Looking into the future: How to adapt antibiotic use based on pharmacokinetics and pharmacodynamics

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C.H.U. *de Charleroi*

CHU "Marie Curie", Lodelinsart
19 December 2017

Disclosures

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- Non-profit Institutions:
  - the Belgian ***Fonds de la Recherche Scientifique*** for basic research on pharmacology antibiotics and related topics
  - The **European Union** for applied research on optimization of β-lactams treatments through on-line monitoring of free serum levels
  - The ***Université catholique de Louvain*** for past personal support
- Industry:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other past and present relationships in relation to this talk

- Belgian Antibiotic Policy Coordination Committee (BAPCOC)
- European Committee for Antibiotic Susceptibility Testing (EUCAST)
- European Medicines Agency (EMA)
- Drive-AB (a EU program for a new economical framework for antibiotics)

Slides: http://www.facm.ucl.ac.be → Lectures

Do we have a problem ?

1. Infections are (most often) treated with an antibiotic dosing regimen related to the severity of the disease rather than the susceptibility of the micro-organism ...

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

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

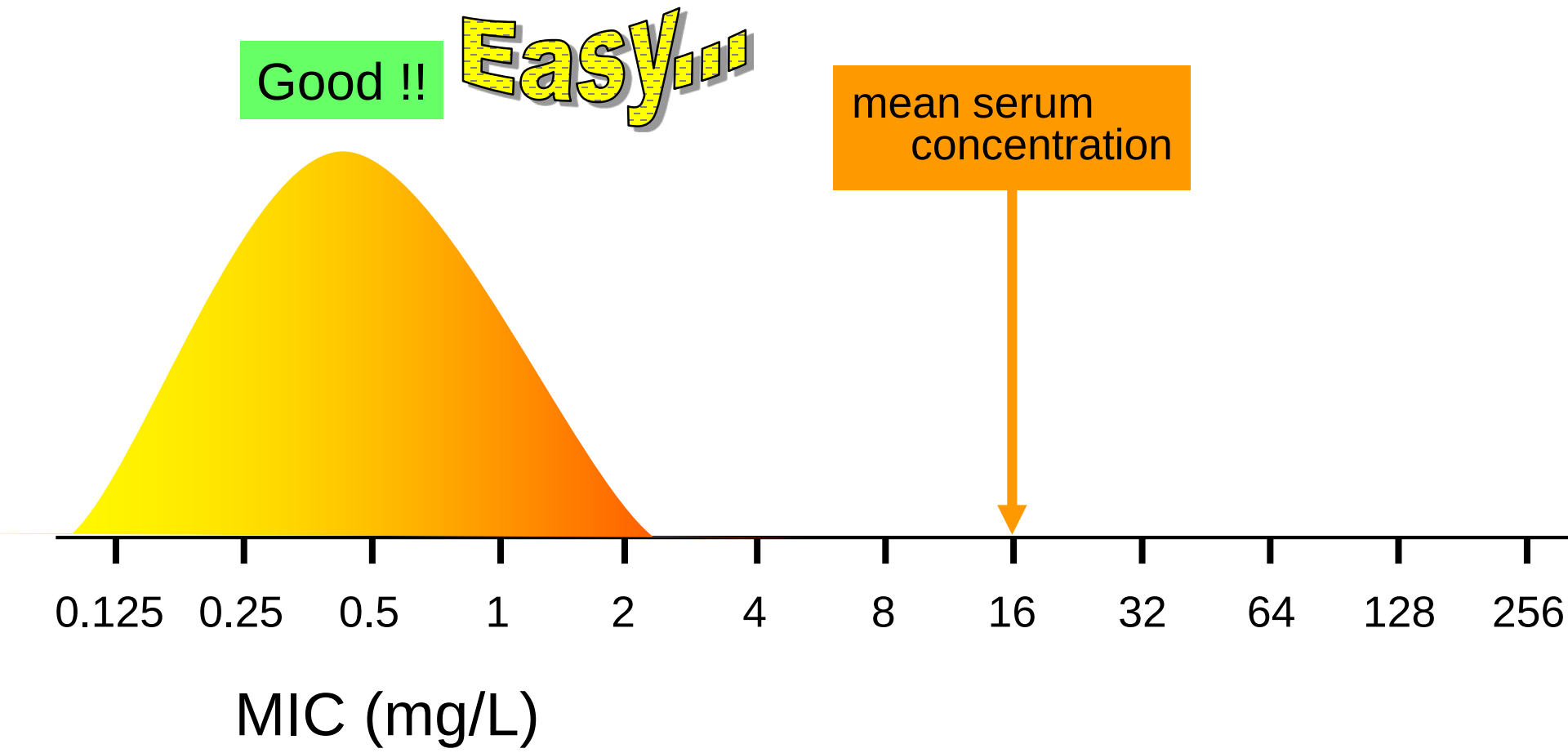
What is a "severe disease" ?

Problem ... #2 (of many)

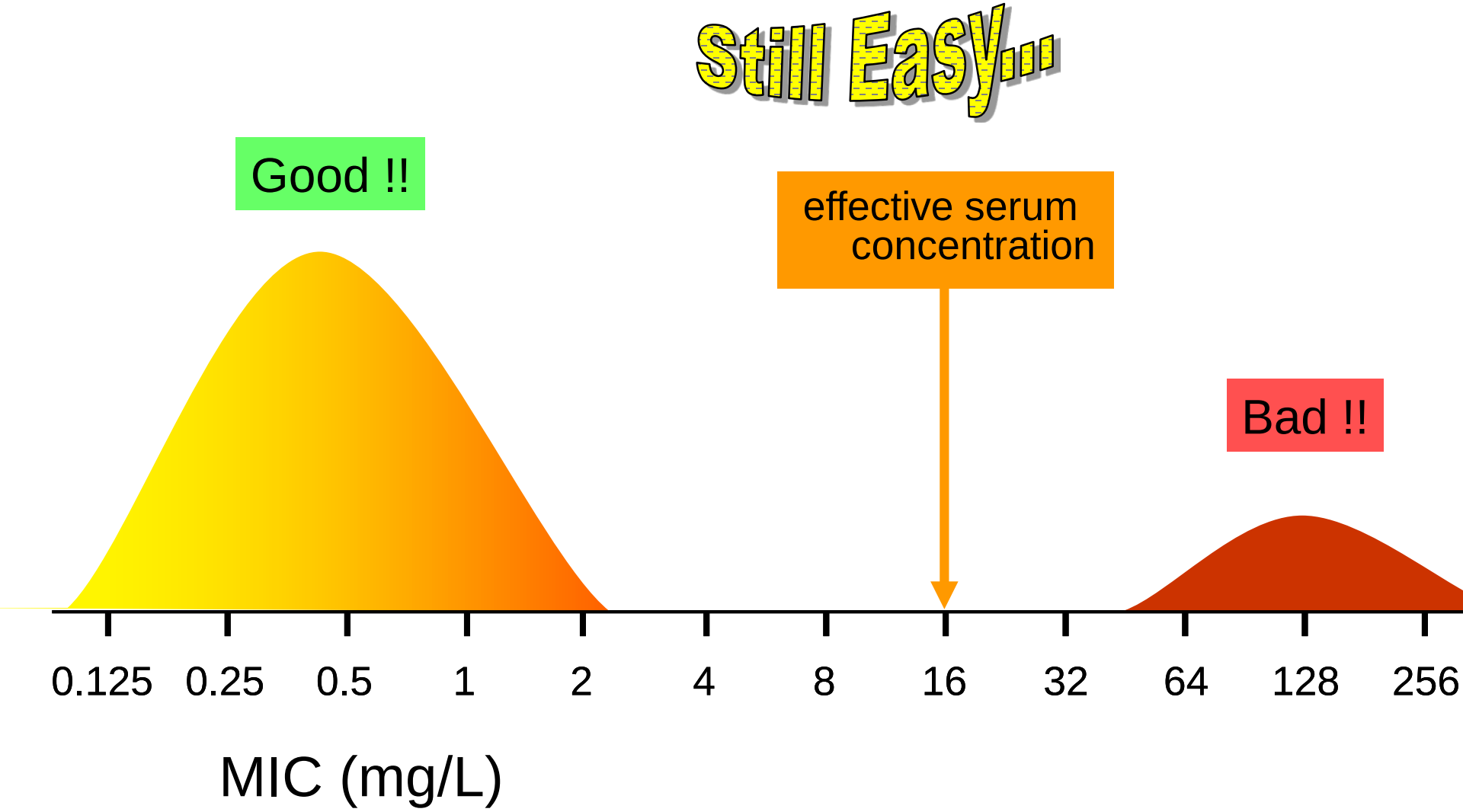
Clinicians tend to ask (and clinical microbiologists to provide only) "S – I – R" answers based on accepted breakpoints …

But, what is a breakpoint ?

