Pharmacodynamics of MASKO Compounds (Macrolides, Azalides, Streptogramins, Ketolides, and Oxazolidinones)

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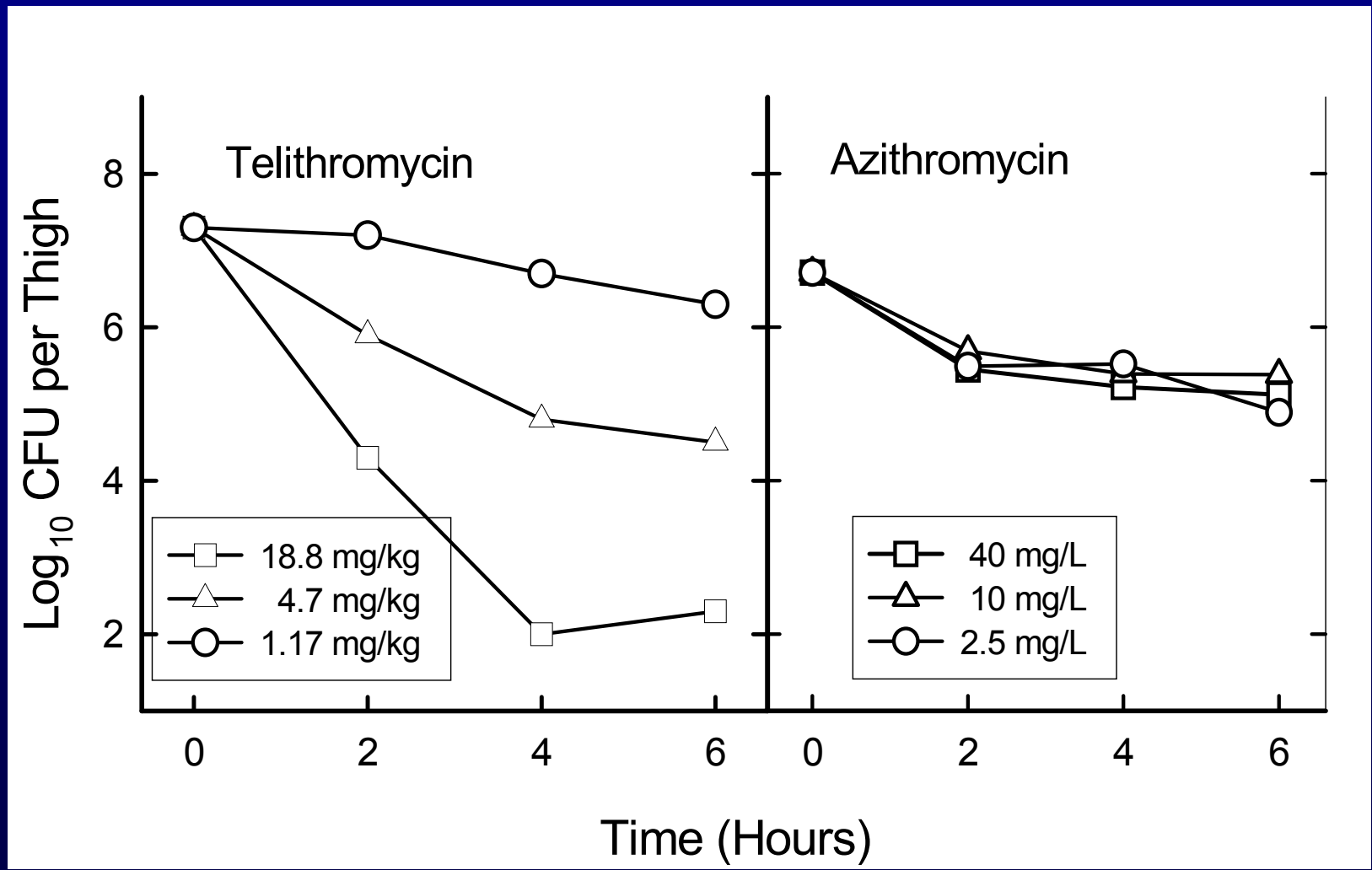
Pharmacodynamics

- Pattern of killing
- PAEs, PA-SMEs, and PALEs
- PK/PD parameters determining efficacy (dose fractionation studies)
- Magnitude of PK/PD targets (importance of protein binding)
- Comparison of different sites of infection
- Effect of neutrophils

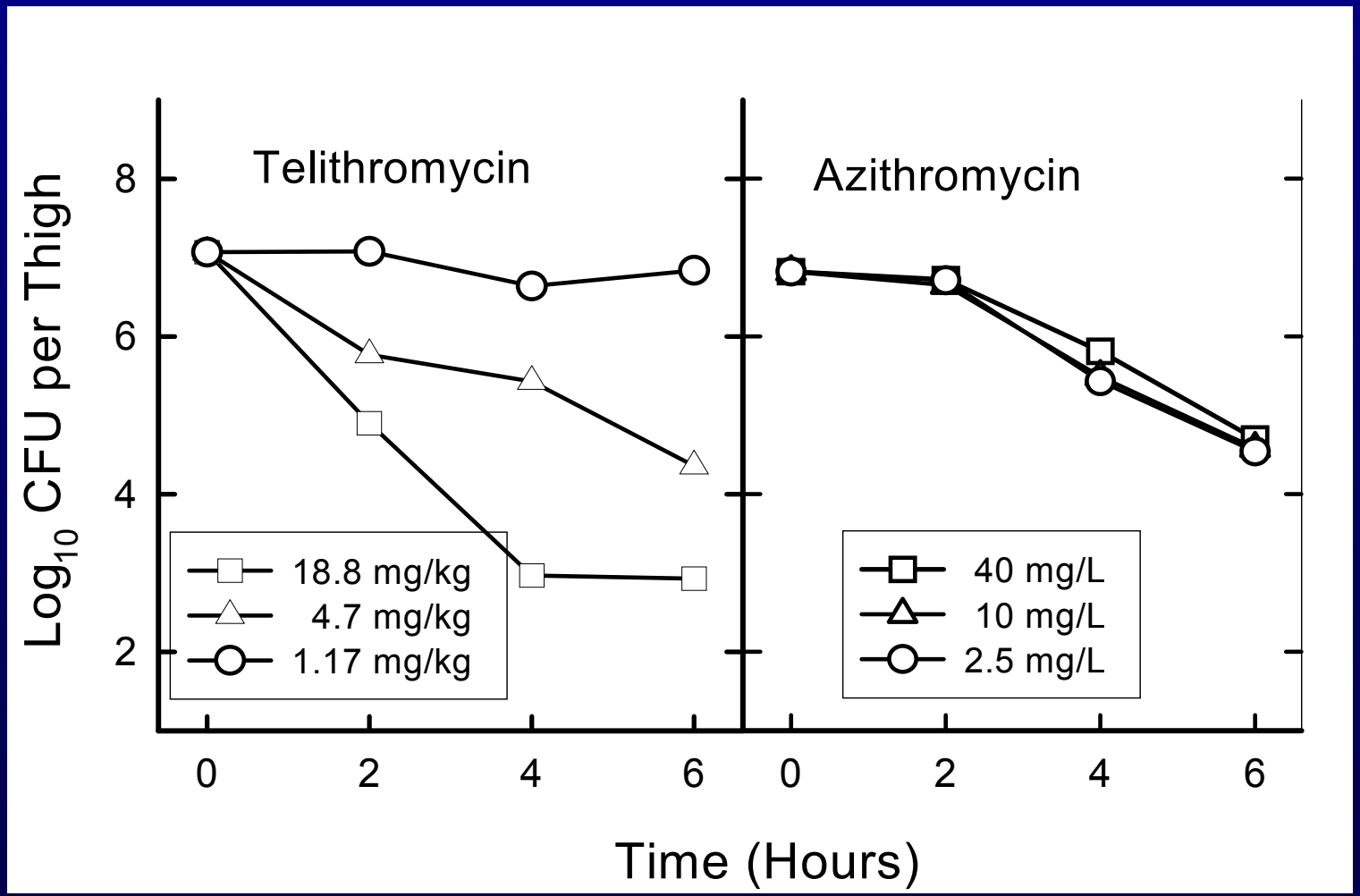
Pattern of Bacterial Killing

- Except for the ketolides, the MASKO compounds show very little concentration-dependent killing both in vitro and in vivo in neutropenic animals
- Killing with concentration-independent drugs is always maximal when levels are above 1-4 times the MIC for 100% of the dosing interval
- In animals with neutrophils, there is a tendency for more concentration-dependent killing

