The basics of pharmacokinetics and pharmacodynamics (PK/PD)

Christian G. Giske
Senior consultant physician/Ass. Professor
Clinical microbiology
Karolinska University Hospital
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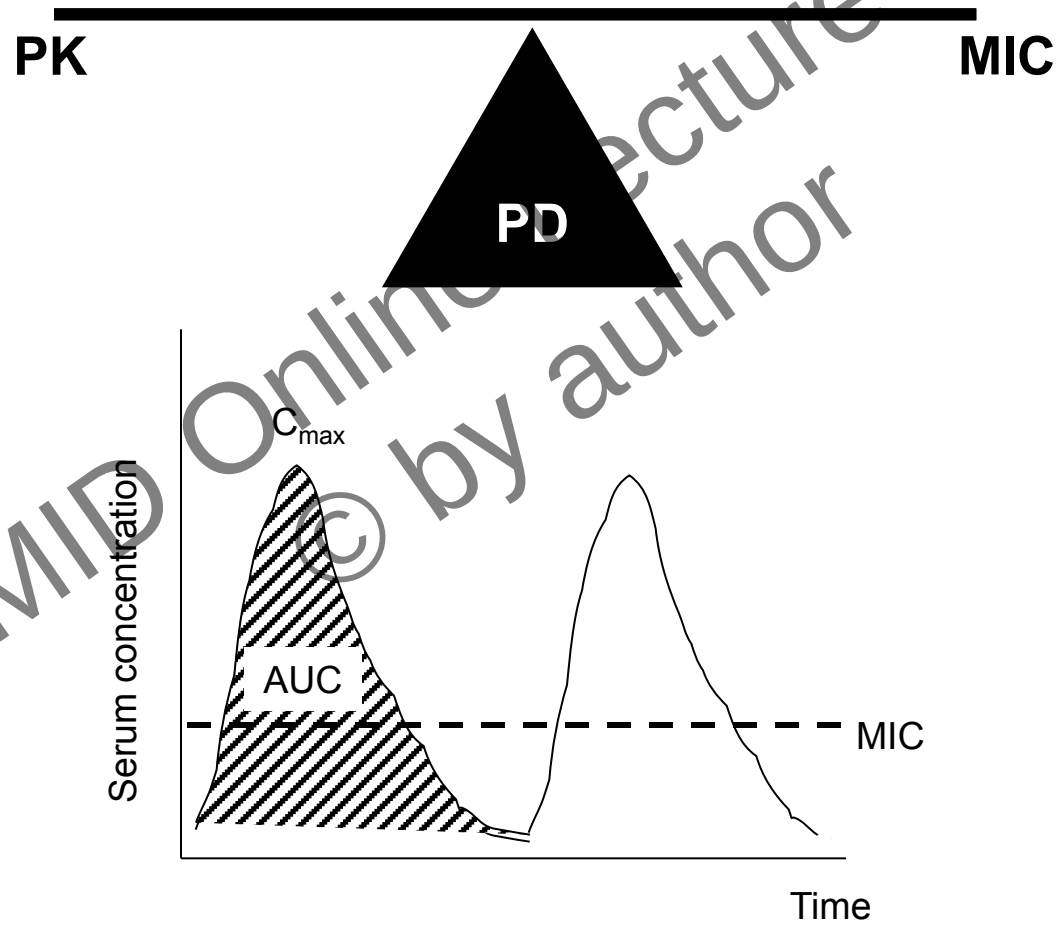
Killing of bacteria: PK/PD



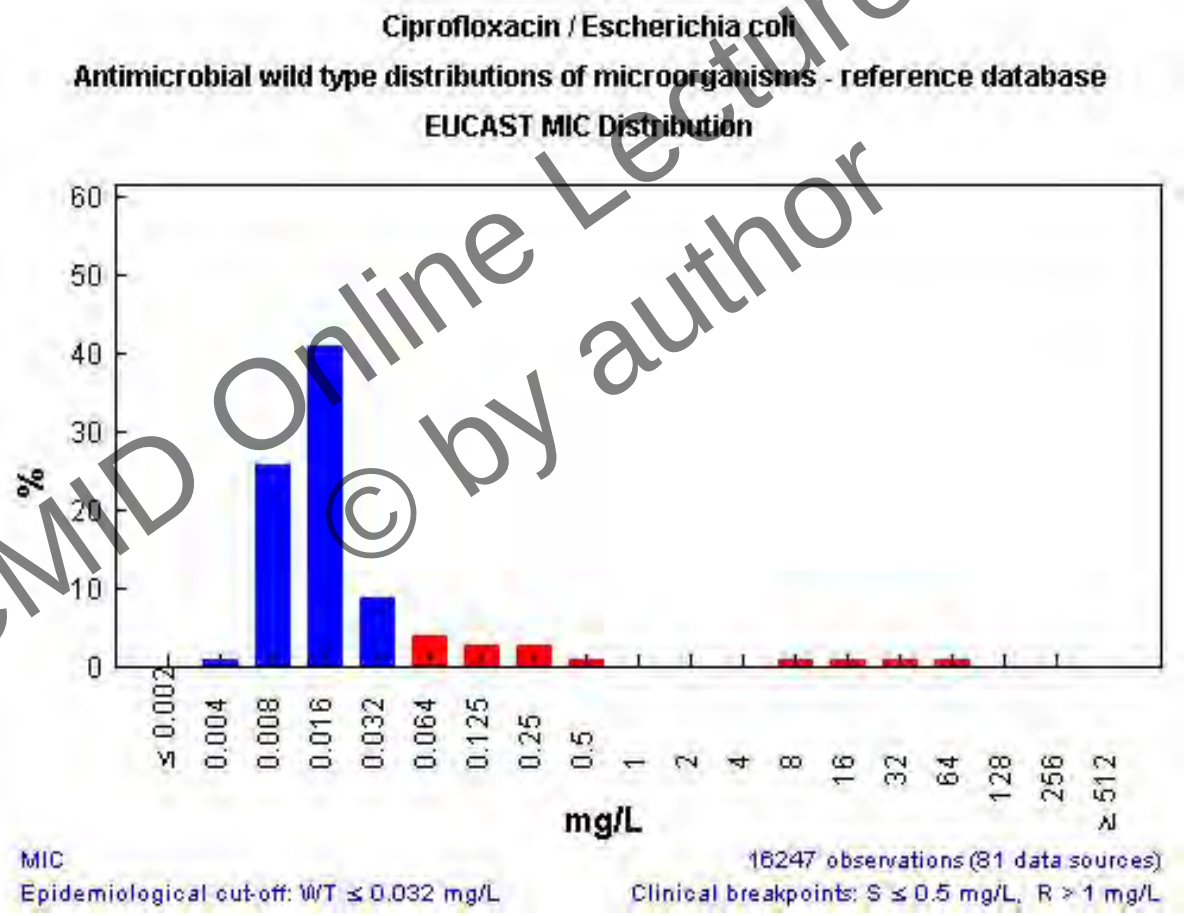
Pioneer work: Eagle (J Bacteriol 1950)

