Basic Concepts of PK/PD
-pharmacodynamic indices-

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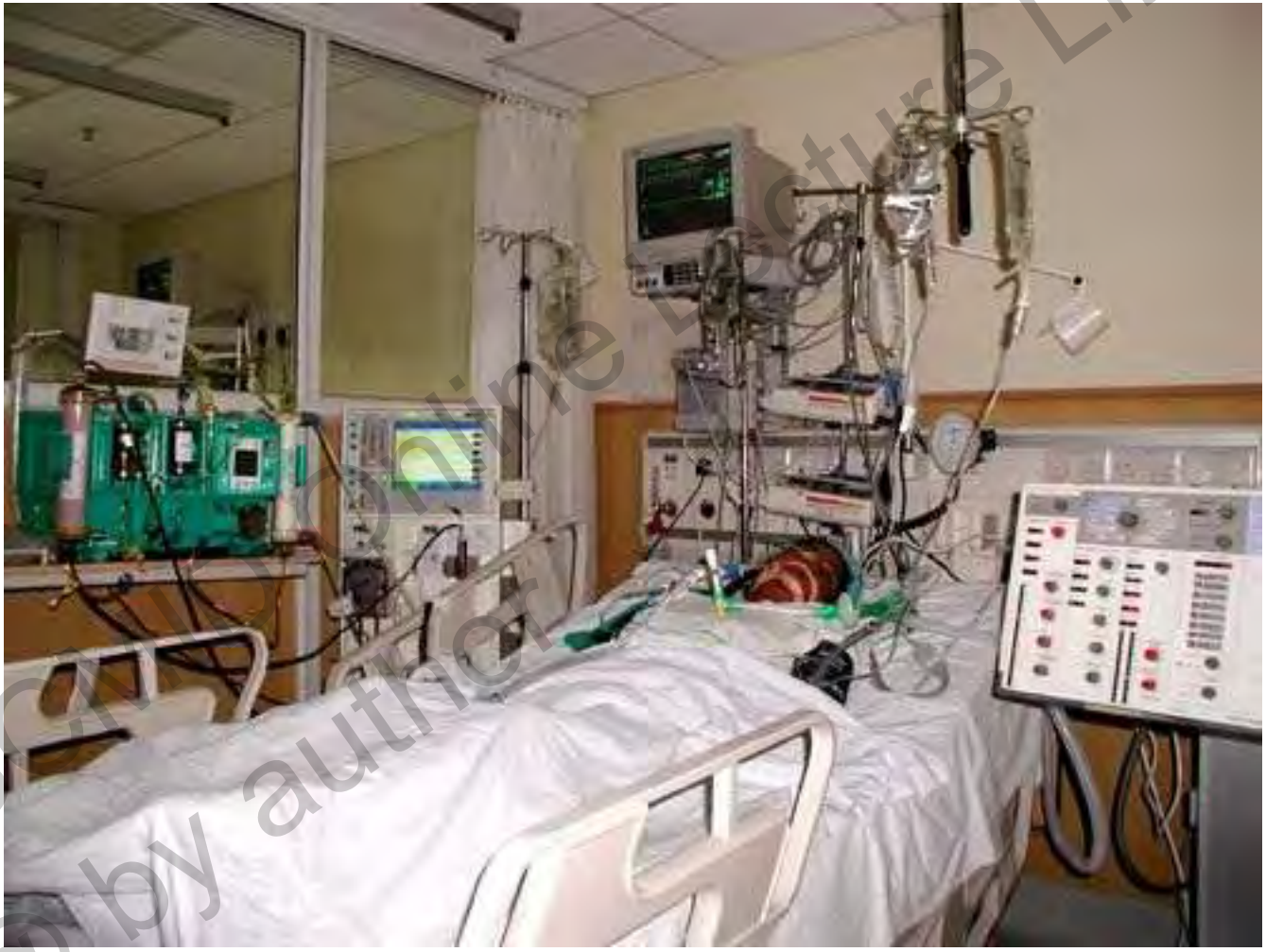
Professor pharmacokinetics and pharmacodymamics



Intensive care patient

Which of the following dosing regimens is best?

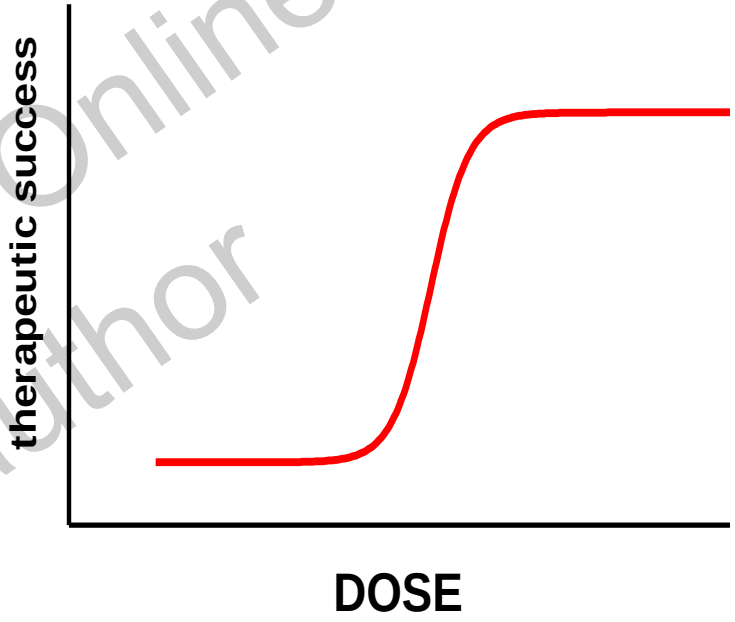
A. 1000 mg q12h

B. 500 mg q6h

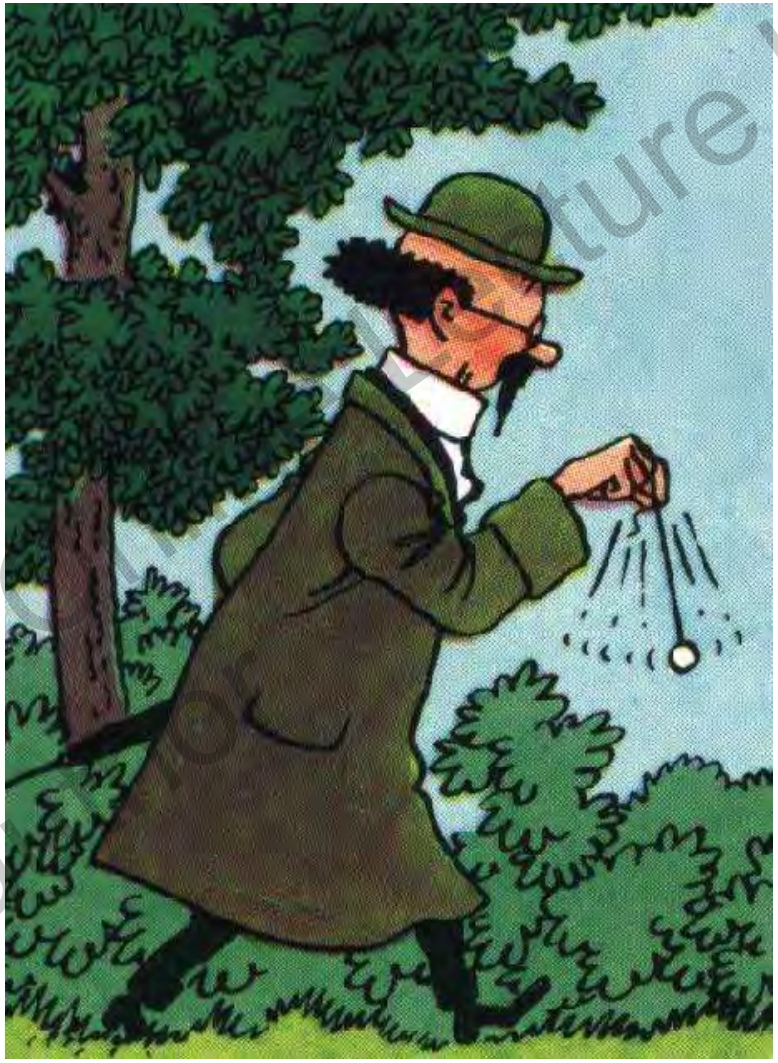
C 2000 mg q12h

D 1000 mg q8h

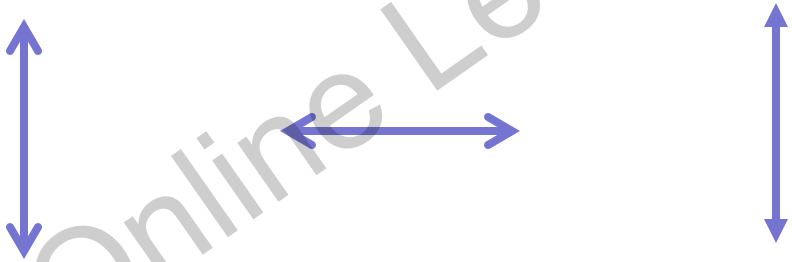
Dosing should be such that the level of antmicrobial activity is associated with a high likelihood of therapeutic success.



Dose Finding - The Past



Efficacy of the drug



Potency of a drug
(MIC)

Exposure to the bug
In vivo
(PK)

ACTVITY
***in vitro* (MIC)**

CONCENTRATIONS
***in vivo* (PK)**

DOSING
regimen

ANTMICROBIAL EFFICACY
(*Microbiological Cure*)

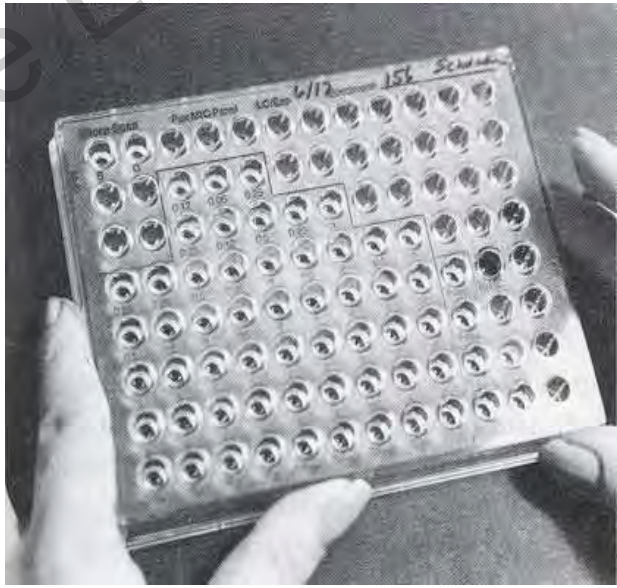
Other factors

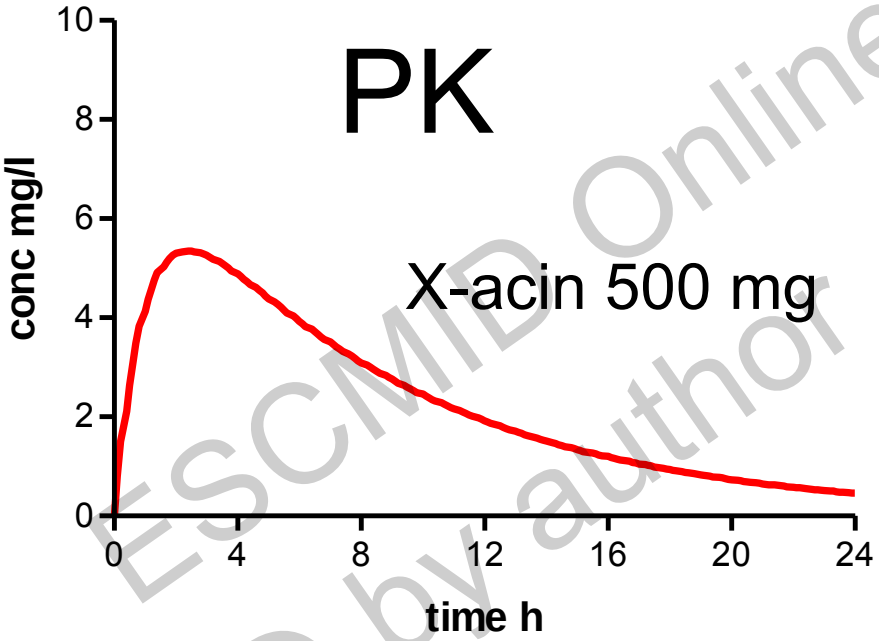
CLINICAL EFFICACY
(*Clinical Cure*)

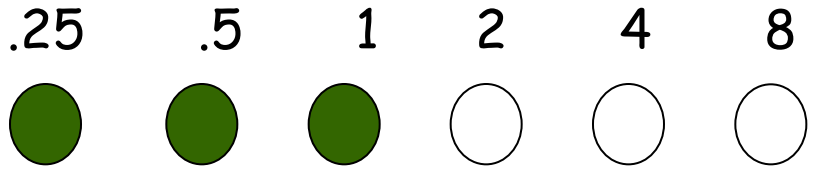
Mouton et al., *Drug Resistance Updates 2011*

MIC

Lowest concentration with no visible growth after 18 hour incubation







MIC = 2 mg/L

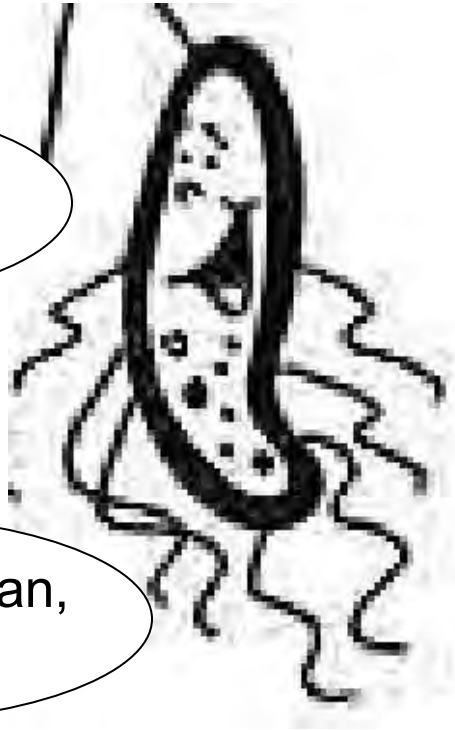
Pharmacokinetic Parameter (and Dose)

MIC

- Thus, we have to:
  - Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
  - Determine which dosing regimens are optimal for Treatment in relation to the MIC

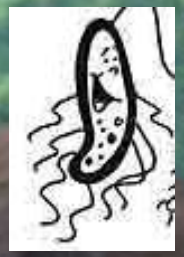
Any idea where we are today?

