Principes van farmacokinetiek en dynamiek bij antibiotica

(met een overzicht van EUCAST breekpunten)

en "*Therapeutic Drug Monitoring*" (TDM)

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Aanvullingen Farmacologie en Farmacotherapie
Truncus Communis 2020-2021

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PK / PD van antibiotica: van waar komen we?

Oorsprong:

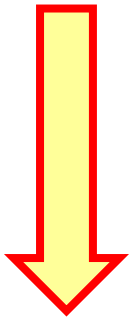
- farmacodynamisch gezien was de anti-infectieuze therapie lange tijd irrationeel en wetenschappelijk niet gefundeerd…
  - toediening van lage dosissen uit vrees voor toxiciteit
  - “fouten” in de dosering bij de registratie
  - verkeerd interpreteren van “optimale toedieningsschema’s”

- farmacokinetiek werd eerder gebruikt om de aanwezigheid van het geneesmiddel te staven dan om de doeltreffendheid te verbeteren door dosisaanpassing

Farmacodynamie van antibiotica was 30 jaar geleden algemeen “*terra incognita*”

PK/PD sedert 1989...

- Het gebruik van bestaande geneesmiddelen werd verbeterd (clinici)
  - **aminoglycosiden** één keer per dag (*once-daily*) (sedert 1995…) *
  - AUC-gebaseerd doseren van **fluorochinolonen** (**)
  - **β-lactams** in continu infuus en/of "extended infusion"
  - **vancomycine** PK/PD en in een continu infuus
  - **linezolid** TDM om neveneffecten te verminderen
  - *Personalized medicine* NEW



(in 2020...)

* eerste studies in België in 1980-1985 …
** Forrest et al., AAC (1993)

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  - Therapeutic Monitoring (*personalized medicine*) NEW (in 2020...)

- Optimalisatie van het gebruik van geneesmiddelen (overheid)
  - registratie van **nieuwe antibiotica** (EMA)
  - breekpunten (EUCAST) voor de **nieuwe antbiotica**
    maar ook voor de **<u>oude en zeer oude moleculen</u>** NEW
  - bepaling **terugbetalingsschema's** en forfait op basis van optimale dosis

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  - bepaling **terugbetalingsschema's** en forfait op basis van optimale dosis

- **Resistentie tegengaan... ← een belangrijk maar ook zeer moeilijke project**

Het programma, alstublieft...

1. Basis microbiologische parameter: MIC

2. Farmacokinetiek (PK) en Farmacodynamiek (PD)
   het concept en de methode
   het gebruik van de voornaamste antibioticaklassen

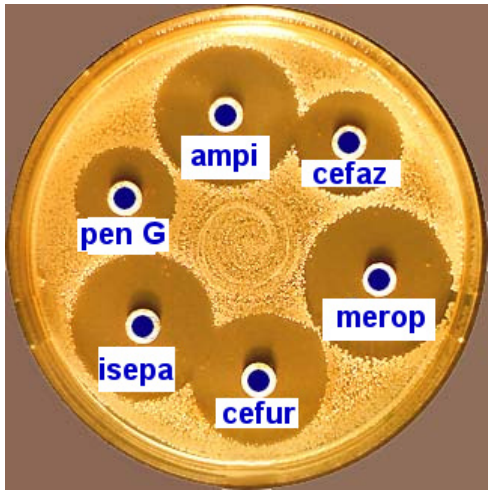
3. Toepassingen
   - EUCAST breekpunten (in het kort)
   - Therapeutic Drug Monitoring
   - continu infuus

4. Resistentie

5. Geselecteerde referenties

Wat u altijd al wilde weten maar niet durfde te vragen…

1. Microbiologie



S-I-R

MIC

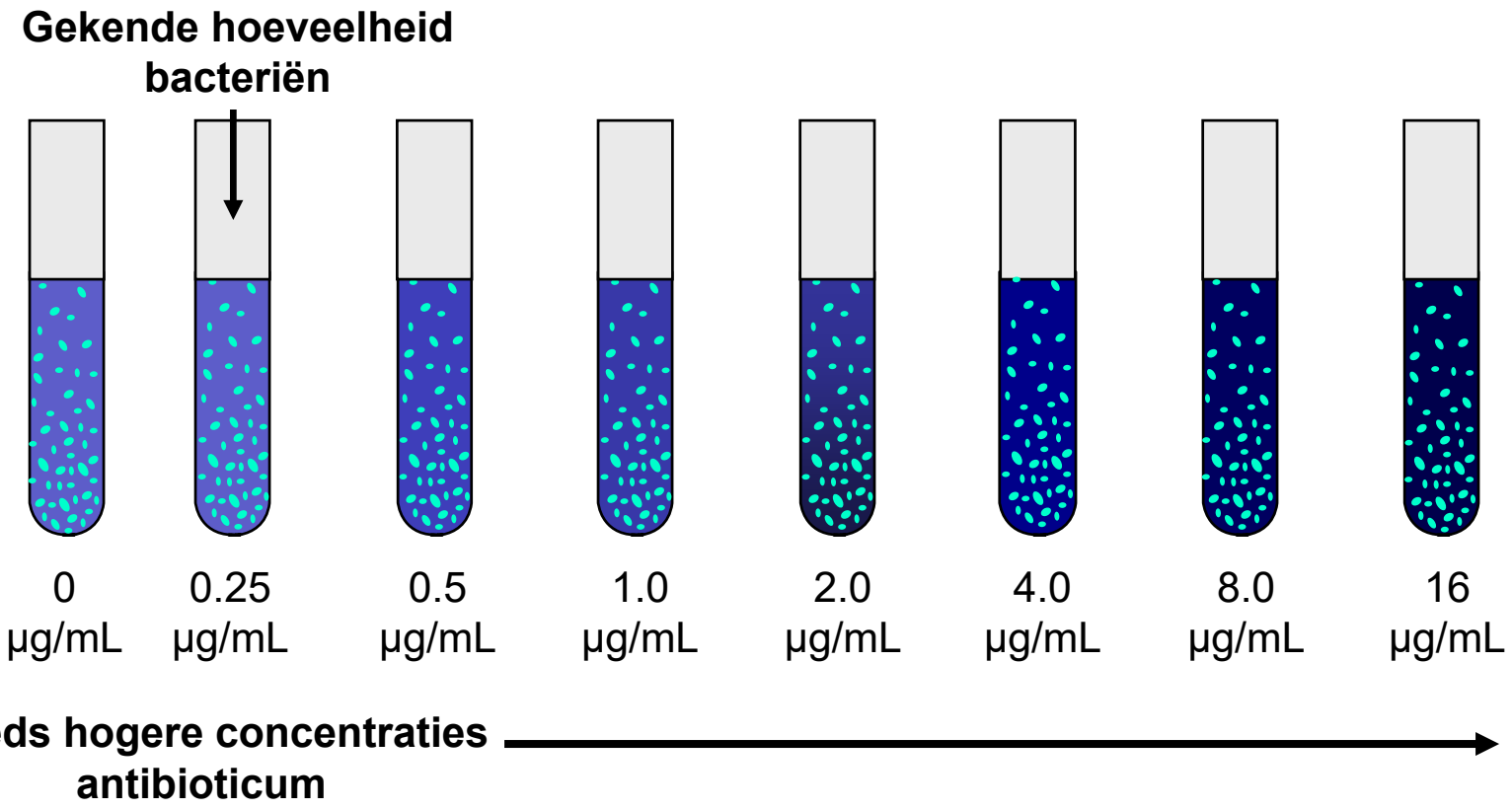
Met welke eigenschappen moet rekening gehouden worden om de therapiekeuze te optimaliseren?

In vitro bepaling van de activiteit van een antibioticum: **MIC**

Minimal inhibitory concentration

⇨ kwantitatieve bepaling

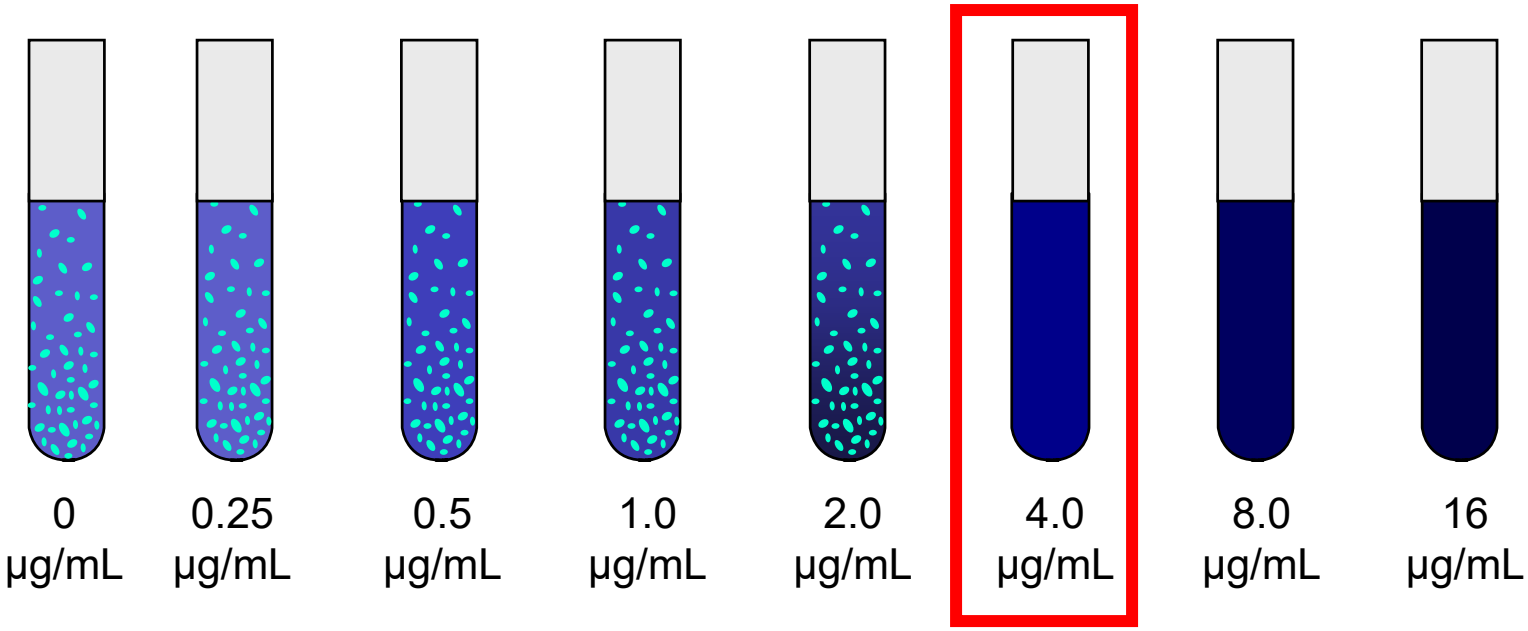
1. Inoculatie



In vitro bepaling van de activiteit van een antibioticum: **MIC**

⇨ kwantitatieve bepaling

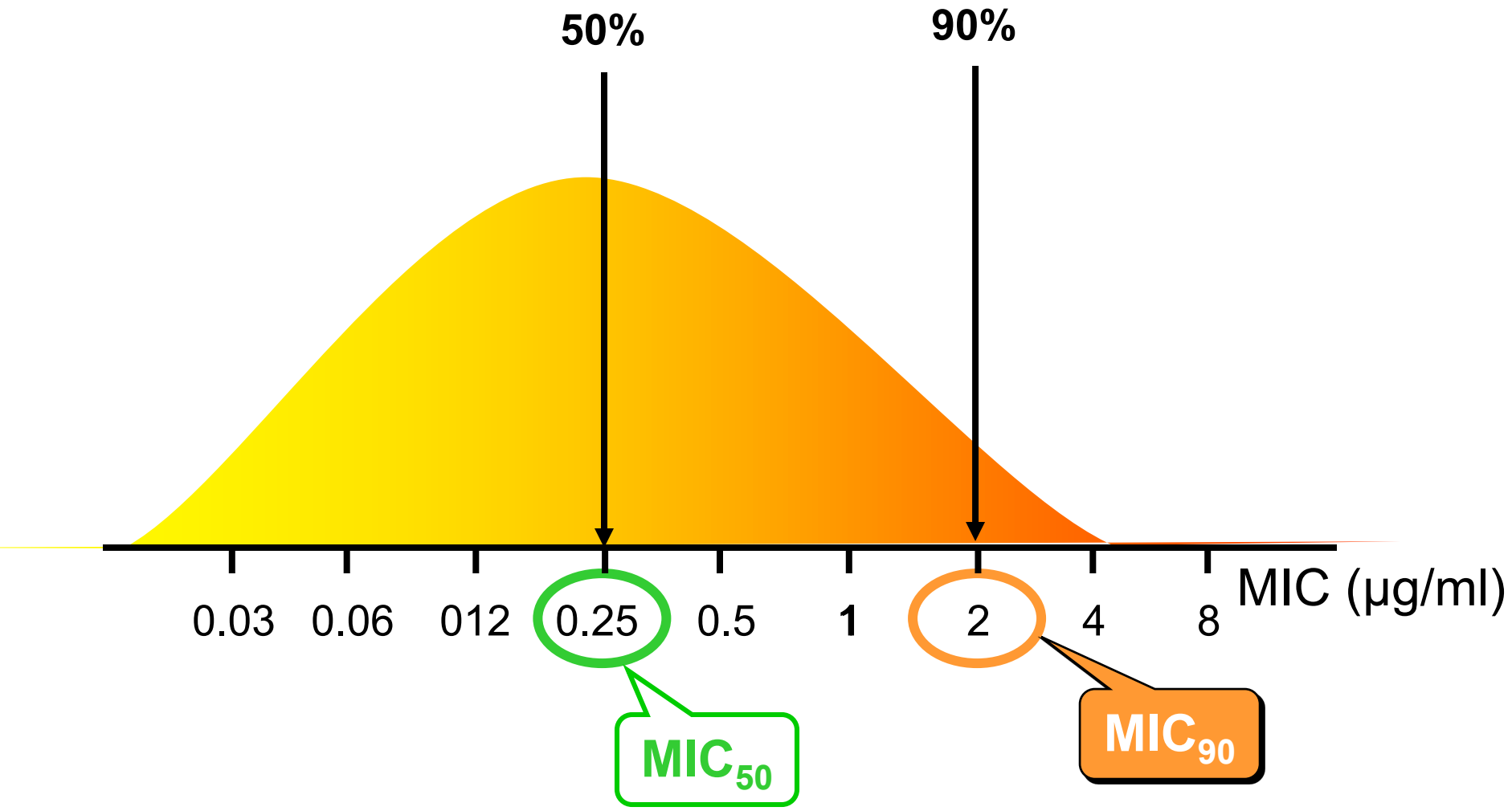
2. incubatie 37°C - 18-24 u



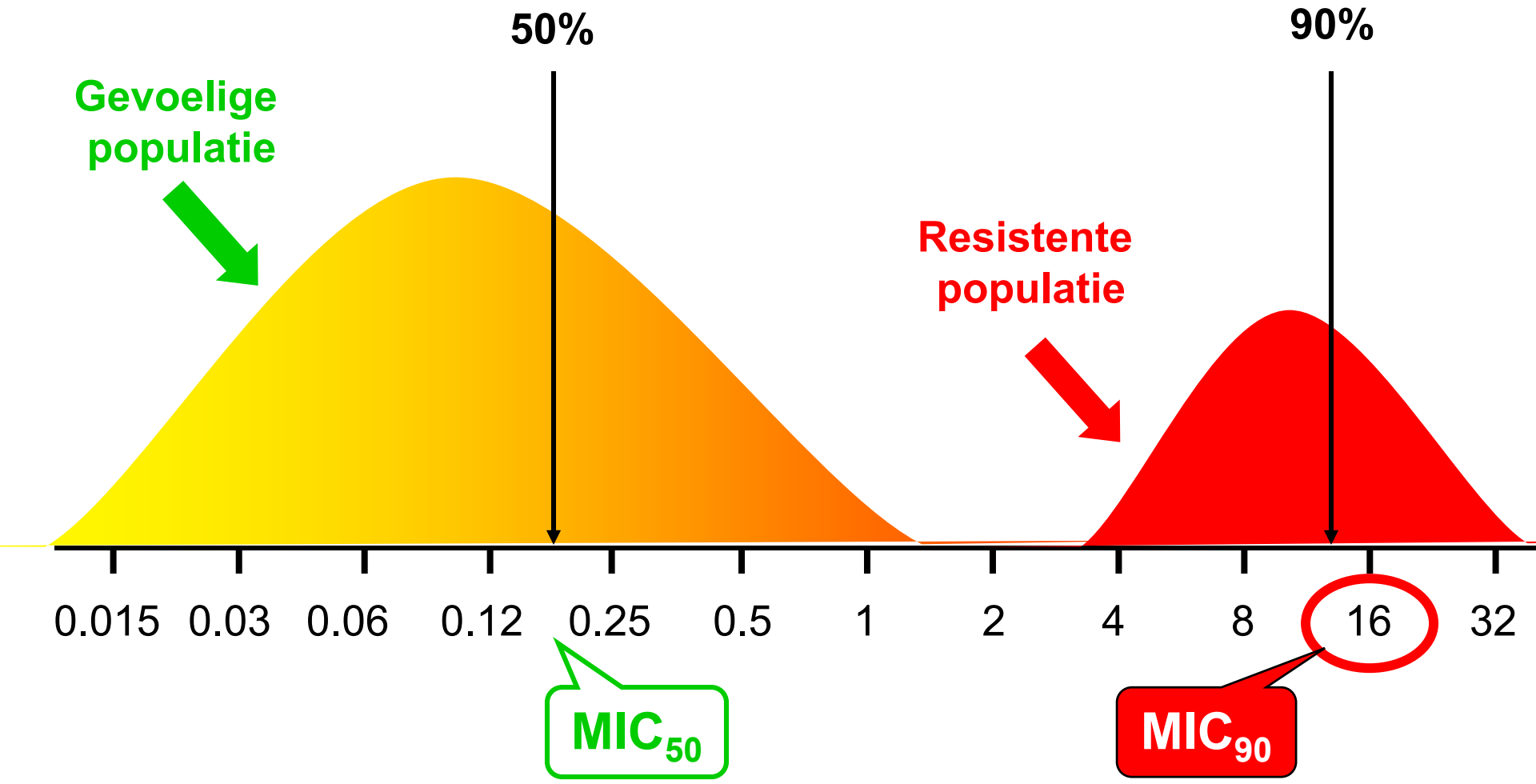
MIC = de laagste antibioticum- concentratie die de bacteriegroei verhindert

Verdeling van de MIC: unimodale populaties

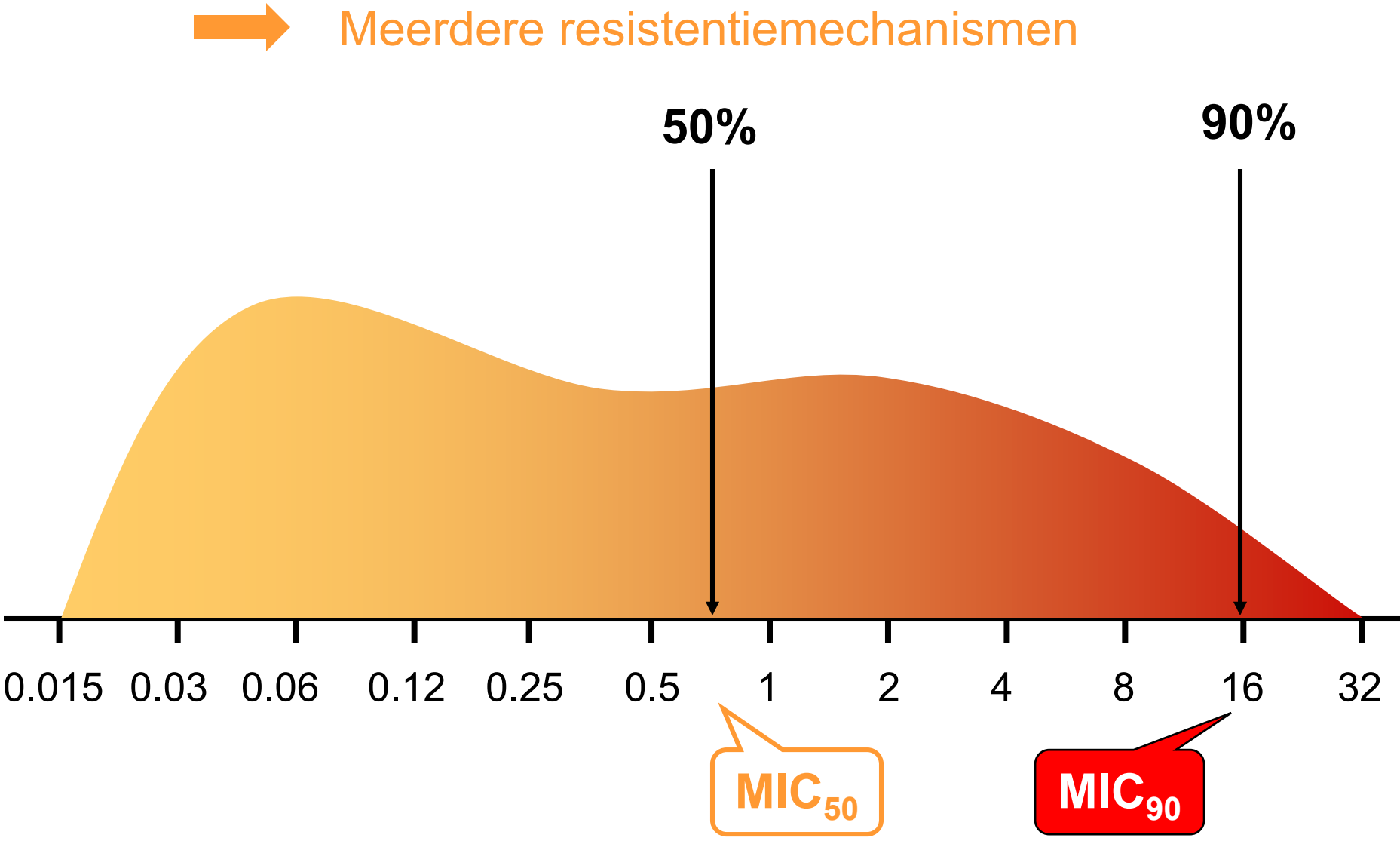
Geen resistentiemechanismen



Verdeling van de MIC: bimodale populaties

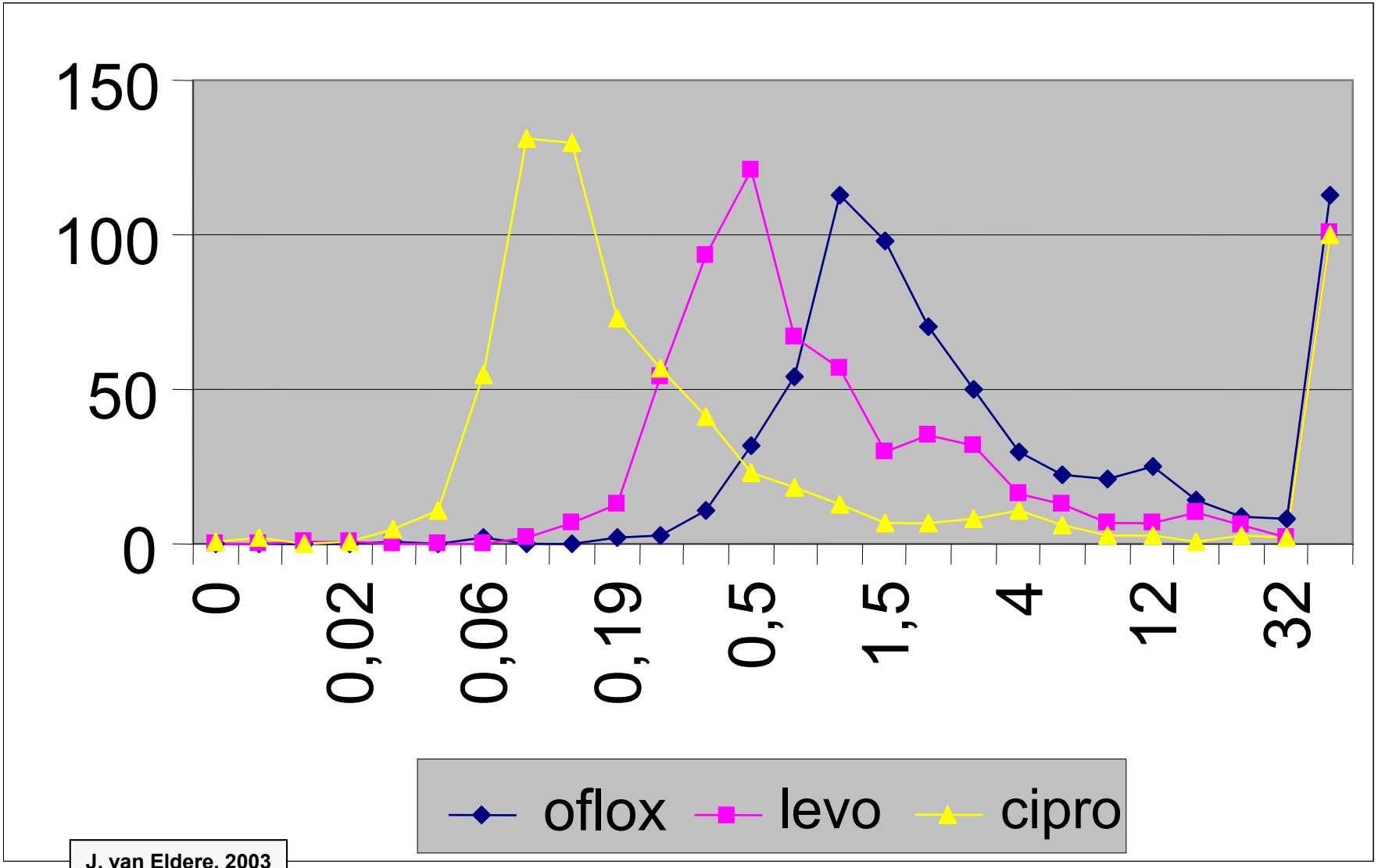


Verdeling van de MIC: populaties met continuum

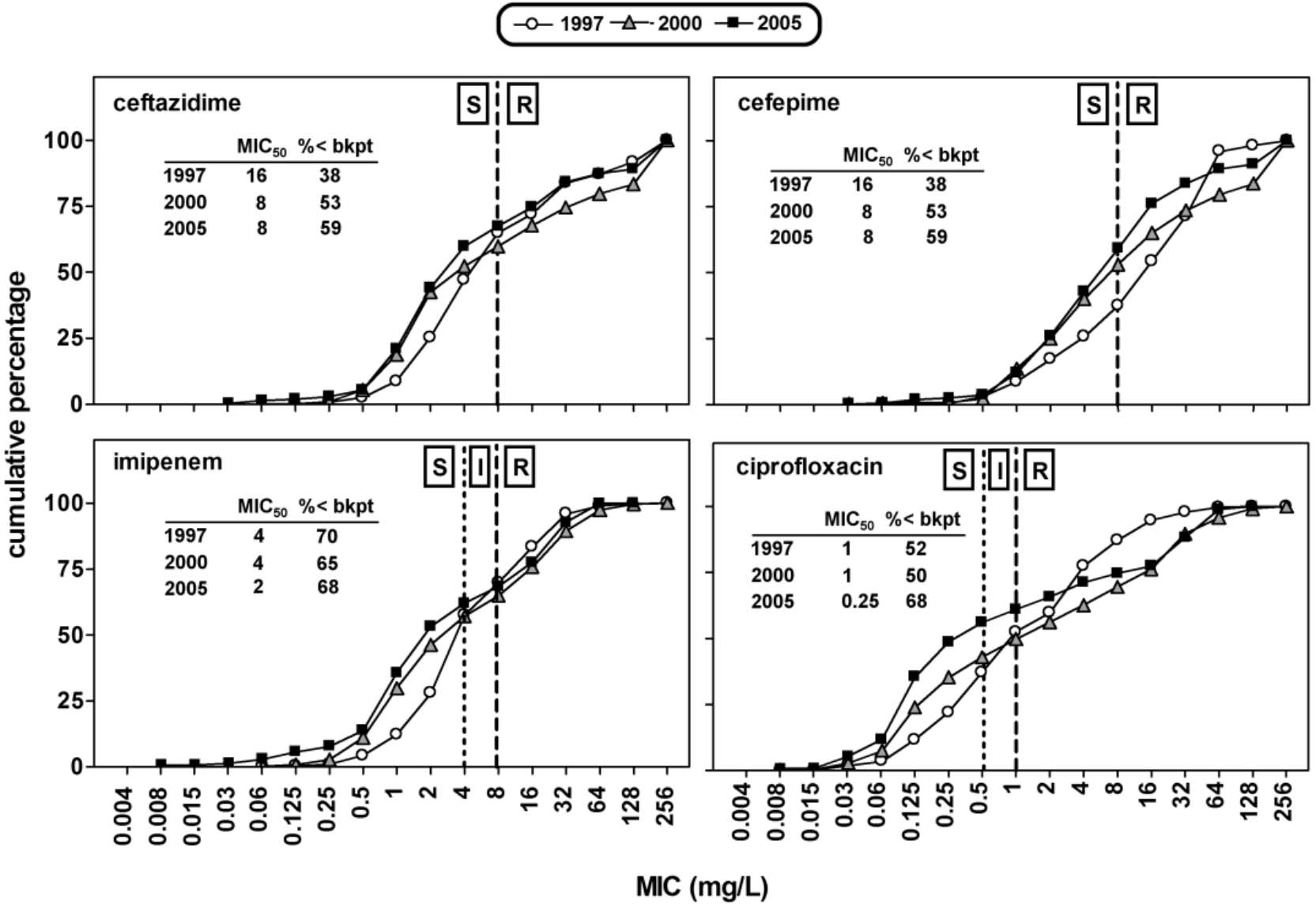


Een voorbeeld...

Verdeling van de MIC-waarden van *P. aeruginosa* te Leuven

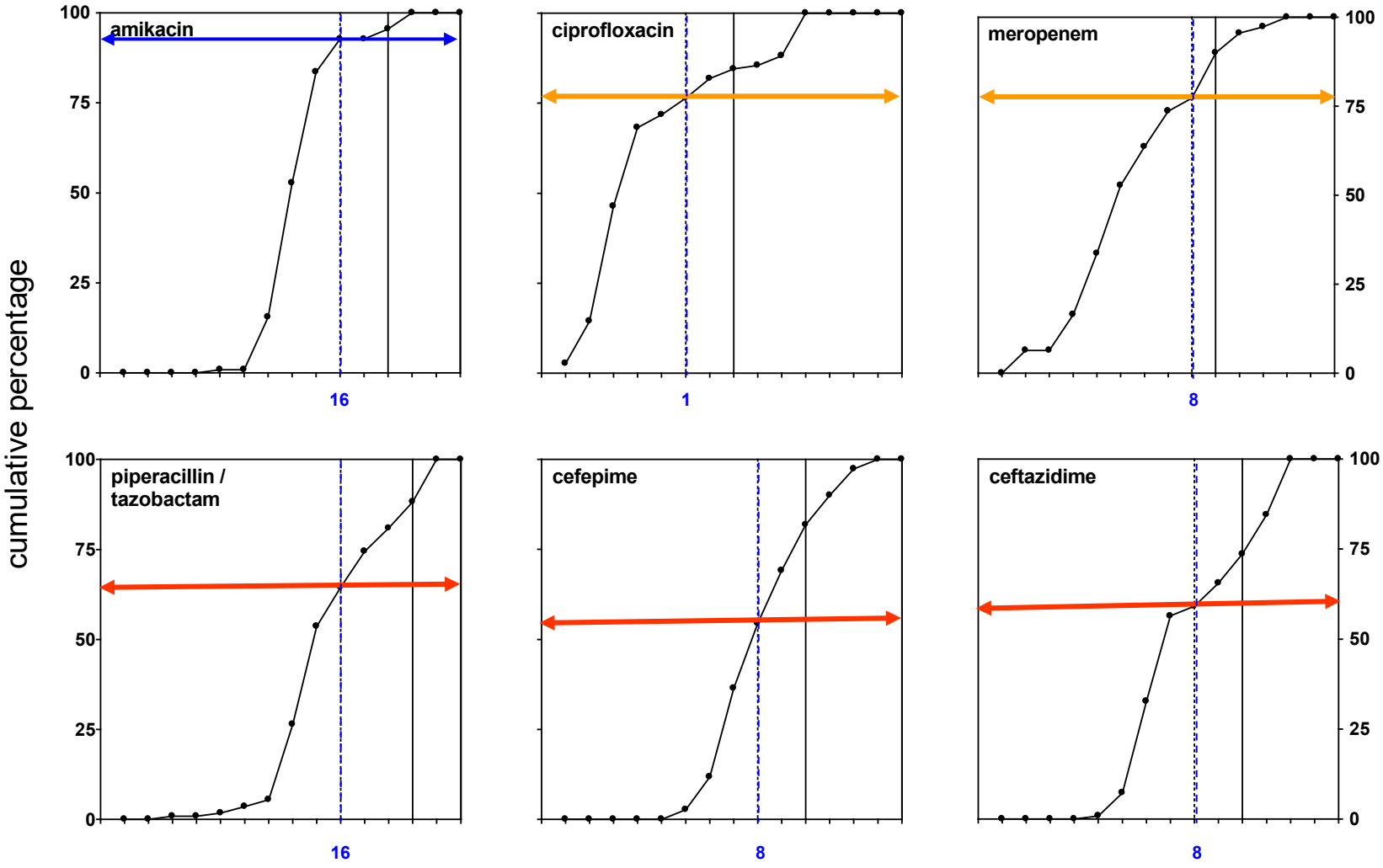


P. aeruginosa in Europa tussen 1997 en 2005



Mesaros et al. CMI (2007) 13: 560–578

P. aeruginosa te Brussel in 2007-2009

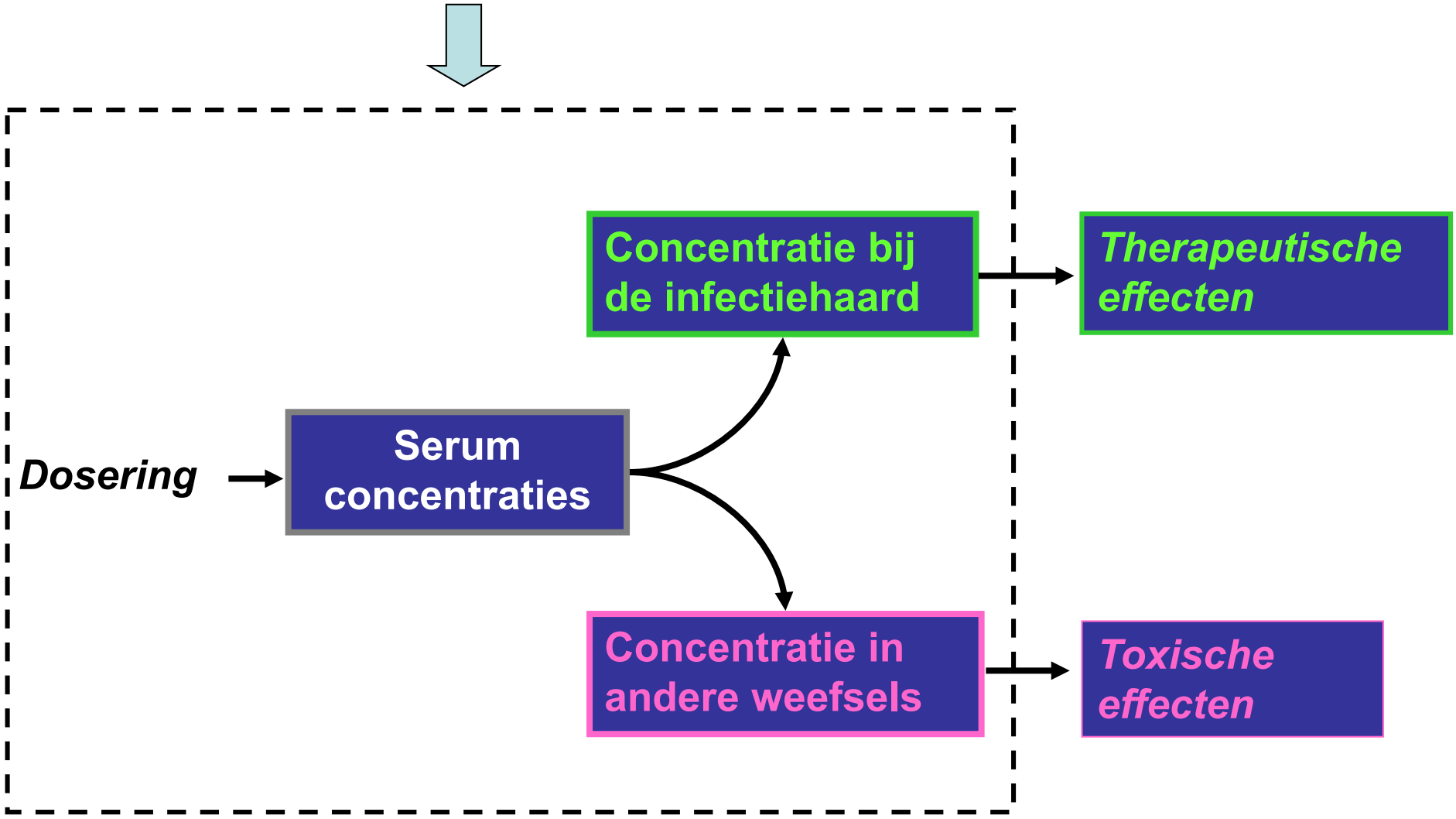


Riou et al. IJAA (2010) 36:513-522

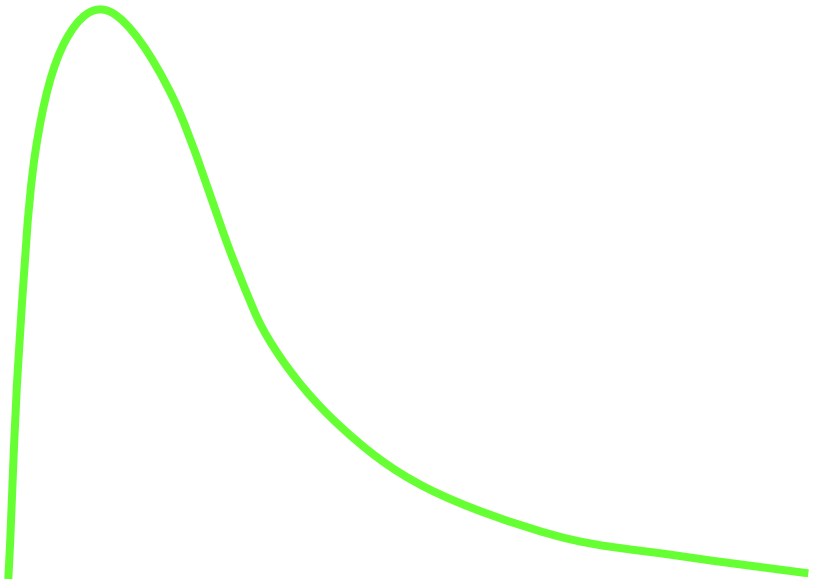
Eerste aandachtspunten…

- **MIC_{50}** en **MIC_{90}** zijn nuttig… maar hebben beperkingen...
  (later zullen we spreken over **breekpunten** en "**S - I - R**")
- De **waarden van de MIC** met micro-dilutie **zijn enkel intrinsiek nauwkeurig** tot **± 1 de verdunningsfactor**
  (zo kan een aflezing van 1 mg/L overeenkomen met 0.5 of 2 mg/L)…
  (dit kan verbeterd worden met E-test…)
- Toch **kunnen de actuele MIC waarden** voor specifieke bacteriën **heel belangrijk zijn** op het niveau van individuele patiënten (in ernstige situaties zoals intensieve zorgen, recidiverende infecties...)
- **MIC verdelingen** zijn nog belangrijker om een correct beeld te krijgen van de gevoeligheid in een bepaalde omgeving (zoals een dienst, een ziekenhuis, een regio…)

2. Farmacokinetiek / Farmacodynamiek (PK/PD)



2.1. Farmacokinetiek



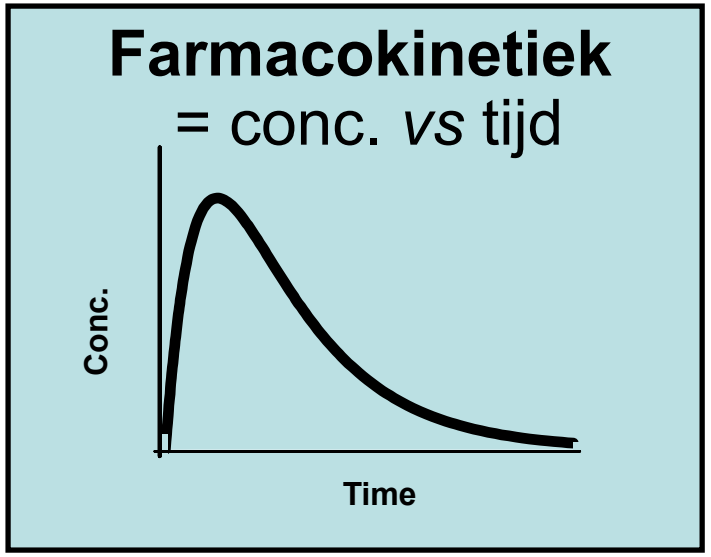
- C_{max}
- klaring
- Vd
- halfwaardetijd
- AUC
- biologische beschikbaarheid
- proteïnebinding

Wat is dit vak jargon?
Is dit belangrijk voor mij?

Wat is het belang van PK?

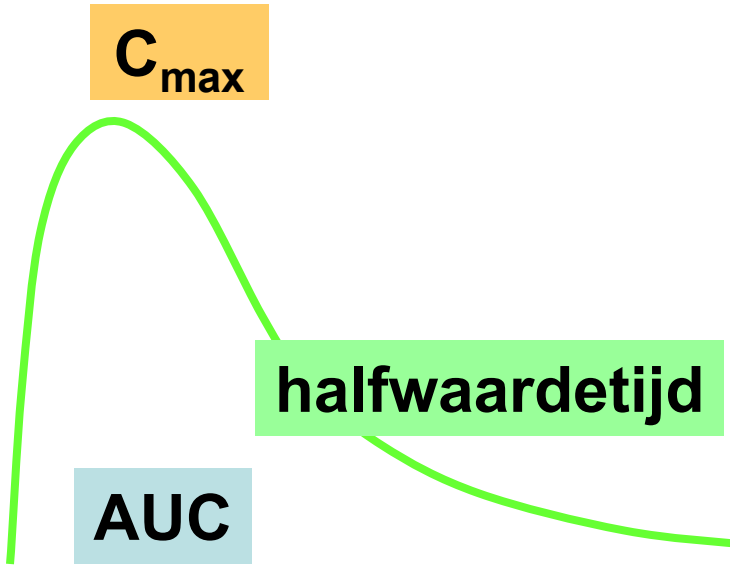
PK helpt om het geneesmiddel zo doeltreffend mogelijk te maken…

- bereikt het middel zijn **doelwit** en in **voldoende hoeveelheden**?
- en **lang genoeg**?
- bereikt het ook **ongewenste doelwitten**?



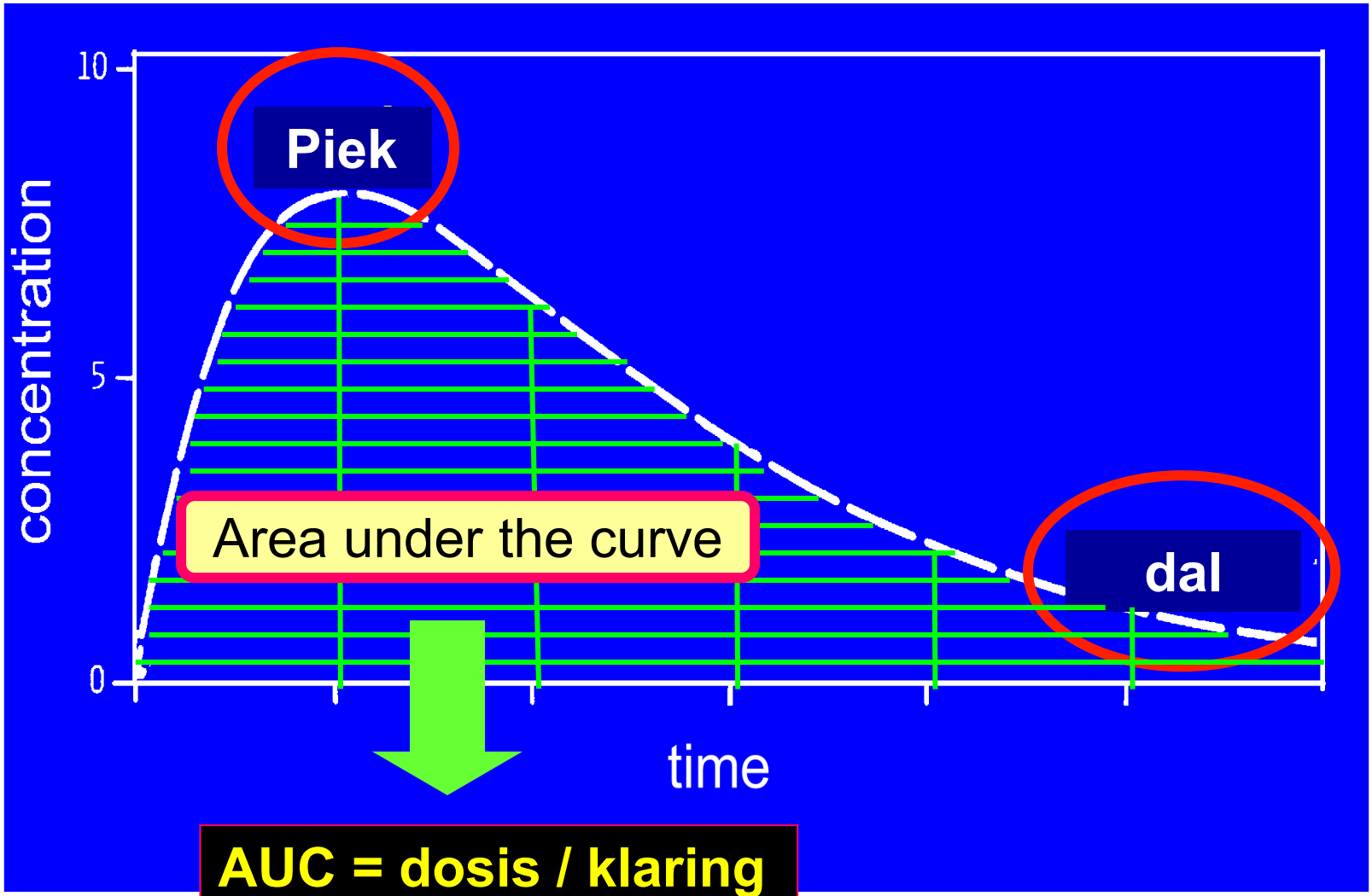
Welke zijn de belangrijkste farmacokinetische parameters (en hun betekenis) voor uw praktijk

parameter	wat is het ?	wordt bepaald door
C_{max}	dosis / Vd	**eenheidsdosis**
$t_{1/2}$	0.693 x Vd / Cl	**klaring** (en V_d)
AUC	dosis / Cl	**dosis** en **klaring**



- **dosis:** wat **U** aan de patiënt geeft ..
- **klaring:** afhankelijk van het **antibioticum** en de **patiënt**

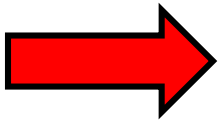
Area under the curve (AUC)



Een andere belangrijke parameter:

Biologische beschikbaarheid

- Kwantificeert de **ABSORPTIEGRAAD** vanuit de plaats van toediening **naar het bloed**
- wordt gemeten door de orale toediening (of een andere toedieningswijze) te vergelijken met intraveneuze toediening



Een gebrekkige biologische beschikbaarheid vermindert zowel de C_{max} als de AUC... waardoor de werkzaamheid sterk afneemt!!!

