Towards clinical Applications of PK-PD

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with many things borrowed from

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& 46th Infectious Diseases Society of America
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The problem ...

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

The problem ...

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

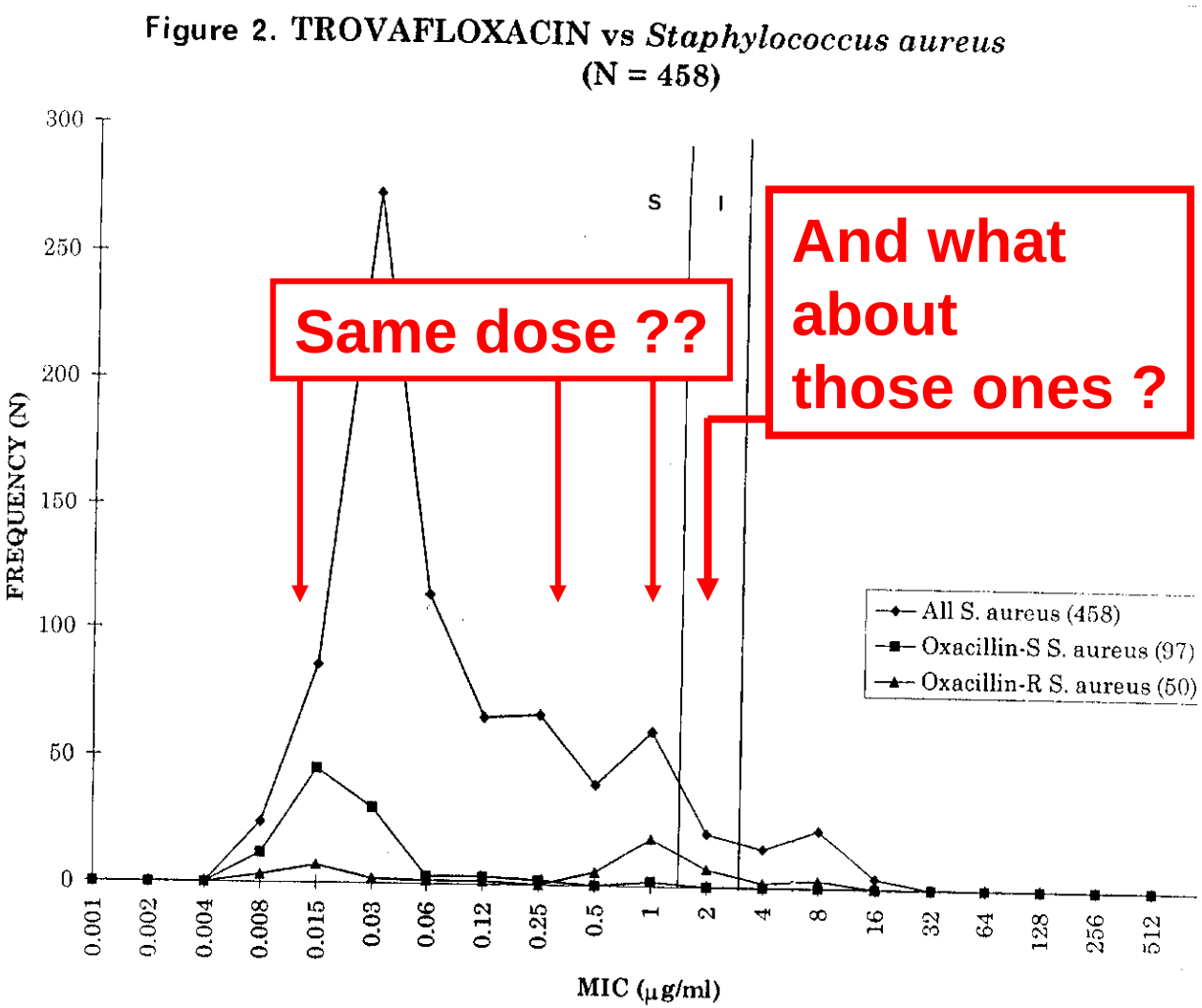
afssaps – Version 1 - Juin 2002

CEFTAZIDIME

Les concentrations critiques séparent les souches sensibles des souches de sensibilité intermédiaire et ces dernières, des résistantes :

S ≤ 4 mg/l et R > 32 mg/l

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

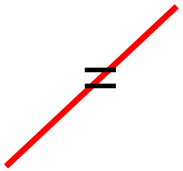


Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...

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

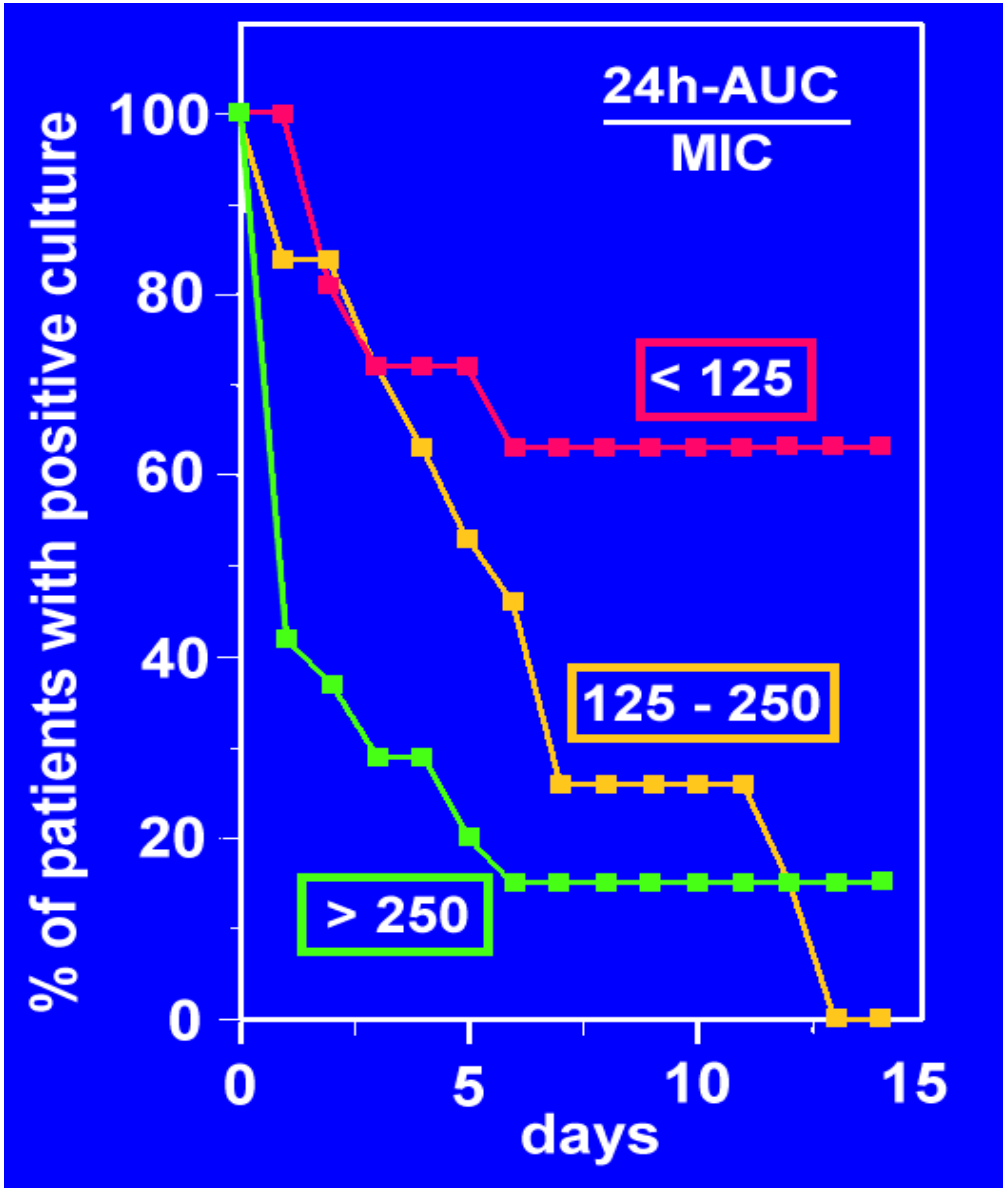
how much and for all ?

