Doseren van Antibiotica
PK/PD

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internist-infectioloog & klinisch farmacoloog

- Farmacokinetiek:

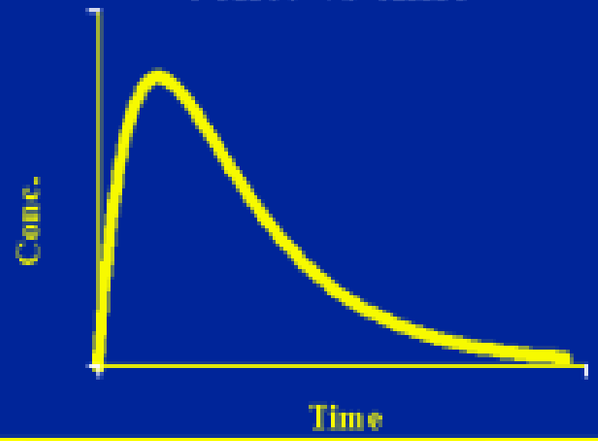
  What the body does to the drug

- Farmacodynamiek:

  What the drug does to the body

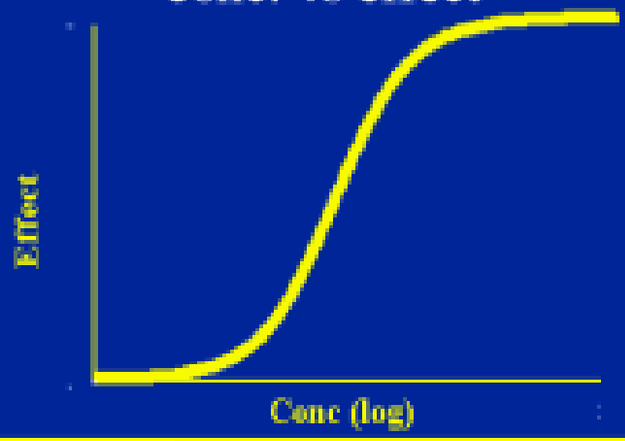
Pharmacokinetics

conc. vs time



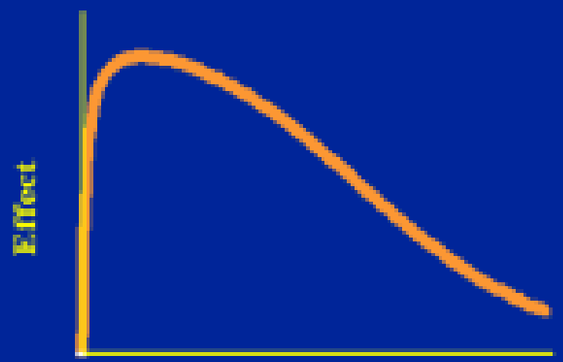
Pharmacodynamics

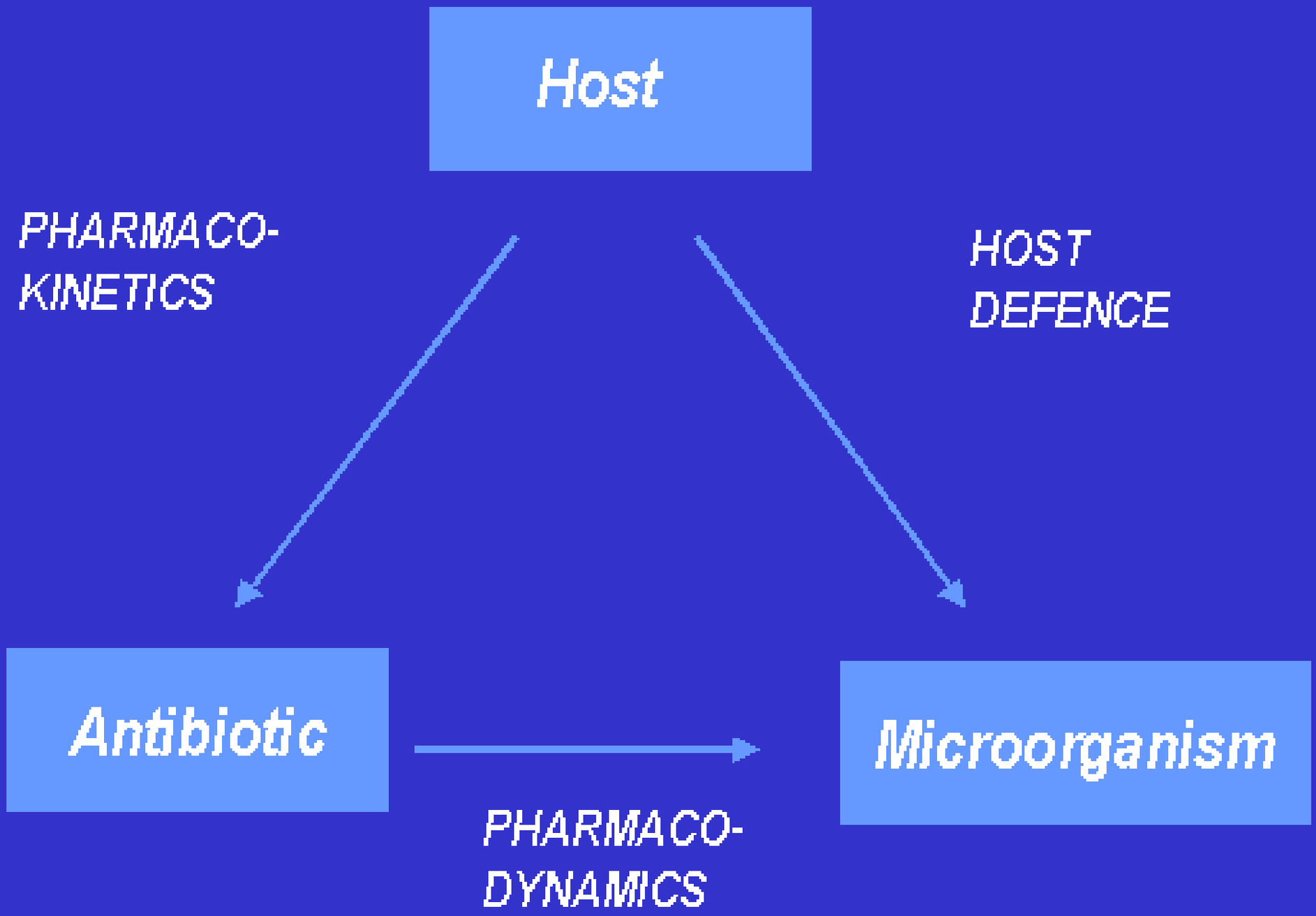
conc. vs effect

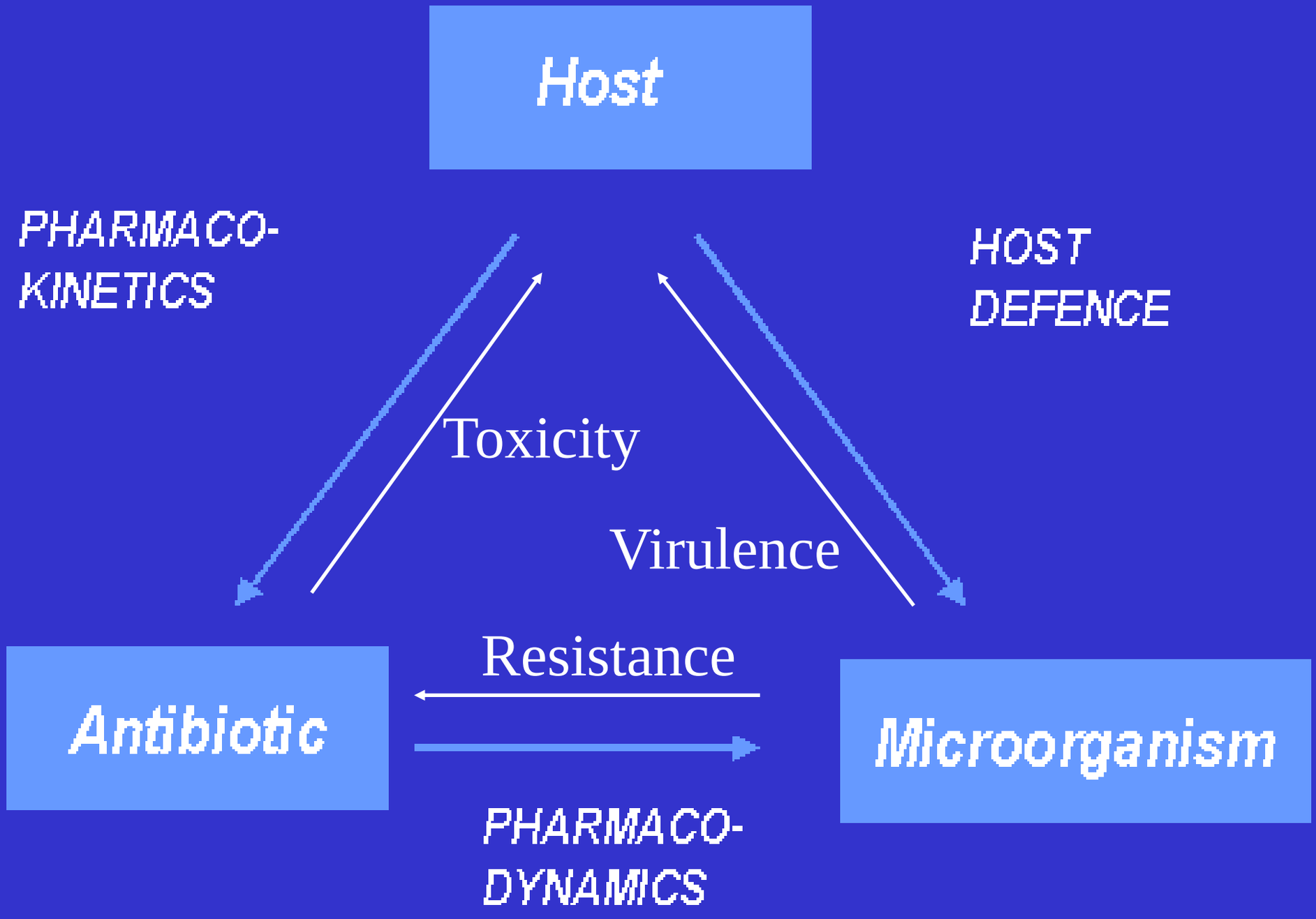


PK/PD

effect vs time




Host
PHARMACO-
KINETICS
HOST
DEFENCE
Antibiotic
Microorganism
PHARMACO-
DYNAMICS


Host
PHARMACO-
KINETICS
HOST
DEFENCE
Toxicity
Virulence
Resistance
Antibiotic
Microorganism
PHARMACO-
DYNAMICS

Keuze van AB kan lastig zijn maar de dosis toch niet ?

- locale richtlijn, SWAB, FK
