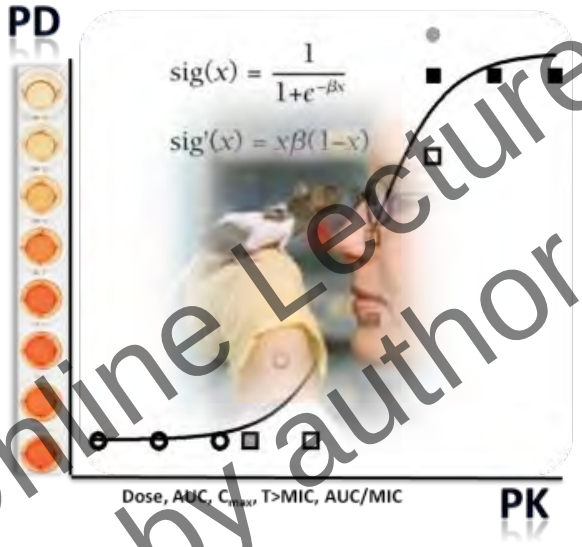


PK/PD analysis in animals

ELEFTHERIA MAVRIDOU

WHY using animal models ?

- Development of new /more effective methods for diagnosing and treating diseases
- assure the safety of new medical treatments
- chimpanzees share more that 99% of DNA with humans and mice share more than 98% DNA with humans
(susceptible to same diseases)

ANTIBIOTICS – In 1940 the value of penicillin as an affective antibiotic was defined

- Ethical considerations

Humane endpoints (reduce sufferring, trauma etc)
3 Rs (Refinement, Reduction, Replacement)

PK/PD clinical trials

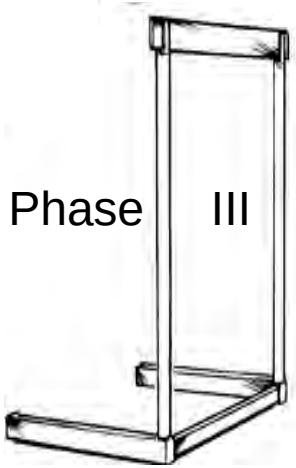
Pre-clinical

In vitro studies
&
Animal models

Clinical Development

- Population PK
- Simulations for Phase 2 dose-selection
- Development of an optimal PK sampling for Phase 2

Phase 2 population PK and PK-PD



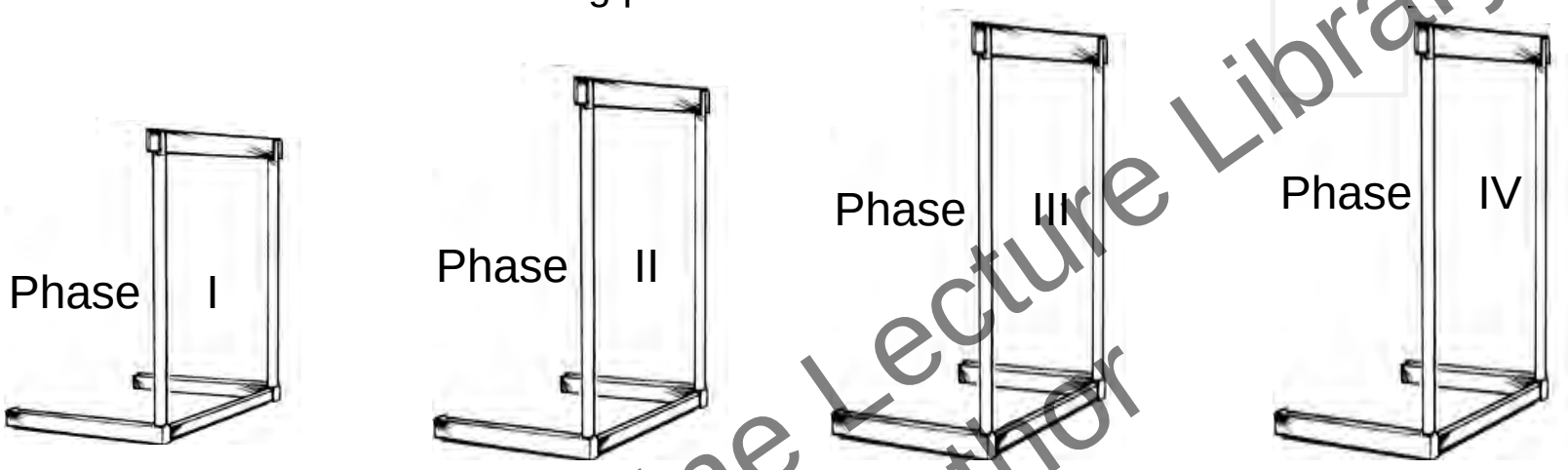
Phase 3 population PK and PK-PD

Screening for safety

Establishing the testing protocol

Final testing

Postapproval studies



Phase 1: test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase 2 : a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

Phase 3: large groups of people (1,000-3,000) to confirm drug effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

Phase 4: postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use

Animal Model PK/PD: A Tool for drug development

- The initial dosage of a drug in first-in-humans clinical trials is based on data from preclinical studies

Animal Model PK/PD: A Tool for drug development

PK/PD index and magnitude should be used to determine the dosage regimens evaluated in Phase 2/3

in vitro/animal models increase the probability of a successful clinical outcome

PD Parameter Prediction> What PK characteristics do I optimize?

How much drug do I need? (PD Magnitude)

- PD Magnitude Variables – What factors impact how much drug I need?

- PD Correlation in humans

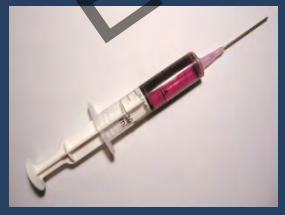
Complexity

PK

Immunity

PD

Virulence



MIC

Susceptibility

Considerations when using Animals Models

Efficacy may depend upon various factors:

– MIC , virulence

– Infection (inoculum, initiation of treatment)

– host immune response

– animal pharmacokinetics (half life time)/protein binding

- Endpoint

• Drug concentrations at the site of infection may differ between animals and humans

- What is the right animal model?

"humanized animal models"

The General Term PK/PD

Pharmacokinetic (PK) studies examine how the body handles drugs, including:

1) Absorption
2) Distribution
3) Metabolism and
4) Elimination

Pharmacodynamic (PD) studies examine the integration of a drug's PK properties and outcome.

PK ➡ is what the body does to a drug

PD ➡ is what the drug does to the body

How can I quantify the activity of an antimicrobial agent?

