Strategies to combat resistance:
Focus on pharmacokinetics/pharmacodynamics with applications to β-lactams and aminoglycosides

Paul M. Tulkens
Unité de pharmacologie cellulaire et moléculaire
Université catholique de Louvain, Brussels, Belgium
&
International Society of Antiinfective Pharmacology
European PK/PD of Anti-infectives Study Group

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

ISAP

With the support of *Wallonie-Bruxelles-International*

WBI Wallonie-Bruxelles International

Antibiotic treatment:
Wat does the clinician want ?

"The" **drug**

Best therapeutic effects

No or minimal toxic effect

The ideal antibiotic ...

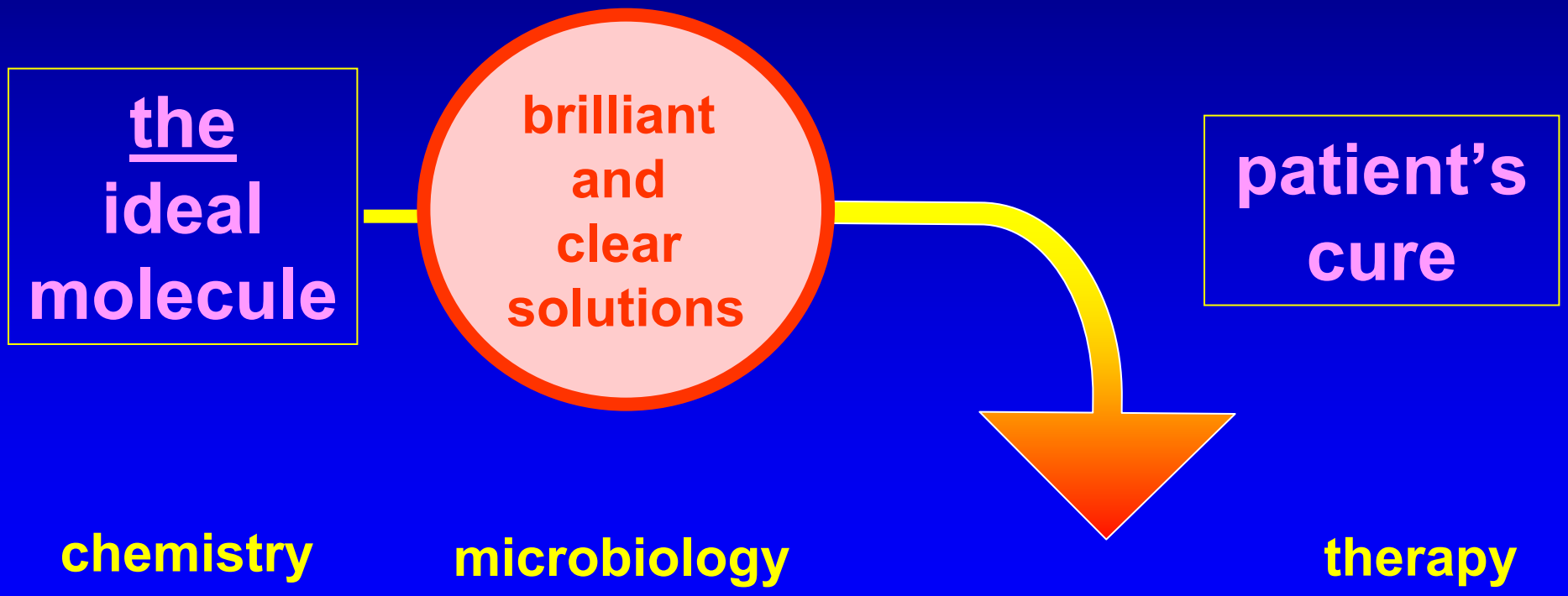
the molecule

brilliant and clear solutions

ent's cure

chemistry **microbiology** **therapy**

Is the molecule always ideal ?



Main causes of antibiotic failures...

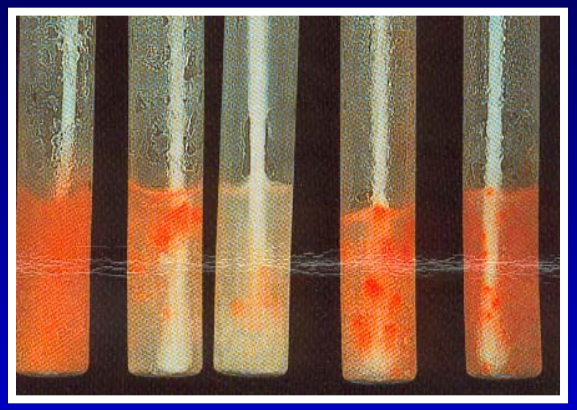
Adapted from Pechère J.C., 1988, 1993, 1998

- **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

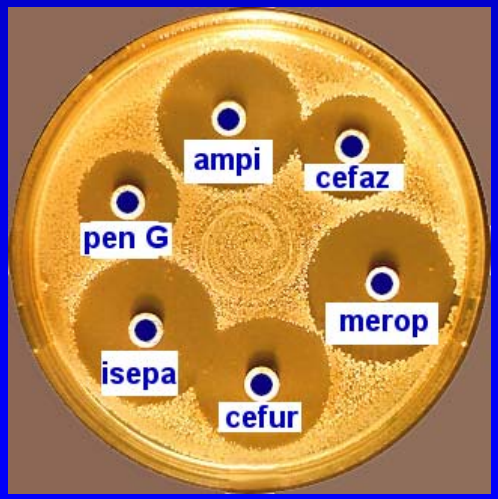
In a nutshell ... so far …

- **Microbiology parameters: MIC !**
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams
- The problems if you underdose
- Take home message

Microbiology



identification



susceptibility ⇒ **S – I – R ***

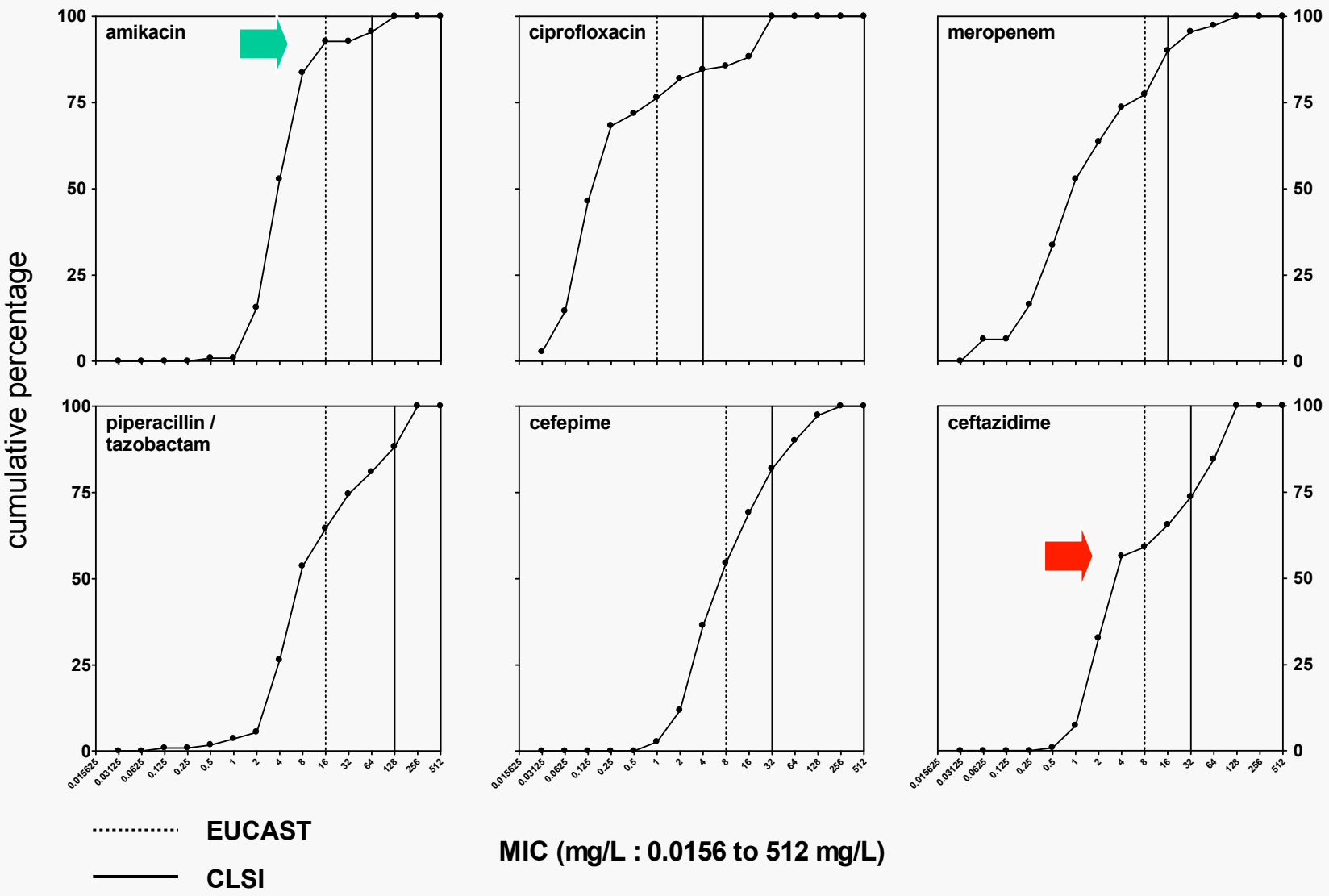
* following CLSI or EUCAST breakpoints system

S – I – R is insufficient...

What do I do in my country ?

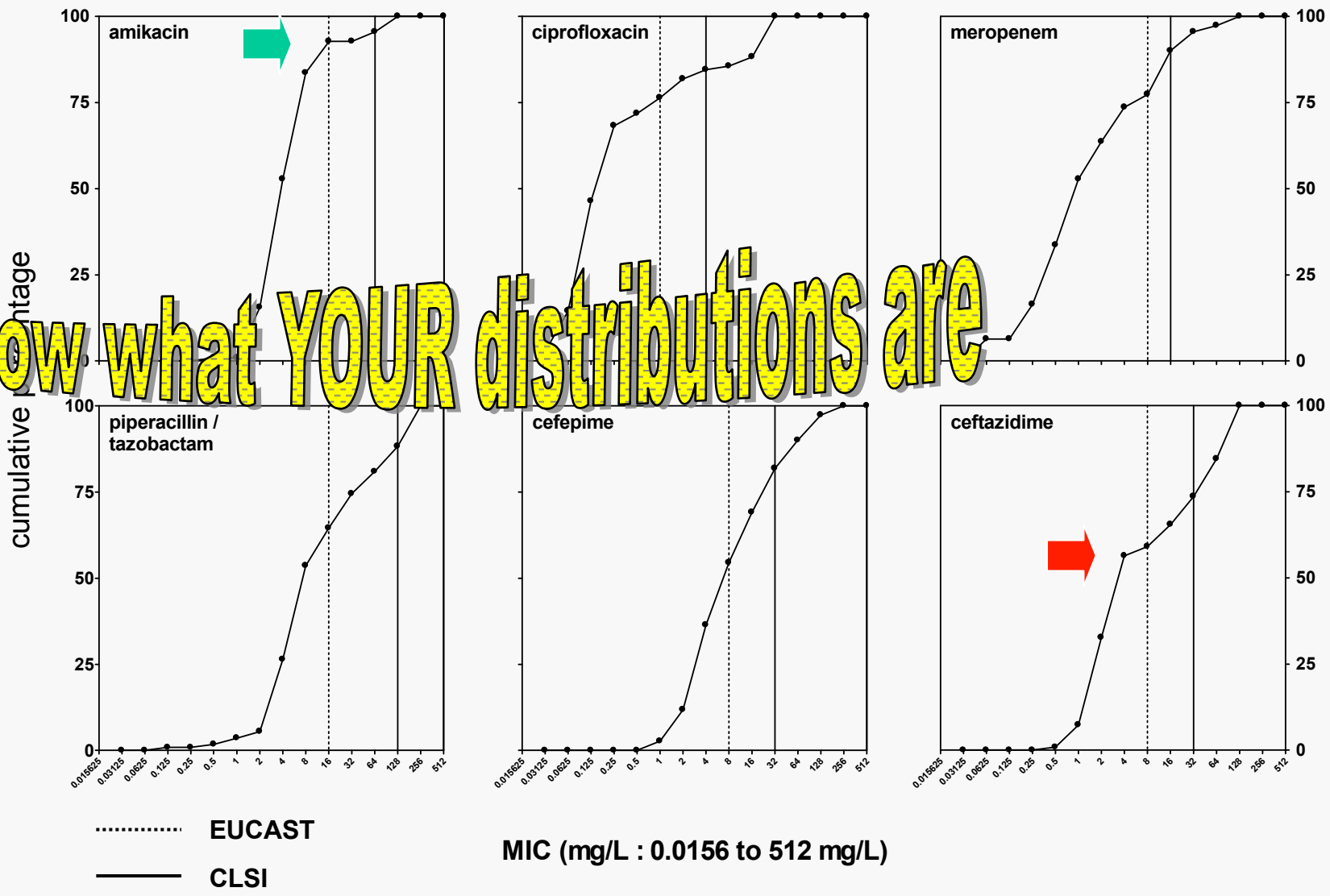
- Survey the level of resistance in Brussels Hospitals and relate it to therapy
- Examine the mechanisms of resistance acquisition (with special reference to efflux pumps)
- Assess new antibiotics and novel approaches (immunotherapy)
- Examine the susceptibility to biocides

What is the situation at day 0 with *P. aeruginosa* in HAP ?



