Φαρμακοκινητικοί – Φαρμακοδυναμικοί Δείκτες (PK/PD index)

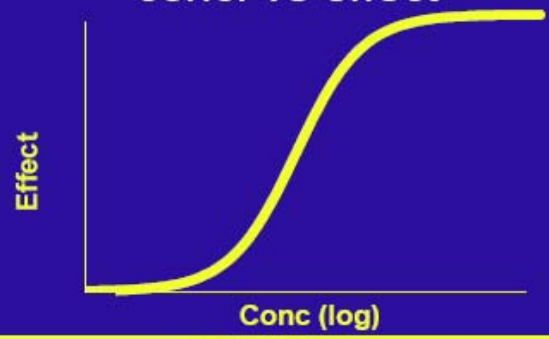
Διαμαντής Πλαχούρας
Λέκτορας Παθολογίας – Λοιμώξεων
Δ' Παθολογική Κλινική

Pharmacokinetics

conc. vs time

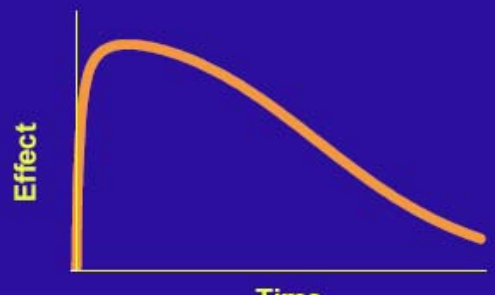
Pharmacodynamics

conc. vs effect



PK/PD

effect vs time



Στόχος αντιμικροβιακής θεραπείας

Αποτελεσματική αντιμετώπιση της λοίμωξης

?

Συγκέντρωση του αντιμικροβιακού > MIC

↓

Παράμετροι που σχετίζονται ποσοτικά με την αποτελεσματικότητα

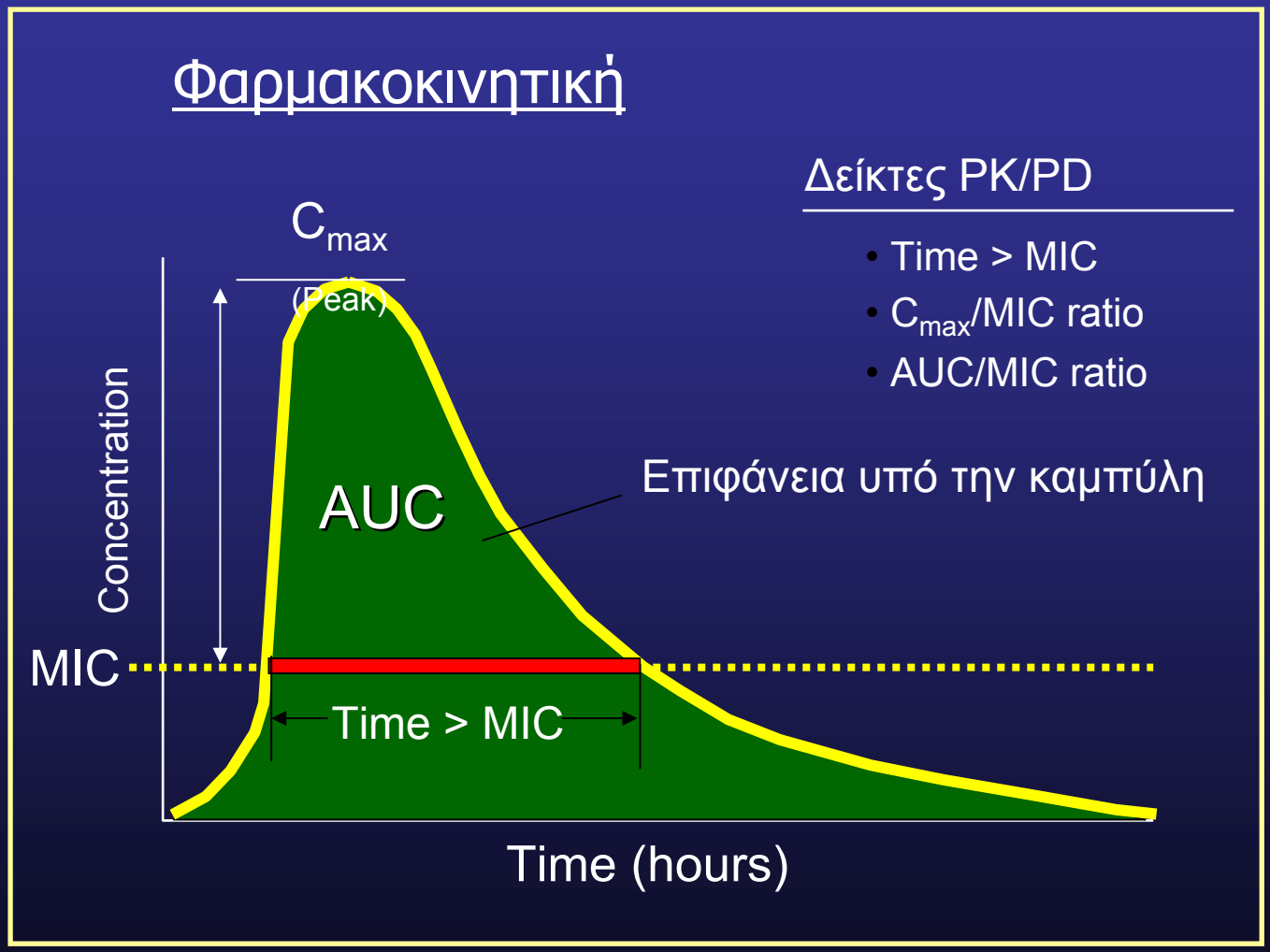
PK/PD δείκτες

T > MIC

AUC / MIC

C_{max} / MIC

Φαρμακοκινητική



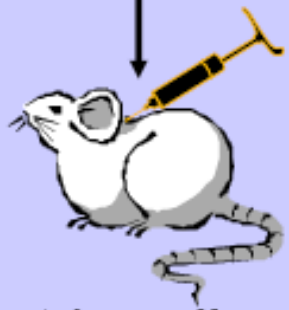
Μοντέλο μηρού ουδετεροπενικού ποντικού

- Λοίμωξη στον μηρό ουδετεροπενικού ποντικού
- Διάφορα δοσολογικά σχήματα
- Υπολογισμός φαρμακοκινητικών παραμέτρων
- Μέτρηση αποικιών μικροβίου (cfu / ml) στις 24 ώρες
- Γράφημα PD παραμέτρων προς αποτέλεσμα