Impact of Increasing Doses on Killing of *Streptococcus pneumoniae* ATCC 10813



Impact of Increasing Doses on Killing of *Streptococcus pneumoniae* CDC 140



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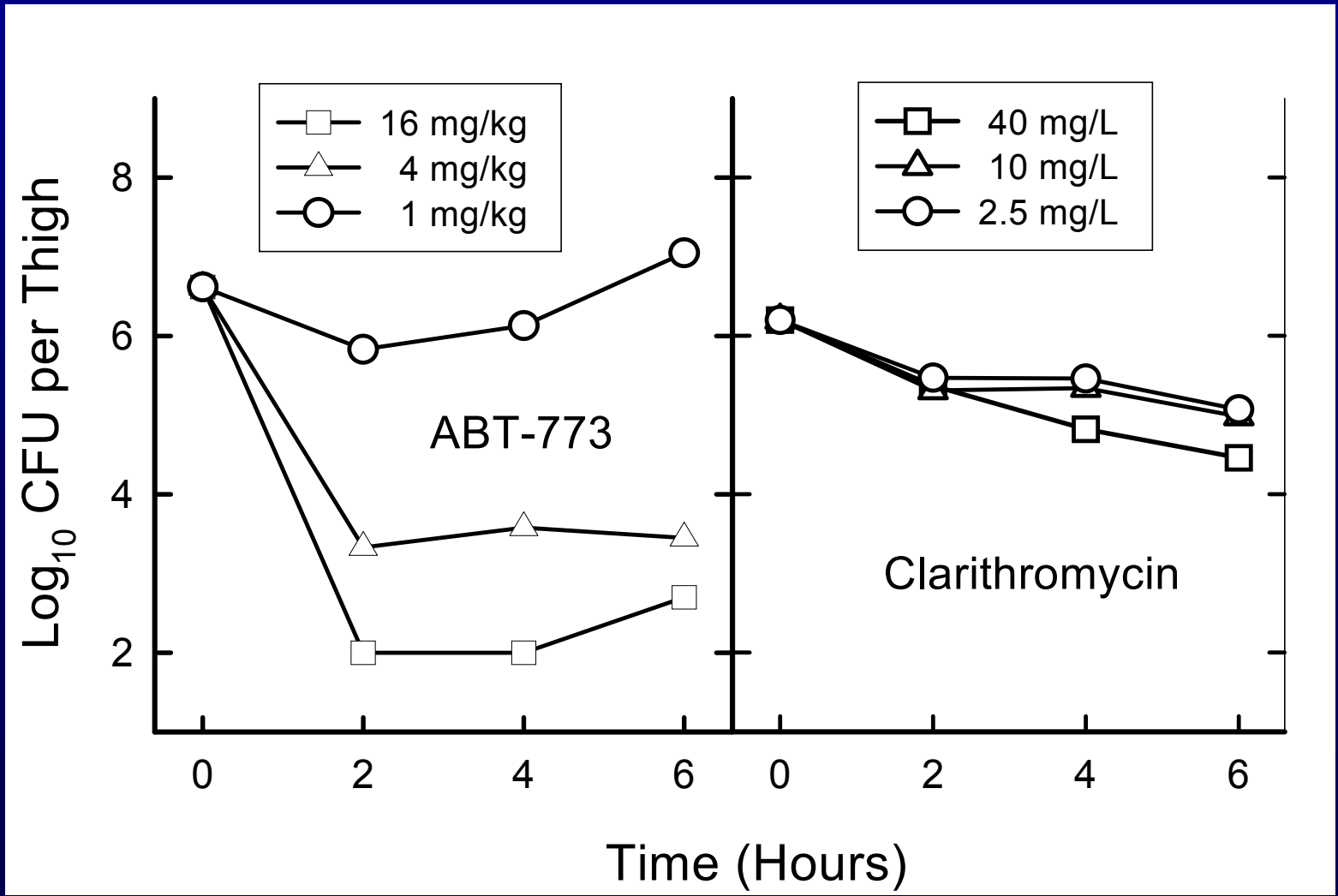
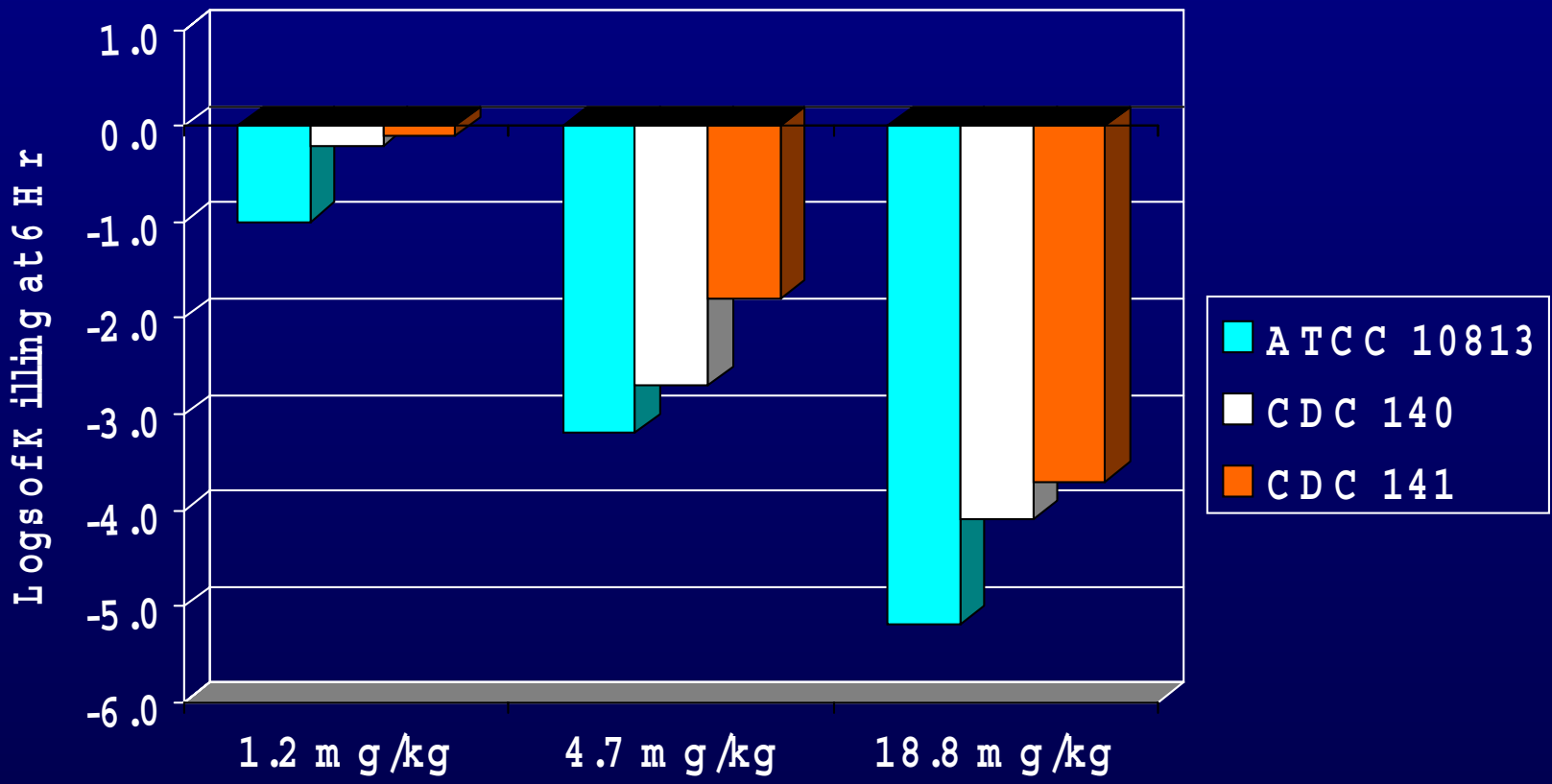
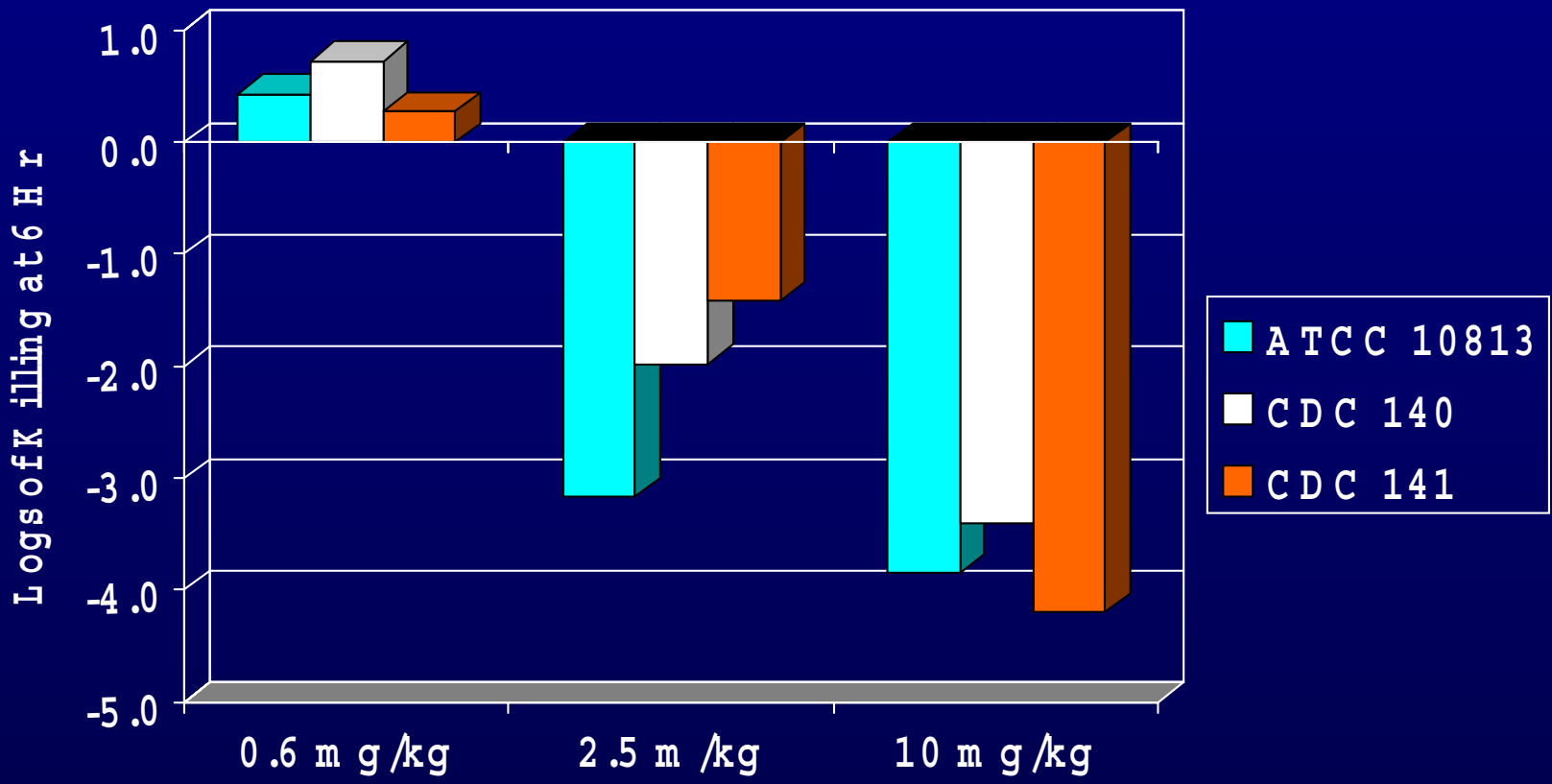


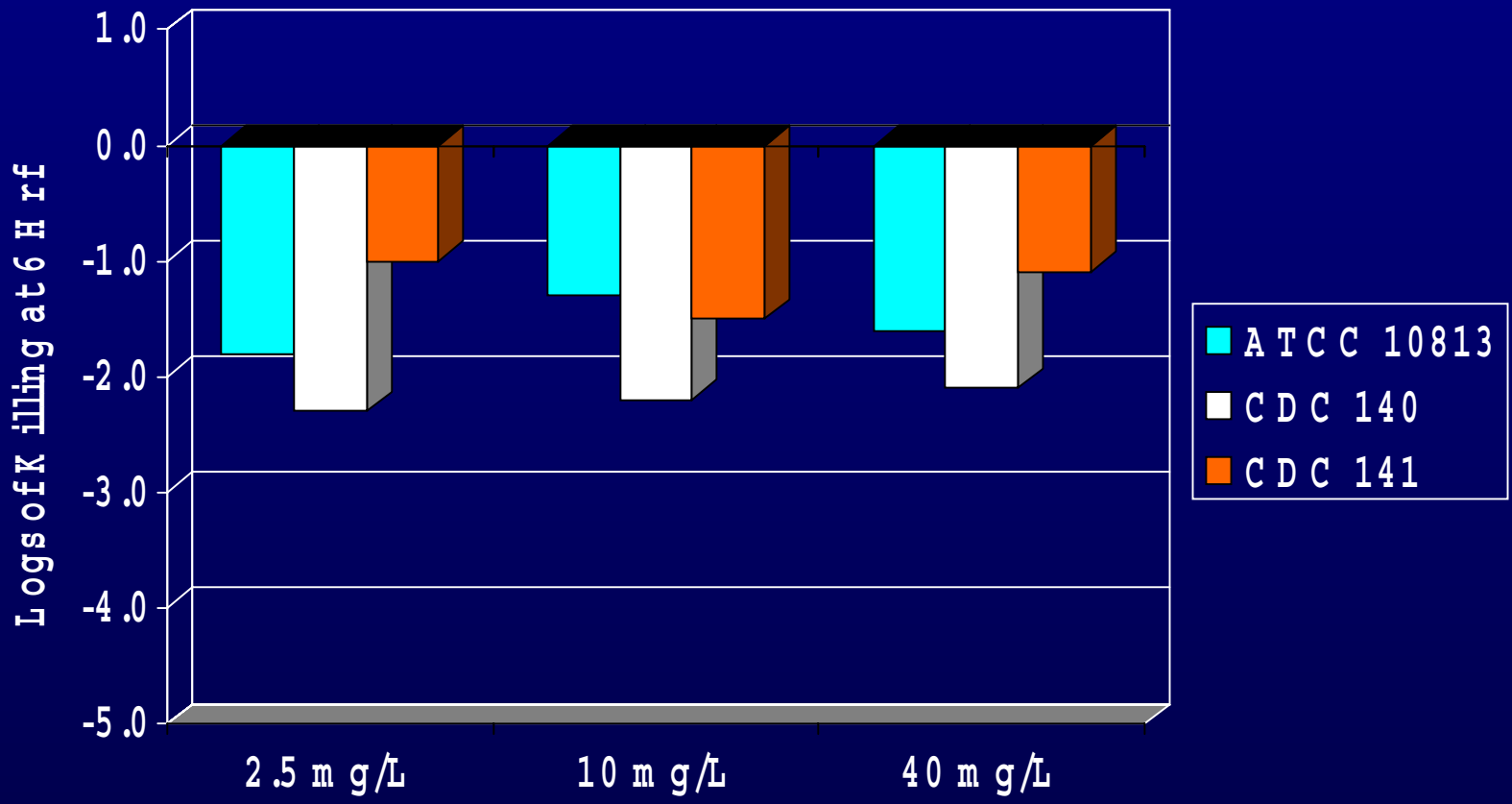
Impact of Increasing Doses of Telithromycin on Killing of *Streptococcus pneumoniae* in Thighs of Neutropenic Mice



Impact of Increasing Doses of ABT 773 on Killing of *Streptococcus pneumoniae* in Thighs of Neutropenic Mice



Impact of Increasing Doses of Azithromycin on Killing of *Streptococcus pneumoniae* in Thighs of Neutropenic Mice



Persistent Effects

MASKO compound produce moderate to prolonged persistent effects wiith various bacteris both in vitro and in vivo

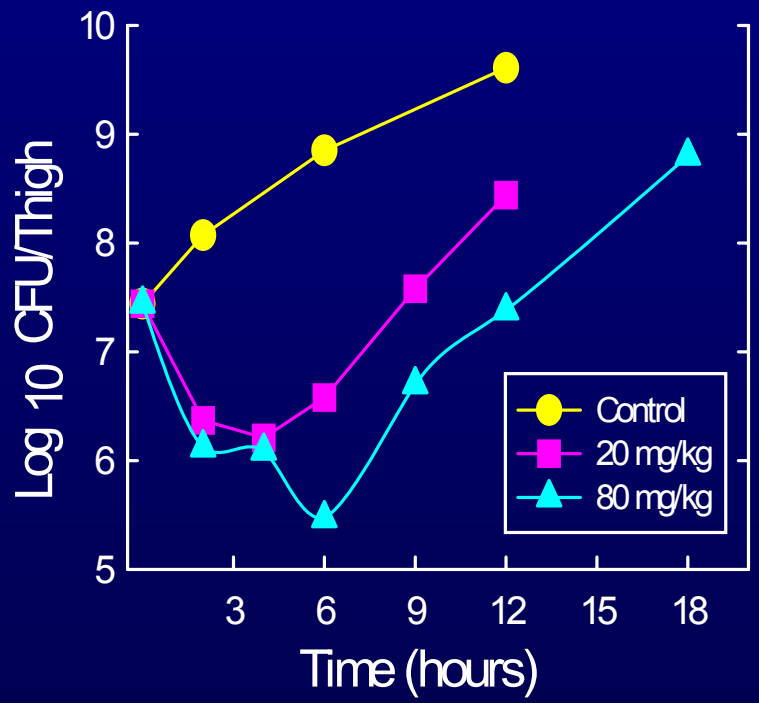
- moderate to prolonged in-vitro PAEs
- moderate to prolonged PA-SMEs
- moderate PALEs
- moderate to prolonged in vivo PAEs (prolonged even longer by the presence of neutrophils)

