Optimising treatment based on PK/PD principles

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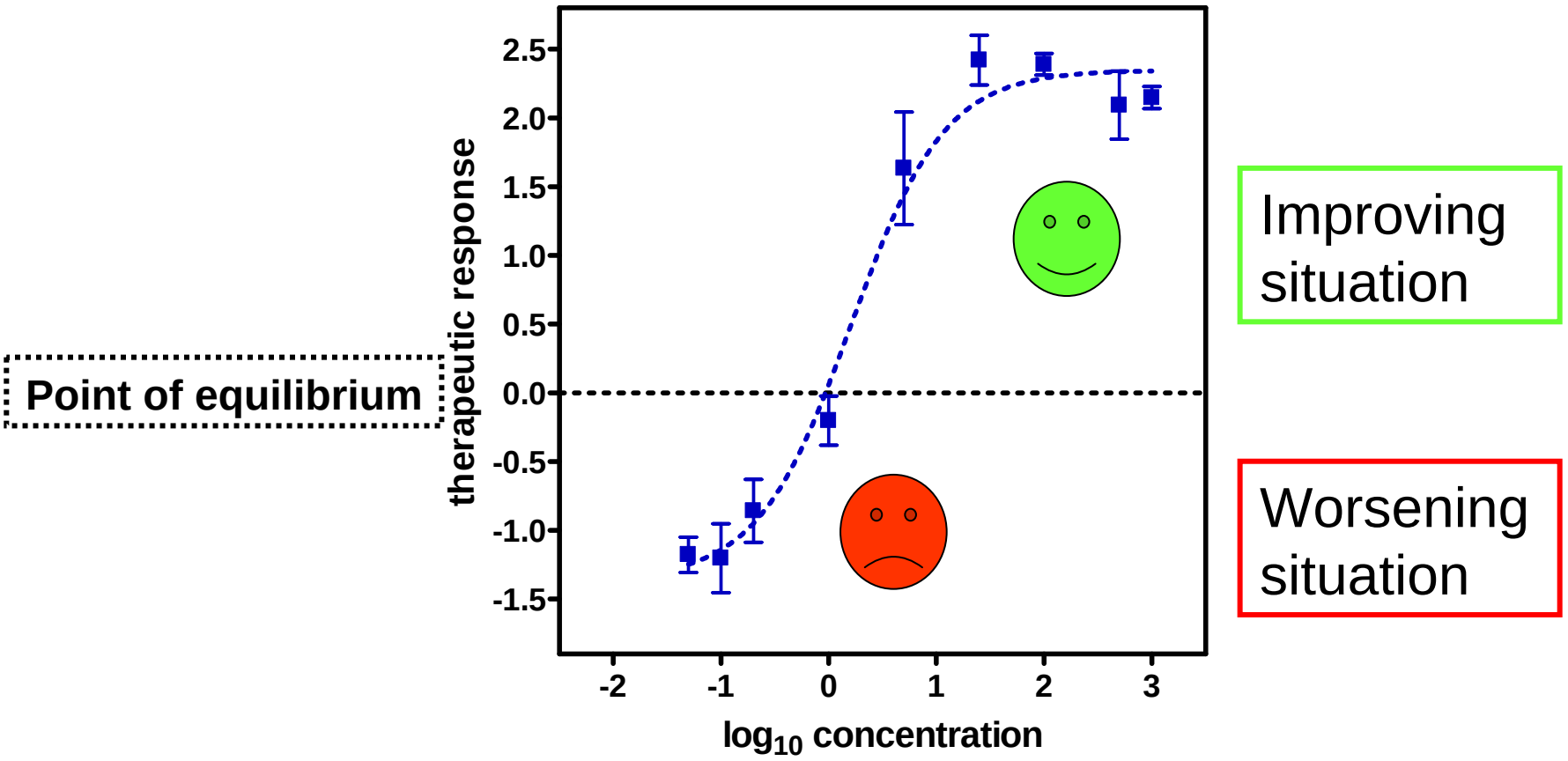
In a nutshell…