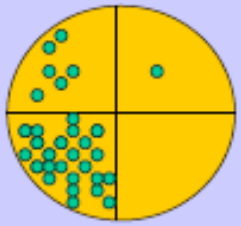
Neutropenic Mouse Thigh-Infection Model

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

2. Bacteria injected into thighs on day 0 (10^{4-7})

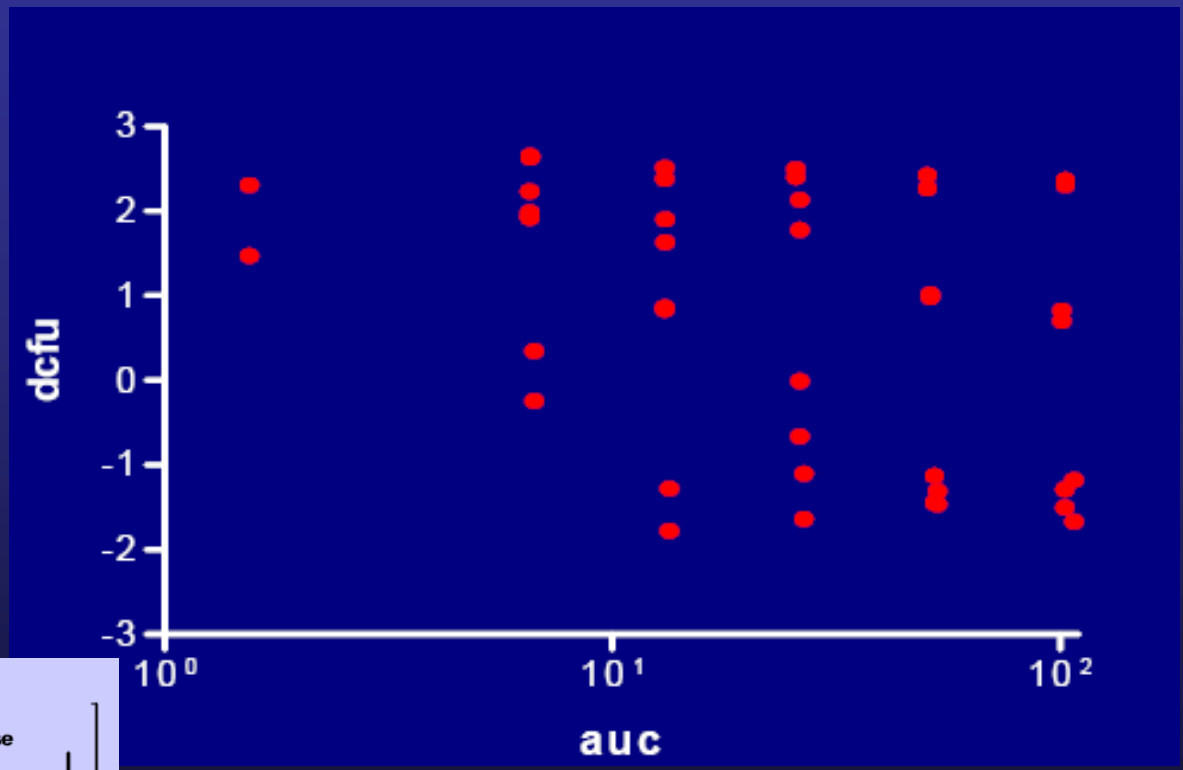


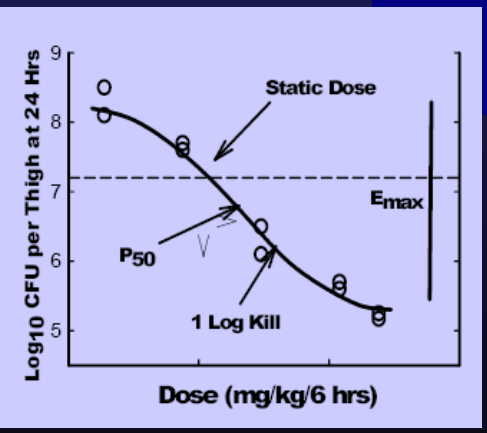
3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days



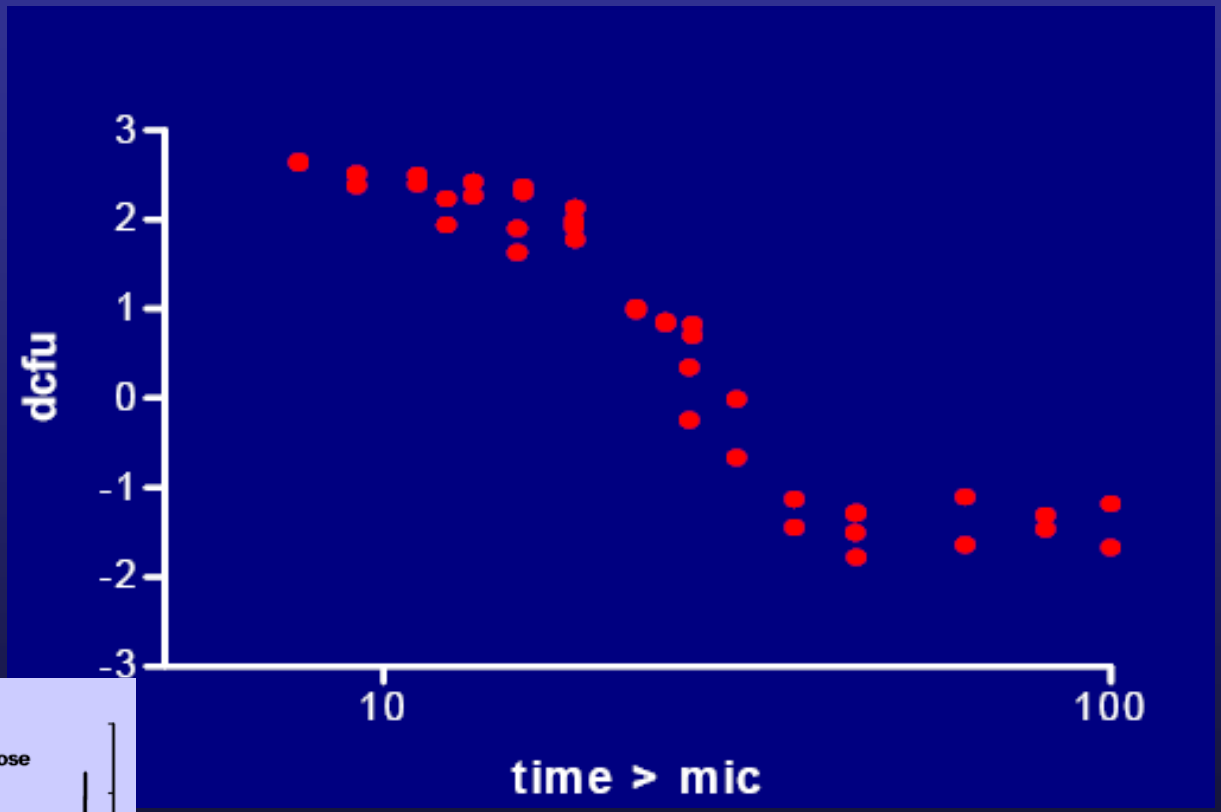
4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