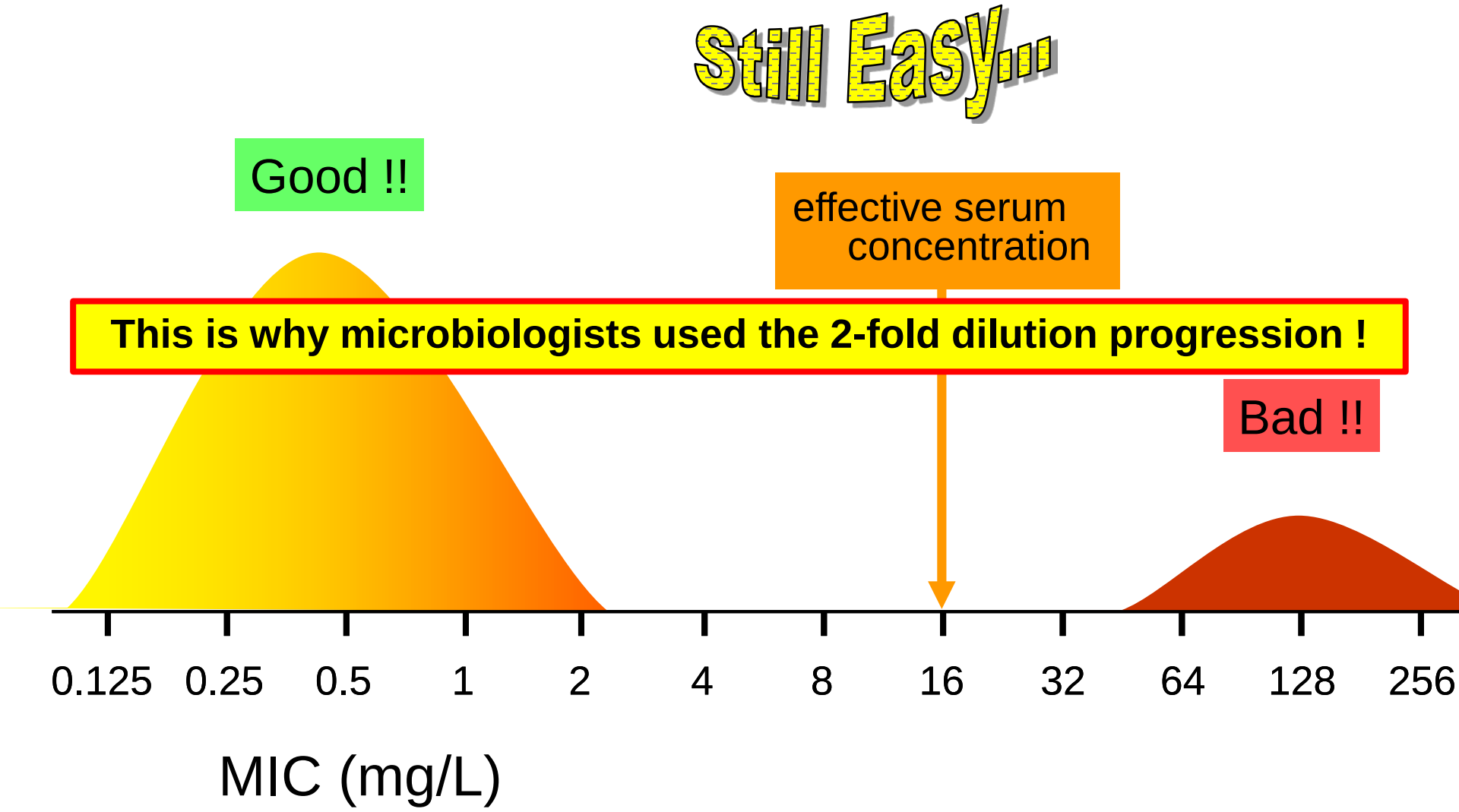
In the good old time…



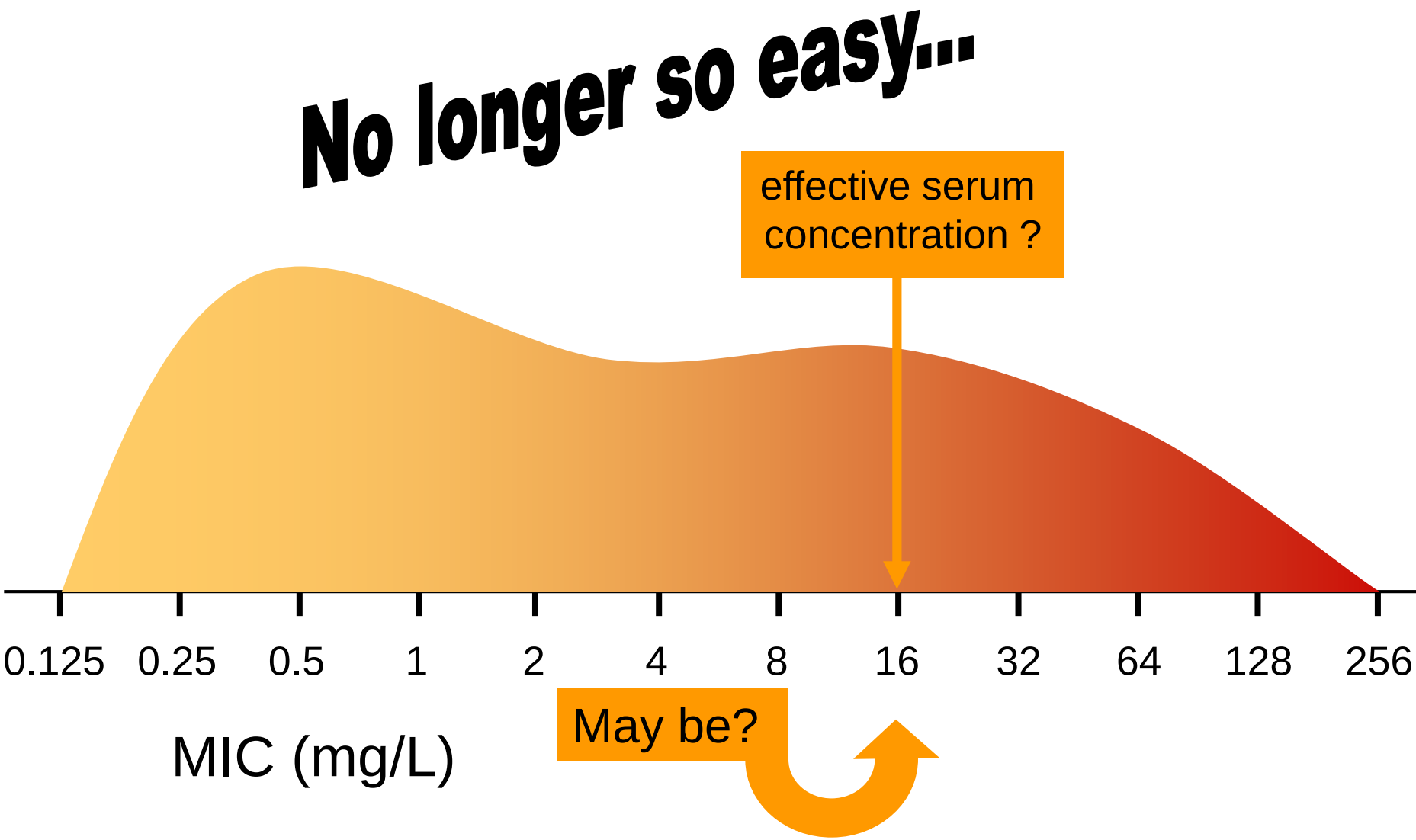
No so old but still good time ….