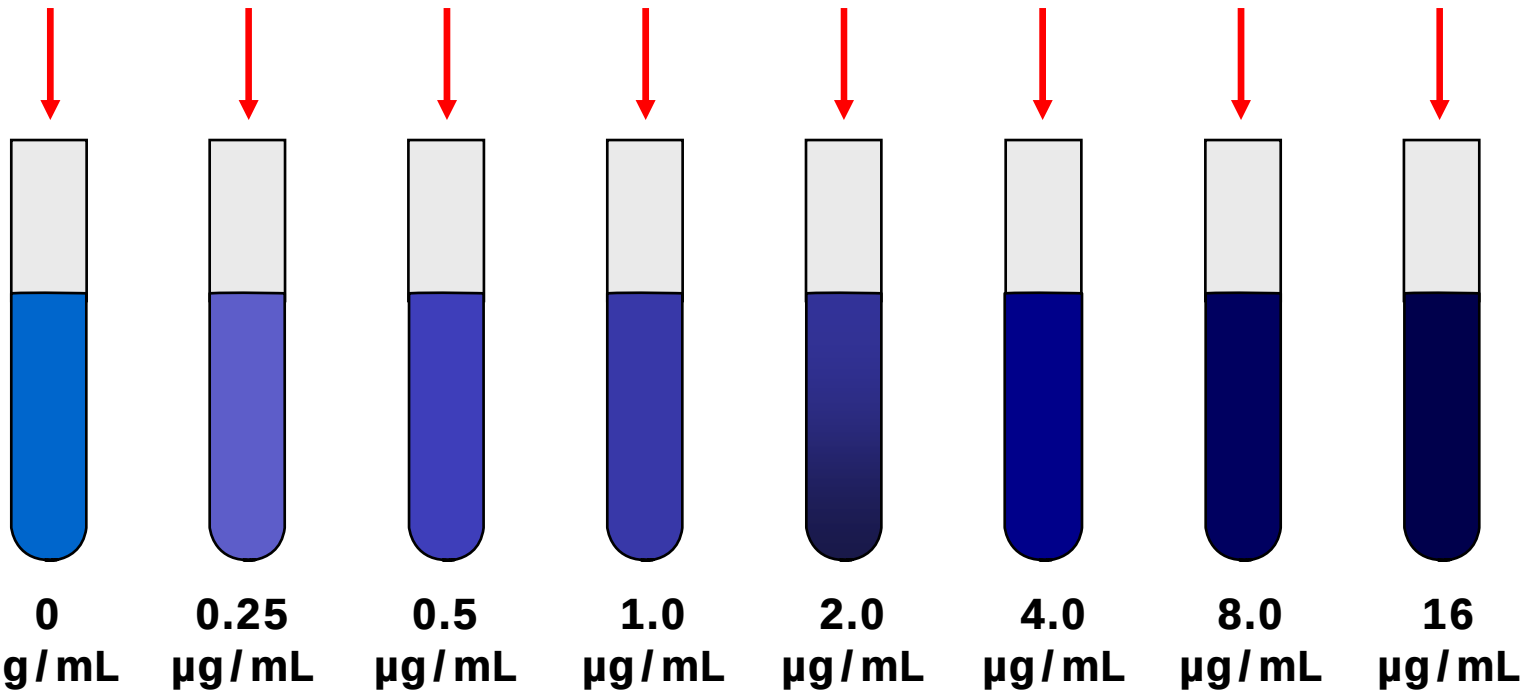
The dose must be adapted to the goal…



In a nutshell…

The target is the bacteria = MIC

Known quantity of bacteria placed into each tube

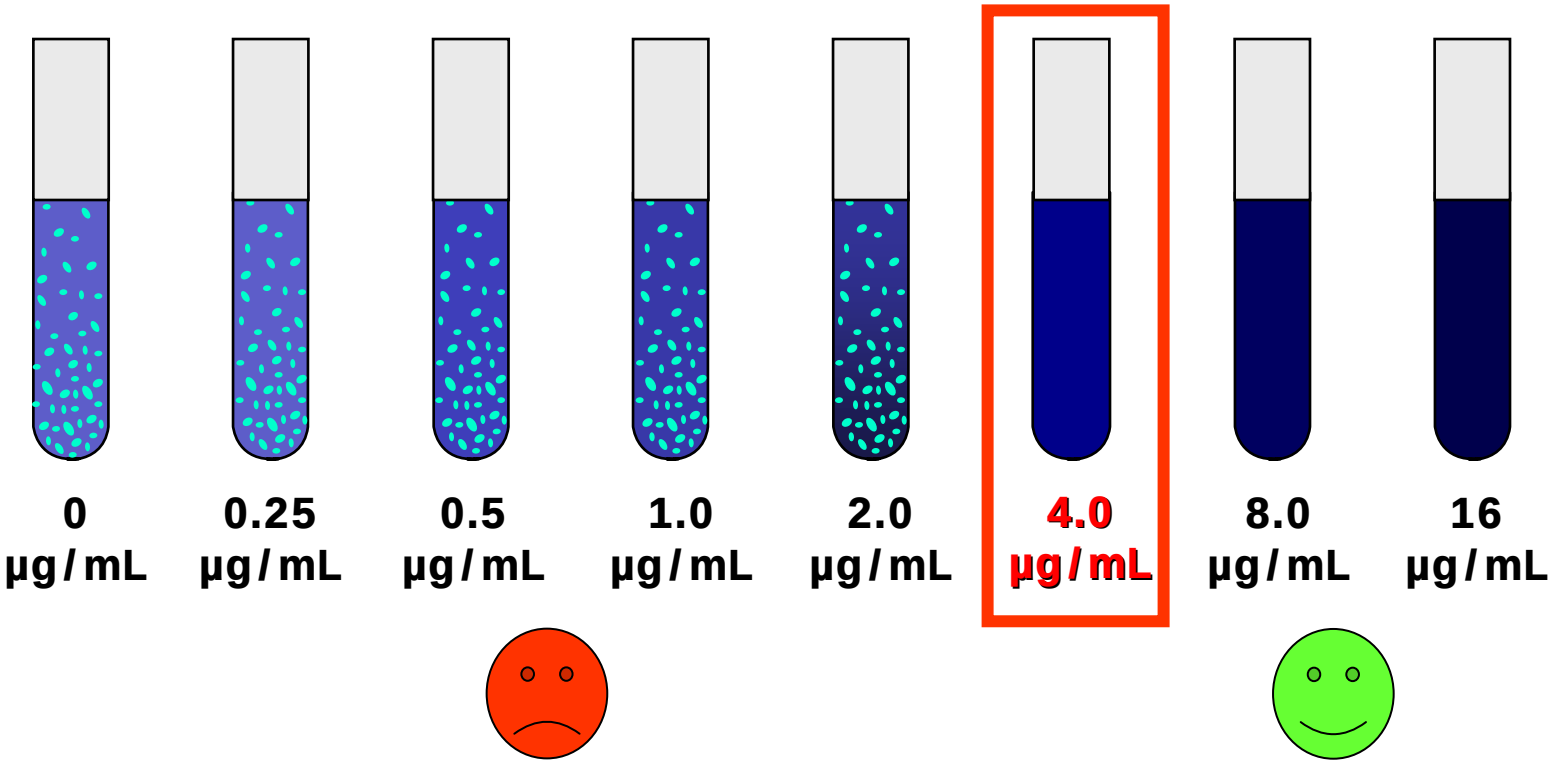


In a nutshell…

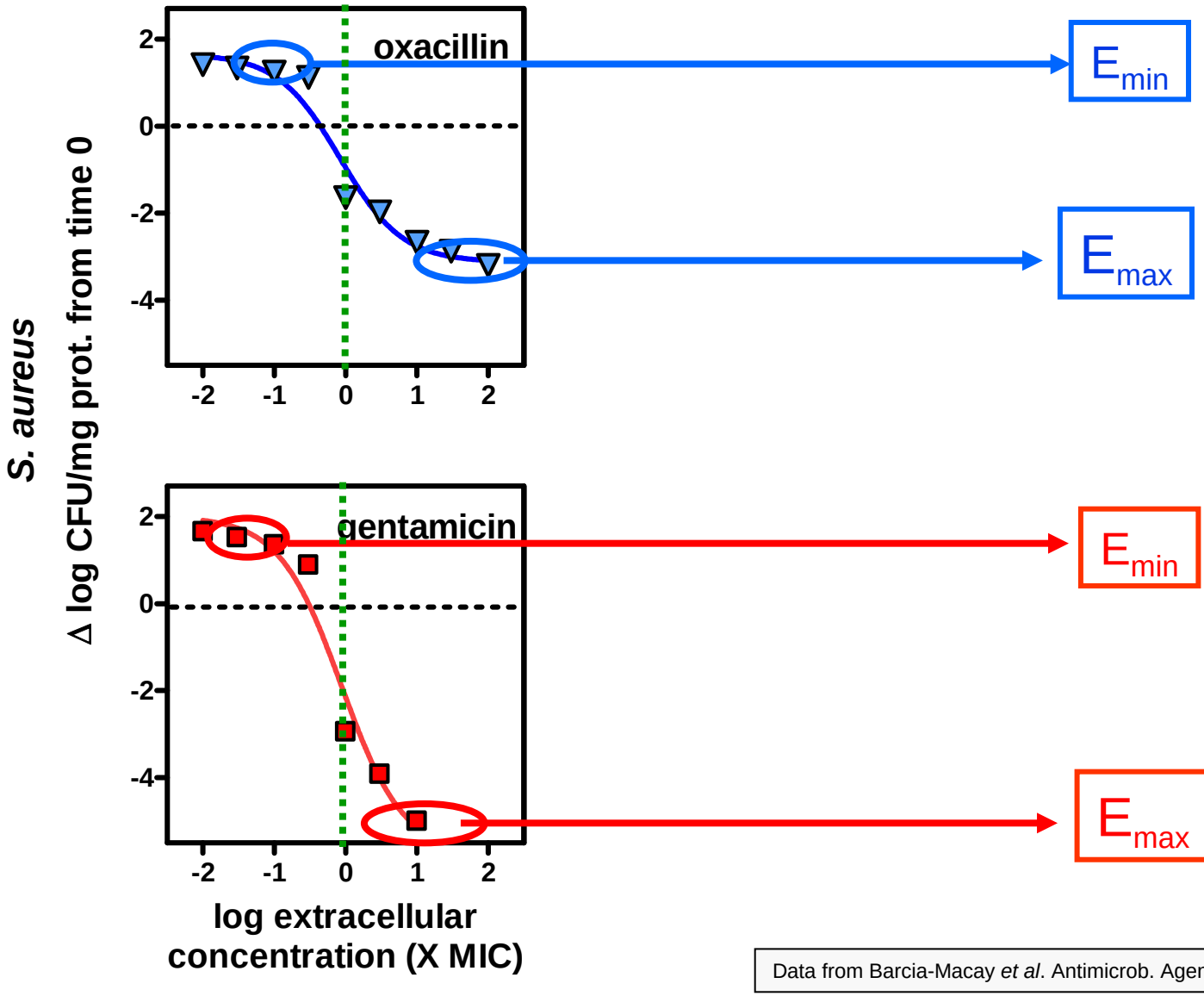
The target is the bacteria = MIC

24h later…

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



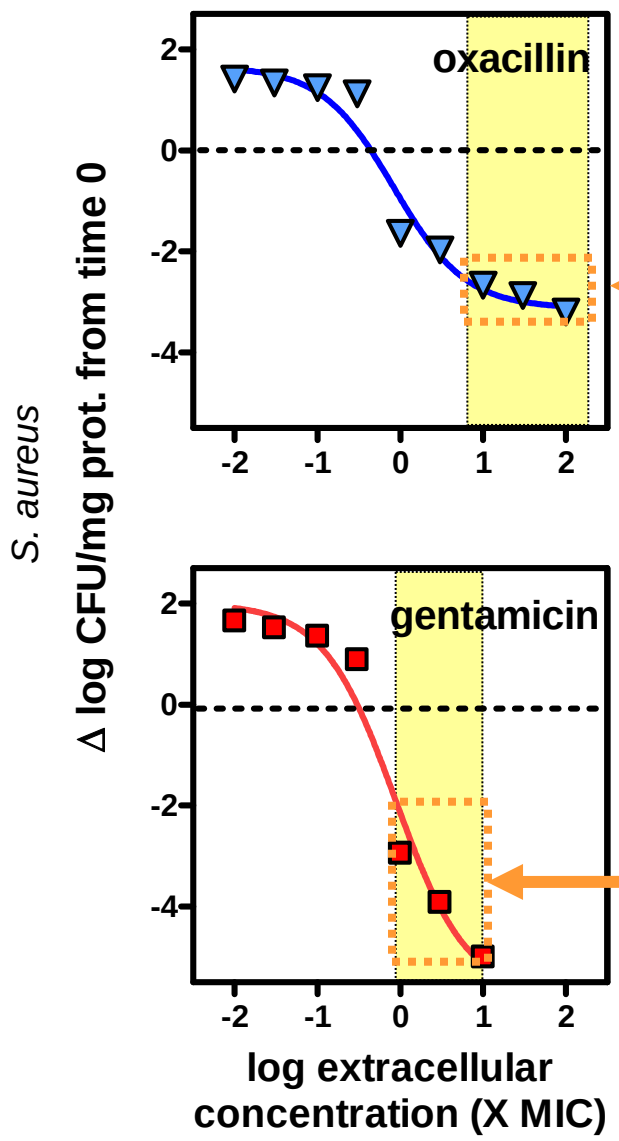
What is the relationship between MIC and effect?



It looks as if they are all concentration-dependent…

Data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851

But here comes pharmacokinetics …



Weak concentration-dependence (max. effect) over the C_{min}–C_{max} range

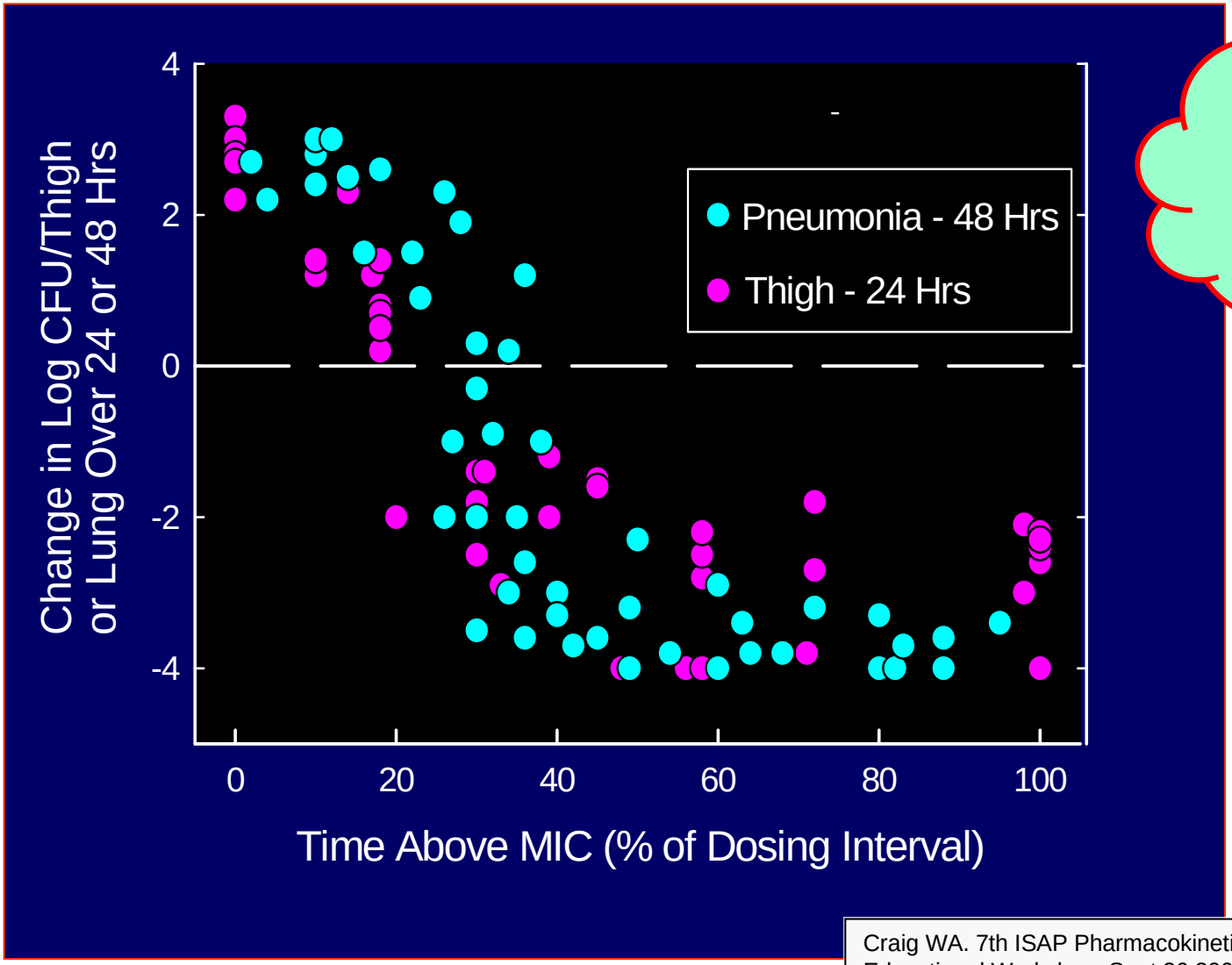
➔ TIME will emerge as the main parameter in vivo

C_{min}–C_{max}

high concentration-dependence over the C_{min}-C_{max} range ➔ the time is less important than the actual concentration

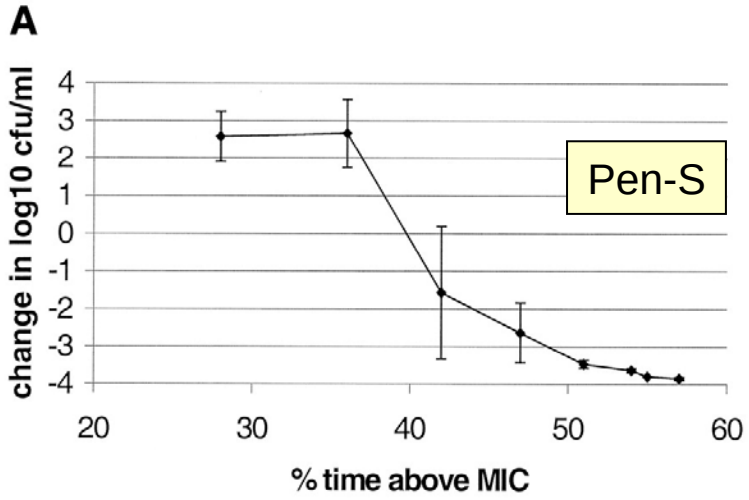
- data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851
- C_{min}-Cmax: Principles and Practice of Infectious Diseases, 7th Ed. Mandell *et al*. eds., Elsevier

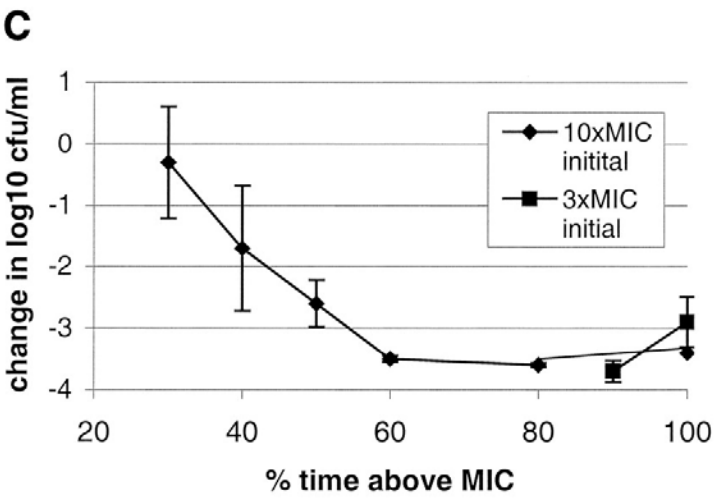
Relationship between T>MIC and efficacy of amoxicillin against *S. pneumoniae* in rat pneumonia and murine thigh infection models



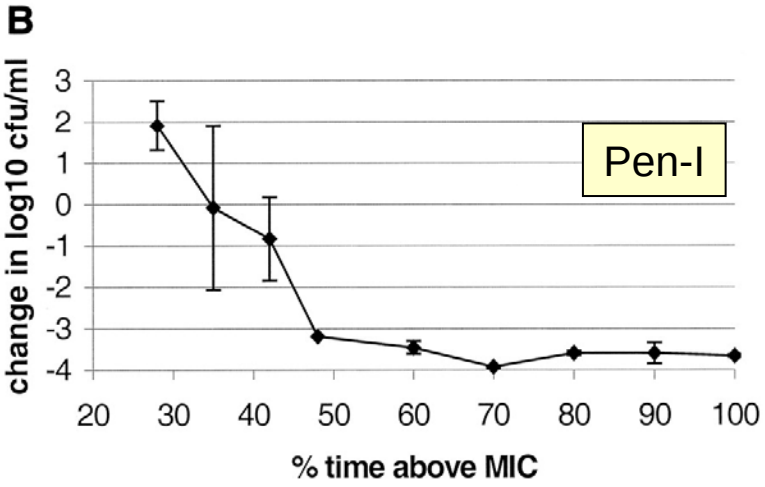
Craig WA. 7th ISAP Pharmacokinetics/Pharmacodynamics (PK/PD) Educational Workshop. Sept 26 2001, San Diego, CA.