3 PK parameters

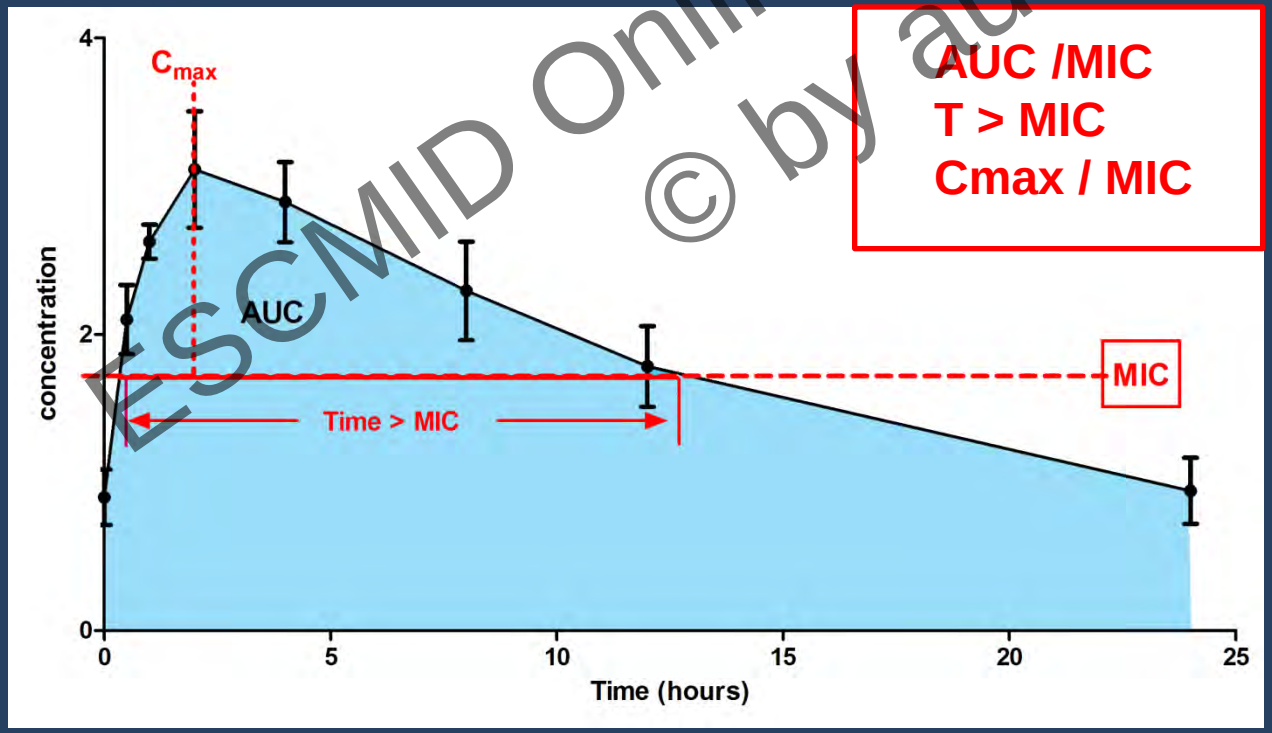
- peak serum level (**Cmax**),
- the trough level (**Cmin**),
- Area Under the serum concentration time Curve (**AUC**)

Integration PK parameters with MIC

3 PK parameter

MIC

PK/PD Indices



- 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

What Bridges PK and PD ?

Pharmacokinetics

Cl V

Pharmacodynamics

E_{max} EC_{50}

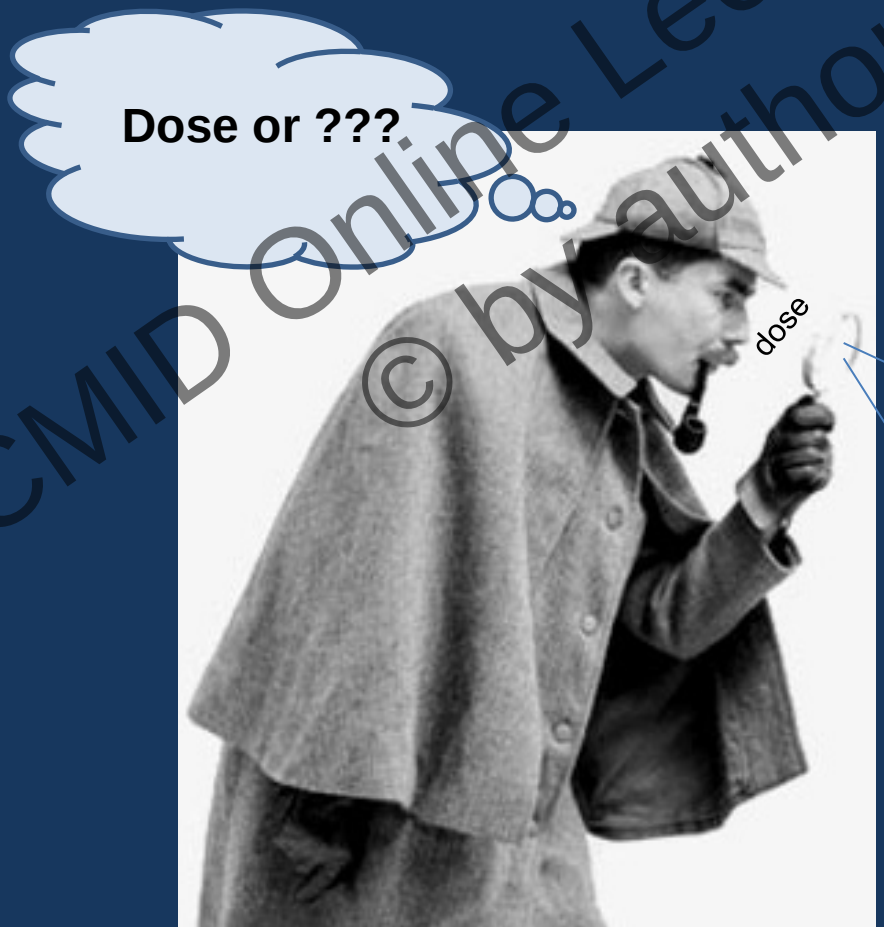
PK : relationship between dose, drug concentrations, and time
PD : relationship between drug concentration and the effect vs time profile)

Drug selection on the basis of effectiveness and selectivity.

Why do we need the PK/PD Index?

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

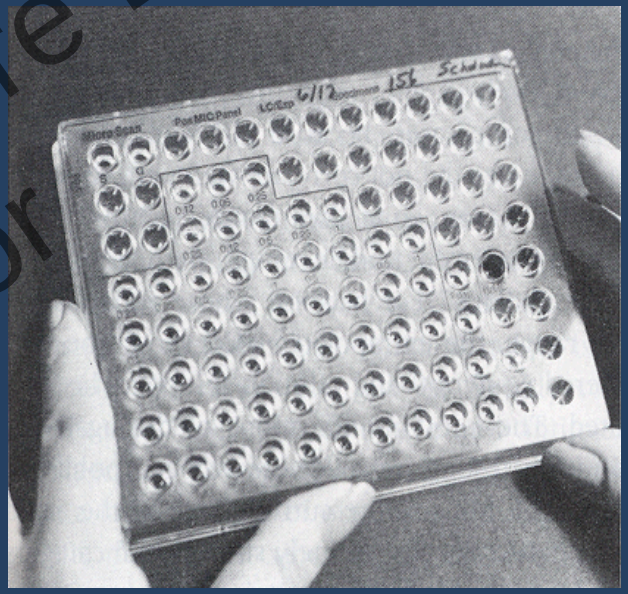
Paracelsus (Philippus Aureolus Theophrastus Bombast von Hohenheim) 1493-1541