TABLE 4

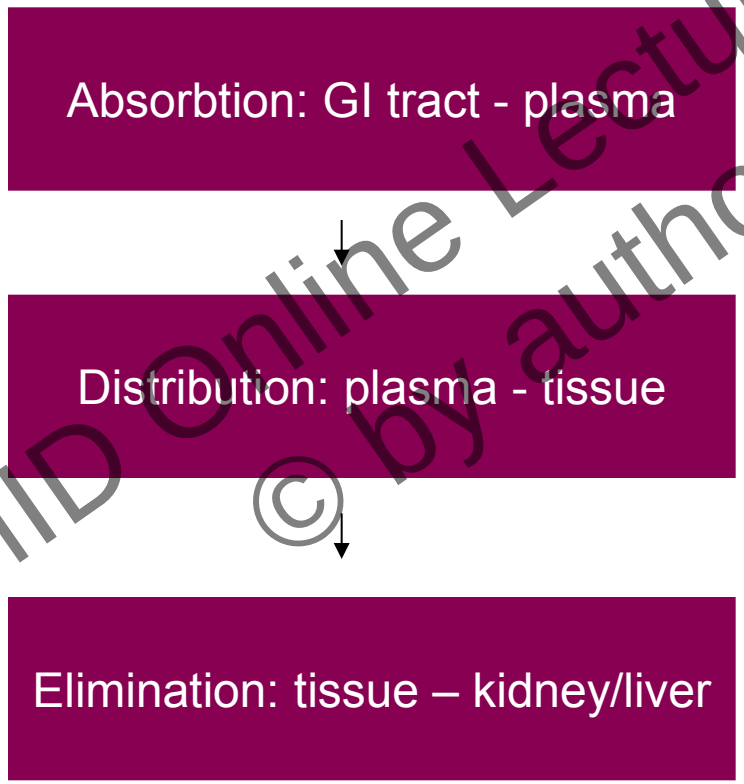
The minimal effective serum concentration of penicillin in a number of experimental infections (based on the dosage of procaine penicillin necessary to abort early infections)

ORGANISM	HOST	ROUTE OF INOCULATION	NO. OF ORGANISMS INOCULATED	(1) DOSAGE THAT ABORTED INFECTION IN HALF THE ANIMALS*	SERUM CONCS. OF PENICILLIN (μG/ML) PROVIDED BY ED50 DOSAGE OF PENICILLIN		(4) ESTIMATED MINIMUM EFFECTIVE SERUM CONC. OF PENICILLIN,
					(2) At time of inoculation†	(3) 1 hour later†	
				mg/kg			*μg/ml*
β-Hemolytic streptococcus, group A	Mice	Intramuscular	100	1.0	0.015‡	0.008‡	0.012
β-Hemolytic streptococcus, group B	Mice	Intramuscular	100	3.0	0.11	0.06	0.08
	Rabbits	Intramuscular	20	0.8	0.14	0.11	0.12
		Subcutaneous	20	0.6	0.1	0.09	0.1
		Intratesticular	20	0.4	0.07	0.065	0.07
		Intrapulmonary	20	0.6	0.1	0.09	0.1
Diplococcus pneumoniae, type I	Mice	Intraperitoneal	100	2.2	0.06	0.035	0.05§
Diplococcus pneumoniae, type III	Mice	Intraperitoneal	100	2.0	0.055	0.03	0.05§
		Intramuscular	100	3.0	0.11	0.06	0.08

