Use of antibiotics in clinical practice:
Two selected topics:
1. Pharmacodynamics/ Pharmacokinetics (including breakpoints)
2. Guidelines (example: Community acquired pneumonia)

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With the support of *Wallonie-Bruxelles-International*

Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillins

Ann. Rev. Biochem. 1979. 48:73–101

USE OF MODEL ENZYMES IN THE DETERMINATION OF THE MODE OF ACTION OF PENICILLINS AND Δ^3-CEPHALOSPORINS[1]

Jean-Marie Ghuysen, Jean-Marie Frère, Mélina Leyh-Bouille, Jacques Coyette, Jean Dusart, and Martine Nguyen-Distèche

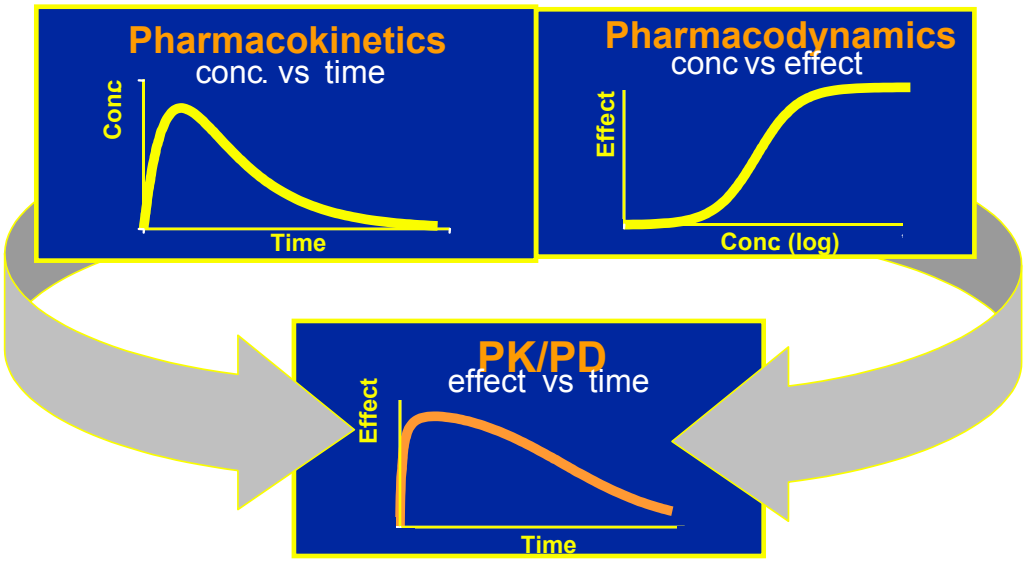
Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

and died from invasive pneumococcal infection …

http://www.cip.ulg.ac.be/newsite/pdf/jmghuysen.pdf

What is my goal ?

- Discuss with you two ways to improve antibiotic treatment (with pneumonia as an example)



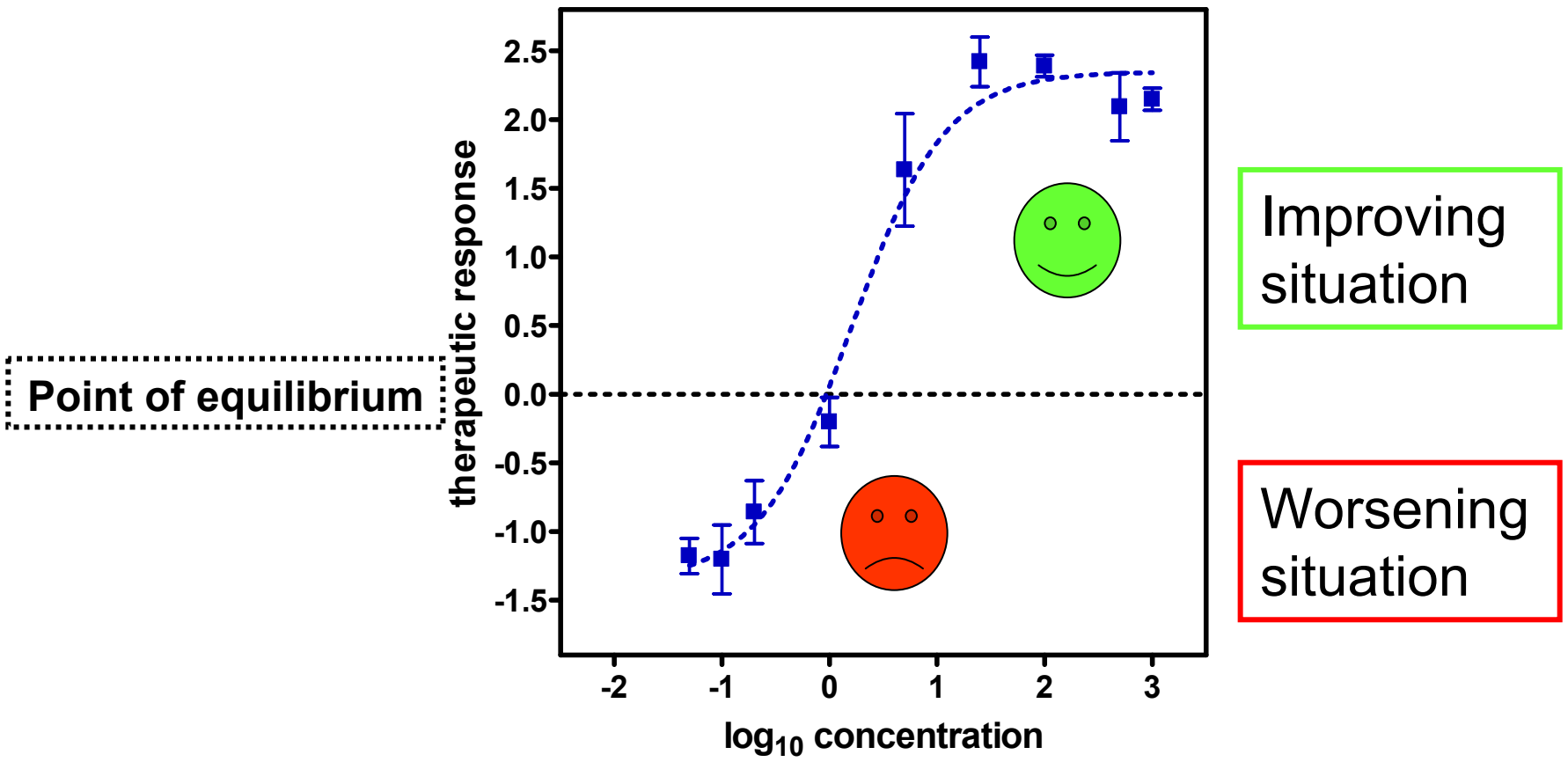
GUIDELINES

- Give a few comments about usefulness of a clinical pharmacist (example with vancomycin)

Part 1: Optimising treatment based on PK/PD principles

In a nutshell…

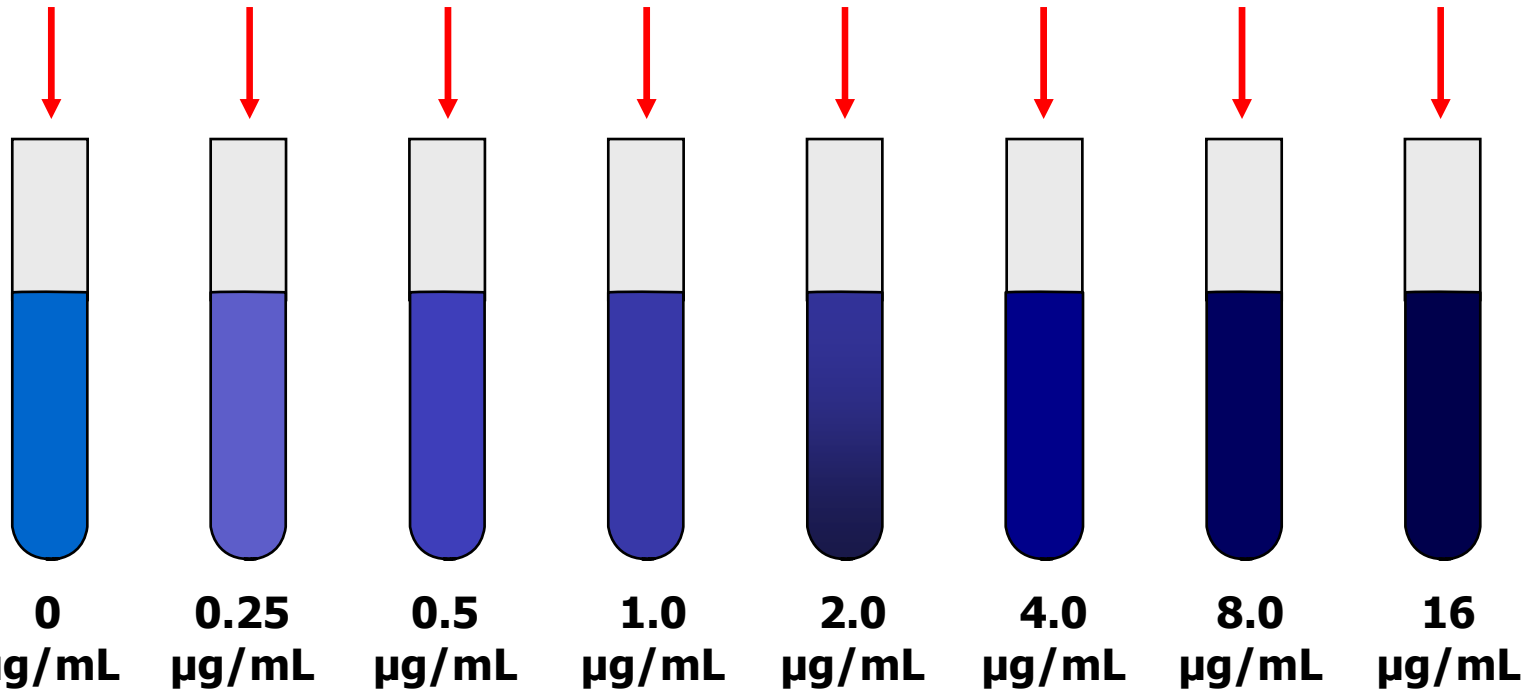
The dose must be adapted to the goal…



In a nutshell…

The target is the bacteria = MIC

Known quantity of bacteria placed into each tube

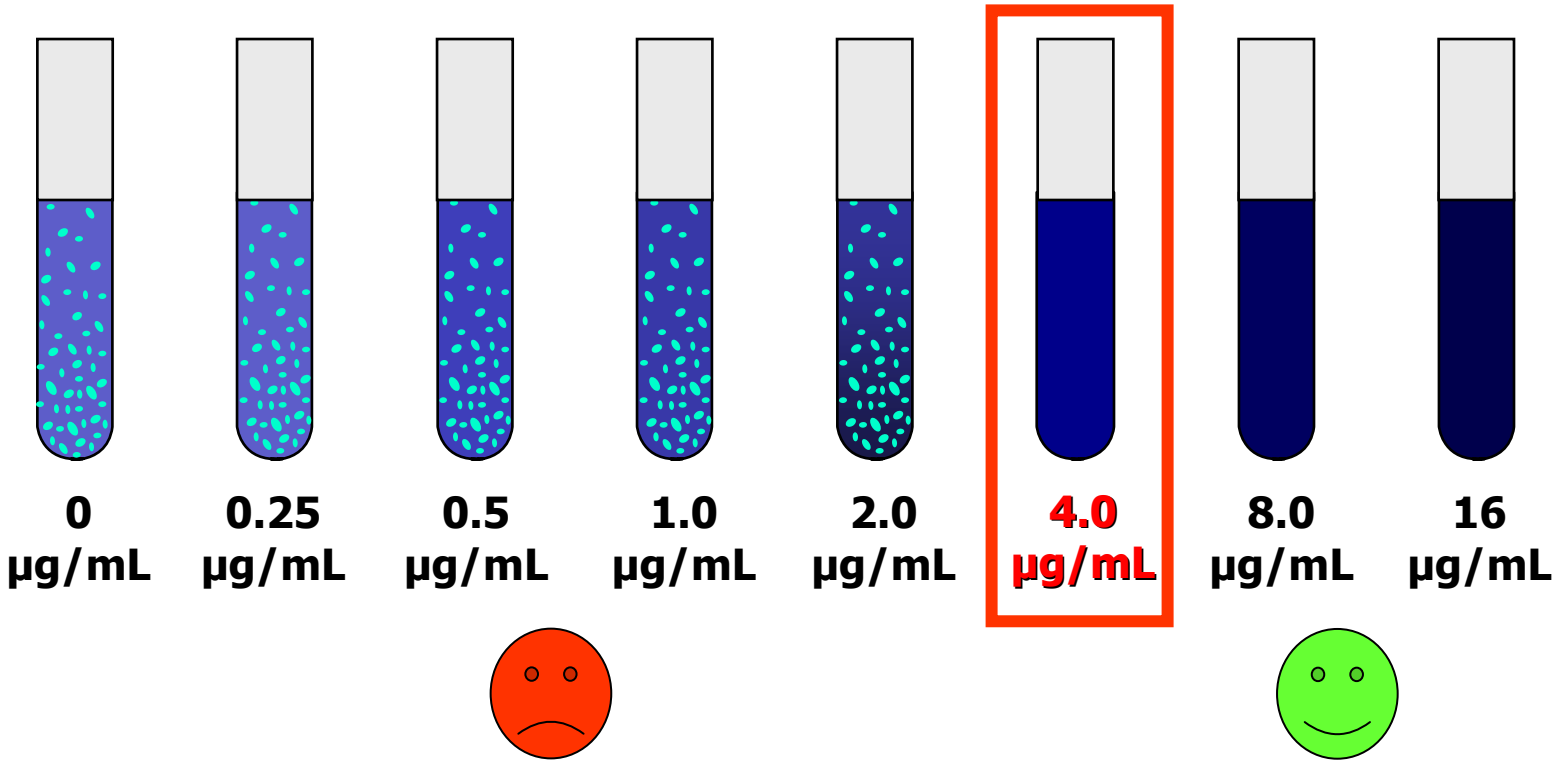


In a nutshell…

The target is the bacteria = MIC

24h later…

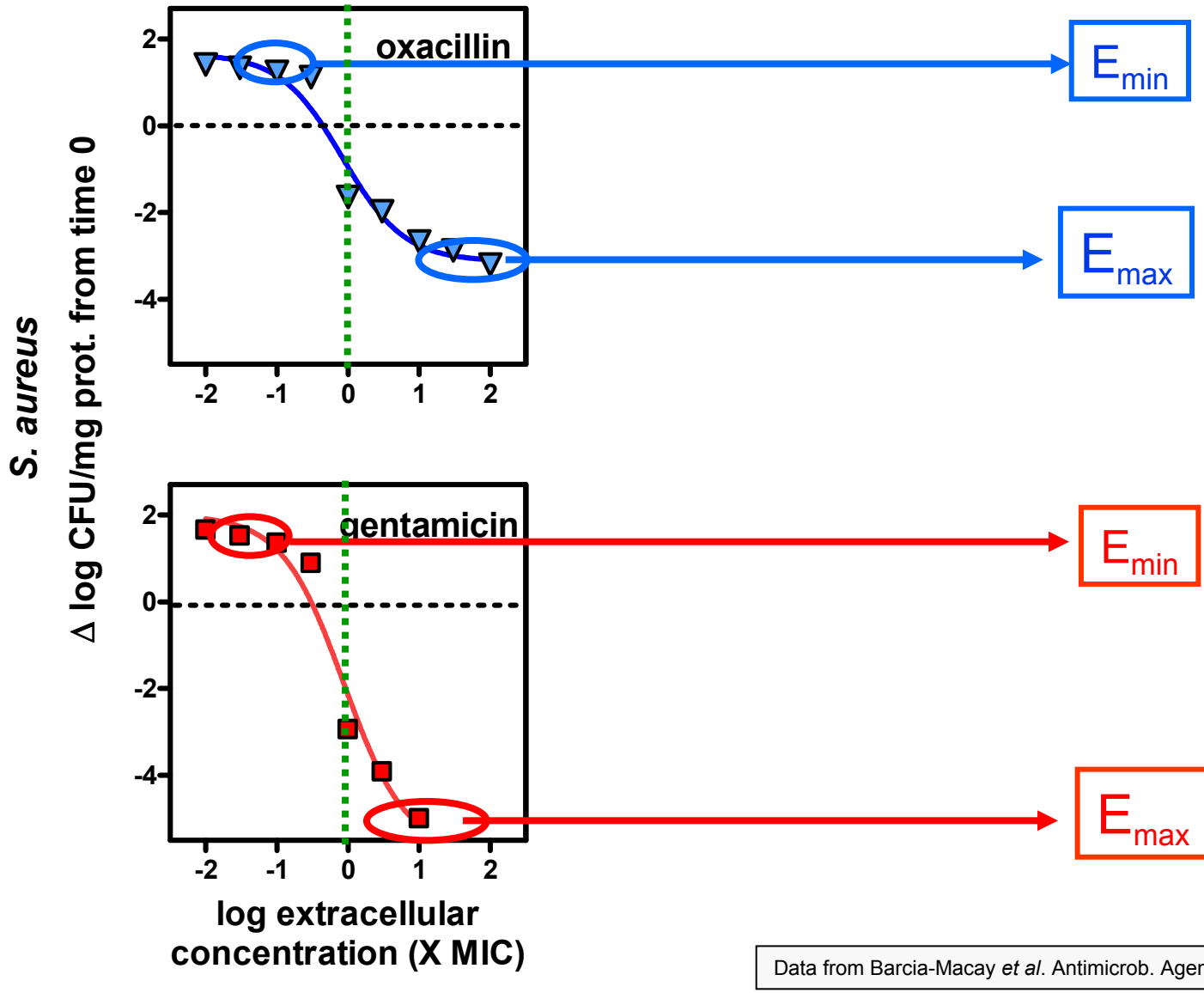
Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



MIC: techniques…

- **broth microdilution is the only ISO standard**
  - by definition, correct values
  - BUT does not inform about heteroresistance...
- **disks or E-test**
  - be careful about poorly diffusible antibiotics (vancomycin, colistin, ...)
  - BUT shows heteroresistance (colonies within the inhibition zone)
- **agar dilution method**
  - shows heteroresistance and gives warning for failures
- **automatic techniques** (Vitek, etc...)
  - "easy" and fast, but possibilities of major mistakes
  - be careful about breakpoints and "expert rules"
  - do NOT show heteroresistance !!!

What is the relationship between MIC and effect?

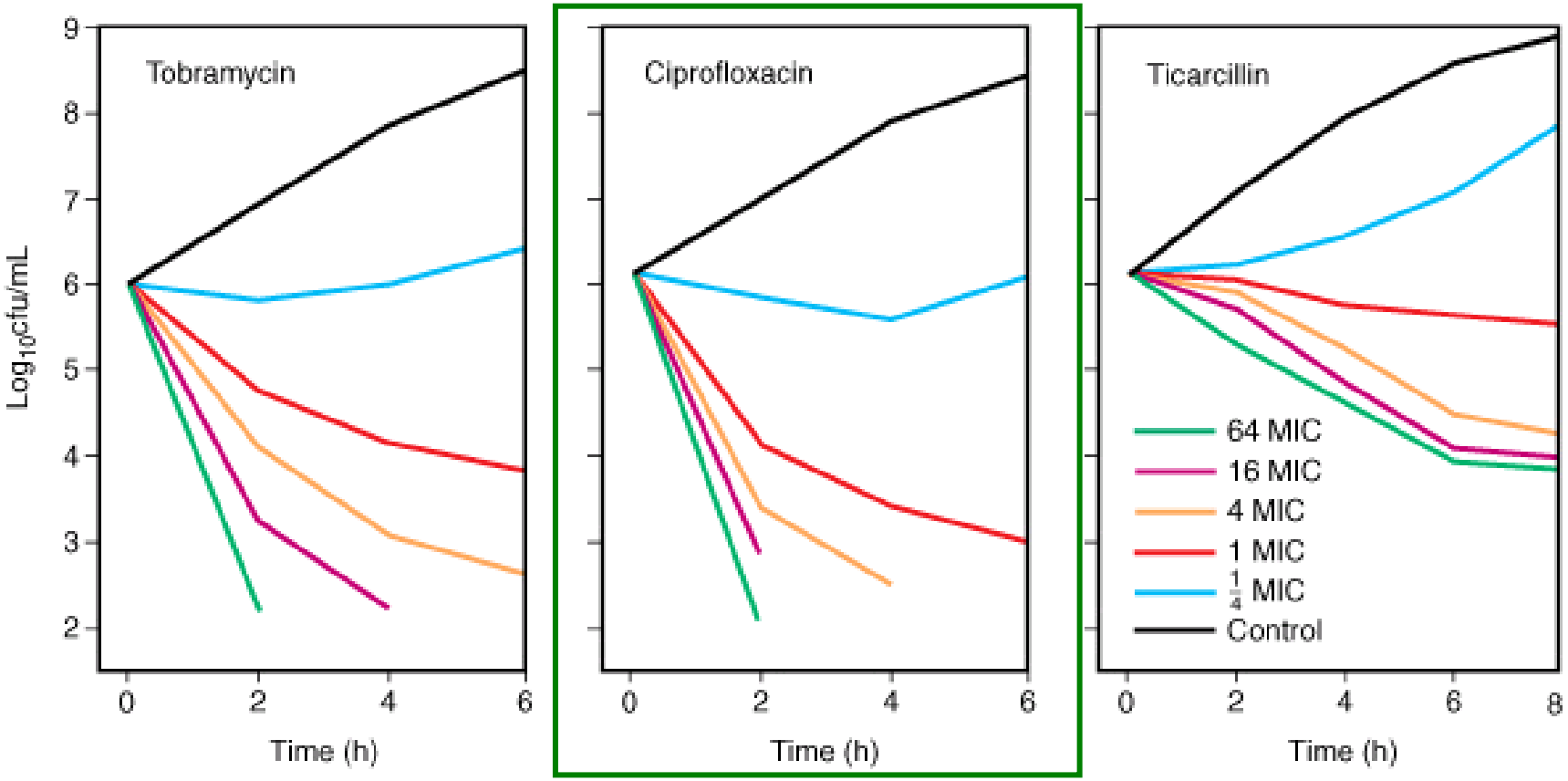


It looks as if they are all concentration-dependent…

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

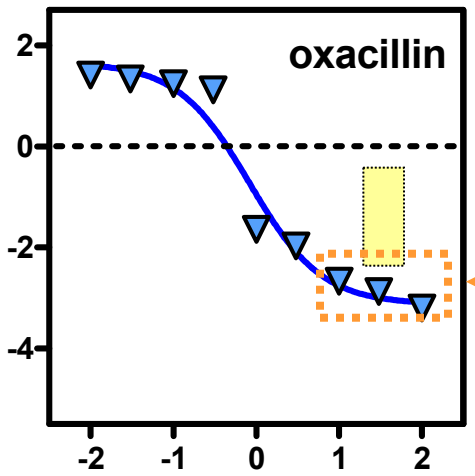
A first comparison: in vitro kill curves vs MIC

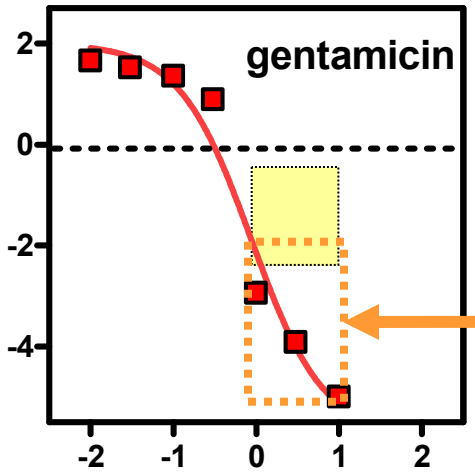
conc. dependent



Time kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration.
(From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. Scand J Infect Dis. 1990;74:63–70.)

But now comes pharmacokinetics …





S. aureus

Δ log CFU/mg prot. from time 0

log extracellular concentration (X MIC)

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

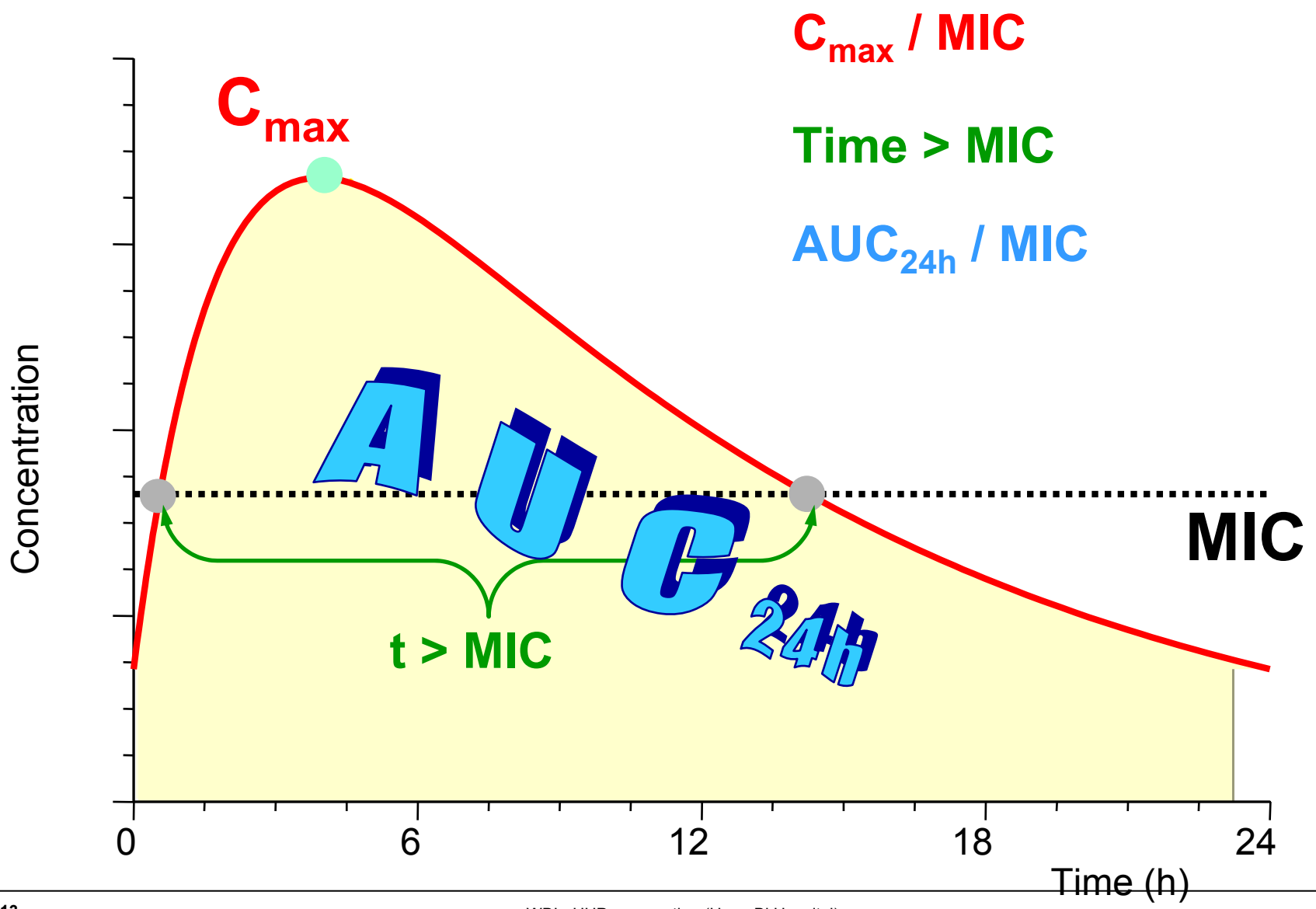
- data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851
- C_{min}-Cmax: Principles and Practice of Infectious Diseases, 7th Ed. Mandell *et al*. eds., Elsevier

First conclusions

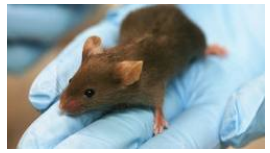
Considering their pharmacokinetics in humans

- β-lactams appear as **"time-dependent"** antibiotics because their serum concentrations is almost always > MICs …
  if you administer them several times a day (most have only short serum half-lives)
- Fluroquinolones (and aminoglycosides) are primarily **"concentration-dependent"** antibiotics as their bactericidal effect increases in proportion to their C_{max}/MIC ratio.