Riou *et al.* IJAA 2010; 36:513-522

What is the situation at day 0 with *P. aeruginosa* in HAP ?



Know what YOUR distributions are

Riou *et al.* IJAA 2010; 36:513-522

Questions ...

- Does your microbiologist discuss infection cases with you ?

1. Each case
2. Few cases
3. Upon asking
4. Never

Asking the question you always wanted to ask ...

- Does your microbiologist gives MIC of antibiotics apart from sensitivity for difficult patients or for important epidemiological surveys ?

1. Each case
2. Few cases
3. upon asking
4. Never

Asking the question you always wanted to ask ...

- Does your microbiologist gives MIC of antibiotics apart from sensitivity for difficult patients or for important epidemiological surveys ?

1. Each case
2. Few cases
3. upon asking
4. Never

No, MIC is not the acronym for "**M**inimal **I**nterest to the **C**linician" !

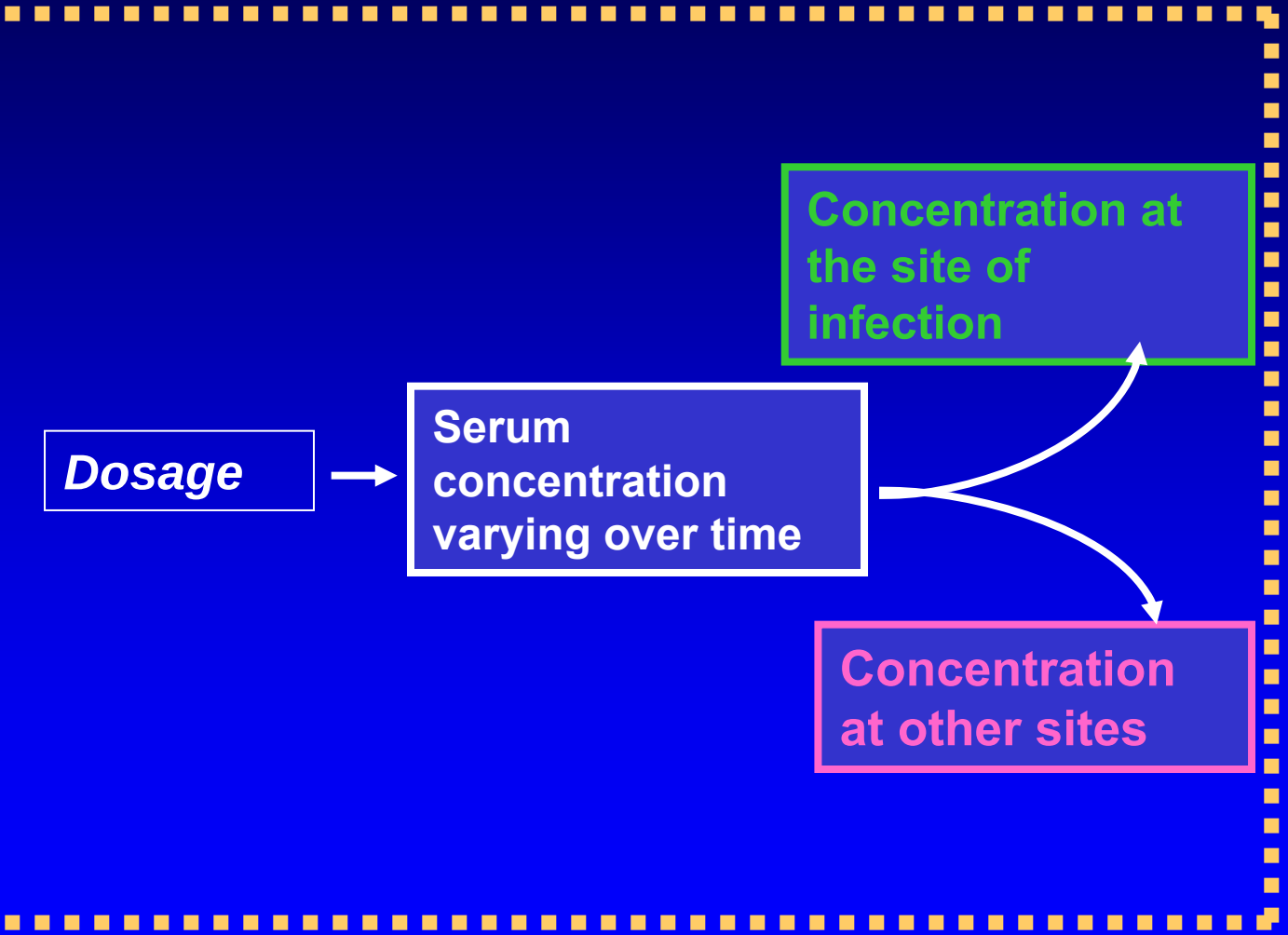
What did the textbooks say about antibiotic dosages and schedules in the 90's ?

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 ...**

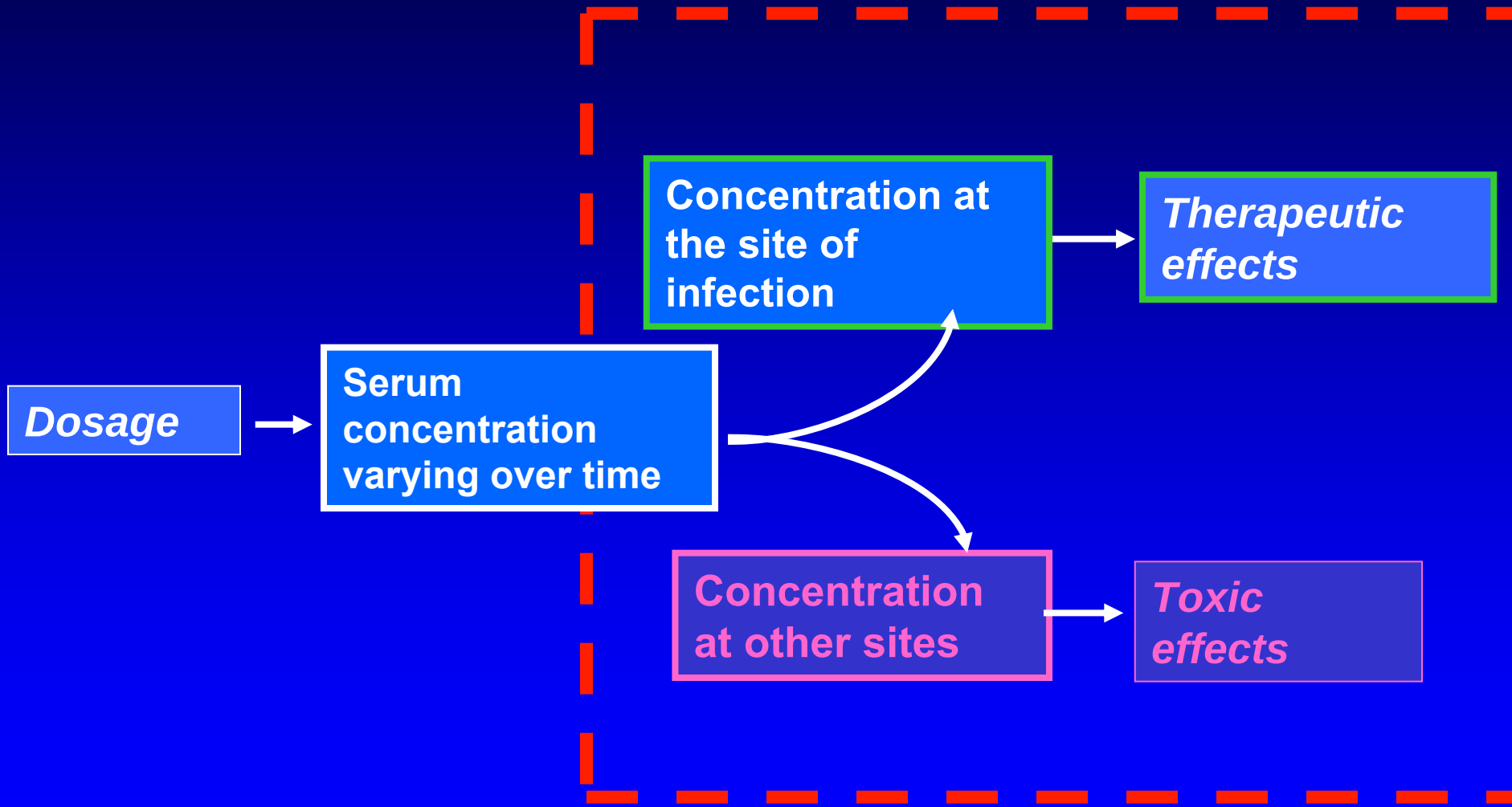
In a nutshell ... so far …

- **Microbiology parameters: MIC !**
- **Pharmacodynamic parameters**
- PK/PD as applied to beta-lactams
- The problems if you underdose
- Take home message

Pharmacokinetics



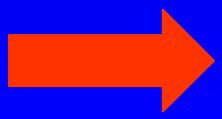
Pharmacodynamics



PK / PD : why does it improve the use of antibiotics ?

The basics:

- anti-infective drug usage was long irrational or not scientifically based on a pharmacodynamic point of view
  - search for low doses for fear of toxicity
  - "errors" in drug dosages at registration
  - misunderstanding of "optimal schedules"
- pharmacokinetics was mostly used to establish "drug presence" rather than to correlate dosing with efficacy

