PK/PD: from theory
to applications in the real world...

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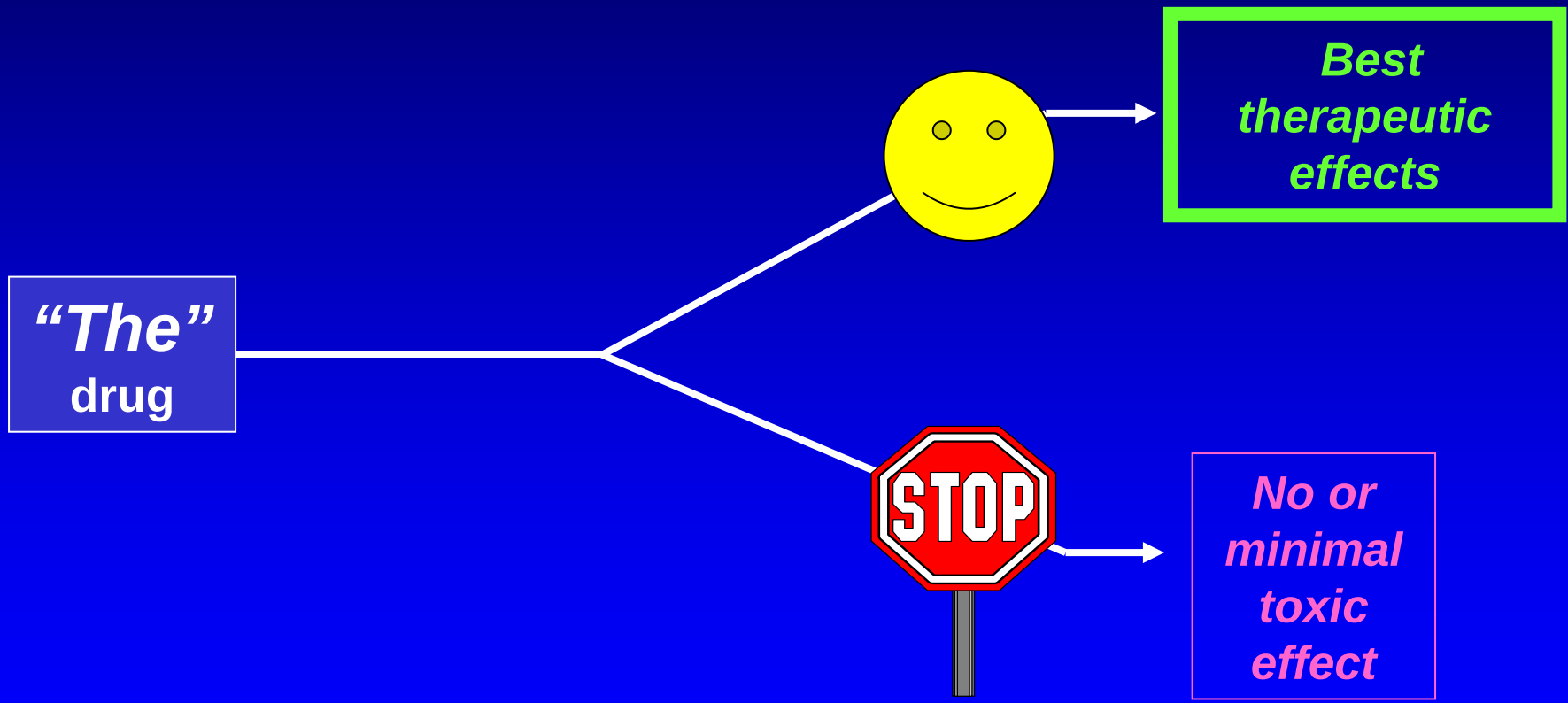
International Society of
Anti-infective Pharmacology

Antibiotic treatment:
Wat does the clinician want ?



The ideal antibiotic ...

the molecule

brilliant and clear solutions

…ent's cure

chemistry **microbiology** **therapy**

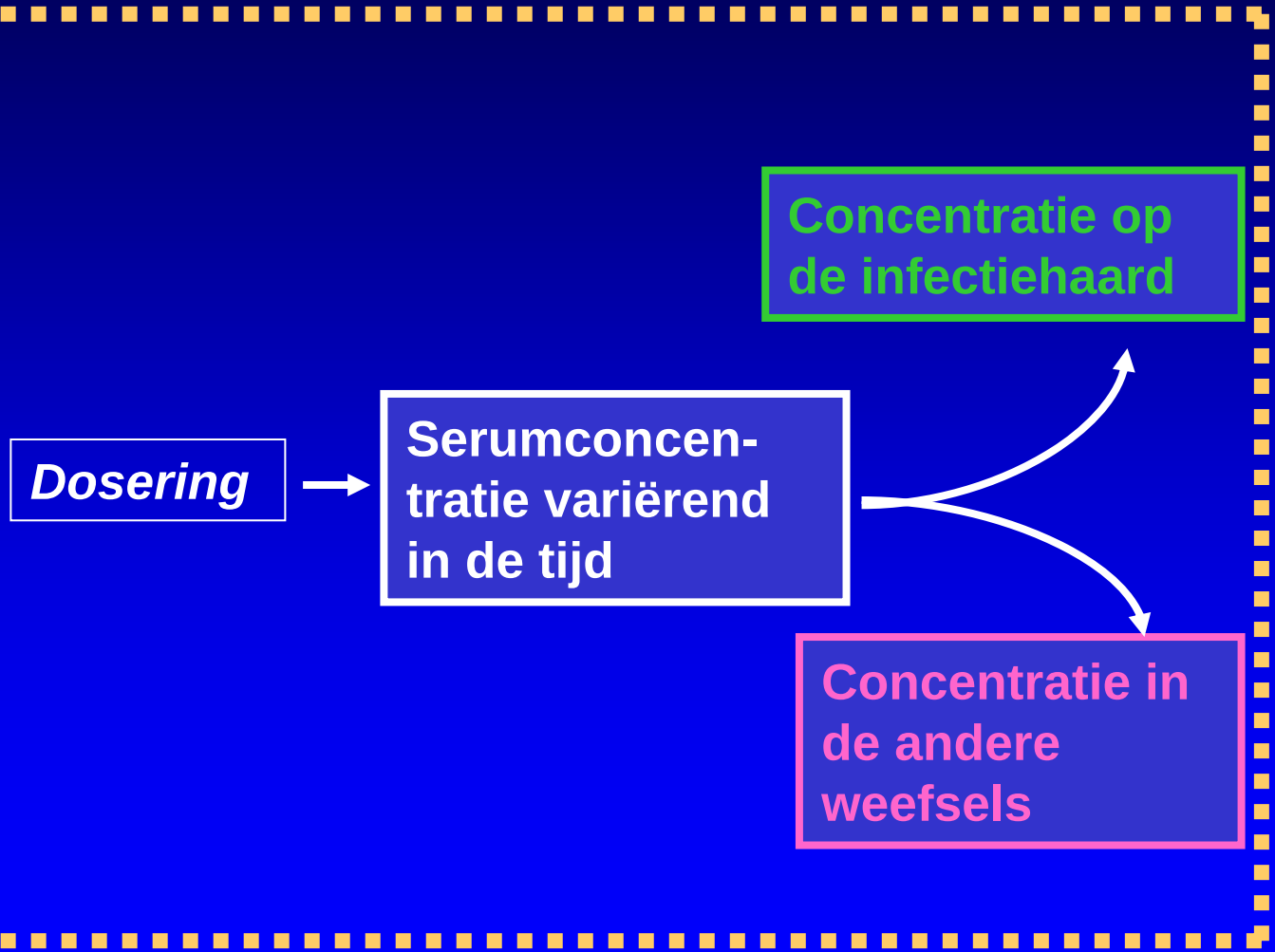
Is the molecule always ideal ?

Main causes of antibiotic failures...