- Je past soms aan bij verminderde nierfunctie
- Je wil een goede AB concentratie ter plaatse (abces, meningen, bot, vegetatie etc)

Penetratie in weefsel

De concentratie van het antibioticum in het weefsel wordt bepaald door:

- concentratiegradiënt
- vascularisatie van het weefsel
- moleculair gewicht
- vetoplosbaarheid
- eiwitbinding
- PK

Niet oraal maar iv

- Neutropenie met indicatie voor klinische behandeling
- Abces zonder goede drainage, ernstige weke delen infectie, osteomyelitis en/of septische artritis
- Staphylococcus aureus bacteriemie
- Endocarditis of endovasculaire infectie
- Meningitis
- Gestoorde gastrointestinale absorptie

Mw. O, septische shock nosocomiale urosepsis?

- SWAB: ceftriaxon + gentamicine

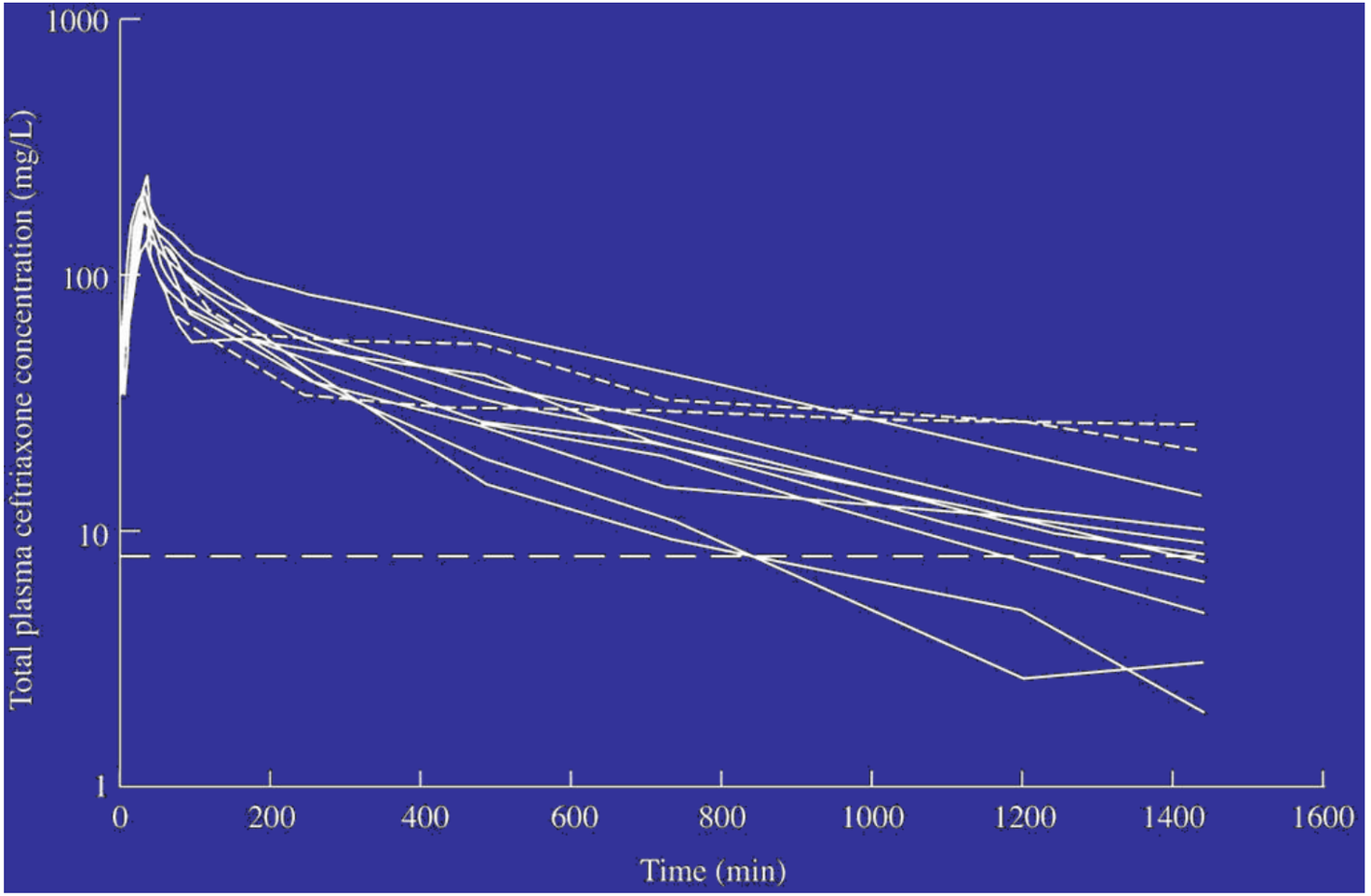
- LO: ziek, lengte 1.68 cm. Gewicht 135 kg.
- Lab: kreat 120 µmol/l

- Welke doses?