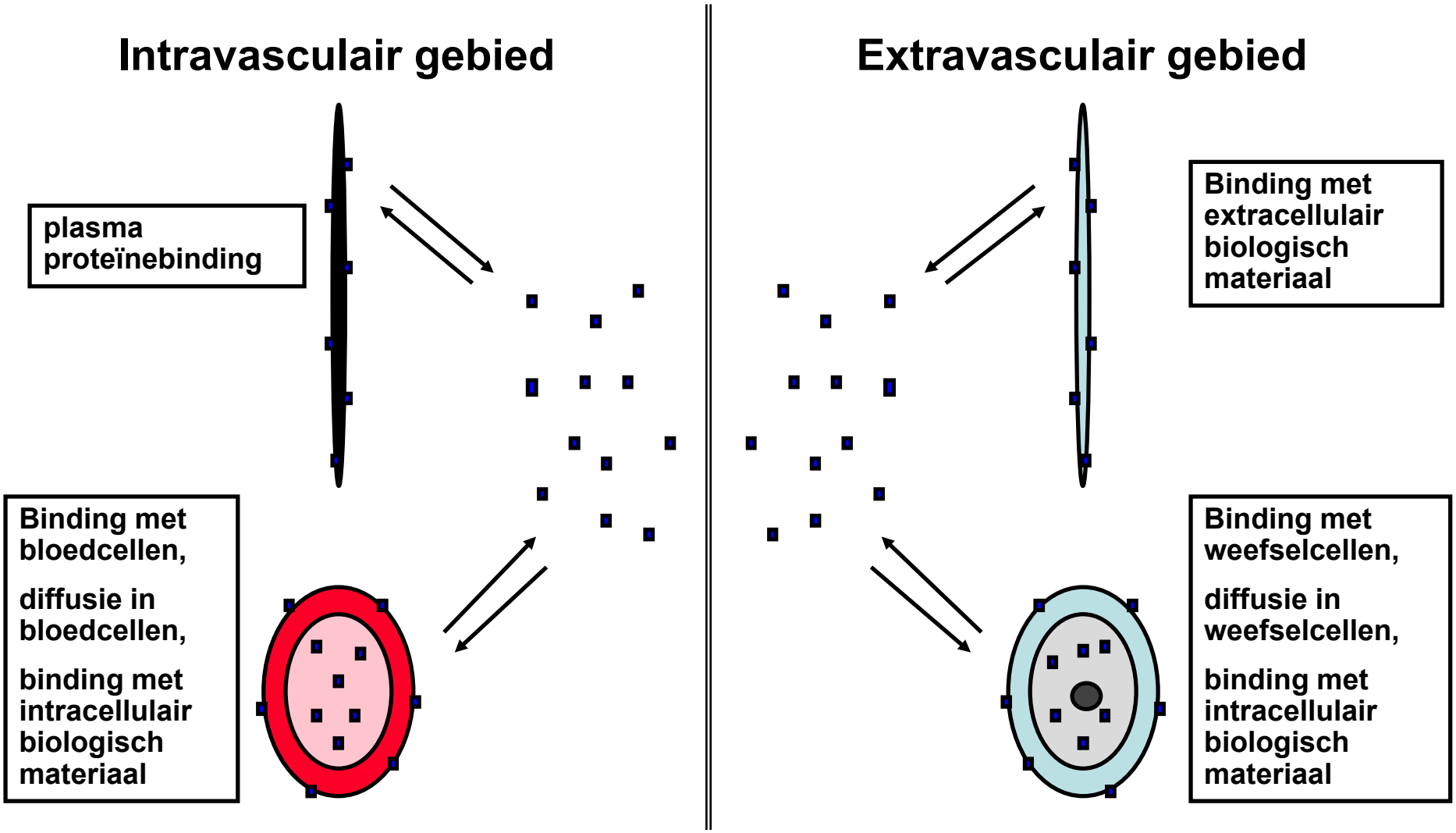
Biologische beschikbaarheid van antibiotica: IV naar perorale switch

molecule	% beschikbaarheid	gevolgen
ampicilline	50	amoxicillin is 1ste keus
amoxicilline	89	
cefuroxime-axetil	37-52	dosis is zeer belangrijk *
ciprofloxacine	70-80	dosis van cipro *vs.* levo is essentieel **
levofloxacine	99	
vancomycine	0	nooit voor system. infecties
linezolid	100	perfect voor perorale switch

* met een maaltijd om beschikbaarheid te verhogen

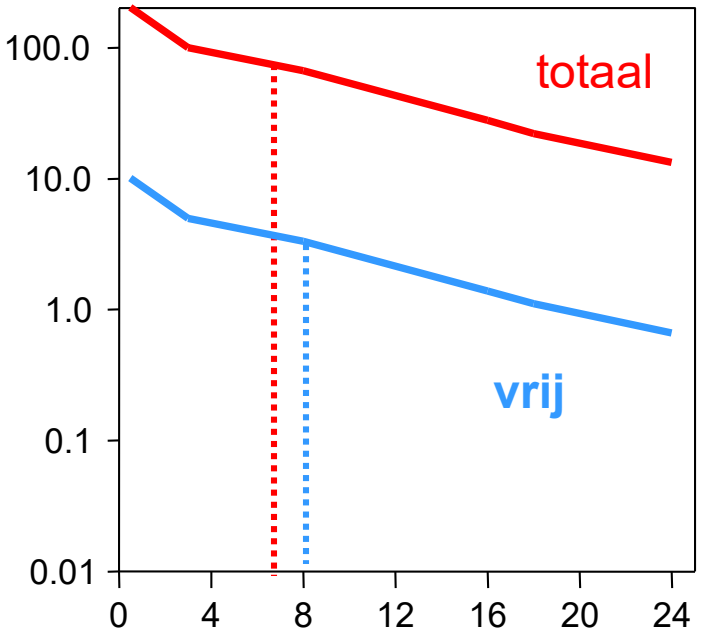
** voor of 2 u na een maaltijd , en niet met Ca^{++}, Mg^{++}, Al^{+++}, of Fe^{++} bevattende medicaties (vorming van onoplosbare complexen).

Proteïnebinding: meestal is het de vrije fractie van het geneesmiddel dat actief is...



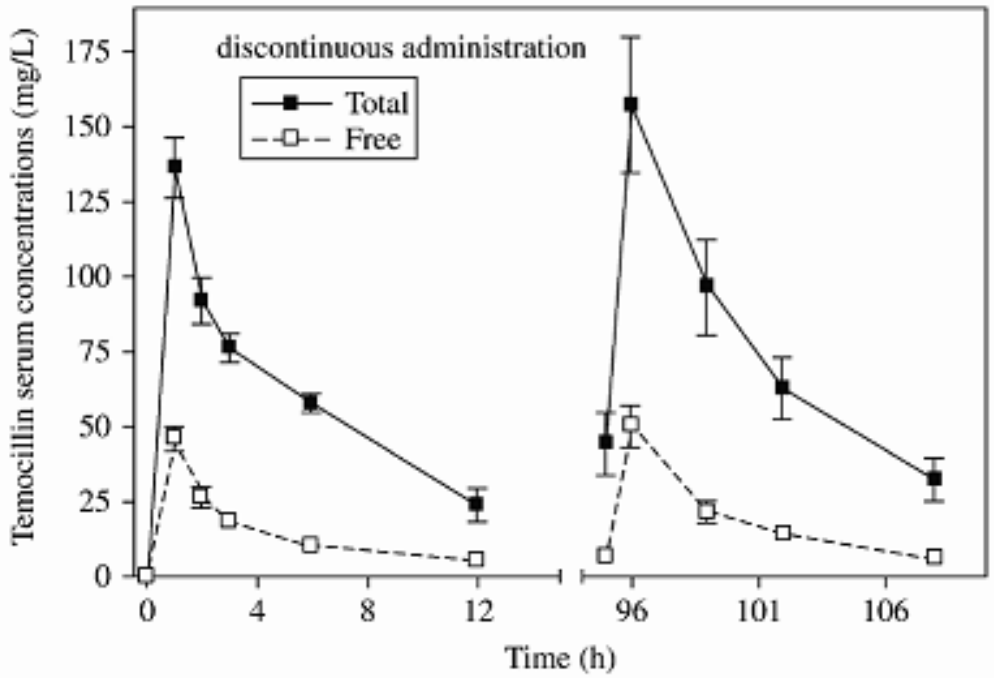
Proteïnebinding vertraagt de eliminatie…
maar alleen de vrije fractie van het antibioticum is actief!

ceftriaxone 1 g



Paradis *et al*, AAC 1992, 36: 2085-2092
Perry & Schentag, Clin Pharmacokinet. 2001, 40: 685-694

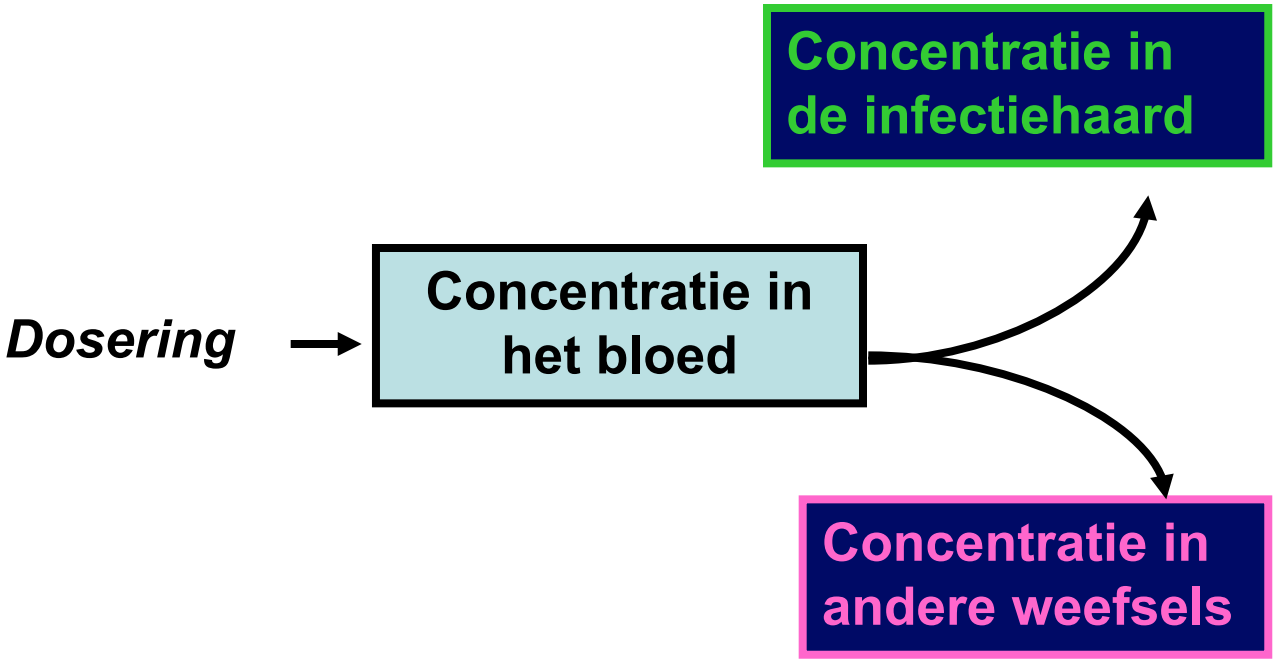
temocilline 2 g



De Jongh et al. J. Antimicrob. Chemother. 2008;61:382-388

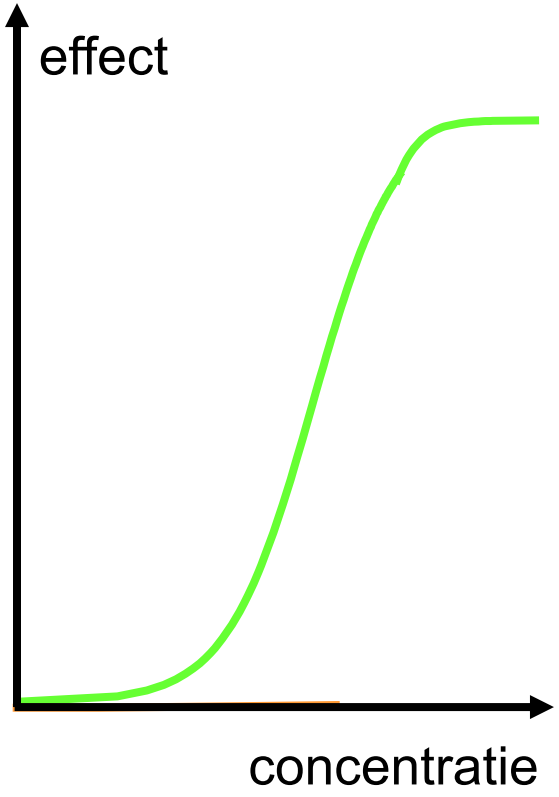
Zover staan we...

Farmacokinetiek



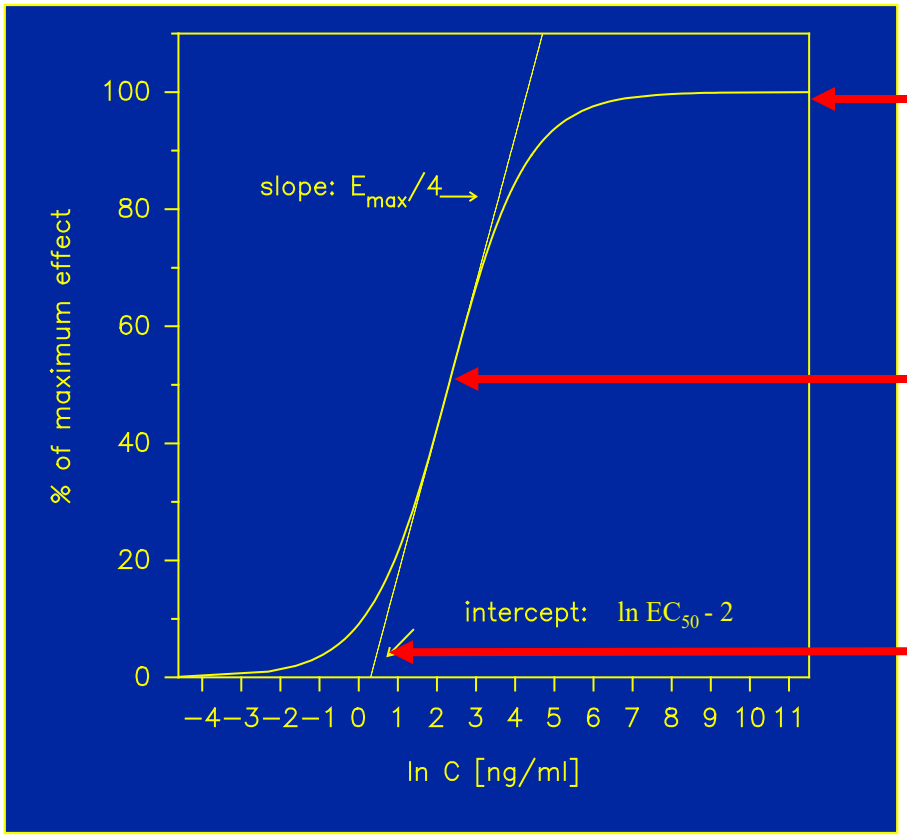
Volgende stap…

2.2. Farmacodynamiek: het concept



- Wat is farmacodynamiek?
- Dosis-respons modellen...
- invloed van de tijd...

Klassieke Farmacodynamiek



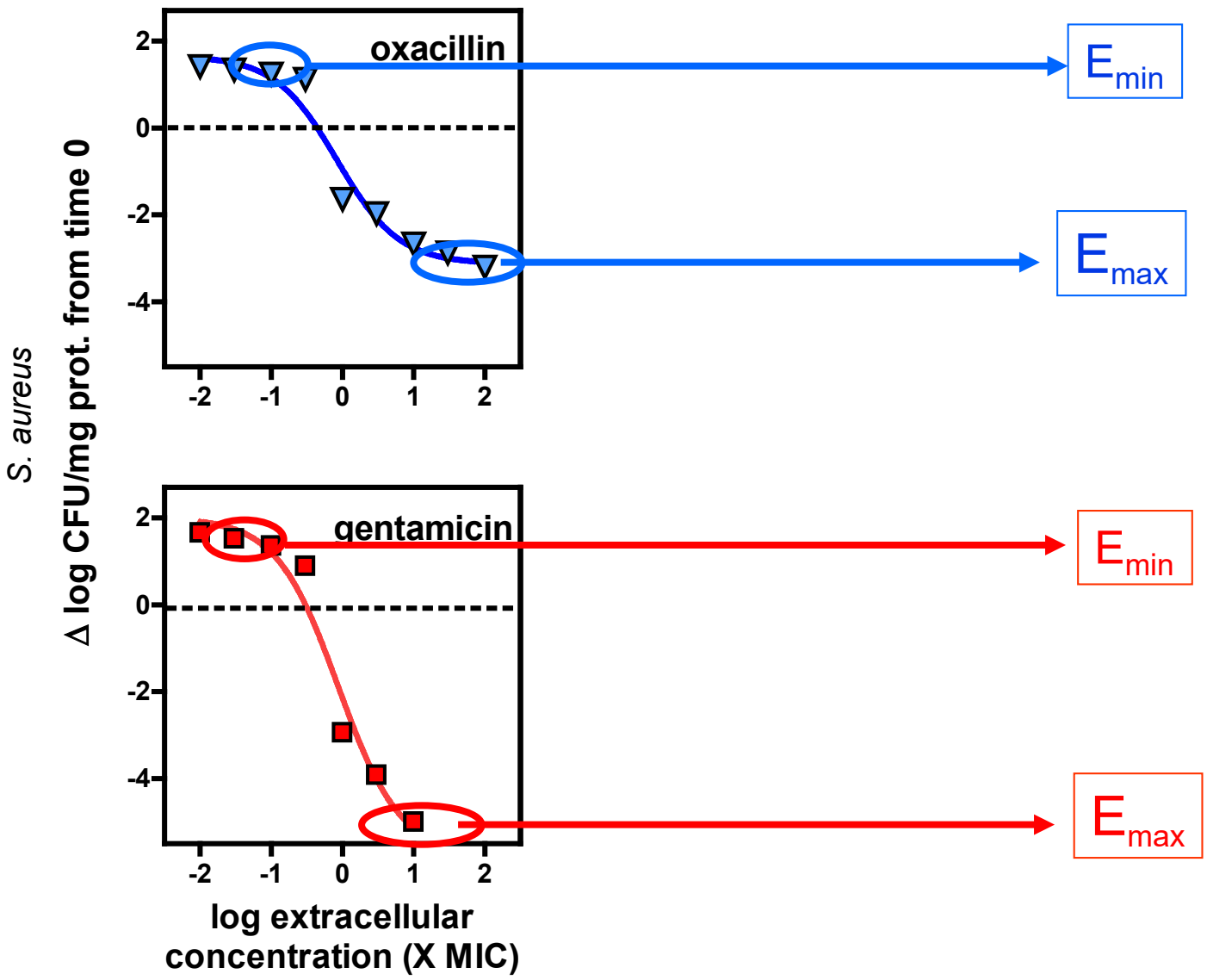
E_{max} **Maximaal effect**

$E_{50\%}$

E_{min} **Minimaal effect**

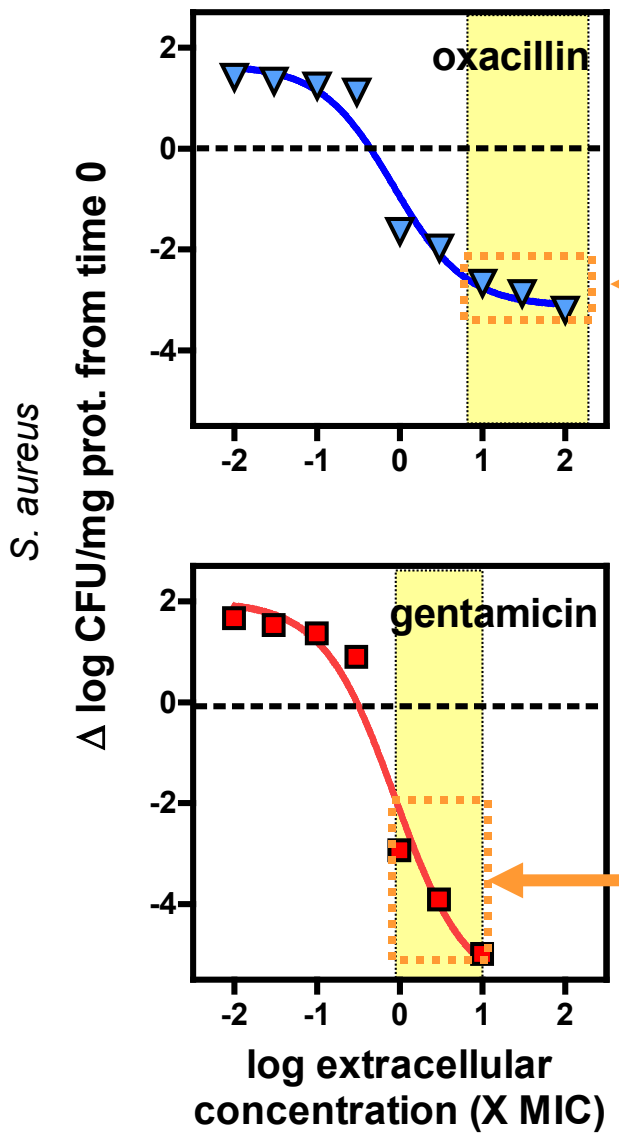
$$E = \frac{E_{max} \times C^n}{EC_{50}^n + C^n}$$

Farmacodynamiek van antibiotica



Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

En met farmacokinetiek...



geringe concentratie-afhankelijkheid over C_{min}-C_{max}

➔ **de tijd wordt de <u>overheersende</u> parameter in de praktijk**

C_{min}-C_{max}

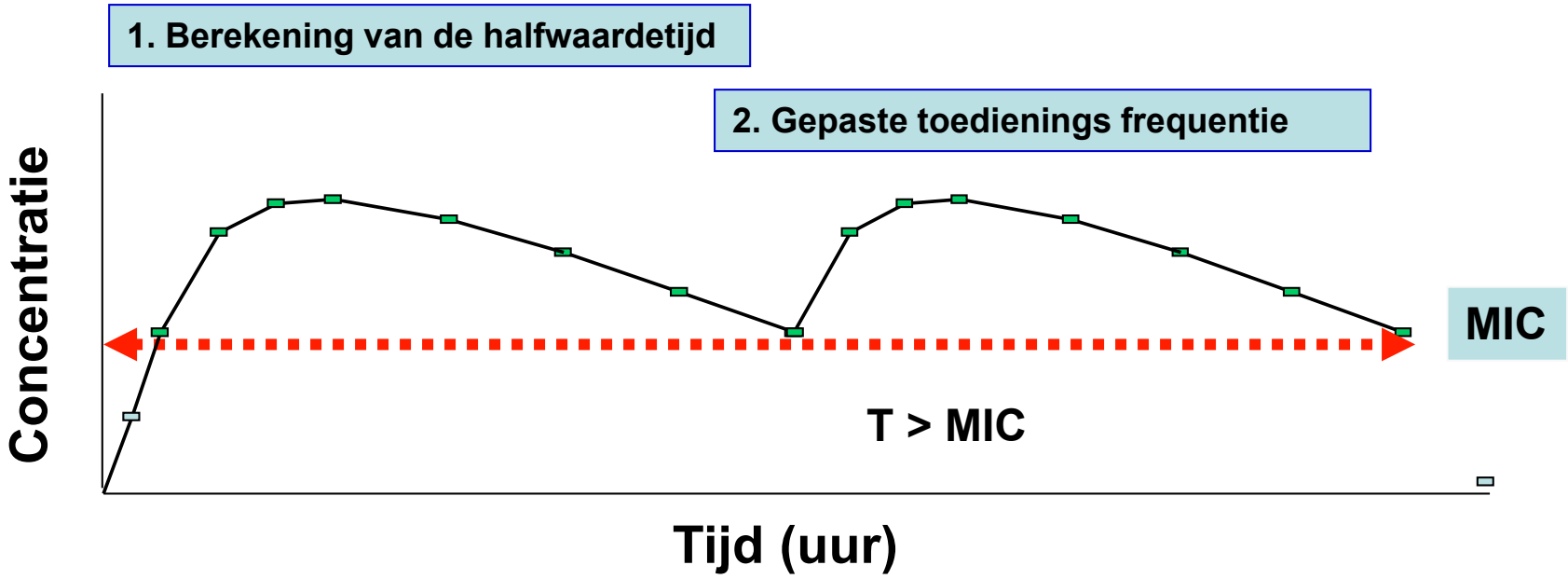
hoge concentratie-afhankelijkheid

➔ **de tijd EN de concentratie zijn de belangrijke parameters in de praktijk**

Eerste conclusies (1 van 3)…

- Alle antibiotica zijn <u>in principe</u> concentratie-afhankelijk…
- **MAAR**: voor β-lactams is de activiteit reeds optimaal vanaf een concentratie hoger dan 3-4 x de MIC. Dit kan al met normale dosissen bereikt worden… en er is geen post-antibiocum effect.

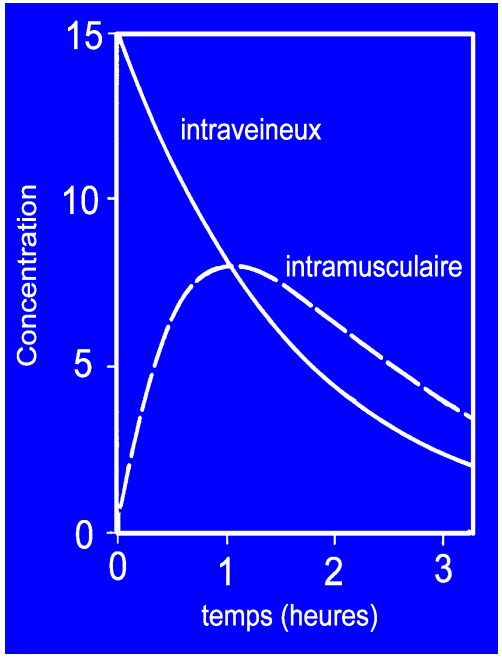
  ➔ Daarom worden de **β-lactams** in de klinische praktijk nu voornamelijk beschouwd als **tijdsafhankelijk**… (→ **tijd boven de MIC**)



Eerste conclusies … (2 van 3)

- De situatie is aanders voor concentratie-afhankelijke antibiotica binnen de normale serumspiegel waarden… met een belangrijk post-antibioticum effect

  ➔ Daarom worden **aminoglycosiden concentratie-afhankelijk…** (→ **piek concentratie**)



Naar Schorderet, 1998

1. Gepaste toedieningsmethode (IV > IM)

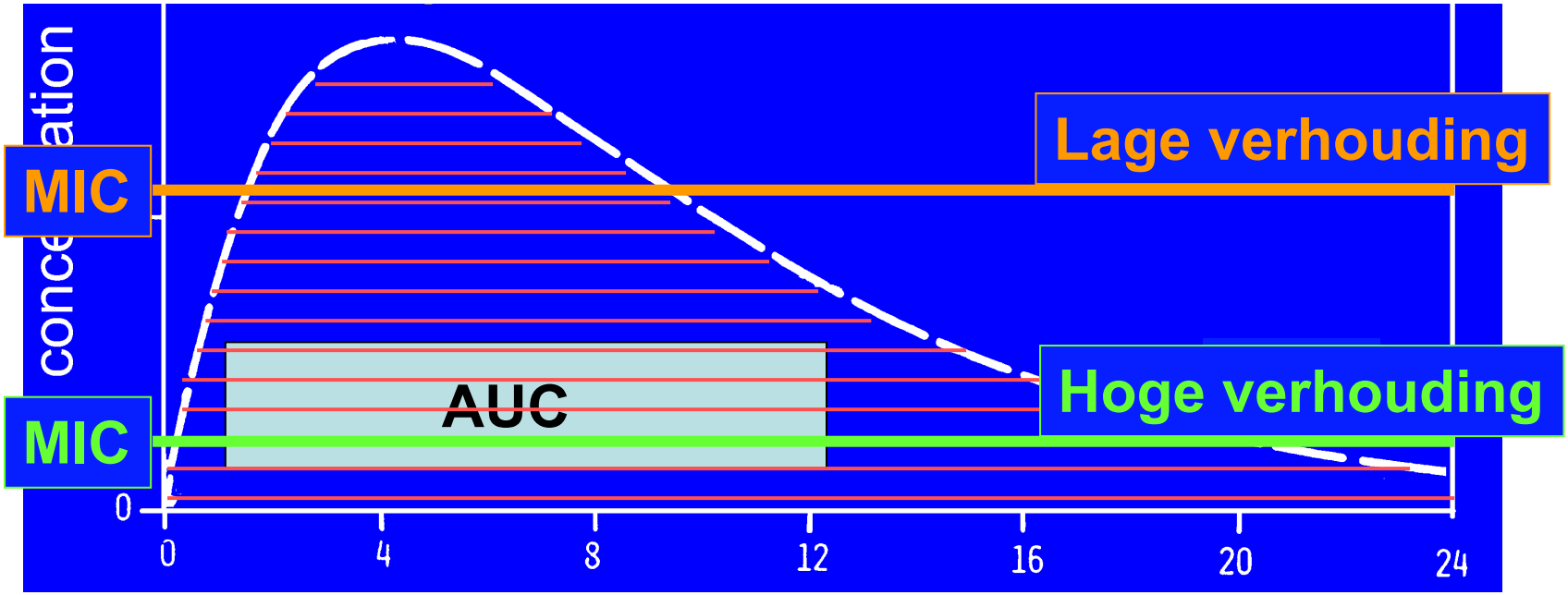
2. Berekening van de gewenste piek

3. Berekening van de gewenste dosis (piek x Vd)

Eerste conclusies... (3 van 3)

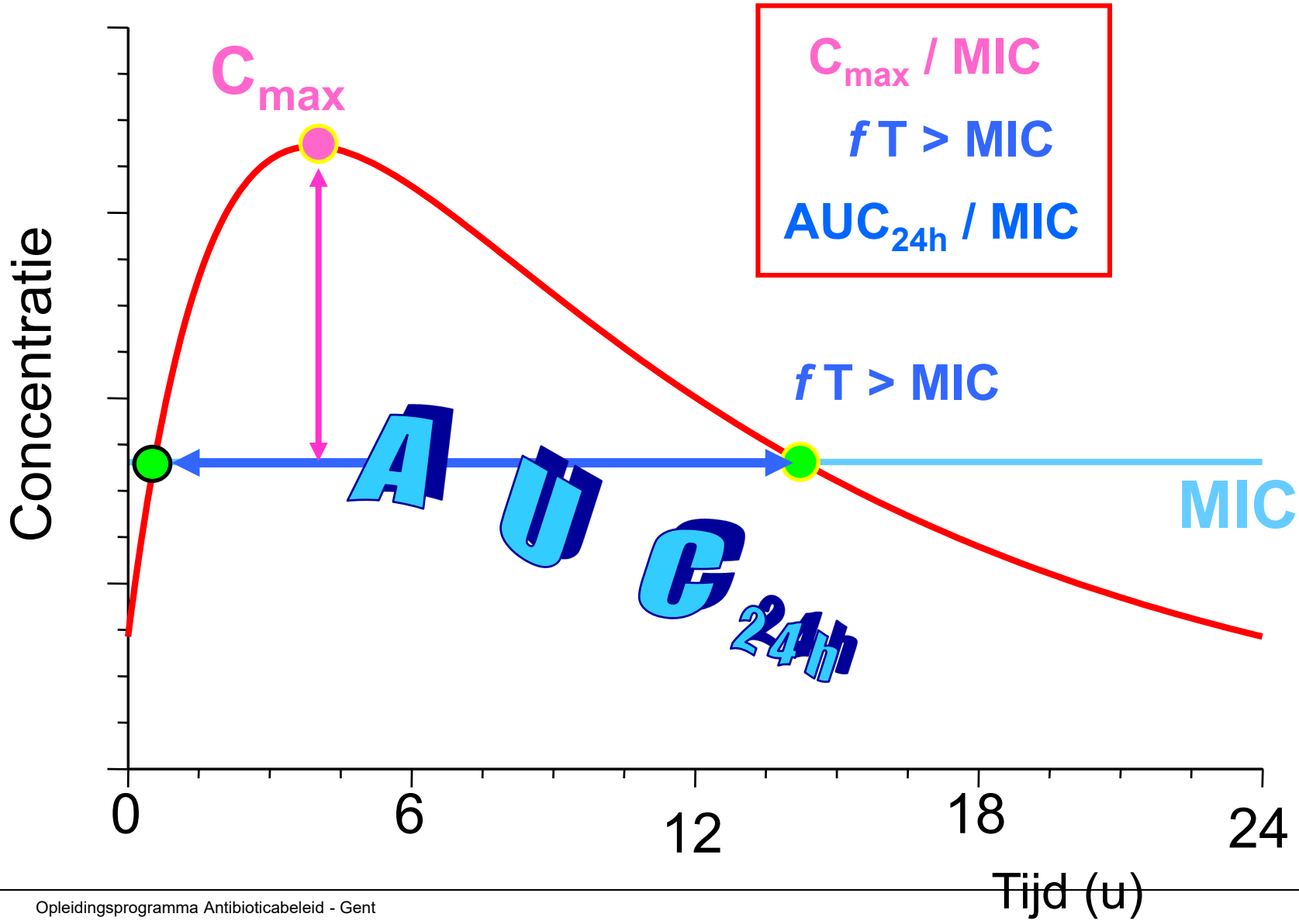
- Voor de meeste andere antibiotica is de situatie een combinatie (**tijds- en concentratie afhankelijk**), met matig tot belangrijk post-antibioticum effect

  ➔ Deze antibiotica worden **AUC-afhankelijk***genoemd



* AUC is dosis / klaring !! → **hogere eenheidsdosis betekent hogere piek, hoger AUC en langere tijd > MIC**

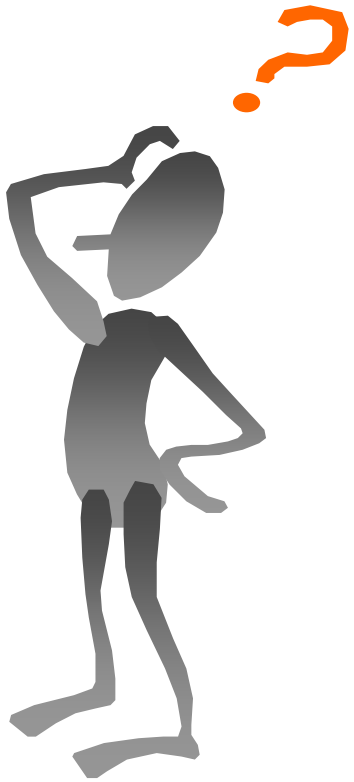
Van farmacokinetiek naar farmacodynamiek...



Voornaamste PK/PD-kenmerken van antibiotica

De huidige antibiotica kunnen in 3 groepen verdeeld worden:

- tijdsafhankelijk (*f* T > MIC)
- AUC_{24h} / MIC - afhankelijk
- tegelijkertijd piek / MIC en AUC_{24h} / MIC-afhankelijk



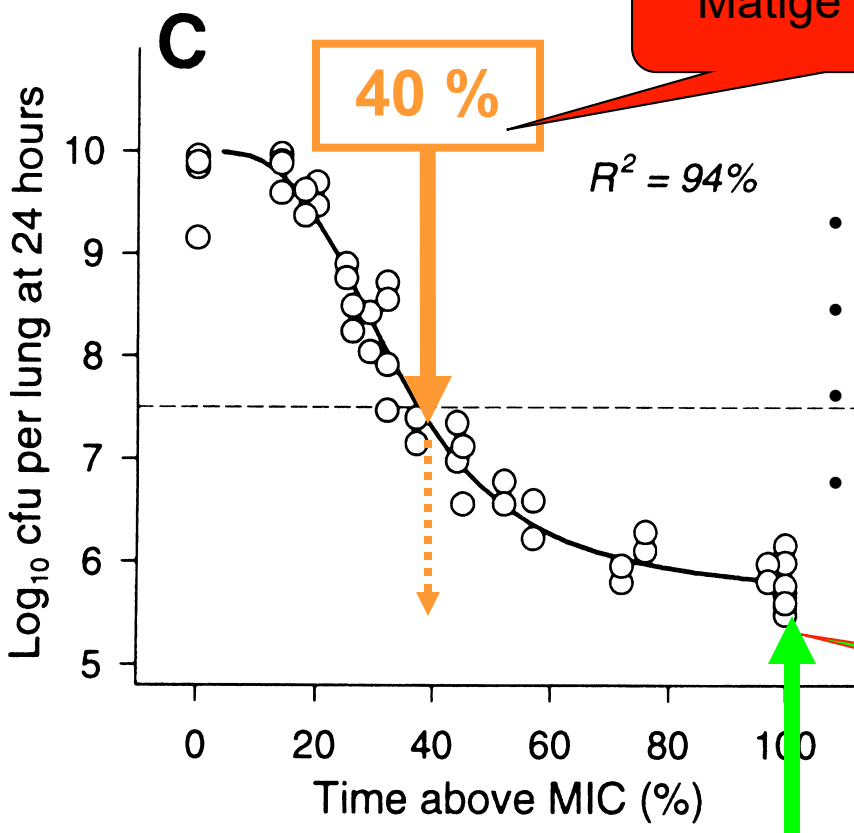
Antibiotica van Groep # 1

(naar W.A. Craig, 2000; herzien in 2002-2005)

1. Antibiotica met tijdsafhankelijke effecten en geen of weinig aanhoudende nawerking (post-antibiotisch effect)

AB	PK/PD-parameter	Doel
β-lactams flucytosine	***f* Tijd > MIC**	Duur van de blootstelling maximaliseren

Hoelang moet men boven de MIC blijven?



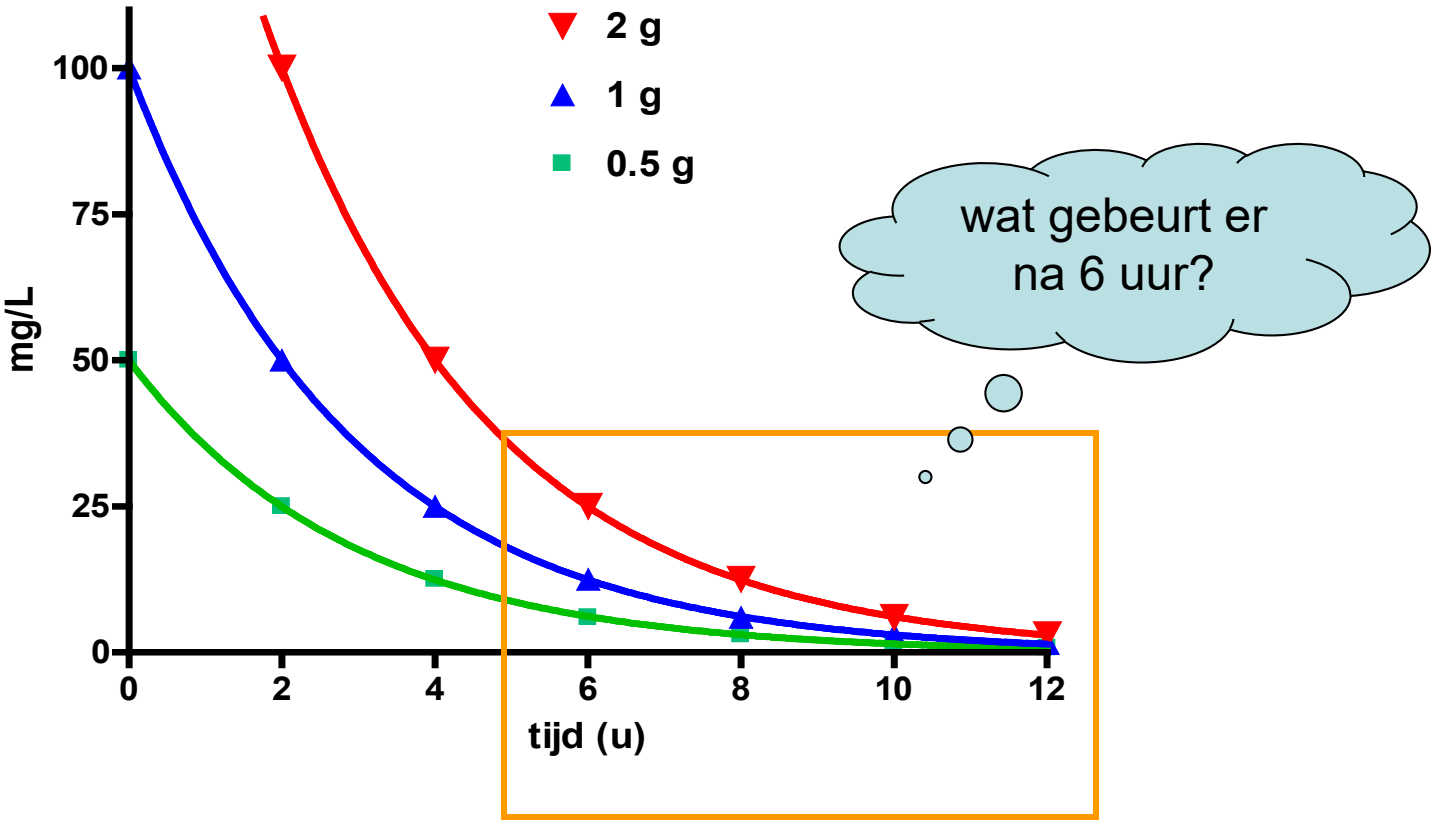
Matige infecties

- cefotaxime
- neutropene muis
- *K. pneumoniae*
- pulmonaire infectie

Ernstige infecties

100 %

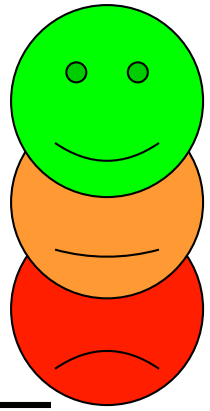
Typische farmacokinetiek van een β-lactam IV*



* éénmalige toediening; halfwaardetijd van 2u ; V_d = 0.2 l/kg

Typische farmacokinetiek van een β-lactam IV*

tijd	serumconcentratie (mg/L) na:		
(uren)	0.5 g	1 g	2 g
Hoelang zou u graag wachten ?			
6	6	12	25
8	3	6	12
12	0.75	1.5	3



* éénmalige toediening; halfwaardetijd van 2u ; V_d = 0.2 l/kg

Optimalisatie van β-lactams IV tegenover "hardnekkige" organismen

- 1 g elke 12 u → ***f* T > MIC = 100 %**
  voor MIC ≤ 1.5 mg/L
- 2 g elke 12 u → ***f* T > MIC = 100 %**
  voor MIC ≤ 3 mg/L !
- 2 g elke 8 u → ***f* T > MIC = 100 %**
  voor MIC ≤ 12 mg/L

Een meer frequente toediening is een goede optie om de activiteitslimiet van β-lactams te verhogen bij moeilijke gevallen...

→ **PK / PD - kritisch punt voor meeste IV β-lactams: MIC = 8 mg/L**

Antibiotica van groep # 2

(naar W.A. Craig, 2000; herzien in 2002-2005)

2. Tijdsafhankelijke antibiotica,
   weinig of niet beïnvloed door de concentratie maar met langere nawerking (post-antibiotisch effect)

AB	PK/PD Parameter	Doel
glycopeptiden * tetracyclinen macroliden linezolid streptograminen	**AUC_{24h} / MIC**	Dag dosis optimaliseren

Later meer over glycopeptiden…

Antibiotica van groep # 3

(naar W.A. Craig, 2000; herzien in 2002)

3. Bactericide antibiotica concentratie-afhankelijk en met lange nawerking (post-antibiotisch effect)

AB	PK/PD parameter	Doel
aminoglycosiden fluorochinolonen daptomycine telithromycine amphotericine	**piek / MIC en AUC_{24h} / MIC**	Piek en dag dosis optimaliseren

Aminoglycosiden: piek is het meest kritiek...

- om nefrotoxiciteit te verminderen is “éénmalige dagelijkse dosering" aanbevolen...
- voor optimale doeltreffendheid moet de piek 8 x de MIC bereiken
- dosis = 8 x MIC x Vd
- gemiddelde patiënten:
  - gentamicine / tobramycine / netilmicine 6 mg/kg
    ➔ piek ~ 16 mg/L ➔ beperking tot MIC ~ 2 mg/L
  - amikacine 15 mg/kg
    ➔ piek ~ 32 mg/L ➔ beperking tot MIC ~ 4 mg/L

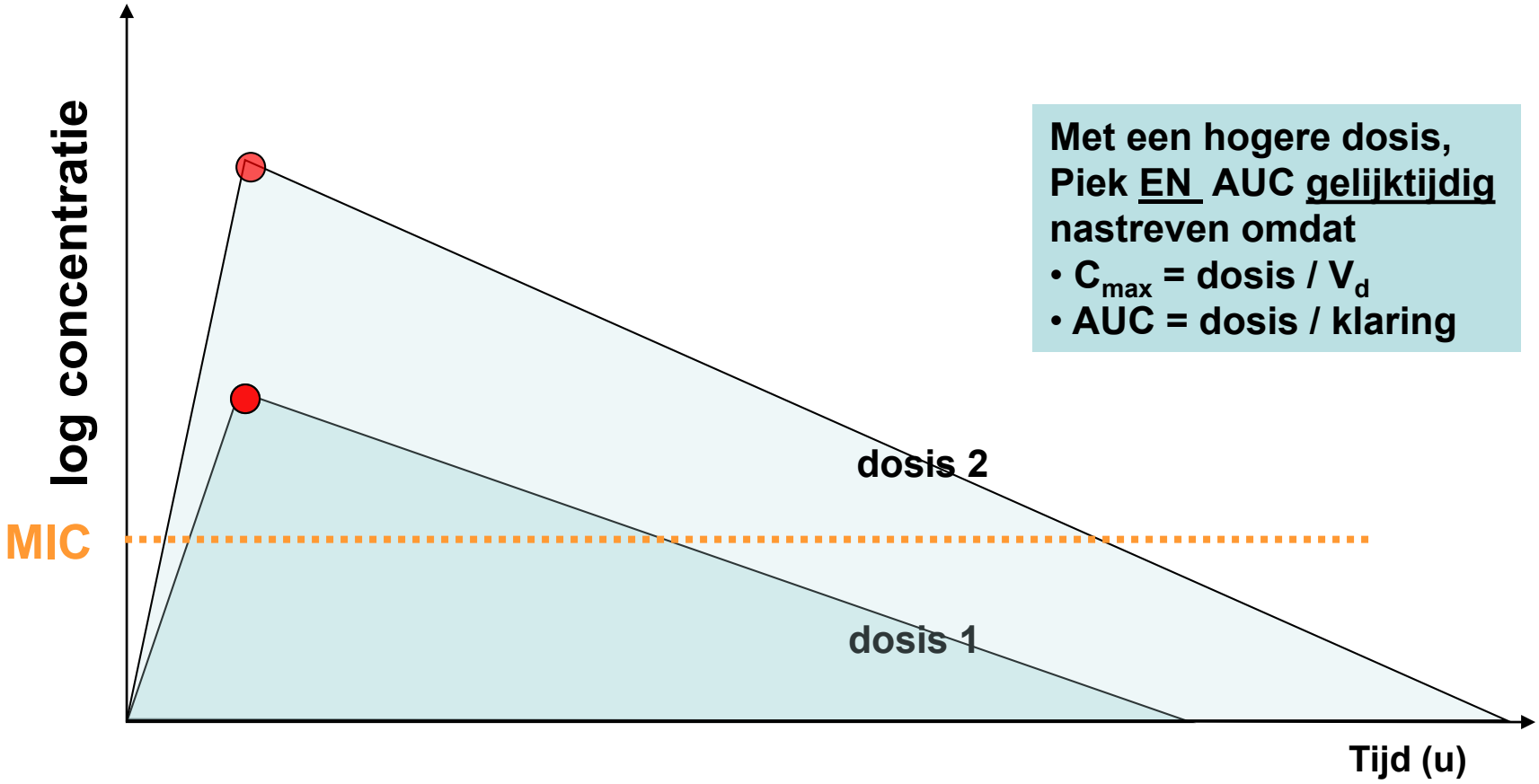
Kritische PK / PD-punten voor aminoglycosiden

- **Genta, Netil, Tobra : 2 mg/L**
- **Amika : 4 mg/L**

Fluorochinolonen: een piek EN een AUC verkrijgen

De toegediende dosis verhogen ter optimalisatie van :

- de AUC/MIC ⇒ zou **> 30-100** moeten zijn
- en de piek/MIC ⇒ zou **> 10** moeten zijn



Met een hogere dosis,
Piek EN AUC gelijktijdig nastreven omdat
- **C_{max} = dosis / V_d**
- **AUC = dosis / klaring**

PK/PD van de fluorochinolonen in 2 woorden…

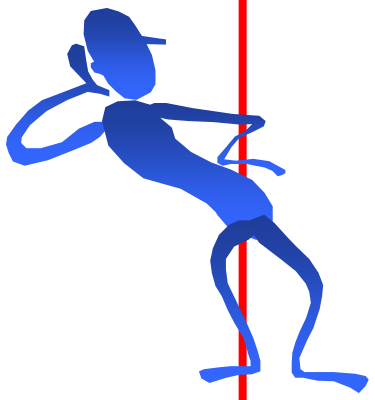
We herhalen:

- De 24u-AUC is evenredig met de dagelijkse dosis
- de piek is evenredig met de eenheidsdosis

- een **24u-AUC /MIC > 30* - 125**** behalen alsook
- een **piek / MIC > 10**

➡ doeltreffendheid

- en dus :
  de totale dagelijkse dosis aanpassen
  en de eenheidsdosis aanpassen



* Gram **+** en immunocompetente patiënt

** Gram **-** en/of immuno-gecompromitteerde patiënt

PK/PD breekpunten voor fluorochinolonen

Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

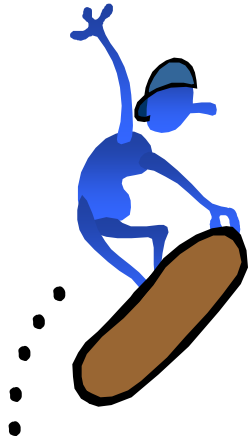
Aanpassing van de dosis volgens de MIC: voorbeeld voor levofloxacine

Dagelijkse dosis levofloxacine	AUC_{24h}*	Grens MIC voor AUC_{24h} / MIC = 125**
250	23	~ 0.2
500	45	~ 0.4
1000	90	~ 0.8

welke zijn de MIC's van levofloxacine in **uw** omgeving?

* gebaseerd op een klaring van 175 mL/min
na veelvuldige dosissen voor een volwassene van 65 kg

** Gram - infectie



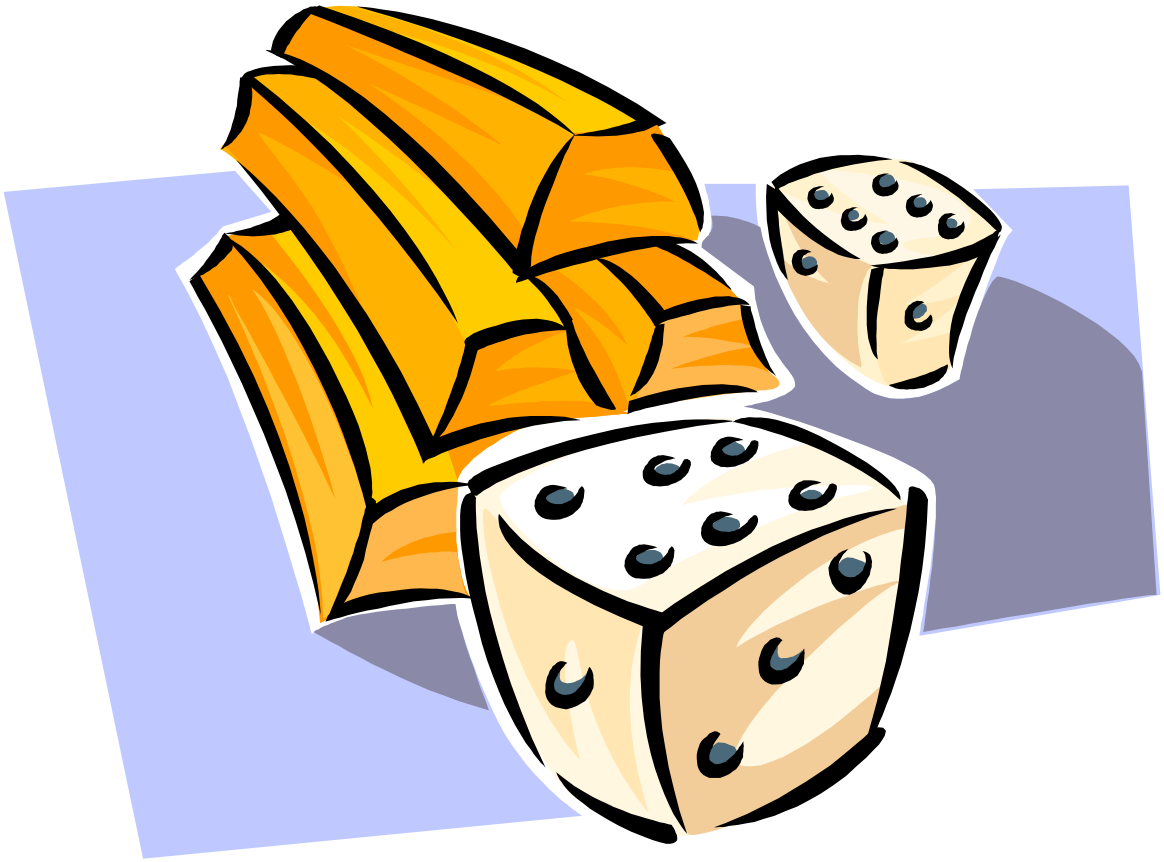
PK/PD: wat moeten we onthouden?

