Towards clinical Applications of PK-PD in specific situations

P.M. Tulkens

Cellular and Molecular Pharmacology
& Center for Clinical Pharmacy,
Catholic University of Louvain,
Brussels, Belgium

with many things borrowed from

J.W. Mouton

Department of Medical Microbiology,

Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands

http://www.isap.org

51th Interscience Conference on Antimicrobial Agents and Chemotherapy
Chicago, Ill.

In a nutshell…

- Why dosing according to susceptibility (MIC) ?
  - Application for the **fluroquinolones** ?
  - Why do you need "good" breakpoints ?
  - Can you do it for intracellular bacteria ?
- Can you optimize **β-lactams**
  - T > MIC: practical approaches
  - Continuous infusion ?
- What about **vancomycin** ?
  - Continuous infusion ?
  - Where do we reach a limit ?

The problem ... #1 of many …

1. Infections are (most often) treated with the same dosing regimen irrespective of the absolute susceptibility of the micro-organism ...

Table 20-7. Dosing Regimens of Cephalosporins in Adults and Children

	Adults		Children
Cephalosporin	***Usual Dose***	***Severe Disease***	***Usual Dose***
First Generation			
Cefazolin	0.5-1 g q8-12h	2 g q6-8h	12.5-33 mg/kg q6-8h
Cephalothin	0.5-1 g q6h	2 g q4-6h	20-25 mg/kg q6h
Cephapirin	0.5-1 g q6h	2 g q4-6h	10-20 mg/kg q6h

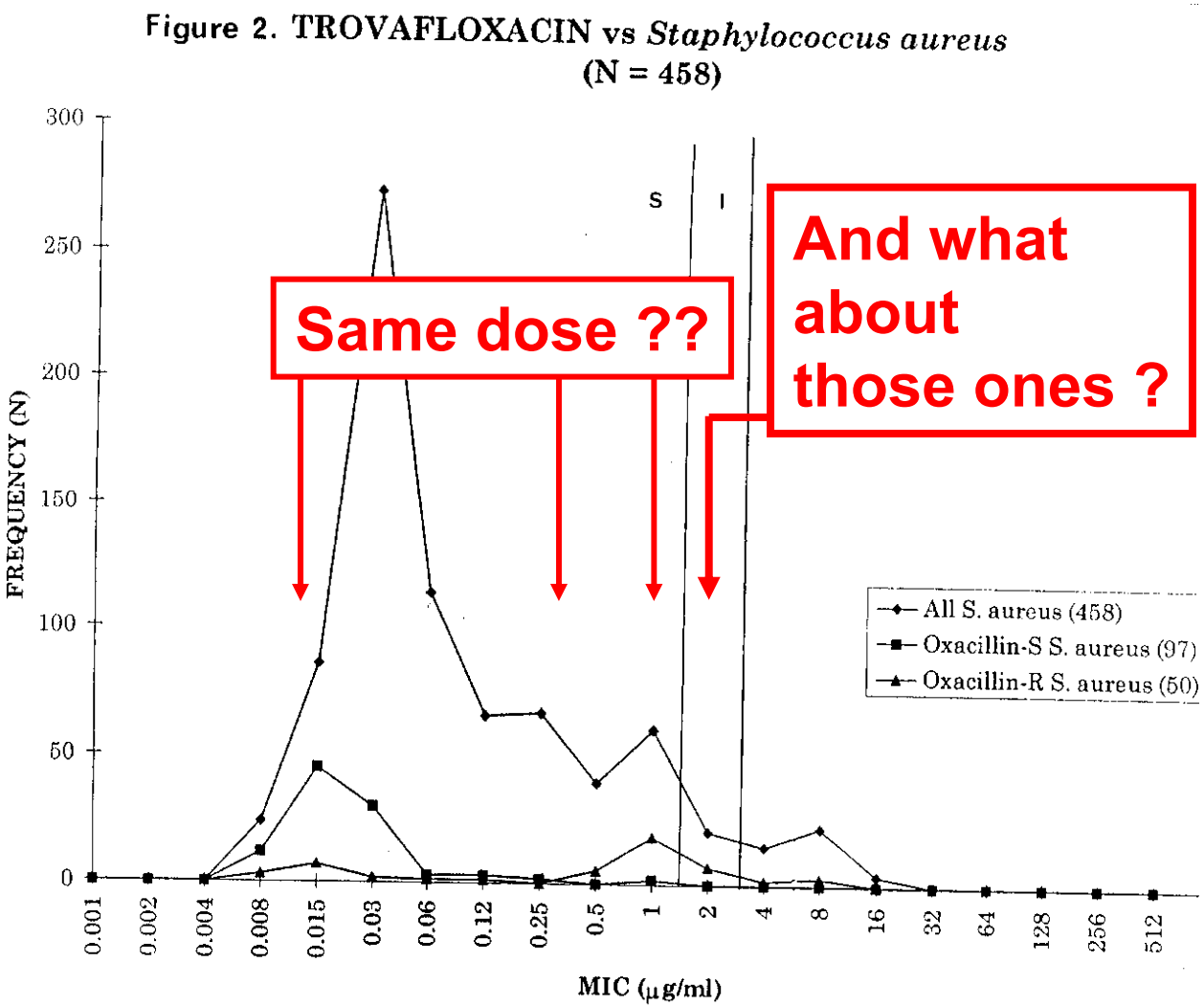
What is s "severe disease ?

The problem ... #2 (of many)

2. Clinicians tend to ask only (and clinical microbiologists to provide only) "S – I – R" answers based on accepted breakpoints …

But, what is a breakpoint ?

The problem as seen from a question of the FDA...



Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...

So, you need to know the enemy ...

For a fluoroquinolone….

MIC = .016 mg/L Susceptible

≠

MIC = 2.0 mg/L Susceptible ?

Which parameter are you going to use in your hospital ?

- AUC_{24h} / MIC
- C_{max} / MIC
- Time above MIC

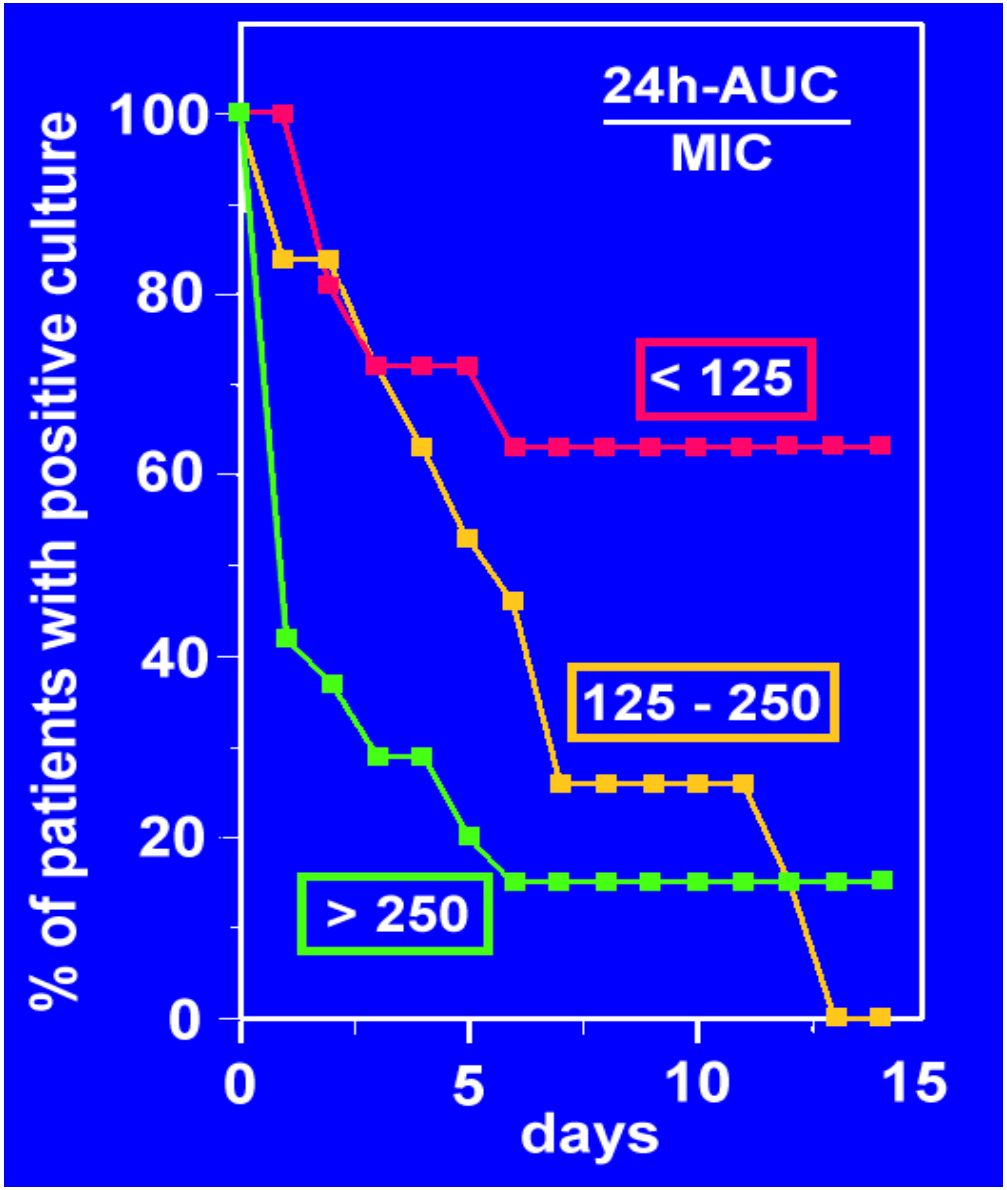
how much and for all ?

Exercise with

- **the fluoroquinolones**
- **the β-lactams**

The saga of the AUC / MIC vs C_{max} / MIC ratio for fluoroquinolones ...

AUC / MIC
is
the parameter ...



