Doseren van Antibiotica
PK/PD

Dr. Michiel van Agtmael,
internist-infectioloog & klinisch farmacoloog

- Farmacokinetiek:

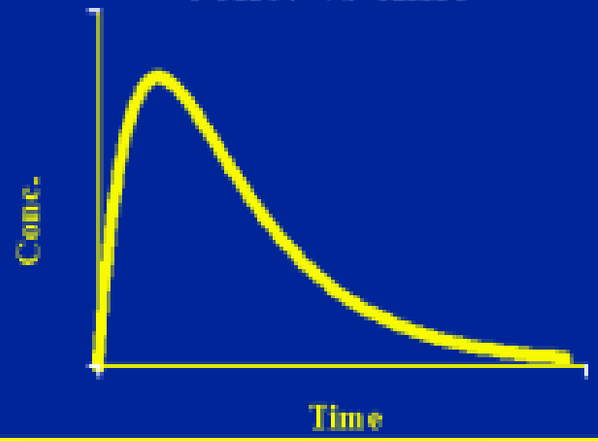
  What the body does to the drug

- Farmacodynamiek:

  What the drug does to the body

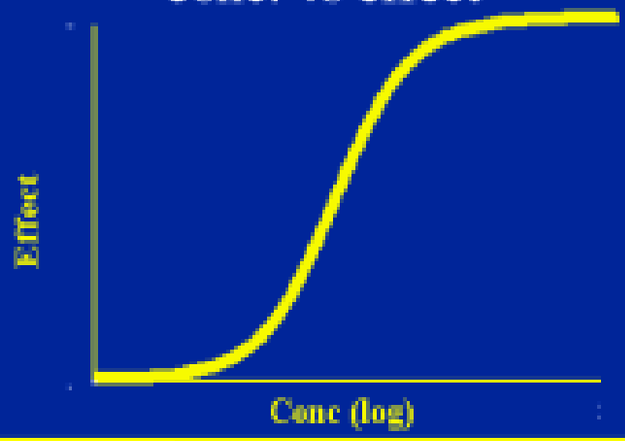
Pharmacokinetics

conc. vs time



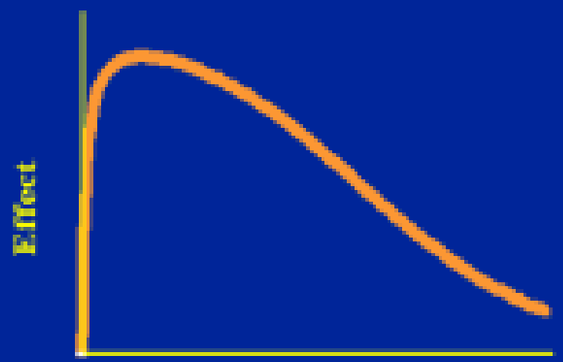
Pharmacodynamics

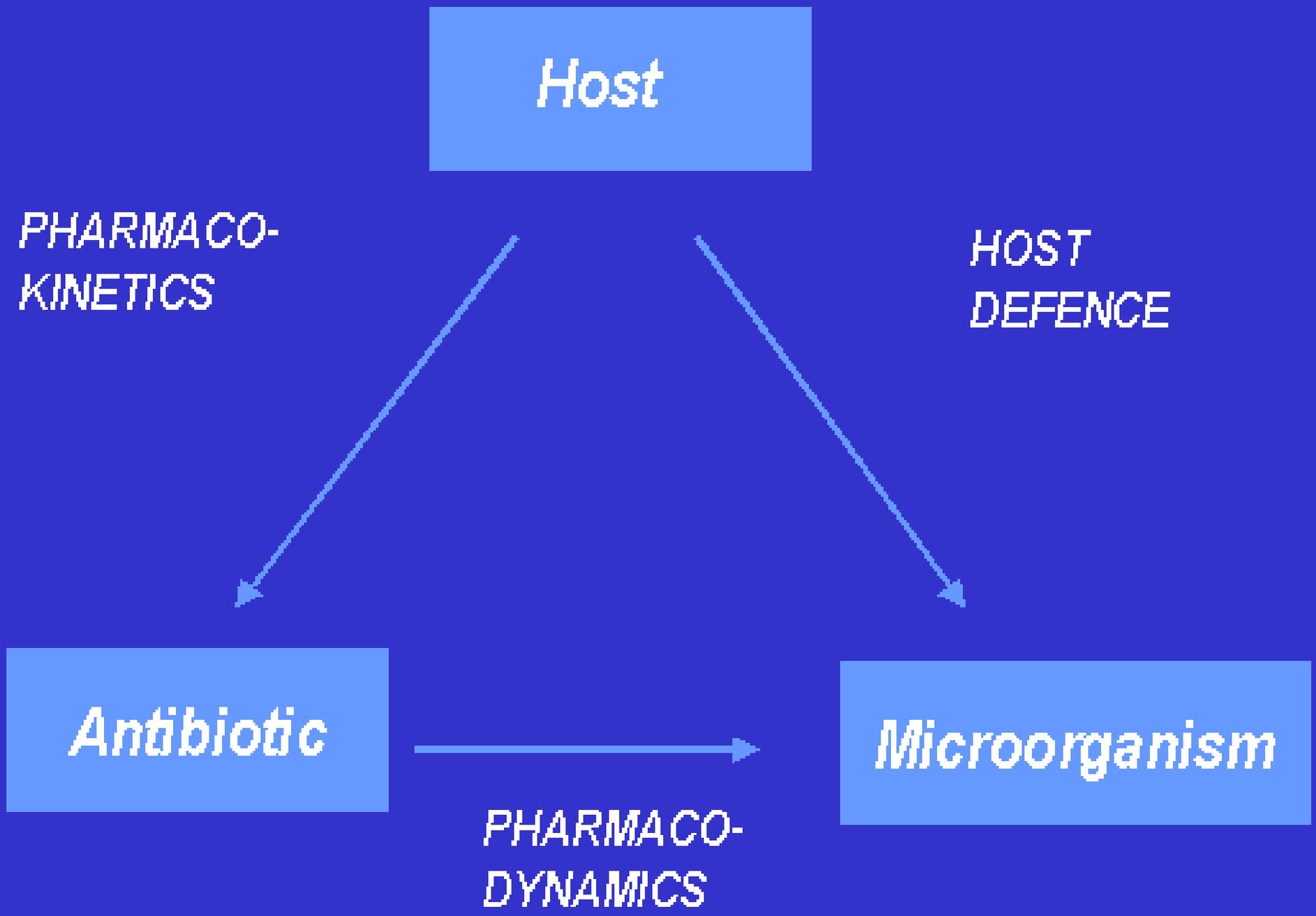
conc. vs effect

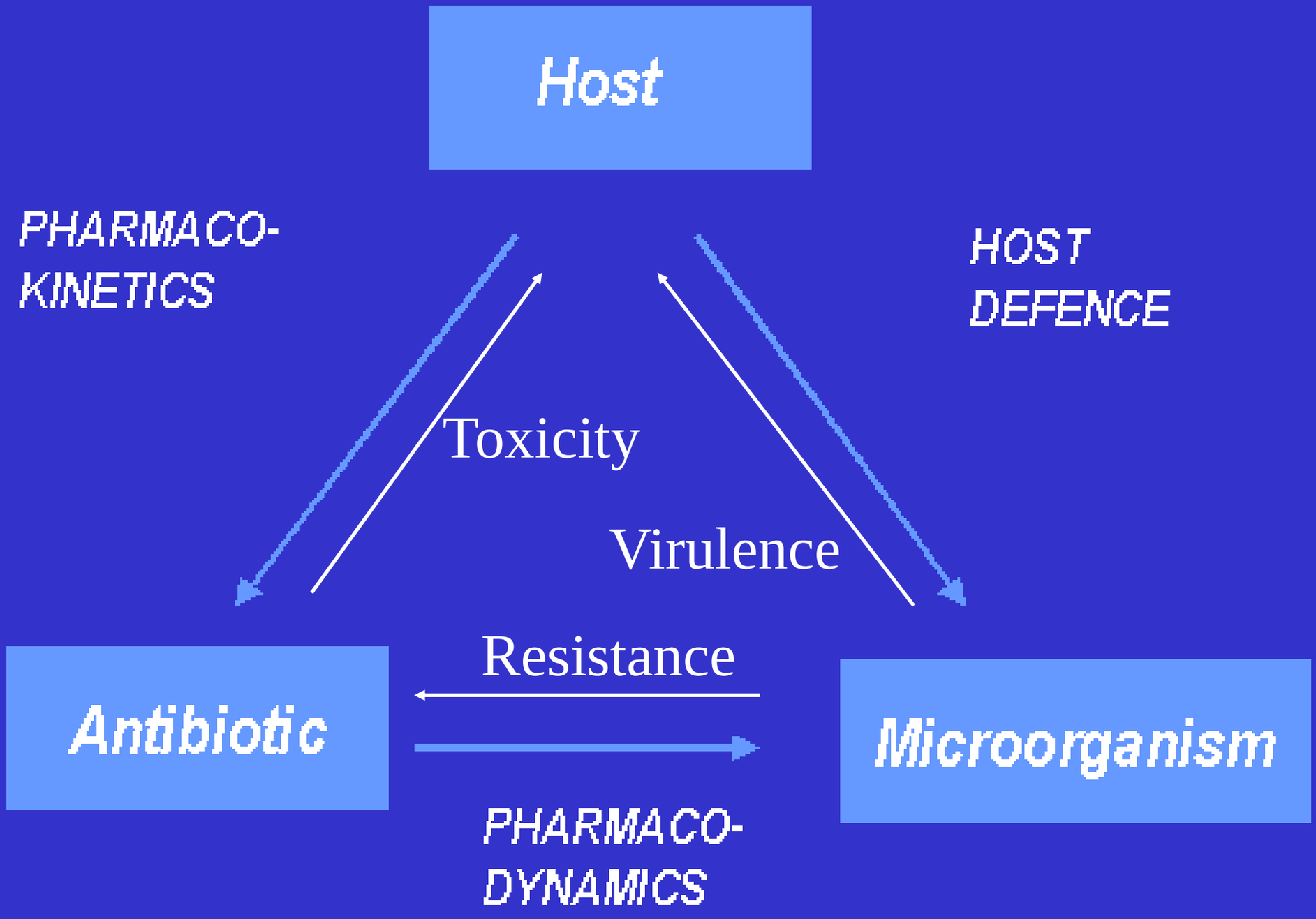


PK/PD

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

(Niet iv maar oraal…. switch ikv stewardship)