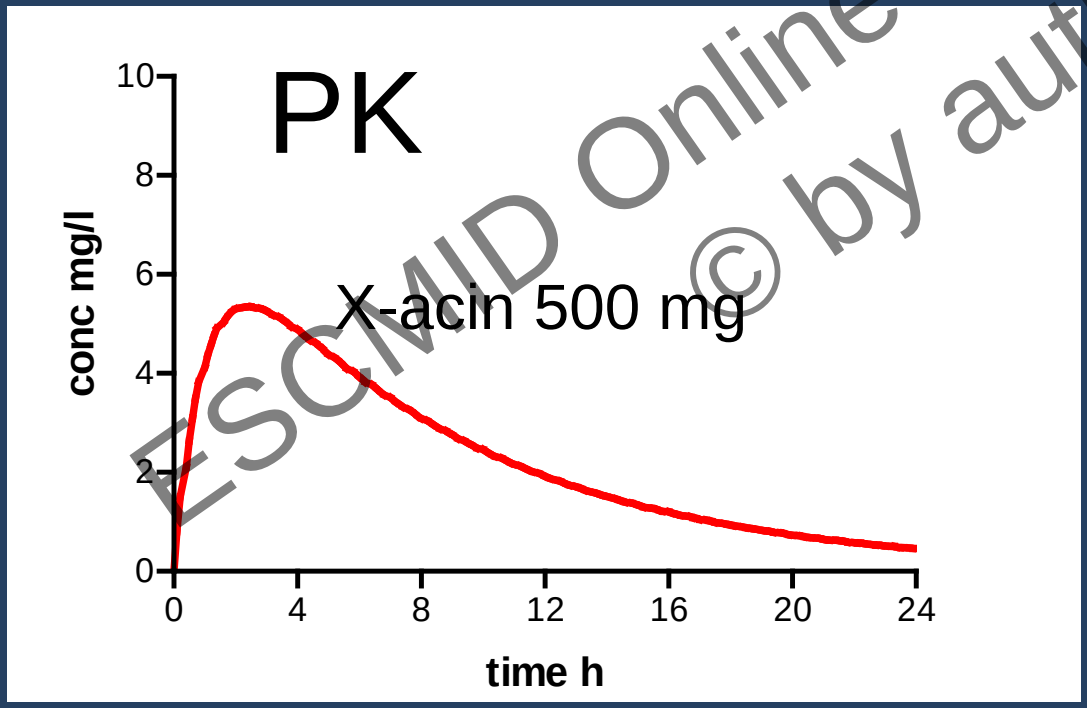
Plasma/serum Concentration was the killer?

MIC

Lowest concentration with no visible growth after x hour incubation



MIC = 2 mg/L



How can PK/PD help here?

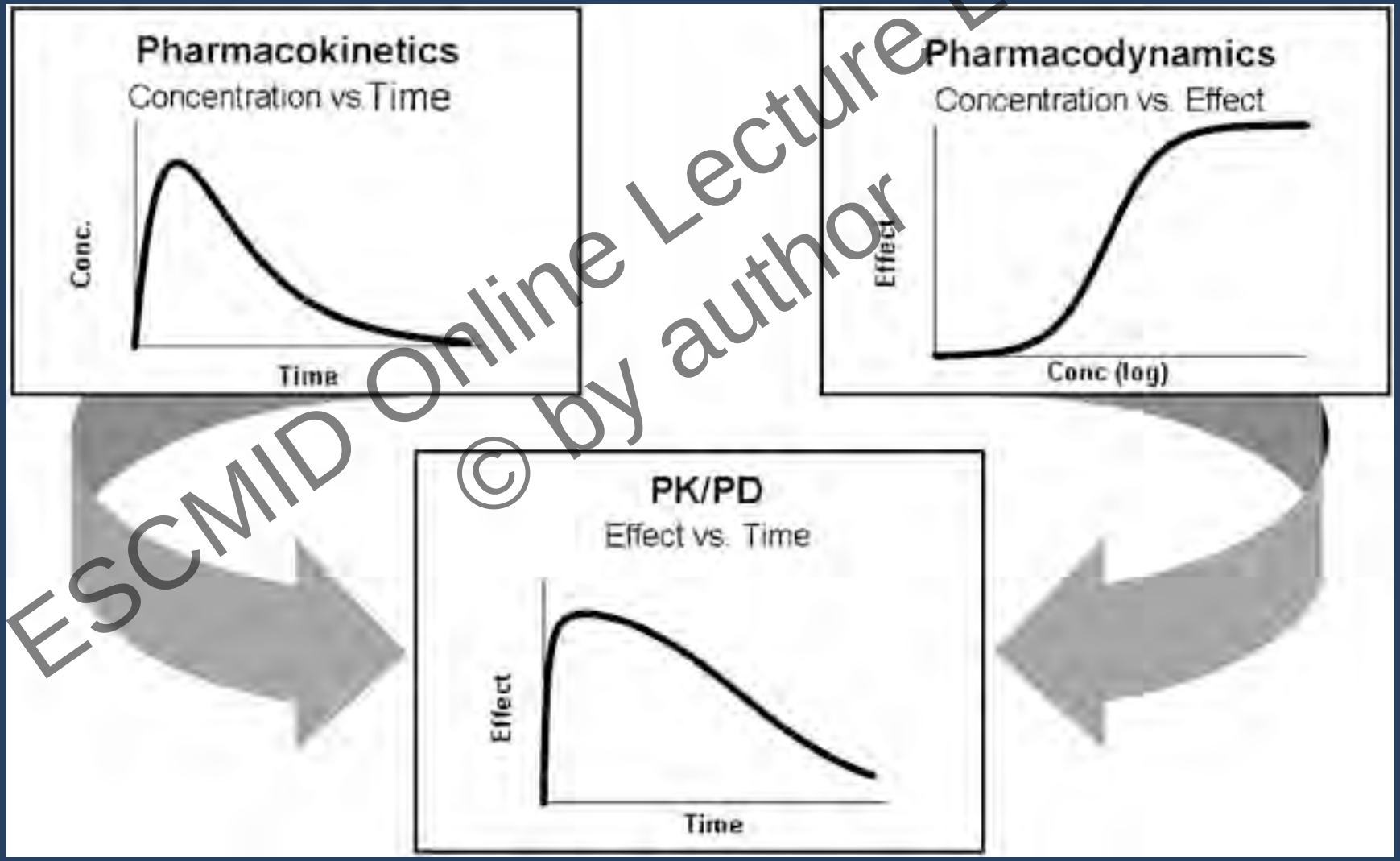
Efficacy of the drug

Potency of a drug
(MIC)

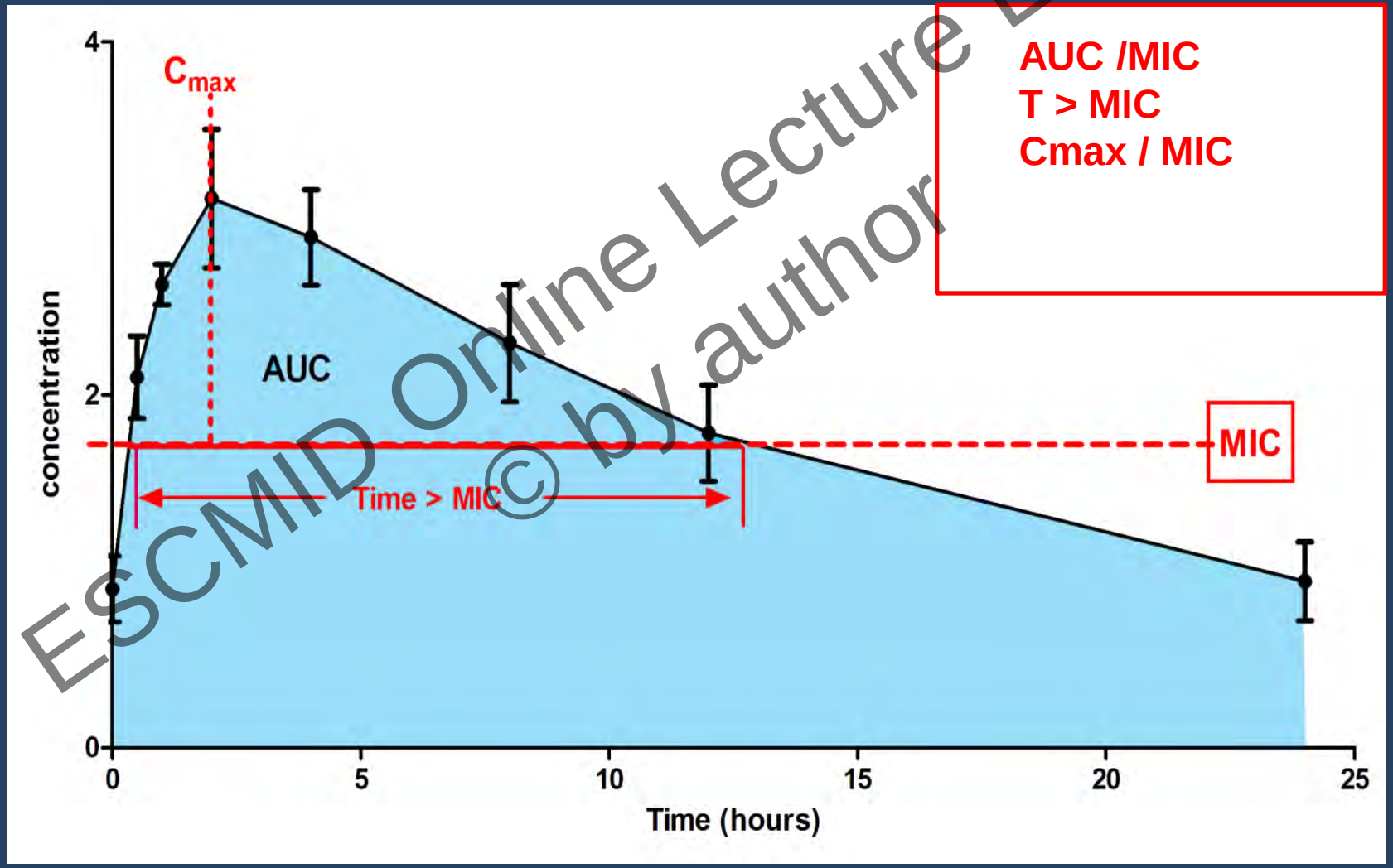
Exposure to the bug
In vivo
(PK)