Forrest et al., AAC, 1993

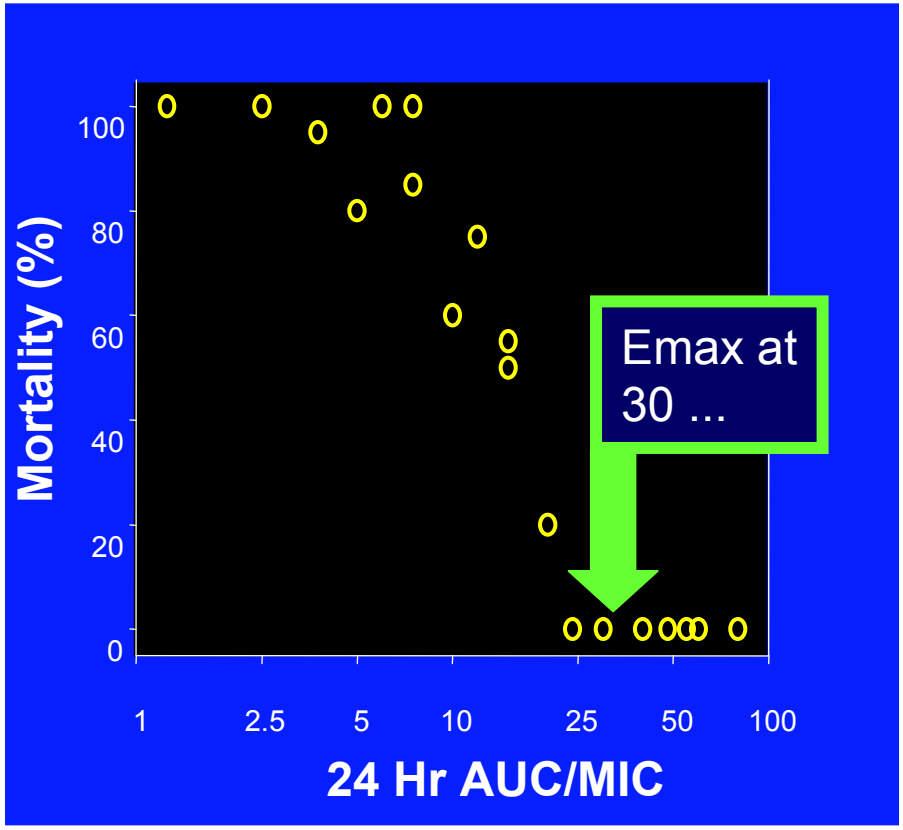
AUC/MIC_{24h} = 125 : a magical number??

125 was the limit below which failure rates became unacceptable because of either

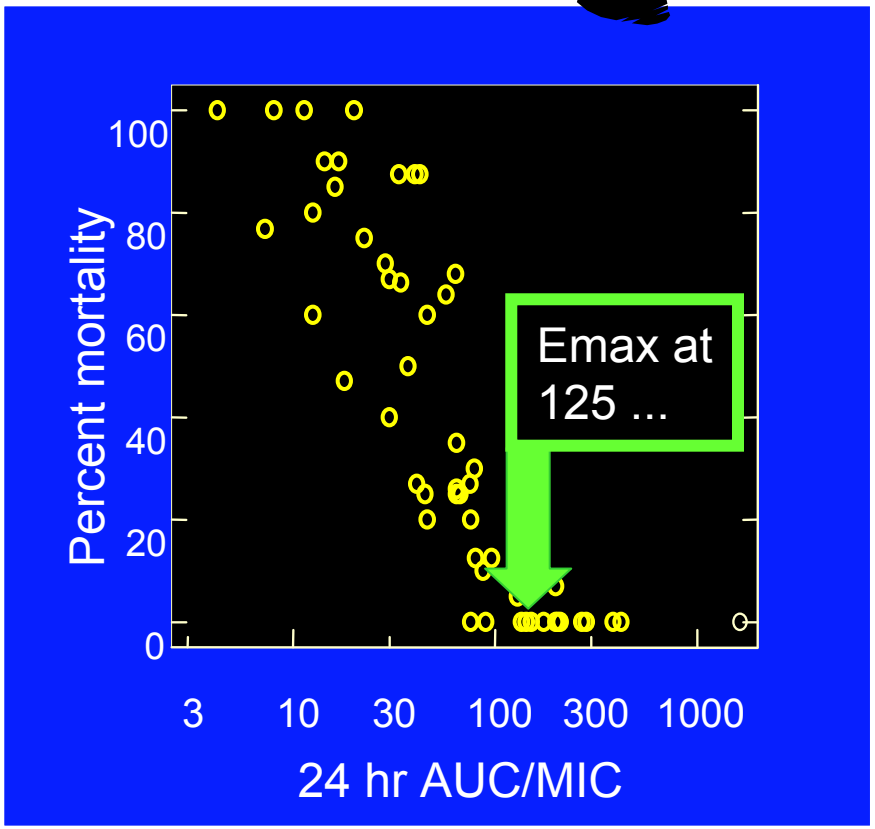
- a large MIC
- or a too low dosage
  (AUC is proportional to the dosage)
- was derived from studies on Gram-negative infections

Is 125 good for all ??

The saga of *S. pneumoniae* ...



non-neutropenic



neutropenic

Conditions That Predispose to Pneumococcal Infection

Defective antibody formation

PrimaryCongenital agammaglobulinemia

Common variable (acquired) hypogammaglobulinemia

Selective IgG subclass deficiency

SecondaryMultiple myeloma

Chronic lymphocytic leukemiaLymphoma

HIV infection

Defective complement (primary or secondary)

Decreased or absent C1, C2, C3, C4

Insufficient numbers of PMNs

PrimaryCyclic neutropenia

SecondaryDrug-induced neutropenia

Aplastic anemia

Poorly functioning PMNs

Alcoholism

Cirrhosis of the liver

Browse Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases

Conditions That Predispose to Pneumococcal Infection

Glucocorticosteroid treatment

Renal insufficiency?

Poorly avid receptors for FCγII (R131 allele)

Defective clearance of pneumococcal bacteremia

PrimaryCongenital asplenia, hyposplenia

SecondarySplenectomy

Sickle cell disease (autosplenectomy)

Multifactorial

Infancy and aging

Malnutrition

Diabetes mellitus

Prior respiratory infection

Influenza

Cigarette smoking

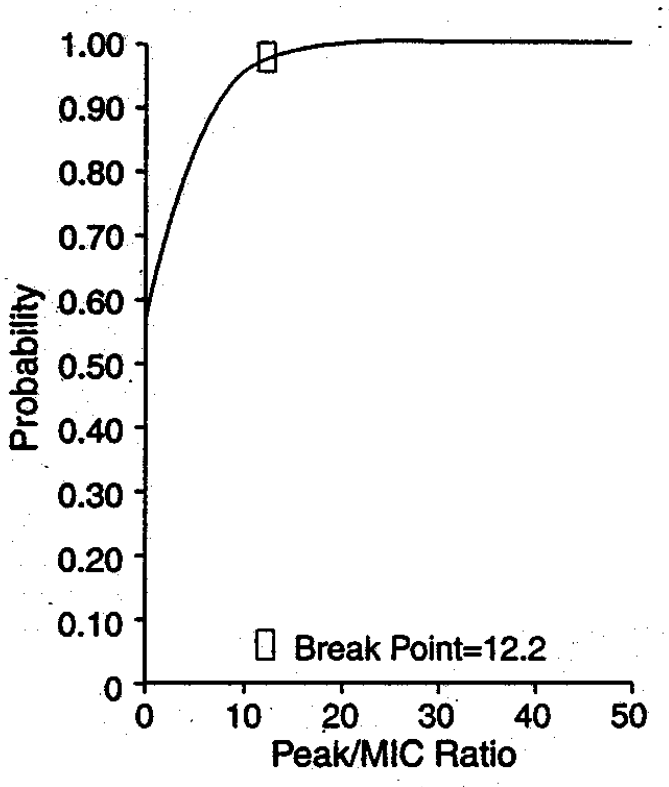
Asthma

COPD

Browse Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases

Quinolones : to peak or not to peak ?

- Three studies have shown AUC/MIC predictive for outcome
- One prospective study showed Peak/MIC to be more predictive



Modelling studies show that :

- **Survival linked to Peak/MIC when ratio > 10/1**
- **Survival linked to AUC/MIC when ratio < 10/1**
- **the risk of resistance is minimized if the peak/MIC > 10**

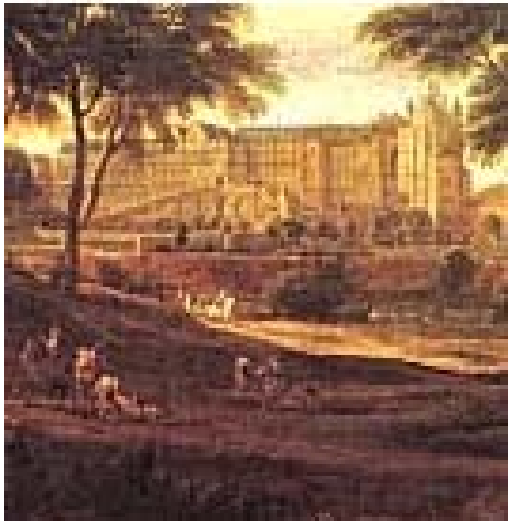
So, let us accept values with some degree of precaution with fluoroquinolones

If you wish to get a faster eradication and reduce mergence of resistant

➔ peak / MIC > 10

If you are interested in global effect …

➔ AUC_{24h} / MIC: 30 to 125



1st Example :
You want to control fluoroquinolone dosing at the level of the patient

- Patient 60 yr, pneumonia and suspected bacteraemia/sepsis
- Ixacin 400 mg IV q8h ➔ AUC = 30
- Gram negative rod …

- E-test MIC=0.01 mg/L
- 30/0.01 ➔3000 !

➢ 100 mg/day is plenty !

- E-test MIC = 1 mg/L
- 30/2 ➔ 30 !

➢ 400 mg q8h may fail

Mouton & Vinks, PW 134:816

Breakpoint issues ...

Drug	PK/PD limits of susceptibility (mg/L)			
	Dosage (mg/24h)	**AUC/MIC*** (24h)	**peak / MIC****	**CLSI "S" Bkpts**
norfloxacin	800	**0.1**	**0.2**	**< 4**
ciprofloxacin	500	**0.1**	**0.2**	**< 1**
ofloxacin	400	**0.2-0.4**	**0.3 - 0**	**< 2**
levofloxacin	500	**0.4**	**0.4 - 0**	**< 2**
gatifloxacin	400	**0.3**	**0.4**	**< 2**
moxifloxacin	400	**0.4**	**0.4**	**< 2**

Based on US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®

* AUC/MIC = 125

** peak / MIC = 10

A proposal for PK/PD based-breakpoints for fluoroquinolones...