Exercice 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

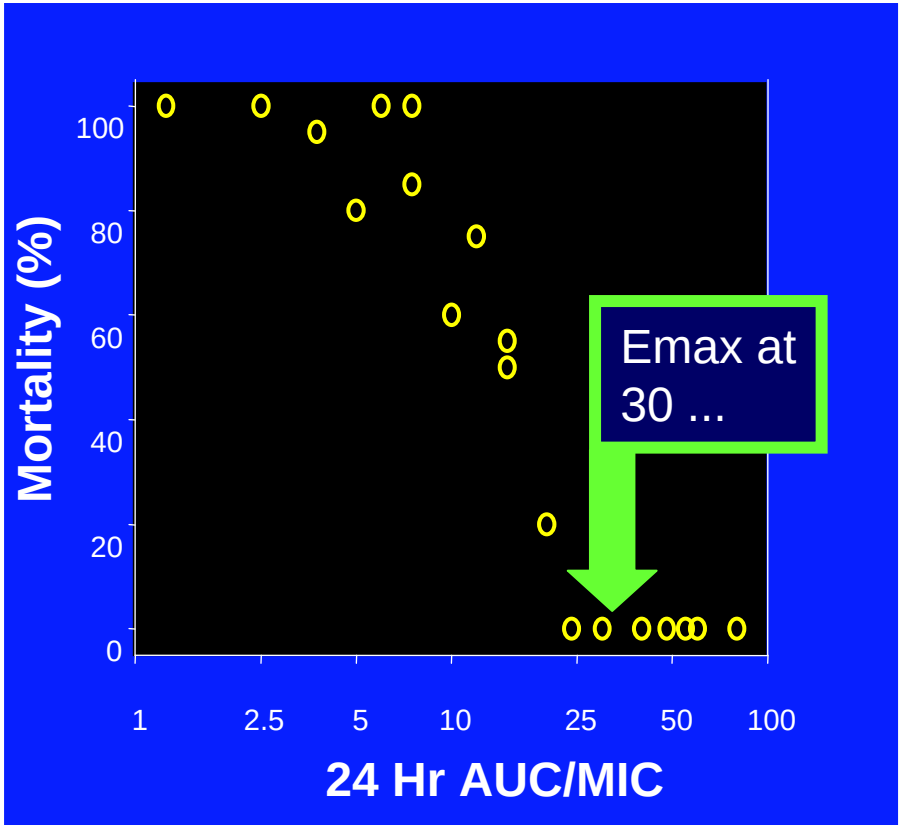
AUC/MIC_{24h} = 125 : a magical number??

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

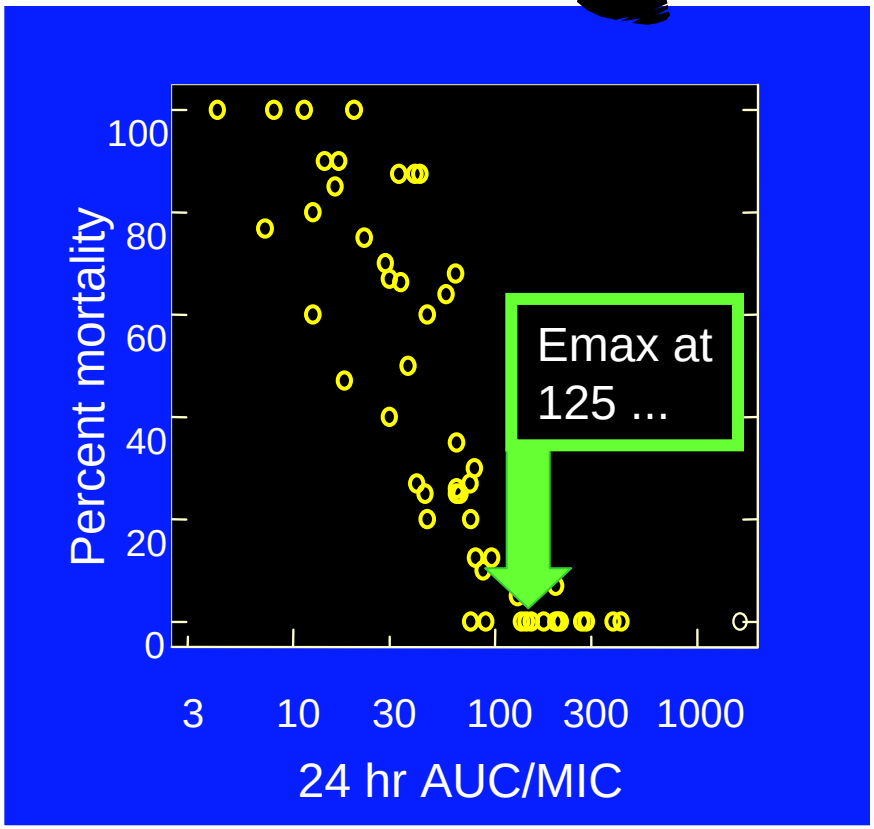
- a large MIC
- or a too low dosage
  (AUC is proportional to the dosage)
- was derived from studies on Gram-negative infections

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

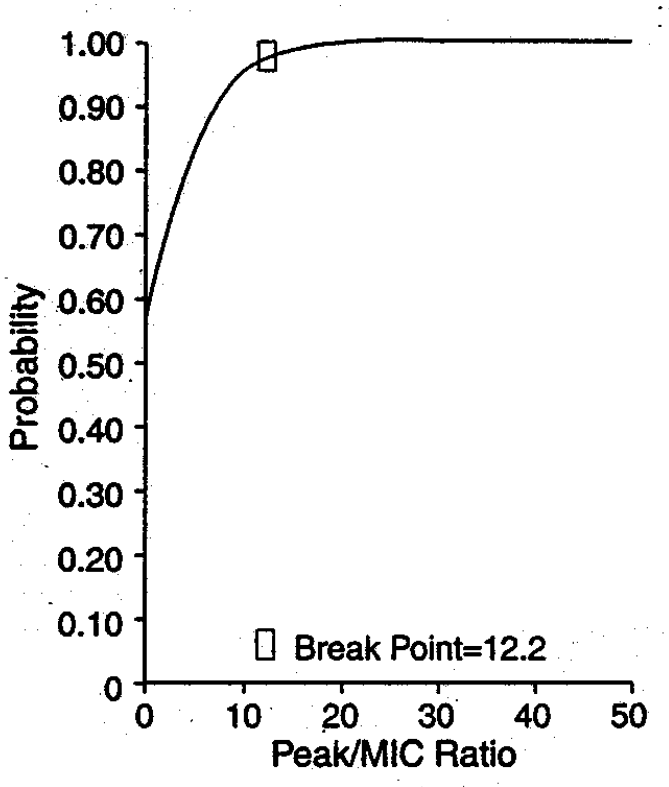
Asthma

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**

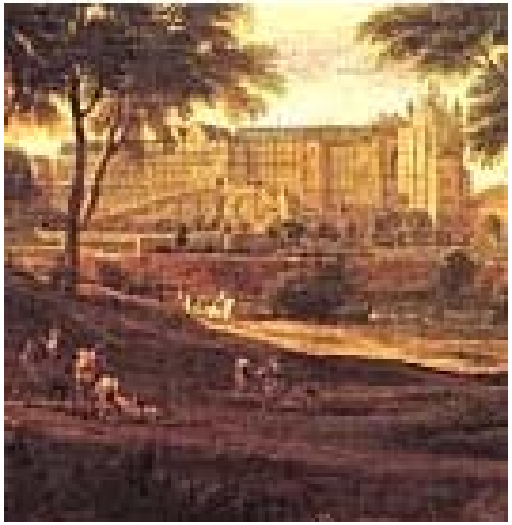
So, let us accept values with some degree of precaution with fluoroquinolones

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 sensitivity(mg/L)			
	Dosage (mg/24h)	**AUC/MIC*** (24h)	**peak / MIC****	**former NCCLS Bkpts**
norfloxacin	800	**0.1**	**0.2**	**< 4**
ciprofloxacin	500	**0.1**	**0.2**	**< 1**
ofloxacin	400	**0.2-0.4**	**0.3 - 0.4**	**< 2**
levofloxacin	500	**0.4**	**0.4 - 0.5**	**< 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...