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?

Bij een vroege sepsis is je [antibioticum]

- A. hoog
- B normaal
- C laag

Bij een vroege fase (d1-d3) sepsis is je [antibioticum]

- A. hoog
- B. normaal
- **C. laag**

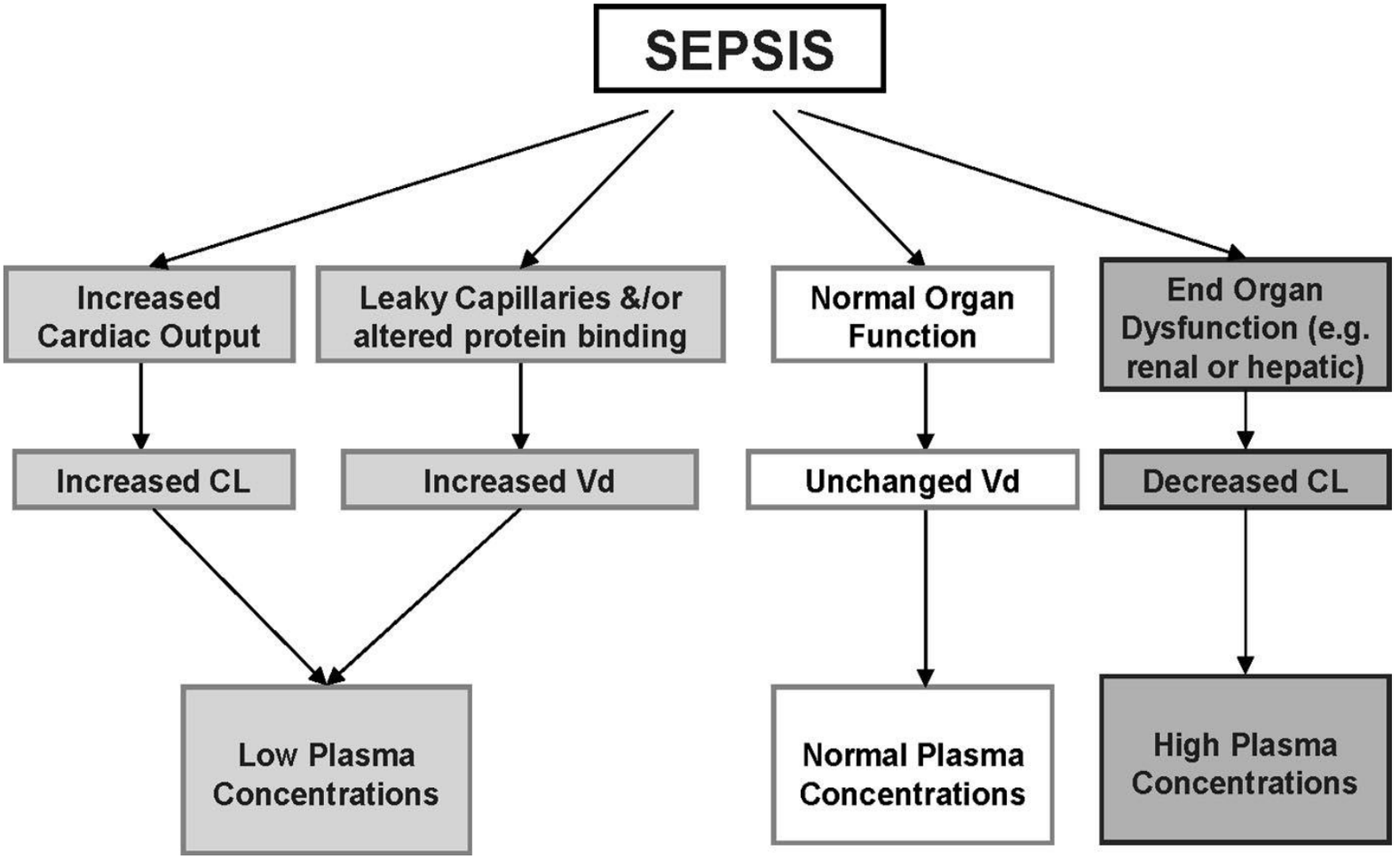
Bij een late fase (>d4) sepsis is je [antibioticum]

- A. hoog
- B normaal
- C laag

Bij een late fase (>d4) sepsis is je [antibioticum]

- **A. hoog**
- B. normaal
- C. laag

Severe sepsis/shock: gewijzigde PK/PD



Vroege fase sepsis (d1-d3)
STARTDOSIS

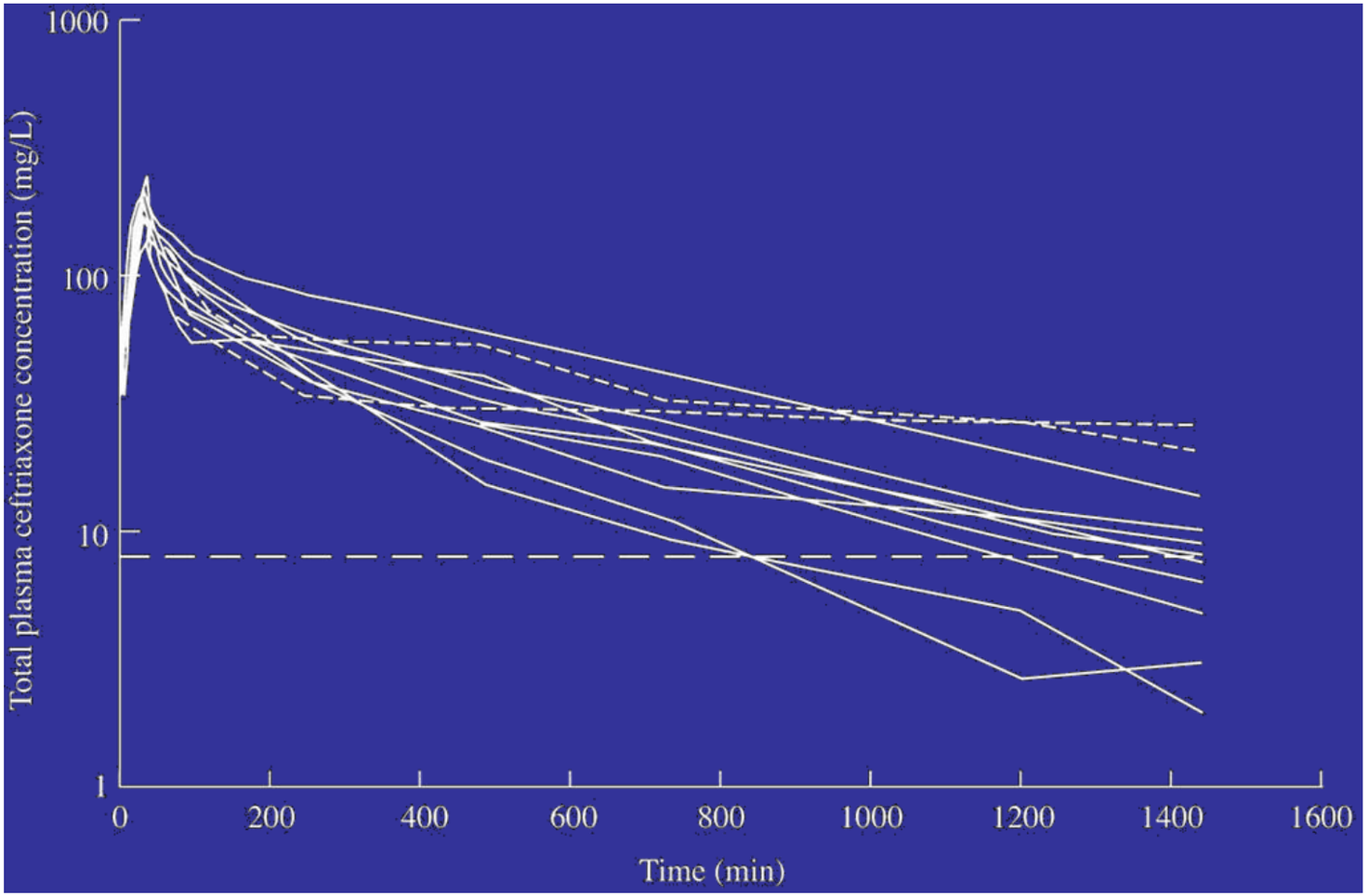
Latere fase sepsis (>=d4), MOF
ONDERHOUDSDOSIS