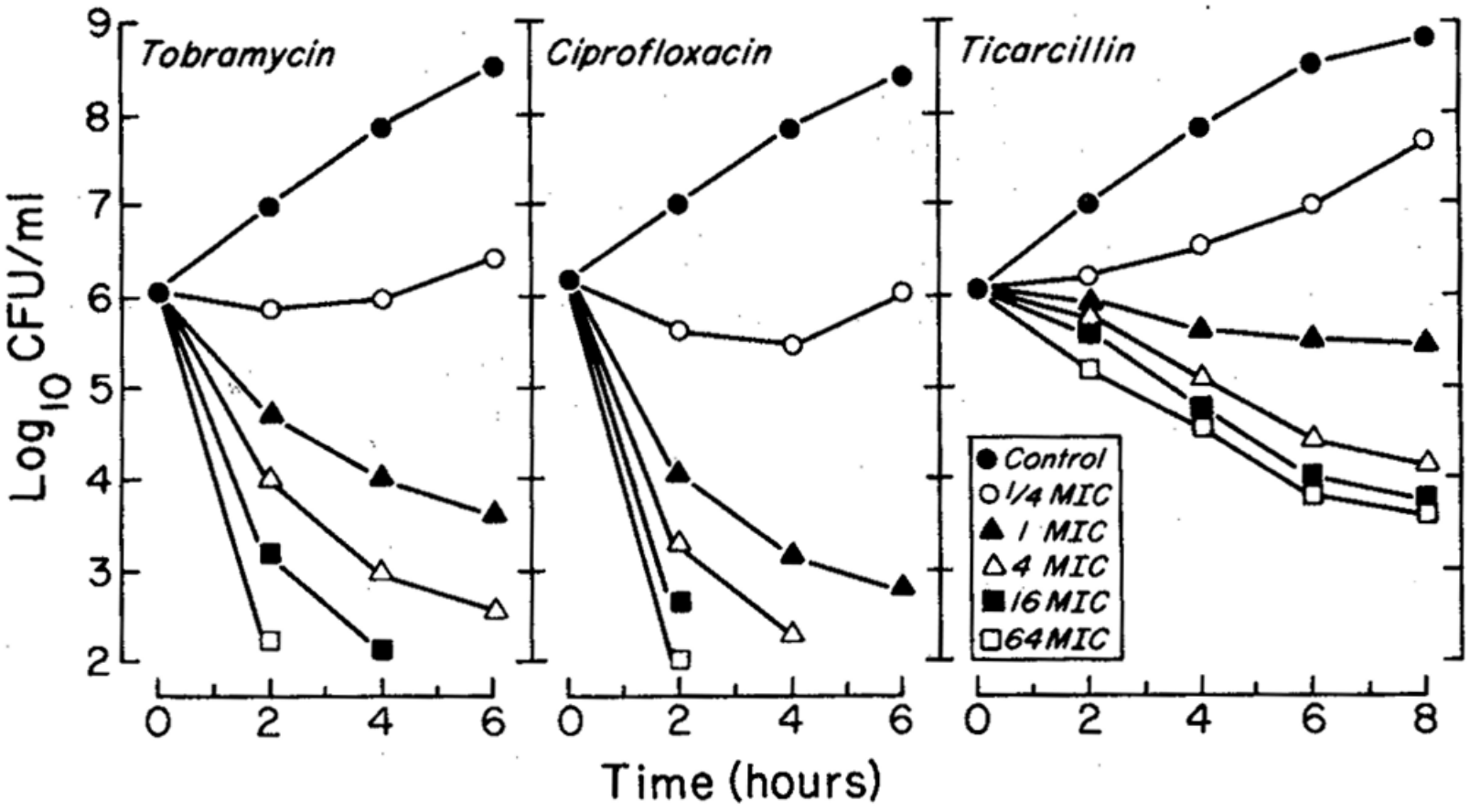


pharmacodynamics of antiinfective drugs was largely "*terra incognita*" 20 years ago

How did it start ?

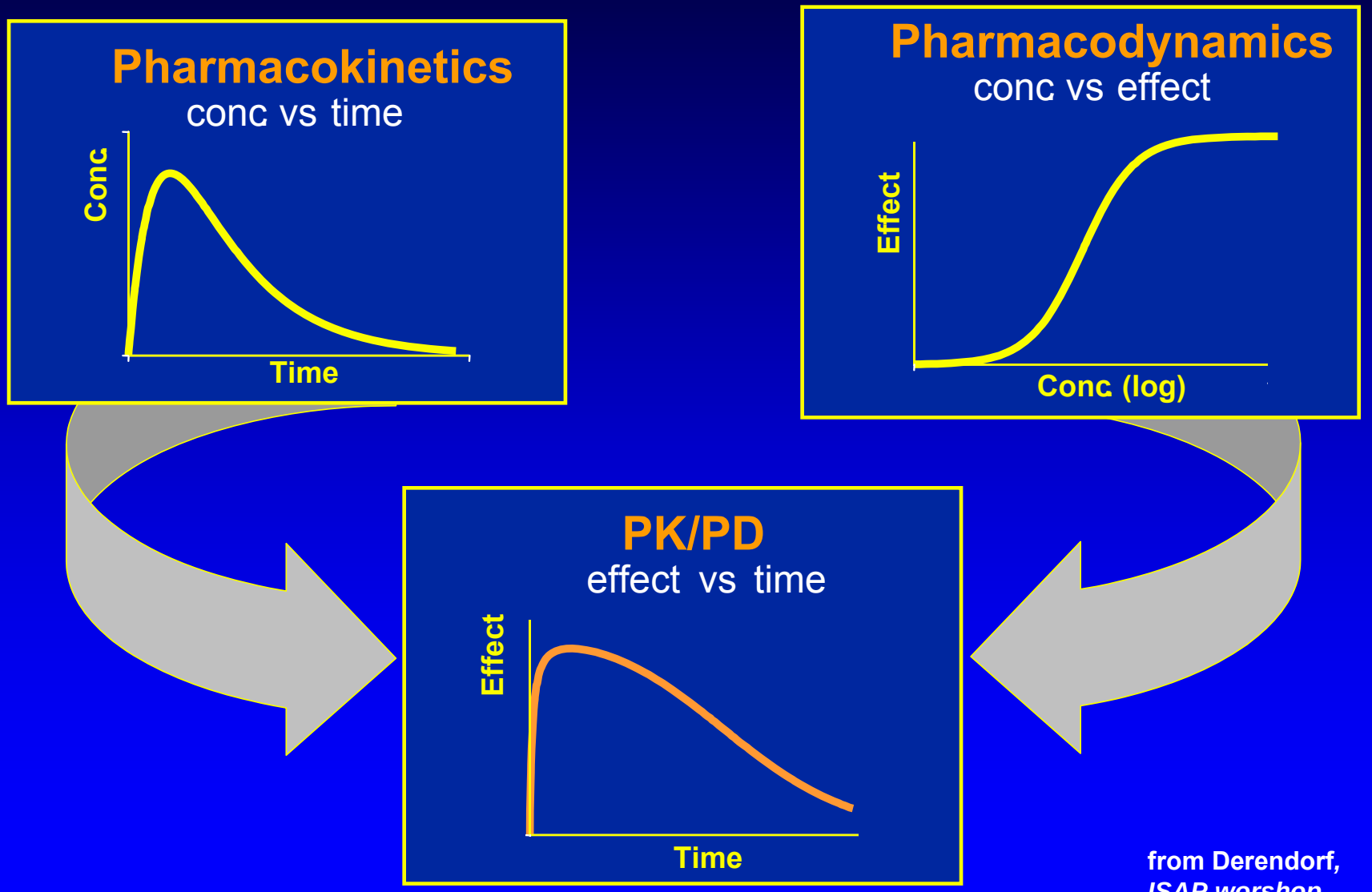
A bunch of good guys met in Stockholm in 1989 ...

Pharmacodynamics : influence of time and concentration ...



Craig *et al.*

Pharmacokinetics - Pharmacodynamics



from Derendorf,
ISAP worshop

More questions …

- Do you agree with the benefit of "HIT HARD and HIT FAST" ?

1. No
2. Yes

More questions …

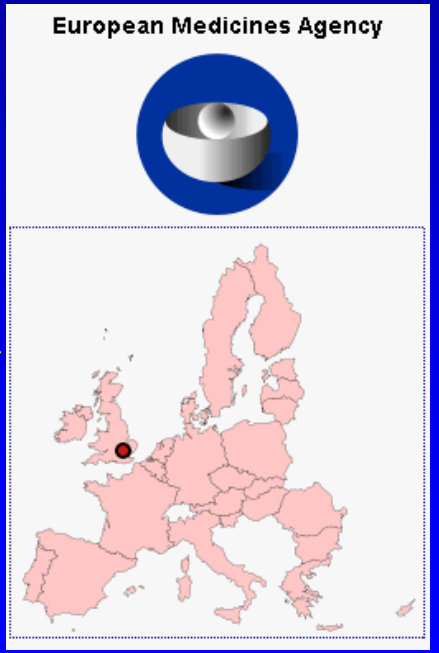
- Do you agree the benefit of "HIT HARD & HIT FAST ?"

Paul Ehrlich:

‚Frapper fort et frapper vite' (Hit hard and early) –

Address to the 17th International Congress of Medicine, 1913

Ehrlich P, Lancet 1913; 2:445–51.



PK /PD and resistance in Europe

" Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties… "

---

* Committee for Proprietary Medicinal Products – European Medicines Agency

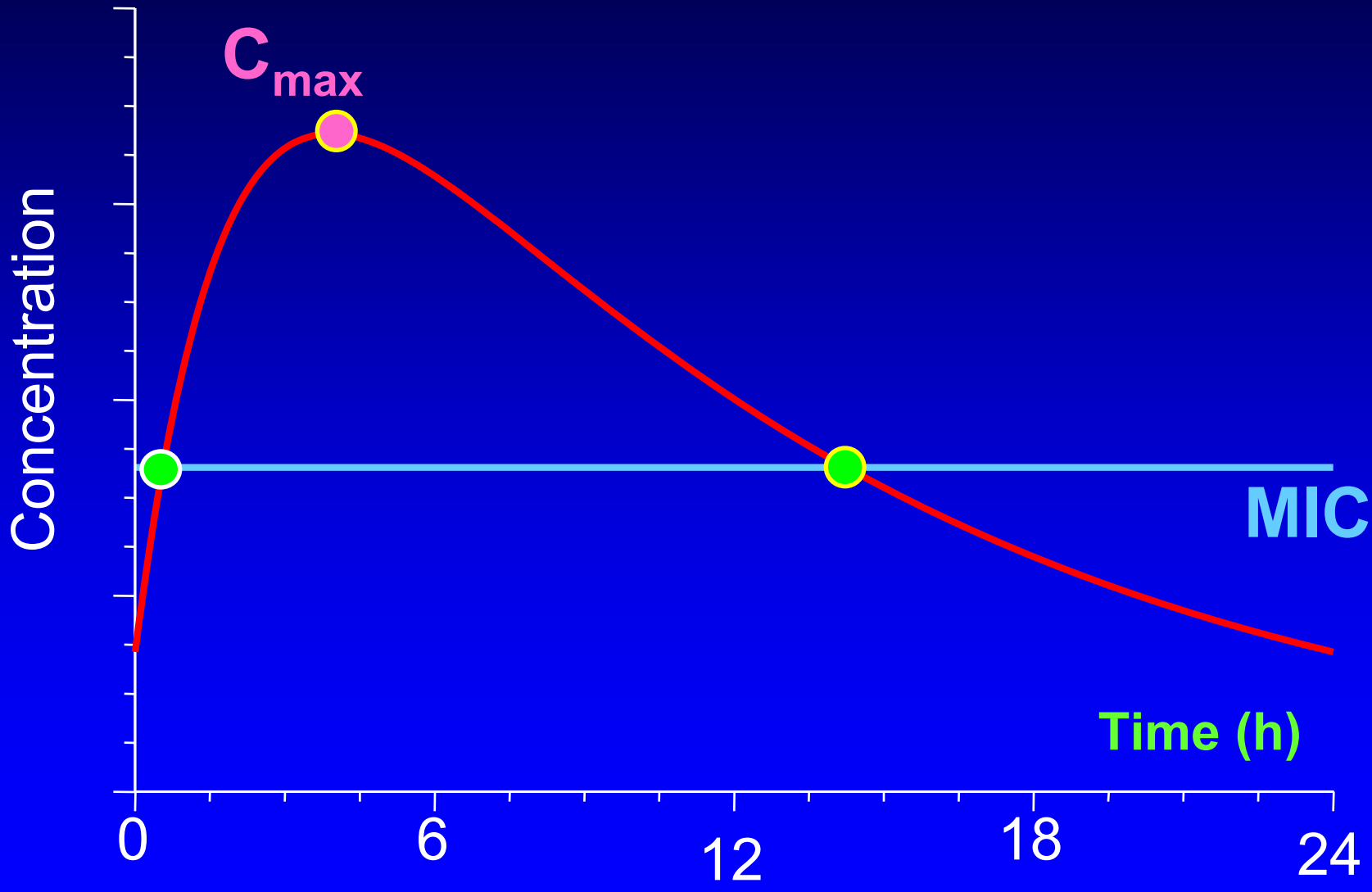
PK-PD properties of antibiotics

Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties :

