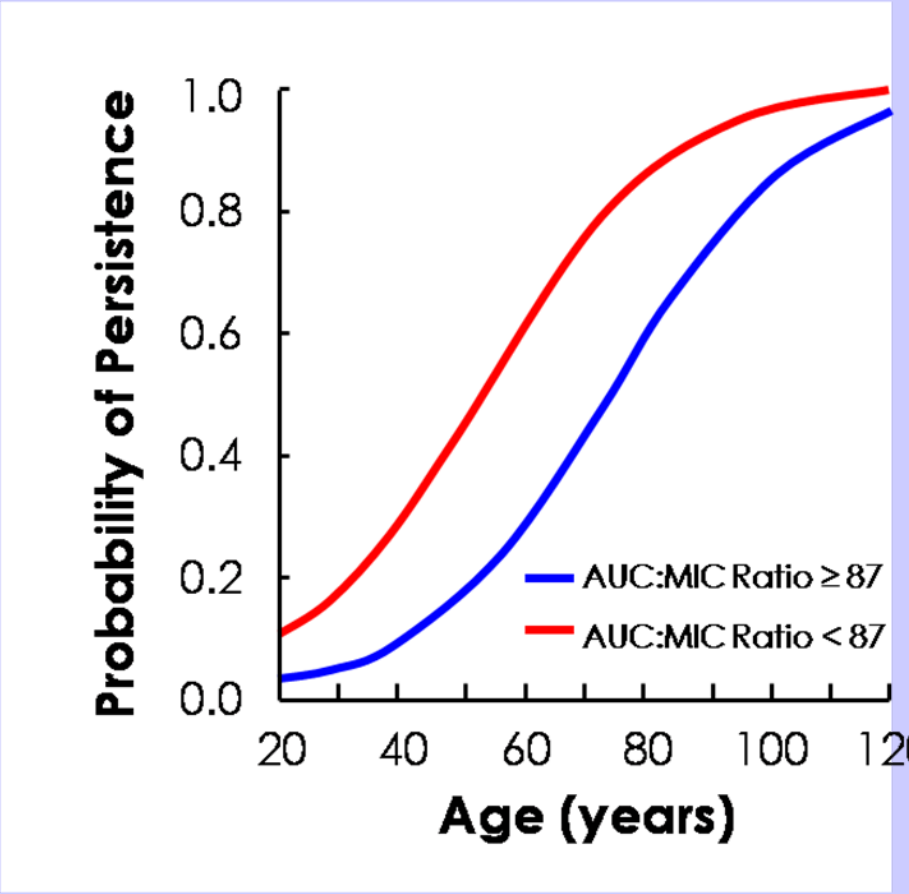


AUC_{24}/MIC >125 = 79-80% clinical and microbioloical cure

Forrest A, Nix SE, Ballow CH, Schentag, JJ. *Antimicrob Agents Chemother.* 1993. 37:1073–1081.

LEVOFLOXACIN

Hospital-Acquired Pneumonia



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

Efficacy of Fluoroquinones against *Enterobacteriaceae* in Animals and Humans

Source	Parameter	Free Drug AUC_{24}/MIC
Animal Non-neutro-penic	Stasis	39 ± 4
	50% Survival	41 ± 7
	1 Log Kill	62 ± 7
	2 Log Kill	105 ± 12
	90% Survival	105 ± 16
Human	80% Clinical Cure	125
	80% Microbiological Cure	87-125

Conclusions

- Animal and in vitro models have been very useful for determining the PK/PD target for efficacy (PK/PD indice and appropriate magnitude required for bacteriologic efficacy and survival)
- 2 Log kill values at 24 hours correlate well with 90% survival with longer treatment courses for most antimicrobials.
- 1 Log kill values in neutropenic animals simulate 2 log kill values in non-neutropenic animals for antimicrobials that have minimal enhancement with the presence of neutrophiles.