Pharmacodynamics: Integrating Concerns about Resistance and Efficacy in the Practical Care of Patients

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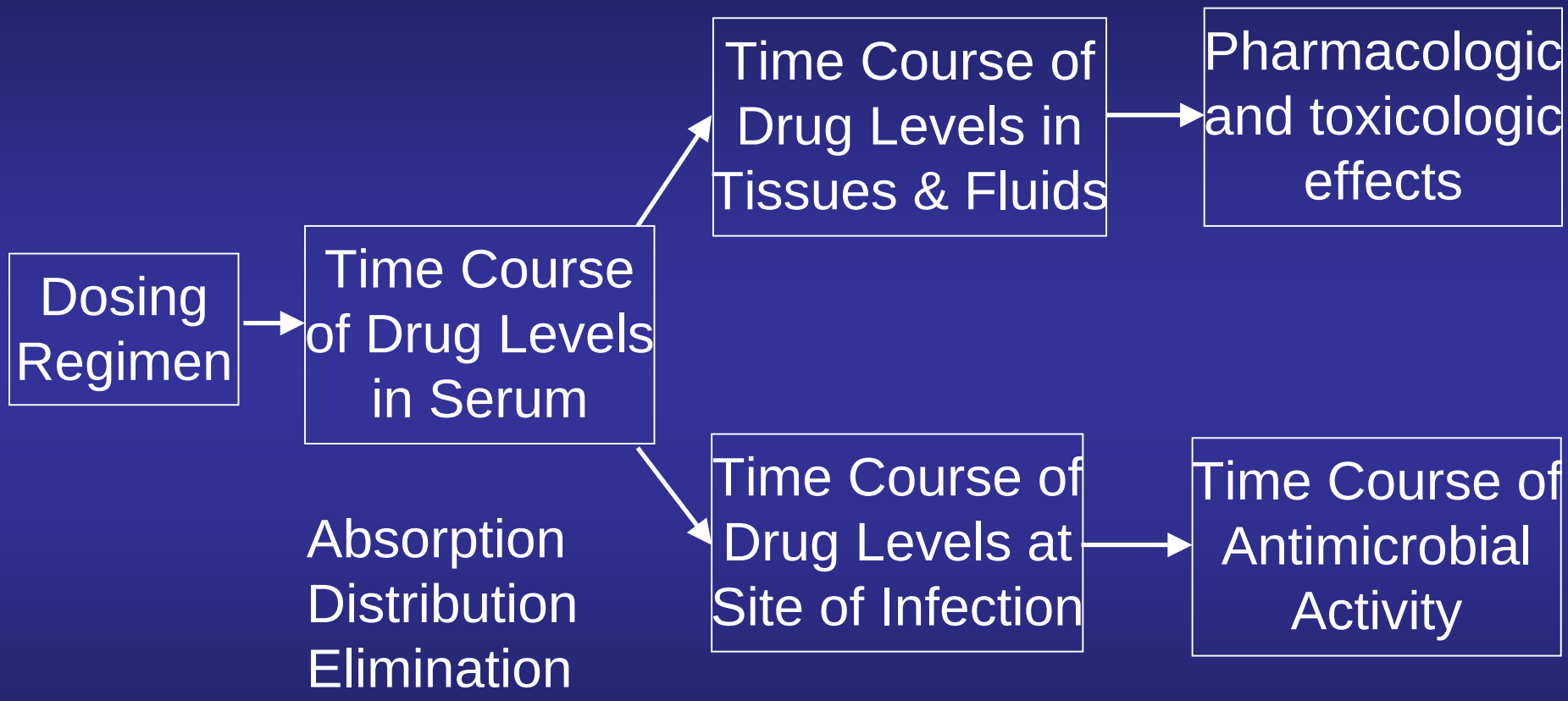
Pharmacology of Antimicrobials