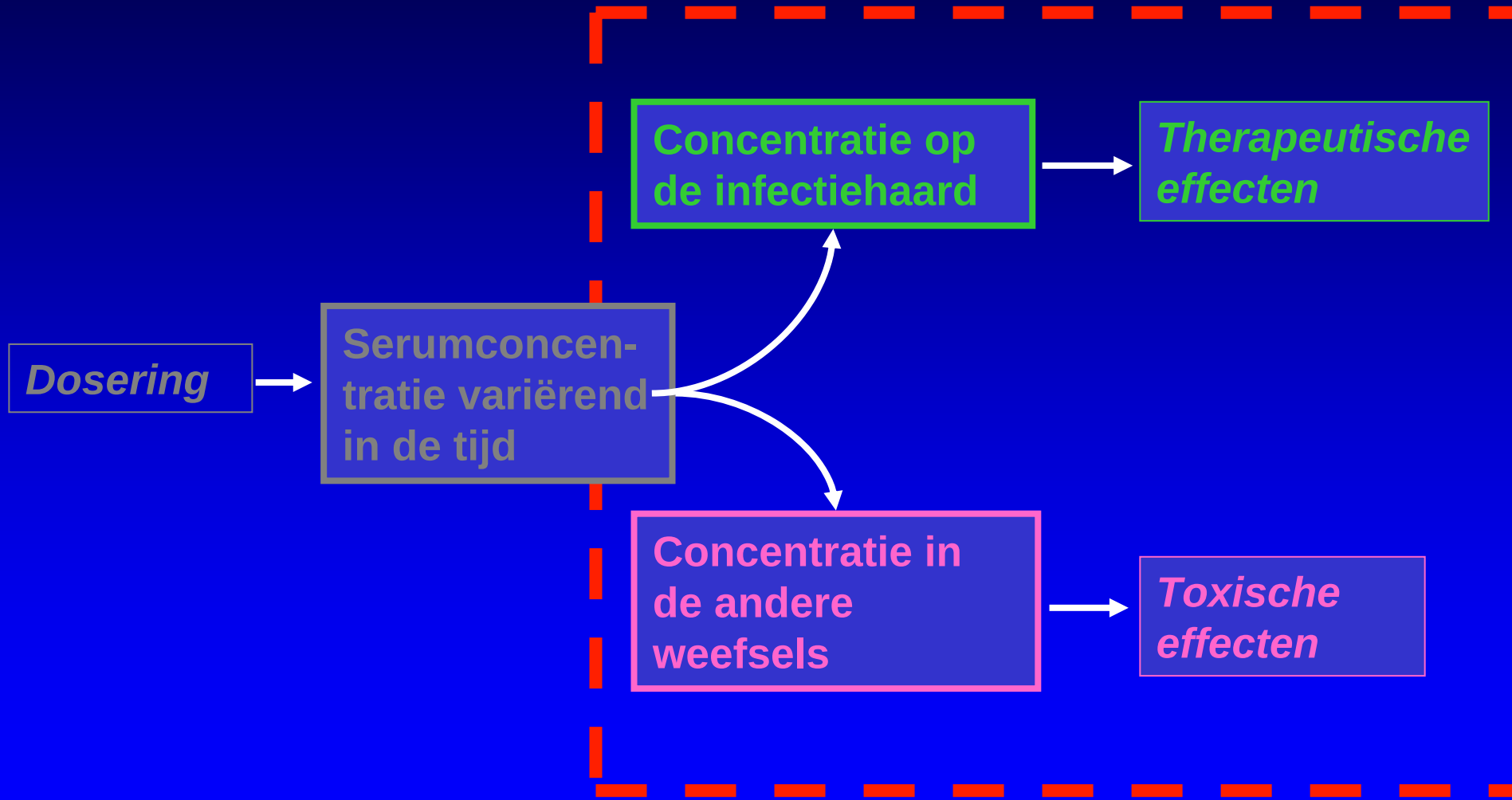
Adapted from Pechère J.C., 1988, 1993, 1998