Crit Care Med 2009 Vol. 37, No. 3

D= Vd x Cp

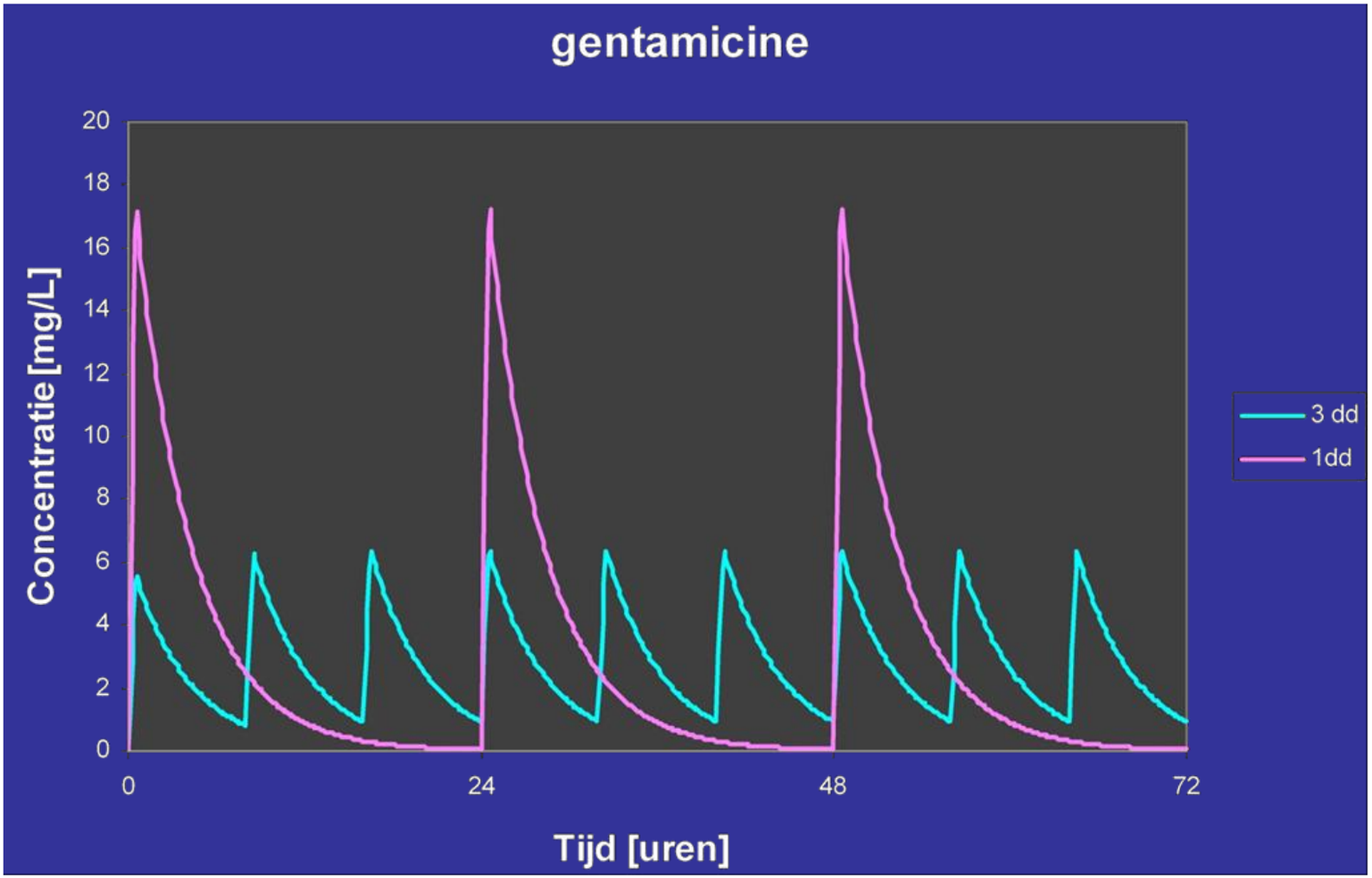
- C= D/Vd in mg/l
- Vd is virtueel en variabel
  - Neemt af bij dehydratie
  - Neemt toe voor hydrofiele AB (cefalo's) bij third spacing/sepsis
  - Neemt toe bij adipositas bij lipofiele AB (macroliden)

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.

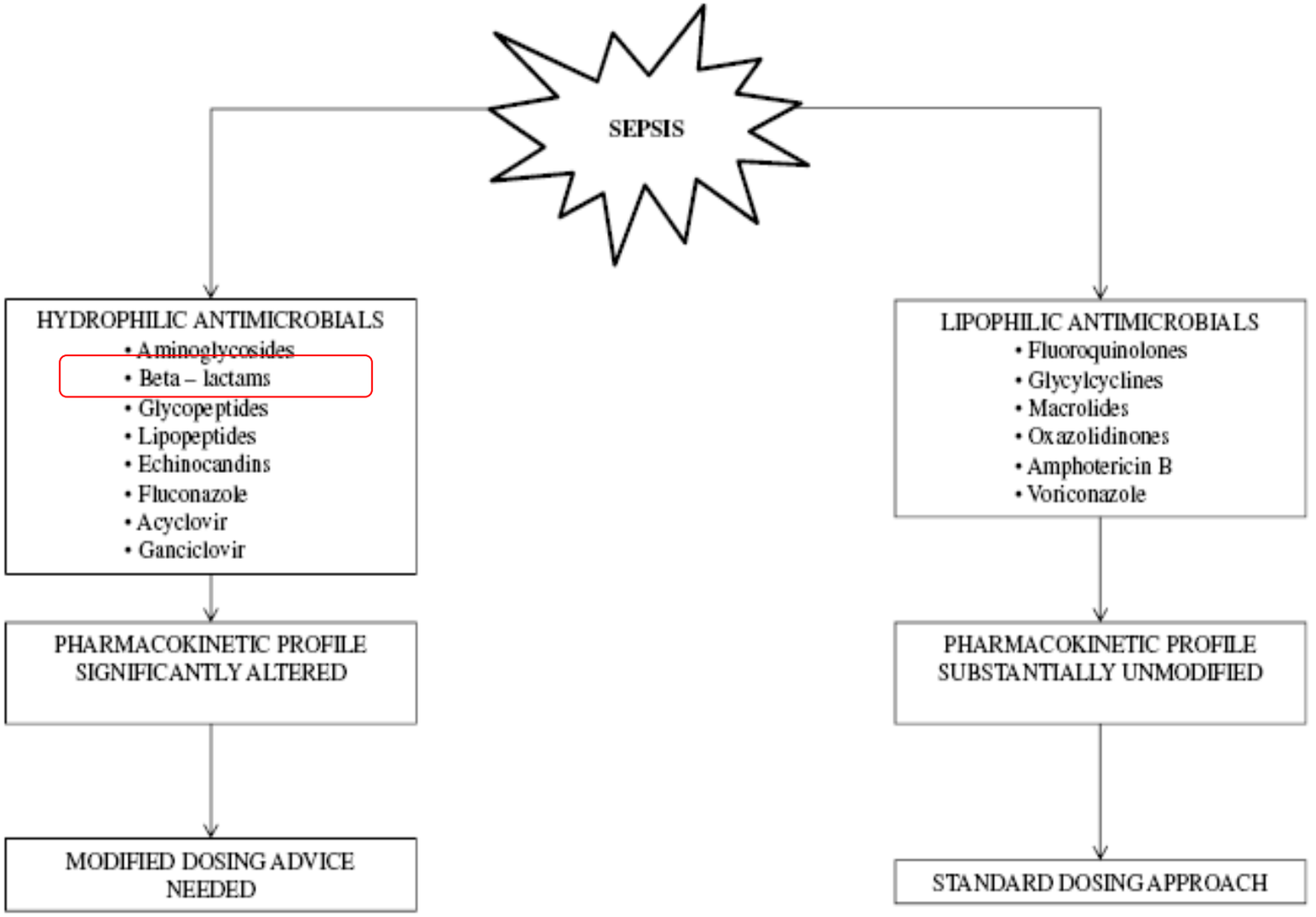
Moore RD. J Infect Dis 1987;155:93-9.