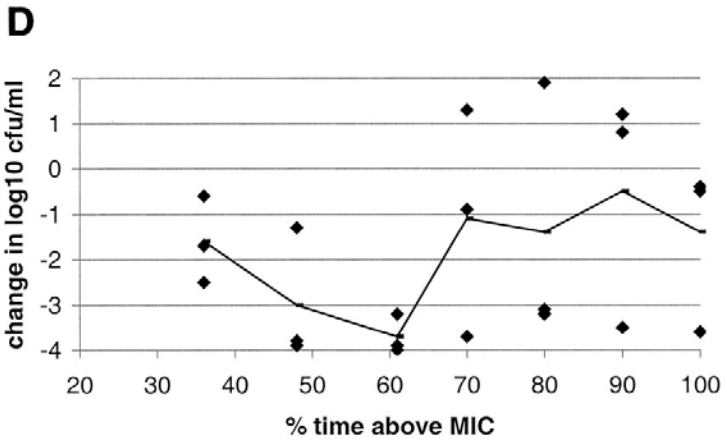
Further modeling the response to amoxicillin over time in an in vitro kinetic model...





Pen-R MIC = 2 mg/L





Pen-R MIC = 4 mg/L

Gustafsson, I. et al. 2001. Antimicrob. Agents Chemother. 45(9):2436-2440

Is this true for all β-lactams?

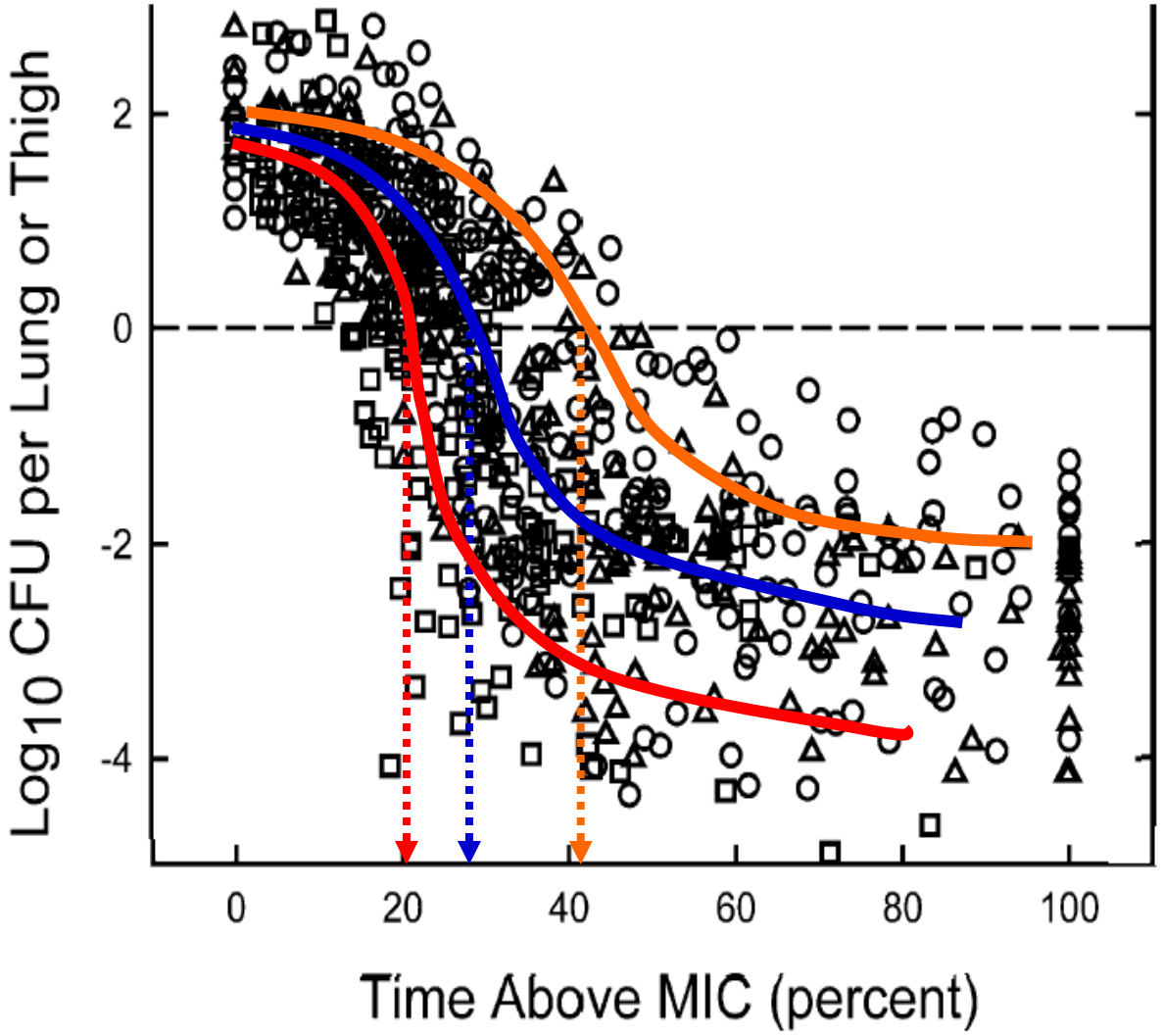
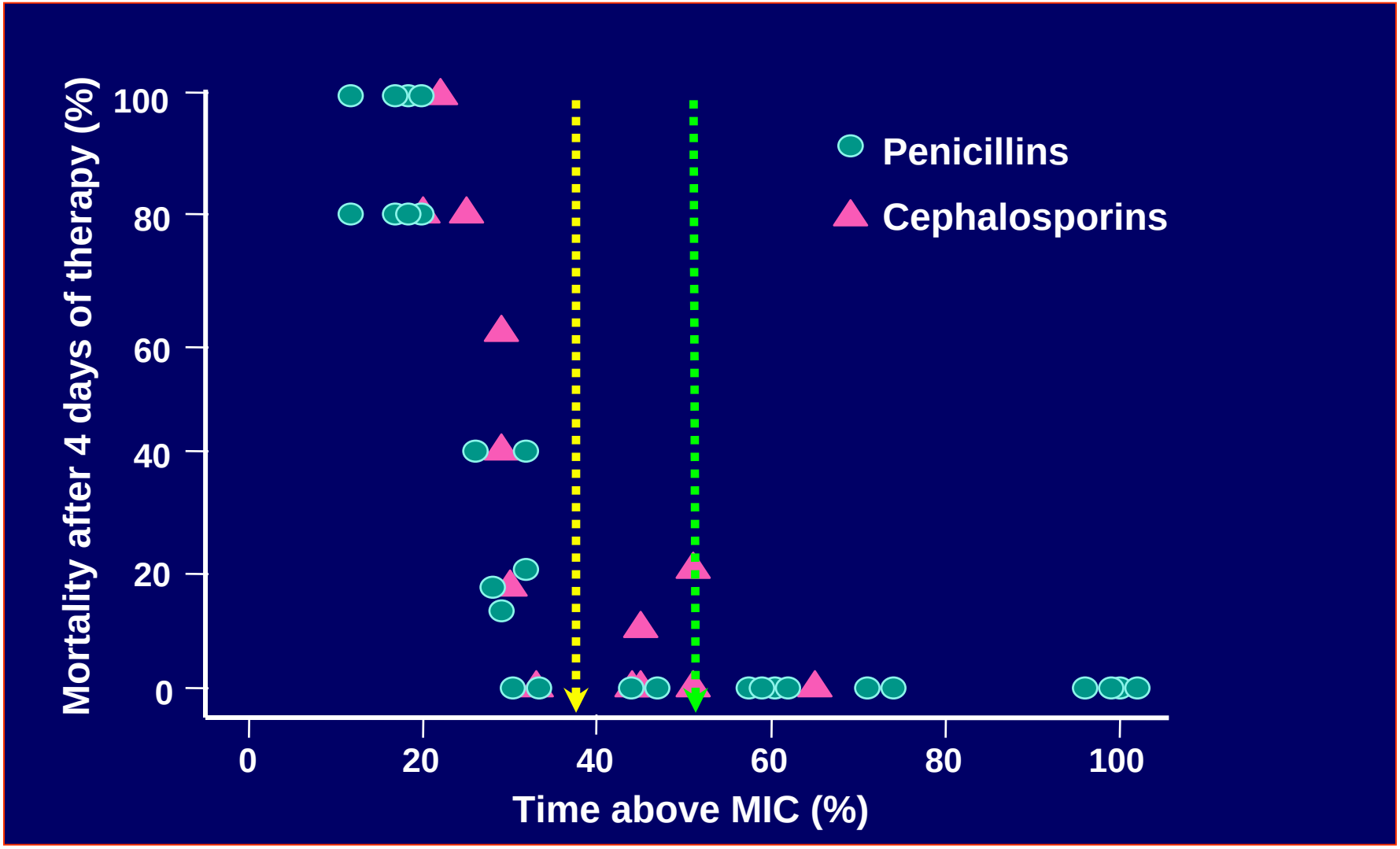