- **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

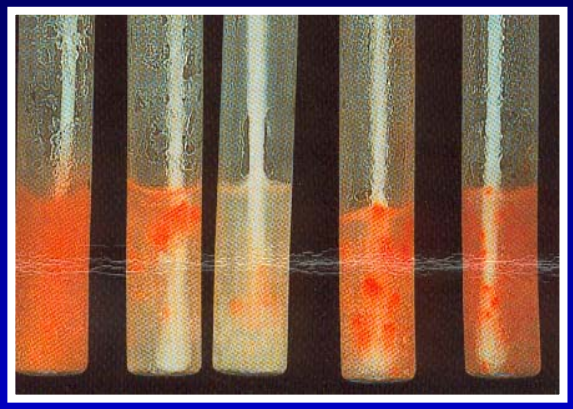
Farmacokinetiek



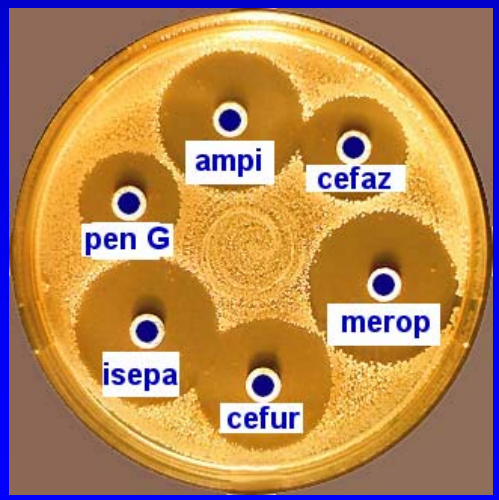
Farmacodynamie



Microbiology



identification



sensitivity

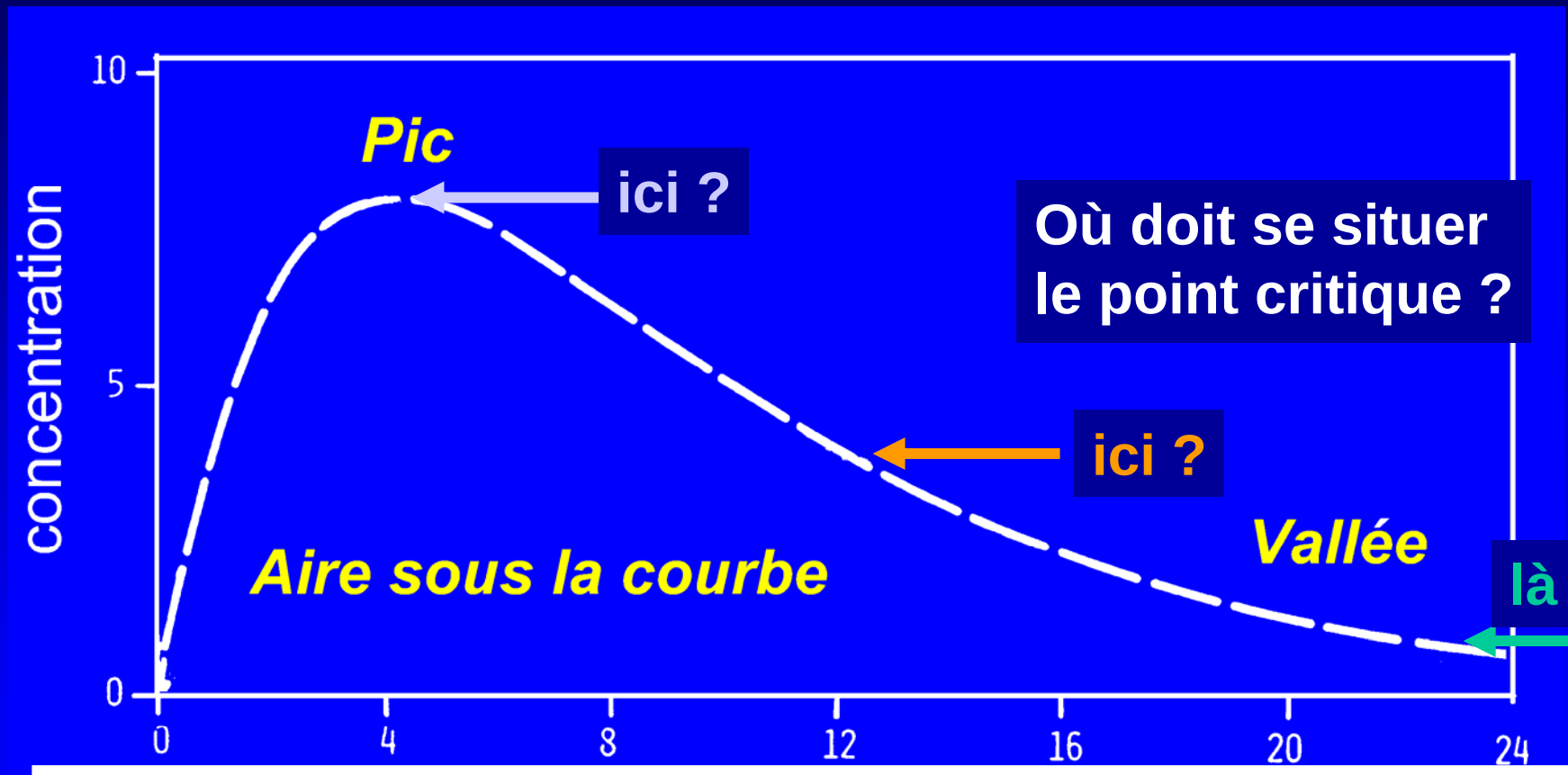
by static techniques

drug concentration stays constant

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

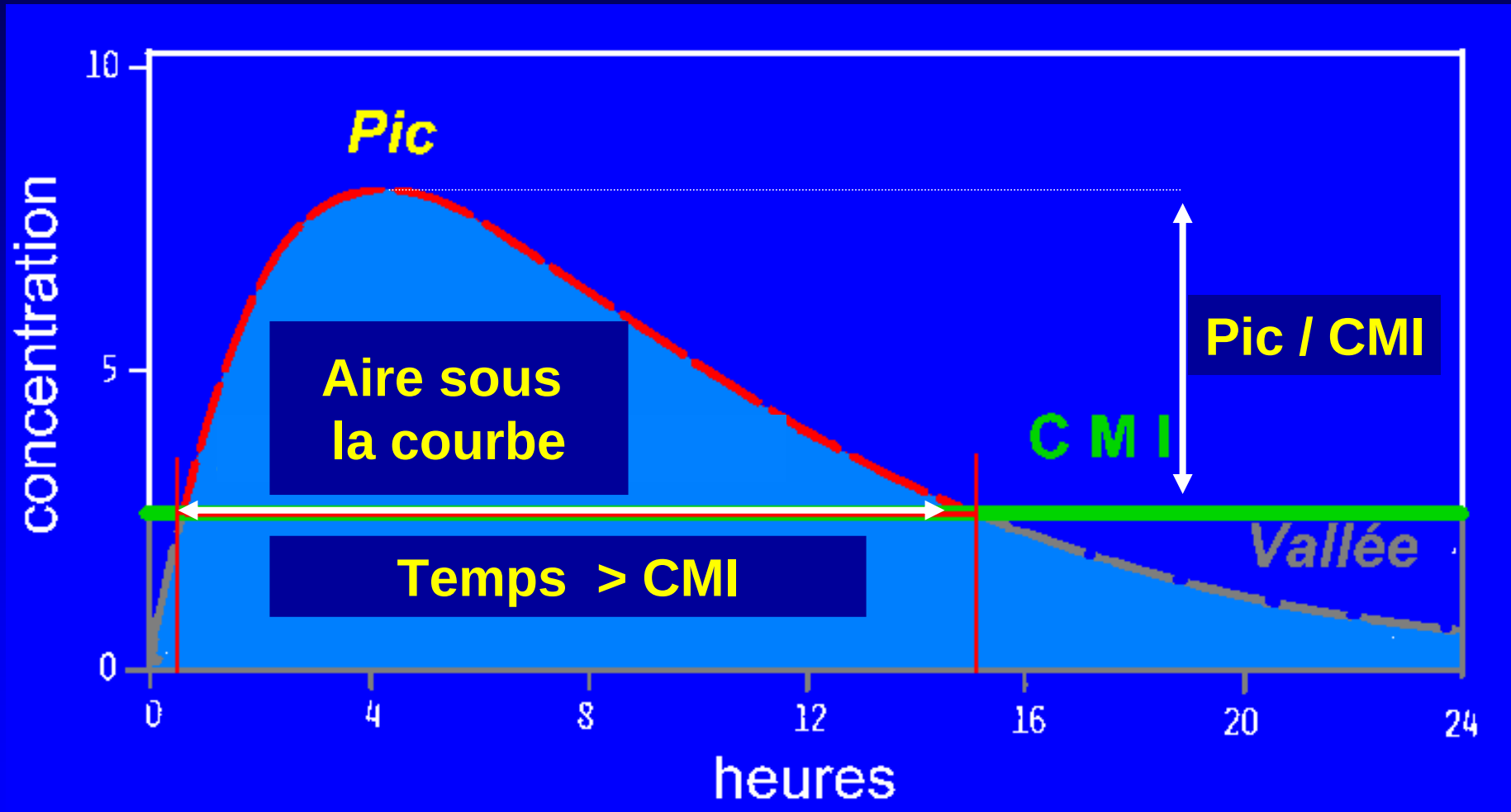
1. Stay above the MIC... **but how much ?**
2. Remain around for a while… **but how long ?**
3. Hope it works... **against everything ?**
4. Hope it is not toxic… **can't do much ...**

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)

Antibiotics Group # 1
(after W.A. Craig, 2000; revised 2003)

1. Antibiotics with **time-dependent effects** and no or little persistent effects

AB	PK/PD parameter	Goal
β-lactams	Time above MIC	Maximize the exposure time

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig, et al. ICAAC 2002; Craig 2003

Antibiotics Group # 2
(after W.A. Craig, 2000; revised 2003)

2. Antibiotics with time-dependent effects, with little or no influence of the concentration BUT with persistent effects

AB	PK/PD parameter	Goal
glycopeptides tétracyclines macrolides streptogramines fluconazole	24h AUC / MIC ratio	Optimize the quantity of AB administered

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig et al., ICAAC 2002; Craig, 2003

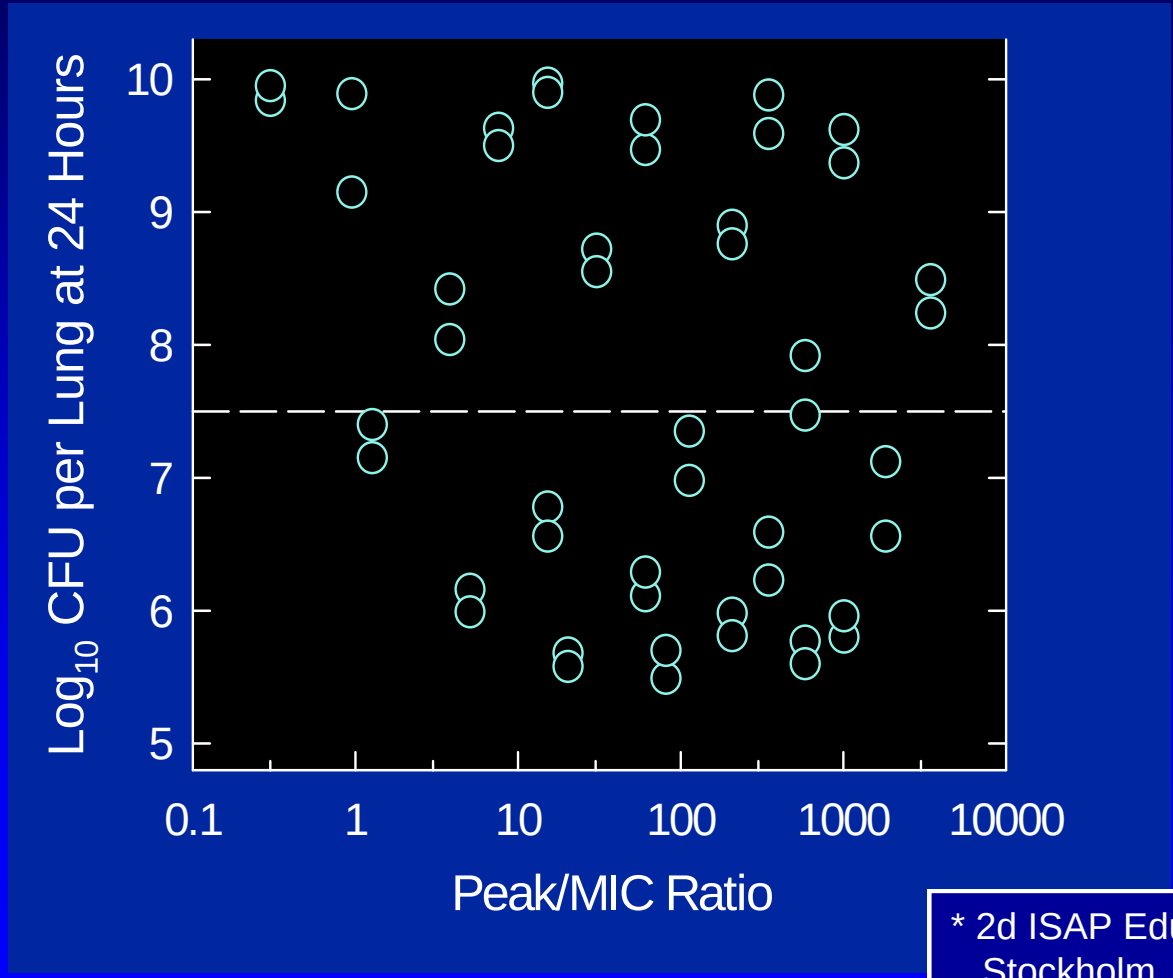
Antibiotics Group # 3
(after W.A. Craig, 2000; revised 2003)