MIC-distributions – definition of the wild-type



Pharmakokinetics

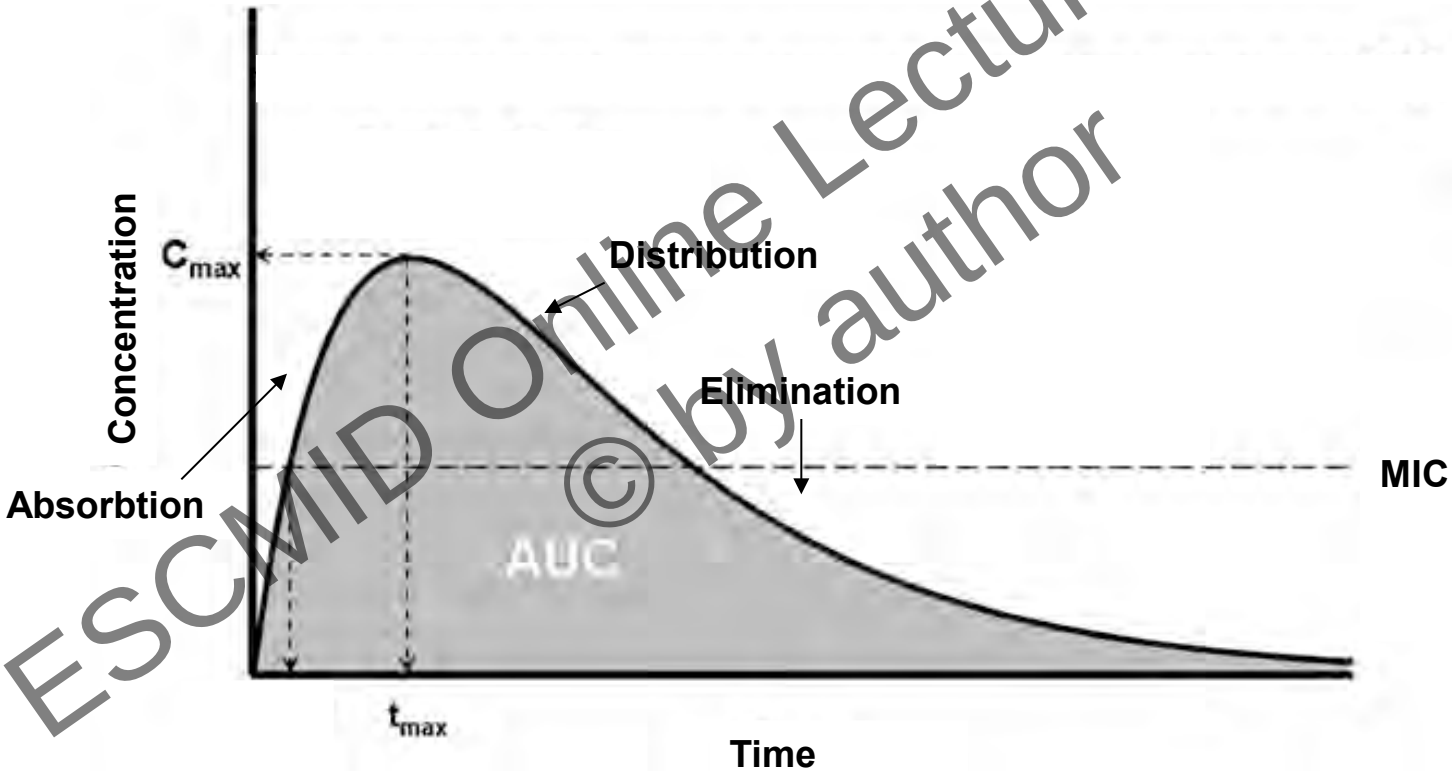


Influenced by
-Passage time
-pH

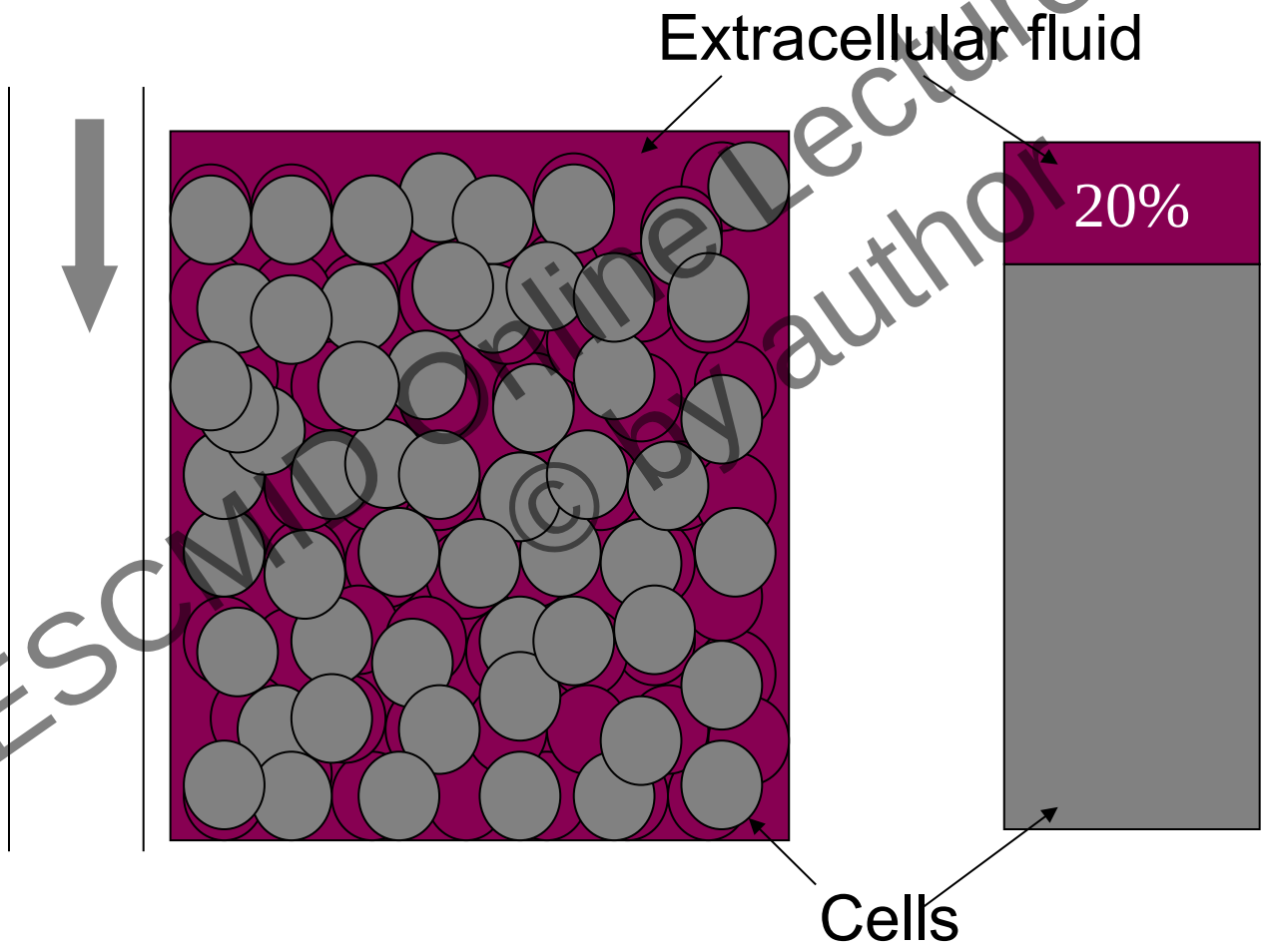
Influenced by:
-Protein binding
-Abscess
-Edema

Influenced by:
-Kidney function

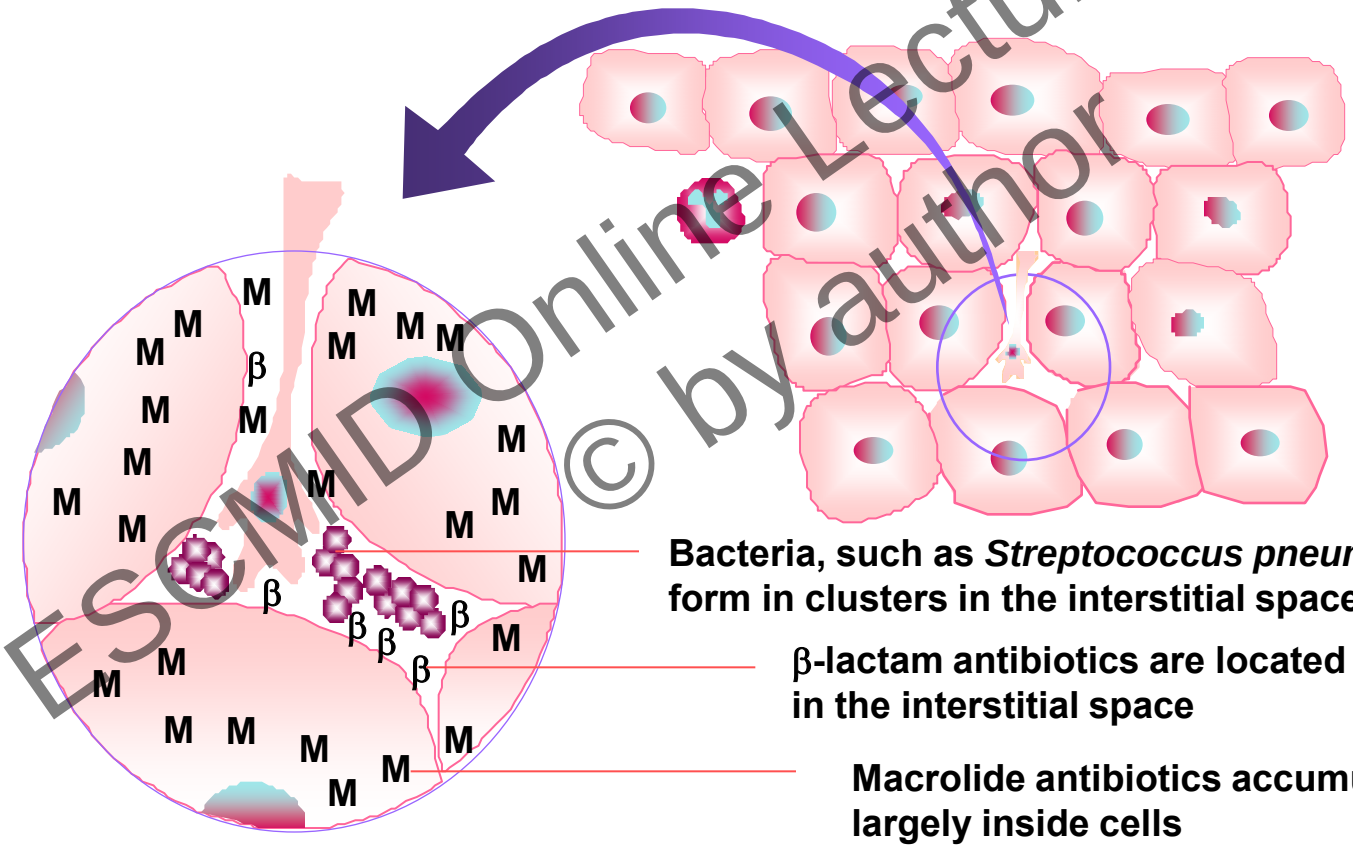
Serum concentration in different phases



Concentration: tissue or serum?



Where are the bacteria?