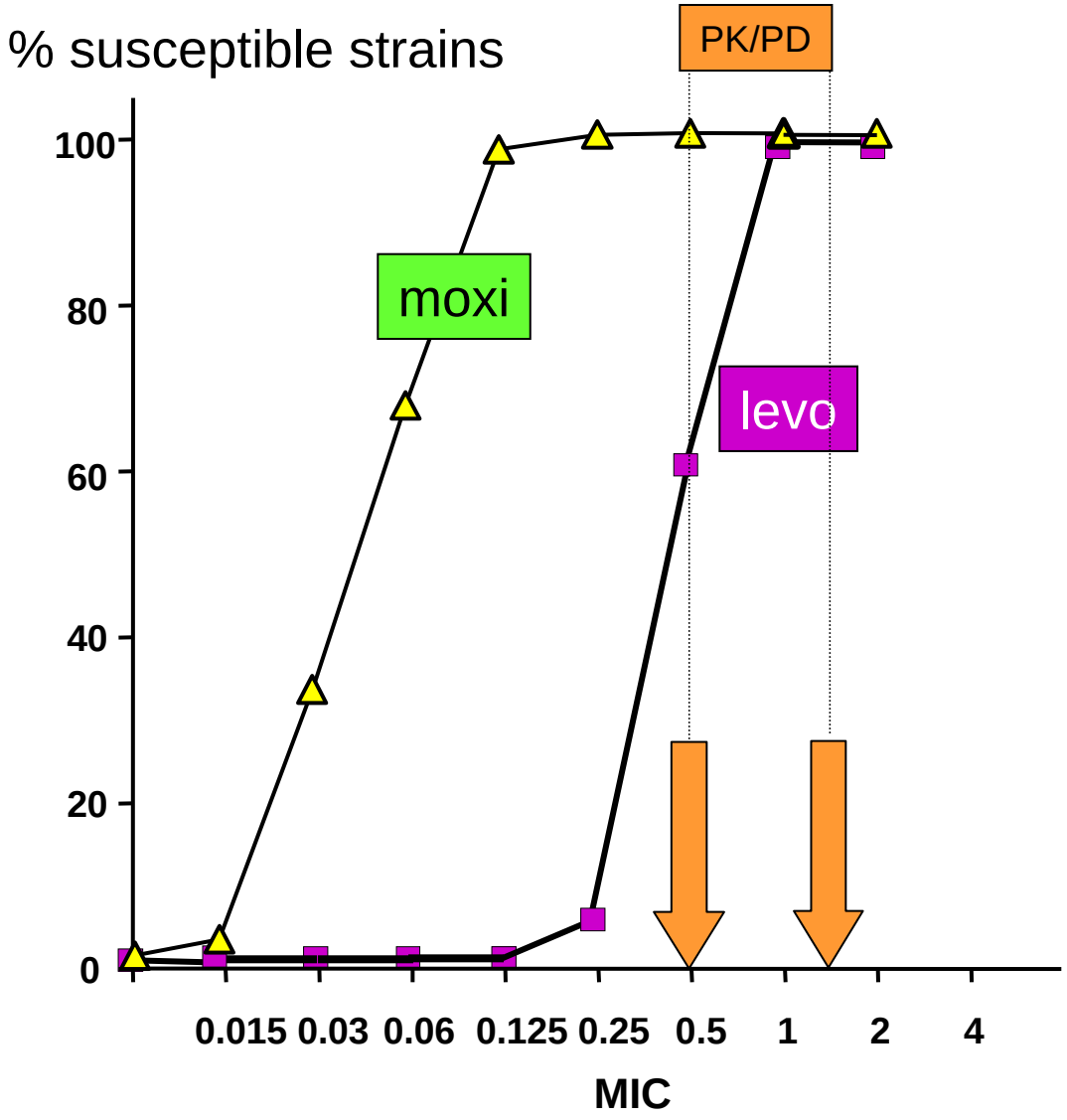
Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75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

- 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

Can you do that in another country ?

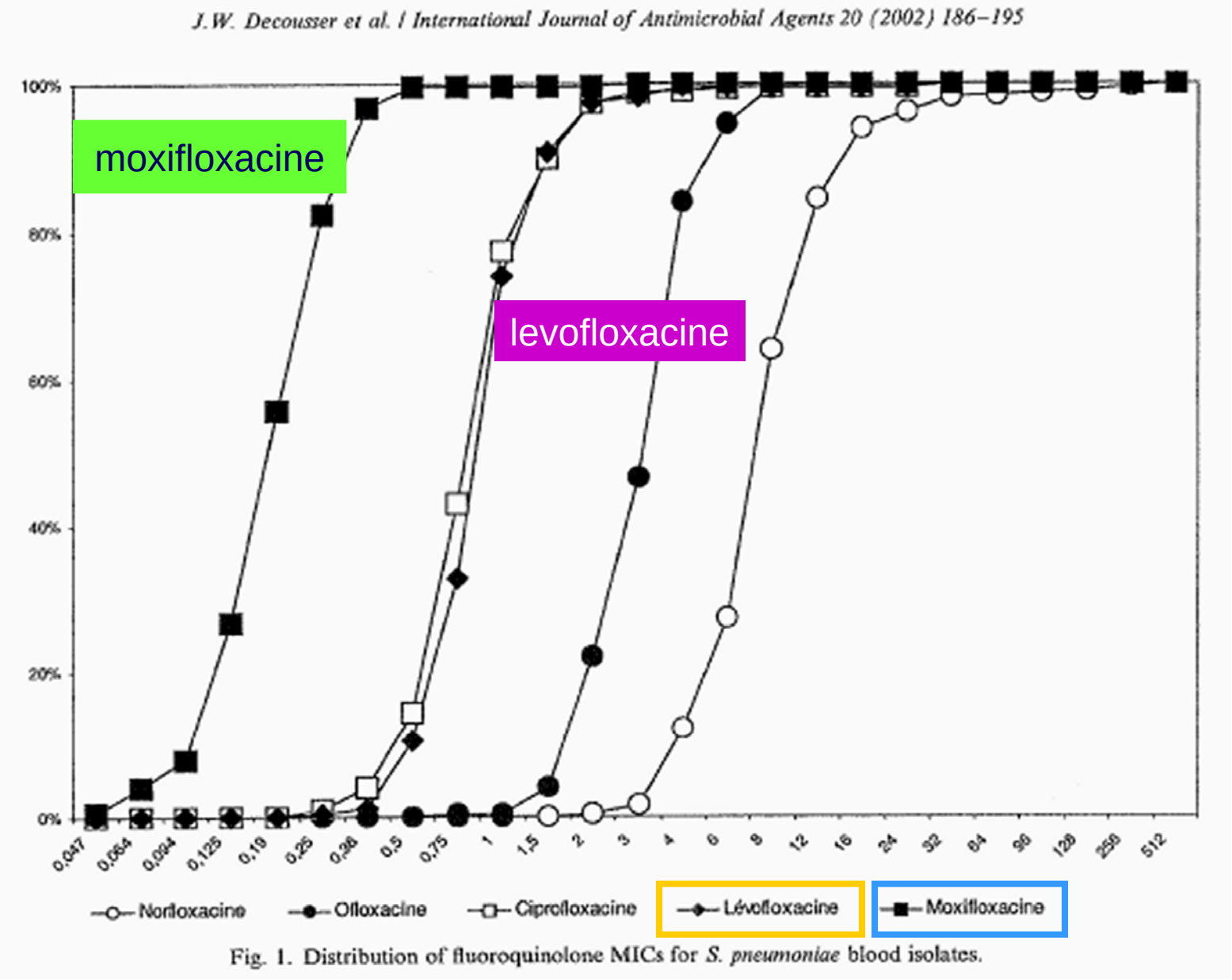


Fig. 1. Distribution of fluoroquinolone MICs for *S. pneumoniae* blood isolates.