1. Voor elk antibioticum moeten we, op basis van PK/PD
   - het toedieningschema bepalen
   - de dagelijkse dosis bepalen

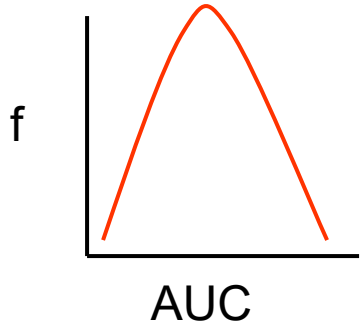
2. De dosering aanpassen aan de gevoeligheid van de bacterie
   - op basis van de MIC van de geïsoleerde kiem
   - bij gebrek hieraan, op basis van de lokale epidemiologie

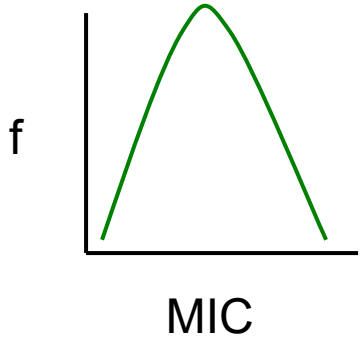
“Monte Carlo”-simulatie

(voor populatie studies)



“Monte Carlo”-simulatie voor pneumococcen (gebaseerd op AUC/MIC)*



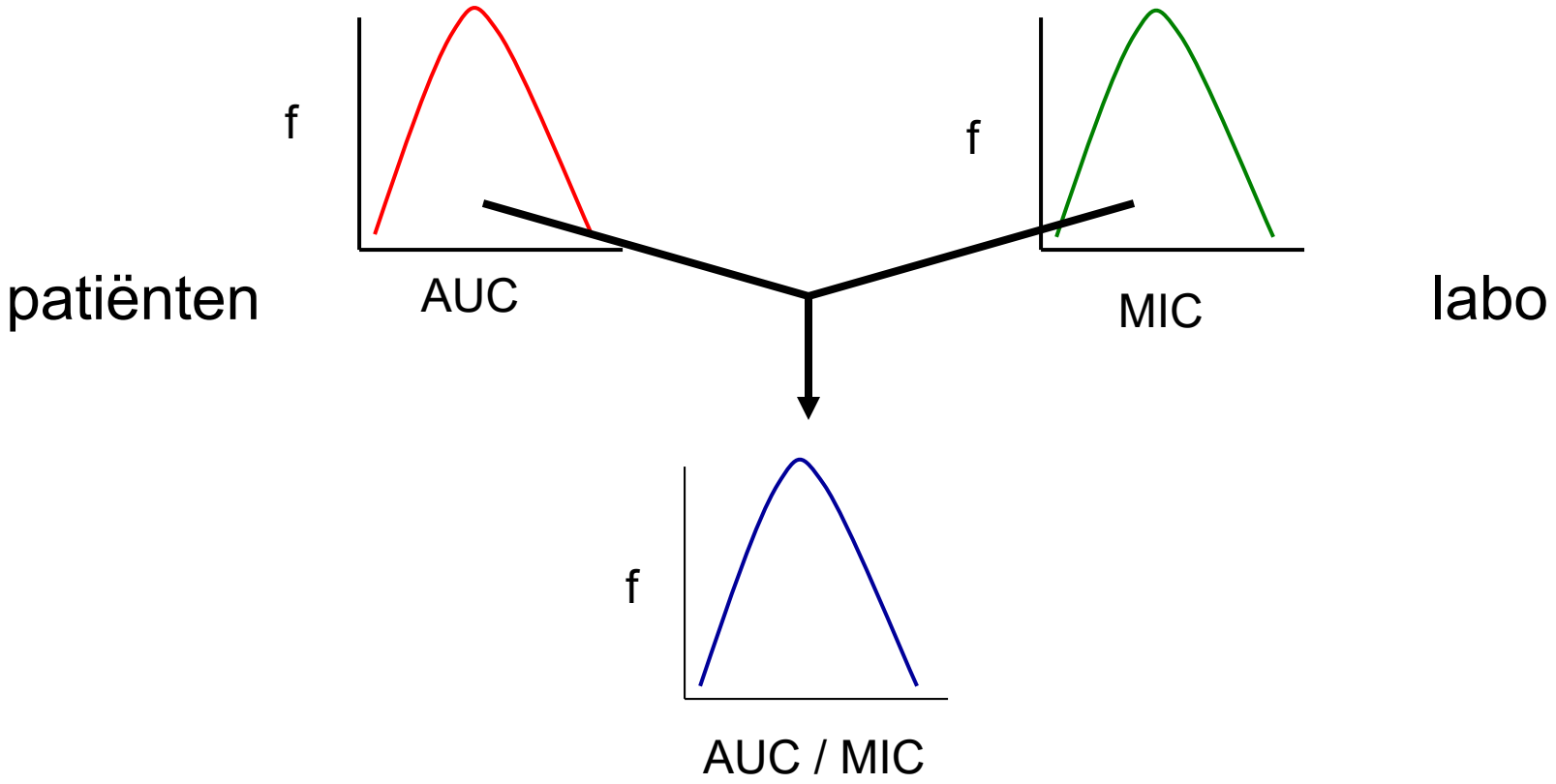


1. AUC-verdeling bij de patiënten (PK)

2. MIC-verdeling van de bacteriën

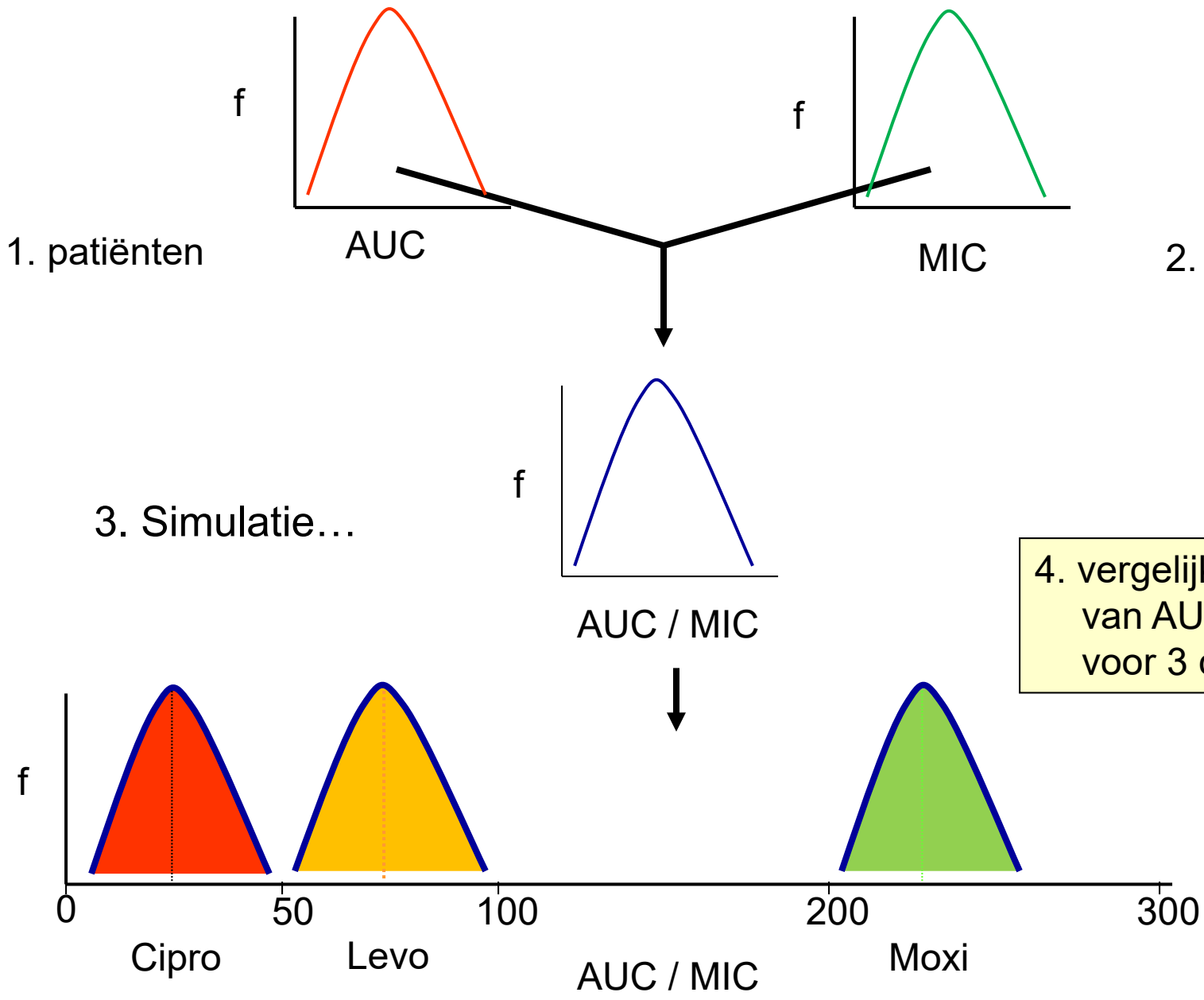
* Dus voor en chinolone...

“Monte Carlo”-simulatie voor pneumococcen (gebaseerd op AUC/MIC)

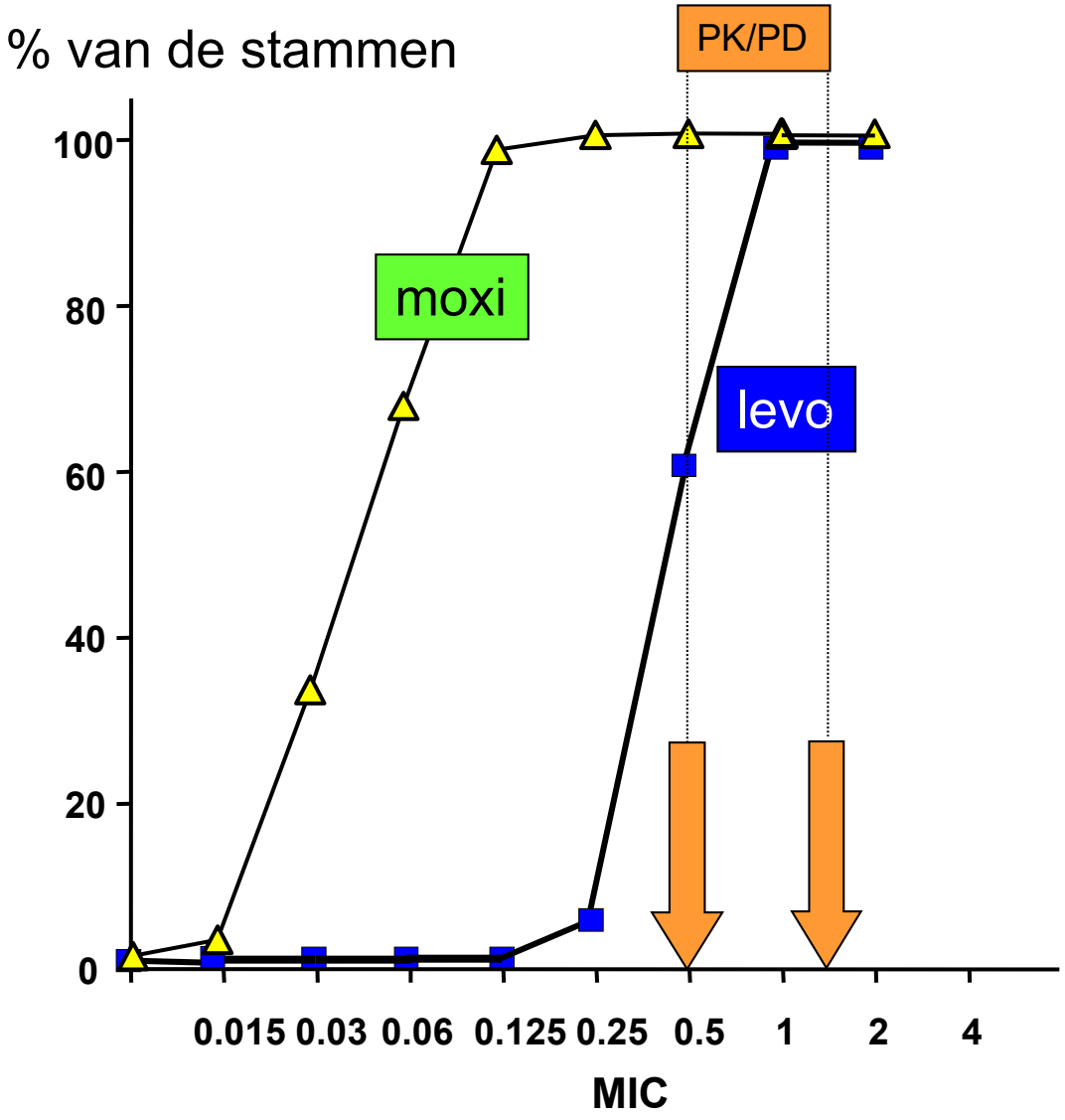


3. Simulatie van AUC/ MIC-verdeling

“Monte Carlo”-simulatie voor pneumococcen (gebaseerd op AUC/MIC)



Vergelijking levofloxacine - moxifloxacine voor pneumococcen in België



Moxifloxacine 400 mg 1x/d

- AUC [(mg/L) x h]: 48
  - ➢ MIC_{max}: ~ 0.4-1.5 *
- piek [mg/L]: 4.5
  - ➢ MIC_{max} : ~ 0.4 **

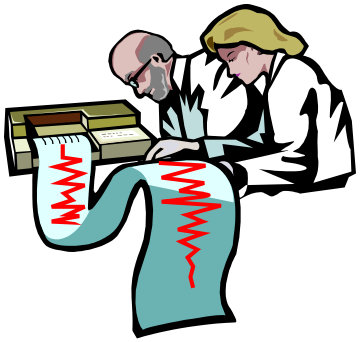
Levofloxacine 500 mg 1x/d

- AUC [(mg/L) x h]: 47
  - ➢ MIC_{max}: ~ 0.5-1.5 *
- piek [mg/L] 5
  - ➢ MIC_{max}: ~ 0.4 **

* AUC/MIC = 30 tot 125
** piek/MIC = 10

MIC gegevens: J. Verhaegen et al., ECCMID 2003
Vergelijkbare warden in 2009 (Vanhoof, ECCMID 2009)
en tussen 1994 en 2014 (Ceyssens et al. PLoS One, 2016: 11:e0154816)

Farmacodynamiek: een mix van verschillende methodes

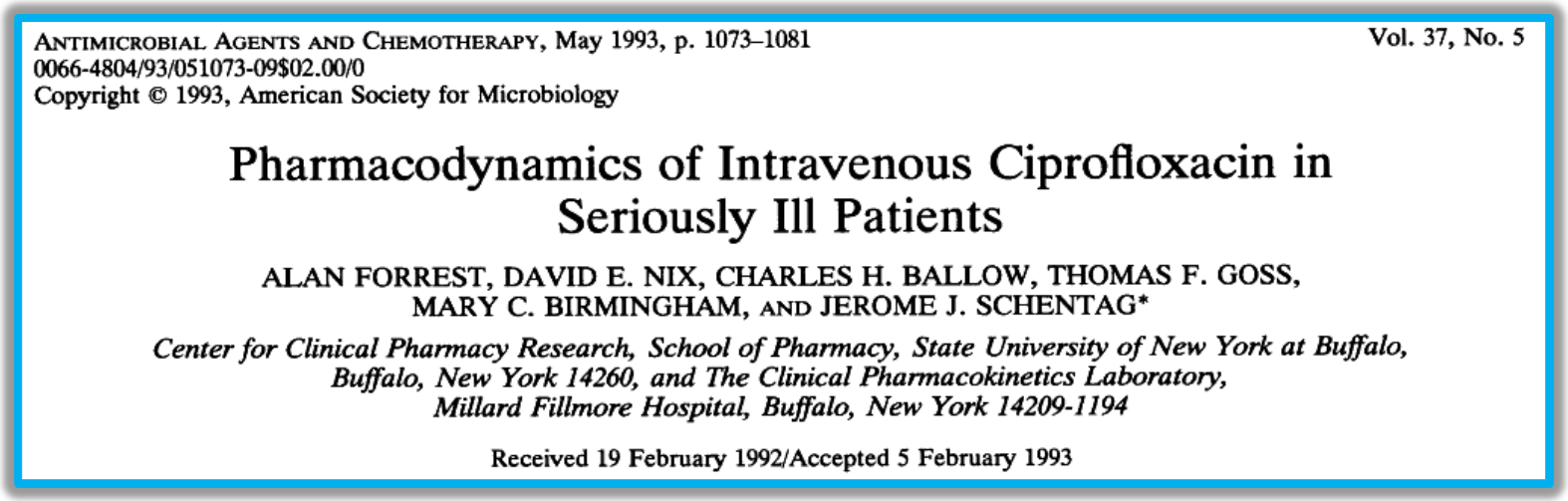


- *in vitro* modellen
- Dierenmodellen
- Klinische studies
- Populatiestudies

Een originele klinische studie…

Fluorochinolonen moeten een voldoende hoge AUC_{24h}/MIC-ratio bereiken (125) voor effectiviteit tegen Gram-negatieve bacteriën te bekomen…

Hoe hebben we dit geleerd ?



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1073–1081 Vol. 37, No. 5
0066-4804/93/051073-09$02.00/0
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Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

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Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194

Received 19 February 1992/Accepted 5 February 1993

Een originele klinische studie…

Fluorochinolonen moeten een voldoende hoge AUC_{24h}/MIC-ratio bereiken (125) voor effectiviteit tegen Gram-negatieve bacteriën te bekomen…

Hoe hebben we dit geleer

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May
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Pharmacodynamic
Se

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Millard Fillmo

Received 1

hier is het !

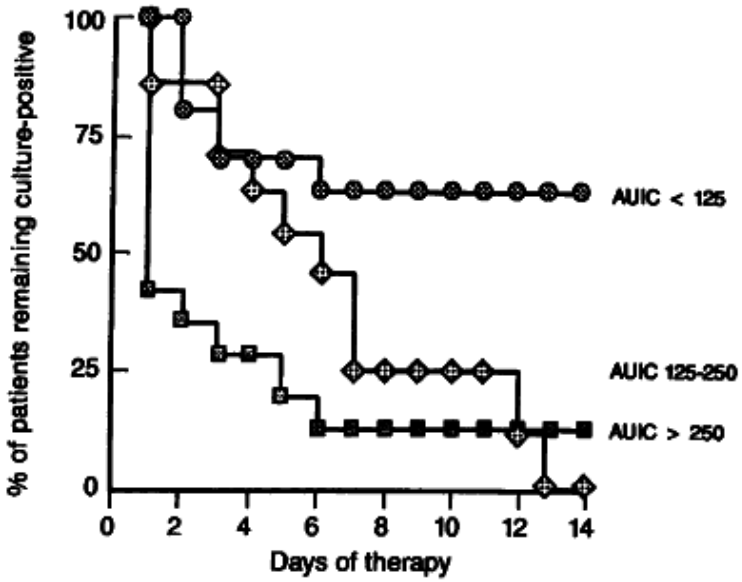


FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).

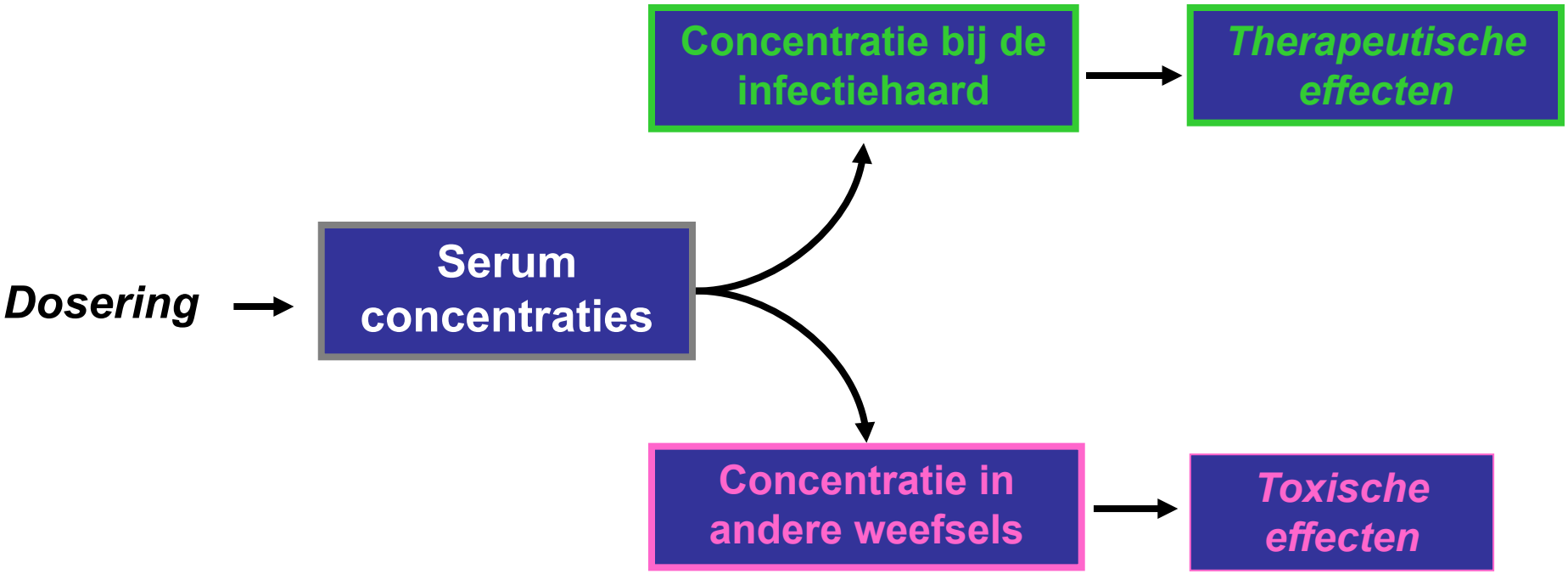
Maar hoe kan IK dit gebruiken?

1. ken het antibioticum en zijn PD parameter
   - ➢ tijd-, AUC_{24h}-, of C_{max}- afhankelijkheid
2. zoek naar de relevante farmacokinetische gegevens voor de aanbevolen dosering…
3. ken de relevante "PK/PD parameter – MIC" verhouding die doeltreffendheid zal bieden
   - – β-lactams: *f* T > MIC = 30 tot 100 % van het dag
   - – aminoglycosiden: C_{max} = 8 x MIC
   - – fluorochinolonen: C_{max} = 10 x MIC en AUC_{24h} = 30-100 MIC
   - – vancomycine: AUC_{24h} = 350 x MIC (en boven)
   - – macroliden: AUC_{24h} = 30 x MIC
   - – tetracyclinen (met tigecycline): AUC_{24h} = 7-10 x MIC
4. kijk of dit in verband is met **uw** epidemiologie… → Vraag aan **uw** microbioloog… zij/hij weet dit

Kijk naar de bijsluiter en publicaties, … of vraag aan de firma… (ze kennen dat !)

Farmacokinetiek

Farmacodynamiek



Waar zijn we aanbeland? ...

1. Basis microbiologische parameter: MIC

2. Farmacokinetiek (PK) en Farmacodynamiek (PD)
   het concept en de methode
   het gebruik van de grootste antibioticaklassen

3. **Toepassingen**
   - **EUCAST breekpunten**
   - **Therapeutic Drug Monitoring**
   - **continu infuus**

4. Resistentie

5. Enkele woorden over toxiciteit

6. Geselecteerde referenties

Breekpunten?

Vérité en-deçà des Pyrénées, erreur au-delà.

The frontispiece of Geert Hofstede's influential book, *Culture's consequences: Comparing values, behaviors, institutions, and organizations across nations* (Hofstede, 2001) includes the following quote: "Vérité en-deça des pyrénées, erreur au-delà". Written about 350 years ago by the French mathematician and physicist Blaise Pascal and included in his *Pensées*, Hofstede's translation is "There are truths on this side of the Pyrenees that are falsehoods on the other."

Waarvoor dienen breekpunten?

Om eerlijk te zijn, heb ik het mij al dikwijls afgevraagd…

Wat is een breekpunt?

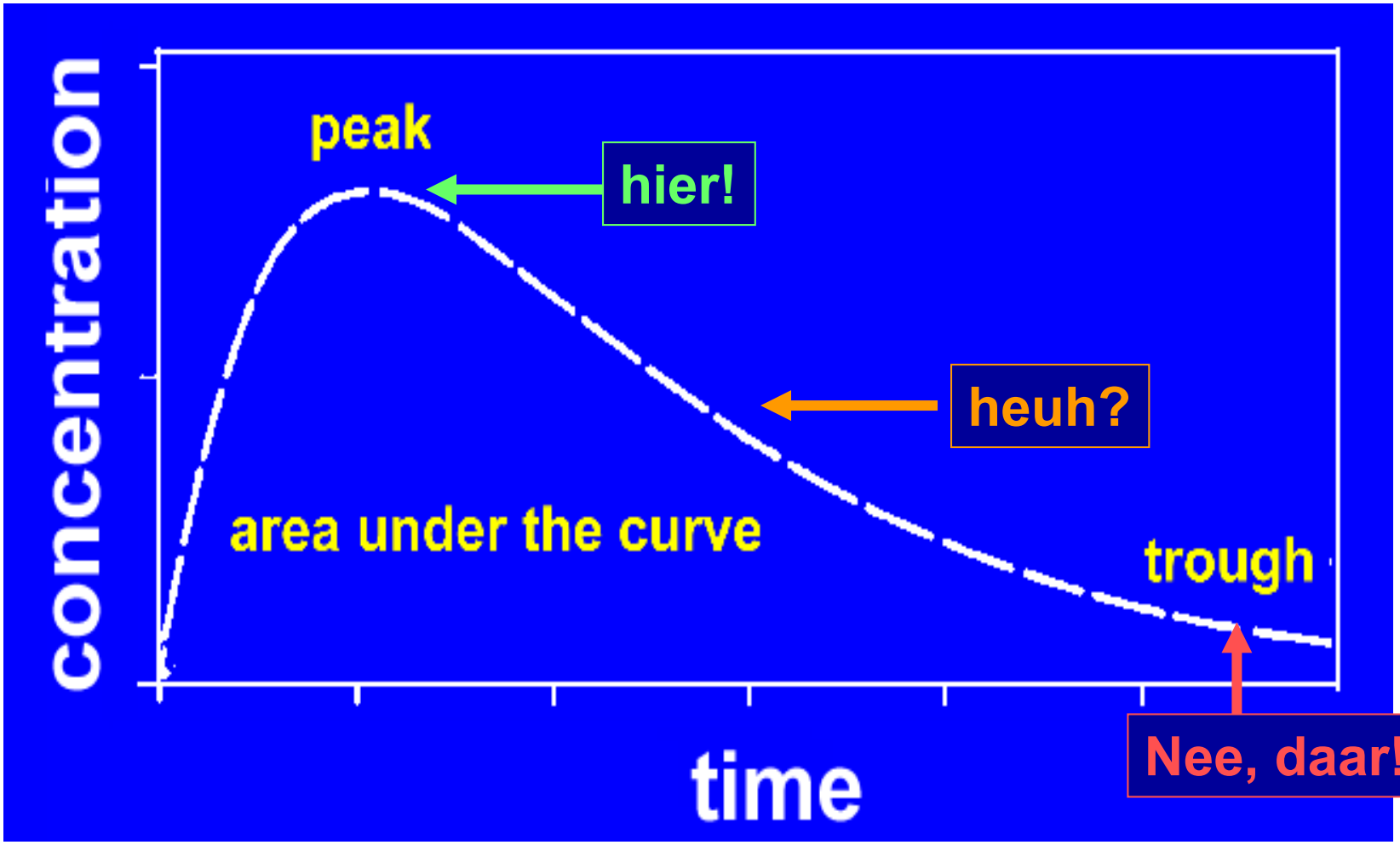
- Een ‘magisch getal’ dat ***in vitro*** bepaald wordt door de microbioloog en dat tot doel heeft te voorspellen of het antibioticum doeltreffend zal zijn ***in vivo.***
- De in vitro verkregen waarden vormen een continue functie. Het verkregen cijfer wordt echter als volgt geïnterpreteerd...
  - gevoelig … **(S)**
  - intermediair… **(I)**
  - resistent … **(R)**

en dit is wat de **clinicus** zal krijgen

Ja, dan moesten normaal de breekpunten PK/PD in rekening brengen …

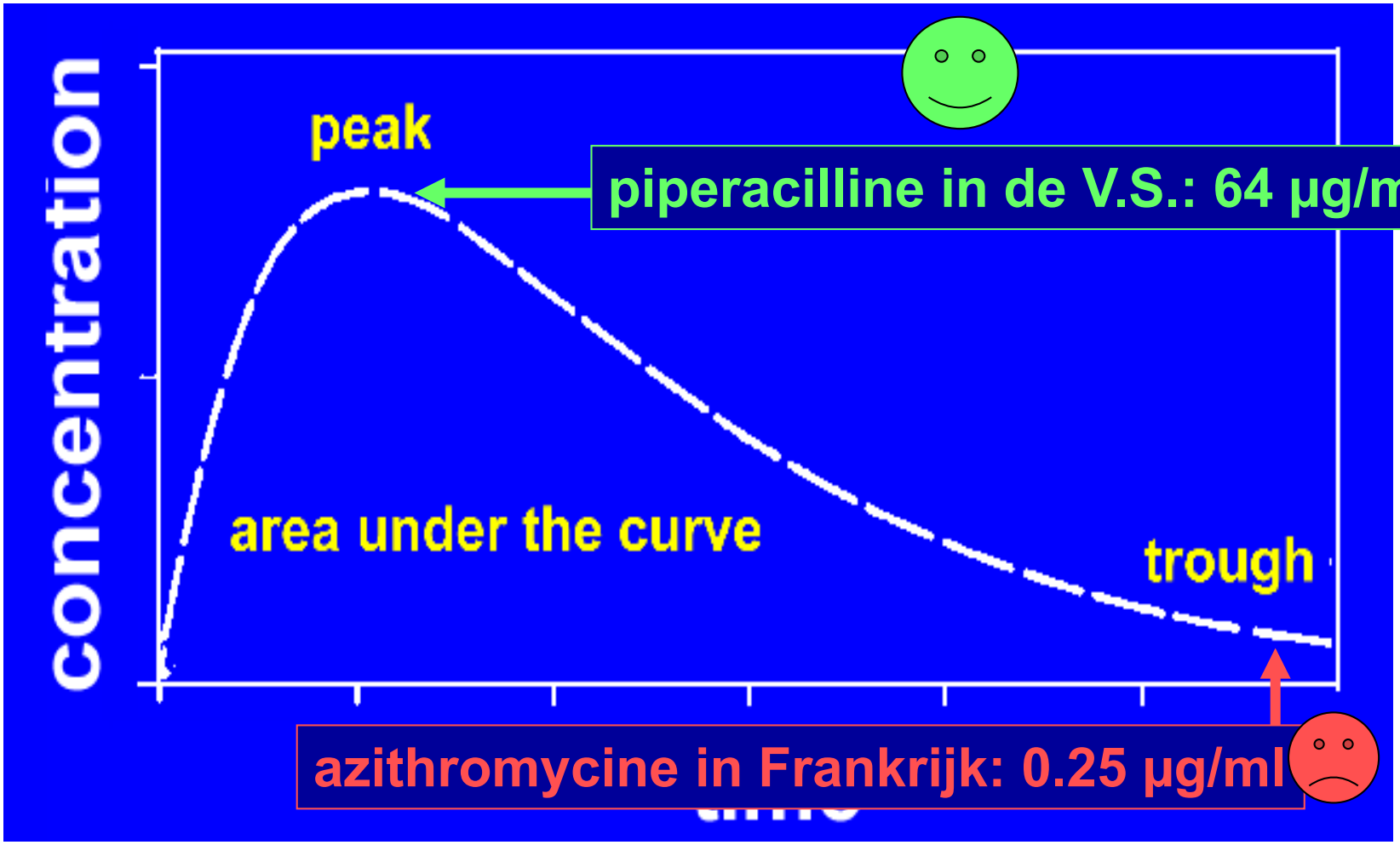
[1] kan omgezet worden in een MIC (zie verder); geautomatiseerde systemen gebruiken groeisnelheid…

Waar moet het breekpunt liggen ten opzichte van de serum concentratie?

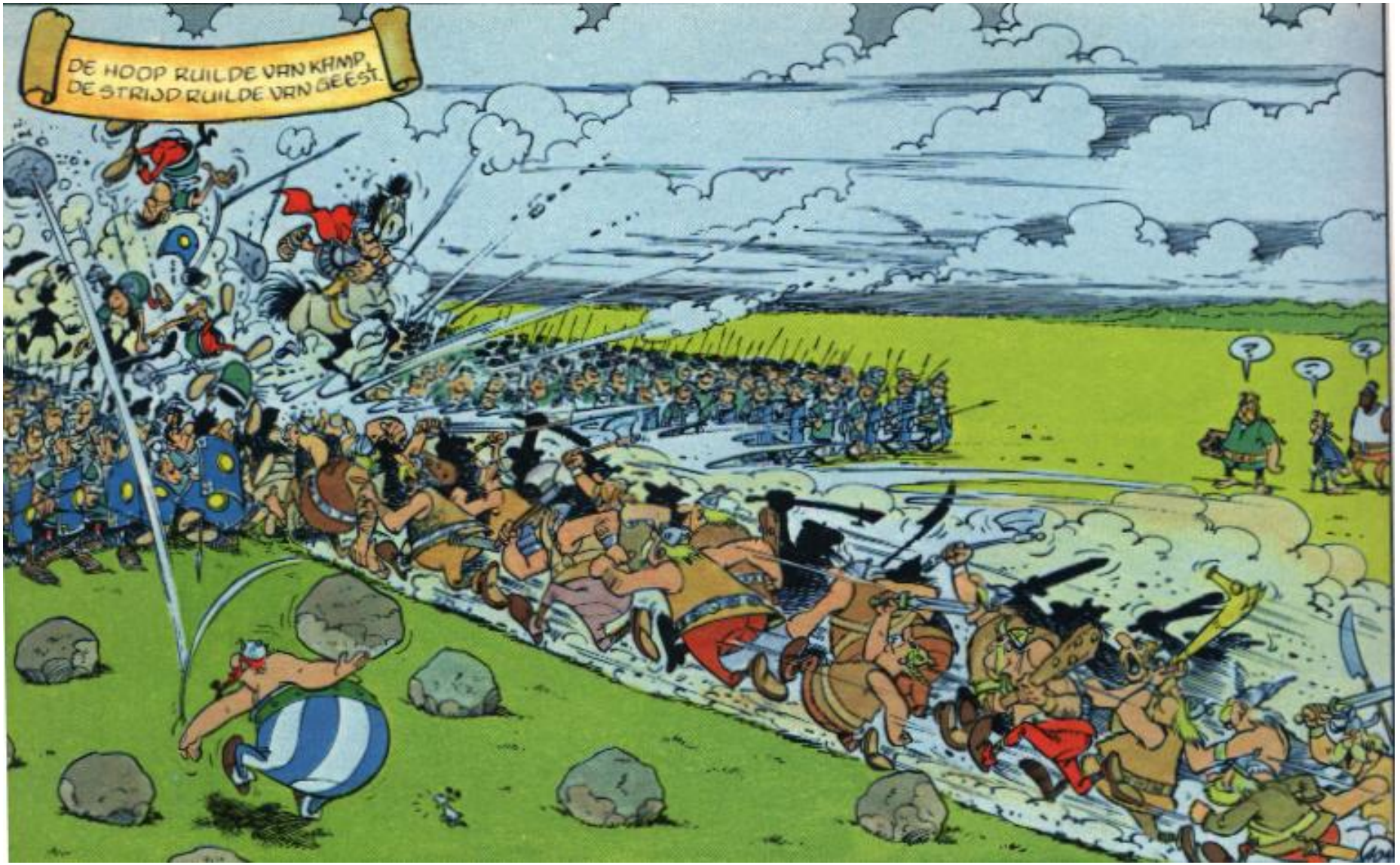


Piek of Dal?

Oude breekpunten: nog een voorbeeld van de verschillen tussen Amerikanen en Fransen !



Maar ook tussen de Europeanen onderling…



Naar Mouton, 8th ISAP symposium, Nijmegen, 2001

Wat was HET probleem?

- Europa had verschillende nationale breekpuntcommissies… en daardoor verschillende breekpunten voor eenzelfde antibioticum… *

- De Amerikaanse breekpunten werden door het NCCLS** vastgesteld. Maar deze waren:
  - niet (altijd) rationeel en realistisch (te hoog!)
  - beïnvloed door de specifieke Amerikaanse situatie (dosering, resistentiepatronen, industrie, enz…)
  - en… verschillend van de nationale breekpunten in Europa

---

* Bij gebrek aan een nationale commissie, gebruikten Belgische microbiologen meestal de NCCLS breekpunten…

** *National (US) Committee for Clinical Laboratory Standards* (nu CLSI)

Een eenvoudig voorbeeld

cefotaxime vs *E.coli*		S≤ / R
BSAC	Verenigd Koningrijk	2 / ≥4
CA-SFM	Frankrijk	4 / >32
CRG	Nederland	4 / >16
DIN	Duitsland	2 / ≥16
NWGA	Noorwegen	1 / ≥32
SRGA	Zweden	0.5 / ≥2
NCCLS	V.S.	8 / ≥64

Desalniettemin gebruikten microbiologen deze breekpunten dagelijks om clinici in te lichten over de gevoeligheid van de bacteriën die zij moesten bestrijden

Wat is EUCAST?

European Committee on Antimicrobial Susceptibility Testing

In het kort!

- in 1997 opgestart
- met steun van
  - *European Society for Clinical Microbiology and Infectious Diseases* (ESCMID)
  - Nationale Breekpuntcommissies in Europa (GB, F, D, NL, N, S)
- *Standard operating procecure agreement* met EMA (*European Medicienes Agency*) voor definitie en vaststelling van breekpunten voor alle nieuwe moleculen

PK-PD en breekpunten vaststelling

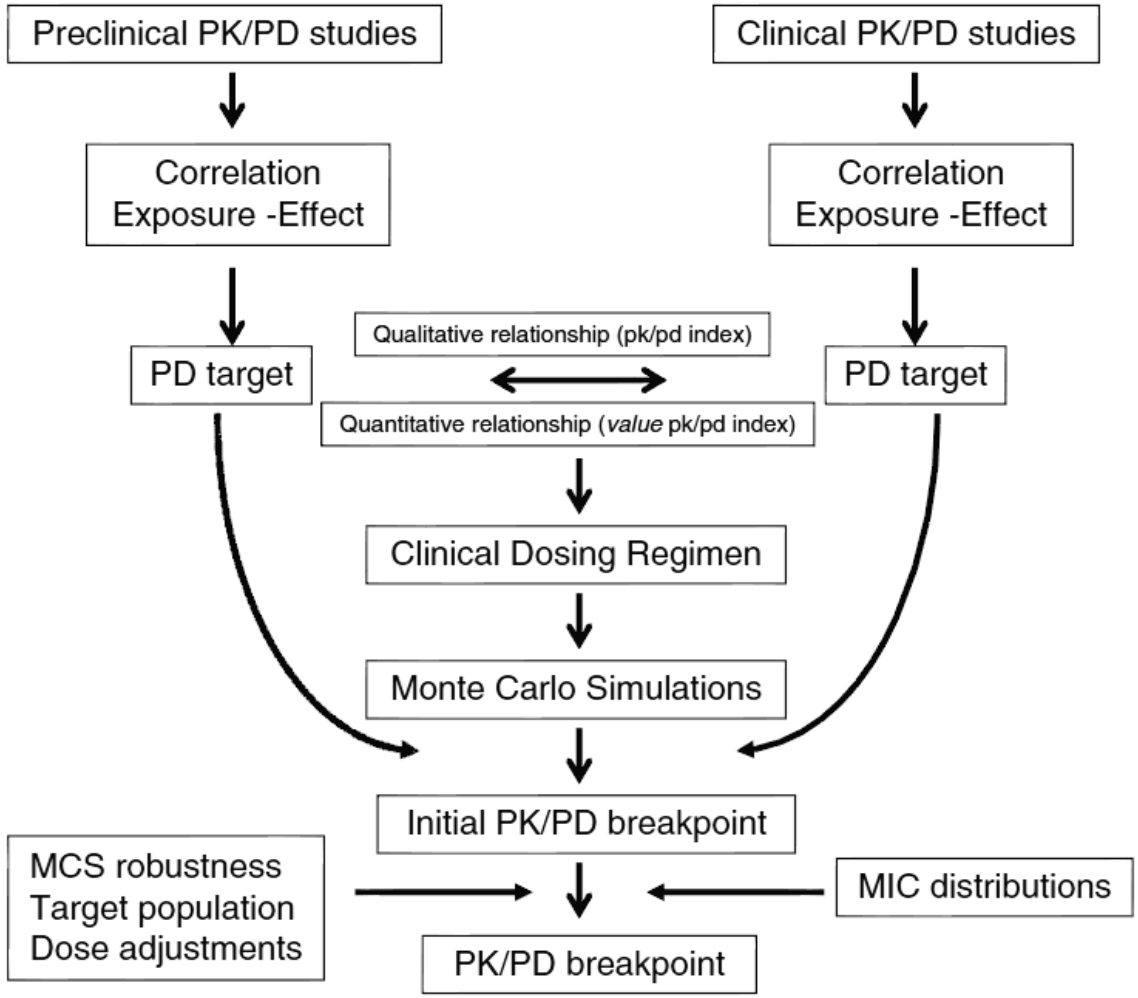


Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, Vinks, Derendorf & Mouton, eds., 2013, Springer

zie zip

Breakpoint instelling: de EUCAST weg

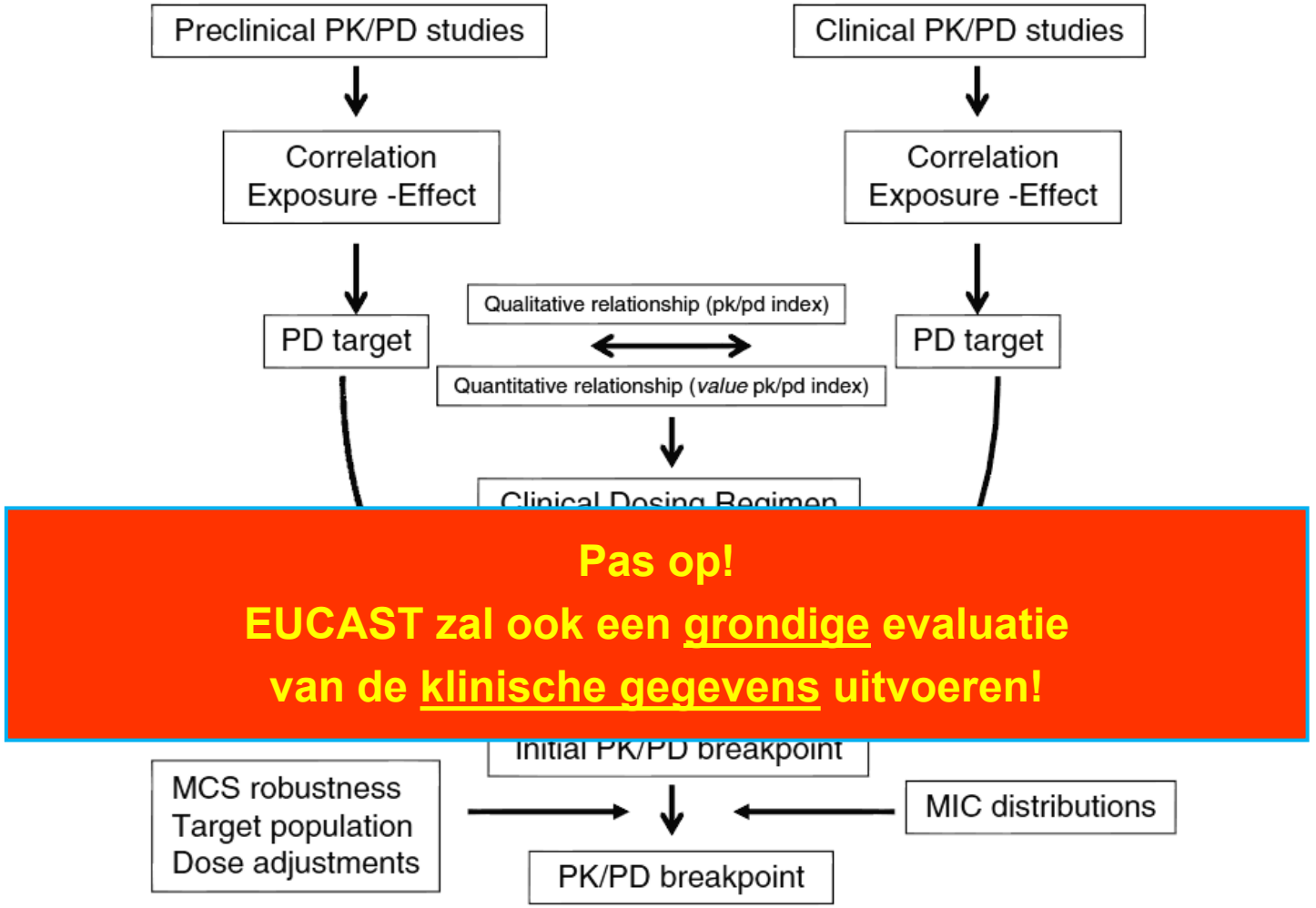


Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, Vinks, Derendorf & Mouton, eds., Springer

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Het resultaat… (op http://www.eucast.org)

Enterobacteriaceae

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin	0.5	1	5	22	19
Ciprofloxacin, *Salmonella* spp.[1]	0.06	0.06		Note[A]	Note[A]
Pefloxacin (screen), *Salmonella* spp.[1]	NA	NA	5	24[B]	24[B]
Levofloxacin	1	2	5	22	19
Moxifloxacin	0.5	1	5	20	17
Nalidixic acid (screen)	NA	NA		NA	NA
Norfloxacin	0.5	1	10	22	19
Ofloxacin	0.5	1	5	22	19

Bron: http://www.eucast.org/clinical_breakpoints/

zie zip

Deze zijn VEEL lager dan 2015 CLSI breekpunten die S ≤1 and R > 4 voor ciprofloxacine en S ≤2 and R > 8 voor ofloxacine zijn

maar dicht bij de PK/PD breekpunten…

PK/PD breekpunten voor fluorochinolonen

Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (µg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[l]	
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.5-1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.5-1
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.5-1
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	1-2
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.5-1

EUCAST breekpunten

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Voor welke antibiotica zijn breekpunten beschikbaar?

EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

- Organization
- EUCAST News
- **Clinical breakpoints**
- Expert rules
- Setting breakpoints
- MIC distributions
- Zone diameter distributions
- Antimicrobial susceptibility testing
- Antifungal susceptibility testing (AFST)
- Frequently Asked Questions (FAQ)
- Meetings
- EUCAST Presentations
- Documents
- Information for industry
- Links

Clinical breakpoints

Clinical breakpoints are for everyday use in the clinical laboratory to a
therapy.
In EUCAST tables, the I-category is not listed. It is implied as the value
S-breakpoint and the R-breakpoint.
For a breakpoint listed as S<=1 mg/L and R>8 mg/L the intermediate category is 2 - 8 (technically >1 - 8) mg/L.
For a breakpoint listed as S>=22 mm and R<18 mm the intermediate category is 18-21 mm.

Clinical breakpoints - bacteria (v 2.0) - pdf file for printing (2012-01-01)
Clinical breakpoints - bacteria (v 2.0) - Excel file for screen (2012-01-01)
A new set of tables for antibacterials were uploaded on Feb 23, 2012, only because all links to MIC distributions were updated because the database was moved.

Ceftaroline clinical MIC and zone diameter breakpoints (addendum 3 October, 2012). Work to determine zone diameter breakpoints for other species than *S. aureus* is ongoing.

Breakpoints published in Addendum during the year will be part of the next version of the full Clinical breakpoint tables valid from early January each year.

voor (bijna) alle antibiotica zijn EUCAST breekpunten nu vrij beschikbaar op http://www.eucast.org (surf naar "Clinical breakpoints")

Ook de meest recente!

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST

Enterobacteriaceae

Cephalosporins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefepime	1	4	30	24	21
Ceftazidime	1	4	10	21	18
Ceftriaxone	1	2	30	23	20

Bron: http://www.eucast.org/clinical_breakpoints/

zie zip

Waarom zo laag?

Herinnering:

PK / PD - kritisch punt voor een β-lactam IV was 8 µg/ml...

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EUCAST

Cephalosporins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
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Ceftazidime	1	4	10	21	18
Ceftriaxone	1	2	30	23	20

Bron: http://www.eucast.org/clinical_breakpoints/

zie zip

Waarom zo laag?

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

Om ESBL met te hoge MIC uit te sluiten...

En voor *Pseudomonas*…

Pseudomonas spp.

	MIC breakpoint (mg/L)	
	S ≤	R >
Piperacillin[1]	16	16
Piperacillin-tazobactam[1,2]	16	16
Ticarcillin[3]	16	16
Ticarcillin-clavulanate[2, 3]	16	16
Cefepime	8[1]	8
Ceftazidime	8[1]	8
Doripenem	1	4
Ertapenem	-	-
Imipenem	4[1]	8
Meropenem	2	8
Ciprofloxacin	0.5	1
Levofloxacin	1	2

Oude piperacilline NCCLS breekpunten voor *Pseudomonas* waren S ≤ 64 en R ≥ 128 !!!