Still good old time ….



But now, what do you do with this ?



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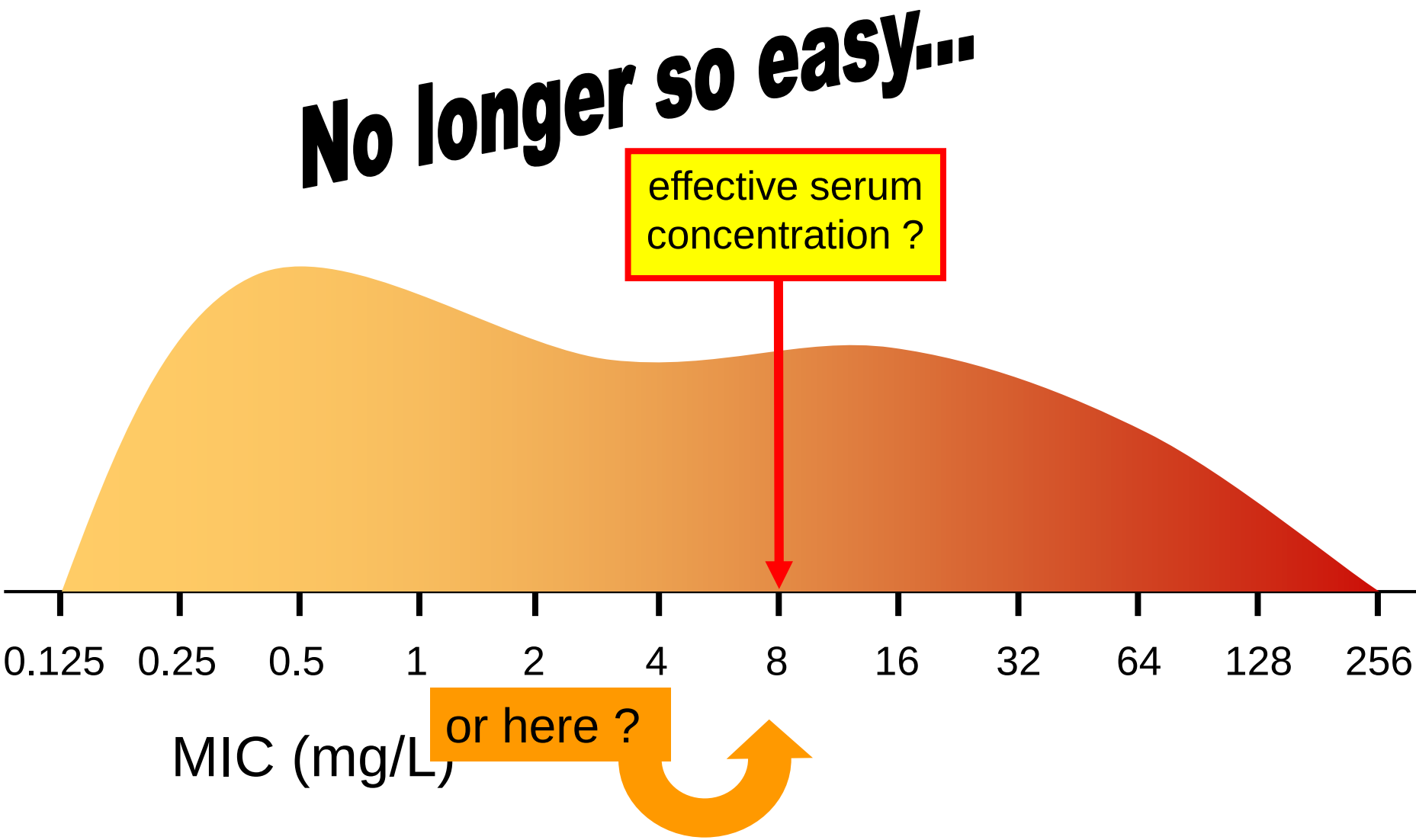

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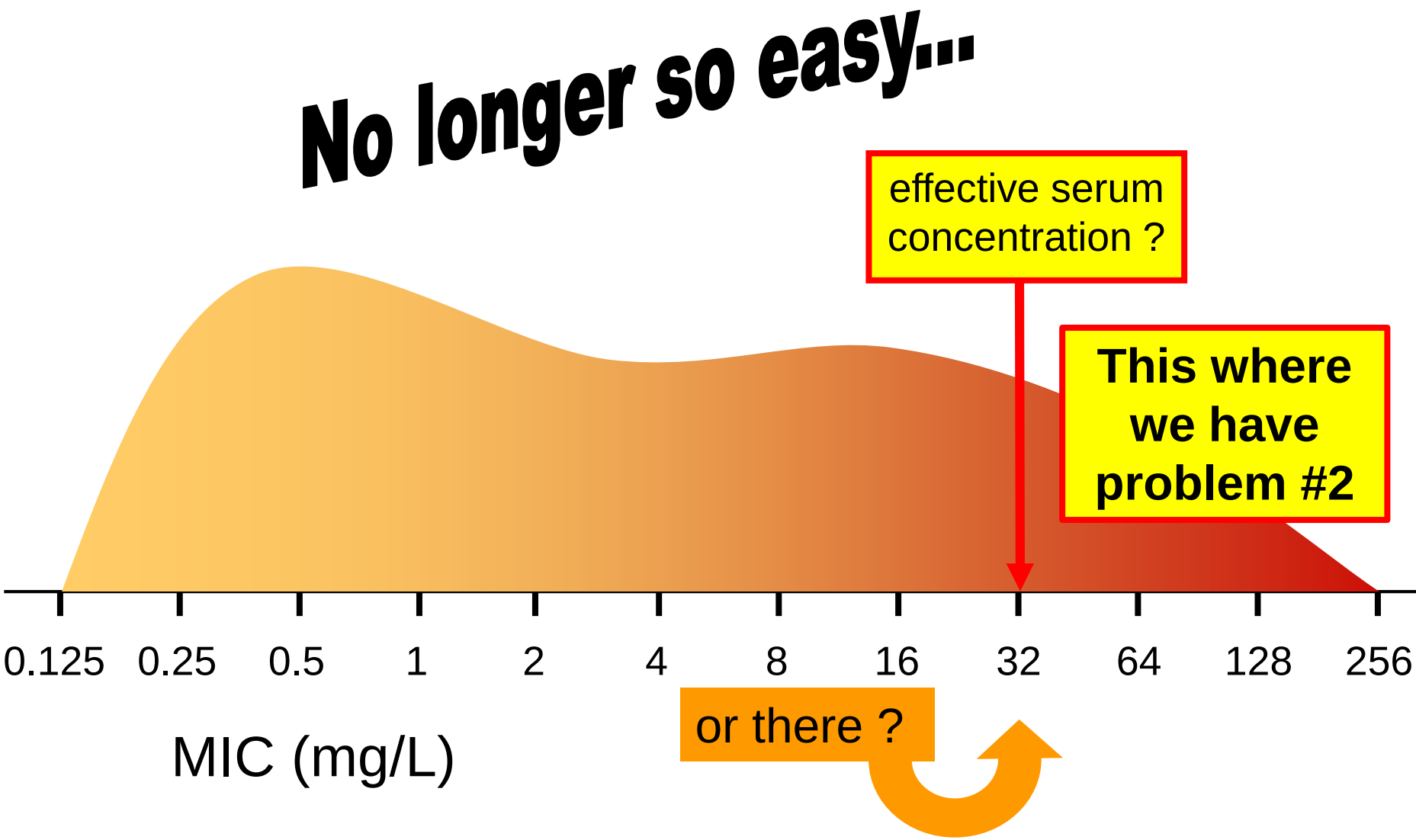


Can breakpoints come to help ?

