β-lactams:
from pharmacodynamics to applications in the real world...

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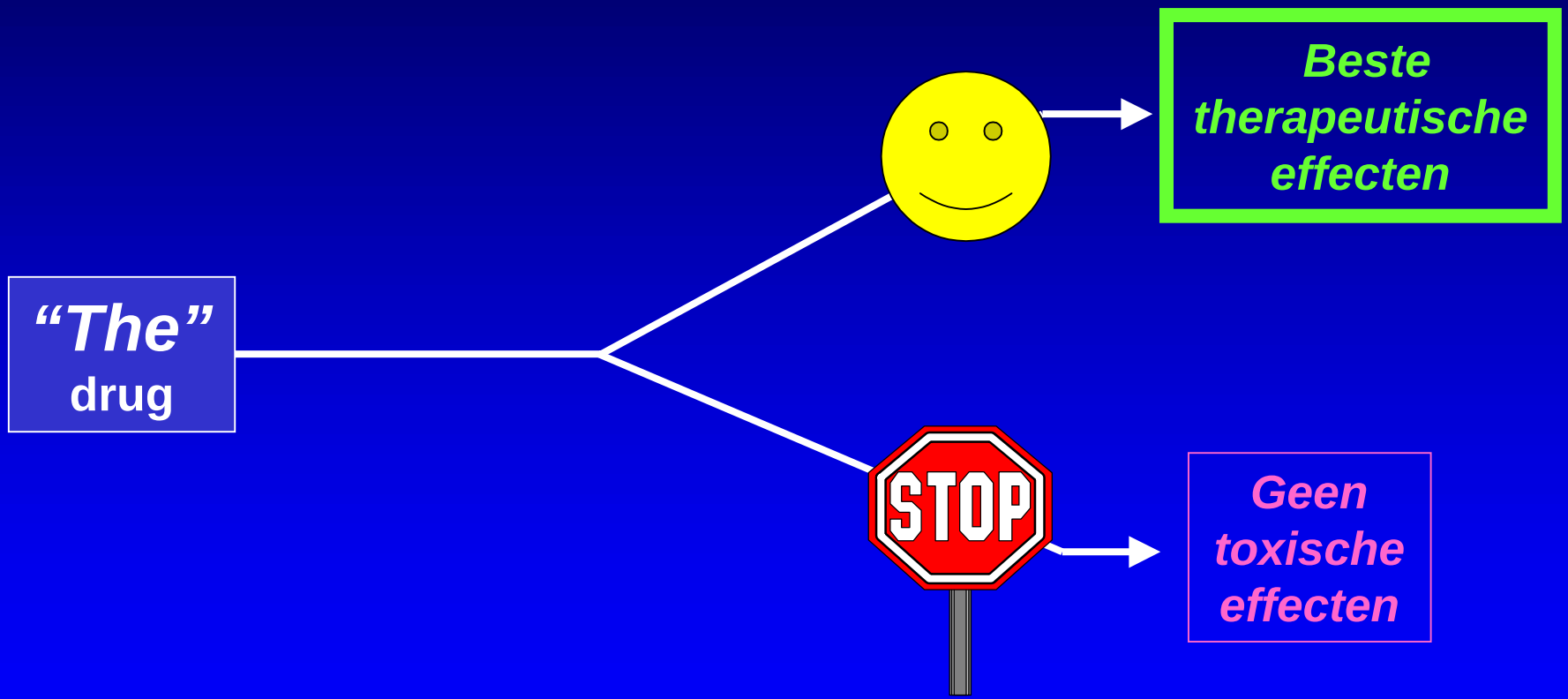
**Belgian Intensive Care Study Group,
Cambridge, UK, September 11th, 2001**

Antibiotic treatment:
Wat does the clinician want ?



The ideal antibiotic ...

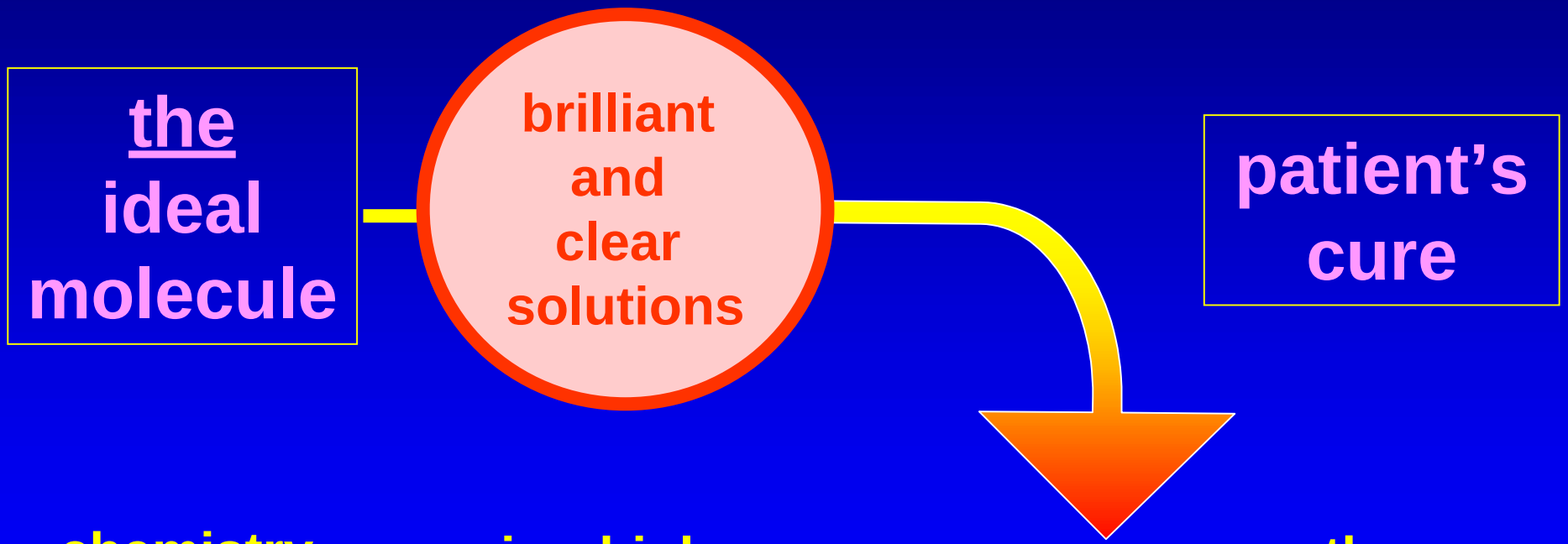
the molecule

brilliant and clear solutions

ent's cure

chemistry **microbiology** **therapy**

Is the molecule always ideal ?

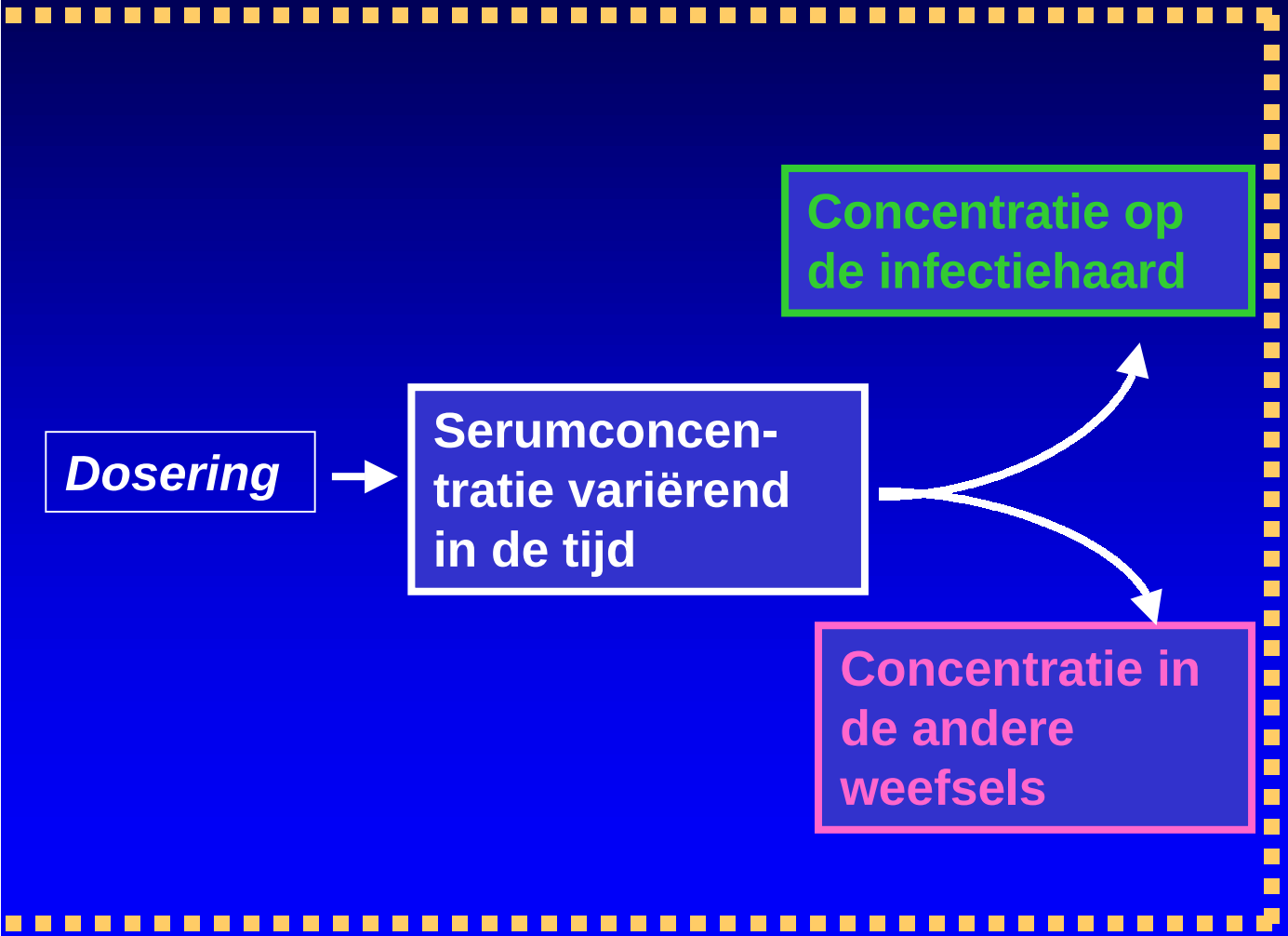


Main causes of antibiotic failures...