D= Vd x Cp

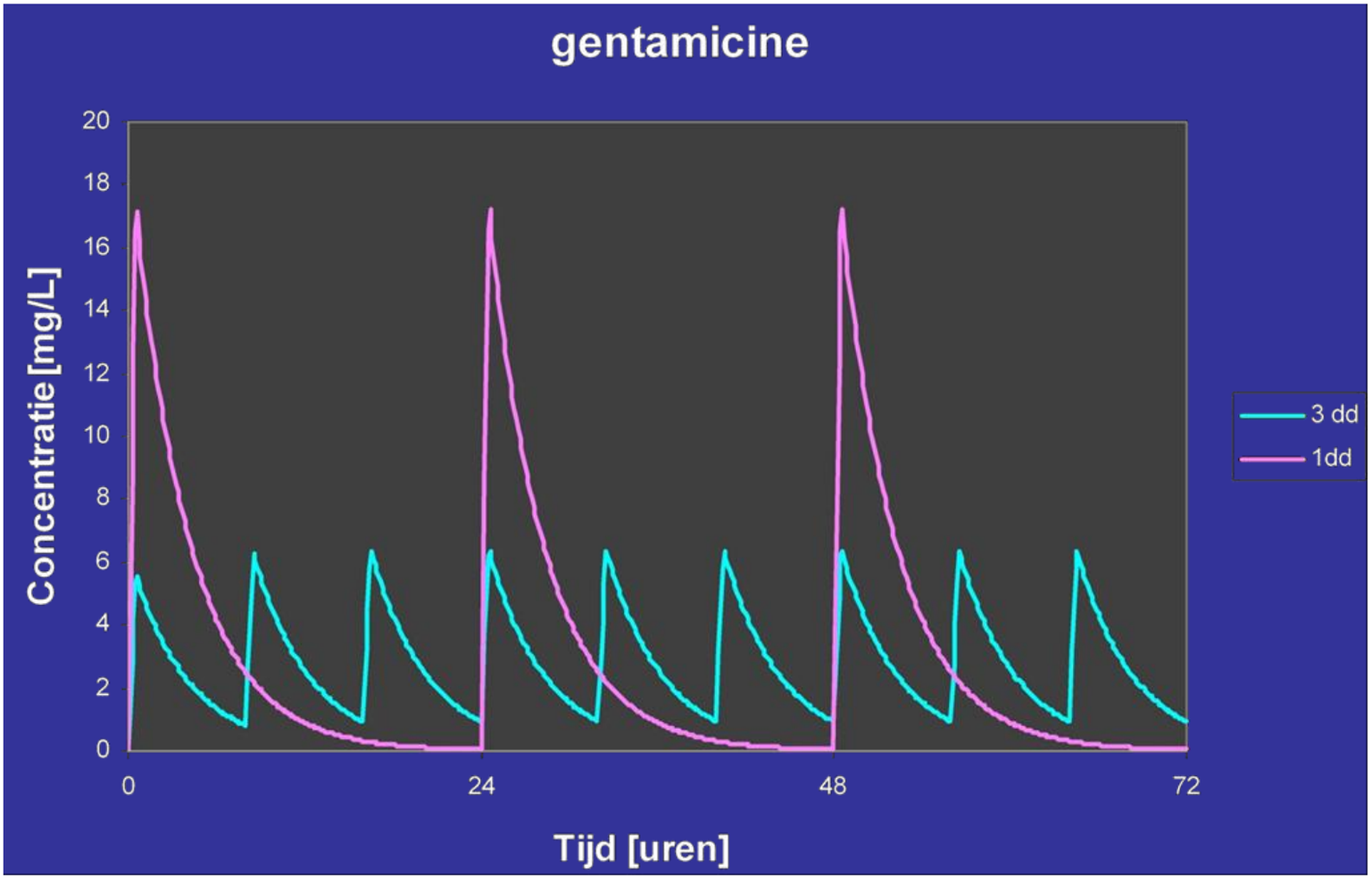
- C= D/Vd
- Vd is virtueel en variabel
  - Neemt af bij dehydratie
  - Neemt toe voor hydrofiele AB (cefalo's) bij third spacing/sepsis
  - Neemt toe bij adipositas bij lipofiele AB (macroliden)

Totale plasma ceftriaxon concentratie van individuele patiënten gedurende 24 uur na iv toediening



Joynt, G. M. et al. J. Antimicrob. Chemother. 2001;47:421-429

Gentamicine 1dd x mg/kg ?



Nicolau DP. Antimicrob Agents Chemother 1995;39:650-5.

Moore RD. J Infect Dis 1987;155:93-9.

Geen genta maar cipro….

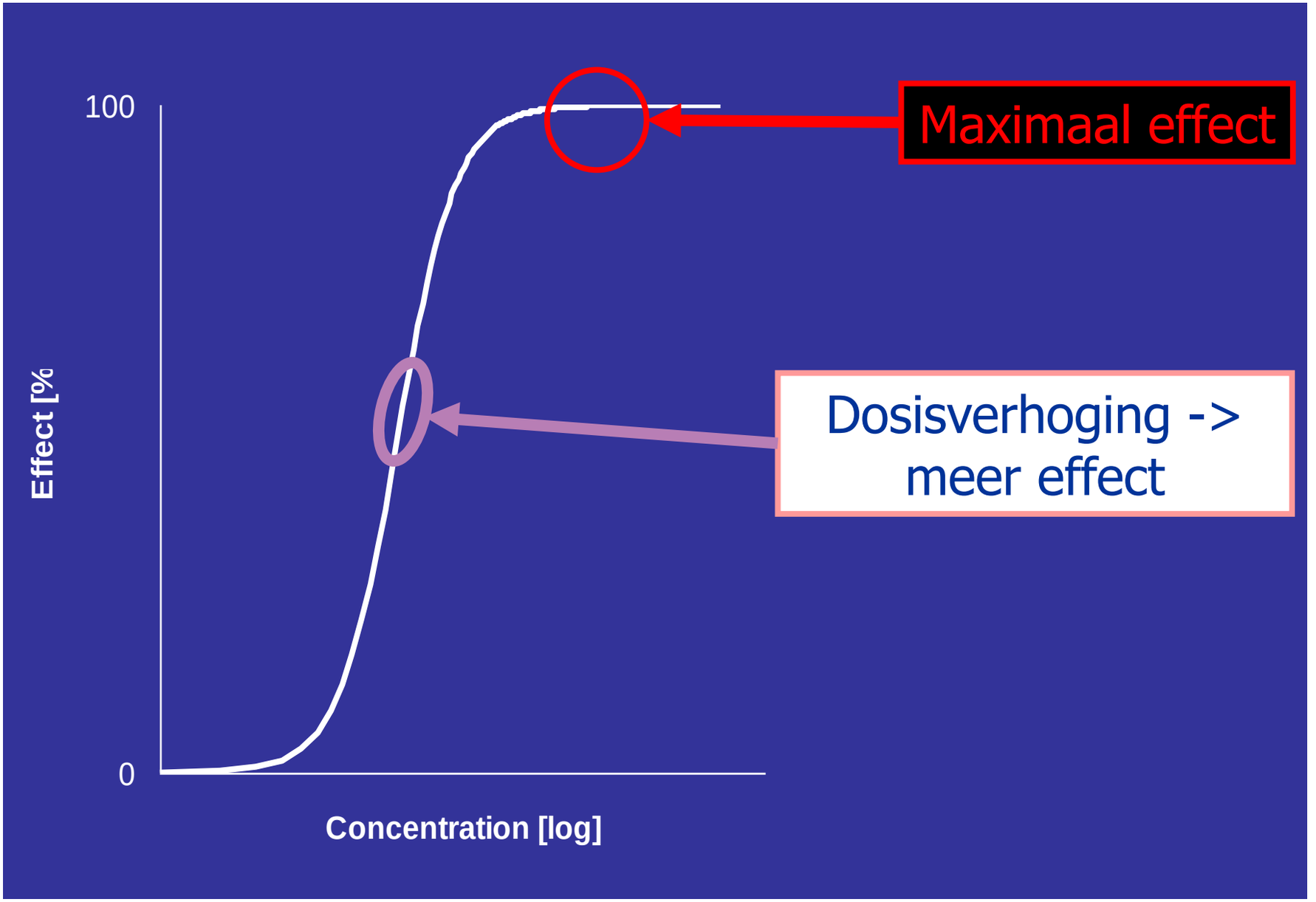
- J Crit Care. 2008
- **Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study.** Girbes AR.

Serum concentrations were measured in 32 intensive care unit patients (age, 68.7 +/- 17.4 years; Sepsis-related Organ Failure Assessment (SOFA) scores, 7.3 +/- 3.4)

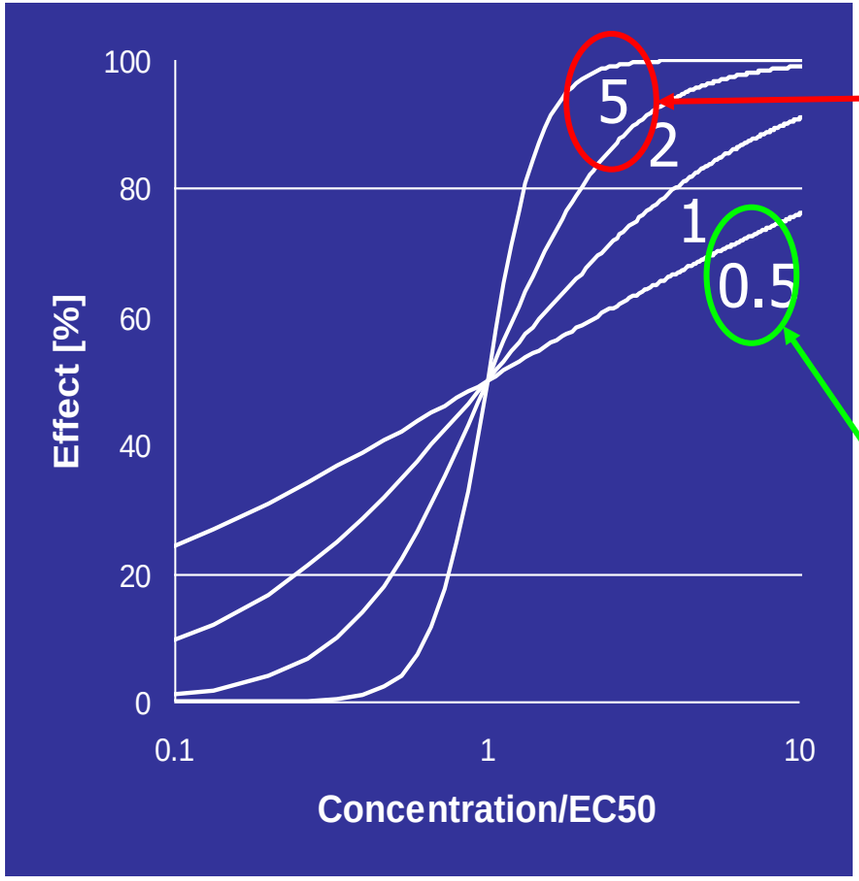
CONCLUSIONS:

- Ciprofloxacin 400 mg bid IV leads to inadequate AUC/MIC and C(max)/MIC ratios in many cases. Effective killing concentrations were only achieved in pathogens with MIC less than 0.25. As bacteria in intensive care unit patients often exceed this threshold, we recommend to use higher doses of ciprofloxacin (1200 mg daily) to ensure optimal bacterial killing and avoid antibiotic resistance.

Sigmoïdaal dosis-respons model



Sommige curves zijn steiler



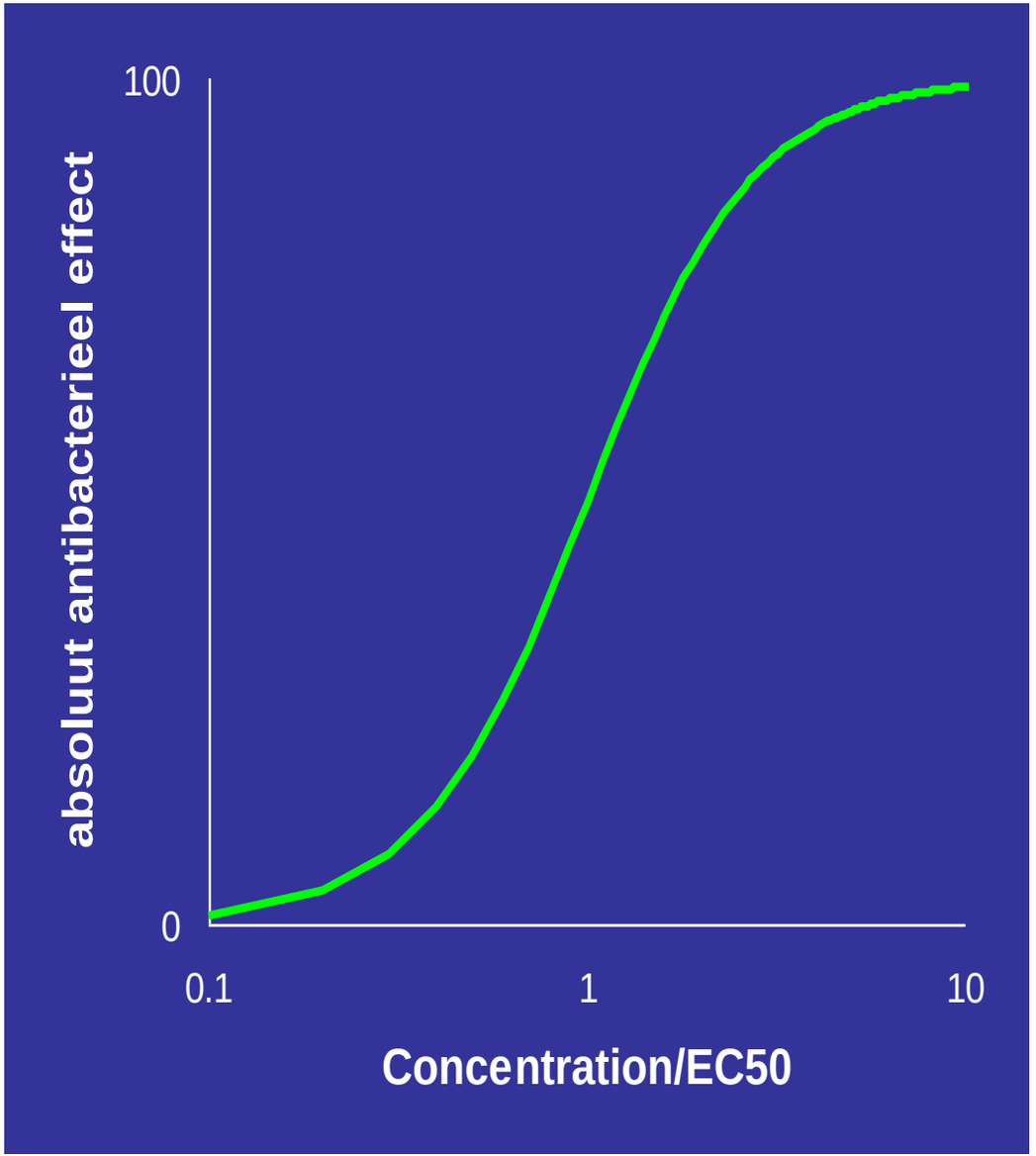
ß-lactams, vancomycine

- Beperkte dosis-respons zone
- Neigt naar alles of niets
- Celwandsynthese

Aminoglycosiden, fluoroquinolonen

- Brede dosis-respons zone
- Concentratieverhoging doet het effect toenemen
- Nucleïnezuur- en eiwitsynthese

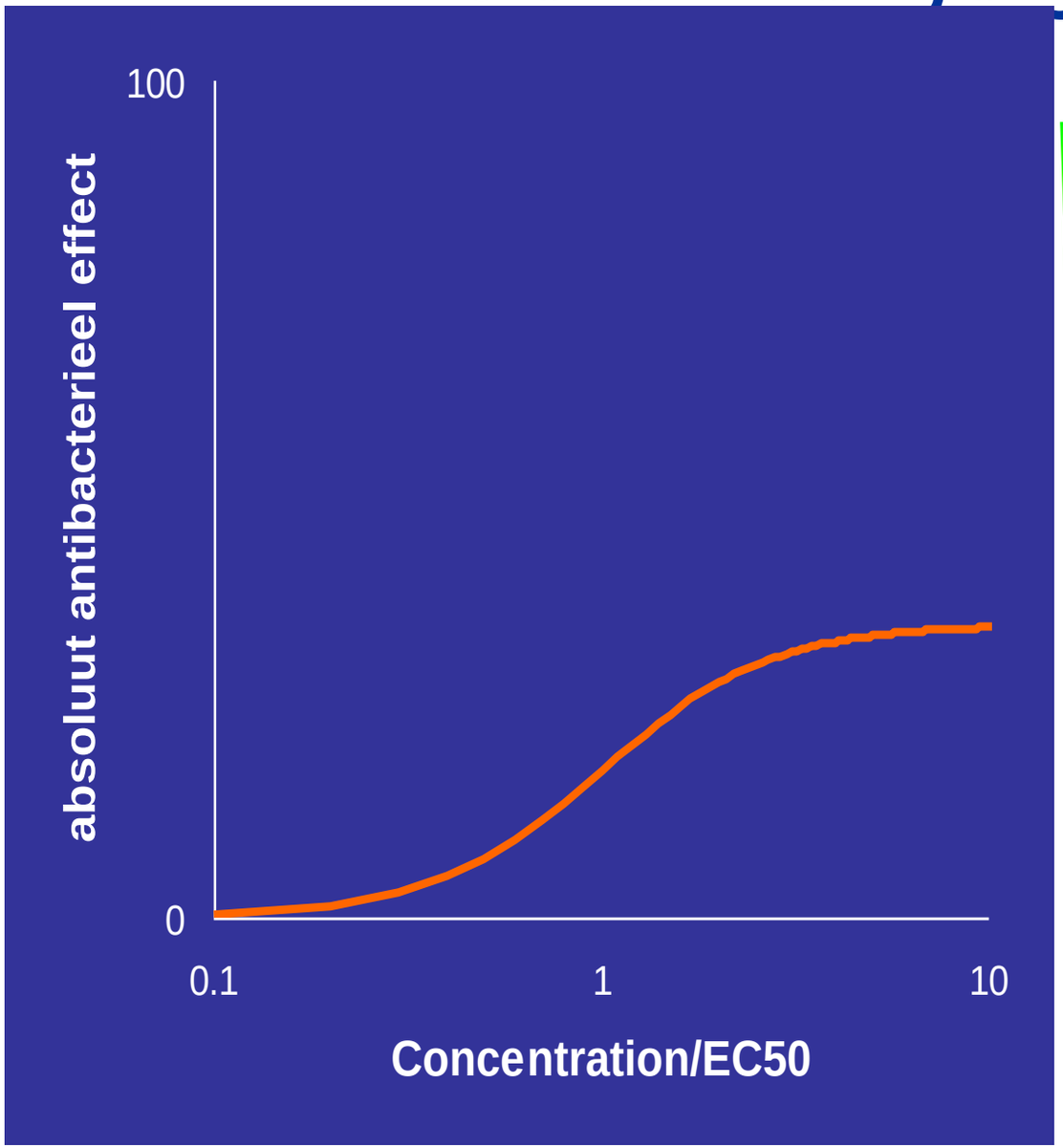
Sommige antibiotica zijn krachtiger dan anderen: vergelijk de E_{max}