“Mathematical Visualization” of the PK/PD Determination Process

The General Term PK/PD

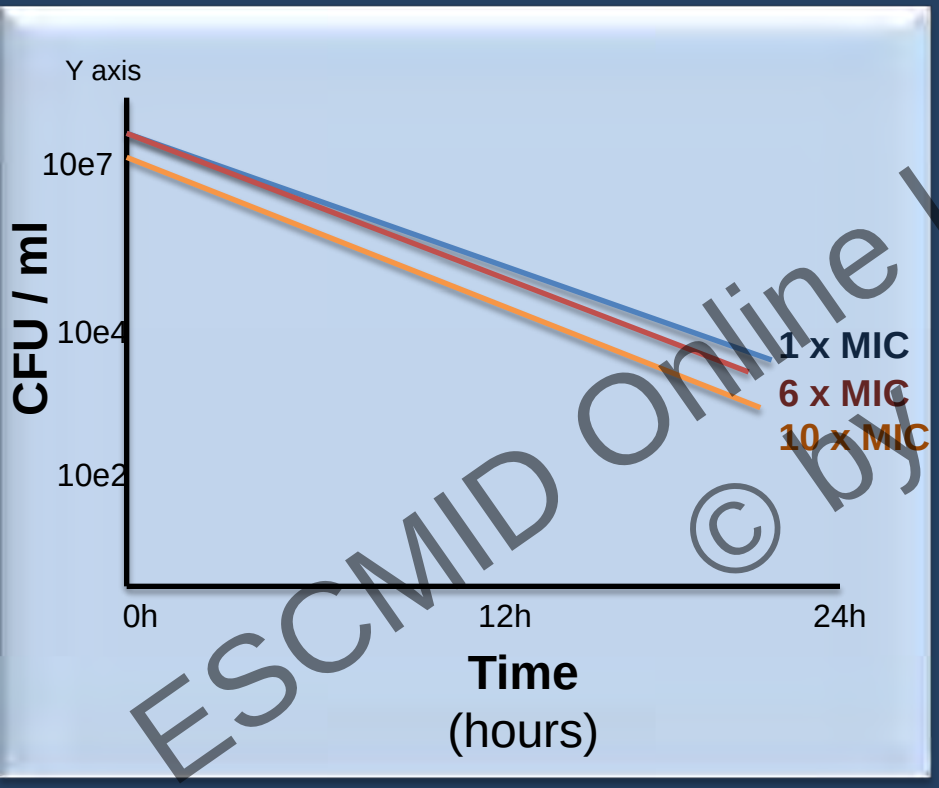


PK/PD Indices



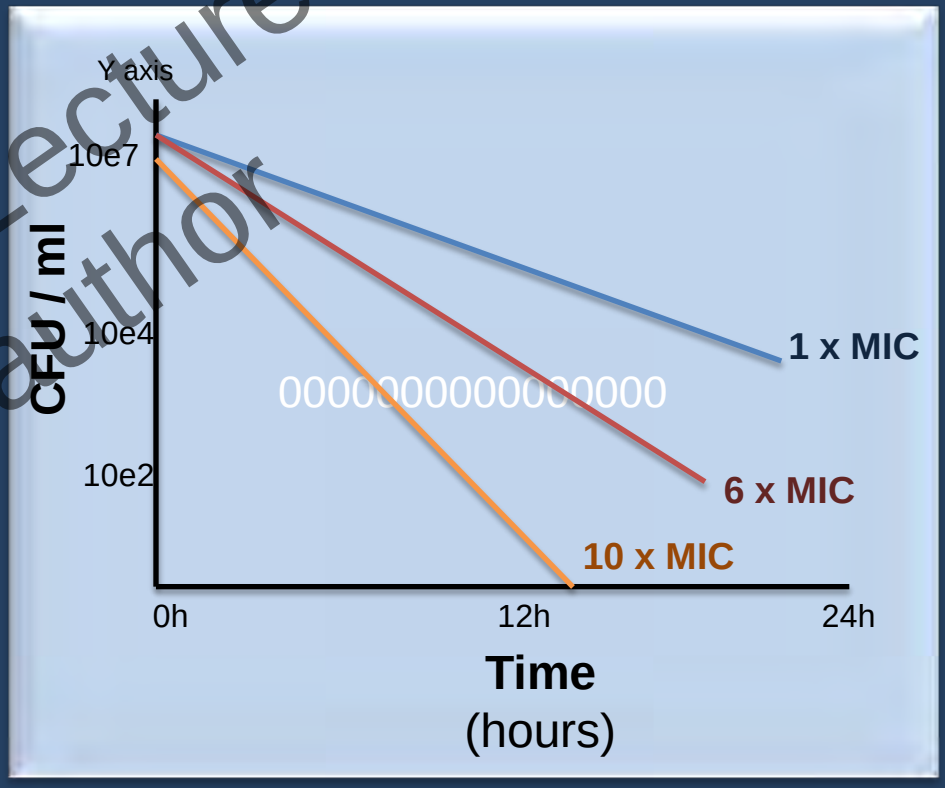
Exposure-response relationship.