Bron: http://www.eucast.org/clinical_breakpoints/

zie zip

Kortom, het gebruik van EUCAST beekpunten zal u helpen om:

- "*zonder iets te weten en op te merken*" PK/PD in uw omgeving te introduceren

- de clinici beter te adviseren over de verwachte doeltreffendheid in verband met de lokale epidemiologie en de gebruikte antibiotica

Opgepast: nieuwe definities van EUCAST sinds 2019…

- ***S - Susceptible, standard dosing regimen:***
  A microorganism is categorized as "susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.

- ***I - Susceptible, increased exposure*:***
  A microorganism is categorized as "susceptible, increased exposure" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.*

- ***R - Resistant:***
  A microorganism is categorised as "resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

Opgepast: nieuwe definities van EUCAST sinds 2019…

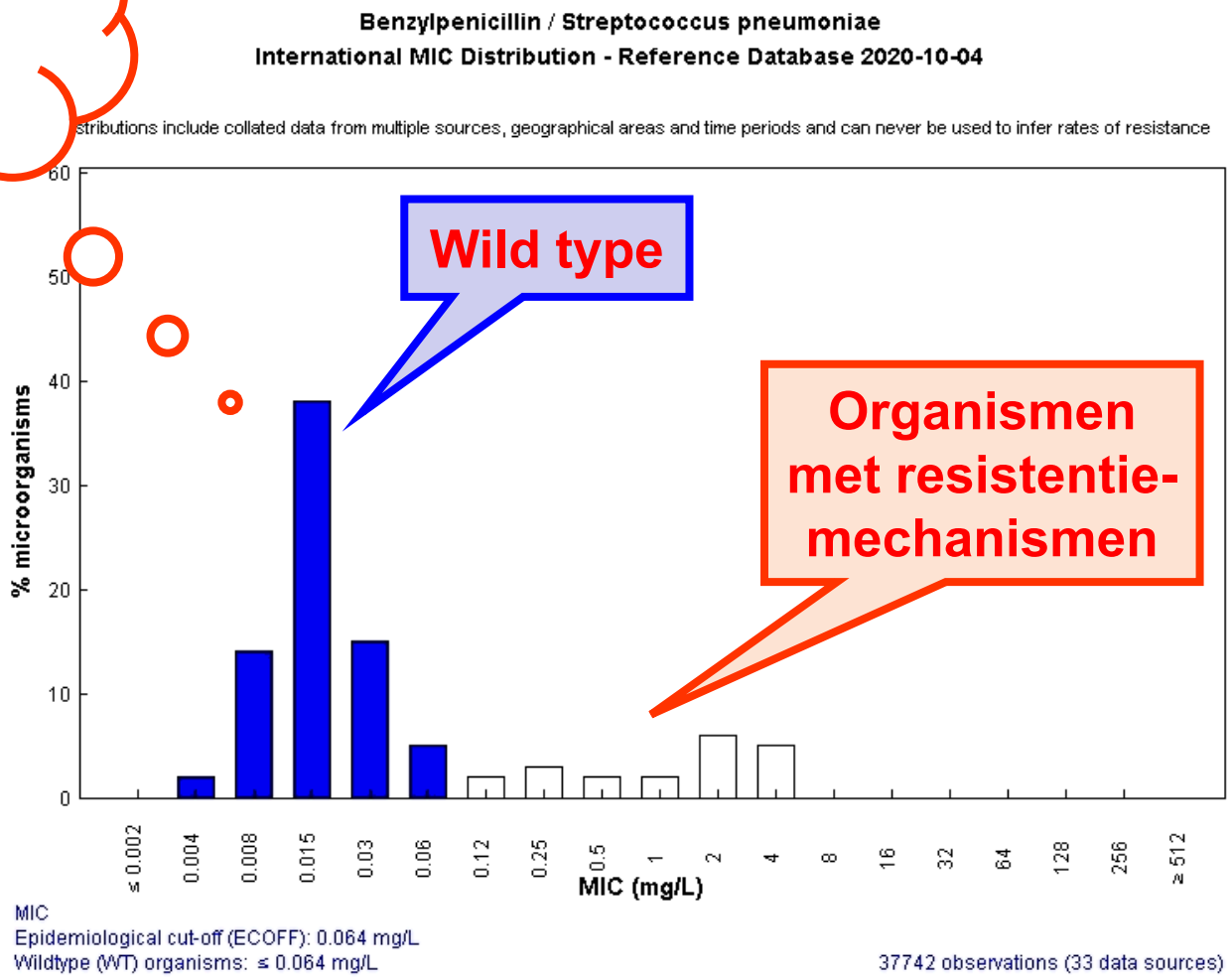
- ***S - Susceptible, standard dosing regimen:***
  Een micro-organisme wordt gecategoriseerd als "gevoelig, standaard doseringsregime", wanneer er een grote kans is op therapeutisch succes bij gebruik van een standaard doseringsregime

- ***I - Susceptible, increased exposure**:*
  *Een micro-organisme wordt gecategoriseerd als "gevoelig, verhoogde blootstelling *" wanneer de kans op therapeutisch succes groot is, omdat de blootstelling aan het medicijn wordt verhoogd door het doseringsschema aan te passen... of door de concentratie hiervan op de infectieplaats.*
- ***R - Resistant:***
  Een micro-organisme wordt gecategoriseerd als "resistent" wanneer de kans op therapeutisch falen zeer groot is, zelfs bij verhoogde blootstelling.

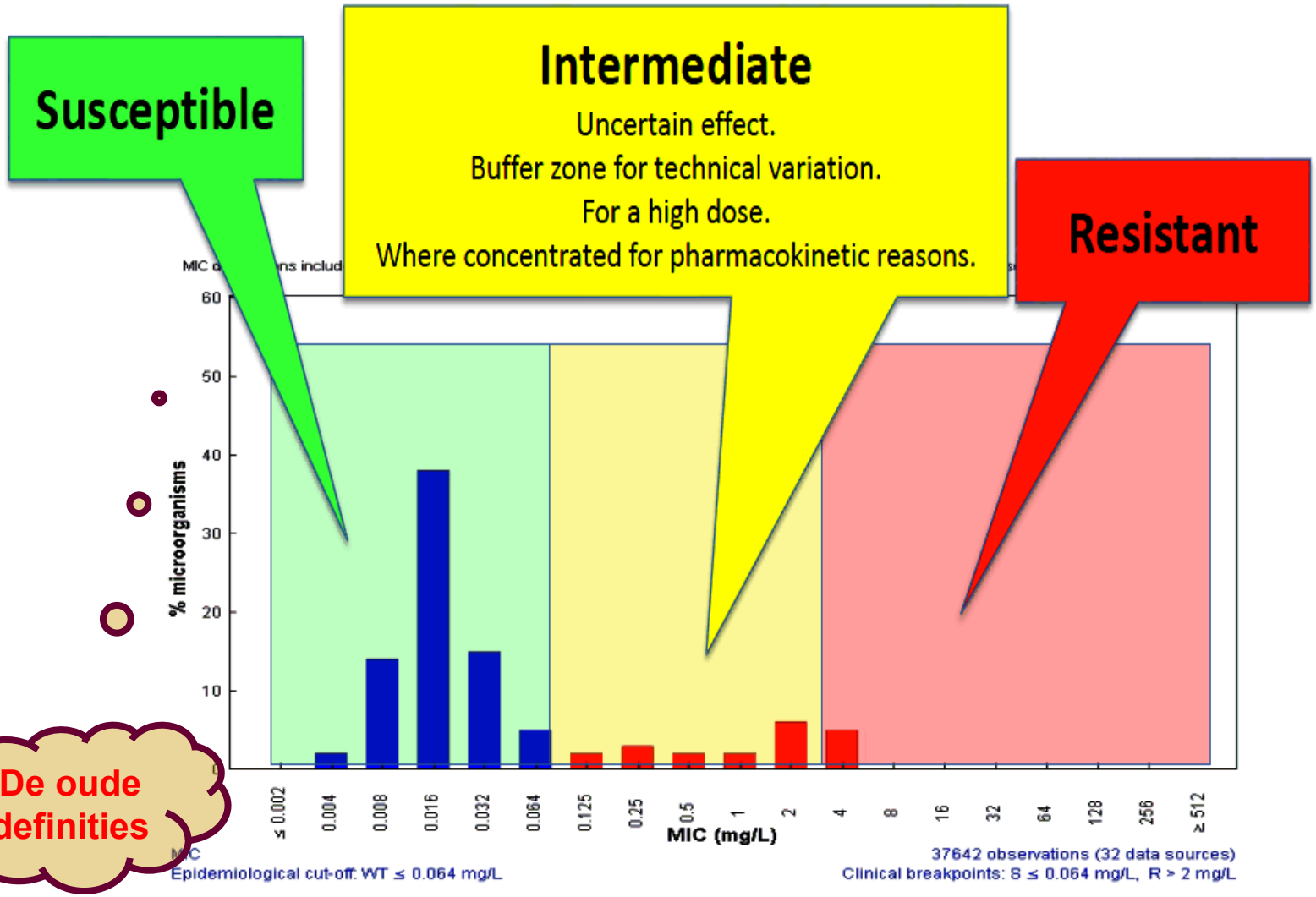
Oude en Nieuwe S-I-R:
Benzylpenicllin en *S. pneumoniae* als voorbeeld...

NEW!

1. MIC verdeling



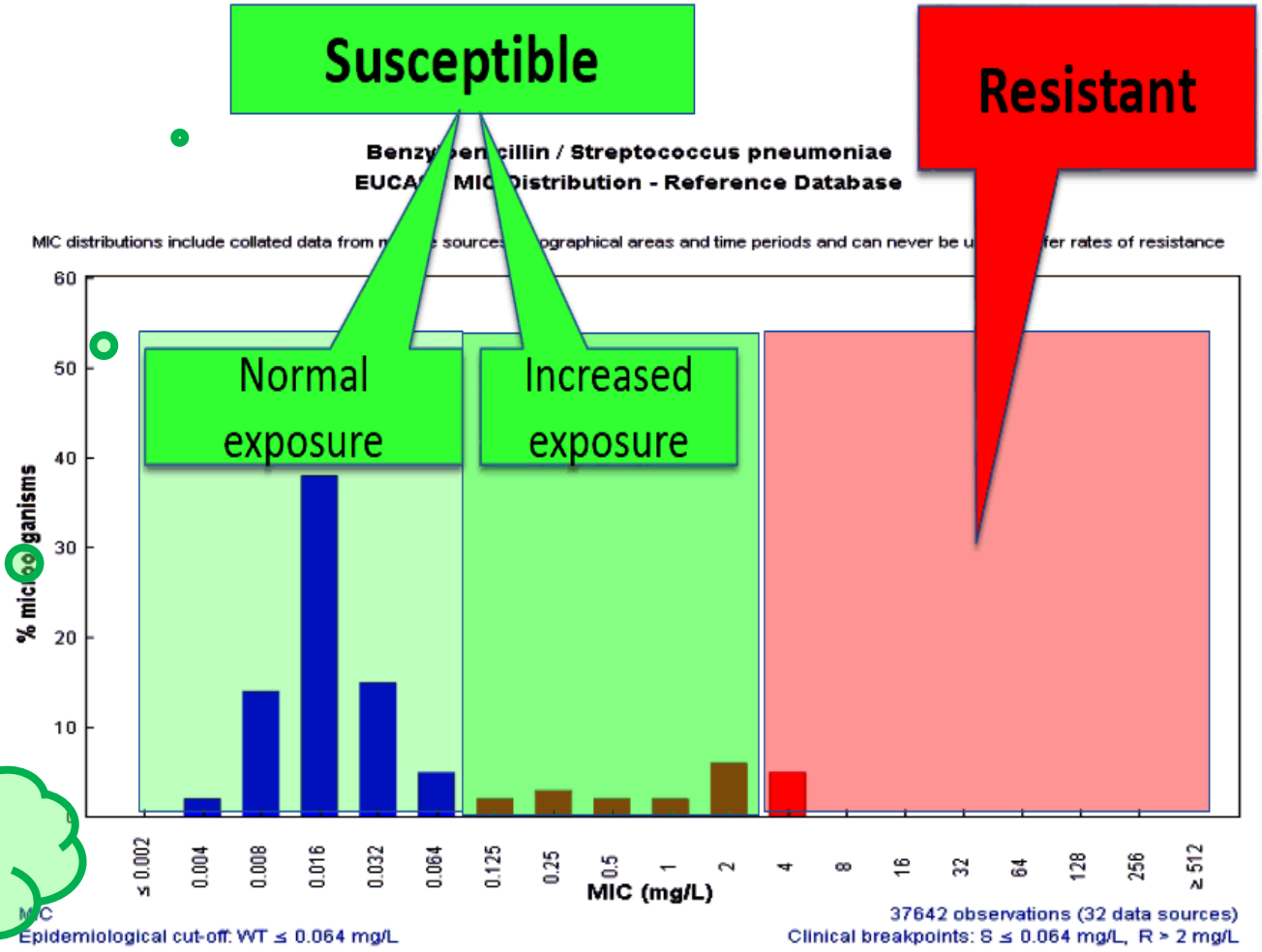
Oude en Nieuwe S-I-R:
Benzylpenicllin en *S. pneumoniae* als voorbeeld...



NEW!

De oude definities

Oude en Nieuwe S-I-R:
Benzylpenicllin en *S. pneumoniae* als voorbeeld...



De nieuwe definities

Maar what is "*exposure* / bloodstelling"?

Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

Blootstelling is een functie van hoe de wijze van toediening, **dosis**, **doseringsinterval**, **infusietijd**, evenals **distributie** en **uitscheiding** van het antimicrobiële middel het infecterende organisme op de infectieplaats zullen beïnvloeden.

Dit betekent PK/PD...

Maar what is "*exposure* / bloodstelling" ?

Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

Blootstelling is een functie van hoe de wijze van toediening, **dosis**, **doseringsi** **ling** van het ant infectieplaa

Video van Gunnar, oprichter van EUCAST, waarin hij de redenen en implementatie van deze veranderingen uitlegt
(zie ook: https://eucast.org/newsiandr/)

Voorbeeld: temocilline

Enterobacterales breakpoints are valid only for E. *coli*, *Klebsiella* spp. (except *K. aerogenes*), *P. mirabilis*: S ≤0.001, R >16 mg/L
The R breakpoint is the same as the ECOFF for most target species. The wild-type population has been placed in the I group to emphasise the need for high exposure to cover the entire wild-type (1 – 16 mg/L) of relevant species.

Clinical breakpoints for temocillin have (following general consultation 2019) been set by EUCAST as follows:

Organisms	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Enterobacterales (*E. coli*, *Klebsiella* spp. (except *K. aerogenes*), *P. mirabilis* only)	0.001	16	30	50[1]	17[1]
PK/PD (non-species related) breakpoints	IE	IE	-	-	-

[1] Ignore isolated colonies within the inhibition zone.

Voorbeeld: temocilline

Dosage	Breakpoints apply to high-exposure dosing regimen of 2 g x 3 iv
Additional comment	Data from mouse non-severe pyelonephritis model supports a breakpoint of R > 16 mg/L, but only with a dosing regimen of 2 g x 3. An "R" breakpoint below 16 mg/L i(for example 8 mg/L, which has been used by some countries) would split the wild type of the relevant species believed to be good targets for temocillin. Using a target %*f*T>MIC of 35%, satisfactory target attainment rates can only be achieved in systemic infections using doses of 2 g every 8 hours, i.e. doses above those currently licensed. High urinary concentrations may permit the use of lower-exposure dosing regimens such as 2g every 12 hours for lower urinary tract infections complicated by comorbidities or caused by species resistant to other drug classes.

Reference. Temocillin Rationale Document v1.0 (http://www.eucast.org/documents/rd/)

Voorbeeld: temocilline

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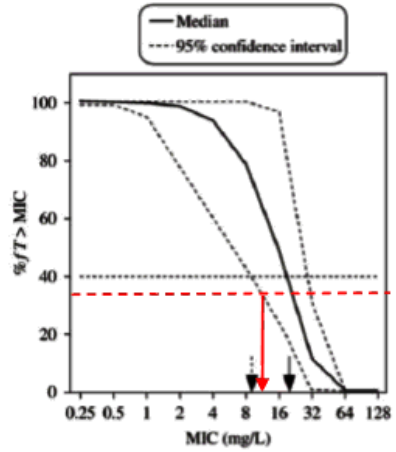
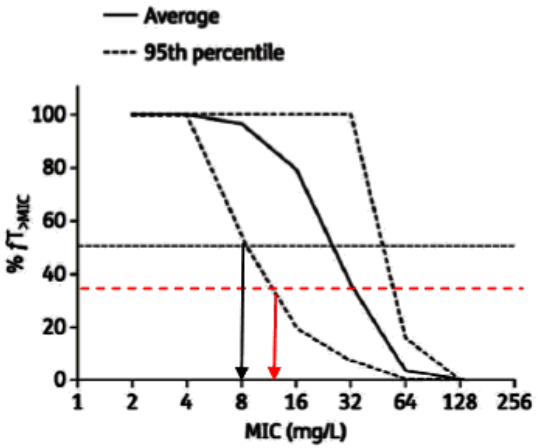
6. Monte Carlo simulations and Pk/Pd breakpoints

Temocillin 2g x 2 (De Jongh et al., JAC 2016)



	fT>MIC (in %) of free temocillin (2 g) given		
MIC (mg/L)	q24 h	q12 h	q8 h
0.50	100.00	100.00	100.00
1.00	87.50	100.00	100.00
2.00	70.60	100.00	100.00
4.00	53.70	100.00	100.00
8.00	36.70	79.70	100.00
16.00	19.40	45.10	80.30
32.00	1.60	9.50	26.90
64.00	0.00	0.00	0.00

Temocillin 2g x 3 (Laterre et al., JAC 2016)



Voorbeeld: temocilline

Journal of Antimicrobial Chemotherapy (2008) **61**, 382–388
doi:10.1093/jac/dkm467
Advance Access publication 10 December 2007

JAC

Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection

Raf De Jongh[1], Ria Hens[1], Violetta Basma[2], Johan W. Mouton[3], Paul M. Tulkens[2]* and Stéphane Carryn[2]

[1]Dienst Voor Intensieve Zorgen, Ziekenhuis Oost-Limburg, B-3600 Genk, Belgium; [2]Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, B-1200 Bruxelles, Belgium; [3]Afdeling Medische Microbiologie en Infectieziekten, Canisius Whilhemina Ziekenhuis, NL-6500 GS Nijmegen, The Netherlands

Voorbeeld: temocilline

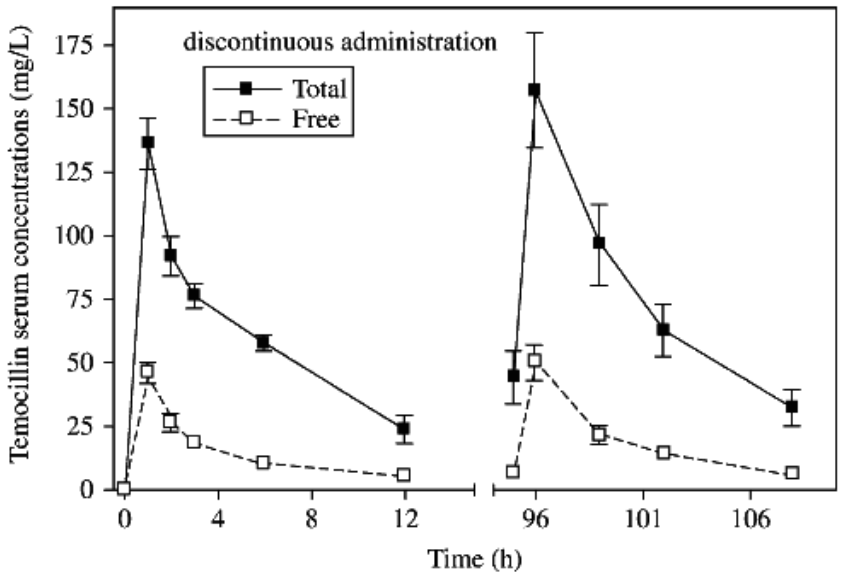


Figure 1. Serum concentrations (total and free) of temocillin in patients receiving temocillin. Upper panel: patients received 2 g every 12 h (discontinuous administration) with samples taken after the first administration (0–12 h) and 1 h before and after the ninth administration (95–108 h). Lower panel: patients received a loading dose of 2 g followed

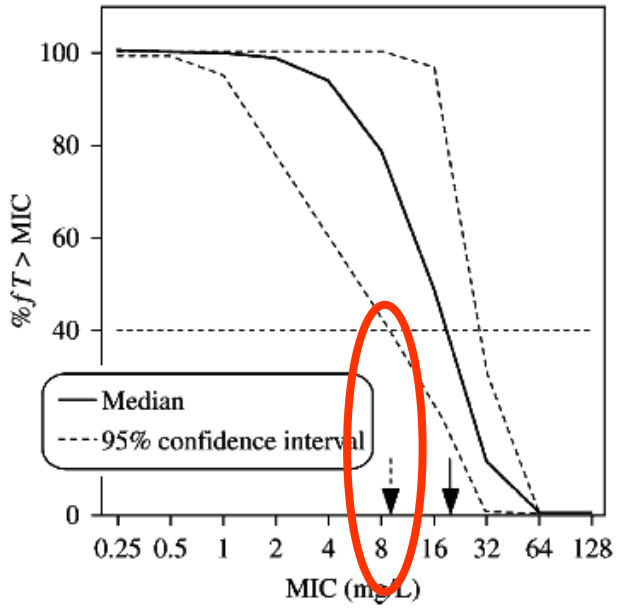


Figure 2. Probabilities of target attainment of temocillin (as obtained with the Monte Carlo simulation: solid line, median value; dotted lines, 95% confidence interval) for the currently registered treatment (2 g every 12 h), using the pharmacokinetic data of the six patients treated according to this dosage and schedule in this study (twice daily group). The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a percentage) during which free serum levels remain above the corresponding MIC. The horizontal dotted line indicates the 40% $fT >$ MIC limit achieving a bacteriostatic effect and survival for penicillins in animal models with Gram-negative bacteria.[1] The highest MIC at which this target will be obtained is shown by the vertical arrows (arrow with solid line, median; arrow with dotted line, 95% probability).

2g elke 12u
Intensieve zorgen,
Z. Oost-Limburg

Voorbeeld: temocilline

J Antimicrob Chemother 2015; **70**: 891–898
doi:10.1093/jac/dku465 Advance Access publication 27 November 2014

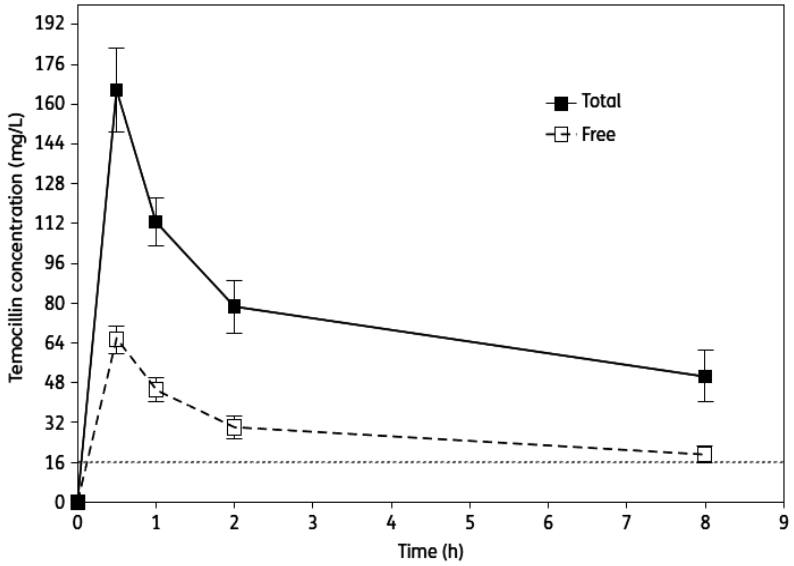
Journal of Antimicrobial Chemotherapy

Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration

Pierre-François Laterre[1], Xavier Wittebole[1], Sebastien Van de Velde[2]†, Anouk E. Muller[3], Johan W. Mouton[4], Stéphane Carryn[2]‡, Paul M. Tulkens[2]* and Thierry Dugernier[1,5]

[1]Department of Critical Care Medicine, St Luc University Hospital, Université catholique de Louvain, Brussels, Belgium; [2]Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [3]Department of Medical Microbiology, Medical Centre Haaglanden (MCH), Den Haag, The Netherlands; [4]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; [5]Department of Critical Care Medicine, St Pierre Hospital, Ottignies, Belgium

Voorbeeld: temocilline



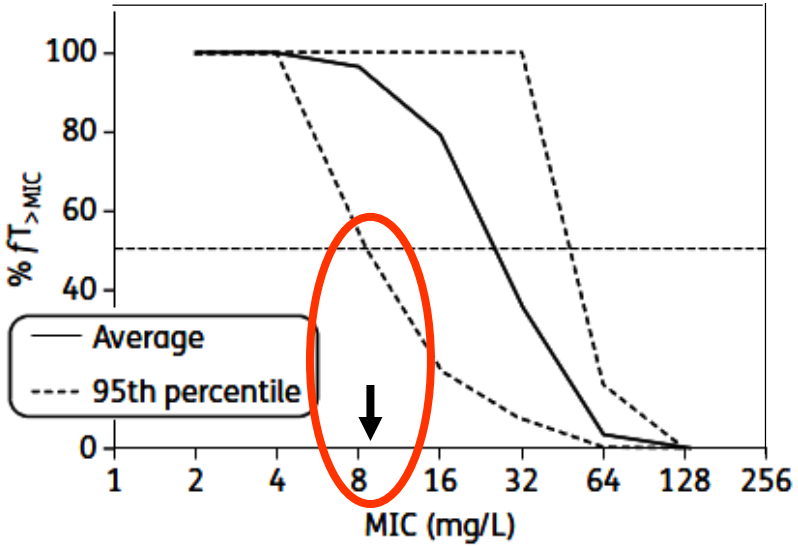


Figure 3. Probabilities of target attainment of temocillin (as obtained with the Monte Carlo simulation) for discontinuous administration of a 6 g daily dose divided into three administrations at 8 h intervals (three times daily). The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a percentage) during which free serum levels remain above the corresponding MIC. The horizontal broken line indicates the 50% $fT_{>MIC}$ limit achieving a bacteriostatic effect and survival for penicillins in animal models with Gram-negative bacteria.[26]

2g elke 8 u
Intensieve zorgen,
Z. St-Luc, Brussel

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Hoe zullen de EUCAST breekpunten in de praktijk ingevoerd worden (bestaande antibiotica)?

- Breekpunten van EUCAST kunnen onmiddellijk door iedereen gebruikt worden op basis van MIC…
- De nationale commissies (GB, F, NL, D, N, S) hebben zich ertoe verbonden om de breekpunten van EUCAST in hun respectievelijke landen te implementeren… en de andere landen volgen nu…
- Het merendeel van de automatische systemen kan vanaf nu geherprogrammeerd worden om breekpunten van EUCAST te gebruiken
  (details op http://www.eucast.org/ast_of_bacteria/compliance_of_manufacturers/)
- Er is nu een Europese standaard voor antibioticum disks beschikbaar

Alle details (en meer) zijn te vinden op **http://www.eucast.org**

En wat voor België / Et en Belgique?

Il y a eu beaucoup de discussions…

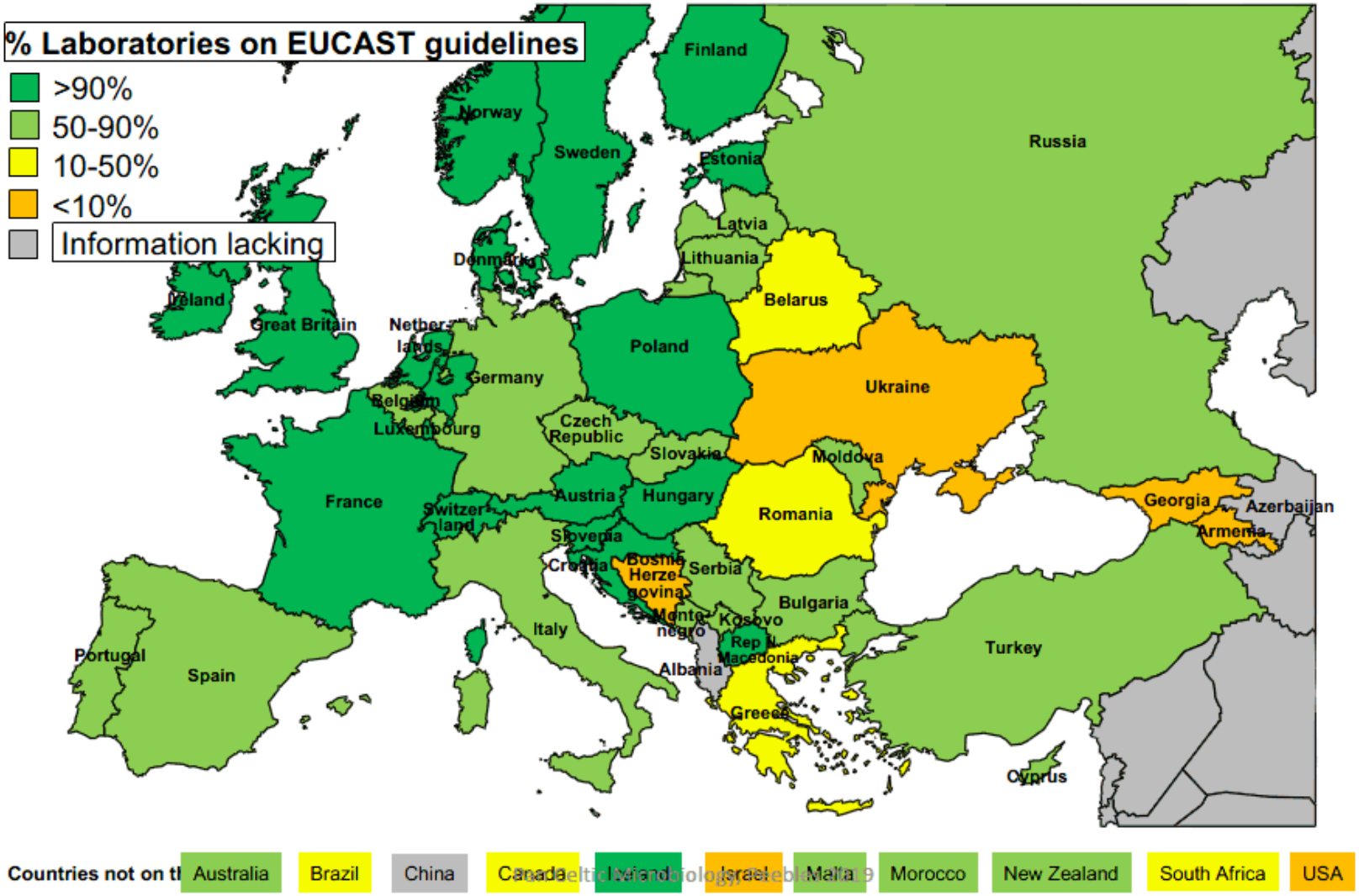
De *Belgische Vereniging voor Infectiologie en Klinische Microbiologie /Société belge d'infectiologie et de microbiologie clinique* heeft de operatie gestuurd…

Er bestaat nu een Belgische "*National Antibiotic Committee*" (NAC; niet te verwarren met BAPCOC) om de lokale situatie op de voet op te volgen en mogelijke problemen op te lossen…

De meeste labo's zijn nu veranderd van CLSI naar EUCAST!

Les francophones en de Nederlandstaligen gaan akkoord!!

Implementation of EUCAST breakpoints/guidelines, May 2019



EMEA – EUCAST SOP

European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
PUBLIC		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

Voor alle nieuwe moleculen zijn de EUCAST breekpunten de
finale officiële Europese breekpunten…

EMEA – EUCAST voor nieuwe antibiotica

- Antibiotica die al geregistreerd werden met EUCAST breekpunten
  - Tigecycline
  - Daptomycine
  - Telavancine
  - Ceftaroline
  - Ceftobiprole (decentralized procedure)
  - Bedaquilin (antituberculosis agent)
  - Ceftozolane/tazobactam (antipseudomonal cephalosporin)
  - Oritavancin (lipoglycopeptide in “once” administration)
  - Dalbavancin (lipoglycopeptide in “once-a-week” administration)
  - Tedizolid (oxazolidinone with less myelotoxicity and shorter duration of treatment)
  - Ceftazidime/avibactam (activity against ESBL [class A, B and some D] not inhibited by tazobactam…
  - plazomycin (nieuw aminoglycoside actief op bacteriën die resistent zijn tegen oudere aminoglycosiden) *
  - eravacycline (nieuw tetracycline actief op bacteriën die resistent zijn tegen oudere tetracyclines)
  - delafloxacin (nieuwe anionisch fluorochinolone met activiteit tegen MRSA)
  - meropeneme/vaborbactam (actief tegen Enterobacteriaceae die ESBL's produceerden inclusief KPC, SME, TEM, SHV, CTX-M, CMY en ACT)

* EMA Application withdrawn for commecrail reasons 16 June 2020

Therapeutic Drug Monitoring: PK/PD target*...

- β-lactamen: *f* T > MIC = 30 to 100 % van de dag
  (*f* C_{min} = 4 x MIC voor om het ontstaan van resistentie voor te komen)
- aminoglycosiden: C_{max} = 8 x MIC en *f* AUC = 21 to 400 x MIC
- fluorochinolonen: C_{max} = 10 x MIC en *f* AUC_{24h} = 30-100 x MIC
- vancomycine: AUC_{24h} = 350 x MIC (en hierboven)
- macroliden: AUC_{24h} = 30 x MIC
- tetracyclinen (met tigecycline): AUC_{24h} = 7-10 x MIC
- linezolid: *f* AUC24h = 100 x MIC (clinical data)

* waarde die wordt gebruikt om EUCAST-breekpunten te berekenen

Therapeutic Drug Monitoring: aminoglycosiden (1)

- C_{max} = 8 x MIC
- EUCAST breekpunten:

Enterobacteriaceae

Aminoglycosides[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Amikacin	8	16	30	16	13
Gentamicin	2	4	10	17	14
Netilmicin	2	4	10	15	12
Tobramycin	2	4	10	15	12

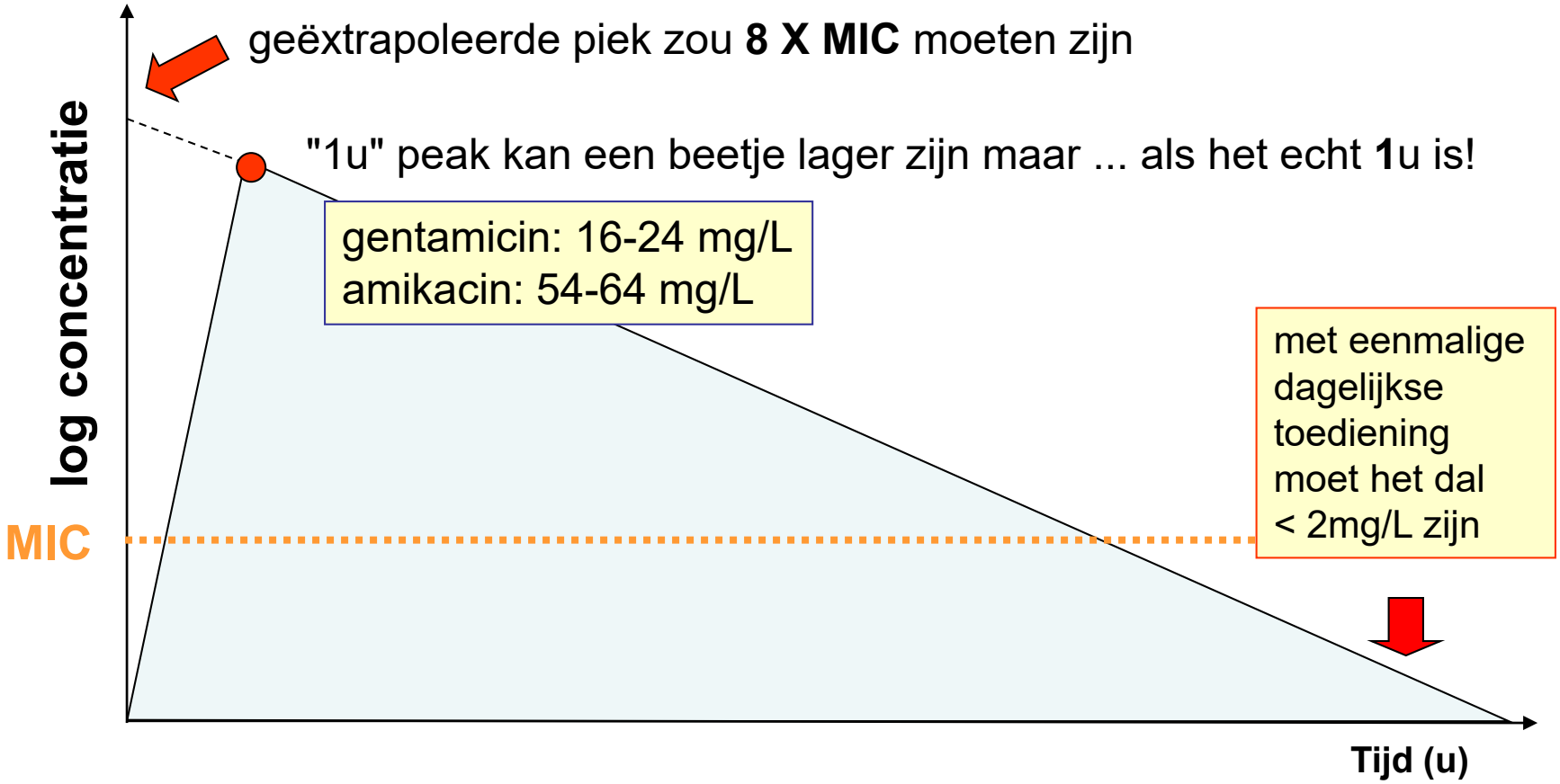
Bron: http://www.eucast.org/clinical_breakpoints/

zie zip

➔ Piek moet tenminste 16 (gentamicin) tot 64 (amikacin) mg/L zijn om de limiet van gevoeligheid (≤ S) te bereiken

Therapeutic Drug Monitoring: aminoglycosiden (2)

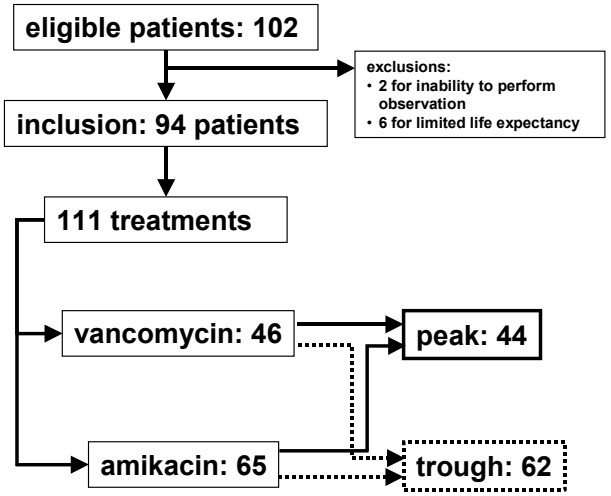
Aminoglycosiden (korte halfwaardetijd!):



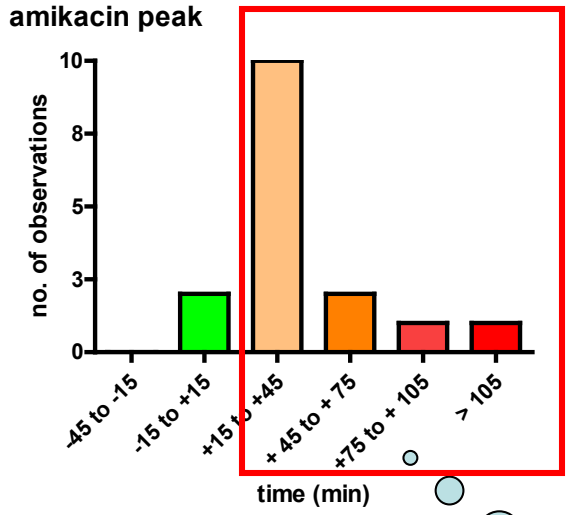
Therapeutic Drug Monitoring: aminoglycosiden (3)

Aminoglycosiden: probleem met de piek is de correcte tijd van staalname of !!

Een "klinische apotheker" studie over de "klassieke toediening" van amikacine (1x/dag en "piek en dal" staalname)



Ampe *et al.*, unpublished



Meeste stalen werden NIET binnen de correcte tijdsperiode afgenomen...

Therapeutic Drug Monitoring: aminoglycosiden (4)

Aminoglycosiden: de "Nicolau" nomogram met ~ 8 u staalname

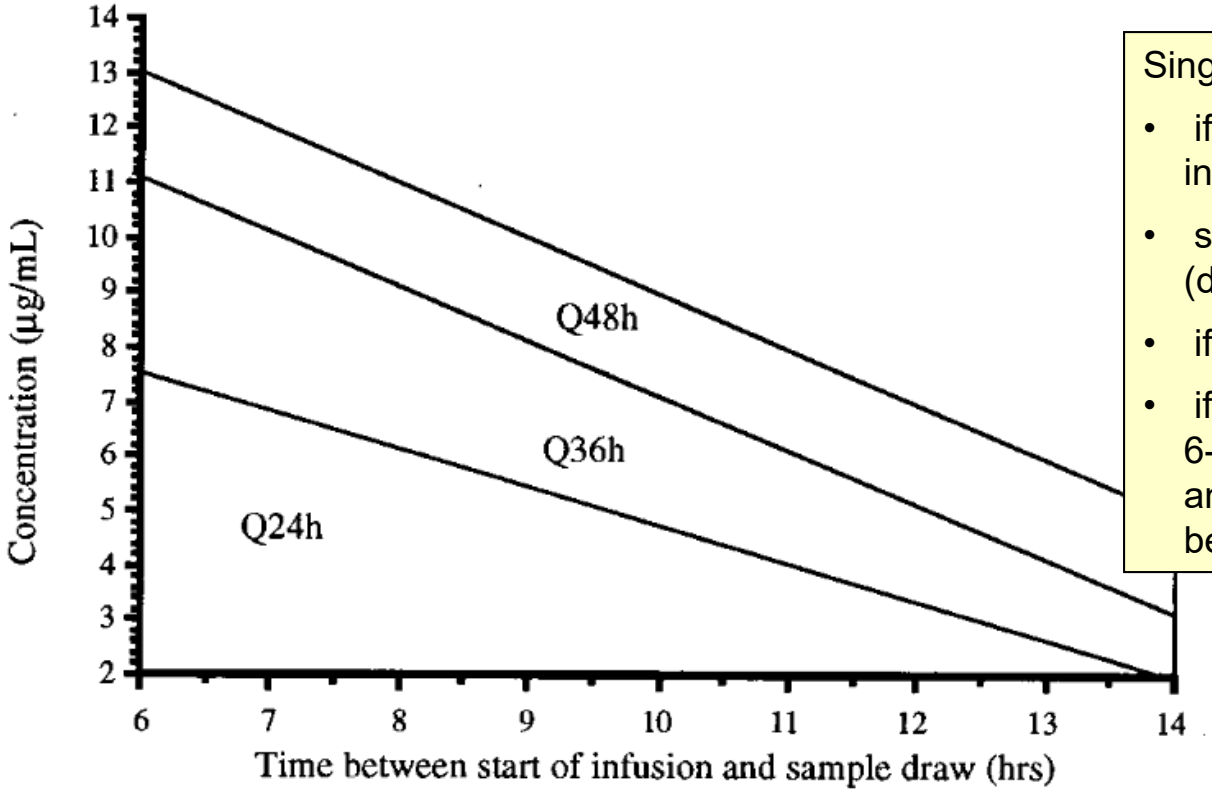


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

Single concentration measured at 8 h

- if level falls in q24h area, dosing interval is q24h
- same applies for areas q36h q48h (decr. creat. clearance).
- if near line, choose longer interval
- if above the nomogram between the 6- and 14-h time points, stop therapy and monitor for concentr. < 1 mg/L before next dose

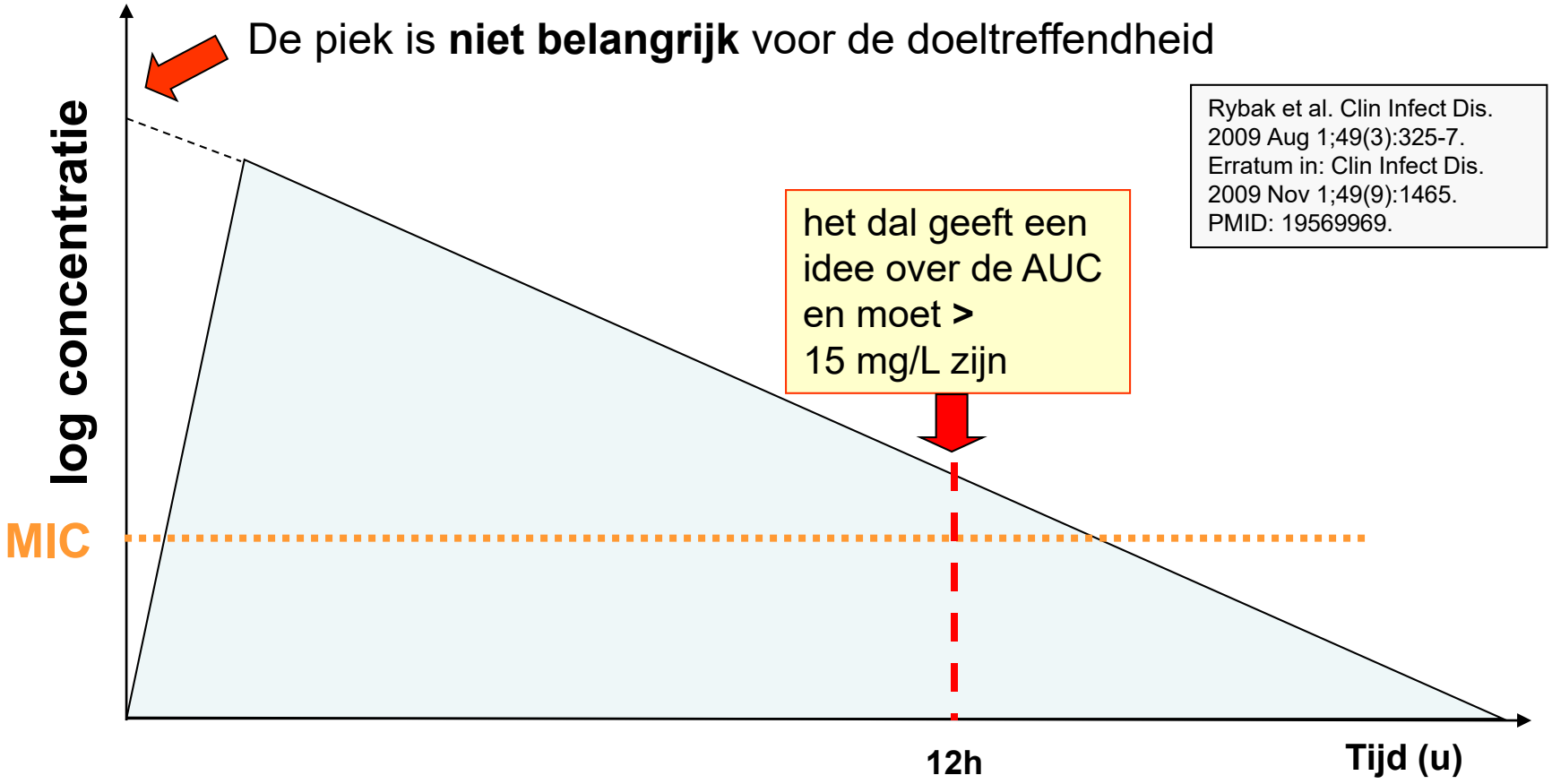
Nicolau et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother. 1995 Mar;39(3):650-5. PubMed PMID: 7793867;

zie zip

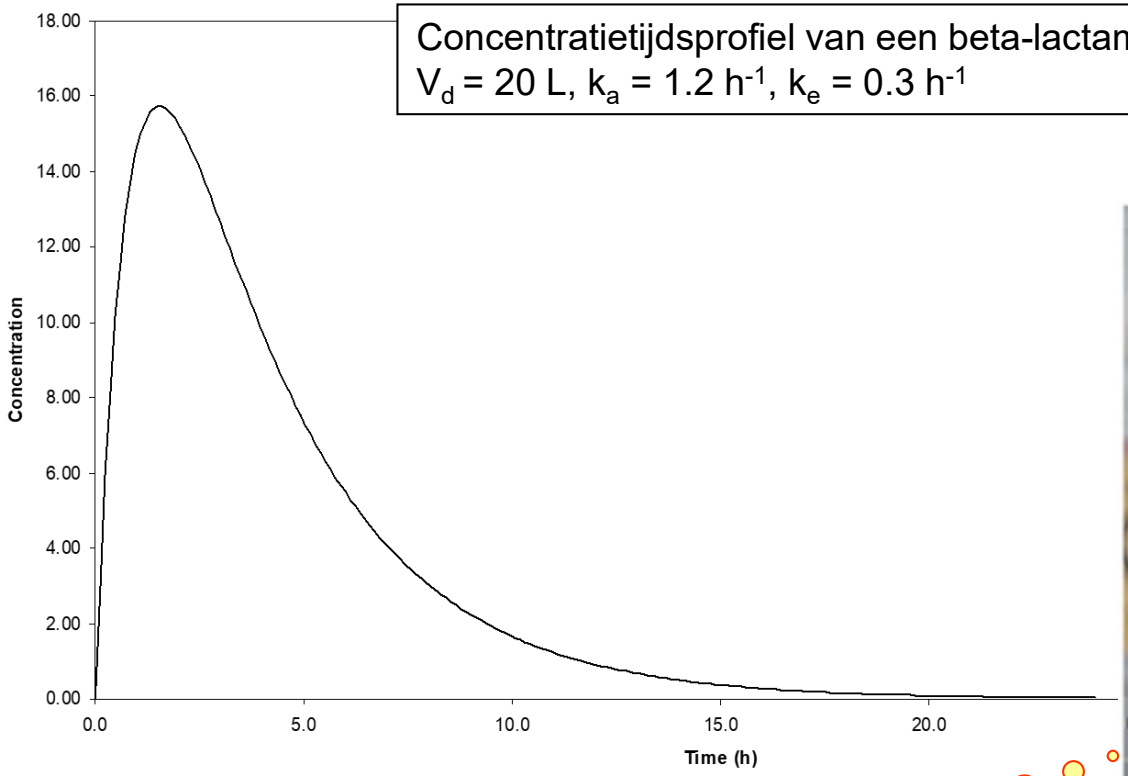
Therapeutic Drug Monitoring: vancomycine

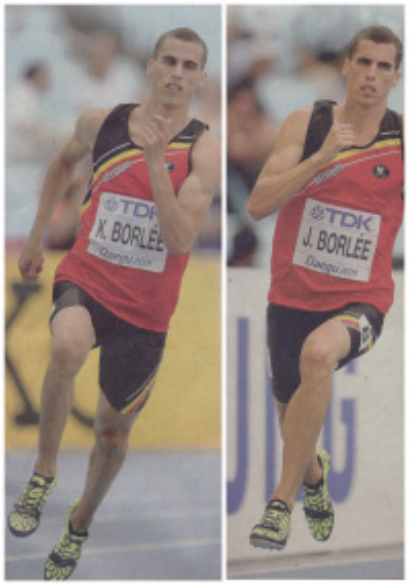
Vancomycine (AUC_{24h}-afhankelijk antibioticum – lange halfwaardetijd)

- dal is genoeg...