hoge E_{max}

hoog bactericide effect
- fluorochinolonen
- aminoglycosiden

Sommige antibiotica zijn krachtiger dan andere: vergelijk de E_{max}

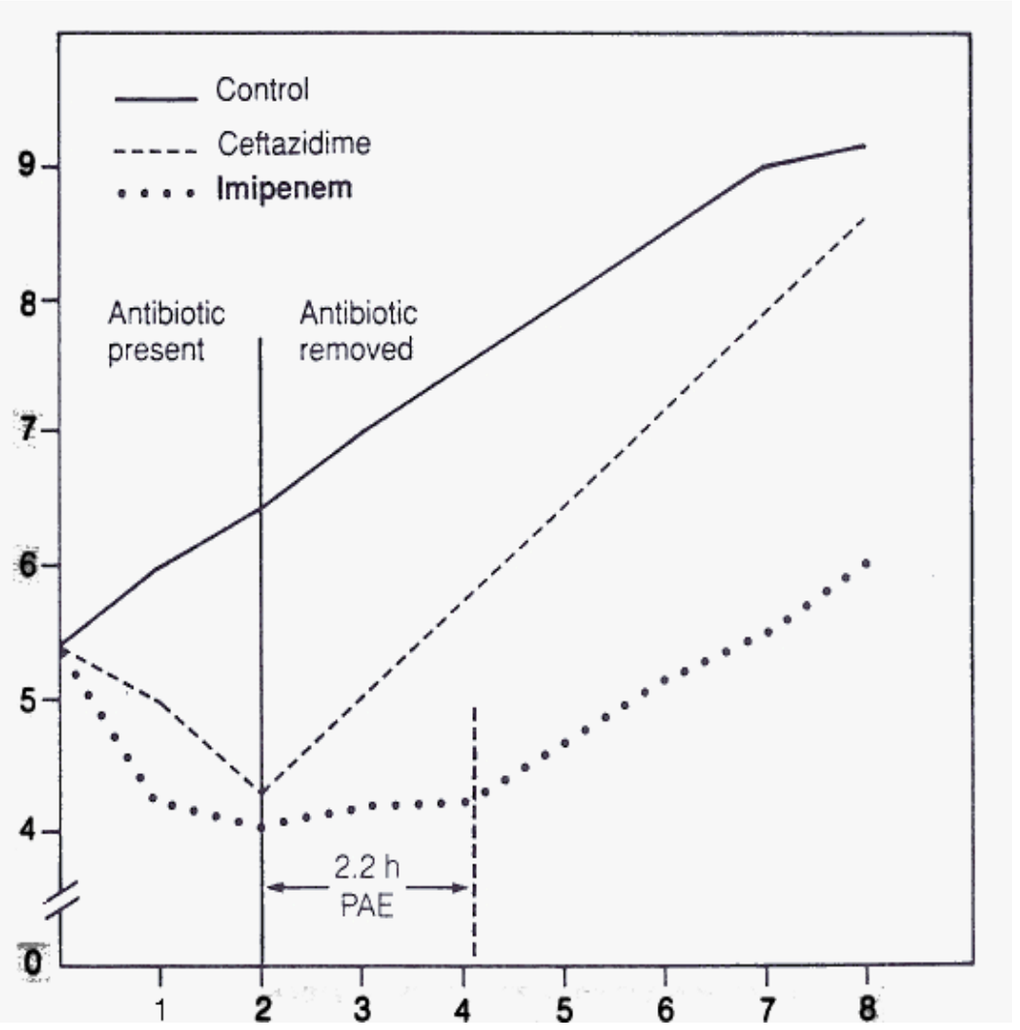


lage E_{max}

gering bactericide effect
- vancomycine
- macroliden
- tetracyclinen

Post Antibiotisch Effect

Tijd dat het effect aanhoudt nadat het antibioticum verdwenen is



Bron: Harris D, Denis Odipo Okumu. Biobio.loc.edu

Post Antibiotisch Effect

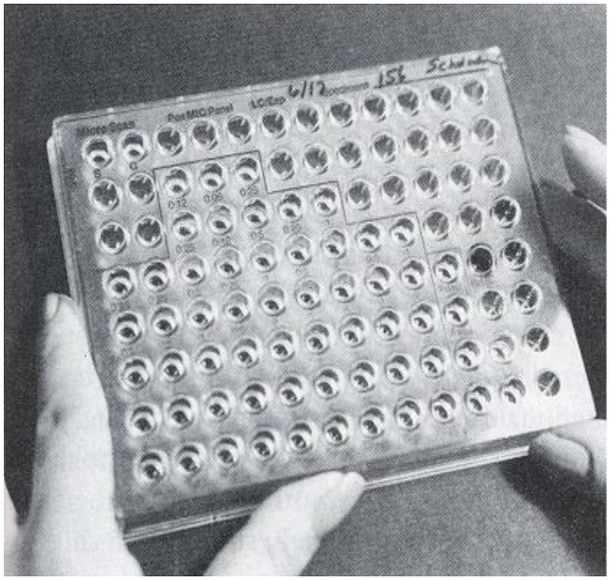
Antibioticum	PAE [uren]
chinolonen	2-3
erytromycin en claritromycine	1-2
clindamycine	2
ß-lactam: penicilline G, amoxicilline en ceftriaxon	1
vancomycine	1
rifampicine	4-5

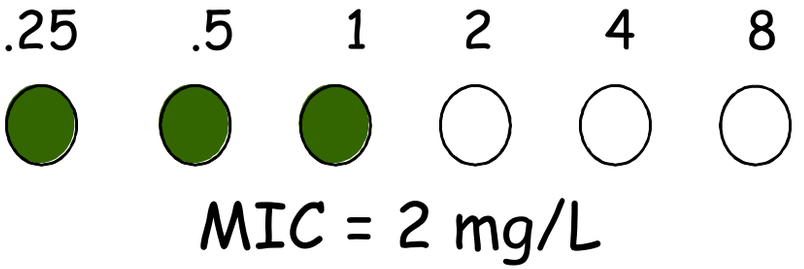
Athamna AJ. Antimicrob. Chemother. 2004;53:609-615