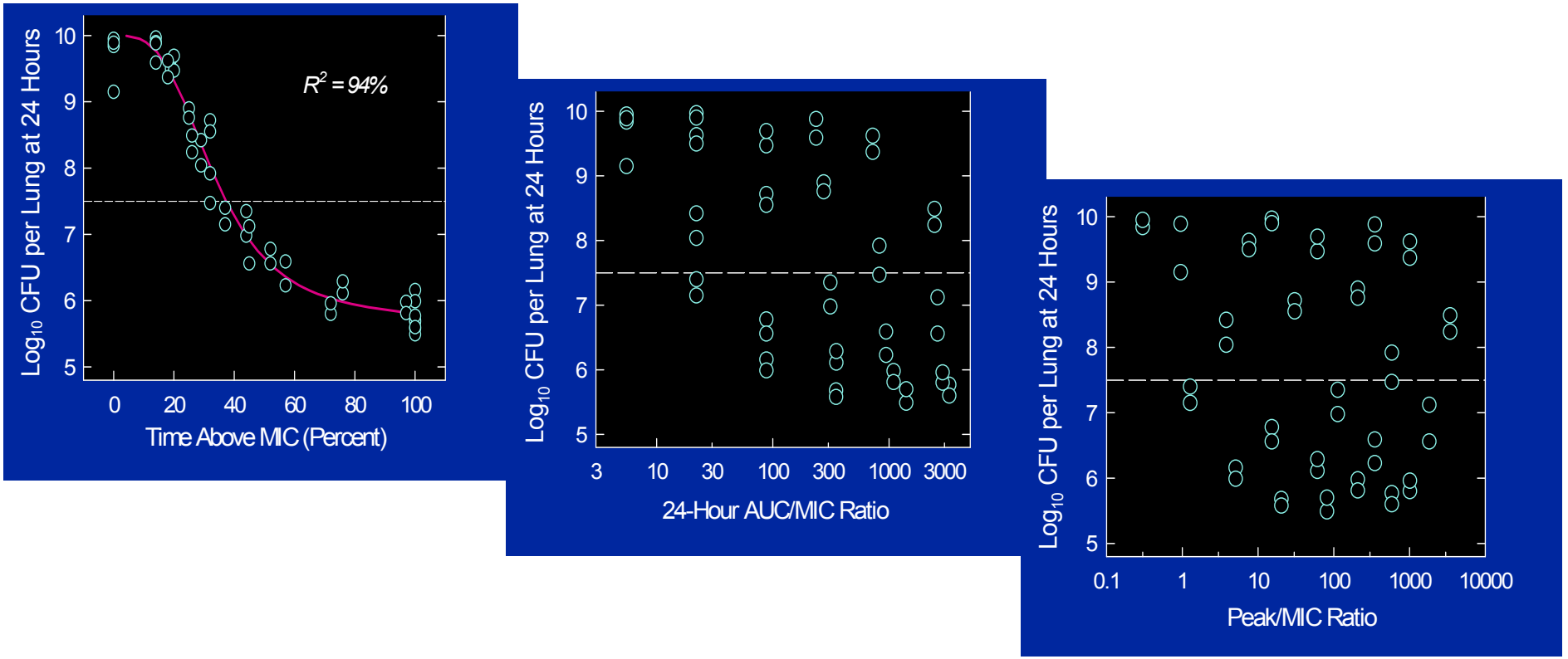
Moving to actual conditions of use



PK/PD in animals: β-lactams

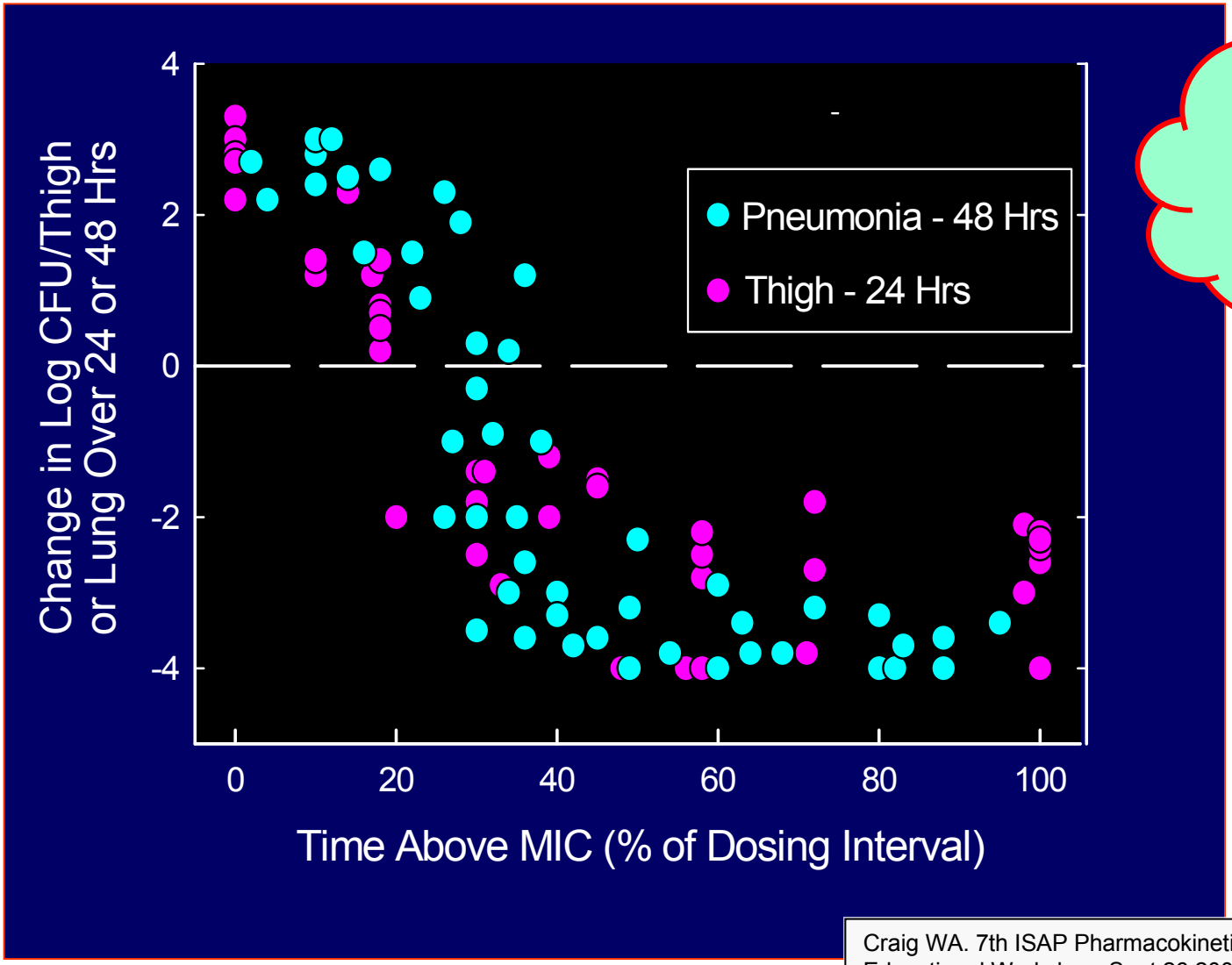


1. For β-lactams, time > MIC is the only key index for efficacy



Correlation of PK/PD Indices with Efficacy of Cefotaxime against Klebsiella pneumoniae in a Murine Pneumonia Model (W.A. Craig – ISAP workshop – Stockholm, Sweden, 2000)

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.

Is this true for all β-lactams?

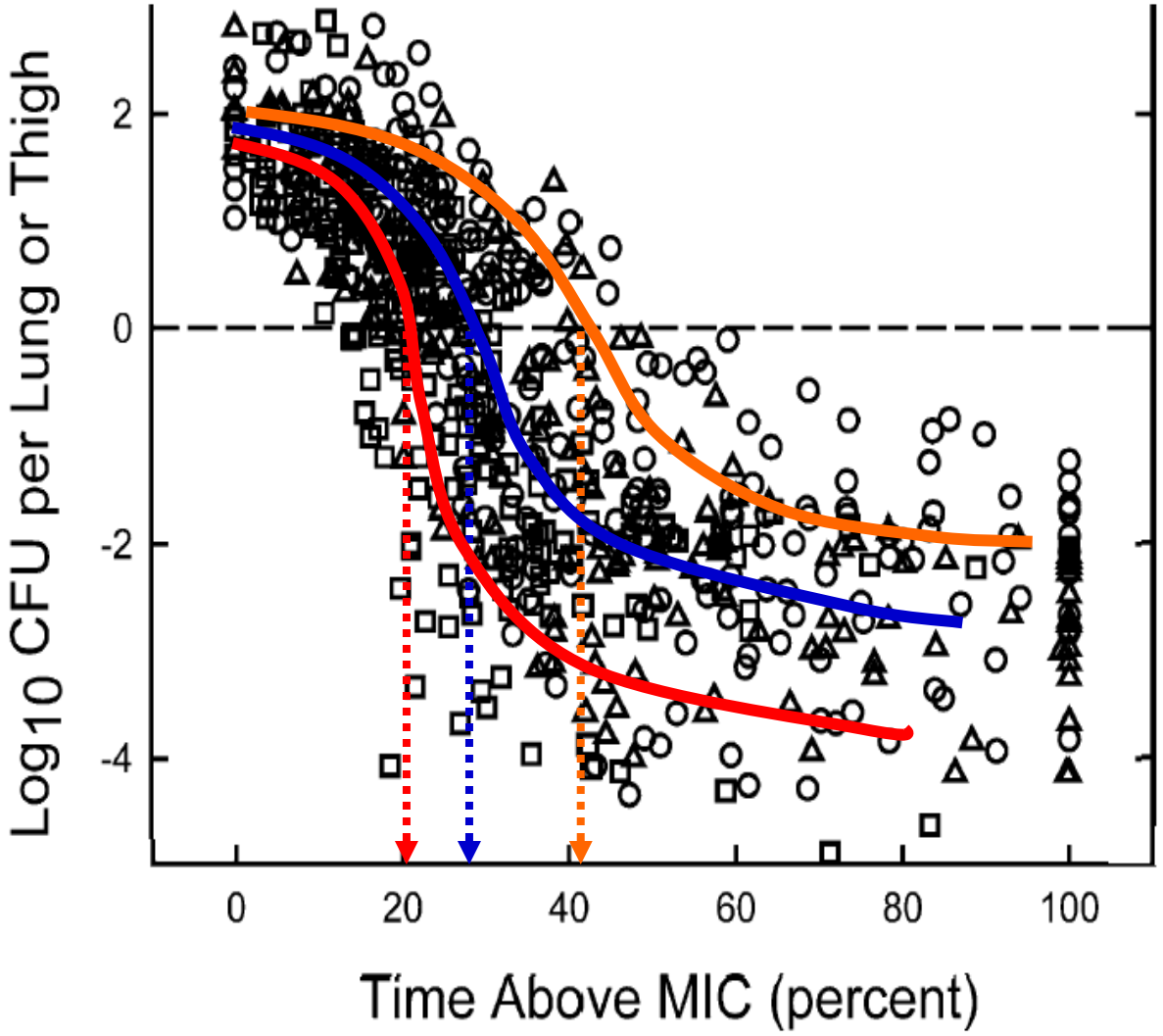
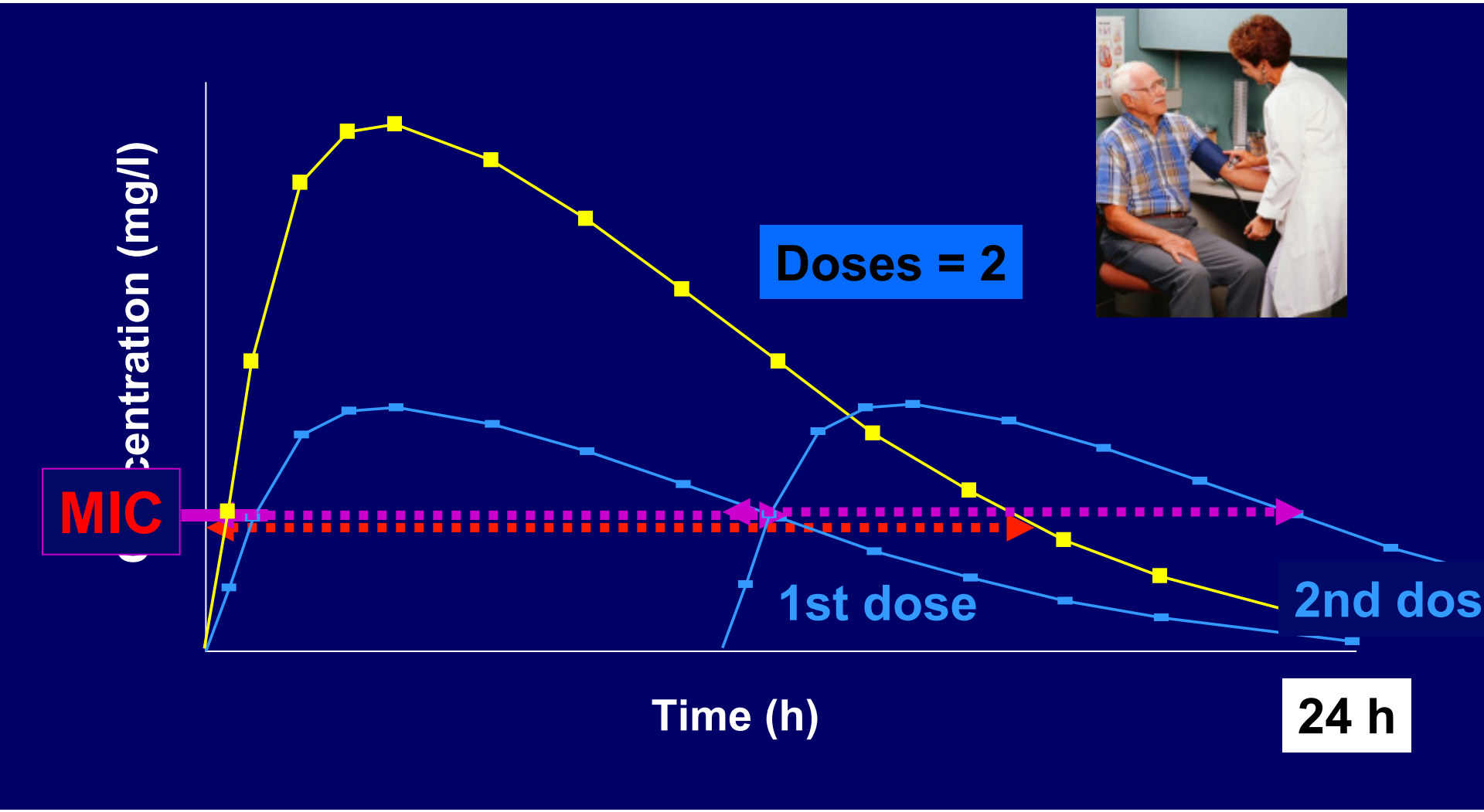


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

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

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



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 ...

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
NCCLS	U.S.A.	8 / ≥64

Is 64 mg/L really "susceptible" ?

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

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

EUCAST

Amoxicillin EUCAST rationale document

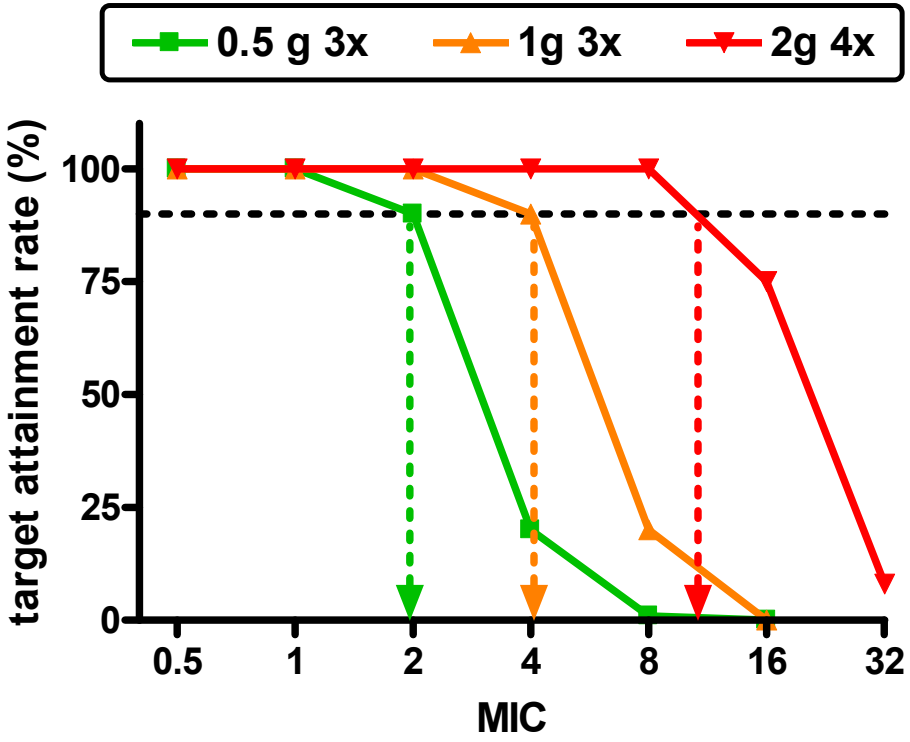
5. Pharmacodynamics

	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*

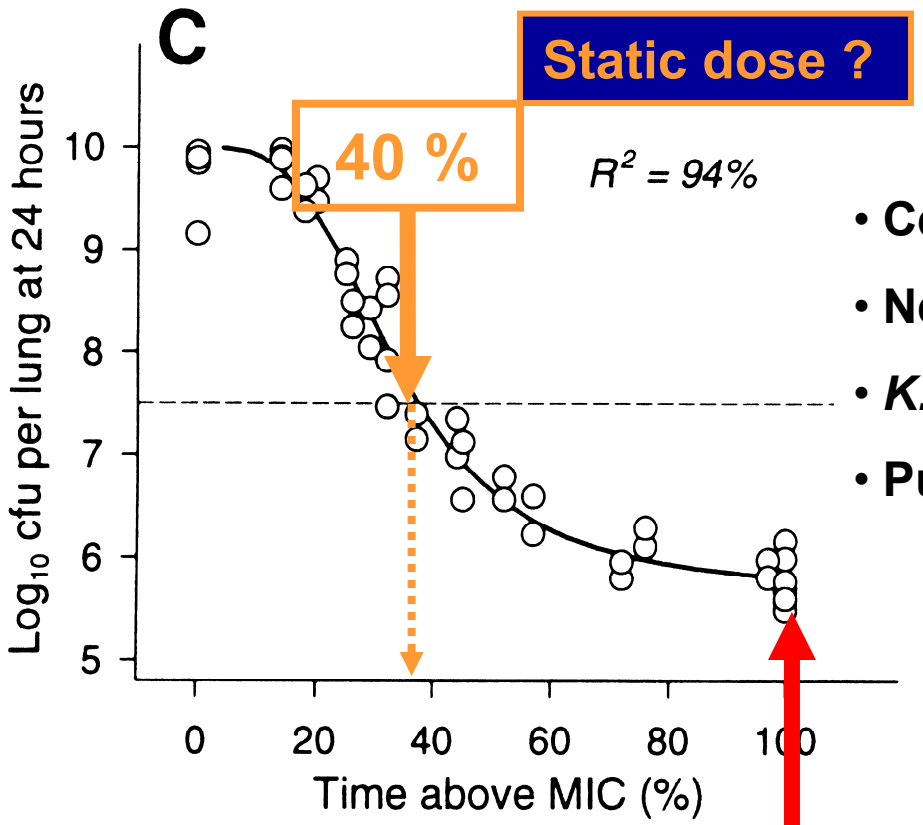


* for *f* T >MIC = 40%

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

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



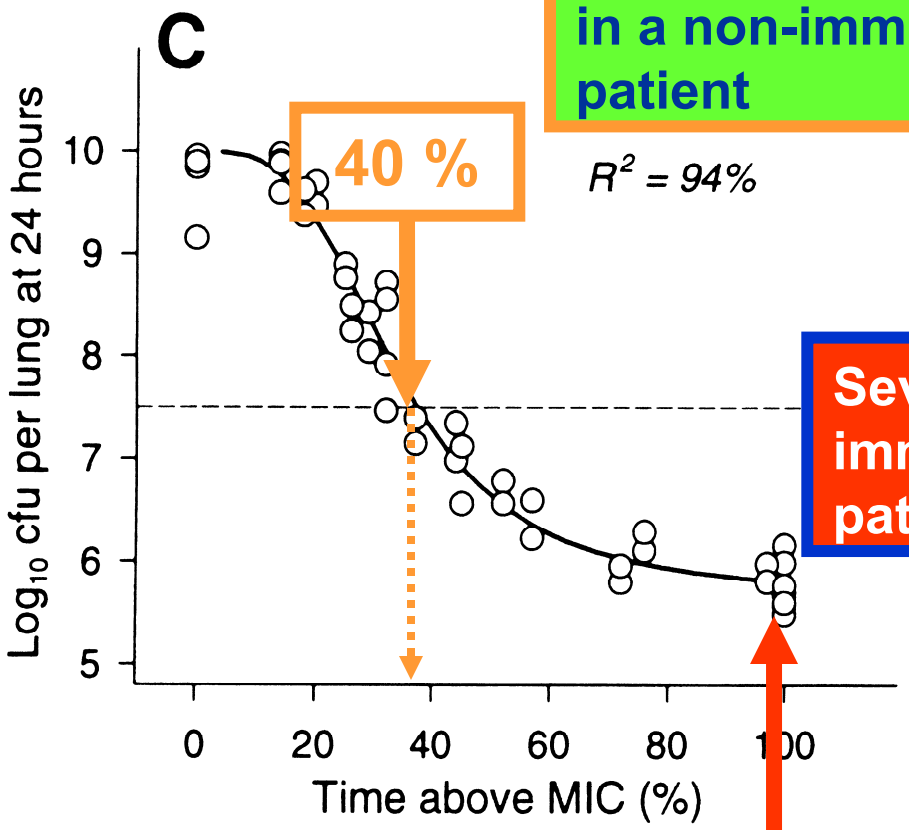
- Cefotaxime
- Neutropenic mice
- *K. pneumoniae*
- Pulmonary infection

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 ...

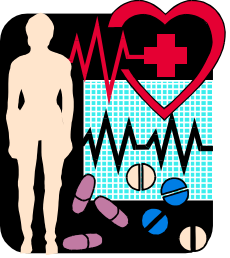
Moderately severe infection in a non-immunosuppressed patient



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



Pharmacokinetics of a typical IV β-lactam *

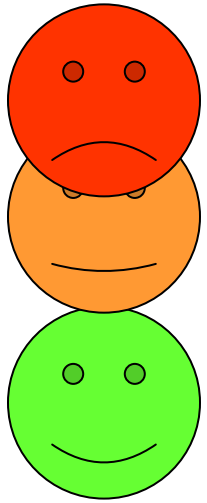
Time (hours)	Serum concentration (mg/L)		
	0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

*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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EUCAST and ESBL

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.

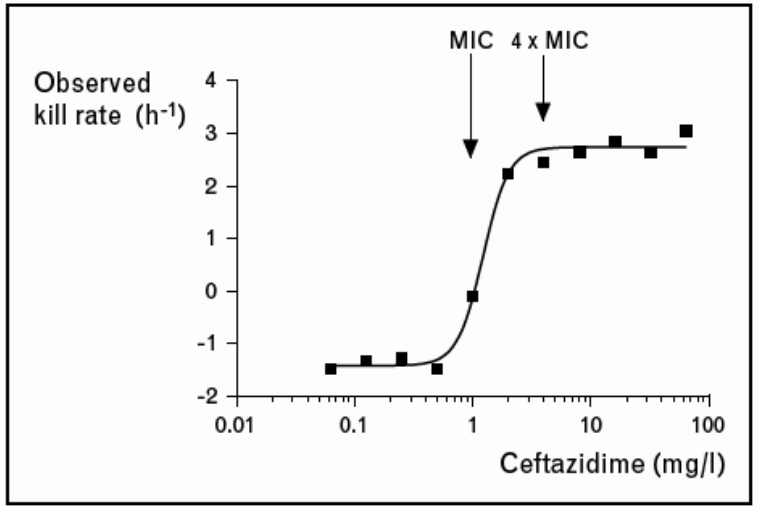
To exclude ESBL

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

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

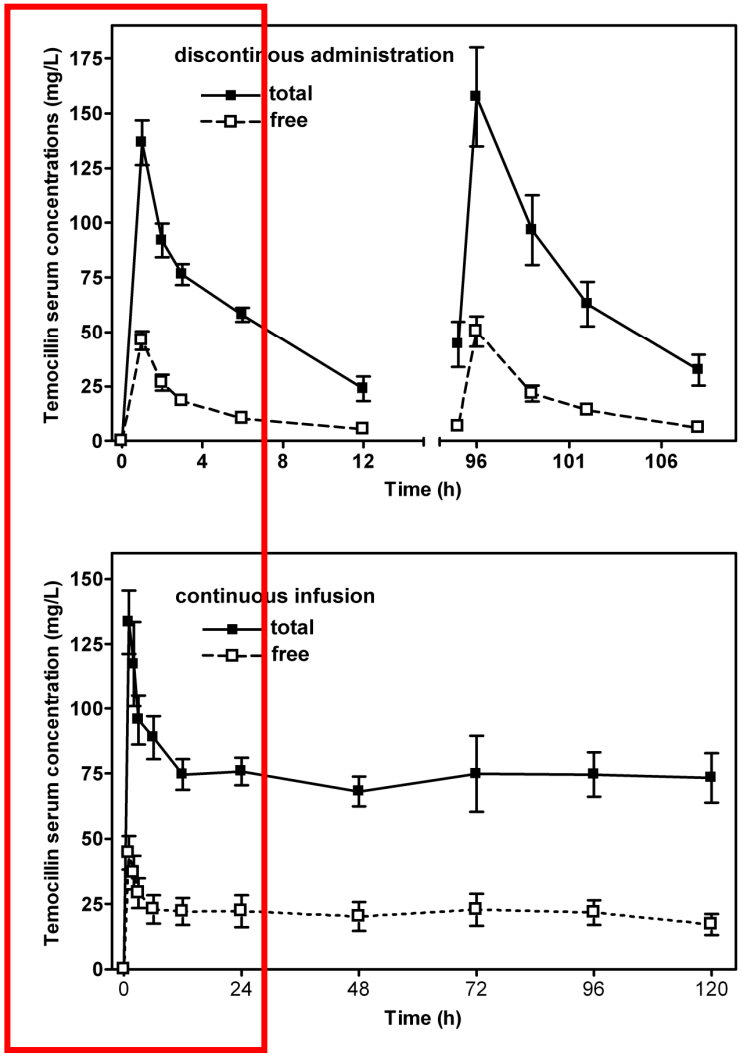


The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (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
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 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
- Clinical data supporting continuous administration are less convincing, but
- **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. *Int J Antimicrob Agents* 2007;30:11-8.

And the other antibiotics...

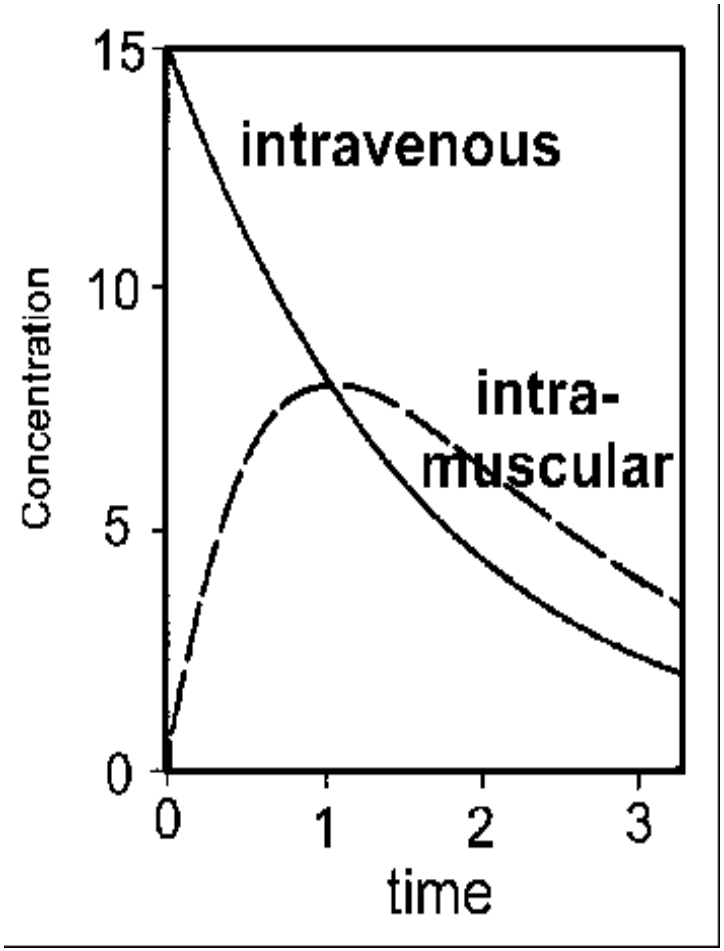
- Only β -lactams are fully time-dependent

- Other antibiotics are divided in two groups
  - those that are "C_{max}/MIC-dependent":
    - aminoglycosides and fluoroquinolones (partially)
  - those "AUC_{24h}/MIC-dependent":
    - most other antibiotics

Aminoglycosides: get a peak !

Aminoglycosides: get a peak !

Peak/MIC > 8



1. **Appropriate mode of administration**

   ⇨ **IV route**

2. **Calculation of the necessary peak value**

   ⇨ **minimal peak: = MIC x 8**

3. **Calculation of the adequate dosis**

   ⇨ **peak = dosis / Vd**

   ⇨ **dosis = peak x Vd**

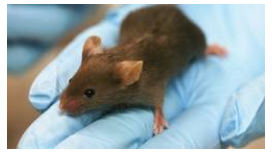
   ⇨ **dosis = MIC x 8 x Vd**

Aminoglycosides...