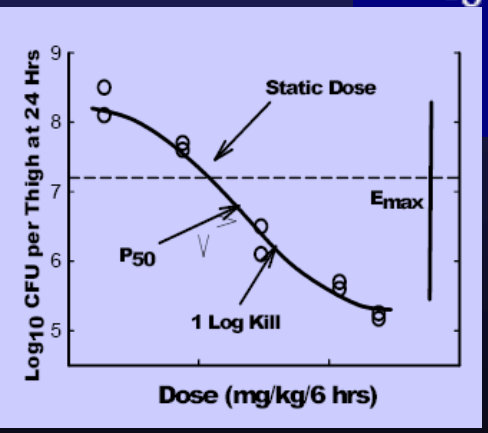
Meropenem vs. Klebsiella



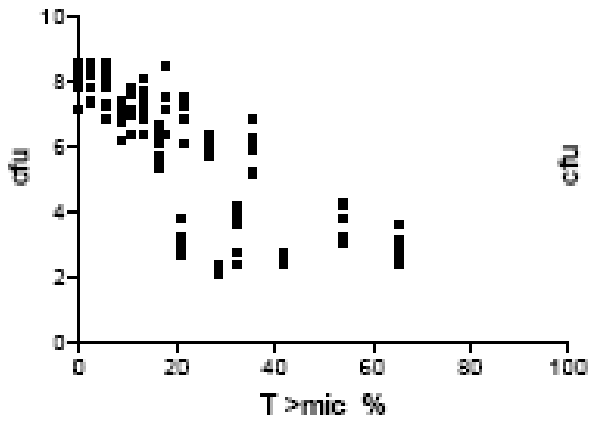


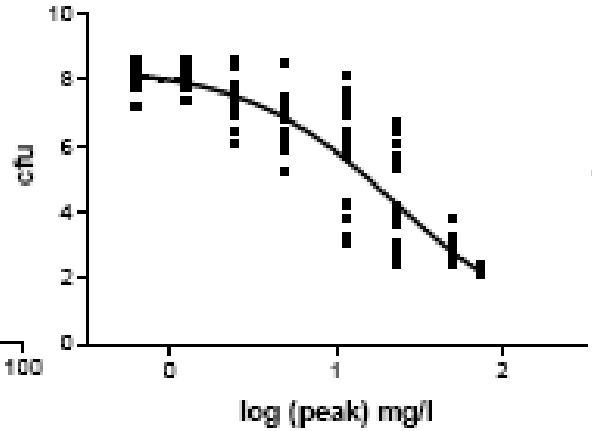
Meropenem vs. Klebsiella

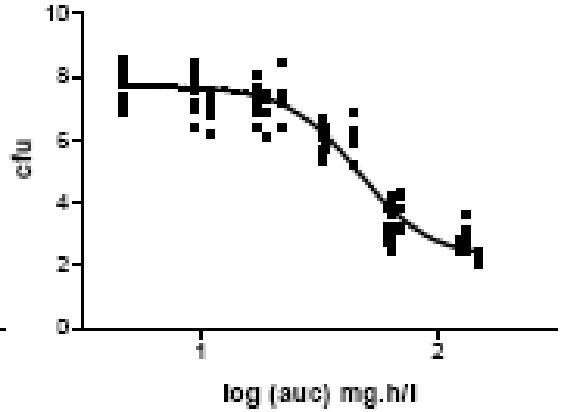




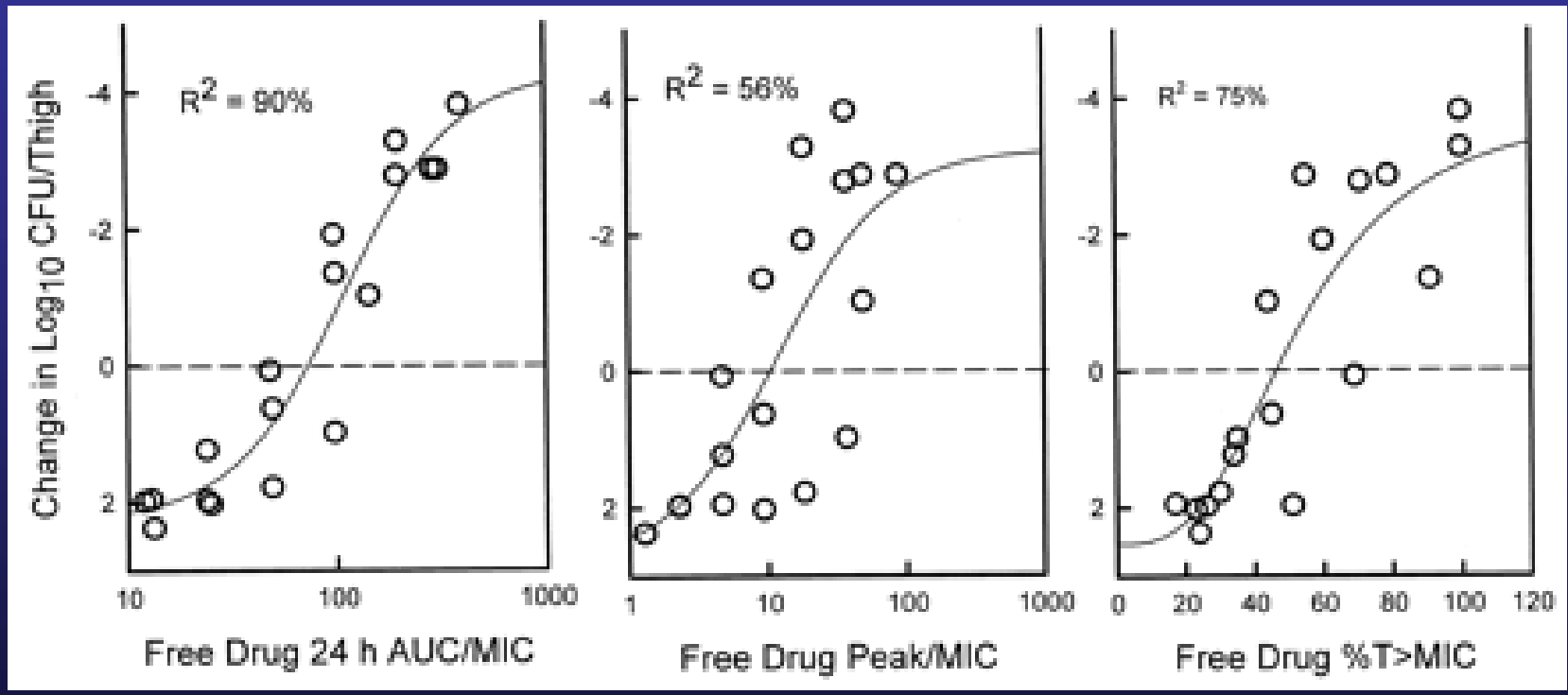
Λεβοφλοξασίνη vs *Streptococcus pneumoniae*