Bacteria, such as *Streptococcus pneumoniae,* form in clusters in the interstitial space

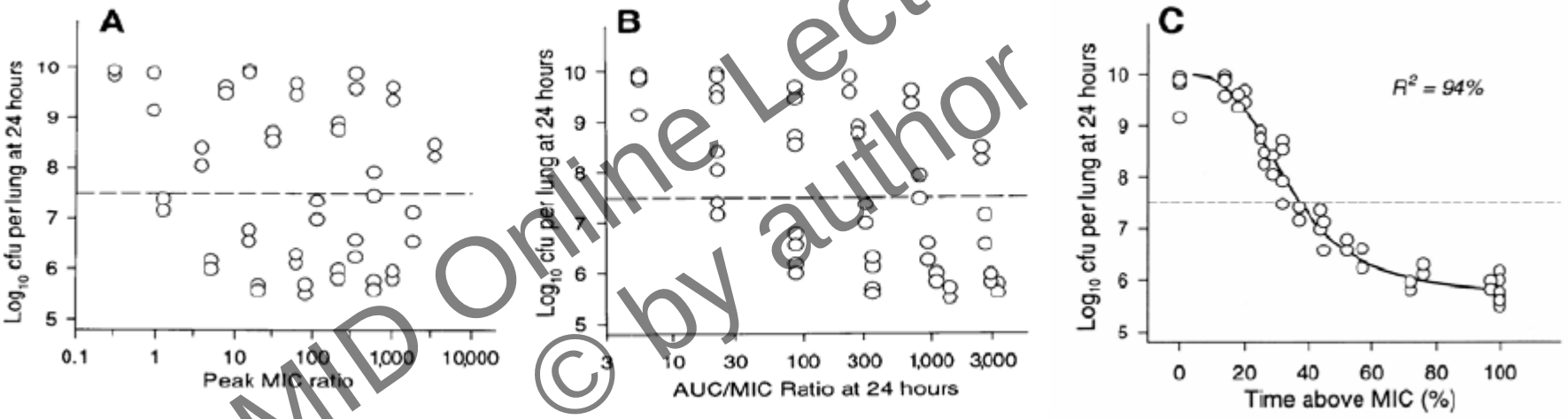
β-lactam antibiotics are located largely in the interstitial space

Macrolide antibiotics accumulate largely inside cells

Why can tissue concentrations be harmful?

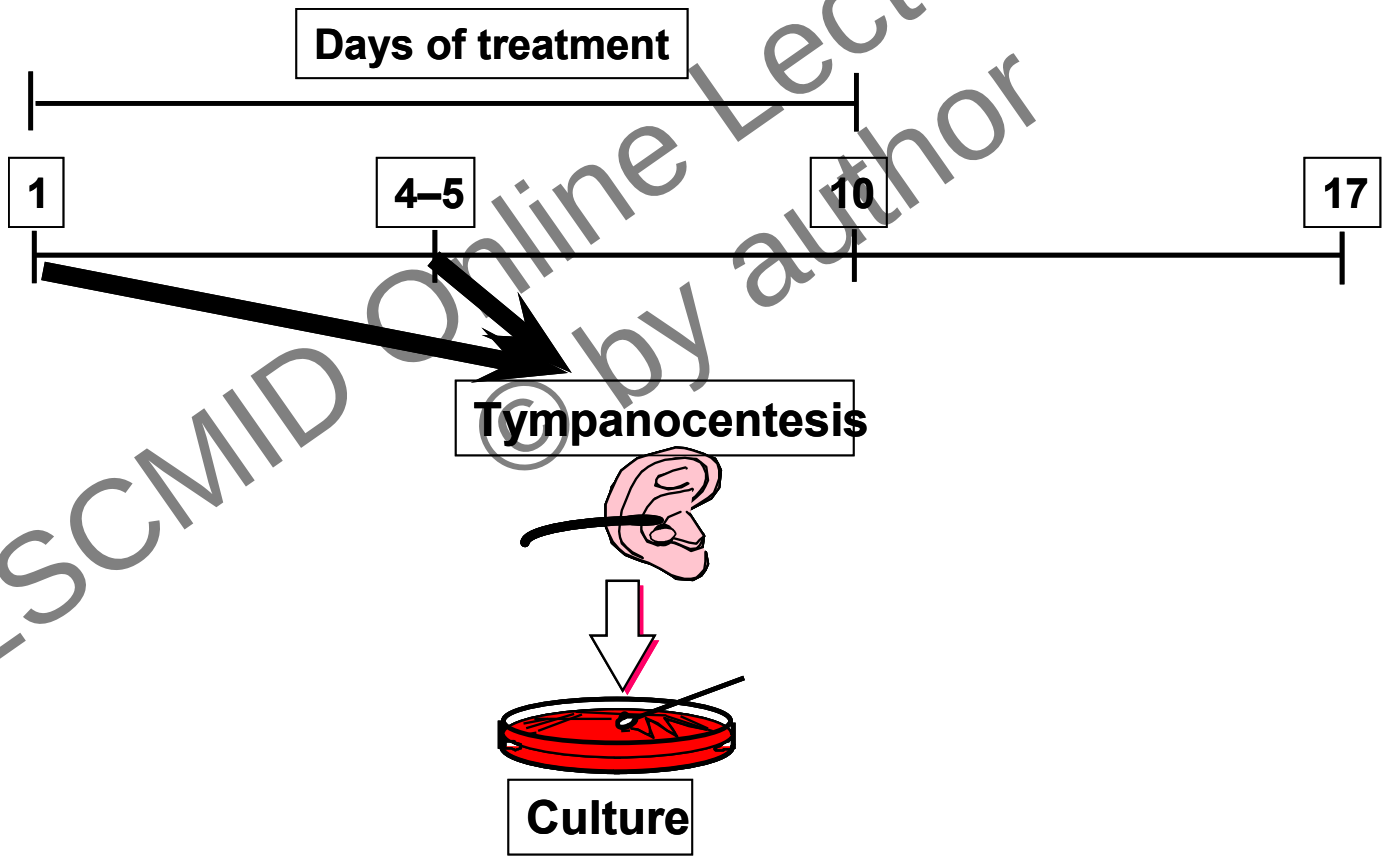
- β-lactams and aminoglycosides
  → Underestimation of local concentration
- Macrolider and fluoroquinolones
  → Overestimation of local concentration (except intracellular bacteria)
- Complex distribution between different compartments – tissue concentrations need to be measured repeatedly
- Serum concentration an excellent surrogate measure for the concentration in the infectious focus
- Some exceptions: epithelial lining fluid and cerebrospinal fluid