Here come EUCAST *

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

- Organization
- EUCAST News
- Clinical breakpoints
- Expert rules and intrinsic resistance
- Resistance mechanisms
- Guidance documents
- Consultations

20 October 2017

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

http://www.eucast.org
Last accessed: 18 Dec 2017

EUCAST breakpoints are the only legal in Europe and are implemented for most new antibiotics since 2005

Can breakpoints come to help ?

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

aka, an MIC !

EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)

- a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success
- a micro-organism is categorized as susceptible (S) by applying the appropriate breakpoint in a defined phenotypic test system
- this breakpoint may be altered with legitimate changes in circumstances

Clinically Resistant (R)

- a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.
- a micro-organism is categorized as resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system
- this breakpoint may be altered with legitimate changes in circumstances

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_SOPs/EUCAST_definitions_of_clinical_breakpoints_and_ECOFFs.pdf
Last updated: 1 Sep 2015; last accessed: 18 Dec 2017

MIC: Minimal Inhibitory Concentration
(the lowest antibiotic concentration at which bacteria stop growing in a defined in vitro system)

But breakpoints must be interpreted…

Enterobacteriaceae

Penicillins[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Piperacillin-tazobactam	8[4]	16[4]

Cephalosporins[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Cefepime	1	4
Ceftazidime	1	4

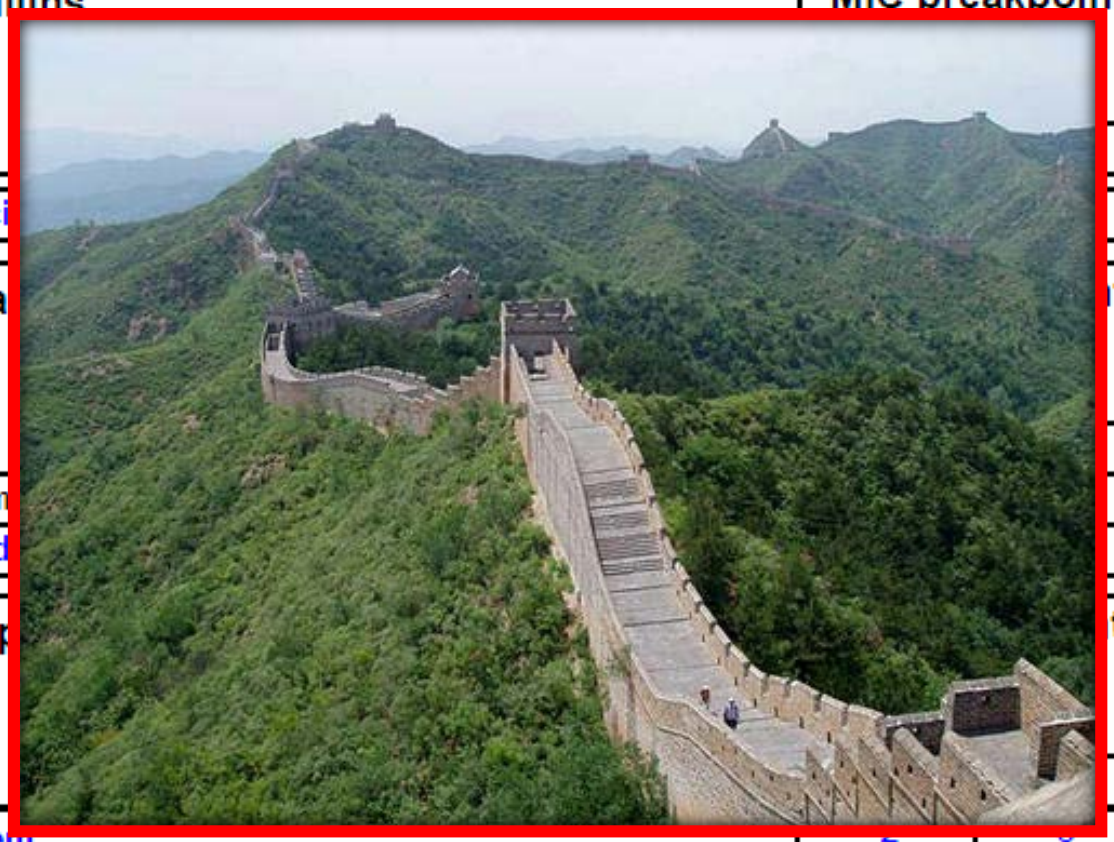
Carbapenems[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Imipenem[2]	2	8
Meropenem	2	8

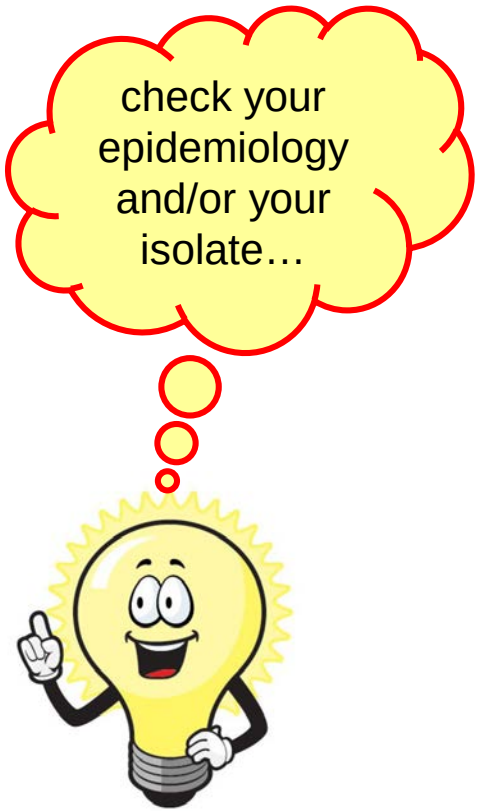
http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf
Last updated: 10 Mar 2017; last accessed: 18 Dec 2017

Simple use of breakpoints in the hospital…

Enterobacteriaceae

Penicillins[1]	MIC breakpoint	
Piperacil		
Cepha		t
Cefepim		
Ceftazid		
Carbap		t
Imipenem	2	8
Meropenem	2	8





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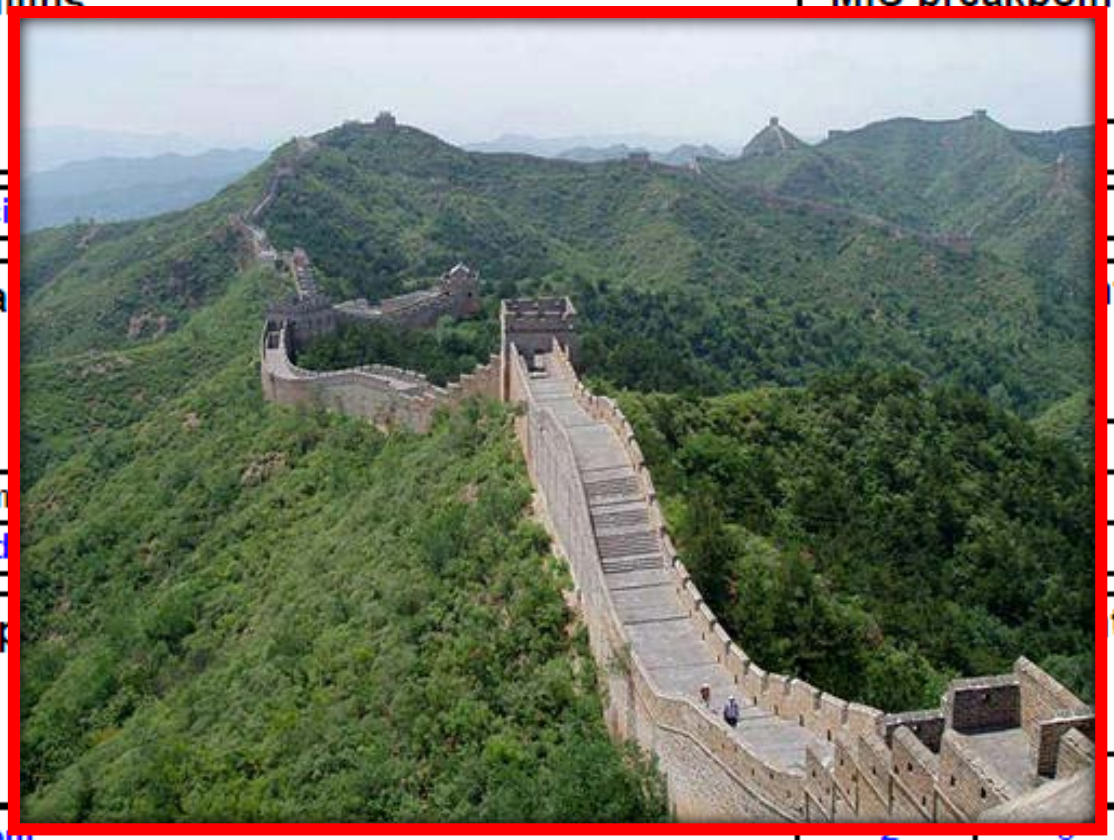