Pharmacokinetics (PK) **Pharmacodynamics (PD)**

Measures of Antimicrobial Activity

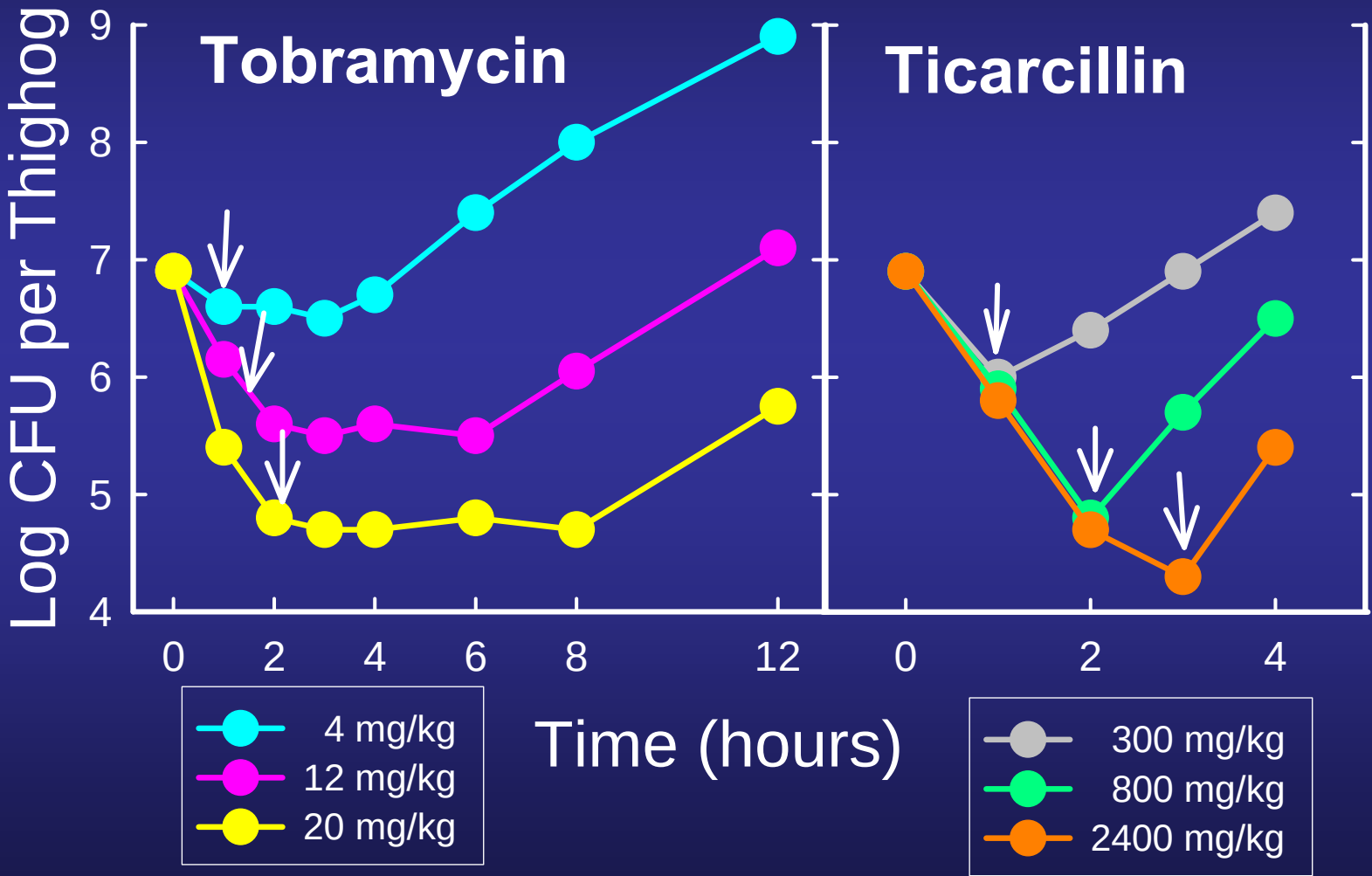
Potency

- MIC
- MBC

Time Course of Activity

- Rate of killing and impact of increasing concentrations (concentration-dependent versus time-dependent killing)
- Persistent effects (postantibiotic effect, postantibiotic sub-MIC effect, postantibiotic leukocyte effect, postantimicrobial effect)

Bactericidal Activity of Tobramycin and Ticarcillin against *Pseudomonas aeruginosa*



Vogelman et al. J Infect Dis 157, 1988

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 – amount of drug and peak level are important

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, glycylcyclines, 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

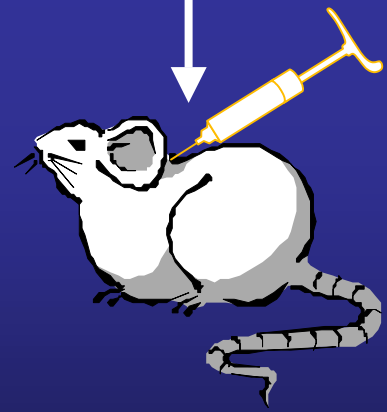
- identify which **PK/PD indice** (T>MIC, AUC/MIC, peak/MIC) best predicts in vivo antimicrobial activity

- determine the **magnitude** of the PK/PD parameter required for in vivo efficacy and to prevent resistance