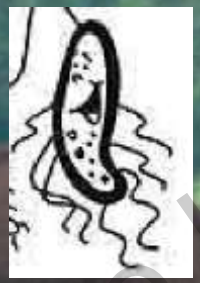
No idea…
may be a mouse?



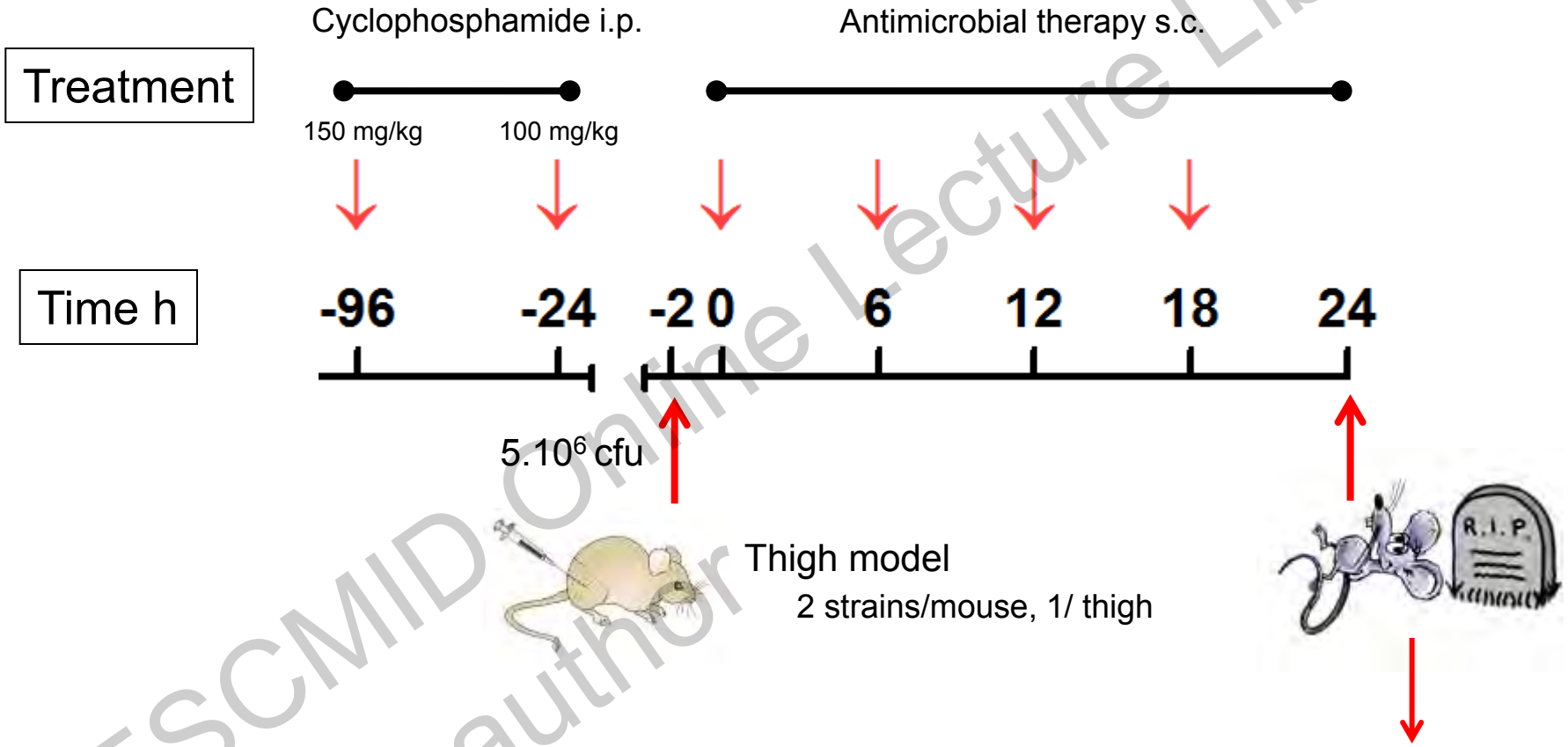
Might be a human,
though…

An elephant….
Today it is an elephant!





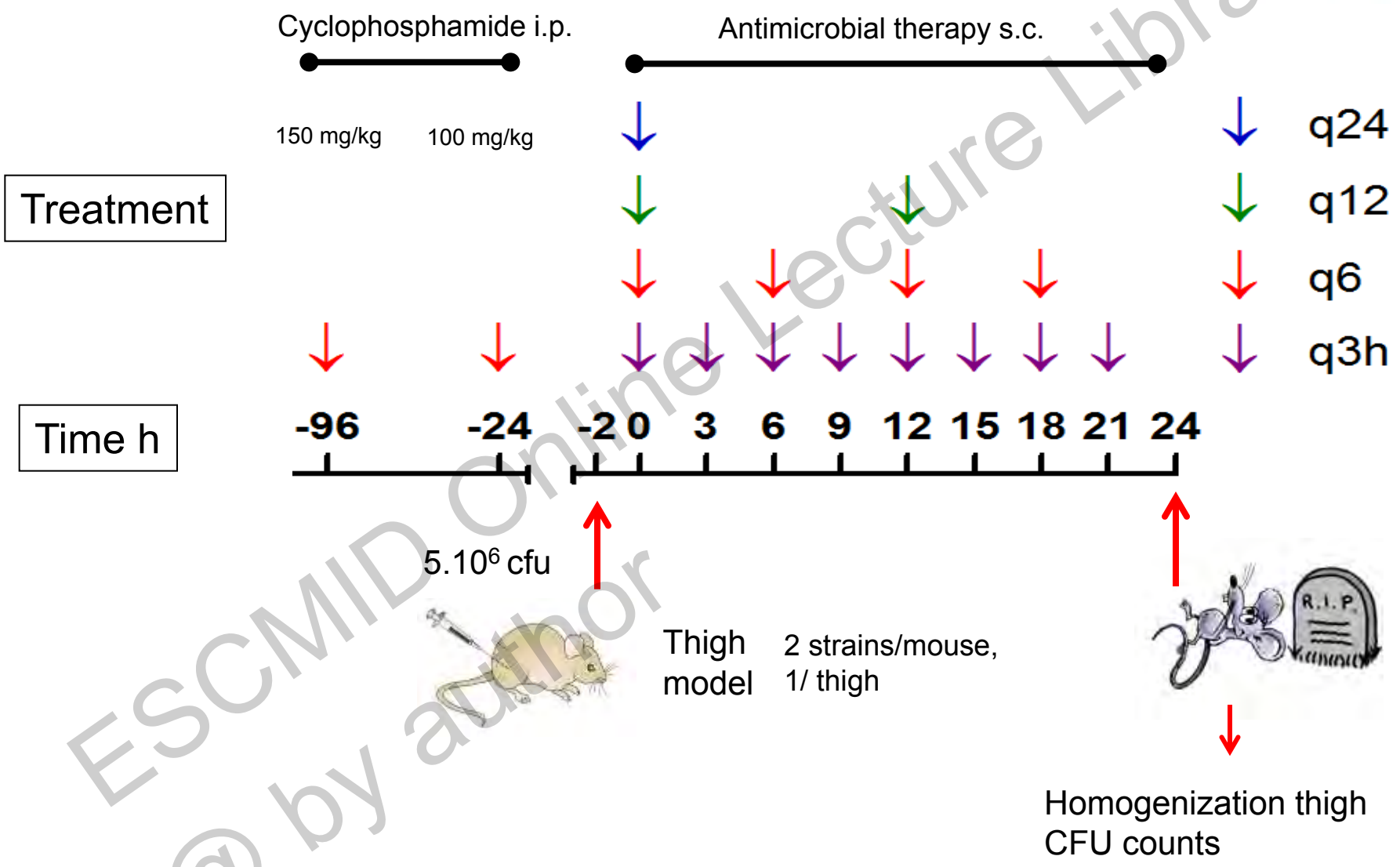
Neutropenic Mouse Model
Example with q6h dosing



PK/PD
dose fractionation studies

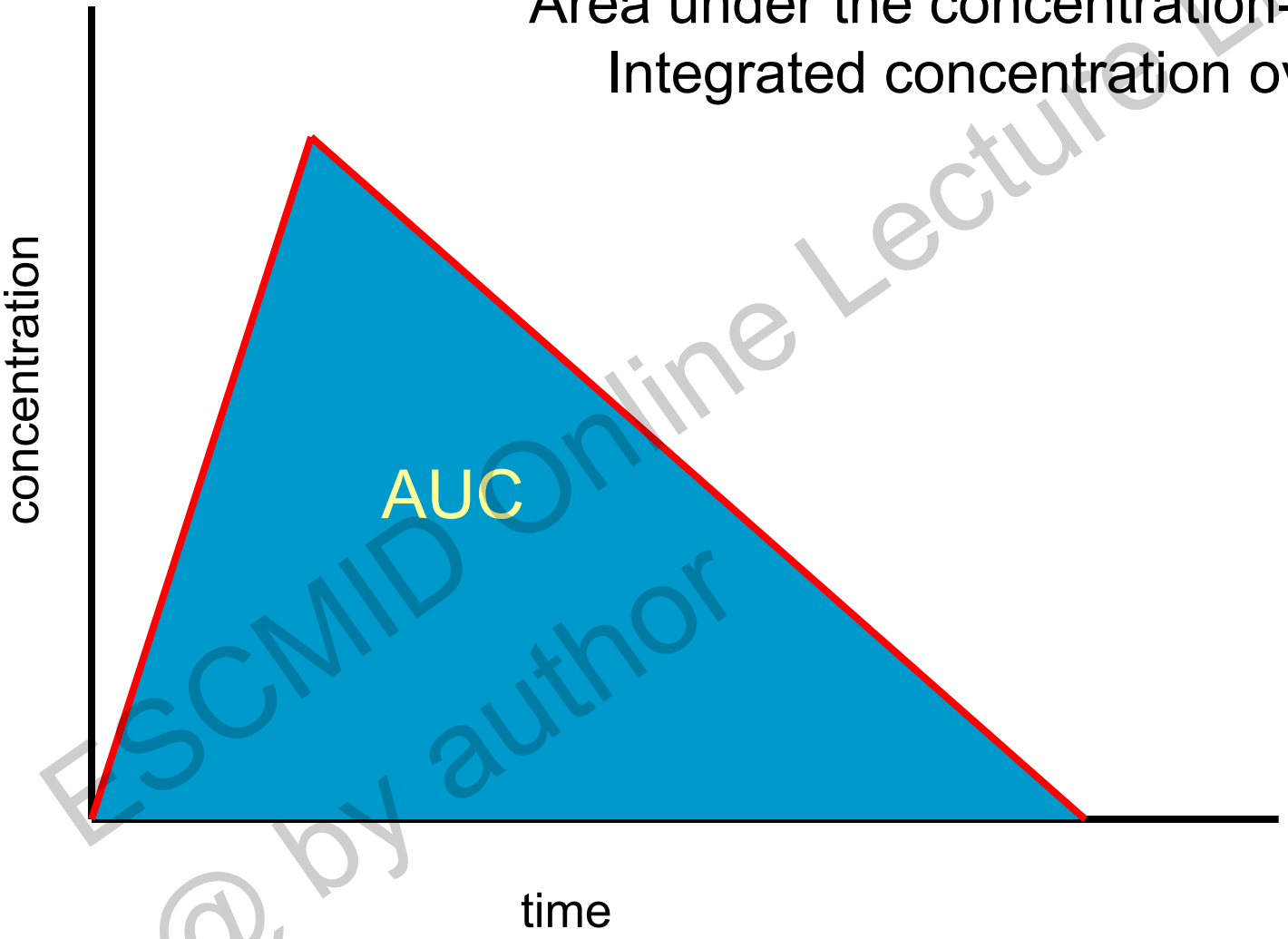
- Neutropenic mouse thigh model 
- Various doses and dosing regimens (q1 to q24)
- Outcome parameter: cfu counts after 24 h
- Plot PK parameter and/or PK/PD index (AUC, Peak %*f*T>MIC) to effect