Time dependent microbe killing



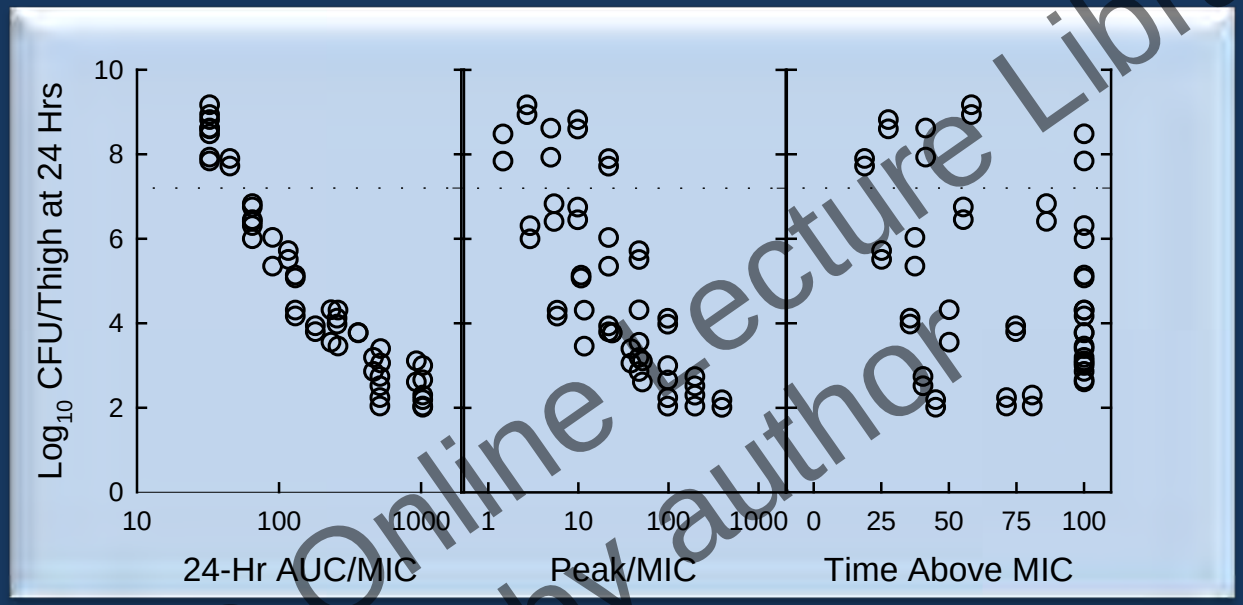
(%T) during the dosing interval that the free drug concentration remains above the MIC (%T >MIC).

Concentration dependent microbe killing

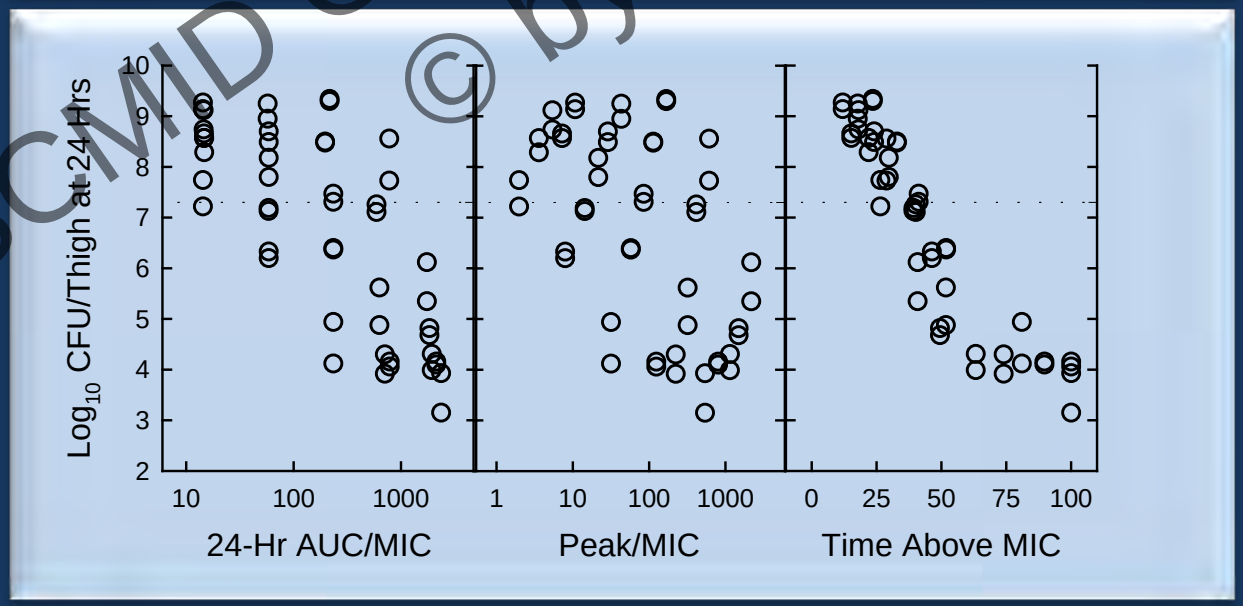


AUC/MIC, Cmax/MIC

PK/PD relationship is Class Dependent



levofloxacin



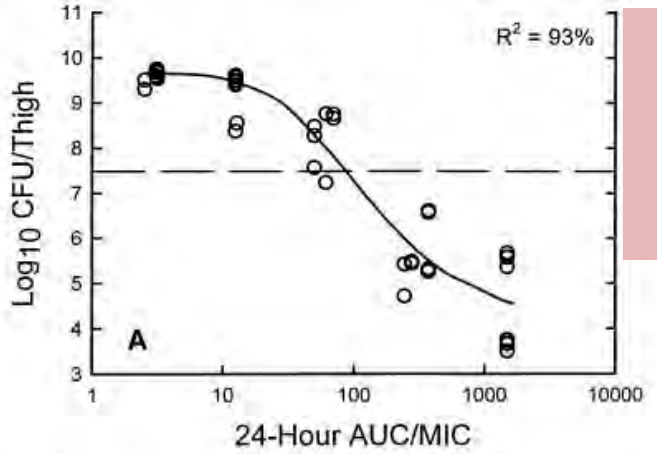
ceftazidim

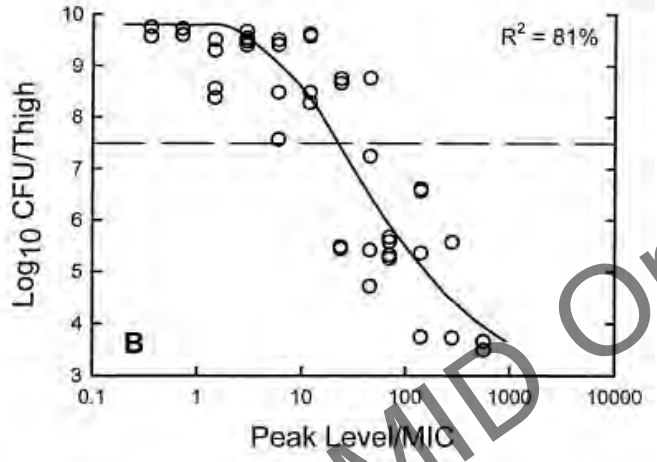
Andes IJAA 2002

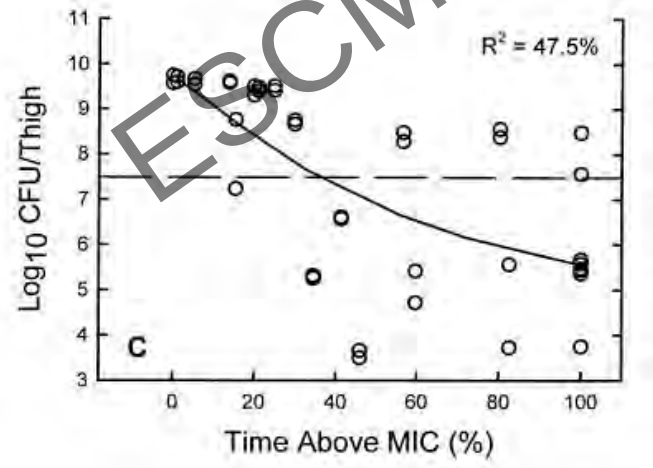
Relationship PK/PD and Effect

Antimicrobial agent	PK-PD measure (s)
Penicillins Cephalosporins Carbapenems Monobactams Tribactams	T >MIC
Aminoglycosides Fluoroquinolones Metronidazole Lipopeptides Ketolides Macrolides Clindamycin Streptogramins Glycopeptides Glycylcyclines Oxazolidinones Tetracyclines Azoles Echinocandins	AUC /MIC and/or Cmax/MIC

Relationships of the gatifloxacin 24-h AUC/MIC , Cmax/MIC, and *T*>MIC for *S. pneumoniae*







Sigmoid dose-effect (exposure-response) model.