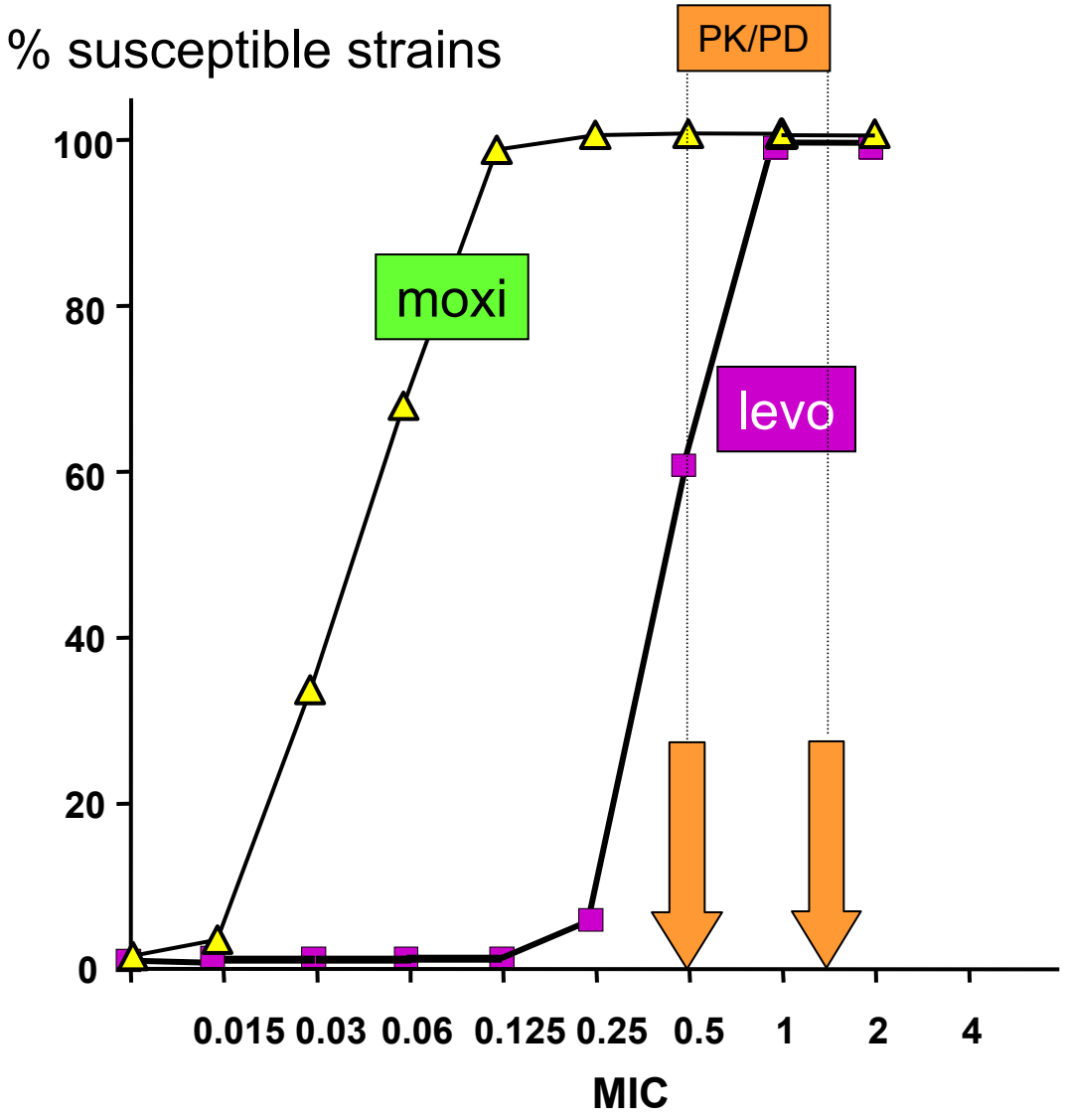
Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (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

2d example: you want to control fluoroquinolone choice and dosing for patients with CAP

- You have two Ixacins: L-xacin and M-xacin
- They have essentially the same pharmacokinetics and tolerance
- Which one will you recommend in YOUR set-up for CAP ?

Application to pneumococci in Belgium



Moxifloxacin 400 mg 1x/d

- AUC [(mg/l)xh]: 48
  - ➢ MIC max: 0.5-1.5
- peak [mg/l]: 4.5
  - ➢ MIC_{max} : ~ 0.5

Levofloxacin 500 mg 1x/d

- AUC [(mg/l)xh] 47
  - ➢ MIC max: 0.5-1.5
- peak [mg/l] 5
  - ➢ MIC_{max} : ~ 0.5

MIC data: J. Verhaegen et al., ECCMID 2003
Similar values in 2009 (Vanhoof, ECCMID 2009)

Can you do that in another country ?

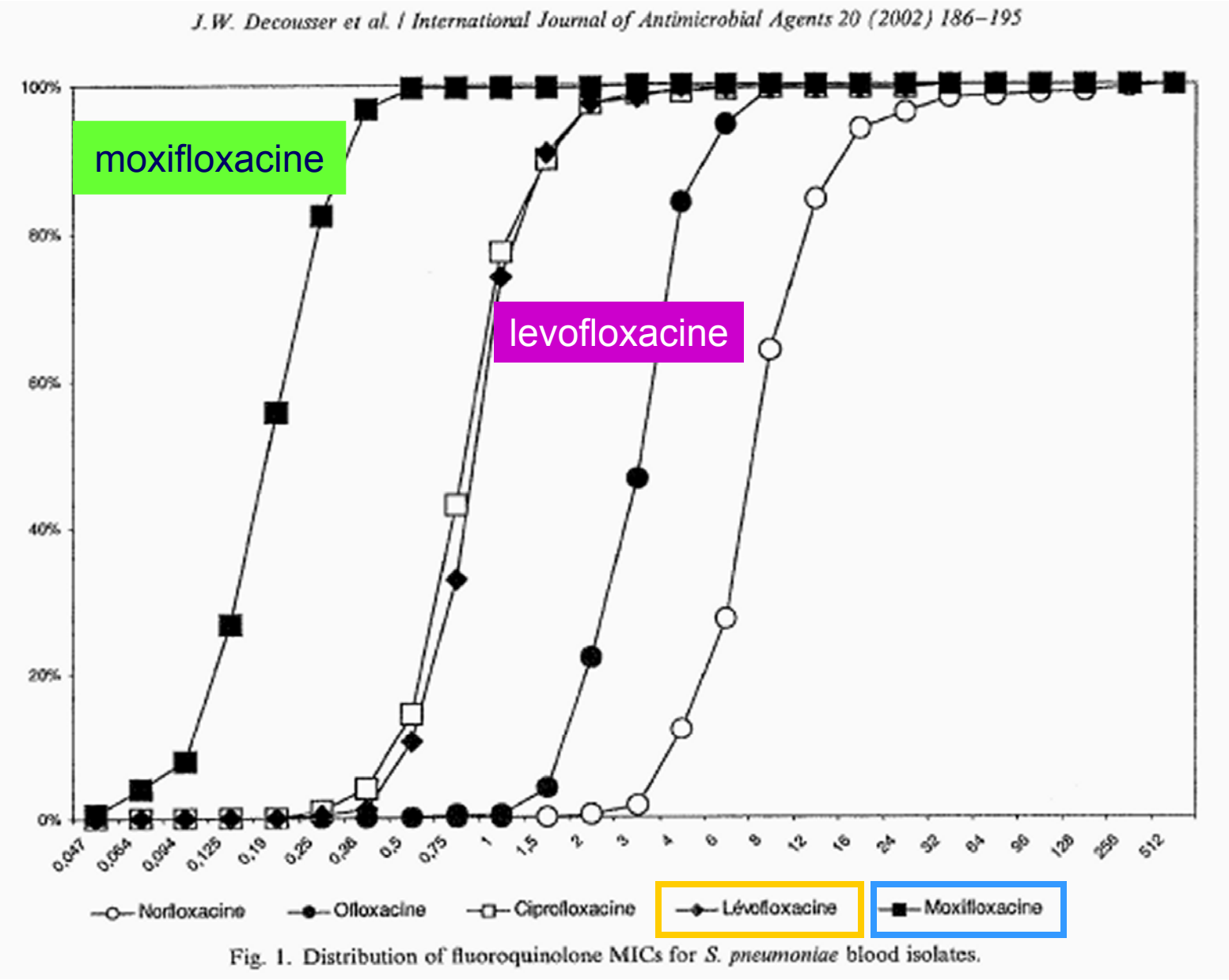


Fig. 1. Distribution of fluoroquinolone MICs for *S. pneumoniae* blood isolates.

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 brakpoints committees in Europe
- sets common breakpoints for surveillance of antimicrobial resistance and harmonize 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

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

EUCAST

Enterobacteriaceae

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin[1]	0.5	1	5	22	19
Levofloxacin	1	2	5	22	19
Moxifloxacin	0.5	1	5	20	17
Norfloxacin	0.5	1	10	22	19
Ofloxacin	0.5	1	5	22	19

This is now close to the PK/PD breakpoints

All EUCAST data are freely available at http://www.eucast.org

Can we define an intra-cellular breakpoint ?