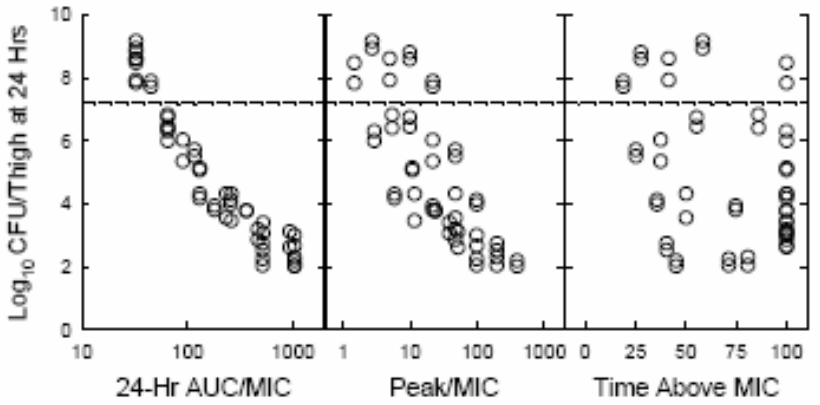




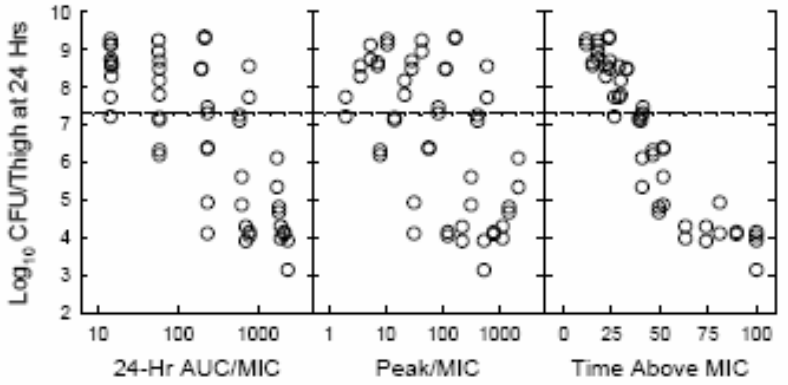
Garenoxacin vs Str. pneumoniae



Andes D, Craig W. Antimicrob Agents Chemother 2003



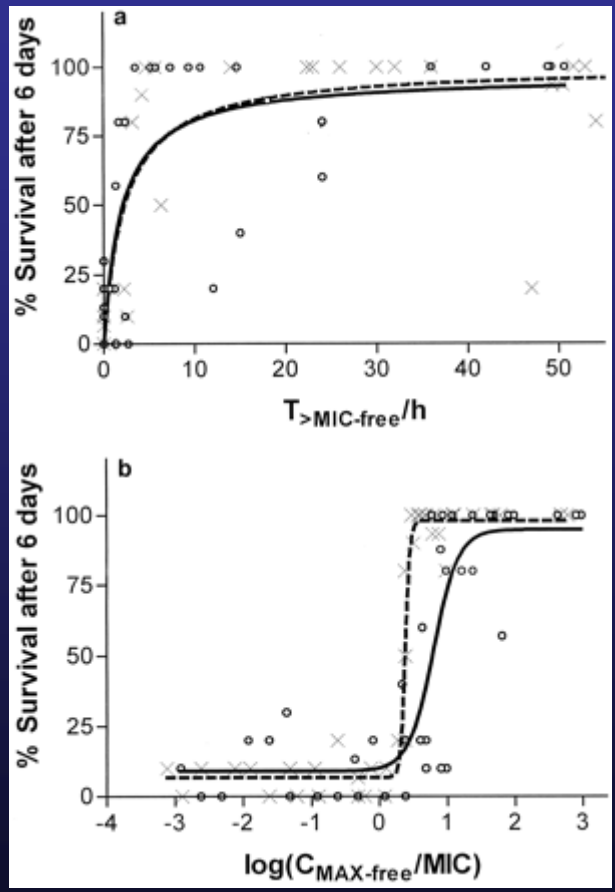
levofloxacin



ceftazidim

Andes IJAA 2002

PK/PD δείκτες και γλυκοπεπτίδια

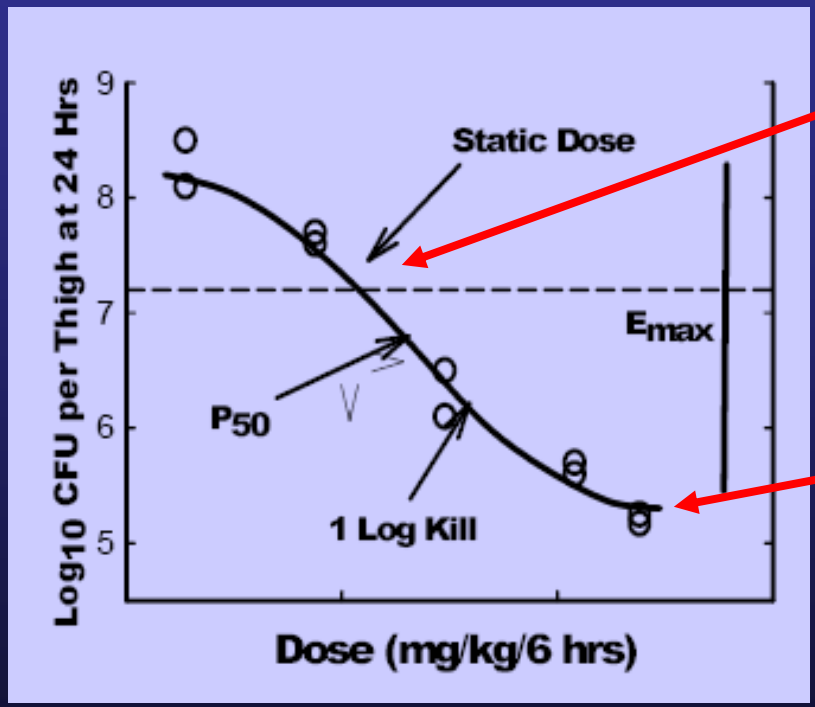


Knudsen JD. *AAC* 2000

T>MIC		AUC
Penicillins		Aminoglycosides
Cephalosporins		Fluoroquinolones
Carbapenems		Metronidazole
Monobactams		Lipopeptides
Tribactams		Ketolides
		Macrolides
		Clindamycin
		Streptogramins
	Glycopeptides	Glycylcyclines
		Oxazolidinones
		Tetracyclines
		Azoles

Μέγεθος δείκτη PK/PD

- Αντιμικροβιακό
- Μικροοργανισμός
- Ανοσολογική επάρκεια ξενιστή
  - Φυσιολογικός
  - Ουδετεροπενικός
- Θέση λοίμωξης
- Πρωτεϊνοδέσμευση
- Μικροβιακό inoculum



Βακτηριοστατικό αποτέλεσμα

- Ανοσοεπαρκείς
- Λοιμώξεις σε «εύκολα» διαμερίσματα

Βακτηριοκτόνο αποτέλεσμα

- Ουδετεροπενικοί
- Ασθενείς ΜΕΘ
- Ενδοκαρδίτιδα, μηνιγγίτιδα

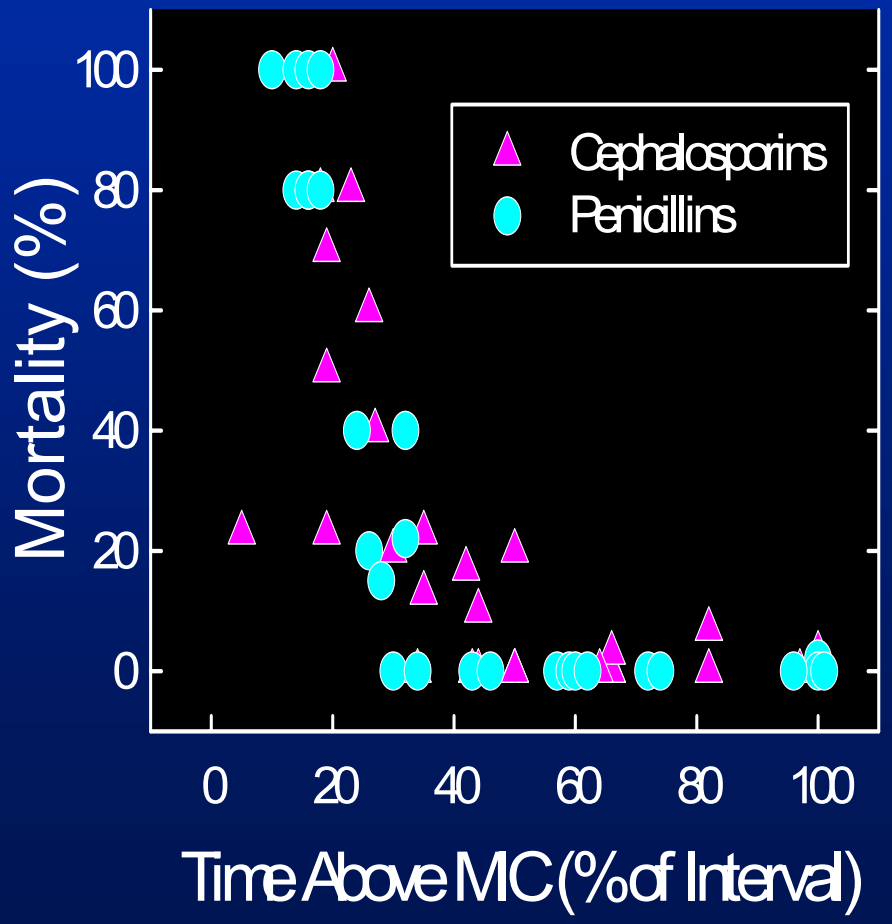
Pharmacodynamic Goals (T>MIC as percent of Interval) with Beta-Lactams

Class	Organism	Stasis	Maximum Killing
Cephalosporins	GNR, pneumo	40-50	70-80
	Staph	20-30	40-50
Penicillins	GNR, pneumo	30-40	60-70
	Staph	20-30	40-50
Carbapenems	GNR, staph	20-30	40-50
	Pneumo	10-20	25-40

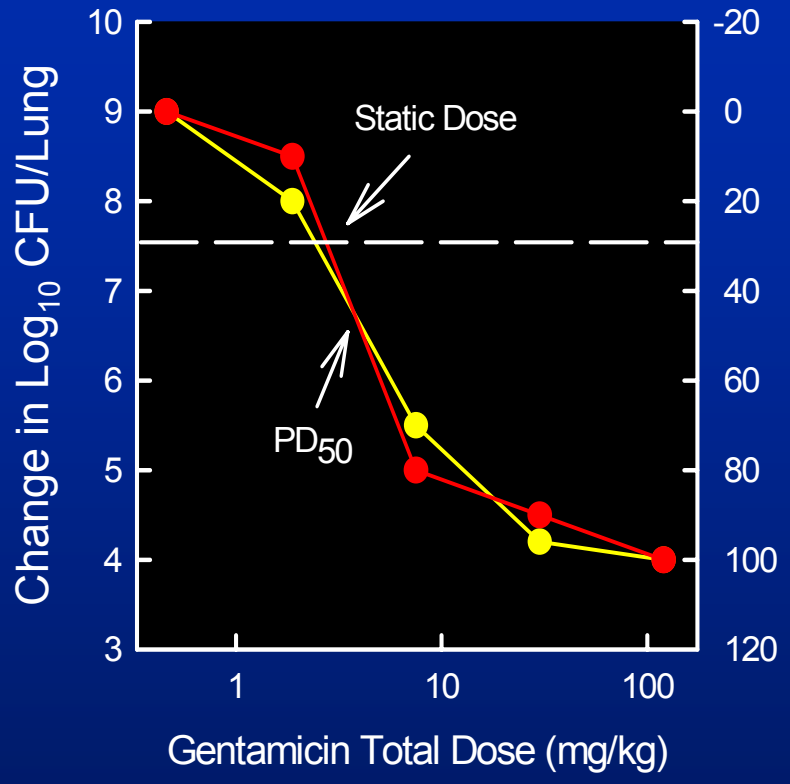
Literature Review for T>MIC for Beta-Lactams Versus Mortality in Animal Models