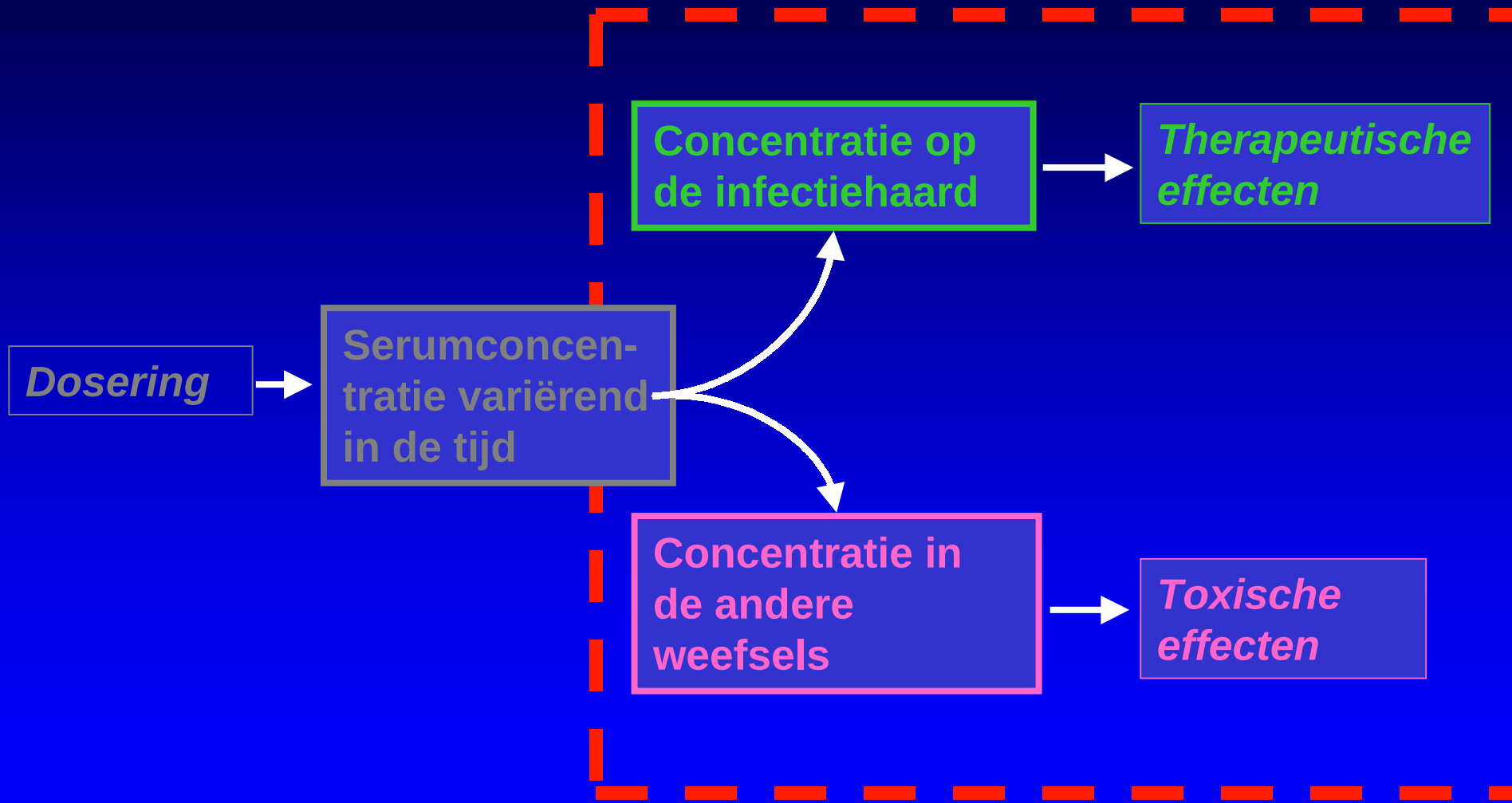
Adapted from Pechère J.C., 1988, 1993, 1998

- **False failures**
  - erroneous diagnosis
  - underlying disease uninfluenced by antibiotics
  - unjustified lack of patience
  - inactivation of the antibiotic
- **Patient related failures**
  - compliance failure (broadly speaking)
  - inappropriate administration route (broadly speaking)
  - immunodepressed hosts
- **Pharmacological failures**
  - **insufficient amount or drug inappropriately administered**
  - **no attention paid to pharmacodynamic parameters**
  - in situ inactivation or lack of drainage
- **Micro-organism related failures**
  - wrong pathogen
  - **resistance acquired during treatment**
  - **insufficient bactericidal activity**
  - inoculum effect

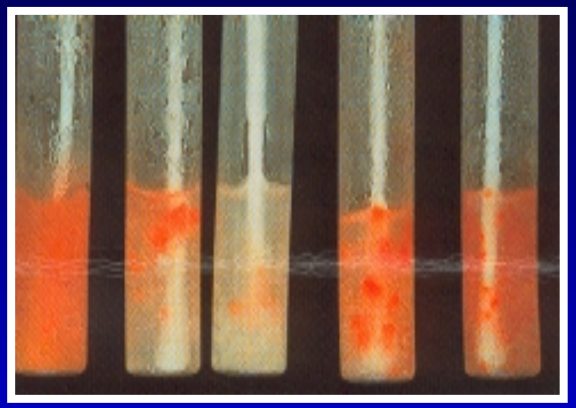
Farmacokinetiek



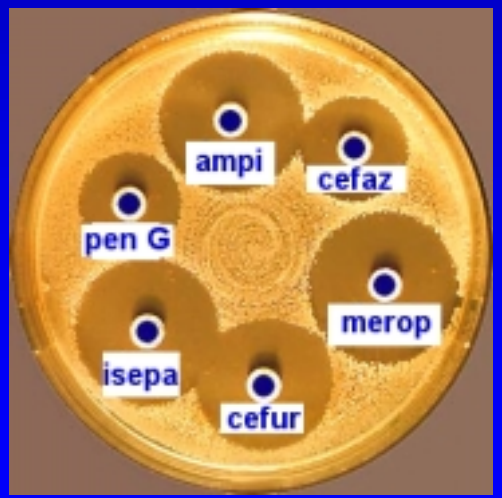
Farmacodynamie



Microbiology



identification



sensitivity

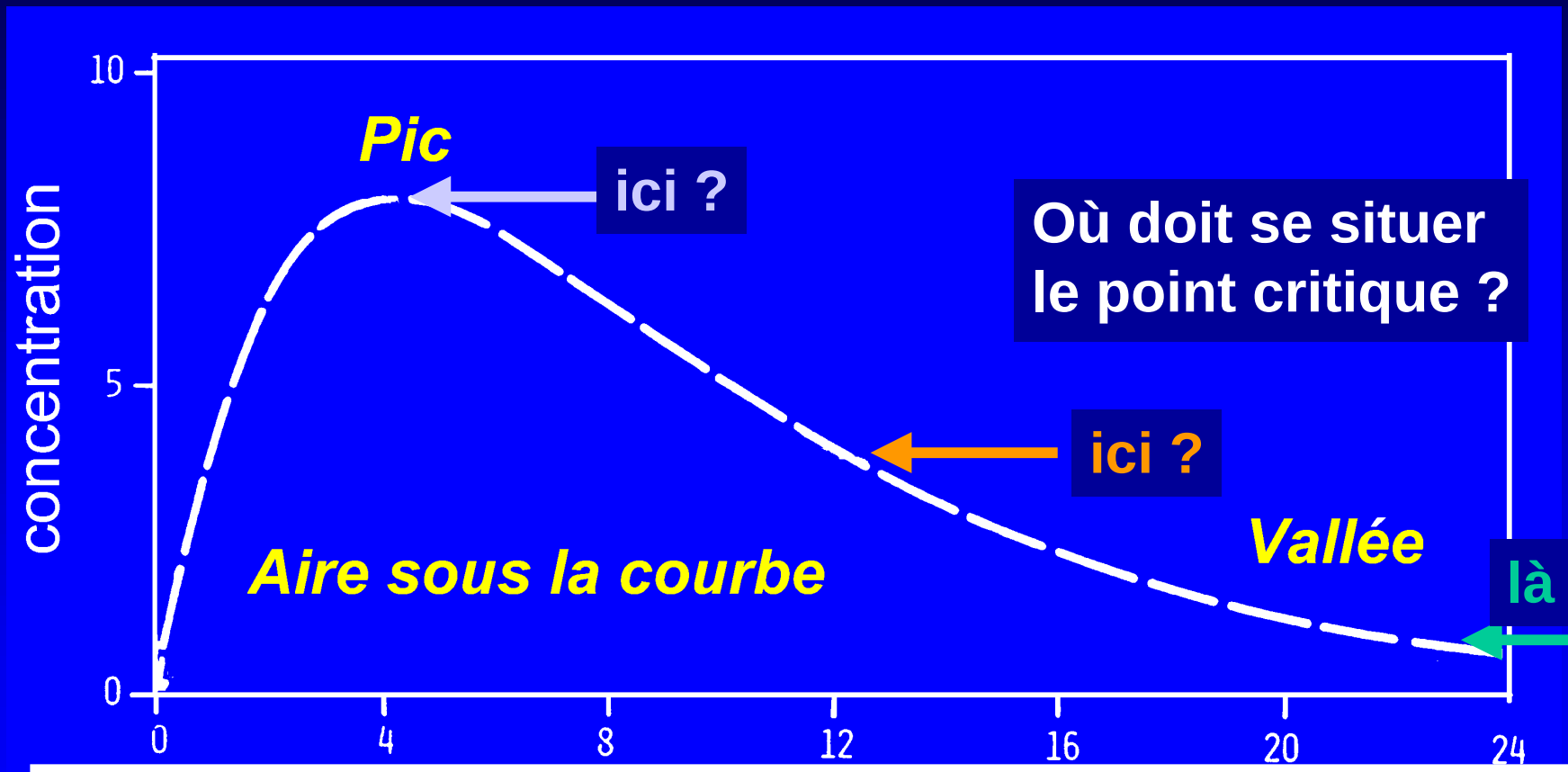
by static techniques

drug concentration stays constant

What did the textbooks say about antibiotic dosages and schedules in the 70's ?