http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf
Last updated: 10 Mar 2017; last accessed: 18 Dec 2017

check your epidemiology and/or your isolate…

and see where YOU are !

Breakpoints are partly based pharmacokinetics …

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

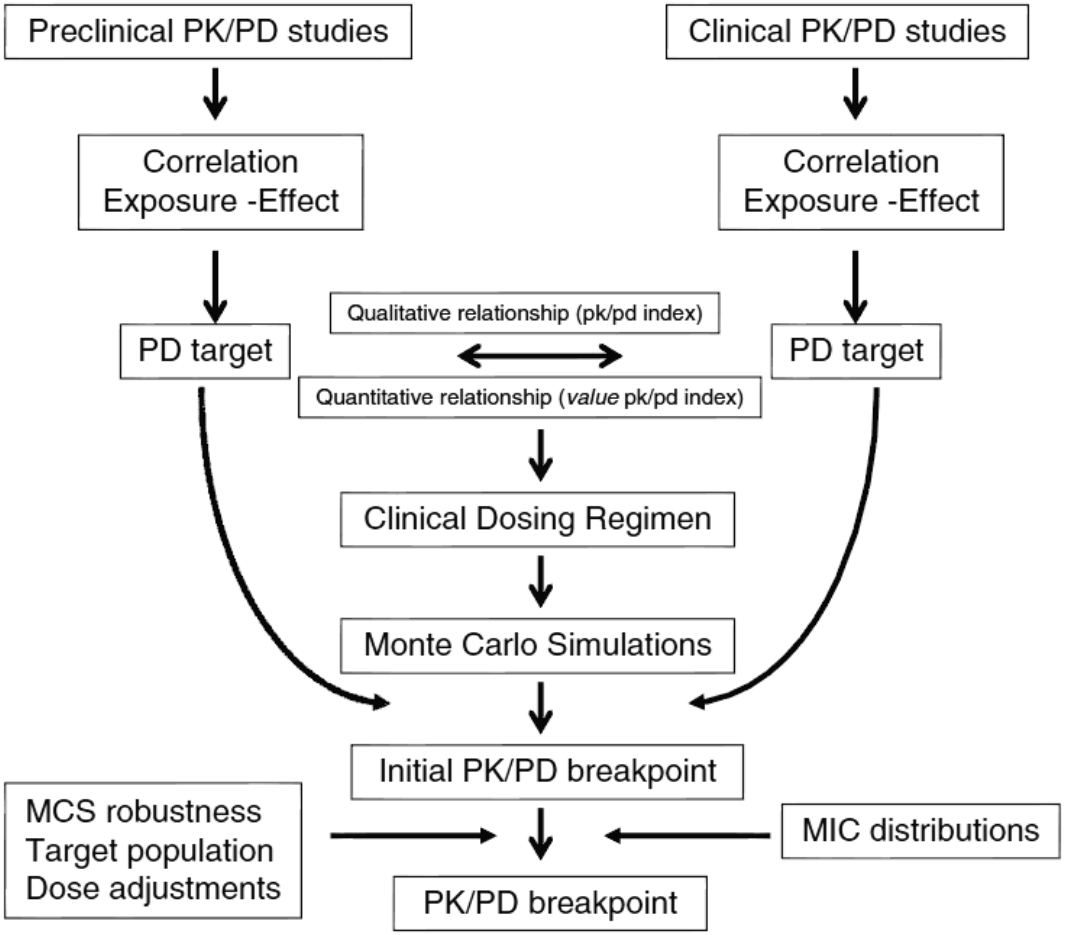
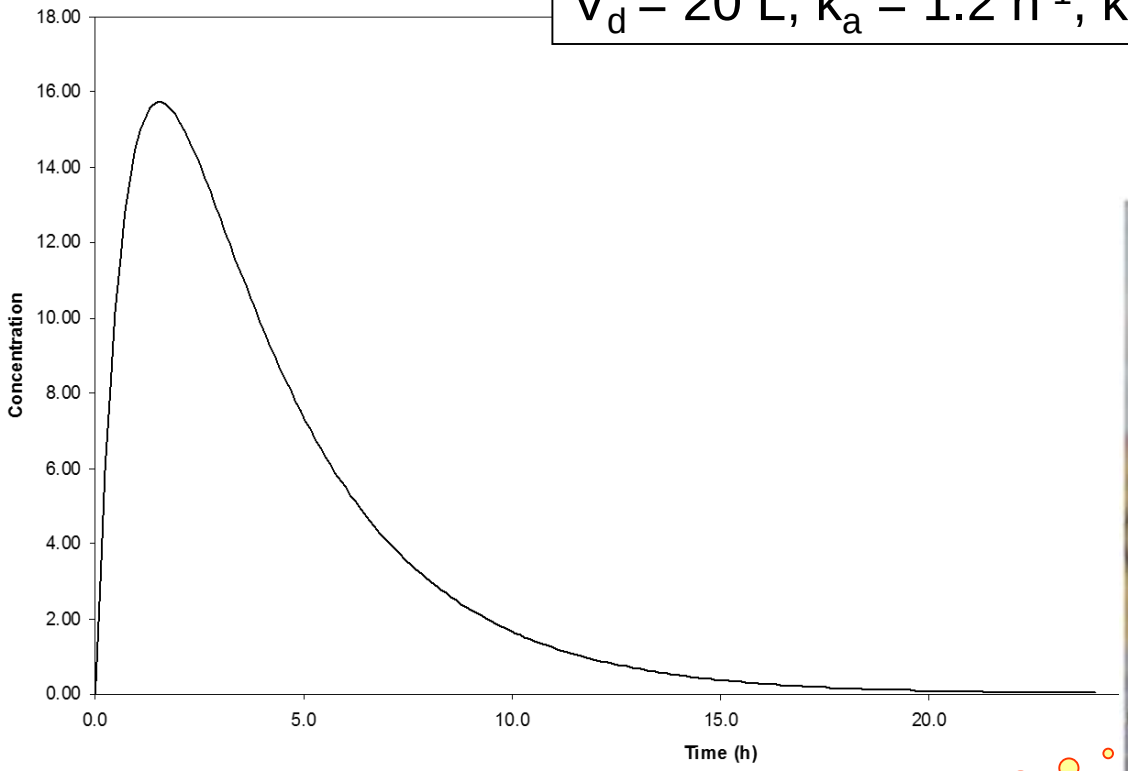
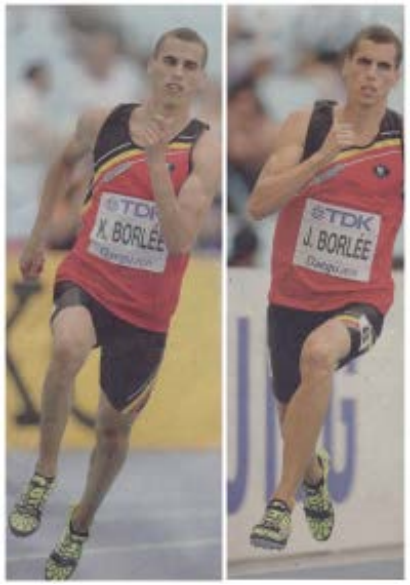


Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

Problem #3: variations of PK in individuals...