The model is derived from the Hill equation,

$$E = (E_{max} \quad D^H) \; / \; (ED_{50}^H + D^H)$$

E is the effect (Log change in the CFU number per thigh after the 24-h)

E_{max} is the maximum effect;

D is the total dose administered over 24 h;

ED_{50} is the dose required to achieve 50% of E_{max}

H is the slope of the dose-effect curve

Andes DR. & Craig WA, AAC 2002; 46: 1665.

Hill Equation

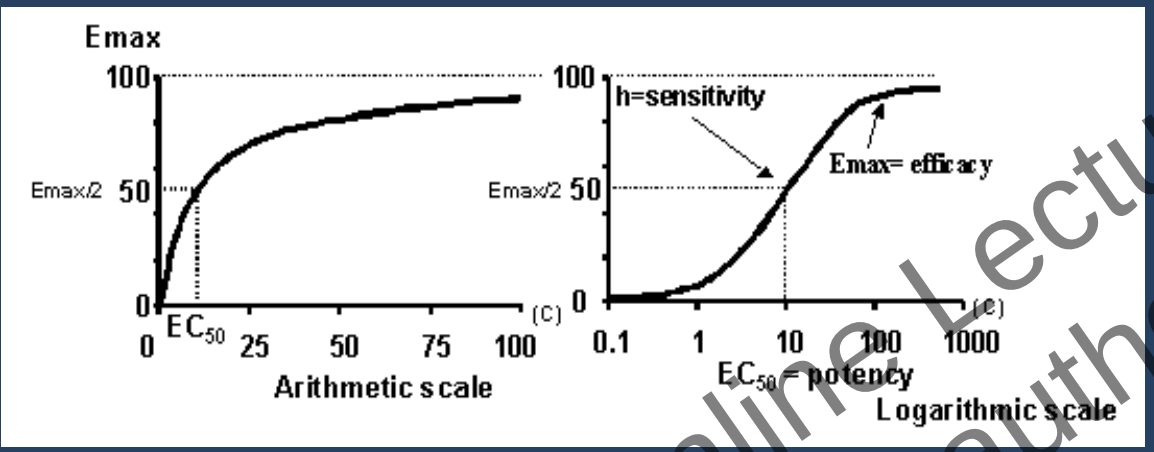
3 parameter equation of a nonlinear relationship between 2 Variables x (independent) and y the (dependent)

$$Y = \frac{y_{max}\, x^{H}}{C^{H} + x^{H}} \qquad \frac{E_{max}\quad D^{H}}{ED_{50}{}^{H} + D^{H}} \qquad E$$

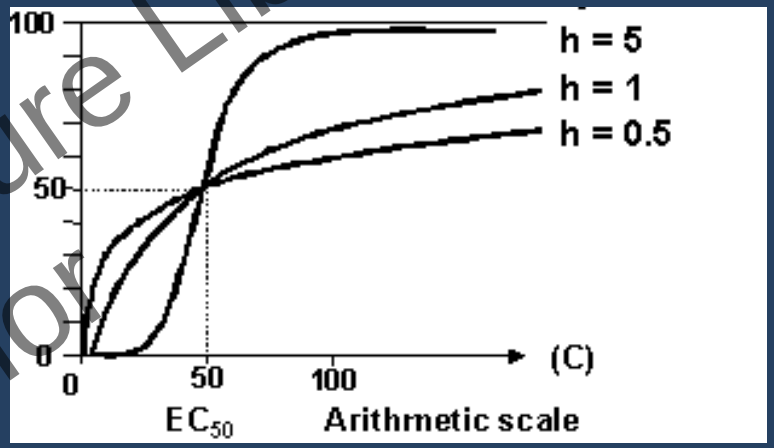
The Emax model is the most fundamental description of the concentration effect relationship

Emax versus sigmoid model.

E_{max} model: h=1



Hill model: h= any value



- **Arithmetic scale**: the concentration-response (C-R) curve is hyperbolic and asymptotically approaches the maximal response (*E max), a measure of clinical efficacy.*

- ***EC 50*** *, the concentration* corresponding to *E max/2, is a measure of drug potency*

- log transformation: S-shaped log of C-Effect curve is obtained. Useful for a wide range of C.
- facilitates comparative examination of different C-E curves (desirable/undesirable effects

$$E = \frac{Emax \cdot C^h(t)}{EC^h_{50} + C^h(t)}$$

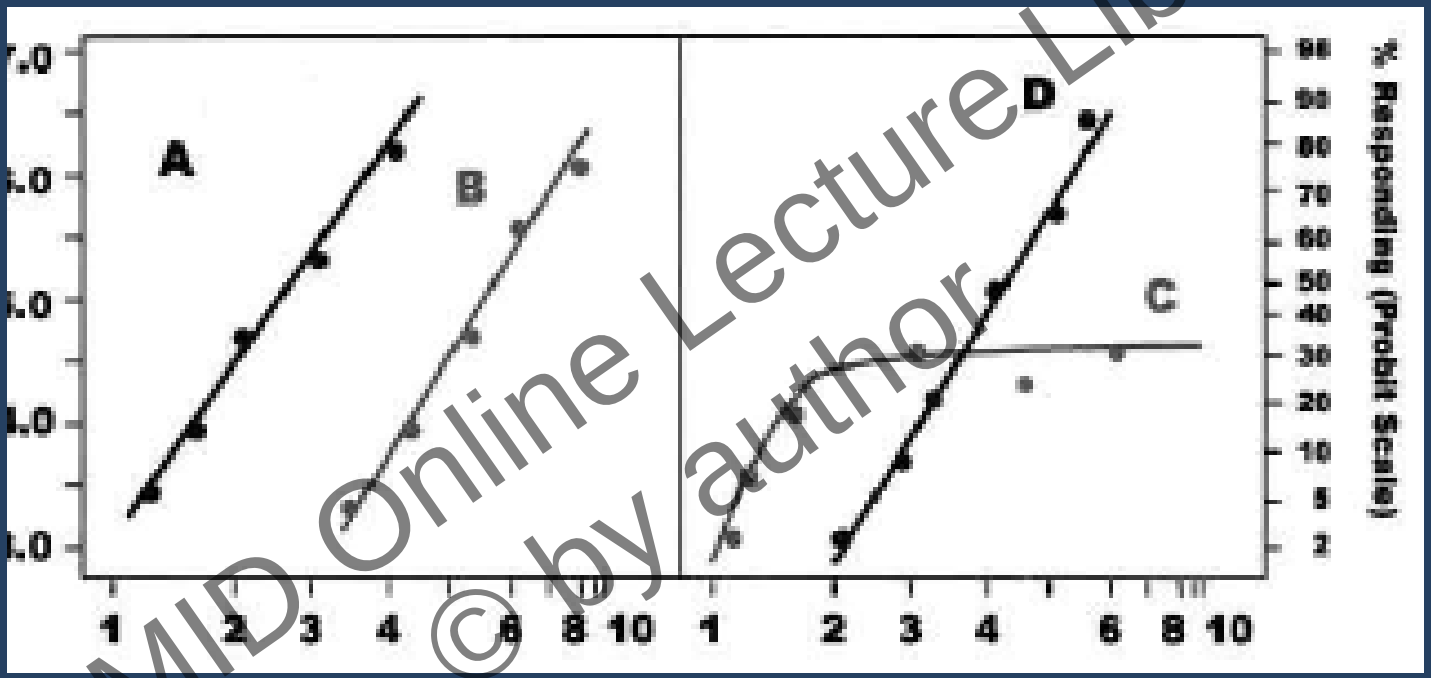
A sigmoid model is an *E max model for which h (the Hill coefficient)* can be other than 1.

The slope of the curve changes as a function of h. For h >1 the curve becomes sigmoid, with a steeper slope in the middle.