General Diagram Dose fractionation studies



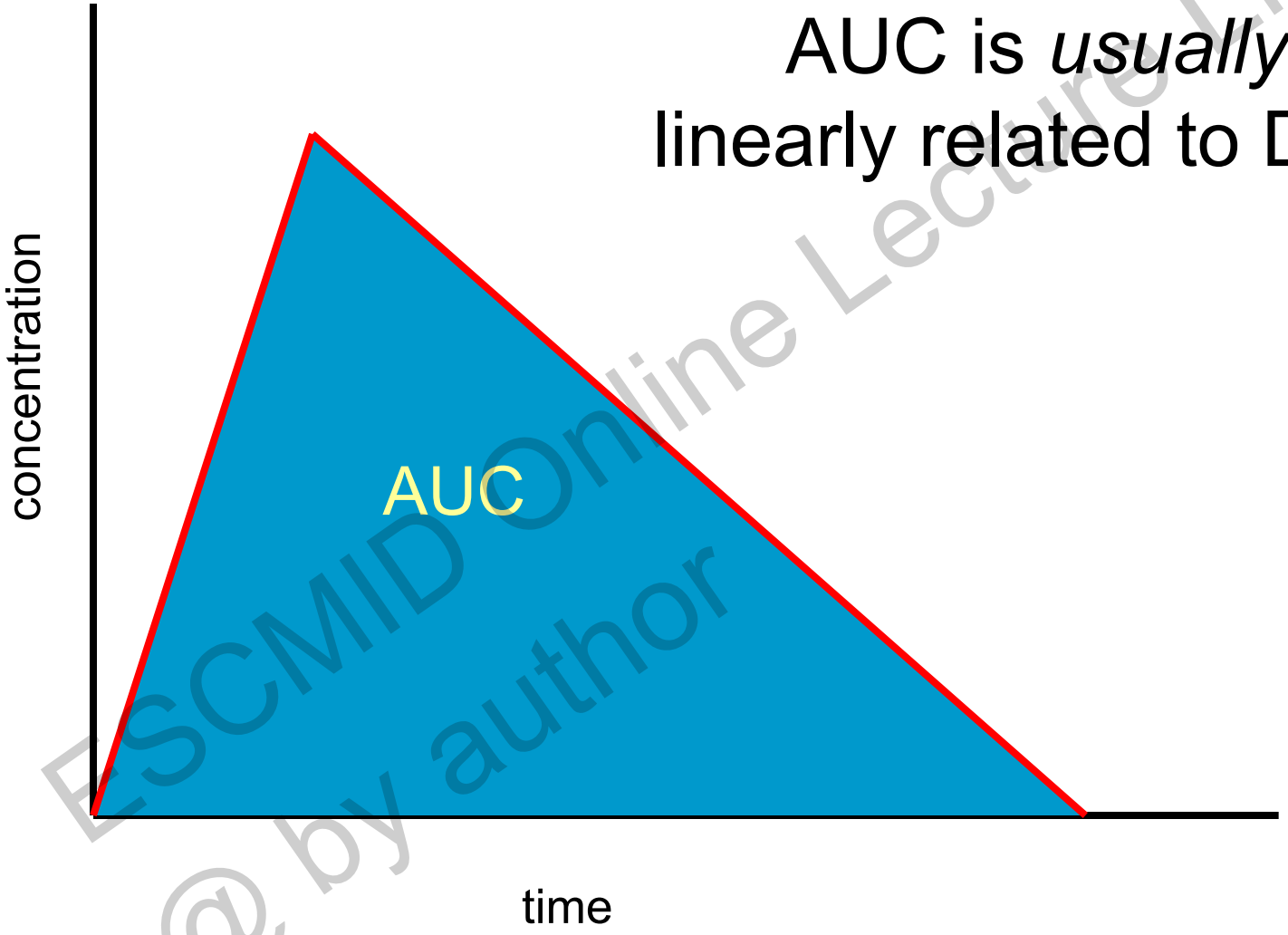
Pharmacokinetic parameters : Measures of Exposure