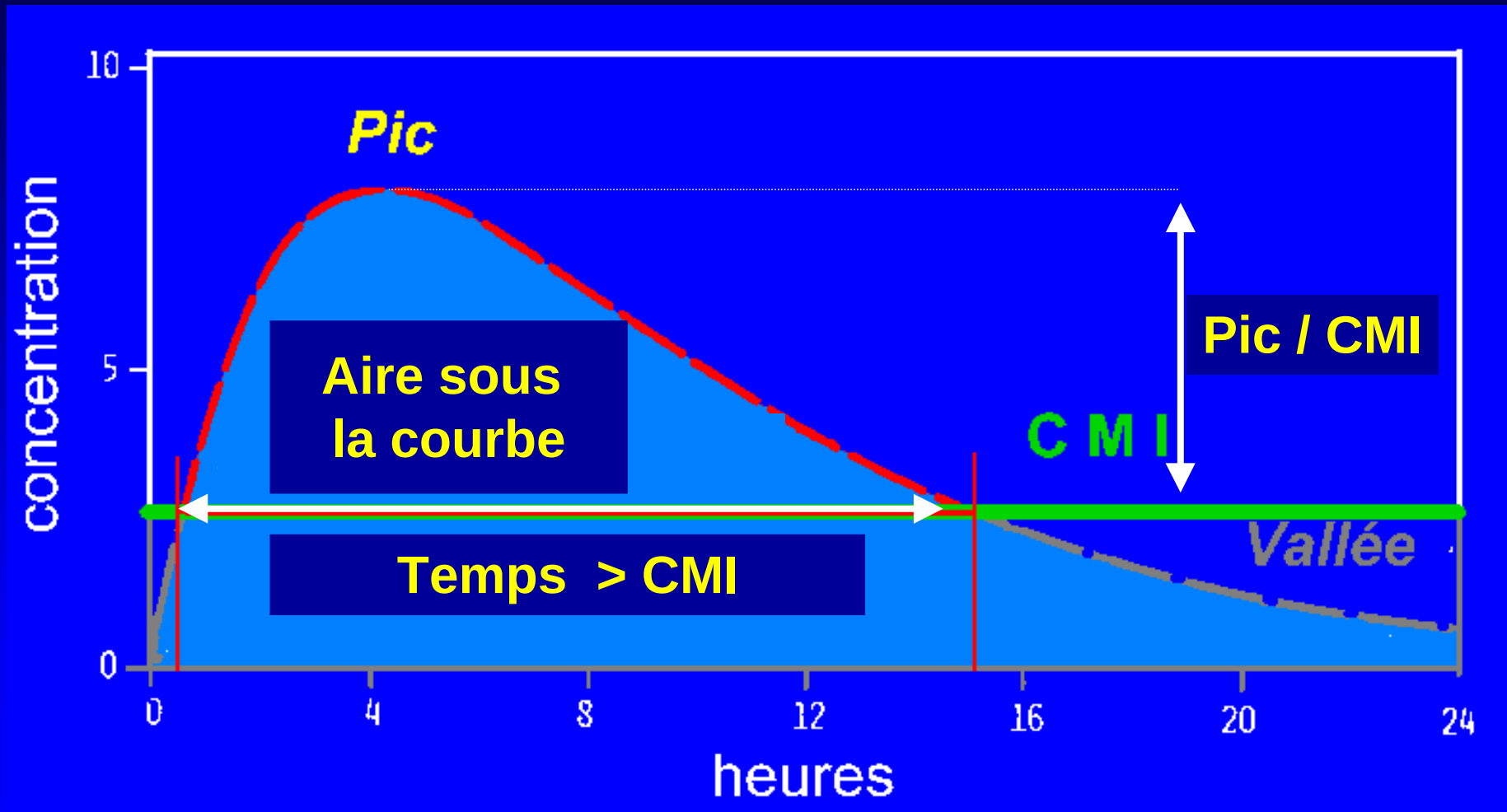
1. Stay above the MIC... **but how much ?**
2. Remain around for a while… **but how long ?**
3. Hope it works... **against everything ?**
4. Hope it is not toxic… **can't do much ...**

Les méthodes statiques sont (souvent) inadaptées pour définir les conditions de sensibilité *in vivo*



Première difficulté: les points critiques ignorent le caractère dynamique des taux sériques de médicament

Pharmacocinétique ➔ Pharmacodynamie



Type de “propriétés PK/PD” des antibiotiques

Les antibiotiques actuellement disponibles peuvent être regroupés en 3 groupes montrant, une dépendance prédominante vis-à-vis soit :

- **du temps (“ T > MIC “)**
- **du rapport AUC / MIC (AUC_{24h}/MIC)**
- **du rapport Pic / MIC (C_{max}/MIC)**

Types de propriétés PK/PD des antibiotiques **(1 de 3)**

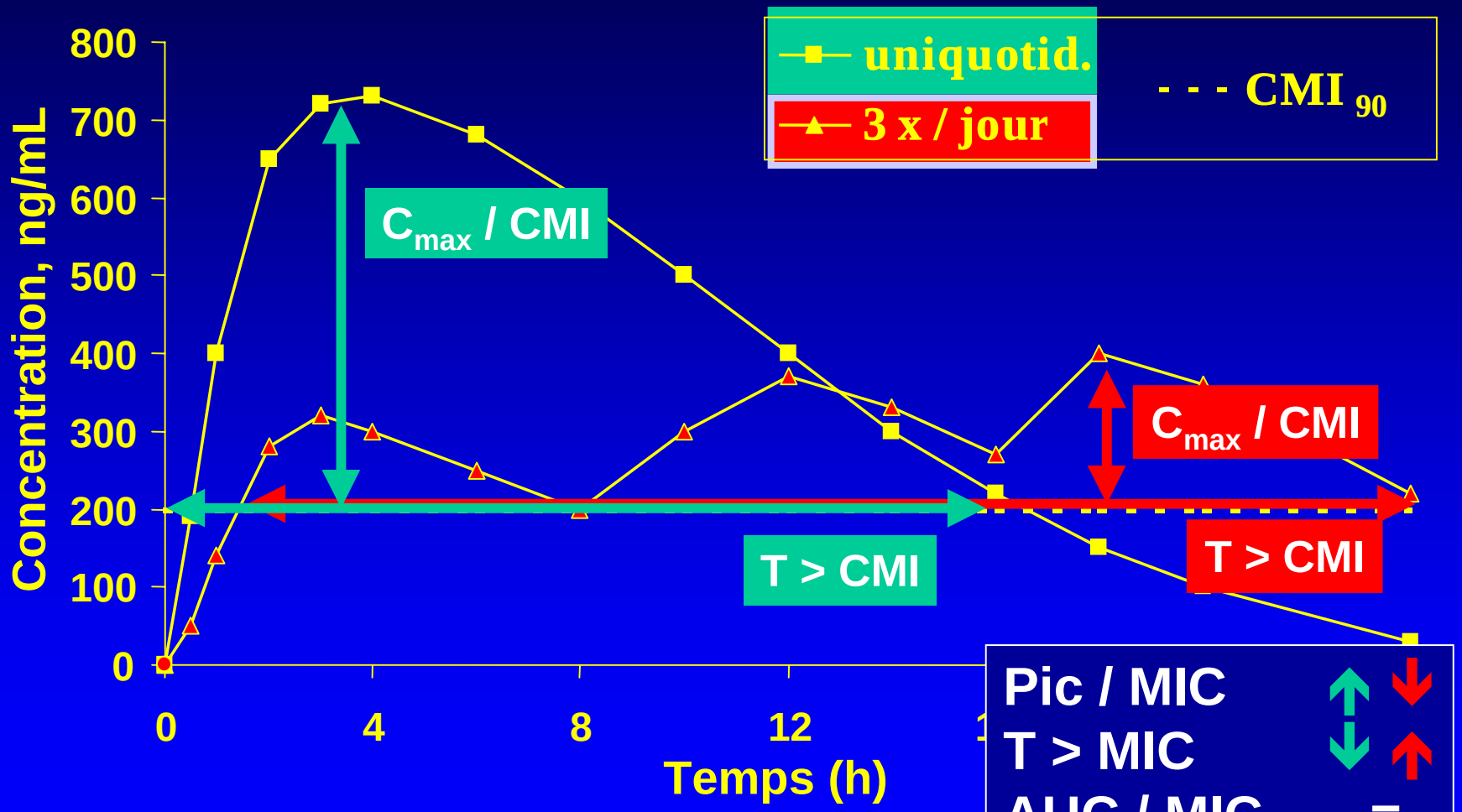
(d'après WA. Craig, 2000)

1. Antibiotiques avec effet **temps-dependent**

- **peu ou pas d'effet de la concentration (si > CMI)**
- **peu ou pas d'effet persistant**