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 harmonise 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

Fluoroquinolones - EUCAST clinical MIC breakpoints 2006-06-20 (v 2.2)

Fluoroquinolone[2] Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)											Non-species related breakpoints[1] S≤/R>
		Entero-bacteriaceae[3]	*Pseudo-monas/*	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*[5]	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.menin-gitidis*[8]	*Gram-negative anaerobes*	
Ciprofloxacin	RD	0.5/1	0.5/1	1/1[4]	1/1[5]	--	--	0.125/2	0.5/0.5[7]	0.03/0.06	0.03/0.06	--	0.5/1
Levofloxacin	RD	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1[7]	IE	IE	--	1/2
Moxifloxacin	RD	0.5/1	--	--	0.5/1	--	0.5/1	0.5/0.5	0.5/0.5[7]	IE	IE	IE	0.5/1
Norfloxacin	RD	0.5/1	--	--	--	--	--	--	--	IE	--	--	0.5/1
Ofloxacin	RD	0.5/1	--	--	1/1[3]	--	--	0.125/4	0.5/0.5[7]	0.12/0.25	IE	--	0.5/1

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).
2. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by national breakpoint committees.
3. *Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case reports of poor response with other *Salmonella* species.
4. The S/I breakpoint has been increased from 0.5 to1 mg/L to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Acinetobacter* species
5. *Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
6. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant. *Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae*.
8. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
RD =Rationale document listing data used for setting EUCAST breakpoints.

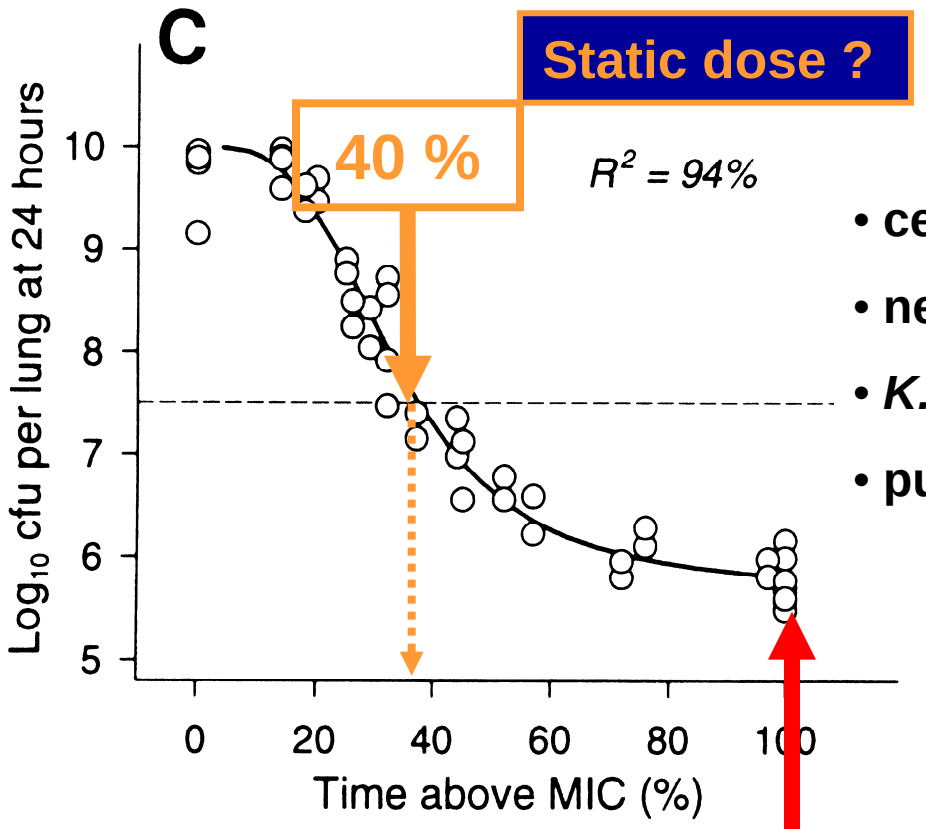
All EUCAST data are freely available at http://www.eucast.org

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 ?

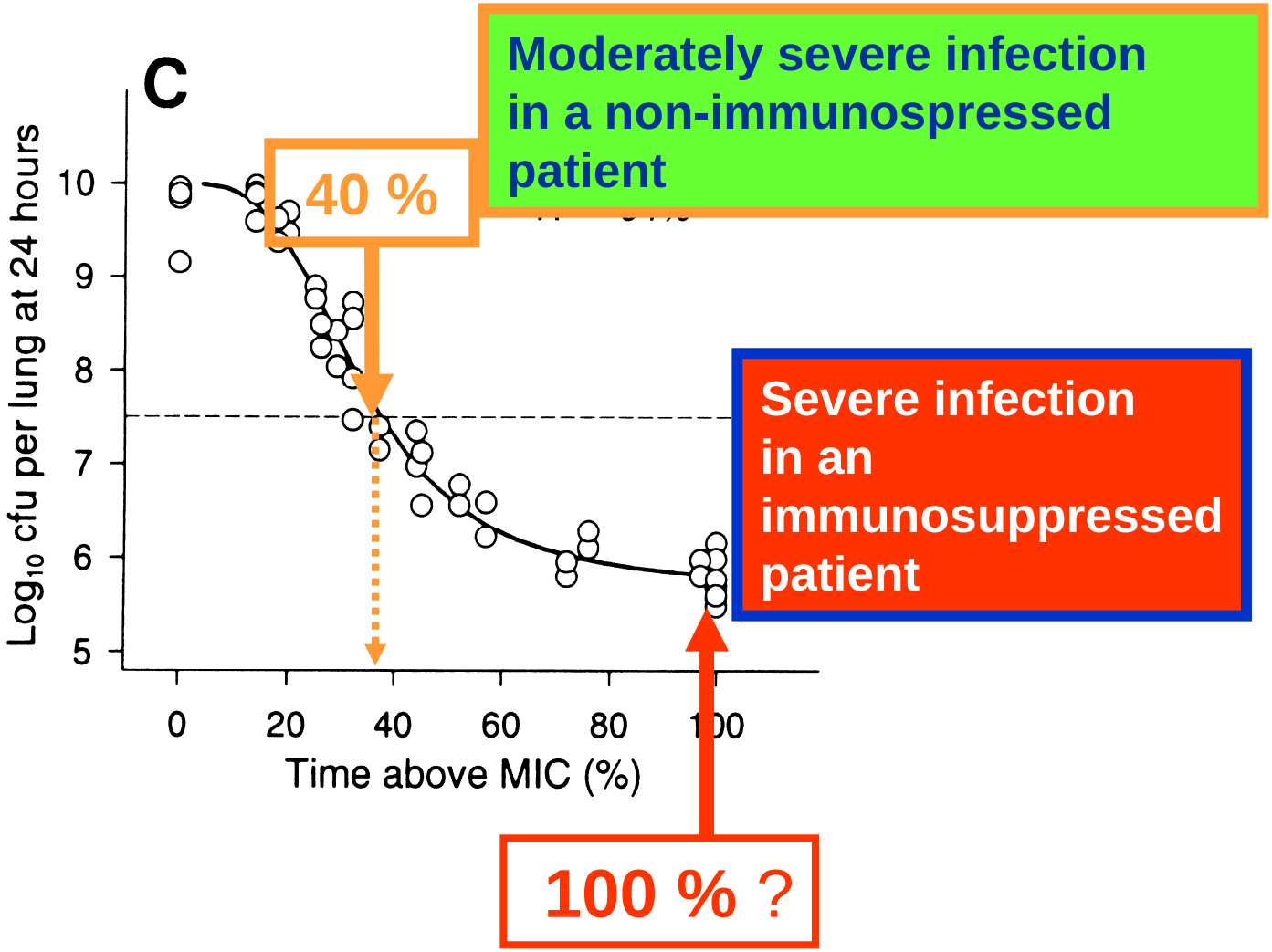
How much time above MIC ?