Area under the concentration-time curve
Integrated concentration over time

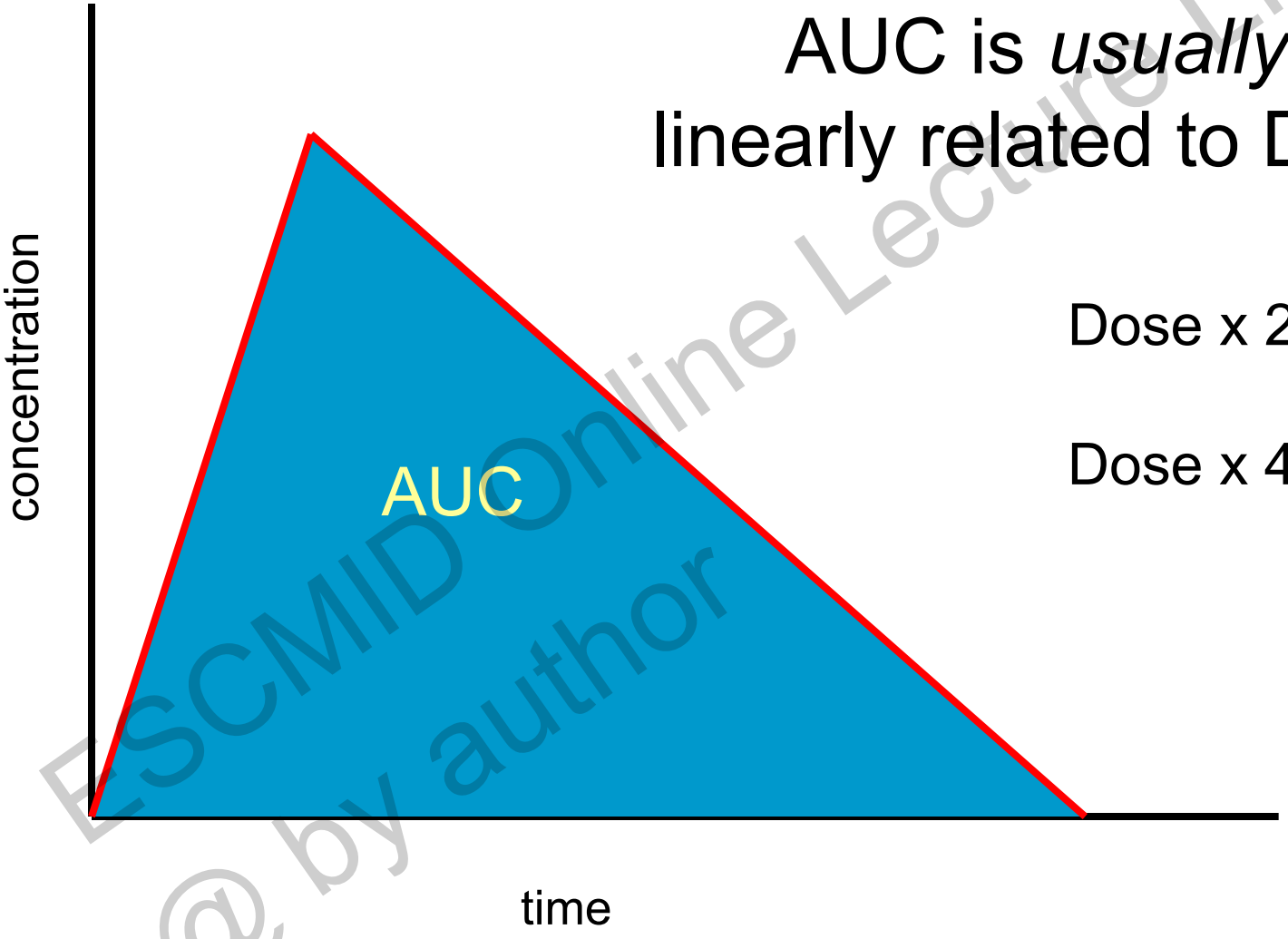


Pharmacokinetic parameters : Measures of Exposure

AUC is *usually* linearly related to Dose



Pharmacokinetic parameters : Measures of Exposure

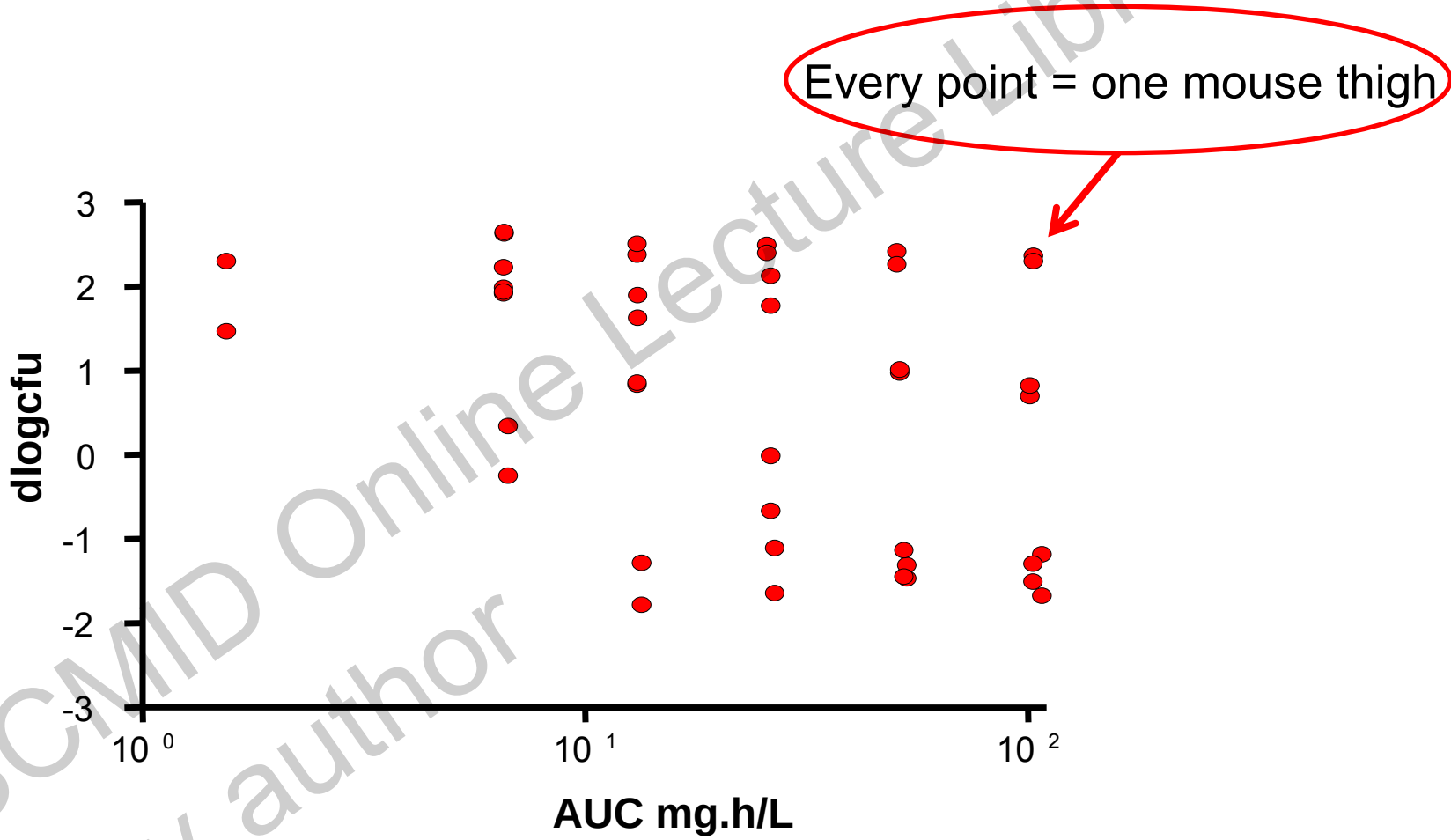


AUC is *usually* linearly related to Dose

Dose x 2 = AUC x 2

Dose x 4 = AUC x 4

K. pneumoniae, imipenem

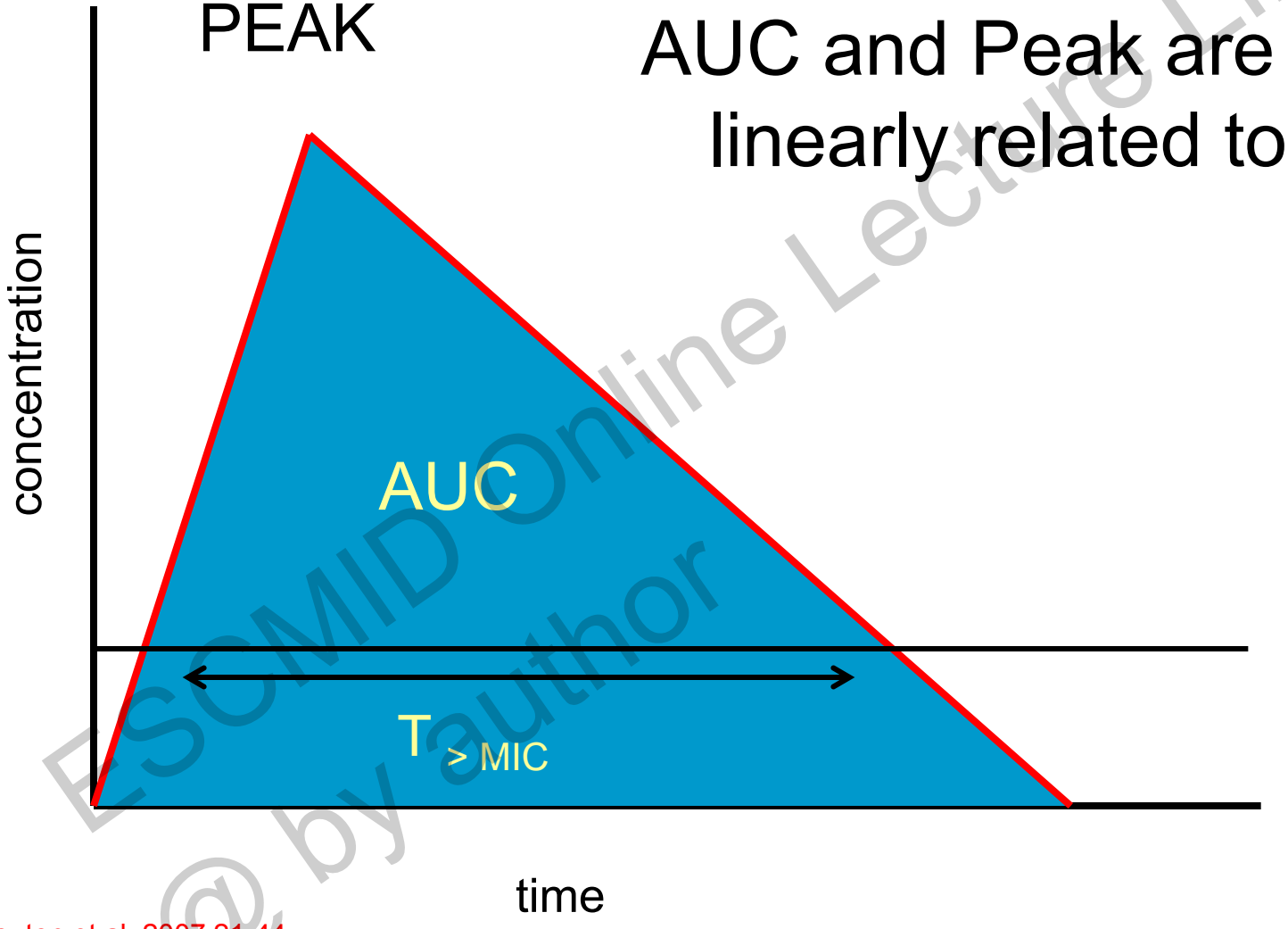


dlogcfu = logcfu (t=24h) – logcfu (t=0h in controls) = net effect of treatment

Based on data from Craig WA

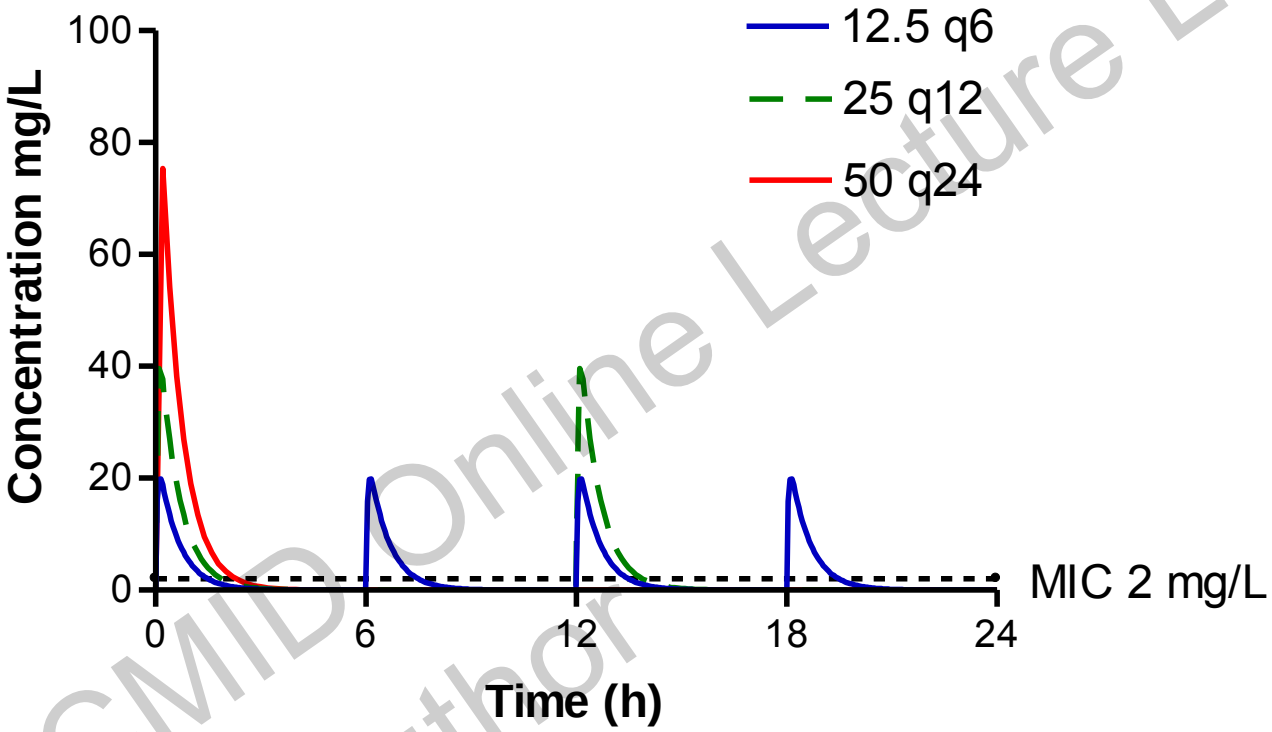
For *K.pneumoniae*, there is no clear relation between AUC (or total daily dose) of imipenem and efficacy in an in vivo model of infection

Pharmacokinetic parameters : Measures of Exposure



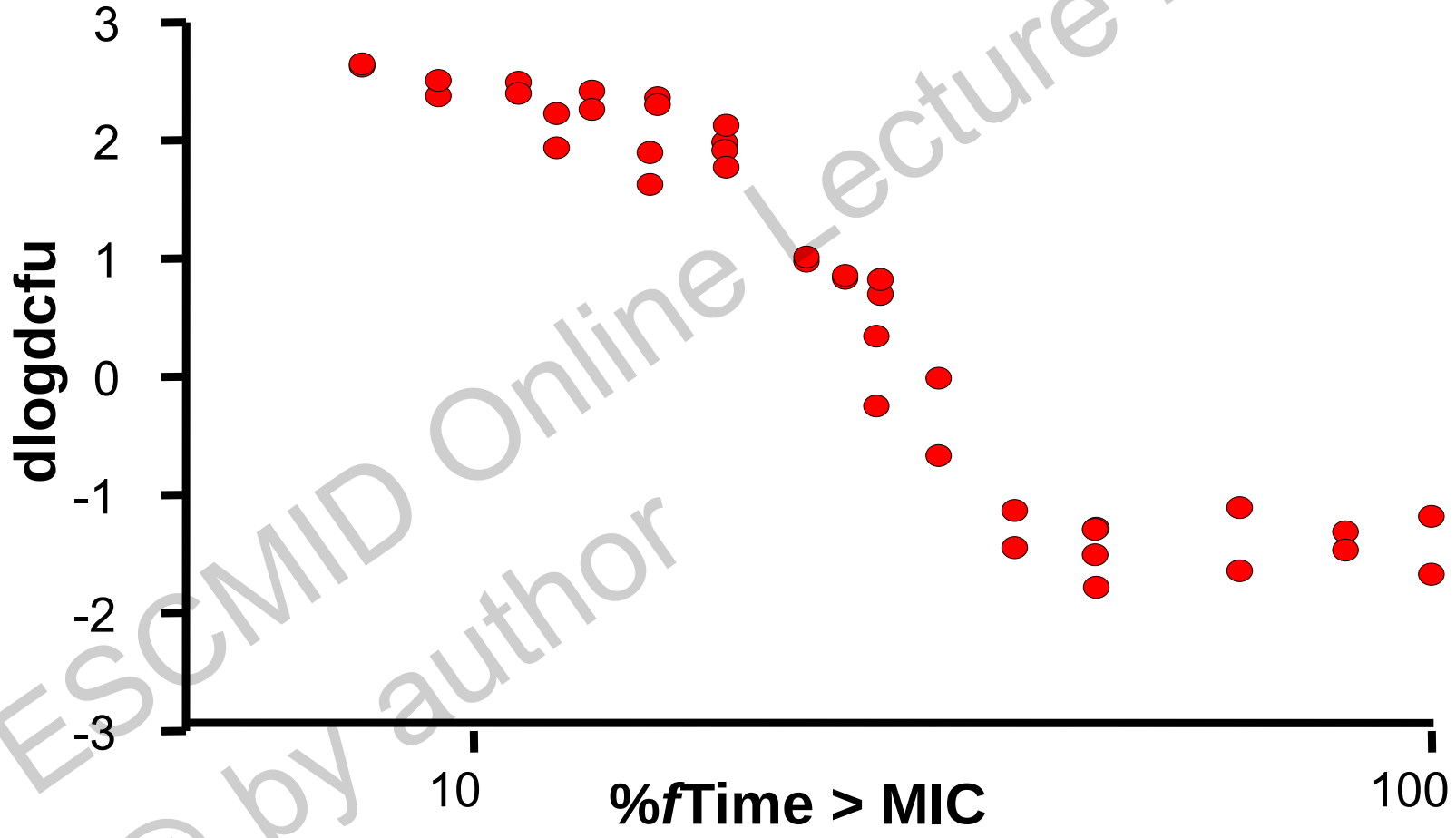
AUC and Peak are *usually* linearly related to Dose