3. Antibiotics with concentration-dependent activity and with persistant effects (PAE)

AB	PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin ketolides amphotericin	C_{max} / MIC **and** 24h AUC / MIC ratios	Optimize **both the peak** and the **quantity** of drug

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig ek al., ICAAC 2002; Craig, 2003

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



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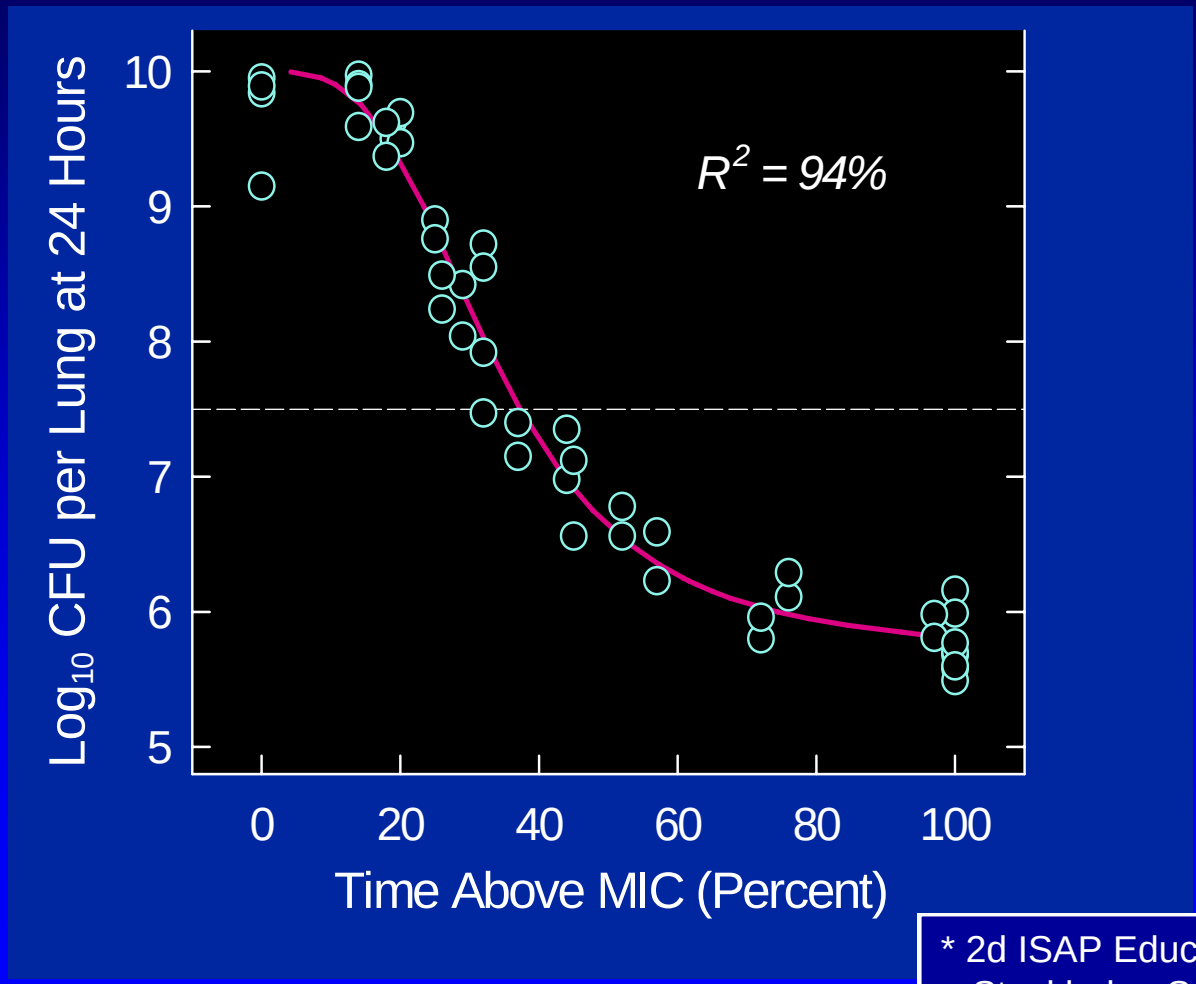
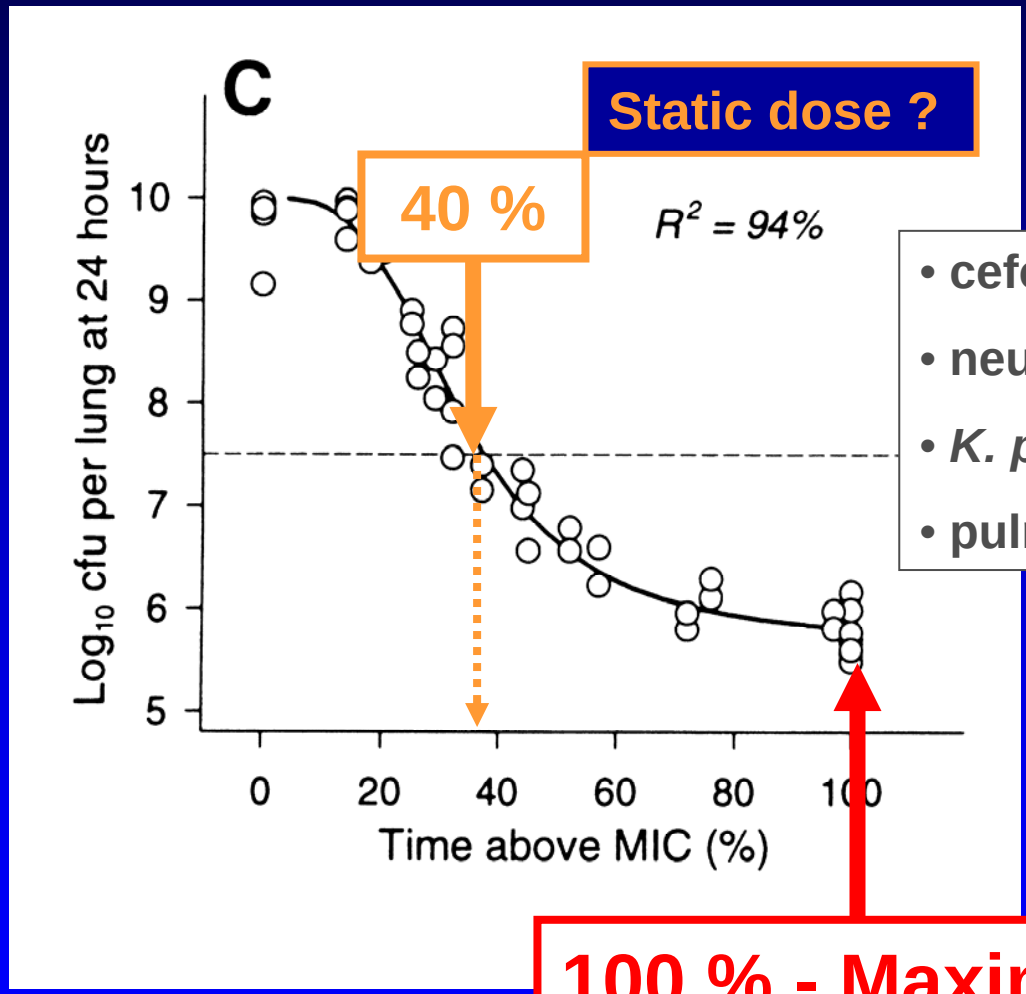


* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Pharmacokinetics / Pharmacodynamics in action ...

What can (and must) the clinician know ?