Pharmacodynamics of Linezolid

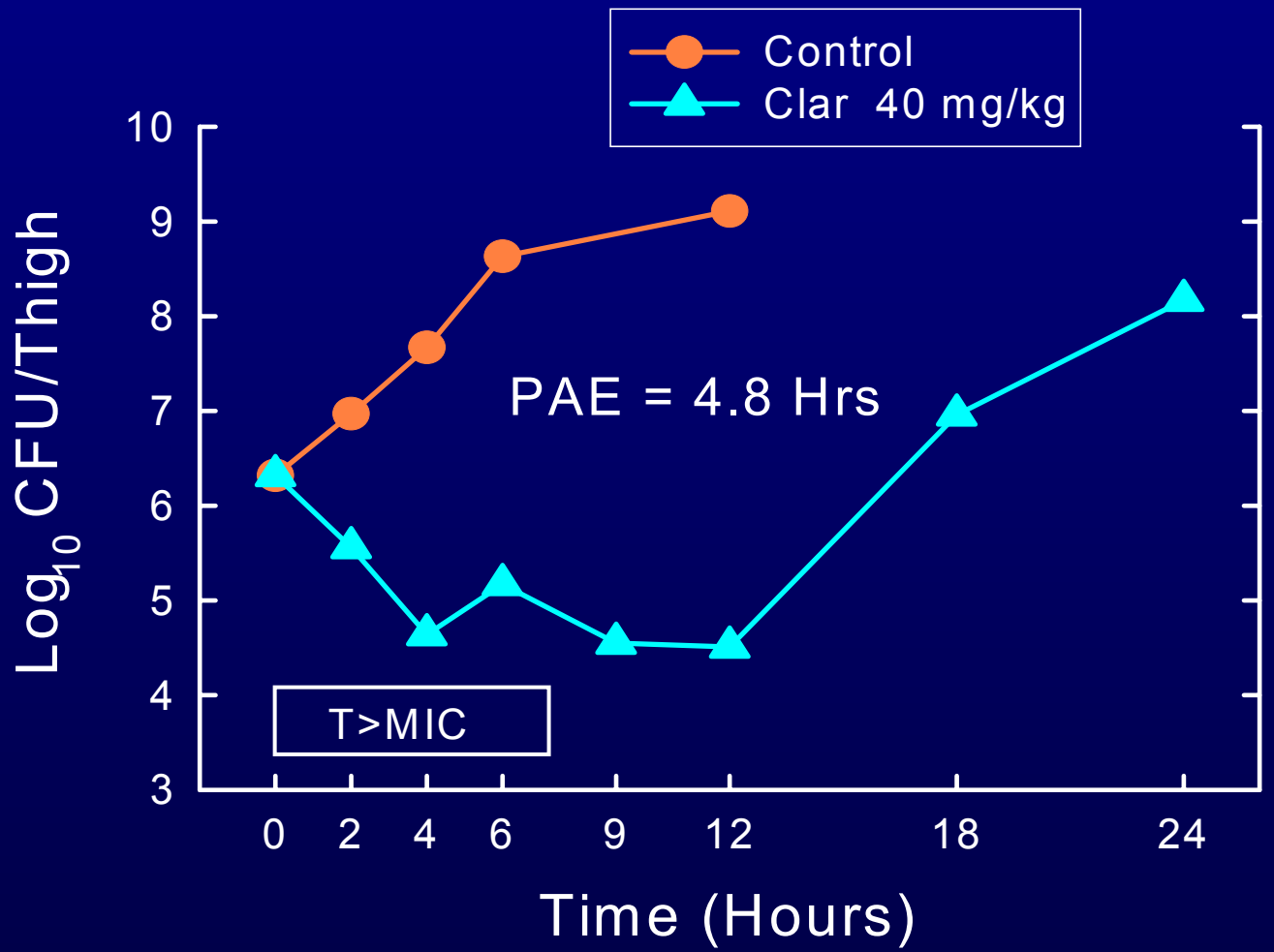
- **Time-Dependent Killing Pattern**
- **Modest In-Vivo PAEs 3.6-3.8 hrs with PSSP**

  3.7-3.9 hrs with MSSA

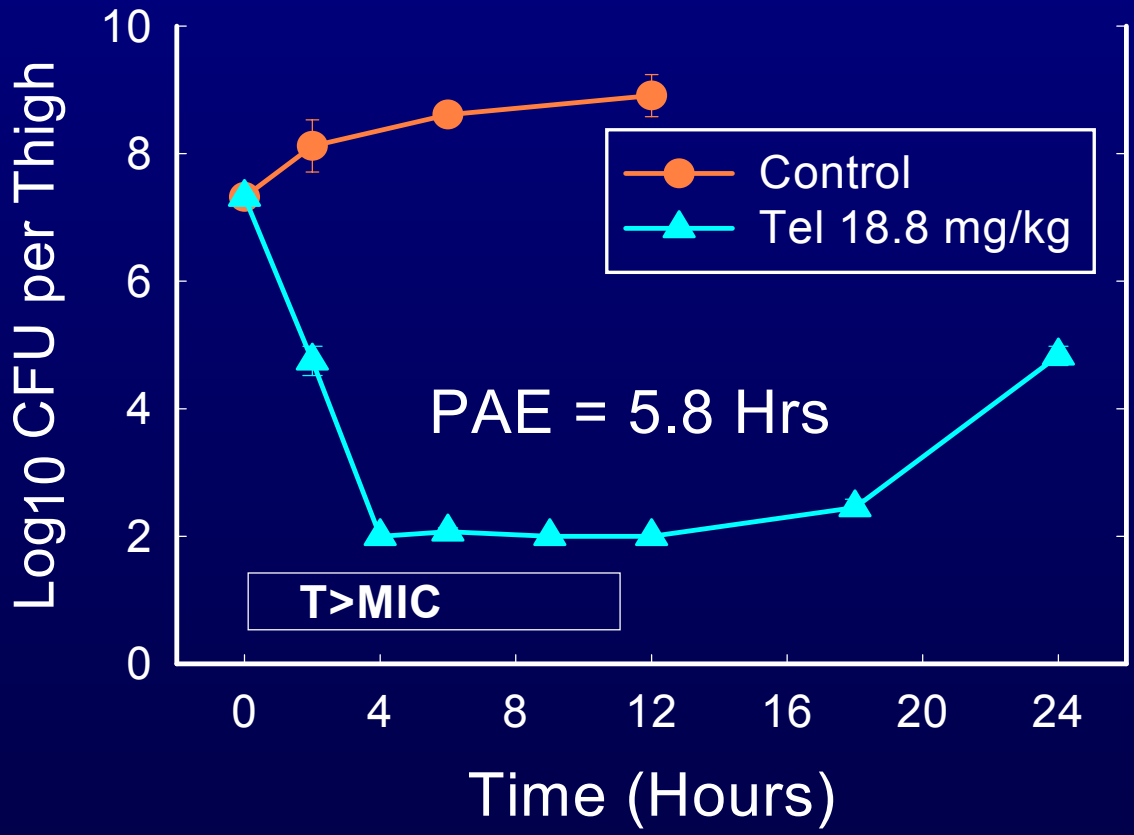
PAE Against S. pneumoniae



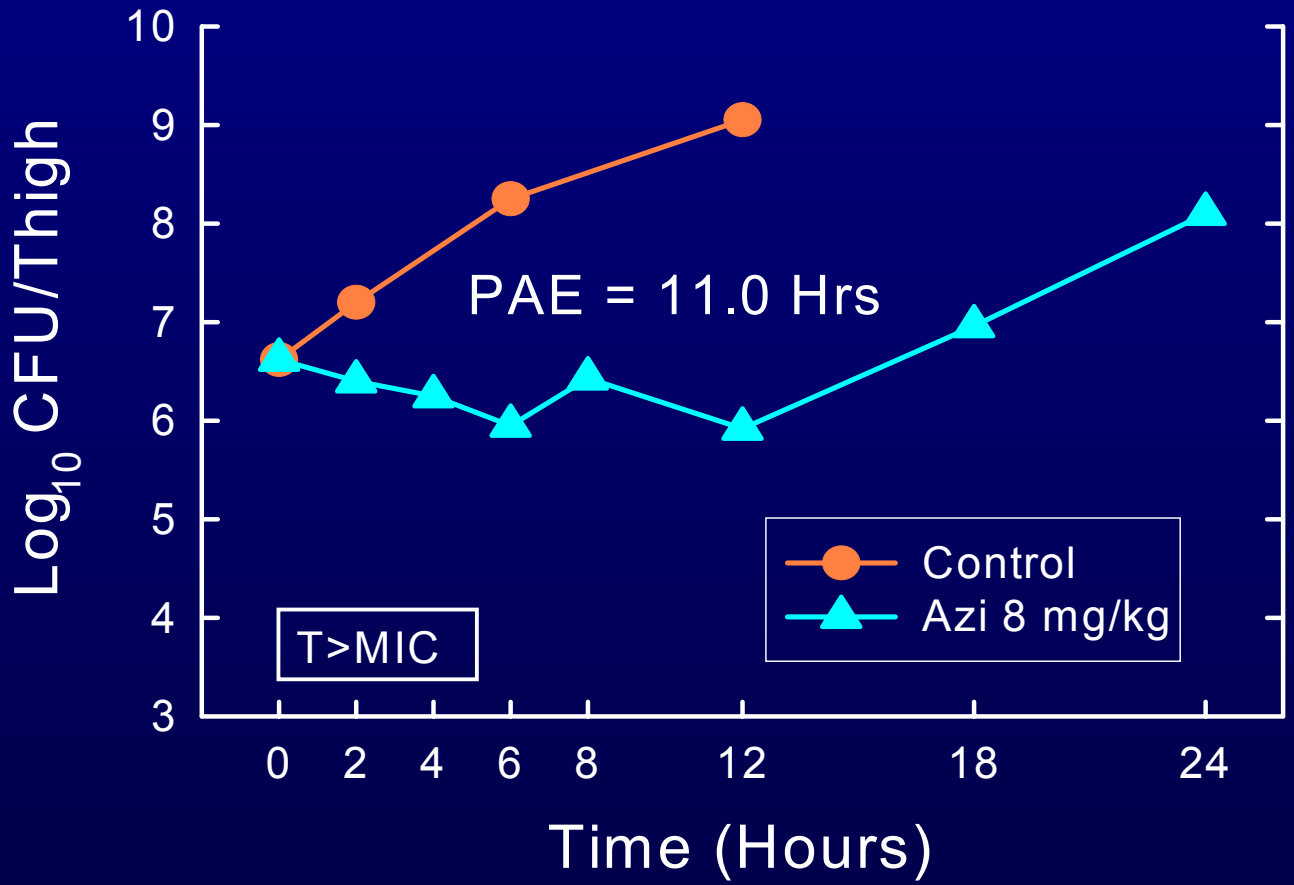
In Vivo PAE of Clarithromycin with *Streptococcus pneumoniae* ATCC 10813 in Thighs of Neutropenic Mice



In Vivo PAE of Telithromycin with *Streptococcus pneumoniae* ATCC 10813 in Thighs of Neutropenic Mice



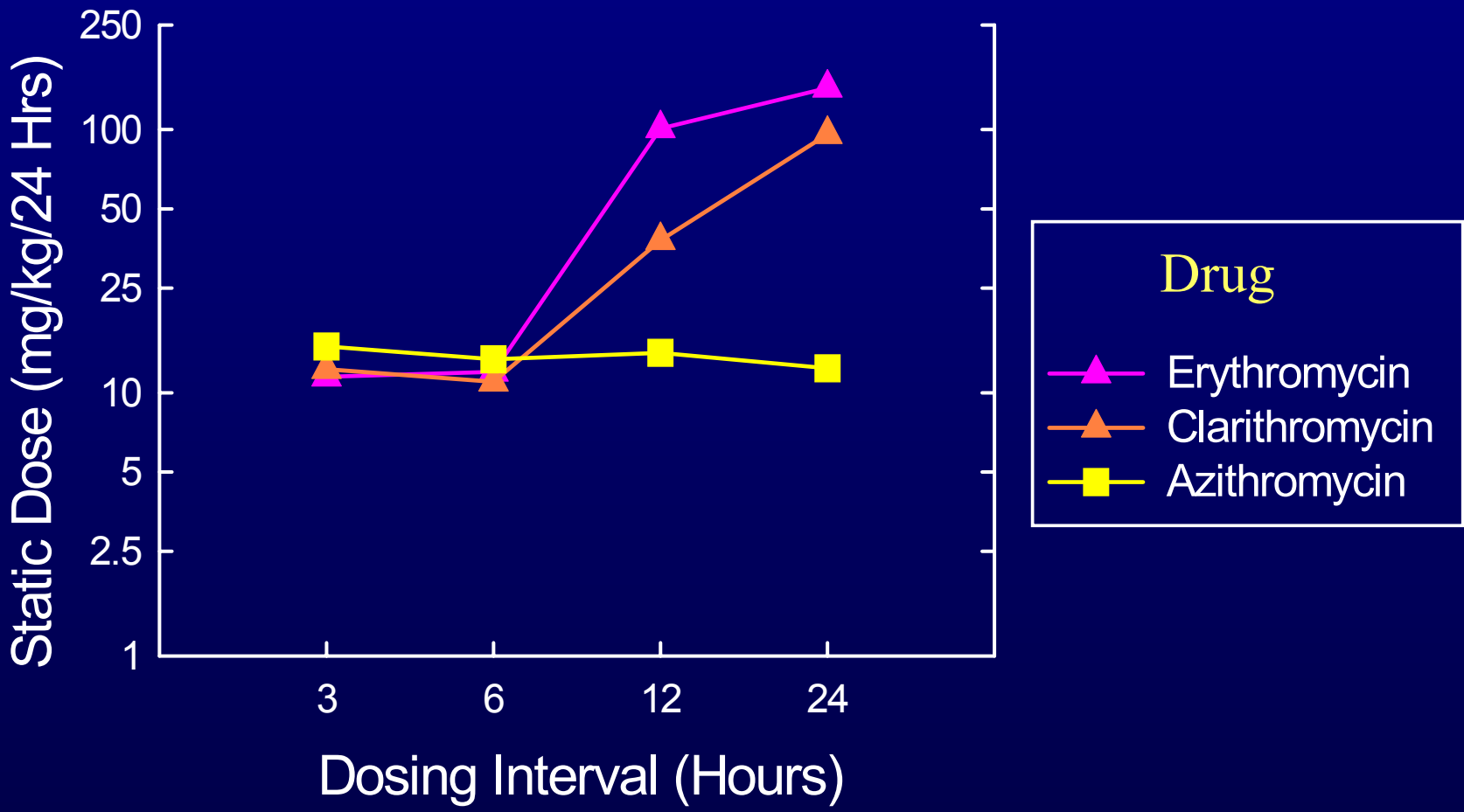
In Vivo PAE for Azithromycin with *Streptococcus pneumoniae* ATCC 10813 in Thighs of Neutropenic Mice