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





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

What is, indeed, a standard patient ?

weight

age

physical condition

Kim Clijsters pose avec sa fille Jada. [illegible]/AFP

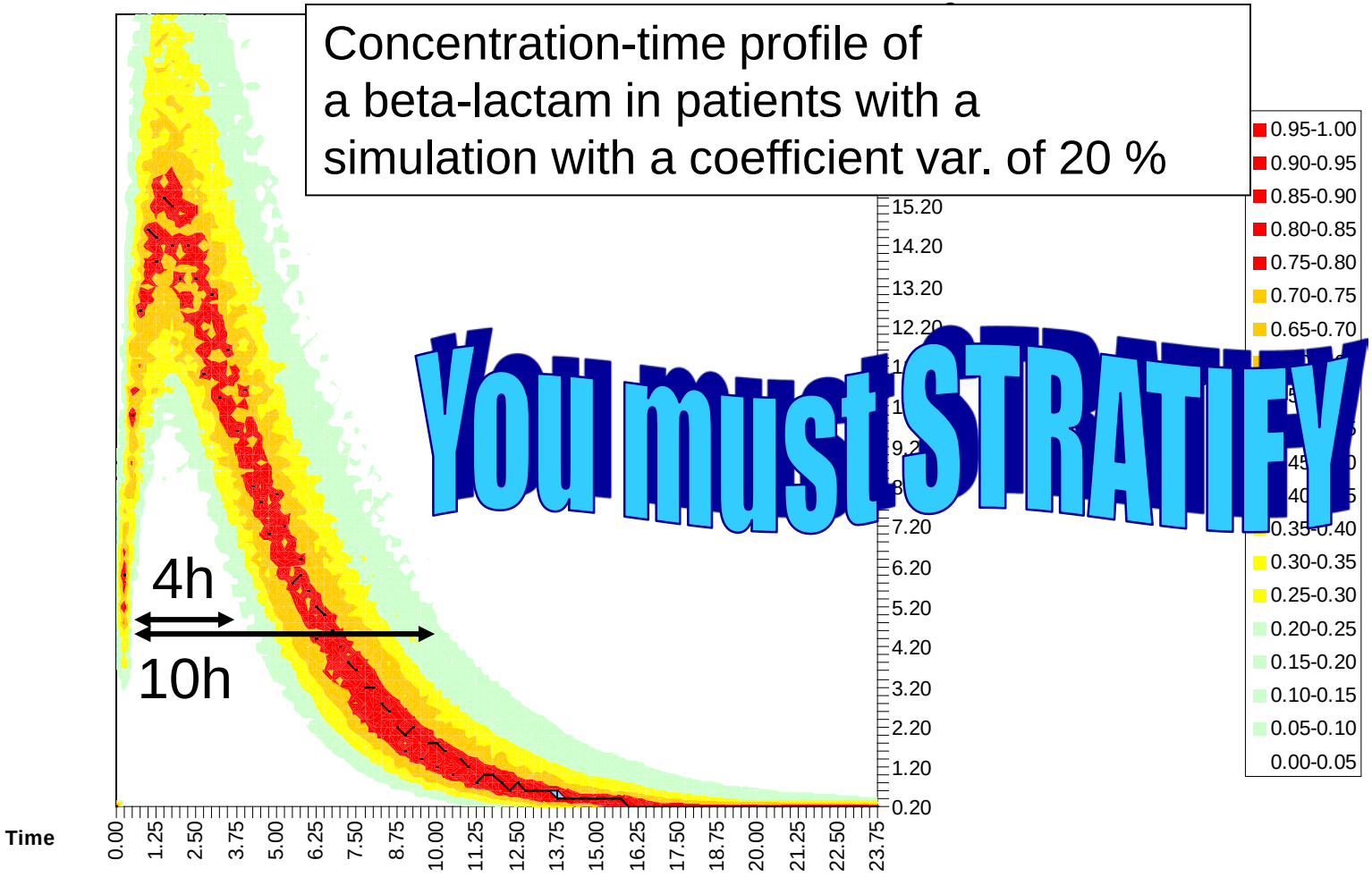
race

size

disease

elimionation functions

Variation of PK in individuals...

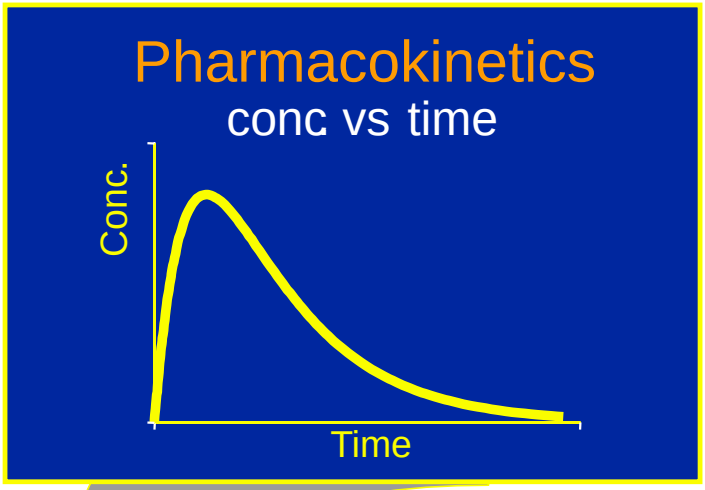


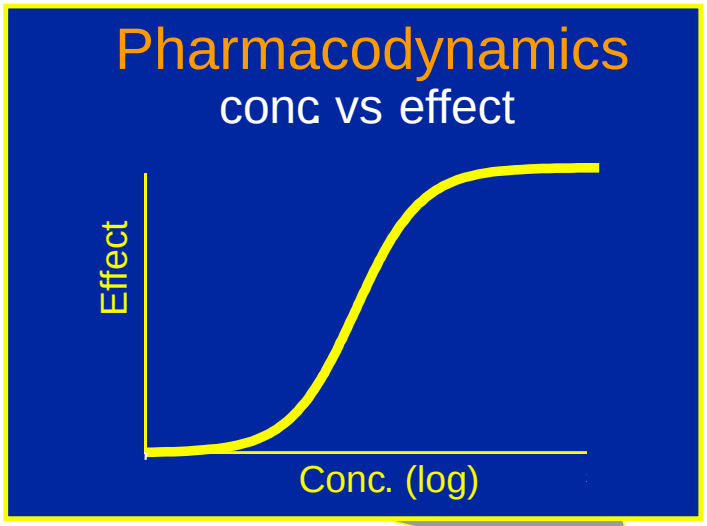
Mouton, Int J Antimicrob Agents april 2002

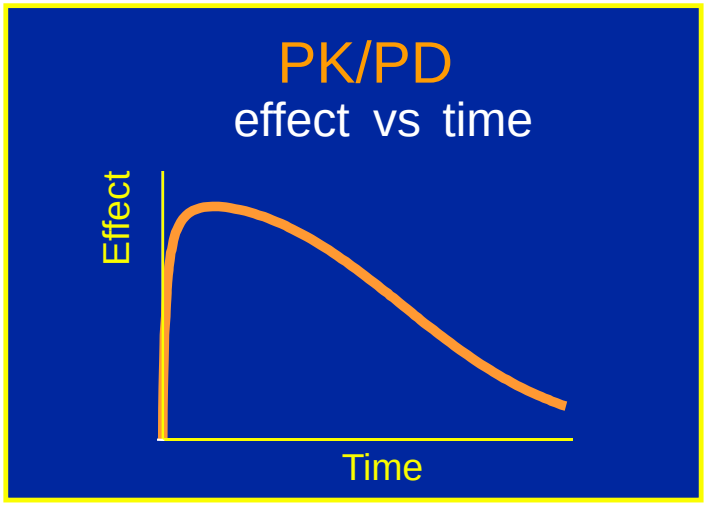
What is, indeed, a standard patient ?