Killing with β-lactams

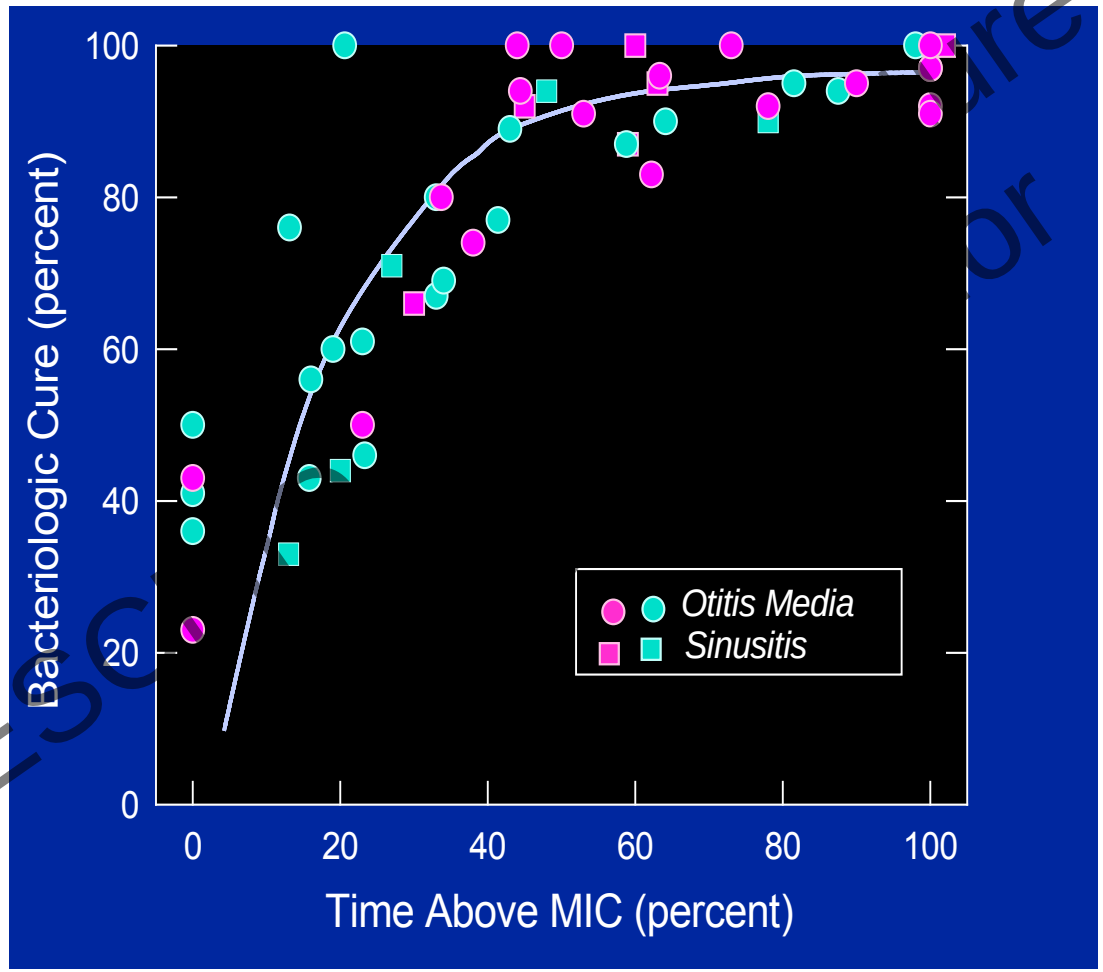


- Neutropenic mouse pneumonia model, *K. pneumoniae*
- Craig WA. CID 1998

Validation in clinical studies – double tap (Dagan et al)

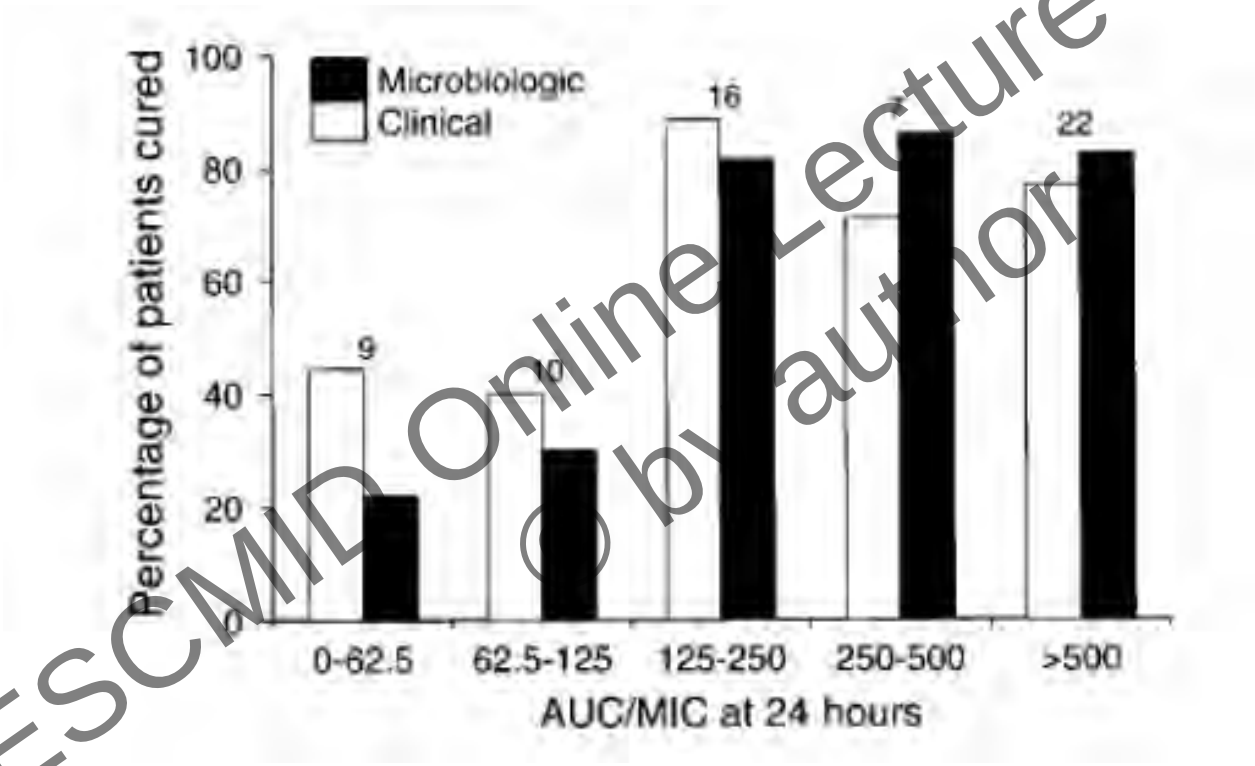


Findings from double-tap studies



Pink: *S. pneumoniae*
Green: *H. influenzae*

Killing with fluoroquinolones



- Forrest et al. AAC 1993
- Critically ill patients

Conclusions regarding PD-targets

Antibiotic	PD parameter	Target
Pencillins	%*f*T>MIC	50
Cephalosporins	%*f*T>MIC	50
Carbapenems	%*f*T>MIC	40
Fluoroquinolones	*f*AUC/MIC	Gram-positive: 40 Gram-negative: 80
Aminoglycosides	fC_{max}/MIC	10
Tigecycline	AUC/MIC	Gram-positive: 12.5 Gram-negative: 7
Vancomycin	*f*AUC/MIC	180

Individual variation

- Not all are healthy fire workers
- Patients are not even healthy…

PK in critically ill patients (Burkhard, JAC 2007)

Parameter	This study[a] (n = 17)	Pletz *et al.*, 2004[b] single dose (n = 10)	Pletz *et al.*, 2004[b] multiple dose (n = 10)
C_{max} (mg/L)	90.5 ± 26.1	253 (15)	275 (19)
$AUC_{0-\infty}$ (mg · h/L)	418.5 ± 171.6	817 (20)[c]	823 (19)[d]
T_{max} (h)	0.5 (0.5–1.0)	0.5 (0)	0.5 (0)
$t_{1/2}$ β (h)	4.15 ± 1.33	4.5 (23)	4.3 (11)
MRT (L)	5.72 ± 1.68	4.7 (13)	4.1 (18)
V_z (L)	17.3 ± 5.93	8.0 (25)	7.5 (20)
V_{ss} (L)	14.8 ± 3.78	5.7 (18)	5.0 (18)
CL_{TOT} (mL/min)	43.2 ± 23.7	20.4 (18)	20.2 (16)
CL_R (mL/min)	31.8 ± 23.3	9.38 (37)	8.62 (46)
f_u (%)	54.8 ± 19.09	45.1 (36)	41.2 (42)