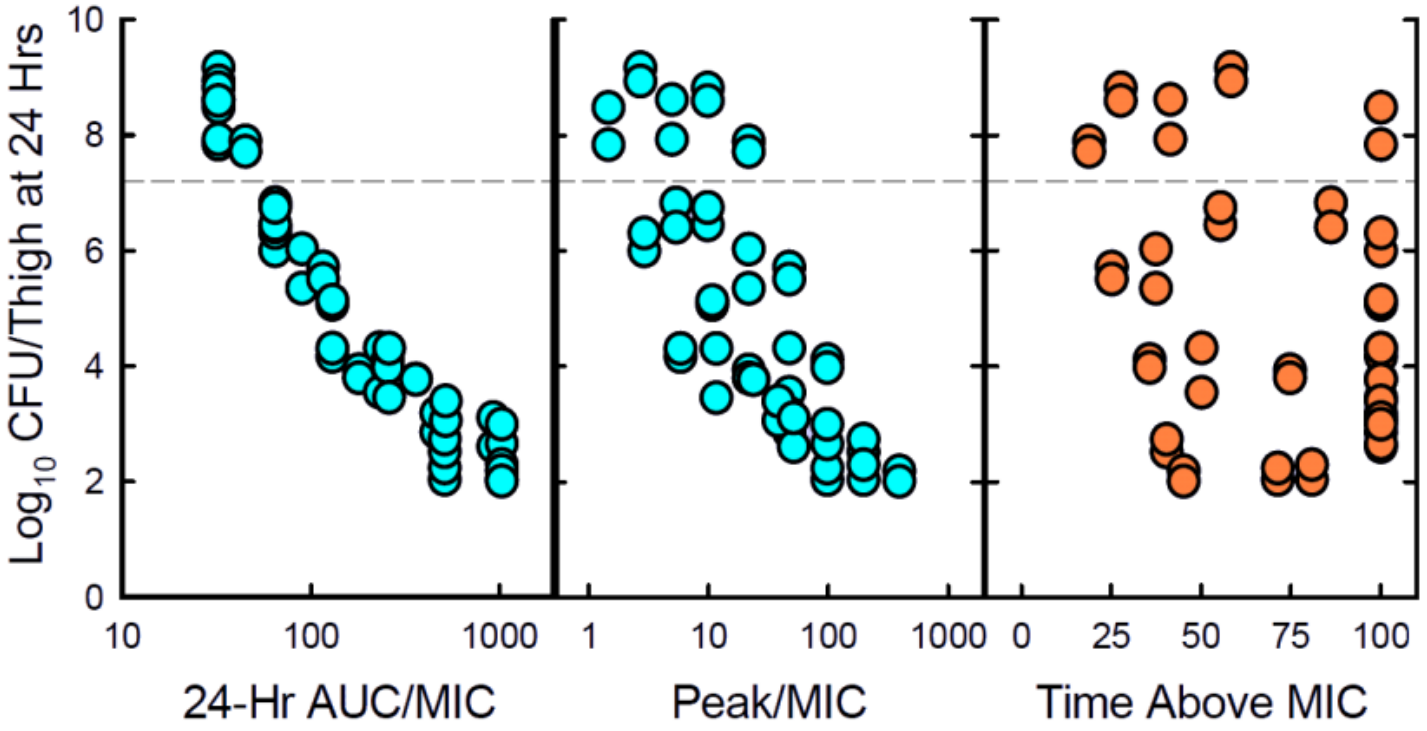
- optimize the peak !
  - must reach 8-10 x the MIC
  - use intravenous only (in 30 min)
  - use once-daily (full dose in one administration)
    - to increase efficacy
    - to reduce toxicity (associated with elevated through levels) [1]

[1] not shown here but ask questions

PK/PD in animals: fluoroquinolones

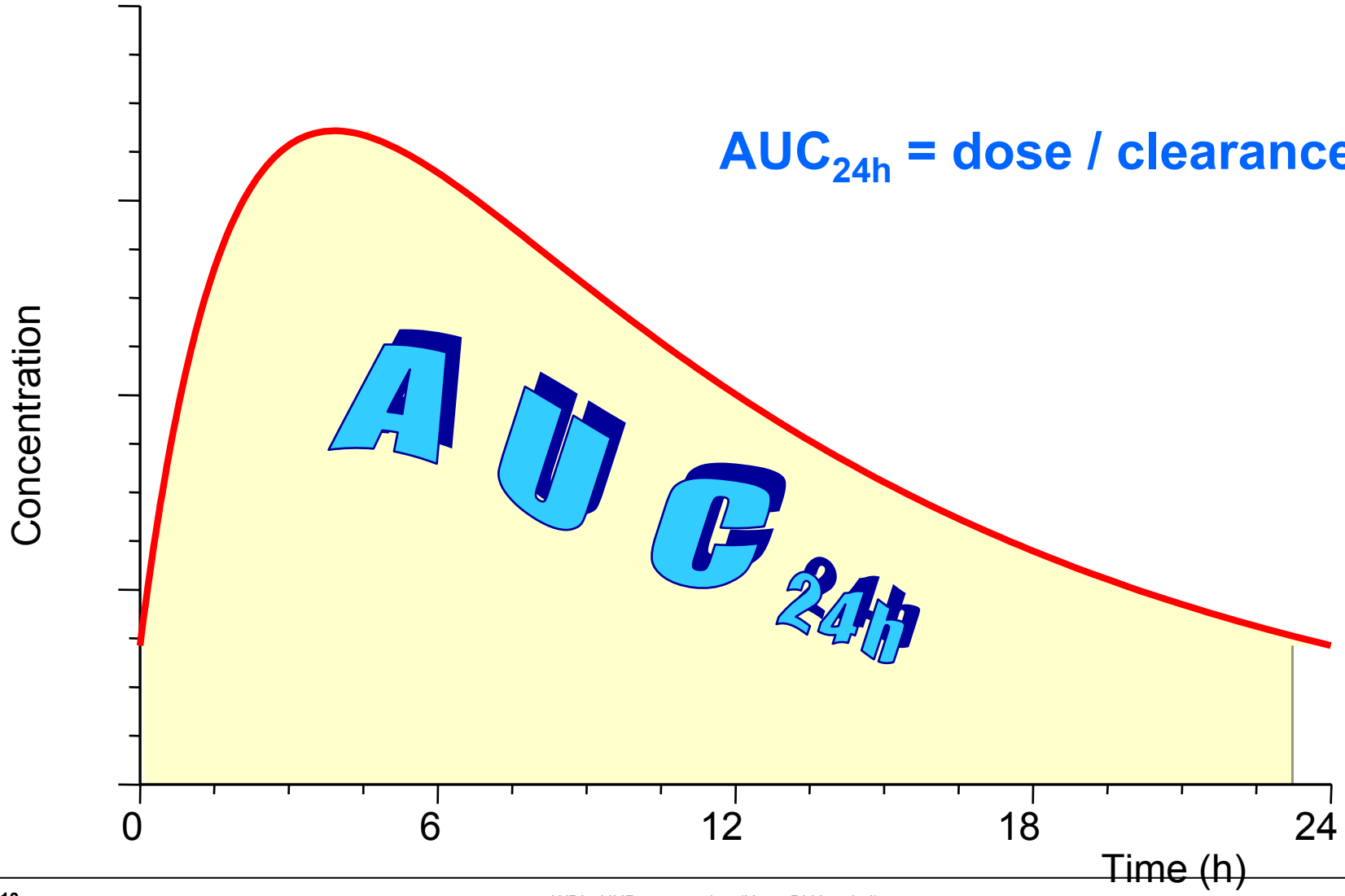


2. For fluoroquinolones, both AUC_{24h}/MIC and C_{max} emerge as key indices



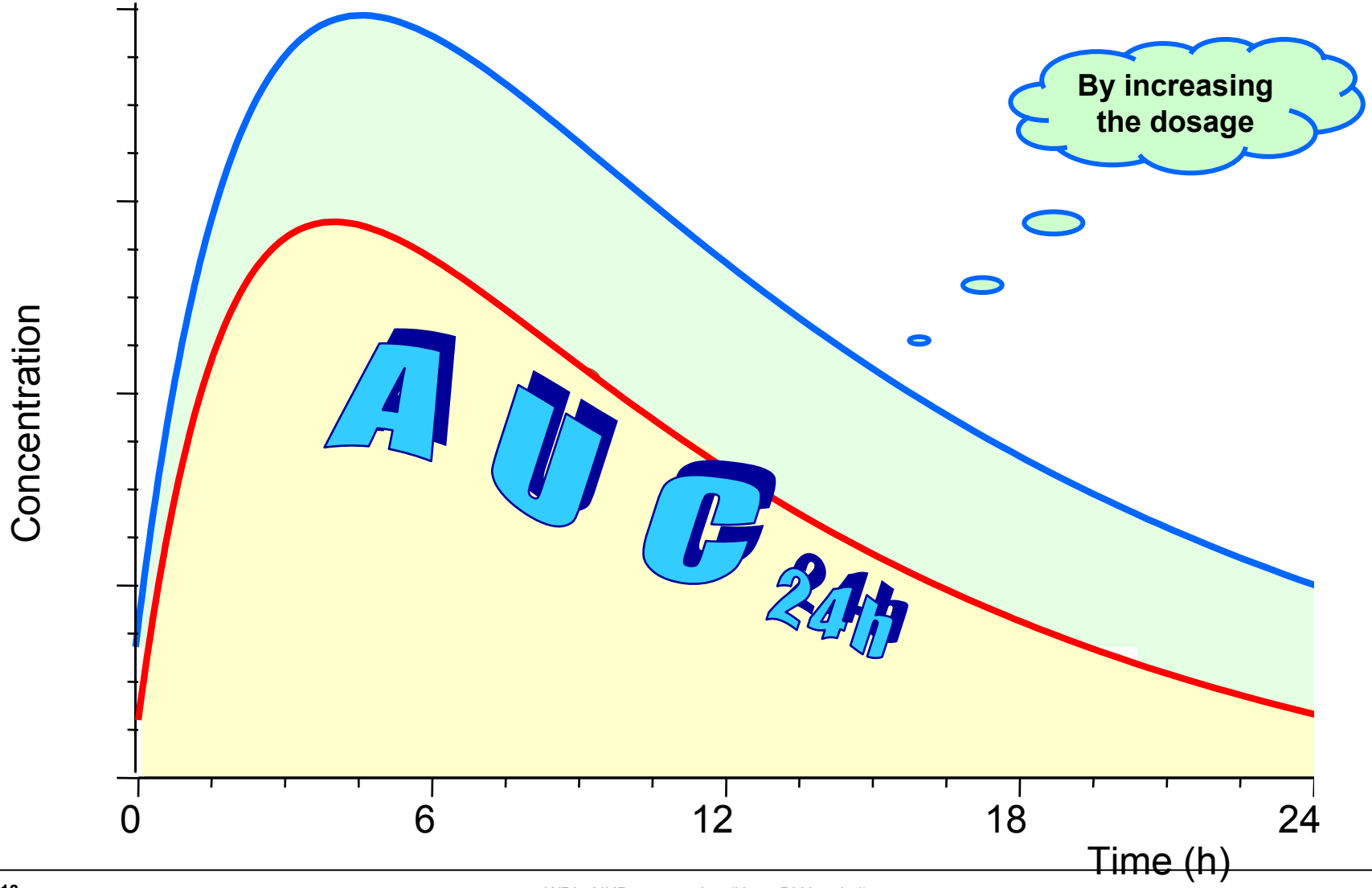
Correlation of PK/PD Indices with Efficacy of Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice (W.A. Craig – ISAP workshop – ICAAC 2009)

What is an AUC_{24h} ?



How do I get a larger AUC_{24h} ?

AUC_{24h} = dose / clearance



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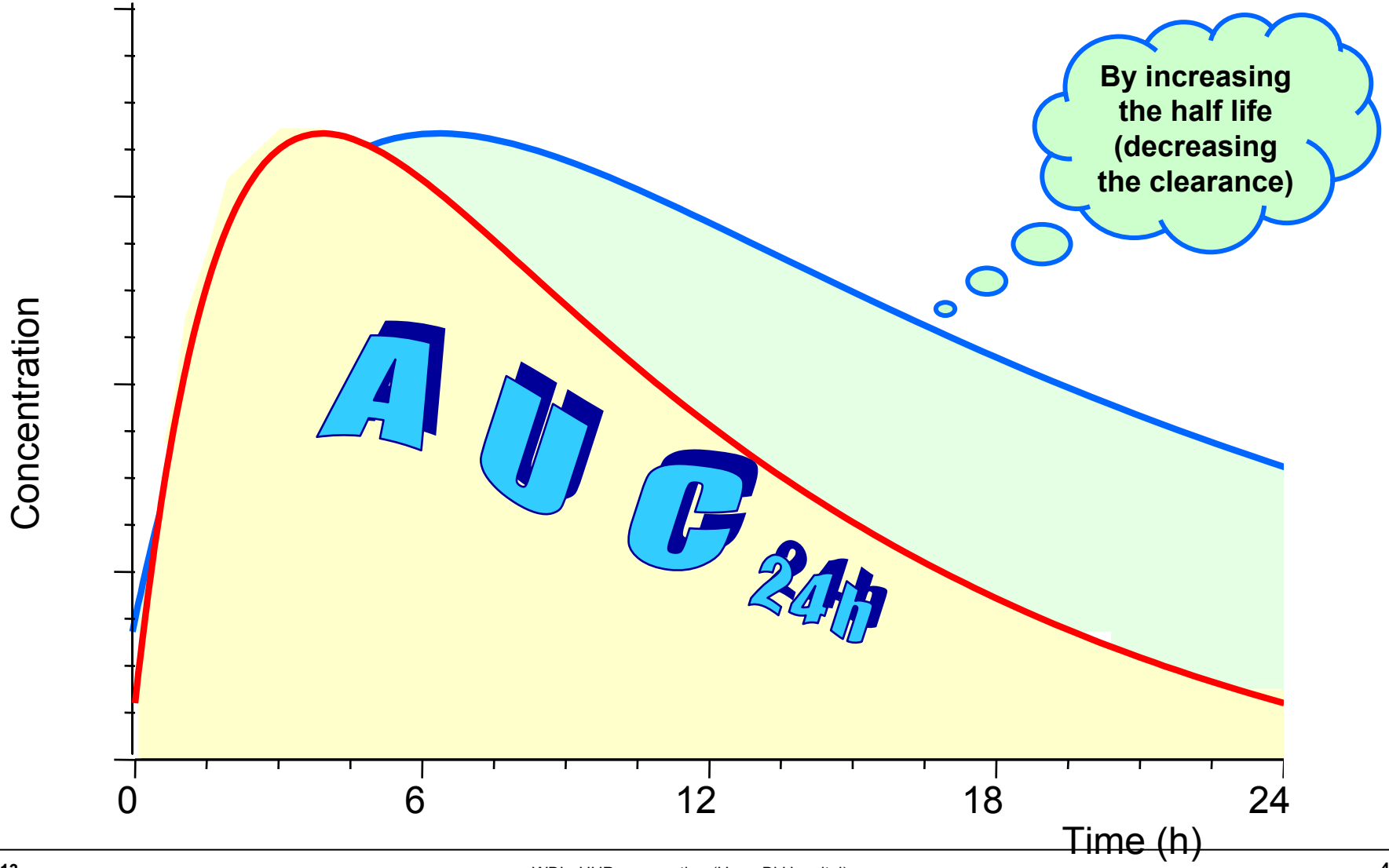
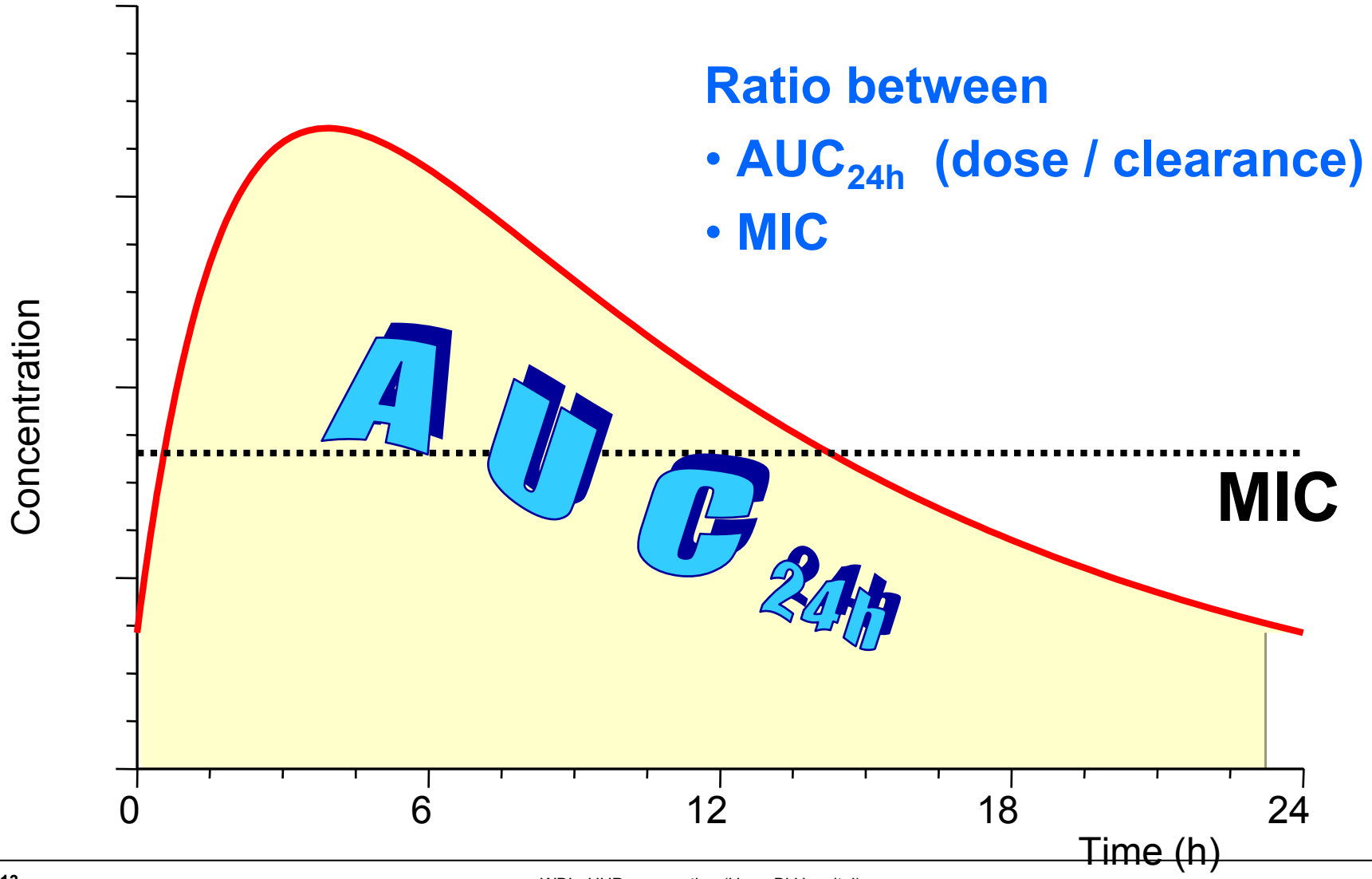
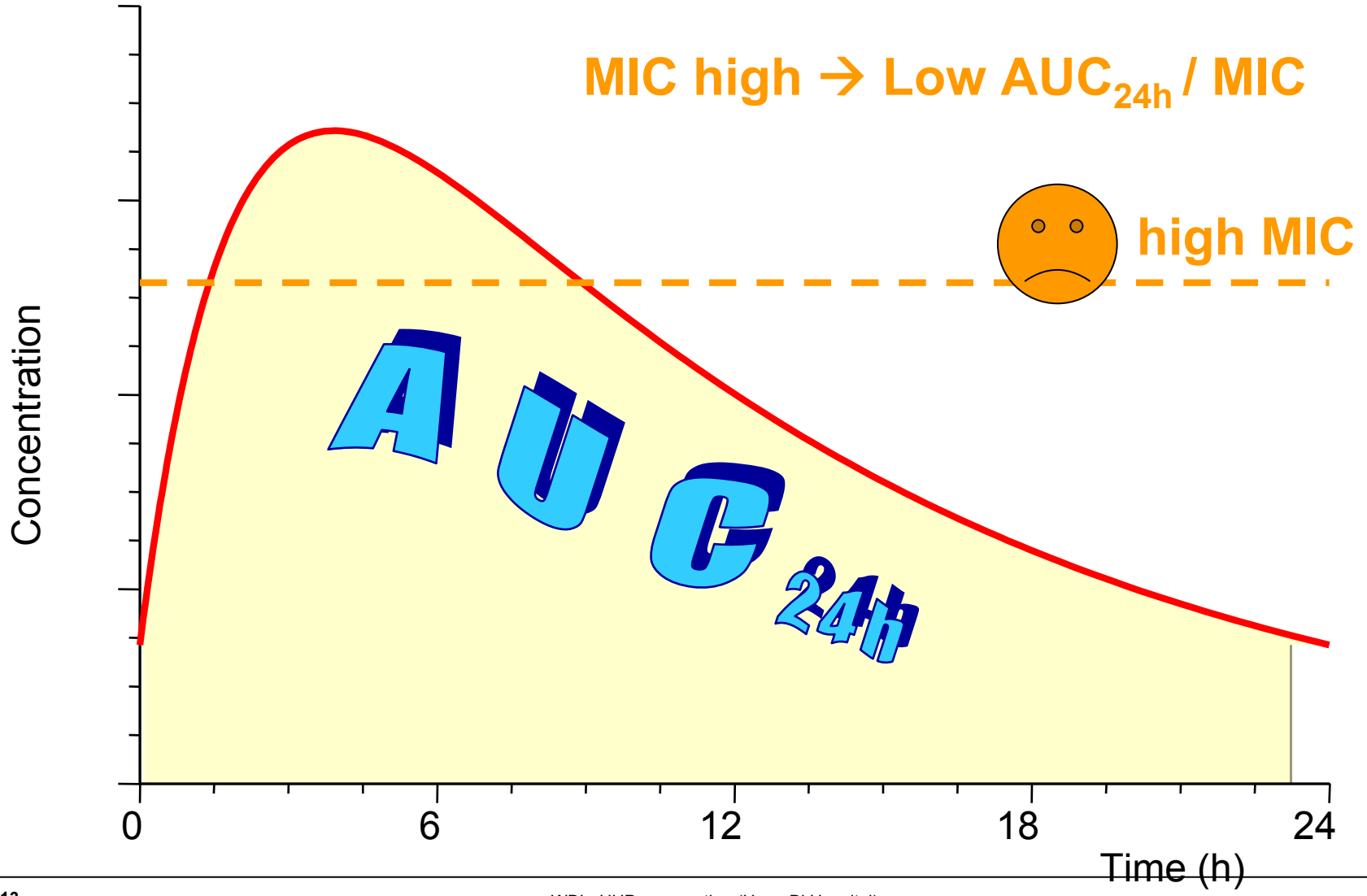
AUC_{24h} = dose / clearance



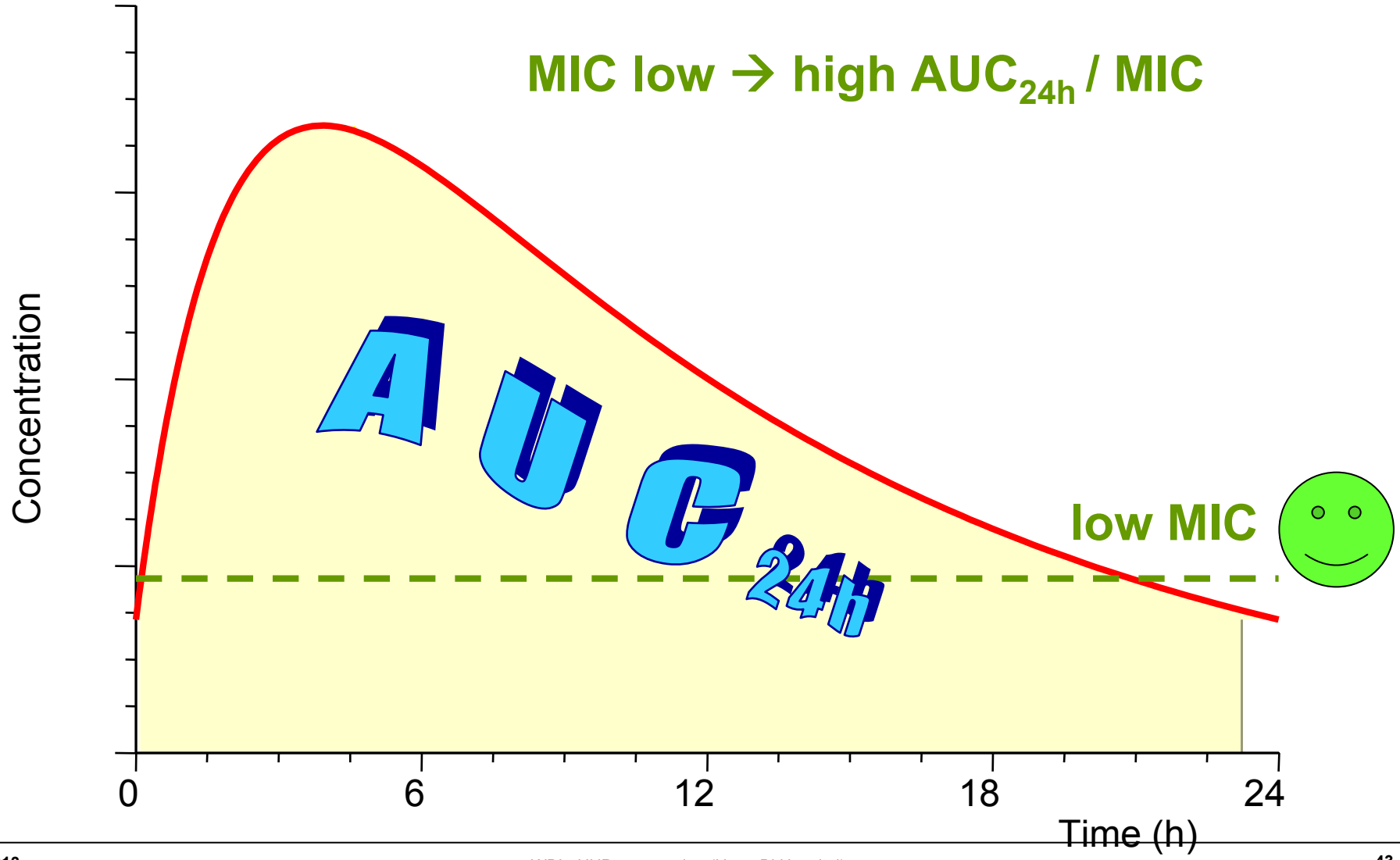
What is an AUC_{24h} / MIC ?



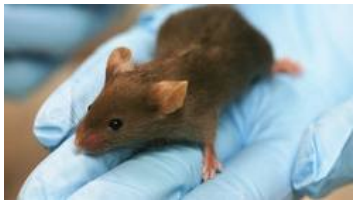
What is an AUC_{24h} / MIC ?



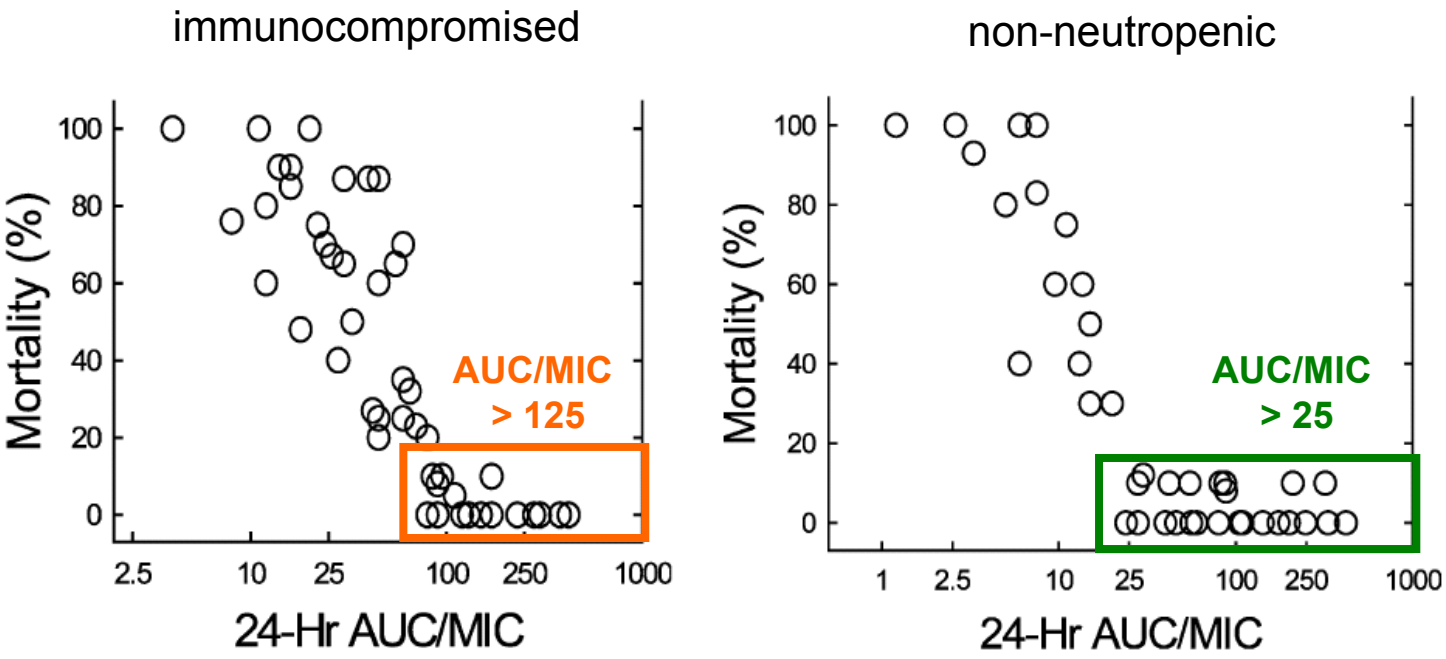
What is an AUC_{24h} ?



PK/PD in animals



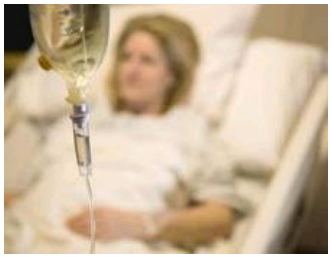
Immune status influences the magnitude of the PK/PD index required for efficacy

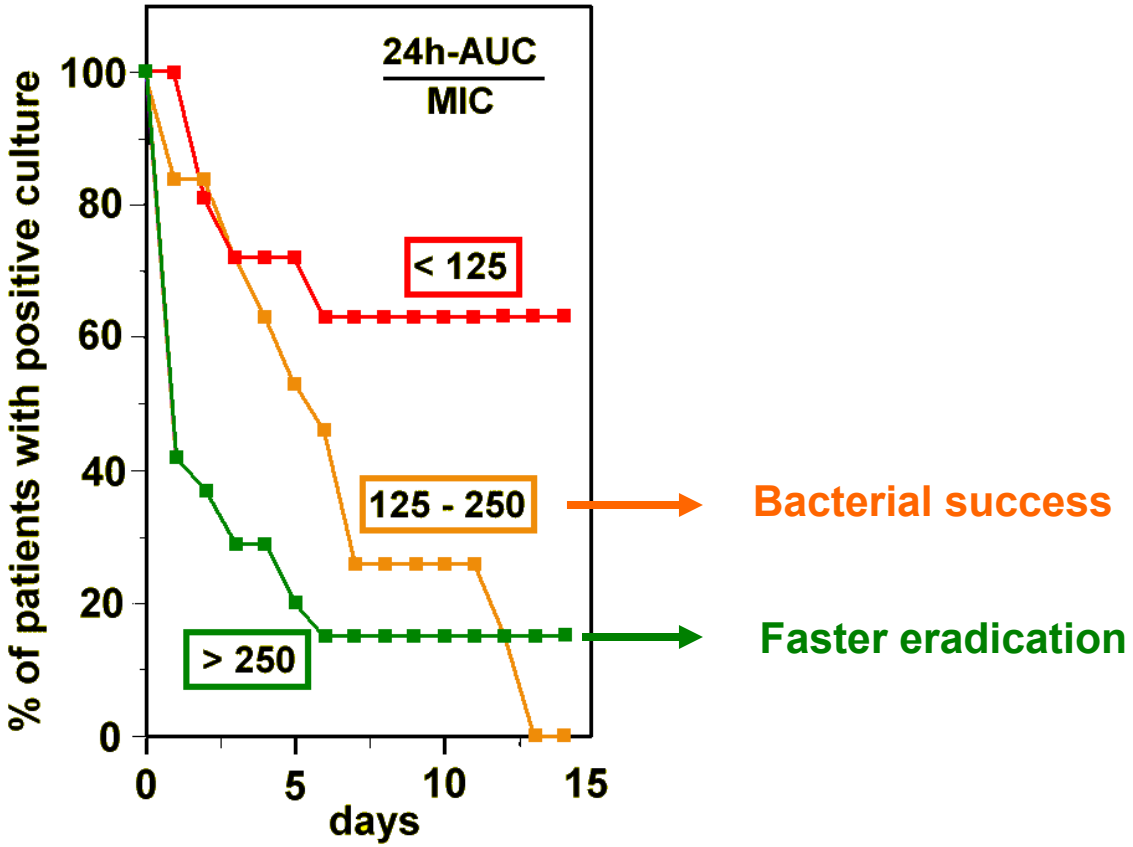


Relationships between mortality at the end of therapy and the 24 h AUC/MIC of fluoroquinolones with multiple pathogens (left panel) in different animal models (mostly immunocompromised) and with S. pneumoniae in non-neutropenic models (right panel).