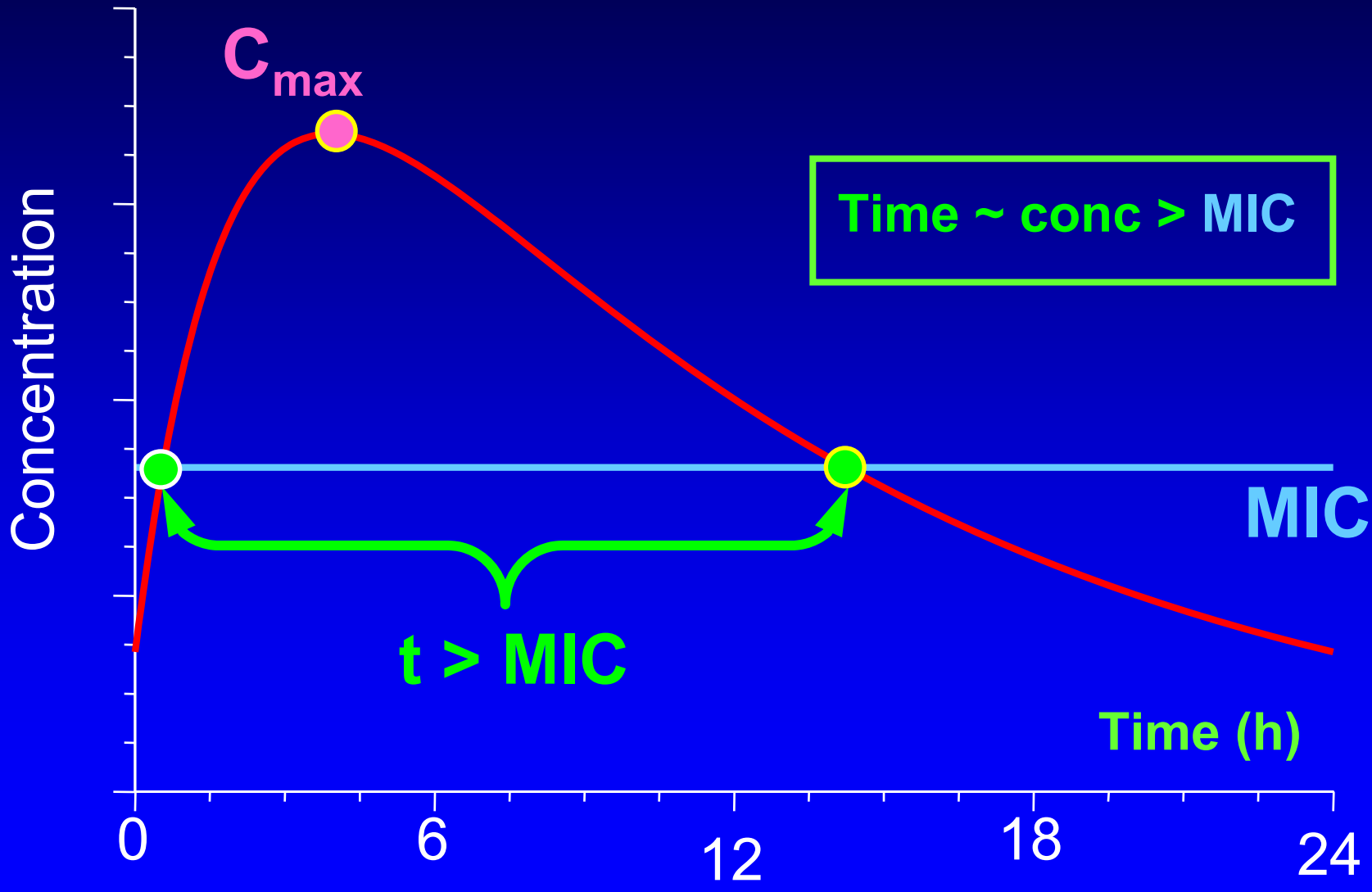
- **Time-dependent (" T > MIC ")**
  → β-lactams (all)
- **Concentration-dependent (" C_{max} / MIC")**
  → aminoglycosides and, for eradication, fluroquinolones
- **Total daily dose-dependent (" AUC / MIC ")**
  → fluroquinolones (for global efficacy) and all others

Those are the main key messages

from pharmacokinetics to pharmacodynamics...



from pharmacokinetics to pharmacodynamics...



PK-PD properties of antibiotics

Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties :

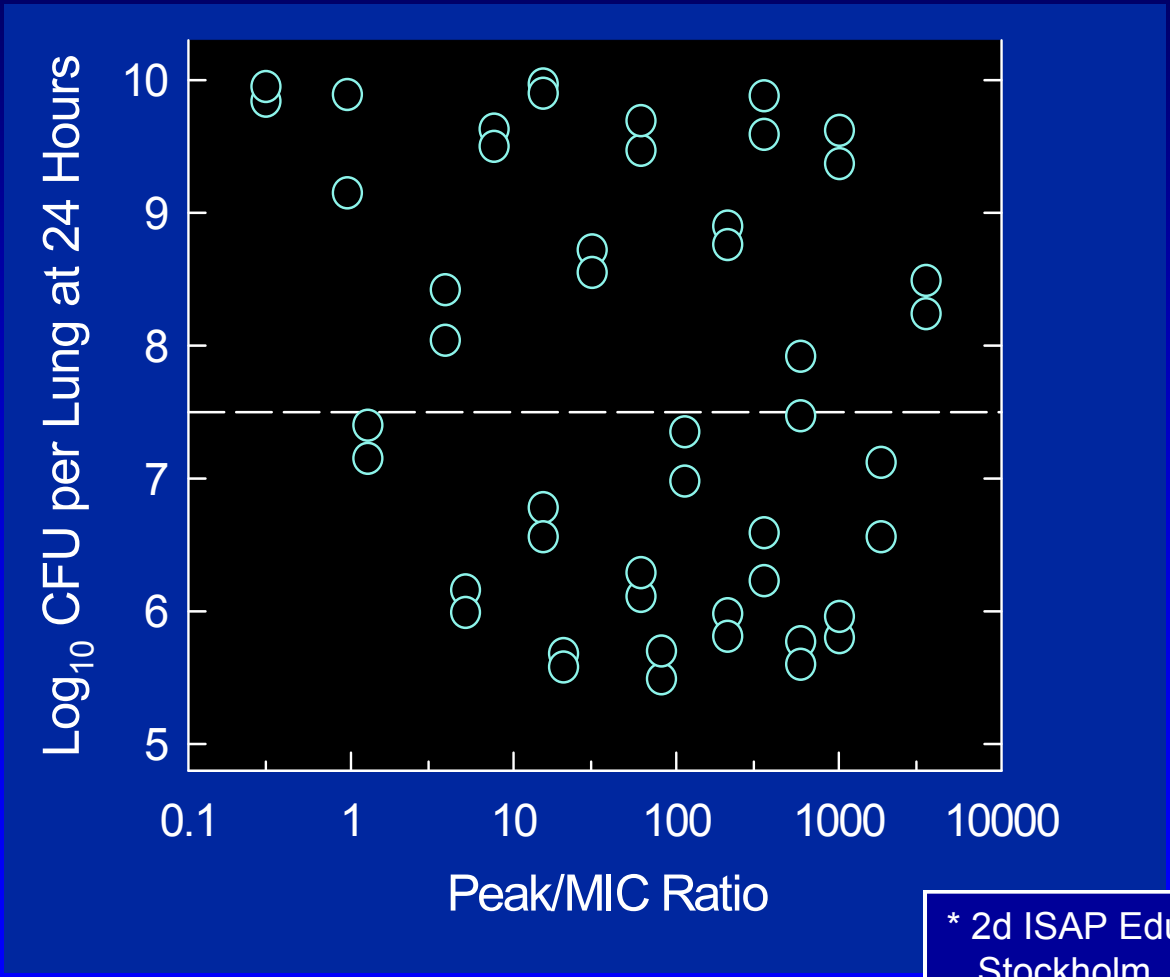
- **Time-dependent (" T > MIC ")**
  → **β-lactams (all)**

- **Concentration-dependent (" Cmax / MIC")**
  → **aminoglycosides and, for eradication, fluroquinolones**

- **Total daily dose-dependent (" AUC / MIC ")**
  → **fluroquinolones (for global efficacy) and all others**

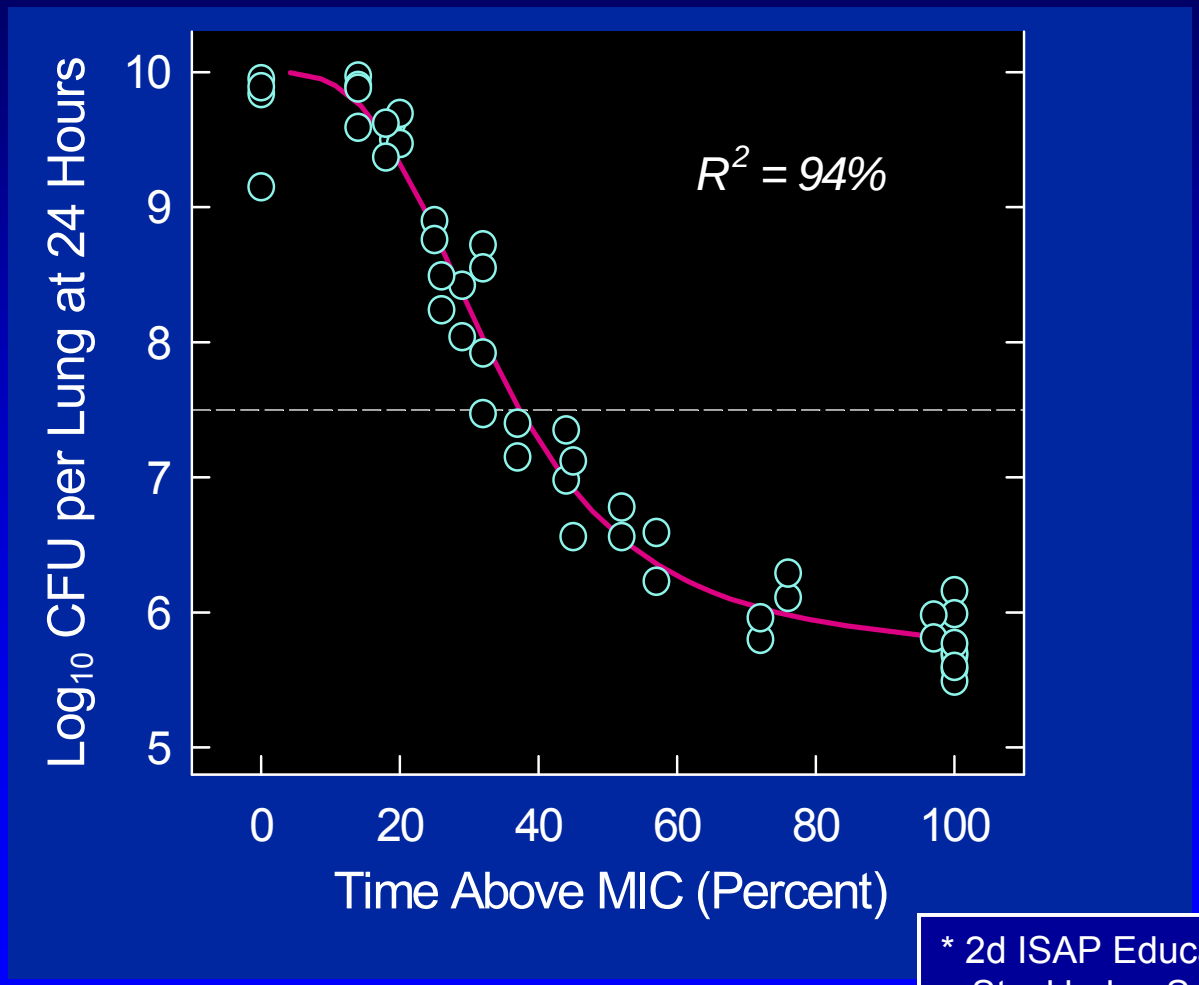
This is the main key message for beta-lactams