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

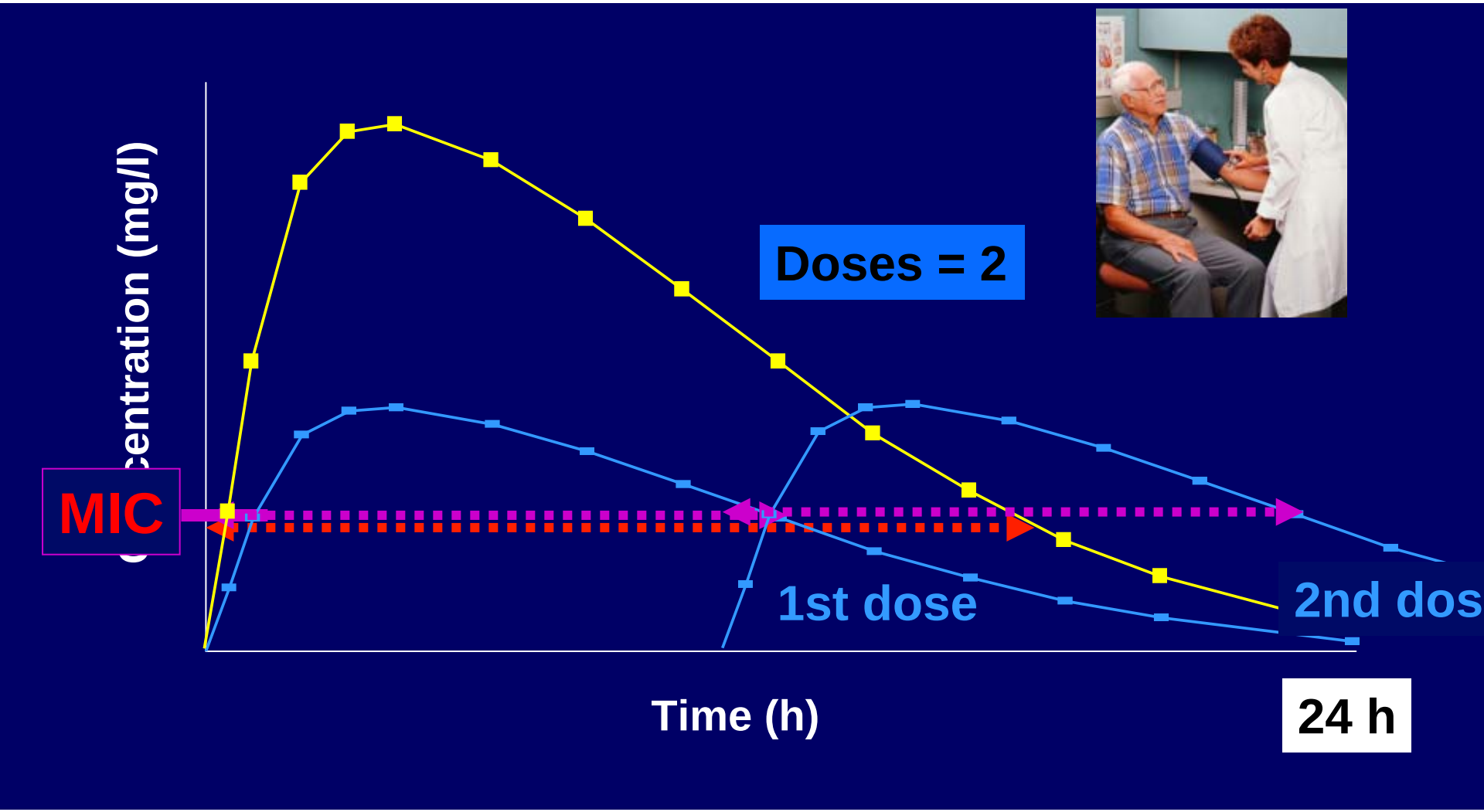
Andes D, Craig WA. Int J Antimicrob Agents 2002; 19: 261-8.

Relationship between time above MIC and mortality in animals infected with *S. pneumoniae*

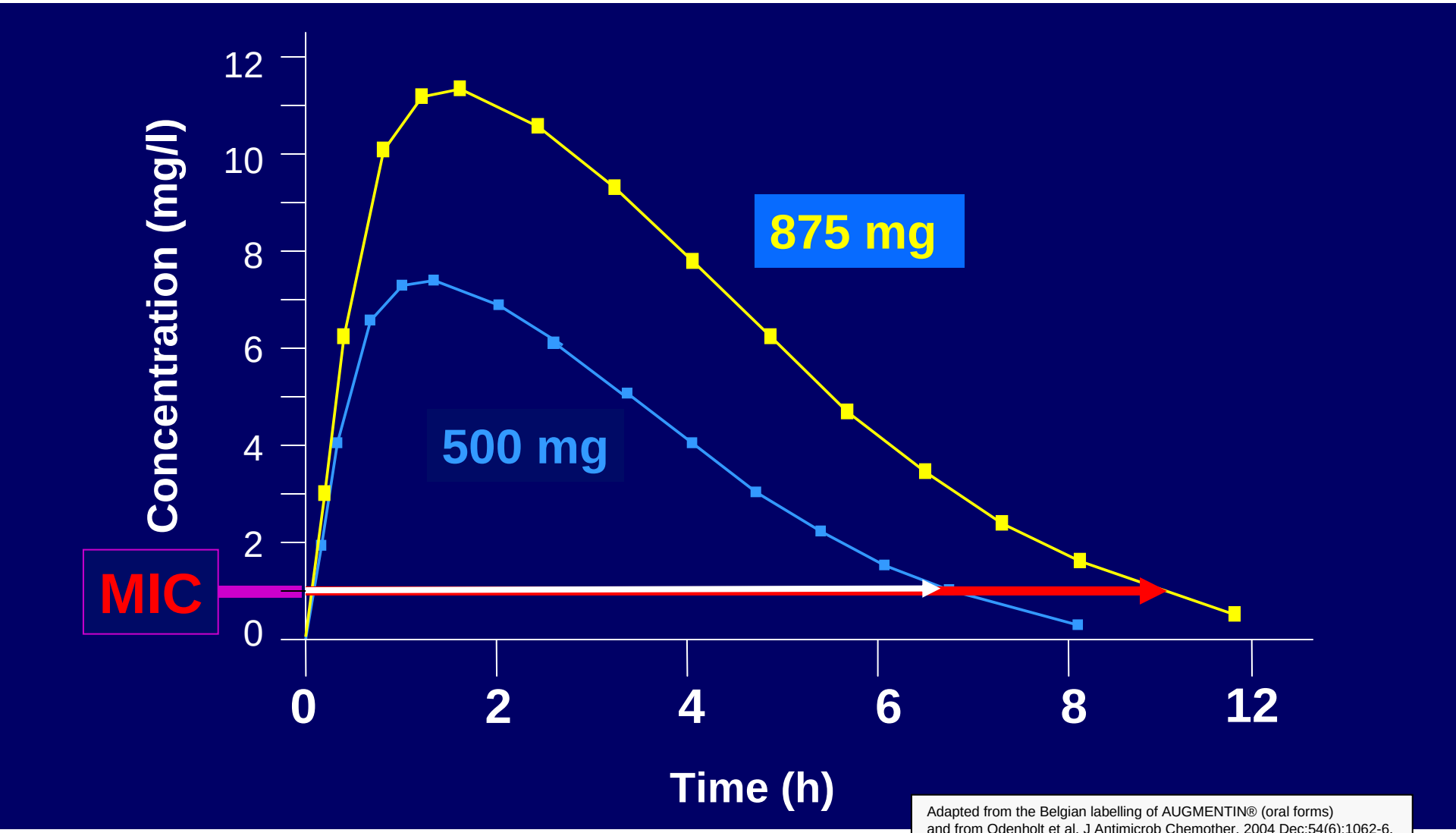


Craig WA. Diagn Microbiol Infect Dis 1996; 25: 213-7.

Oral penicillins: How to increase "Time > MIC" ?



Augmentin 875/125 q12h *versus* 500/125 q12h...



Adapted from the Belgian labelling of AUGMENTIN® (oral forms)
and from Odenholt et al. J Antimicrob Chemother. 2004 Dec;54(6):1062-6.

The next problem... (of many)

Clinicians tend to ask only (and clinical microbiologists to provide only) ‘S (susceptible) – I (intermediate susceptible) – R (resistant)’ answers based on accepted breakpoints…

But what is a breakpoint?

The situation 15 years ago…

cefotaxime vs. *E. coli*		**S≤ / R**
BSAC	United Kingdom	2 / ≥4
CA-SFM	France	4 / >32
CRG	The Netherlands	4 / >16
DIN	Germany	2 / ≥16
NWGA	Norway	1 / ≥32
SRGA	Sweden	0.5 / ≥2

Yet, these breakpoints were used everyday by clinical microbiology laboratories to advise clinicians about which antibiotic(s) they could sucessfully use against the bacteria they were supposed to fight …

Using USA (NCCLS / CLSI) breakpoints was not a real help for the patient ...

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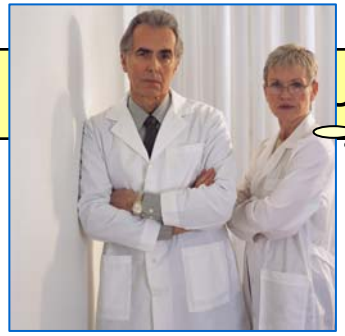
SRGA	Sweden	0.5 / ≥2
NCCLS	U.S.A.	8 / ≥64



Is 64 mg/L really "susceptible" ?

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

EUCAST

- Formed in 1997
- Convened by the main ad-hoc scientific and breakpoints committees in Europe
- Sets common breakpoints for surveillance of antimicrobial resistance and harmonizes clinical breakpoints for existing drugs
- Sets breakpoints for all newly registered antimicrobials for inclusion in the labeling (SPC) through ongoing agreement with the European Medicines Agency (EMEA)
- All breakpoints are based on a combination of
  - PK/PD data (in vitro, animals, …)
  - PK in humans with Monte-Carlo simulations and target attainment rates with dose simulations
  - Clinical data

http://www.eucast.org

The pros and cons of using CLSI or EUCAST breakpoints

CLSI

Pros

- available for antibiotics registered in the US mainly
- proposed and implemented by an independent committee
- backed by an extensive set of guidelines and recommendations for testing…

Cons

- no real control and non-fully transparent procedures for breakpoint setting
- no real access to decision by non- US countries
- high impact of industry
- CLSI can no longer set breakpoints for new molecules in the US (decision is made by FDA)
- not freely available ($$$)

EUCAST

Pros

- available for all current antibiotics used in Europe and free
- proposed and implemented by a committee working in close contact with ECCMID and the ECDC, and with representation of all EU countries
- backed by extensive and strict PK/PD considerations
- EUCAST breakpoints are transferred to the EMA for implementation in labels throughout all EU countries (= legal in EU)

Cons

- insufficient representation of non-EU countries
- less extensive guidelines and method description

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EUCAST

Amoxicillin EUCAST rationale document

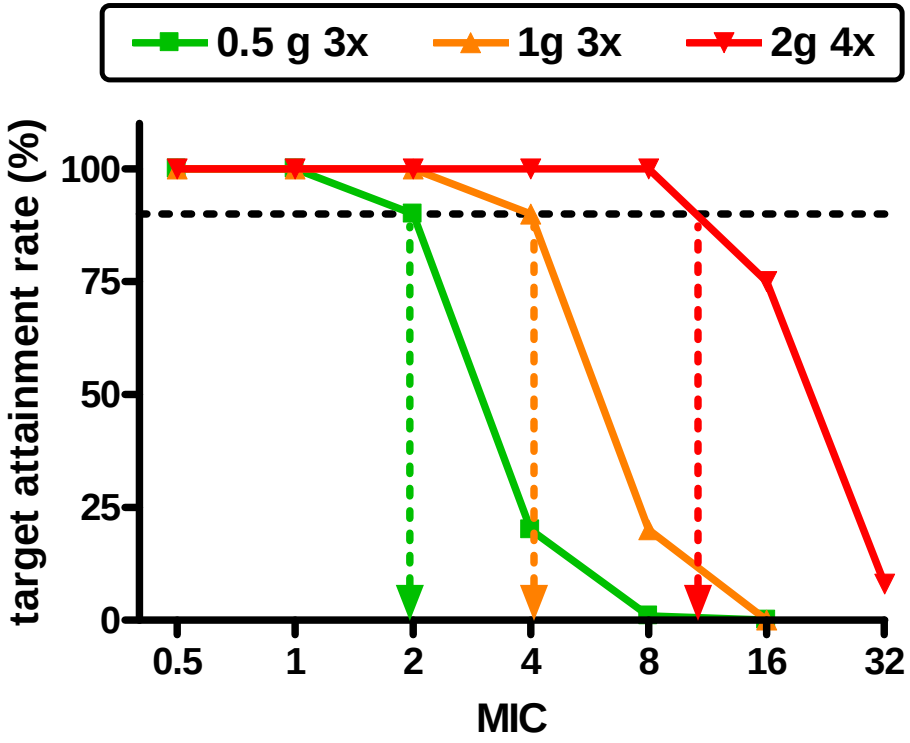
5. Pharmacodynamics

	Enterobacteriaceae	*Streptococcus pneumoniae*	*Haemophilus influenzae*
%*f*T>MIC for stasis : exp	30 – 35	25 – 35	25 – 35
%*f*T>MIC for 2 log drop : exp		35 – 45	35 - 45
%*f*T>MIC from clinical data		40	40
References	• Gerber AU et al. *J Infect Disease* 1986; 153: 90-97 • Craig WA et al. 33rd ICAAC 1993; Abstract 86 • Craig WA. In Antimicrobial Pharmacodynamics Theory and Clinical Practice 2002. Ambrose. Marcel Dekker Inc, Basel: 1-22 • MacGowan AP. *Clin Microbiol Infect* 2004: 52: 6-11		