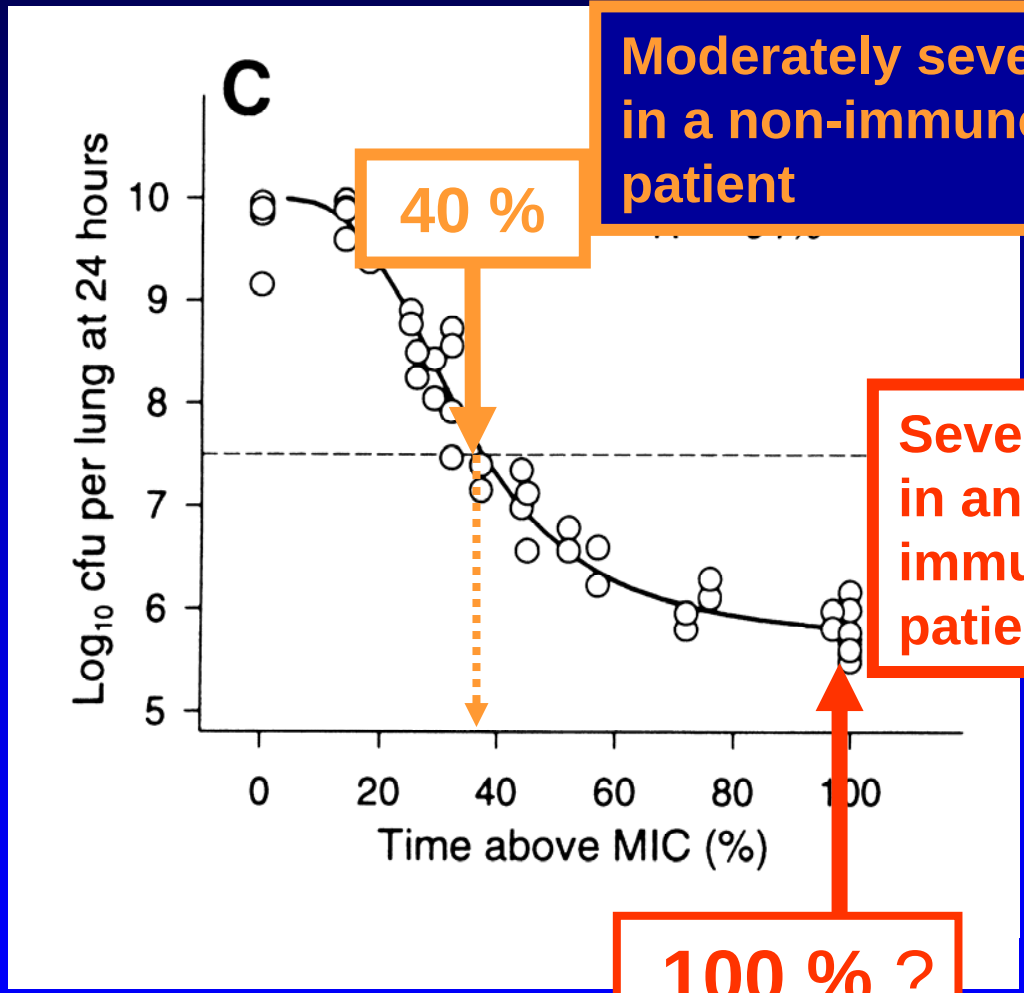
How much time above MIC ?



- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100 % - Maximal effect ?

Here is a proposal ...



Moderately severe infection in a non-immunospressed patient

40 %

Severe infection in an immunosuppressed patient

100 % ?

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

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

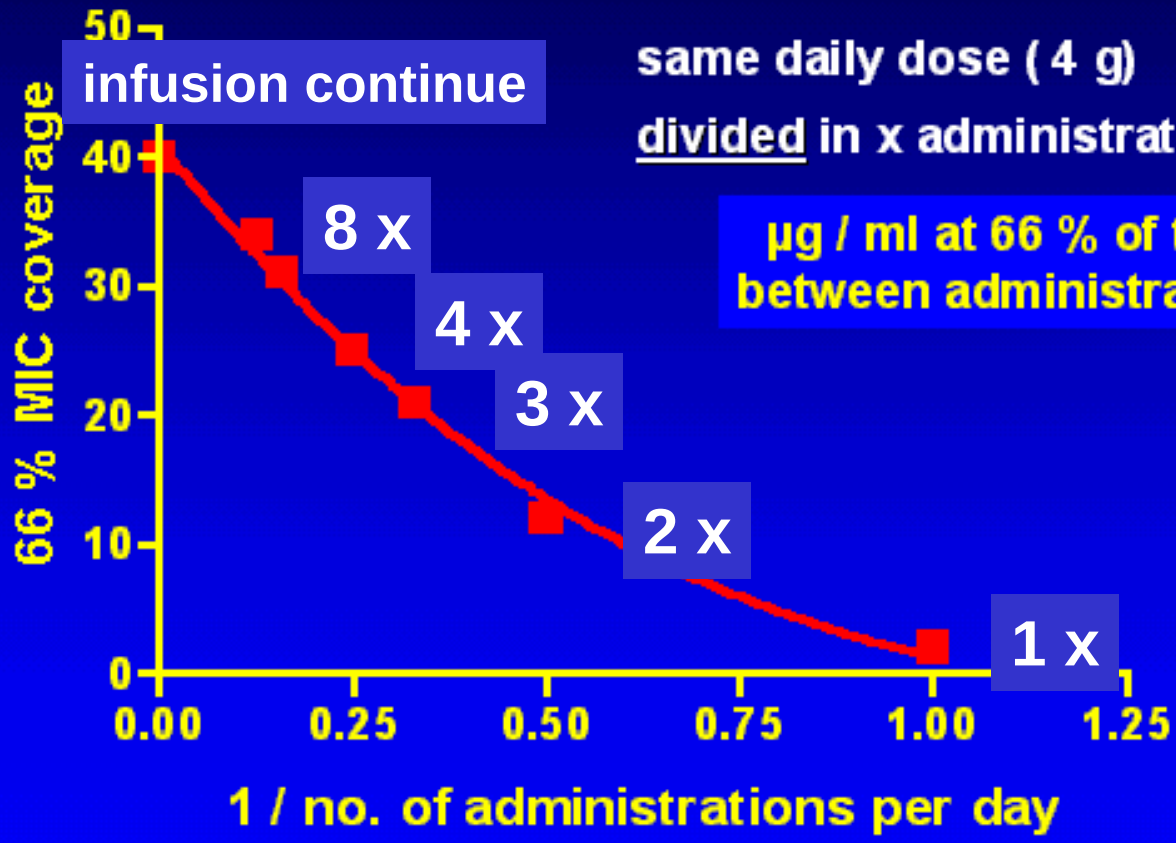
Pharmacokinetics / Pharmacodynamics in action ...

β- lactams : what can you really do ?

I guess 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

Reducing β - lactams interval: where can we go ?