You must STRATIFY according to the patient

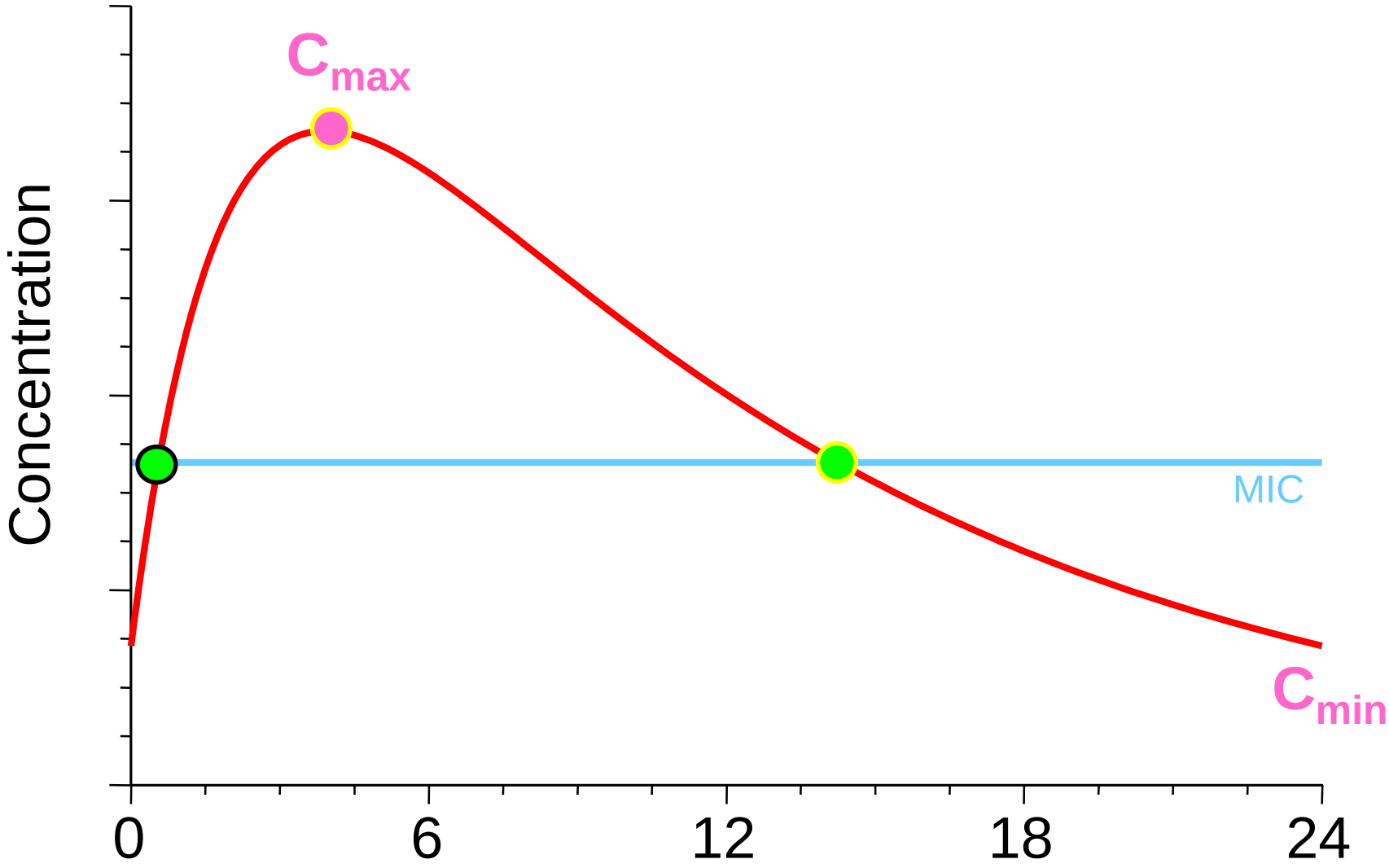
But what is the relation between pharmacokinetics and efficacy ?







From pharmacokinetics to pharmacodynamics.



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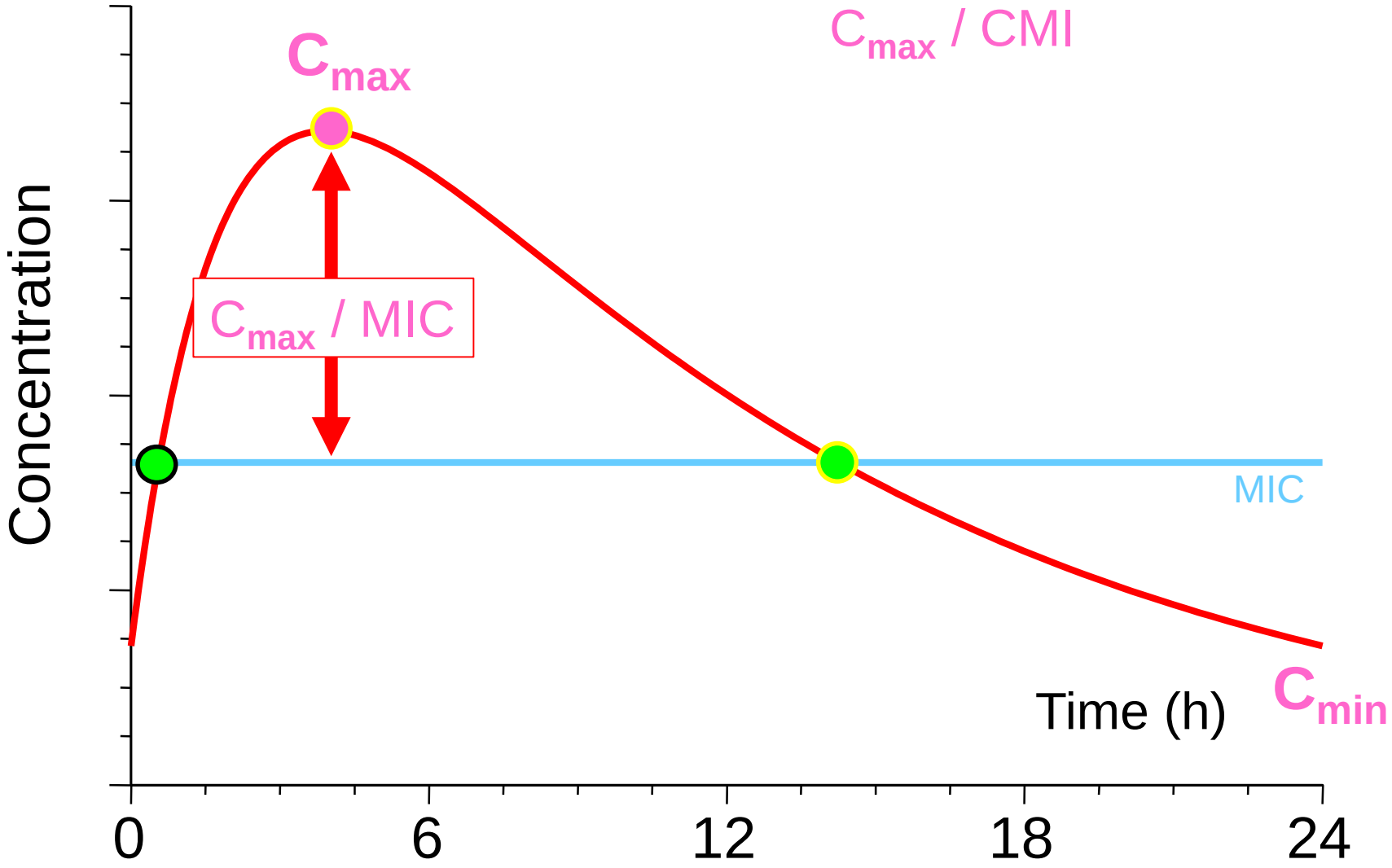