MIC
Measure of Potency

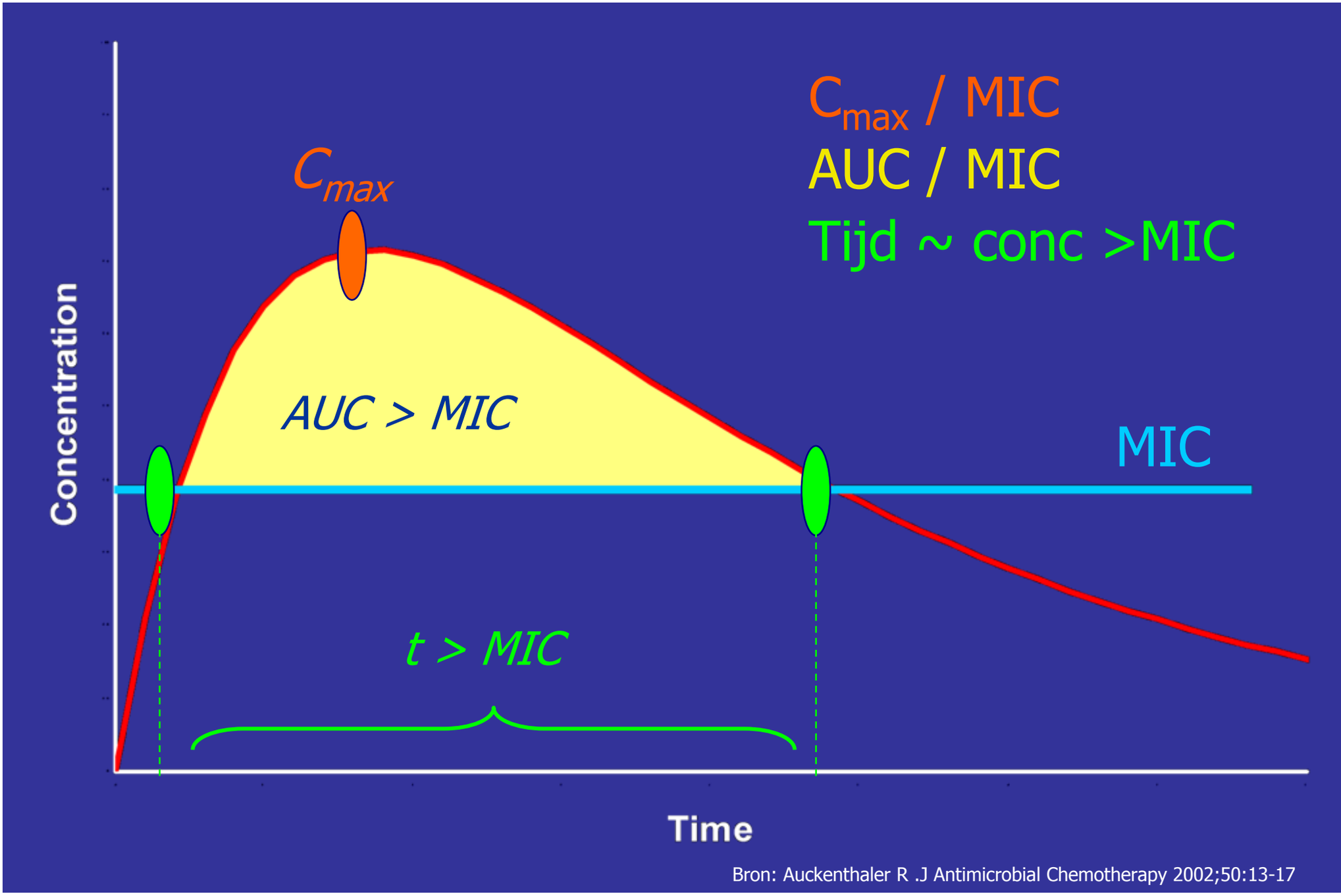
MIC

Lowest concentration with no visible growth after 18 hour incubation

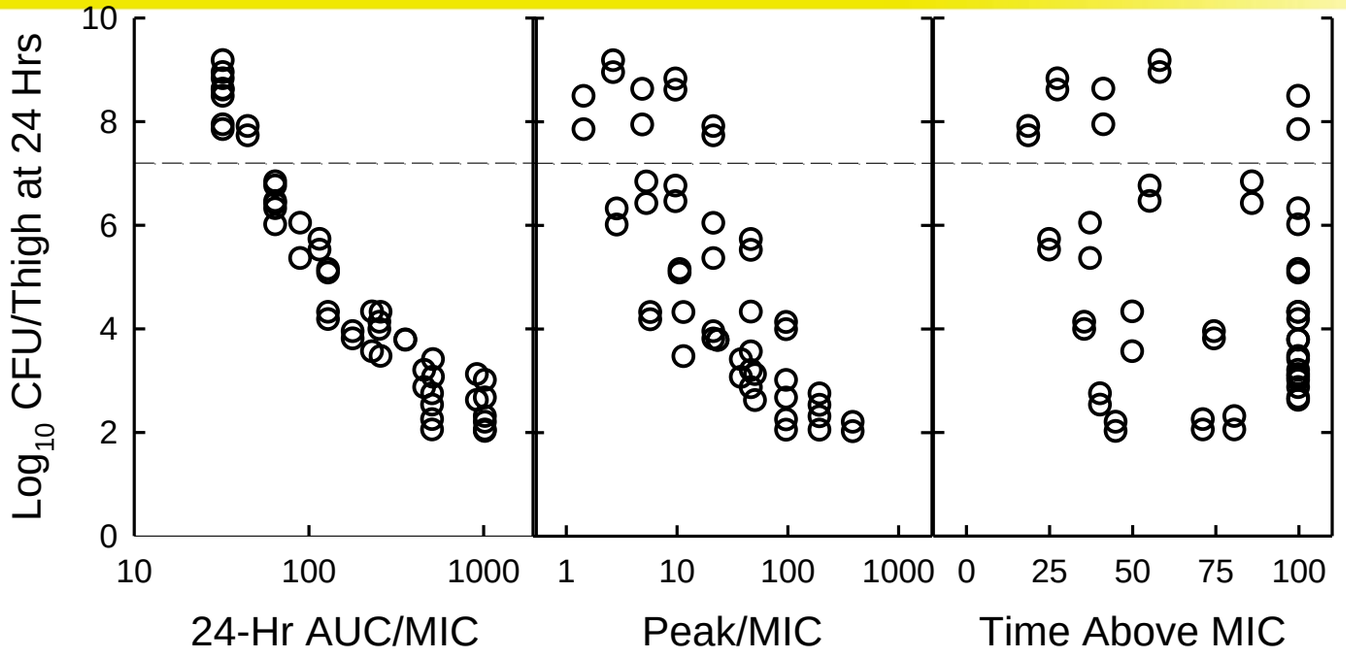




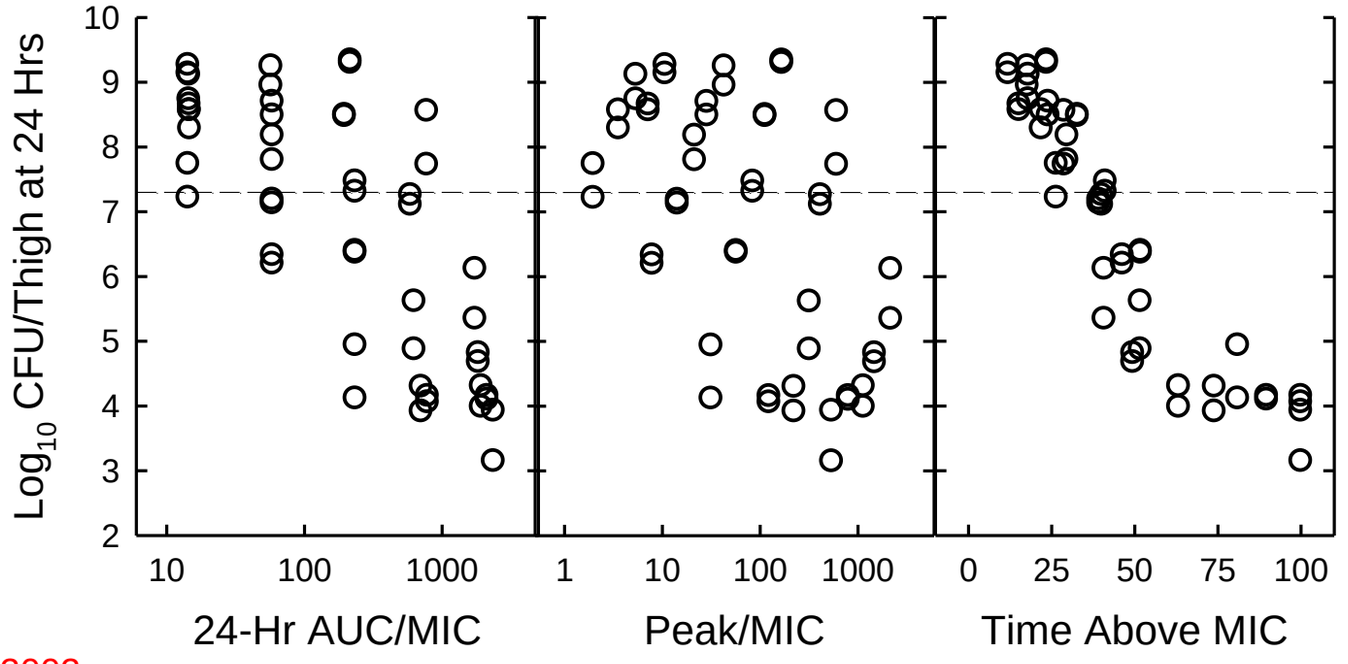
PK/PD relaties



Bron: Auckenthaler R .J Antimicrobial Chemotherapy 2002;50:13-17



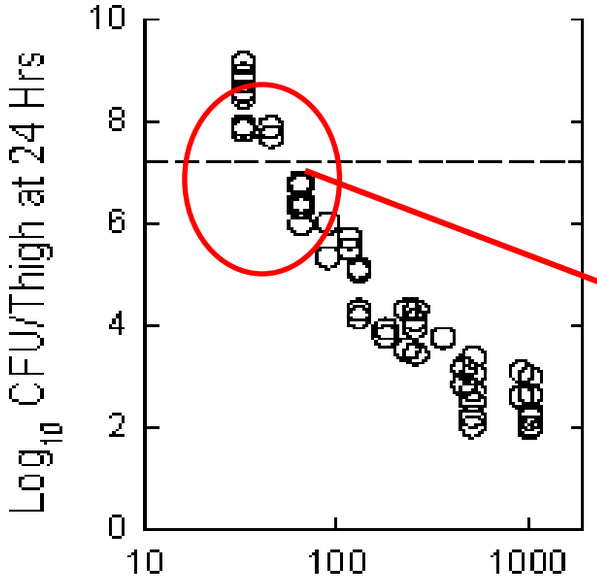
levofloxacin

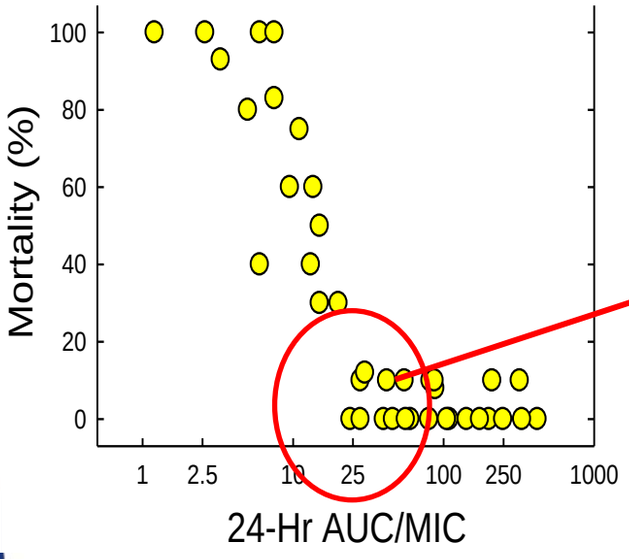


ceftazidim

Andes IJAA 2002

Quantitative relationship : exposure in mice and men

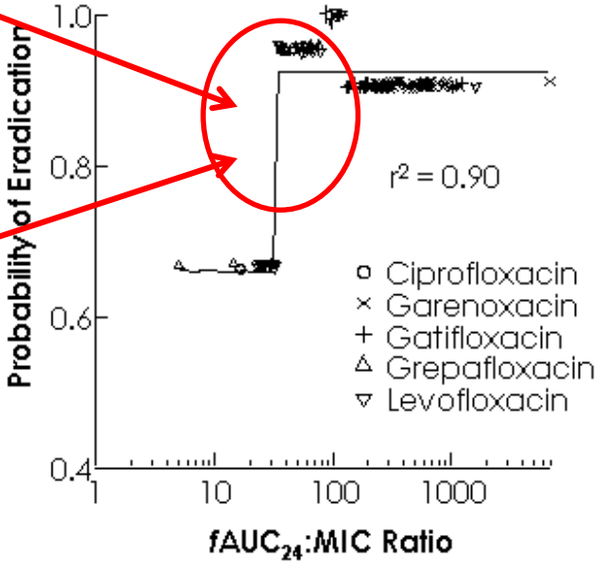




AUC/MIC mouse

~ 30-35

AUC/MIC human



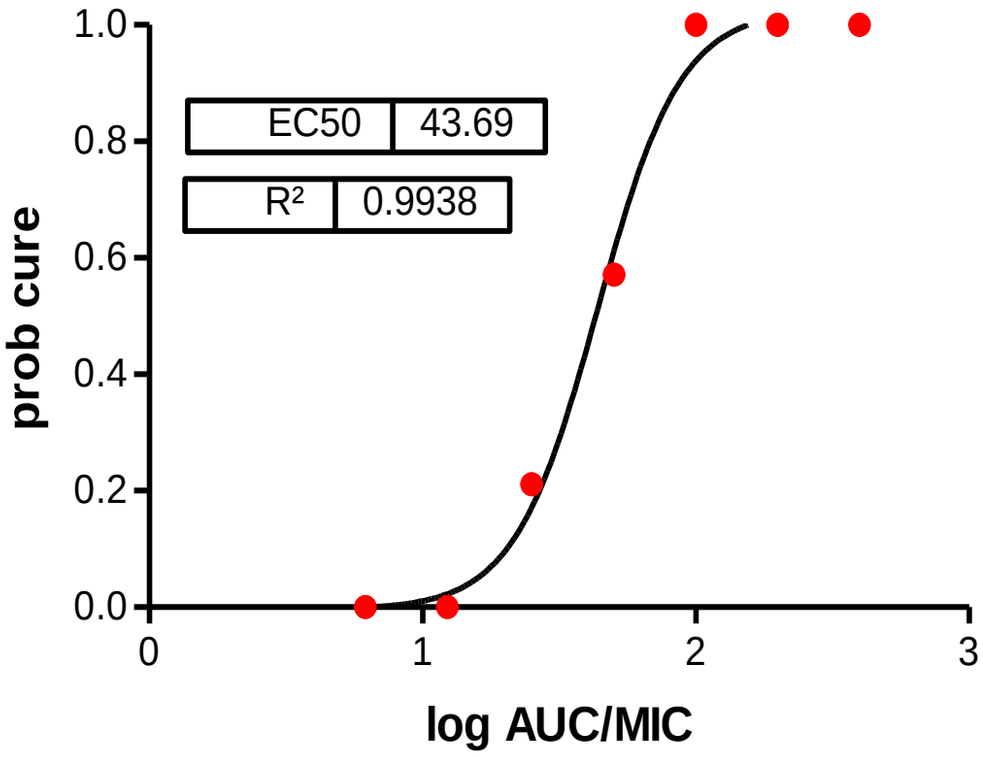
It is not only for Mice

Disease state, drug	Clinically-derived PK-PD target [reference(s)]	Animal infection model; organism studied	Animal-derived PK-PD target [reference(s)]
Hospital-acquired pneumonia			
Quinolones	*f*AUC$_{0-24}$:MIC ratio, 62–75 [11, 12]	Neutropenic mouse thigh; gram-negative bacilli	*f*AUC$_{0-24}$:MIC ratio, 70–90 for 90% animal survival or 2 log-unit kill [13, 14]
Community-acquired respiratory tract infections			
Quinolones	*f*AUC$_{0-24}$:MIC ratio, 34 [22]	Immunocompetent mouse thigh; *Streptococcus pneumoniae*	*f*AUC$_{0-24}$:MIC ratio, 25–34 for 90% animal survival or 2 log-unit kill [23]