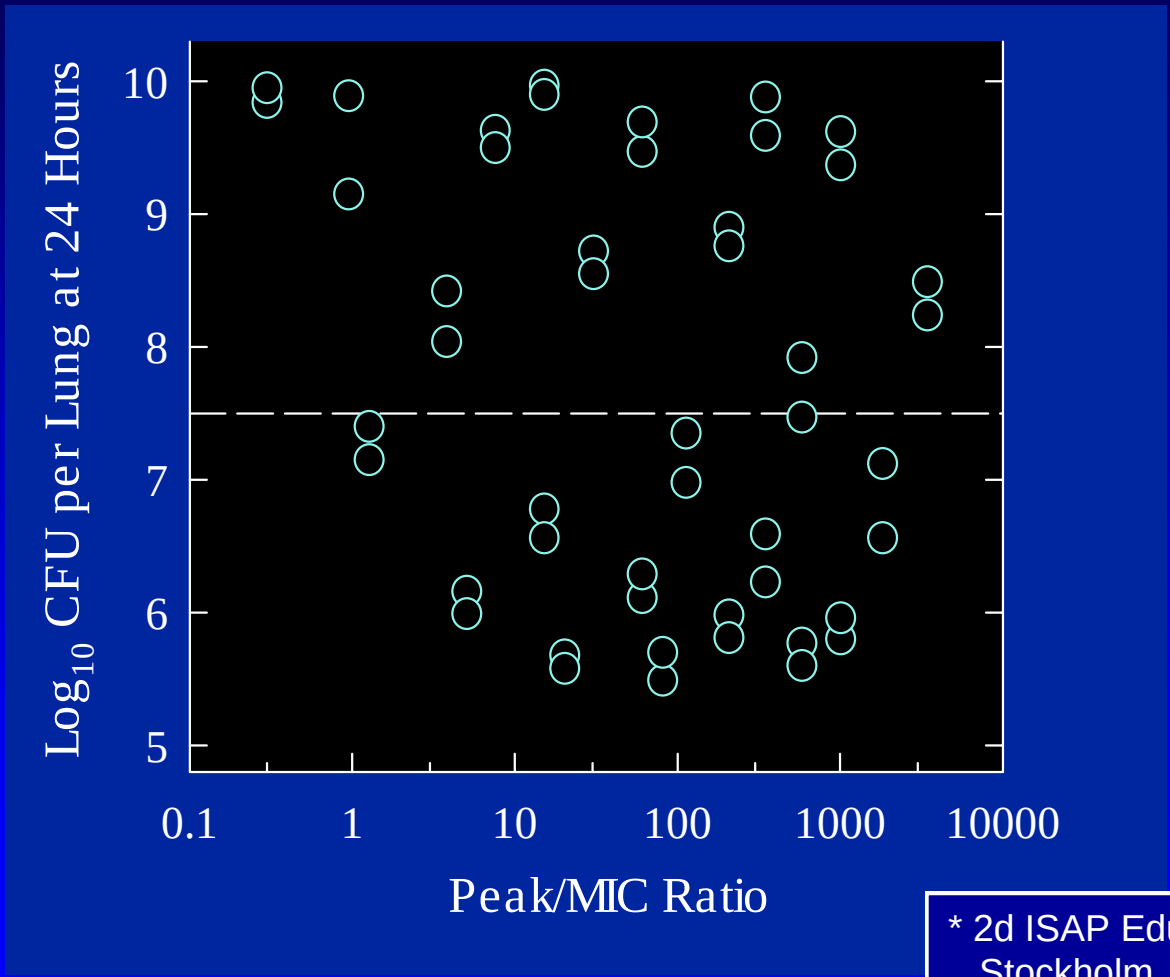
AB	paramètre PK/PD	But
β-lactames clindamycine oxazolidinones macrolides flucytosine	**Temps au-delà de la CMI**	**Maximiser ce temps au-delà de la CMI**

Dissocier les co-variables pharmacocinétiques



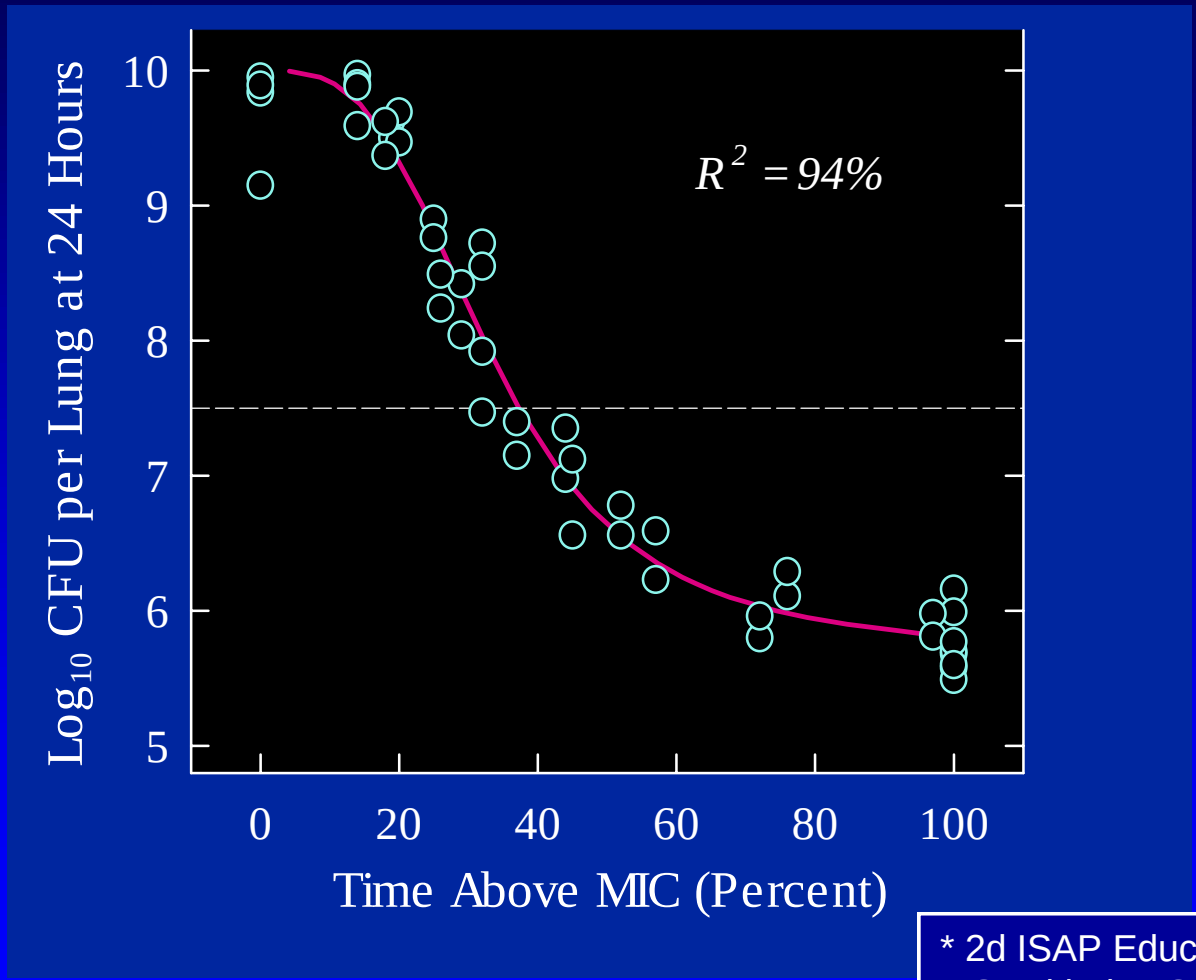
Adapté de F. O. Ajayi, ISAP-FDA Workshop, 1999

Relationship between peak/MIC and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

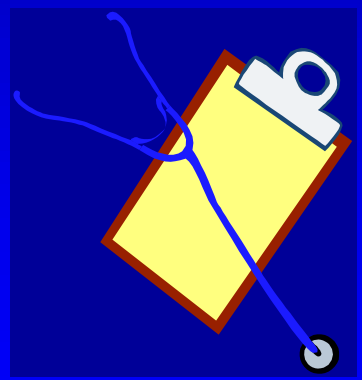
Relationship between time above MIC (T>MIC) and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)



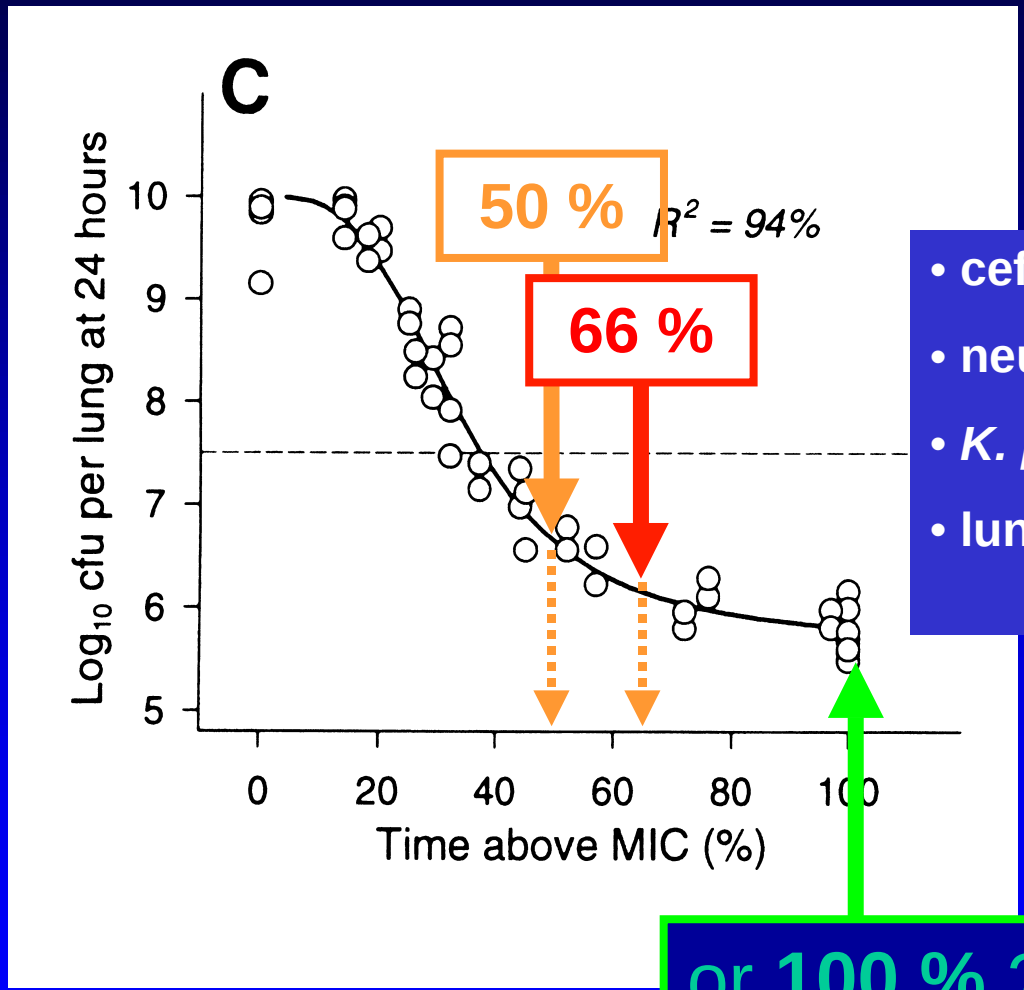
* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Pharmacokinetics / Pharmacodynamics in action ...