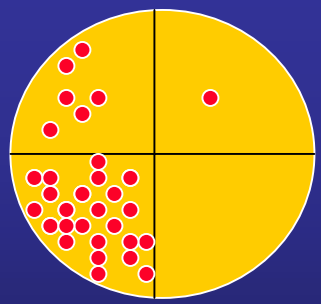
Neutropenic Mouse Thigh-Infection Model

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

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

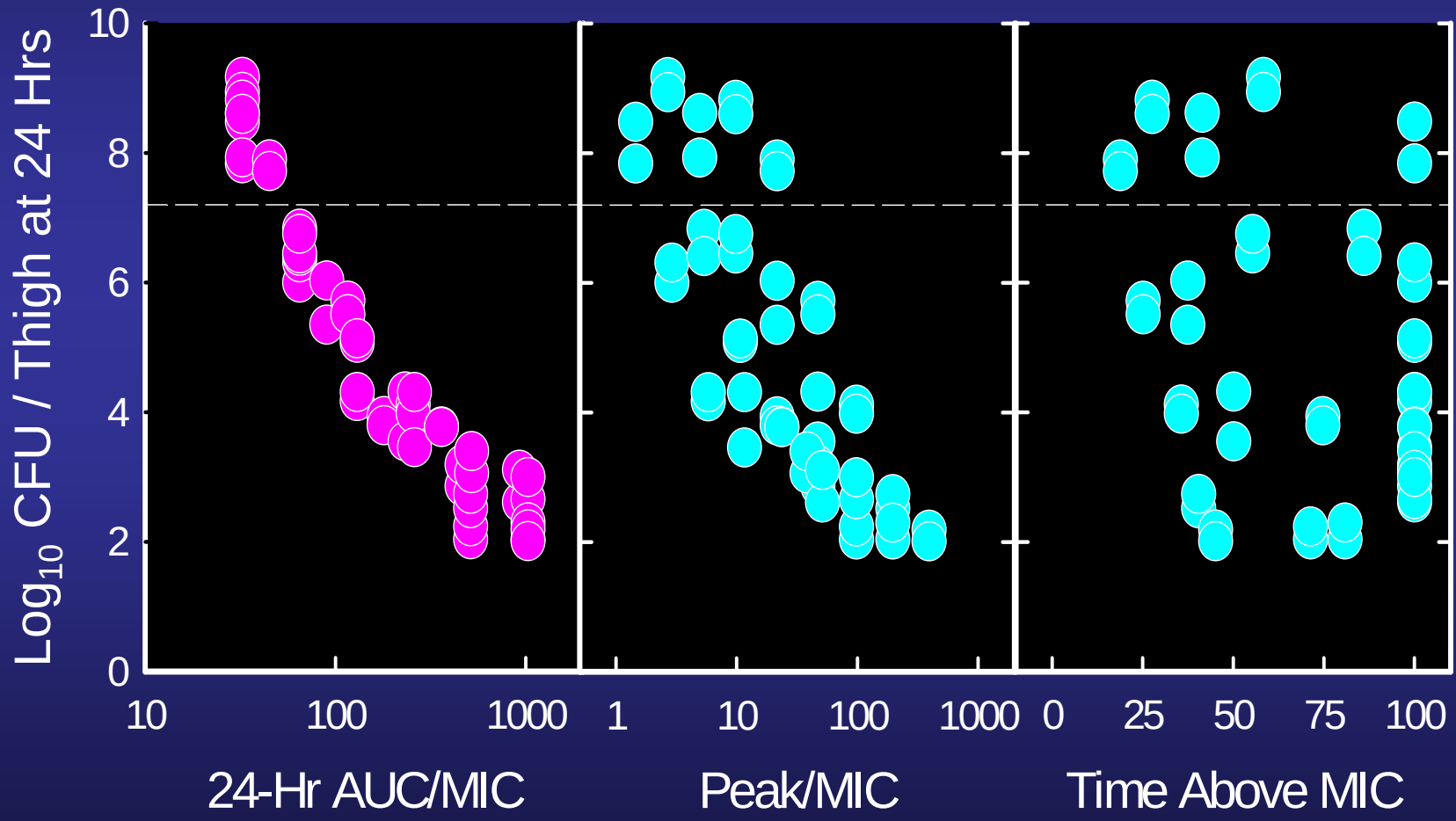


3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days



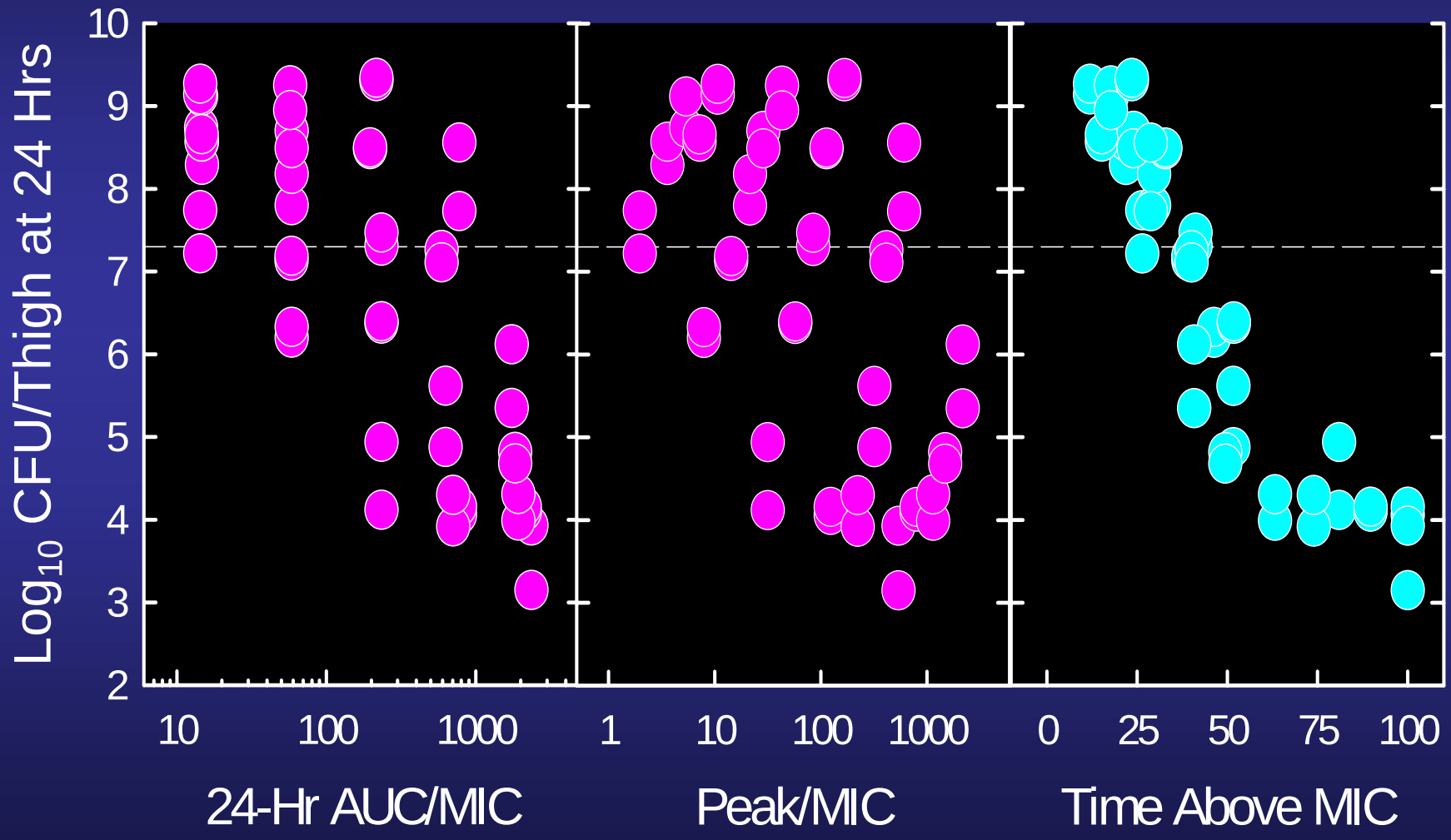
4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