Time > MIC dependent on dose frequency



total length of bars corresponds to Time > MIC

K. pneumoniae, imipenem



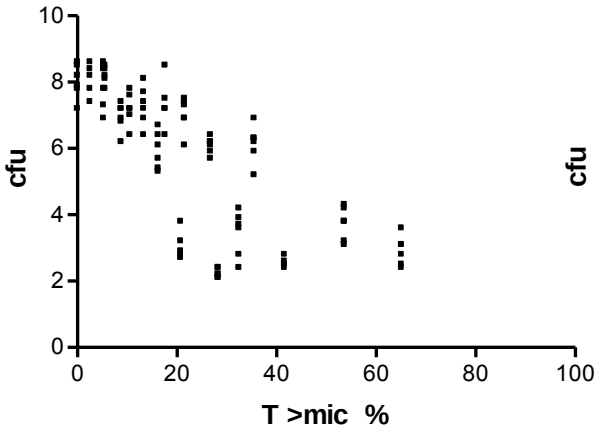
Based on data from Craig WA

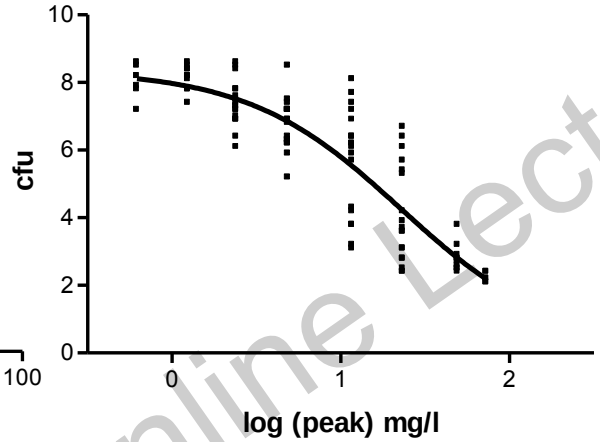
For beta-lactams, there is a direct

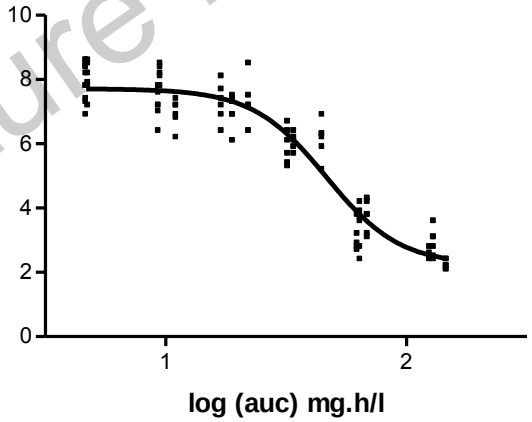
relation between

Time > MIC and efficacy

Levofloxacin in *S. pneumoniae* infection in mice





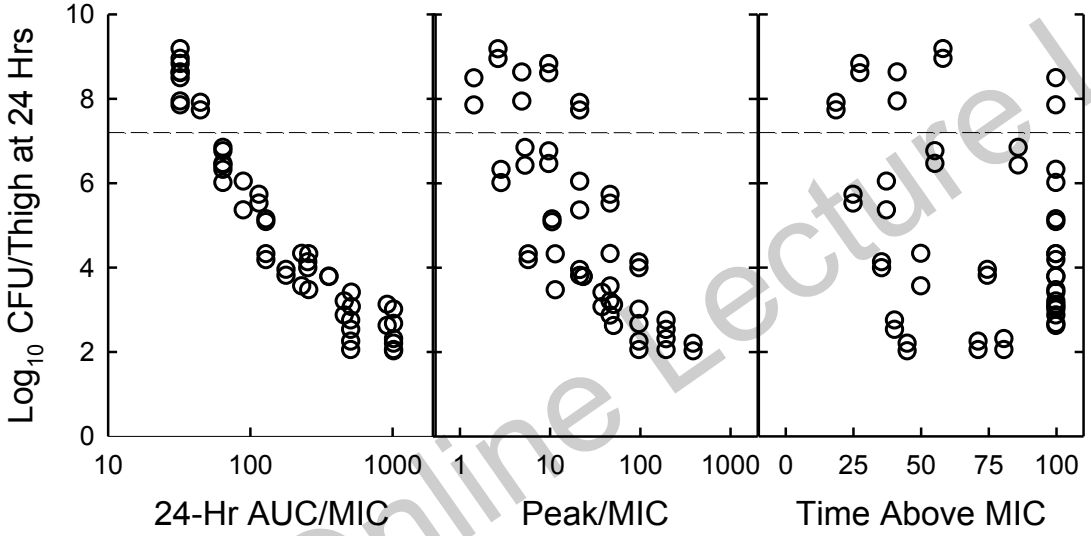


Relationship between T>MIC , Peak, AUC

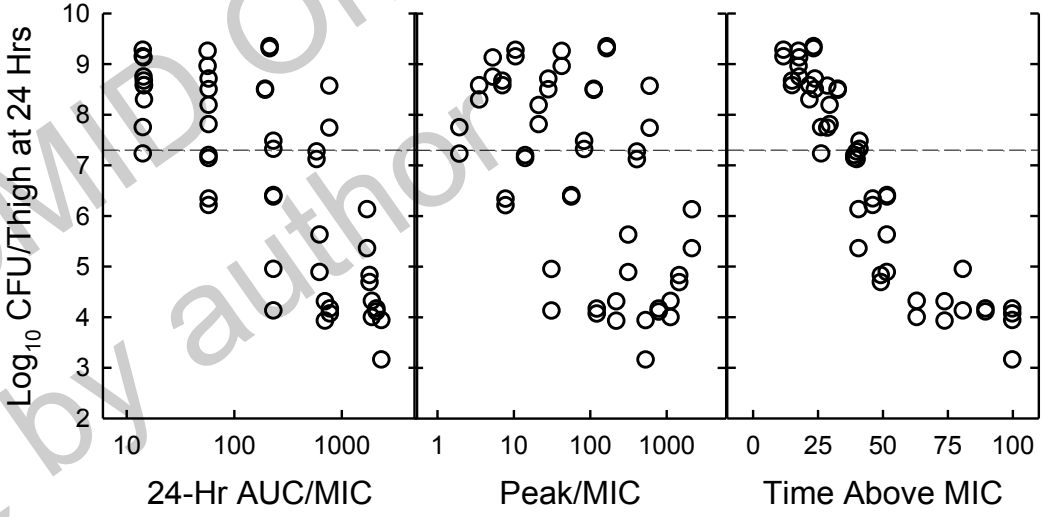
Each dot represents one mouse / dosingregimen.

Based on data from Scaglione & Mouton, 2001, 2003

PK/PD relationship is Class Dependent



levofloxacin



ceftazidim

Andes IJAA 2002

3 Possible Outcomes of Dose fractionation (in general)

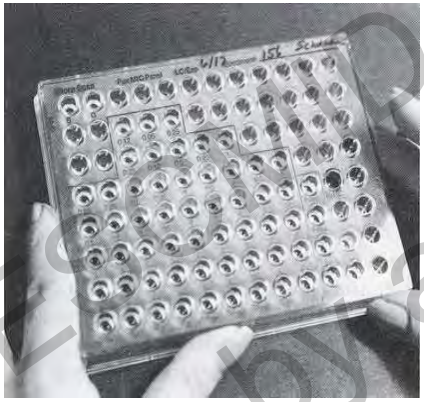
Efficacy Q3 > Q6 > Q12 > Q24	Primarily Time dependent (f)
Efficacy Q3 < Q6 < Q12 < Q24	Primarily Cmax (D) dependent
Efficacy Q3 = Q6 = Q12 = Q24	Primarily AUC (TDD) dependent

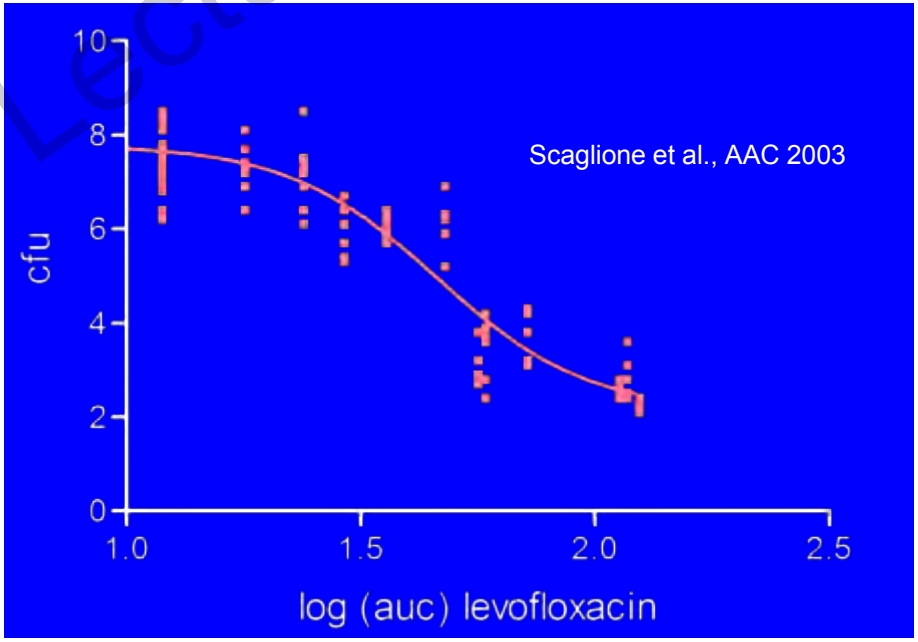
Relationship PkPd and Effect

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

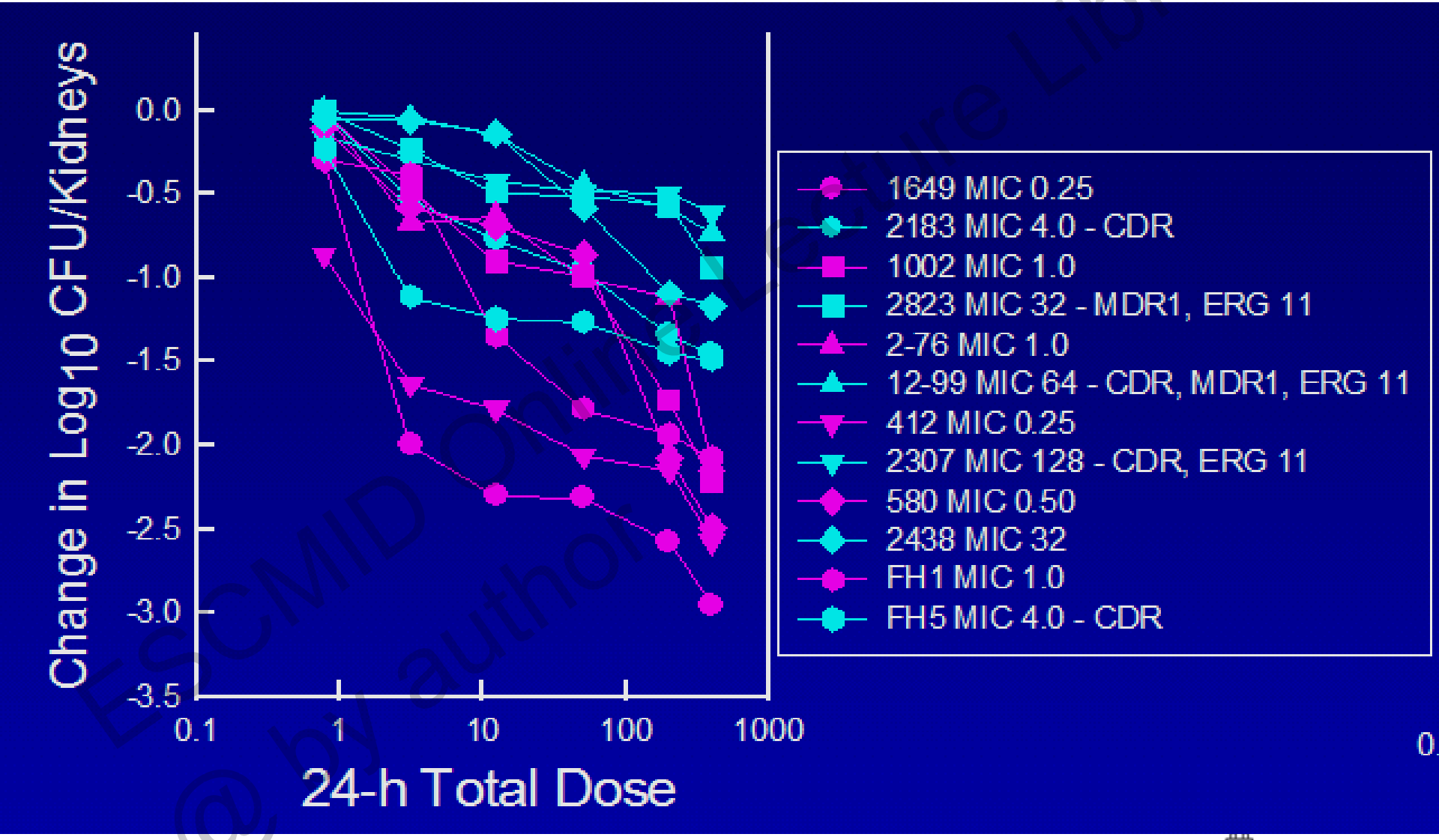
Relationship AUC and effect

- What has the MIC to do with this?



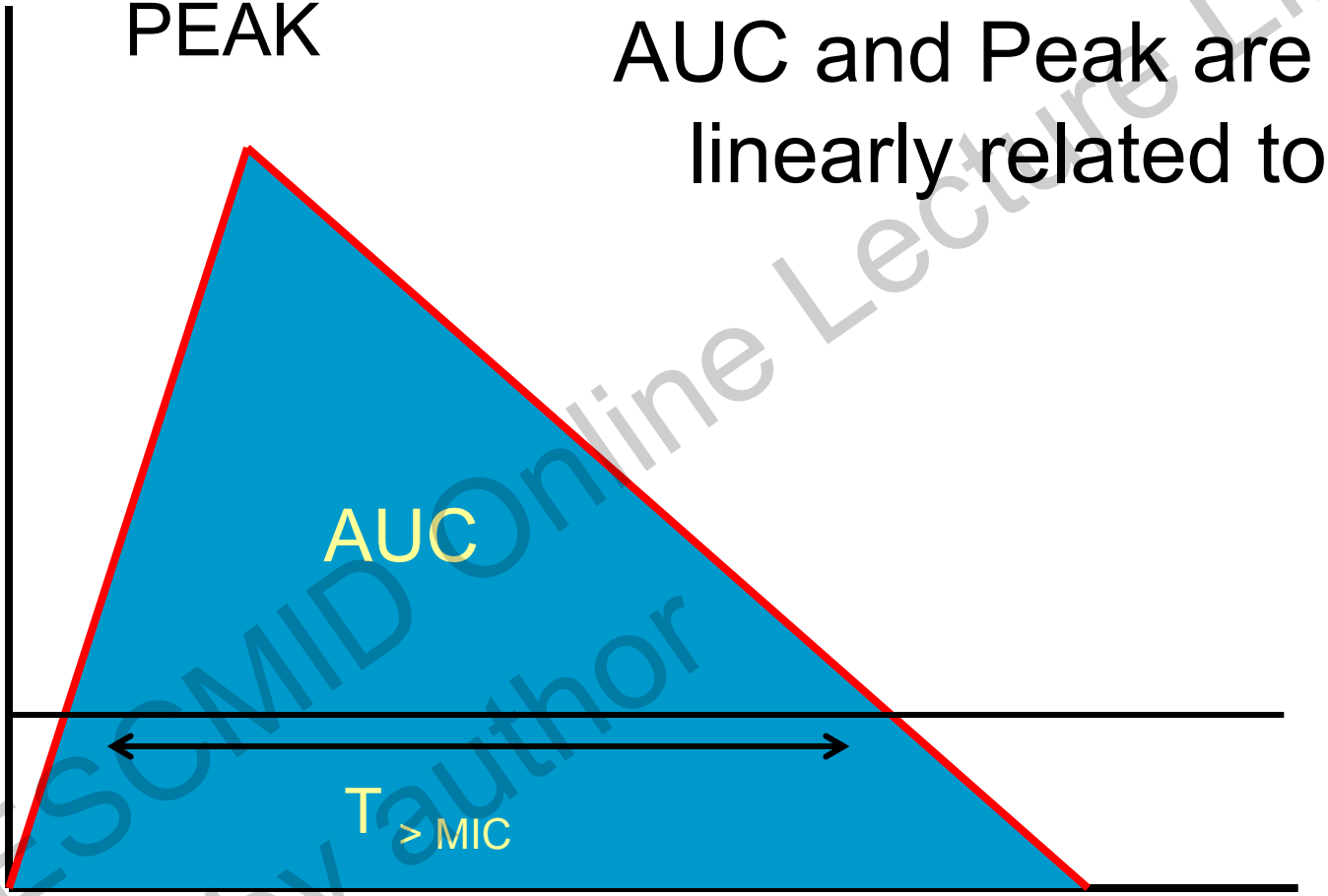


Fluconazole efficacy in mice
Dose *vs MIC*



Andes et al ISHAM 2003

Pharmacokinetic parameters : Measures of Exposure



AUC and Peak are *usually* linearly related to Dose

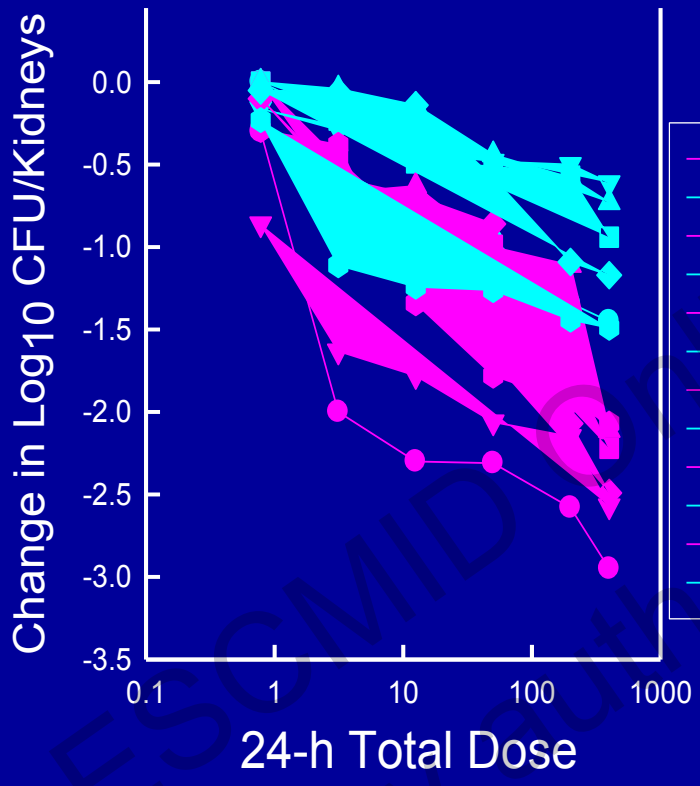
'Normalizing pk/pd relationships'