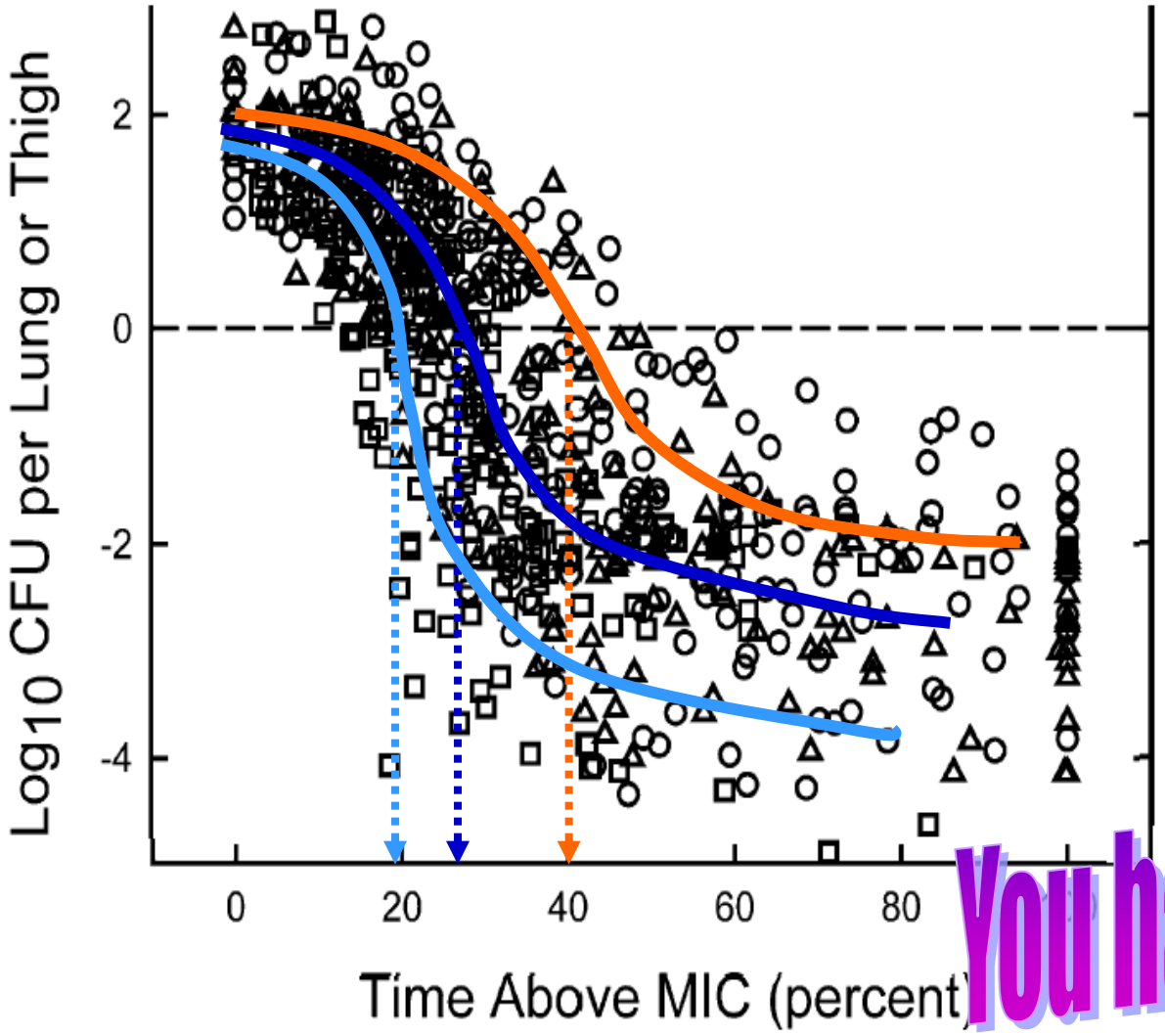


- **cefotaxime**
- **neutropenic mice**
- ***K. pneumoniae***
- **pulmonary infection**

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

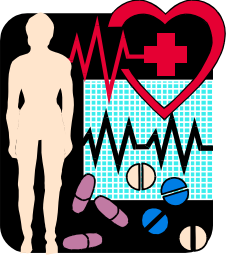
The same for all microorganims ?

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

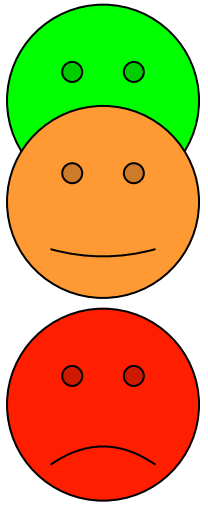
time (hours)	serum concentration for 0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

* 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 clinical MIC breakpoints - cephalosporins - Mozilla Firefox

File Edit View Go Bookmarks Tools Help

http://www.srga.org/eucastwt/MICTAB/MICcephalosporins.html

Cephalosporins Click on antibiotic name to see wild type MIC distributions.		Species-related breakpoints (S≤/R>)							
		Enterobac-teriaceae[2]	*Pseudo-monas*[3]	*Acineto-bacter*	*Staphylo-coccus*[4]	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influen M.catarrh*
Cefazolin	RD	--	--	--	note[4]	--	--	--	--
Cefepime	RD	1/8	8/8	--	note[4]	--	0.5/*0.5*[6]	1/2	0.25/*0.2*
Cefotaxime	RD	1/2	--	--	note[4]	--	0.5/*0.5*[6]	0.5/2[6]	0.12/*0.1*
Ceftazidime	RD	1/8	8/8	--	--	--	--	--	--
Ceftriaxone	RD	1/2	--	--	note[4]	--	0.5/*0.5*[6]	0.5/2[6]	0.12/*0.1*
Cefuroxime	RD	8/8[5]	--	--	note[4]	--	0.5/*0.5*[6]	0.5/1	1/2

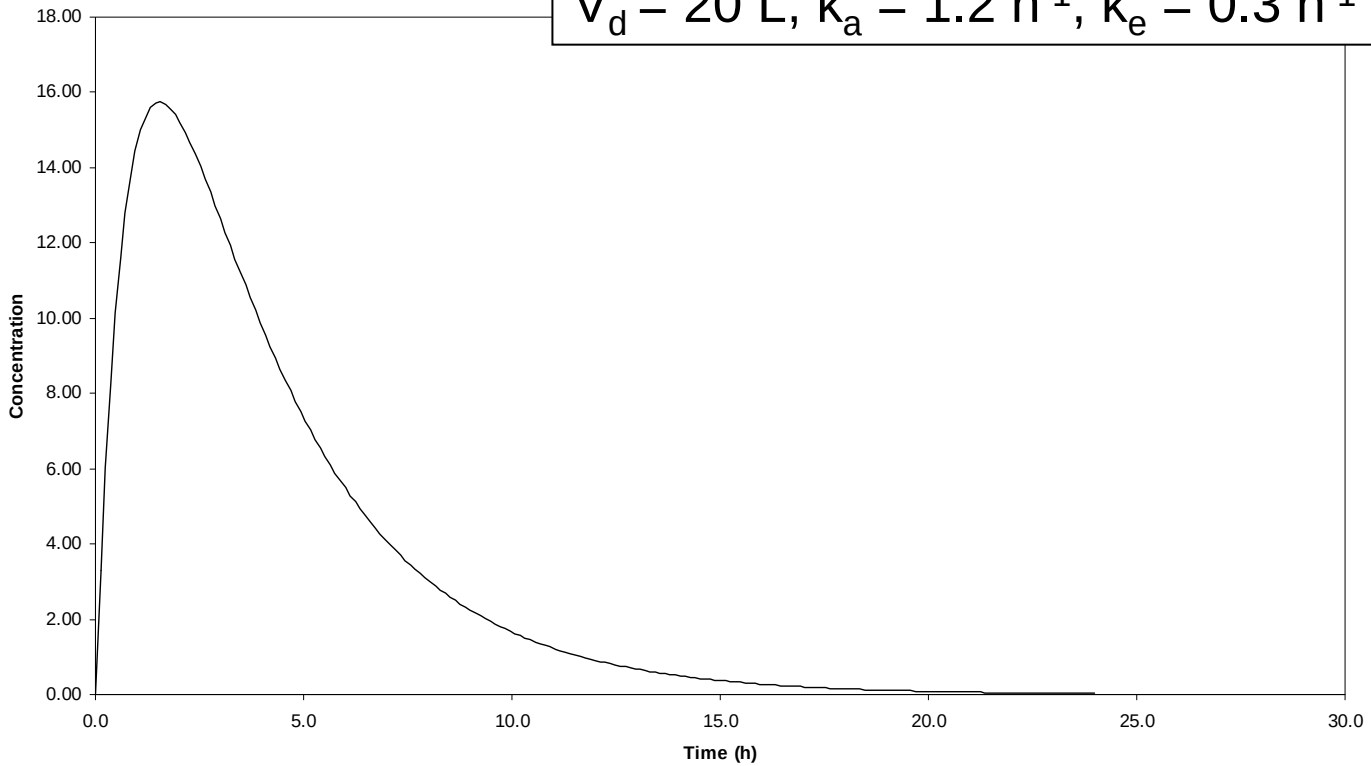
1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriacae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.
6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
RD = rationale document listing data used by EUCAST for determining breakpoints.