Het PK profiel bij sepsis verandert vooral bij:

- A. Hydrofiele antibiotica
- B. Lipofiele antibiotica

Het PK profiel bij sepsis verandert vooral bij:

- **A. Hydrofiele antibiotica**
- B. Lipofiele antibiotica



Pea F. Curr Clin Pharmacol 2013; 8: 5-12

Geen genta maar cipro….

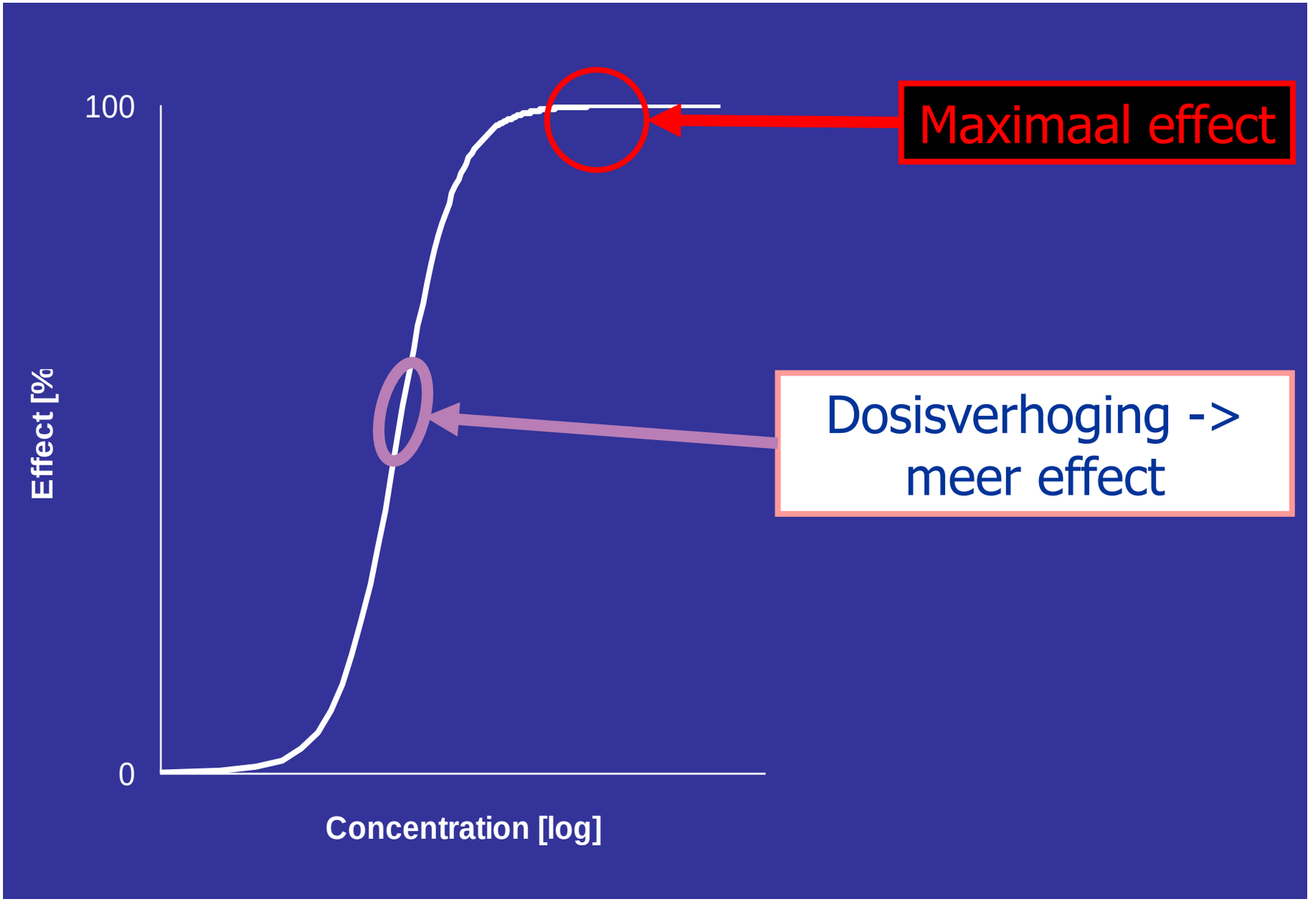
- J Crit Care. 2008
- **Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study.** Girbes AR.

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)

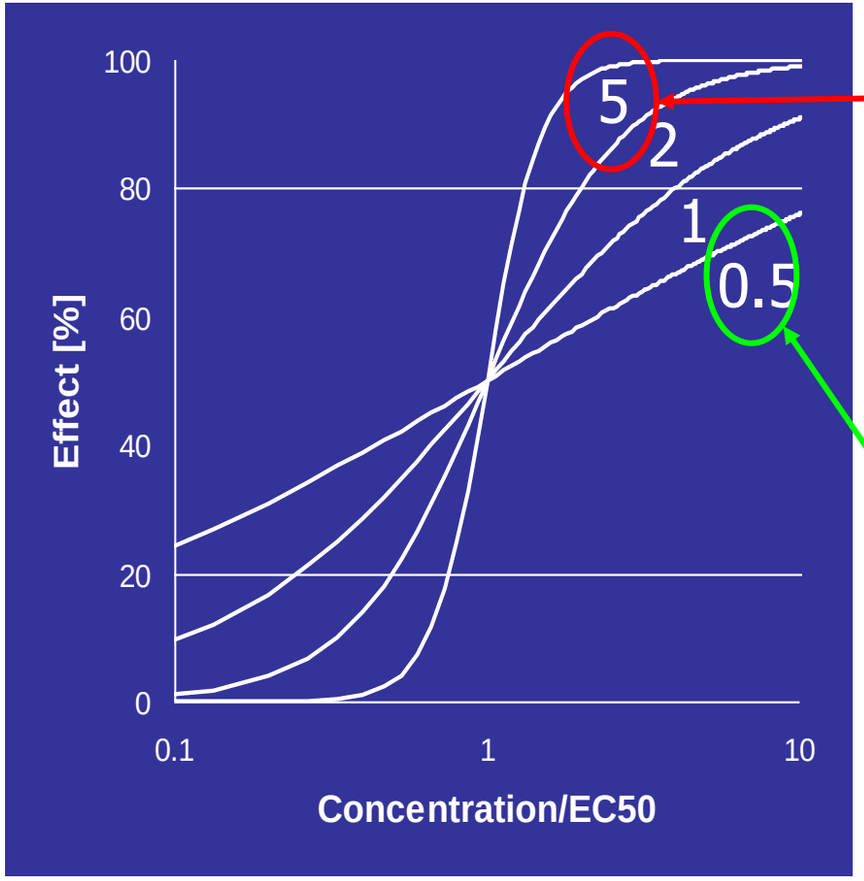
CONCLUSIONS:

- 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



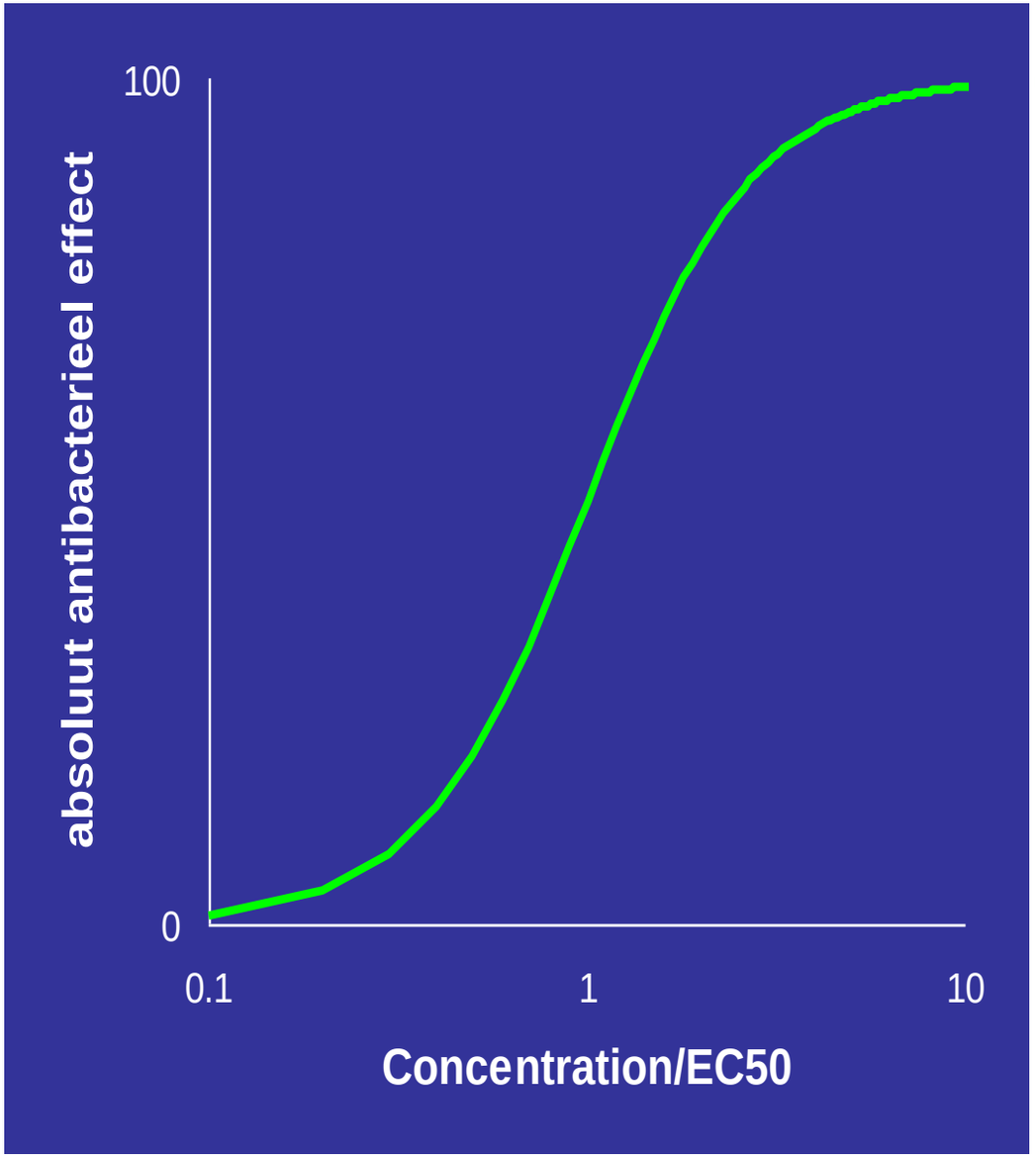
ß-lactams, vancomycine

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

Aminoglycosiden, fluoroquinolonen

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

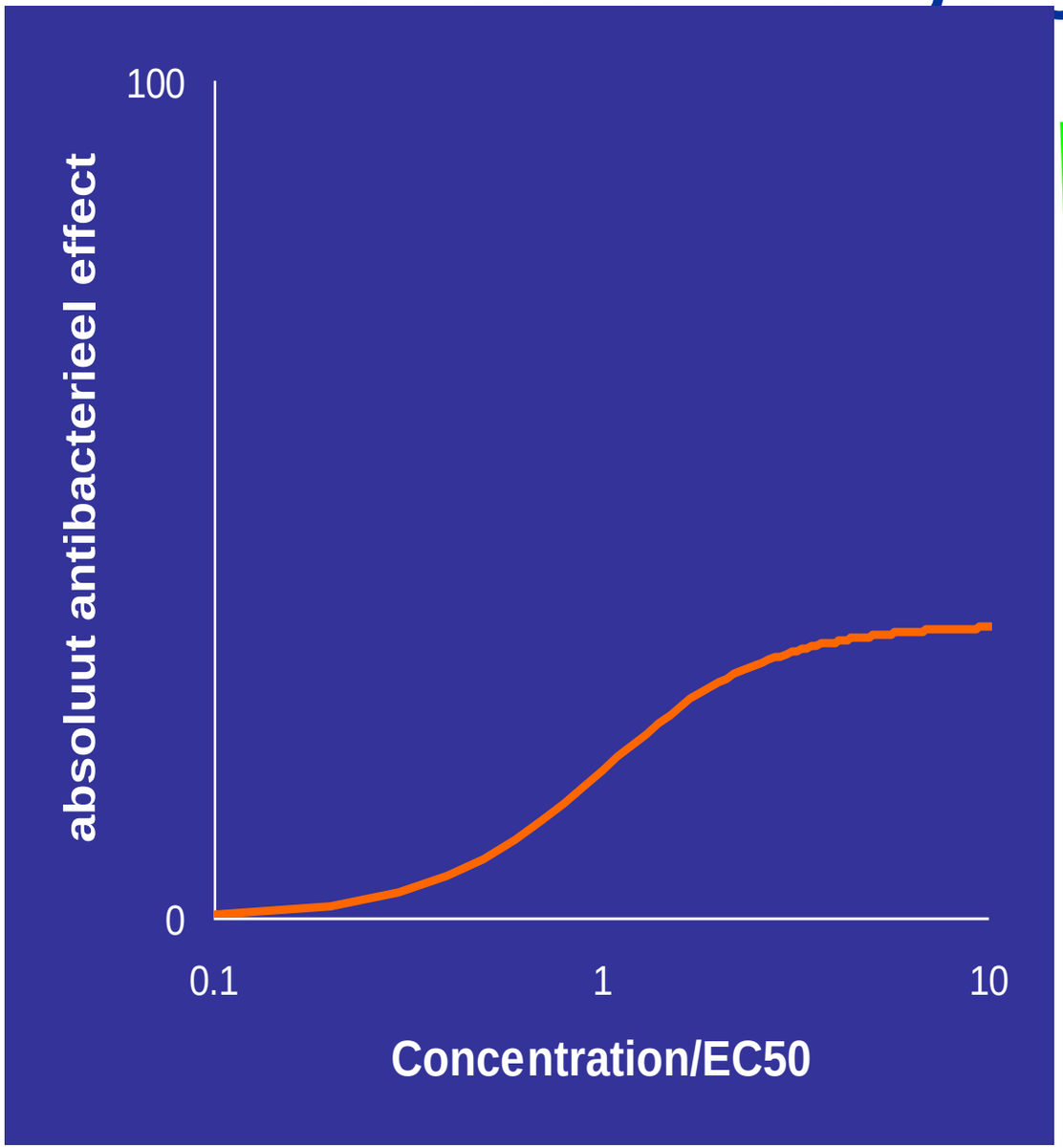
Sommige antibiotica zijn krachtiger dan anderen: vergelijk de E_{max}