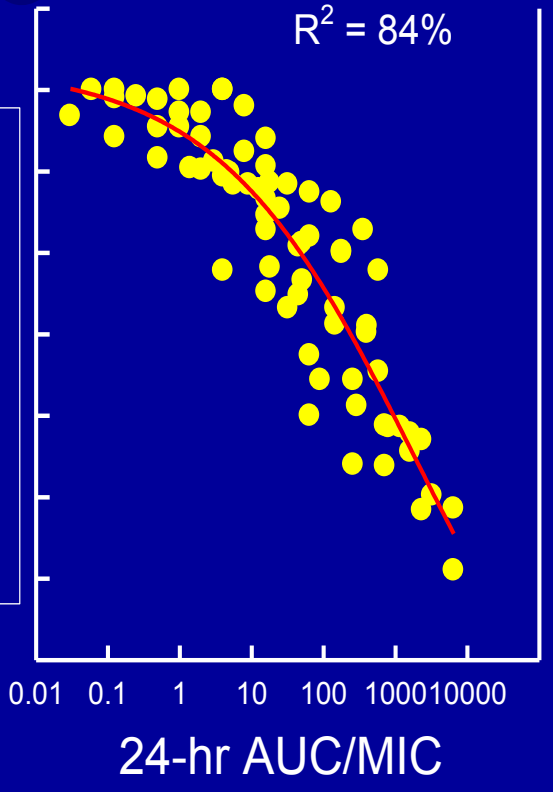
Pharmacokinetic parameter

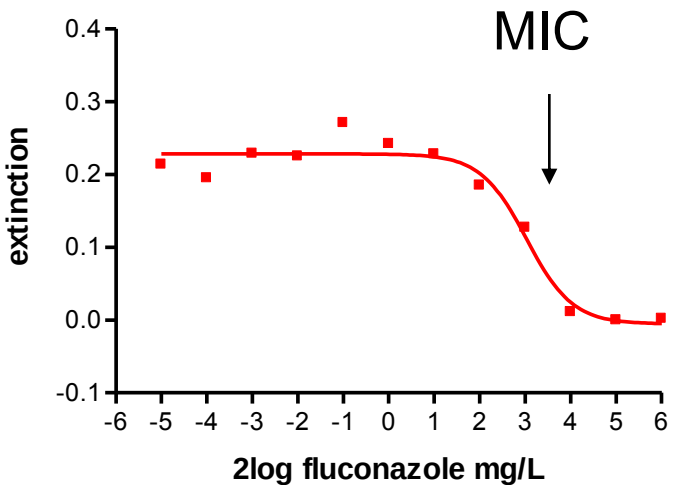
MIC

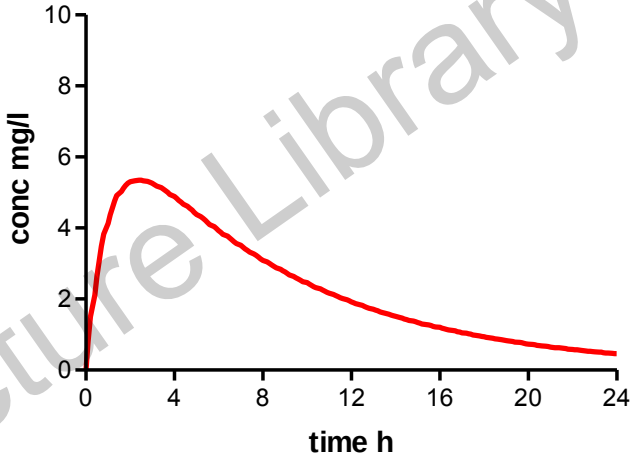
Pharmacodynamic index
(AUC/MIC, Peak/MIC, T>MIC)

Fluconazole Pharmacodynamics Against Isogenic Strain Pairs of Susceptible and Resistant C. albicans



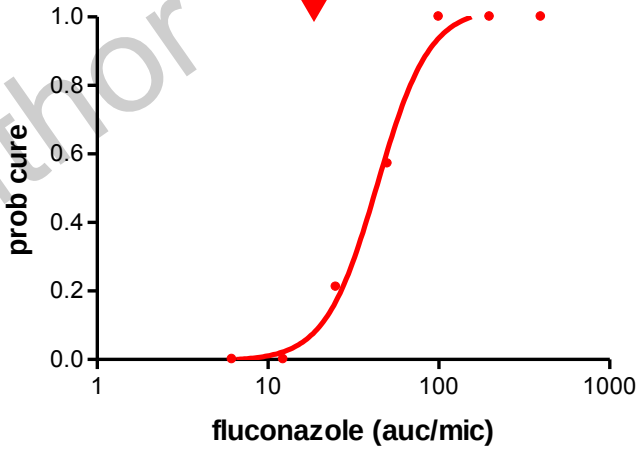






In vitro effect
at fixed concentrations

In vivo CT profile
dynamic concentrations



Response Curve

Probability of cure after treatment with fluconazole Oropharyngeal Candidiasis n=132

Treatment with fluconazol
Doses 50 – 800 mg

↓

Individual Dose

Culture-results with
MIC-values

↓

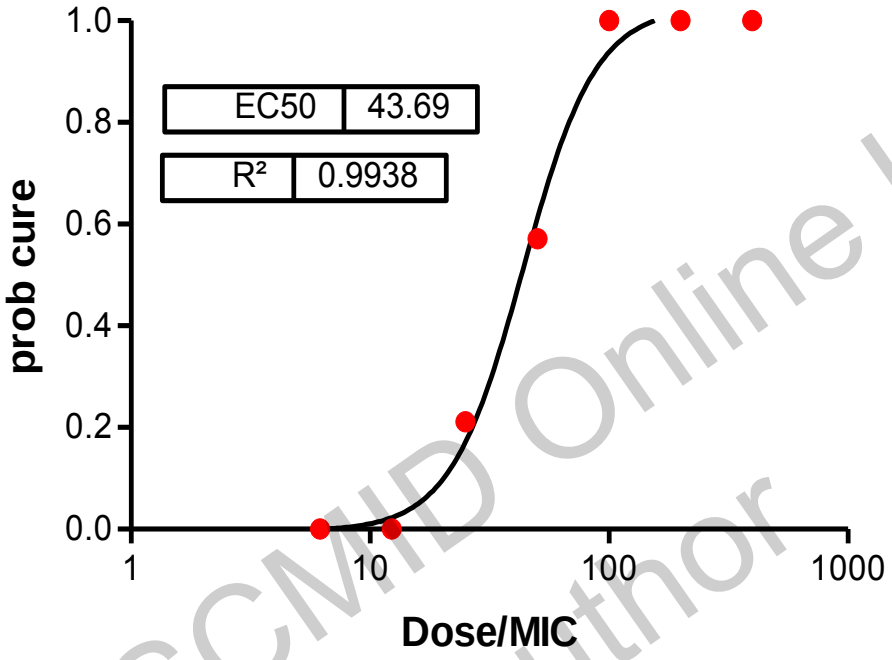
MIC-values per individual

Determine Dose/MIC for each patient

↕

Microbiological outcome (candida cured)
Clinical outcome

Probability of cure after treatment with fluconazole Oropharygeal Candidiasis n=132



- Prob cure correlates with Dose/MIC
- POSITIVE correlation with dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value

Rodriguez- Tudela et al, AAC 2007

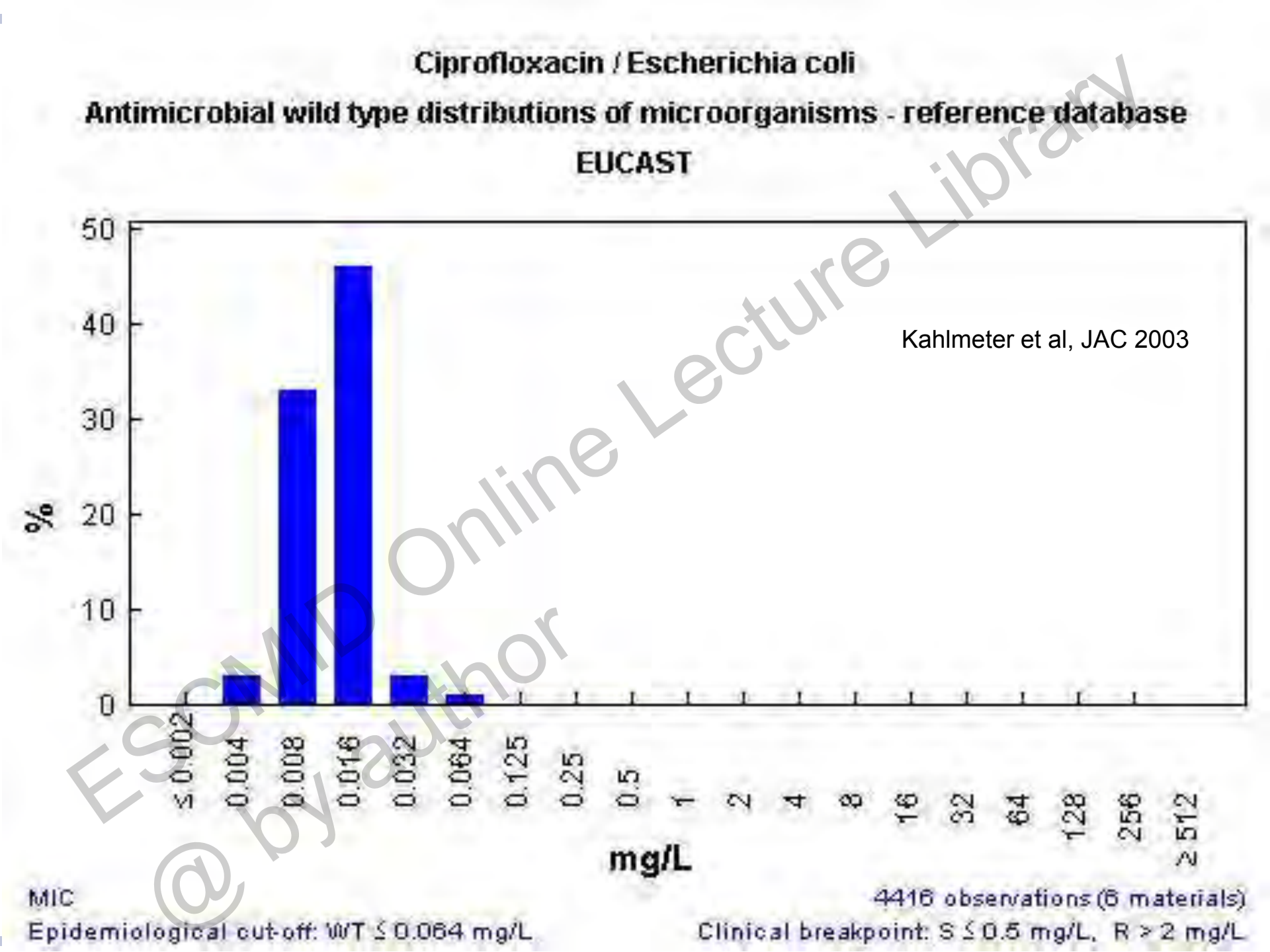
Why is the term pk/pd index used instead of pk/pd parameter?

-a ratio (e.g.) of two independent parameters, not a parameter by itself

Mouton et al, J Antmicrob Chemother 2005 55:601.
Available from ISAP site (www.isap.org)

Thus, 2 factors influence the value of the pk/pd index:

MIC and its Errors/variation
Pharmacokinetics and its variation



- Growth and/or kill rate dependent :
  - strain, species
  - medium composition, brand
    - MH, supplements, ISO
  - number of bacteria
  - inoculum
    - 5.10^5 (CLSI) vs 10^5 (BSAC)
  - temperature (35^o vs 37^o)
  - growth phase
  - CO^2
  - etc.