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



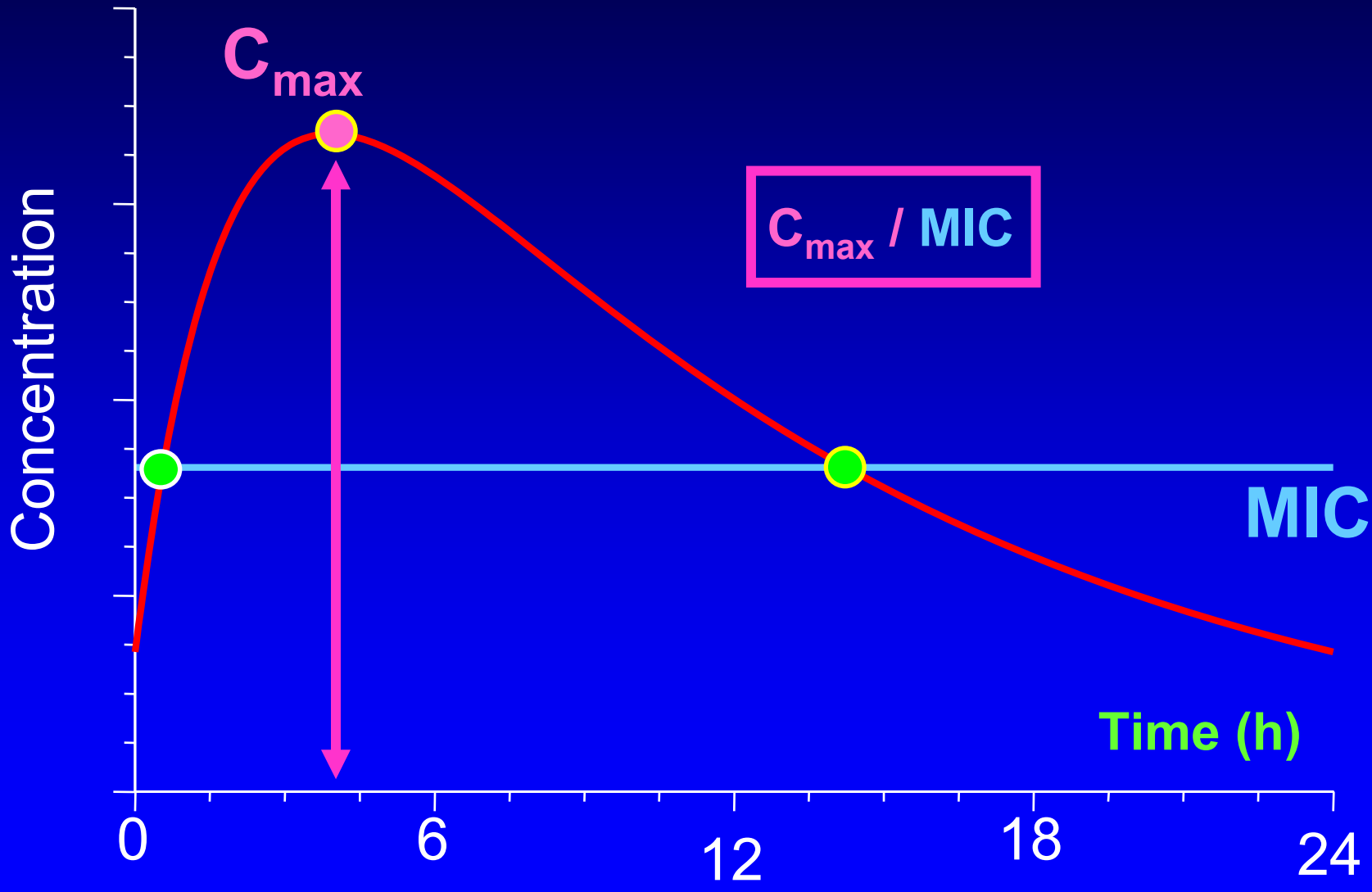
* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

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

From pharmacokinetics to pharmacodynamics...



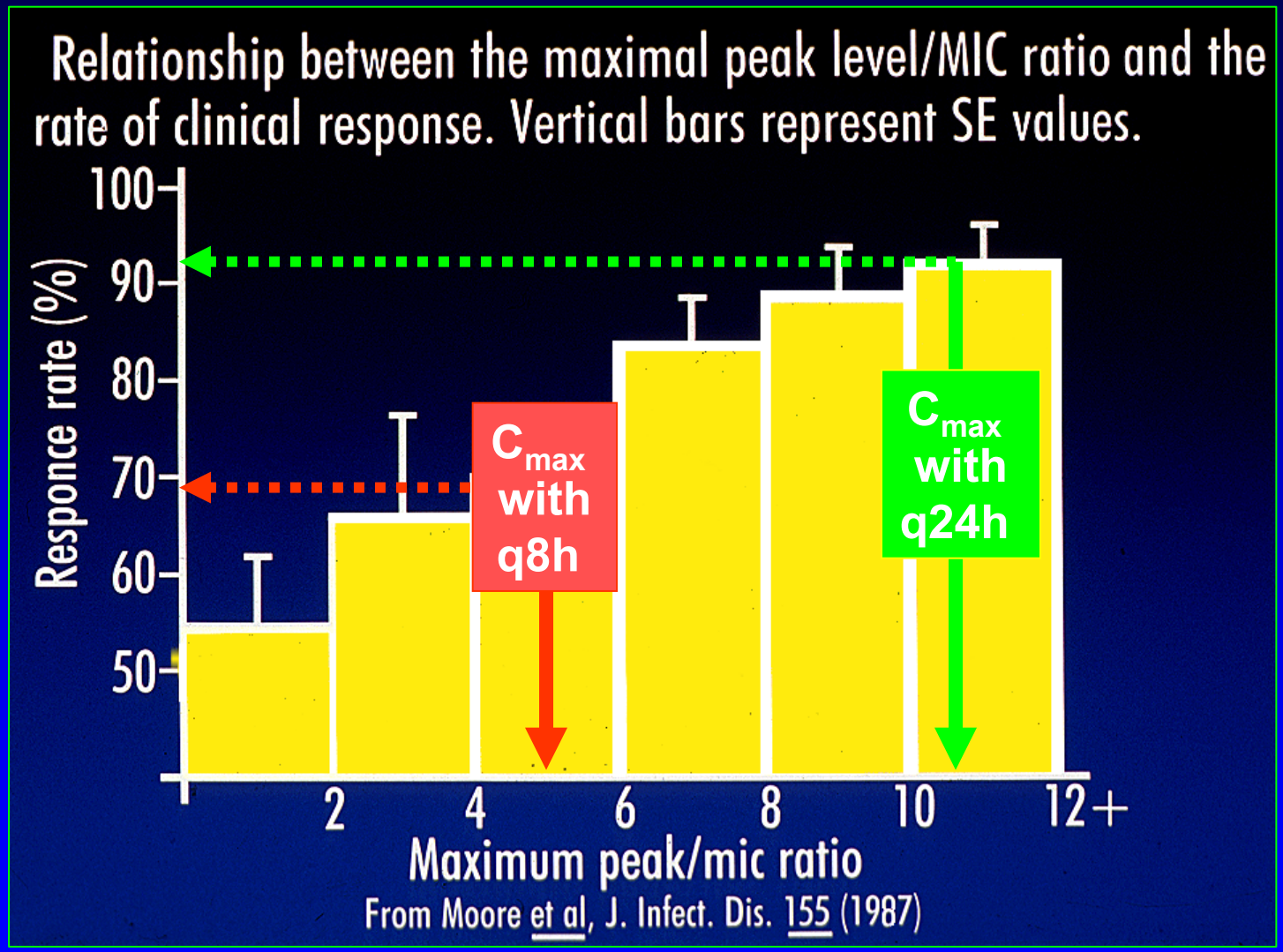
PK-PD properties of antibiotics

Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties :

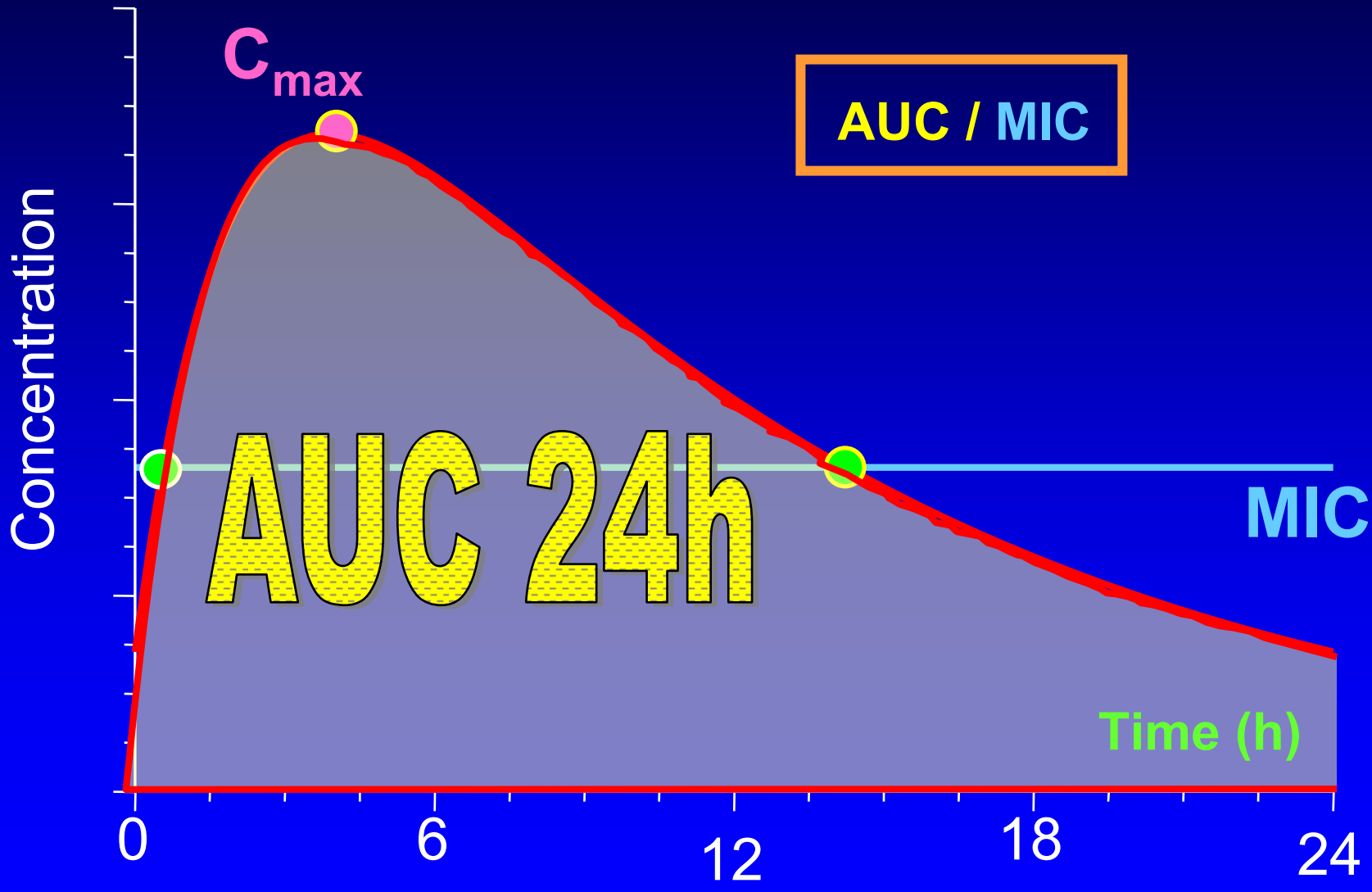
- Time-dependent (" T > MIC ")
  → β-lactams (all)
- **Concentration-dependent (" Cmax / MIC")**
  → aminoglycosides and, for eradication, fluroquinolones
- Total daily dose-dependent (" AUC / MIC ")
  → fluroquinolones (for global efficacy) and all others

This is the main key message

Aminoglycoside peak / MIC ratio is predictive of clinical efficacy



From pharmacokinetics to pharmacodynamics...