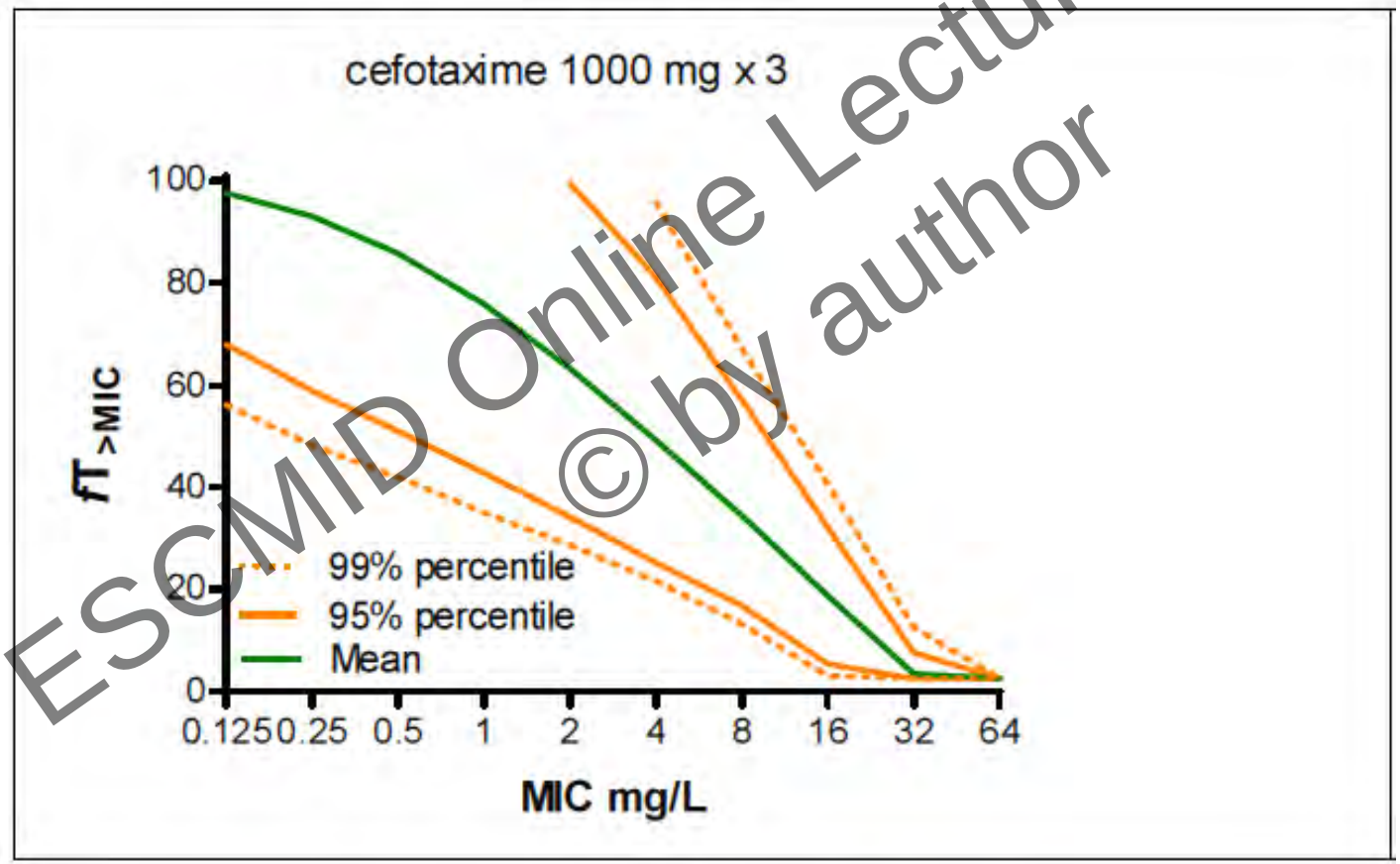
Can we simulate individual variation?

Goddard Cartoon ©PharmaVentures; all rights reserved

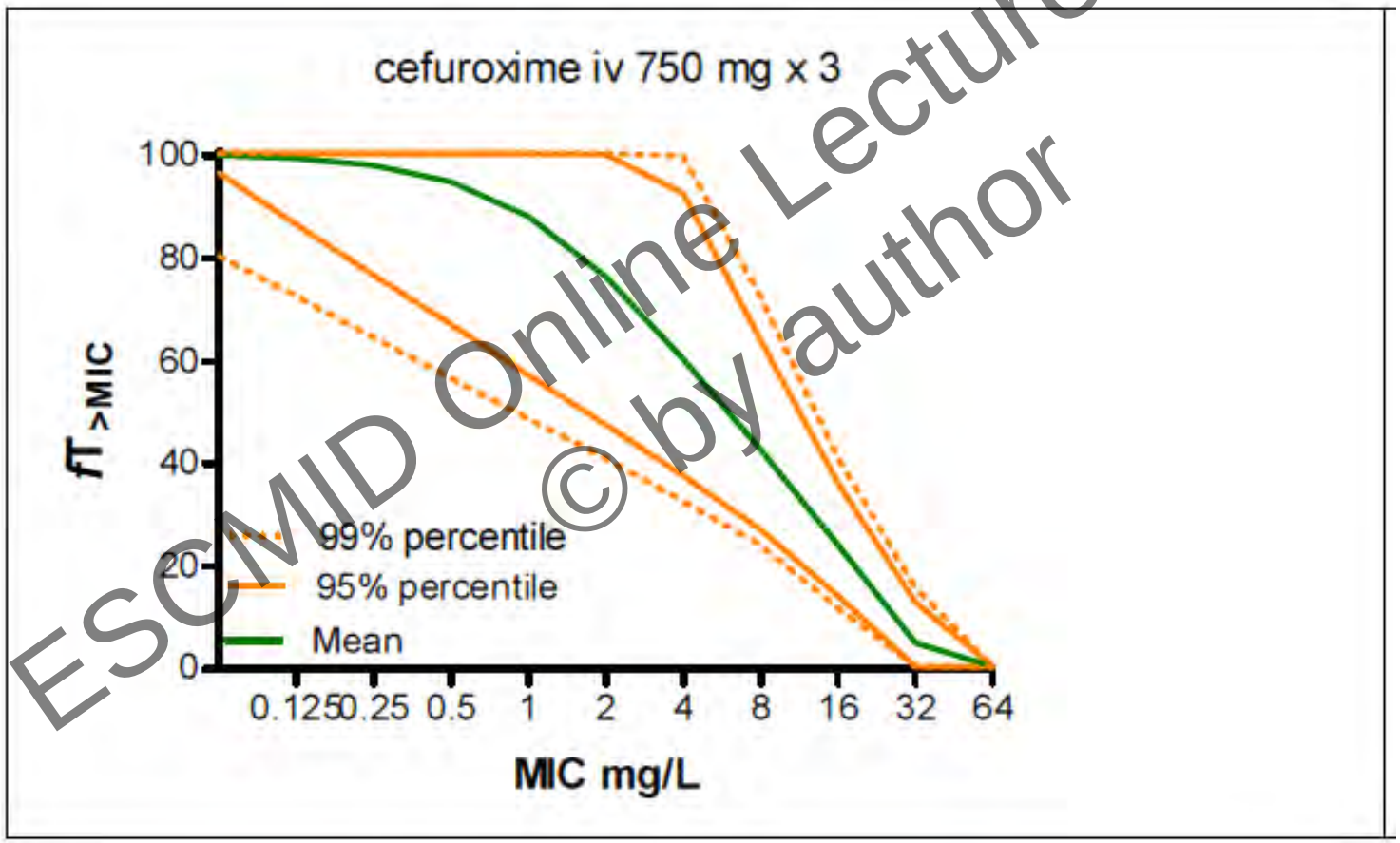
How does a Monte Carlo simulation work?