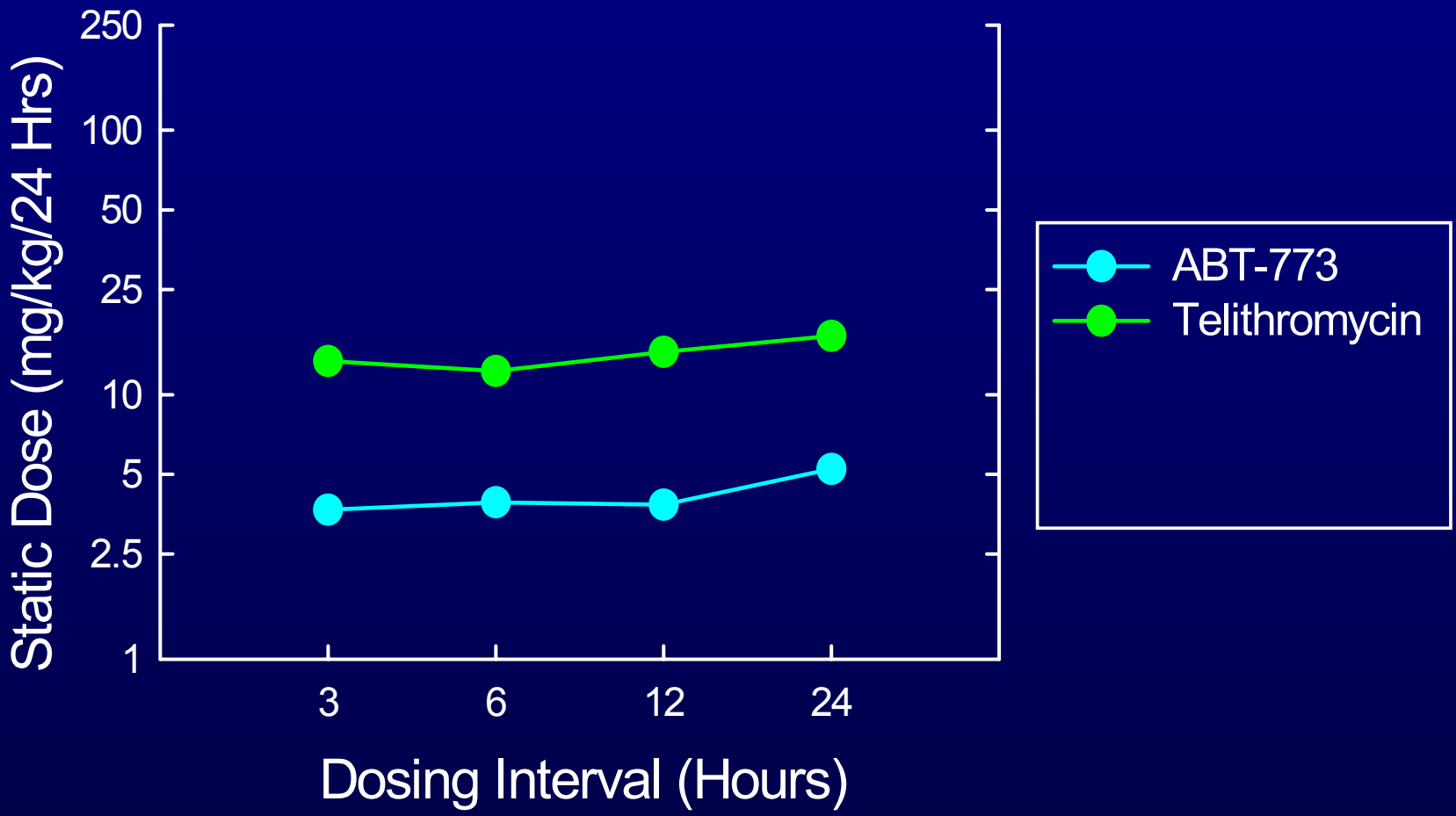
Pharmacodynamic Characterisitics

Drug	Killing Pattern	Persistent Effects
Macrolides	Time-Dependent	Moderate
Azithromycin	Time-Dependent	Prolonged
Ketolides	Conc-Dependent	Moderate
Streptogramins	Time-Dependent	Mod-prolonged
Oxazolidinones	Time-Dependent	Mod-prolonged

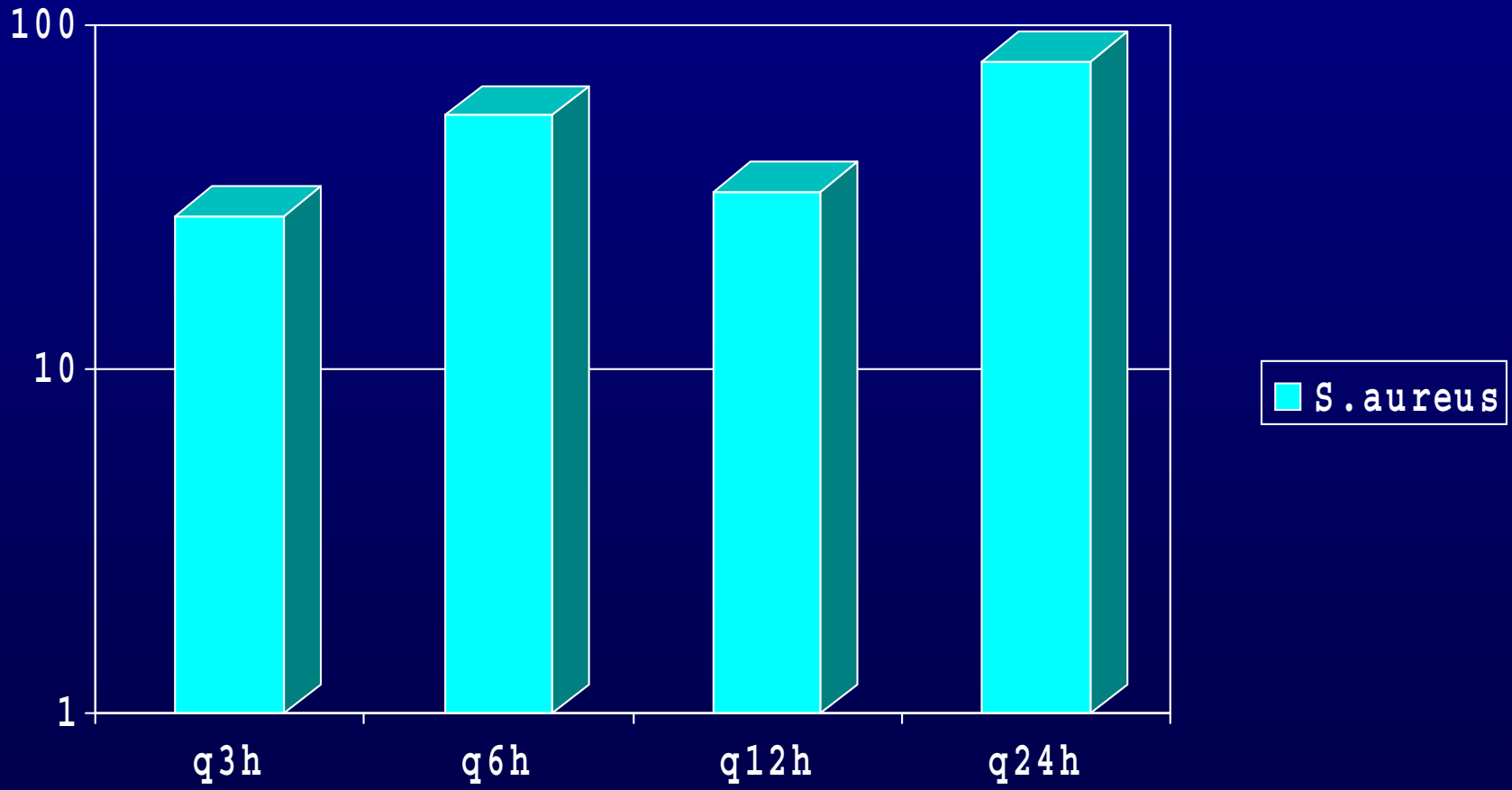
Impact of Dosing Frequency on Static Dose for Macrolides and Azalides with *Streptococcus pneumoniae* ATCC 10813



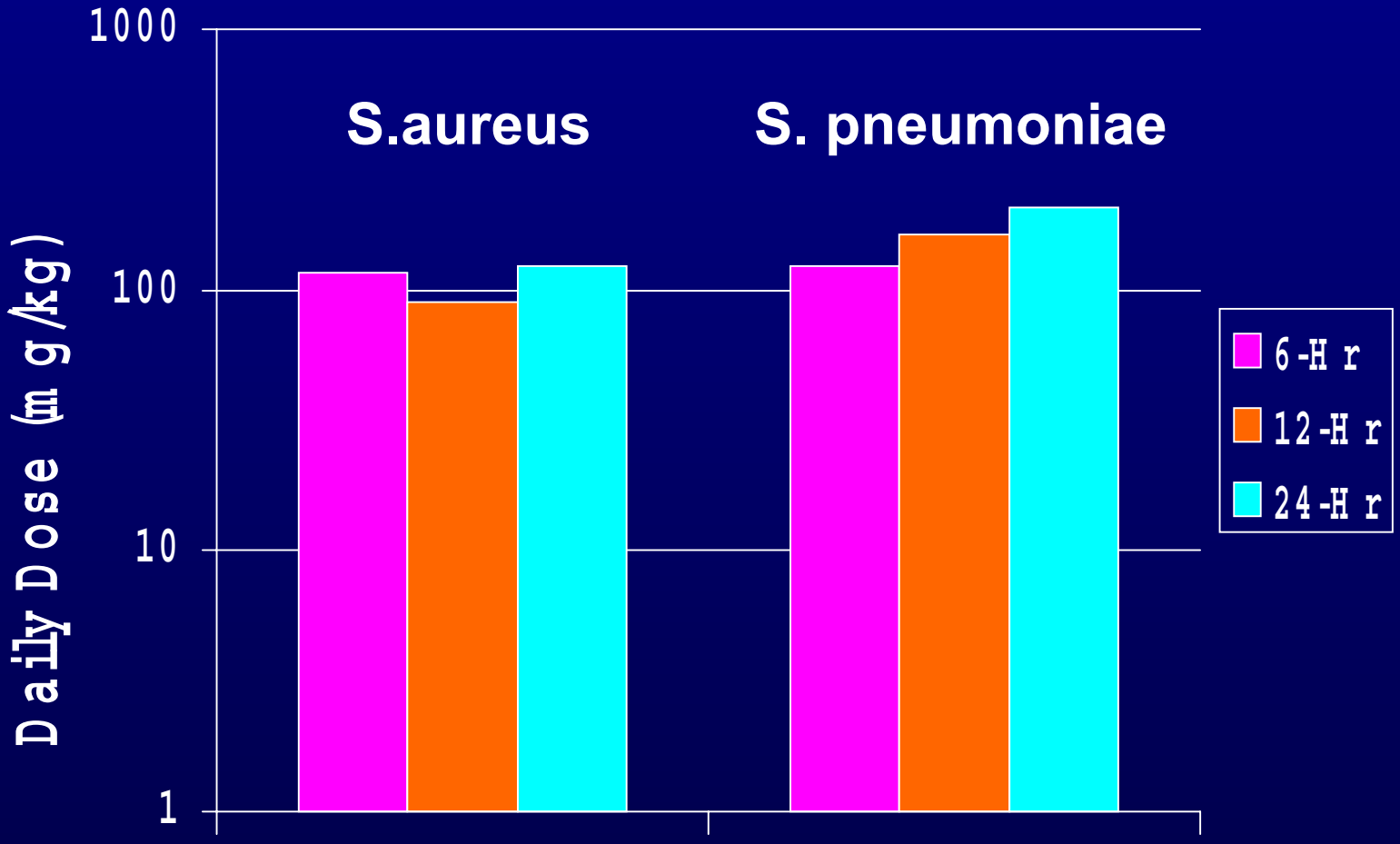
Impact of Dosing Frequency on Static Dose for Macrolides, Azalides and Ketolides with *Streptococcus pneumoniae* ATCC 10813



Impact of Dosing Interval on Static Doses for ABT-773 Against *S. aureus* ATCC 29213

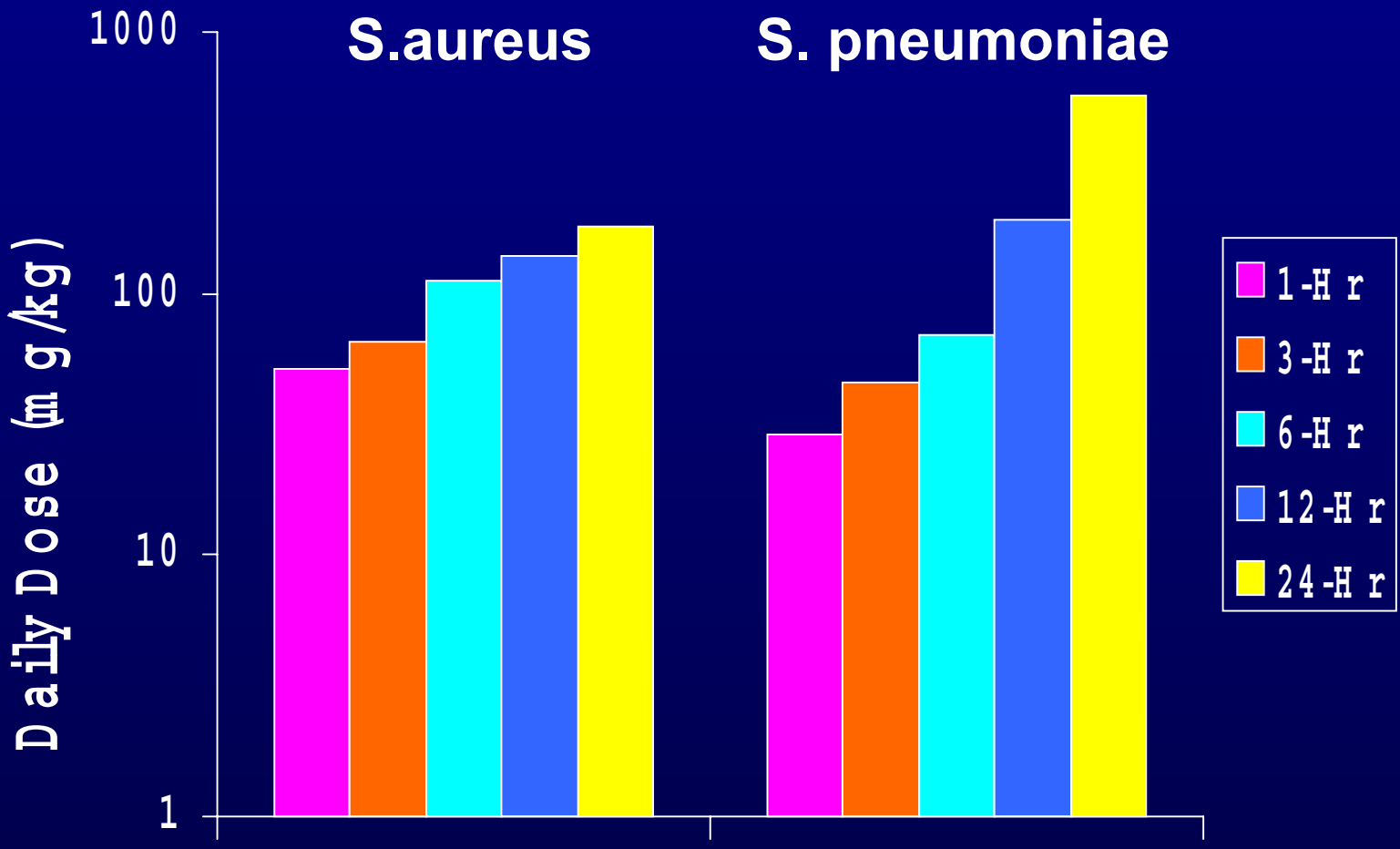


Impact of Dosing Interval on Doseof Synercid (Quinupristin + Dalfopristin) Required for Efficacy in Neutropenic Mice