En voor β-lactams?





Maar zijn we allemaal echt gelijk?

Wat is een "standaard" patiënt?

gewicht

leeftijd

fysieke conditie

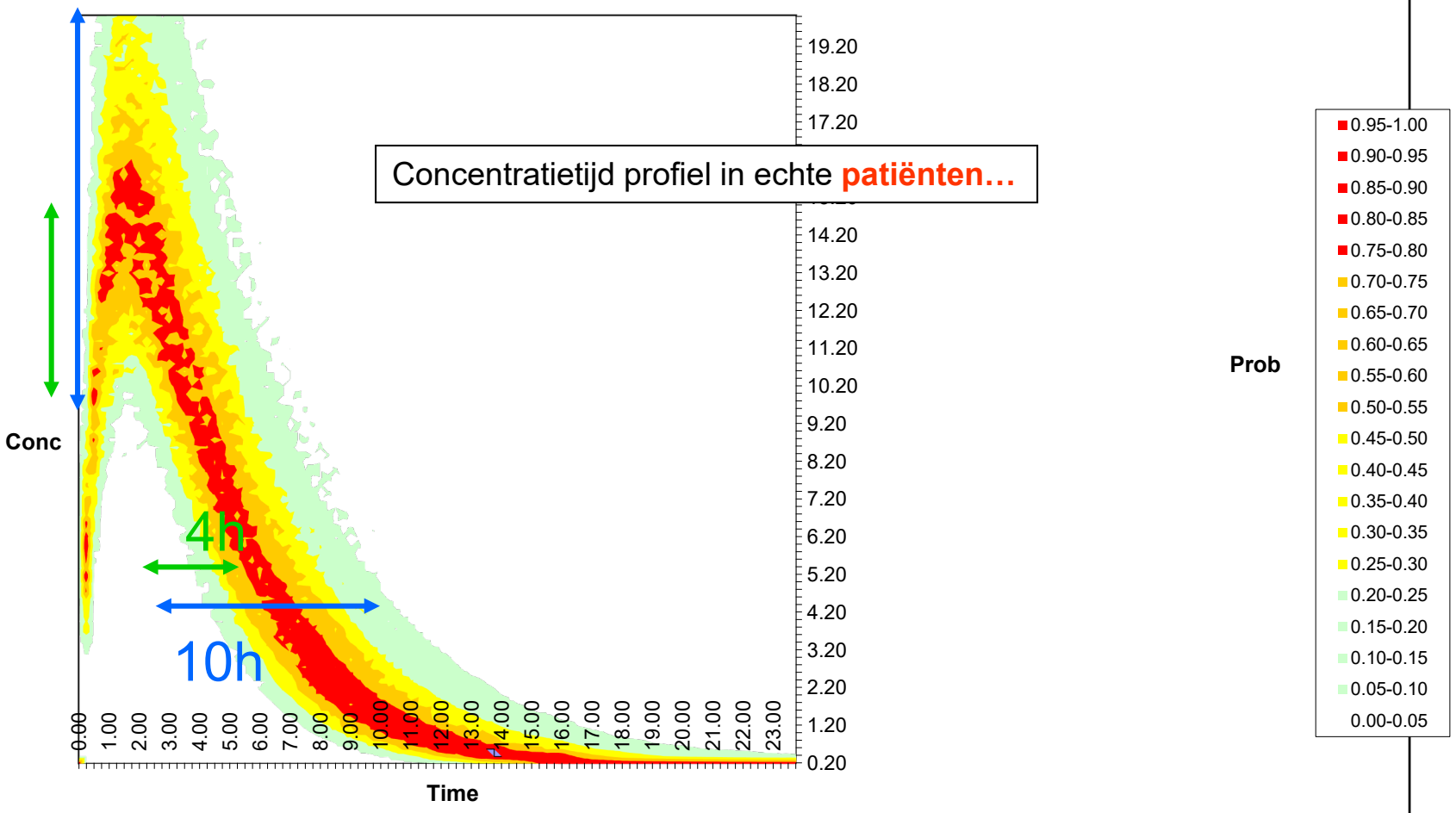
ras

lengte

ziekte

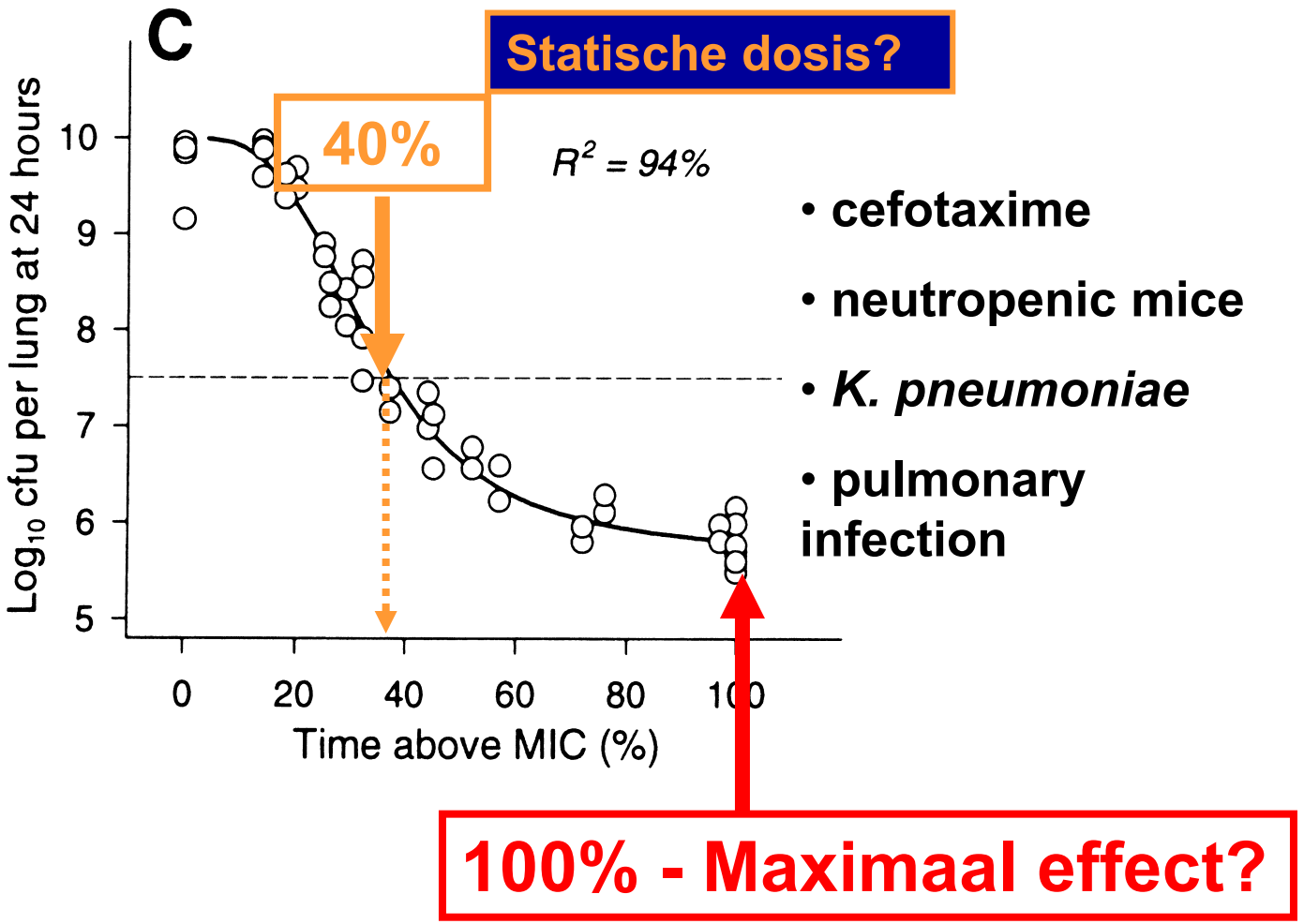
eliminatie functies

Dit is de dagelijkse realiteit…



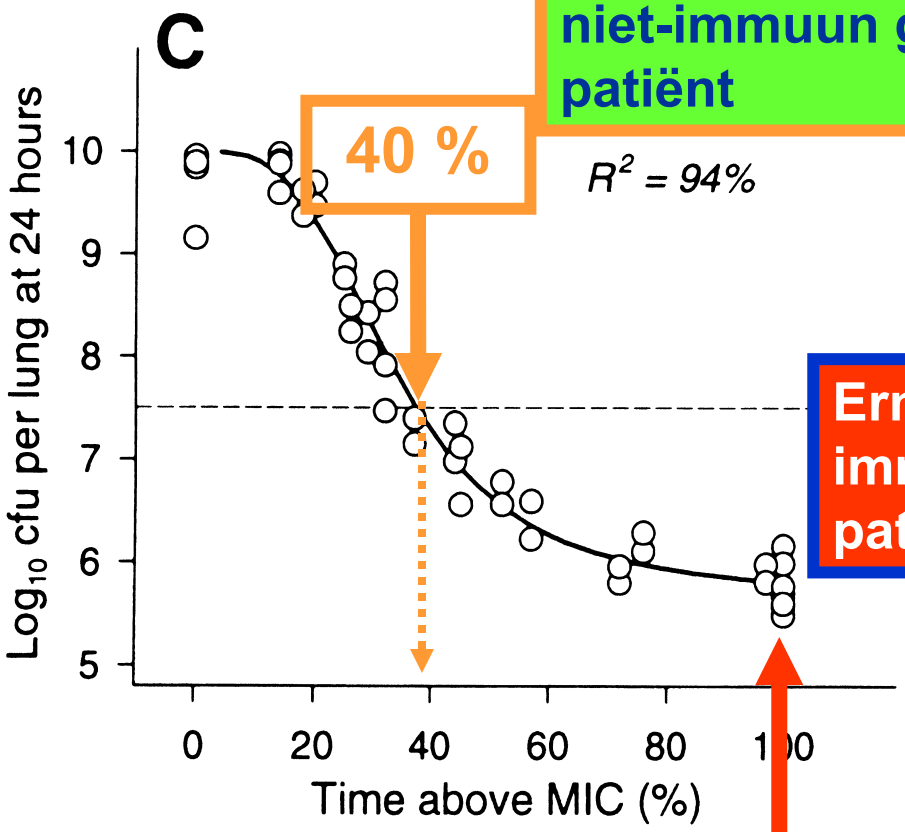
Mouton, Int J Antimicrob Agents april 2002

Wat is bovendien het correcte target?



Correcte target voor UW patiënt?

Matig tot ernstige infectie in een niet-immuun gecompromitteerde patiënt



Ernstige infectie in een immuun gecompromitteerde patiënt

100% ?

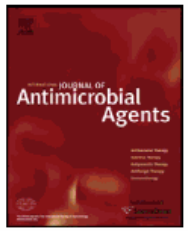
Vandaag wordt monitoring van β-lactams mogelijks de realiteit

International Journal of Antimicrobial Agents 36 (2010) 332–339

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag



Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

Jason A. Roberts[a,b,c,*], Marta Ulldemolins[a,d], Michael S. Roberts[e,f], Brett McWhinney[g], Jacobus Ungerer[g], David L. Paterson[h,i], Jeffrey Lipman[a,c]

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[b] Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia
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[d] Critical Care Department, Vall d'Hebron University Hospital; Institut de Recerca Vall d'Hebron-Universitat Autònoma de Barcelona (UAB)-CIBER Enfermedades Respiratorias, Barcelona, Spain
[e] Therapeutics Research Unit, The University of Queensland, Brisbane, Australia
[f] School of Pharmacy, University of South Australia, Adelaide, Australia
[g] Department of Chemical Pathology, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia
[h] Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane, Australia
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Vandaag wordt monitoring van β-lactams mogelijks de realiteit

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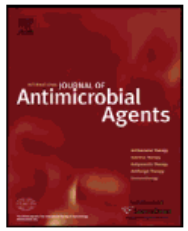

Therapeutic drug monitoring of β-lact
proof of concept

Jason A. Roberts[a,b,c,*], Marta Ulldemolins[a,d], M
Jacobus Ungerer[g], David L. Paterson[h,i], Jeffre

[a] Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, A
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[h] Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane, Australia
[i] University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Australia

meer over monitoring
in het verdere verloop
van de presentatie…

Continu infuus…

Continu infuus: welke antibiotica?

antibiotica	dosis-respons	invloed van de tijd	klinische consequenties
Ja! • β-lactams • glycopeptiden (*)	gering	kritiek	• Blootstelling aan geneesmiddel is belangrijk • Zeer hoge concentraties zijn onbelangrijk
Nee! • aminoglycosiden • fluoroquinolonen (**)	belangrijk	beperkt	• Concentraties zijn wél belangrijk • Tijdsduur is niet bepalend

* globaal AUC afhankelijk maar met gering post-antibiotisch effect

** piek is ook belangrijk voor preventie van resistentie

Continu infuus in het praktijk:
1. ladingsdosis

Serum "*target*" concentratie

$C_t = D_l / Vd$

distributie volume

ladingsdosis

ladingsdosis (in mg) = C_t (mg/L) x **Vd** (L)

* **ladingsdosis is afhankelijk van het distributievolume, en dus, van het gewicht van de patiënt EN zijn/haar medische situatie…**
  Typische distributievolumes:
  - **β-lactam: 0.2 - 0.4 L/kg**
  - **vancomycine: 0.7 - 0.8 L/kg**

Continu infuus in het praktijk:
2: infusie

Serum "*target*" concentratie

$C_{ss} = K_o / Cl$

klaring

infusiesnelheid

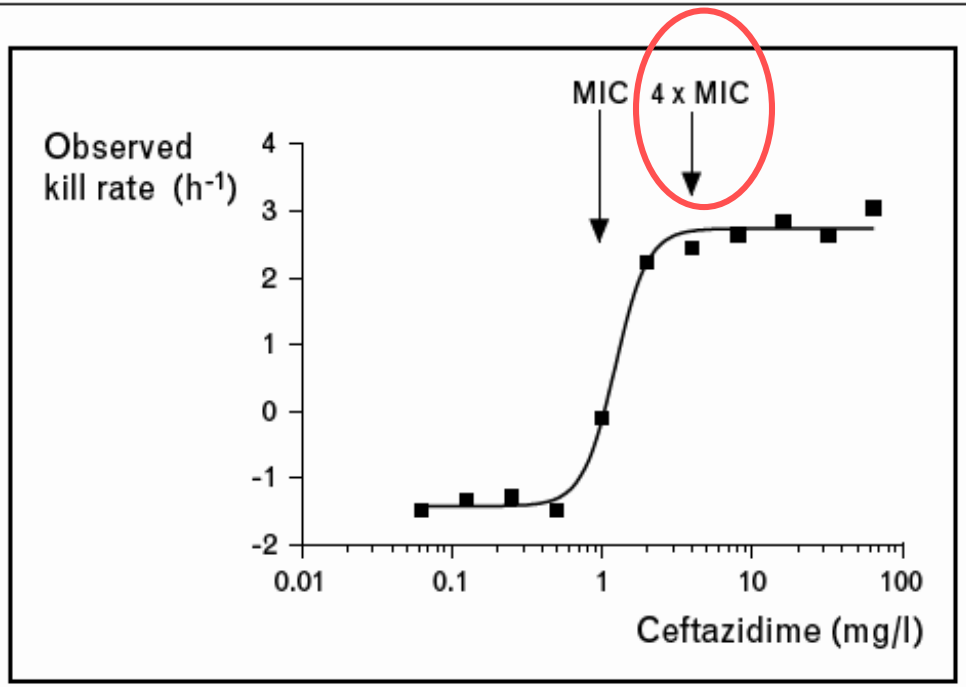
dagelijkse dosis (in mg) = 24 x **totaal klaring** (L/h) x **Css**

*** gedurende de infusie is de dosis uitsluitend afhankelijk van de klaring (dus is het gewicht niet meer van belang)**

β-lactams:

hoe hoog?

Figure 2 Relationship between concentration of ceftazidime and kill rate



The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

Mouton JW, Vinks AA. Curr Opin Crit Care. 2007 Oct;13(5):598-606.

Continu infuus van β-lactam antibiotica: een voorbeeld…

Continuous versus Intermittent Infusion of Temocillin in Intensive Care Patients

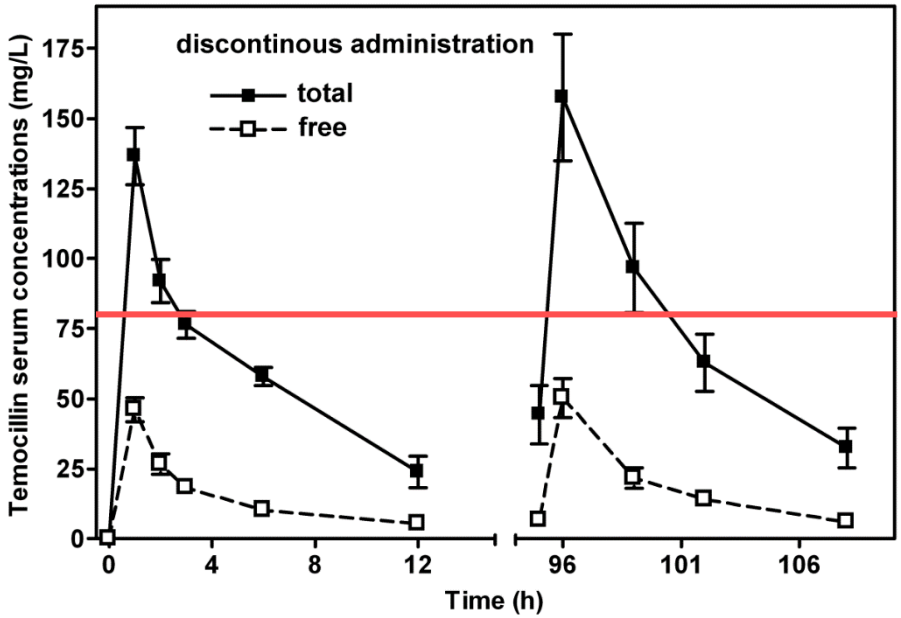
V. Basma, R. de Jongh, F. Van Bambeke, M.P. Mingeot-Leclercq, P.M. Tulkens
(Unité de pharmacologie cellulaire et moléculaire, Université catholique de Louvain, Bruxelles;
Dienst voor intensieve zorgen, Ziekenhuis Oost-Limburg, Genk; Belgium

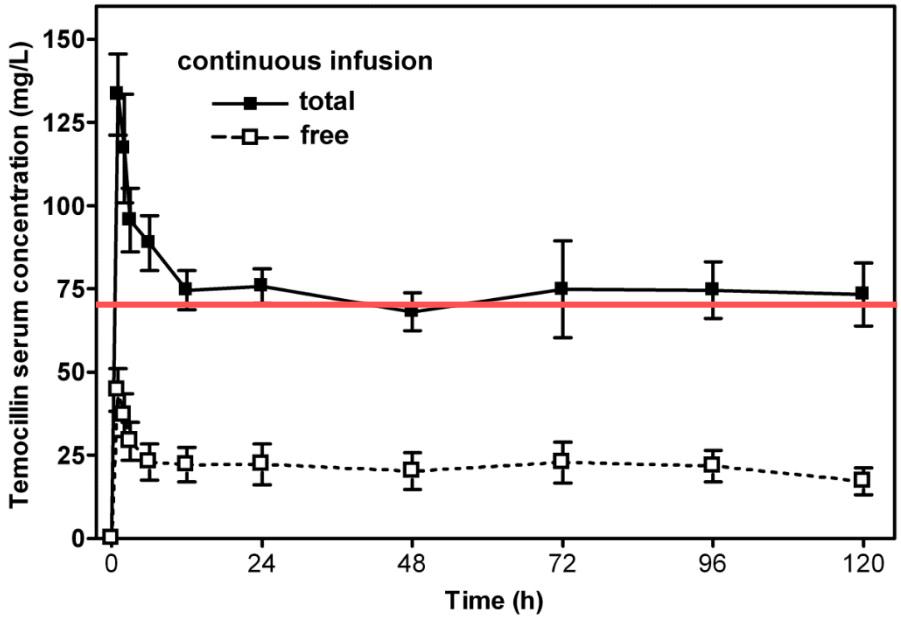
- **target level: 64 mg/L** (max. MIC: 16 mg/L; Belgian bkpt van temocilline = 16 mg/L])
- ladingsdosis: 2g (overshoot !)
- infusie: 4g/dag (2.778 mg/min; assumed clearance: 40 ml/min)

  [drug diluted in 48 ml of water; infusion through motor-operated syringe at a rate of 2 ml/h; temperature: 25°C or lower].

- RICAI, Paris, Frankrijk (december 2004)
- J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

Farmacokinetiek van temocilline 4g/dag

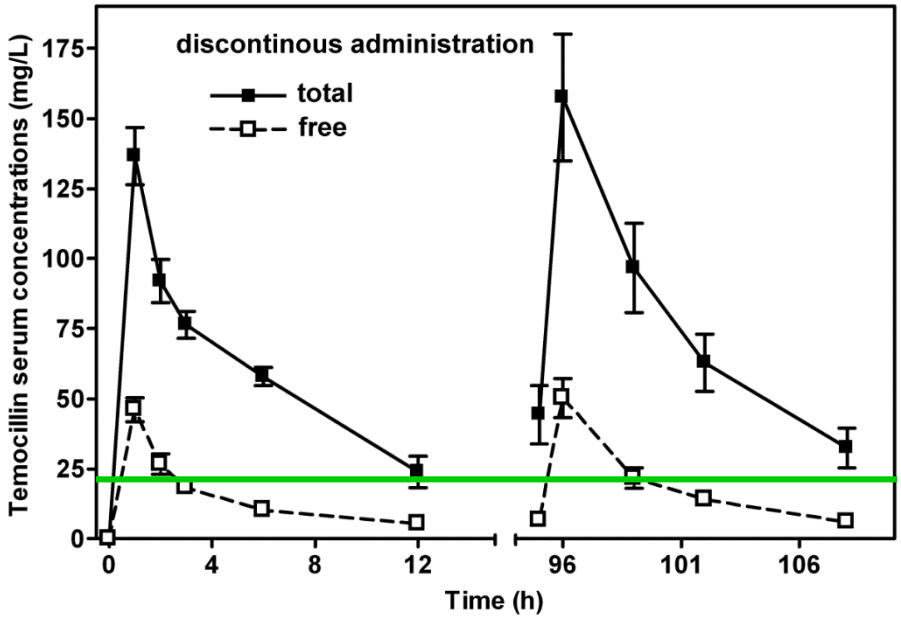


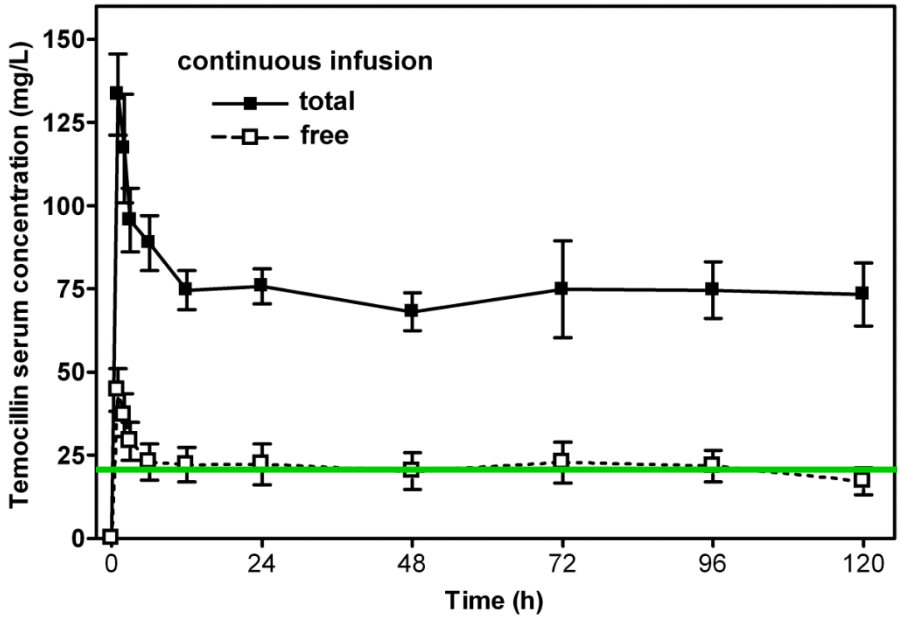


Concentration at equilibrium (total): 73 ± 3 (40 - 142)

J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

Farmacokinetiek met temocilline 4g/dag





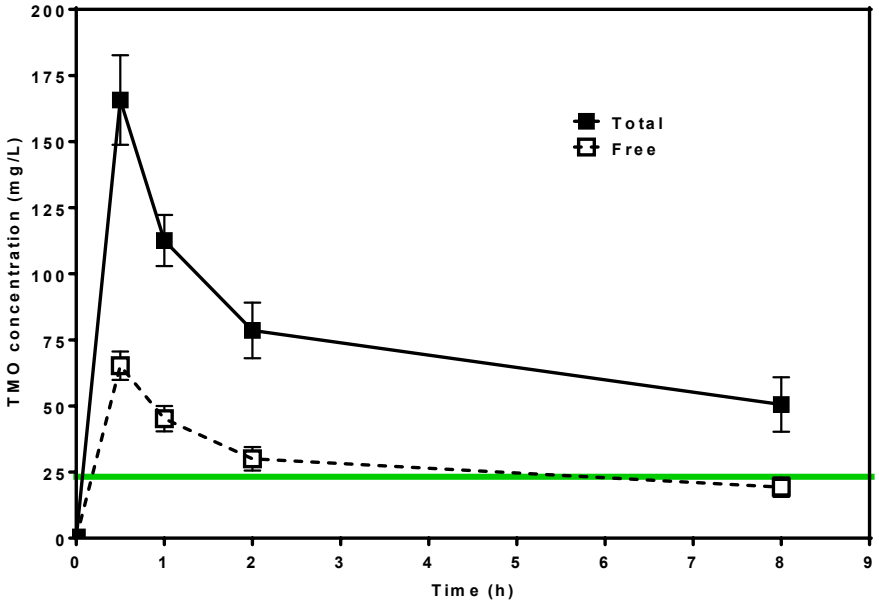
Concentration at equilibrium (free): 23 ± 2 (12 - 42)

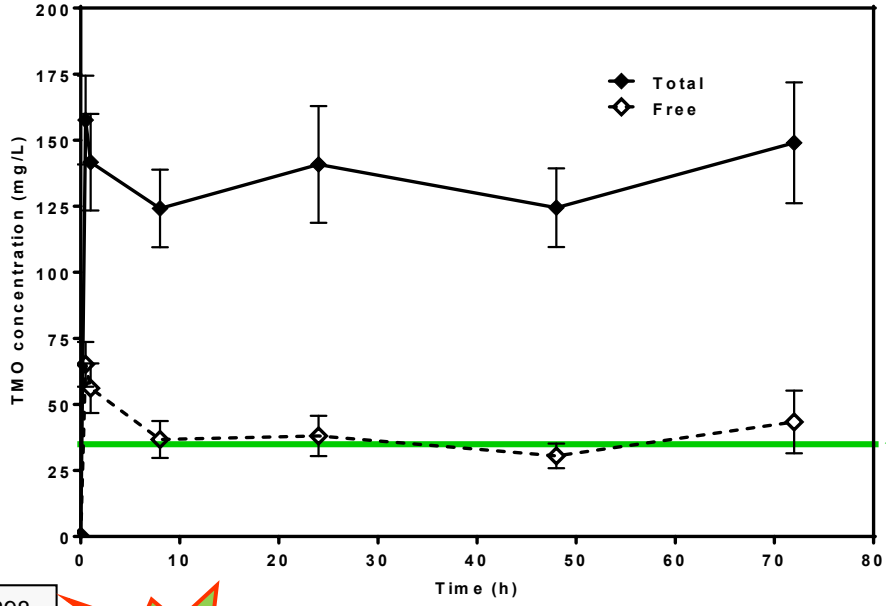
J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

En met 6g/dag

(3 x 2g)

op Intensieve Zorgen?





Concentration at equilibrium (free): 30 ± 17 (12 - 42)

Laterre *et al.* J. Antimicrob. Chemother. (2015) 70:891–898

zie zip

Continu infuus van β-lactams: een overzicht…

- The exact role of continuous infusion of β-lactam antibiotics in the treatment of severe infections remains unclear...
- However, increasing evidence is emerging that suggests potential benefits
  - better attainment of pharmacodynamic targets for these drugs
  - More reliable pharmacokinetic parameters in seriously ill patients
  - when the MIC of the pathogen is ≥4 mg/L (empirical therapy where the susceptibility of the pathogen is unknown)
- Clinical data supporting continuous administration are less convincing, but
  - Some studies have shown improved clinical outcomes from continuous infusion
  - none have shown adverse outcomes.
  - clinical and bacteriological advantage are visible in seriously ill patients requiring at least 4 days of antibiotic therapy.
- **Seriously ill patients with severe infections requiring significant antibiotic courses (≥4 days) may be the subgroup that will achieve better outcomes with continuous infusion.**

Roberts et al., Intern. J. Antimicrob. Agents 30 (2007):11-18

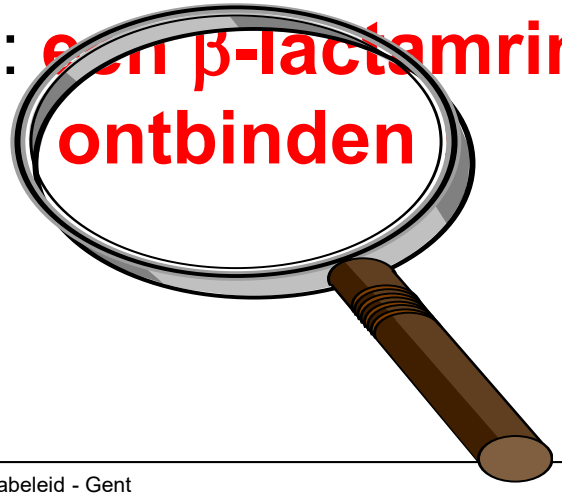
Continu infuus van β-lactams in de praktijk: farmaceutische aspecten...

Probleem:

Zijn ze chemisch stabiel genoeg?

antwoord : testen is de boodschap

reden : **een β-lactamring kan spontaan ontbinden**



Is continu infuus mogelijk voor alle β-lactams?

Elk molecule moet afzonderlijk getest worden voor zijn

- stabiliteit
- compatibiliteit
  (met andere geneesmiddelen in dezelfde infusie-set)

- **compatibiliteitsgegevens** zijn gepubliceerd voor **ceftazidime** (**AAC 2001;45:2643-7**), **cefepime** (**JAC 2003; 51:651-8**), **temocilline** (**JAC 2008;61:382-8**), **meropenem** (**Minerva Anestesiol. 2015;81:283-7)** en **vancomycine** (**JAC 2013;68:1179-82)** (meer gegevens over meropenem generieken binnenkort)
- **stabiliteitgegevens:** zie dezelfde publicaties en ook **AAC 2002;46:2327-32** en **Curr Opin Crit Care. 2007;13:598-606.**

Welke β-lactam antibiotica zijn stabiel genoeg voor continu-infuus?

(24 u in 8-12% oplossing)

	molecule	stabiliteitsgrens	referentie
voldoende	temocilline	> 24u op 37°C *	De Jongh et al. JAC 2008
	aztreonam	> 30u op 37°C	Chanteux et al. (abstract)
	piperacilline	24u op 37°C	Viaene et al. AAC 2002
matig	ceftazidime	24u op 25°C / 8u op 37°C	Servais et al. AAC 2001
problematisch	cefepime	verkleuring binnen 6u	Baririan et al. JAC 2003
onvoldoende	imipenem	< 5u	Viaene et al. AAC 2002
	meropenem	< 5u	Viaene et al. AAC 2002
	doripenem	~ 6-10u	Berthoin et al. JAC 2010

voor deze is een 3-4u infusie het maximum wat U kan doen!
(zie Berthoin et al., JAC (2010) 65:1073-1075)

* kan tot 3 weken aan 4°C behouden worden (voor thuis-medicatie bij mucoviscidose) (Carryn et al., JAC 2010; 65:2045-2046)

Wat is er nog van belang bij een continu-infuus

Van Herendael *et al. Annals of Intensive Care* 2012, **2**:22
http://www.annalsofintensivecare.com/content/2/1/22

Annals of Intensive Care
a SpringerOpen Journal

REVIEW **Open Access**

Continuous infusion of antibiotics in the critically ill: The new holy grail for beta-lactams and vancomycin?

Bruno Van Herendael[1*], Axel Jeurissen[2], Paul M Tulkens[3], Erika Vlieghe[4,5], Walter Verbrugghe[6], Philippe G Jorens[6] and Margareta Ieven[1]

Abstract

The alarming global rise of antimicrobial resistance combined with the lack of new antimicrobial agents has led to a renewed interest in optimization of our current antibiotics. Continuous infusion (CI) of time-dependent antibiotics has certain theoretical advantages toward efficacy based on pharmacokinetic/pharmacodynamic principles. We reviewed the available clinical studies concerning continuous infusion of beta-lactam antibiotics and vancomycin in critically ill patients. We conclude that CI of beta-lactam antibiotics is not necessarily more advantageous for all patients. Continuous infusion is only likely to have clinical benefits in subpopulations of patients where intermittent infusion is unable to achieve an adequate time above the minimal inhibitory concentration (T > MIC). For example, in patients with infections caused by organisms with elevated MICs, patients with altered pharmacokinetics (such as the critically ill) and possibly also immunocompromised patients. For vancomycin CI can be chosen, not always for better clinical efficacy, but because it is practical, cheaper, associated with less AUC_{24h} (area under the curve >24 h)-variability, and easier to monitor.

Keywords: Continuous infusion, Intermittent infusion, Vancomycin, Beta-lactam, Antibiotic(s), Critically ill, Pharmacokinetic/pharmacodynamic

zie zip

Meer over continu infuus…

J Antimicrob Chemother 2018; **73**: 1330–1339
doi:10.1093/jac/dkx526 Advance Access publication 7 February 2018

Journal of Antimicrobial Chemotherapy

Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model

Iris K. Minichmayr[1,2], Jason A. Roberts[3,4], Otto R. Frey[5], Anka C. Roehr[5], Charlotte Kloft[1]*† and Alexander Brinkmann[5]†

Meer over continu infuus: meropenem nomogram…

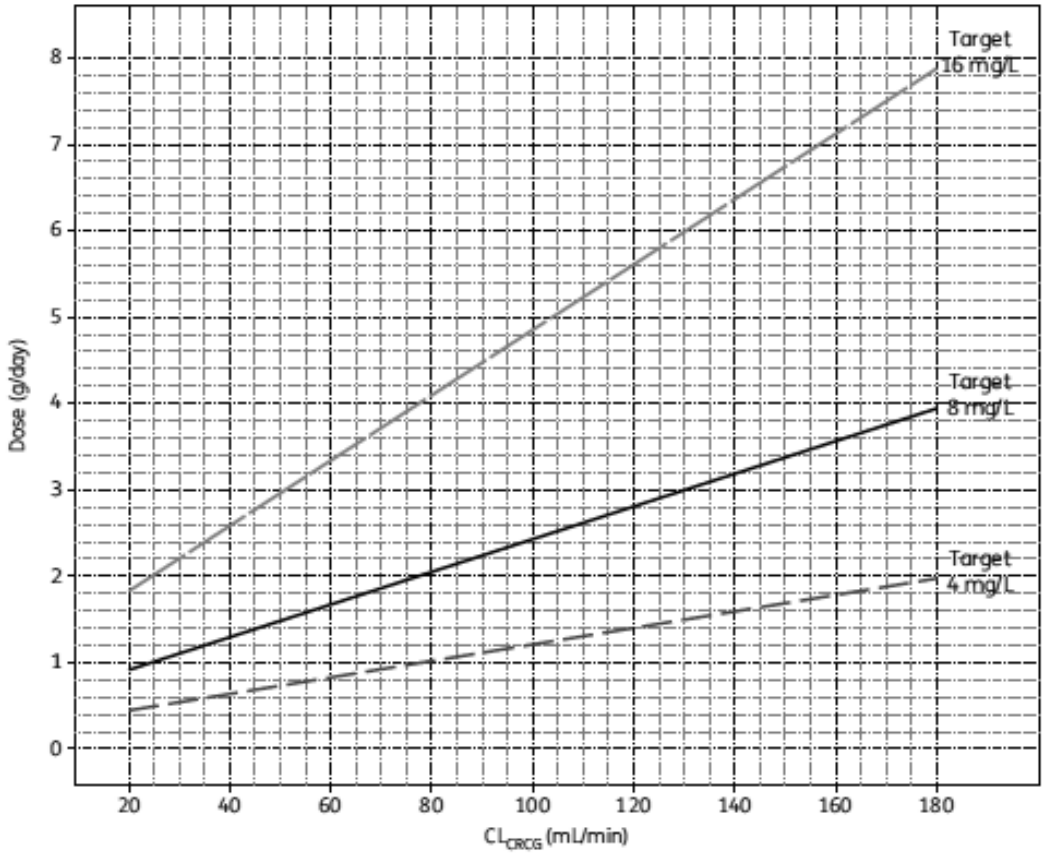
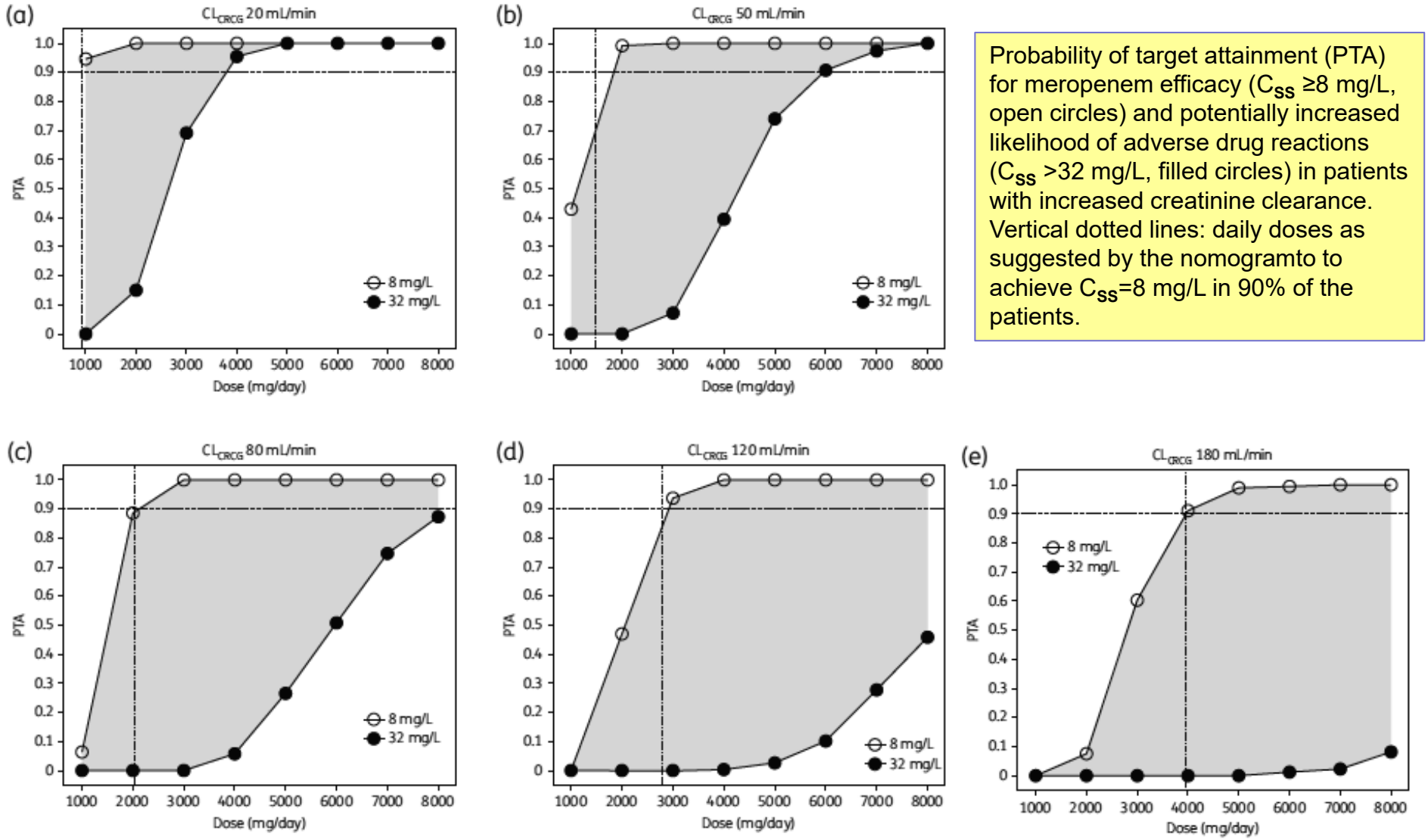


Figure 4. Nomogram depicting the daily doses of continuous-infusion meropenem required to achieve specific target steady-state concentrations (4, 8 and 16 mg/L) in 90% of the critically ill cohort given different creatinine clearance values (CL_{CRCG_WT}, calculated according to Cockcroft and Gault). Relationships between daily dose (DD) and CL_{CRCG_WT} for specific target steady-state concentrations (C_{SS}) were as follows: (a) target 4 mg/L: $DD_{CSS_4} = 0.00945 \cdot CL_{CRCG_WT} + 0.267$; (b) target 8 mg/L: $DD_{CSS_8} = 0.0189 \cdot CL_{CRCG_WT} + 0.534$; (c) target 16 mg/L: $DD_{CSS_16} = 0.0378 \cdot CL_{CRCG_WT} + 1.07$; (d) general target $DD_{CSS_TARGET} = C_{SS_TARGET}(0.00236 \cdot CL_{CRCG_WT} + 0.0665)$.

Meer over continu infuus: meropenem doeltreffendheid en risico tot toxiciteit…



Probability of target attainment (PTA) for meropenem efficacy (C_{ss} ≥8 mg/L, open circles) and potentially increased likelihood of adverse drug reactions (C_{ss} >32 mg/L, filled circles) in patients with increased creatinine clearance. Vertical dotted lines: daily doses as suggested by the nomogramto to achieve C_{ss}=8 mg/L in 90% of the patients.

Monitoring van β-lactams?

International Journal of Antimicrobial Agents 35 (2010) 500–503

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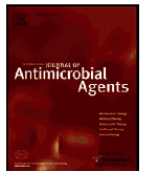

Short communication

Daily serum piperacillin monitoring is advisable in critically ill patients

Nicolas Blondiaux[a,*], Frédéric Wallet[a], Raphaël Favory[b], Thierry Onimus[b], Saad Nseir[b], René J. Courcol[a], Alain Durocher[b], Micheline Roussel-Delvallez[a]

[a] *Pôle de Microbiologie, Centre de Biologie-Pathologie, Centre Hospitalier Régional Universitaire (CHRU) de Lille, Boulevard du Pr. J. Leclercq, F-59037 Lille, France*
[b] *Service de Réanimation Médicale, Hôpital A. Calmette, Centre Hospitalier Régional Universitaire (CHRU) de Lille, Boulevard du Pr. J. Leclercq, F-59037 Lille, France*

Monitoring van β-lactams?

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Short communication

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[a] Pôle de Microbiologie, Centre de Biologie-Pathologie, Centre Hospitalier Régional Universitaire (CHRU
[b] Service de Réanimation Médicale, Hôpital A. Calmette, Centre Hospitalier Régional Universitaire (CHR

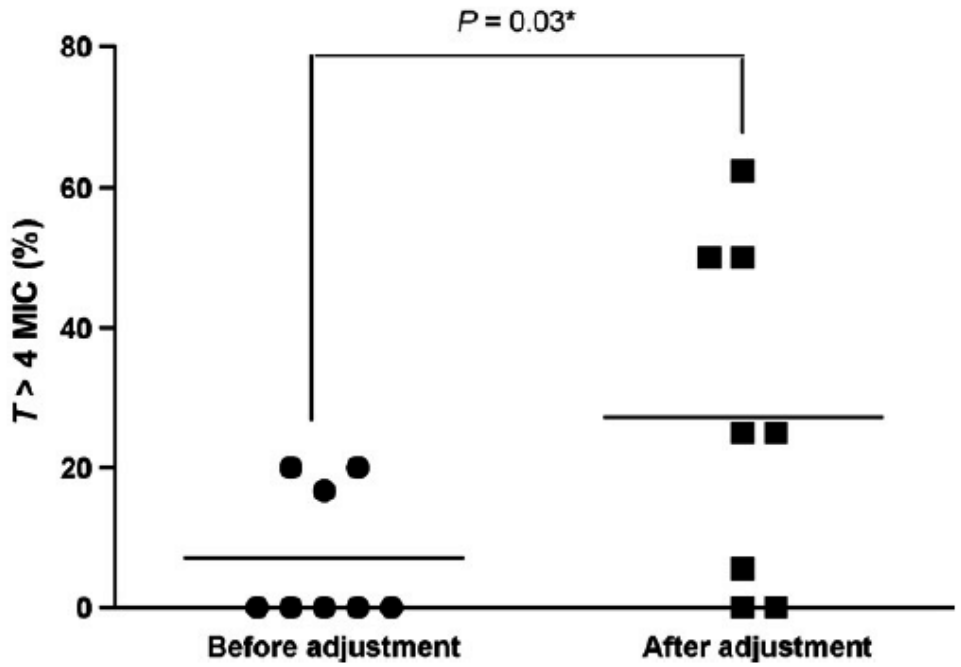

Fig. 1. Change in percentage of time during which the concentration remained above 4x the minimum inhibitory concentration (%$T > 4\times$ MIC) for patients who received dosage adjustment due to below-target serum concentrations. Horizontal bars represent the mean %$T > 4\times$ MIC.

Monitoring (TDM) van β-lactams?

DE GRUYTER Clin Chem Lab Med 2015; 53(9): e227–e230

Letter to the Editor

Mieke Carlier*, Jan J. De Waele, Alain G. Verstraete and Veronique Stove

Exploration of the pre-analytical stability of β-lactam antibiotics in plasma and blood – implications for therapeutic drug monitoring and pharmacokinetic studies

Monitoring (TDM) van β-lactams?

DE GRUYTER

Letter to the Editor

Mieke Carlier*, Jan J. De Waele, Alain G. Ve

**Exploration of the pre-
β-lactam antibiotics in
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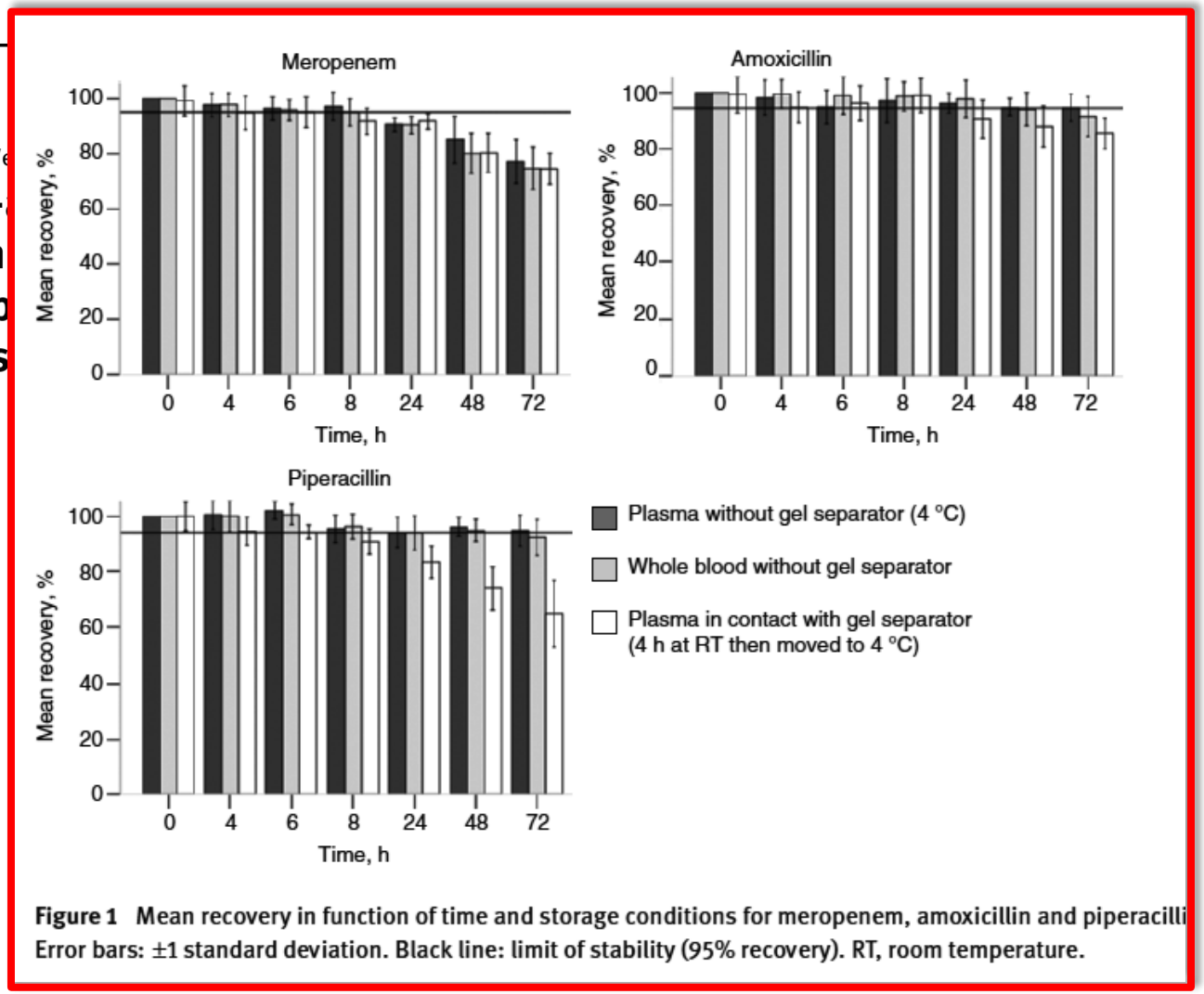

Figure 1 Mean recovery in function of time and storage conditions for meropenem, amoxicillin and piperacilli
Error bars: ±1 standard deviation. Black line: limit of stability (95% recovery). RT, room temperature.