For *h >5 :an all-or-none response curve.*
For h <1 the initial portion is above the hyperbolic curve at low concentrations but shallower after reaching *EC 50 . Inset: Equation for E max (h* =1) or Hill (*h ≠ 1) model.*

Potency

Maximal efficacy



- **range of concentration over which a drug produces increasing responses. A > B; C > D.**

- limit of dose (concentration)-response relationship. A=B; C<D.

Why is the Slope of a curve so important ?

Example

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

MIC and its Errors/variation

Pharmacokinetics and its variation

Data of Animal Models

- Murine model of disseminated aspergillois

- 4 strains (1 susceptible, 3 Resistant,
  MIC range: 0.03 -0.5, 0.5, 16 mg/L)

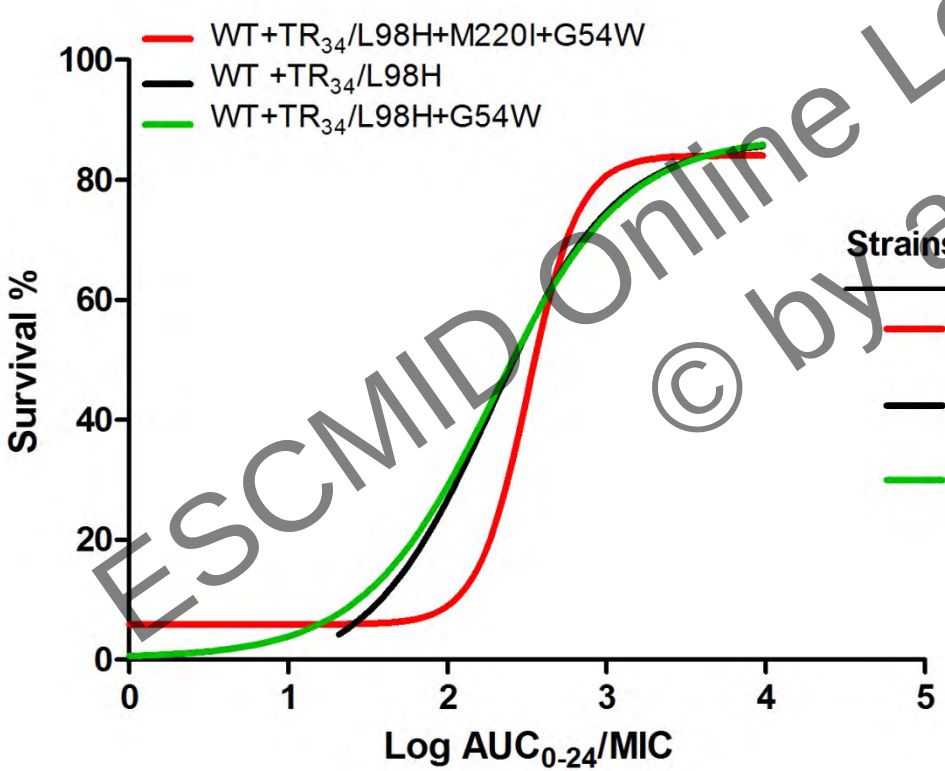
- AUC/MIC
- EC50= 321 EC90 = 1000

Endpoint:survival

Another model; pulmonary aspergillosis
1 WT strain

EC50 = 170

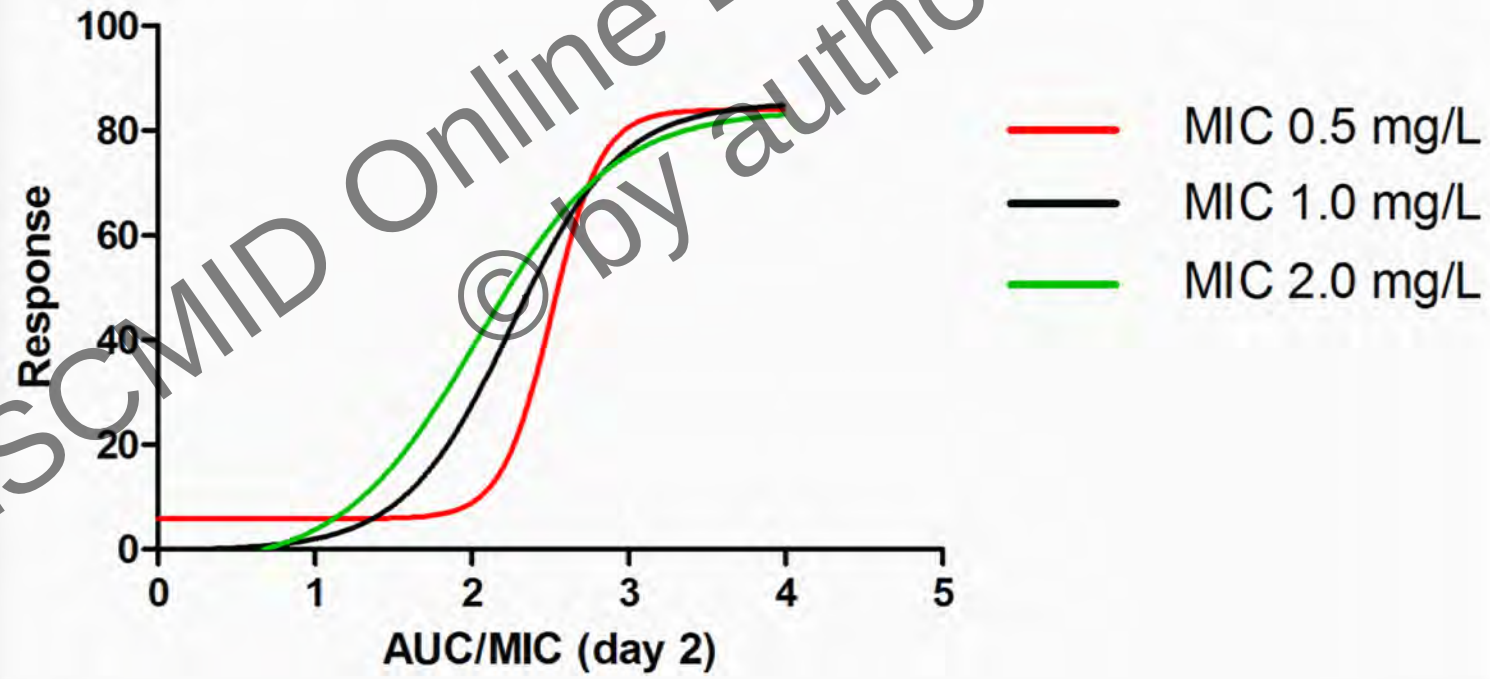
The MIC Range



Strains	EI_{50}	EI_{60}	EI_{65}	EI_{70}	EI_{75}	EI_{80}	Hillslope
	321	433	486	560	675	929	2.73
	189	405	524	705	1028	1782	1.11
	195	409	535	729	1076	1879	1.06

The MIC Error/variability

	MIC 0.5 mg/L	MIC 1 mg/L	MIC 2 mg/L
HillSlope	2.734	1.259	0.9991
EC50	321.3	178.2	108.8