PK-PD properties of antibiotics

Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties :

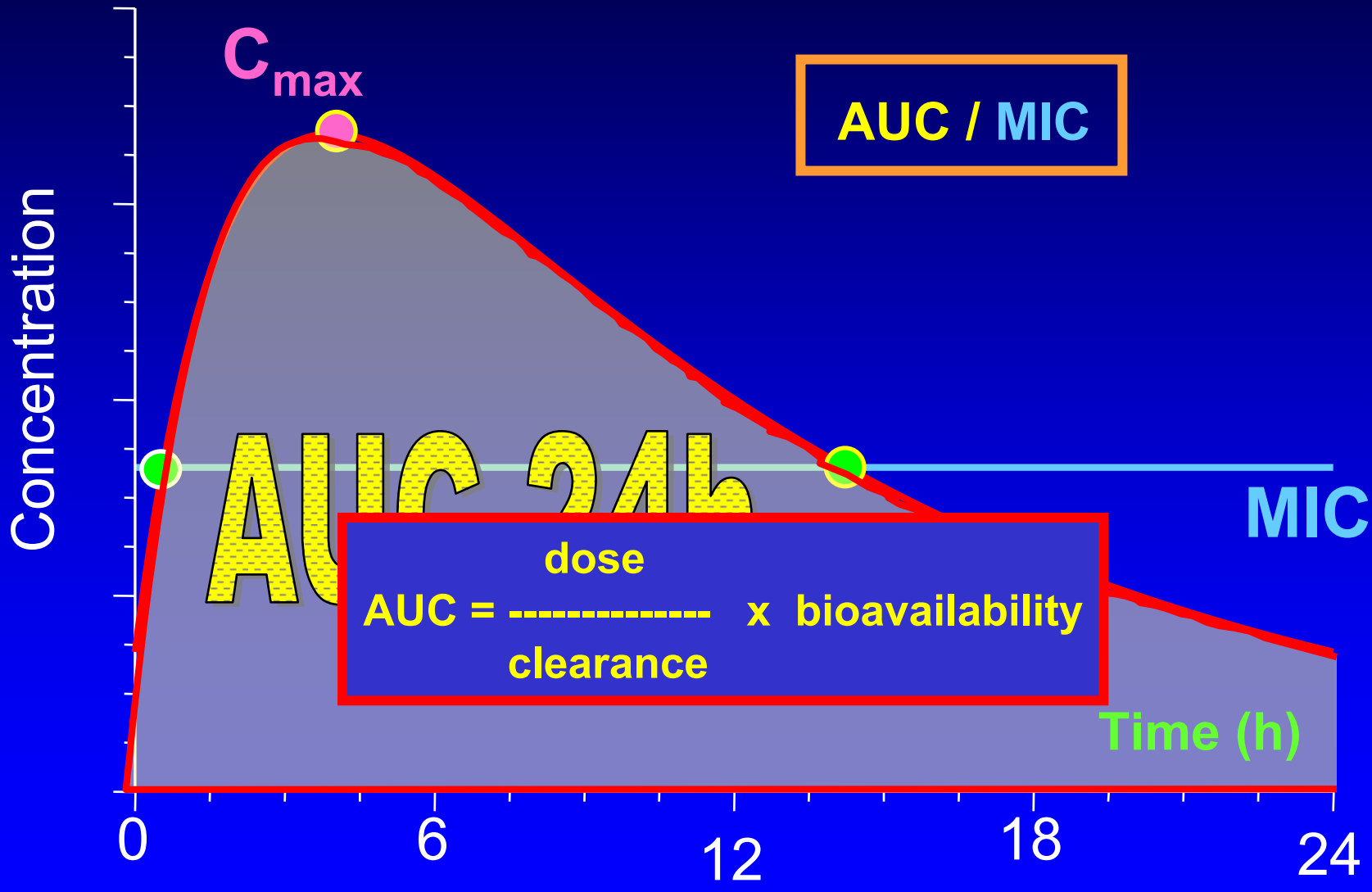
- **Time-dependent (" T > MIC ")**
  → **β-lactams (all)**

- **Concentration-dependent (" Cmax / MIC")**
  → **aminoglycosides and, for eradication, fluroquinolones**

- **Total daily dose-dependent (" AUC / MIC ")**
  → **fluroquinolones (for global efficacy) and all others**

This is the main key message

from pharmacokinetics to pharmacodynamics...



In a nutshell ... so far …

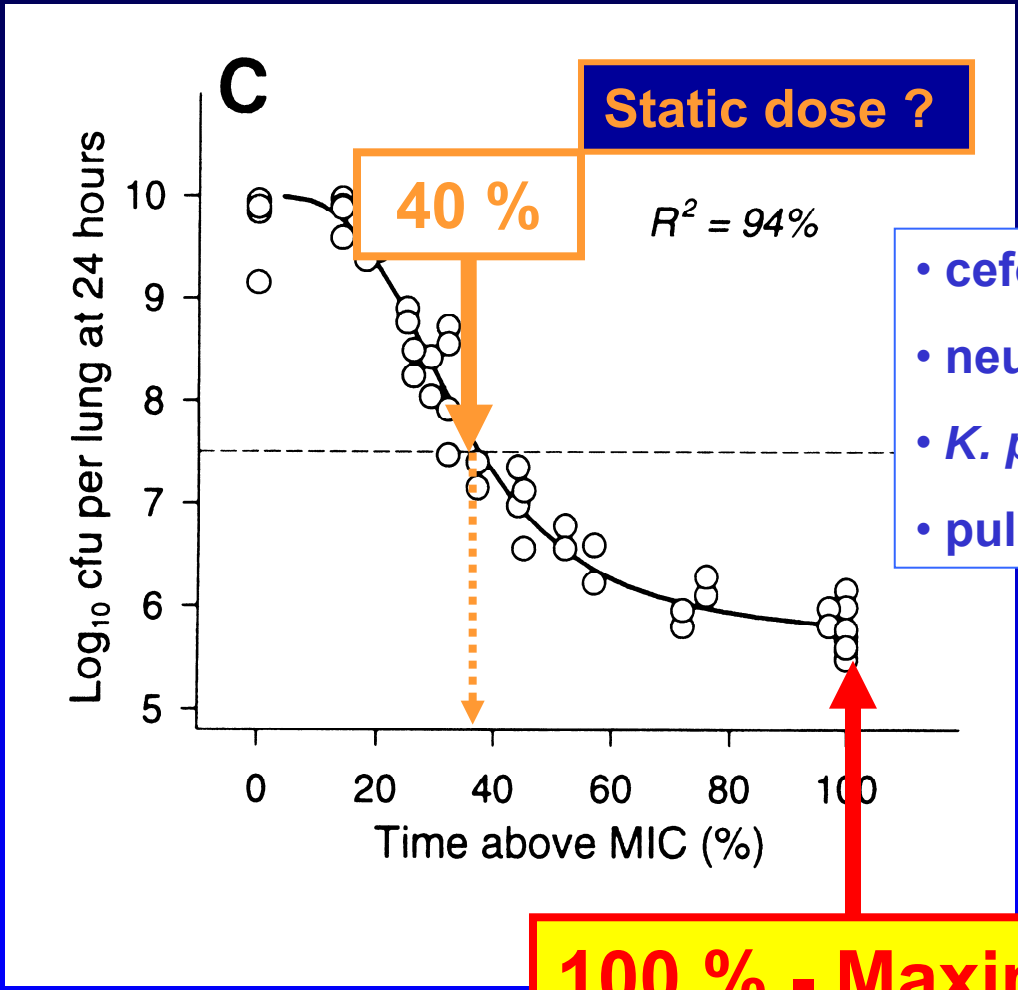
- **Microbiology parameters: MIC !**
- **Pharmacodynamic parameters**
- **PK/PD as applied to beta-lactams**
- The problems if you underdose
- Take home message

β-lactams : T > MIC … but …

You know it is "time above MIC", but…

- How much / How frequent ?
  (Static dose *vs* maximum effect ?)
- The same for all beta-lactams ?
  (Free fractions of the drug (*Fu*) ?)
- The same for all micro-organisms ?
- The same for all infections ?
- Can you apply to all patients ?

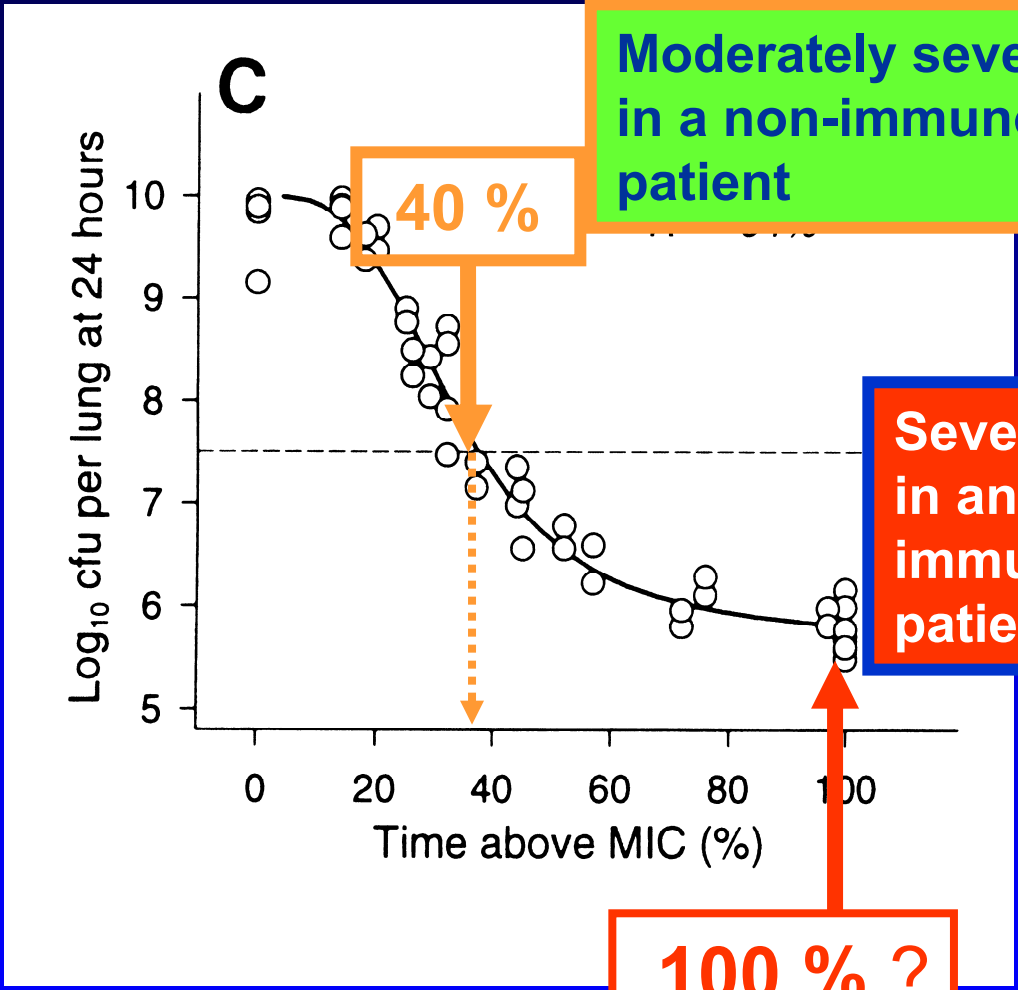
How much time above MIC ?



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

100 % - Maximal effect ?

Here is a proposal ...



Moderately severe infection in a non-immunospressed patient

Severe infection in an immunosuppressed patient

100 % ?

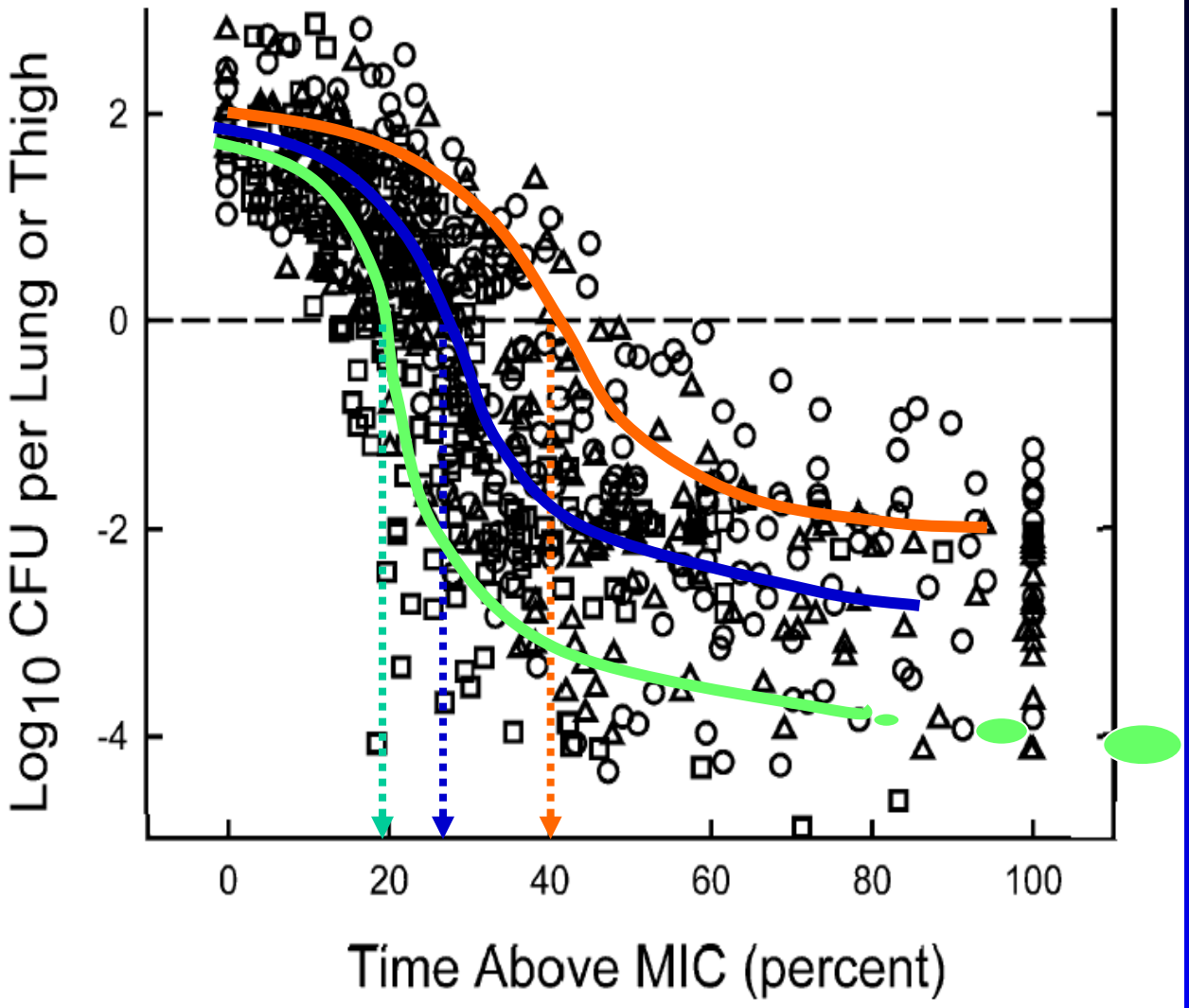


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

The same for all β-lactams ?