Vandaag wordt monitoring van β-lactams mogelijks realiteit… in België

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

International Journal of Antimicrobial Agents 46 (2015) 367–375

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Assays for therapeutic drug monitoring of β-lactam antibiotics: A structured review

Mieke Carlier[a,b,*], Veronique Stove[a], Steven C. Wallis[c], Jan J. De Waele[b], Alain G. Verstraete[a], Jeffrey Lipman[c,d], Jason A. Roberts[c,d,e]

[a] Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium
[b] Department of Critical Care Medicine, Ghent University, Ghent, Belgium
[c] Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Queensland, Australia
[d] Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
[e] Institute of Translational Medicine, University of Liverpool, Liverpool, UK

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Methods of analysis
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Unbound

ABSTRACT

In some patient groups, including critically ill patients, the pharmacokinetics of β-lactam antibiotics may be profoundly disturbed due to pathophysiological changes in distribution and elimination. Therapeutic drug monitoring (TDM) is a strategy that may help to optimise dosing. The aim of this review was to identify and analyse the published literature on the methods used for β-lactam quantification in TDM programmes. Sixteen reports described methods for the simultaneous determination of three or more β-lactam antibiotics in plasma/serum. Measurement of these antibiotics, due to low frequency of usage relative to some other tests, is generally limited to in-house chromatographic methods coupled to ultra-violet or mass spectrometric detection. Although many published methods state they are fit for TDM, they are inconvenient because of intensive sample preparation and/or long run times. Ideally, methods used for routine TDM should have a short turnaround time (fast run-time and fast sample preparation), a low limit of quantification and a sufficiently high upper limit of quantification. The published assays included a median of 6 analytes [interquartile range (IQR) 4–10], with meropenem and piperacillin being the most frequently measured β-lactam antibiotics. The median run time was 8 min (IQR 5.9–21.3 min). There is also a growing number of methods measuring free concentrations. An assay that measures antibiotics without any sample preparation would be the next step towards real-time monitoring; no such method is currently available.

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Monitoring van β-lactams in speciale populaties (1)

Wong *et al. BMC Infectious Diseases* 2014, **14**:288
http://www.biomedcentral.com/1471-2334/14/288

BMC Infectious Diseases

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients?

Gloria Wong[1†], Fekade Bruck Sime[2,3†], Jeffrey Lipman[1,4] and Jason A Roberts[1,2,4*]

Monitoring van β-lactams in speciale populaties (1)

Wong *et al. BMC Infectious Diseases* 2014, **14**:288
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BMC Infectious Diseases

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcor
critically ill pati

Gloria Wong[1†], Fekade Bruck Sime[1]

Table 1 Summary of common factors associated with altered pharmacokinetics of antibiotics in critically ill patients

Increased V_d	Decreased Cl	Increased Cl	Variable changes in V_d and/or Cl
Hypoalbuminaemia, leading to increased unbound drug	Renal hypoperfusion	Augmented renal clearance	Extracorporeal interventions (eg RRT, ECMO)
Capillary leakage	Acute kidney injury		
Fluid resuscitation	Renal/hepatic dysfunction		
Third space loss			

Monitoring van β-lactams in speciale populaties (1)

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BMC Infectious Diseases

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcor
critically ill pati

Gloria Wong[1†]

Table 1 Summary of common factors associated with altered pharmacokinetics of antibiotics in critically ill

- In the context of critical illness, there is strong data demonstrating that standard dosing regimens for many antibiotics frequently fail to provide optimal PK/PD exposure in critically ill patients.
- Given that pharmacokinetic exposures can be very difficult-to-predict in some patients, TDM is valuable to identify these patients and guide dose optimization.
- TDM can ensure attainment of PK/PD surrogate indicators of antibiotic efficacy, and therefore potentially improve patient outcome.

Monitoring van β-lactams in speciale populaties (2)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

β-Lactam Dosage Regimens in Septic Patients with Augmented Renal Clearance

Alexandra Jacobs,[a,b] Fabio Silvio Taccone,[a] Jason A. Roberts,[c,d,e,f] Frédérique Jacobs,[b] Frederic Cotton,[g] Fleur Wolff,[g] Jacques Creteur,[a] Jean-Louis Vincent,[a] Maya Hites[b]

Jacobs et al. Antimicrob Agents Chemother. 2018;62:pii: e02534-17 - PMID: 29987138

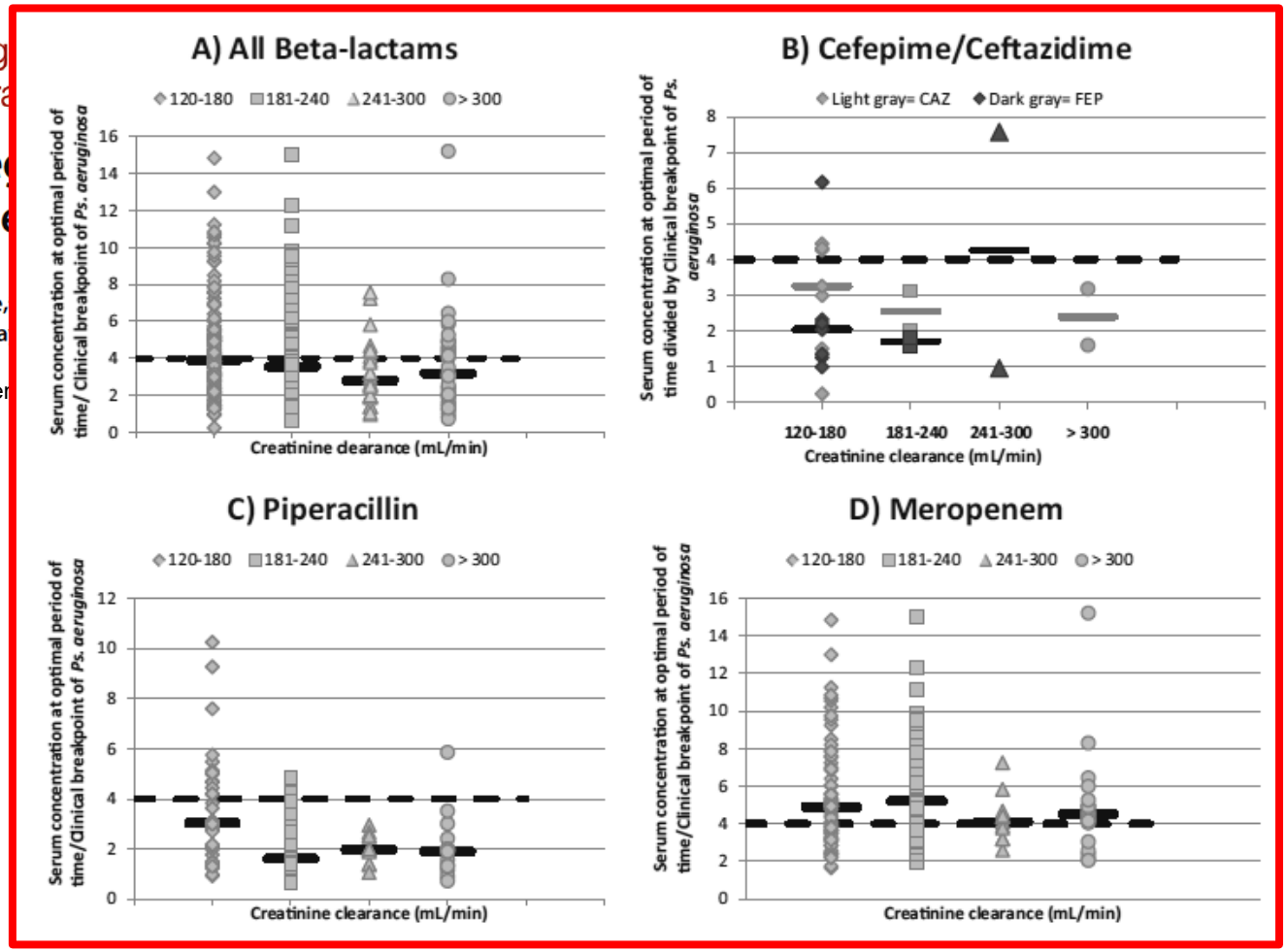
Monitoring van β-lactams in speciale populaties (2)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Ag and Chemothera

β-Lactam Dosage Re Augmented Renal Cl

Alexandra Jacobs,[a,b] Fabio Silvio Taccone, Jacques Creteur,[a] Jean-Louis Vincent,[a] Ma

Jacobs et al. Antimicrob Agents Chemother



Serum concentrations of β-lactams (at optimal period of time divided by clinical breakpoints of *Pseudomonas aeruginosa*), in function of quartiles of mCLCR, as indicated. Solid horizontal black lines, median serum concentrations; dashed horizontal black lines, pharmacodynamic target of 4x MIC of the clinical breakpoints for *Pseudomonas aeruginosa*. Serum concentration at optimal period of time is the serum concentration at 40%, 50%, or 70% of the dosage interval of MEM, TZP, or FEP/CAZ, respectively.

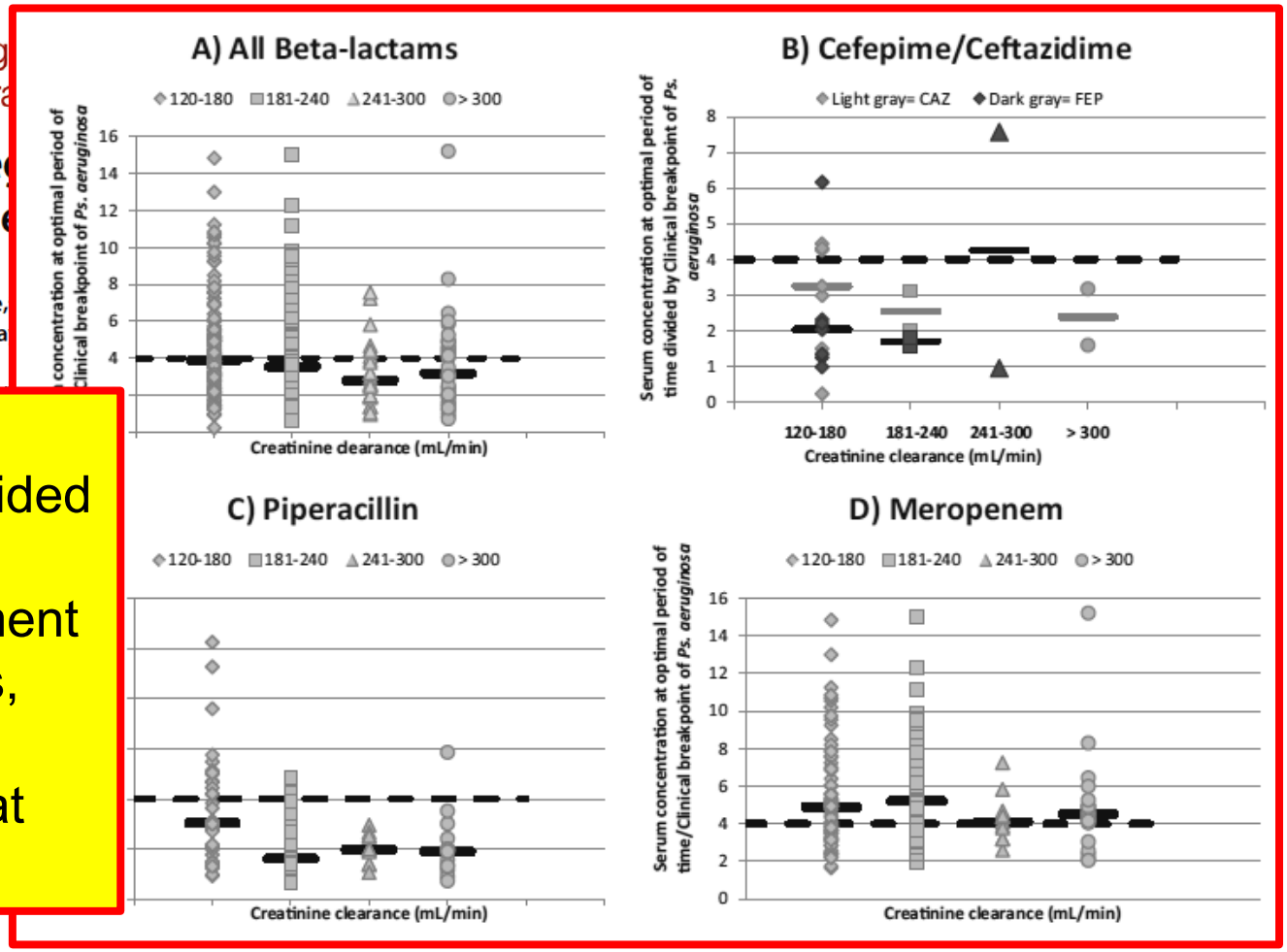
Monitoring van β-lactams in speciale populaties (2)

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Ag and Chemothera

β-Lactam Dosage Re Augmented Renal Cl

Alexandra Jacobs,[a,b] Fabio Silvio Taccone, Jacques Creteur,[a] Jean-Louis Vincent,[a] Ma

Currently, we recommend TDM-guided therapy to optimize PK/PD target attainment in critically ill patients, when possible, and particularly in those at risk of ARC.



Serum concentrations of β-lactams (at optimal period of time divided by clinical breakpoints of *Pseudomonas aeruginosa*), in function of quartiles of mCLCR, as indicated. Solid horizontal black lines, median serum concentrations; dashed horizontal black lines, pharmacodynamic target of 4x MIC of the clinical breakpoints for *Pseudomonas aeruginosa*. Serum concentration at optimal period of time is the serum concentration at 40%, 50%, or 70% of the dosage interval of MEM, TZP, or FEP/CAZ, respectively.

Monitoring van β-lactams in speciale populaties (3)

Repeated Piperacillin-Tazobactam Plasma Concentration Measurements in Severely Obese Versus Nonobese Critically Ill Septic Patients and the Risk of Under– and Overdosing*

Boris Jung, MD, PhD[1,2]; Martin Mahul, MD, MSc[1,2]; Dominique Breilh, PharmD, PhD[3]; Rachel Legeron, PharmD[3]; Jeremy Signe, MD[1,2]; Helene Jean-Pierre, MD[4]; Anne-Catrin Uhlemann, MD, PhD[5]; Nicolas Molinari, PhD[6]; Samir Jaber, MD, PhD[1,2]

Jung et al. Crit Care Med. 2017;45:e470-e478 - PMID: 28240688

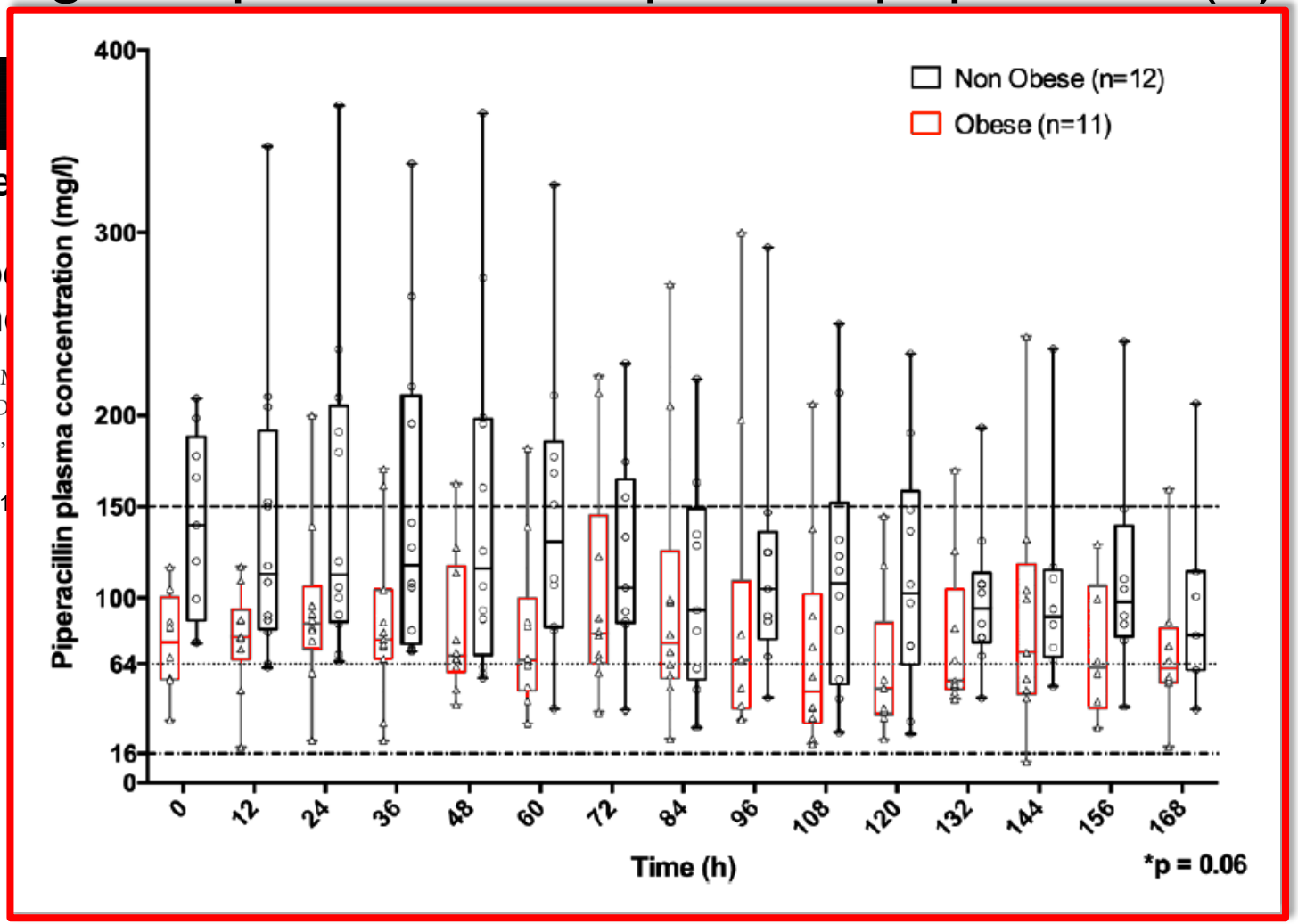
Monitoring van β-lactams in speciale populaties (3)

Online Clinical

**Repeated Pipe
Concentration
Versus Nonob
the Risk of Un**

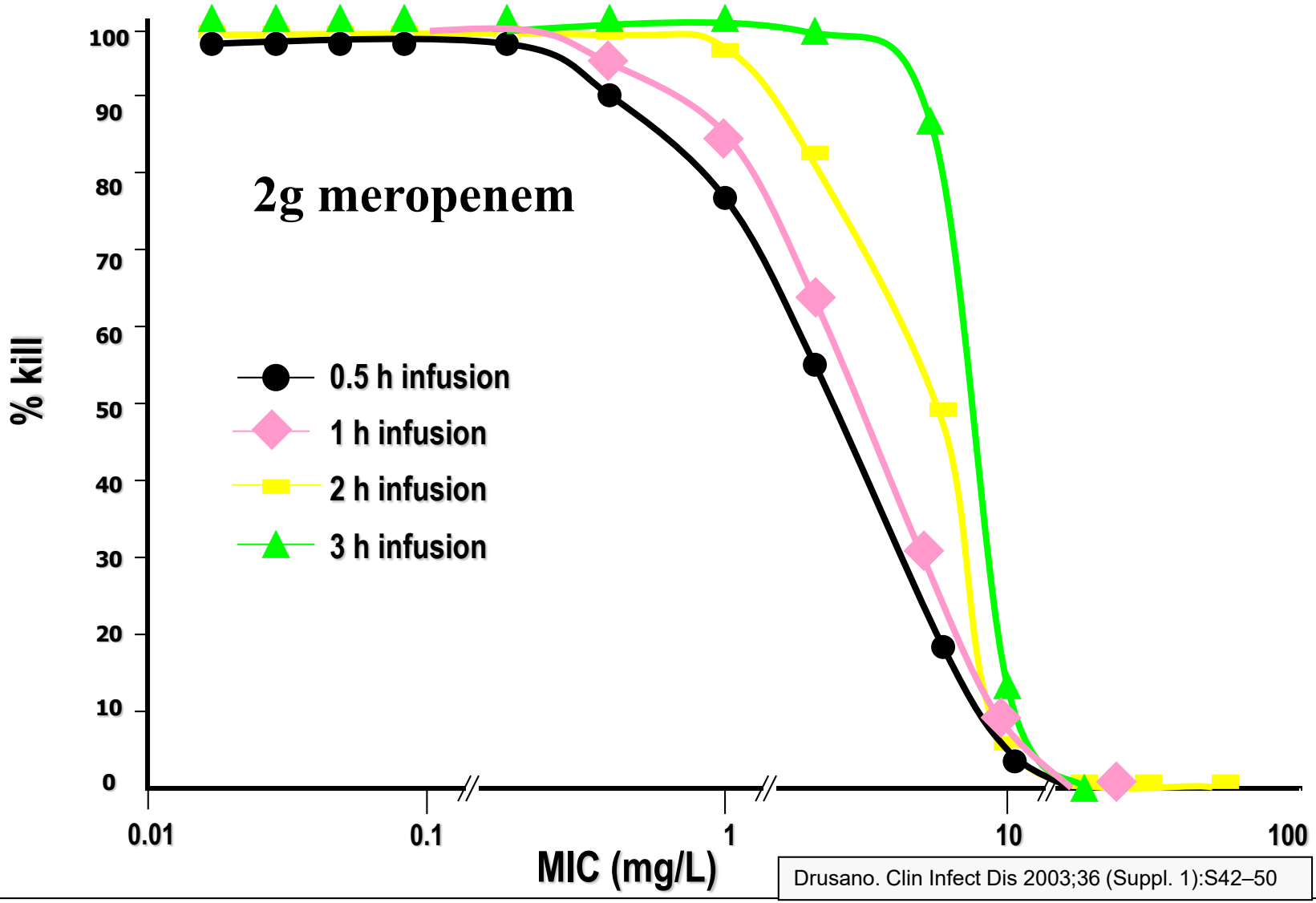
Boris Jung, MD, PhD[1,2]; M
Rachel Legeron, PharmD
Anne-Catrin Uhlemann,

Jung et al. Crit Care Med. 201



Piperacillin blood concentrations (median, quartiles, and individual values) over the 7-d study period for non-obese (*n* = 12) and severely obese (*n* = 11) patients. The *Pseudomonas aeruginosa* minimal inhibitory concentration breakpoint (16 mg/L), 4-fold the breakpoint (64 mg/L), and the potential piperacillin toxic concentration threshold (150 mg/L) are represented as *dashed lines*.. *Between obese and non-obese patients over time, adjusted to SOFA score.

Verbeterde potentiële doeltreffendheid van meropenem door een 3u infuus in vergelijking met standaard 0.5u infuus



Drusano. Clin Infect Dis 2003;36 (Suppl. 1):S42–50

3-uur infuus: een consensus?

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift
An open access, online journal • www.smw.ch

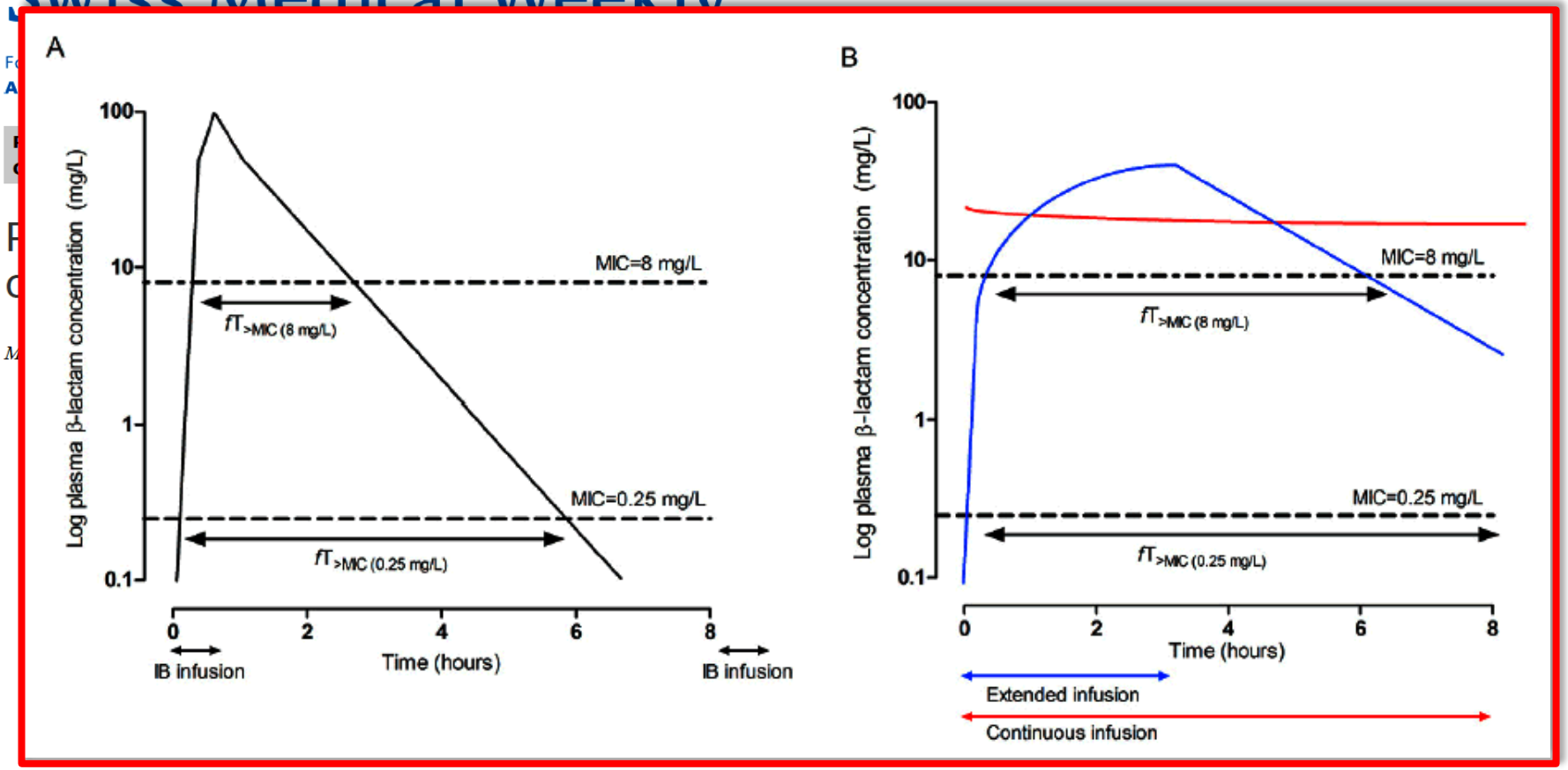
Review article: Biomedical intelligence | Published 10 October 2016, doi:10.4414/smw.2016.14368
Cite this as: Swiss Med Wkly. 2016;146:w14368

Prolonged administration of β-lactam antibiotics – a comprehensive review and critical appraisal

Michael Osthoff[a,b], Martin Siegemund[c], Gianmarco Balestra[d], Mohd H. Abdul-Aziz[e,f], Jason A. Roberts[f,g,h]

3-uur infuus: een consensus?

Swiss Medical Weekly



Differences in the time that β-lactam concentrations exceed the MIC (*f*T>MIC) of two different pathogens (MIC of 0.125 mg/l and 8 mg/l, respectively) according to the mode of β-lactam administration. (A) Intermittent bolus administration. (B) Extended infusion (blue line) and continuous infusion (red line).IB = intermittent bolus administration; MIC = minimal inhibitory concentration; *f*T>MIC = time that the free drug concentration is above the MIC

3-uur infuus: een consensus ?

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift
An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 10 October 2016, doi:10.4414/smw.2016.14368
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Prolonged administration of β-lactam antibiotics – a comprehensive review and critical appraisal

Michael Osthoff[a,b], Martin Siegemund[c], Gianmarco Balestra[d], Mohd H. Abdul-Aziz[e,f], Jason A. Roberts[f,g,h]

Universal administration of β-lactam antibiotics as prolonged infusion, even if supported by therapeutic drug monitoring, is not yet ready for “prime time”, as evidence for its clinical benefit is modest. There is a need for prospective randomized controlled trials that assess patient-centred outcomes (e.g. mortality) of a personalized approach in selected critically ill patients including prolonged infusion of β-lactams compared with the current standard of care.

Antibiotica van groep # 2

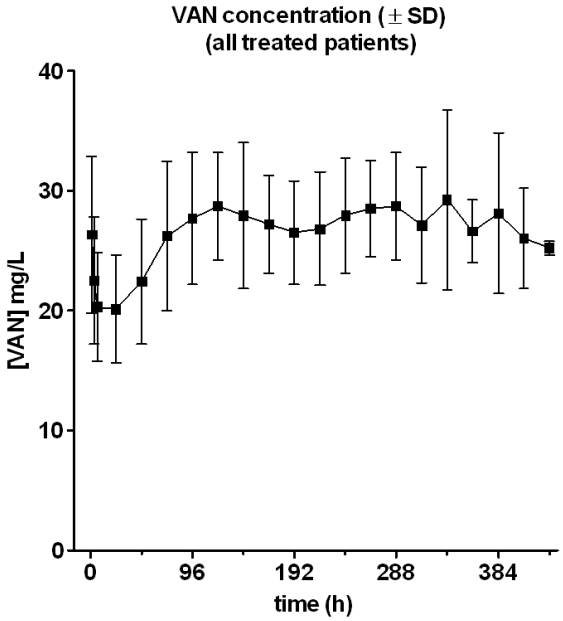
(naar W.A. Craig, 2000; herzien in 2002-2005)

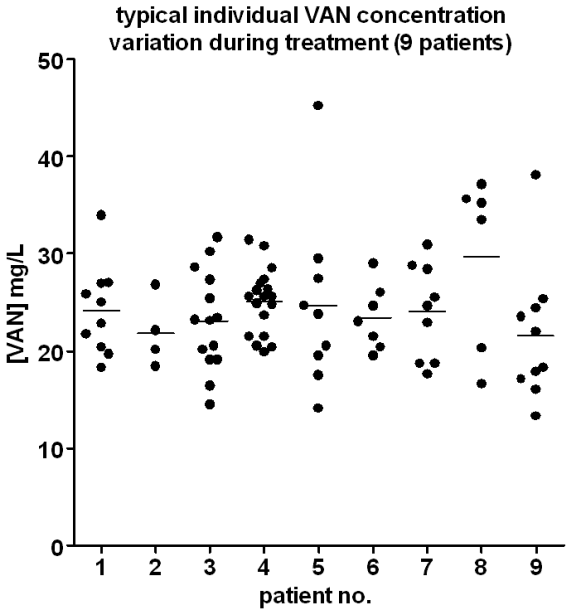
2. Tijdsafhankelijke antibiotica,
   weinig of niet beïnvloed door de concentratie, maar met langere nawerking (post-antibiotisch effect)

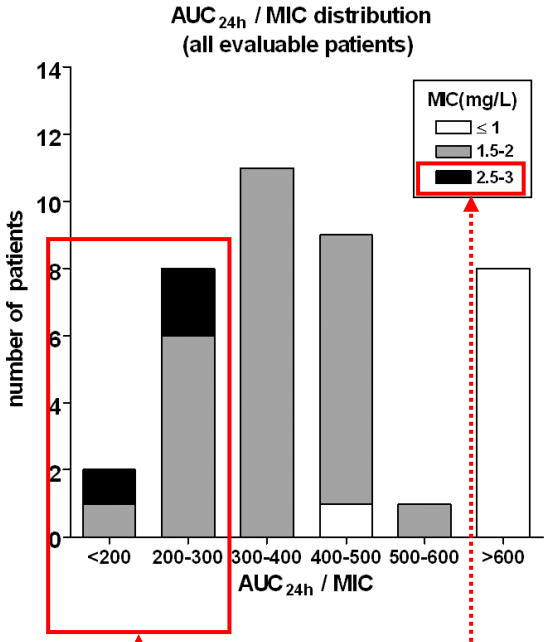
AB	PK/PD Parameter	Doel
glycopeptiden *	AUC_{24h} / MIC	Dag dosis optimaliseren
tetracyclinen		
macroliden		
linezolid		
streptograminen		

Wat kan U doen?…

Ervaring met vancomycine in continu infuus in Mont-Godinne







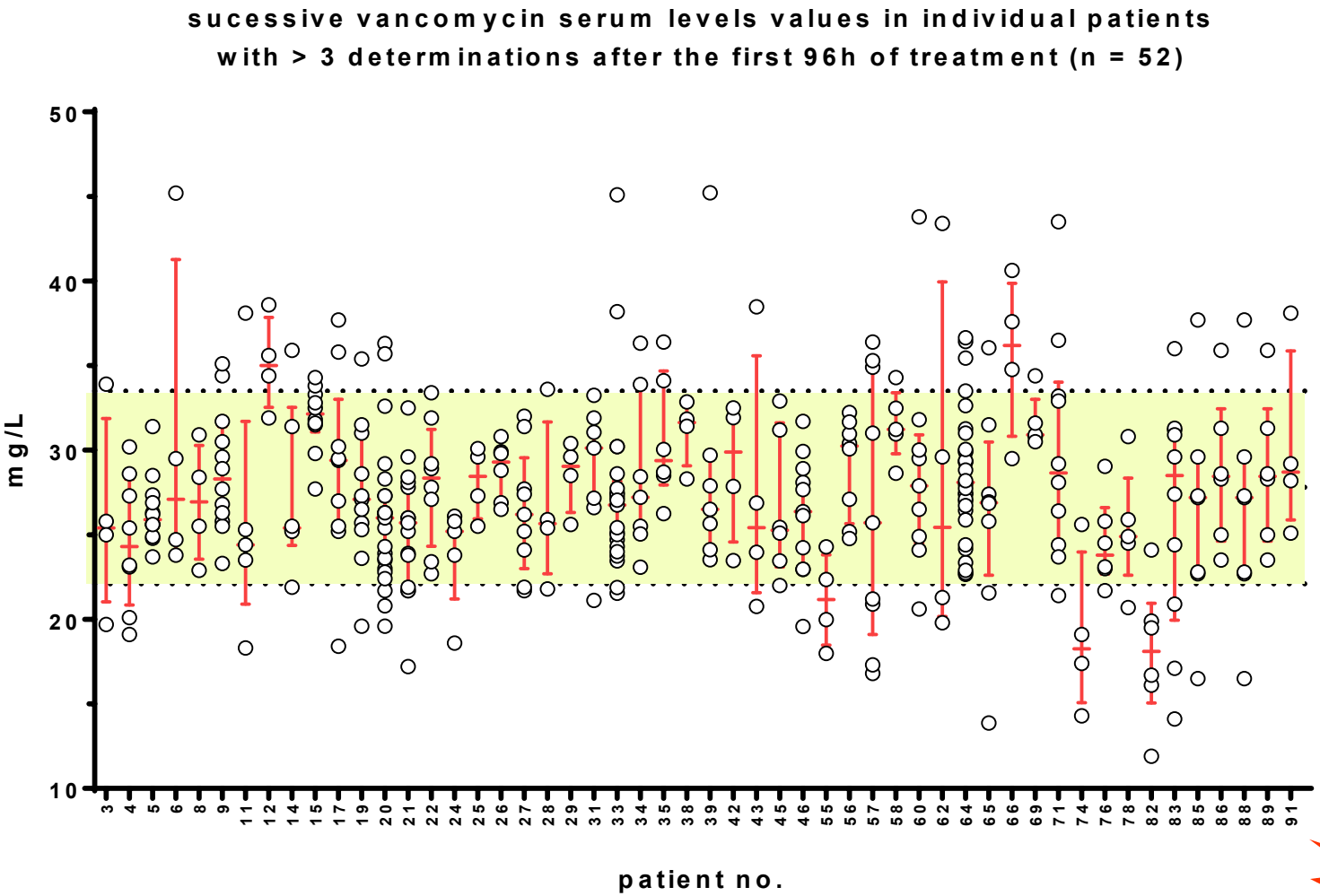
- 54 patients (40 documented infections)
- target concentration: 25-30 mg/L
- loading dose: 20 mg/kg;
- infusion rate: 2.5 g/day
  (adapted to renal function and corrected by therapeutic drug monitoring)

patiënten met risico van onvoldoende "*target attainment*"

zie zip

Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

Maar hoge variatie in serum spiegels



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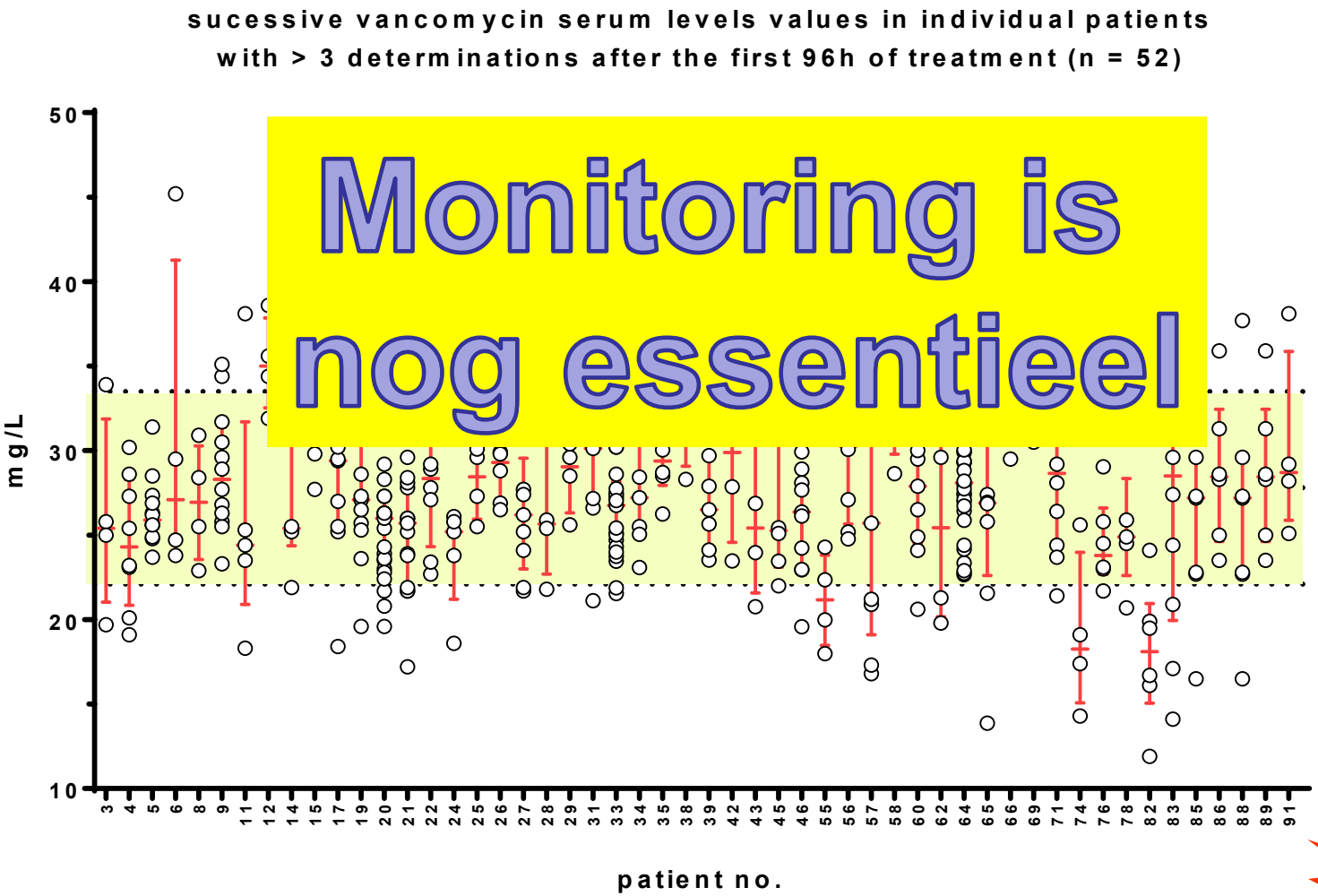
Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

Maar hoge variatie in serum spiegels



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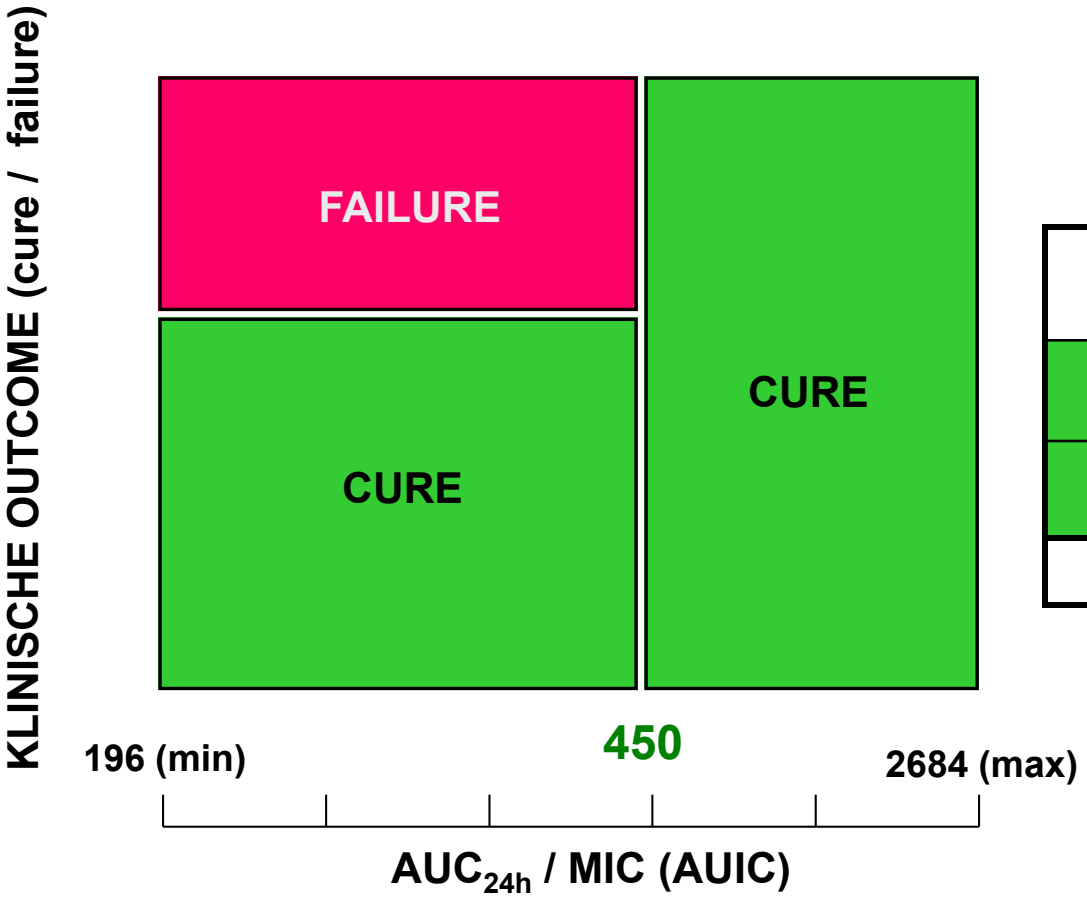
Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

Resultaten qua doeltreffendheid zijn toch duidelijk…

relatie tussen AUC_{24h} / MIC (E-Test) en klinische doeltreffendheid (n=19)



AUIC < 450	
cure	failure
5/9	4/9
P < 0.05	

zie zip

Ampe *et al.*, International Journal of Antimicrobial Agents (2013) 41:439-446

Gebruik en aanbevelingen voor "*extended*" (3u) en continu-infuus van antibiotica in België

Eur J Clin Microbiol Infect Dis (2013) 32:763–768
DOI 10.1007/s10096-012-1803-7

zie zip

ARTICLE

A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals

F. M. Buyle · J. Decruyenaere · J. De Waele · P. M. Tulkens · T. Van Audenrode · P. Depuydt · G. Claeys · H. Robays · D. Vogelaers

Gebruik en aanbevelingen voor "*extended*" (3u) en continu-infuus van antibiotica in België

Eur J Clin Microbiol Infect Dis (2013) 32:763–768
DOI 10.1007/s10096-012-1803-7

ARTICLE

zie zip

Table 2 Recommended dosing regimens for intermittent, prolonged and continuous infusions

	Intermittent	Prolonged	Continuous
Ceftazidime	2 g q8h/30 min		2 g/30 min loading dose+6 g q24h/24 h
Cefepime	1 g q8h/30 min	2 g q8h/3 h	2 g/30 min loading dose+2 g q8/8 h
	2 g q8h/30 min		2 g/30 min loading dose+6 g q24/24 h
Piperacillin–tazobactam	4/0.5 g q8h/30 min 4/0.5 g q6h/30 min	4/0.5 g q6h/3 h 4 g/0.5 g/30 min loading dose+4/0.5 g q6h/3 h	16 g/2 g q24h/24 h
Meropenem	0.5 q6h/30 min 1 g q8h/30 min	1 g q8h/3 h 1 g/30 min loading dose+1 g q8h/3 h	1 g/30 min loading dose+1 g q6h/6 h
	1 g/30 min loading dose+0.5 g q4h/30 min	2 g/30 min loading dose+1 g q8h/3 h 2 g q8h/3 h	
	2 g q8h/30 min	2 g/30 min loading dose+2 g q8h/3 h	
Vancomycin	15 mg/kg q12h/1 h		15 mg/kg/2 h loading dose+30 mg/kg q24h/24 h
	20 mg/kg q12h/1 h		20 mg/kg/2 h loading dose+30 mg/kg q24h/24 h

Linezolid: een probleem van toxiciteit?

- Een wel bekent en belangrijke neveneffect van linezolid is thrombocytopenia
- De SPK (samenvatting van productkenmerken) lijkt gunstig...

Bijkomende ongewenste reacties die tijdens de ervaring na het op de markt brengen werden gemeld, zijn in de tabel opgenomen onder de frequentiecategorie "Niet bekend", daar de werkelijke frequentie met de beschikbare gegevens niet kan worden bepaald.

Systeem/orgaan-klasse	Vaak (≥ 1/100 tot < 1/10)	Soms (≥ 1/1.000 tot < 1/100)	Zelden (≥ 1/10.000 tot < 1/1.000)	Zeer zelden (< 1/10.000)	Niet bekend (kan met de beschikbare gegevens niet worden bepaald)
Bloed- en lymfestelsel-aandoeningen	anemie*†	leukopenie*, neutropenie, trombocytopenie*, eosinofilie	pancytopenie*		myelosuppressie*, sideroblastische anemie*

Samenvatting van de productkenmerken BEL 19J23

Toxicodynamiek van linezolid

Modellering linezolid toxiciteit

Clinical Population Pharmacokinetics and Toxicodynamics of Linezolid

Lauren M. Boak,[a]* Craig R. Rayner,[a,b] M. Lindsay Grayson,[c,d] David L. Paterson,[e]* Denis Spelman,[f] Sharmila Khumra,[c,h] Blair Capitano,[e]* Alan Forrest,[g] Jian Li,[a] Roger L. Nation,[a] Jurgen B. Bulitta[a,g,h]

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Australia[a]; d3 Medicine LLC, Parsippany, New Jersey, USA[b]; Department of Medicine, Austin Hospital, Melbourne, Australia[c]; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia[d]; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[e]; Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia[f]; School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, Buffalo, New York, USA[g]; Centre for Medicine Use and Safety, Monash University (Parkville campus), Parkville, Australia[h]

Antimicrob Agents Chemother 2014;58:334–2343

Toxicodynamiek van linezolid

Modellering linezolid toxiciteit

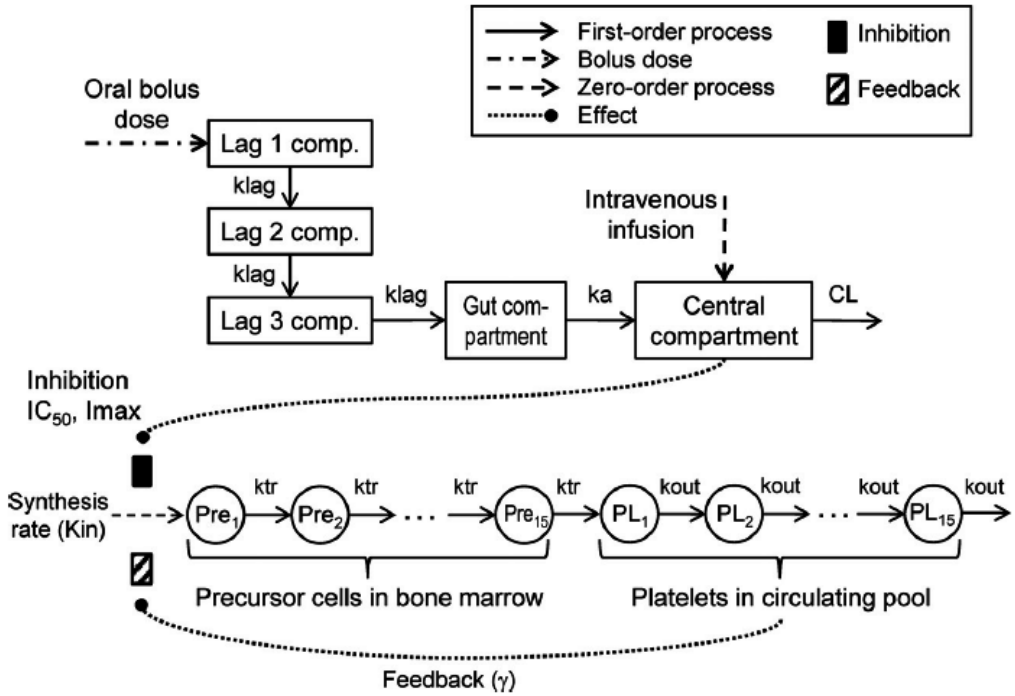


FIG 1 Structure of the final mechanism-based population pharmacokinetic/toxicodynamic model. The pharmacokinetic model is comprised of three absorption lag compartments, a gut compartment, and a central compartment. One series of 15 transit compartments was used to describe platelet precursor cells in the bone marrow, and another series of 15 transit compartments to describe platelets in the circulating pool. Platelets displayed a feedback effect on the synthesis of platelet precursor cells. A lack of platelets in the circulating pool compared to the platelet count at steady state caused a stimulation of platelet precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.