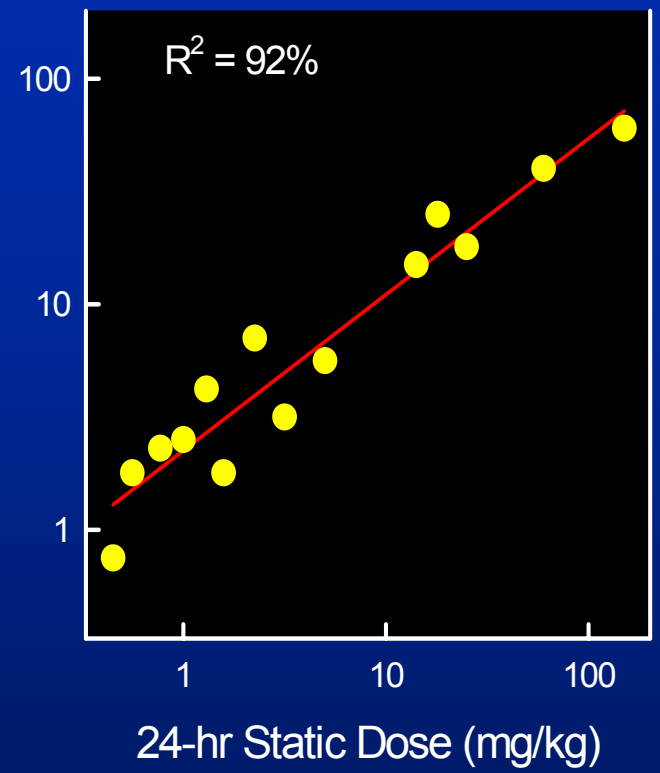
- **At least 48 hours of treatment**
- **Mortality 80-100% in untreated controls**
- **Pharmacokinetics provided to calculate magnitude of PK/PD parameter**
- **Mortality recorded within 24 hrs after last dose of drug**
- **Data from 3 animal species and 4 sites of infection**

Streptococcus pneumoniae



Correlation Between Bacterial Numbers After 24-hr of Therapy and Survival After 4-5 Days of Therapy



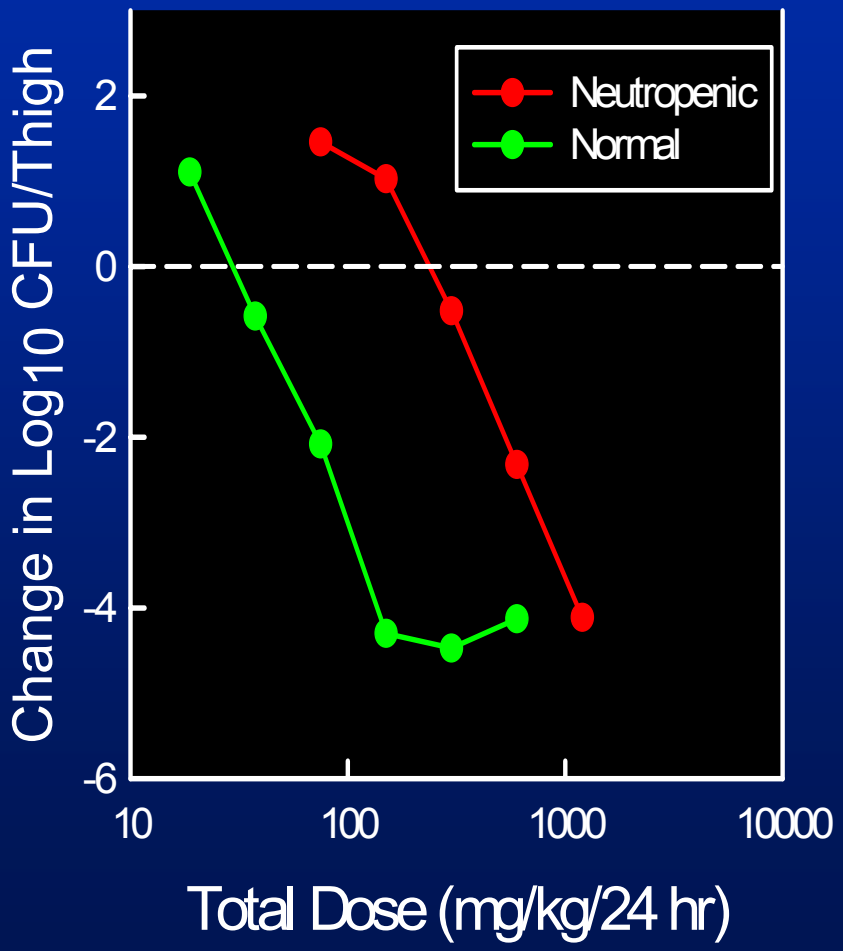


3 Quinolones
2 Aminoglycosides
4 B-lactams

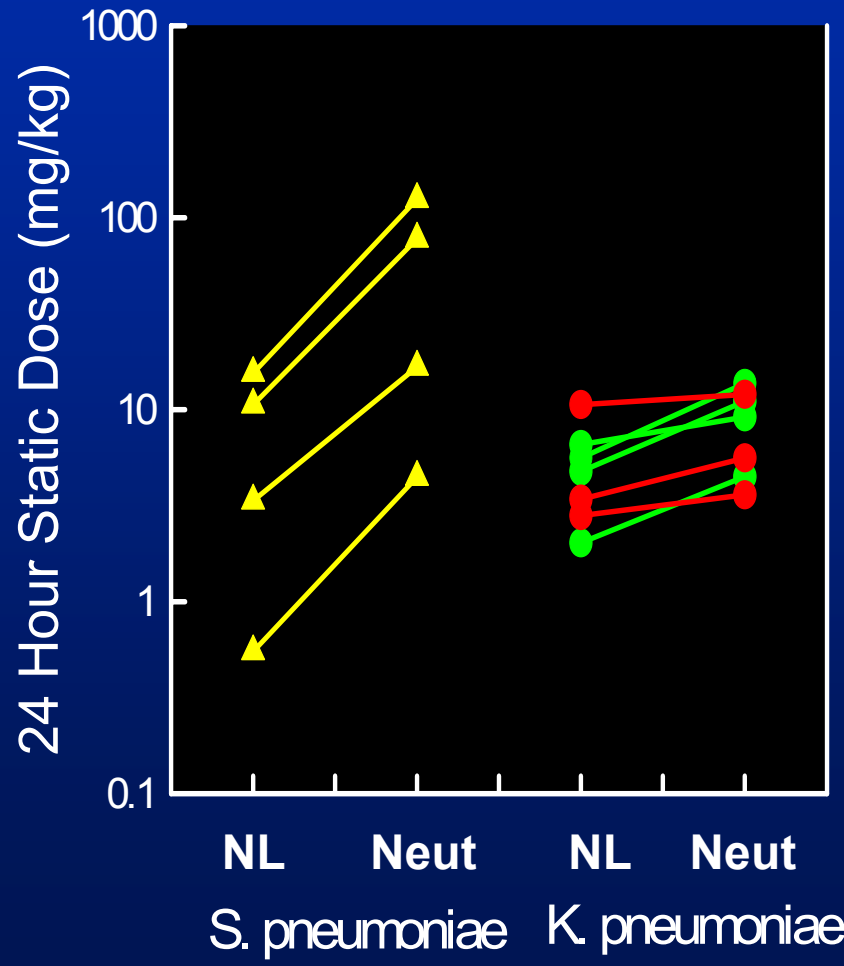
K. pneumoniae
P. aeruginosa
S. pneumoniae

Thigh
Lung

Ciprofloxacin Dose-Response Relationship Against S. pneumoniae in Both Normal and Neutropenic Mice