Craig and Ebert, ICAAC 1996

Impact of Dosing Interval on Dose of Linezolid Required for Efficacy in Neutropenic Mice

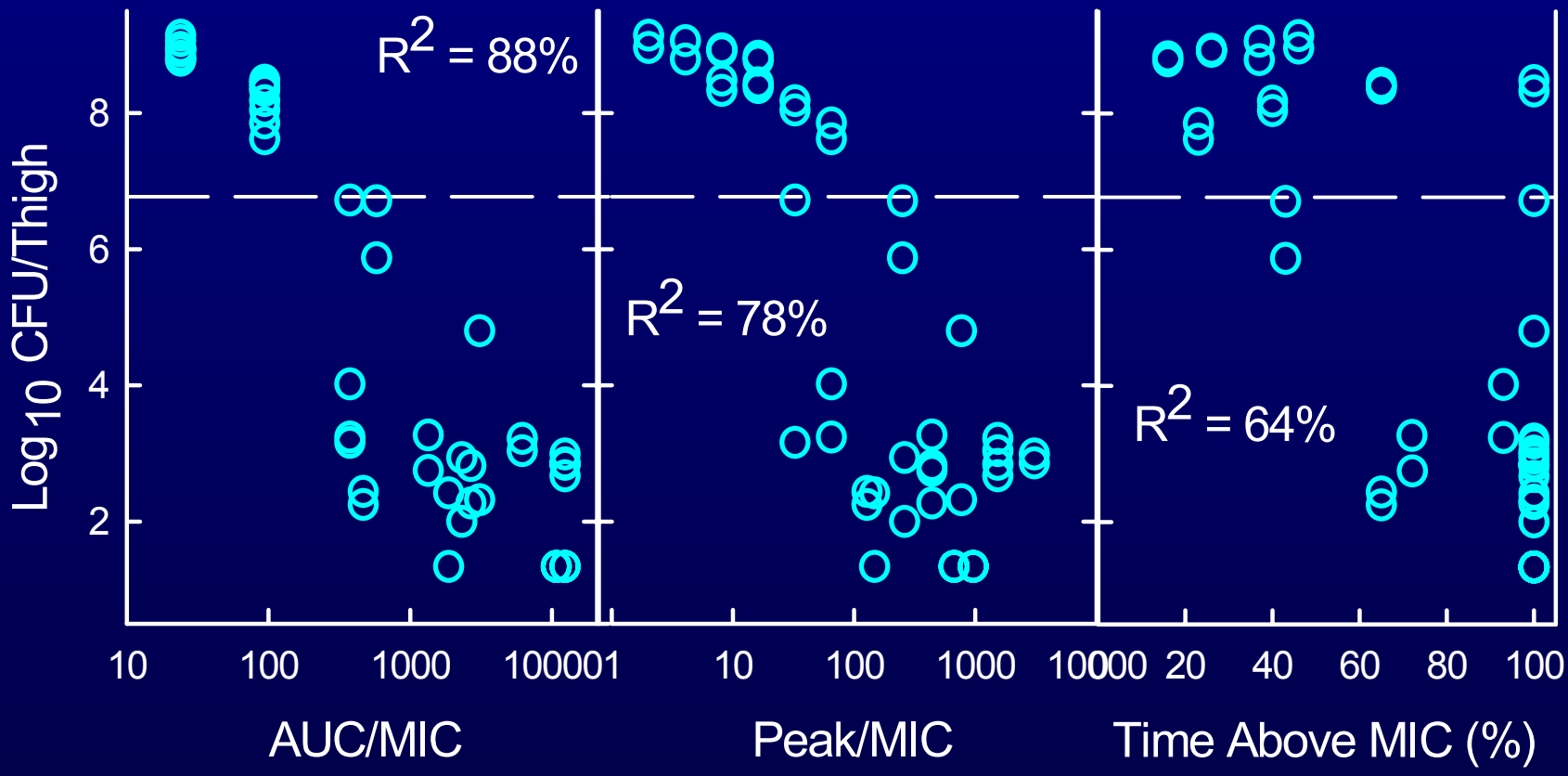


Andes et al, ICAAC 1996

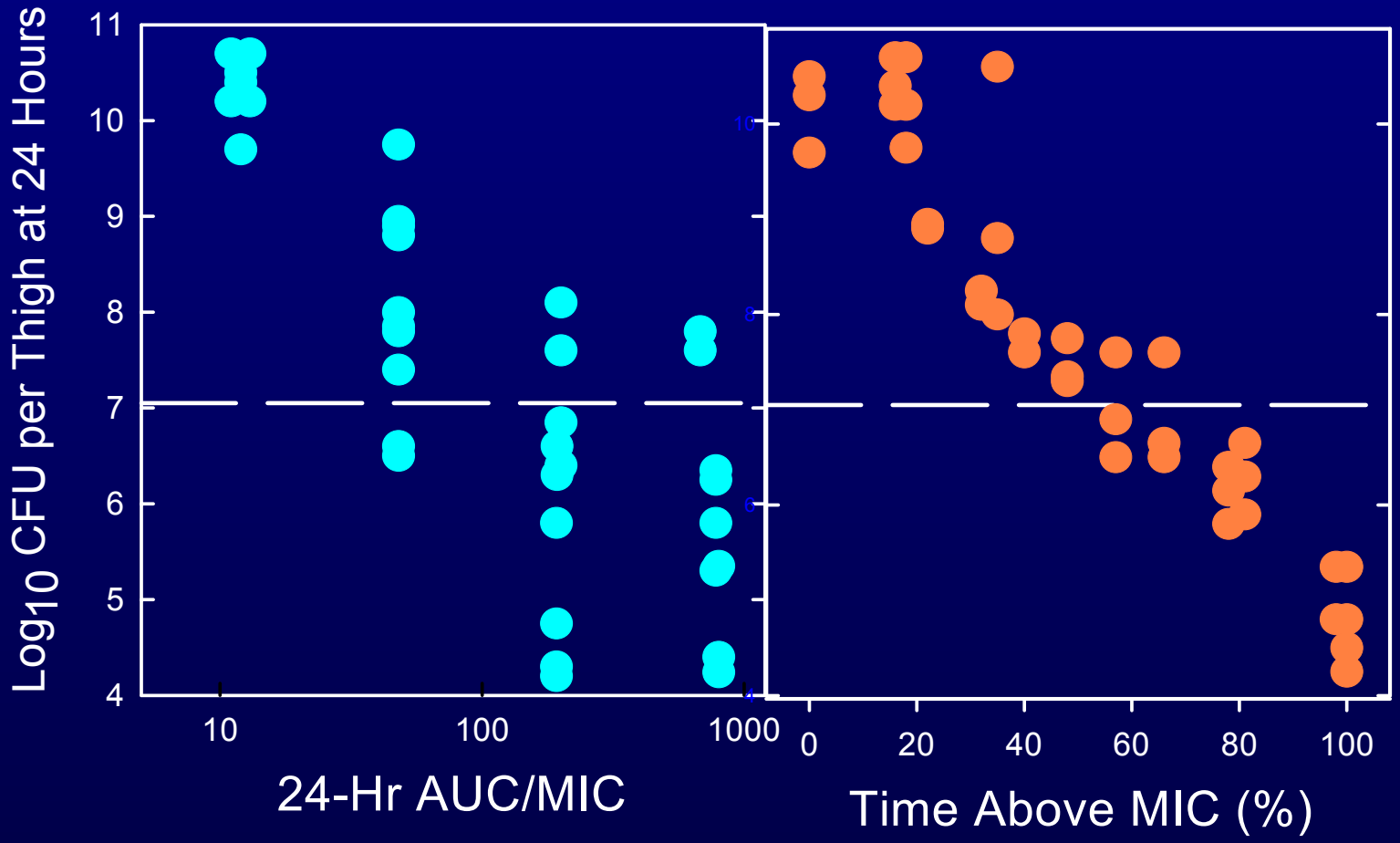
Pharmacokinetics of Macrolides, Azalides and Ketolides in Infected Neutropenic Mice at a Dose of 18.8 mgkg

Drug	Cmax	Half-life	AUC
Erythromycin	2.8	0.8	4.0
Roxithromycin	2.7	0.8	3.9
Clarithromycin	3.0	1.1	5.5
Azithromycin	1.9	1.8	4.1
Telithromycin	8.5	2.5	30
HMR 3004	6.2	0.9	10
ABT-773	7.2	2.6	28

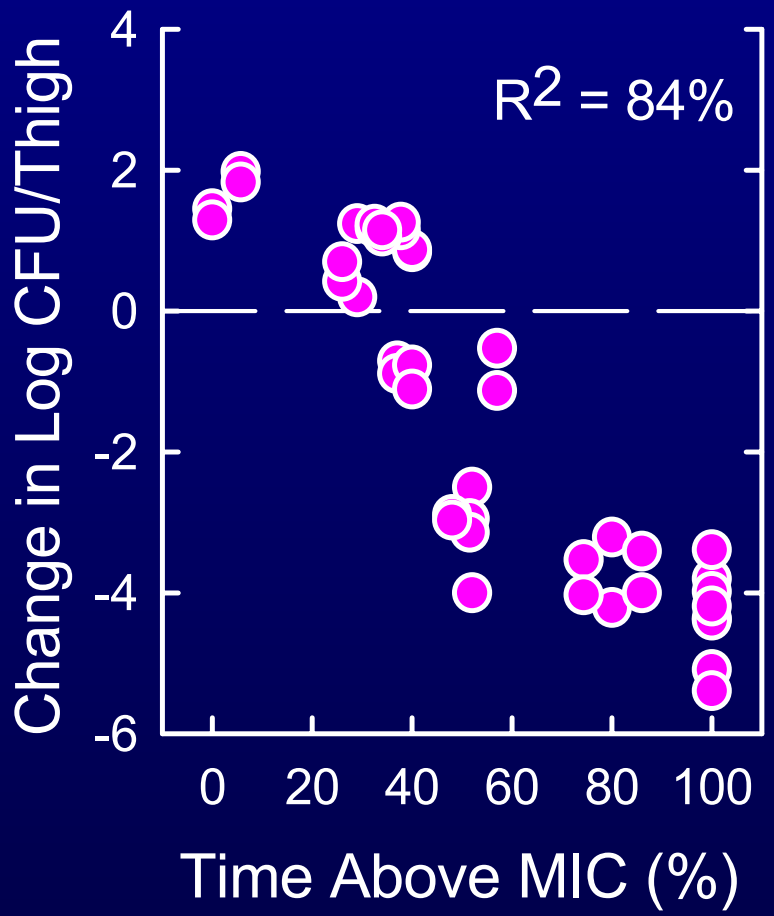
Relationships Between PK/PD Parameters and Efficacy of ABT-773 with *Streptococcus pneumoniae* ATCC 10813



Relationship Between PK/PD Parameters and Efficacy of Clarithromycin with *Streptococcus pneumoniae* ATCC 10813



Relationship Between PK/PD Parameters and Log_{10} CFU/Thigh After 24 Hrs of Therapy with Linezolid at Different Dosing Intervals