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf

EUCAST

Amoxicillin EUCAST rationale document: Target attainment rate*



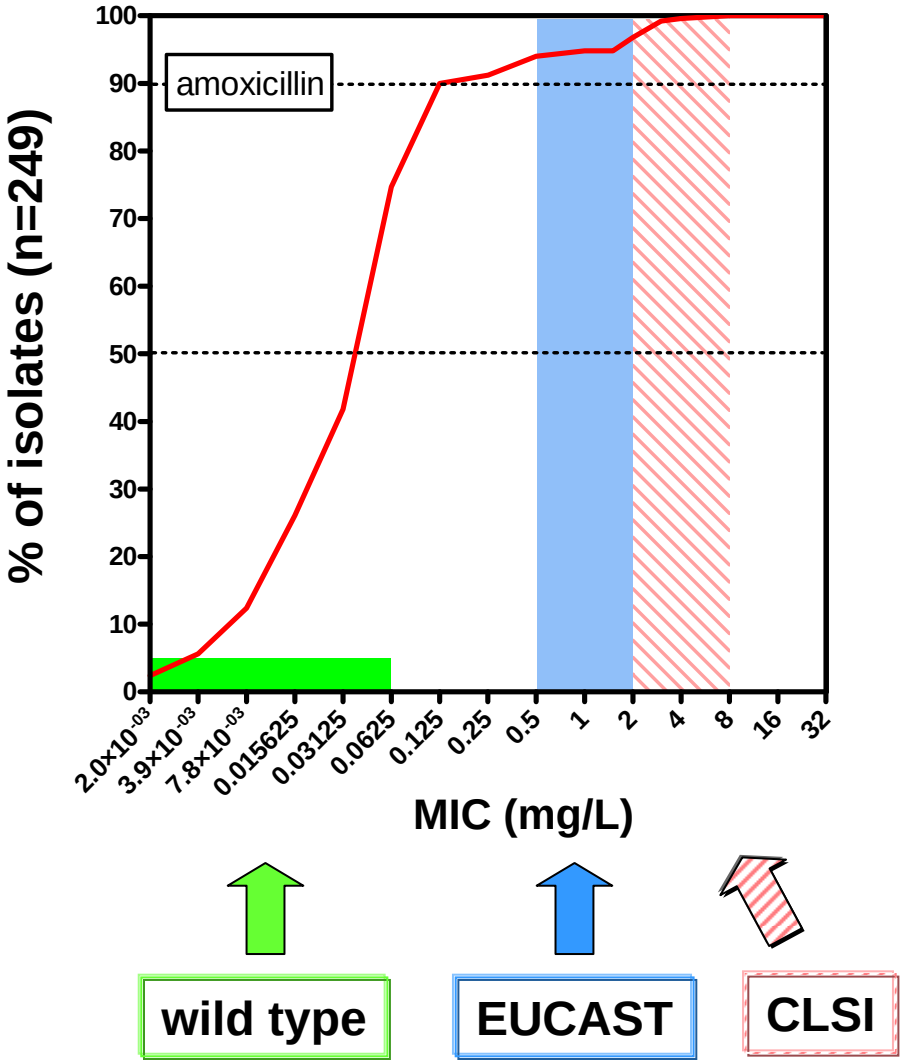
*** for *f* T >MIC = 40%**

Depending on the dose and schedule, you may cover bacteria with MIC from 0.5 to 8 mg/L

Graph prepared from data in http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf

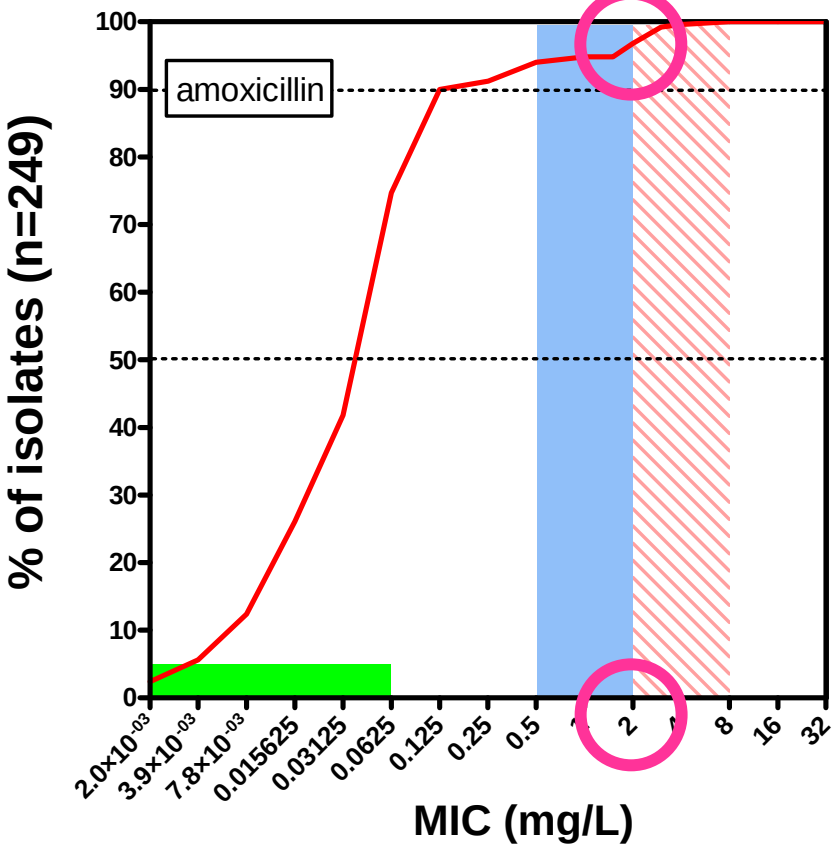
Looking at local MIC distributions…

isolates collected from confirmed cases of CAP from Belgium



Lismond *et al. 19th* ECCMID 2009, Helsinki, Finland; and submitted for publication

And making decisions….



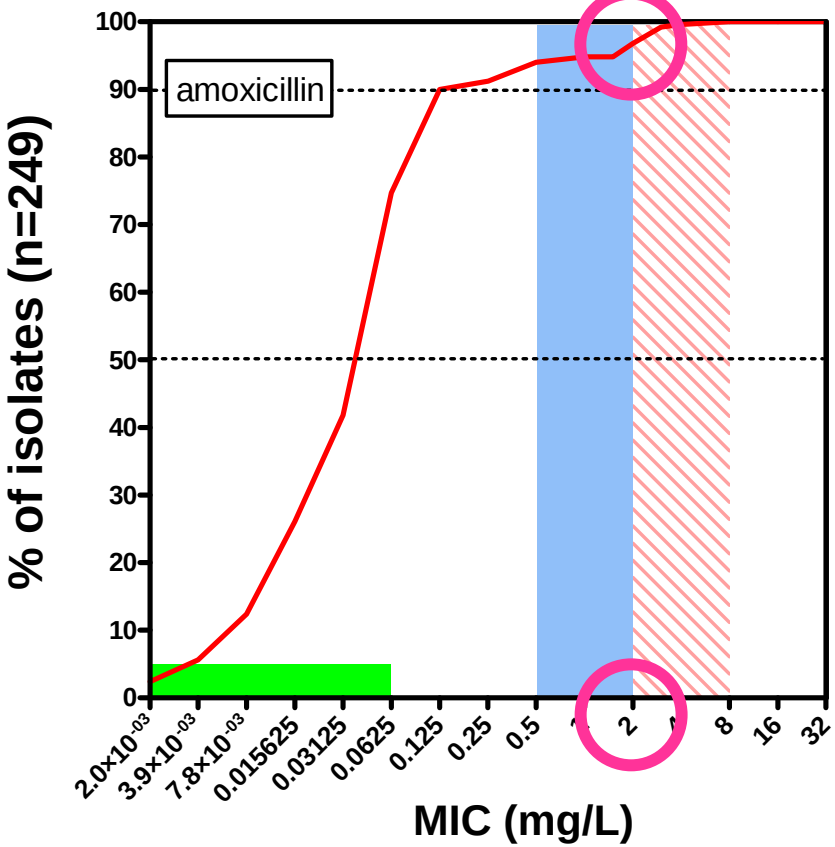
the dose of 0.5 g 3x/day will be almost perfect in **Belgium…**

wild type

EUCAST

CLSI

And making decisions….



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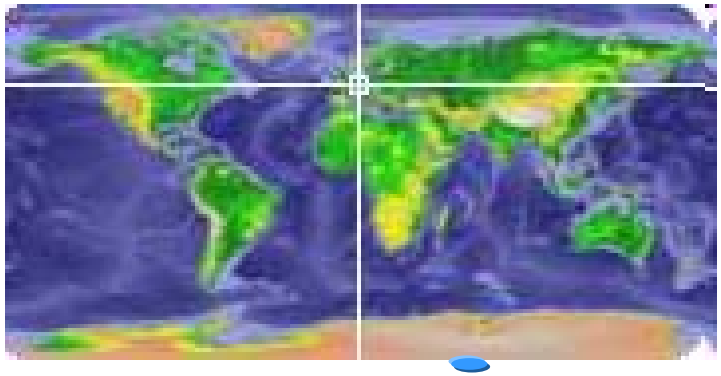