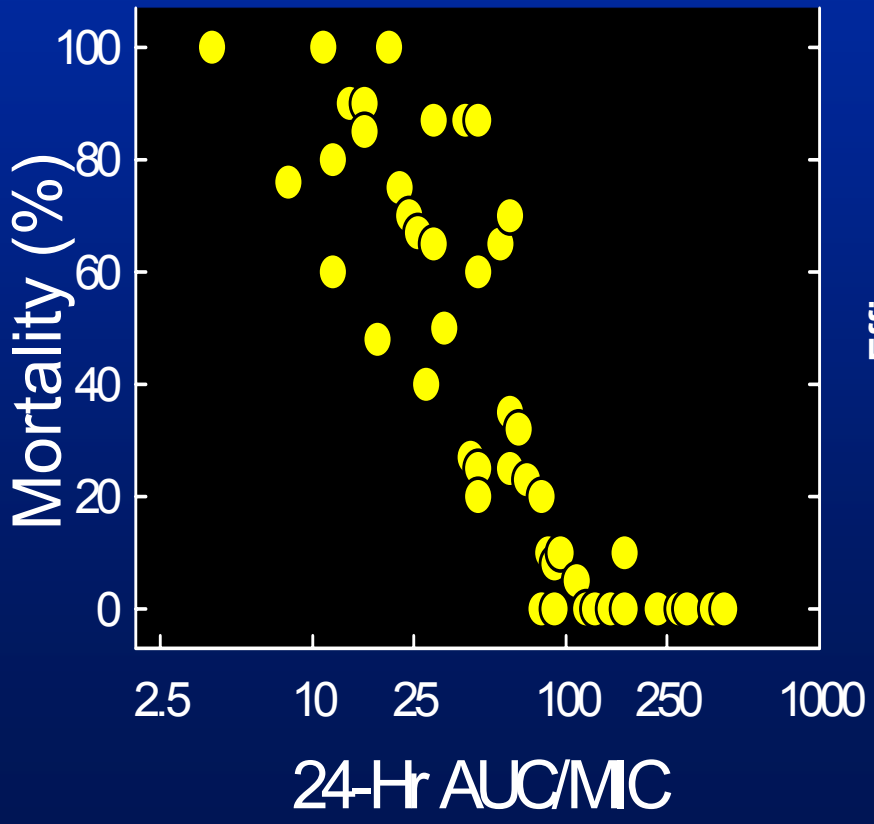


Impact of Neutrophils on the 24 hr Static Dose of Selected Quinolones Against S. pneumoniae and K. pneumoniae



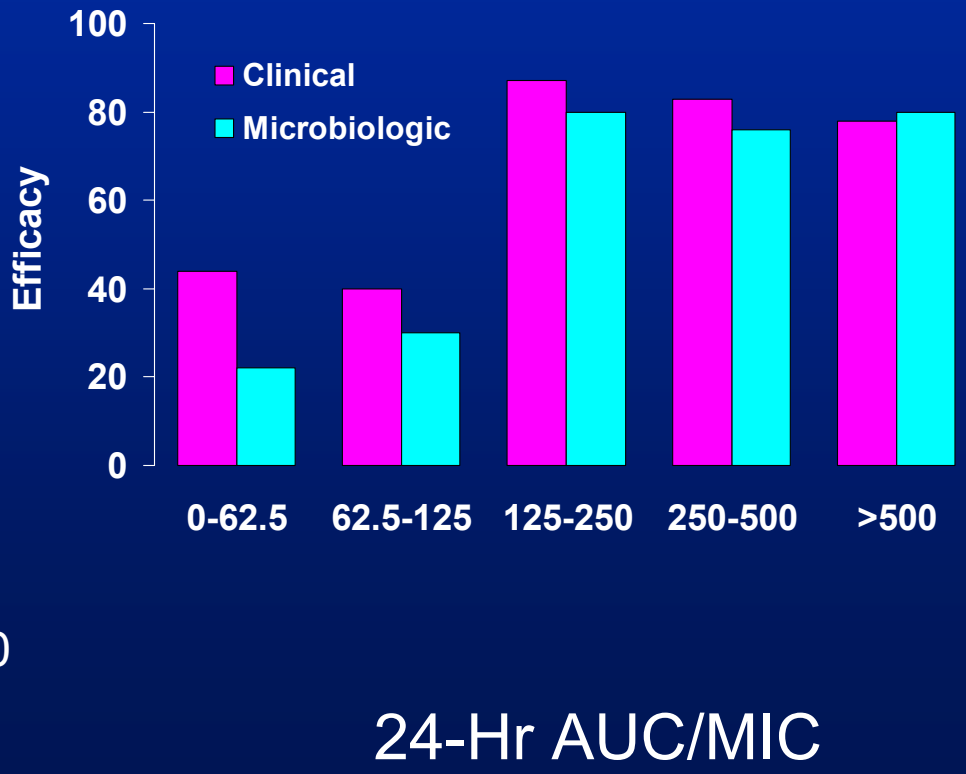
Comparison of the Relationships Between Efficacy and 24-Hr AUC/MIC for Fluoroquinolones in Animal Models and Infected Patients

Animals - Literature Review



Andes, Craig Int J Antimicrob Agents, 2002

Seriously ill patients + Ciprofloxacin



Forrest et al. AAC 37:1073, 1993

Inoculum effect

Impact of Inocula on Static Dose against Staphylococci for Different Antibacterials

Drug	Increase in Static Dose for Inocula from 10^5 to 10^7
Vancomycin	13- to 25-fold
Linezolid	2- to 8-fold
Daptomcyin	3- to 7-fold
Ceftobiprole	2- to 5-fold

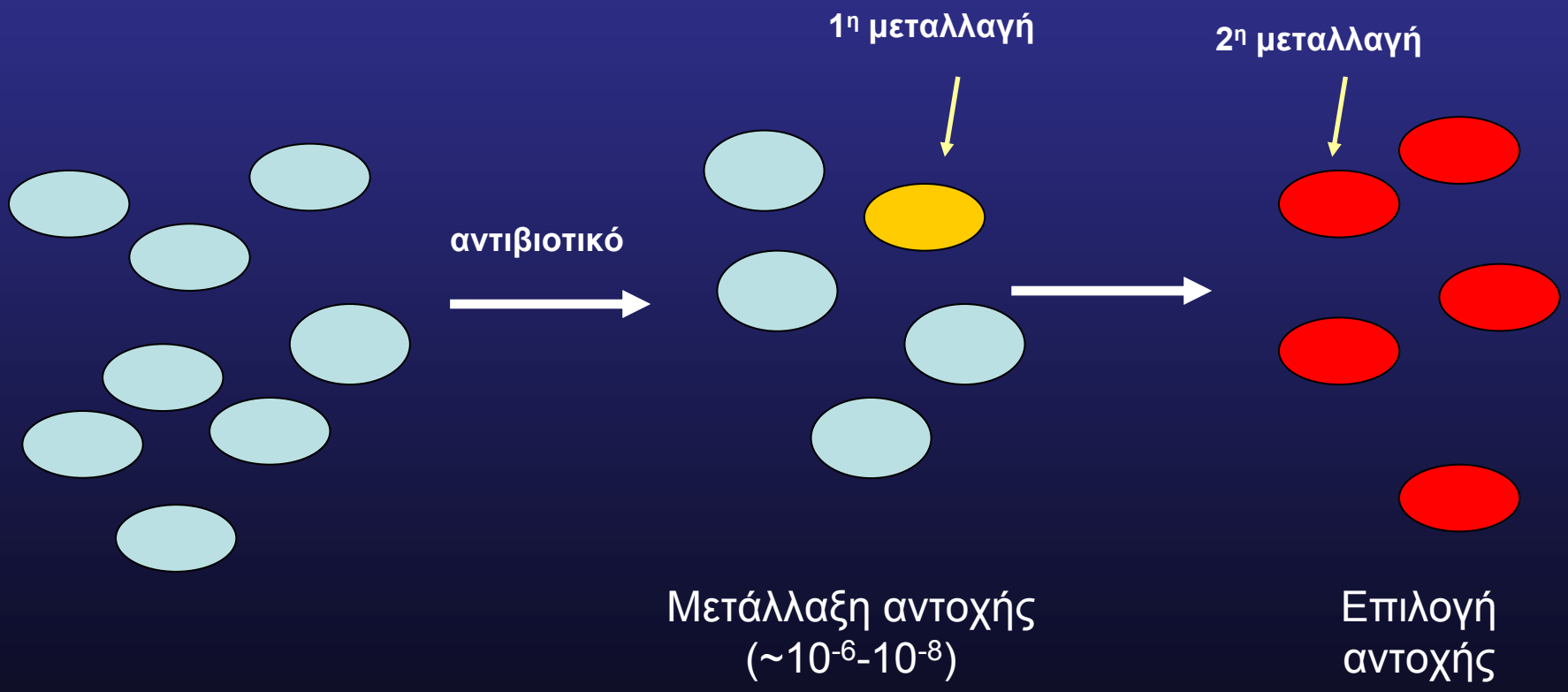
Lee et al ICAAC 2007

PK PD και αντοχή

Μπορούμε να χρησιμοποιήσουμε τις αρχές PK/PD με σκοπό να προλάβουμε την

ΑΝΑΠΤΥΞΗ ΑΝΤΟΧΗΣ;

Μοντέλο ανάπτυξης αντοχής



From CLIN INFECT DIS 33(S3):S147-S156.