Carbapenems tend to require less time above MIC

Andes & Craig Int. J. Antimicrob. Agents 2002, 19: 261-268

The same for all microorganims ?

T> MIC for static effect

Drug	Enterobacteriaceae	*S. pneumoniae*
Ceftriaxone (free)	38 (34-42)	39 (37-41)
Cefotaxime	38 (36-40)	38 (36-40)
Ceftazidime	36 (27-42)	39 (35-42)
Cefpirome	35 (29-40)	37 (33-39)
Meropenem	22 (18-28)	
Imipenem	24 (17-28)	

How do you adjust the dose for a given "Time > MIC" ?

- "out of the package insert" PK data
- Monte-Carlo simulations and target attainment approaches *

---

* will be presented in October 2011

Typical pharmacokinetics of an IV β-lactam

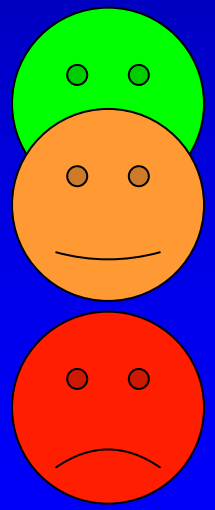
time (hours)	serum concentration for 0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

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

Reading the labeling (package insert)

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

Where would you like to be ?



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

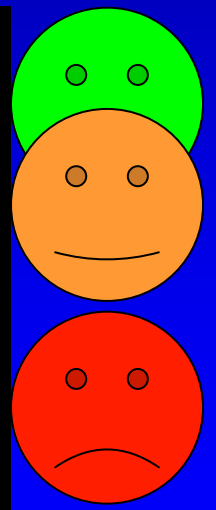
Reading the labeling (package insert)

time	serum concentration for		
(hours)	0.5 g	1 g	2 g
2	25		

Where would you like to be ?

A more detailed calculator will be made available soon on our web site

http://www.facm.ucl.ac.be



Single administration unique; half-life 2h ; V_d = 0.2 l/kg

Simple optimisation of IV β-lactams for "difficult" organisms

- 2 g every 12 h → **T > MIC = 100 % if MIC ≤ 3 mg/L !**
- 2 g every 8 h → **T > MIC = 100 % if MIC ≤ 12 mg/L**

More frequent administrations is the best way to increase the activity of β-lactams in difficult-to-treat infections...

PK / PD breakpoint for

IV β-lactams : MIC = 8 µg/ml

To be practical

In an environment where susceptibilities are compromised (MICs > 4 mg/L) but still "acceptable" (MIC < 16 mg/L) *

- cefepime: 2 g every 8 h
- ceftazidime: 2 g every 8 h

- meropenem: 2 g every 8 h
- imipenem: 1 g every 6 h

International labelling (SmPC)

Doses up to 2 g three times daily in adults ...may particularly be suited for treating nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter* spp.

To be practical

In an environment where susceptibilities are compromised (MICs > 4 mg/L) but still "acceptable" (MIC < 16 mg/L) *

- cefepime: 2 g every 8 h
- ceftazidime: 2 g every 8 h

- meropeneme: 2 g every 8 h
- imipeneme: 1 g every 6 h

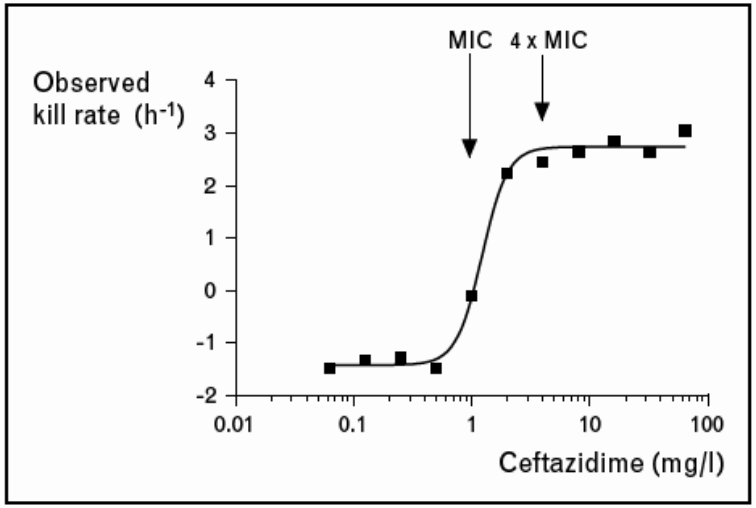
The label of all EU countries limit the dose of imipenem to 4 g/day ! (risk of seizures)

* **see presentation about breakpoints on our web site: http://www.facm.ucl.acbe.**

Target Concentration for β-lactams: **continuous infusion**

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection

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.

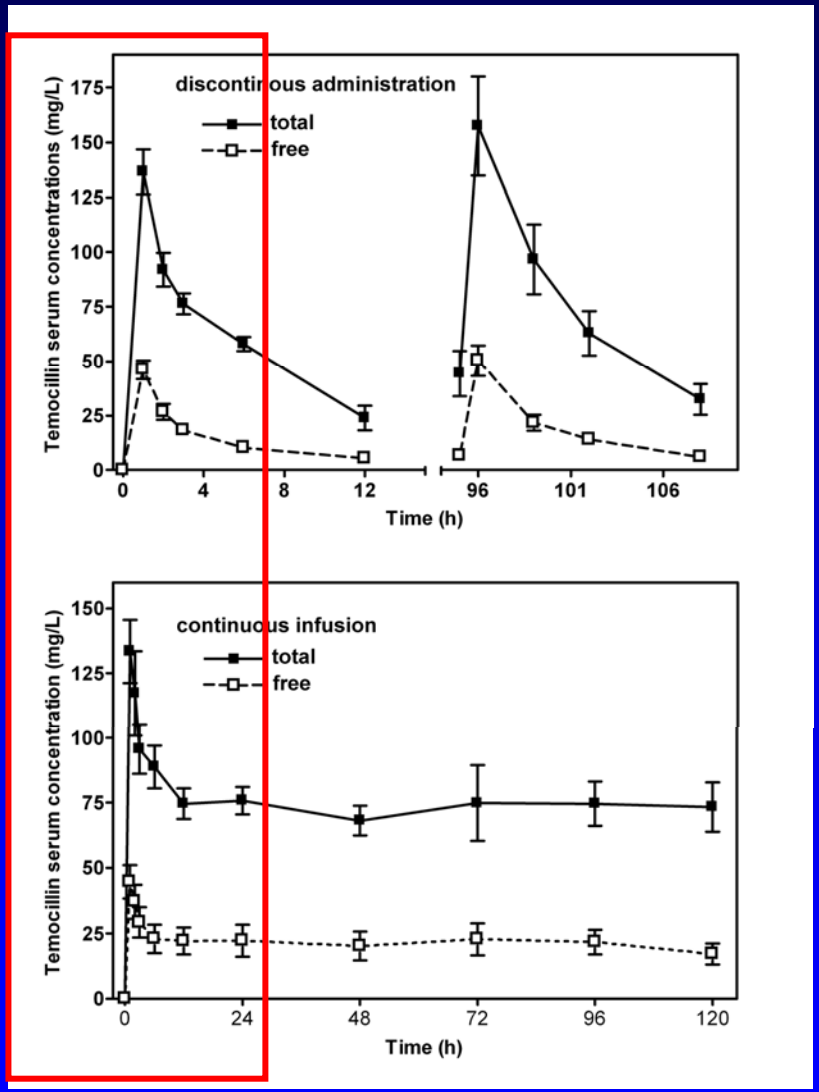
Continuous infusion of β-lactams: an overview…

- 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.**

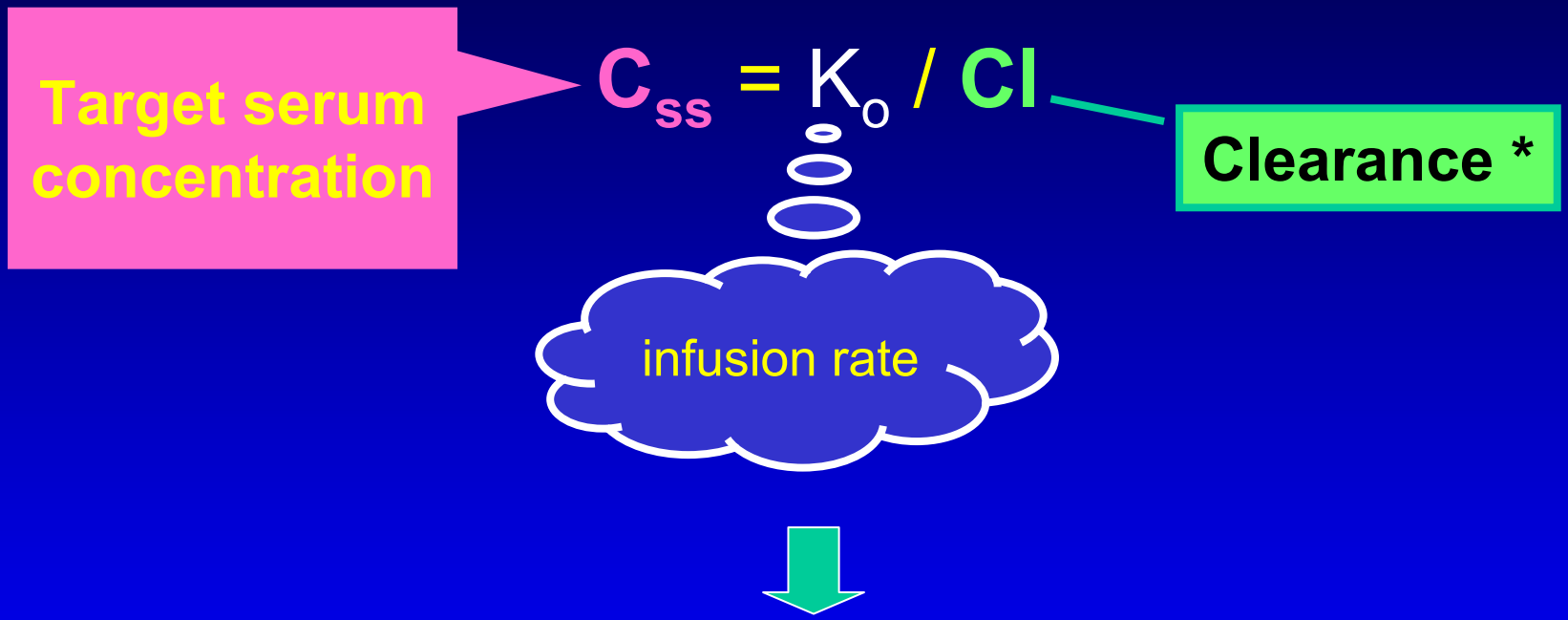
Roberts et al., Intern. J. Antimicrob. Agents 30 (2007):11-18

Continuous infusion in practice
1. loading dose: a simplified (useful) scheme

- Because β-lactams have a low intrinsic toxicity, transient overshooting may not be a major problem…
- Conventional treatments (discontinuous) is by means of bolus or short infusions…
- Why not giving the loading dose as a single bolus or short infusion of a classical dose (1-2 g) ?