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



Andes & Craig, Int J Antimicrob Agents, 2002

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

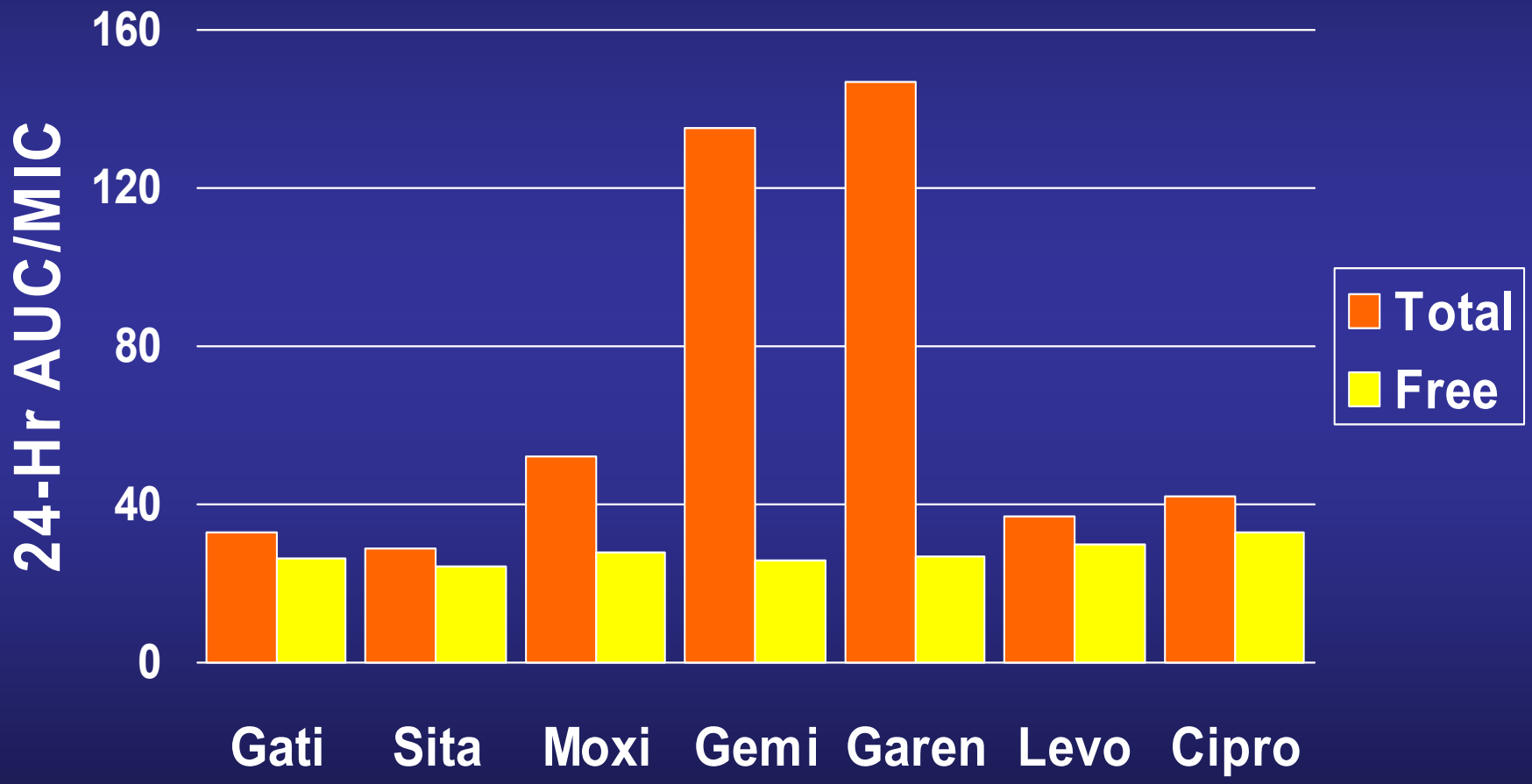


Craig Antimicrobial Pharmacodynamics in Theory and Practive 2002

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

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



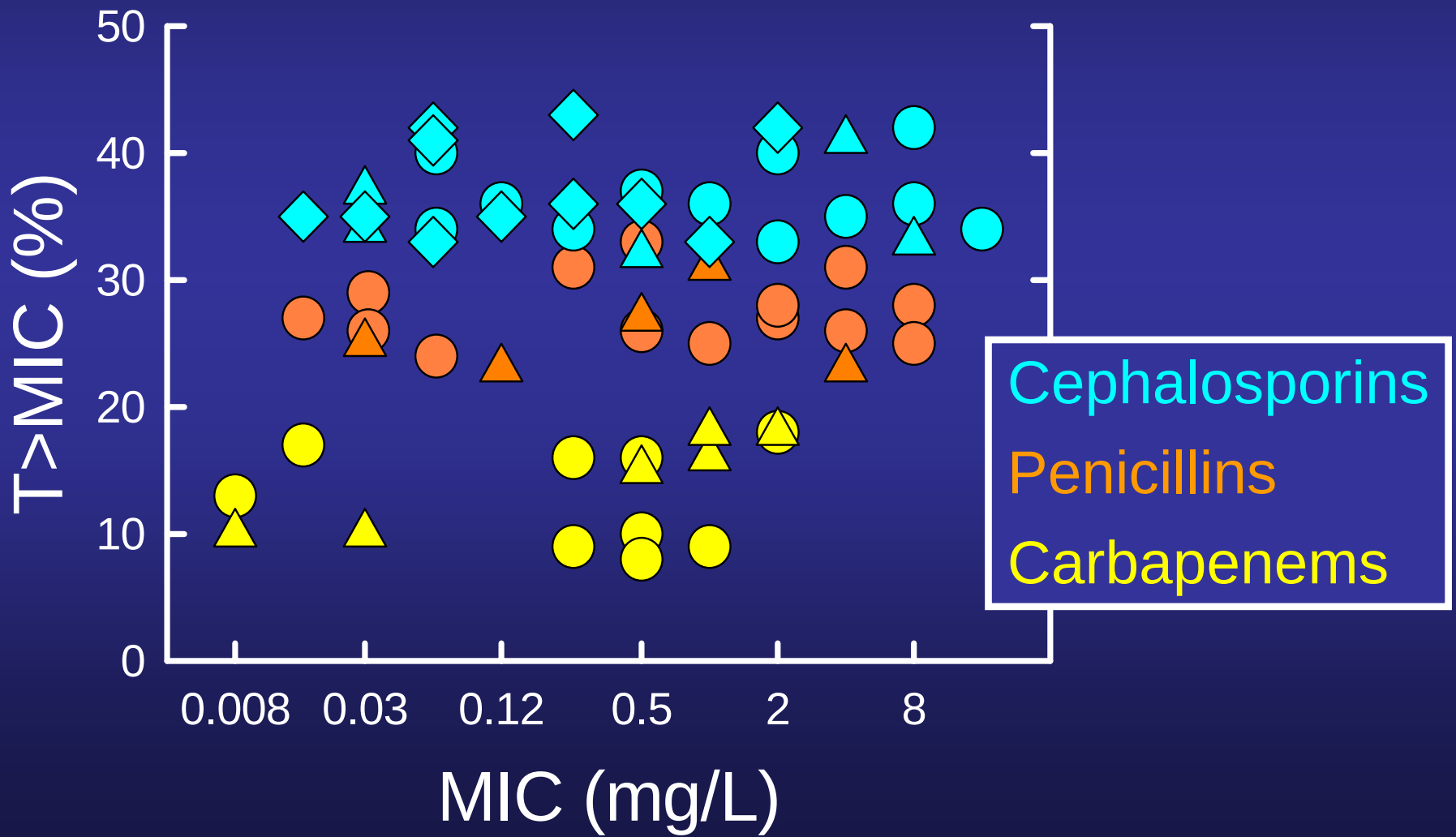
Andes & Craig 40th and 41st ICAAC, 2000 and 2001