β - lactams by continuous infusion

$C_{ss} = K_o / Cl$

Serum concentration

clearance

rate of infusion

Servais & Tulkens, AAC, *September 2001*

stability of the molecule …

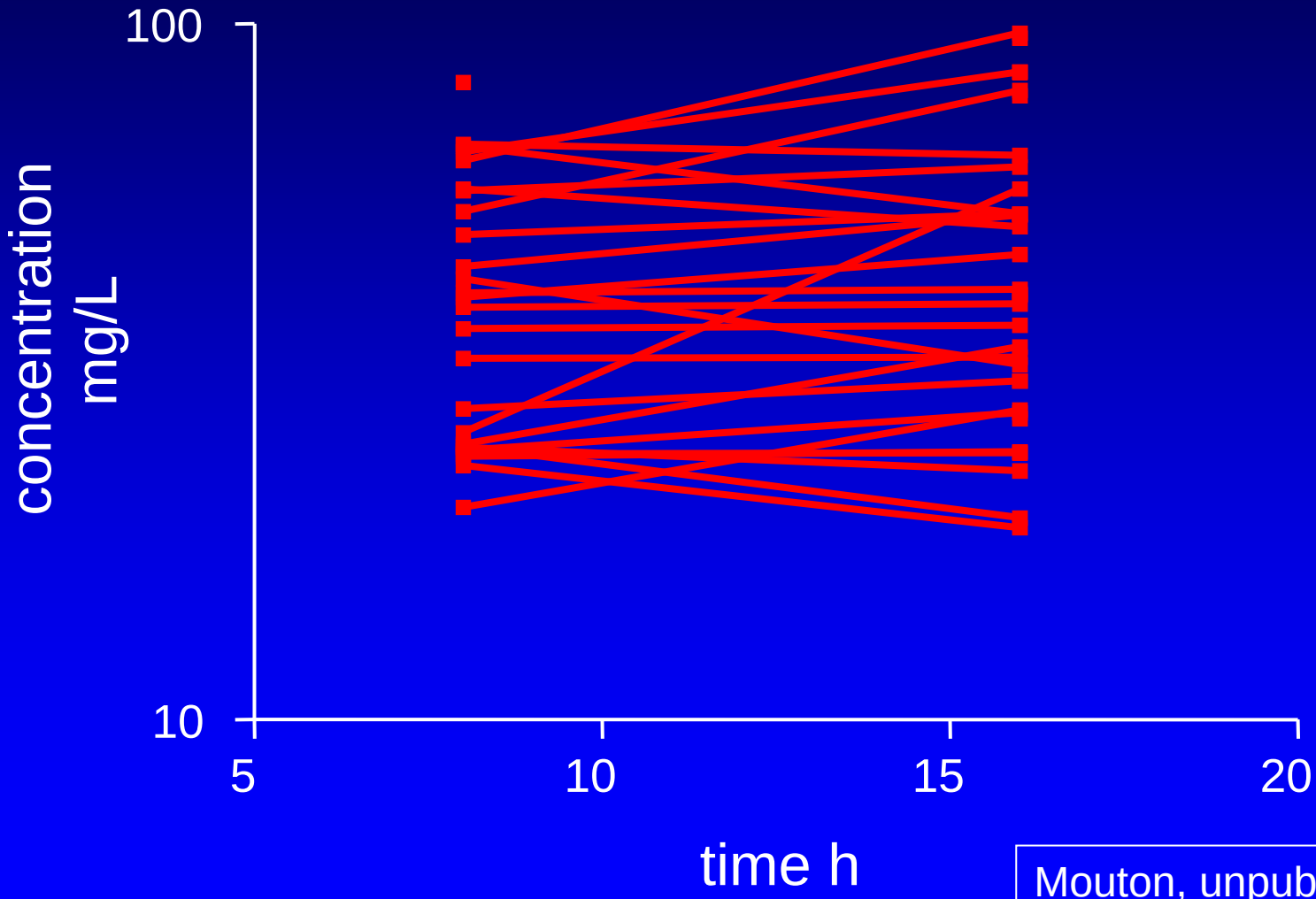
specific applications …

Nosocomial pneumonia, cystic fibrosis, … in progress

Problems with continuous infusion ...

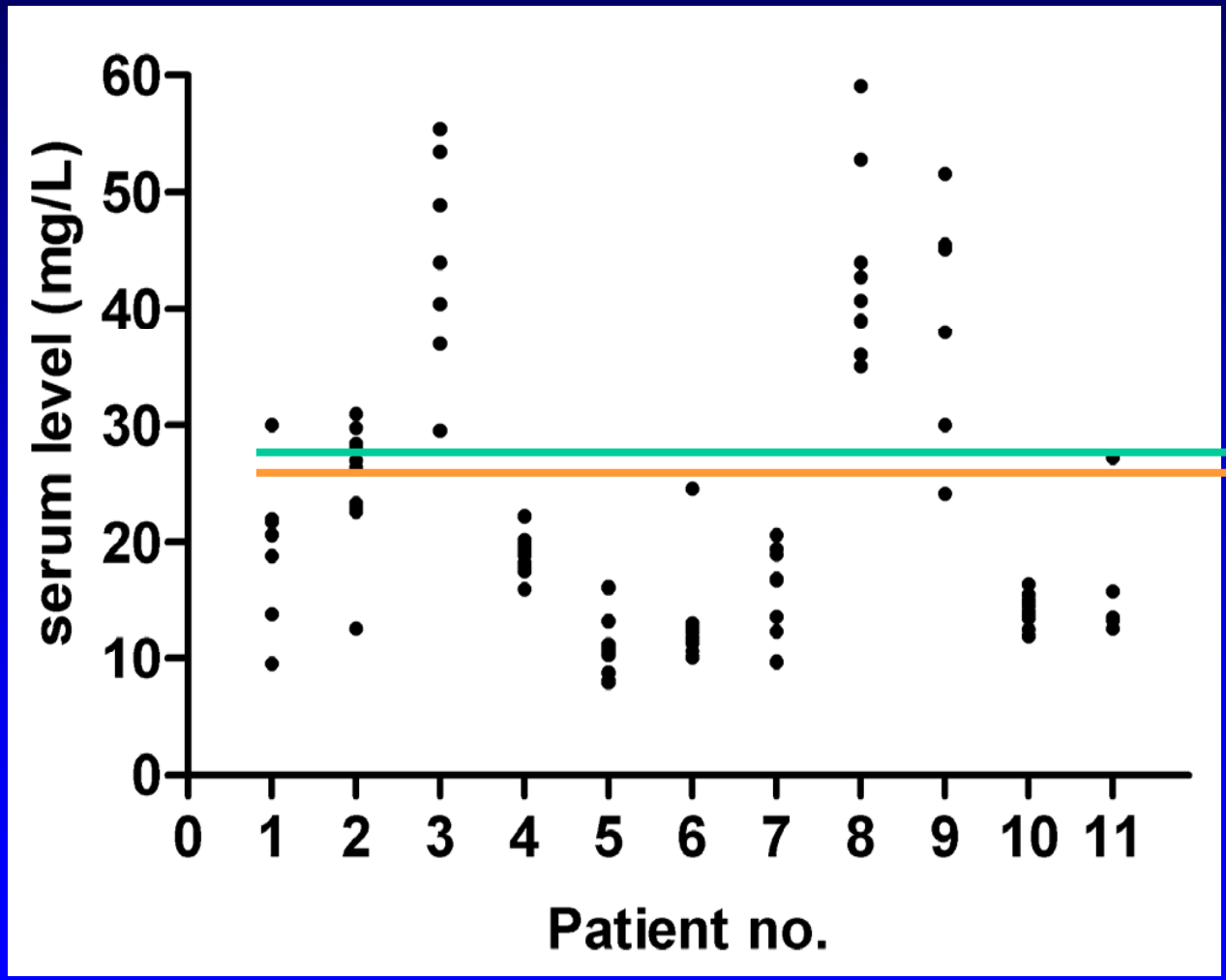
- Clearance estimates
- Variations in clearance (ICU)
- Non-linear clearance
- drug instability

Ceftazidime concentrations (ICU patients)



Mouton, unpublished

Ceftazidime concentrations in ICU patients (successive determinations)



Laterre et al., ICAAC 2002

What about meropenem ?