The reference method

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

↓

International Organization for Standardization

2003 20 june DIN Berlin
CEN TC140/WG10

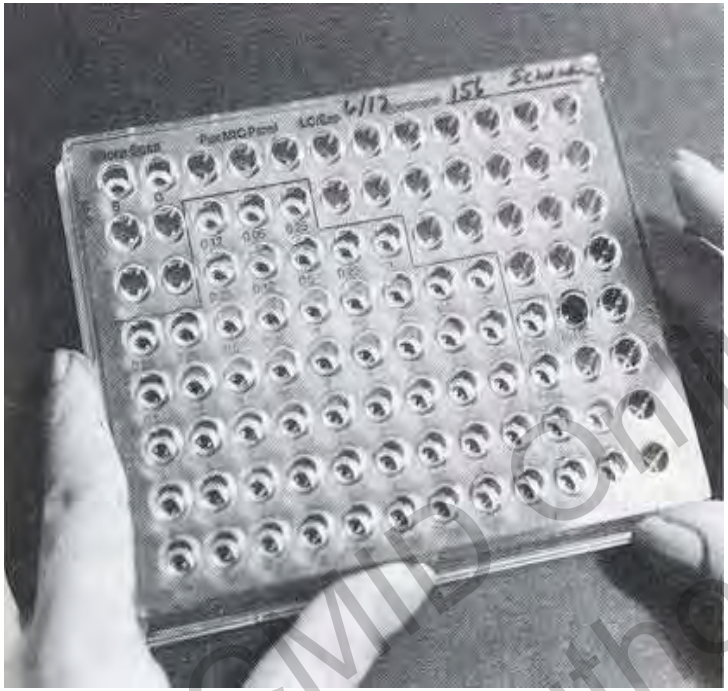
2004 22 april DIN Berlijn
Combined meeting with
ISO ISO/TC 212 WG4
Vienna Agreement

2005 Vote on first draft and comments by all Member Countries

2006 Final version 27 October 2006, 8th CEN, 6th ISO meeting
ISO 20776-1

2007 Final version validation ISO 20776-2.

The reference method - Microdilution

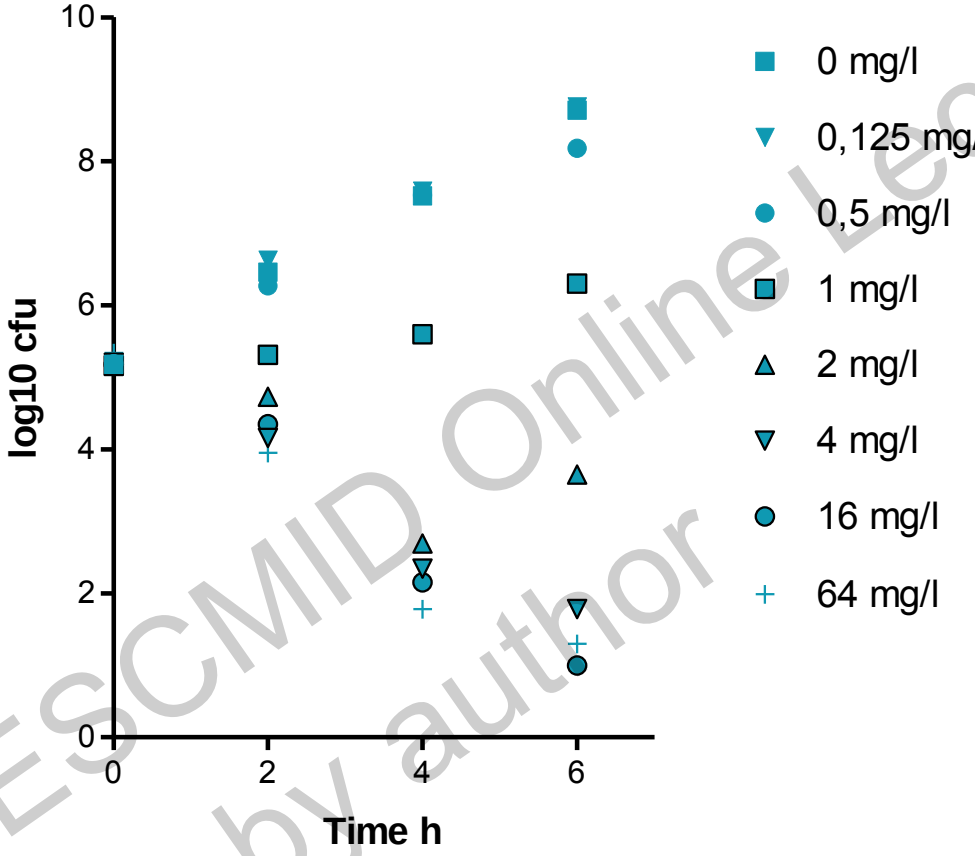


- Microdilution, 0.1 ml
- Mueller Hinton (1941, Corn starch)
- Inoculum 5 (2-8) .10E5 cfu/ml
- 36 ± 1 °C
- 18 ± 2 h incubation

The reproducibility of the MIC test is within 2 2 2fold dilutions. The variation introduced in the AUC/MIC and Peak/MIC values by the MIC is there for at least 0.5 tot 2 x the pk/pd index value!

Why is outcome of beta-lactams %*f*T>MIC related?
And aminoglycosides AUC related?

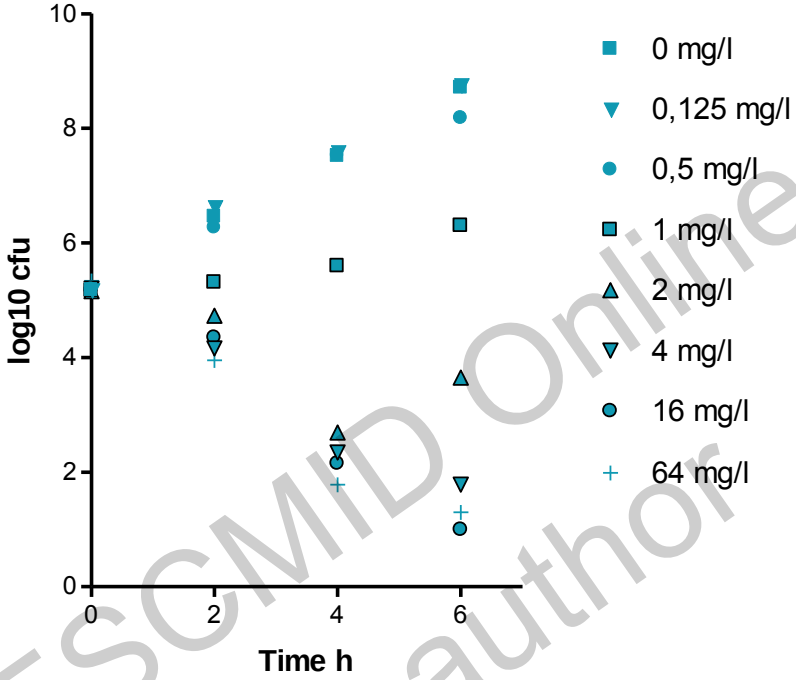
In vitro activity of ceftazidime – exposure-response relationship



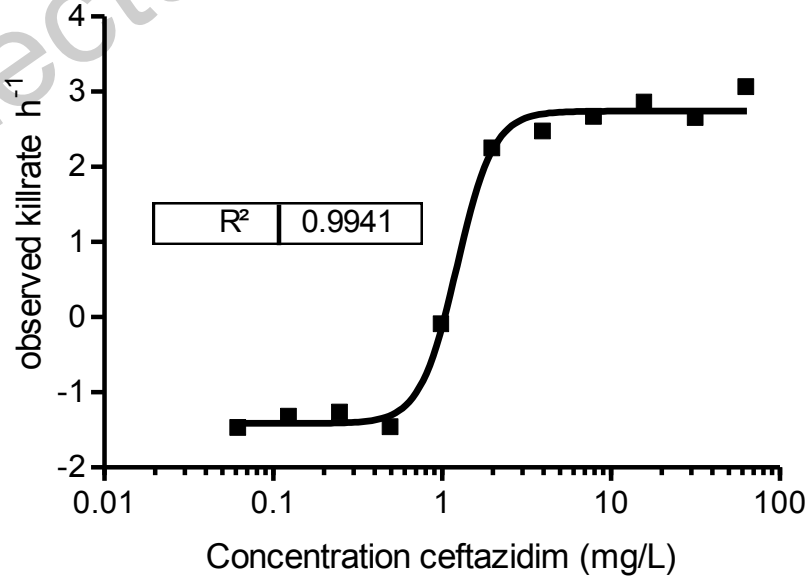
- Incubate inoculum at increasing concentrations
- Sample every two h

Mouton et al. AAC 2007 51:3449

Modelling Kill Kinetics



Killrates

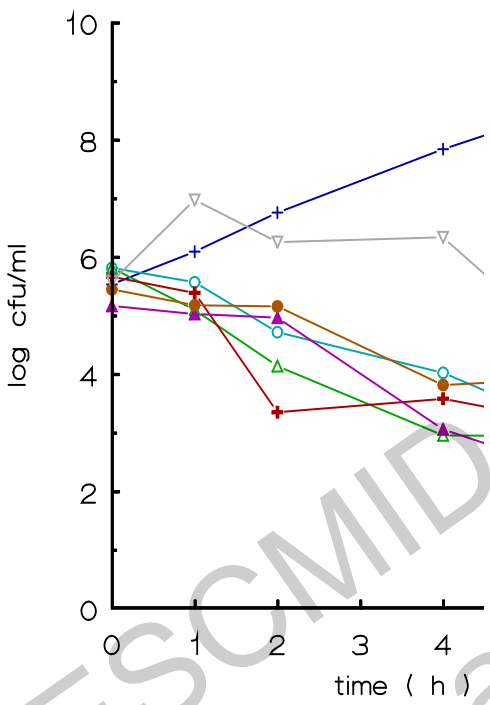


$$E = Emax * C^{\gamma} / (C^{\gamma} + EC^{\gamma})$$

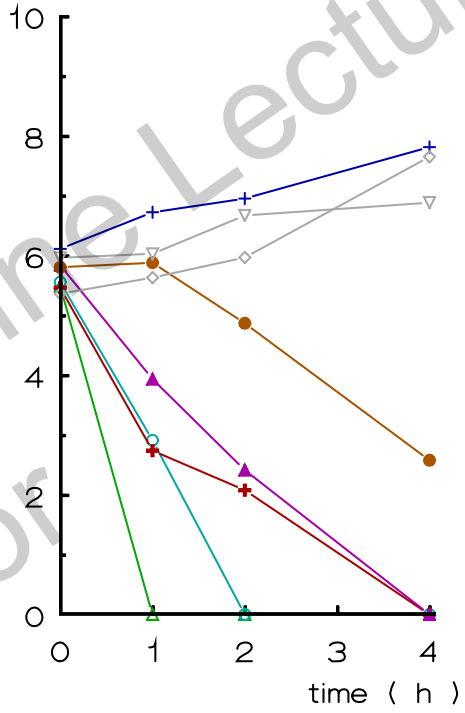
Mouton et al. AAC 2007 51:3449

Patterns of activity: Kill curves of P. aeruginosa

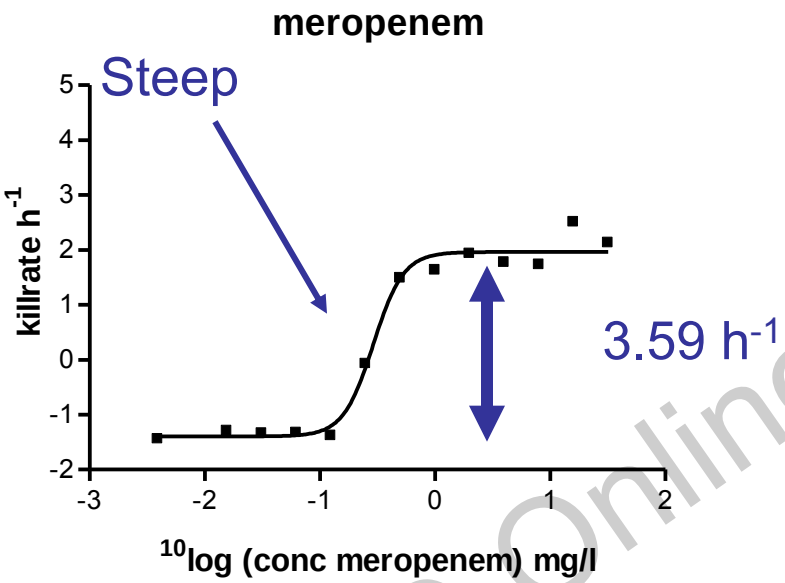
ceftazidime

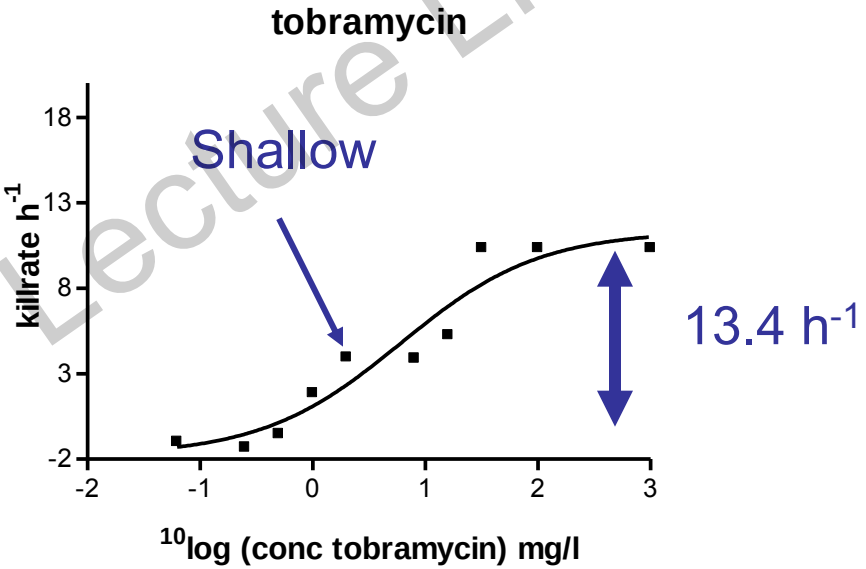


tobramycin



Mouton JW Thesis 1993





1a

1b

γ high : steep slope
'concentration independent'