Time Above MIC Required for a Static Effect with 4 Cephalosporins

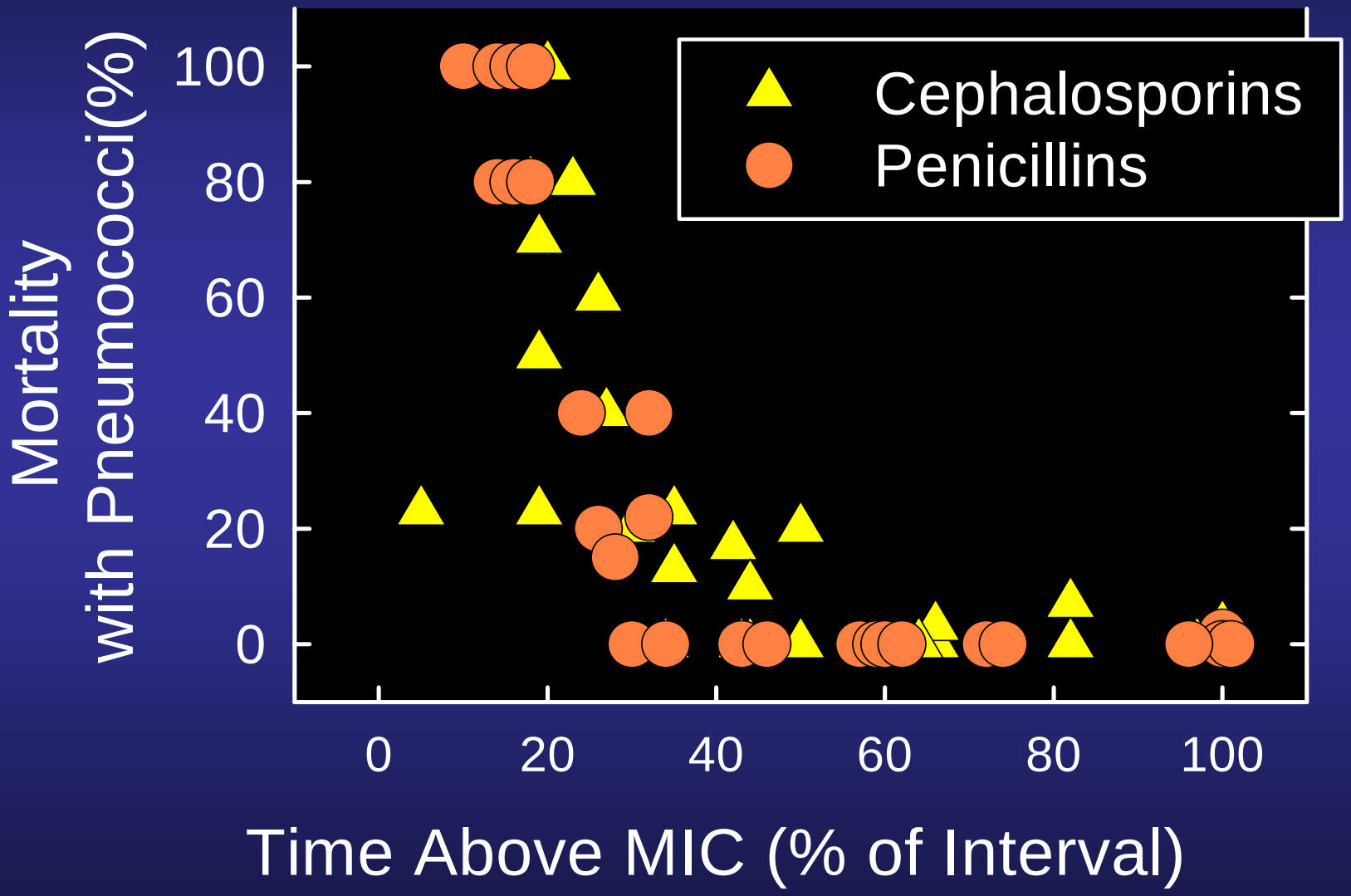
	Time Above MIC (% of Dosing Interval)		
Drug	GNB	S. pneumoniae	S.aureus
Ceftazidime	36 (27-42)	39 (35-42)	22 (19-24)
Cefpirome	35 (29-40)	37 (33-39)	22 (20-25)
Cefotaxime	38 (36-40)	38 (36-40)	24 (20-28)
Ceftriaxone	38 (34-42)	39 (37-41)	24 (21-27)

Craig Diagn Microbiol Infect Dis 22:89, 1995

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



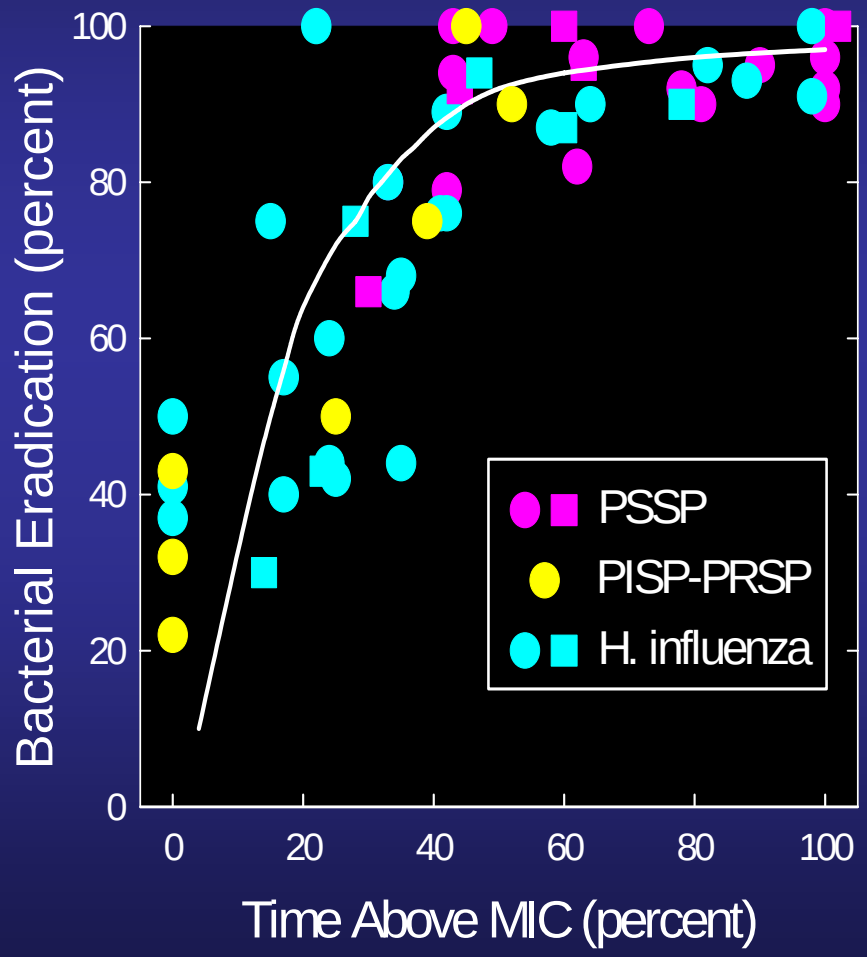
T>MIC for ß-Lactams Versus Mortality in Animal Models: Literature Review