Continuous infusion in practice
2. Infusion

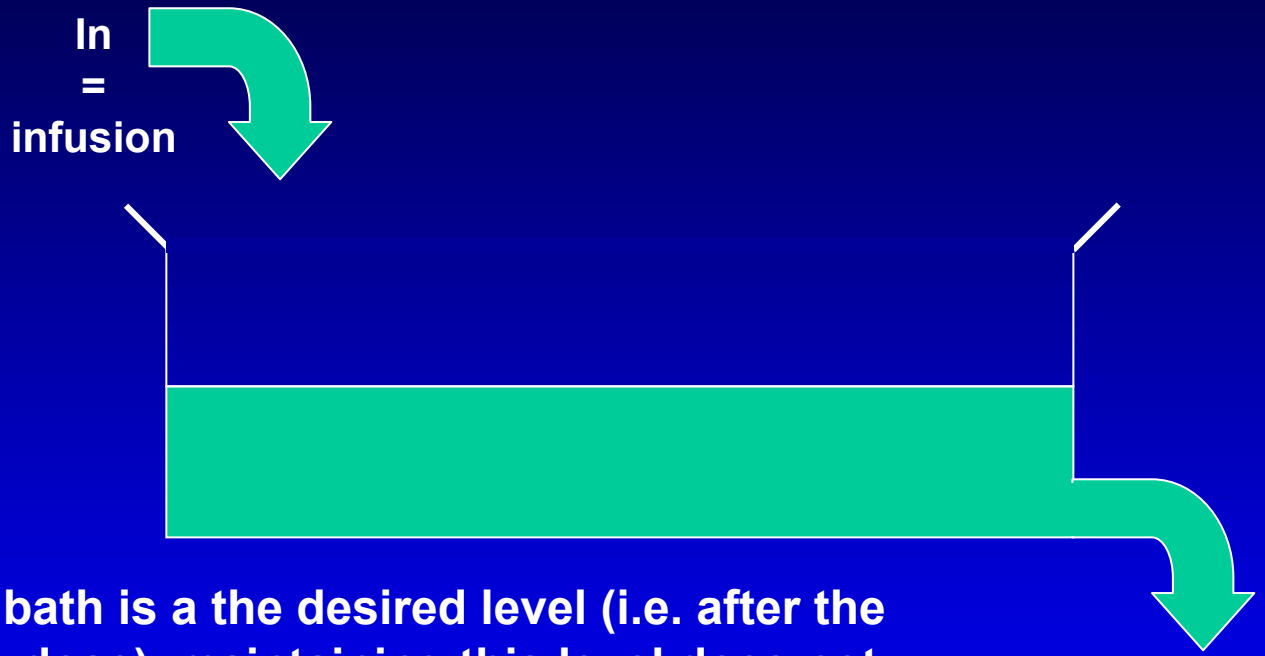


daily dose (in mg) = 24 x **clearance** (L/h) x **Css**

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the **clearance** and not the weight of the patient

* assuming linear pharmacokinetics (almost always the case for β-lactams)

Continuous infusion in practice: why clearance only ?



once a bath is a the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which must be equal: in = out…)

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the **clearance** and not the weight of the patient

Continuous infusion of β-lactams: a simplified practical scheme for patientw with normal renal function

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

example of β-lactam

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*

- loading dose: **2 g** — **the conventional unit dose**
- infusion: **4 g/day** (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].

Continuous infusion of β-lactams: a simplified practical scheme for patients with normal renal function

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

example of β-lactam

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

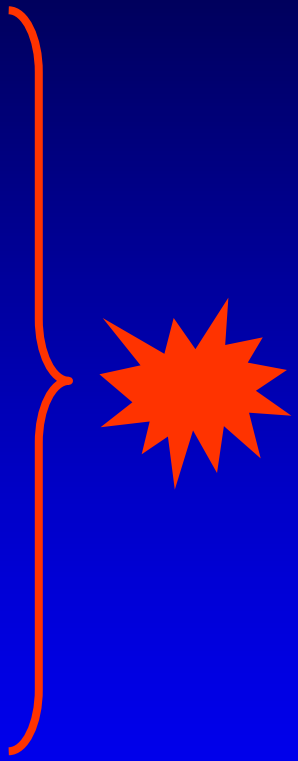
[1]*Dienst Voor Intensieve Zorgen, Ziekenhuis Oost-Limburg, B-3600 Genk, Belgium;* [2]*Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, B-1200 Bruxelles, Belgium;* [3]*Afdeling Medische Microbiologie en Infectieziekten, Canisius Whilhemina Ziekenhuis, NL-6500 GS Nijmegen,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

- loading dose: **2 g**
- infusion: **4 g/day** (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].

the conventional daily dose

Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- **drug instability**



Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance

you may like to monitor the serum levels if MICs ≥ 4 (also for discontinuous administration)

- **drug instability**

!! carbapenems are unstable (3-4 h max.)

To be practical wit carbapenems: 3 h infusion

for patients with normal renal function

- 1st administration: loading dose in 30 min
  - 2 g (meropenem)
- followed immediately by an 3 h infusion of
  - 2 g (meropenem)
  - Repeat step 2 every 8 h

In a nutshell ... so far …

- **Microbiology parameters: MIC !**
- **Pharmacodynamic parameters**
- **PK/PD as applied to beta-lactams**
- **The problems if you underdose**
- Take home message

A simple experiment …

Exposure of *E. aerogenes* to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC determination

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 8 April 2011

A simple experiment …

Exposure of *E. aerogenes* to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC determination

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen et al., presented at the 8th ISAAR, Seoul, Korea, 8 April 2011

sub-MIC concentrations create resistance !

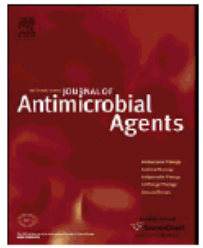
And in the clinics ?

International Journal of Antimicrobial Agents 36 (2010) 513–522

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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



In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

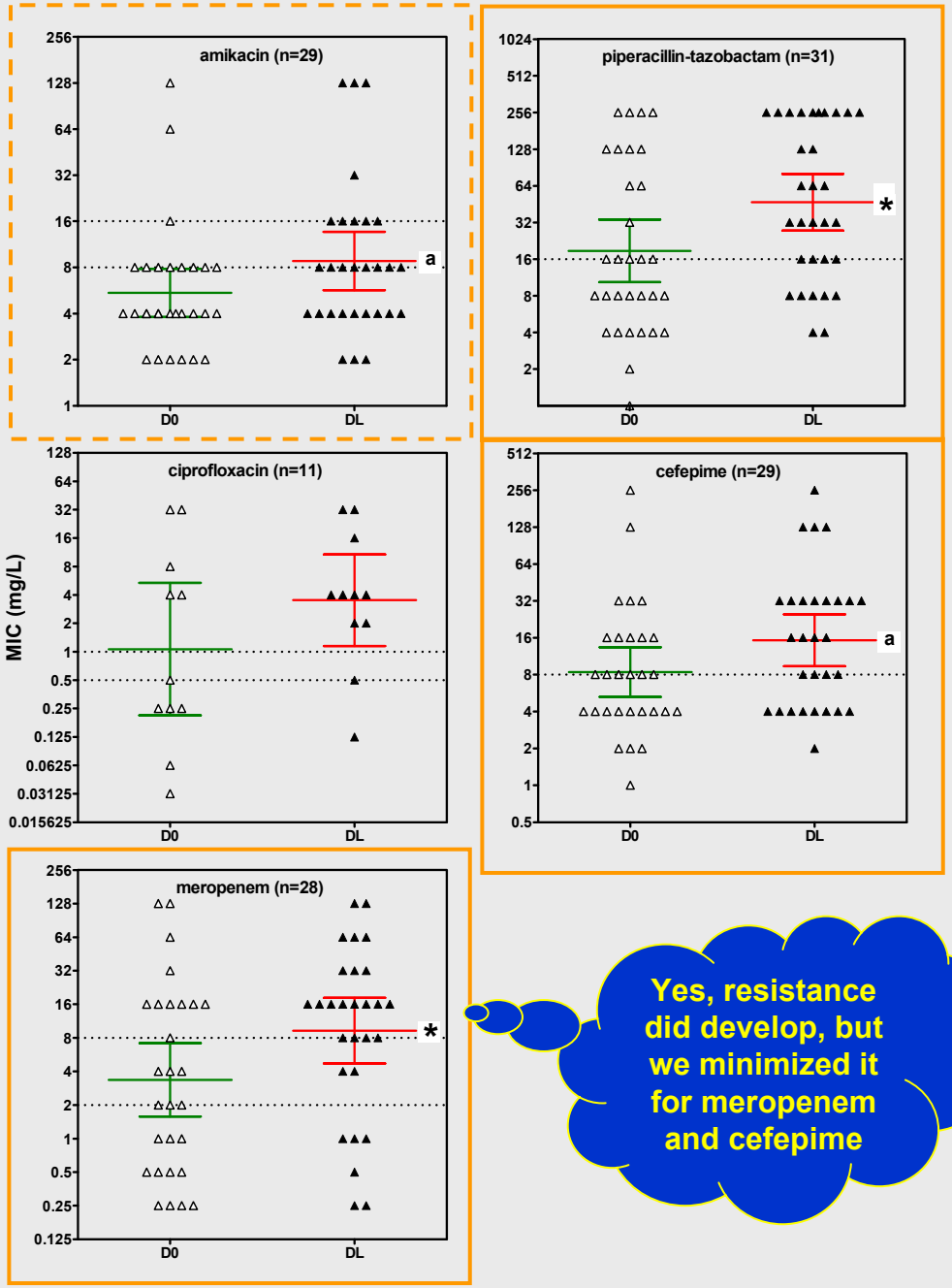
What happens during treatment ?

- 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)



PK / PD in action for science and clinics

Some other achievements:

- **once-daily dosing of aminoglycosides registration or reregistration in several countries**
  - **amikacin, netilmicin, tobramycin, gentamicin: from tid or bid to qd**
  - **24h AUC / MIC and C_{max} / MIC ratios used as guides for fluroquinolones**
  - **moxifloxacin: correct dose at registration !**
  - **levofloxacin, ciprofloxacin: increase of dosages !**

“Take home” message

- dosage is one key to success and protection against resistance... (NOT the only key !)
- dosage should match bacterial susceptibility... and knowledge of MIC is essential
- for β-lactams, get TIME > MIC to reach maximal efficacy … and dose appropriately…
  ➔ 3h infusion of meropenem may help
- Use of correct breakpoints * will also help in avoiding the use of "weak antibiotics" … or to decide dosage escalation to avoid emergence of resistance …

---

* see presentation on EUCAST breakpoints

Do NOT forget hygiene measures !

(an example for *Acinetobacter baumanii* in Thailand)

- Most outbreaks can be terminated with multi-faceted, comprehensive infection control programs
- Measures always include education, hand hygiene (5-moments), contact isolation, environmental cleaning, targeted active surveillance culture in high risk area, and antimicrobial control program
- Recent reports also suggested the role of 4% chlorhexidine total body wash

Dancer SJ. JHI 2009
Rodriguez-Bano J, AJIC 2009
Valencia R, ICHE 2009
Gill CJ, CID 2009
Borer A, JHI 2007
Chan PC, ICHE 2007

From: Anucha Apisarnthanarak, MD
Division of Infectious Diseases
Thammasat University Hospital, Thailand
Presented at the 2011 ISAAR, Seoul, Korea
(used with permission)

What to do to Control *MDR-Acinetobacter* in Resource-Limited Settings?

Resource-full

- Molecular epidemiology
- Environmental culture
- Active Surveillance
- Enhanced environmental cleaning
- Enhanced isolation precaution
- Antibiotic management

Resource-Limited

- Stratified unit specific infection rate
- Line listing and/or case-control study (identify common source outbreak)
- Implement emergency measure for highly alert pathogen
- Initial environmental culture (per finding from line listing)
- Modified Active Surveillance Cultures
- Enhanced isolation precaution
- Environmental cleaning
- Antibiotic management program

From: Anucha Apisarnthanarak, MD
Division of Infectious Diseases
Thammasat University Hospital, Thailand
Presented at the 2011 ISAAR, Seoul, Korea
(used with permission)

WHO statement 2000

The most effective strategy against antibiotic resistance is:

- "to unequivocally destroy microbes"
- "thereby defeating resistance before it starts"

WHO Overcoming Antimicrobial Resistance, 2000

All slides will be available from our web site: http://www.facm.ucl.ac.be ➔ Adanced courses

But a complementary message is probably…

Have multi-rooted actions...