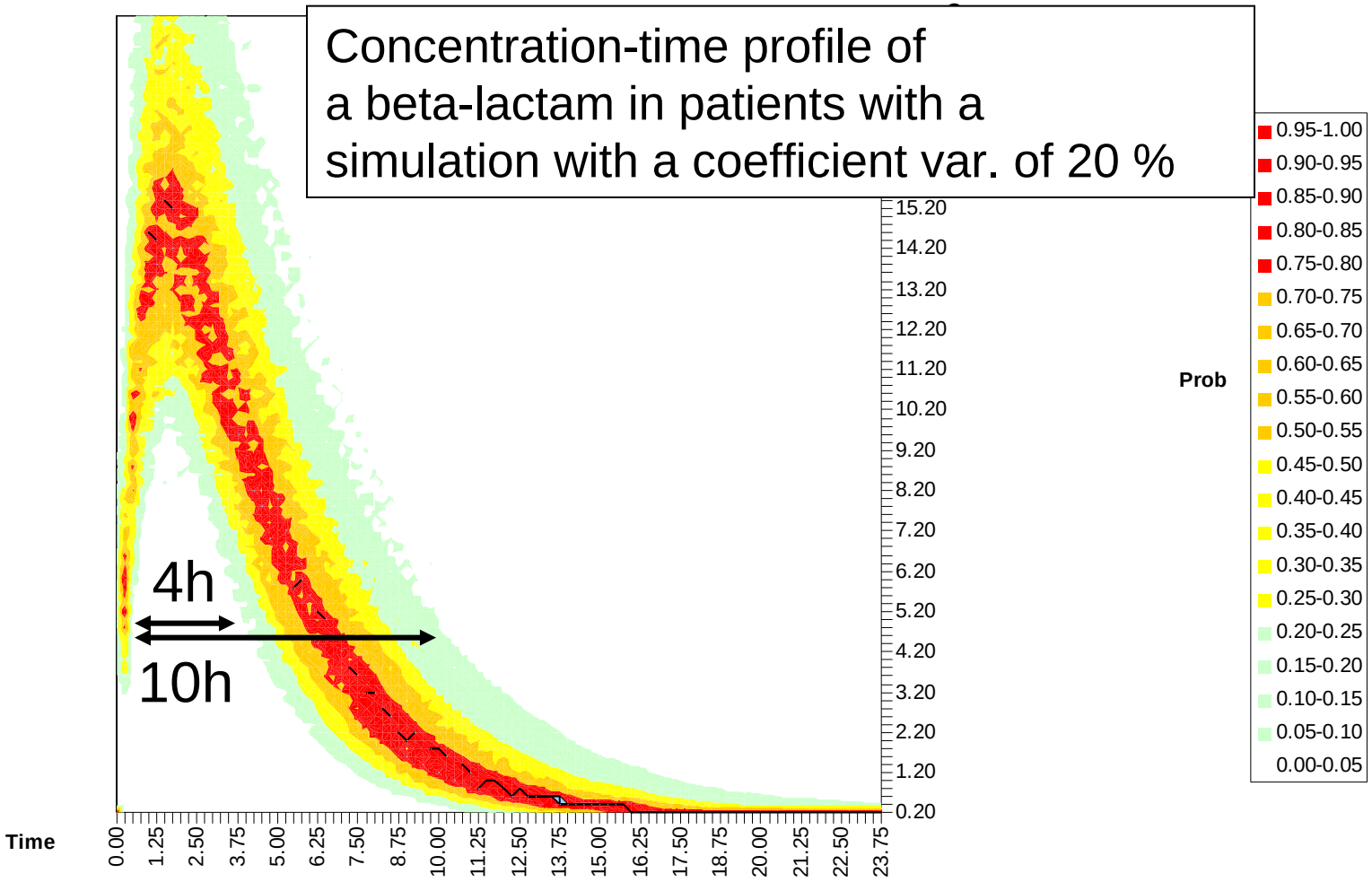
Done Now: Partly Cloudy, 7° C Mon: 12° C Tue: 10° C

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}



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…

Monte Carlo Simulations in PK/PD: application to ceftobiprole

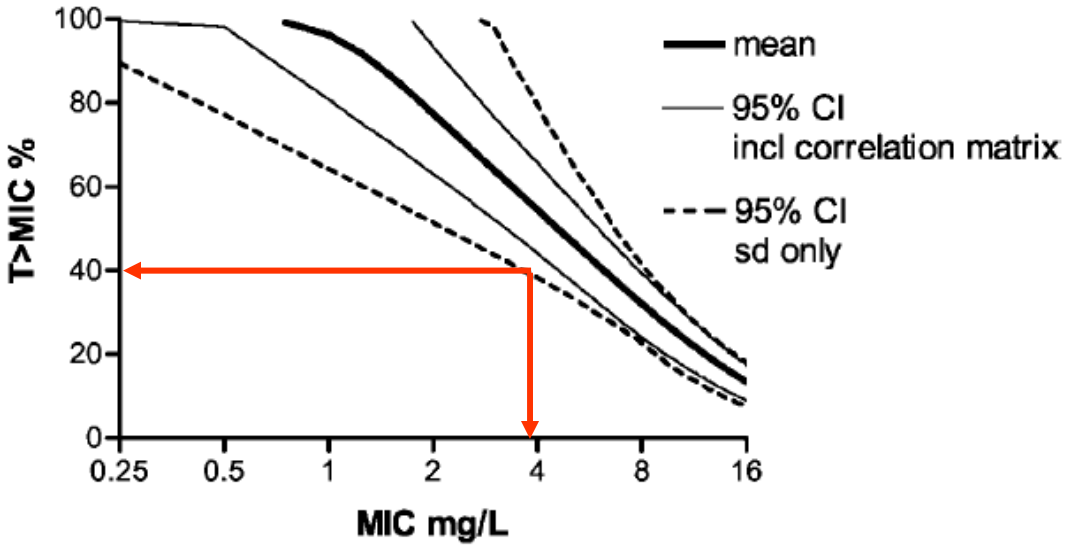


FIG. 4. TARs and 95% CI (thus, attainment rates at 2.5 and 97.5%, respectively) as obtained with simulations using means and SDs with or without the full covariance matrix.