γ low: shallow slope
'concentration dependent'

Conclusions

- The overall effect of antimicrobial therapy is dependent on exposure AND MIC
- The effect differs by antibiotic class
  - Beta-lactams : %*f*T>MIC related
  - Most others : AUC related
- Exposure response relationship can be explained by the pd characteristics
  - Fast vs slow kill (speed of killing)
  - Maximum kill rate (extend of killing)
  - Concentration effect (hill slope)
- Adjust dosing regimens based on pkpd!
  - For beta-lactams : adjust dose : frequency matters!
  - For most others : adjust frequency

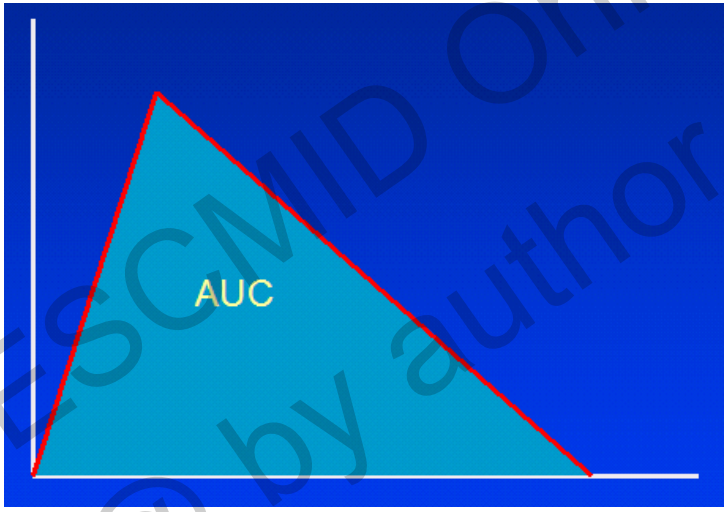
PHARMACOKINETIC parameters

AUC

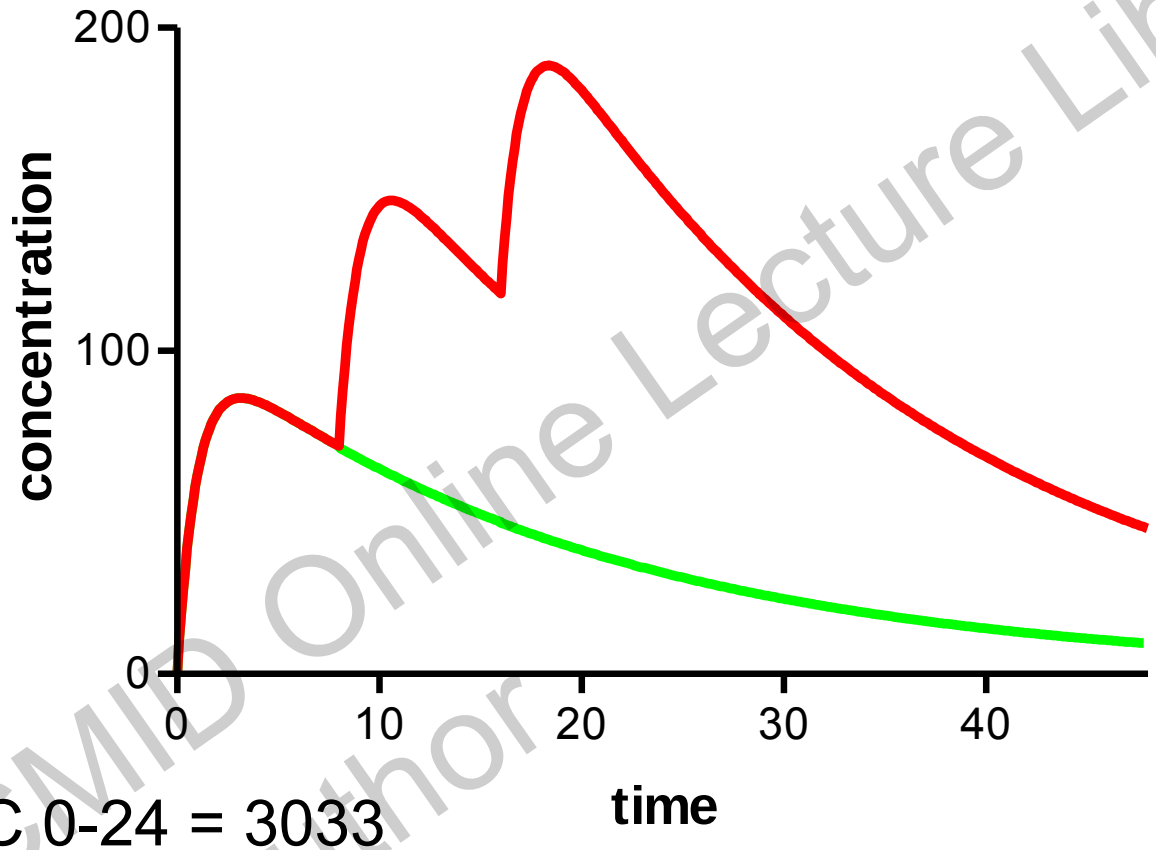
Definition : The Area under the Concentration-time curve over 24 hours.

Note: ….. It should be stated how the AUC is determined :
based on (log) linear trapezoideal rule,
based on clearance,
or based on microconstants.

Dimensions : concentration x time e.g. mg.h/L or μg.h/mL



Mouton et al, J Antmicrob Chemother 2005.
Available from ISAP site



AUC 0-24 = 3033
AUC inf = 5100
AUC 0-24 sd = 1361
AUC inf sd =1700

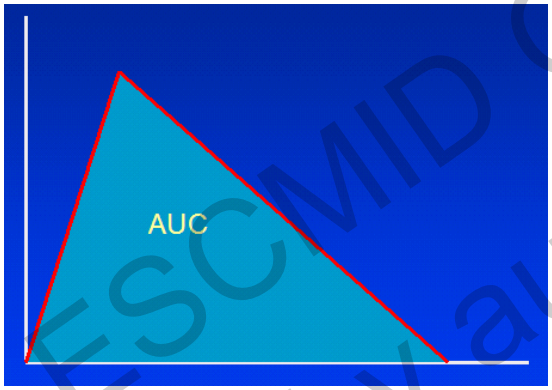
Mg.h/L

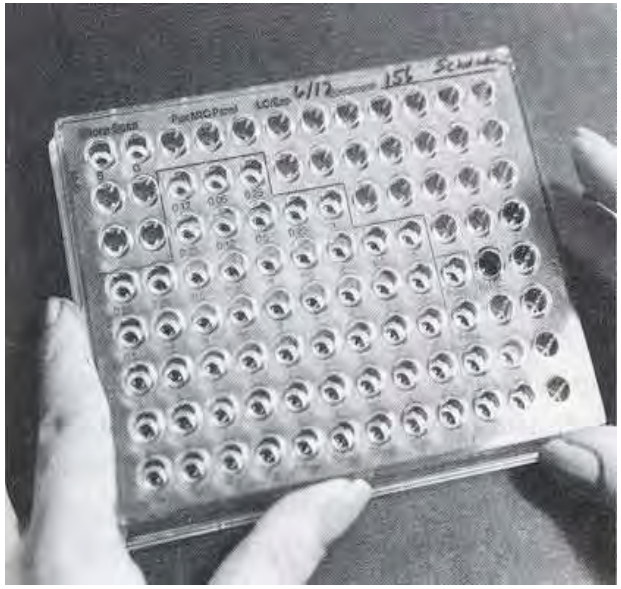
WHICH AUC?

- AUC $_{0\text{-}24h}$ or AUC $_{\infty}$
- Steady State?
- (log) trapezodeal rule?
- Derived ? (A/α +B/β or other)

AUC/MIC

Definition : The area under the concentration-time curve over 24 hours in steady state divided by the MIC. ….
Note : ….For unbound fraction of the drug, use ***fAUC/MIC***
Dimensions : no dimensions





Mouton et al, J Antmicrob Chemother 2005
Available from ISAP site

AUIC

Definition :The Area under the inhibitory curve over 24 hours.
Note: the AUIC should be reserved for those cases where actual inhibitory titers have been measured and used in the calculations. The AUIC is not equal to the AUC/MIC. See also Flaherty et al, *AAC* 1988;32(12):1825-29; Hyatt JM et al *AAC* 1994;38(12):2730-7; Occhipinti DJ et al, *AAC* 1997;41(11):2511-7.

Dimensions : none

Mouton et al, J Antmicrob Chemother 2005
Available from ISAP site

Peak/MIC

Definition : the peak level divided by the MIC.

Dimensions : no dimensions.

Mouton et al, J Antmicrob Chemother 2005
Available from ISAP site

WHICH PEAKLEVEL?

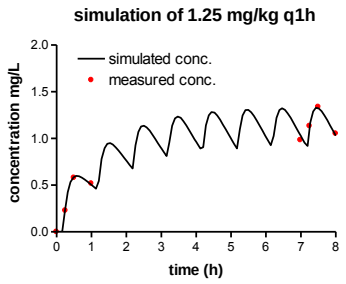


fig 2a

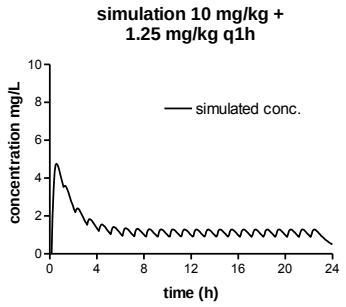


fig 2b

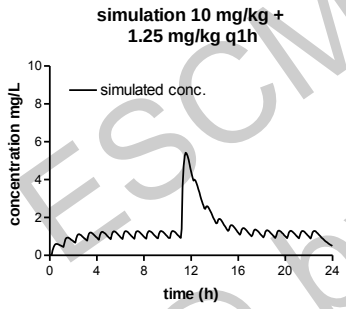


fig 2c

- After the 1st, 2nd or later dose?
- If more than one compartment, the peak level in compartment 1, 2 or even 3?

Scaglione et al, AAC 2003

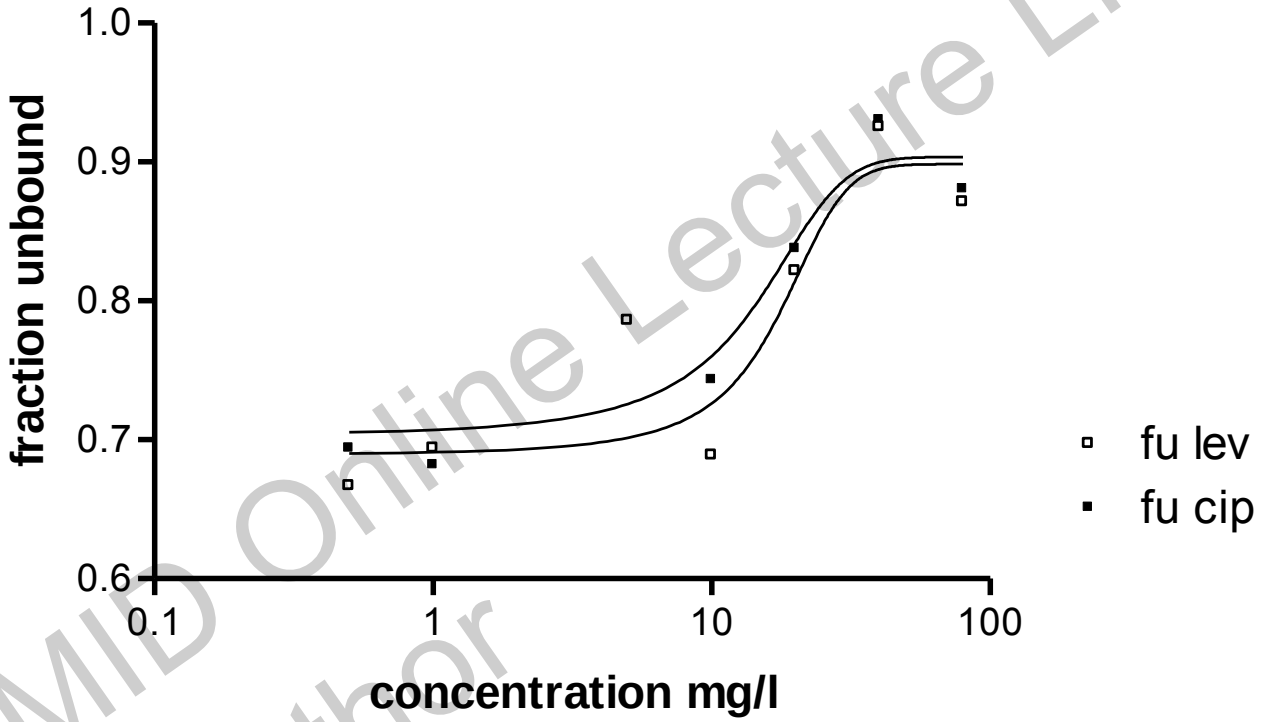


fig 1

Scaglione et al, AAC 2003

Time > MIC

Definition : the % of time above the MIC over a period of 24 hours.

Note : if the period is other than 24 h, this should be stated explicitly.

Dimensions : %.

Mouton et al, J Antmicrob Chemother 2005
Available from ISAP site

Variation in *methods, definitions*

Variation in *estimation*

Variation in *population*

For all indices :

how are they determined
how are they calculated
what is the error?

Only when these questions have been answered do we know the true impact and value of the index.