β-Lactams	T>MIC, 40% of the dosing interval [14]	Immunocompetent mouse thigh; *S. pneumoniae*	T>MIC, 30–40% of the dosing interval for 90% animal survival [14]
Telithromycin	AUC$_{0-24}$:MIC ratio, 3.375 [20]	Neutropenic mouse thigh; *S. pneumoniae*	AUC$_{0-24}$:MIC ratio, 1000 for stasis [24]
Bacteremia			
Oritavancin	*f*T>MIC, 22% of the dosing interval for *Staphylococcus aureus* [25]	Neutropenic mouse thigh; *S. aureus*	*f*T>MIC, 20% of the dosing interval for a 0.5 log-unit kill [26]
Linezolid	AUC$_{0-24}$:MIC ratio, 85 for *S. aureus* or *Enterococcus faecium* [27]	Neutropenic mouse thigh; *S. aureus*	AUC$_{0-24}$:MIC ratio, 83 for stasis [33]
Complicated skin and skin structure infections			
Tigecycline	AUC$_{0-24}$:MIC ratio, 17.9 [28]	Neutropenic mouse thigh; *S. aureus*	AUC$_{0-24}$:MIC ratio, 15–20 for stasis [29]
Linezolid	AUC$_{0-24}$:MIC ratio, 110 [27]	Neutropenic mouse thigh; *S. aureus*	AUC$_{0-24}$:MIC ratio, 83 for stasis [33]

NOTE. AUC$_{0-24}$:MIC, the ratio of the area under the concentration-time curve at 24 h to the MIC; C_{max}:MIC, the ratio of the maximal drug concentration to the MIC; T>MIC, duration of time a drug concentration remains above the MIC.