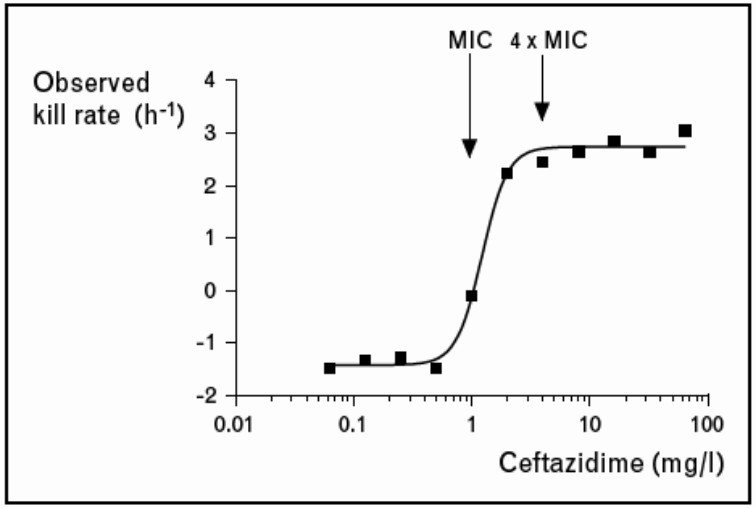
ceftobiprole should be effective (static) up to an MIC of 4 mg/L

Mouton et al. Antimicrob Agents Chemother. 2004; 48:1713-8.

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

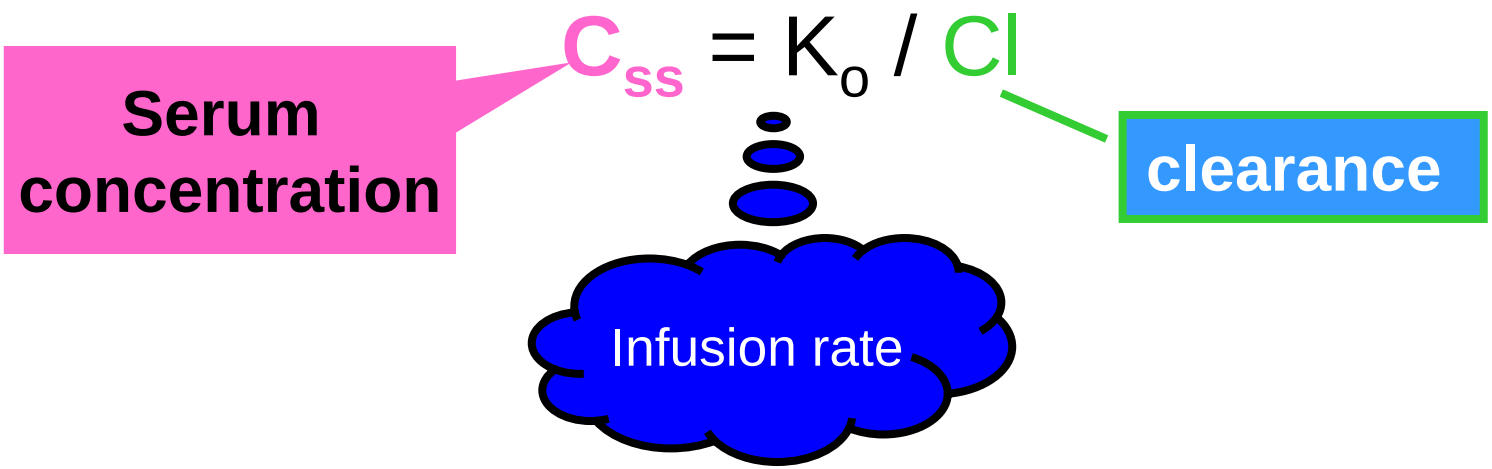


The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration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

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

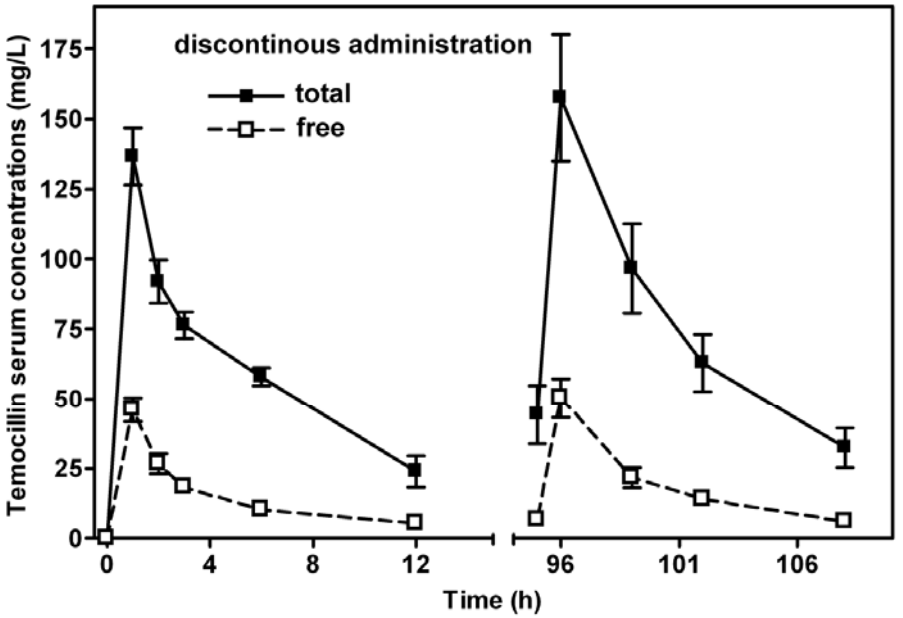
Dose Calculations for continuous infusion

- Total Clearance estimate
- Elimination rate constant

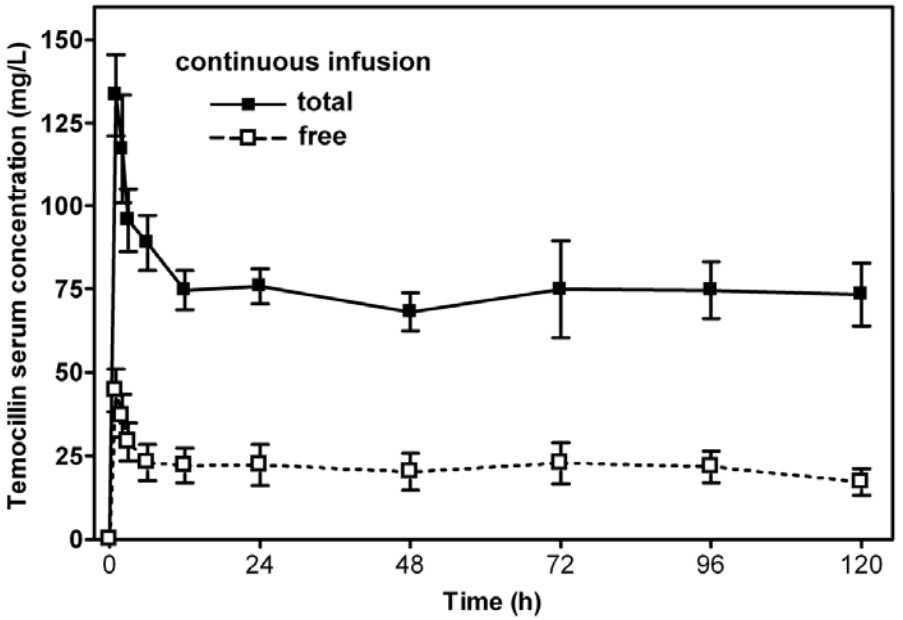


- Volume of distribution for the initial loading dose (loading dose = C_{target} / Vd)

An example of application with temocilin (a stable, narrow spectrum β-lactam with high protein binding): comparison with BID



- dose:
  - 2 g/12h *vs.*
  - 2 g loading dose followed by 4g over 24h
- assay: free and total drug