Craig Antimicrobial Pharmacodynamics in Theory and Practive 2002

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

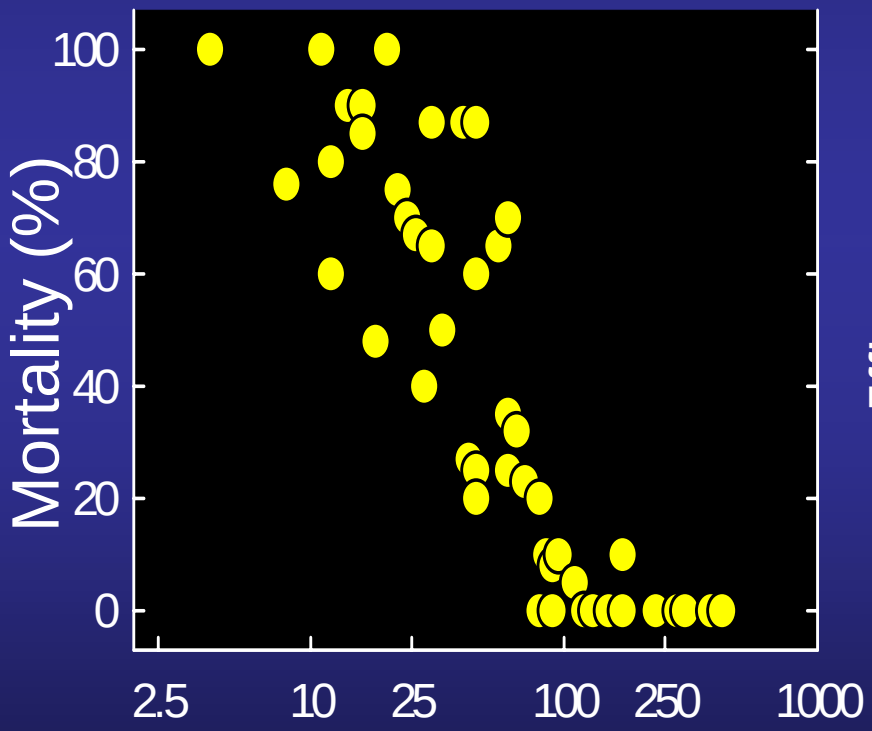
- Bacteriologic cure for beta-lactams with *S. pneumoniae* and *H. influenzae* from double-tap studies in acute otitis media and acute maxillary sinusitis
- Time above MIC calculated from serum levels and MICs



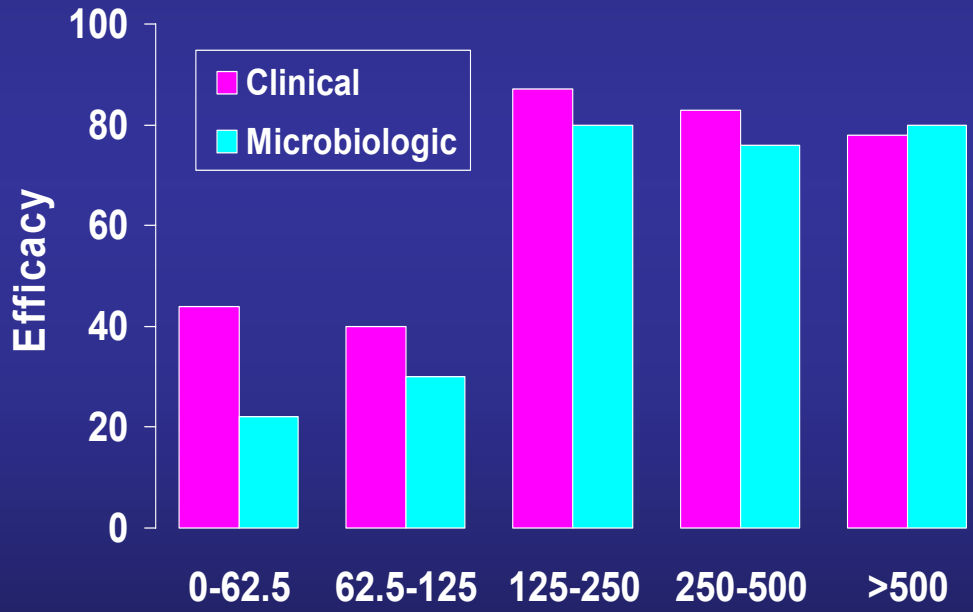
Craig & Andes, Pediatr Infect Dis J 15:255, 1996; Dagan et al JAC 47:129, 2001; Dagan et al Pediatr Infect Dis J 20:829, 2001

Comparison of the Relationships Between Efficacy and 24-Hr AUC/MIC for Fluoroquinolones in Animal Models and Infected Patients

Animals - Literature Review



Seriously ill patients
+ Ciprofloxacin

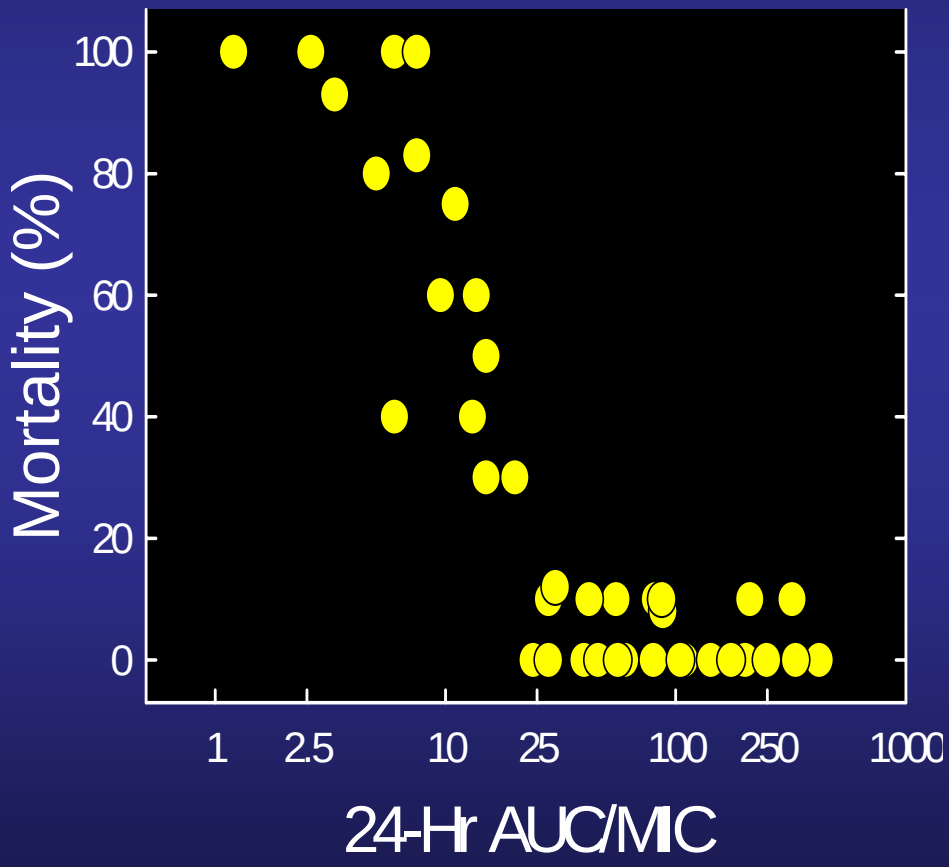


Andes, Craig Int J Antimicrob Agents, 2002

Forrest et al. AAC 37:1073, 1993

Comparison of the Relationships Between 24-Hr AUC/MIC and Efficacy against Pneumococci for Fluoroquinolones in Animals and Patients