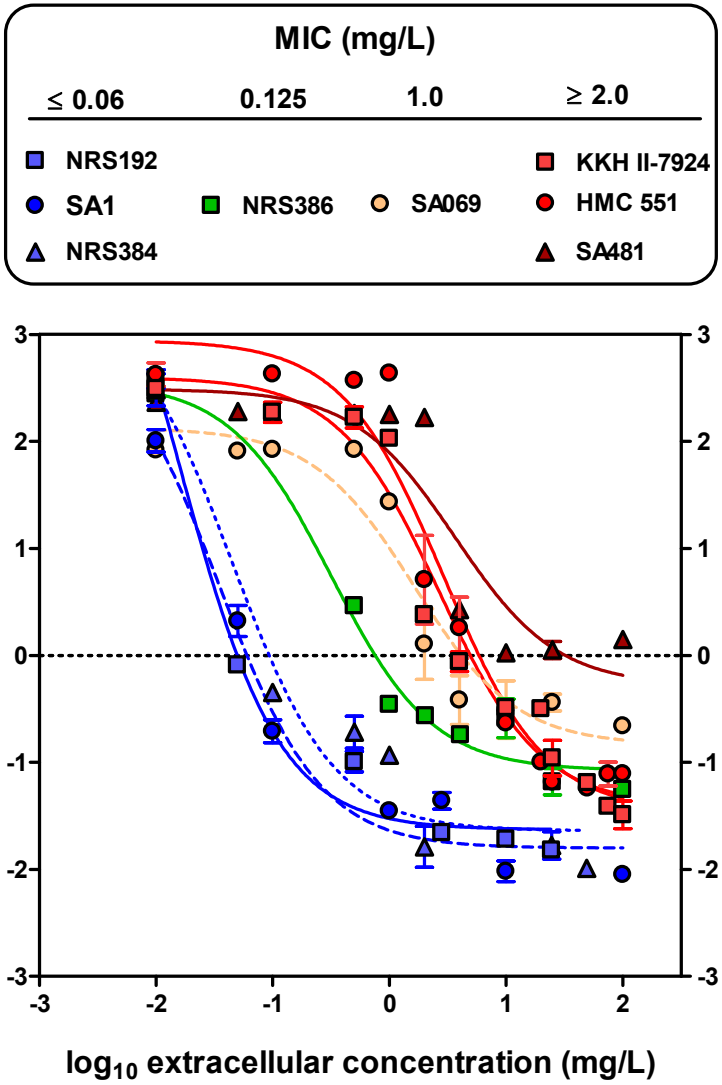
An exercise with moxifloxacin and intracellular *S. aureus* …

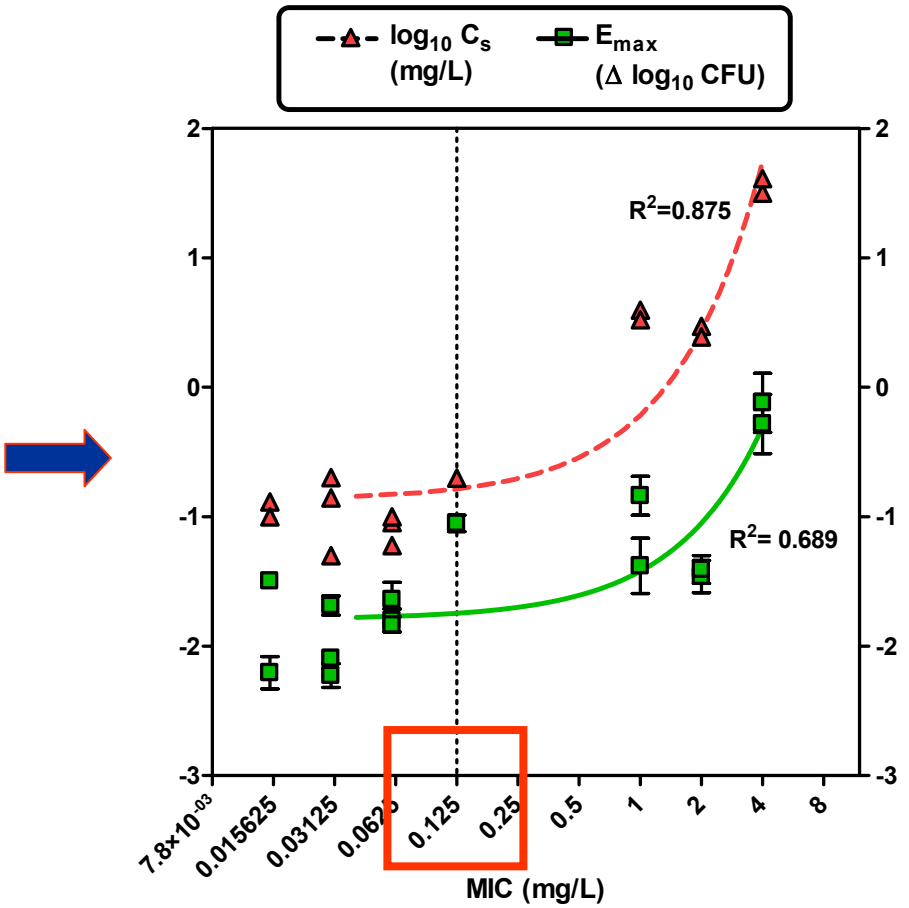
- Use a model of S. aureus phagocytized by macrophages *
- Take a collection of *S. aureus* with increased MIC towards moxifloxacin (MSSA, CA-MRSA, HA-MRSA, …)
- Test for activity over a wide range of extracellular concentration
- Plot the results against the MIC

---

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

Can we define an intra-cellular breakpoint ?



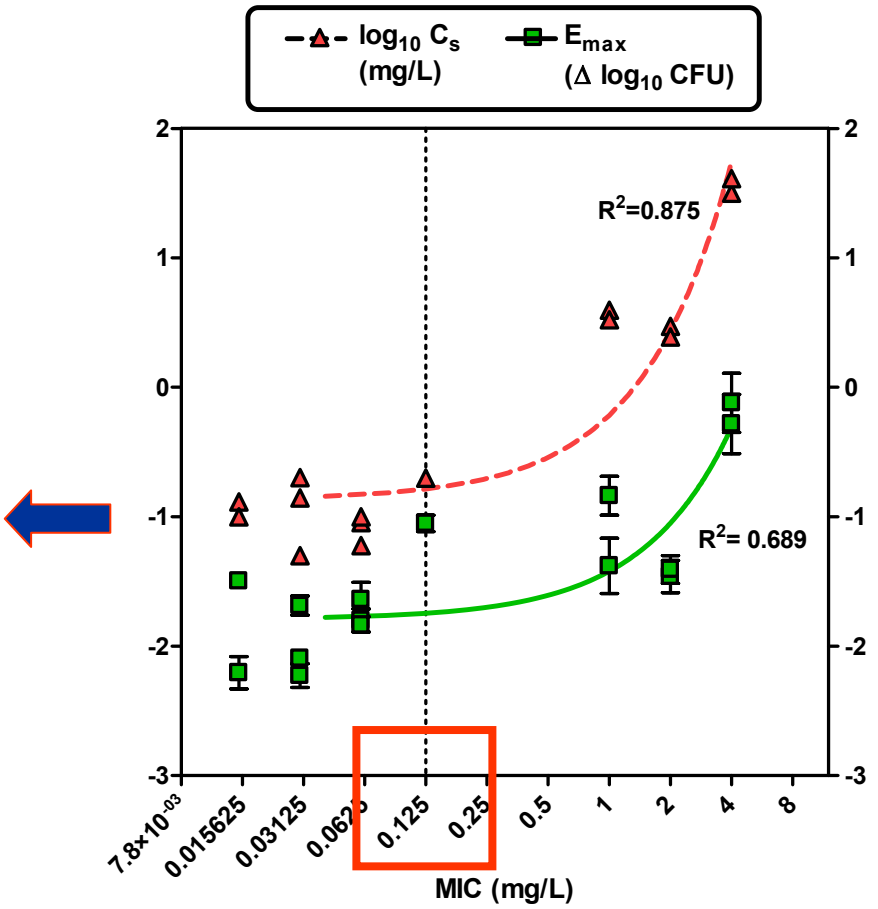


Lemaire et al. J Antimicrob Chemother. 2011 Mar;66(3):596-607.

Can we define an intra-cellular breakpoint ?

EUCAST breakpoints

Fluoroquinolones	MIC breakpoint (mg/L)	
	S ≤	R >
Ciprofloxacin[1]	0.5	1
Levofloxacin	1	2
Moxifloxacin	0.5	1
Norfloxacin	0.5	1
Ofloxacin	0.5	1



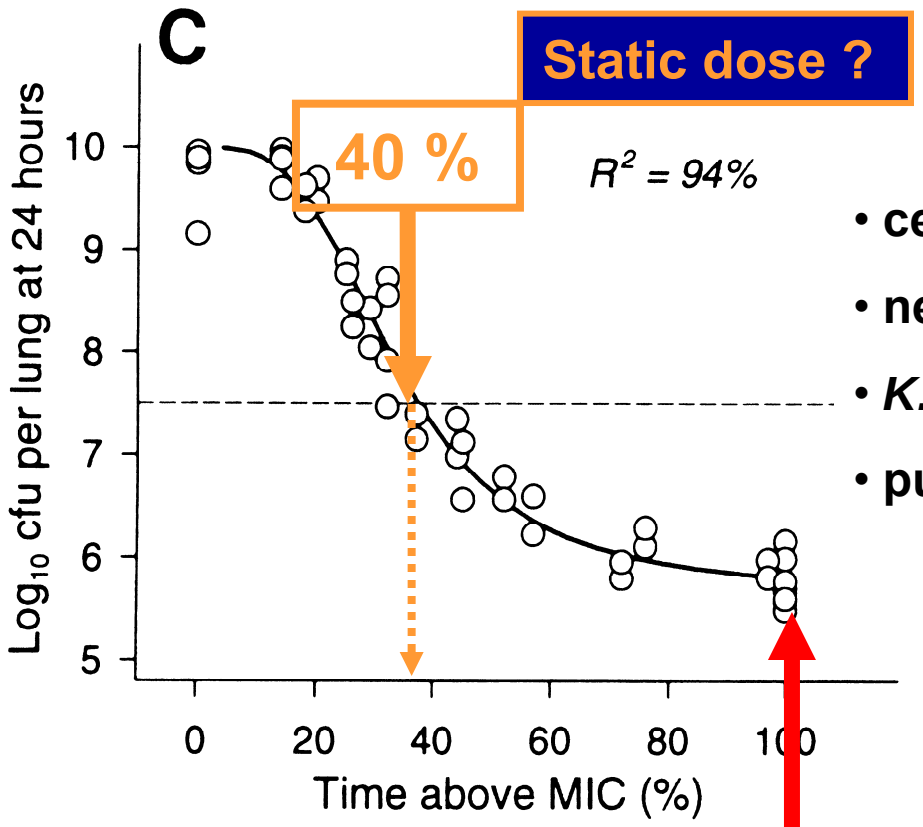
Lemaire et al. J Antimicrob Chemother. 2011 Mar;66(3):596-607.

2d example: β-lactams : T > MIC …

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 ?