Andes & Craig. Int. J. Antimicrob. Ag. (2002) 19: 261-68

AUC_{24h}/MIC in patients



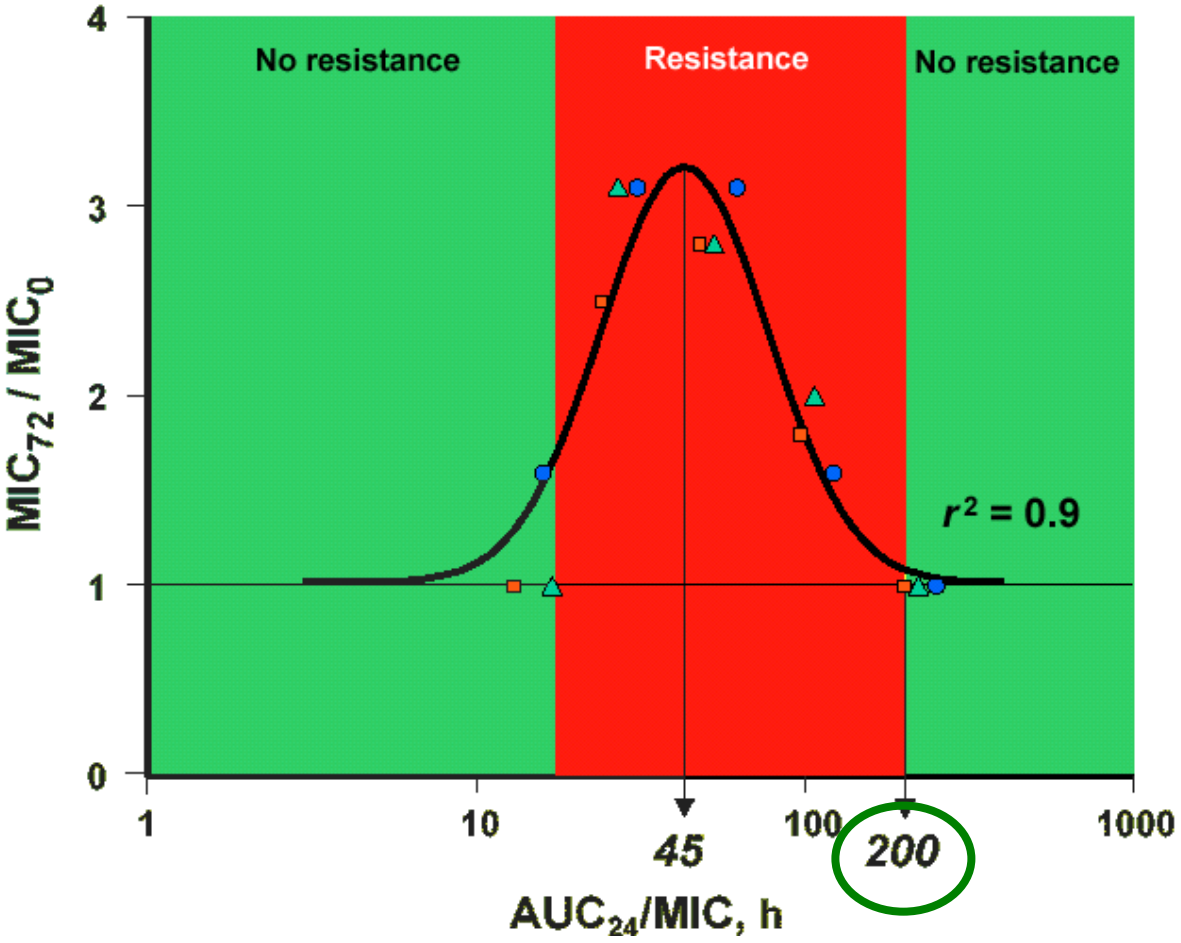


Time (days of therapy) to bacterial eradication versus AUC/MIC in severely ill patients treated with ciprofloxacin
The three groups differed significantly (P < 0.005).

Forrest et al AAC (1993) 37:1073-81

AUC_{24h}/MIC and prevention of resistance

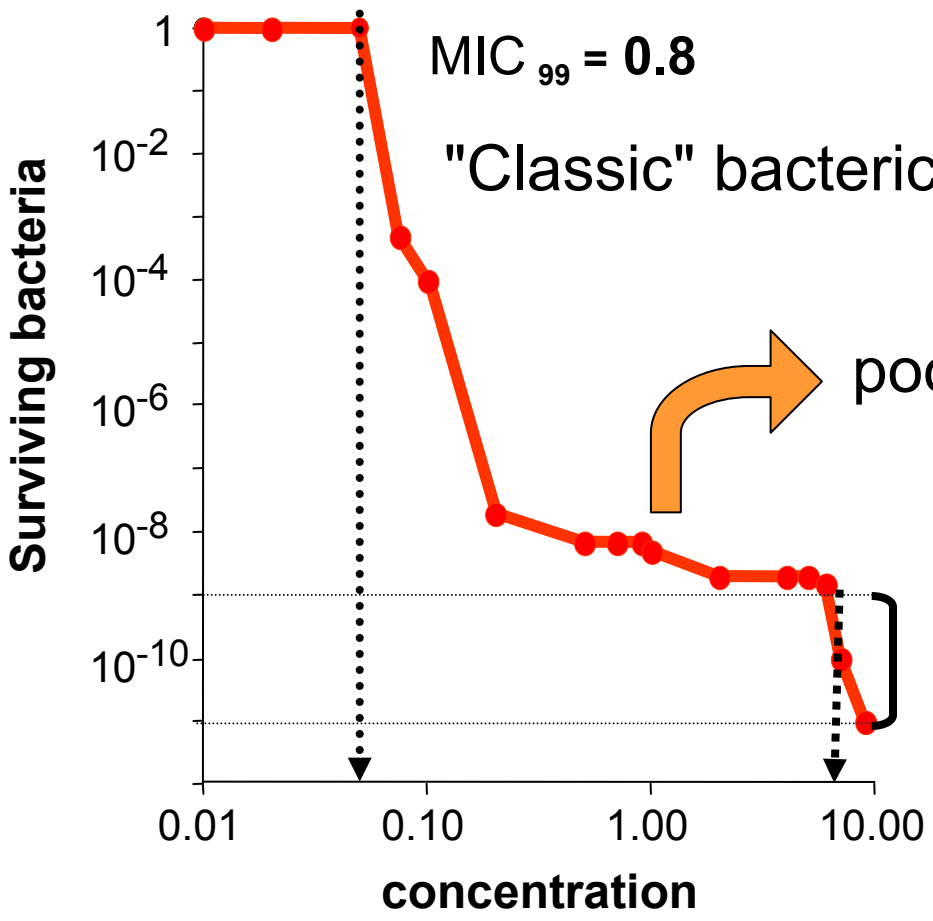
Change in susceptibility of *S. aureus* after exposure to fluoroquinolones



AUC/MIC >> 125
&
Peak/MIC > 8
to prevent resistance selection

Firsov *et al.* In vitro pharmacodynamic evaluation of the mutant selection window hypothesis using four fluoroquinolones against *Staphylococcus aureus*. Antimicrob Agents Chemother. 2003 May;47(5):1604-13.

C_{max} and the "Mutant Prevention Concentration" (MPC) …



MIC $_{99}$ = **0.8**

"Classic" bactericidal effect

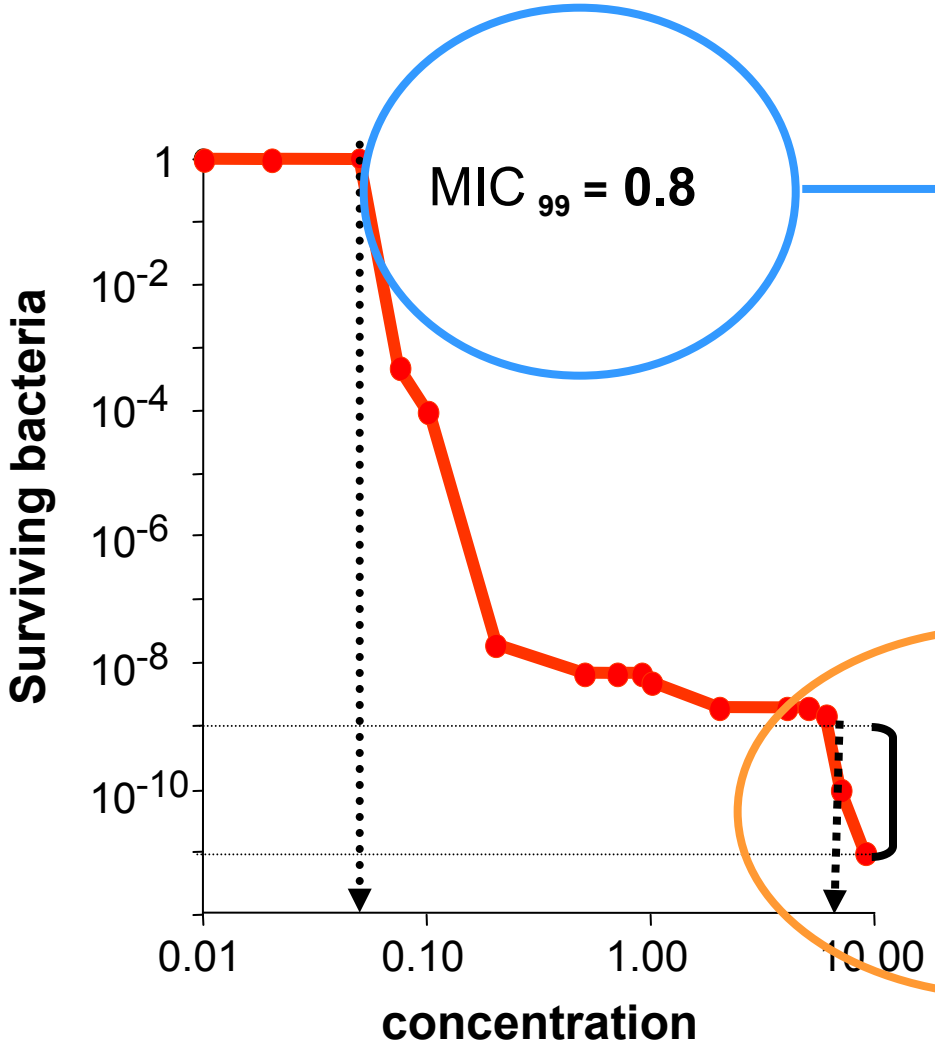
poorly sensitive organisms…

Elimination of resistant organisms

MPC $_{10}$ = **9**

Dong *et al:* AAC 1999; 43:1756-1758

"Mutant Prevention Concentration …"

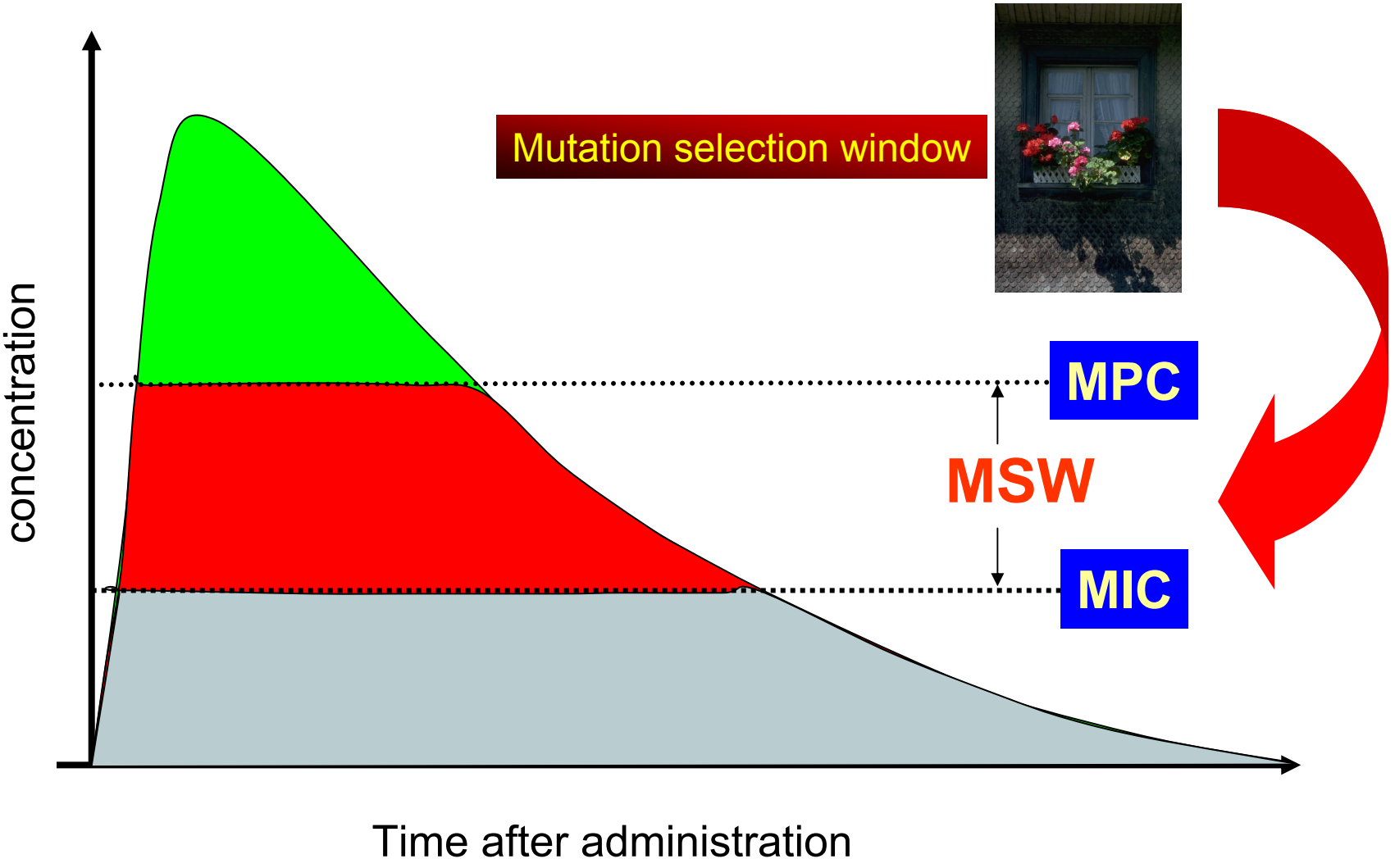


Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

Dong *et al*; AAC 43:1756-1758

"Window" where selection of mutants/resistants may take place …



concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

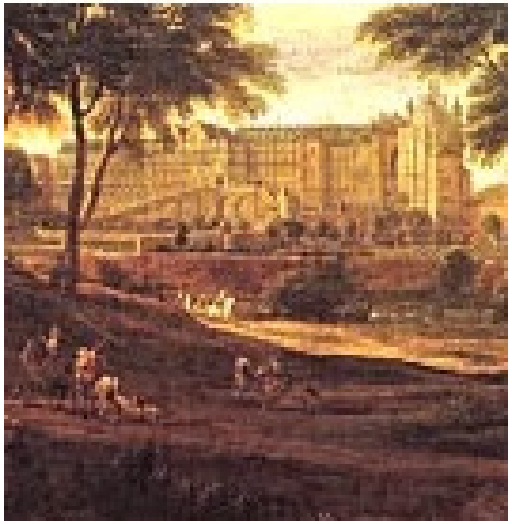
For fluoroquinolones, optmise both the C_{max}/MIC and the AUC_{24h}/MIC ratios

If you wish to get a faster eradication and reduce emergence of resistance

➔ C_{max} / MIC > 10

If you are interested in global effect …

➔ AUC_{24h} / MIC: 30 to 125

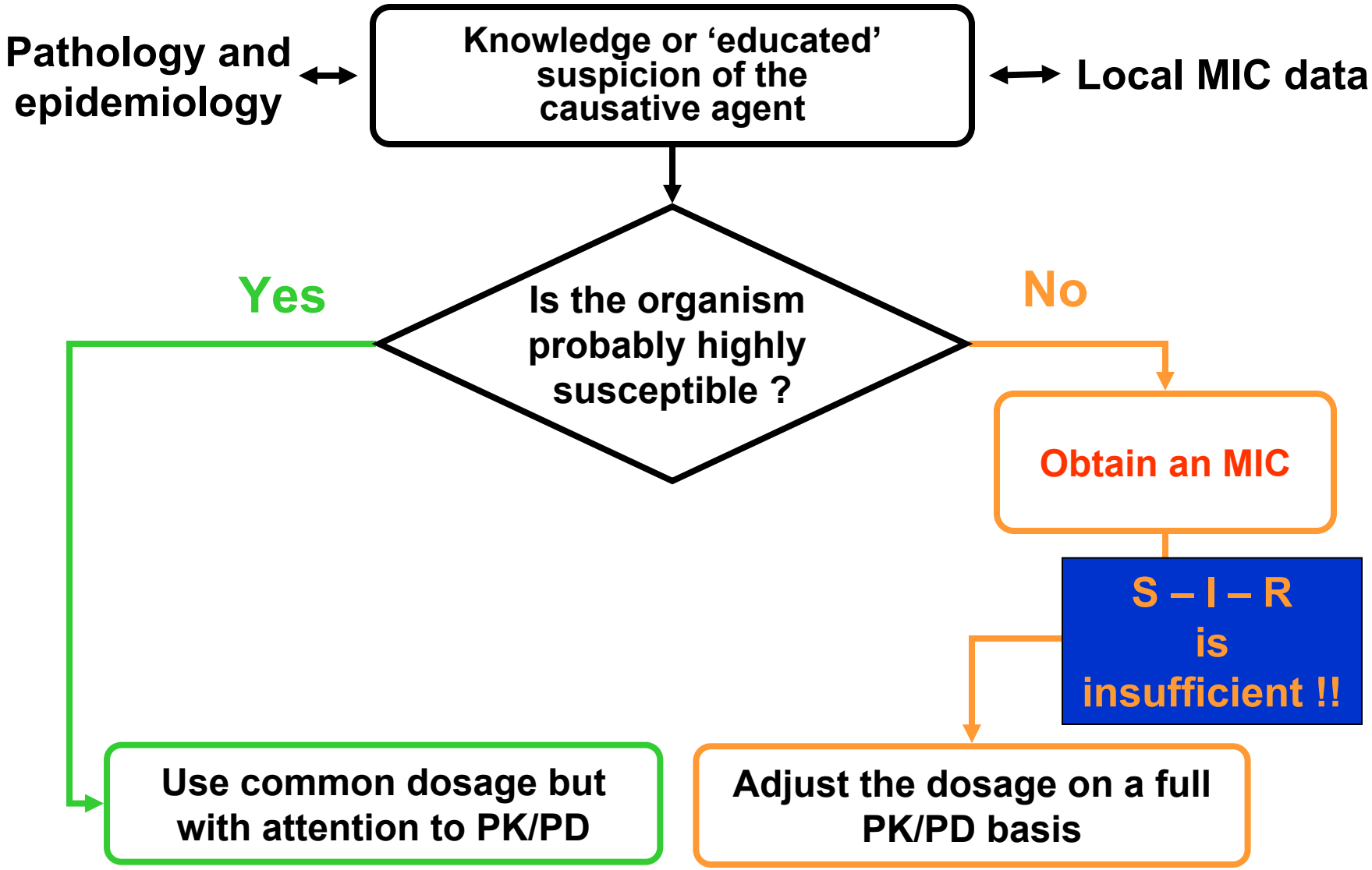


For all other antibiotics, optimize the AUC_{24h}/MIC ratio

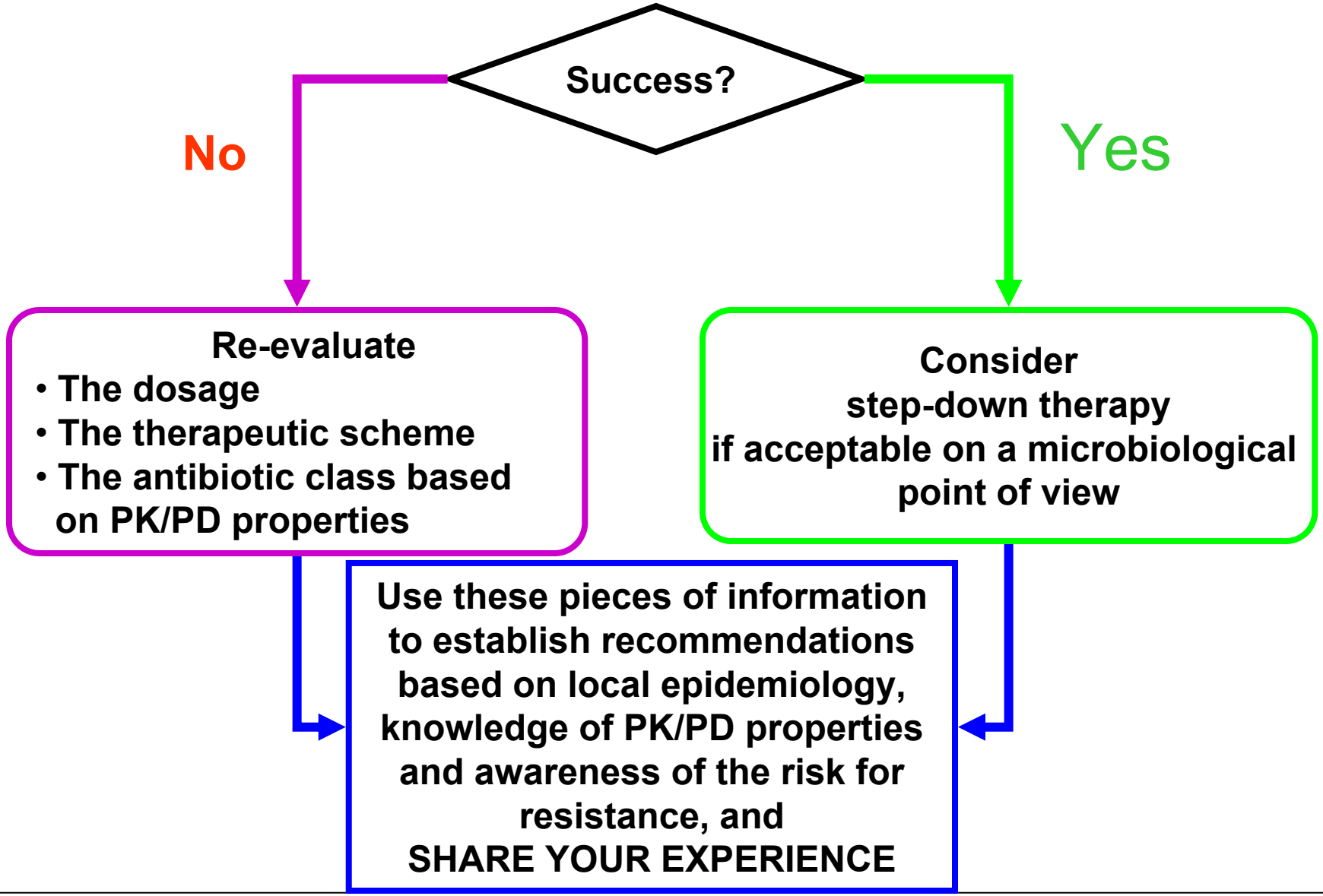
Simple rules:

- AUC = (dose x bioavailability) / clearance
- **Dose:** this is what you give...
- **Bioavailability:** this is what is absorbed by the patient
- **Look for a daiy dose that is sufficient for the MIC_{90}**
  (check EUCAST web site and rational documents)
  (low doses will promote the selection of resistance)

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.

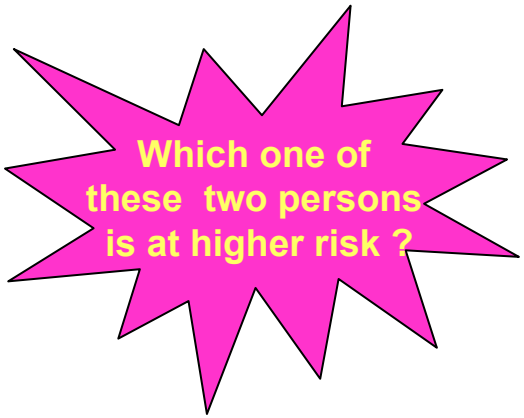
- **For all of you:** ***"New"*** antibiotics are not necessarily superior and may even be risky if the highest MIC they can safely cover is too close from the upper limit of the wild type population…

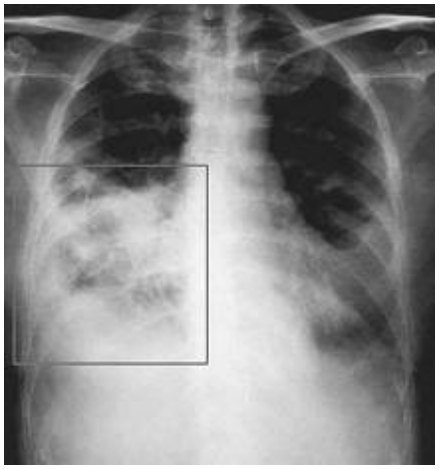
* get this information from your pharmacist, the literature, EUCAST, and industry …

Part 2: Setting guidelines for treatment optimization

Do we have a problem with "simple pneumonia"?

- CAP:
  - remains a major acute cause of death (3rd to 7th);
  - mortality varies from < 2% to 30% of more depending largely of co-morbidities, host defenses status, and age;
  - *Streptococcus pneumoniae* is the most commonly identified pathogen, but other bacteria may be critical in specific environments (the causative organisms remains, however, unidentified in 30% to 50% of cases).

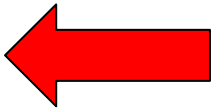




CAP: community acquired pneumonia

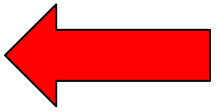
Guidelines: origin, basis and use

- Clinical guidelines aim at **guiding decisions and criteria** regarding diagnosis, management, and treatment

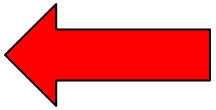


- Guidelines have been used since the beginning of medicine

- Modern medical guidelines are supposed to be based on **critical examination of current evidence**, with emphasis on **evidence-based** rather than eminence-based medicine

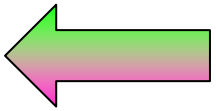


- More and more, healthcare professionals must not only know about, but **apply guidelines** or **justify why they do not follow them** for an individual patient or a group of patients

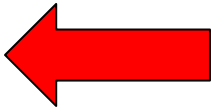


Guidelines: content and goals

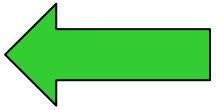
- Modern clinical guidelines should identify the **most valuable evidence** and integrate this knowledge to build **optimized decisions trees** that should be applicable to the **majority of patients**, while being sufficiently flexible to accommodate a sufficient level of **individual variation**



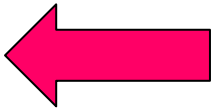
- But guidelines are also often seen as a mean to **standardize medical care** with 2 potential consequences/goals:



  - to **raise quality of care** while *reducing the risks* to patients

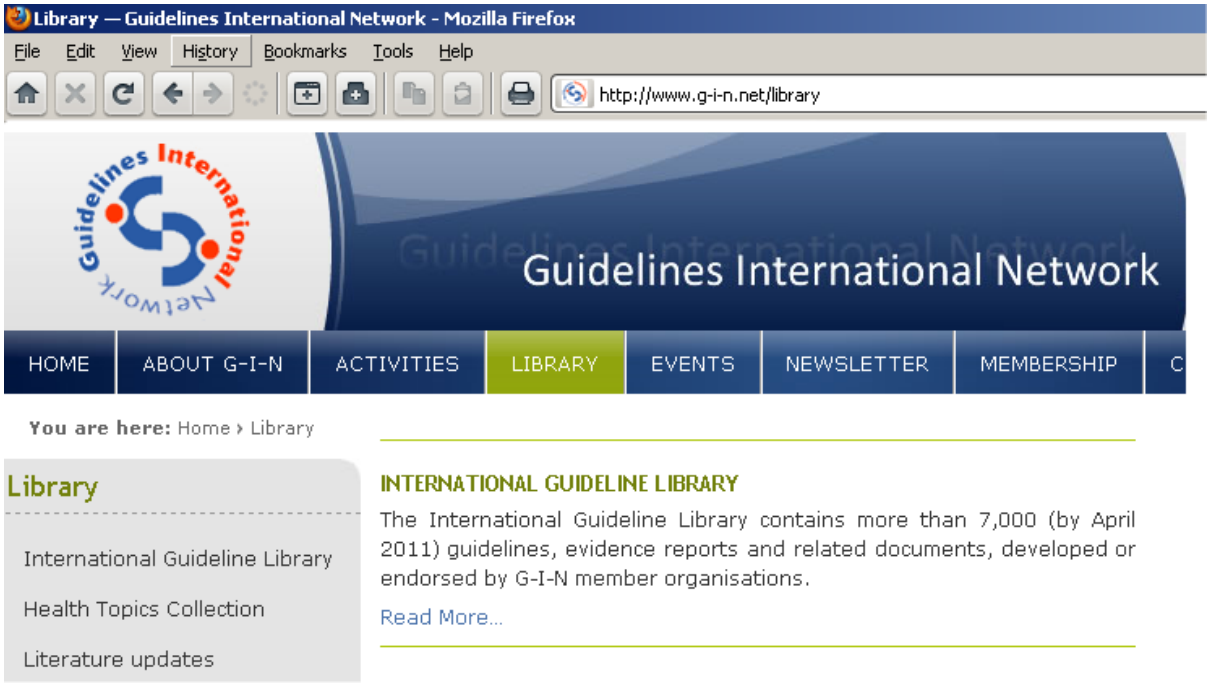


  - to achieve the **best balance between cost and medical efficacy** (broadly speaking)



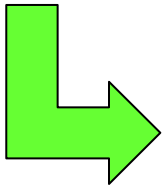
Guidelines: who and where?

- Guidelines at national or international level by experts and associations that should represent not only healthcare professionals but also patients (individual level) and society (societal level), and published in a variety of forms…
- Guidelines International Network (G-I-N) is the largest web-based database of medical guidelines worldwide



How to judge guidelines ?