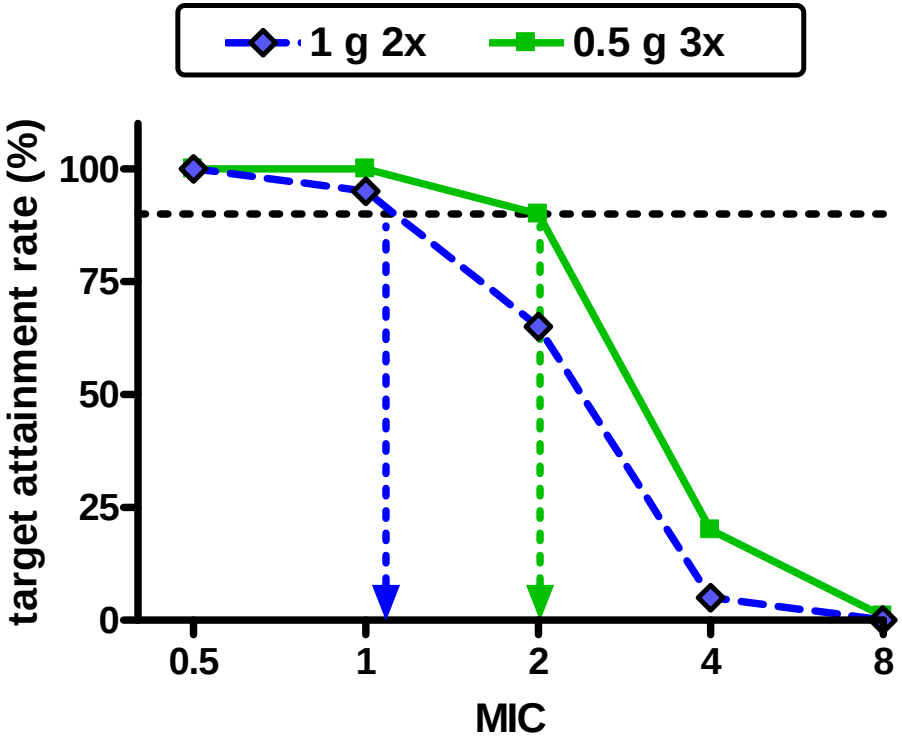
wild type

EUCAST

CLSI

You can do the same exercise for other countries or regions

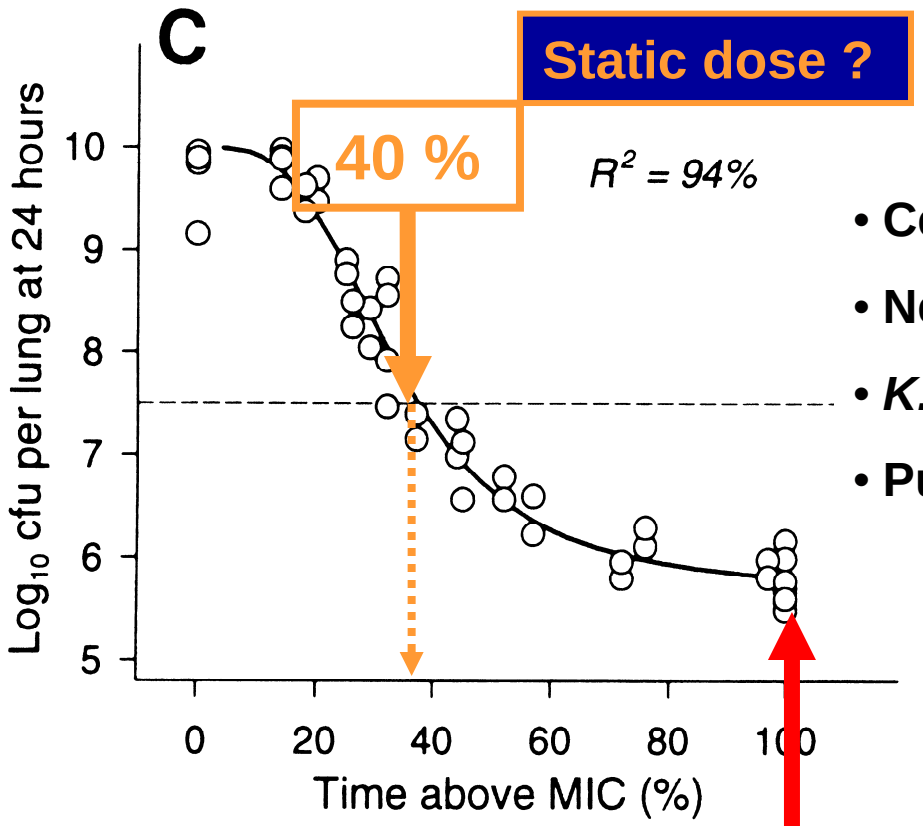
BID also works
but is intrinsically less efficient



*** for *f* T >MIC = 40%**

Graph prepared from
- data in http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf
- recalculation for 1 g 2x/day

The next problem: Is 40% T >MIC sufficient?



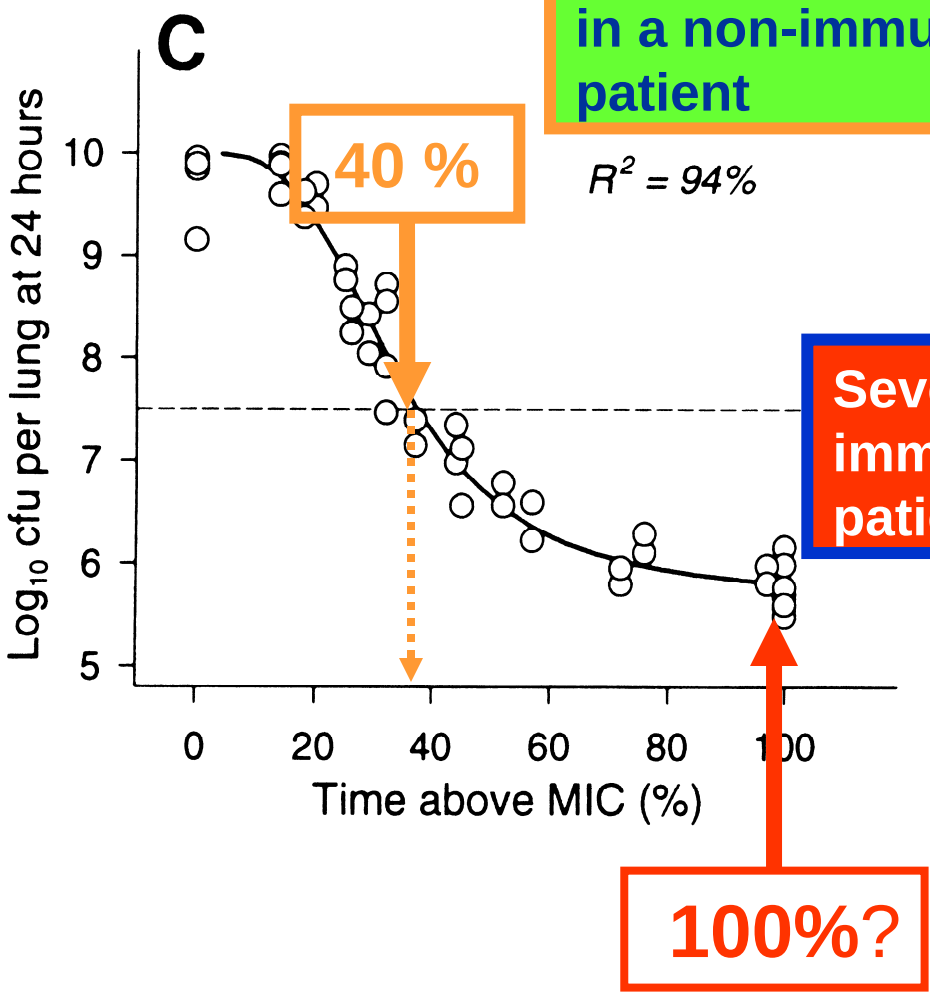
- Cefotaxime
- Neutropenic mice
- *K. pneumoniae*
- Pulmonary infection

100% – Maximal effect?

- Data: W.A. Craig, 2d ISAP Educational Workshop, Stockholm, Sweden, 2000 (see also Intern. J. Antimicrob. Agents 19 (2002) 261-268)
- Interpretation: P.M. Tulkens, ICAAC - ISAP PK/PD Workshop - Clinical Implications of PK/PD Modelling, Chicago, IL, 2005

Here is a proposal ...

Moderately severe infection in a non-immunosuppressed patient



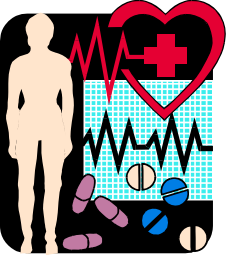
Severe infection in immunosuppressed patient

100%?

- Data: W.A. Craig, 2d ISAP Educational Workshop, Stockholm, Sweden, 2000 (see also Intern. J. Antimicrob. Agents 19 (2002) 261-268)
- Interpretation: P.M. Tulkens, ICAAC - ISAP PK/PD Workshop - Clinical Implications of PK/PD Modelling, Chicago, IL, 2005

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

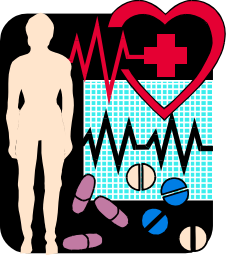
- ‘Out of the package insert’ PK data
- Monte-Carlo simulations and target attainment approaches



Pharmacokinetics of a typical IV β-lactam *

Time (hours)	Serum concentration (mg/L)		
	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

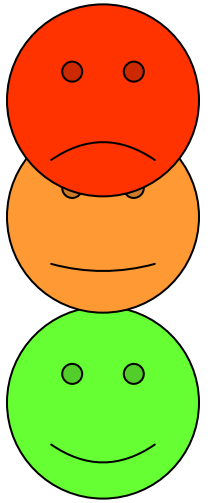
*Modelled according to typical PK data of ceftazidime single administration - half-life, 2h; V_d = 0.2 l/kg



Pharmacokinetics of a typical IV β-lactam *

Where would you like to be ?

Time (hours)	Serum concentration (mg/L)		
	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



*Modelled according to typical PK data of ceftazidime single administration - 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**

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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

Why so low ?

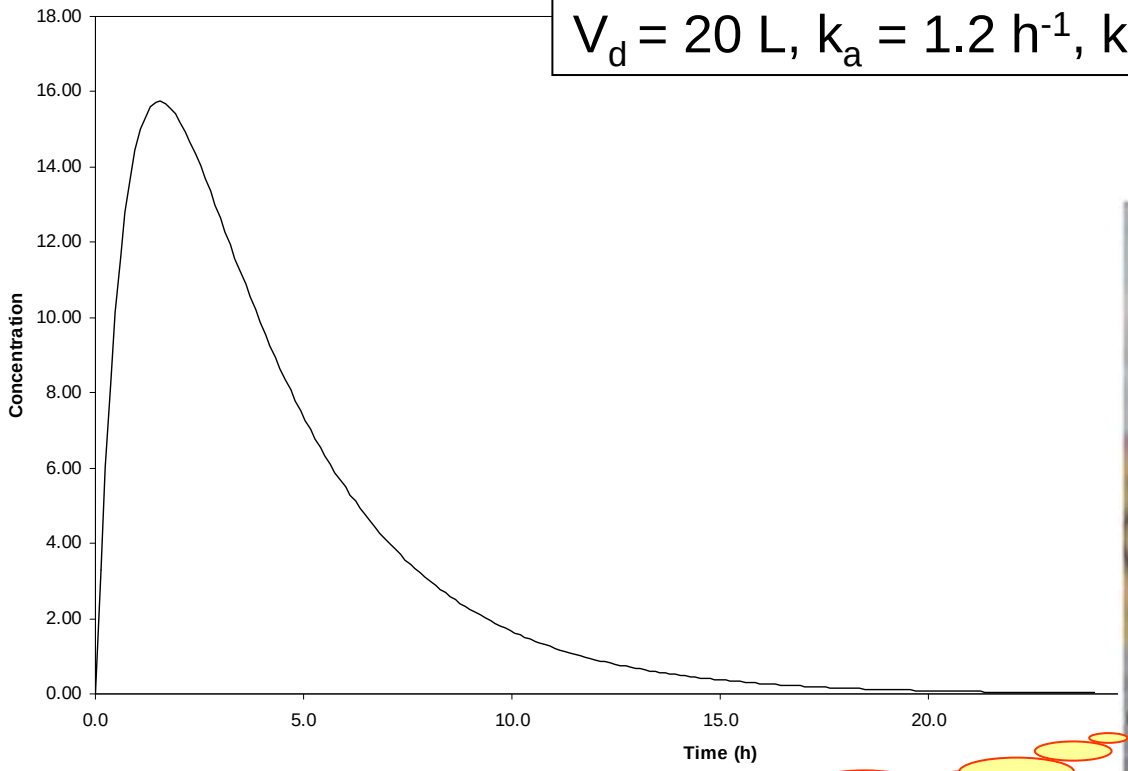
1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should 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.

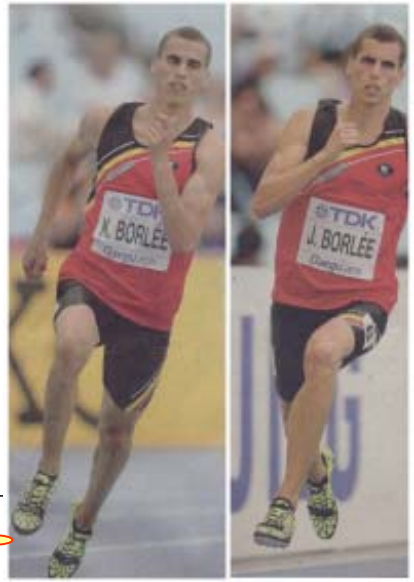
To exclude ESBL

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/EUCAST_breakpoints_v1.3_pdf.pdf

But there are variations in PK between individuals...