hoge E_{max}

hoog bactericide effect
- fluorochinolonen
- aminoglycosiden

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

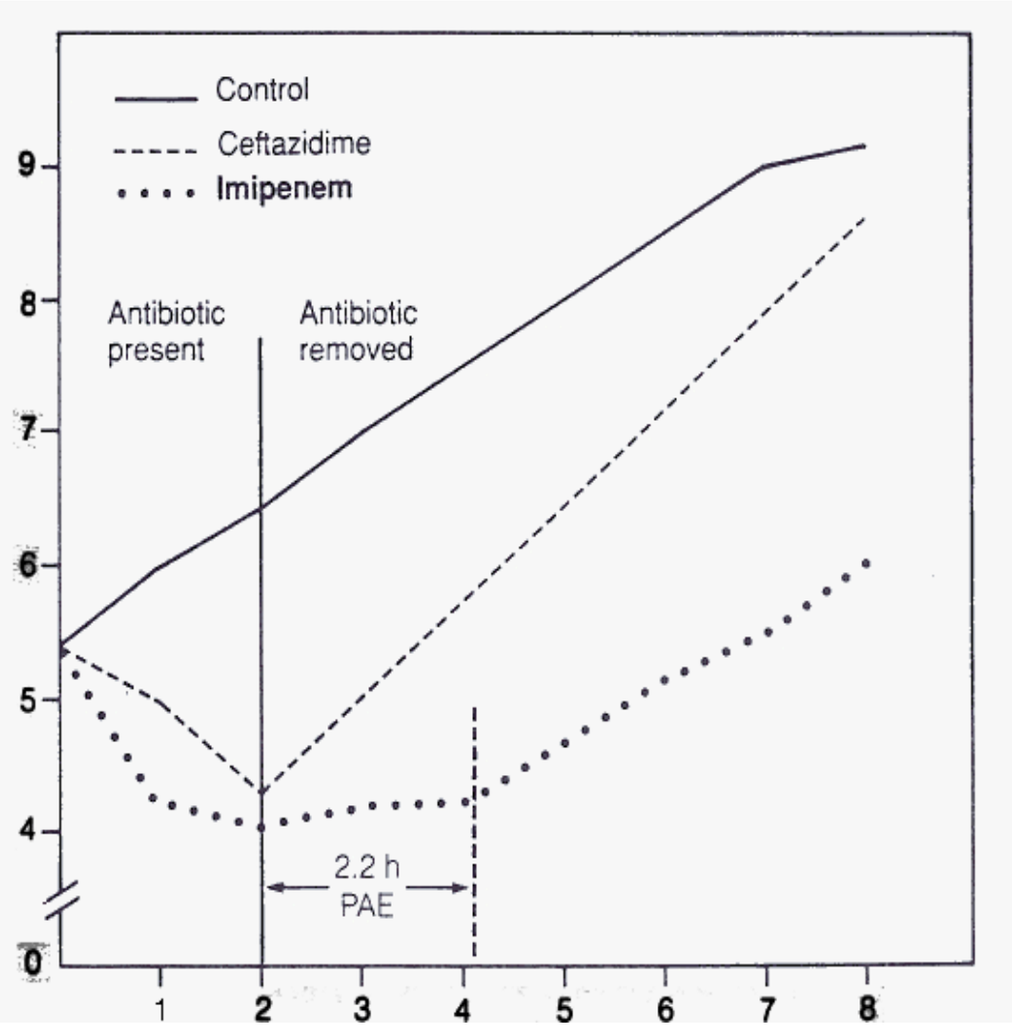


lage E_{max}

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

De effectiviteit van een B lactam wordt bepaald door:

- A. Cmax
- B. T>MIC
- C. AUC

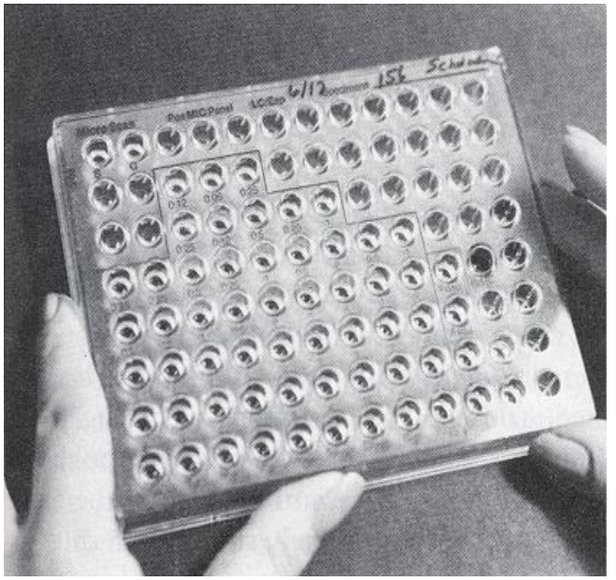
De effectiviteit van een B lactam wordt bepaald door:

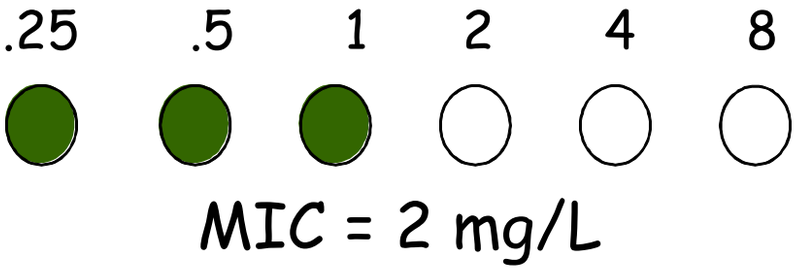
- A. Cmax
- **B. T>MIC**
- C. AUC

MIC
Measure of Potency

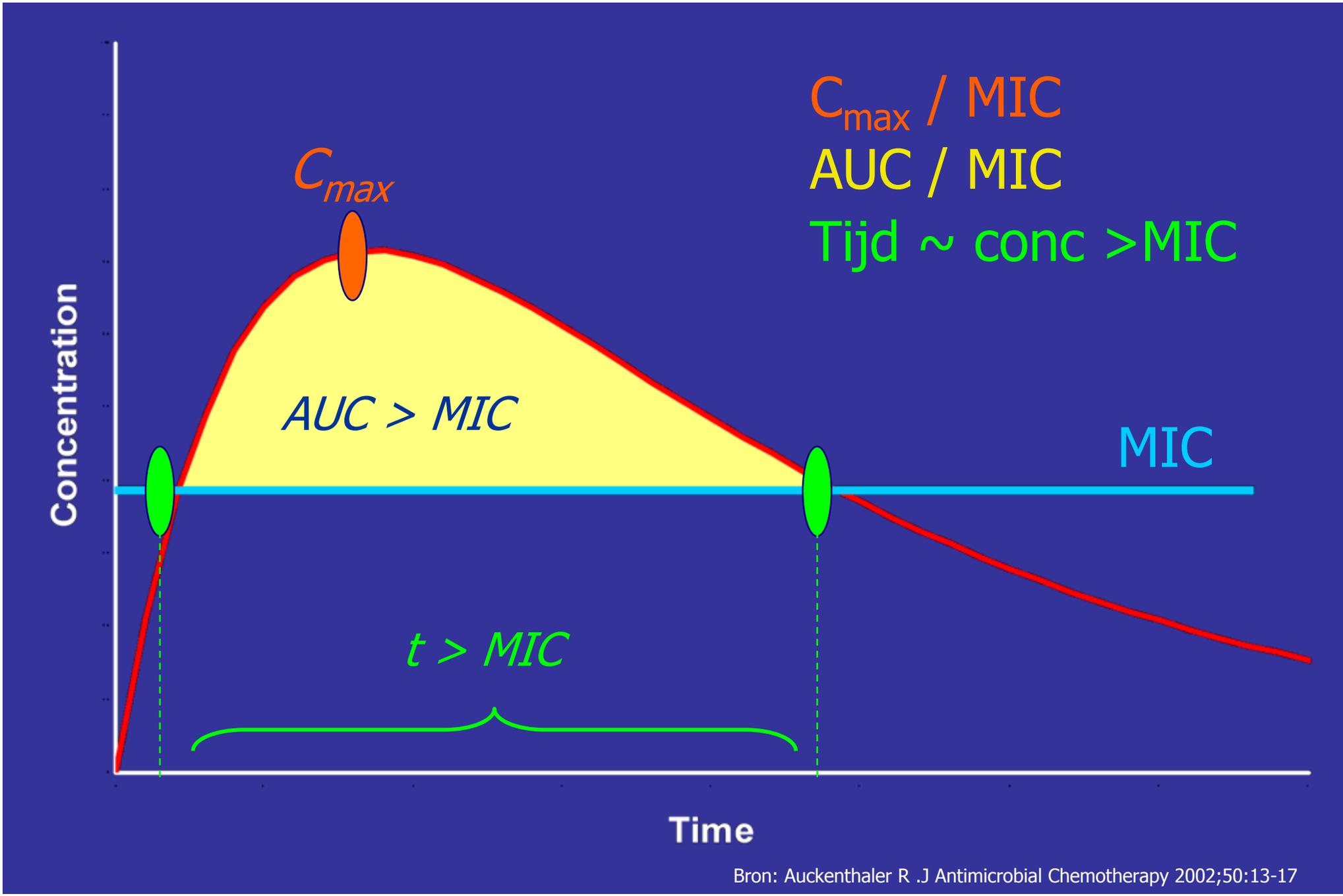
MIC

Lowest concentration with no visible growth after 18 hour incubation

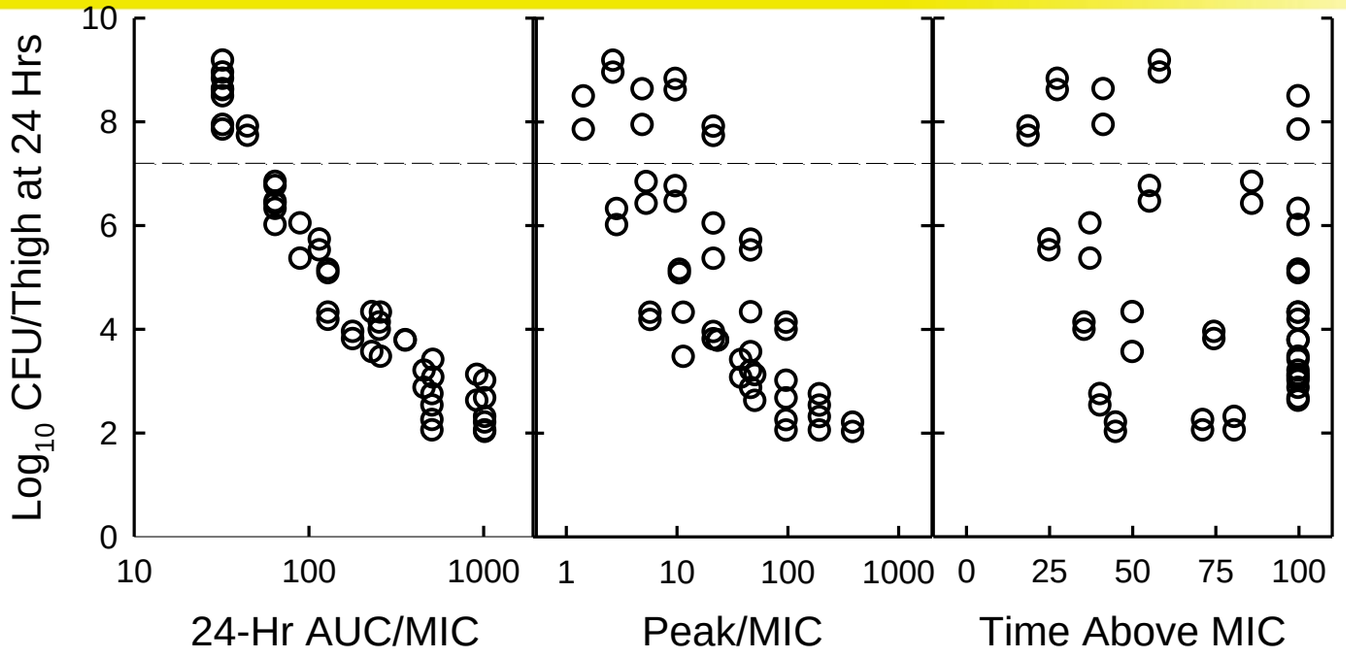




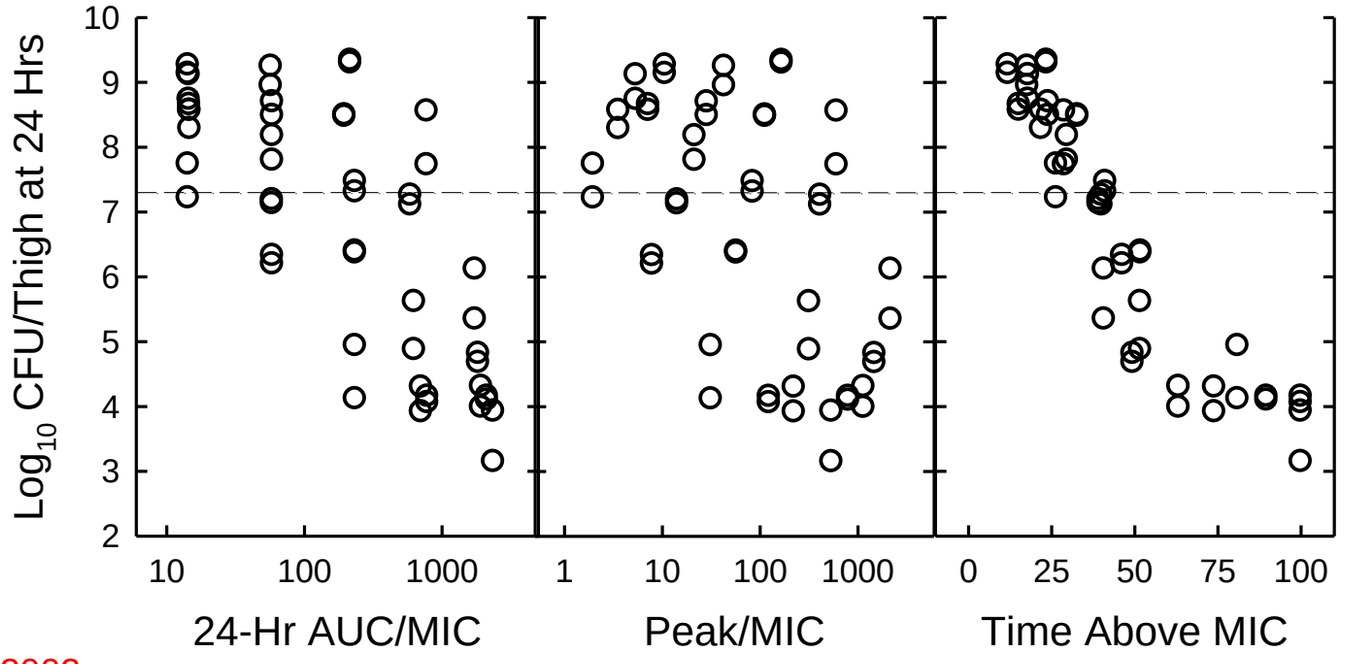
PK/PD relaties



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



levofloxacin



ceftazidim

Andes IJAA 2002

Kennis antimicrobiële PKPD targets anno 2014

VUmc

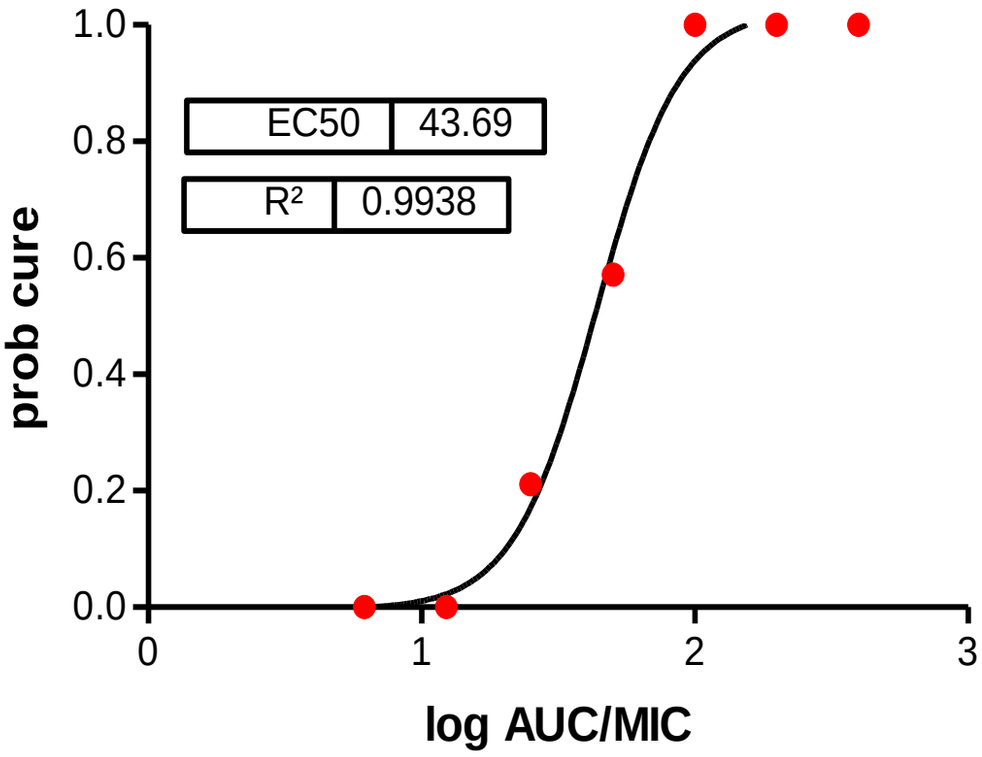
	Preclinical studies		Clinical studies	
Concentration-dependent				
Aminoglycosides	Maximum killing[43]	AUC_{0-24}/MIC 80–100	Clinical cure[82–86]	C_{max}/MIC 8–10; AUC/MIC >70
	Resistance suppression[87]	C_{max}/MIC 10–30	Microbiological cure	..
Time-dependent				
Carbapenems	Maximum killing[88]	40% $T_{>MIC}$	Clinical cure[89]	75% $T_{>MIC}$; C_{min}/MIC 5
	Resistance suppression[90, 91]	16 × MIC; C_{min}/MIC >6·2	Microbiological cure[17]	54% $T_{>MIC}$
Cephalosporins	Maximum killing[11]	60–70% $T_{>MIC}$	Clinical cure[92]	100% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[16,93]	60–100% $T_{>MIC}$; 95% $T_{>4·3×MIC}$
Penicillins	Maximum killing[11]	40–50% $T_{>MIC}$	Clinical cure	..
	Resistance suppression[94]	40–50% $T_{>MIC}$	Microbiological cure[95]	40–50% $T_{>MIC}$
Concentration-dependent and time-dependent				
Fluoroquinolones	Maximum killing[11,96]	AUC_{0-24}/MIC >30–100	Clinical cure[15,86,96,97,98]	AUC_{0-24}/MIC ≥125–250; C_{max}/MIC ≥8
	Resistance suppression[99,100,101]	AUC_{0-24}/MIC >160; AUC_{0-24}/MPC ≥22	Microbiological cure[14,86,102]	AUC_{0-24}/MIC ≥34–125; C_{max}/MIC ≥8
Vancomycin	Maximum killing[103]	AUC_{0-24}/MIC 86–460	Clinical cure[20,21]	AUC_{0-24}/MIC ≥400–450
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure[20]	AUC_{0-24}/MIC ≥400
Linezolid	Maximum killing	..	Clinical cure[22]	AUC_{0-24}/MIC ≥85; 85% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[22]	AUC_{0-24}/MIC 80–120; 85% $T_{>MIC}$
Tigecycline	Maximum killing[105]	50% $T_{>MIC}$	Clinical cure[106,107,108]	AUC_{0-24}/MIC >12·8–17·9; *f* AUC_{0-24}/MIC ≥0·9
	Resistance suppression	..	Microbiological cure[109,110]	AUC_{0-24}/MIC 6·9–17·9
Daptomycin	Maximum killing[111,112]	AUC_{0-24}/MIC 38–442	Clinical cure	..
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure	..
Colistin	Maximum killing[113,114]	AUC_{0-24}/MIC 7–23	Clinical cure	..
	Resistance suppression	..	Microbiological cure	..

AUC_{0-24}/MIC=ratio of area under the concentration time curve from 0 to 24 h to minimum inhibitory concentration. C_{max}/MIC=ratio of maximum concentration of antibiotic in a dosing interval to minimum inhibitory concentration. $T_{>MIC}$=percentage of dosing interval that the antibiotic concentration is maintained above the minimum inhibitory concentration. AUC_{0-24}/MPC=ratio of the AUC_{0-24} to the concentration that prevents mutation. C_{min}=minimum concentration of antibiotic in a dosing interval, *f*=free concentration or fraction of drug not bound to plasma proteins. *Where the index is reported as a range, data included might have been derived from different infection models with different bacteria. Specific data for the contributing values can be found in the associated references. Data for the various indices has been reported in different studies according to total and free (unbound) concentrations of drug.

***Table 1*: Studies reporting pharmacokinetic/pharmacodynamic indices from preclinical and clinical assessments, by antibiotic class**

Roberts JA, Lancet Infect Dis 2014; 14: 498-509

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

PK/PD kenmerken van antibiotica

3 groepen te onderscheiden

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

t>MIC

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

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

AUC/MIC

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

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

Cmax>MIC

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

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

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Clin Infect Dis. 2013 Jan;56(2):236-44. doi: 10.1093/cid/cis856. Epub 2012 Oct 16.

Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial.

Dulhunty JM[1], Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Lipman J.

Author information

Abstract