What can (and must) the clinician know ?



How long do you need to remain above the MIC ?



- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection)

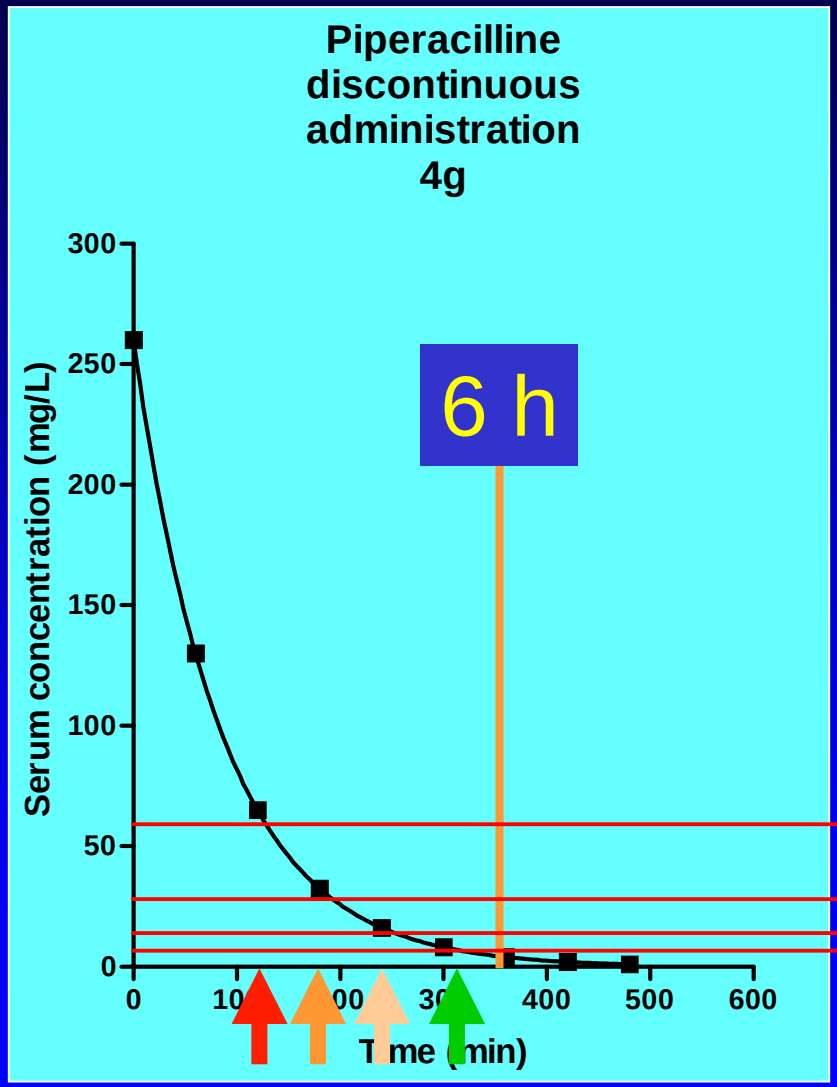
Typical pharmacokinetics of a model β-lactam *

How much do **you** want at 8h ?

time	serum concentration (mg/L) for		
	0.5 g	1 g	2 g
	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

* single administration; 2h half-life; V_d = 0.2 l/kg

Applying this to piperacillin q8h



Where should be your breakpoint ?