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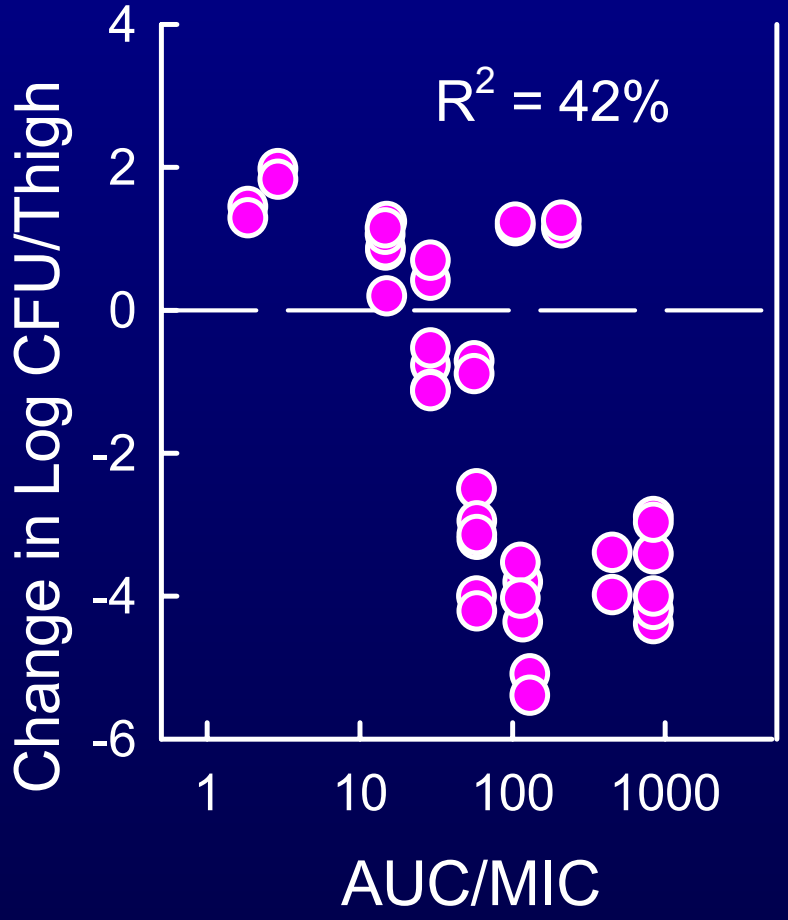
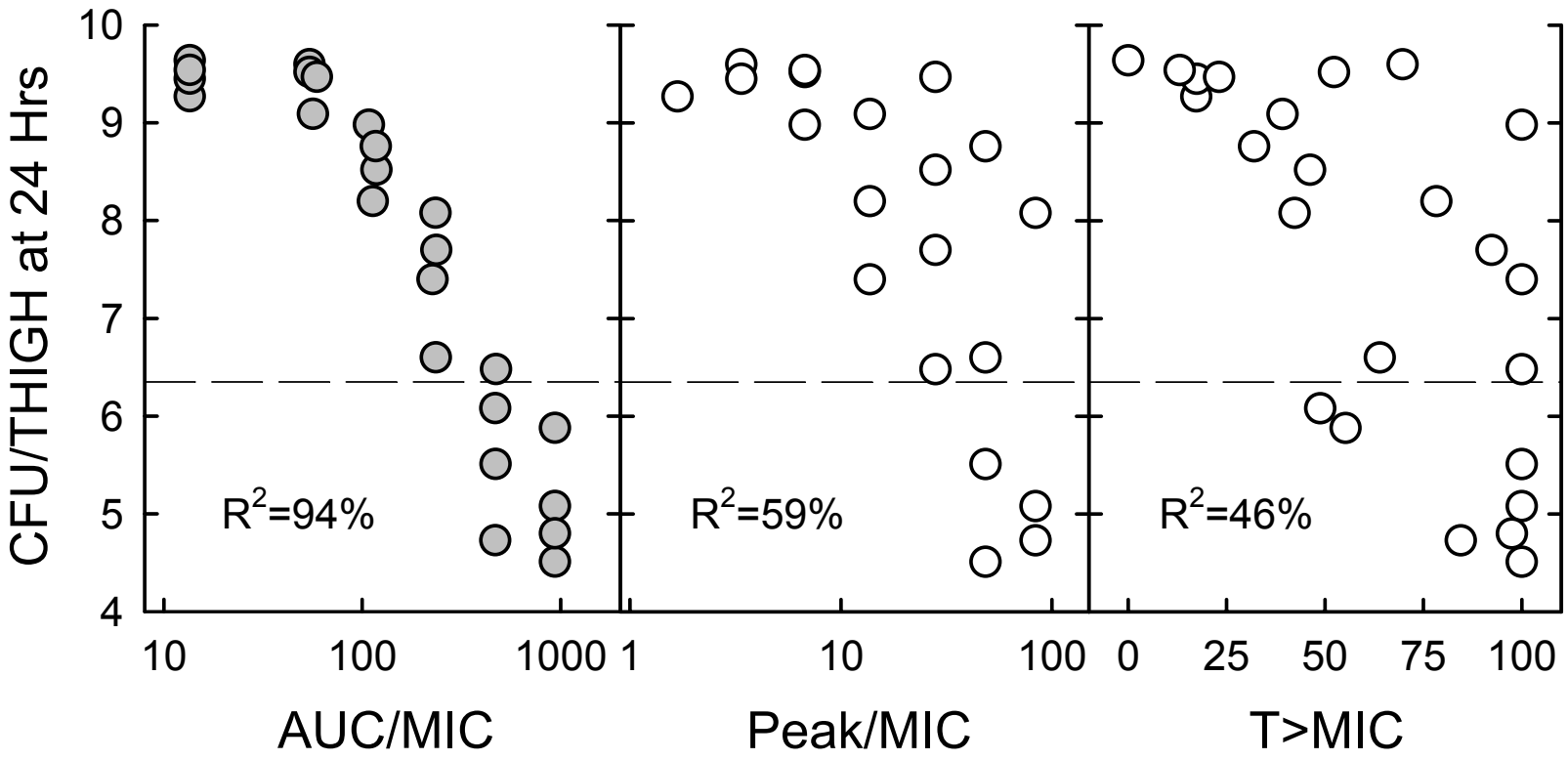


Relationship Between PK/PD Parameters and Efficacy of AZD2562

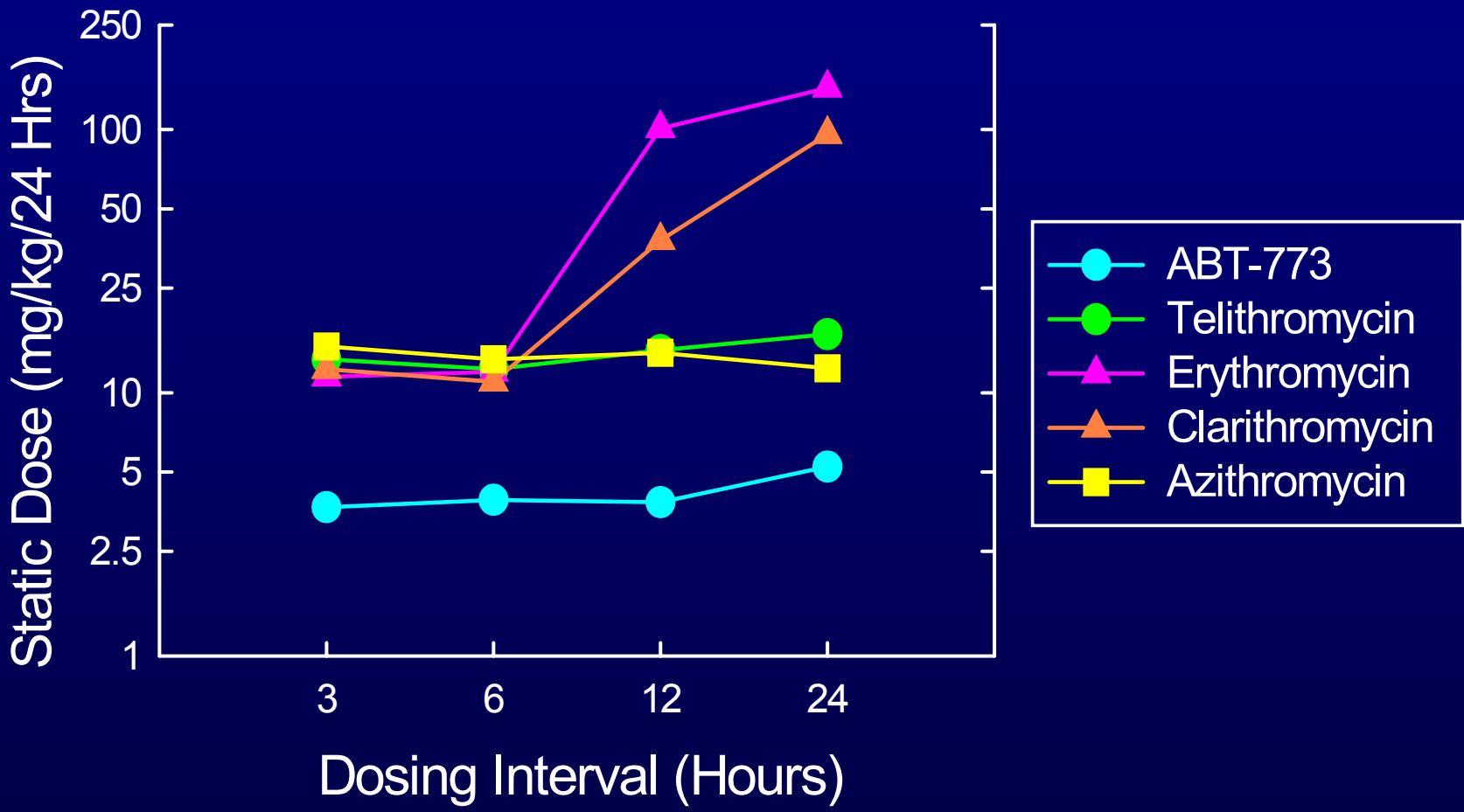
Figure 4. Relationships Between PK/PD Parameters and CFU/Thigh of *S. pneumoniae* ATCC 10813



PK/PD Parameters and Efficacy

Drug	PK/PD Parameter
Macrolides	Time above MIC
Azithromycin	24-Hr AUC/MIC
Ketolides	24-Hr AUC/MIC
Streptogramins	24-Hr AUC/MIC
Oxazolidinones	Time above MIC - 24-Hr AUC/MIC

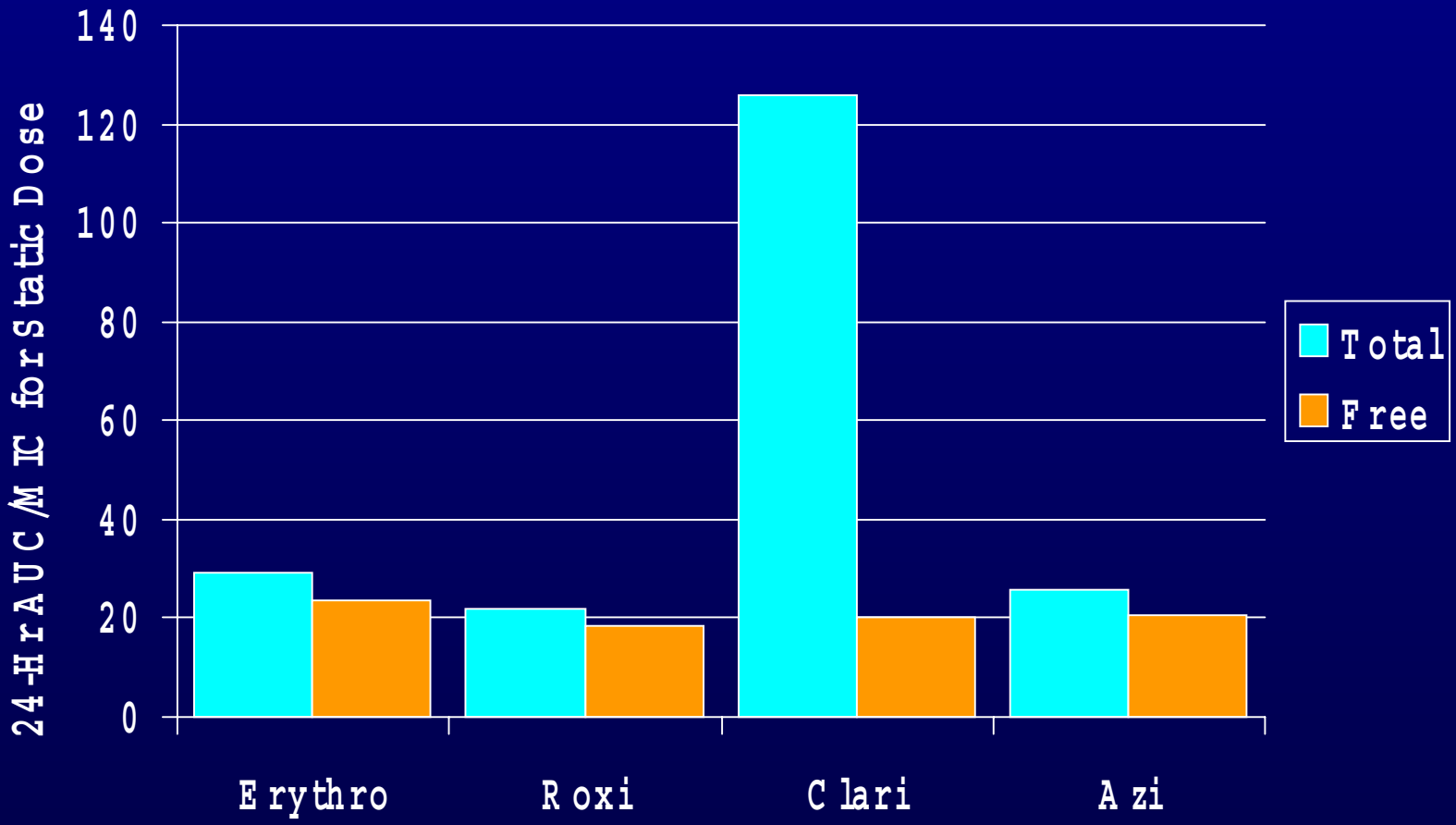
Impact of DosingFrequency on Static Dose for Macrolides, Azalides and Ketolides with *Streptococcus pneumoniae* ATCC 10813



PK/PD Parameters and Efficacy

Drug	PK/PD Parameter
Macrolides	24-hr AUC/MIC
Azithromycin	24-Hr AUC/MIC
Ketolides	24-Hr AUC/MIC
Streptogramins	24-Hr AUC/MIC
Oxazolidinones	24-Hr AUC/MIC