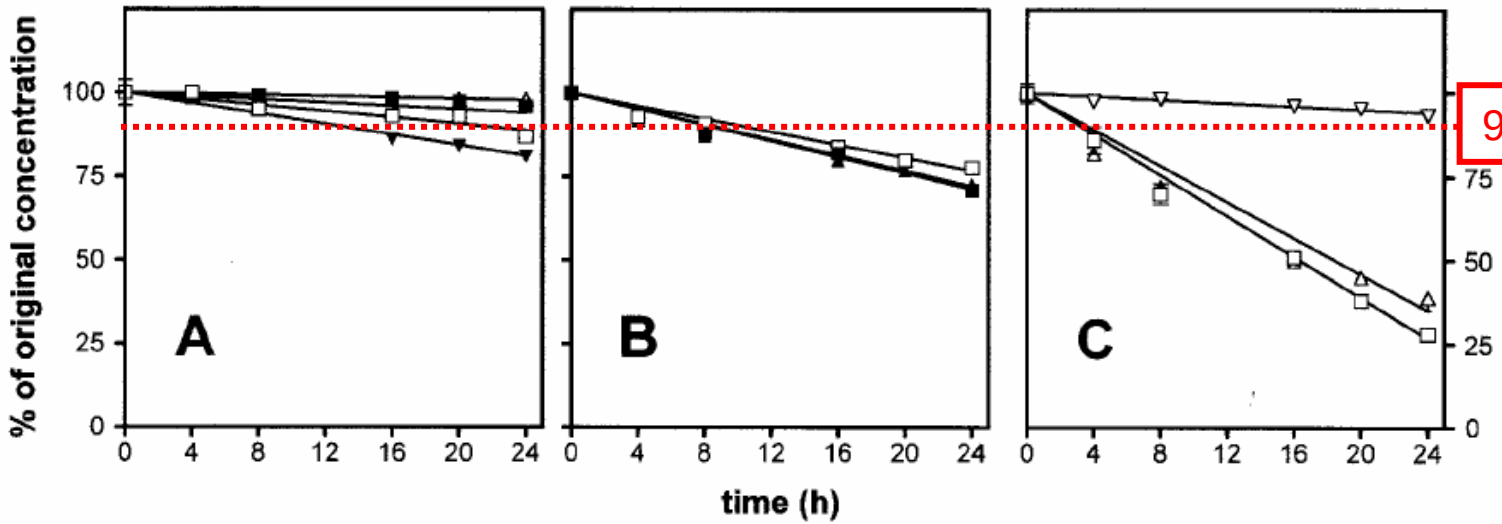
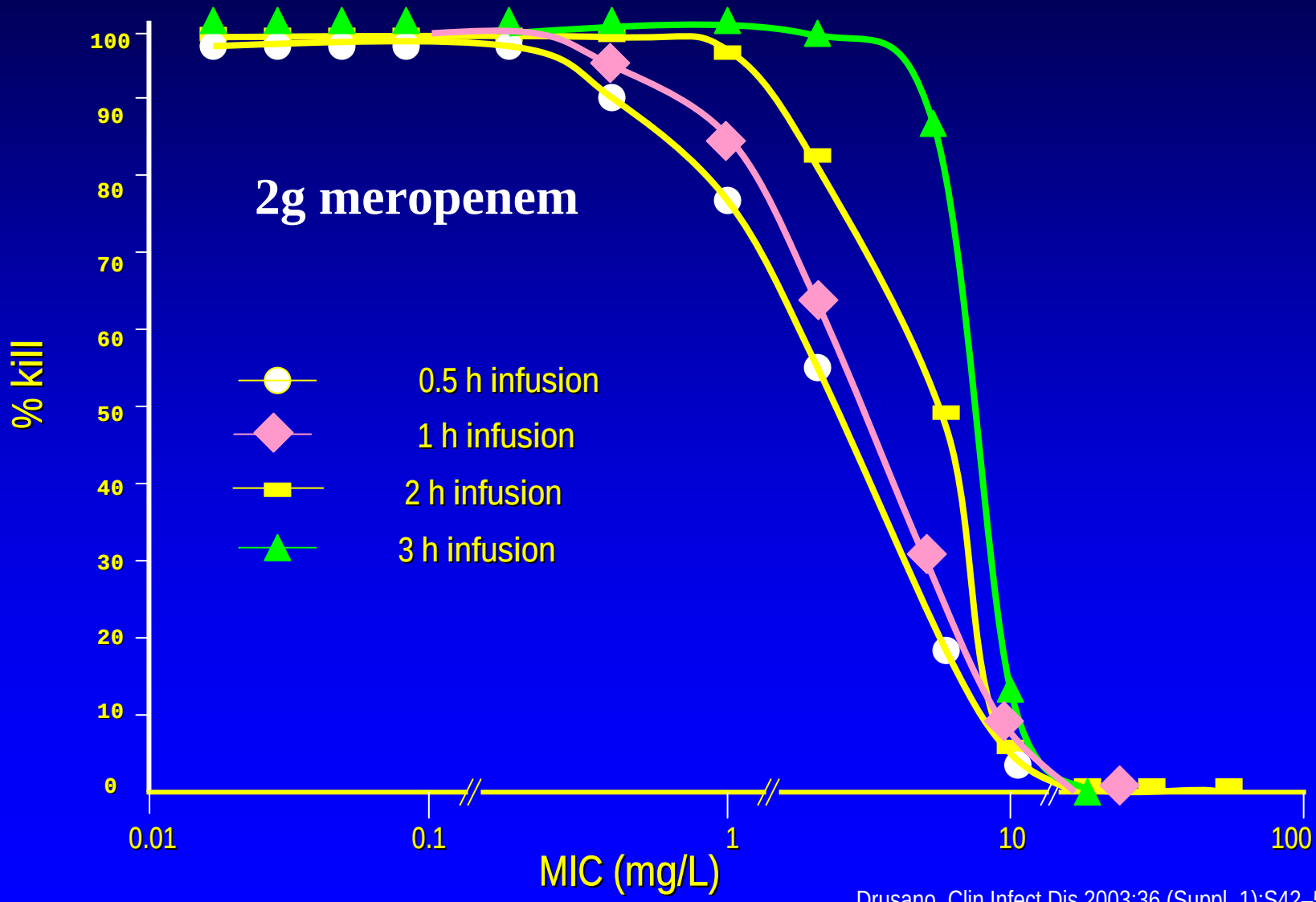


FIG. 1. Stability of the β-lactams in water at 37°C over time at the maximum concentration tested. (A) Symbols: △, 10% aztreonam; □, 12.8% piperacillin; ■, 12.8% piperacillin plus tazobactam (since the slope for 12.8% azocillin was almost identical to that for piperacillin-tazobactam, it was omitted for the sake of clarity); ▼ 12.8% mezlocillin. (B) Symbols: ■, 12% ceftazidime; □, 5% cefepime; ▲, 3.2% cefpirome. (C) Symbols: □, 0.8% imipenem plus cilastatin; △, 6.4% meropenem; ▽, 6.4% faropenem. All values are the means of three independent determinations ± the standard deviation (SD; symbols without bars indicate values for which the SD is smaller than the symbol size).

Viaene et al., AAC 2002; 46:2327-2332

The stability of meropenem is more limited than for other β-lactams ➔… Infusion must be limited to 3h

Use a long infusion of meropenem vs. *P. aeruginosa*



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

Meropenem with prolonged infusion …

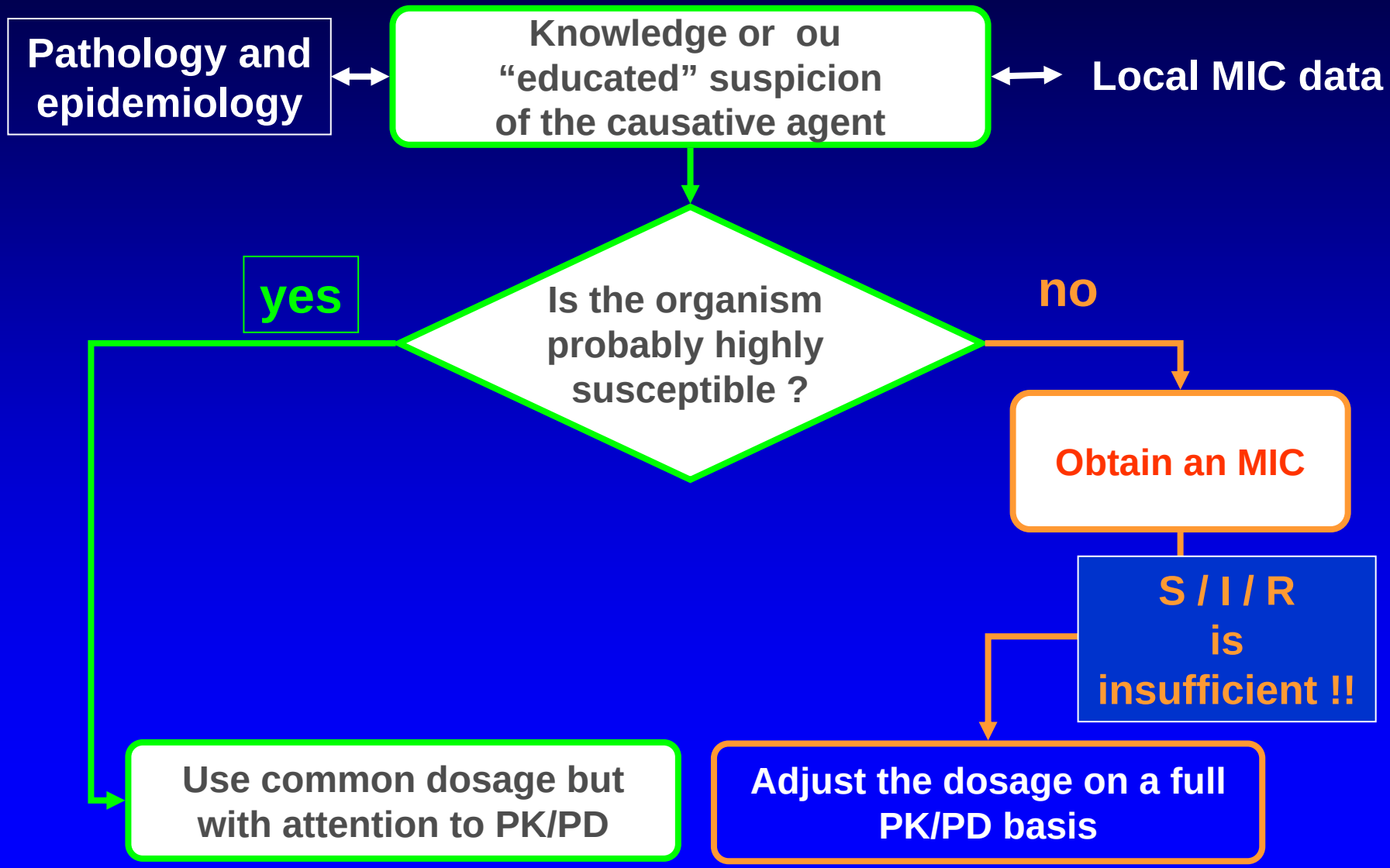
TABLE 5. Meropenem target attainment against *P. aeruginosa* using four different dosing regimens