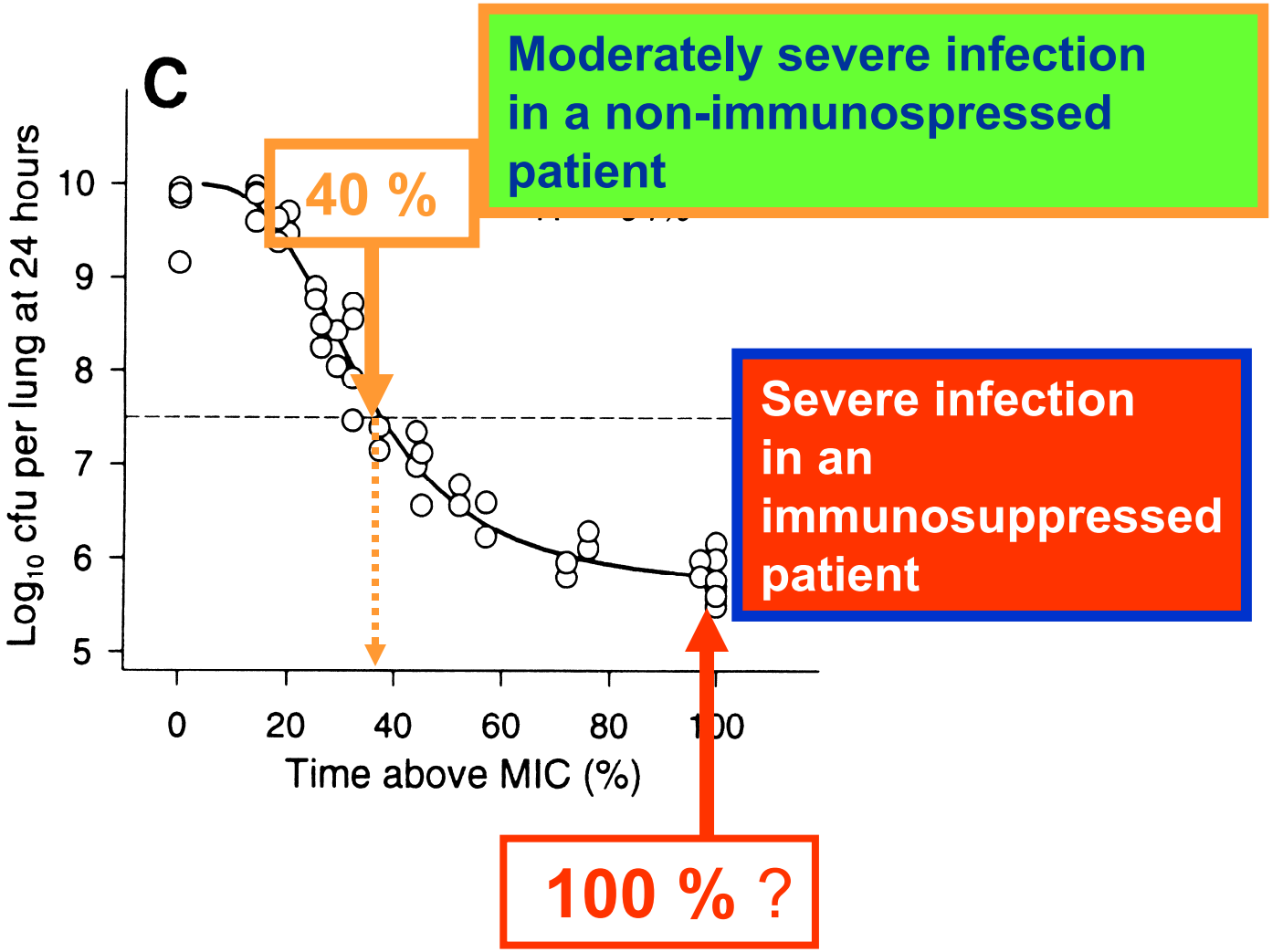
How much time above MIC ?

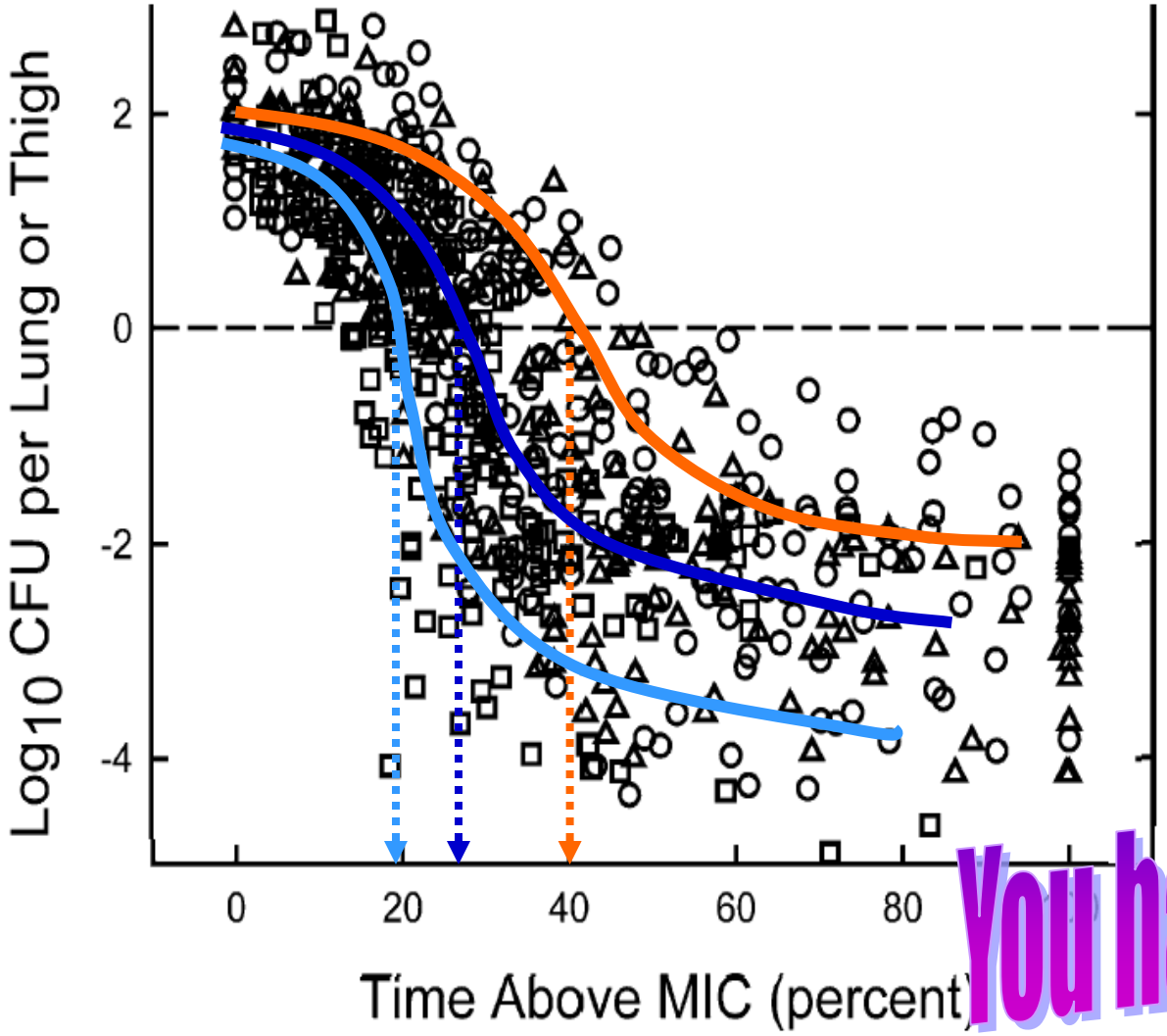


- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100 % - Maximal effect ?

Here is a proposal ...





The same for all β-lactams ?

You have seen this...

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

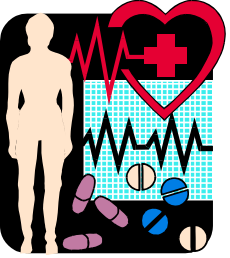
The same for all microorganims ?

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" ?

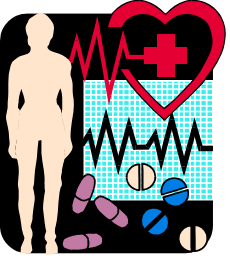
- "out of the package insert" PK data
- Monte-Carlo simulations and target attainment approaches



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

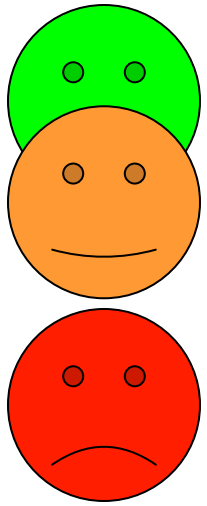
* Single administration unique; half-life 2h ; V_d = 0.2 l/kg



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

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**

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

EUCAST

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

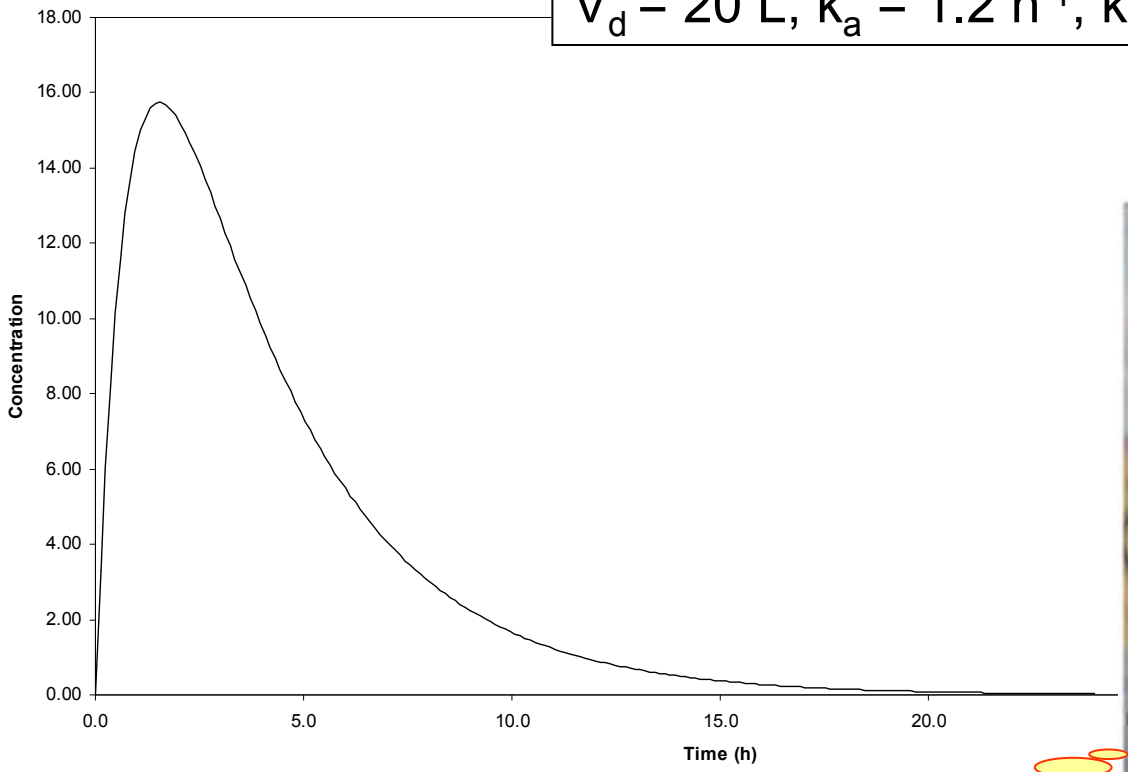
Why so low ?