Animals - Literature Review



Patients with CAP and AECB

- 58 patients enrolled in a comparative trial of levofloxacin vs gatifloxacin
- Free-drug 24-hr AUC/MIC **<33.7**, the probability of a microbiologic cure was **64%**
- Free-drug 24-hr AUC/MIC **>33.7**, the probability of a microbiologic cure was **100%**

Andes, Craig Int J Antimicrob Agents, 2002 Ambrose et al AAC 45:2793, 2001

Uses of Pharmacodynamic Studies

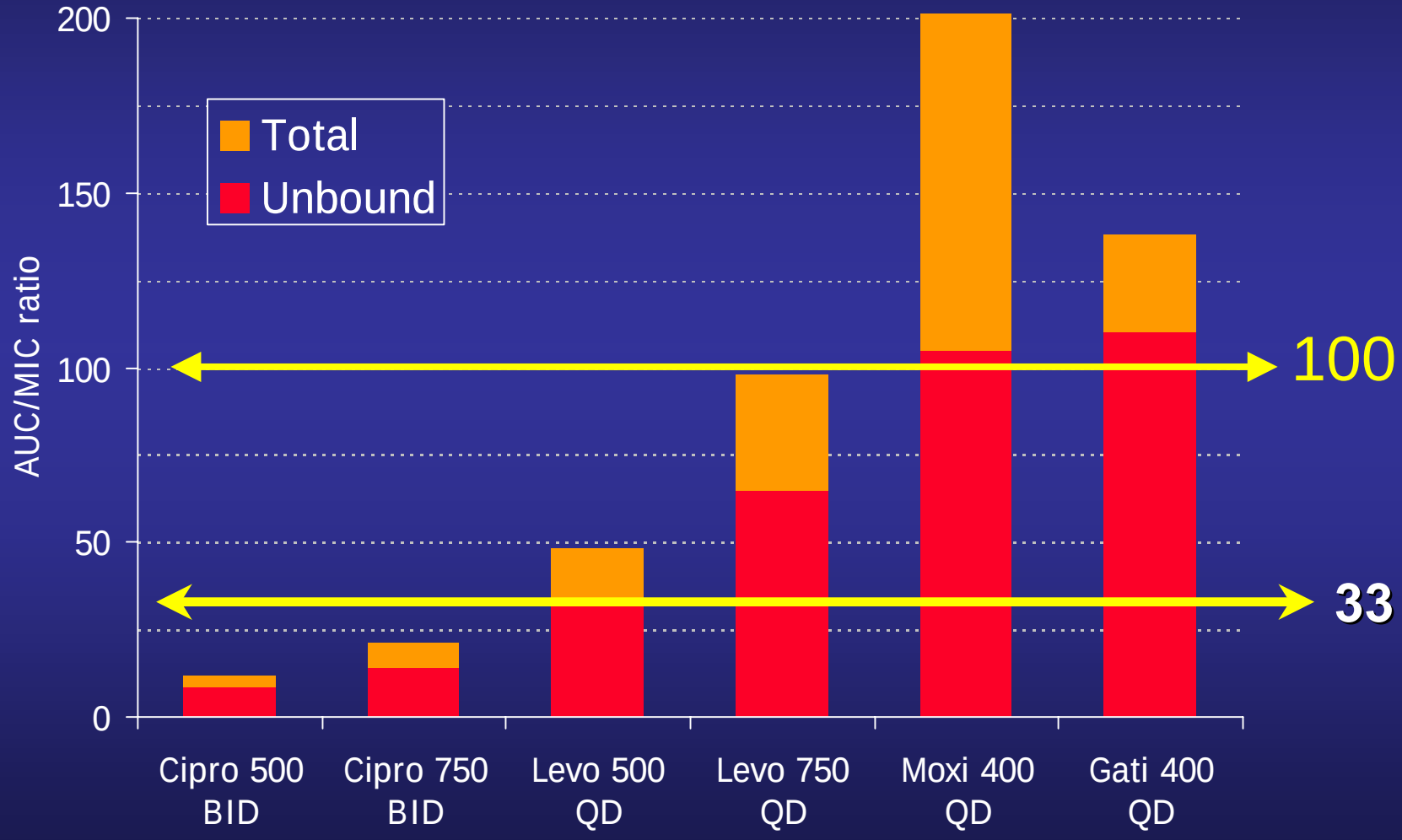
- Drug development
  - new formulations active against organisms with high MICS (e.g. high dose amoxicillin/clavunate)
  - dosage regimens for phase II and III clinical trials
  - drug selection for clinical studies

- 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
- Modifications of susceptibility and resistance breakpoints
  - parenteral cephalosporins for *S. pneumoniae*
  - fluoroquinolones for *S. aureus*
- Identify problem drug-organism combinations with specific MICs

Fluoroquinolone AUC/MIC$_{90}$ Ratios for *S. pneumoniae*



Jacobs MR. *Clin Microbiol Infect* . 2001;7:589-596.