Ambrose et al, CID 2007

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



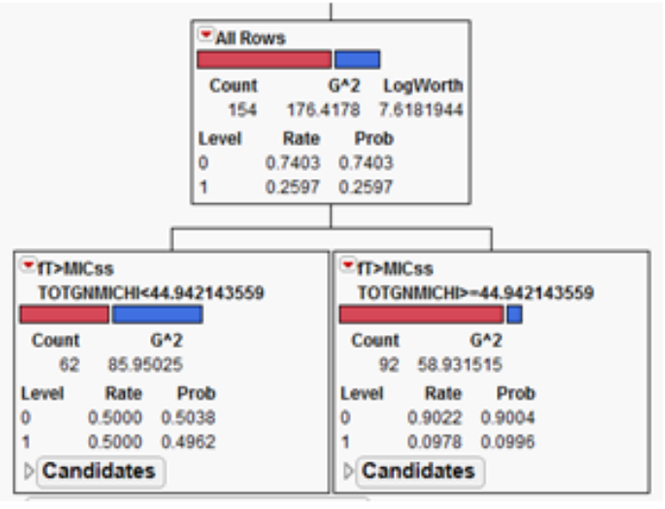
- Prob cure correlates with AUC/MIC
- POSITIVE correlation with EXPOSURE
- INVERSE correlation with MIC

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

Rodriguez- Tudela et al, AAC 2007

Ceftazidime in patients with nosocomial pneumonia

CART analysis



- to differentiate between lower and higher response rate

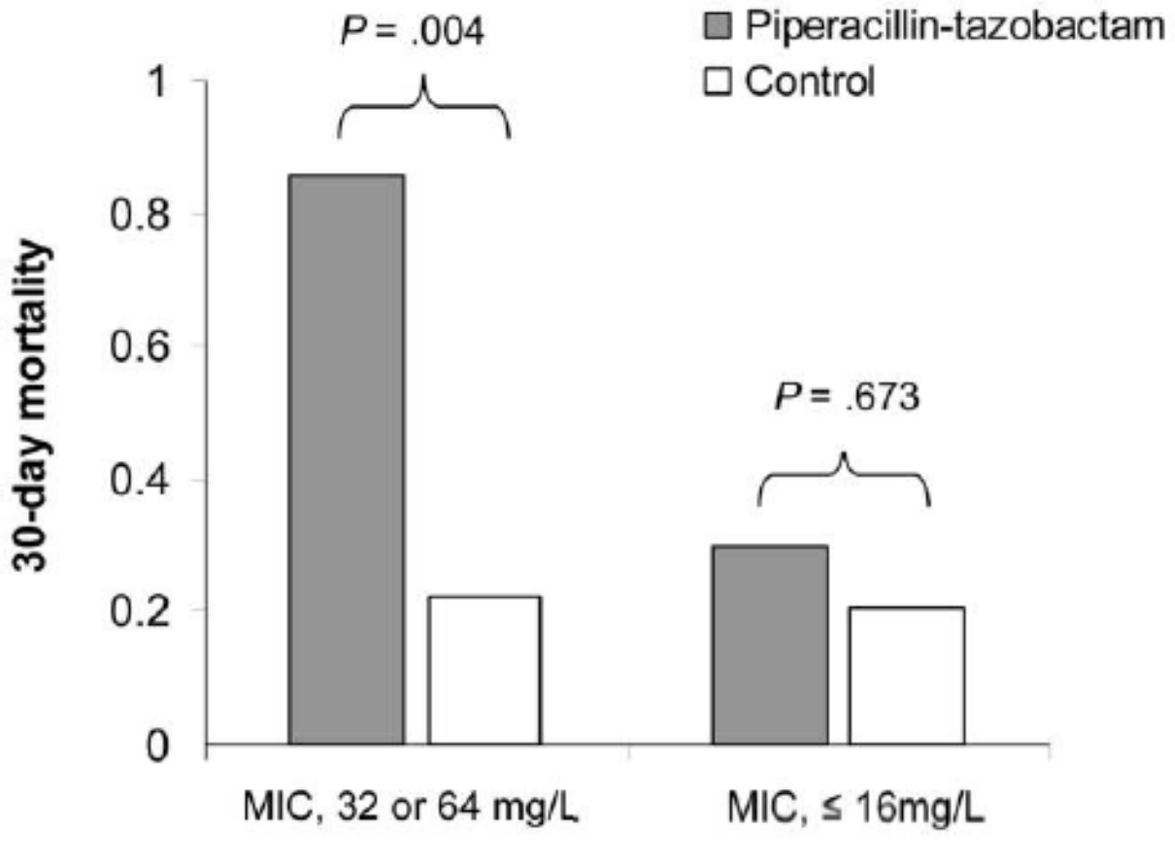
%*f*T>MIC breakpoint = 44.9 %

P< 0.0001

%*f*T>MIC	Success	Failure
≥44.9	83 (90.2%)	9 (9.8%)
<44.9	31 (50%)	31 (50%)

Muller et al, JAC 2013 68:900-906

Outcomes of Bacteremia due to *P.aeruginosa* with reduced Susceptibility to Piperacillin-Tazobactam:



Tam et al 2008 CID 46::862

PK/PD kenmerken van antibiotica

3 groepen te onderscheiden

- tijdsafhankelijk (t > MIC)
- AUC / MIC afhankelijk
- AUC / MIC *en* C_{max} / MIC afhankelijk

Antibiotica van groep 1

- Antibiotica met tijdsafhankelijke effecten en geen of weinig aanhoudende effecten (PAE)
- Duur van de blootstelling maximaliseren

AB	Tijd > MIC
Penicillinen	> 90 %
Cefalosporinen	> 40 %
Carbapenems	> 50 %
Aztreonam	> 30%
Clindamycine	> 40 %

Craig, WA. Infect.Dis.Clin.North Am. 2003;17:479

Antibiotica van groep 2

Antibiotica vooral beïnvloed door blootstelling

- De hoeveelheid antibioticum optimaliseren

AB	AUC / MIC
azitromycine	>25
vancomycine	345
teicoplanin	345
linezolid	82.9
fluconazol	25

Craig, WA. Infect.Dis.Clin.North Am. 2003;17:479

Antibiotica van groep 3

Bactericide antibiotica met concentratie-afhankelijk effect en aanhoudende effecten (PAE)

- Piek en hoeveelheid antibioticum optimaliseren

AB	Cmax/MIC	AUC/MIC
aminoglycosiden	10	200
fluorochinolonen	10	125
daptomycine	59	388

Craig, WA. Infect.Dis.Clin.North Am. 2003;17:479

Therapeutic Drug Monitoring

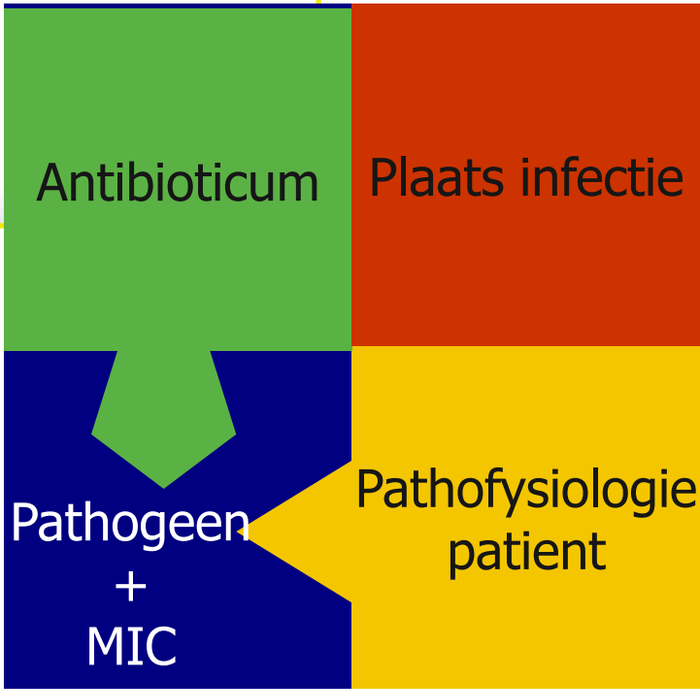
- Optimaliseren van de farmacotherapie op basis van geneesmiddel concentraties in bloed

- Wanneer zinvol:

  - Sensitieve, specifieke, snelle bepaling
  - Klinische effectiviteit is vertraagd of moeilijk direct te meten
  - Significante inter-patient variatie in farmacokinetiek
  - Correlatie tussen geneesmiddelconcentratie en klinisch effect/toxiciteit (PK/PD relatie)

Wat bepaalt de keuze en dosis van het AB?

- Identiteit ziekteverwekker
- Gevoeligheid micro-organismen, MIC
- Status van de patiënt, incl PK
- Penetratie in weefsel
- Resistentie ontwikkeling



Conclusie

- Respons op antibiotica is variabel
  - Patiënt karakteristieken
  - Karakteristieken bacteriën
  - Kinetiek/dynamiek
  - Het gaat om de plaats van werking!

- TDM kan helpen dosering te optimaliseren (MIC based therapy)