64 µg/ml

32 µg/ml

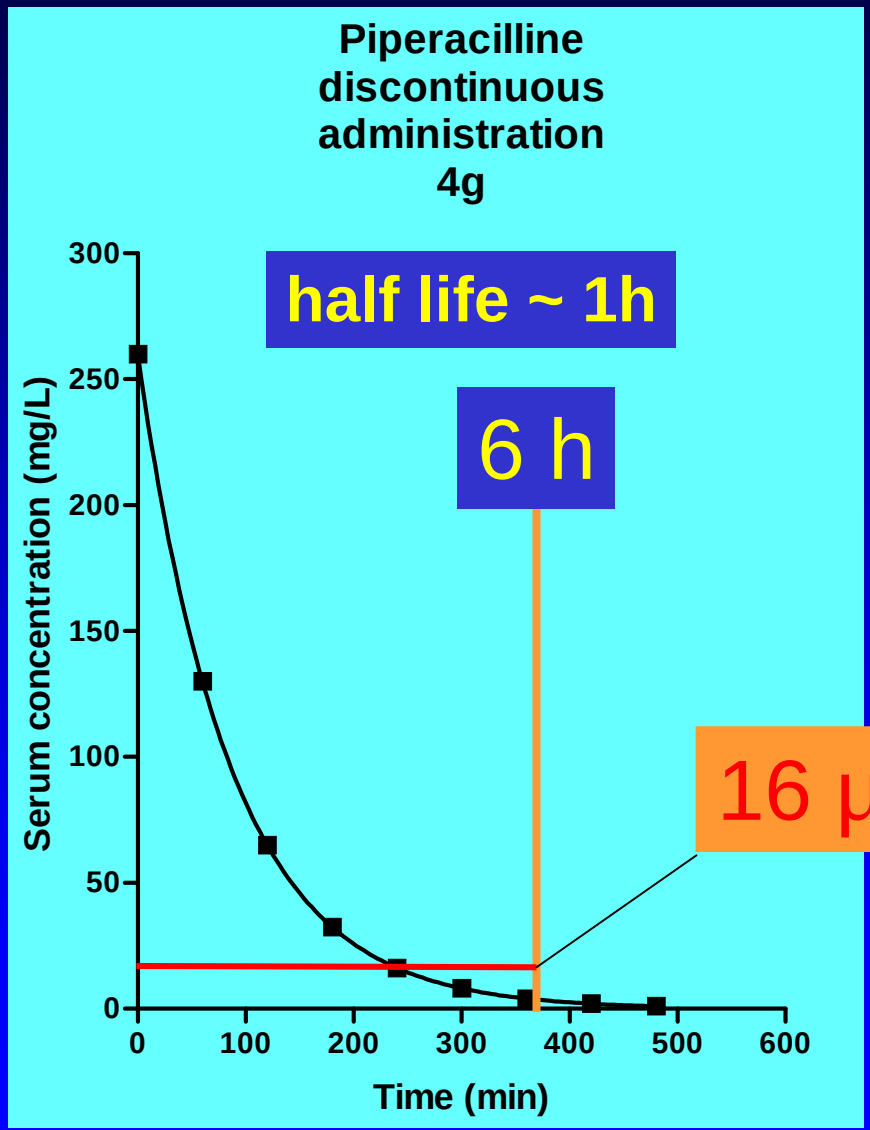
16 µg/ml

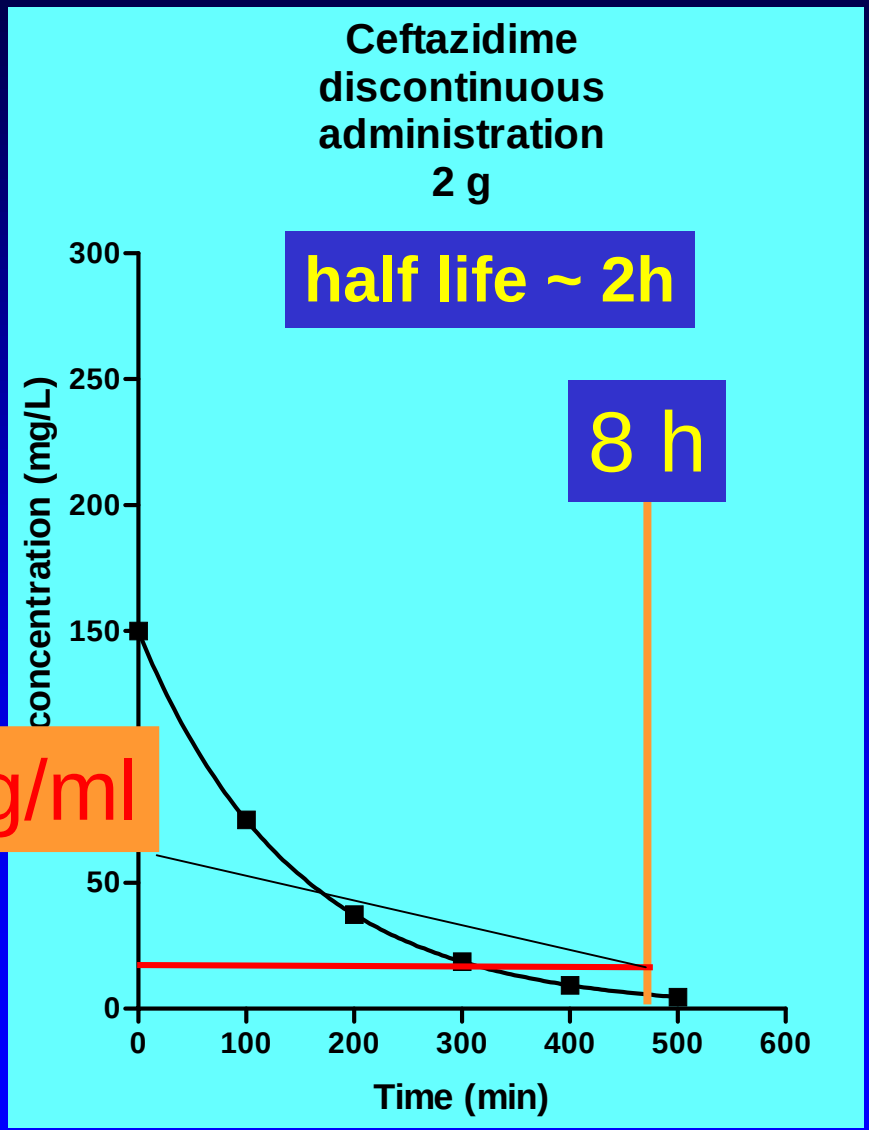
8 µg/ml

A conflict of breakpoints?

From Mouton, 8th ISAP symposium, Nijmegen, 2001

comparing piperacillin and ceftazidime





Pharmacokinetics / Pharmacodynamics in action ...

β- lactams : what can you really do ?

I guess an organism with a MIC ~ 10 µg/ml is the limit if you use it optimally (2 to 3 x / day and up to a total of 4 to 6 g/day…)

PK / PD breakpoints for β-lactams: 8 µg/ml

Pharmacokinetics / Pharmacodynamics in action ...

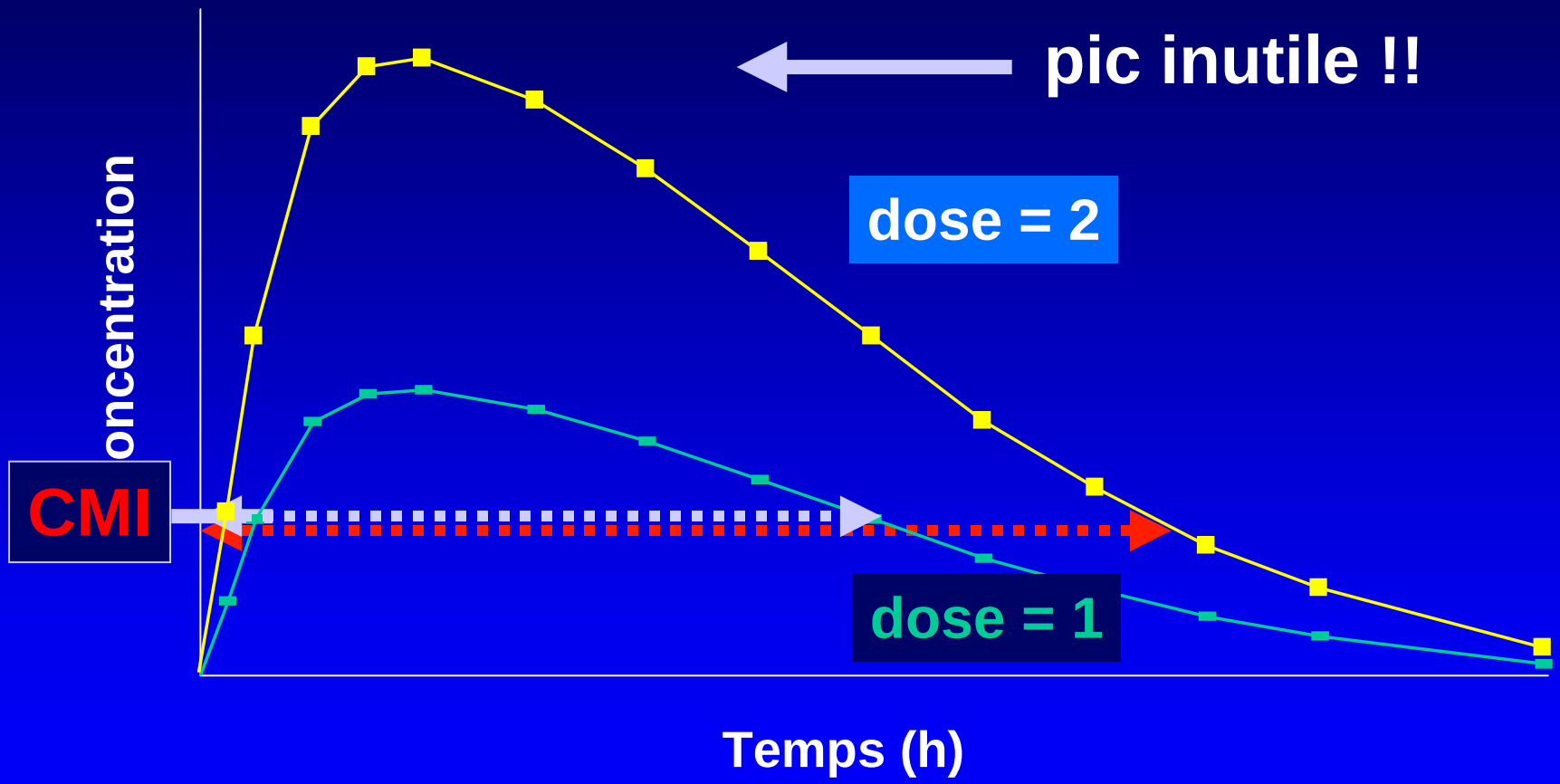
β- lactams: if you have reached the limits ...

- increase the frequency of administration to get enough time > MIC

→ efficacy

- high peaks are unnecessary and may cause toxicity

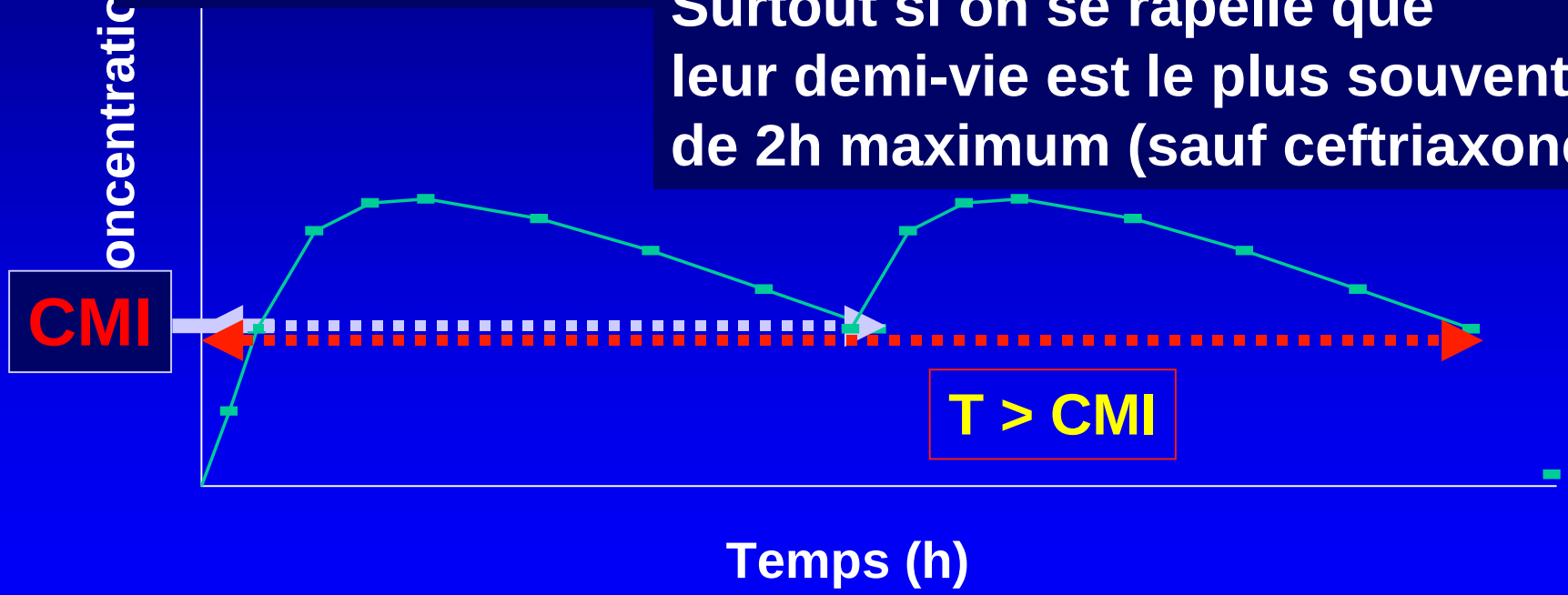
Augmenter la dose unitaire ...