- Guidelines should take enough parameters into account (qualitatively and quantitatively) to be pertinent
- Guidelines must be linked to the specific variables of the environment in which they will apply
- Guidelines must be applicable and regularly updated
- Guidelines should not be recipes



Editorial

Clinical practice guidelines: towards better quality guidelines and increased international collaboration

R Grol*,[1], FA Cluzeau[2] and JS Burgers[1]

[1]University Medical Centre Nijmegen, Nijmegen, The Netherlands; [2]St George's Hospital Medical School, London, UK

British Journal of Cancer (2003) **89**(Suppl 1), S4–S8. doi:10.1038/sj.bjc.6601077 www.bjcancer.com

Keywords: practice guidelines; quality assessment; international network

The AGREE instrument

- Originally developed through a grant from the European Union
- Published in its version 1 in 2001
- Updated as version 2 in 2010 (translations available in French and Chinese)

http://www.agreetrust.org/

The 6 main domains

AGREE II INSTRUMENT

I. Domain 1. Scope and Purpose

II. Domain 2. Stakeholder Involvement

III. Domain 3. Rigour of Development

IV. Domain 4. Clarity of Presentation

V. Domain 5. Applicability

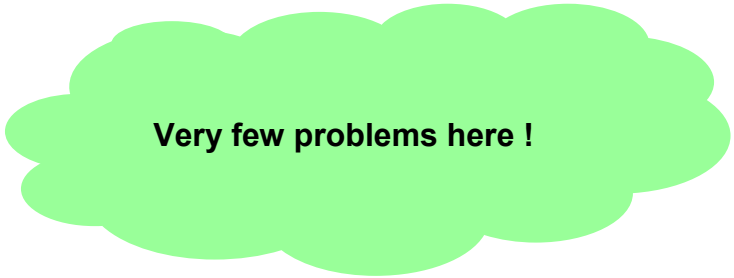
VI. Domain 6. Editorial Independence

***A**ppraisal of **G**uidelines **R**esearch and **E**valuation – developed through an EU-funded research project and available on http://www.agreetrust.org/

Looking at the main subdomains

I. Scope and purpose

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.



Looking at the main critical subdomains

II. Stakeholder involvement

1. **The guideline development group includes individuals from all relevant professional groups.**
2. **The views and preferences of the target population (patients, public, etc.) have been sought.**
3. The target users of the guideline are clearly defined.

Did you really take the patient into consideration ?

Looking at the main critical subdomains

III. Rigour of development

1. Systematic methods were used to search for evidence.
2. The criteria for selecting the evidence are clearly described.
3. The strengths and limitations of the body of evidence are clearly described.
4. The methods for formulating the recommendations are clearly described.
5. The health benefits, side effects, and risks have been considered in formulating the recommendations.
6. There is an explicit link between the recommendations and the supporting evidence.
7. The guideline has been externally reviewed by experts prior to its publication.
8. **A procedure for updating the guideline is provided.**

Perhaps a most critical point…

Looking at the main critical subdomains

III. Rigour of develop

1. Systematic method
2. The criteria for sele
3. [illegible] y
4. [illegible] ben[illegible]
   considered in fo[illegible]
6. There is an explicit
   supporting evidence
7. The guideline has b
   its publication.
8. **A procedure for updating the guideline is provided.**

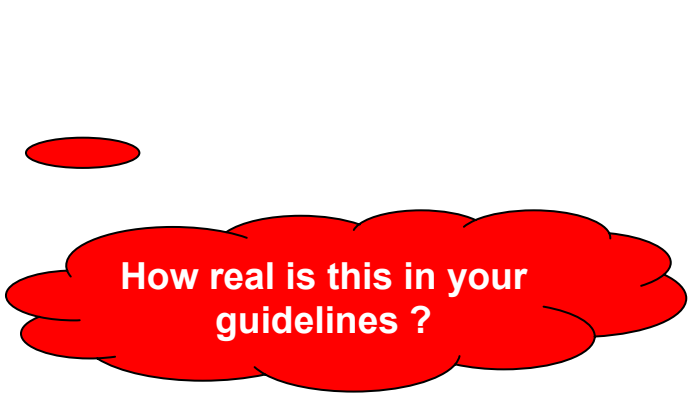
using this map may not be the best way to walk in Ho Chi Minh !!

Perhaps a most critical point…

Looking at the main critical subdomains

V. Applicability

1. **The guideline describes facilitators and barriers to its application.**
2. The guideline provides advice and/or tools on how the recommendations can be put into practice.
3. **The potential resource implications of applying the recommendations have been considered.**
4. **The guideline presents monitoring and/or auditing criteria.**



Looking at the main critical subdomains

V. Applicability

1. **The guideline (its application.**
2. The guideline p recommendatio
3. **The potential r recommendati**
4. **The guideline criteria.**

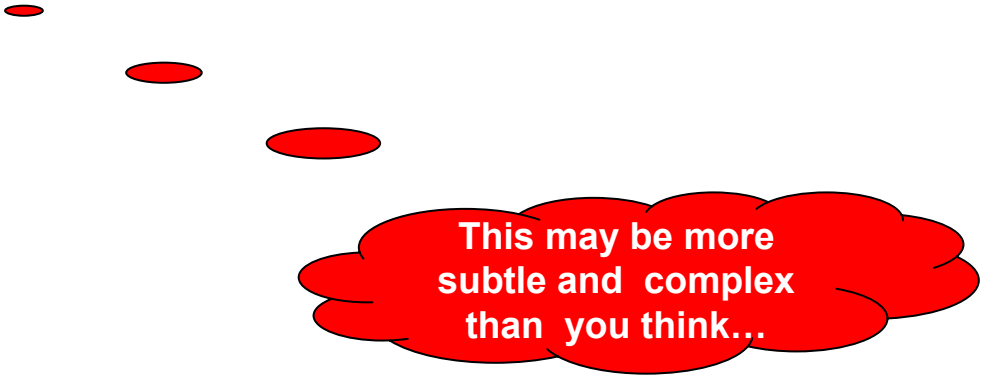
Can you find easily which connection is faulty ?

How real is this in your guidelines ?

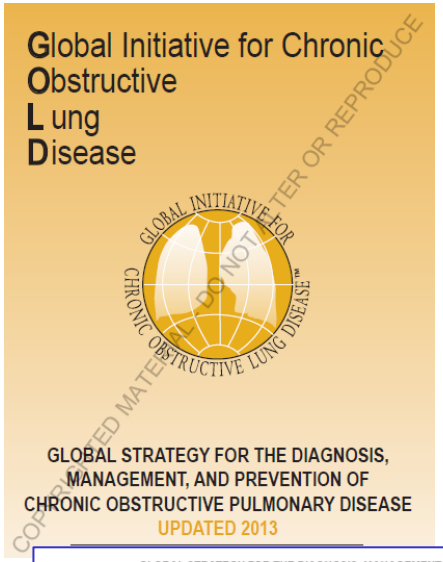
Looking at the main critical subdomains

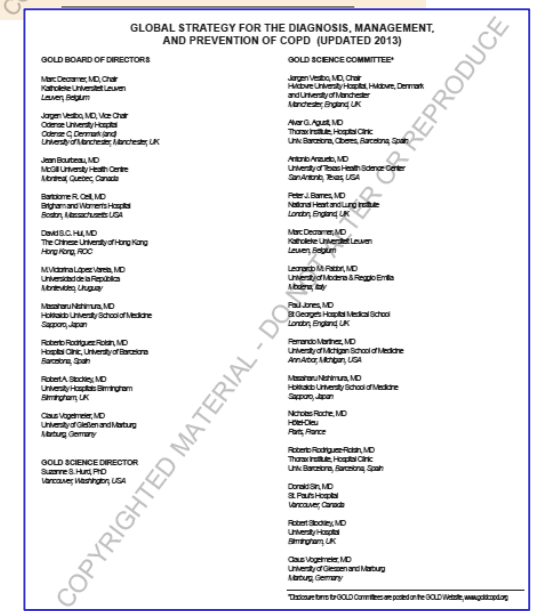
VI. Editorial Independence

1. **The views of the funding body have not influenced the content of the guideline.**
2. **Competing interests of guideline development group members have been recorded and addressed.**



Editorial independence is more than declaring...




GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (UPDATED 2013)

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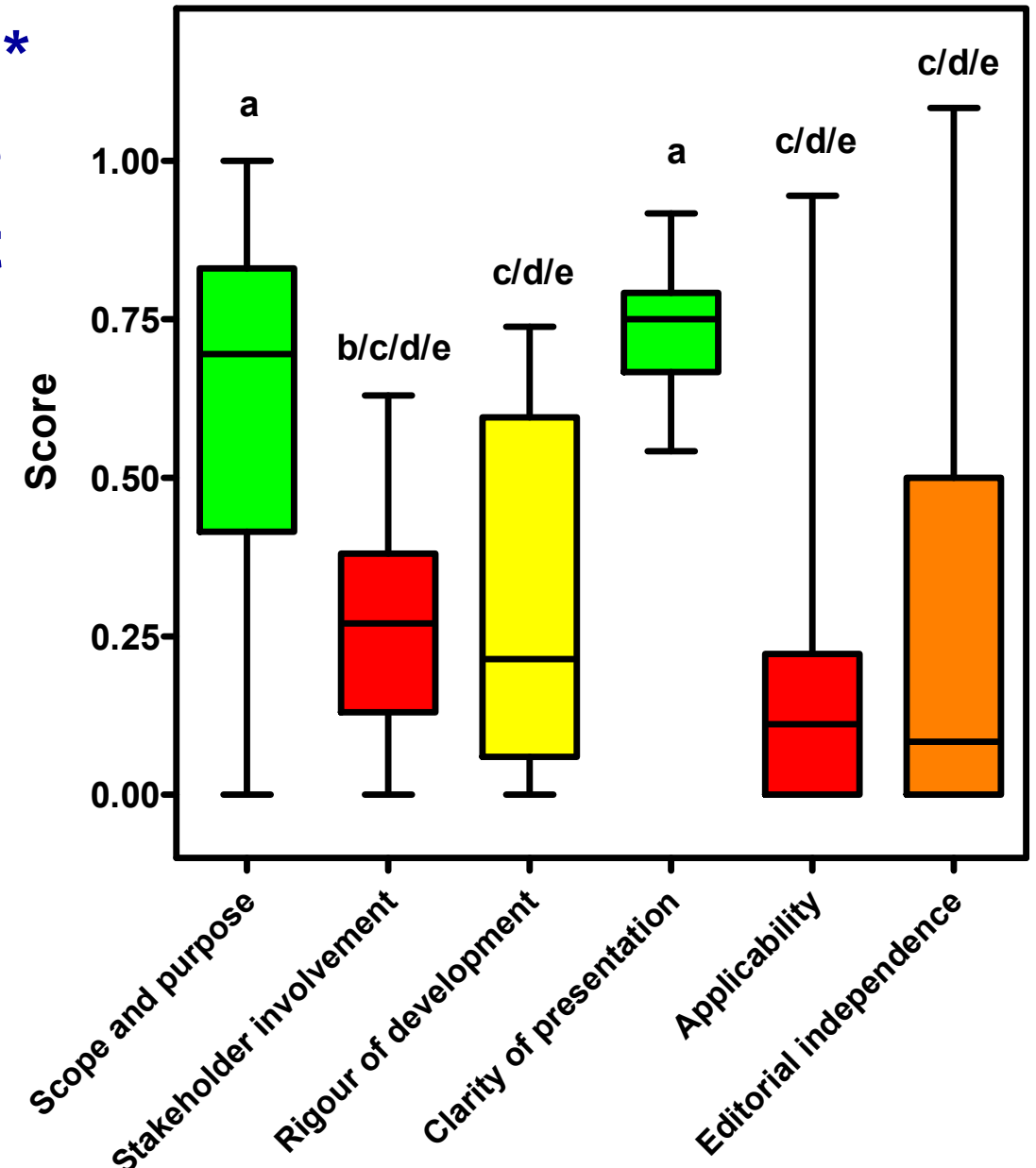
Analysis of 30 CAP * guidelines with the AGREE Instrument

* CAP: community acquired pneumonia

- Mean scores presented as ‘boxes and whiskers’ (lowest to highest with 25 -75% and median.
- Scores of domains with different letters are significantly different from each other (Kruskal-Wallis test with Dunn's Multiple Comparison Test)

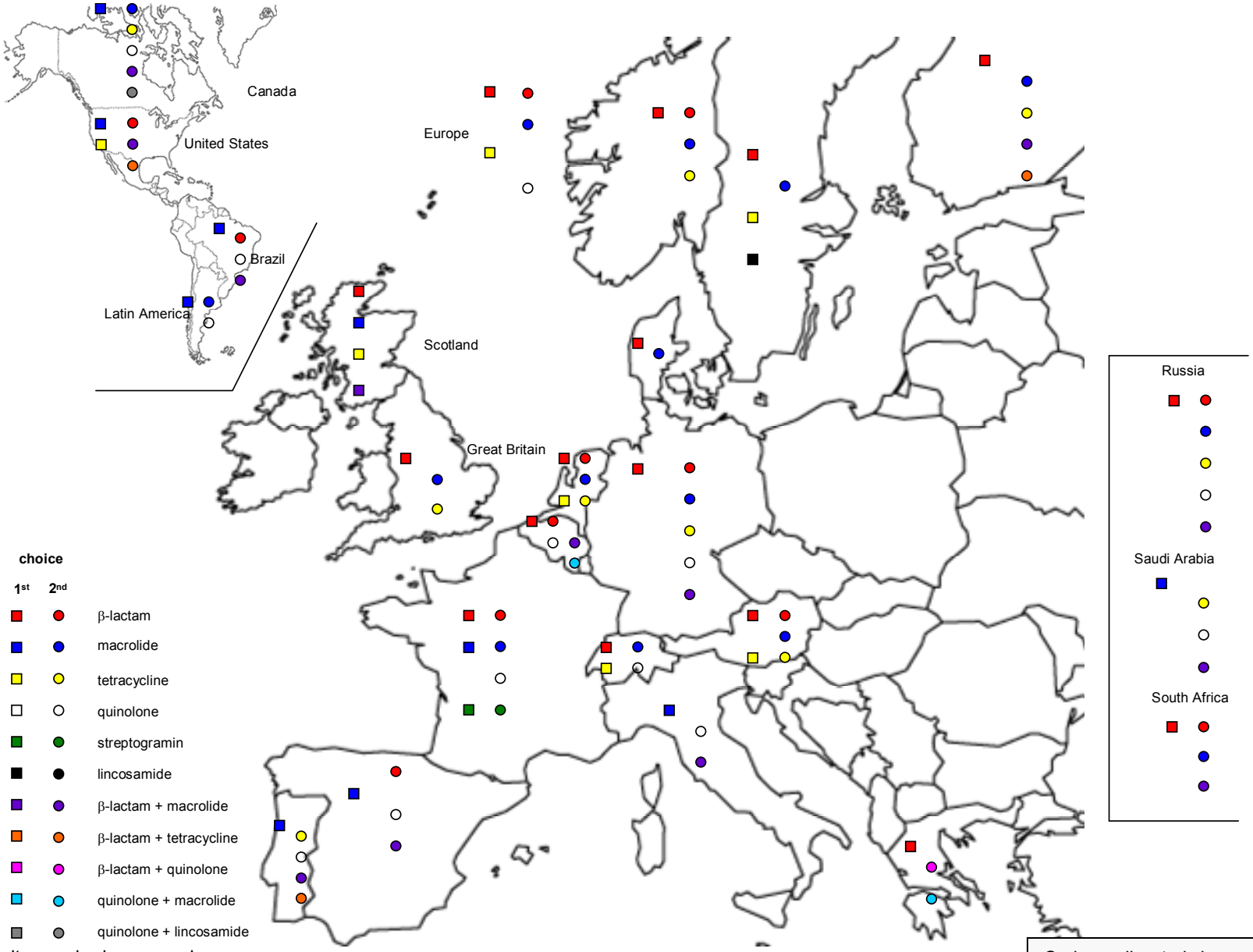


Carbonnelle *et al.*, in preparation

Guidelines: are they homogenous?

- They need not be, if:
  - the diseases are different between geographical areas or groups of patients
  - for infectious diseases, if the epidemiology is different between areas
  - if drug availability is not uniform…
  - if medical and pharmaceutical resources are different
- However, variations are often much larger than may be anticipated from the above considerations…

CAP guidelines: many variations



CAP: community acquired pneumonia

Carbonnelle *et al.*, in preparation

A (short)* summary of variations in Europe… (moderate CAP; empiric)

+ = 1st line **(+)** = alternative

Organization [a] (country or region)	β-lactam [b]	macrolide	tetracycl.	quinolone [c]	strepto-gramin [d]	β-lactam + macrolide	β-lactam + tetracycl.
ERS/ESCMID[1] ***Europe***	**+** (+)	(+)	**+**	(+)			
AFSSAPS[2] France	**+** (+)	**+** (+)		(+)	**+** (+)		
BTS[3] Great Britain	**+**	(+)	(+)				
PESC[4] Germany	**+** (+)	(+)	(+)	(+)		(+)	
SEPAR[5] Spain	(+)	**+**		(+)		(+)	
SPP[6] Portugal		**+**	(+)	(+)		(+)	(+)

* the full list (30 guidelines) is available upon request

[a] see back-up slides for definition of acronyms

[b] amoxicillin most often cited

[c] levofloxacine or moxifloxacin

[d] pristinamycin

1. Woodhead et al. Clin Microbiol Infect 2011; 17(Suppl. 6): E1–E59 – doi: 10.1111/j.1469-0691.2011.03672.x
2.Rev. Mal. Resp. 2003; 20:462-469 (http://www.em-consulte.com/showarticlefile/143561/pdf_51690.pdf)
3. http://www.thepcrj.org/journ/vol19/19_1_21_27.pdf
4. http://media.econtext.de/v1/stream/16-236/acbdd299911a2e9c099c465d9d011062/1274968644/16/236.econtext
5 Arch Bronconeumol. 2005;41(5):272-89 (http://www.archbronconeumol.org/en/pdf/13075322/S300/)
6. http://www.sppneumologia.pt/sites/sppneumologia.pt/files/pdfs/RPP_2005_3_243_Praticas.pdf

A comparison of two CAP guidelines separated by an ocean …

Clinical situation	North American guidelines	UK guidelines
Initial antibiotic choice for adults hospitalized with low-moderate severity CAP treated in the commu	• selected patients with no cardiopulmonary disease or modifying factors → **macrolide alone *** • outpatients with cardiopulmonary disease or 'modifying factors': – monotherapy with a **quinolone** – combination **β -lactam (high dose) + macrolide or tetracycline.**	Most patients can be adequately treated with oral antibiotics **Oral therapy with amoxicillin is preferred** When oral therapy is contraindicated, recommended parenteral choices include **iv amoxicillin or benzylpenicillin, or clarithromycin**
Initial antibiotic choice for adults hospitalized with severe CAP	If no pseudomonal risk factors • **β -lactam +macrolide** or • **antipneumococcal quinolone** (gemifloxacin [oral] > moxifloxacin [oral/IV] > levofloxacin [oral/IV]) Note: quinolone > macrolides if suspected or proven *Legionella* infection If pseudomonas risk factor • **antipseudomonal β -lactam + ciprofloxacin / high-dose levofloxacin** • combination **aminoglycoside + macrolide or antipneumococcal quinolone**	**IV β -lactamase stable β-lactam (amoxi-clav) + clarithromycin** In penicillin-allergic patients, → 2^{d}/3^{d} generation cephalosporin + clarithromycin If *Legionella* is strongly suspected, consider adding levofloxacin

Adapted from NM.S. Niederman Community-acquired pneumonia. *In* Infectious Diseases (3d edition; J. Cohen, W. Powderly & S. Opal, eds), chap. 27 Elsevier/Mosby, 2010 (ISBN 978-0-323-04579-7). Available on line at http://www.expertconsult.com

A comparison of two CAP guidelines separated by an ocean …

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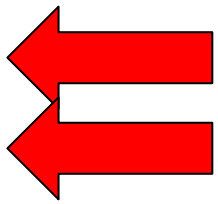
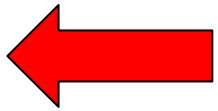
Key questions to ask when setting guidelines in infectious diseases (with application to CAP/COPD)

- How sure are you of the diagnosis ?
- **Which are the main pathogens ?**
- **What are their current resistance patterns ?**
- How should the therapy be initiated (empiric *vs.* directed) ?
- **Which level of adverse effects is acceptable ?**
- Which patients do you mainly treat?
- Does cost matter?
- What are your real choices?



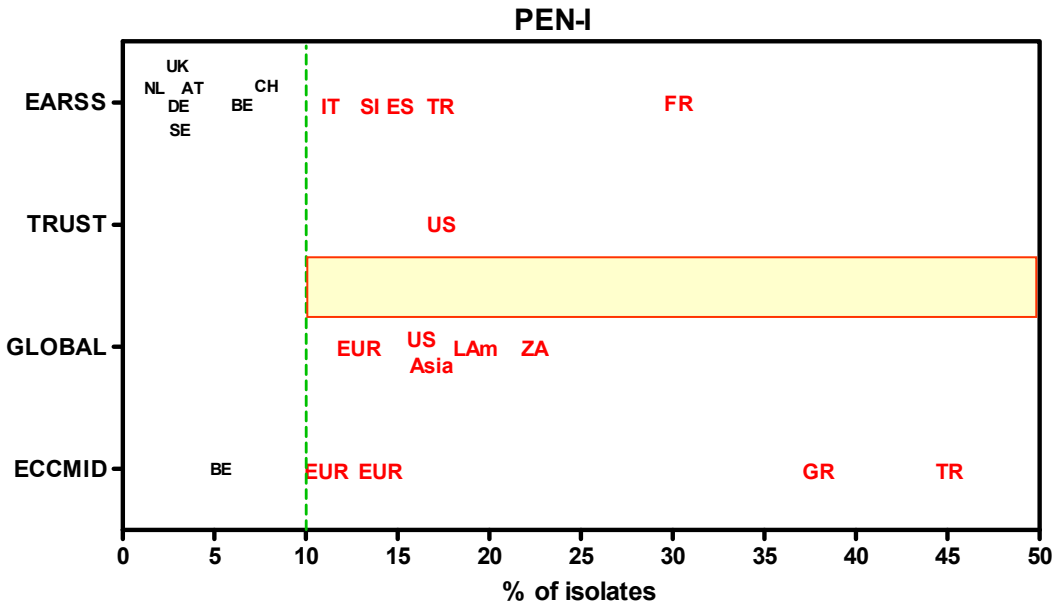


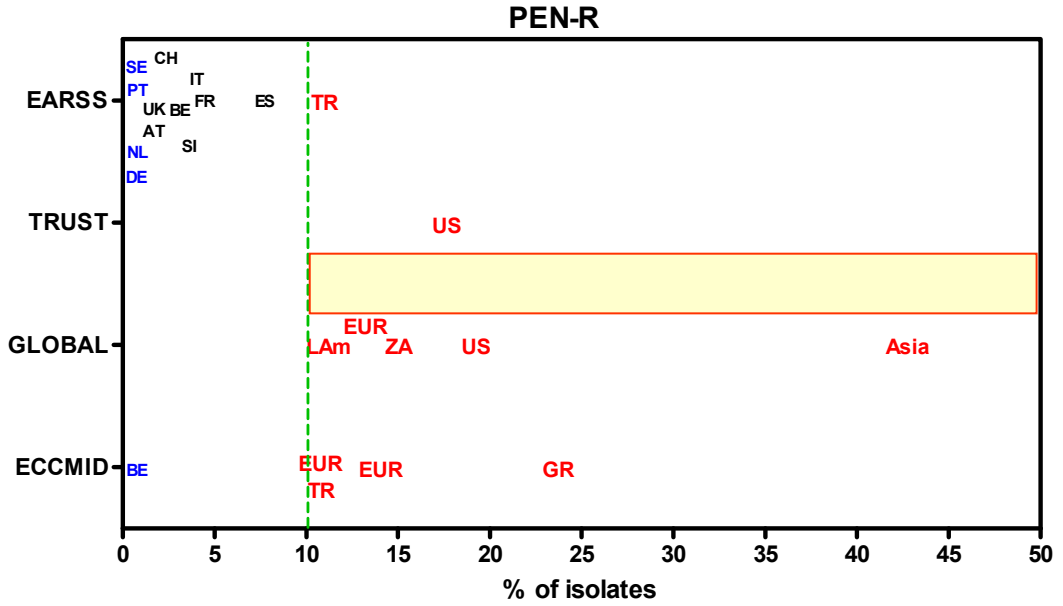
CAP: community acquired pneumonia
COPD: chronic obstructive pulmonary disease

Resistance of *S. pneumoniae* *

*Analysis of resistance to penicillins (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

- **EARSS**: European Antimicrobial Surveillance system
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **ECCMID**: abstracts of the 18-20th European Congress of Clinical Microbiology and Infectious Diseases





Lismond *et al.*, in preparation

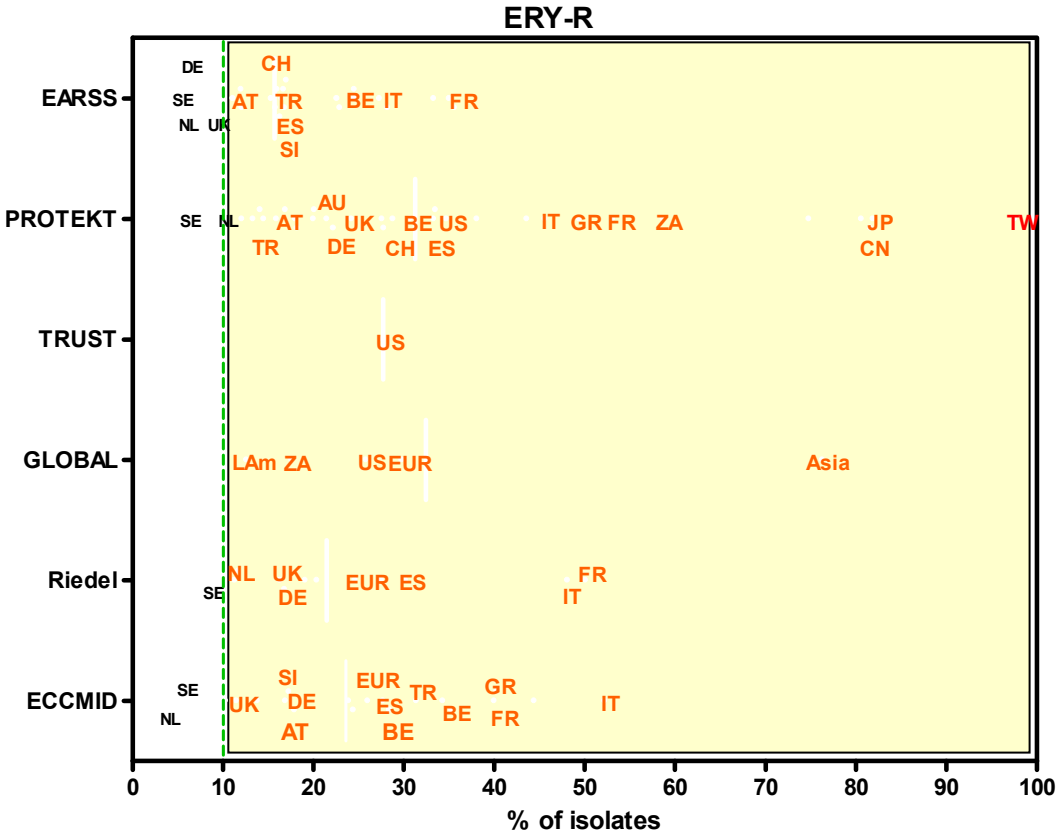
CAP: community acquired pneumonia

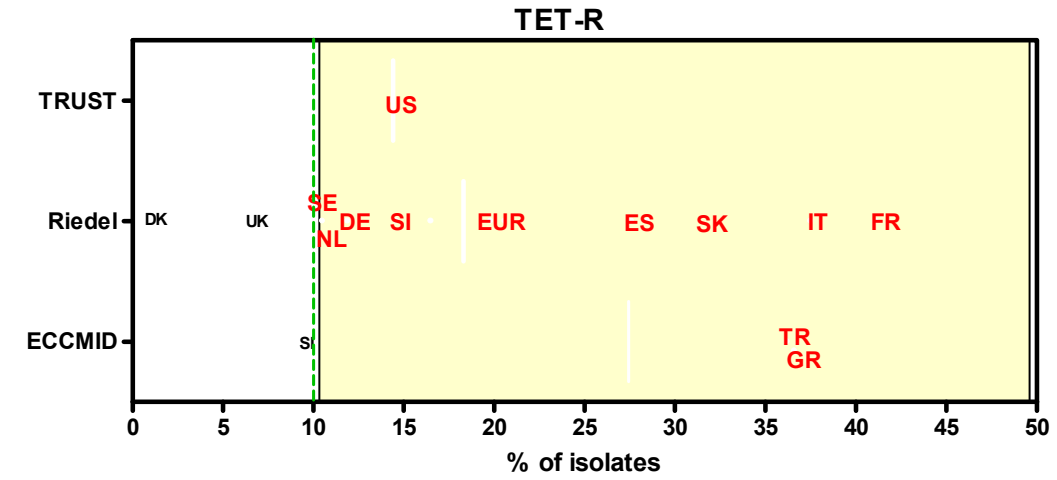
Resistance of *S. pneumoniae* *

*analysis of resistance of eryhromycin and doxycycline (with CAP as main indication) in surveillance systems or publications (*S. pneumoniae*)

- **EARSS**: European Antimicrobial Surveillance system
- **PROTEKT**: Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
- **TRUST**: Tracking Resistance in the United States Today
- **GLOBAL**: Global Landscape On the Bactericidal Activity of Levofloxacin
- **Riedel:** Eur J Clin Microbiol Infect Dis. 2007 Jul;26(7):485-90.
- **ECCMID**: abstracts of the 18th European Congress of Clinical Microbiology and Infectious Diseases

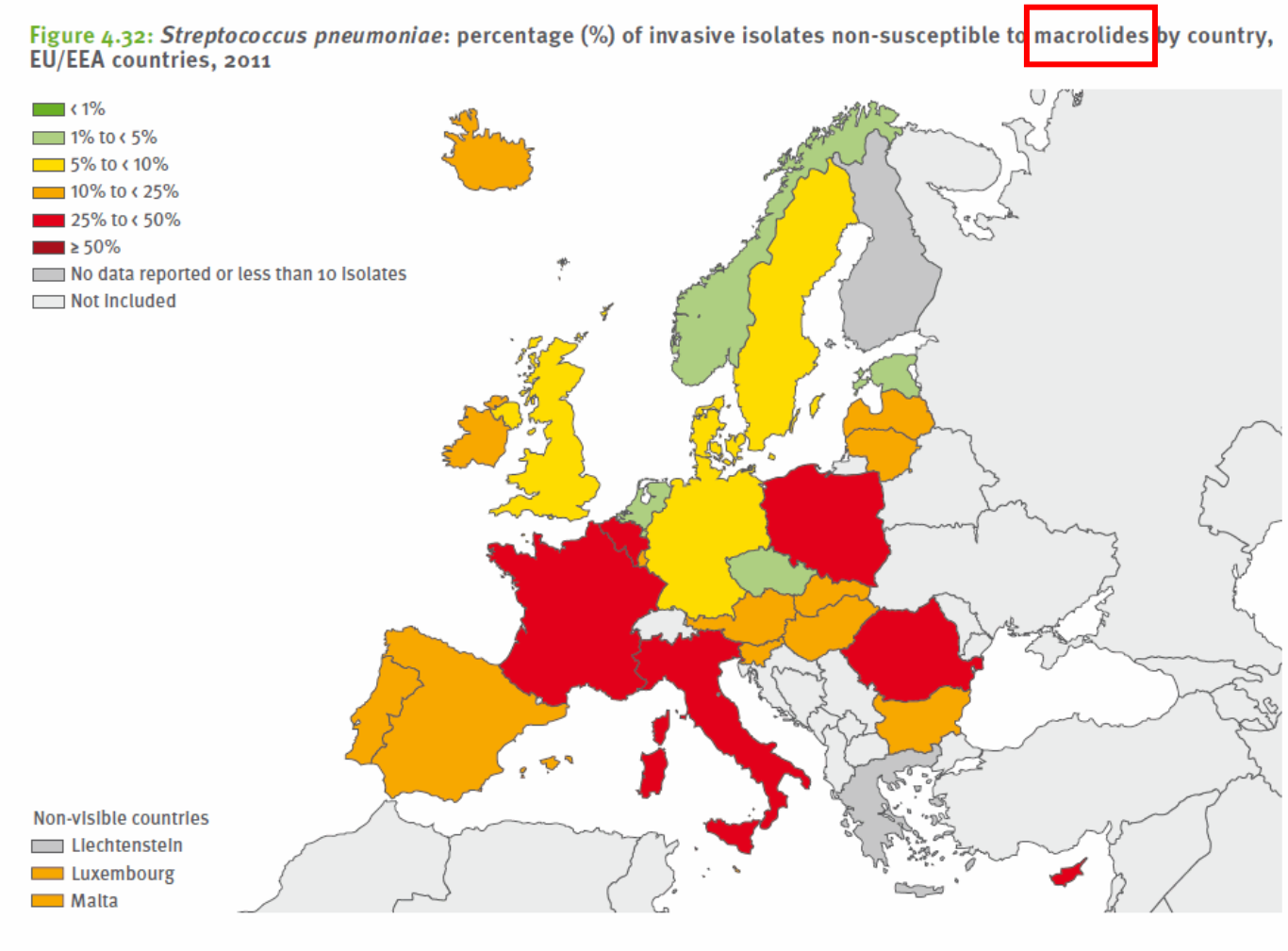
Lismond *et al.*, in preparation





The message: make and use surveillance studies

Countries / Regions should know THEIR resistance patterns !