Bridge the PK/PD animal data

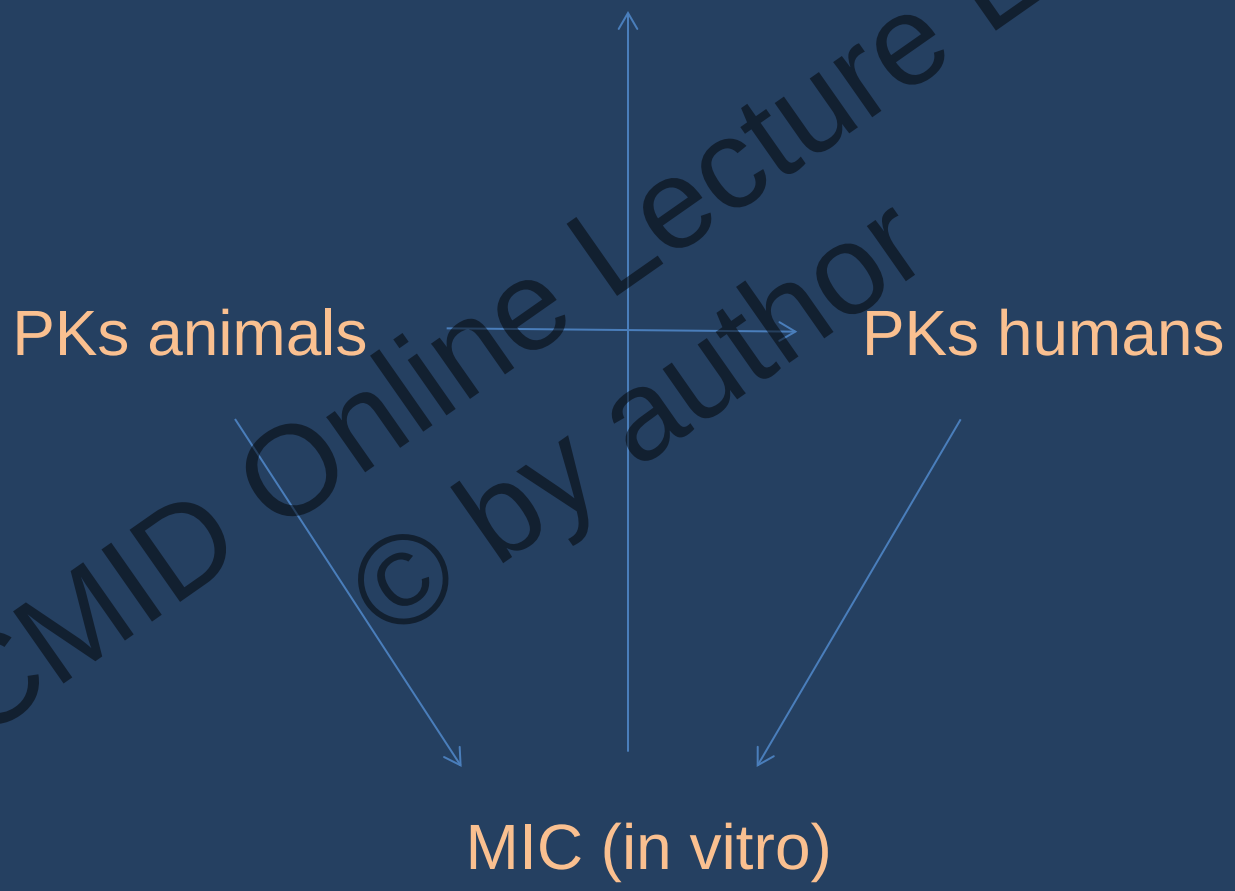
With

Human PK data

Probability of cure when infected with strains Of MIC???

PK/PD Indices	Guidelines for treatment of Mycosis	Recommendations for treatment of disseminated invasive Aspergillosis
	Drug	Drug
Therapeutic C_{min}	1.2 mg/L	>1.5 mg/L
Therapeutic AUC_{0-24}	30 mg h/L	≥ 54 mg h/L(EI_{75}) ≥ 90 mg h/L (EI_{50})
[3]MIC (mg/L) (Clinical Breakpoints)	No data	≤ 0.06 (EI_{75}) ≤ 0.5 (EI_{50})

To summarize



Kapplan Meier Analysis (survival analysis)

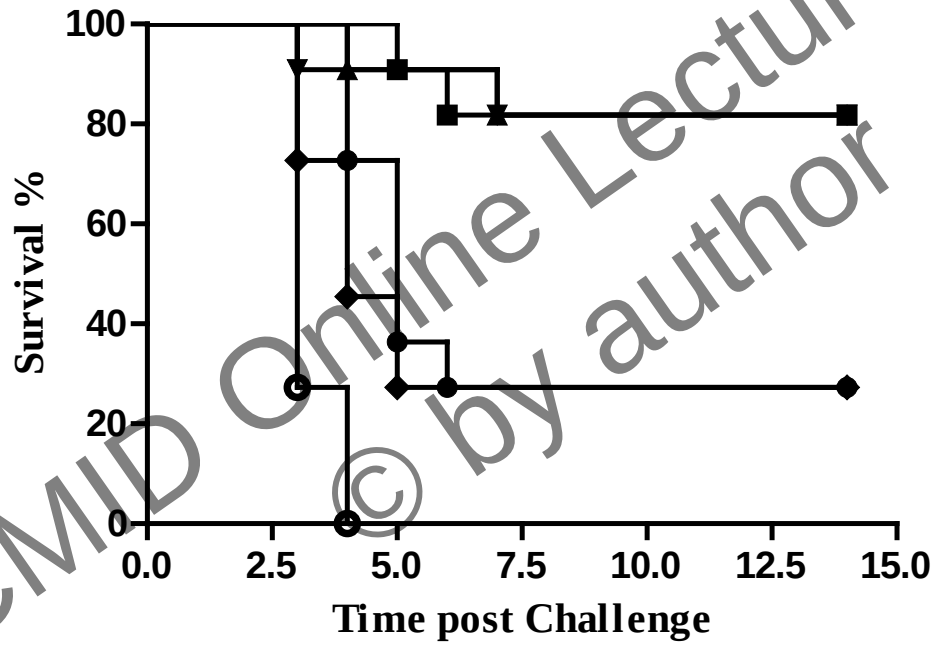
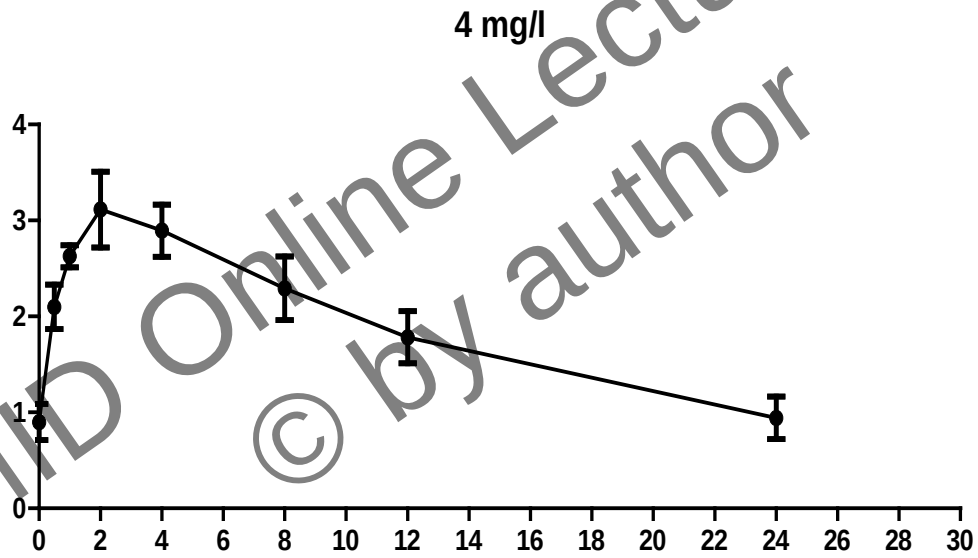


FIG. 1a. Survival curve for CD-1 mice infected with a WT isolate (panel a) and treated with various posaconazole doses. ●— Posaconazole 128mg/kg ■— Posaconazole 64mg/kg, ▲— Posaconazole 16 mg/kg, ▼— Posaconazole 4 mg/kg, ◆— Posaconazole 1 mg/kg, ⊖— Placebo

Determination of AUC



Dose-Response Relationship