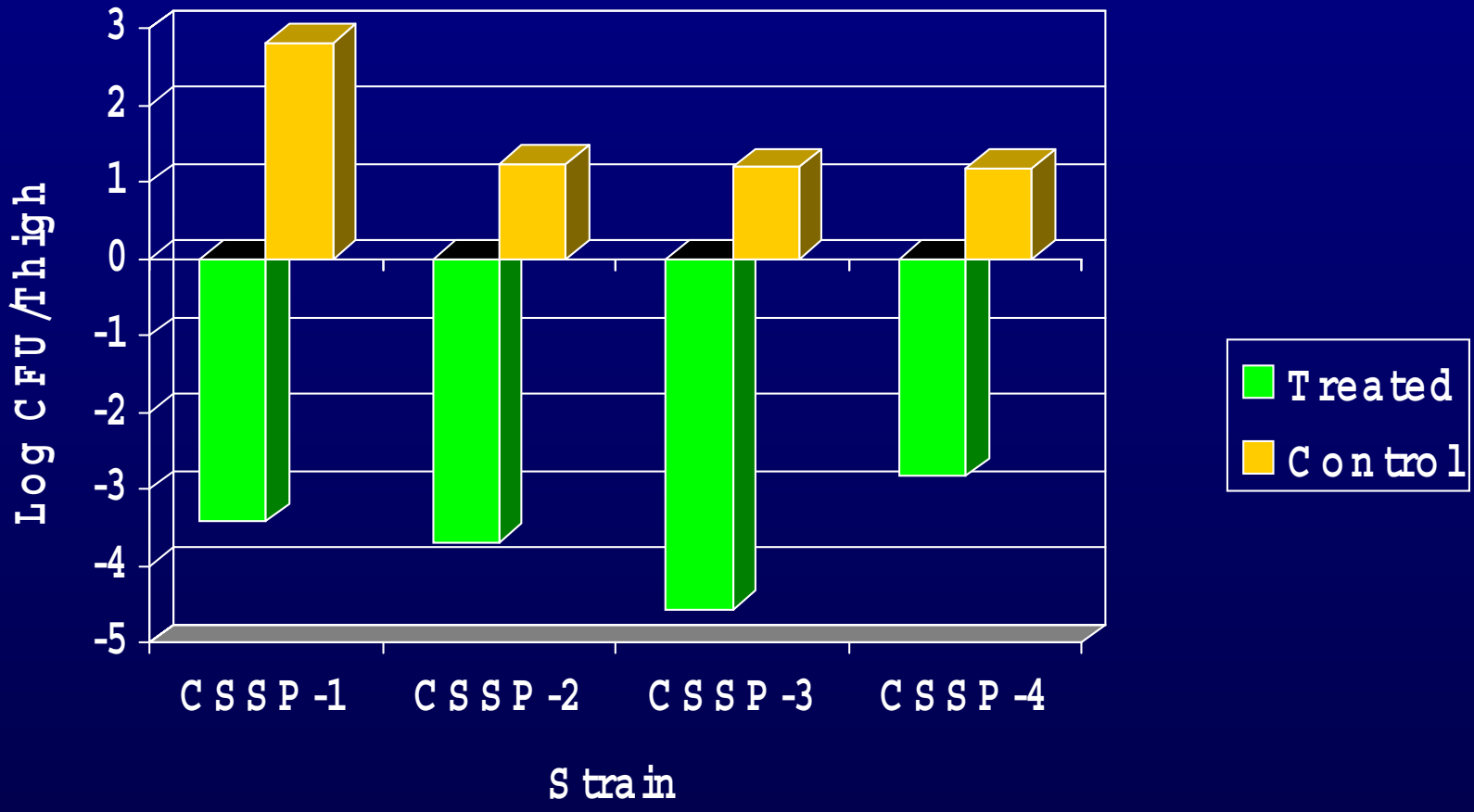
24-Hr AUC/MIC with Total and Free Drug for the Static Dose of Different Macrolides with *S. pneumoniae* ATCC 10813



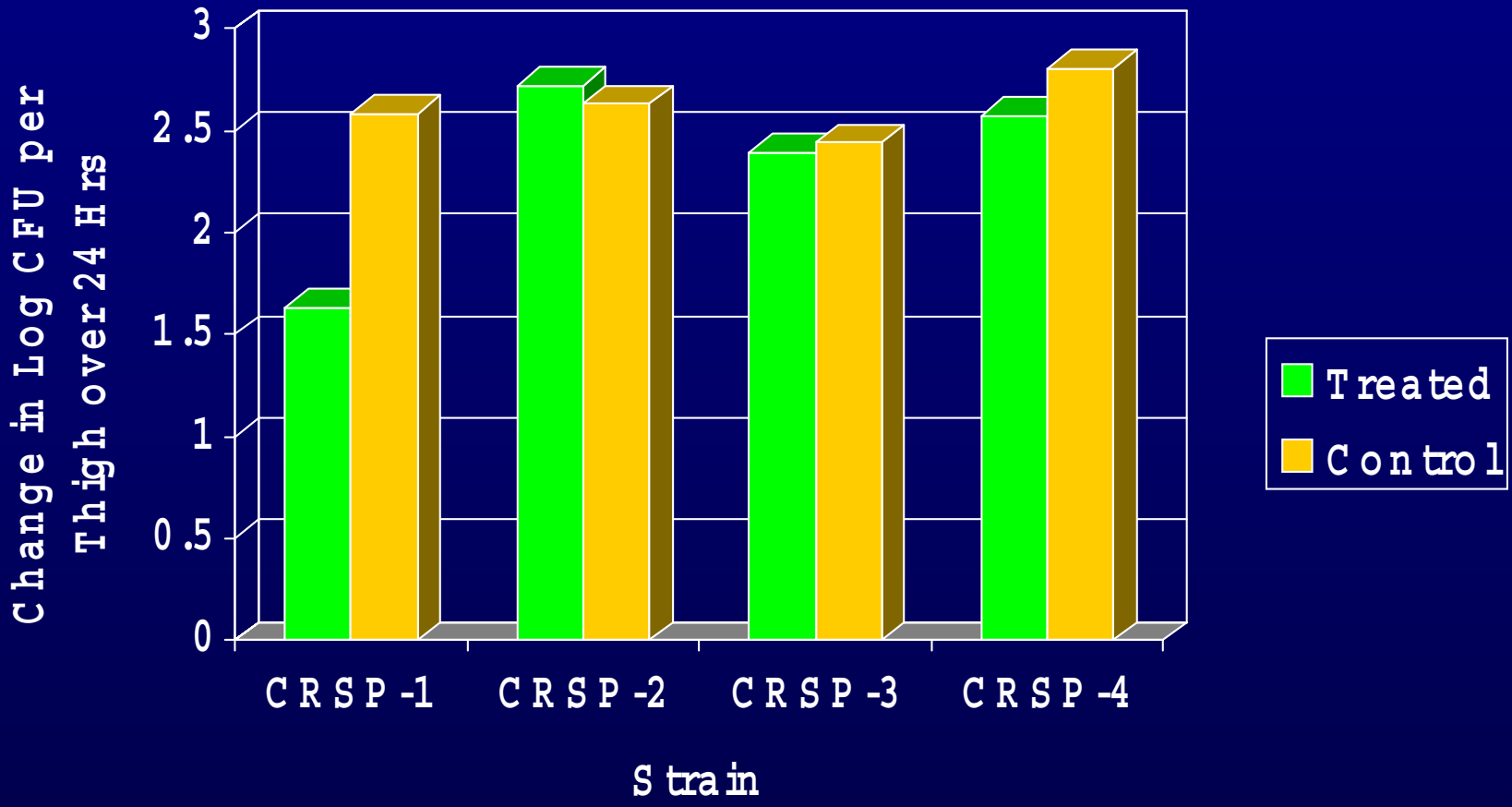
RESULTS

Strains	Clarithromycin MICs (mg/L)
MSSP	0.03-0.06
MRSP (Erm)	8->128
MRSP (Mef)	0.5-4

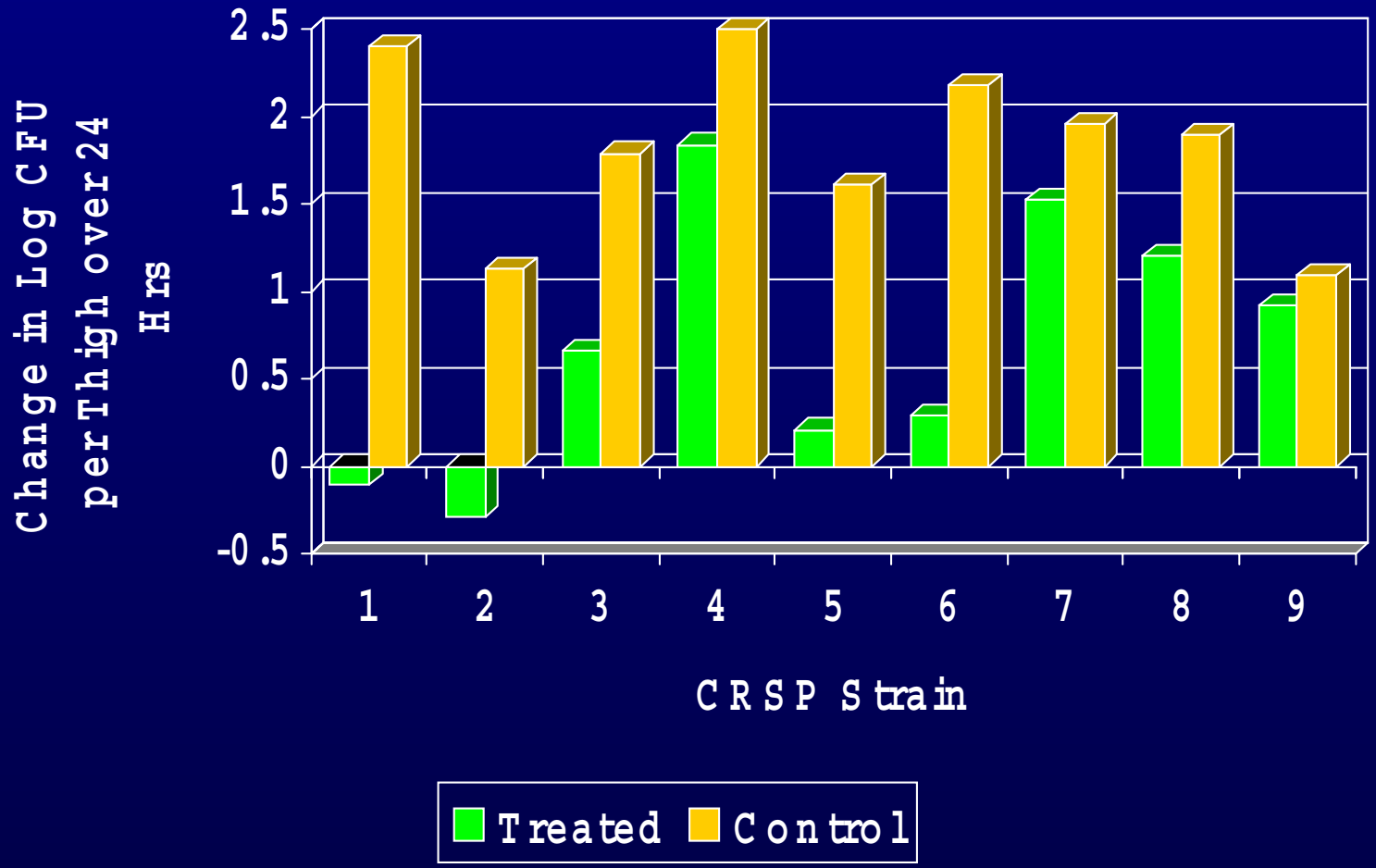
Change in CFU/Thigh with Strains of CSSP after 24 Hrs of Treatment (48 mg/kg/6 hrs) and in Control Neutropenic Mice



Change in CFU/Thigh with Strains of CRSP (due to Erm) after 24 Hrs of Treatment (48 mg/kg/6 hrs) and in Control Neutropenic Mice



Change in CFU/Thigh with Strains of CRSP (due to Mef) after 24 Hrs of Treatment (48 mg/kg/6 hrs) and in Control Neutropenic Mice



24-Hr AUC/MIC for Free Drug with Susceptible and Resistant Strains of *Streptococcus pneumoniae*

Drug	None	ERM	MEF
Clarithromycin	24(13-34)	NM	27 (NM)
Azithromycin	24(13-31)	NM	20 (NM)
Telithromycin	121(66-182)	132(74-228)	86(16-164)
ABT-773	34(26-40)	50(34-58)	56(10-108)

NM = not measurable

Static Doses (mg/kg/24 hrs) in Lungs and Thigh with Azithromycin

Organism	MIC	Thigh	Lung
ATCC 10813	0.06	12.2	14.3
3427	1.0	134	NM

Static Doses (mg/kg/24 hrs) in Lung and Thigh with Clarithromycin

Organism	MIC	Thigh	Lung
ATCC 10813	0.03	3.6	5.7
3427	1.0	182	163

Impact of Resistance to Quinupristin or Dalfopristin on Activity in Animal Models

- Dalfopristin Resistance: No reduction in in-vivo activity with staphylococci (rabbit endocarditis and thigh infection) or pneumococci (thigh infection)