European Antimicrobial Resistance Surveillance Network
http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

The message: make and use surveillance studies

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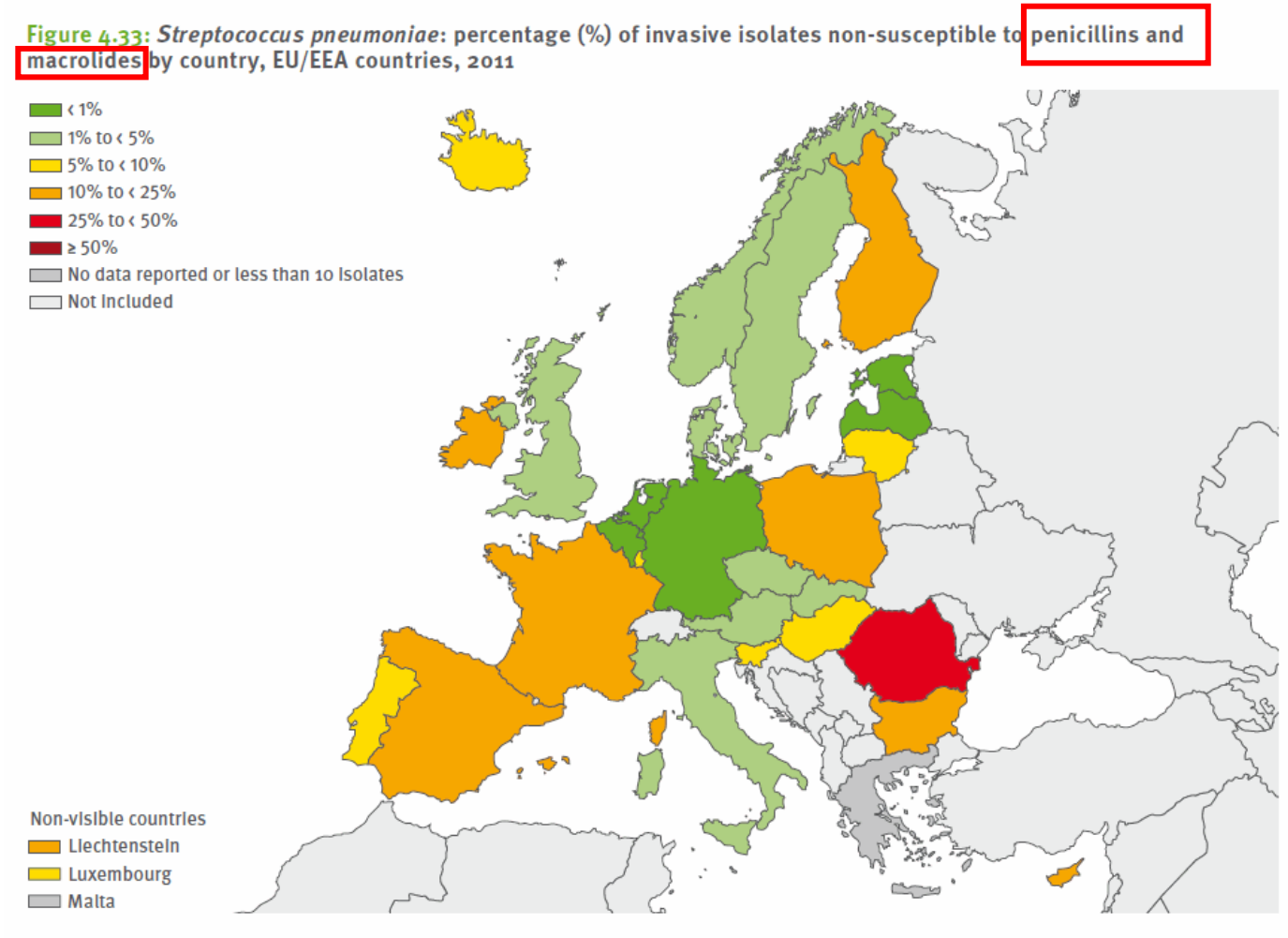


European Antimicrobial Resistance Surveillance Network
http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

An example of national surveillance…

Pathologie Biologie 58 (2010) 147–151

ELSEVIER MASSON

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

10th Survey of antimicrobial resistance in noninvasive clinical isolates of *Streptococcus pneumoniae* collected in Belgium during winter 2007–2008

Dixième surveillance de la résistance aux antibiotiques dans des souches non invasives de Streptococcus pneumoniae collectionnées en Belgique pendant l'hiver 2007 à 2008

R. Vanhoof [a,*], K. Camps [b], M. Carpentier [c], S. De Craeye [a], J. Frans [d], Y. Glupczynski [e], P. Goffinet [f], B. Gordts [g], D. Govaerts [h], L. Ide [i], P. Lefèvre [j], M. Lontie [k], R. Cartuyvels [l], F. Meunier [m], B. Mulongo [n], I. Philippart [o], I. Surmont [p], E. Van Bossuyt [a], J. Van Eldere [q], J. Verhaegen [q]

[a] *WIV/ISP, Unit of Antibiotic Research, Institute of Public Health, 642, Engelandstraat, 1180 Brussel, Belgium*
[b] *AZ Stuivenberg, 2060 Antwerpen, Belgium*
[c] *Hôpital de la Citadelle, 4000 Liège, Belgium*
[d] *Imeldaziekenhuis, 2820 Bonheiden, Belgium*
[e] *Clinique universitaire de Mont-Godinne, 5530 Yvoir, Belgium*
[f] *Cliniques du Sud-Luxembourg, 6700 Arlon, Belgium*
[g] *AZ St. Jan, 8000 Brugge, Belgium*
[h] *CHU André-Vésale, 6110 Montignies-le-Tilleul, Belgium*
[i] *AZ Jan Palfijn, 9000 Gent, Belgium*
[j] *Hôpital Princesse-Paola, 6900 Marche-en-Famenne, Belgium*
[k] *Medisch Centrum Huisartsen, 3000 Leuven, Belgium*
[l] *Virga-Jessesiekenhuis, 3500 Hasselt, Belgium*
[m] *Hôpital de Jolimont, 7100 Haine St. Paul, Belgium*
[n] *Clinique Saint-Étienne, 1210 Bruxelles, Belgium*
[o] *Hôpital de Warquignies, 7300 Boussu, Belgium*
[p] *H.-Hartziekenhuis, 8800 Roeselare, Belgium*
[q] *National Reference Centre Pneumococci, UZ Gasthuisberg, 3000 Leuven, Belgium*

Vanhoof *et al.* Pathologie Biologie 2010; 147-151

Analyzing one guideline (CAP in Belgium)

http://www.health.belgium.be/eportal/Myhealth/Care/Properuse/Antibiotics/15616531_FR?ie2Term=Guide%20belge%20des%20traitements%20anti-infectieux%20en%20pratique%20ambulatoire&ie2section=83

Comparing guidelines (CAP / oral)

Categories

- no comorbidity*, low lethal risk* and no pejorative condition ***
  - *S. pneumoniae*
- if comorbidities
  - *S. pneumoniae*
  - *H. influenzae*

* COPD; diabetes; renal, hepatic or neurological disease; cardiac insufficiency; cancer

** lethal risk: resp. freq. 30/min ; art. press. < 90/60 mmHg; température > 40C o' < 35C; confusion; cyanosis; heart rate > 125/min

*** pejorative conditions: age >65 years, previous hospitalization for pneumonia, recent antibiotic treatment, unfavouravle socioeconomic status, poor compliance; severe emesis

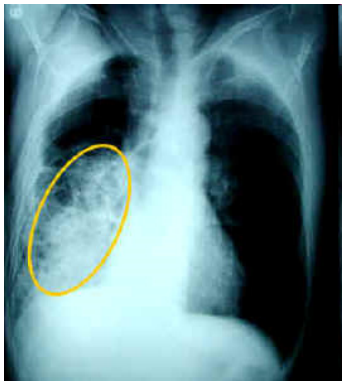
Antibiotics

- no comorbidity, low lethal risk and no pejorative condition
  - **amoxicilline 1 g q8h**
- if comorbidity:
  - **amoxicillin-clavulanic acid**
- if non-IgE-mediated allergy to penicillin:
  - **cefuroxime axetil**
- if IgE-mediated allergy to penicillin
  - **moxifloxacin 400 mg/day**
- if no improvement within 48 h
  - **add a macrolide (clarithromycin, azithromycin)**

Guide Belge des traitements anti-infectieux en pratique ambulatoire (http://www.health.belgium.be)

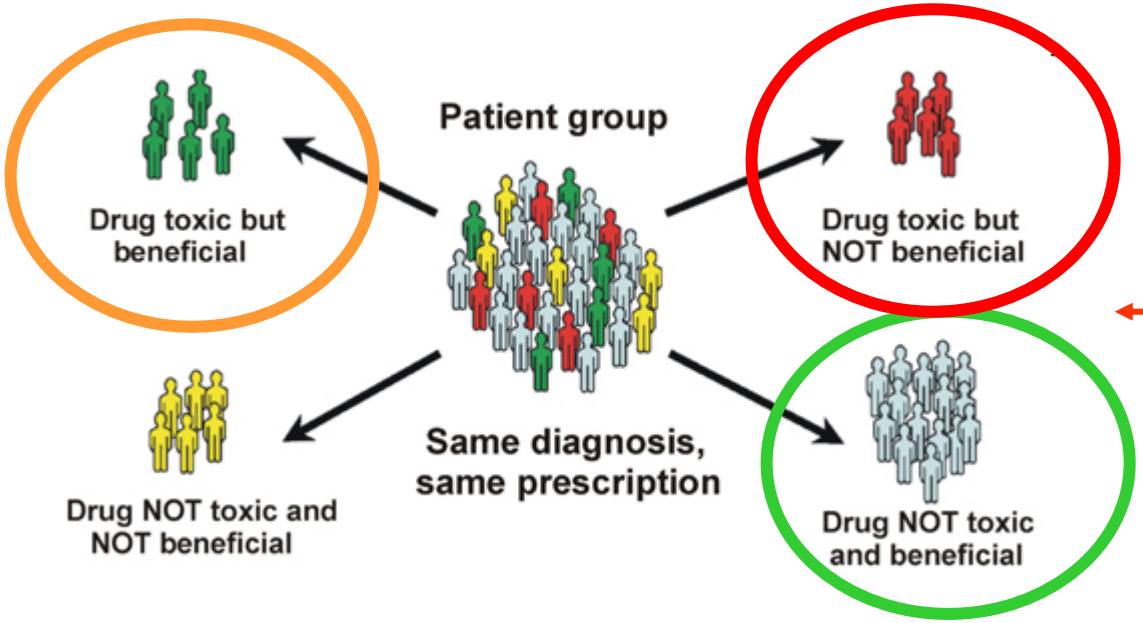
CAP: community acquired pneumonia

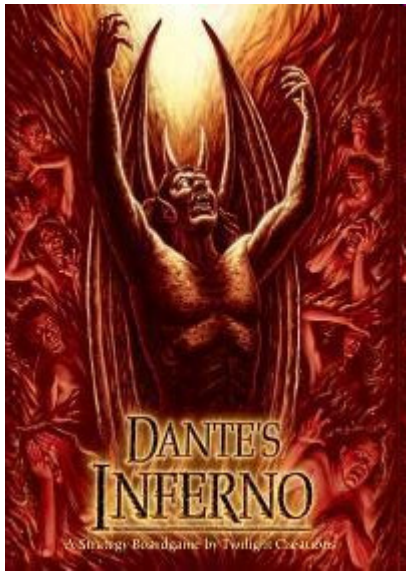
But what about side effects…



therapy ?

side effects ?





All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
β-lactams	**amoxicillin**	• **Anaphylactic reactions** ← • *Clostridium difficile*-associated colitis • Digestive tract: diarrhoea, nausea • CNS: agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness.
	amoxicillin – clavulanic acid	• **Anaphylactic reactions** ← • *Clostridium difficile*-associated colitis • **Hepatic toxicity, including hepatitis and cholestatic jaundice** ← • Digestive tract: diarrhoea, nausea • CNS : agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness
	cefuroxime	• **Anaphylactic reactions and cutaneous eruptions** ← • Nephrotoxicity (aggrav. with loop diuretics) • Hepatic toxicity • *Clostridium difficile*-associated colitis
	ceftriaxone	• **Anaphylactic reactions and cutaneous eruptions** ← • Digestive tract:diarrhoea, nausea • *Clostridium difficile*-associated colitis • Hematologic disturbances (éosinophilia, leucopenia, granulopenia, thrombopenia) • Hepatic and biliary toxicities (precipitation of Ca^{++} salt) • CNS: cephalalgia, vertigo

* based on an analysis of the respective labelling (European SmPC or equivalent)

Carbonelle et al. , in preparation

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
Macrolides	**clarithromycin**	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • **Drug interactions (CYP450)** • **Hepatic toxicity, including hepatitis and cholestatic jaundice** • **Palpitations, arrhythmias including prolonged QTc** • Digestive tract: diarrhoea, nausea, vomiting, abnormal taste • CNS: headache, confusion, …
	azithromycin	• Anaphylactic reactions • *Clostridium difficile*-associated colitis • Drug interactions (CYP450), less frequent than with other macrolides • **Hepatic toxicity, including hepatitis and cholestatic jaundice** • Digestive tract: diarrhoea, nausea, abdominal pain • CNS: dizziness, fatigue, vertigo, … • Genitourinary: nephritis, vaginitis
	telithromycin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity** • Visual disturbance • Loss of consciousness • Respiratory failure in patients with myastenia gravis • **QTc prolongation** • **Drug interactions (CYP450)** • Digestive tract: diarrhoea, nausea, vomiting, dysgueusia • CNS: headache, dizziness

* based on an analysis of the respective labelling (European SmPC or equivalent)

Carbonelle et al. , in preparation

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
fluoroquinolones	levofloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • Hematologic toxicity • **Hepatotoxicity (ALT-AST elevation [common])** • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Musculoskeletal: tendinopathies** • Peripheral neuropathy • Prolongation of the QTc interval (cardiac disorders [rare]) • **Hypoglycaemia (rare)** • **Digestive tract: nausea, diarrhoea**
	moxifloxacin	• Anaphylactic reactions and allergic skin reactions • *Clostridium difficile*-associated colitis • **Hepatotoxicity (ALT-AST elevation [common])** • **Musculoskeletal: Tendinopathies** • Peripheral neuropathy • Prolongation of the QT interval (cardiac disorders [rare]) • Central nervous system effects: headache, insomnia, dizziness, convulsions • **Digestive tract: nausea, diarrhoea**

* based on an analysis of the current respective labelling (European SmPC)
- common: 1/10 to 1/100
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:

- *For [community-acquired pneumonia], TAVANICc should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*
- *Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.*

Carbonelle *et al.* , in preparation

All antimicrobials have associated risks

Conclusions so far:

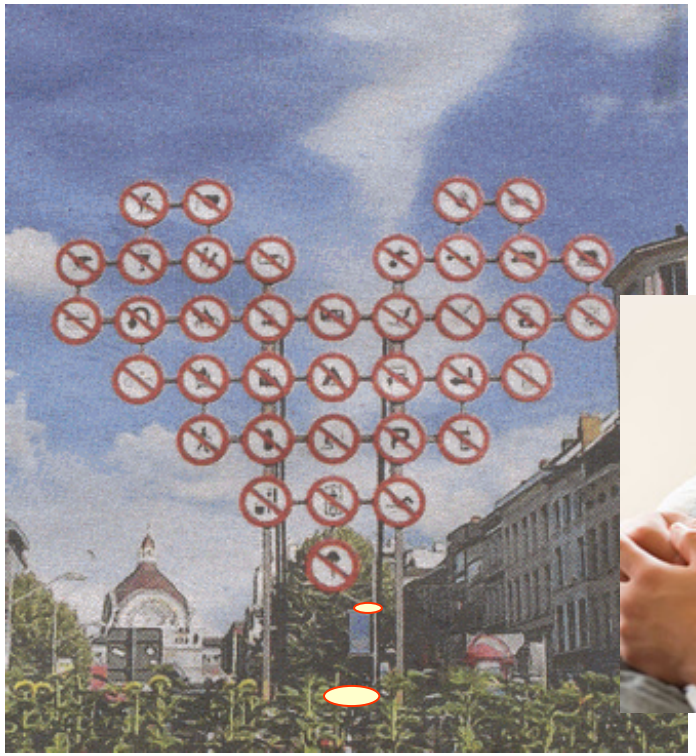
- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the **specific environment** and for the **specific patient**

Never say that …

and check for specific risks

RTI: respiratory tract infection

The 3 major "points for attention" in guidelines



Are they not too dogmatic ?

Are they geared to the REAL patient ?

Are they regularly updated and modernized ?

Conclusions (and food for thought)

- Guidelines are **interesting** and most probably **useful**
- Their writing is a **difficult exercise** and their implementation is a long journey (unsurprisingly)… that **never ends** (no surprise either) …
- They MUST remain open to accommodate for **local** and special situations, with the primary emphasis on **epidemiology** and the second on **real patients**…
- At the end of the day, it will be the doctor's choice, but that choice MUST be rational and based on **best evidence applied to the patient**
- Societal responsibility (in this case, the **emergence of resistance**) should not be ignored*
- Economic responsibility is also important, although the acquisition costs of antibiotics are MUCH lower than those of many other drugs*

***Not addressed in this lecture but do ask questions…**

Disclosures

Financial support from

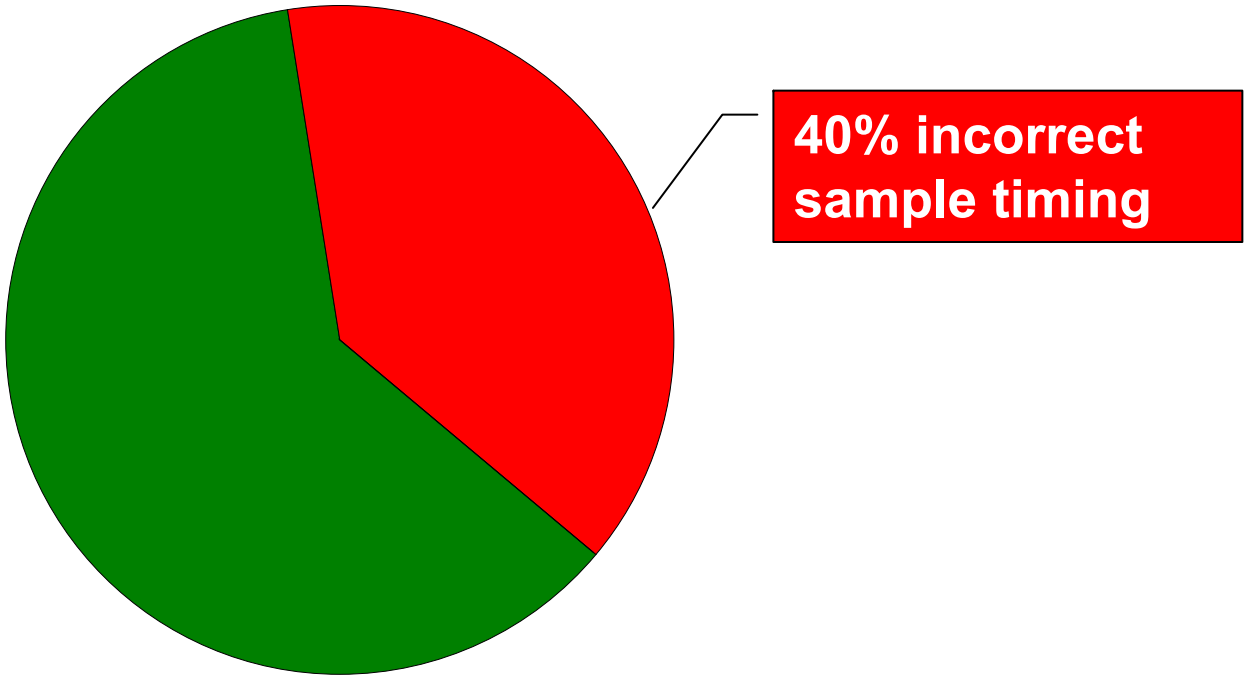
- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics…
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - Belgian Transparency and Reimbursement Committees
  - Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones

Part 3: Usefulness of a clinical pharmacist

Vancomycin: continuous infusion

- Why
- How
- Does it work in a whole hospital ?

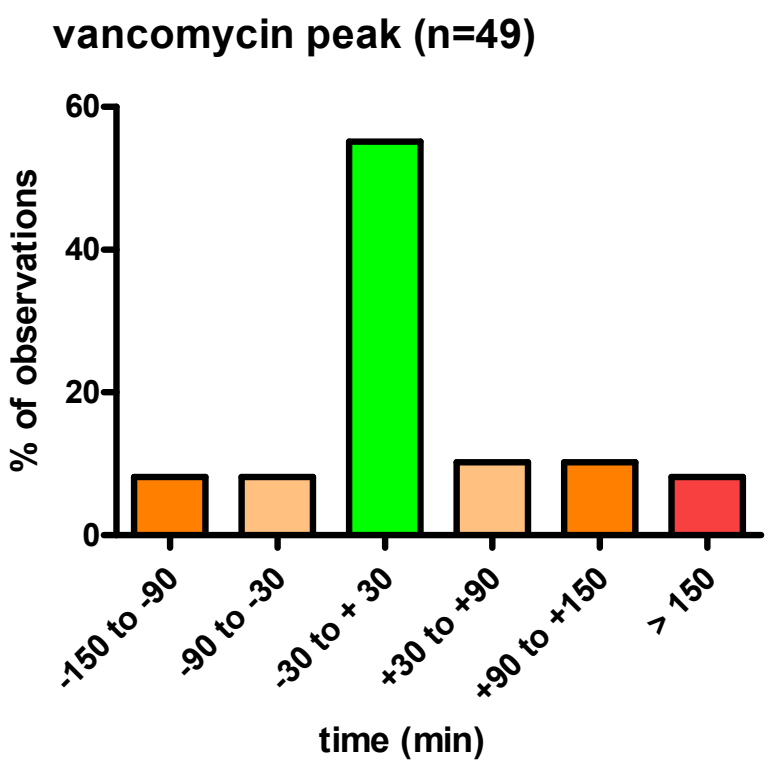
Observational study – results

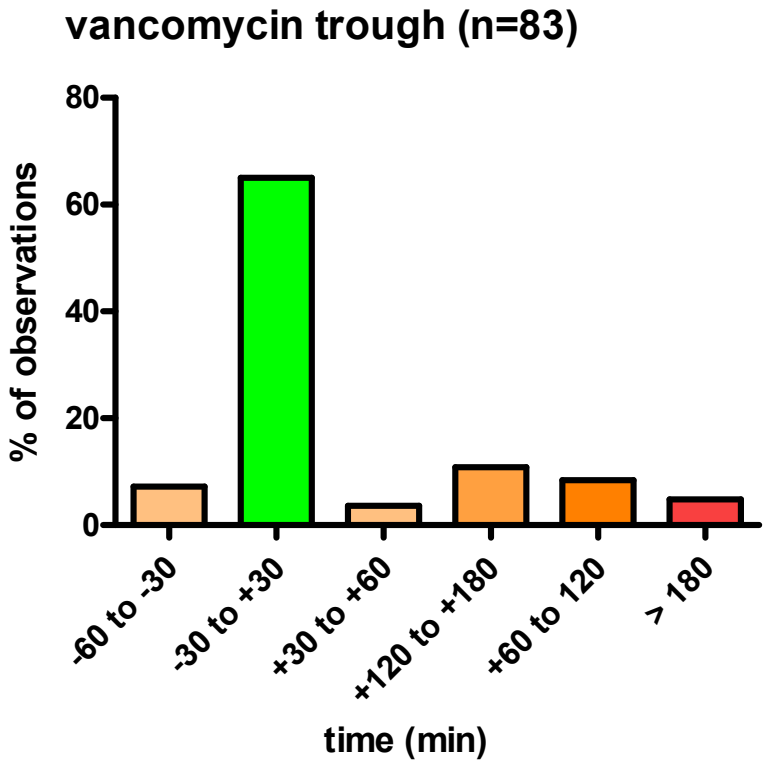


*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

Observational study – results

Observed deviations (in min) from recommended sampling times at baseline.





*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

Observational study – results

TDM process measures for twice daily (BID; baseline) mode of administration of vancomycin

Criterium	BID
Sample timing within 30 min. from scheduled time	61.3% [81/132] [a]
Implementation of TDM dose recommendations	32 % [21/66]
Prescribed daily dose in accordance with hospital guidelines	17% [95/560]
% of serum levels in the recommended ranges	33.3% [37/112] [b]

[a] number of total observations (see Table 1 for the number of patients)
[b] most deviations were towards lower than expected values (average: 20 %)

Qualitative methods in healthcare

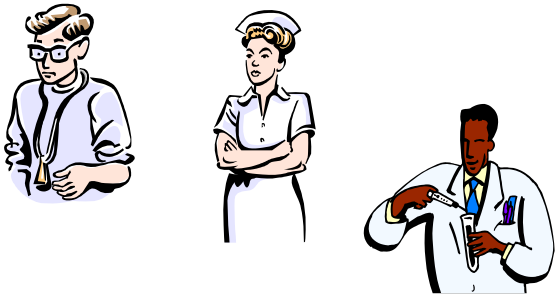
Quantitative methods (clinical trials)	Qualitative methods (interviews, observations, notes)
'how many'?	'why?' and 'how?' (hypothesis generating)
what is the % of inappropriate TDM? what is the impact of x on this %?	*why/how does inappropriate TDM occur?*
large, random samples	small, purposive samples

Qualitative study – results

Emerging themes identified during the analysis of the transcripts of the focus groups and related to low TDM performance and deviations from local TDM guidelines during the baseline phase (BID).