PK/PD Parameters versus Emergence of Resistance for Fluoroquinolones

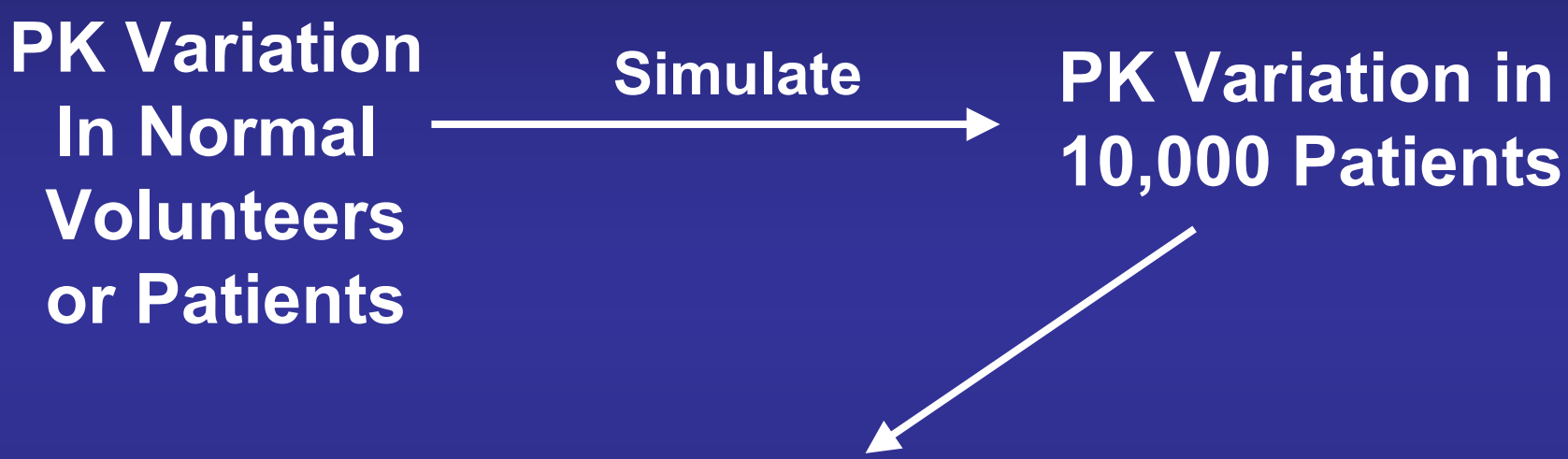
	Resistance Developed	
24-Hr AUC/MIC	*P. aeruginosa*	Other GNB
<100 - Monotherapy	80%	100%
>100 – Monotherapy	33%	10%
Combinations	11%	0%
	25%	12%

Thomas et al. AAC 42:521, 1998

Magnitude of PK/PD Parameters for Common Drugs Used Against Pseudomonas aeruginosa

Drug	Dose	MICs	Peak/MIC	AUC/MIC
Ciprofloxacin	400mg q8	0.25-1	20/4	144/36
Levofloxacin	750mg q24	0.5-4	12/3	125/31
Tobramycin	7 mg/kg q24	1-4	24/6	84/21

Monte Carlo Simulation



Drusano et al

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

	T>MIC with 1g every 8 hr				
MIC	**30%**	**40%**	**50%**	**60%**	**70%**
0.5	100	99	97	89	73
1	99	98	89	71	49
2	98	91	67	41	22
4	92	62	29	11	4
8	58	15	3	0	0
16	12	0	0	0	0

Ambrose & Dudley, ICAAC 2002

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

Outcome	MIC ≤1 µg/L	MIC 2 µg/L	MIC 4 µg/L	MIC 8 µg/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

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

	T>MIC of 40% with doses of:	
MIC	0.5g q8 (1h inf)	0.5g q8 (3h inf)
0.5	95	100
1	90	100
2	65	99
4	32	80
8	4	14
16	0	1

Lomaestro & Drusano AAC 2004

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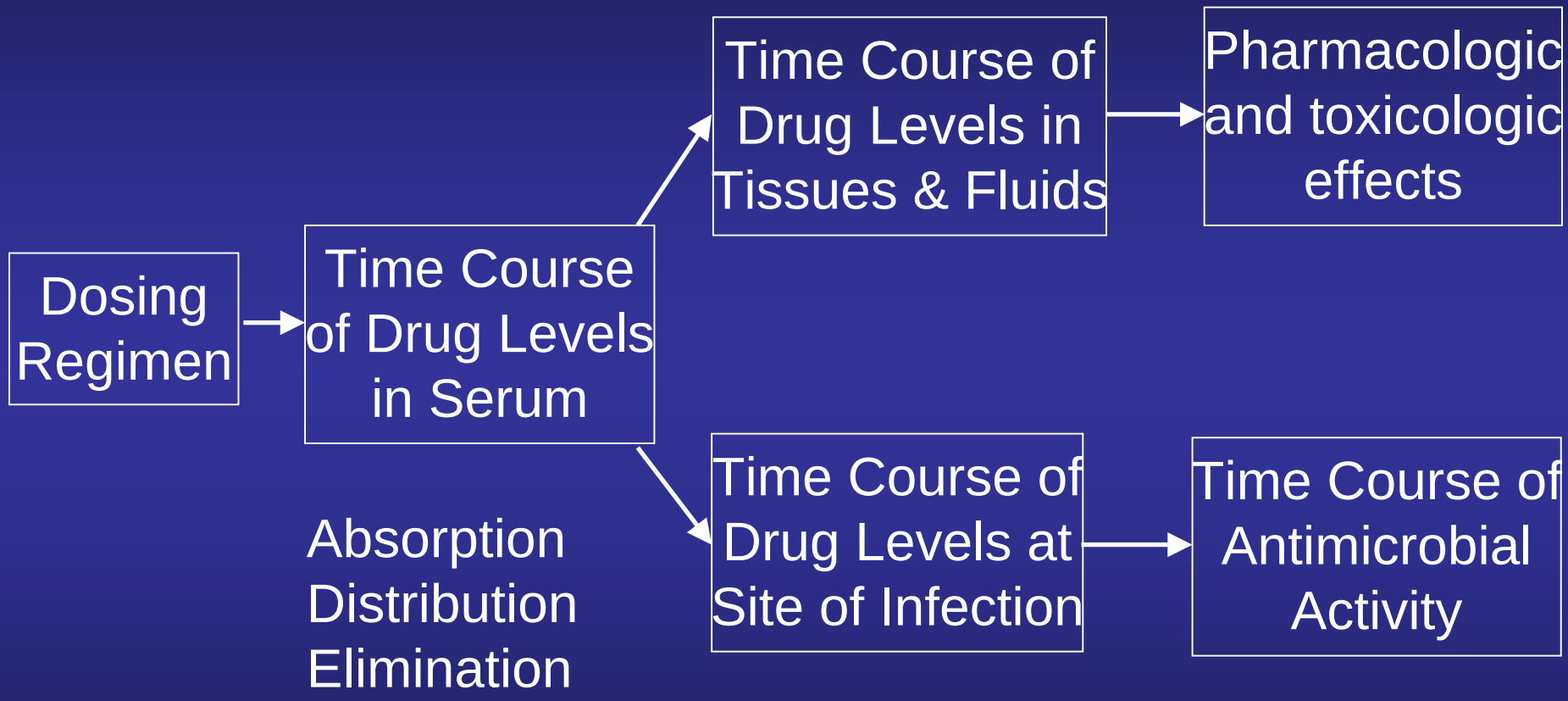

Pharmacokinetics (PK) **Pharmacodynamics (PD)**