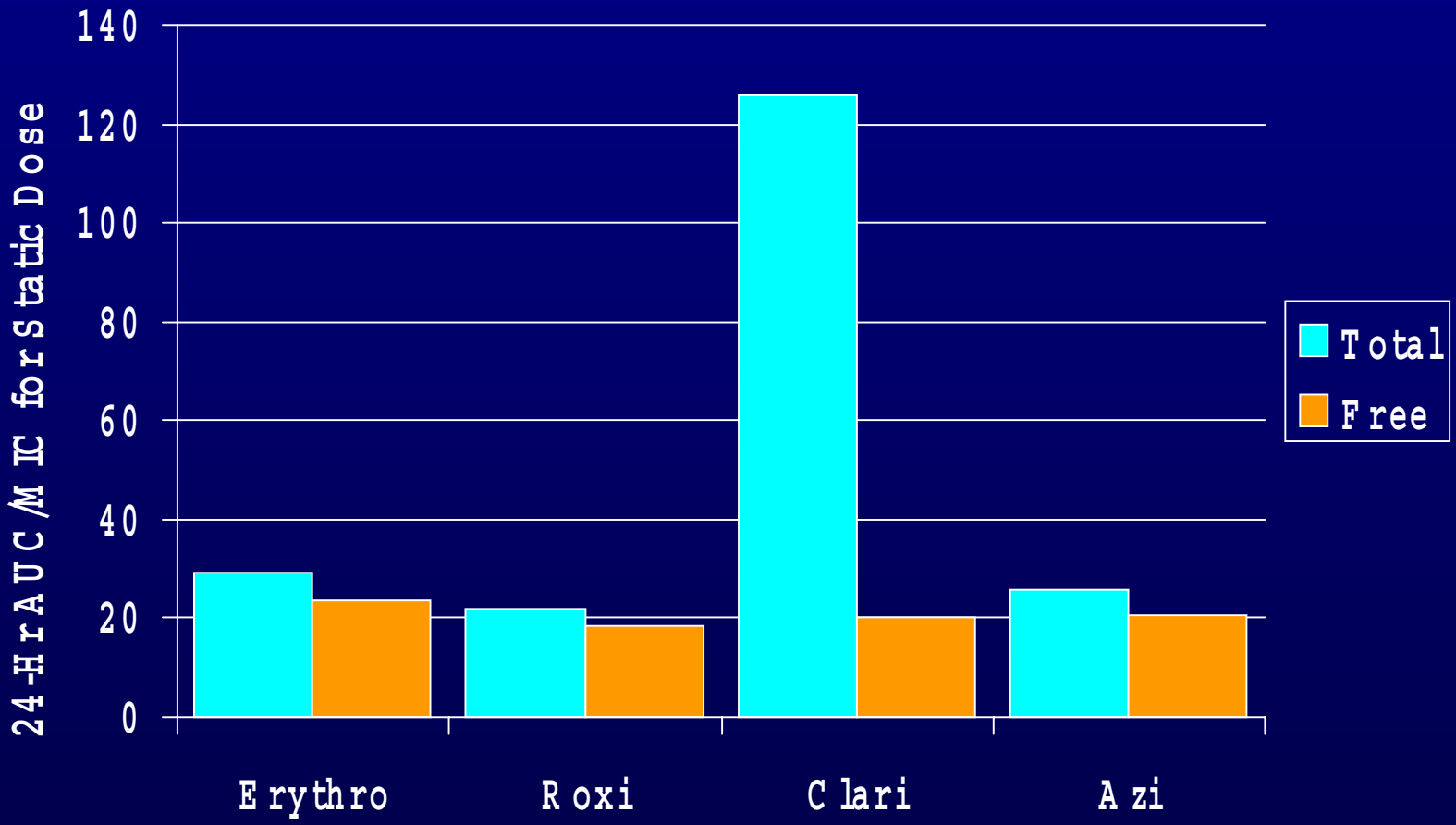
- Quinupristin Resistance: Reduced in-vivo activity (2- to 4-fold) with staphylocci (rabbid endocarditis and thigh infection) and pneumococci (thigh infection)

Fantin et al AAC 39:400, 1995
Zarrouk et al AAC 44:1168, 2000
Vesga et al ICAAC 1996

Impact of Neutrophils on Activity of Macrolides, Azalides, Ketolides and Oxazolidinones with Strains of *Streptococcus pneumoniae*

Drug	Normal	Neutropenic	Difference
Roxithromycin	5.0, 10	23, 29	4.6, 2.9
Clarithromycin	1.6, 8.2	11, 18	6.7, 2.2
Azithromycin	2.3, 4.2	7.4, 14	3.2, 3.4
Telithromycin	1.2, 4.4	5.5, 11	4.6, 2.5
HMR 3004	2.4, 4.4	7.9, 17	3.3, 3.9
ABT-773	1.5	3.9	2.6

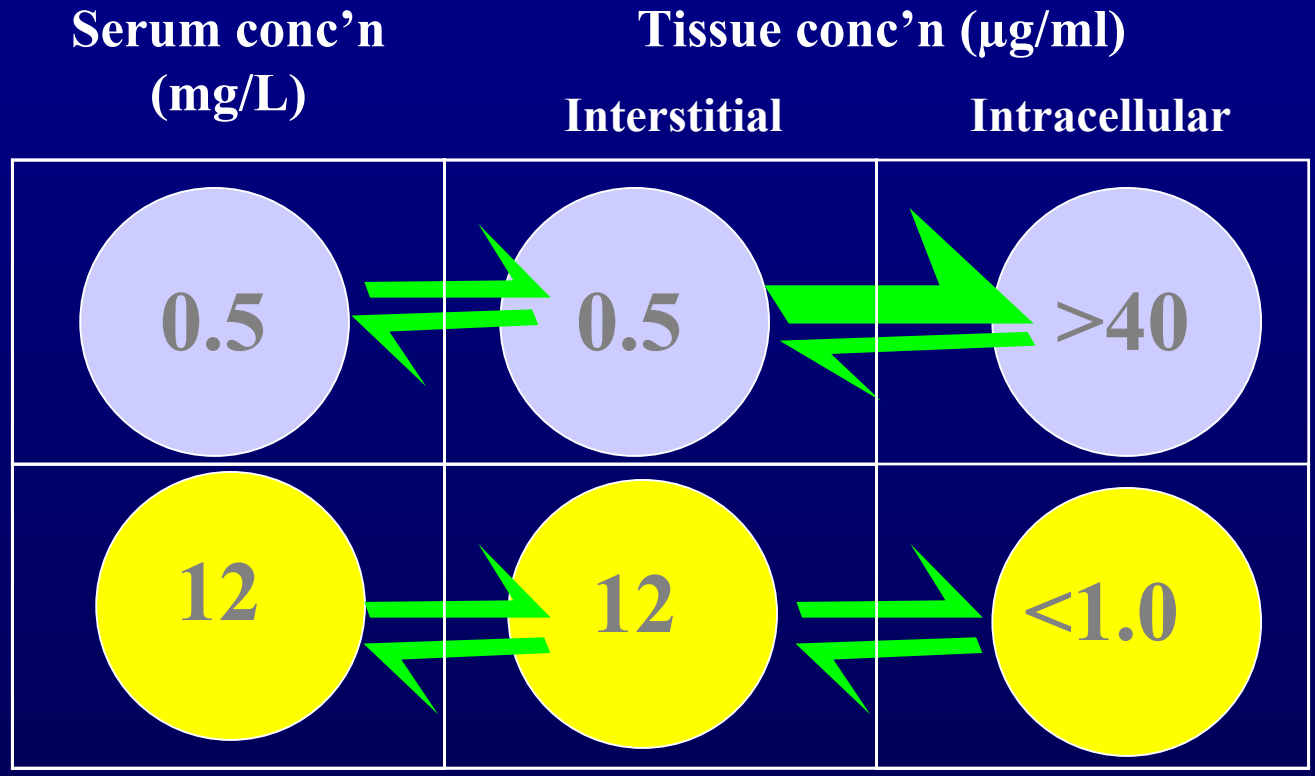
24-Hr AUC/MIC with Total and Free Drug for the Static Dose of Different Macrolides with *S. pneumoniae* ATCC 10813



Conclusions

- For most drugs the 24-hr AUC/MIC of free drug is 20-35 for the static doses in neutropenic mice and 5-15 in normal mice
- This is equivalent to averaging 1-1.5 times the MIC over 24 hrs in neutropenic mice and 0.2-0.6 times the MIC over 24 hrs in normal mice.
- 90-100% survival is associated with a 2-2.5 log drop in CFU at 24 hours.

Distribution of Antibiotics in the Body Affects Bacteriological Efficacy



Parmacodynamic Breakpoints for New Macrolides

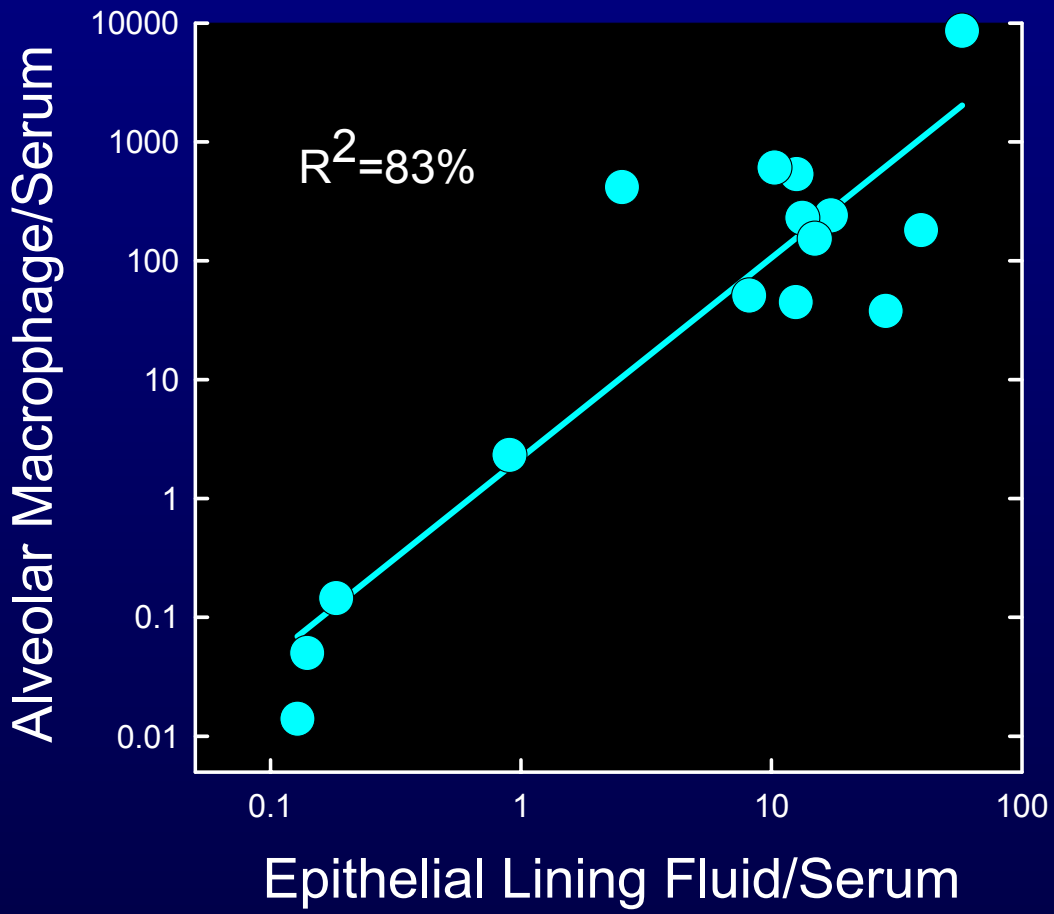
Drug	Site	PD Breakpoint
Clarithromycin	Serum	0.5-2
Azithromycin	Serum	0.12-0.5

Clarithromycin and Azithromycin Levels in Plasma and Epithelial Lining Fluid (ELF) of Healthy Adults

	Clarithromycin		Azithromycin	
Time	Plasma	ELF	Plasma	ELF
4 Hrs	2.0	34.5	0.08	1.0
8 Hrs	1.6	26.1	0.09	2.2
12 Hrs	1.2	15.1	0.04	1.0
24 Hrs	0.2	4.6	0.05	1.2
AUC	25	550	1.4	28

Rodvold et al. Antimicrob Agents Chemother 41:1399, 1997

Relationship Between Epithelial Lining Fluid/Serum Ratio and Alveolar Macrophage/Serum Ratio



Problems in Evaluating Macrolides in Animal Models

- Do not know if rodent models have the same magnitude of ELF/serum levels as seen in humans
- Many of the pneumococcal strains studied are also penicillin-resistant
- Penicillin-resistant pneumococci are less virulent in non-neutropenic rodents

Parmacodynamic Breakpoints for New Macrolides

Drug	Site	PD Breakpoint
Clarithromycin	Serum	0.5-2
Azithromycin	Serum	0.12-0.5
Clarithromycin	ELF	16-64
Azithromycin	ELF	1-4

Relationship Between Magnitude of PK/PD Parameter and Efficacy in Double Tap Studies in Otitis Media due to *S. pneumoniae*

Drug	MIC	Magnitude of PK/PD Parameter	Bacteriologic Cure
Erythromycin	S	AUC/MIC=124	14/15 (93%)
Clarithromycin	S	AUC/MIC=250	12/12 (100%)
Azithromycin	S	AUC/MIC=50	15/16 (94%)
	R	AUC/MIC<0.1	3/14 (21%)

Klein Ped Inf Dis 12:973, 1993; Dagan et al AAC 44:43, 2000, Dagan et al Ped Inf Dis 19:95, 2000

Relationship Between Magnitude of PK/PD Parameter and Efficacy in Double Tap Studies in Otitis Media due to *H. influenzae*

Drug	MIC	Magnitude of PK/PD Parameter	Bacteriologic Cure
Erythromycin	R	AUC/MIC = 0.8	3/20 (15%)
Clarithromycin	S (4) ?	AUC/MIC = 2	3/15 (20%)
Azithromycin	S (2) ?	AUC/MIC = 1.5	13/35 (37%)

Klein Ped Inf Dis 12:973, 1993; Dagan et al AAC 44:43, 2000, Dagan et al Ped Inf Dis 19:95, 2000

Pneumococcal Breakthrough Bacteremia in Patients Treated with Macrolides for Community-Acquired Pneumonia

- 10% (4/41) outpatients treated with macrolides for CAP due to *S. pneumoniae* had breakthrough bacteremia - all strains had moderate resistance (efflux mechanism)
- 20-22% of cases of pneumococcal bacteremia due to macrolide-resistant strains occurred while on treatment with macrolides - about half these strains had moderate resistance (efflux mechanism)

Kelley et al Clin Infect Dis 31:1008, 2000
Garau & Mederios ICMASKO, 2000

Resistance and Efficacy in CAP

- MICs of failures have been 4 mg/L or higher
- Values are close to predicted ELF values for azithromycin and lower than predicted ELF values for clarithromycin
- Protein present in ELF; could reduce efficacy of clarithromycin

Increasing Macrolide Resistance in Eight Counties Surrounding Atlanta