Concentration-time profile of a typical ß-lactam in volunteers
V_d = 20 L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}

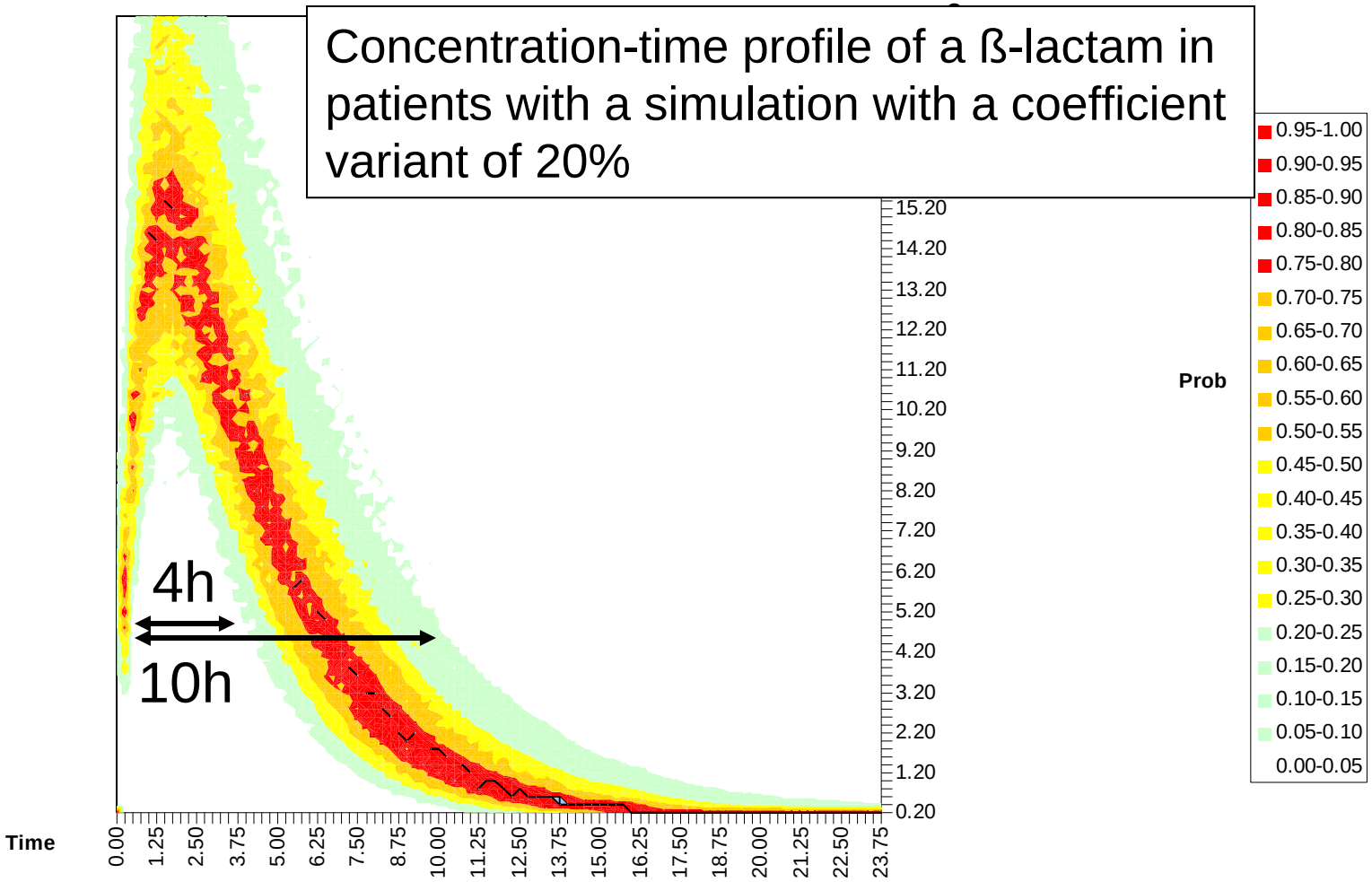




Unlike the Belgian 400 m sprint team, we are not all (almost) equal

Mouton JW. *Int J Antimicrob Agents* 2002;19:323-31.

Variation of PK in individuals...



Mouton JW. *Int J Antimicrob Agents* 2002;19:323-31.

Monte Carlo Simulations in PK/PD

- Use PK parameter values and a measure of their dispersion to simulate PK curves in a large number of patients
- Use MIC distribution values in the target population
- With those two sets of data, calculate a **probability** of attaining the desired target in the corresponding population.

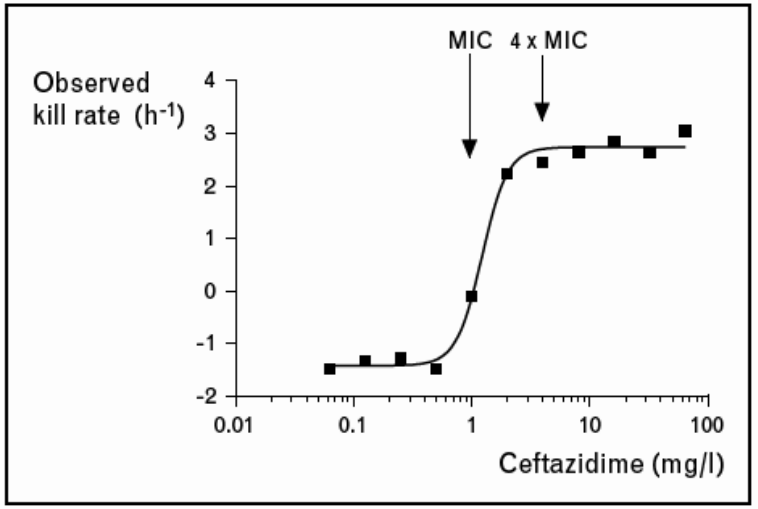
Recent example:
Landersdorfer *et al.* Bone penetration of amoxicillin and clavulanic acid evaluated by population pharmacokinetics and Monte Carlo simulation. Antimicrob Agents Chemother. 2009 Jun;53(6):2569-78.

> For a 30-min infusion of 2,000 mg/200 mg amoxicillin-clavulanic acid every 4 h, amoxicillin achieved robust (> or = 90%) probabilities of target attainment (PTAs) for MICs of < or = 12 mg/liter in serum and 2 to 3 mg/liter in bone and population PTAs above 95% against methicillin-susceptible *Staphylococcus aureus* in bone and serum.

The next frontier to reach the target for β-lactams: continuous infusion

- Maximum effect time-kill at 4 x MIC [1]
- Maximum effect *in vitro* 4 x MIC [2]
- Effect in endocarditis model 4 x MIC [3]
- 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].

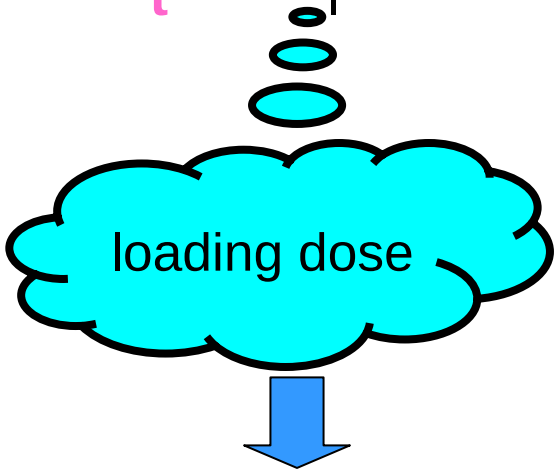
1.Mouton JW, Vinks AA. Curr Opin Crit Care 2007;13:598-606.
2.Craig WA & Ebert SC, Antimicrob Agents Chemother. 1992; 36:2577-83.
3.Xiong YQ, Potel G, Caillon J, et al. 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 4-7 1994, Orlando, FL. A88.

Continuous infusion in practice
1. loading dose (the correct scheme)

Target serum concentration

$C_t = D_l / Vd$

volume of distribution



loading dose (in mg) = C_t (mg/L) x **Vd** (L)

The loading dose is only dependent upon the volume of distribution and is directly influenced by the weight of the patient and his/her medical situation

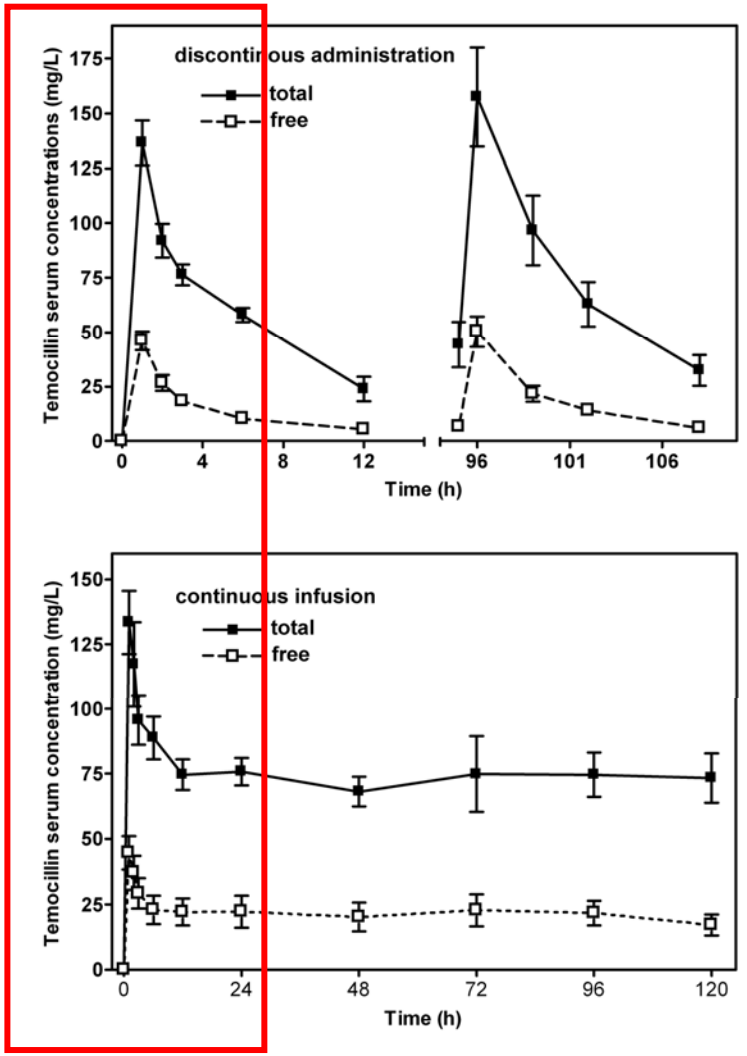
Typical volumes of distribution of a β-lactam are between 0.2 L/kg (volunteers) and 0.4-0.5 L/kg (Intensive Care and burned patients)

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

Tulkens PM. Meet-the-Experts – session 202.
49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 2009

Continuous infusion in practice
Loading dose: a simplified scheme

- Because β-lactams have a low intrinsic toxicity, transient overshooting may not be a major problem…
- Conventional treatment (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) ?