Socio-cultural and structural elements	-inertia of practice
	-lack of motivation and personal involvement
	-insufficient interdisciplinary collaboration
	-unclear definition of responsibilities
	-ill-adapted techniques
Training and information	-insufficient (post-) graduate education
	-'teacher-centred' learning approach
	-incomplete and/or difficult to apply local guidelines
	-conflict between local guidelines and external guidelines
harm-benefit ratio of TDM	-patient too frail
	-unnecessary samplings for the information gained

Qualitative study – results



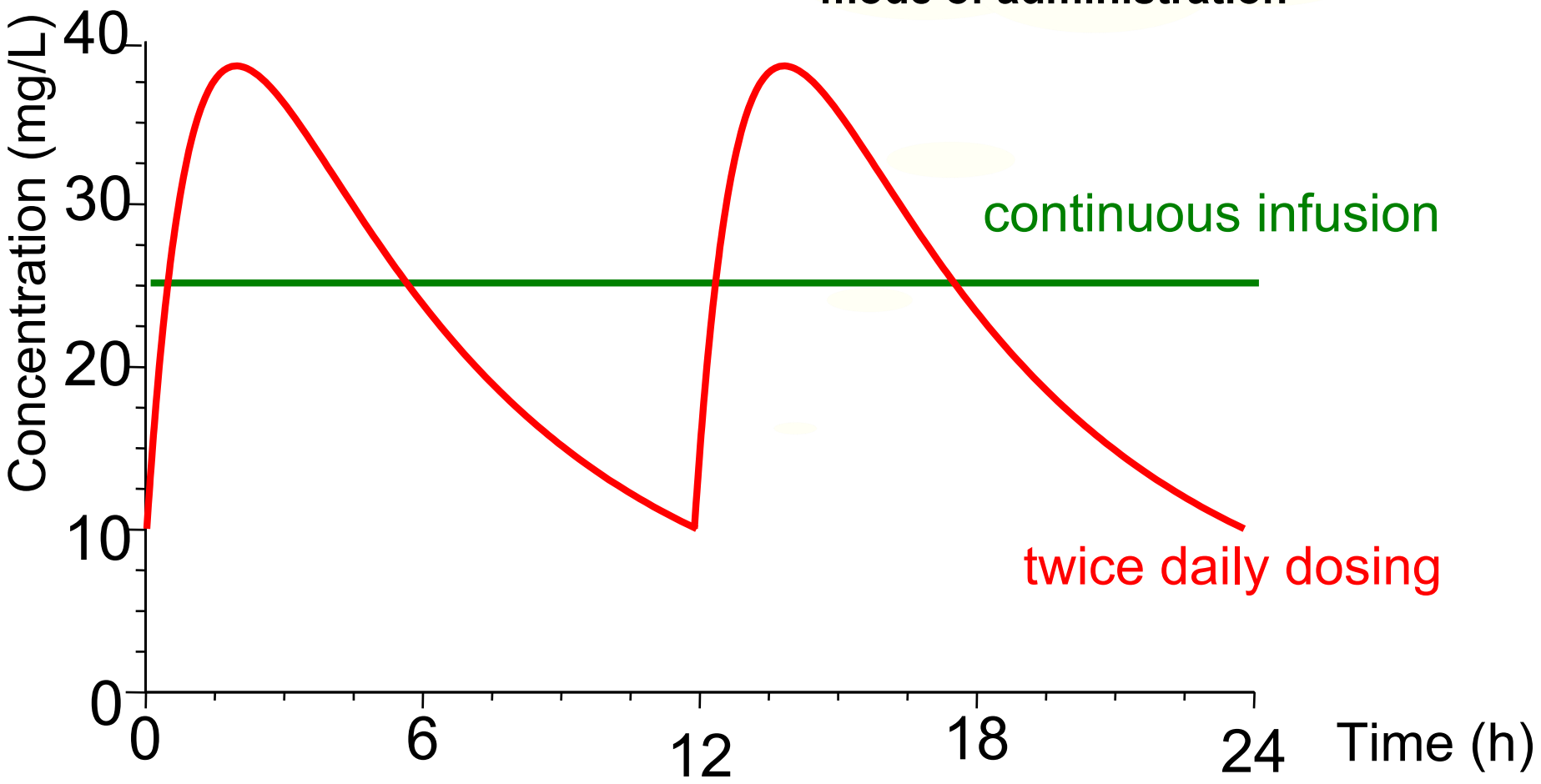
M2: "I'm convinced that there are pharmacokinetic calculations on which we will base [our next dosing] and which are erroneous because the sample drawing and the timing of the administration have not been made correctly, it is completely random, I mean… "

M1: "It is forbidden, on my ward, to follow the therapeutic recommendations of the laboratory, what the lab proposes."

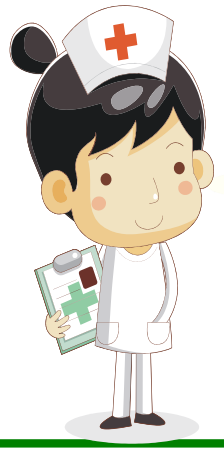
N2: *"It represents a lot of additional samples for frail patients. Sometimes, I ask myself whether all these samples are necessary."*

Vancomycin is a AUC_{24h}/MIC–dependent antibiotic

AUC24h /MIC independent of the mode of administration



how to optimize vancomycin treatment



“Continuous infusion is easier because it allows to control the duration of administration and samples can be taken at any time”

Vancomycin administration and therapeutic drug monitoring from a PK/PD perspective

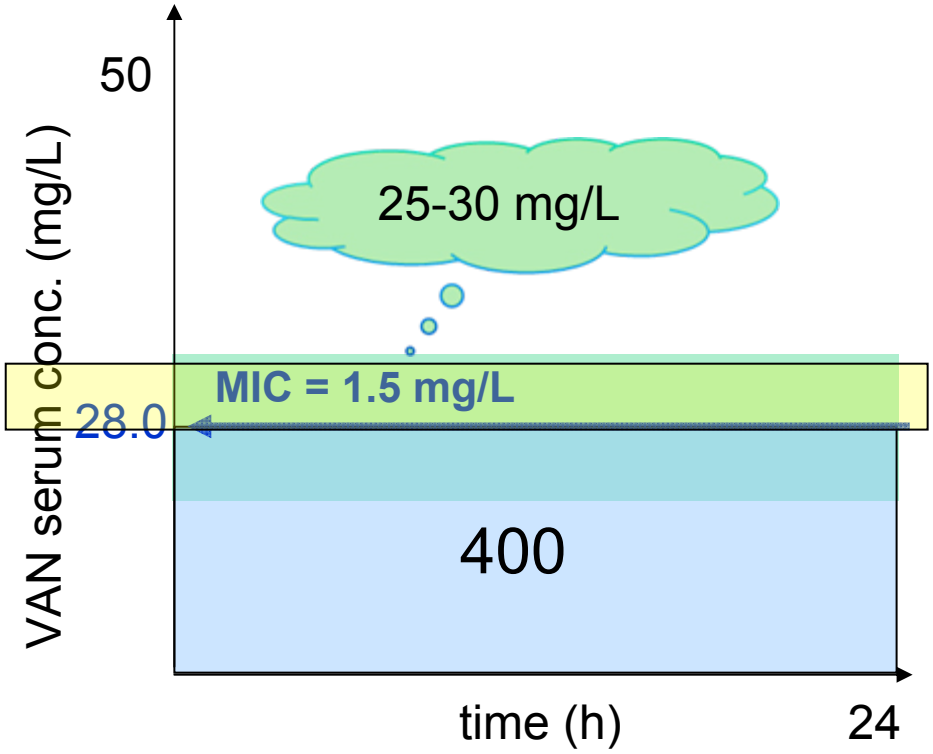
Implementation of a Protocol for Administration of Vancomycin by Continuous Infusion: Pharmacokinetic, Pharmacodynamic and Toxicological aspects

E. Ampe, PharmD; B. Delaere, MD; J.D. Hecq, PharmD, PhD; P.M. Tulkens, MD, PhD; Y. Glupczynski, MD

Int J Antimicrob Agents. 2013 May;41(5):439-46

vancomycin CI: which serum concentration should we target?

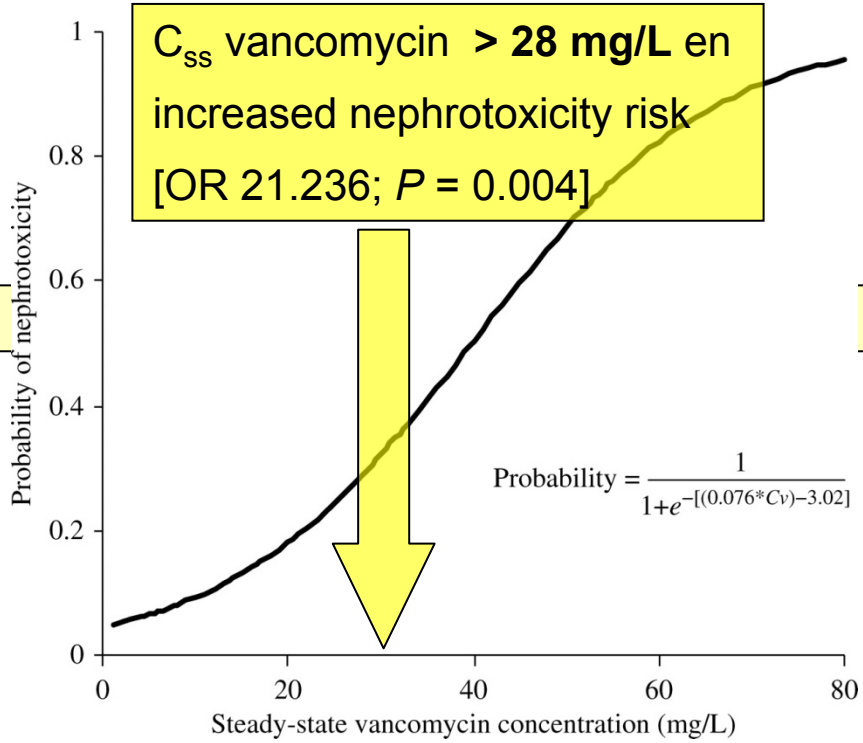
efficacy



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

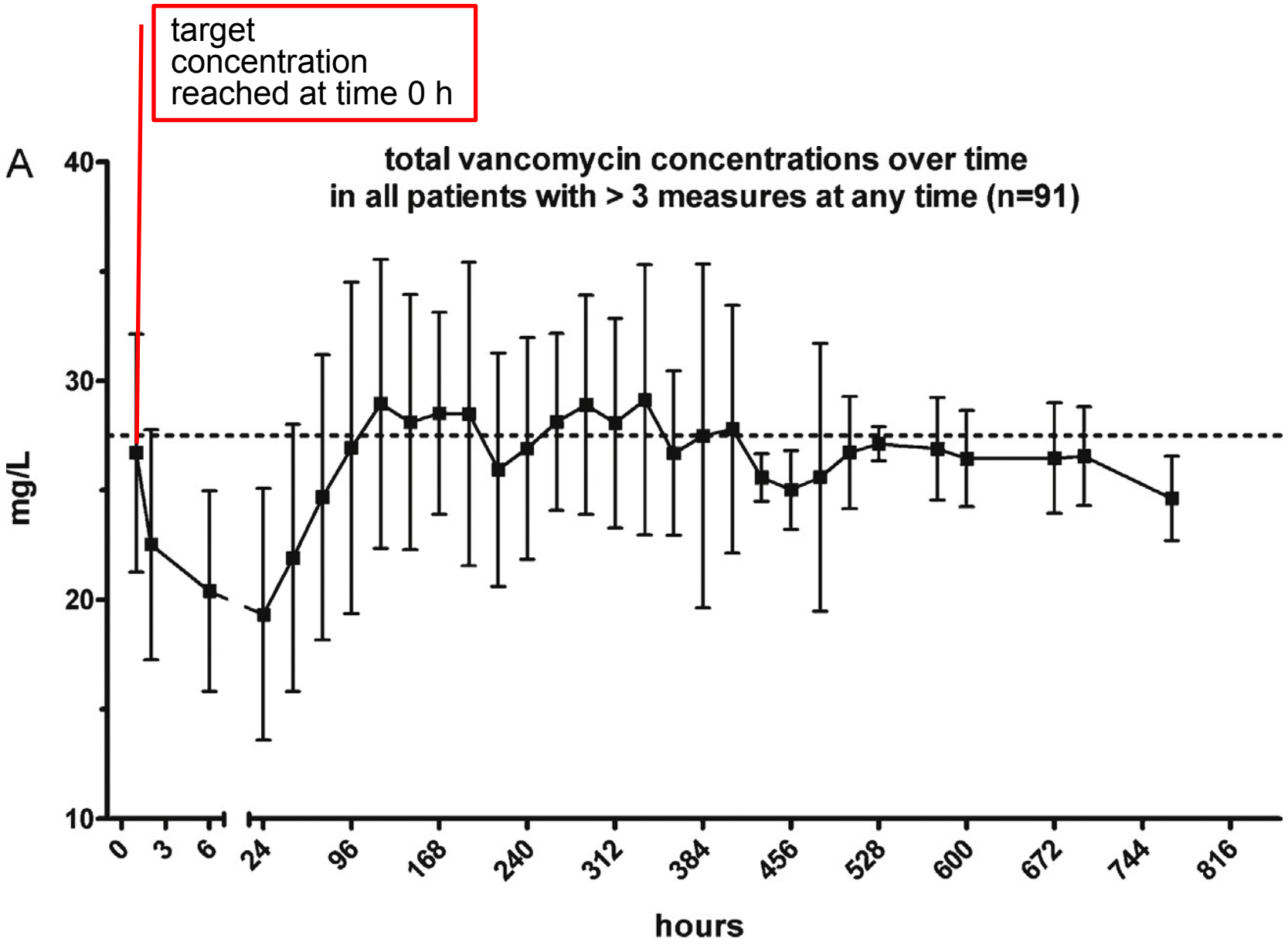
toxicity

C_{ss} vancomycin **> 28 mg/L** en increased nephrotoxicity risk [OR 21.236; *P* = 0.004]

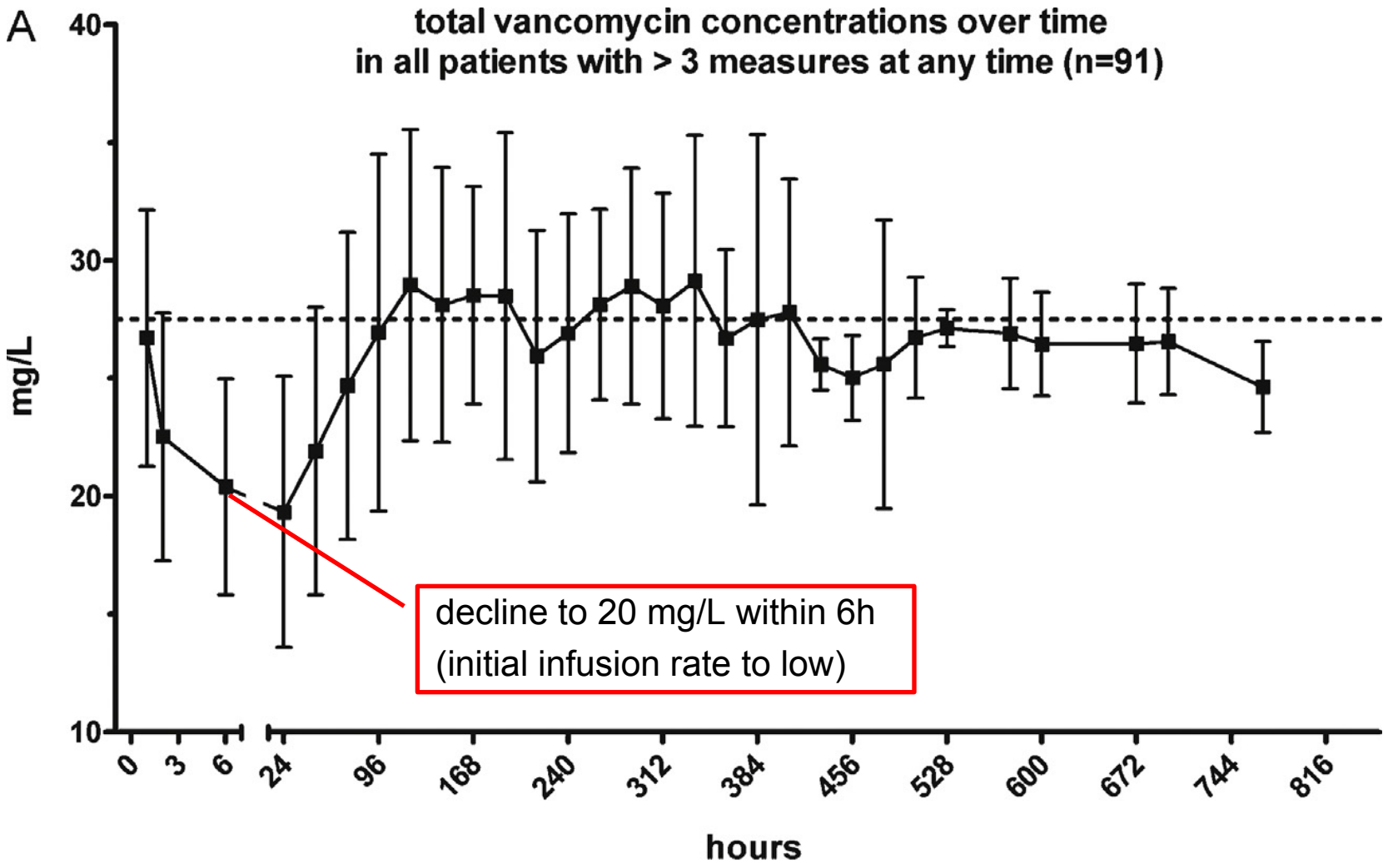


Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

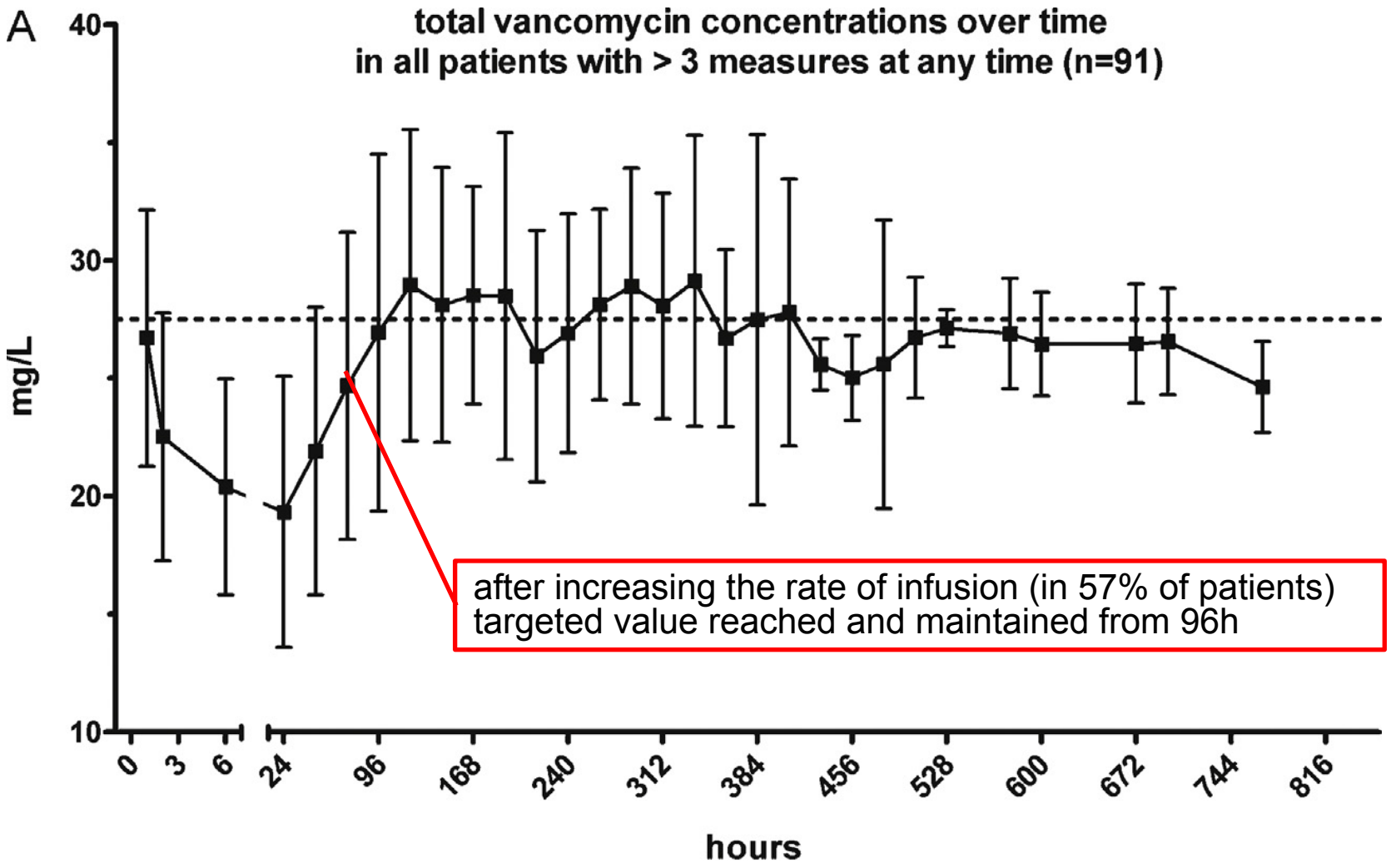
7. Total vancomycin serum concentrations



7. Total vancomycin serum concentrations



7. Total vancomycin serum concentrations



4. Efficacy in clinically evaluable patients (n=59)

- clinical cure:

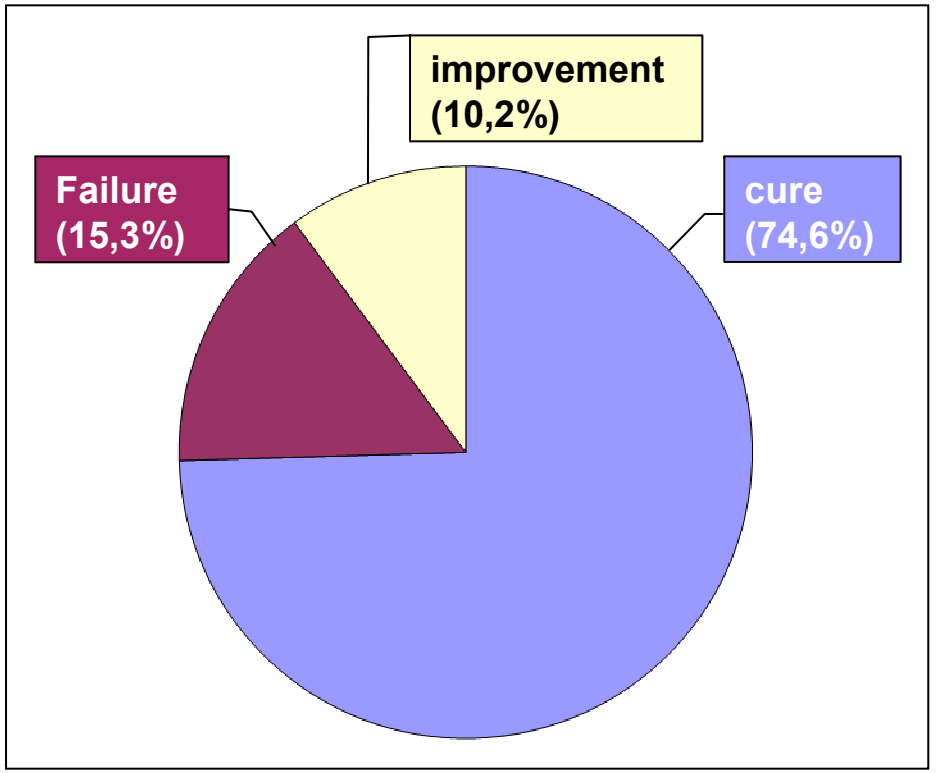
  (i) disappearance of all major signs of infection;

  (ii) normalization of body temperature;

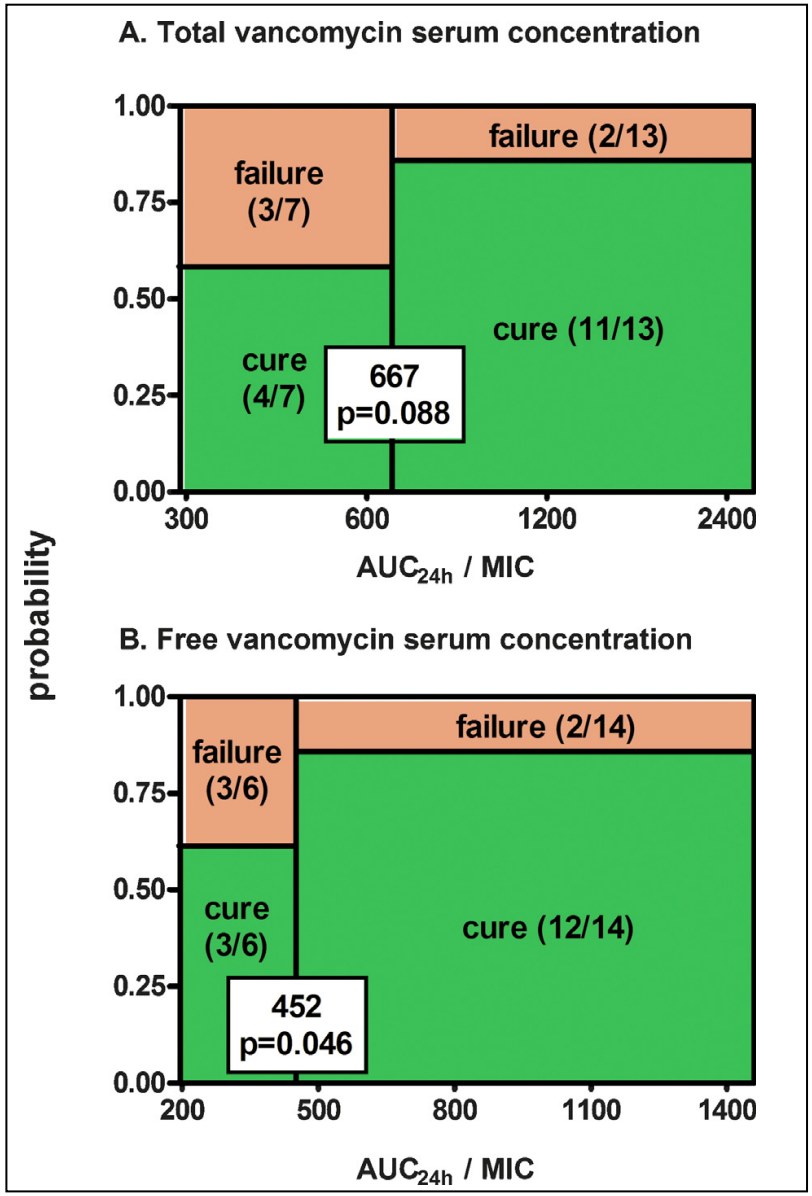
  (iii) marked decrease of CRP.

- at EOT and at 6 months
- assessment retrospectively validated

  by 2 ID physicians



9. AUC_{24h}/MIC predictive of clinical success/failure (n=20)

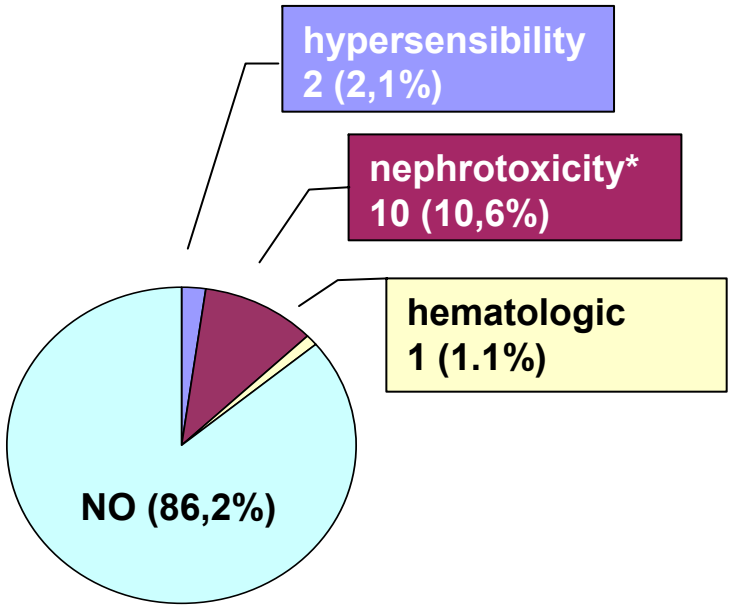


- Recursive partitioning analysis
- best AUC/MIC split value separating failure from success:
  - 667 (total serum concentration)
  - 452 (free serum concentration)

3. Toxicity

Adverse events observed in all enrolled patients (n = 94).

- at least 1 adverse event: 13.8%
- nephrotoxicity 'possible' ADE multiple RF
- treatment discontinuation in only 2 cases



*IDSA consensus statement def. of vancomycin nephrotoxicity (Rybak et al. Am J Health-Syst Pharm 2009):
2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR ≥ 50% increase from baseline after several days of vancomycin therapy.

Observational study – results after implementation of CI

TDM process measures for twice daily (BID; baseline) mode of administration of vancomycin

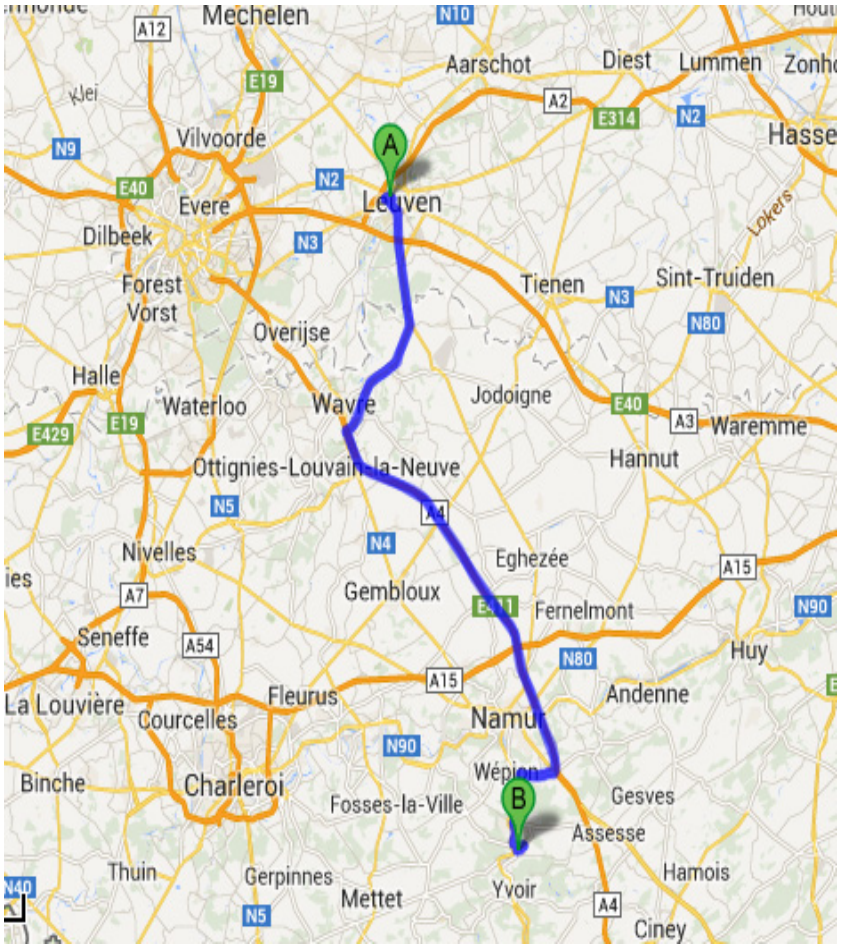
Criterium	BID	continuous infusion	p-value
Sample timing within 30 min. from scheduled time	61.3% [81/132] [a]	97.0% [217/224]	p<0.0001*
Implementation of TDM dose recommendations	32 % [21/66]	94.4% [205/218]	p<0.0001*
Prescribed daily dose in accordance with hospital guidelines	17% [95/560]	86% [1395/1622]	p<0.0001 **
% of serum levels in the recommended ranges	33.3% [37/112] [b]	66.8% [159/238]	p<0.0001*

* Fisher exact test two sided
** Chi-square two sided (because of the large number of observations)
[a] number of total observations (see Table 1 for the number of patients)
[b] most deviations were towards lower than expected values (average: 20 %)

qualitative study – results one year after the end of the study

Implementation of CI by physicians

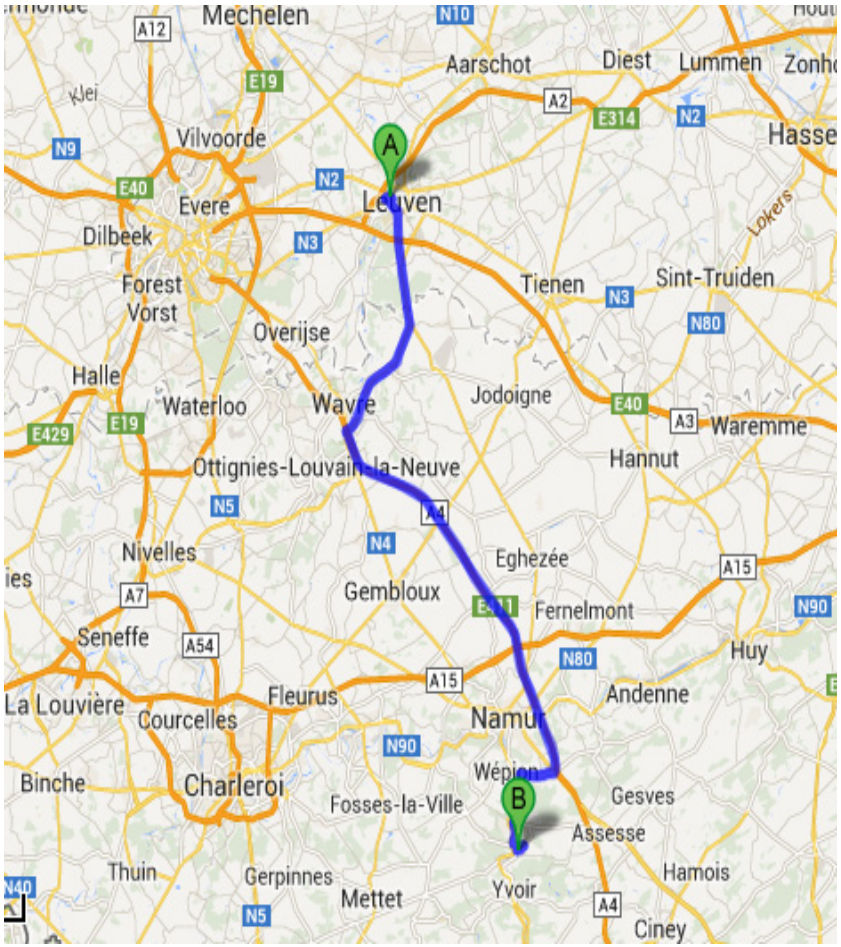
	mean (%)	min-max
Frequency of CI	99	95-100
Follow-up TDM recommendations	96	95-100



qualitative study – results one year after the end of the study

global satisfaction of HCP with CI

	global satisfaction score* (/5)	min-max
Physicians** (n=7)	4.5	4-5
nurses (n=10)	4.3	3.5-5
laboratory personnel (n=8)	4.4	4-5



Qualitative study – results after implementation of CI

M7: "Before even trough samples were obtained incorrectly. They were often just performed together with the other blood sampling without taking care of correct sample timing. Now with CI, samples are always performed correctly."