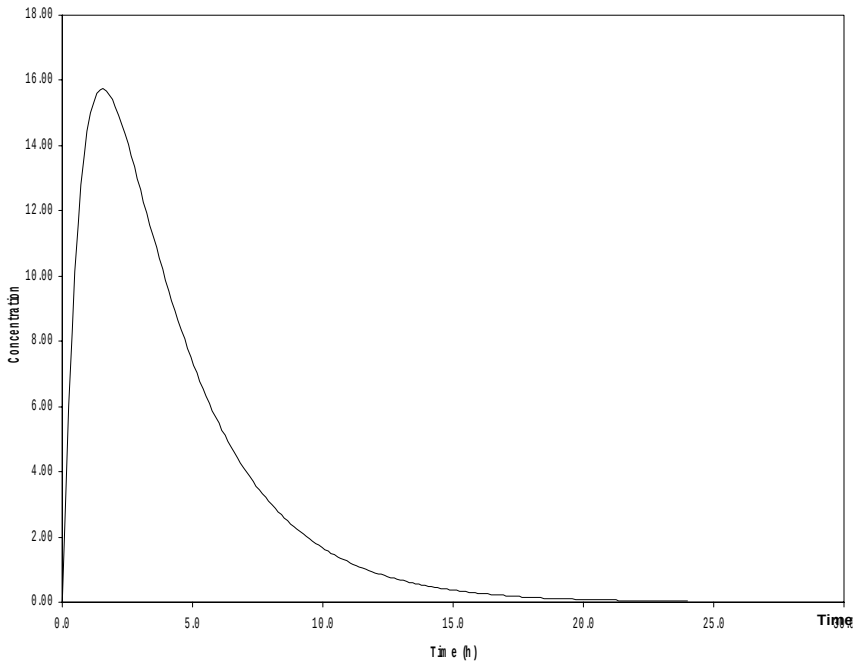
Augmenter la fréquence d'administration ...

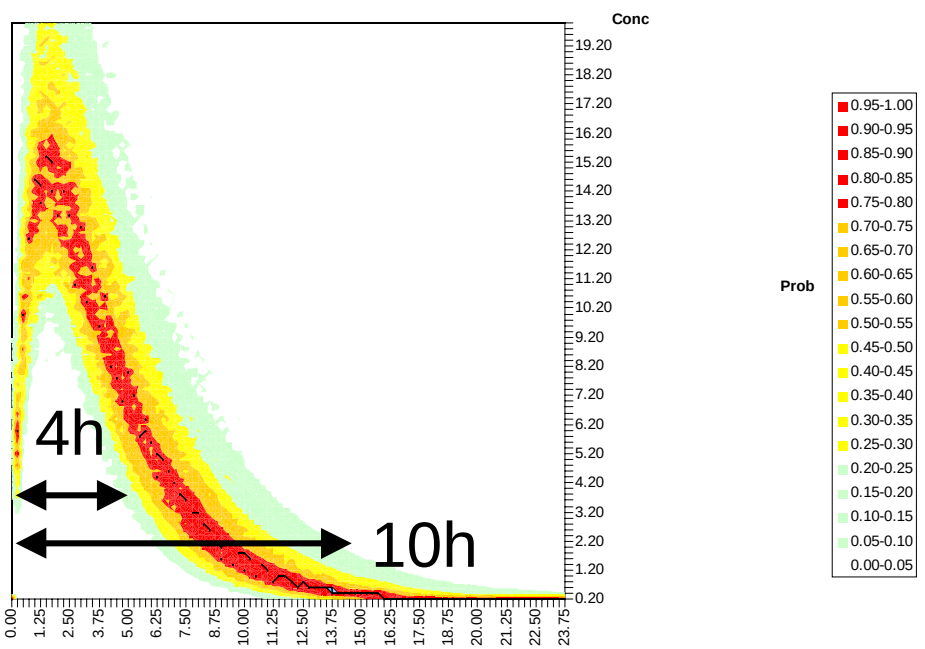
L'augmentation de la fréquence d'administration des β-lactames semble une démarche nettement plus logique ...

Surtout si on se rapelle que leur demi-vie est le plus souvent de 2h maximum (sauf ceftriaxone)



The difficulty is that patients are not models...



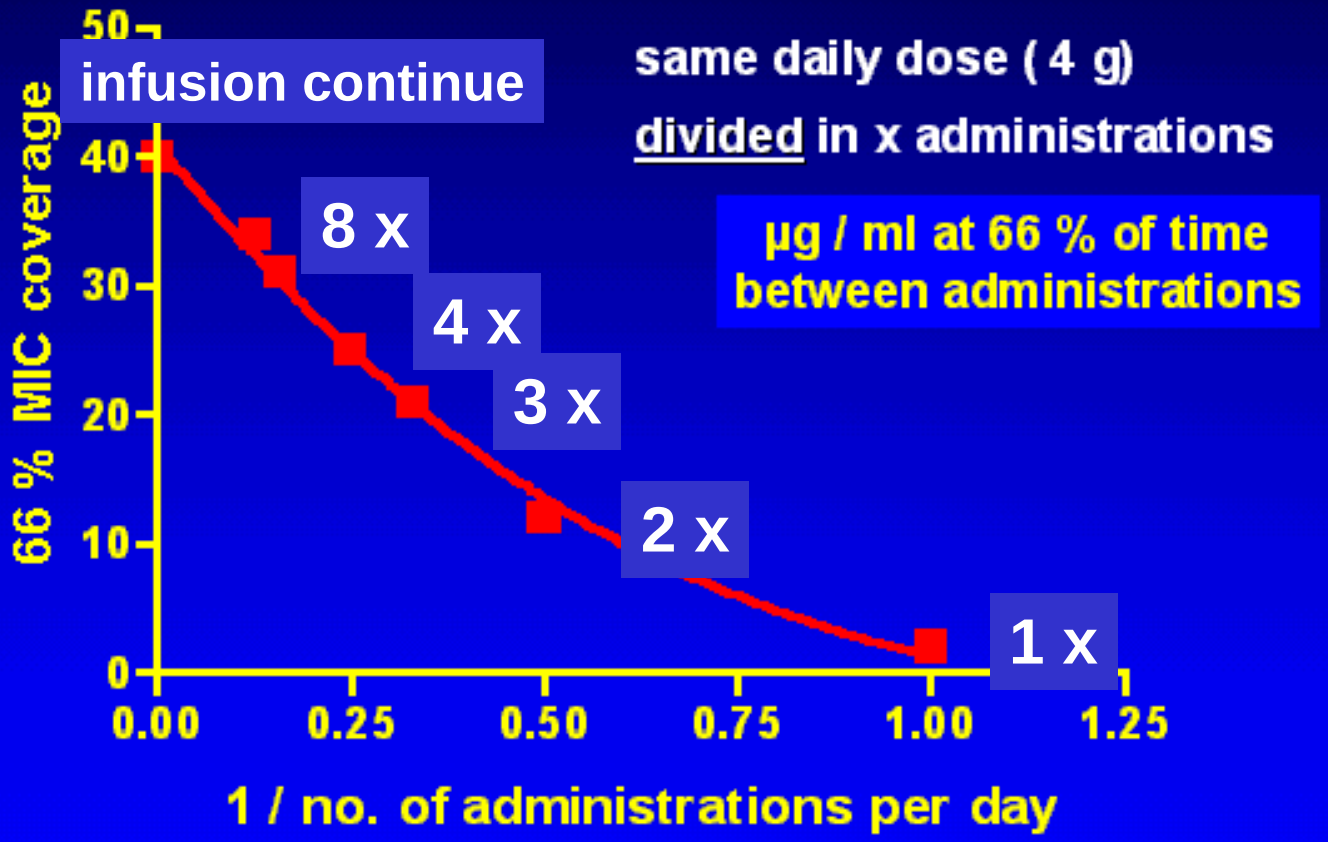


Concentration-time profile of beta-lactam
Vd = 20 L, Ka = 1.2 h^{-1}, Ke = 0.3 h^{-1}

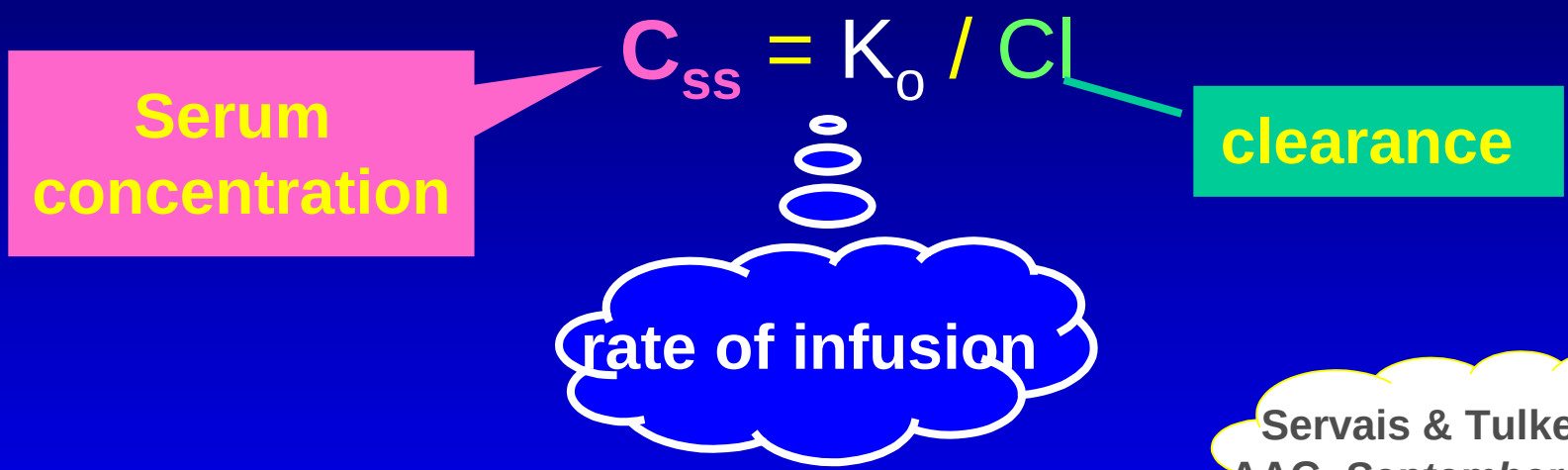
Monte Carlo Simulation of beta-lactam
in patients with the same "basic parameters

From Mouton, 8th ISAP symposium, Nijmegen, 2001

Reducing β - lactams interval: where can we go ?