•De Jongh *et al.* J. A,timicrob. Chemother. (2008) 61:382-388

Continuous infusion in practice 2: infusion *

Target serum concentration

$C_{ss} = K_o / Cl$

Clearance *

infusion rate

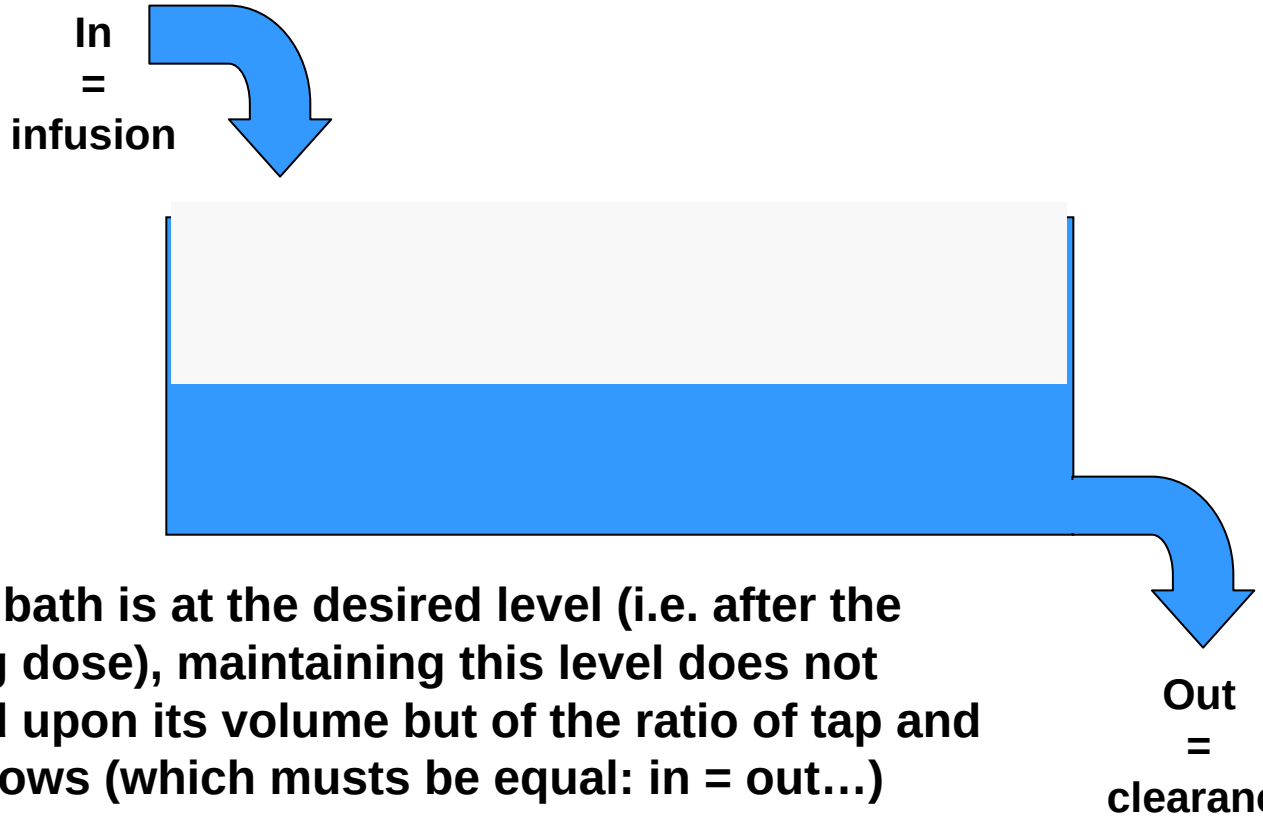
daily dose (in mg) = 24 x **clearance** (L/h) x **Css**

*** 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)

Tulkens PM. Meet-the-Experts – session 202.
49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 2009

Continuous infusion in practice
2: infusion



once a bath is at 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 musts 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**

Tulkens PM. Meet-the-Experts – session 202.
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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 JA, Paratz J, Paratz E, Krueger WA, Lipman J. *Int J Antimicrob Agents* 2007;30:11-8.

Problems with continuous infusion…

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

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

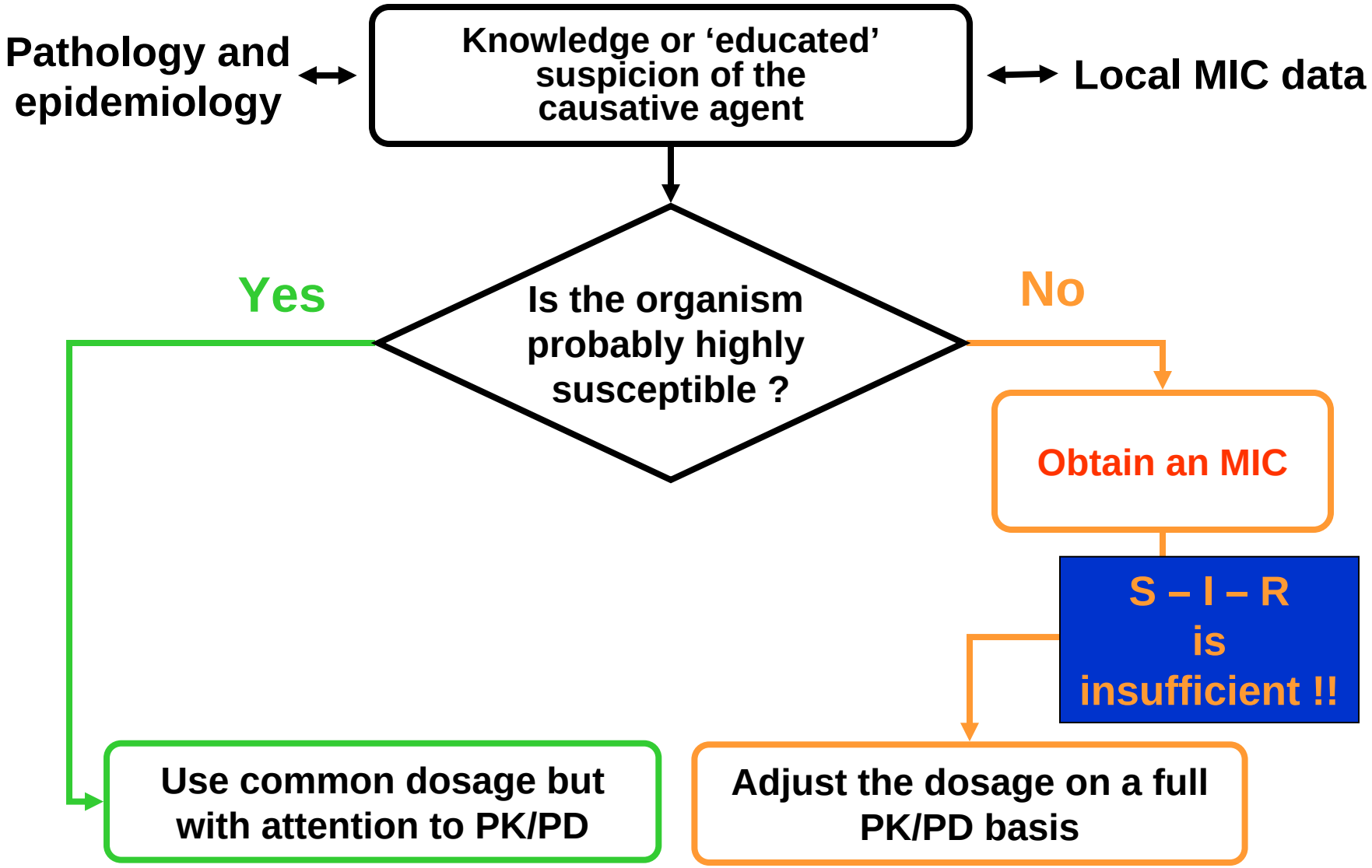
Problems with continuous infusion…

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burns patients…)
- Non-linear clearance
- **Drug instability**

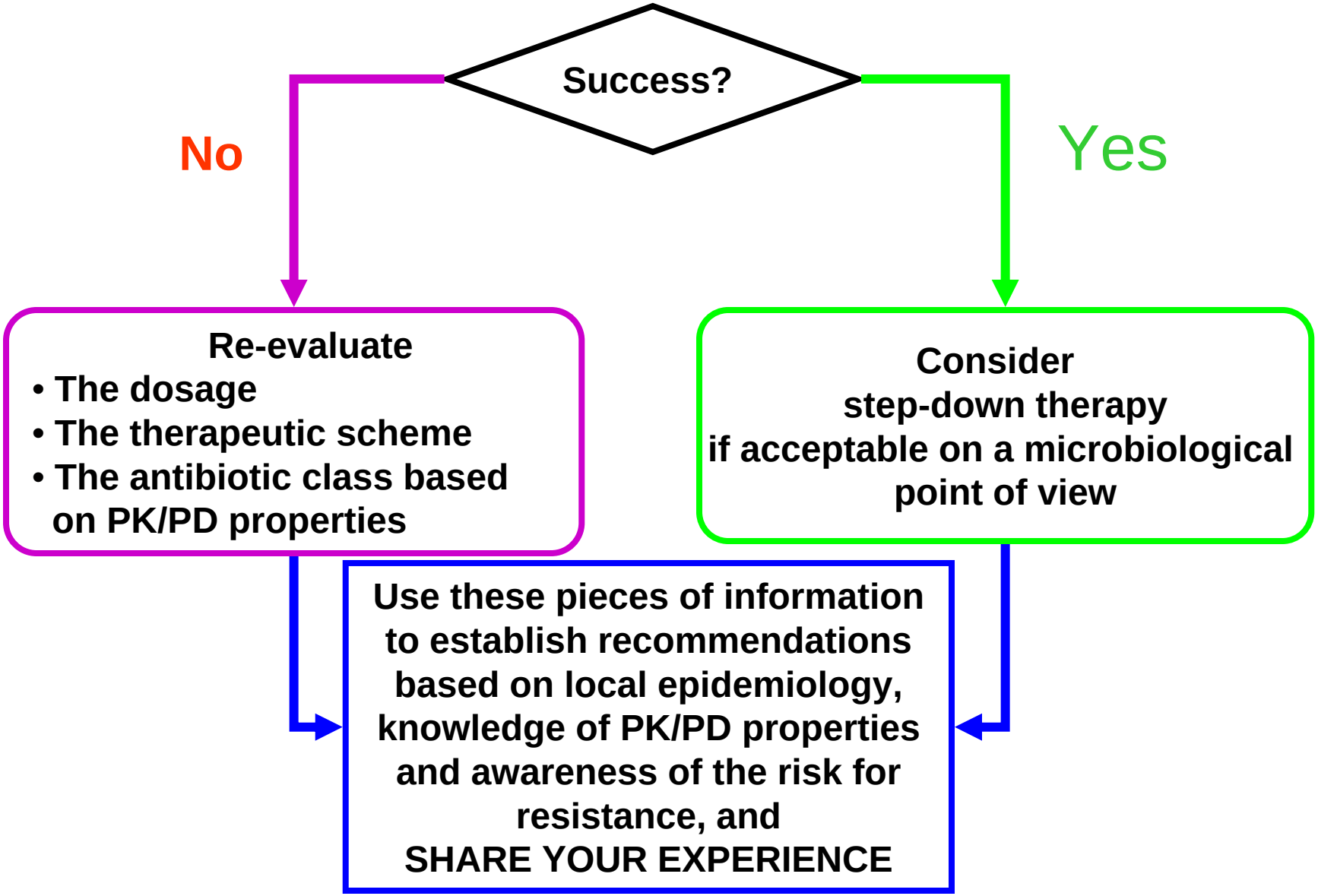
temocillin > piperacillin > ceftazidime > cefepime …
!! carbapenems are unstable (3–4h max.)

- Berthoin et al. J. Antimicrob. Chemother. (2010) 65:1073-1075
- De Jongh et al. J. A,timicrob. Cheomther. (2008) 61:382-388
- Barirain et al. J. Antimicrob. Chemother. (2003) 51:651-658
- Viaene et al. Antimicrob. Agents Chemother. (2002) 46:2327-2332
- Servais et al. Antimicrob. Agents Chemother. (2001) 45:2643-2647

A clinical algorithm or a path to success…



A clinical algorithm (followed)…



Conclusions … or what do you need to consider for any antibiotic…

- **For the microbiologist:** Know and inform about susceptibility data in YOUR clinical/community environment
  - ➔ MICs are best….; use the methodology that suits your needs (CLSI, EUCAST, other…) but make interpretation based on EUCAST breakpoints

- **For the clinician:** use all available information (AUC *, peak *) and/or frequency of administration (time *) to make sure the drug your prescribe will be effective against the organisms you are fighting ...

- **For both and the pharmacists:** re-examine at regular intervals whether the choices made remain appropriate for YOUR patients… with the drug and the dose that were prescribed.

- **For all of you:** ***"New"*** antibiotics are not necessarily superior and may even be risky if the highest MIC they can safely cover is too close from the upper limit of the wild type population…

* get this information from your pharmacist, the literature, EUCAST, and industry …