MIC	% of isolates inhibited by:				
	1 g q8h (3 h)[a]	1 g q8h (1 h)	500 mg q8h (3 h)	500 mg q8h (1 h)	500 mg q6h (1 h)
0.008	100	100	100	99.95	100
0.016	100	100	100	99.8	100
0.125	100	99.99	100	99.45	100
0.25	100	99.97	100	98.65	99.84
0.5	100	99.82	100	95.4	99.36
1.0	100	99.28	100	89.65	97.04
2.0	100	96.21	99.25	65.45	88.04
4.0	99.1	81.08	79.6	31.9	63.02
8.0	79.6	23.12	14.2	4.4	19.08
16.0	14.2	0	0	0	0
32.0	0	0	0	0	0
Target attainment	86.4	79.5	79.3	67.5	76.4

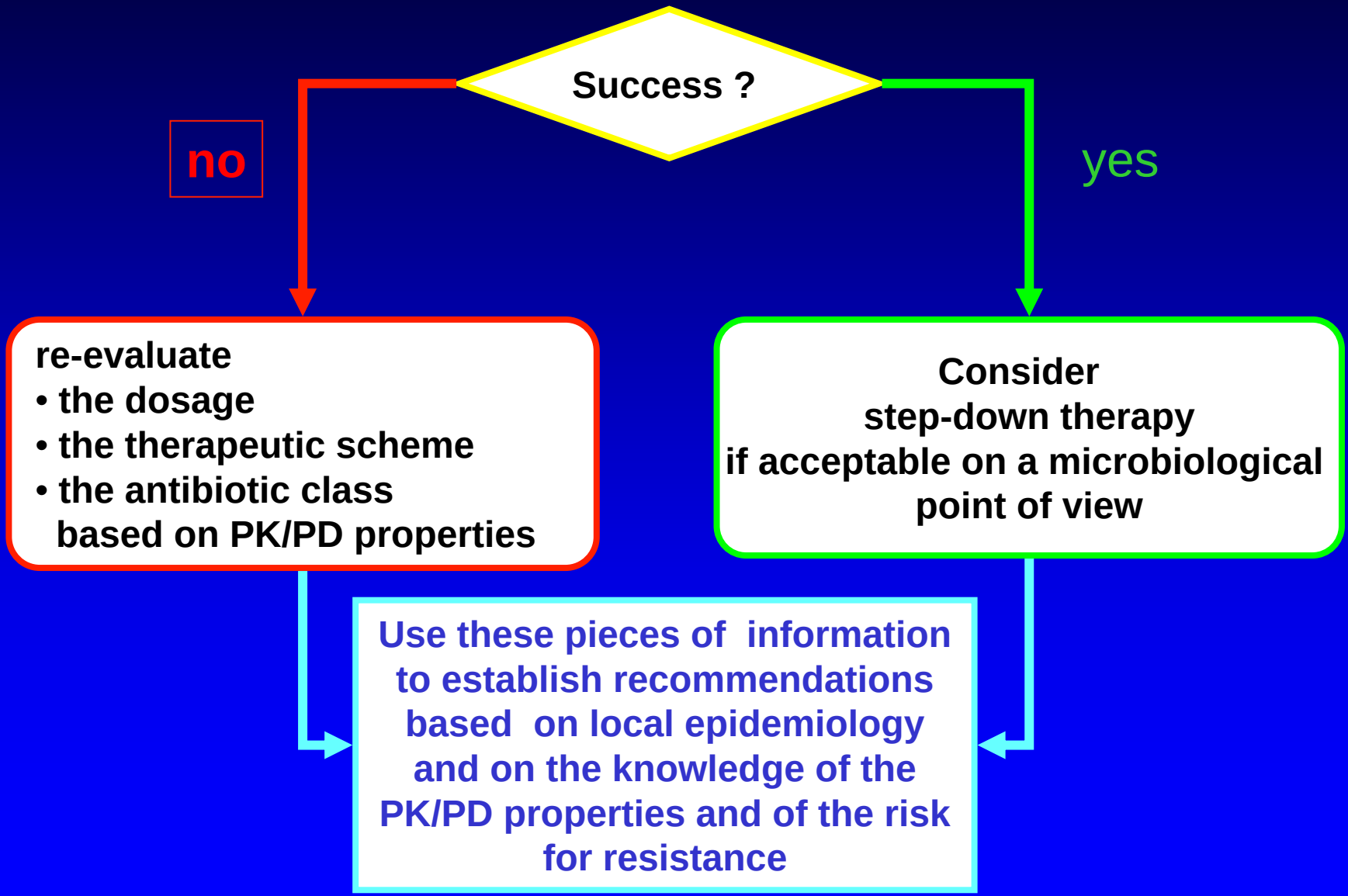
[a] Values in parentheses are infusion times.

Lomaestro & Drusano, Antimicrob Agents Chemother. 2005 Jan;49(1):461-3.

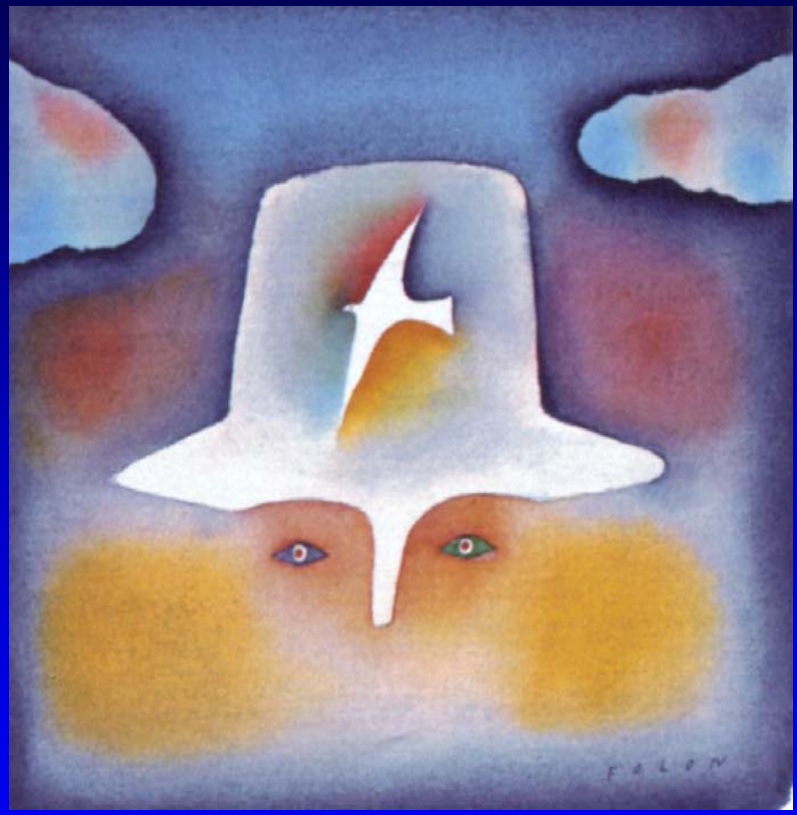
A clinical algorithm ...



A clinical algorithm (follow.) ...



β-lactames and PK/PD



It 's a brilliant idea....

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