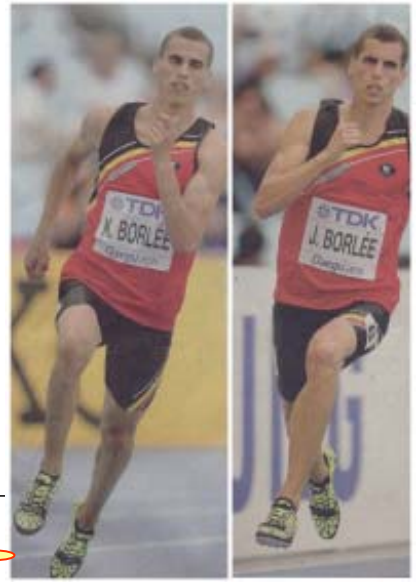
1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should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

But there are variation of PK in individuals...

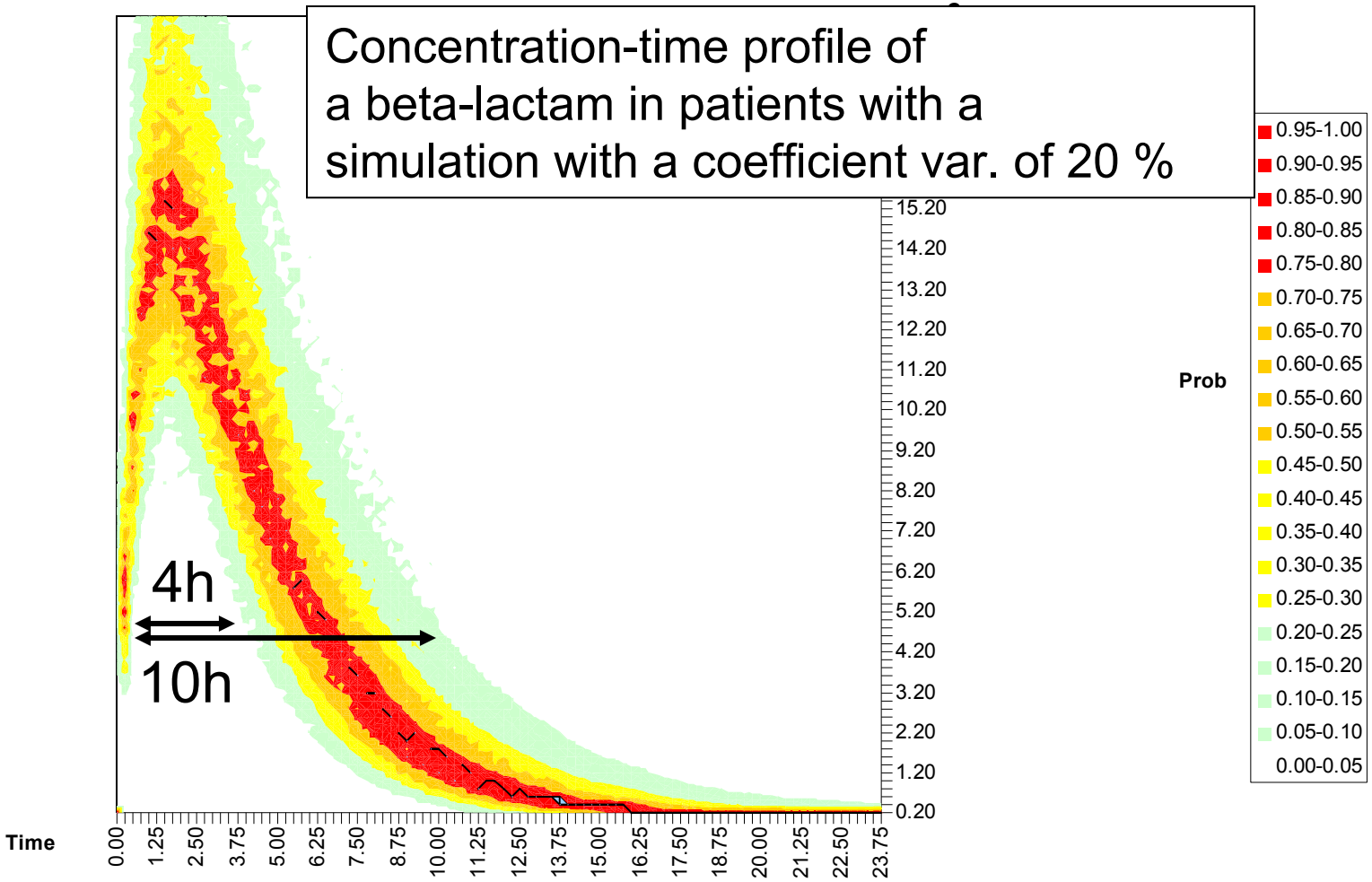
Concentration-time profile of a beta-lactam in volunteers
V_d = 20 L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}





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

Variation of PK in individuals...



Mouton. Int J Antimicrob Agents april 2002

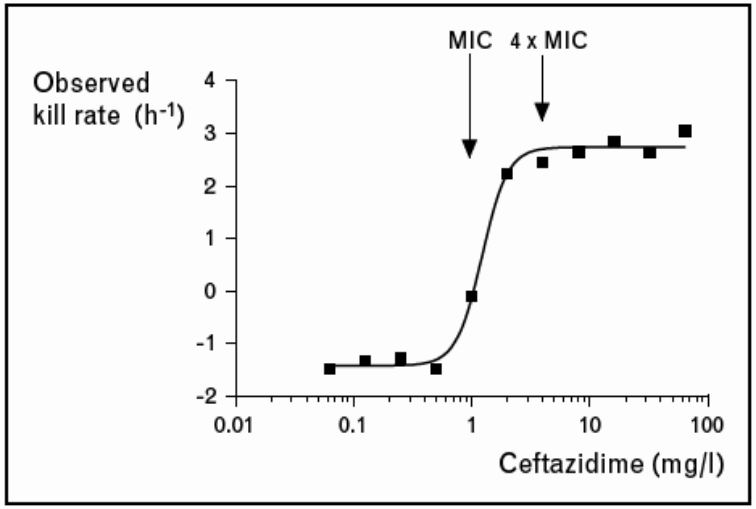
Monte Carlo Simulations in pk/pd

- Have estimates of PK parameter values and a measure of their dispersion (usually SD)
- Simulate PK curves
- use MIC distribution values in the the target population
- calculate a probability of attaining the desired target
- examine if this is feasible in clinical practice…

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

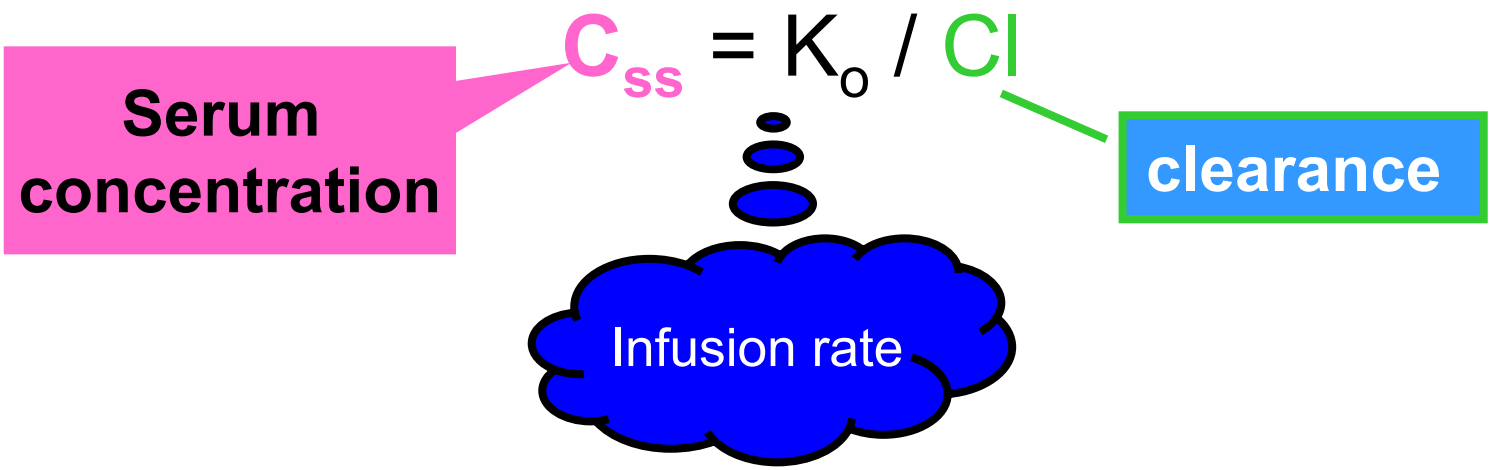


The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration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

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

Dose Calculations for continuous infusion

- Total Clearance estimate
- Elimination rate constant



- Volume of distribution for the initial loading dose (loading dose = C_{target} / Vd)

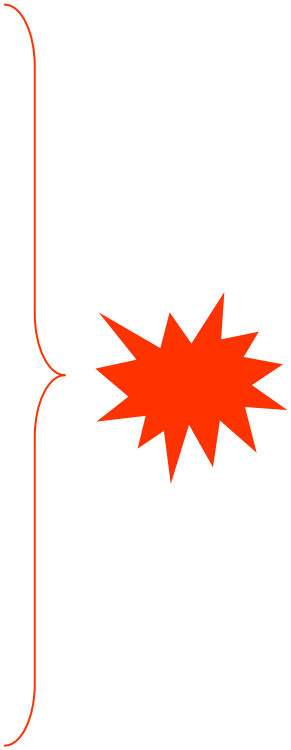
Continuous infusion of β-lactams: an overview…

- 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

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
- drug instability

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

temocillin > piperacillin > ceftazidime > cefepime …

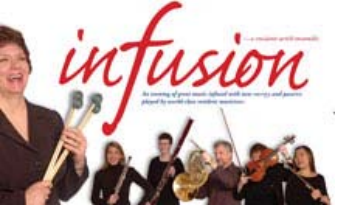
!! carbapenems are unstable (3-4h max.)