M7: "We follow dose recommendations. In my opinion treatment follow up is better now and I feel patients are treated correctly."

N1: "We perform just one sampling in the morning for all the scheduled blood analysis. We hardly ever perform additional samples for TDM only anymore."

Conclusions for the Clinical Pharmacists gained from this study

- Hospital-wide implementation of a new protocol is feasible and well accepted by health care professionals if scientifically sound and providing an added value.
- Centralized preparation of drugs facilitates nursing and is often contributing to the quality of care, but it needs to be presented and implemented by the clinical pharmacist
- Clinical Pharmacists can play an important role in the development and implementation of transversal quality improvement strategies

Disclosures and slides availability

Financial support from

- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics and for support to a PhD fellow (D. Das)
- the Université catholique de Louvain for support to E. Ampe (vancomycin studies)
- the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Research grant from Bophar Pharmaceuticals B.V., importer of colistimethate in Belgium (from Forest Pharmaceuticals UK)
- Wallonie-Bruxelles International for this presentation and my activities in Vietnam

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

Backup slides (for vancomycin)

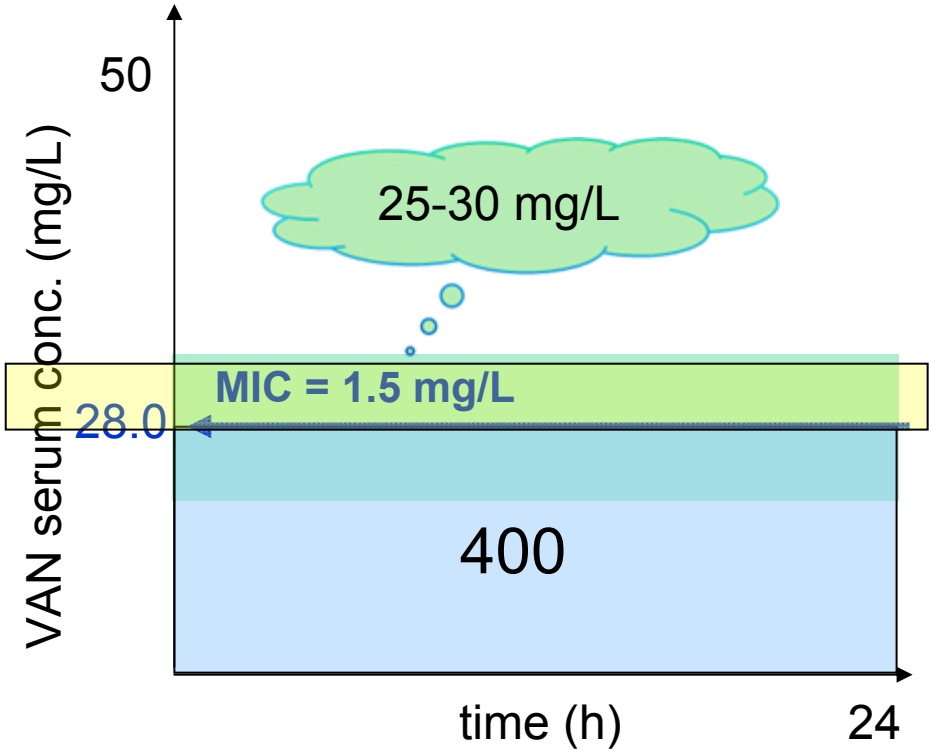
Vancomycin CI: which serum concentration should we target?

Data from a recent study point at a vancomycin AUC_{24h}/MIC of at least 400 to obtain optimal clinical outcome in patients with *S. aureus* lower respiratory tract infections (Moise-Broder et al., Clin Pharmacokinet. 2004;43(13):925-42)

MIC (mg/L)	minimal AUC ($mg*L^{-1}*h$)	target Css (mg/L)
1	400	16.6
2	800	33.3
4	1600	66.6

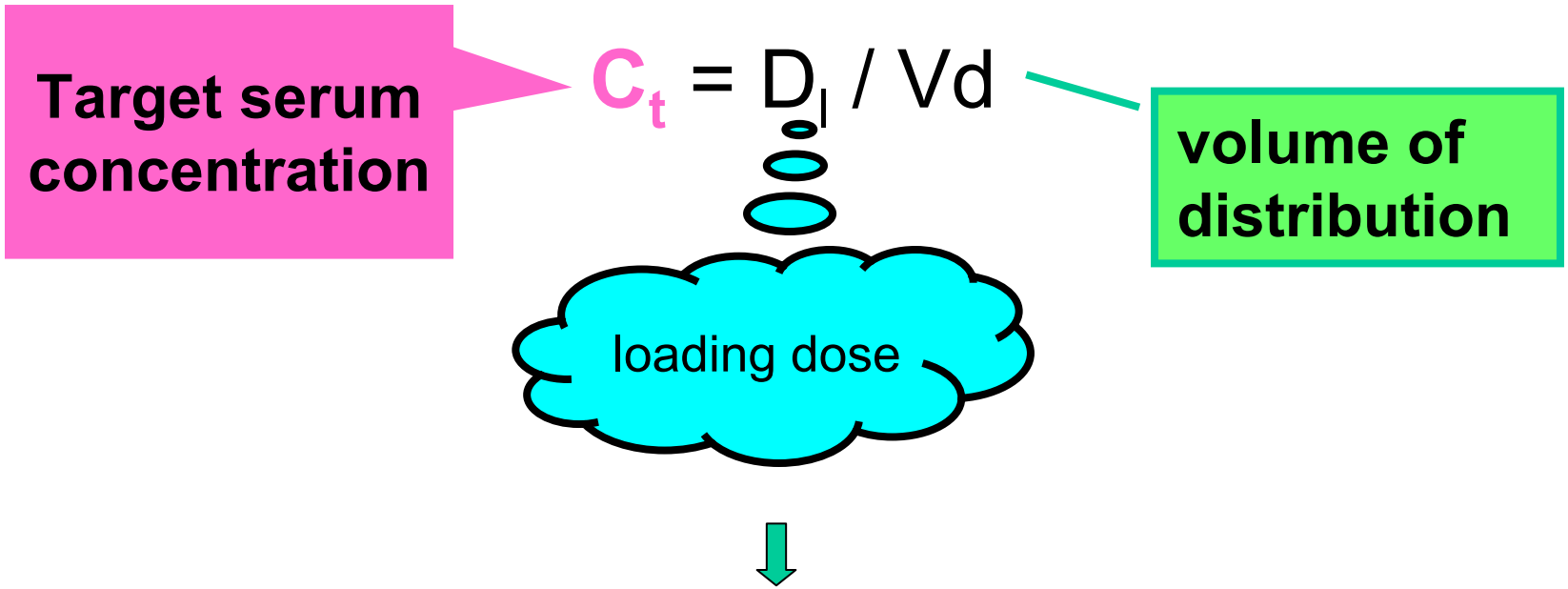
vancomycin CI: which serum concentration should we target?

efficacy



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

How to reach the serum target concentration target with CI?
1. loading dose: the correct scheme *

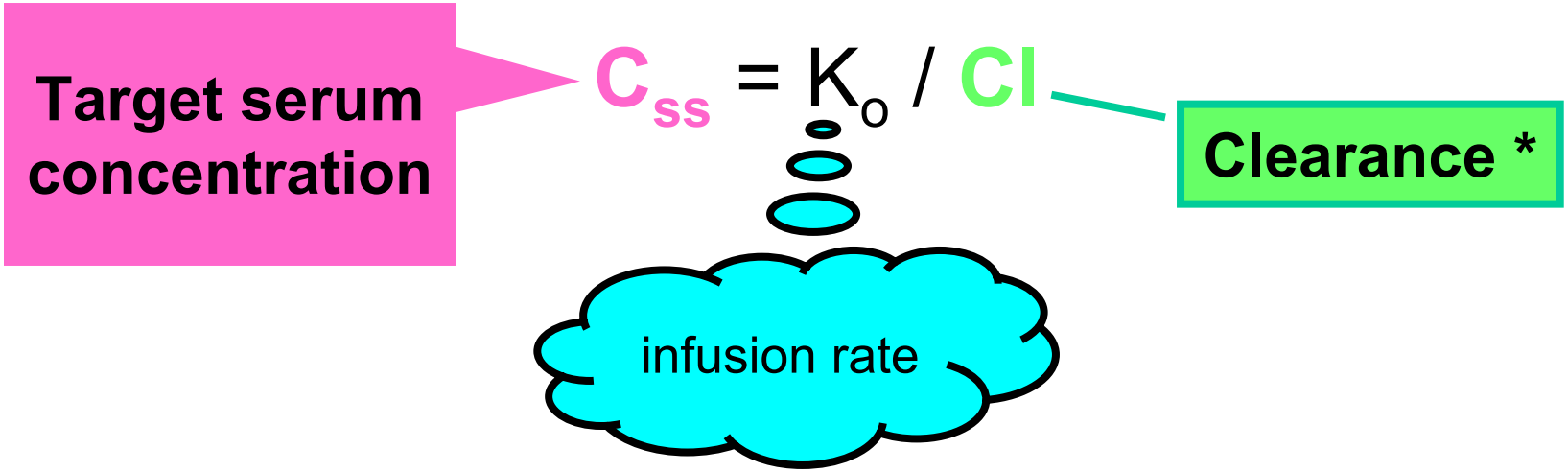


loading dose (in mg/kg) = C_t (mg/L) x **Vd** (L/kg)

loading dose (in mg/kg) = 20 mg/kg = **25** (mg/L) x **0.8** (L/kg)

* assuming linear pharmacokinetics

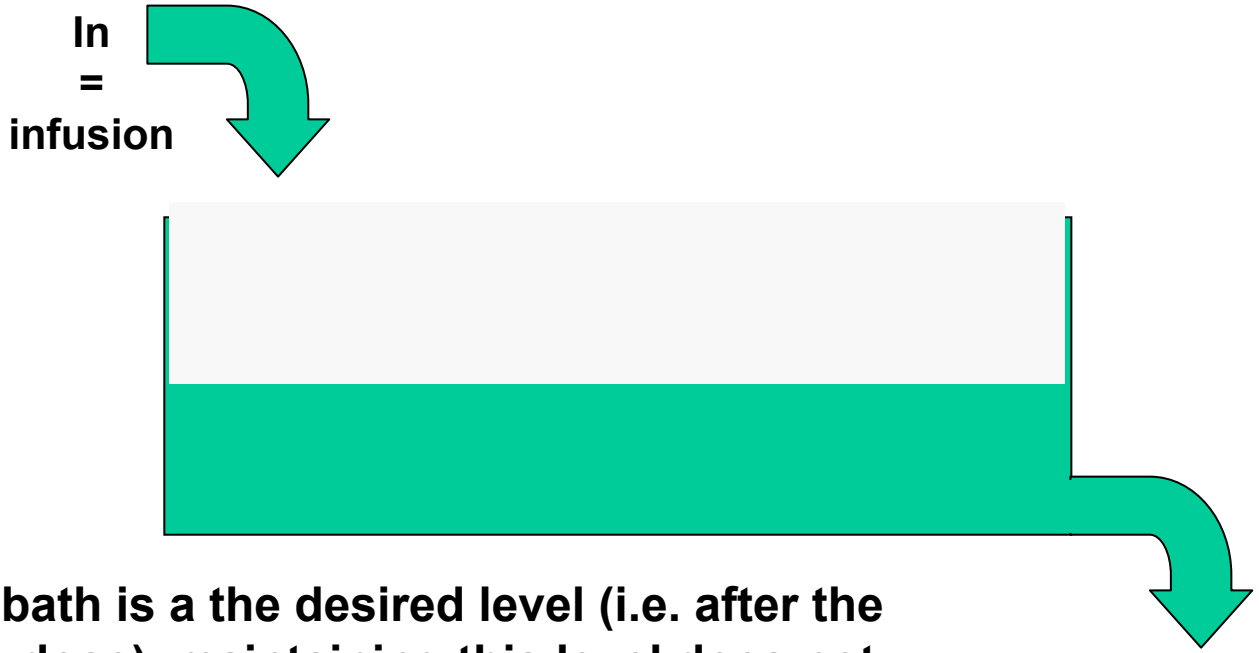
How to reach the serum target concentration target with Cl? 2: infusion *



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

* assuming linear pharmacokinetics

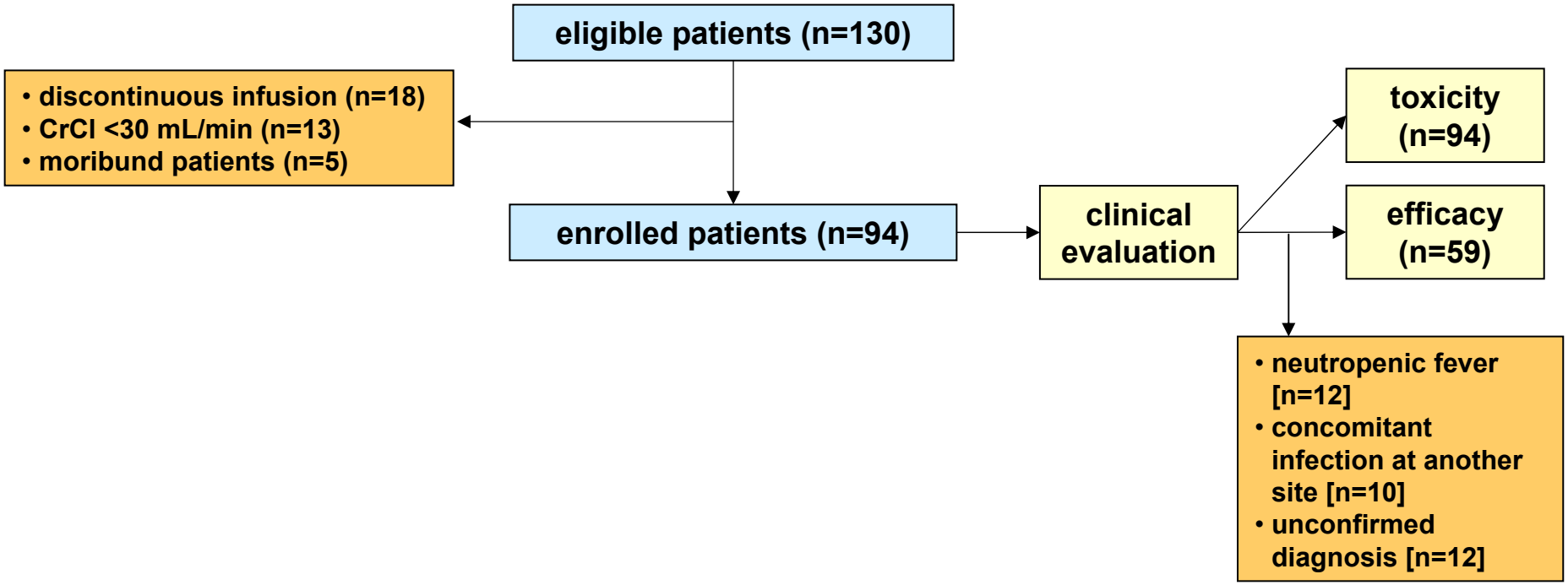
How to reach the serum target concentration target with CI?
2: infusion *



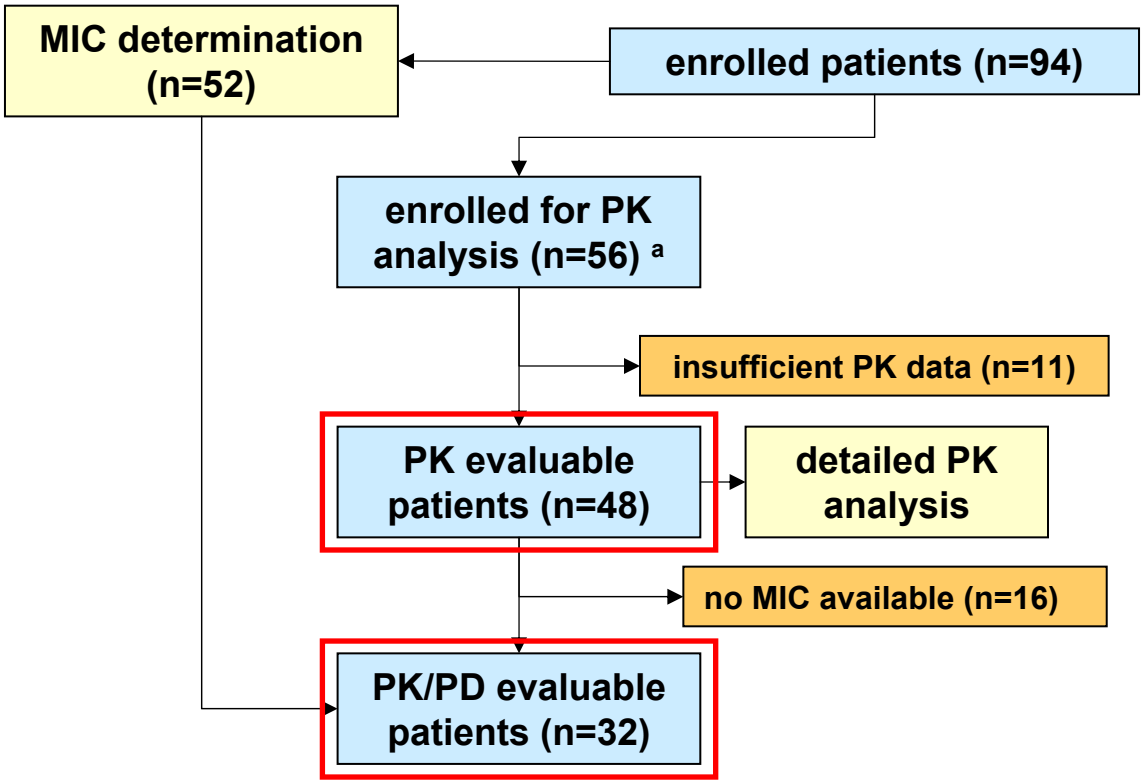
once a bath is a the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which musts be equal: in = out…)

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance

2. Clinical evaluation: study outline

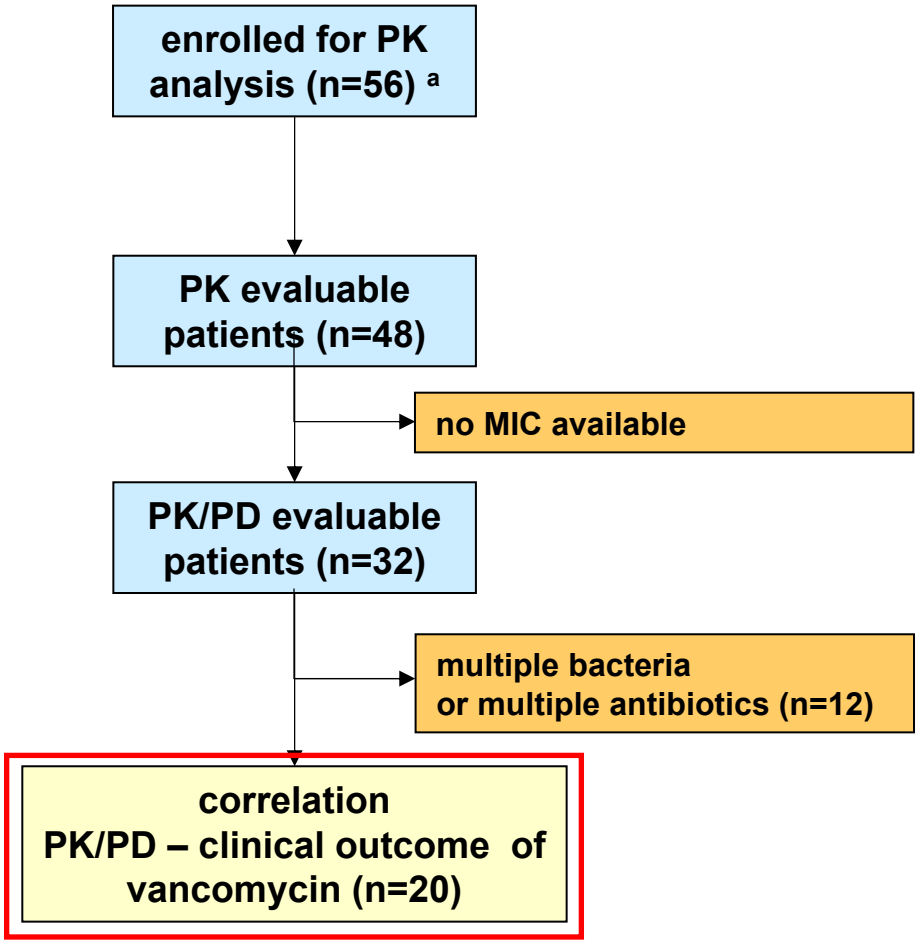


2. Pharmacokinetic evaluation: study outline



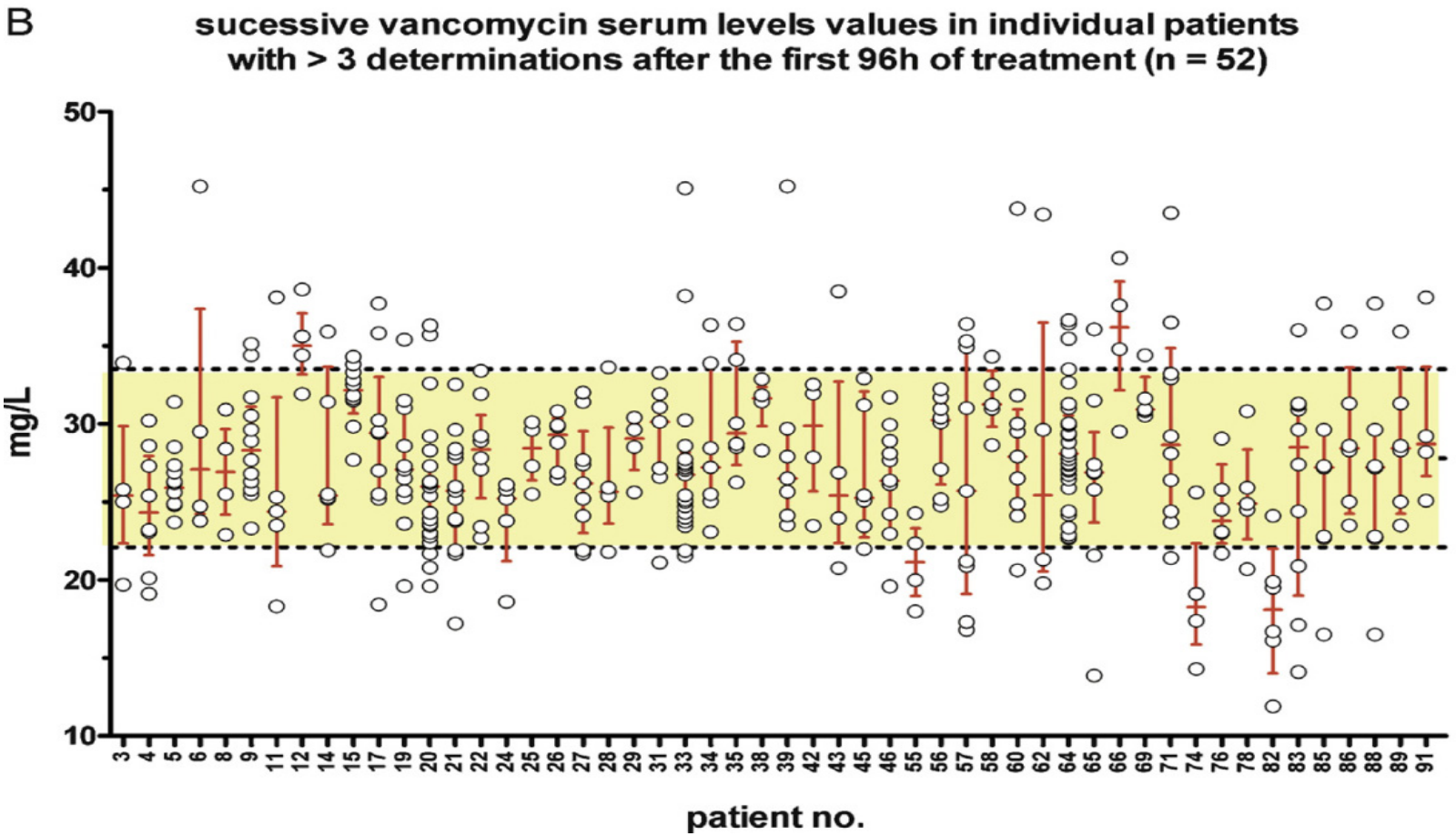
[a] signed informed consent for additional blood sampling
[b] standard of care only

2. Relationship between AUC_{24h}/MIC and clinical efficacy: outline



[a] signed informed consent for additional blood sampling
[b] standard of care only

7. Total vancomycin serum concentrations



- deviations of >10 mg/L according to the recommended range
  - ↘ if increased CCrCl (threshold at >104 mL/min)
  - ↗ if concomitant use of diuretics

Vancomycin continuous infusion: dose adaptation

Table SP1: Dose adaptations for deviations of the targeted serum level

Target level: 25-30 mg/L

Actual concentration (measured)	Dose adaptation
0-5 mg/L	• Add a loading dose (20 mg/kg) Increase of the rate of infusion (+ 8 mL/h) [a]
6-10 mg/L	• Add a loading dose (15 mg/kg) • Increase of the rate of infusion (+ 6 mL/h) [a]
11-15 mg/L	• Add a loading dose (10 mg/kg) • Increase of the rate of infusion (+ 4 mL/h) [a]
16-25 mg/L	• Increase of the rate of infusion (+ 2 mL/h) [a]
26-30 mg/L	• No change
31-35 mg/L	• Decrease of the rate of infusion (- 2 mL/h) [a]
> 35 mg/L	• STOP infusion for 6 h • Decrease of the rate of infusion (- 4 mL/h) [a] • Control serum level the next day

[a] standard infusion solution at 10 mg/mL

Vancomycin continuous infusion: how does it work

- Loading dose
  - 20 mg/kg (based on actual body weight and an estimated distribution volume of 0.7 L/kg [10-12]) administered over 1 h for doses < 2 g or over 2 h for larger doses.
- Infusion:
  - "bags" are prepared in the Central pharmacy at 10 g/L in 5% glucose solution for infusion and transferred to the wards
  - the preparation is infused with voumetric infusion pump (Volumed 7000®; Arcomed AG, Regensdorf, Switzerland).

Note: vancomycin is stable at 37°C for at least 3 days...

(Raverdy V, Ampe E, Hecq JD, Tulkens PM. Stability and compatibility of vancomycin for administration by continuous infusion. J Antimicrob Chemother. 2013 May;68(5):1179-82).

Discussion

- Steady state target concentration reached and maintained
- Efficacy comparable to other studies
- Acceptable safety profile despite higher target range (25-30 mg/L)
- High inter- and intra-patient variability => need for TDM
- Limited number of patients, heterogeneous patient population, no prospective control group
- Re-evaluation of initial infusion rate
- Higher AUC_{24h}/MIC-ratio of 667 necessary for optimal efficacy in our context … MIC of 1 mg/L is probably the limit for vancomycin…

Conclusions for continuous infusion

- Hospital-wide implementation of CI is feasible and well accepted by health care professionals.
- Centralized preparation facilitated nursing and was perceived as contributing to the quality of care
- Clinical Pharmacists can play an important role in the development and implementation of transversal quality improvement strategies
- CI may help optimizing vancomycin usage in the absence of pharmacokinetic services and may improve the quality of these services if available