Toxicodynamiek van linezolid

Modellering linezolid toxiciteit: effect van de dosis !

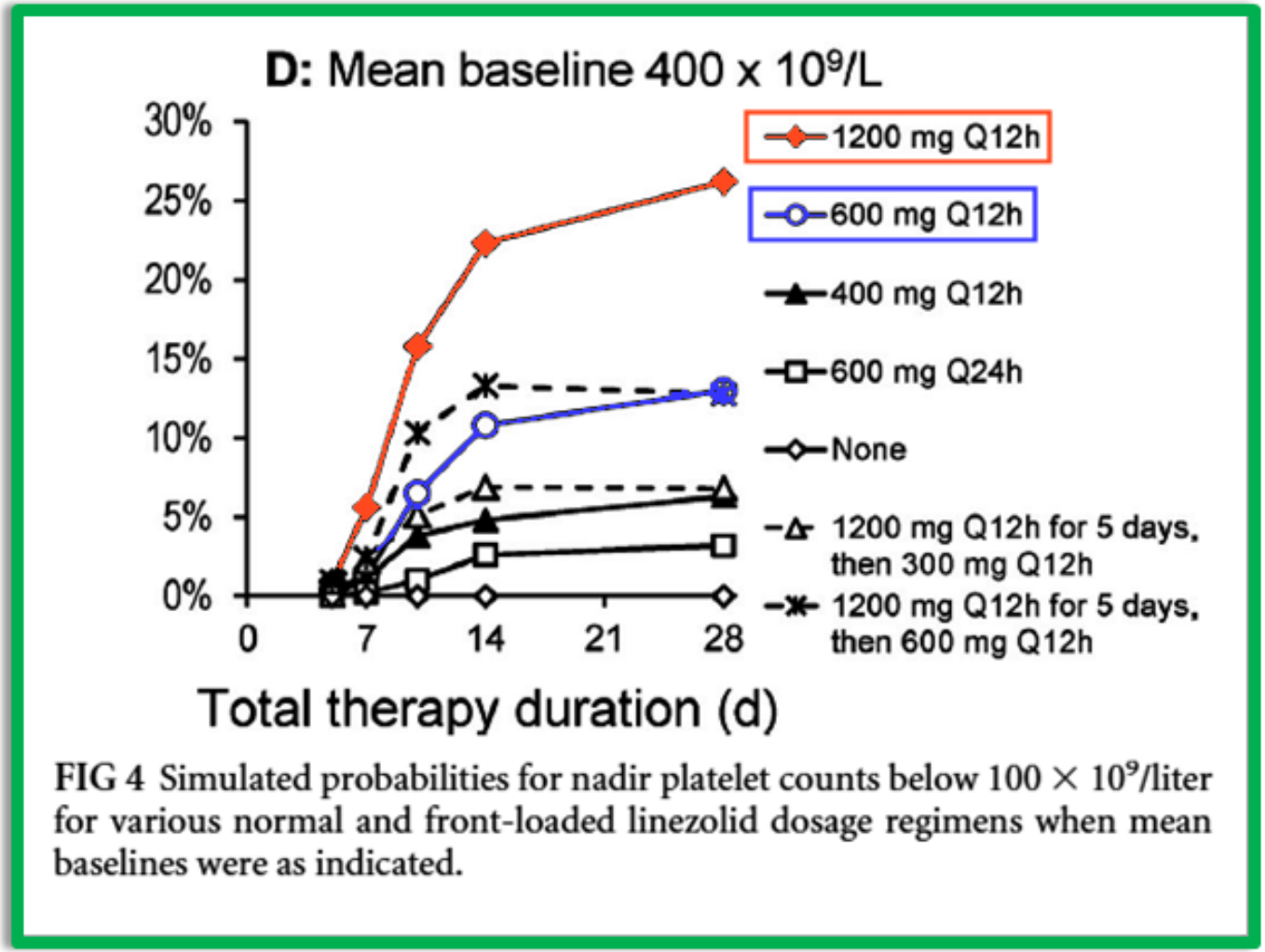


FIG 4 Simulated probabilities for nadir platelet counts below 100 × 10⁹/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

Wat is de realiteit bij patiënten ...

(Pharmacotherapy 2010;30(9):895–903)

Analysis of Linezolid-Associated Hematologic Toxicities in a Large Veterans Affairs Medical Center

Quentin Minson, Pharm.D., and Chris A. Gentry, Pharm.D.

Patients. Four hundred forty-four patients (mean age 63.7 yrs) who received 544 courses of linezolid from 2004–2007.

Conclusion. The overall rates of thrombocytopenia and anemia for patients receiving linezolid were found to be higher than those in phase III clinical trials. This may be attributable in part to the inclusion of patients with comorbidities that were exclusion criteria in the phase III clinical trials. Clinicians should be aware of variables associated with the development of severe thrombocytopenia and anemia in patients receiving linezolid so that they may predict which patients are likely to develop these toxicities and consider potential alternative therapies in those patients.

Minson & Gentry. Pharmacotherapy 2010;30:895-903 - PMID: 20795845

Stratificatie is belangrijk

Patients with thrombocytopenia			
no	yes	grade 1-2	grade 3-4
435 (87.2 %)	**64 (12.8 %)**	38 (7.6 %)	26 (5.2%)

grade 1: 75–99.9 x $10^3/mm^3$; grade 2: 50–74.9 x $10^3/mm^3$;
grade 3: 20–49.9 x $10^3/mm^3$; grade 4: < 20 x $10^3/mm^3$.

Minson & Gentry. Pharmacotherapy 2010;30:895-903 - PMID: 20795845

En u ziet waarom hier !

Patients with thrombocytopenia			
no	yes	grade 1-2	grade 3-4

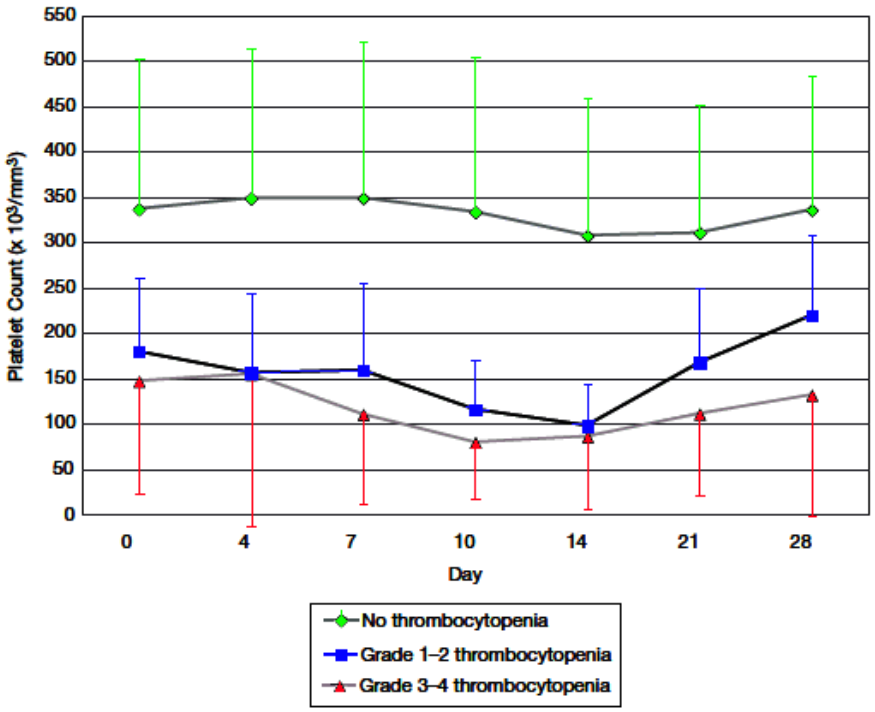


Figure 1. Mean ± SD platelet count during and/or after linezolid therapy in patients who subsequently developed no thrombocytopenia, grade 1–2 thrombocytopenia, and grade 3–4 thrombocytopenia. Platelet counts were significantly different between the no thrombocytopenia group and each of two thrombocytopenia groups at each time point ($p<0.0001$ by Tukey-Kramer analysis of variance). Platelet counts were not significantly different between the grade 1–2 and grade 3–4 toxicity groups at any time point.

En een andere realiteit....

Clinical Infectious Diseases 2006; 42:66–72

MAJOR ARTICLE

High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

Vin-Cent Wu,[1,2] Yu-Ting Wang,[2] Cheng-Yi Wang,[2] I.-Jung Tsai,[3] Kwan-Dun Wu,[2] Juey-Jen Hwang,[1,2] and Po-Ren Hsueh[2,4]

[1]Department of Internal Medicine, Yun-Lin Branch, and Departments of [2]Internal Medicine, [3]Pediatrics, and [4]Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

En een andere realiteit....

Clinical Infectious Diseases 2006; 42:66–72

MAJOR ART

High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

Vin-Cent Wu,[1,2] Yu-Ting Wang,[2] Cheng-Yi Wang,[2] I.-Jung Tsai,[3] Kwan-Dun Wu,[2] Juey- and Po-Ren Hsueh[2,4]

[1]Department of Internal Medicine, Yun-Lin Branch, and Departments of [2]Internal Medicine, [3]Pediatrics, and National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

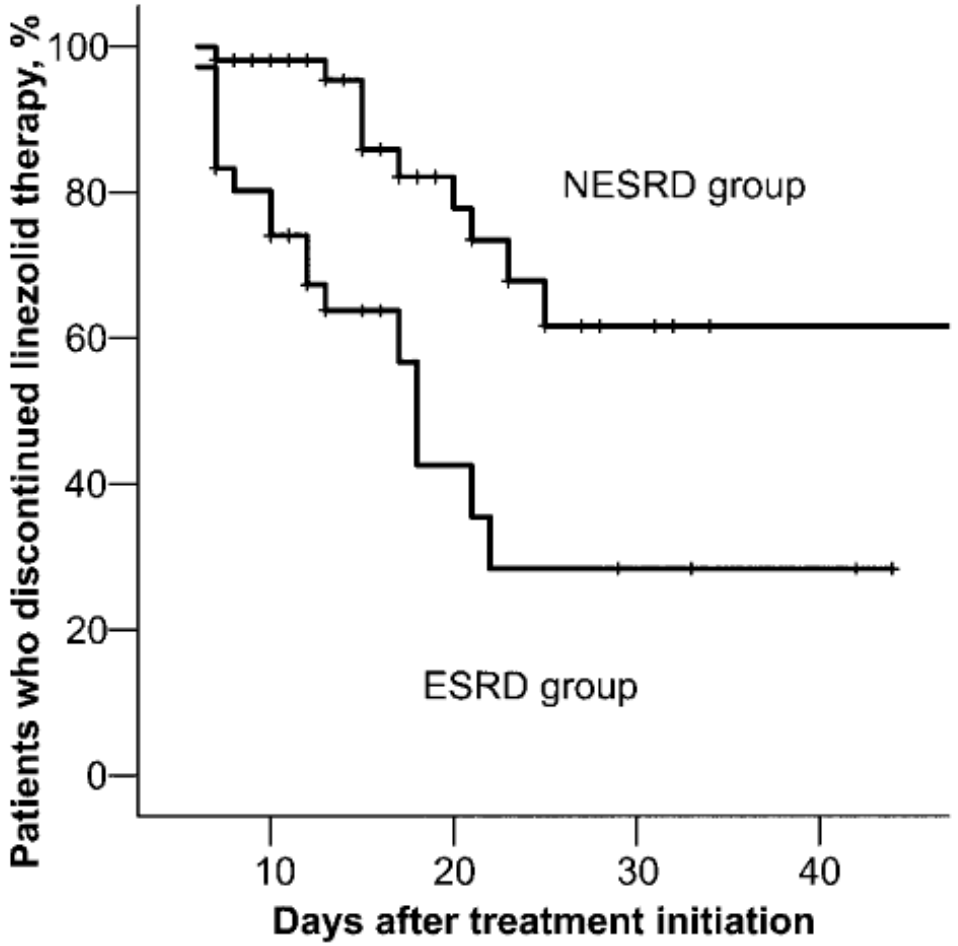


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

Kunnen bloedspiegels van linezolid variabel zijn?

International Journal of Antimicrobial Agents 51 (2018) 745–751

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Population pharmacokinetics/pharmacodynamics of linezolid in sepsis patients with and without continuous renal replacement therapy

Takeshi Ide [a,*], Yoshio Takesue [b], Kazuro Ikawa [c], Norifumi Morikawa [c], Takashi Ueda [b], Yoshiko Takahashi [d], Kazuhiko Nakajima [b], Kenta Takeda [a], Shinichi Nishi [a]

[a] *Division of Intensive Care Unit, Hyogo College of Medicine, Hyogo, Japan*
[b] *Department of Infection Control and Prevention, Hyogo College of Medicine, Hyogo, Japan*
[c] *Department of Clinical Pharmacotherapy, Hiroshima University, Hiroshima, Japan*
[d] *Department of Pharmacy, The Hospital of Hyogo College of Medicine, Hyogo, Japan*

Bloedspiegels zijn erg variabel !

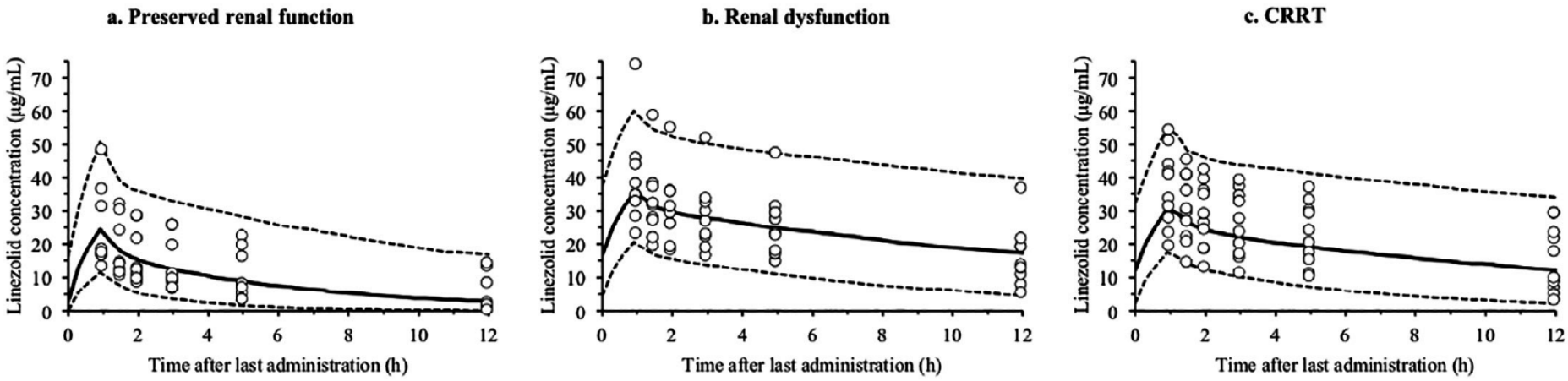


Fig. 1. Observed plasma concentrations and simulation curves for linezolid after the last administration of 600 mg q12h (1-h infusion) in patients with preserved renal function, patients with renal dysfunction, and patients on continuous renal replacement therapy (CRRT). The solid lines represent the median predicted concentrations and the dashed lines represent the 95% confidence intervals of the predicted concentrations, respectively, based on each population pharmacokinetic parameter (1000 replicates using visual predictive check method).

Een andere evidentie...

Zoller et al. Critical Care 2014, 18:R148
http://ccforum.com/content/18/4/R148

CRITICAL CARE

RESEARCH Open Access

Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study

Michael Zoller[1], Barbara Maier[2], Cyrill Hornuss[1], Christina Neugebauer[1], Gundula Döbbeler[1], Dorothea Nagel[2], Lesca Miriam Holdt[2], Mathias Bruegel[2], Thomas Weig[1], Béatrice Grabein[3], Lorenz Frey[1], Daniel Teupser[2], Michael Vogeser[2] and Johannes Zander[2*]

Abstract

Introduction: Severe infections in intensive care patients show high morbidity and mortality rates. Linezolid is an antimicrobial drug frequently used in critically ill patients. Recent data indicates that there might be high variability of linezolid serum concentrations in intensive care patients receiving standard doses. This study was aimed to evaluate whether standard dosing of linezolid leads to therapeutic serum concentrations in critically ill patients.

Methods: In this prospective observational study, 30 critically ill adult patients with suspected infections received standard dosing of 600 mg linezolid intravenously twice a day. Over 4 days, multiple serum samples were obtained from each patient, in order to determine the linezolid concentrations by liquid chromatography tandem mass spectrometry.

Results: A high variability of serum linezolid concentrations was observed (range of area under the linezolid concentration time curve over 24 hours (AUC_{24}) 50.1 to 453.9 mg/L, median 143.3 mg*h/L; range of trough concentrations (C_{min}) < 0.13 to 14.49 mg/L, median 2.06 mg/L). Furthermore, potentially subtherapeutic linezolid concentrations over 24 hours and at single time points (defined according to the literature as AUC_{24} < 200 mg*h/L and C_{min} < 2 mg/L) were observed for 63% and 50% of the patients, respectively. Finally, potentially toxic levels (defined as AUC_{24} > 400 mg*h/L and C_{min} > 10 mg/L) were observed for 7 of the patients.

Conclusions: A high variability of linezolid serum concentrations with a substantial percentage of potentially subtherapeutic levels was observed in intensive care patients. The findings suggest that therapeutic drug monitoring of linezolid might be helpful for adequate dosing of linezolid in critically ill patients.

Trial registration: Clinicaltrials.gov NCT01793012. Registered 24 January 2013.

Een andere evidentie...

Zoller et al. Critical Care 2014, 18:R148
http://ccforum.com/content/18/4/R148

CRITICAL CARE

RESEARCH Open Access

Variability of linezolid concentrations after standard dosing in critically ill patients: a ... l study

...leugebauer[1], Gundula Döbbeler[1], Dorothea Nagel[2], ...atrice Grabein[3], Lorenz Frey[1], Daniel Teupser[2],

...how high morbidity and mortality rates. Linezolid is an ...Recent data indicates that there might be high variability ... receiving standard doses. This study was aimed to ...rapeutic serum concentrations in critically ill patients.

...lly ill adult patients with suspected infections received ...day. Over 4 days, multiple serum samples were obtained ...centrations by liquid chromatography tandem mass

...s was observed (range of area under the linezolid ...3.9 mg/L, median 143.3 mg*h/L; range of trough ...g/L). Furthermore, potentially subtherapeutic linezolid ...fined according to the literature as AUC_{24} < 200 mg*h/L ...e patients, respectively. Finally, potentially toxic levels ... observed for 7 of the patients.

...rations with a substantial percentage of potentially ...nts. The findings suggest that therapeutic drug ...ng of linezolid in critically ill patients.

...ed 24 January 2013.

Resultaten:

Er werd een grote variatie in serum linezolidconcentraties waargenomen...

- bereik van AUC24h: 50,1 tot 453,9 mg / L,
- bereik van Cmin <0,13 tot 14,49 mg / L
- potentieel sub-therapeutische linezolid concentraties
  AUC24h < 200 mg * u/L en C_{min} <2 mg / L) voor respectievelijk 63% en 50% van de patiënten.
- potentieel toxische niveaus
  (AUC24h > 400 mg * h / L en C_{min}> 10 mg / L bij 7/30 de patiënten (23%)).

What could be the response?

- Give more?
- Give less?
- Give something else ?

Wat moet het antwoord zijn?

- Meer geven?
- Minder geven?
- Geef iets anders ?

Geef wat nodig is → voer therapeutische monitoring uit

The same may happen for linezolid …

Doe dat niet !

Een goed uitgevoerde studie

J Antimicrob Chemother 2012; **67**: 2034–2042
doi:10.1093/jac/dks153 Advance Access publication 2 May 2012

Journal of Antimicrobial Chemotherapy

Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients

Federico Pea[1]*, Pierluigi Viale[2], Piergiorgio Cojutti[1], Barbara Del Pin[2], Eleonora Zamparini[2] and Mario Furlanut[1]

[1]Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Department of Experimental and Clinical Medicine, Medical School, University of Udine, Udine, Italy; [2]Clinic of Infectious Diseases, Department of Internal Medicine, Geriatrics and Nephrologic Diseases, University of Bologna, Bologna, Italy

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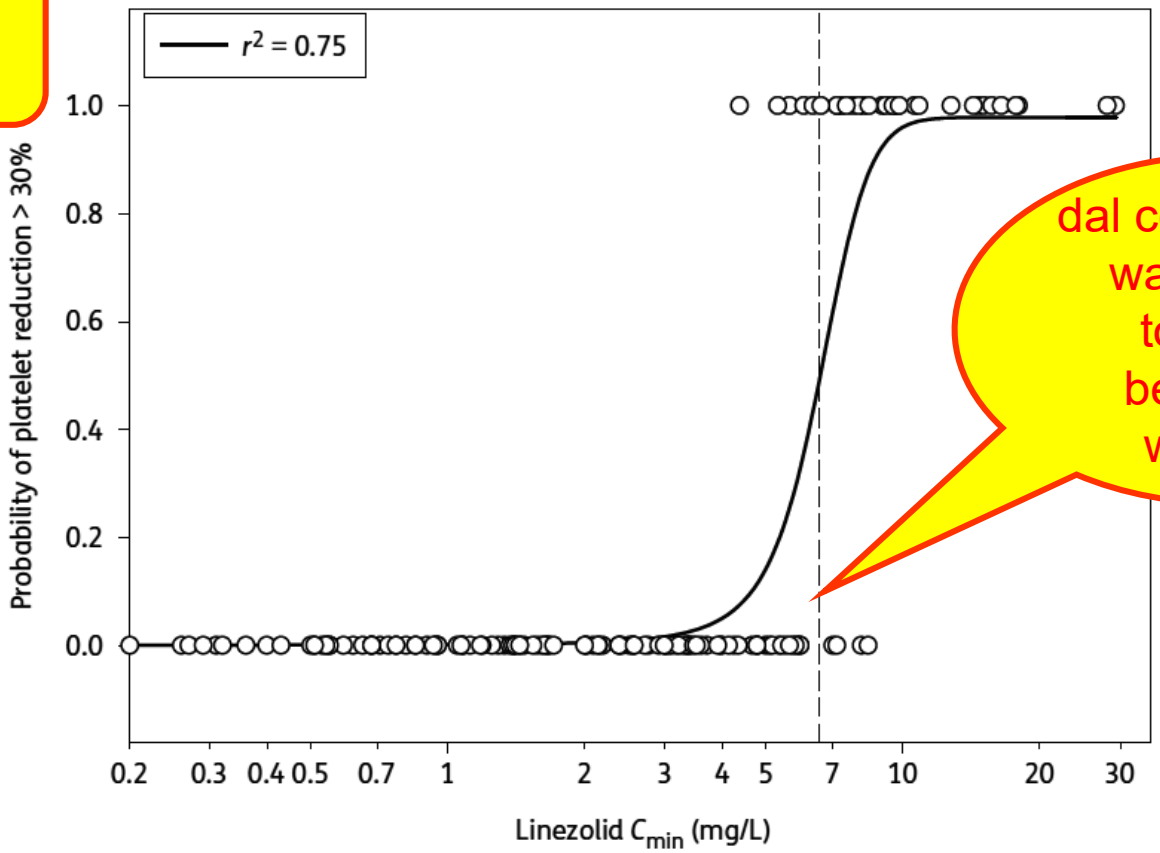
Received 23 February 2012; accepted 1 April 2012

Objectives: Prolonged treatment with linezolid may cause toxicity. The purpose of this study was to define pharmacodynamic thresholds for improving safety outcomes of linezolid.

Linezolid: relatie tussen toxiciteit en C_{min}

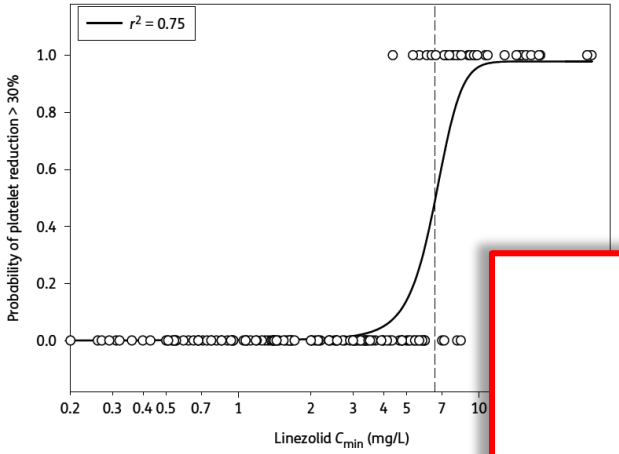
kans op bloedplaatjes vermindering



dal concentratie waarboven toxiciteit belangrijk wordt…

Figure 3. Linezolid C_{min} and logistic regression model for thrombocytopenia. The symbols refer to the C_{min} observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the C_{min} value predicting 50% probability of thrombocytopenia.

De relatie houdt stand voor C_{min} zoals voor AUC *



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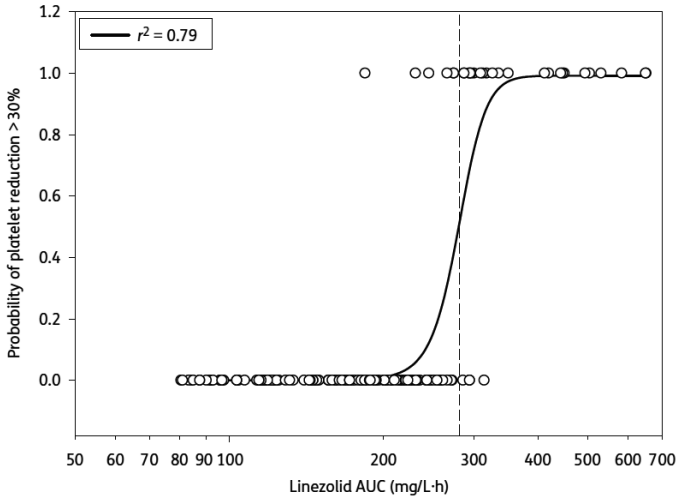


Figure 4. Linezolid AUC_{24} and logistic regression model for thrombocytopenia. The symbols refer to the AUC_{24} estimates over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the AUC_{24} predicting 50% probability of thrombocytopenia.

* covariabelen in de klinische opzet

Conclusions: Maintenance over time of C_{min} between 2 and 7 mg/L and/or of AUC_{24} between 160 and 300 mg/L·h may be helpful in improving safety outcomes while retaining appropriate efficacy in adult patients receiving prolonged linezolid treatment.

Linezolid monitoring mogelijkheden

Observational Study > Basic Clin Pharmacol Toxicol. 2017 Oct;121(4):303-308. doi: 10.1111/bcpt.12797. Epub 2017 Jun 19.

A 10-Year Experience of Therapeutic Drug Monitoring (TDM) of Linezolid in a Hospital-wide Population of Patients Receiving Conventional Dosing: Is there Enough Evidence for Suggesting TDM in the Majority of Patients?

Federico Pea [1 2], Pier Giorgio Cojutti [1 2], Massimo Baraldo [1 2]

Affiliations + expand

PMID: 28419737 DOI: 10.1111/bcpt.12797

Free article

Onze studie suggereert dat TDM een waardevolle benadering zou kunnen zijn bij het optimaliseren van de blootstelling aan linezolid bij de meeste patiënten.

> J Antimicrob Chemother. 2019 Dec 1;74(12):3588-3595. doi: 10.1093/jac/dkz374.

Proactive therapeutic drug monitoring (TDM) may be helpful in managing long-term treatment with linezolid safely: findings from a monocentric, prospective, open-label, interventional study

Pier Giorgio Cojutti [1 2], Maria Merelli [3], Matteo Bassetti [1 3], Federico Pea [1 2]

Affiliations + expand

PMID: 31504570 DOI: 10.1093/jac/dkz374

Proactieve TDM van linezolid kan nuttig zijn bij het voor-komen of herstellen van dosis-afhankelijke trombo-cytopenie, zelfs als de behandeling langer dan 28 dagen duurt.

Waar zijn we aanbeland?...

1. Basis microbiologische parameter: MIC

2. Farmacokinetiek (PK) en Farmacodynamie (PD)
   het concept en de methode
   het gebruik van de grootste antibioticaklassen

3. Toepassingen
   - EUCAST breekpunten
   - Therapeutic Drug Monitoring
   - continu infuus

4. Resistentie

5. Geselecteerde referenties

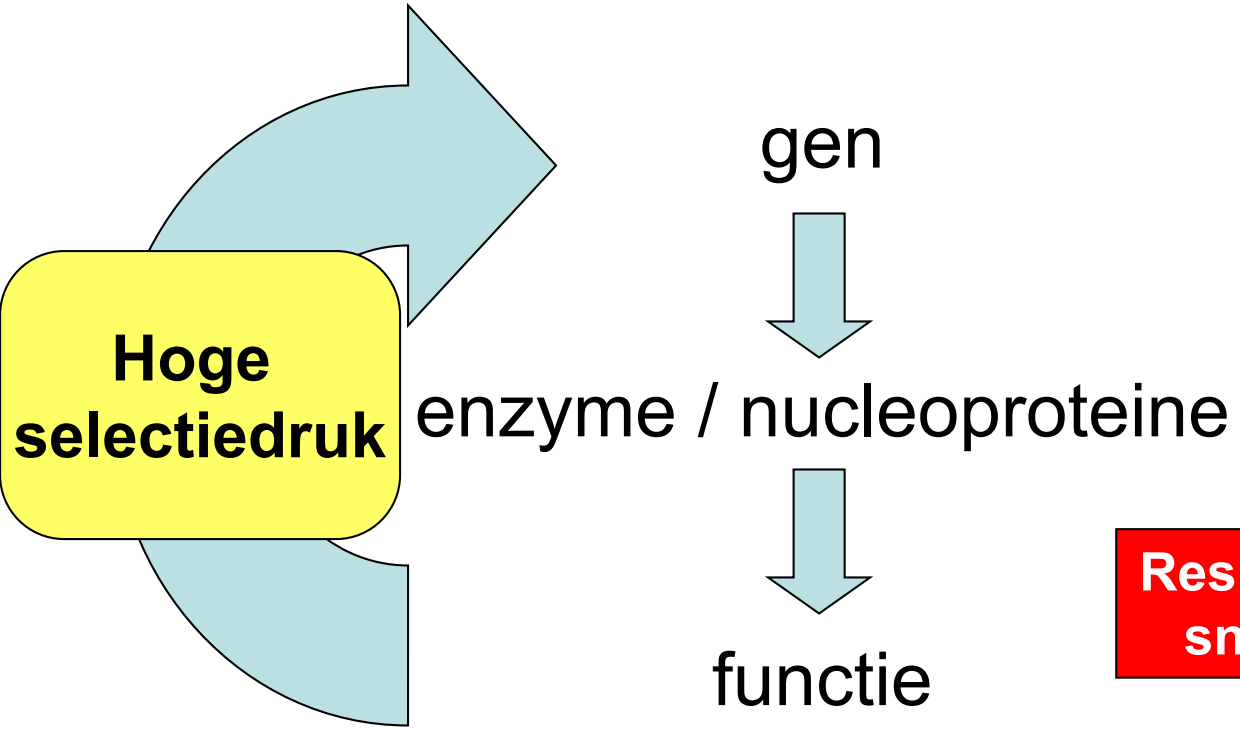
PK/PD en resistentie:
Hoe kunnen we hier tegen vechten (in enkele dias)

- Uitroeien van
  - Mutaties
  - Effluxpompen
- Concentraties die mutaties en/of efflux voorkomen
- En in de praktijk (voorbeeld met chinolonen)…

De vier reden om bacteriën uit te roeien…

- Dode bacteriën muteren niet meer…
  (eenvoudige toepassing op de principes van Darwin…)
- Als ze dood zijn kunnen ze hun buur niet meer contamineren…
  (basisprincipe van acties in de epidemiologie…)
- Hoe dan ook, als Pasteur gelijk heeft (en hij heeft gelijk…), moet men de ziekteverwekker niet uitschakelen om te genezen?
  (fysiopathologisch principe van infectieziekten…)
- Wenst u niet dat uw patiënt veel sneller geneest en voor goed?
  (een tevreden patiënt is er één die niet terugkomt… voor hetzelfde probleem)

Selectie van mutanten: de rol van antibiotica...



antibioticum
weinig efficiënt...

Resistente bacteriën kunnen snel geselecteerd worden

Een directe visualisatie…

ANTIBIOTIC RESISTANCE

Spatiotemporal microbial evolution on antibiotic landscapes

Michael Baym,[1] Tami D. Lieberman,[1]* Eric D. Kelsic,[1] Remy Chait,[1]† Rotem Gross,[2] Idan Yelin,[2] Roy Kishony[1,2,3]‡

A key aspect of bacterial survival is the ability to evolve while migrating across spatially varying environmental challenges. Laboratory experiments, however, often study evolution in well-mixed systems. Here, we introduce an experimental device, the microbial evolution and growth arena (MEGA)–plate, in which bacteria spread and evolved on a large antibiotic landscape (120 × 60 centimeters) that allowed visual observation of mutation and selection in a migrating bacterial front. While resistance increased consistently, multiple coexisting lineages diversified both phenotypically and genotypically. Analyzing mutants at and behind the propagating front, we found that evolution is not always led by the most resistant mutants; highly resistant mutants may be trapped behind more sensitive lineages. The MEGA-plate provides a versatile platform for studying microbial adaption and directly visualizing evolutionary dynamics.

Baym *et al*. Science. 2016; 353:1147-51

zie zip

Een directe v

ANTIBIOTIC RESISTANCE

Spatiotemporal mi on antibiotic lands

Michael Baym,[1] Tami D. Lieberman,[1]* Eric
Idan Yelin,[2] Roy Kishony[1,2,3]‡

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Baym *et al*. Science. 2016; 353:1147-5

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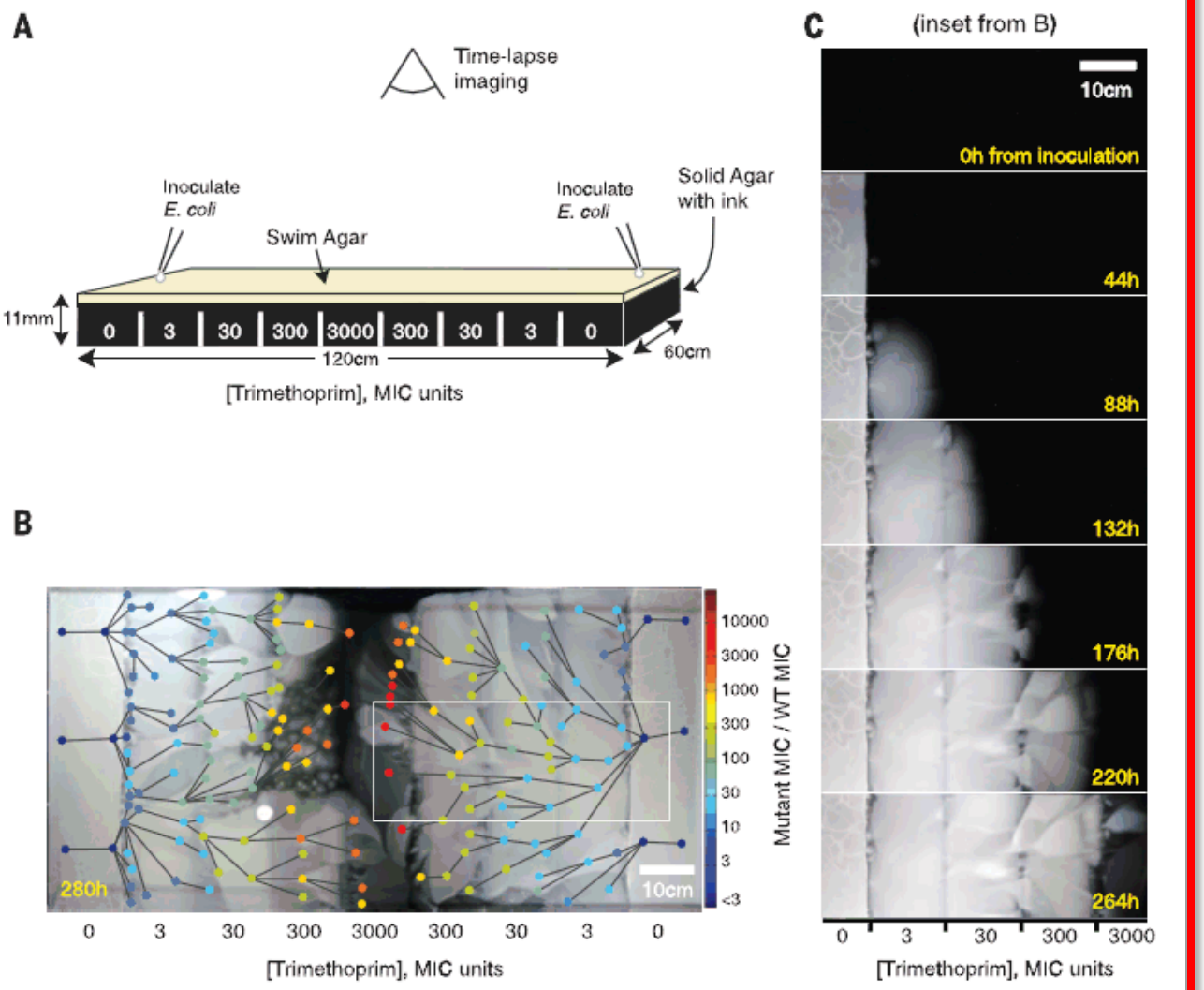

Fig. 1. An experimental device for studying microbial evolution in a spatially structured environment. (**A**) Setup of the four-step gradient of trimethoprim (TMP). Antibiotic is added in sections to make an exponential gradient rising inward. (**B**) The four-step TMP MEGA-plate after 12 days. *E. coli* appear as white on the black background. The 182 sampled points of clones are indicated by circles, colored by their measured MIC. Lines indicate video-imputed ancestry. (**C**) Time-lapse images of a section of the MEGA-plate. Repeated mutation and selection can be seen at each step. Images have been aligned and linearly contrast-enhanced but are otherwise unedited.

Een directe visualisatie…

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Baym *et al*. Science

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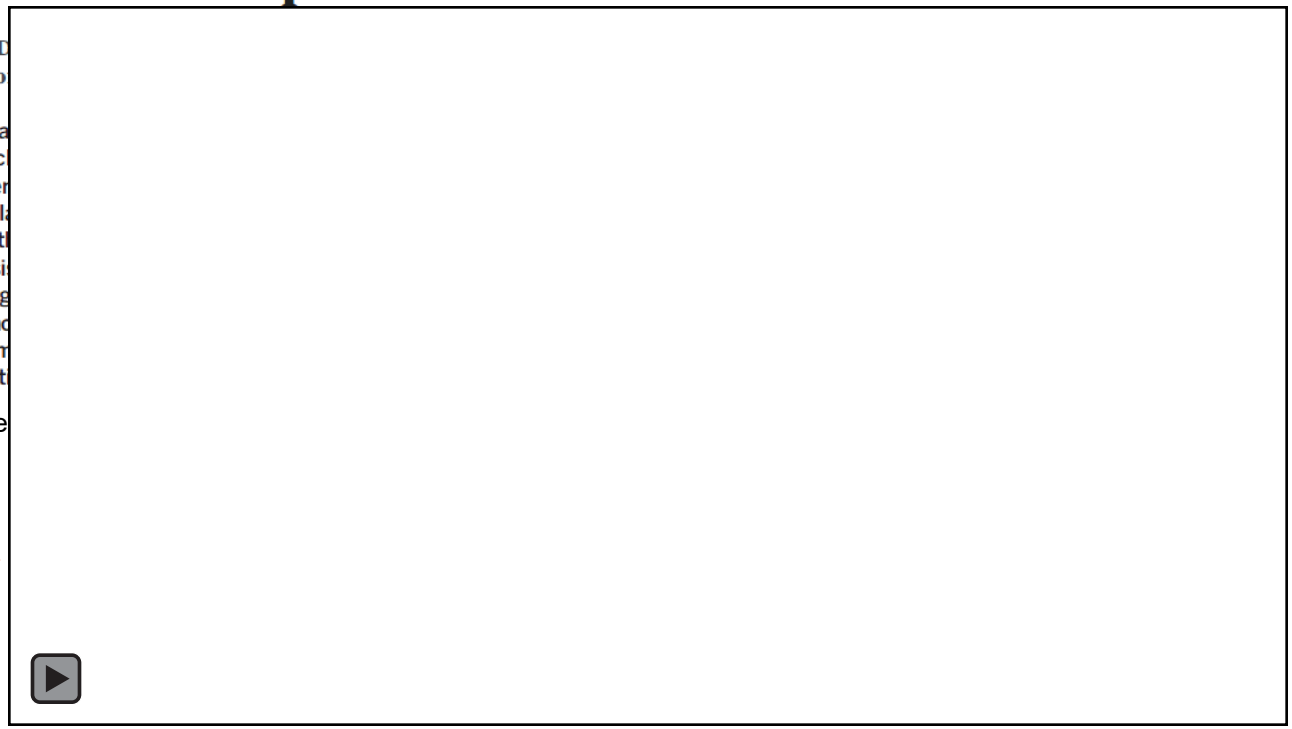

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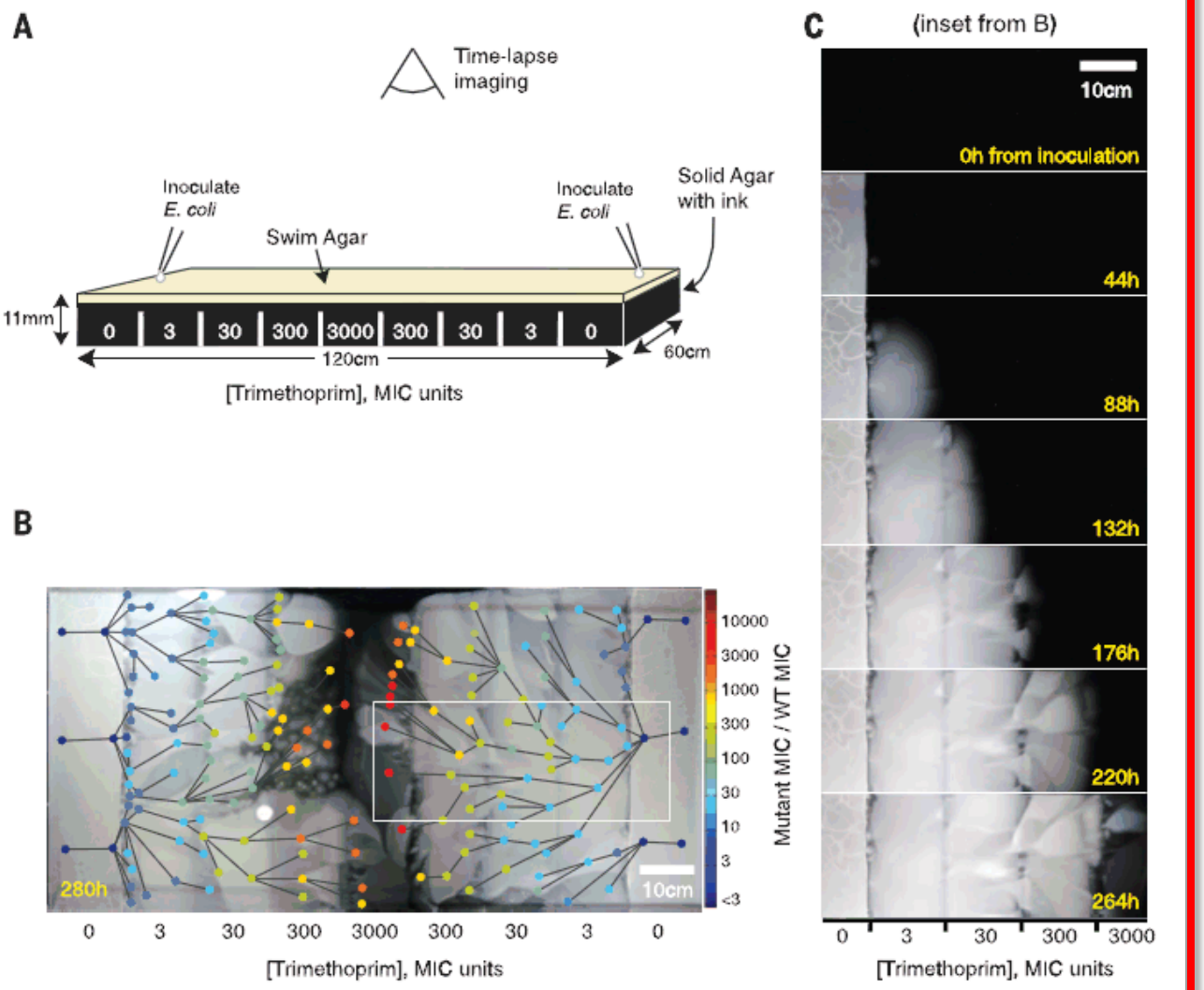

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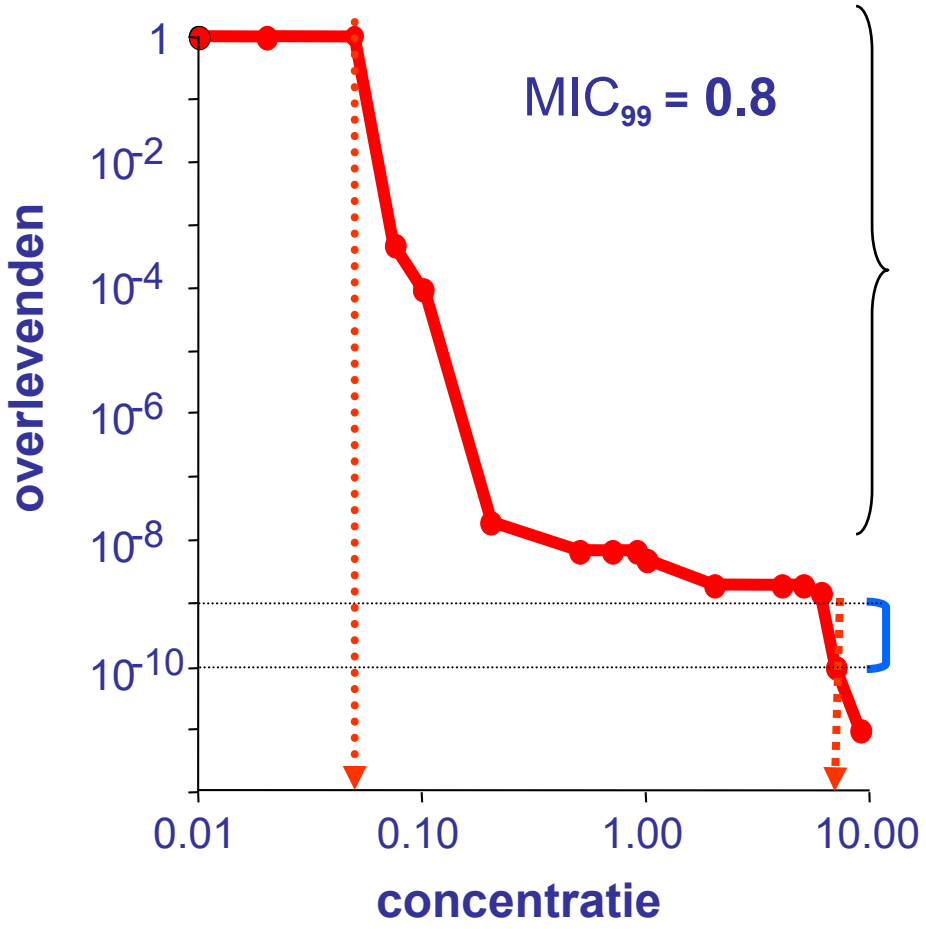
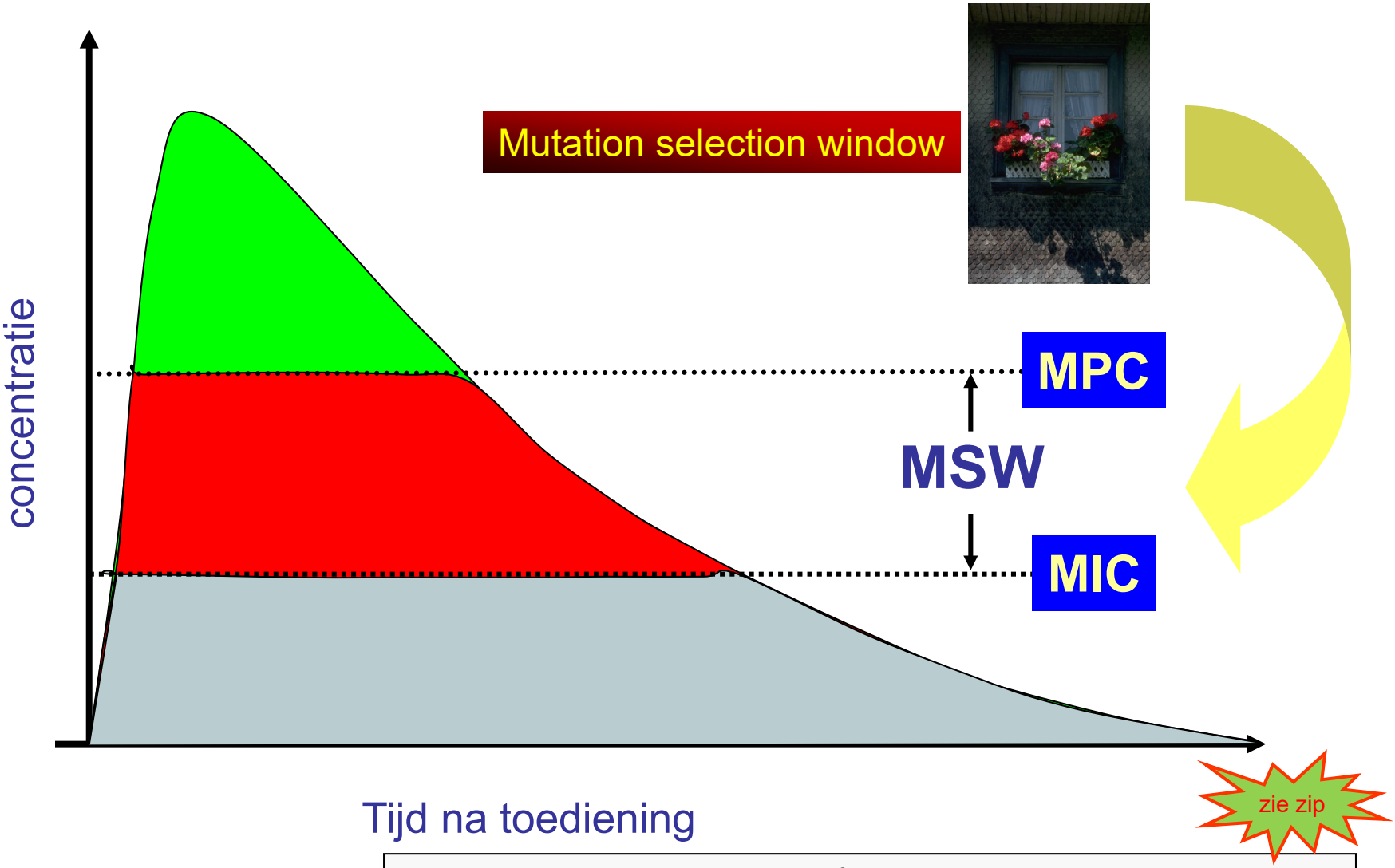
Concentratie die mutaties/efflux voorkomt...
(Mutation Preventing Concentration [MPC])

Voorbeeld: bactericide werking van een FQ tegenover *Mycobacterium bovis*



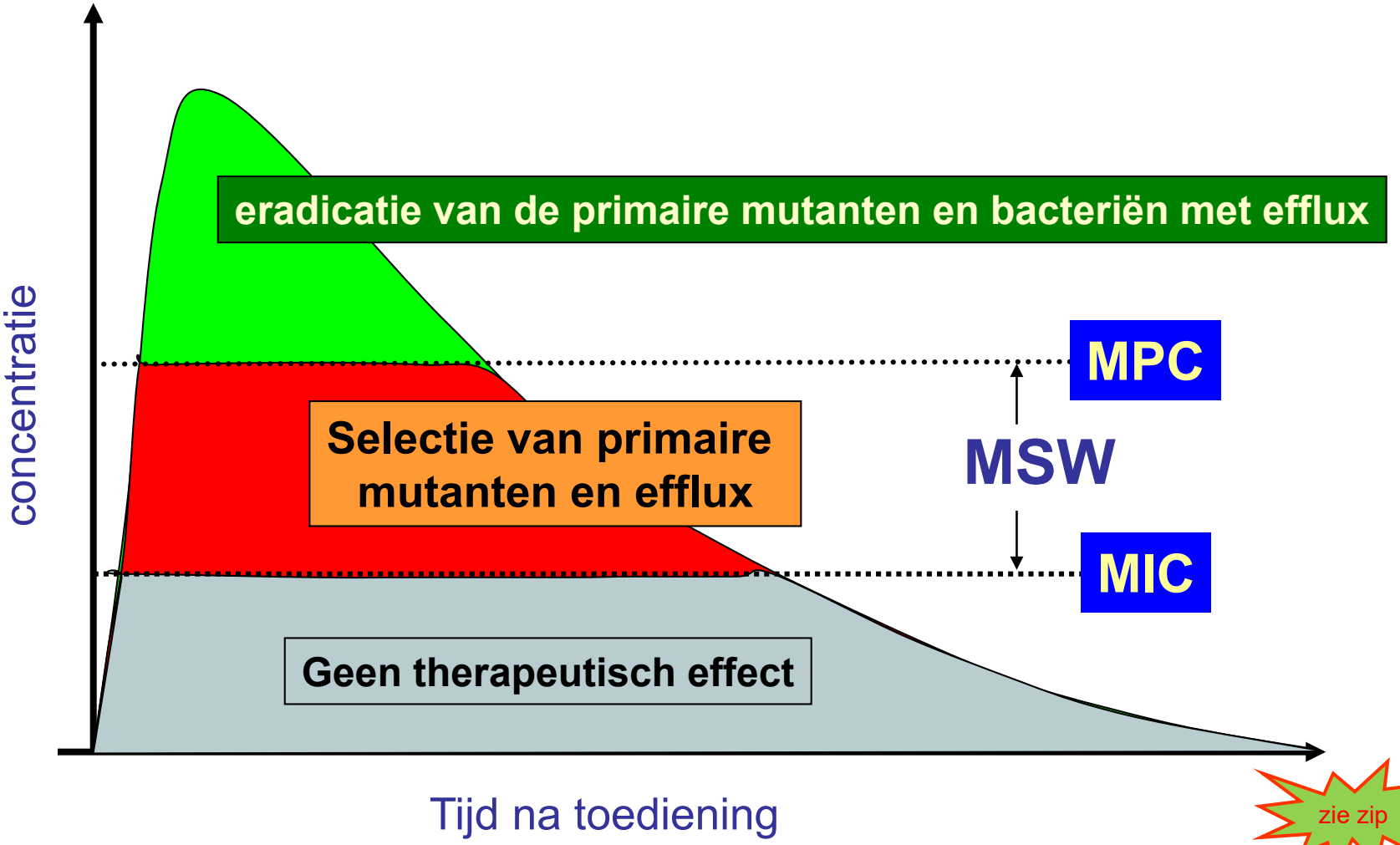
Dong *et al*; AAC 43:1756-1758

Venster waarbinnen selectie van mutaties en efflux plaatsvindt…



concept overgenomen van Drlica & Zhao, *Rev. Med. Microbiol*. 2004, 15:73-80
en *Journal of Antimicrobial Chemotherapy* 2008, 62:434–436

Venster waarbinnen selectie van mutaties plaatsvindt…



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en *Journal of Antimicrobial Chemotherapy* 2008, 62:434–436

PK/PD en resistentie: toepassing voor chinolonen

Preventie van resistentie en doeltreffendheid:

- piek / MIC > 10
  (om de MPC te bereiken)
- AUC / MIC > 100
  (niet volledig immuuncompetente patiënt)

pieken en AUC…

Nota: dit kan ook het geval zijn door te laagste AUC_{24h} voor

- vancomycine (selectie van zo-genoemd "hetero-VISA")
- tigecycline en macroliden (overexpressie of efflux pompen)

AUC_{24h} / MIC = 125 en Piek / MIC > 10 als limietwaarden voor de gevoeligheid aan FQ

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free	Proposed PK/PD upper limit of sensitivity (µg/ml) for: Efficacy[b]	Proposed PK/PD upper limit of sensitivity (µg/ml) for: Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

zie zip

Een voorstel voor β-lactams?