Continuous infusion with vancomycin ?

2. Time-dependent antibiotics with weak concentration effect but with post-antibiotic effect

AB	PK/PD Parameter	Goal
glycopeptides * tetracyclines macrolides linezolid streptogramins	AUC_{24h} / MIC	Daily dose optmization

What can YOU do ?…



Continuous infusion of vancomycin

Infusion will push music to its limits

- Will maxime antibiotic effects…
- Will allow for an easier administration scheme

Studies *	indications	conclusions
1. controlled studies with clinical endpoints		
9 [a]	VAP, Gram + osteomyelitis, other serious infections (ICU, open heart surgery)	equivalence (6) superiority (3)

* Only papers in 'peer-reviewed' journals

a Wysocki 2001; Rello 2005; Hutschala 2009; James1996; Wysocki 1995; Kitzis 2006; Vuangnat 2004; Boffi 2004; Di Filippo 1998

A typical example…

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

MARC WYSOCKI,[1*] FREDERIQUE DELATOUR,[2] FRANÇOIS FAURISSON,[2] ALAIN RAUSS, YVES PEAN,[4] BENOIT MISSET,[5] FRANK THOMAS,[6] JEAN-FRANÇOIS TIMSIT,[7] THOMAS SIMILOWSKI,[8] HERVE MENTEC,[9] LAURENCE MIER,[10] DIDIER DREYFUSS,[10] AND THE STUDY GROUP†

Medico-Surgical Intensive Care Unit[1] and Microbiology,[4] Institut Mutualiste Montsouris, Medico-Surgical Intensive Care Unit, Hôpital Saint-Joseph,[5] Medico-Surgical Intensive Care Unit, Hôpital de Diaconesses,[6] INSERM U13[2] and Infectious Diseases Critical Care Unit,[7] Hôpital Bichat-Claude Bernard, and Respiratory Intensive Care Unit, Hôpital de la Pitié-Salpêtrière,[8] Paris, Medico-Surgical Intensive Care Unit, Hôpital V. Dupouy, Argenteuil,[9] and Medical Intensive Care Unit, Hôpital Louis Mourier, Colombes,[10] France

Received 28 June 2000/Returned for modification 2 January 2001/Accepted 5 June 2001

AAC 45:2460-2467, 2001

- 119 critical care patients with multi-resistant organisms (bacteriemia, 35%; pneumonia, 45%).
- Microbiological and clinical outcomes,
- Safety, pharmacokinetics, ease of administration, cost …

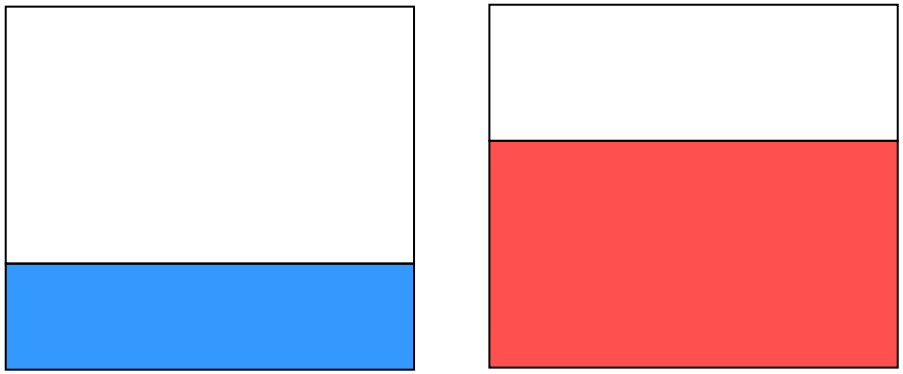
  ➔ clinical outcome and safety: equivalence
  ➔ target concentrations (20-25 mg/L) reached faster
  ➔ less samples needed for blood levels follow up
  ➔ AUC_{24h} less varaible
  ➔ costs: 23% less !

Continuous infusion of vancomycine in daily practice …

- Loading dose

$C_t = Dose/V_d$

$Dose = C_t \times V_d$



Vancomycine: target concentr. 25 µg/ml

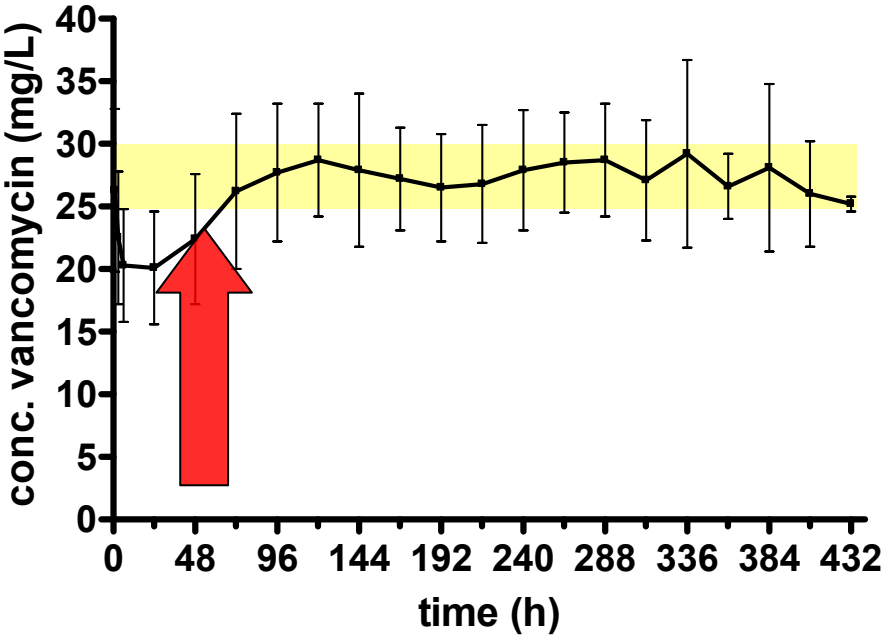
Vd (L/kg):	0.5	0.6	**0.7** *	0.8
dose (mg/kg):	12.5	15.0	**17.5**	20.0

* Vdss of vancomycin: 0.39 to 0.97 L/kg

Matzke et al. Clin Pharmacokinet. 1986 Jul-Aug;11(4):257-82.

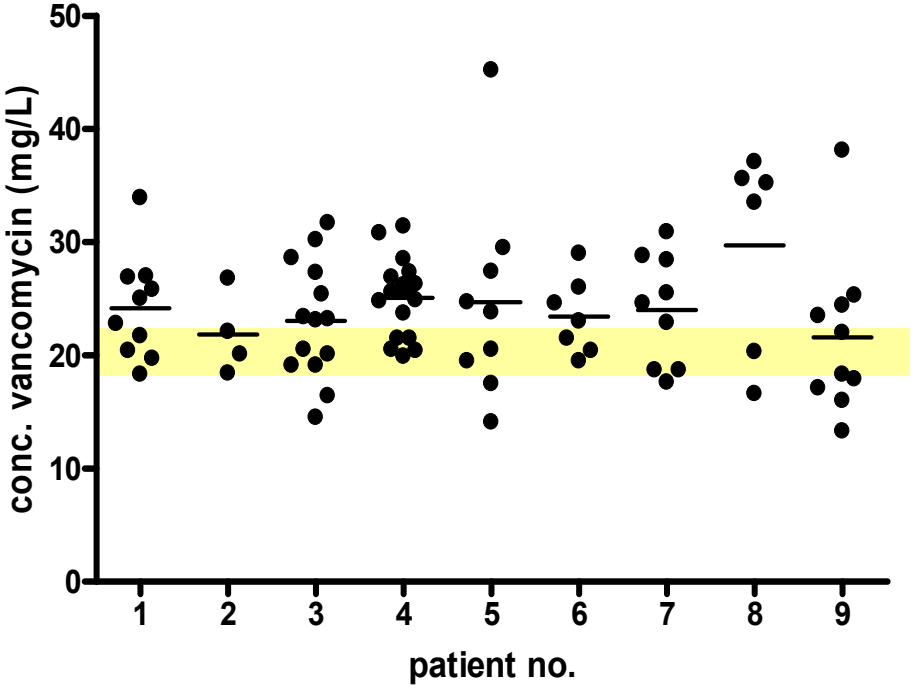
Results

concentration of vancomycin
as a function of the time
in patients treated with continuous infusion



The target concentration was reached after 48 h with the help of the clinical pharmacist…

variability of VAN concentrations
during continuous infusion
(example from typical patients)

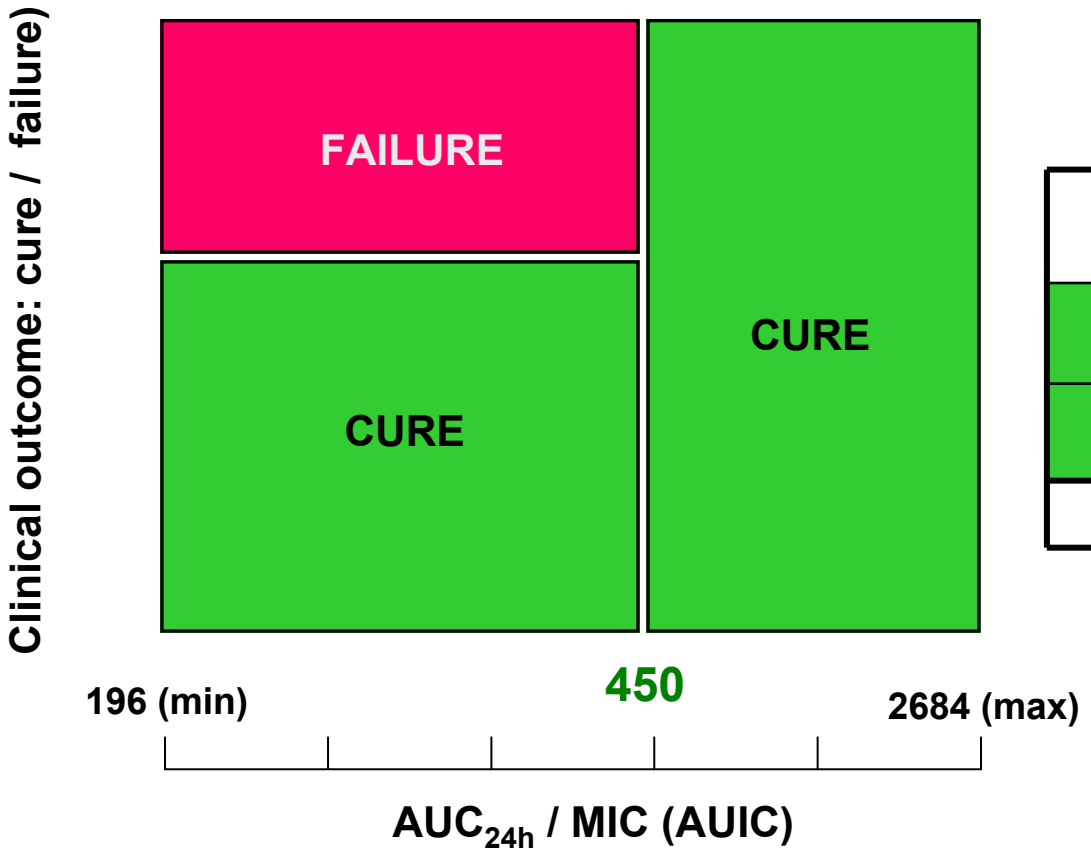


There was, however, a large inter- and intra-individual variability in vancomycin serum concentrations