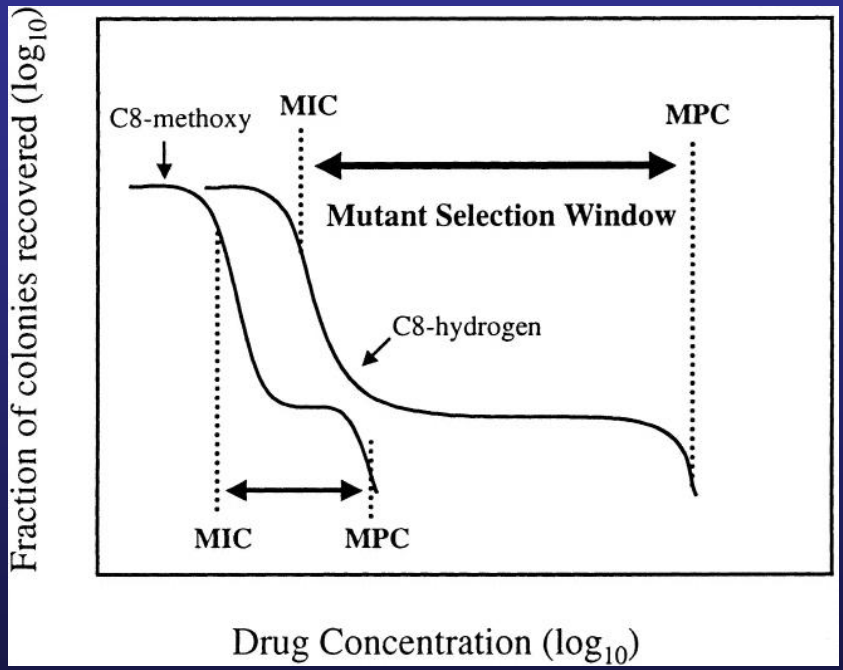
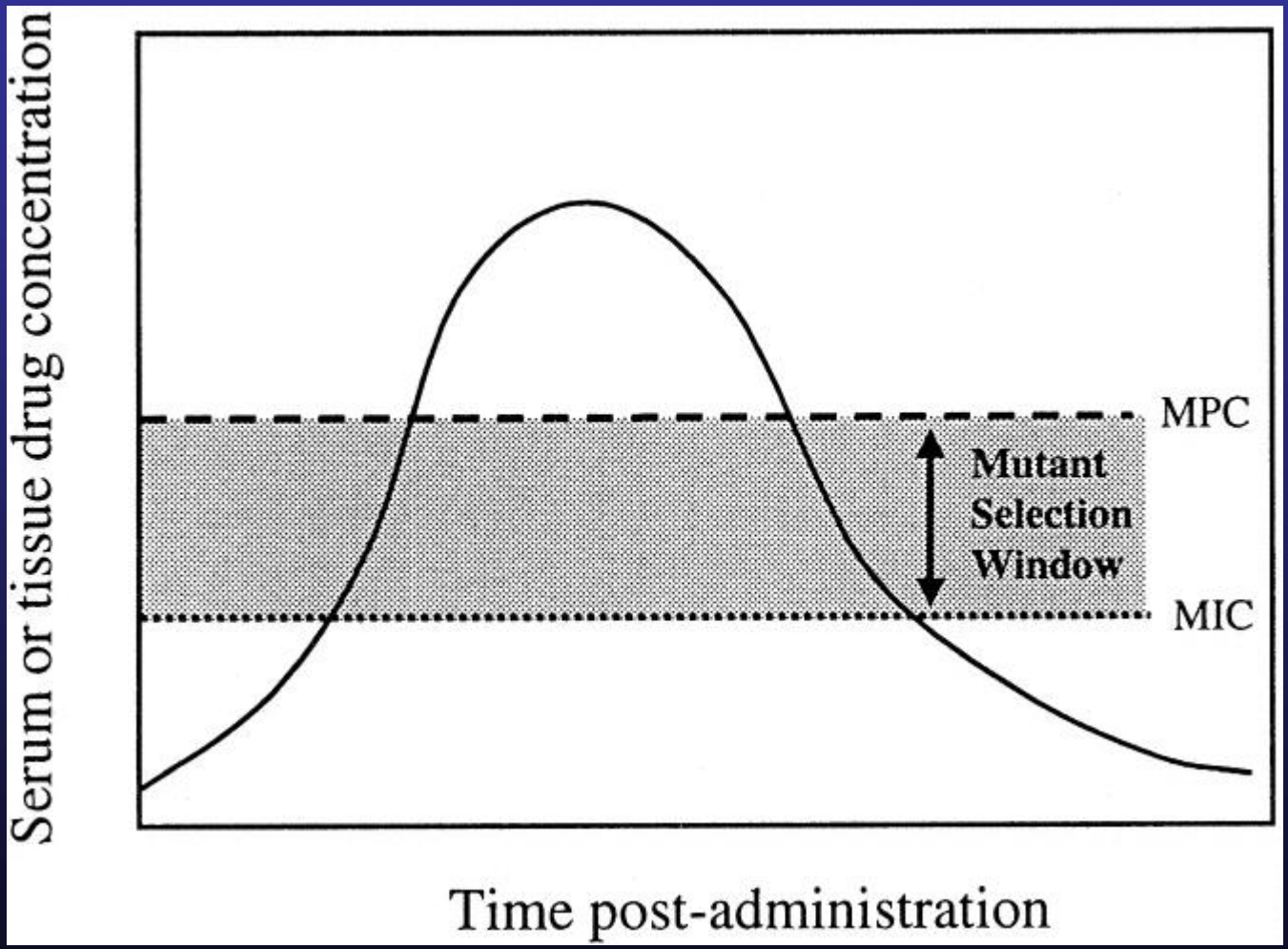
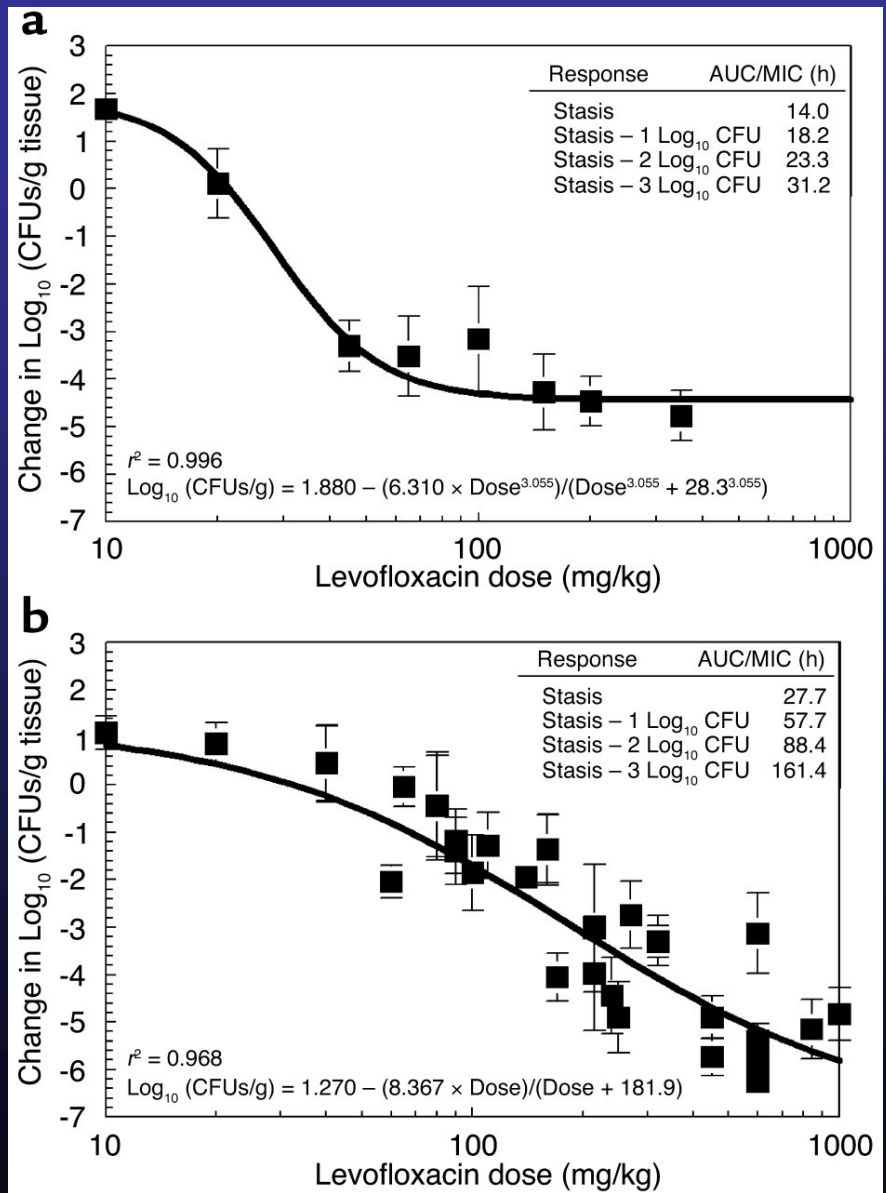