J Antimicrob Chemother 2017; **72**: 1421–1428
doi:10.1093/jac/dkx001 Advance Access publication 31 January 2017

Journal of Antimicrobial Chemotherapy

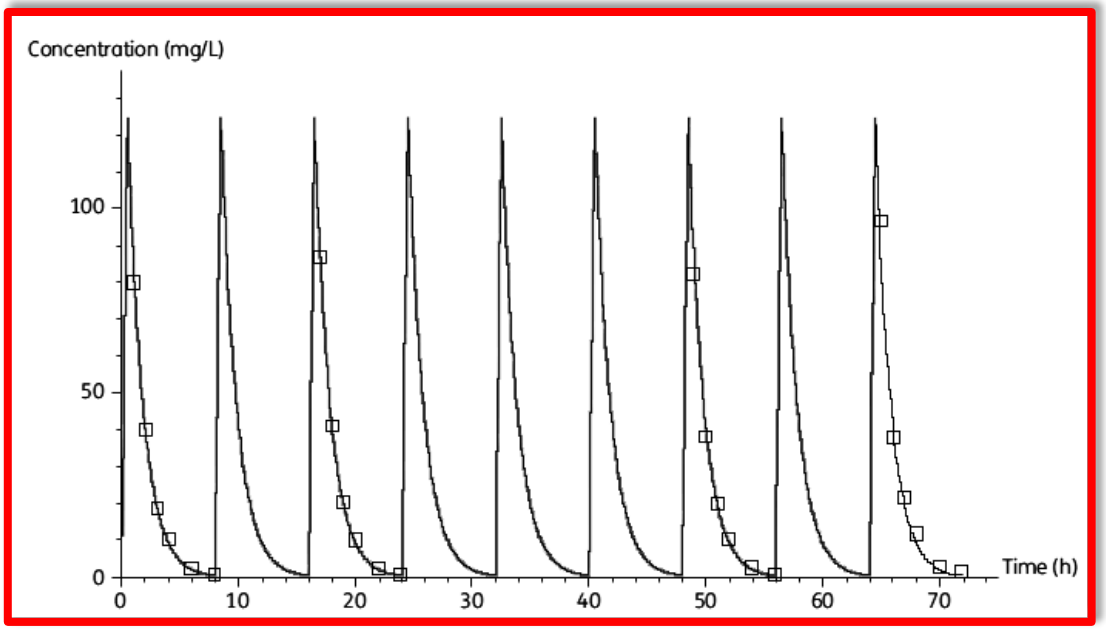
Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam[1]*, Kai-Tai Chang[1], Jian Zhou[1], Kimberly R. Ledesma[1], Kady Phe[1], Song Gao[1], Françoise Van Bambeke[2], Ana María Sánchez-Díaz[3], Laura Zamorano[4], Antonio Oliver[4] and Rafael Cantón[3]

[1]University of Houston, Houston, TX, USA; [2]Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; [3]Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [4]University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain

Tam *et al.* J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Verschillende dosissen en blootstellingen van β-lactams werden gesimuleerd in een holvezel (*hollow fiber*) infectiemodel



Een voorstel voor β-lactams?

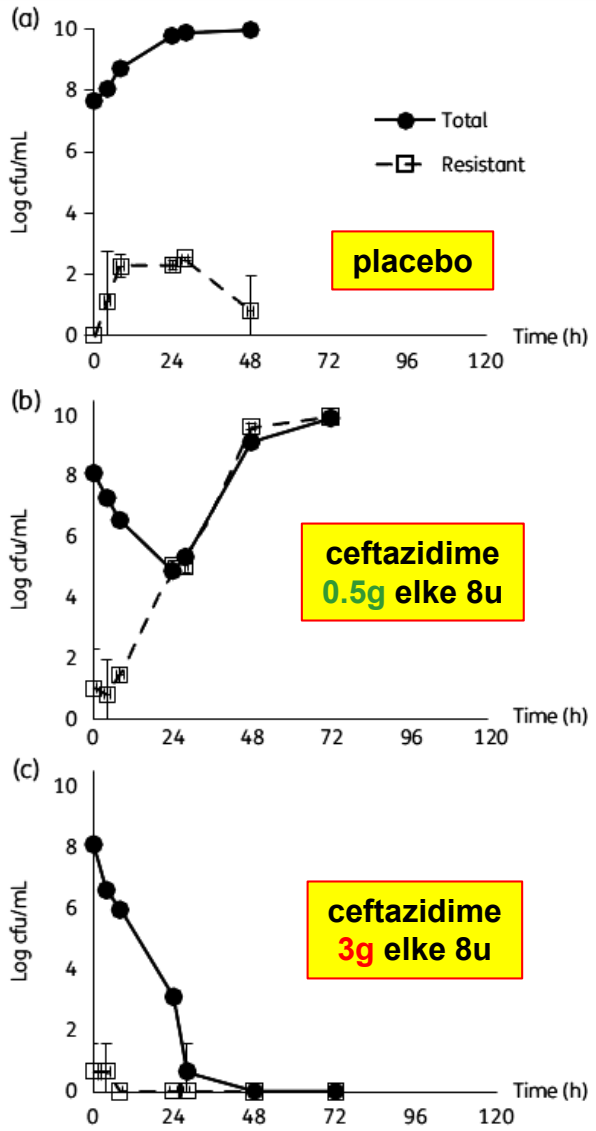


Figure 2. Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h (C_{min}/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h (C_{min}/MIC = 7.7) (c). Data are shown as mean ± SD.

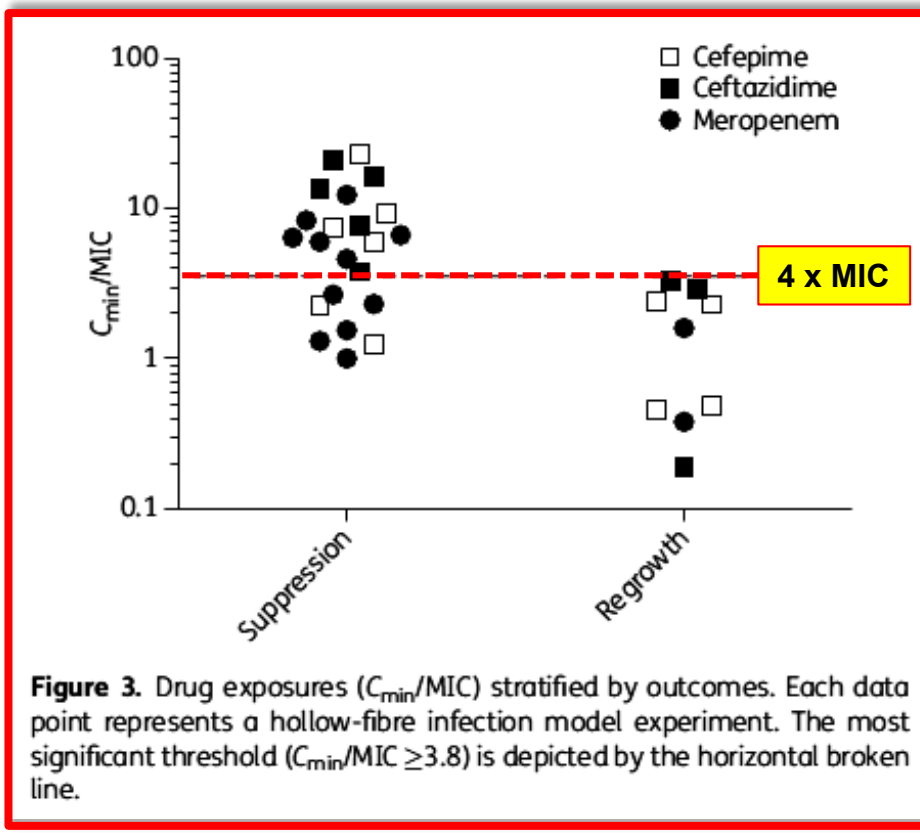


Figure 3. Drug exposures (C_{min}/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold (C_{min}/MIC ≥3.8) is depicted by the horizontal broken line.

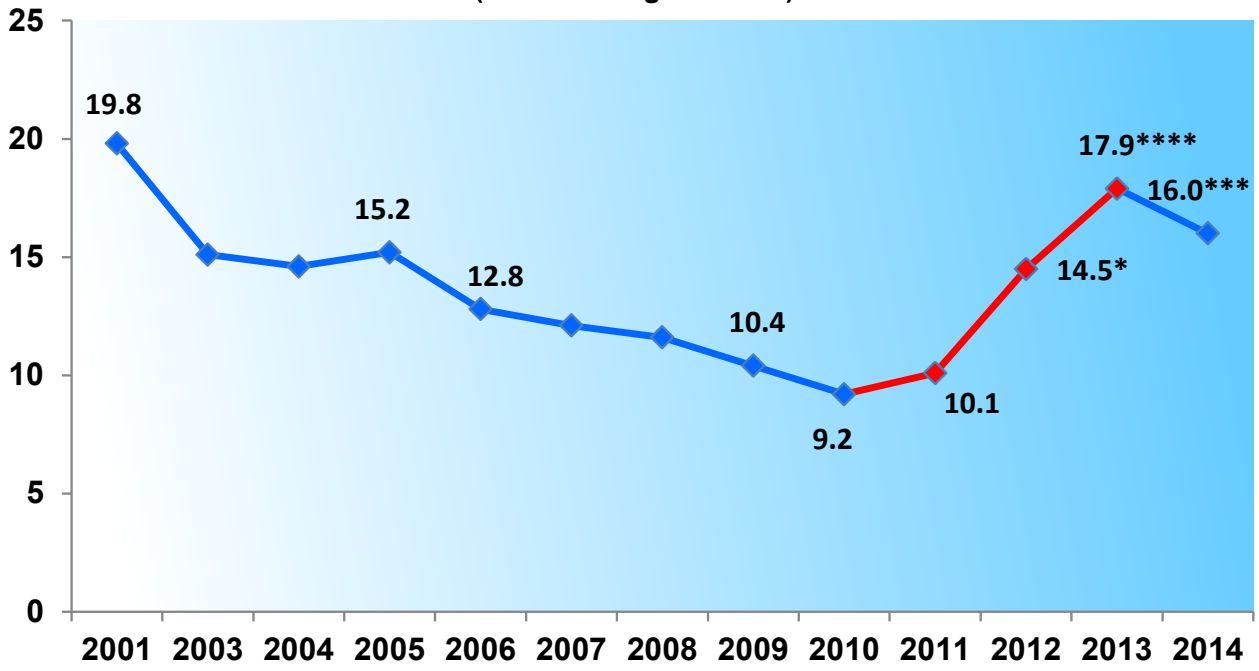
Om resistentie te voorkomen moet de C_{min} van β-lactams > 4 x MIC (gemiddelde) blijven … wat hogere doseringen dan wordt goedgekeurd kan vereisen…

Tam et al. J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Nu, opgepast: variatie van resistentie doorheen de tijd …

S. pneumoniae – Belgische gegevens

Fig. 14: Evolution of Penicillin Non-susceptibility Rates (%)
(*: level of significance)



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INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE

http://bacterio.wiv-isp.be/reporting/reportspdf/SP3013avec%20couverture.pdf

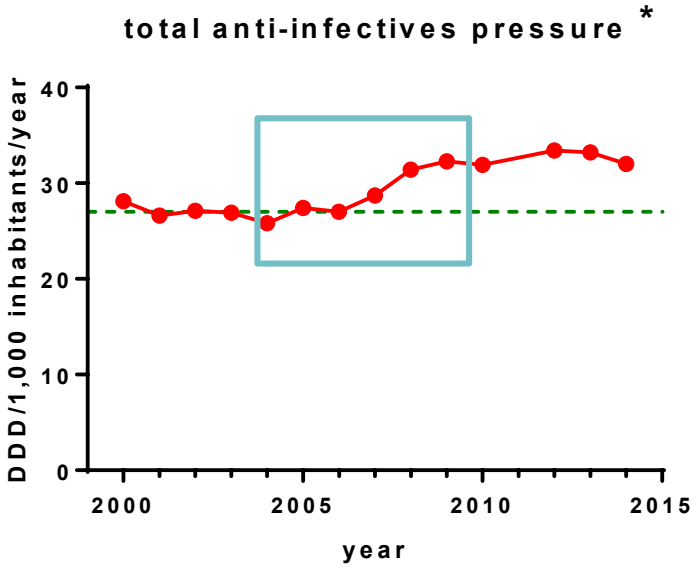
Belgische campagnes: ieder jaar sinds 2000…

http://www.red-antibiotica.org/ (Nederlands)
http://www.antibiotiques.org/ (Frans)

http://www.belgium.be/fr/actualites/2013/news_campagne_antibiotiques_2013

http://www.gebruikantibioticacorrect.be/nl/lees-tante-biotica-online

Magere lange termijn (officiële) resultaten qua antibiotica gebruik…



* defined as DDD's of ATC class J drugs (anti-infectives for systemic use) reimbursed in the community (~ 85% antibiotics)

Oorspong:
http://www.inami.fgov.be/fr/statistiques/medicament/Pages/statistiques-medicaments-pharmanet-01.aspx#.V1wBn6JYyE0
(Frans)
http://www.inami.fgov.be/nl/statistieken/geneesmiddel/Paginas/statistieken-geneesmiddelen-farmanet-01.aspx#.V1wDHKJYyE0
(Nederlands)

Or estimation of no. of

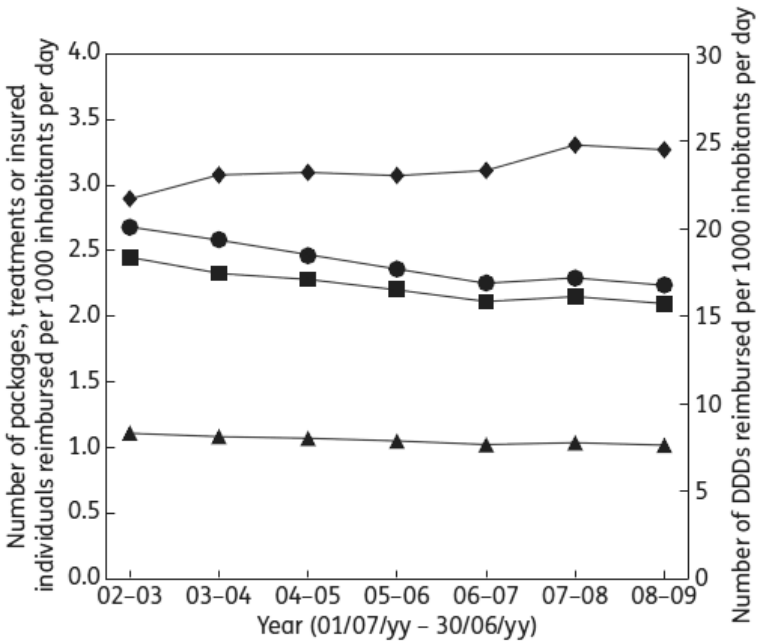
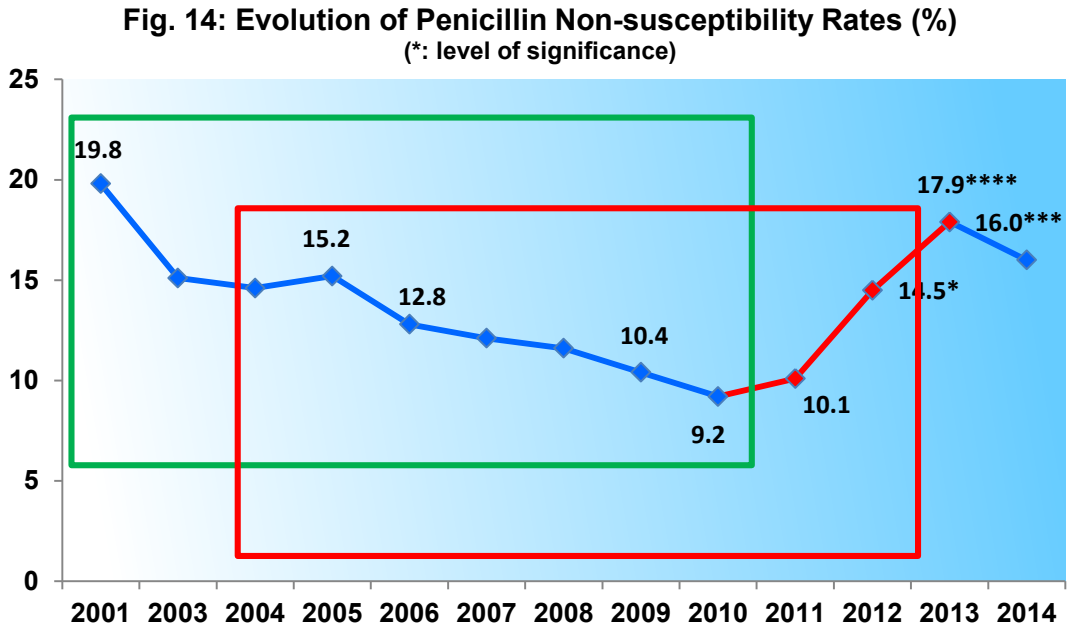
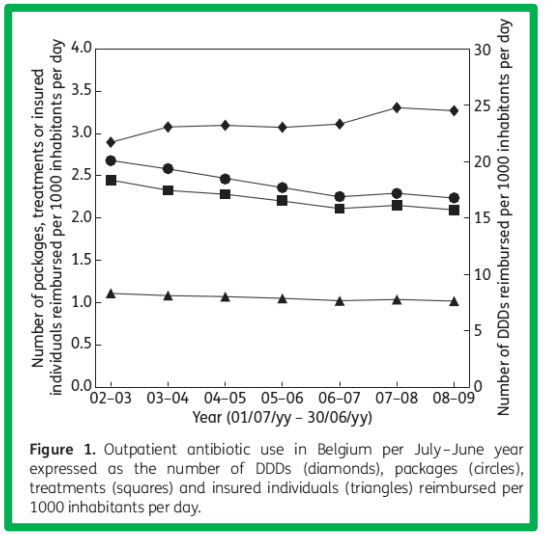


Figure 1. Outpatient antibiotic use in Belgium per July–June year expressed as the number of DDDs (diamonds), packages (circles), treatments (squares) and insured individuals (triangles) reimbursed per 1000 inhabitants per day.

Coenen *et al.* J Antimicrob Chemother 2014; 69: 529–534 – PMID: 24084641

Dus waarom een daling en daarna een stijging in resistentie ?





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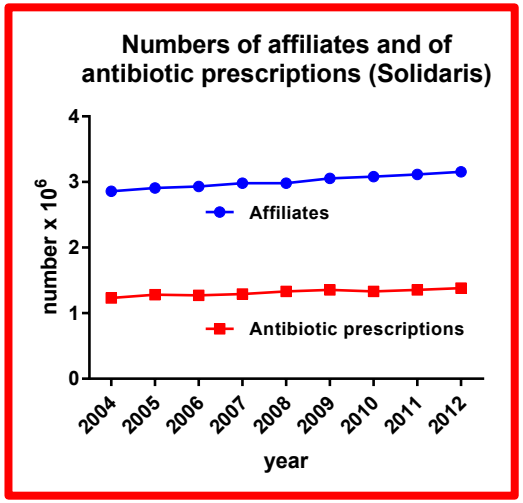


Relaties zijn zeker niet lineair…

Oorsprong van resistentie gedurende de behandeling

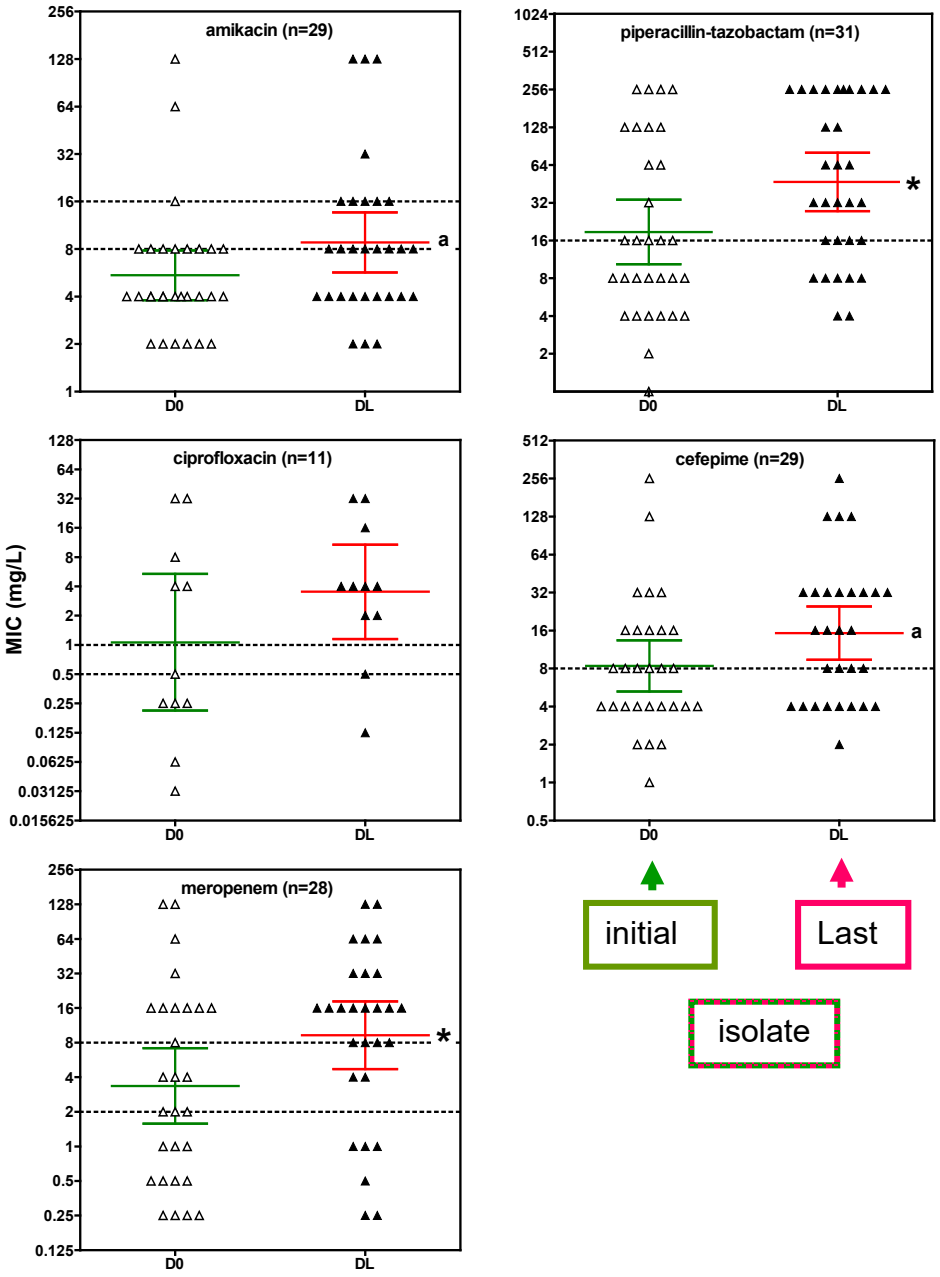
P. aeruginosa successive clonal isolates from the same patient (all patients treated with large doses of 1 to 3 antibiotics)

- D0: initial isolate
  DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

[a] $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)



Riou, *et al. Int J Antimicrob Agents.* 2010;36:513-22

Wat kan resistentie veroorzaken… en wat kunt u daaraan doen?

- Totaal aantal antibiotica?

Ja, maar niet de enige reden…

- Te breed spectrum antibiotica?
  - neveneffecten op de commensale flora
  - resistentie in "non-target" doelwitten

Het is nu tijd voor betere en sneller diagnostische tools…

- Te lage dosering?
  - onvoldoende uitroeien van het doelwit
  - gemakkelijke selectie van een laag niveau van resistentie (efflux, bv.) dat tot een hoog niveau van resistentie kan leiden

Denk aan TDM…
- **β-lactam**
- **chinolonen**
- **linezolid**

- Te lange behandeling?
  - meer kans op selectie van resistente organismen
  - accumulatie van mutaties en expressie veranderingen

Gebruik van voorspellende infectie biomarkers

Waar zijn we aanbeland?...

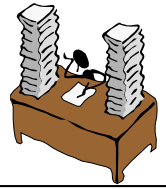
1. Basis microbiologische parameter: MIC

2. Farmacokinetiek (PK) en Farmacodynamiek (PD)
   het concept en de methode
   het gebruik van de voornaamste antibioticaklassen

3. Toepassingen
   - EUCAST breekpunten (in het kort)
   - Therapeutic Drug Monitoring
   - continu infuus

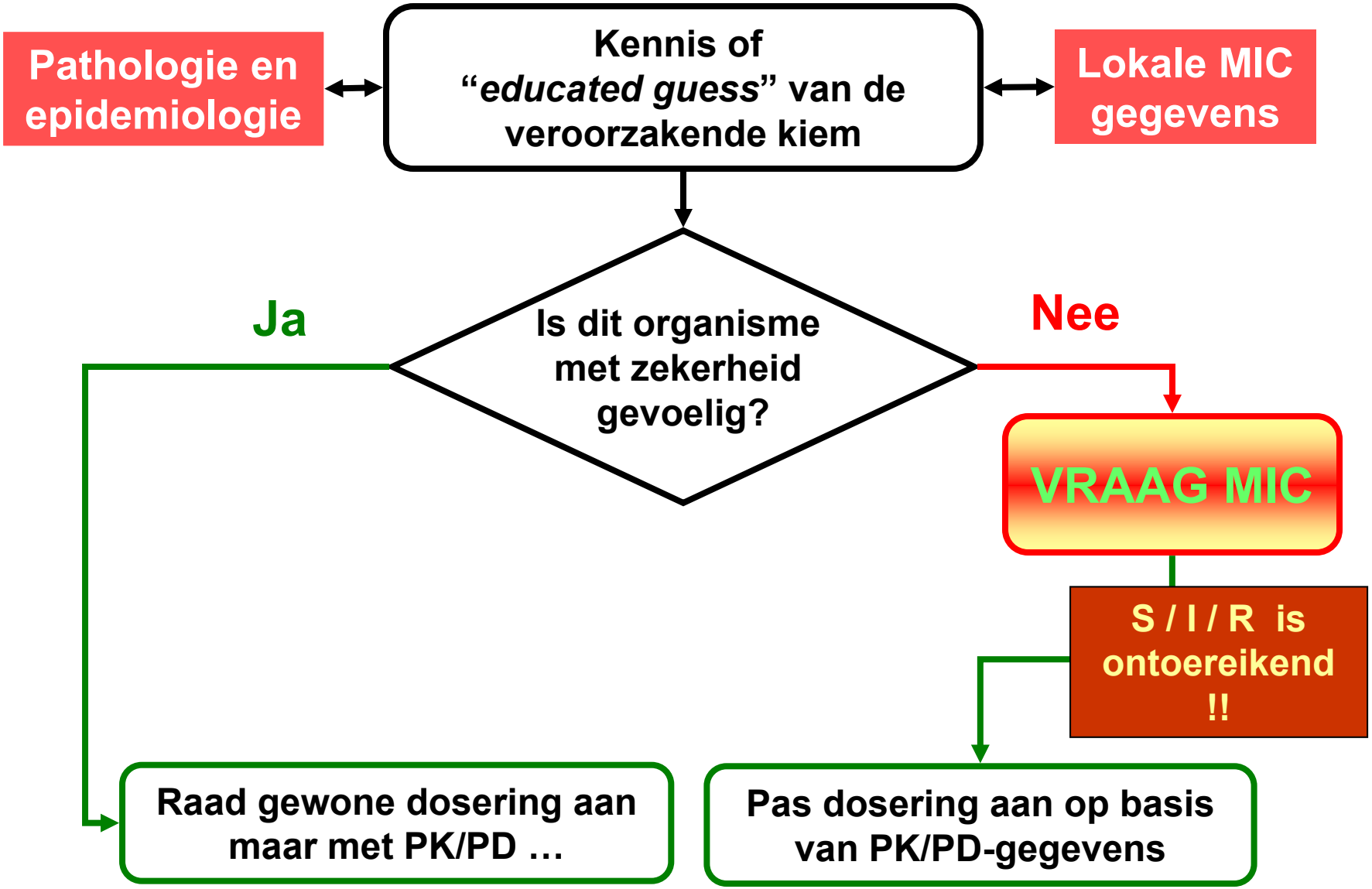
4. Resistentie

5. Geselecteerde referenties

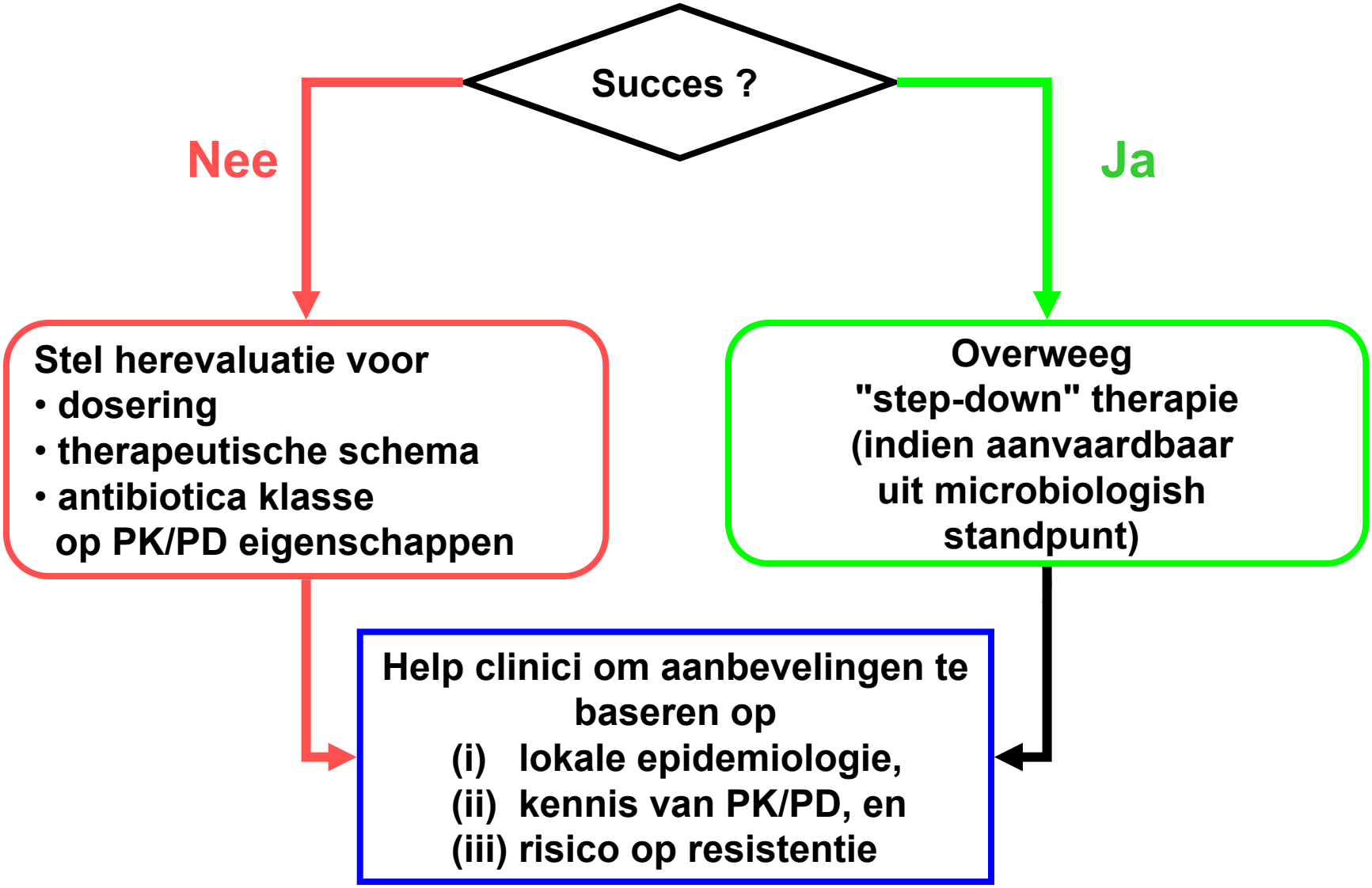


Tot slot !

Enkele sleutels tot succes…



Enkele sleutels tot succes (vervolg…)



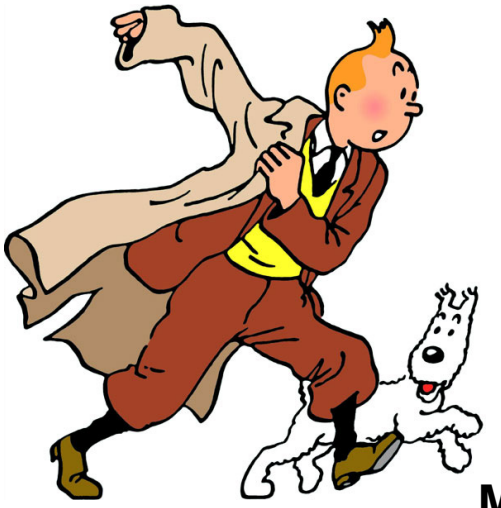
En als U nu een antibioticum moet kopen…

- Ken de lokale epidemiologie…
  - ➢ **distributie van de MIC-waarden …**
- Bereken het PK profiel dat men nodig heeft voor een optimale activiteit tegenover > 90 % van de beoogde kiemen
  (in termen van tijd boven de MIC, AUC en/of piek)
  - ➢ **neem een veiligheidsmarge in acht (MPC…)**
- Vergelijk de verschillende voorstellen…
- koopjes zijn goed zo lang ze echter goedkoper blijven in de praktijk…

En om af te sluiten…

Laat ons de mogelijkheden niet uit de weg gaan

ook successen in antibioticabeleid samen uit te bouwen



Maar nu is er tijd…

Belangenconflicten… en dankbetuigingen

- Belangenconflicten
  - onderzoekstoelagen van Bayer, Pfizer, Wyeth, GSK, AstraZeneca…
  - Vergoedingen voor voordrachten: AstraZeneca, Aventis, Bayer,…
  - Penninggeld van RIZIV en FOD "Volksgezondheid"

- Dankbetuigingen
  - W. Craig, J.J. Schentag, G. Drusano, K. Drlica (voor concepten van PK/PD)
  - Gunnar Kalhlmeter (voor dias en discussies over EUCAST)
  - Johan Mouton (voor inleiding tot de populatiefarmacokinetiek, dias, discussies) en Els Ampe voor veel werk met vancomycin en klinische farmacie
  - Els Ampe en Stefanie Thevelin voor taal herziening…

Referenties (PDF)…

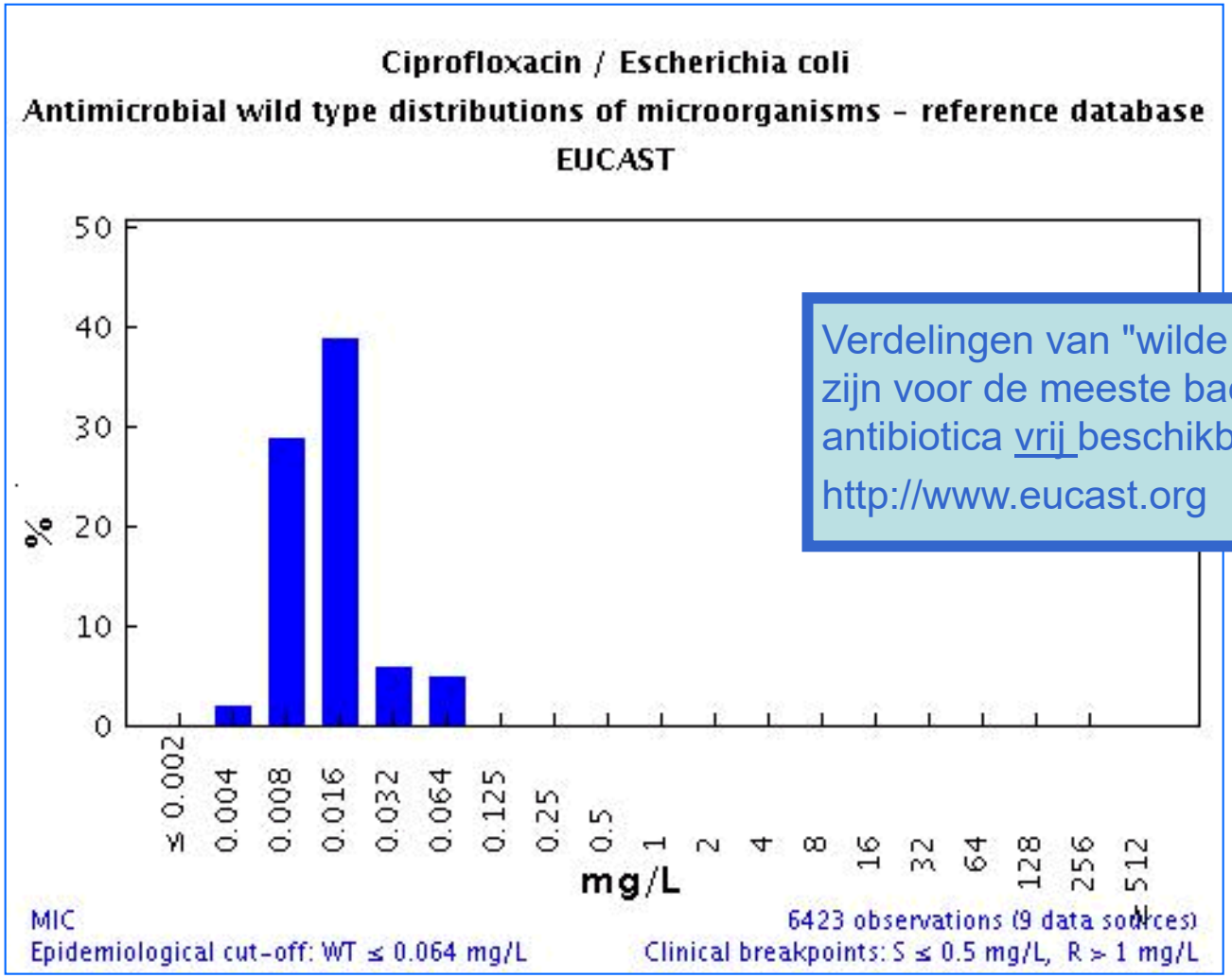
beschikbaar (met de dias) op

http://www.facm.ucl.ac.be/facm-conferences-nl.htm

Kijk naar zip !

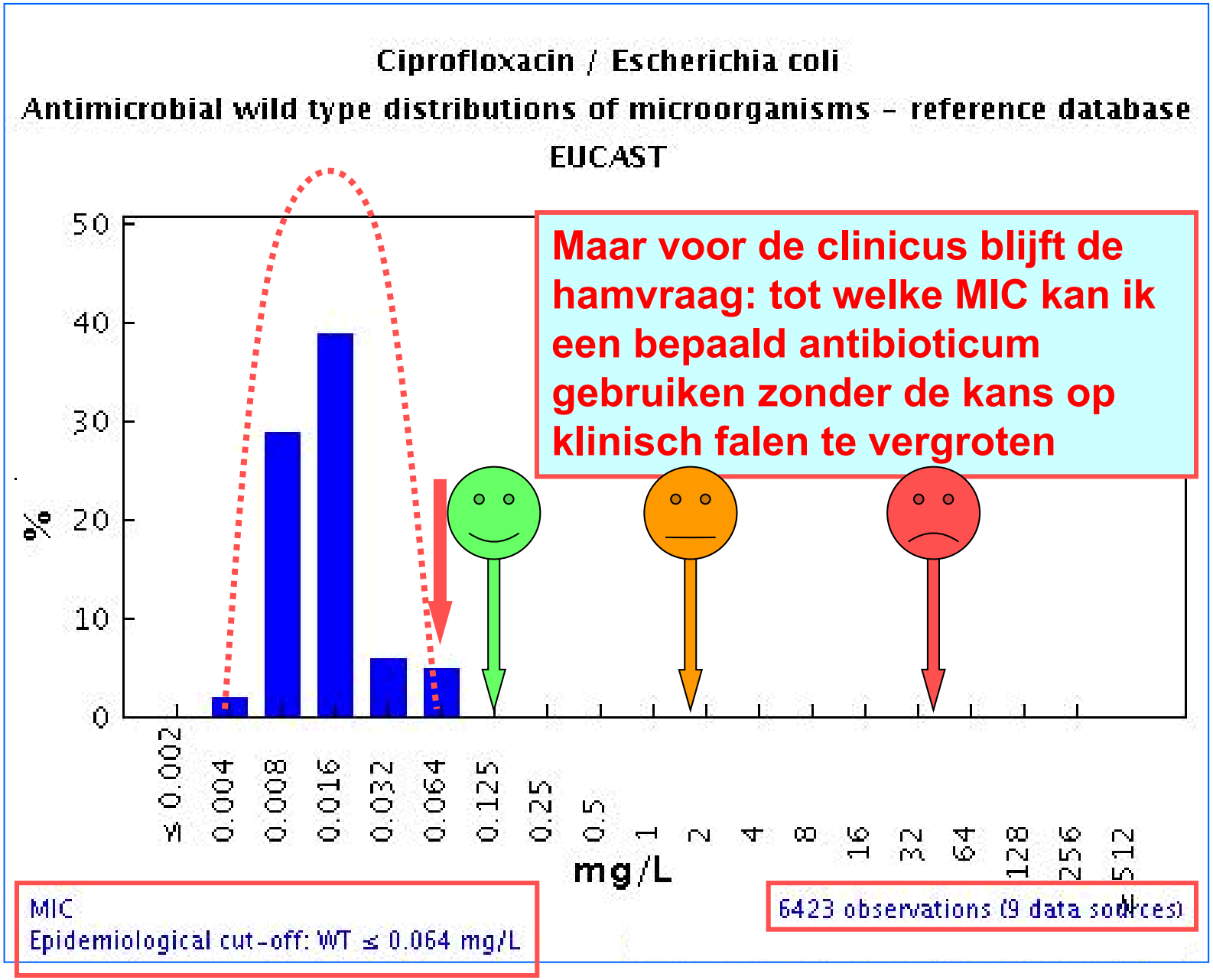
Back-up

EUCAST 1ste stap: definitie van MIC verdelingen voor epidemiologische "*cut off*" waarden ("wilde stammen")



Verdelingen van "wilde stammen" zijn voor de meeste bacteriën en antibiotica vrij beschikbaar op http://www.eucast.org

Epidemiologische "cut-off" waarden veranderen niet naargelang de omstandigheden…


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database EUCAST
Maar voor de clinicus blijft de hamvraag: tot welke MIC kan ik een bepaald antibioticum gebruiken zonder de kans op klinisch falen te vergroten
%
mg/L
MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
6423 observations (9 data sources)

2de stap: EUCAST bepaling van klinische breekpunten

Klinisch gevoelig (S)

- Niveau van antibacteriële doeltreffendheid met hoge kans op therapeutische succes

Klinisch intermediair (I)

- Niveau van antibacteriële doeltreffendheid dat geen eenduidige conclusie over de kans op therapeutisch succes toelaat… (noch mossel noch vis…☺)

Klinisch resistent (R)

- Niveau van antibacteriële doeltreffendheid met hoge kans op therapiefalen

Klinische breekpunten kunnen aangepast worden aan wijzigende omstandigheden (verandering van dosering, bv.)

Hoe bepaalt EUCAST de klinische breekpunten voor bestaande antibiotica ? (in het kort)

1. Evaluatie van dosering, formulering, klinische indicaties en doelwit-organismen

2. Bepaling van de epidemiologische cut-off van de "wild-type" stammen

3. Inzameling en evaluatie van PK/PD parameters en PK gegevens

- doeltreffenheidsparameters (C_{max}/MIC; AUC/MIC, *f* t > MIC): *in vitro* en *in vivo* modellen gevalideerd in klinische studies
- farmacokinetiek: meestal van patiënten (met behulp van populatiefarmacokinetische modellen indien nodig)

4. Grondige evaluatie van klinische gegevens aan de hand van PK/PD

5. Discussies met experten, industrie, nationale breekpuntcommissies en met iedereen die geïnteresseerd is via het forum van de EUCAST website

6. Publicatie van de breekpunten op de EUCAST website http://www.eucast.org

7. Provisoire breekpunten werden aan de Nationale Commissies (GB, F, NL, N, N, S) voorgelegd voor commentaar

8. Raadpleging van:
   - EUCAST General Committee
   - specifieke commissies van deskundigen indien nodig (*Neisseria*, anaeroben, …)
   - Farmaceutische Nijverheid
   - Fabrikanten van toestellen
   - iedereen via EUCAST website

9 . Publicatie van een "*rationale document*" op de website http://www.eucast.org