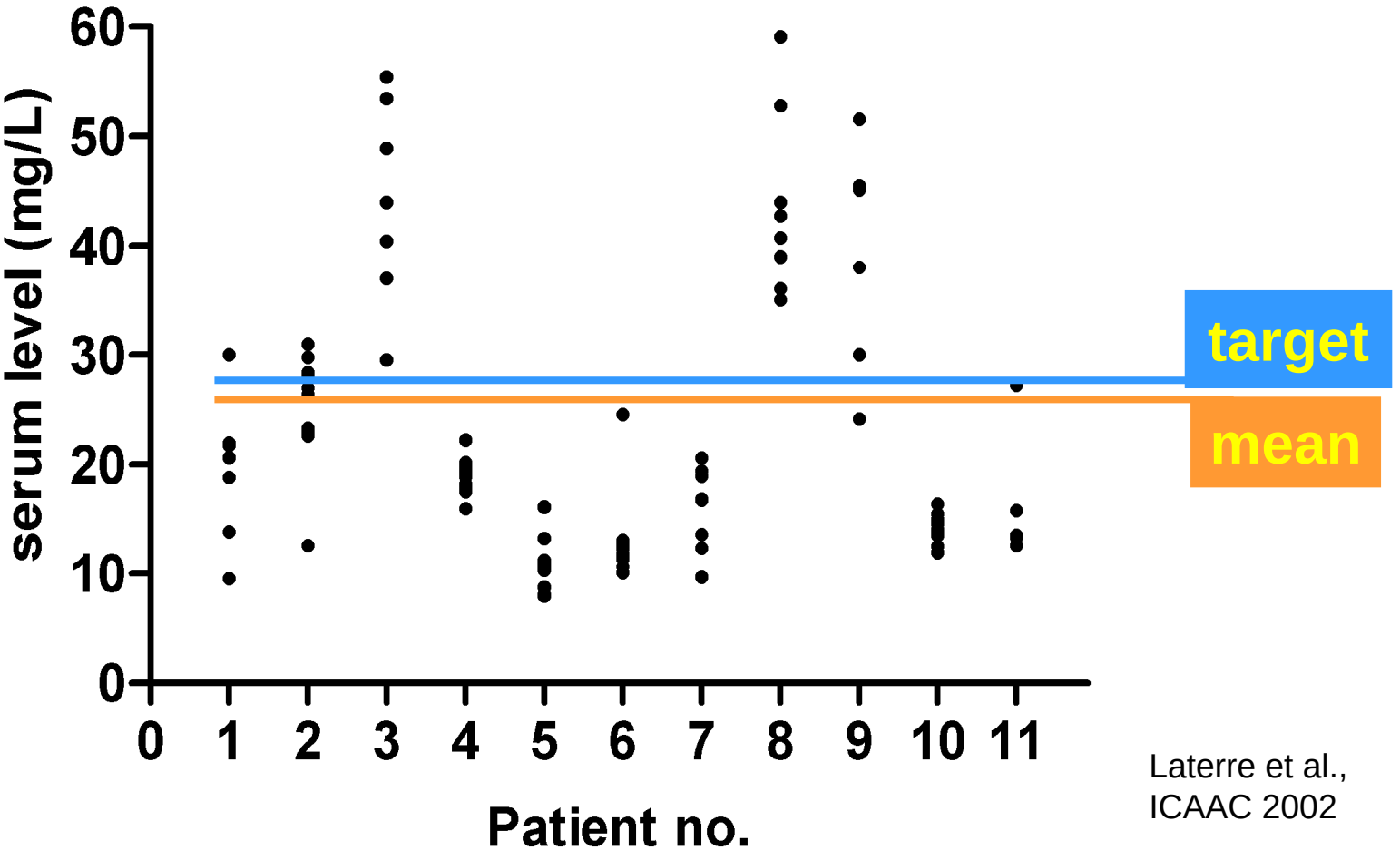


De Jongh et al., submitted

Problems with continuous infusion ...

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

Ceftazidime concentrations in ICU patients (successive determinations) during continuous infusion (4 g/day)



Laterre et al., ICAAC 2002

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.)

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

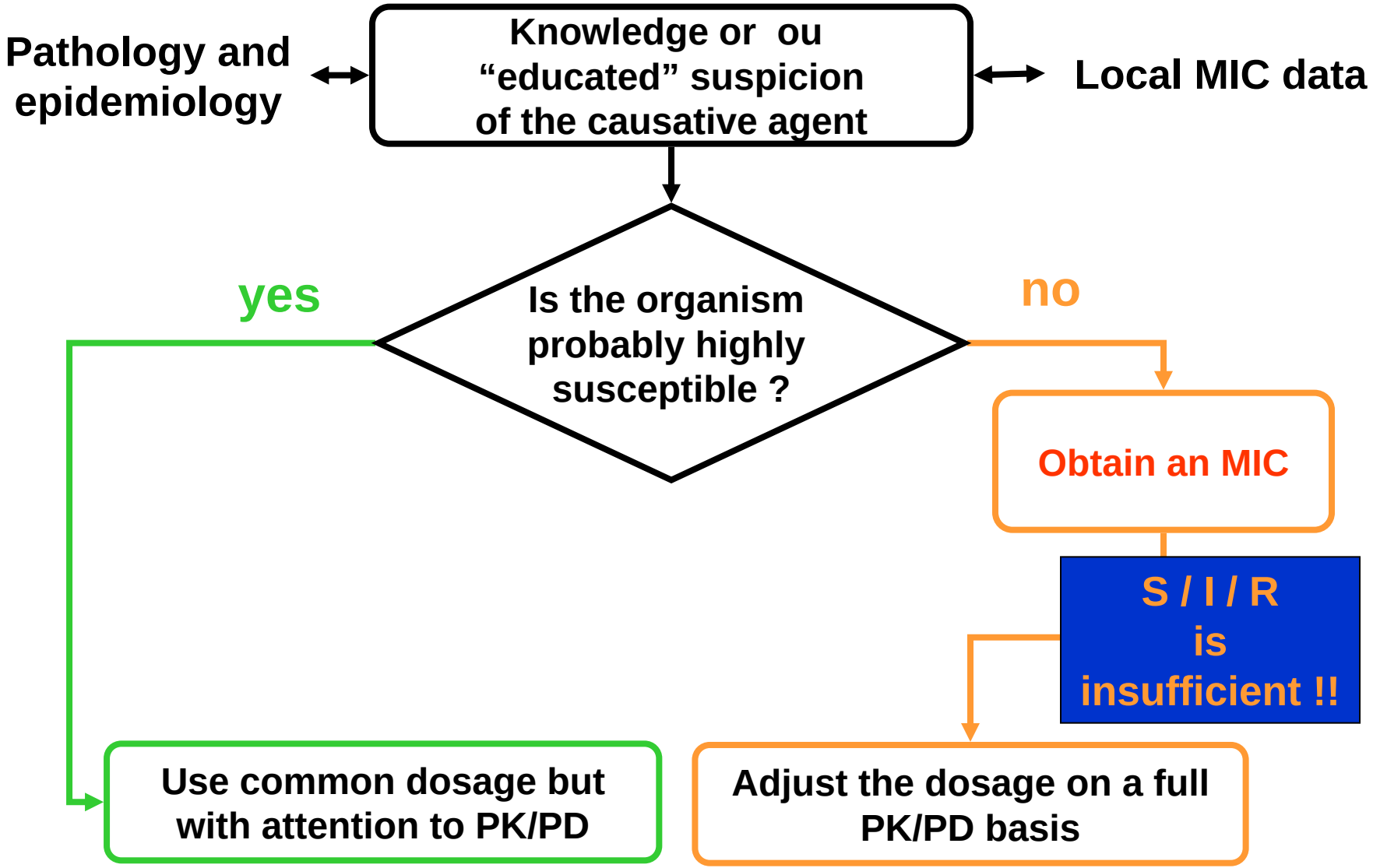
- Obtain MIC distributions in YOUR clinical environment

- 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… <u>with the drug you want to use</u>

* get these informations from your pharmacist and/or the Industry …

A clinical algorithm or a path to sucess...



A clinical algorithm (follow.) ...