β - lactams by continuous infusion



Servais & Tulkens, AAC, *September 2001*

Studies are under way

stability of the molecule …

specific applications …

Nosocomial pneumonia, cystic fibrosis, … in progress

Continu-infuus van β - lactamen in intensieve zorgen:

een amerikaanse studie…(3 g/dag)

	Intermittent *(n=17)*	*Continuous* *(n=17)*
C max (mg/ml)	106.5 (34.6)	18.2 (6.5)
C min (mg/ml)	10.3 (16.0)	16.5 (5.7)
C mean (mg/ml)		17.4 (6.1)
$t_{½}$ (h)	3.2 (2.5)	
AUC_{0-24h}	777.4 (474.6)	419.7 (141.5)
Cl (ml/min)	142.5 (58.7)	133.2 (37.0)

-**Pharmacokinetocs and Pharmacodynamics of continuous and intermittent ceftazidime during the treatment of nosocomiale pneumonia.** D.P. Nicolau et al. *Clin Drug Invest 1999:18(2):133-139.*

Continuous infusion: a bunch of other studies...

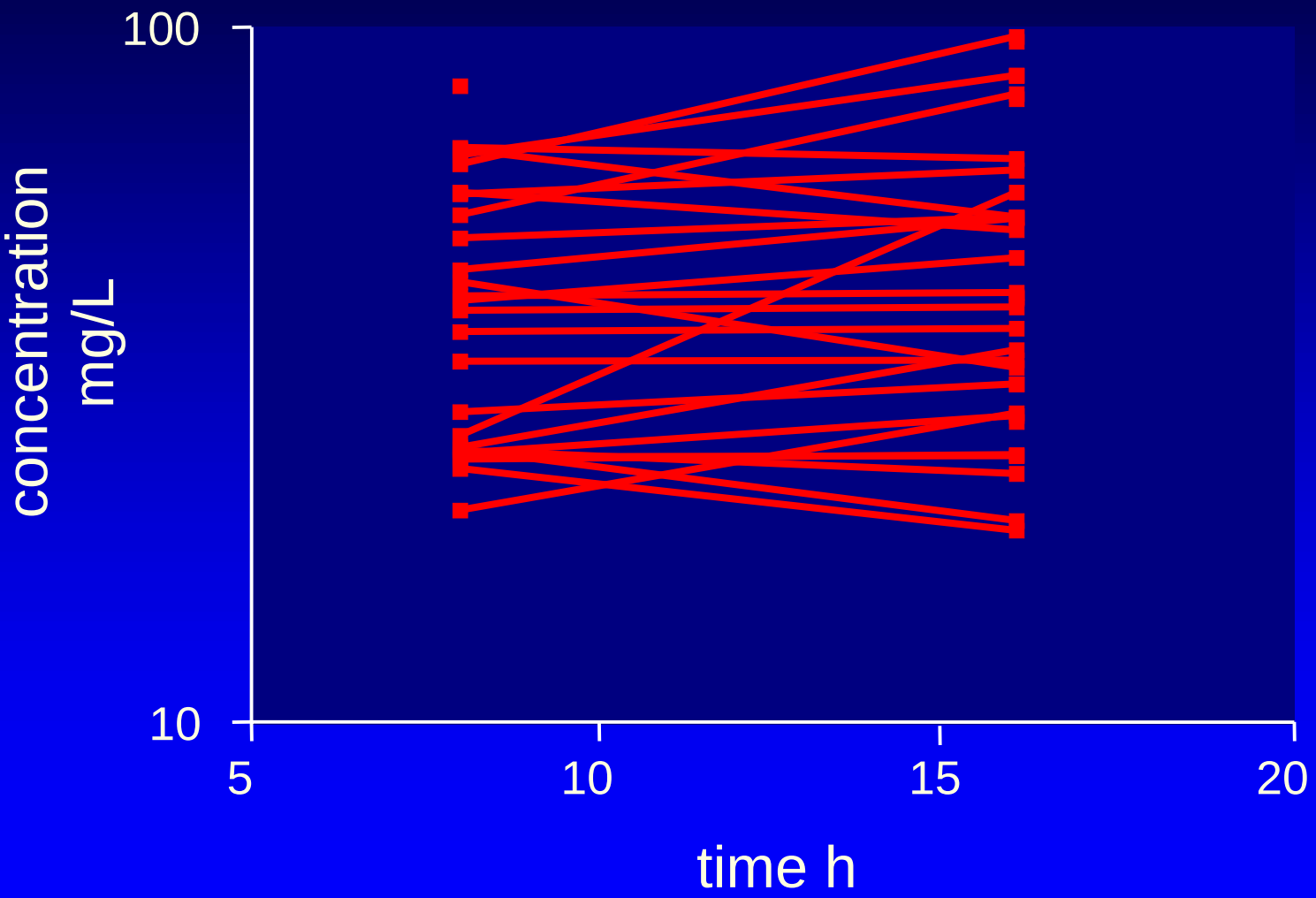
- suspected Gram (-) infections in critically-ill patients
  Benko et al., AAC 1996
- severe infections in Intensive Care patients (5 studies)
  Domenig et al., Transplantation, 2000
- septicemia (2)
  Angus et al., Brit. J. Clin. Pharmacol. 2000
- severe sepsis
  Leder et al., JAC, 1999
- cystic Fibrosis (3 25).
  Rapaz et al., Eur. J. Ped. 2000

β-lactams and continuous infusion

It 's a brilliant idea....

But don't let you fool your self...

Ceftazidime concentrations variations in ICU patients



From Mouton, 8th ISAP symposium, Nijmegen, 2001

Pharmacockinetics / Pharmacodynamics of anti-infectives

I love complicated models...

tissues are unimportant...

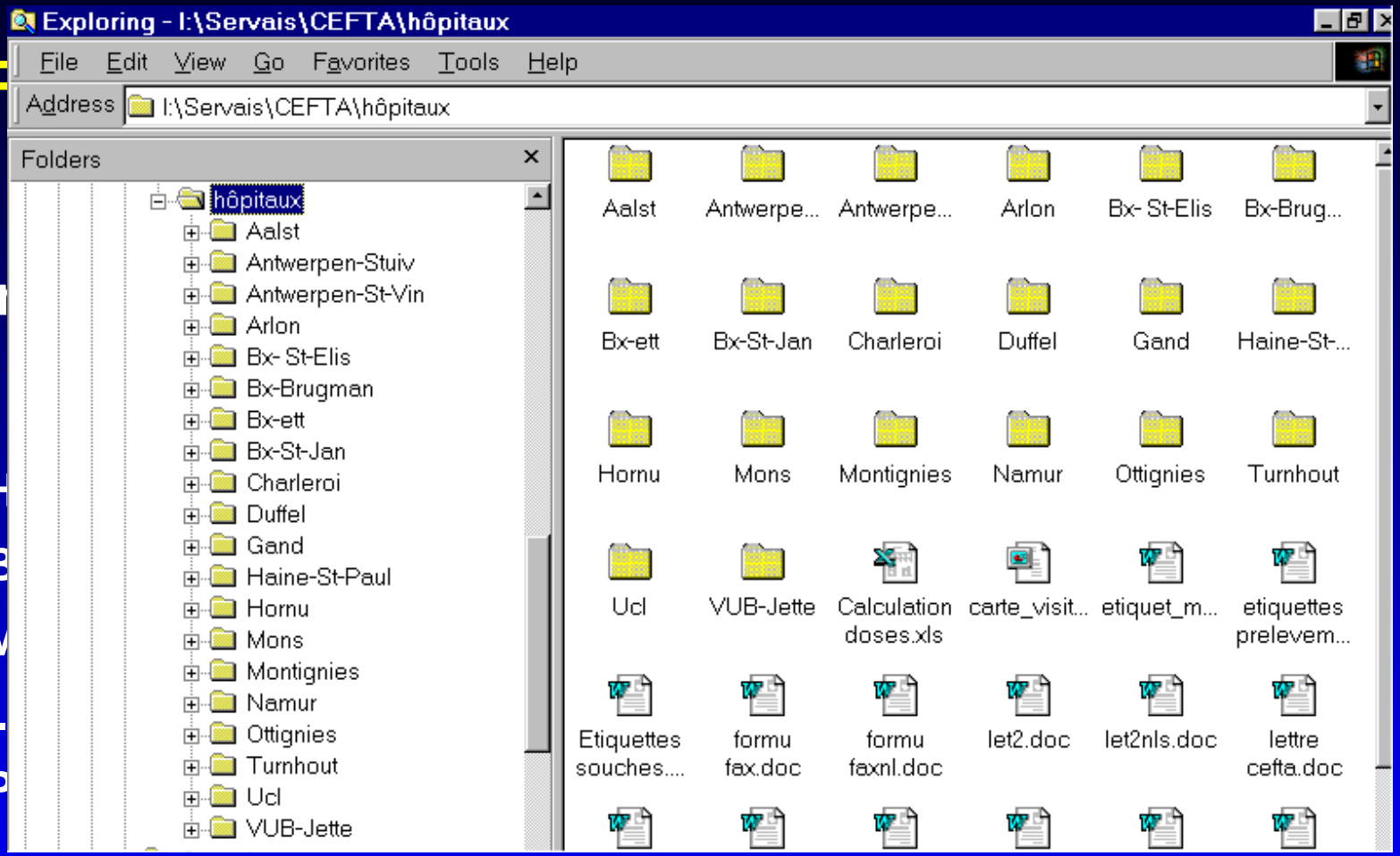
anyway, the clinical trial will fail at the end...

AUIC is good for all...

postantibiotic effect will explain everything...

I should have kept with the aminoglycosides

http://www.isap.org



Et les collaborations cliniques...

[1] mucoviscidose;
[2] concepten en algemene hulp;
[3] farmacokinetische parameters van CF patiënten
[4] ceftazidime studie

and Thank you also to AstraZeneca… and Cambridge...