- Robust PK-data from several studies
- Simulate 10,000 PK-curves = introduce variability
- Calculate probability for e.g. 95% of the population reaching a certain goal – e.g. fT>MIC 50%
- Probability related to MIC-values
- Choosing the MIC-value with best target attainment = pharmacodynamic breakpoint
- Each simulation is done for a given dosing regimen

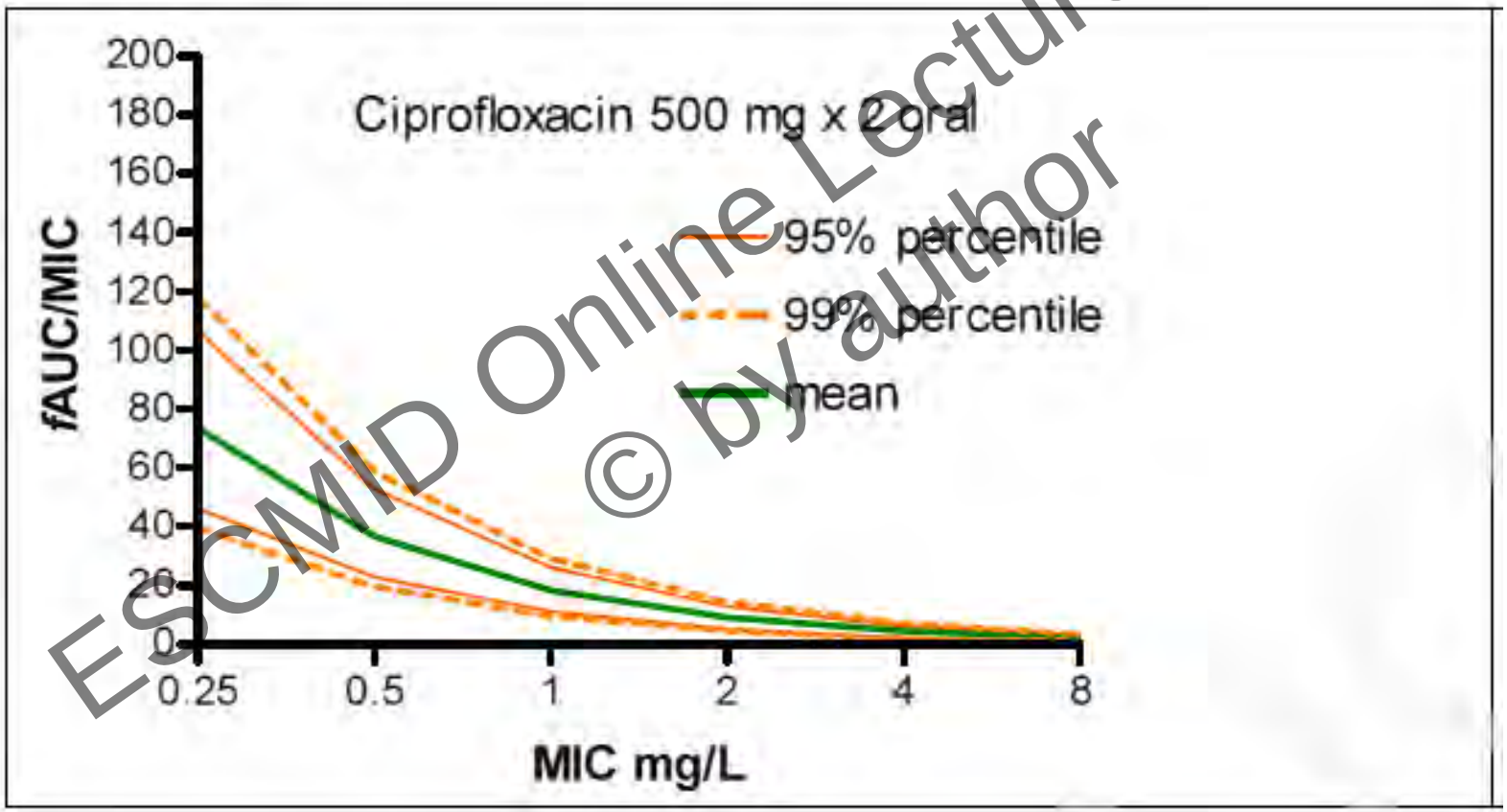
MC-simulation – cefotaxime



MC-simulation cefuroxime



MC-simulation: ciprofloxacin



Quick and dirty Monte Carlo…

- Simple calculations based on worst case scenarios in the literature regarding PK-parameters
- For a very conservative estimate it is possible to decrease deduced breakpoint with one dilution step
- In most cases in agreement with MC-simulations, although not equally convincing to other people….(can it really be that simple…)

Calculation aminoglycosides

Antibiotic	Free C_{max} (dosage)
Gentamicin	3.8 mg/L (1 mg/kg) 7.6 mg/L (2 mg/kg) 11.4 mg/L (3 mg/kg) 22.8 mg/L (6 mg/kg) 26.6 mg/L (7 mg/kg)

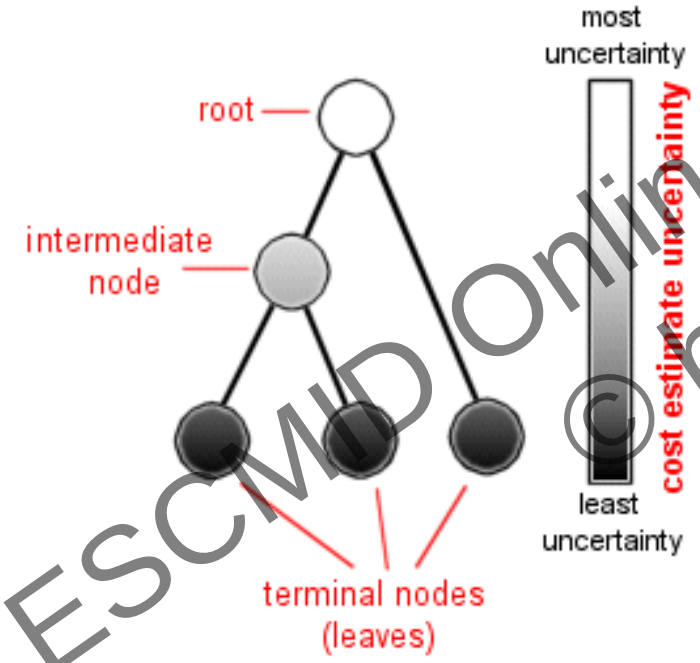
- Target: free C_{max}/MIC=10
- MIC 2 mg/L: need at least 20 mg/L

Calculation fluoroquinolones

Antibiotic	Free C_{max} (dosage)	Free AUC
Ciprofloxacin	1.7 mg/L (0.5 g x 2 p.o.) 2.2 mg/L (0.4 g x 2 i.v.) 2.2 mg/L (0.75 g x 2 p.o.)	13 15 27
Levofloxacin	4.6 mg/L (0.5 g x 1) 6.7 mg/L (0.75 g x 1)	34 43

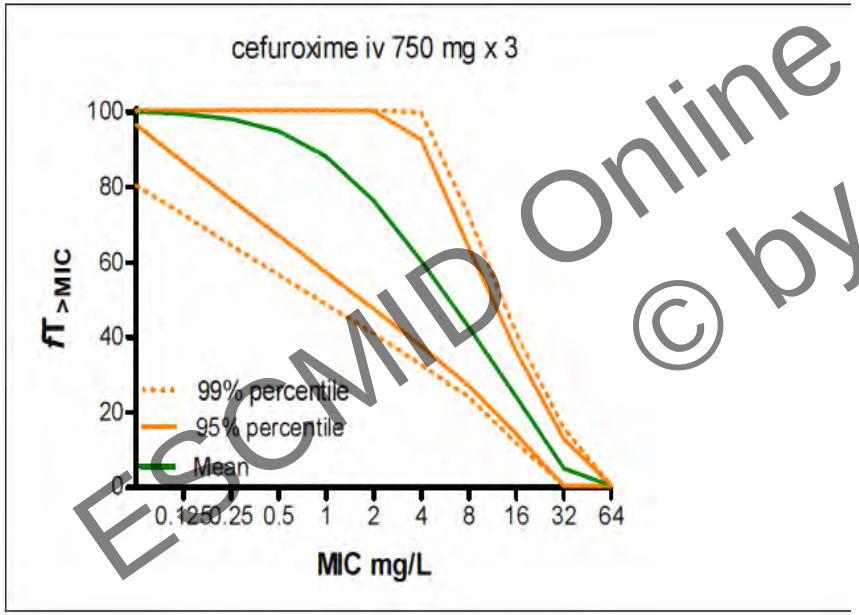
- Target ciprofloxacin: free AUC/MIC=40
- MIC 0.5 mg/L: need at least AUC 20
- Normally 0.5 g x 2 works well, but probably because urinary tract focus