BACKGROUND: Beta-lactam antibiotics are a commonly used treatment for severe sepsis, with intermittent bolus dosing standard therapy, despite a strong theoretical rationale for continuous administration. The aim of this trial was to determine the clinical and pharmacokinetic differences between continuous and intermittent dosing in patients with severe sepsis.

METHODS: This was a prospective, double-blind, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate conducted in 5 intensive care units across Australia and Hong Kong. The primary pharmacokinetic outcome on treatment analysis was plasma antibiotic concentration above the minimum inhibitory concentration (MIC) on days 3 and 4. The assessed clinical outcomes were clinical response 7-14 days after study drug cessation, ICU-free days at day 28 and hospital survival.

RESULTS: Sixty patients were enrolled with 30 patients each allocated to the intervention and control groups. Plasma antibiotic concentrations exceeded the MIC in 82% of patients (18 of 22) in the continuous arm versus 29% (6 of 21) in the intermittent arm (P = .001). Clinical cure was higher in the continuous group (70% vs 43%; P = .037), but ICU-free days (19.5 vs 17 days; P = .14) did not significantly differ between groups. Survival to hospital discharge was 90% in the continuous group versus 80% in the intermittent group (P = .47).

CONCLUSIONS: Continuous administration of beta-lactam antibiotics achieved higher plasma antibiotic concentrations than intermittent administration with improvement in clinical cure. This study provides a strong rationale for further multicenter trials with sufficient power to identify differences in patient-centered endpoints.

Comment in

Are prolonged/continuous infusions of β-lactams for all? [Clin Infect Dis. 2013]
Saving lives with optimal antimicrobial chemotherapy. [Clin Infect Dis. 2013]
Reply to Soman et al. [Clin Infect Dis. 2013]

PMID: 23074313 [PubMed - indexed for MEDLINE] Free full text

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-negative infections in : [A
Review Continuous infus
antibiotics in seve [Int J A
Review Continuous infus
implications for beta-la [M
Cited by 6 PubMed C
Assessment of pharmaco
meropenem durir [BMC P
Review An alternate path
of sepsis and septic shoc
Impact of Bolus dosing ve
infusion of [Antimicrob A

Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropenia: a retrospective observational study

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Objectives: Information on the efficacy of extended meropenem administration in neutropenic patients is scarce. Our objective was to determine whether the administration of meropenem in a 4 h extended infusion (EI) leads to a better clinical outcome in patients with febrile neutropenia than the conventional short infusion (SI).

Methods: This was a retrospective observational study. The subjects were neutropenic patients who presented with fever after receiving haematopoietic stem-cell transplantation or induction chemotherapy for acute myeloid leukaemia. The primary endpoint was the success of treatment after 5 days of meropenem therapy, defined as follows: the disappearance of fever leading to a maintained ($\geq$24 h) feverless state; the resolution or improvement of the clinical signs and symptoms of infection; the absence of persistent or breakthrough bacteraemia; and no additional antibiotics prescribed because of an unsatisfactory clinical evolution.

Results: Eighty-eight patients received meropenem (1 g/8 h) in SI and 76 received the same dose in EI. Treatment success on day 5 was superior in the EI group [52/76 (68.4%) versus 36/88 (40.9%); $P<0.001$]. Meropenem administered in EI was independently associated with success (OR 3.13, 95% CI 1.61–6.10). Fewer additional antibiotics were prescribed in the EI group during the first 5 days of treatment [20/76 (26.3%) versus 44/88 (50.0%); $P=0.002$]. Using Kaplan–Meier survival analysis a more prompt defervescence and a faster decrease in C-reactive protein concentration were observed in the EI group ($P=0.021$ and $P=0.037$, respectively). There were no significant differences in the length of hospital stay and in the mortality rate.

Conclusions: Meropenem administration in EI results in a better clinical outcome for febrile neutropenia episodes, with fewer additional antibiotics needed.

Keywords: prolonged antibiotic infusion, β-lactams, neutropenic fever

Conclusie

- Pas op voor onderdosering in de vroege fase van sepsis
- Overweeg continu infusie van B lactams
- TDM kan helpen dosering te optimaliseren (MIC- based therapy)