Ampe *et al.*, in preparation

Results: efficacy

Correlation between AUC_{24h} / MIC (E-Test *) and clinical efficacy (n=19)

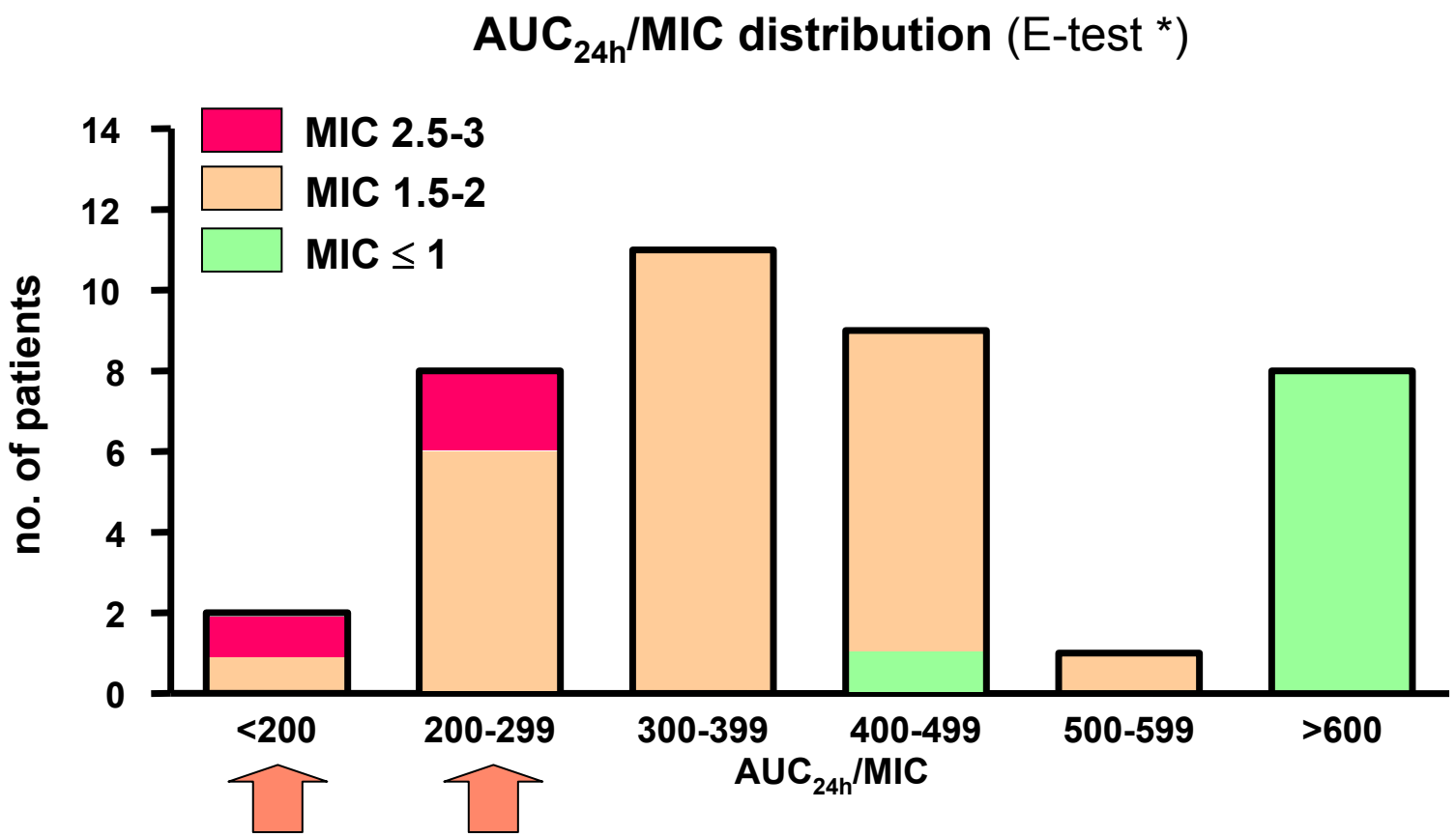


AUIC < 450	
cure	failure
5/9	4/9
P < 0.05	

Ampe *et al.*, in preparation

* E-test overestimates vancomycin MIC by ~ 1 dilution

Which were the isolates where we failed ?



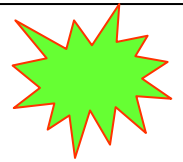
Low "target attainment" in patients with organisms with MIC's ≥ 1,5 mg/L

* E-test overestimates vancomycin MIC by ~ 1 dilution

Ampe *et al.*, in preparation

Conclusions … or what do you need with any antibiotic for "difficult to treat patients" or environments where susceptibility is no longer to its best… ?

- Obtain MIC distributions in YOUR clinical environment



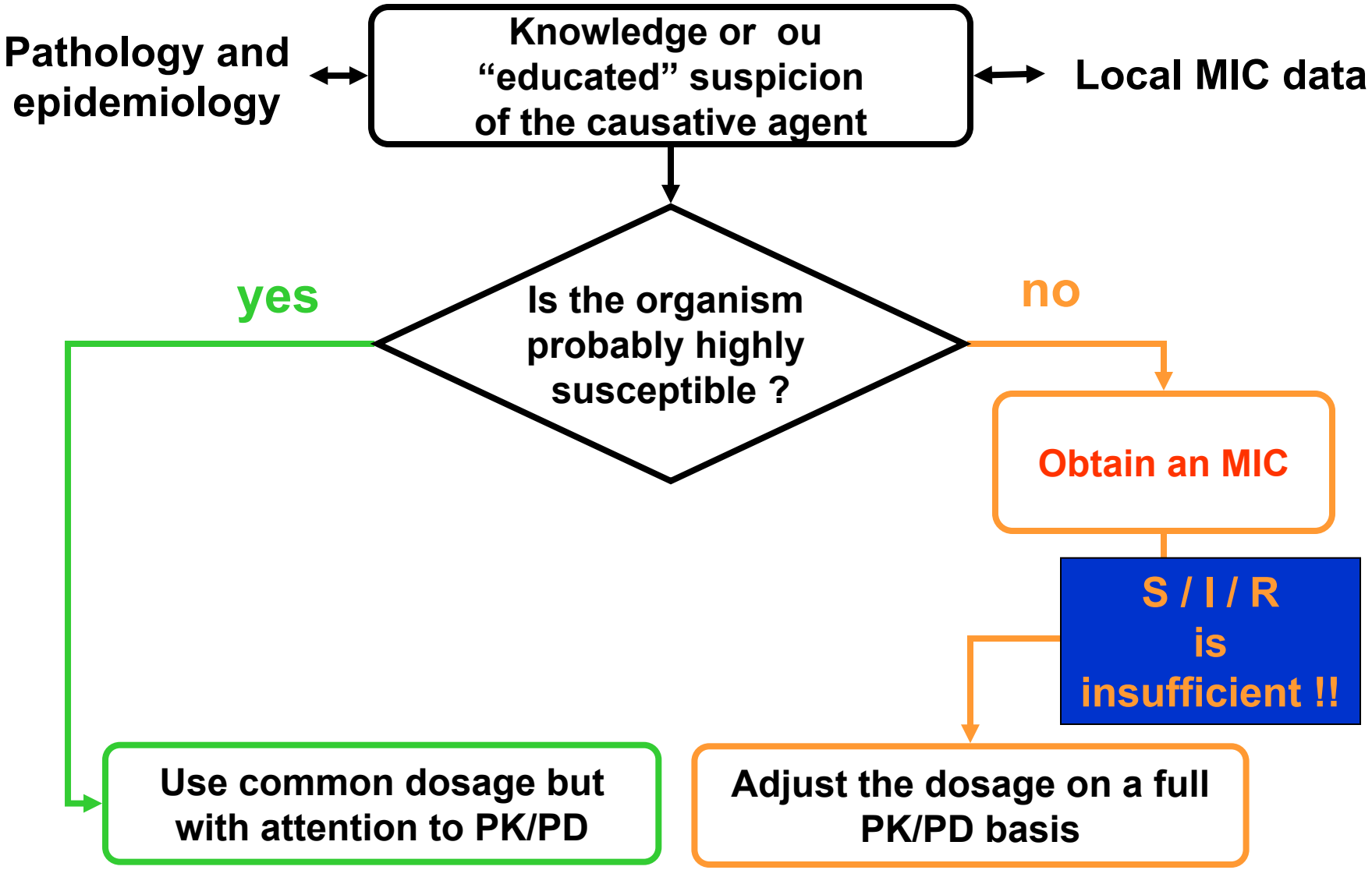
- On this basis, construct nomograms to examine which doses (AUC *, peak *) and/or frequency of administration (time *) are necessary for the MIC you are interested in ...

- Examine whether this is feasible for YOUR patients… with the drug you want to use

- The situation may be critical for **"new"** antibiotics (telavancin, doripenem, …) for which the EUCAST/FDA breakpoints are close to the upper limit of the wild type distribution…

* get this information from your pharmacist, the literature, and/or the Industry …

A clinical algorithm or a path to success...



A clinical algorithm (follow.) ...