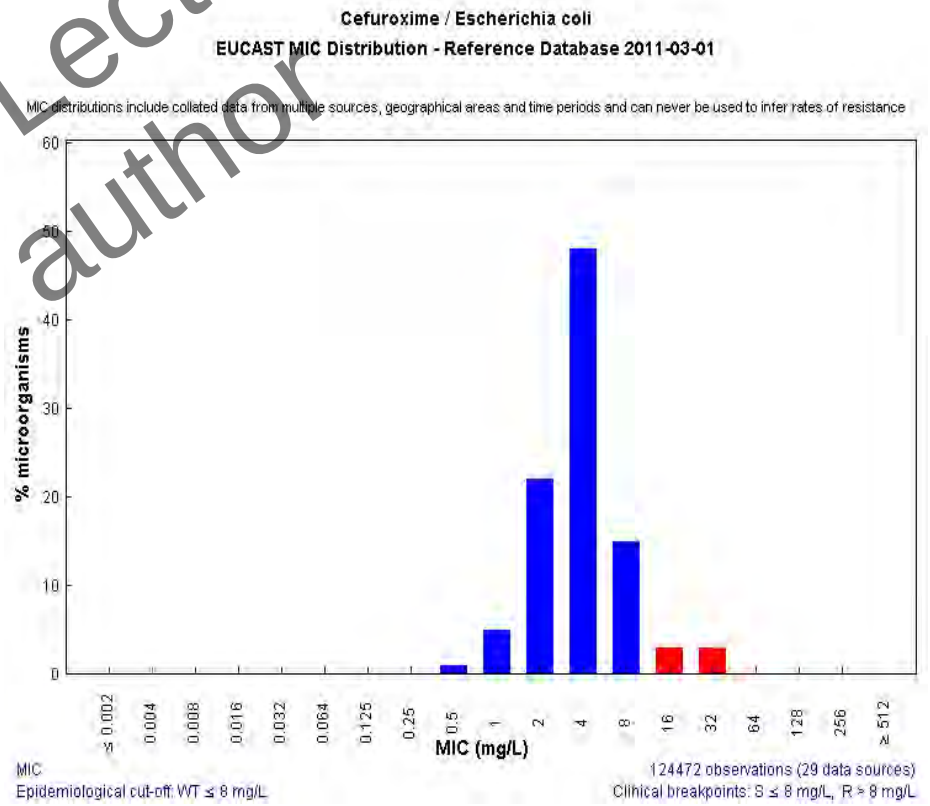
Clinical data: CART-analysis



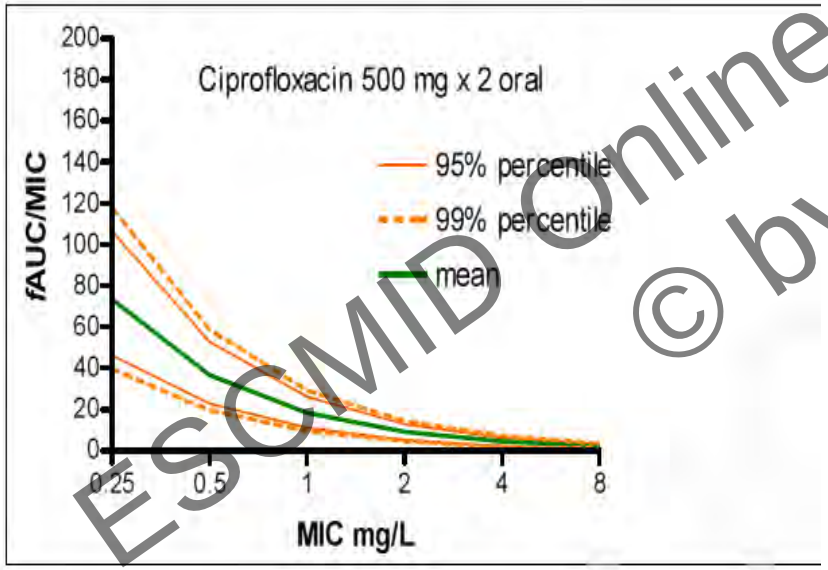
- Classification And Regression Tree
- Define individual AUC/MIC or T>MIC for analyzed patients
- Start recursive splitting in success and failure
- Identify node that will give best separation of success from failure
- The node corresponds to a CART-based breakpoint

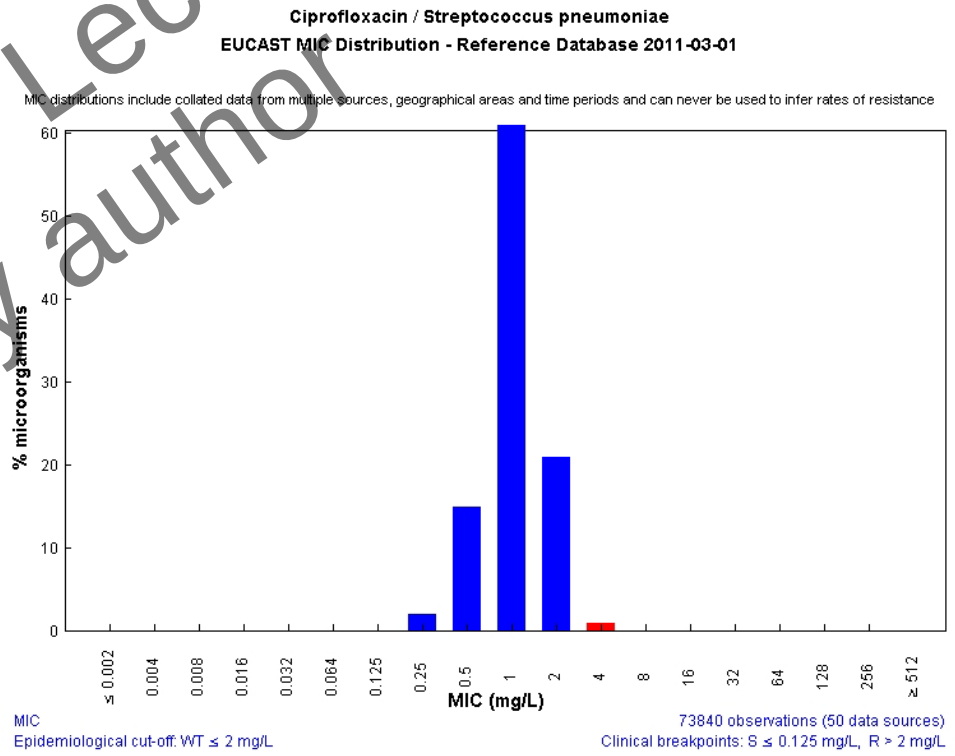
Synthesis of all data – cefuroxime and Enterobacteriaceae





Synthesis of all data: ciprofloxacin and *S. pneumoniae*





Conclusions

- PK/PD: very useful tool in setting of breakpoints
- Simulation of target attainment must take into consideration the considerable pharmacokinetic interindividual variation
- Some patient categories have considerably larger variation than what is reflected in Monte Carlo simulations
- Integration of data
  - → CART-analysis
    - → PK/PD
    - → Wild-type distributions