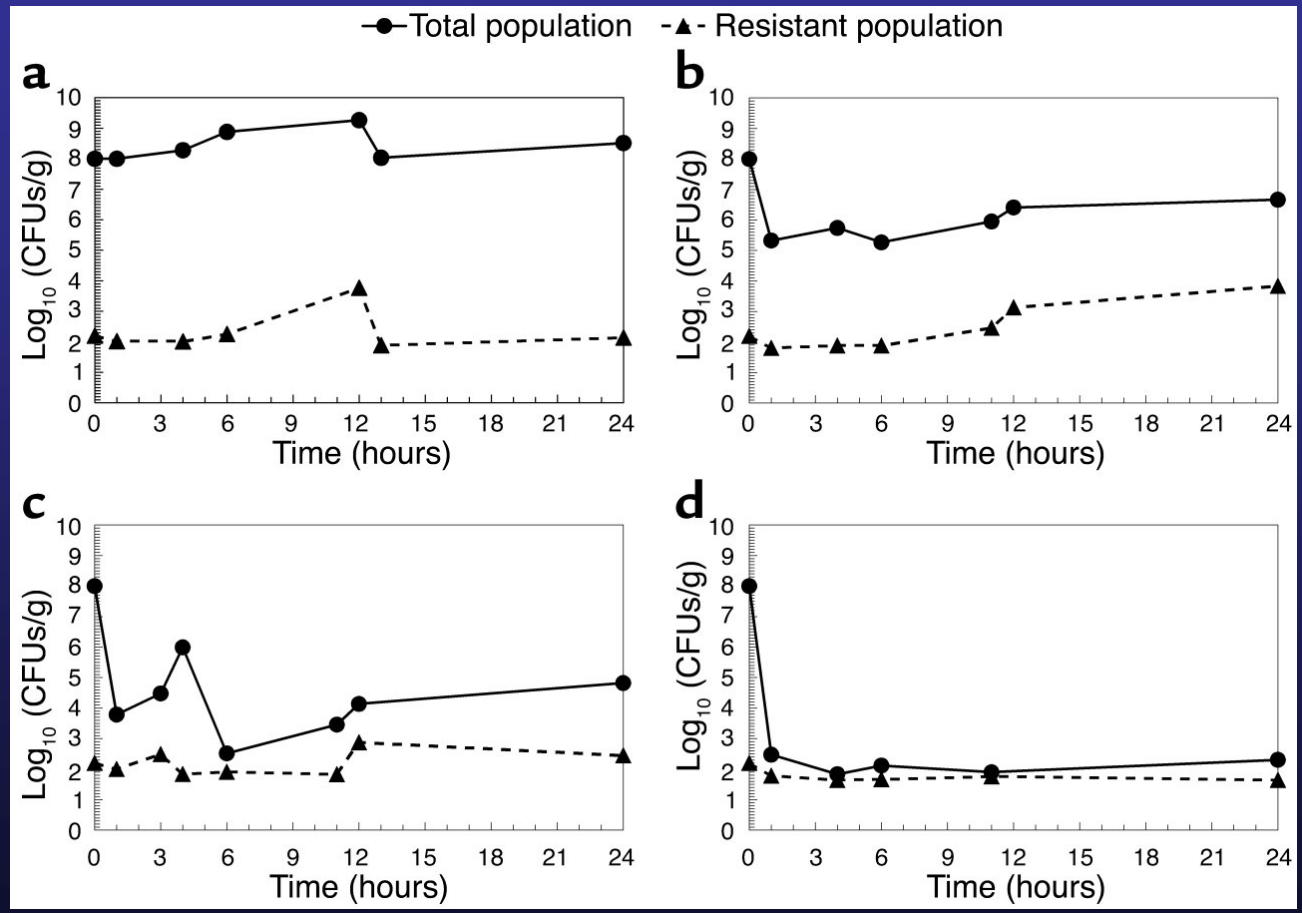
Figure 2. Effect of fluoroquinolone concentration on selection of resistant mutants. Mycobacterium bovis BCG was applied to agar plates containing various concentrations of fluoroquinolone, and, after suitable incubation, colonies were counted. The figure is stylized from data in [24], and the fraction of cells recovered at the plateaus was about 1 in 108. MIC and mutant prevention concentration (MPC) are indicated by dotted lines, and the mutant selection windows are indicated by the double‐headed arrows. In principle, the lower boundary of the window occurs at the drug concentration where growth inhibition of susceptible cells begins, a concentration that is difficult to determine. We use MIC for inhibition of 99% of the cells in a population to approximate this limit. MICs determined according to the NCCLS standards can also be used for approximation of the lower limit.

Mutant selection window





Jumbe L. JCI 2003


Total population
Resistant population
a
b
c
d
Log10 (CFUs/g)
Time (hours)
0
1
2
3
4
5
6
7
8
9
10
0
3
6
9
12
15
18
21
24

MPC κινολονών

	Δόση	MIC	MPC	Cmax	t 1/2
Λεβοφλοξασίνη	500 mg	1	8	5.7	8
Μοξιφλοξασίνη	400 mg	0.25	2	4.5	12

Blondeau JM. *Antimicrob Agents Chemother* 2001

Brief Report

RESISTANCE TO LEVOFLOXACIN AND FAILURE OF TREATMENT OF PNEUMOCOCCAL PNEUMONIA

ROSS DAVIDSON, PH.D., RODRIGO CAVALCANTI, M.D., JAMES L. BRUNTON, M.D., DARRIN J. BAST, PH.D., JOYCE C.S. DE AZAVEDO, PH.D., PAMELA KIBSEY, M.D., CHRISTINE FLEMING, M.L.T., AND DONALD E. LOW, M.D.

N Engl J Med, Vol. 346, No. 10 · March 7, 2002

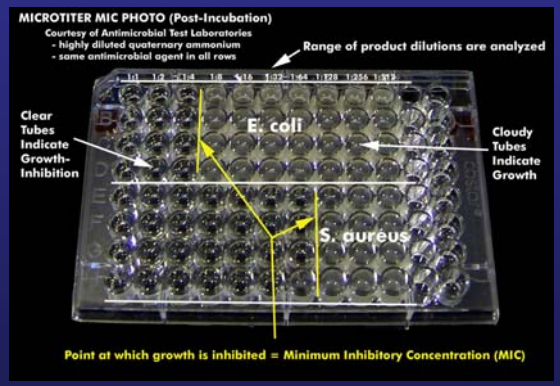
MAJOR ARTICLE

Emergence of Levofloxacin-Resistant Pneumococci in Immunocompromised Adults after Therapy for Community-Acquired Pneumonia

Kevin B. Anderson,[1] James S. Tan,[1] Thomas M. File, Jr.,[1] Joseph R. DiPersio,[1] Barbara M. Willey,[2] and Donald E. Low[2]

[1]Summa Health System, Akron, Ohio; and [2]Toronto Medical Laboratories/Mount Sinai Hospital Department of Microbiology, University of Toronto, Toronto, Ontario, Canada

Clinical Infectious Diseases 2003; 37:376–81


MICROTITER MIC PHOTO (Post-Incubation)
Courtesy of Antimicrobial Test Laboratories
- highly diluted quaternary ammonium
- same antimicrobial agent in all rows
Range of product dilutions are analyzed
Clear Tubes Indicate Growth-Inhibition
E. coli
Cloudy Tubes Indicate Growth
S. aureus
Point at which growth is inhibited = Minimum Inhibitory Concentration (MIC)

Ευχαριστώ