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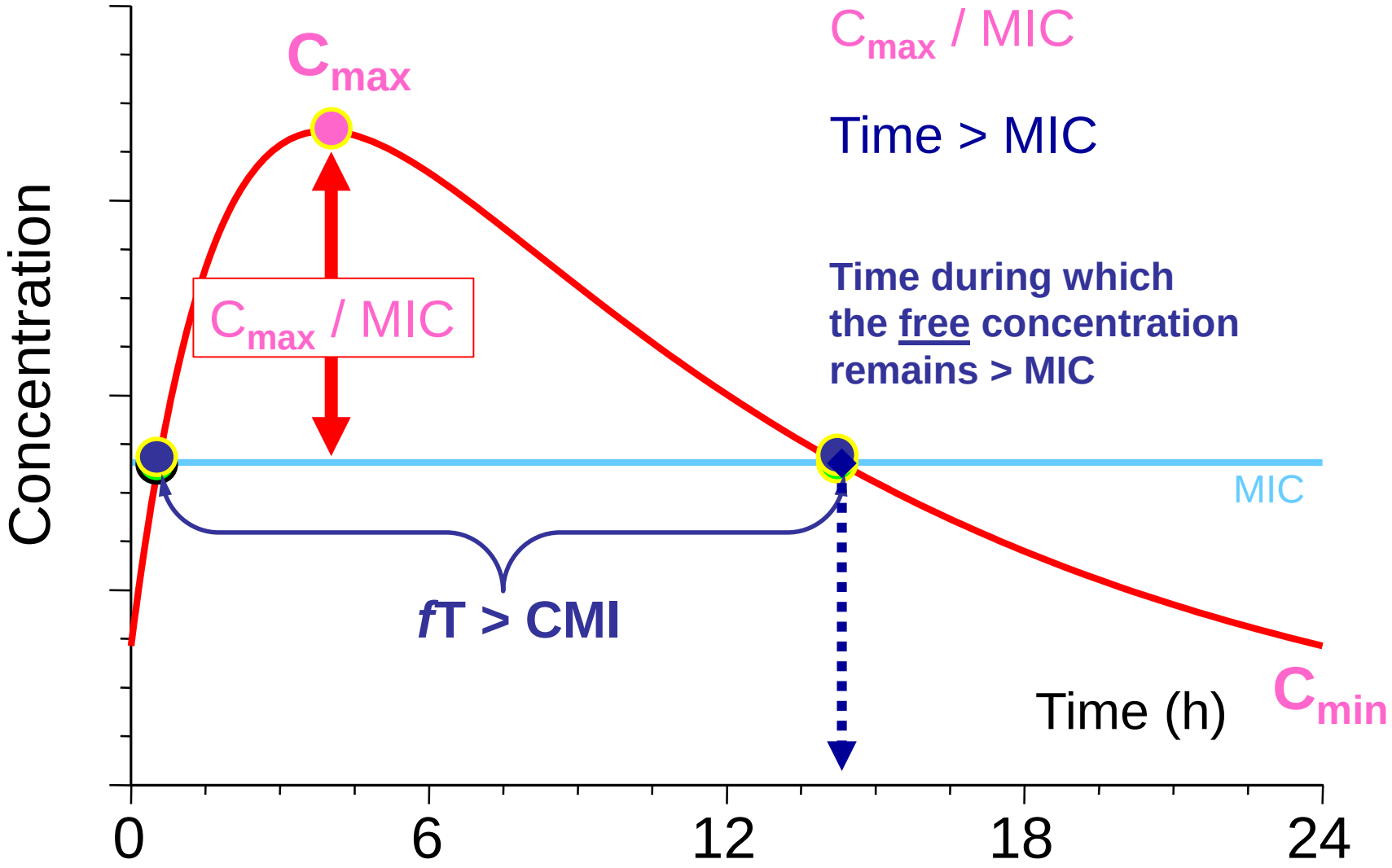
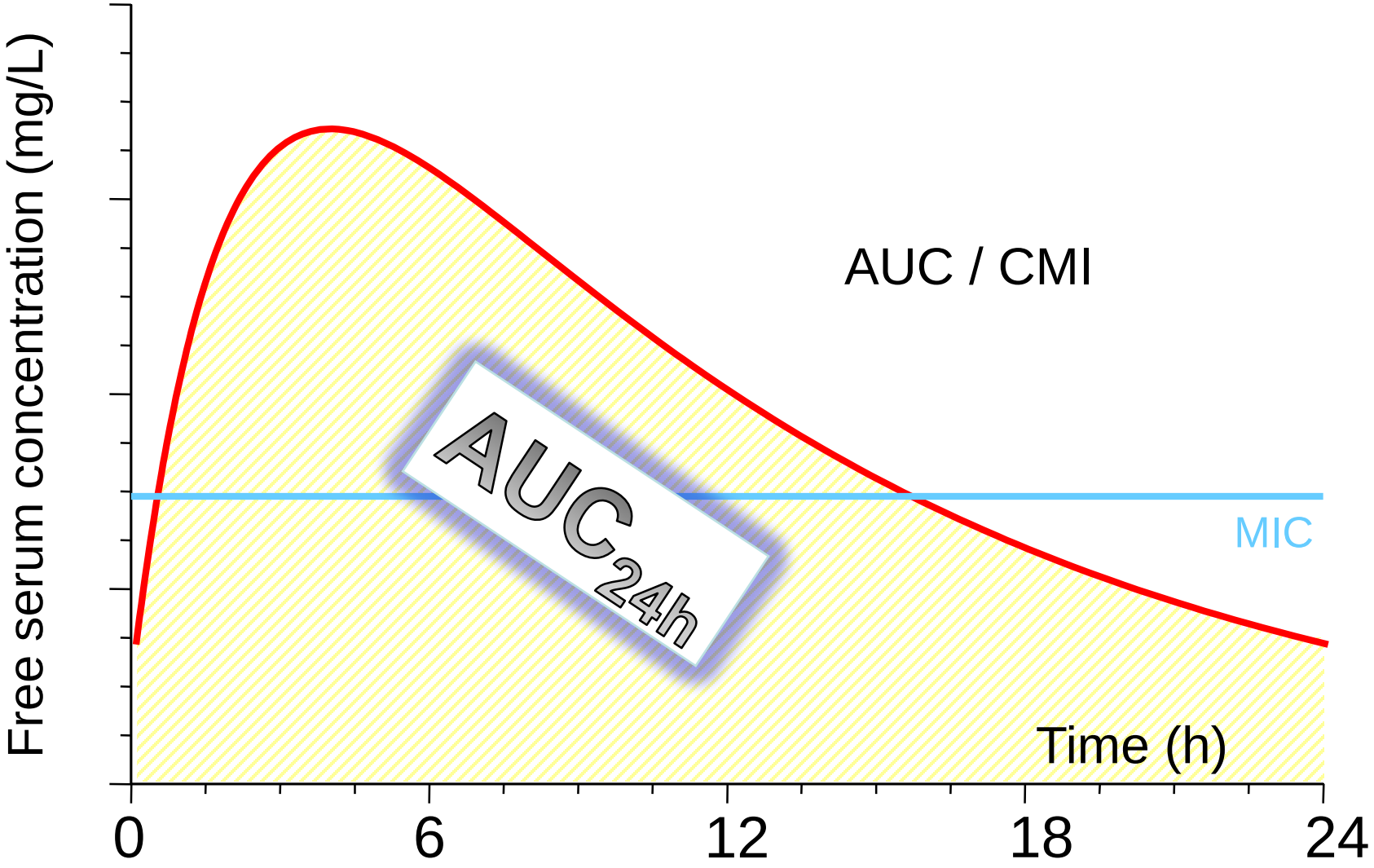


Which pharmacokinetic parameter drives the activity of β-lactams ?



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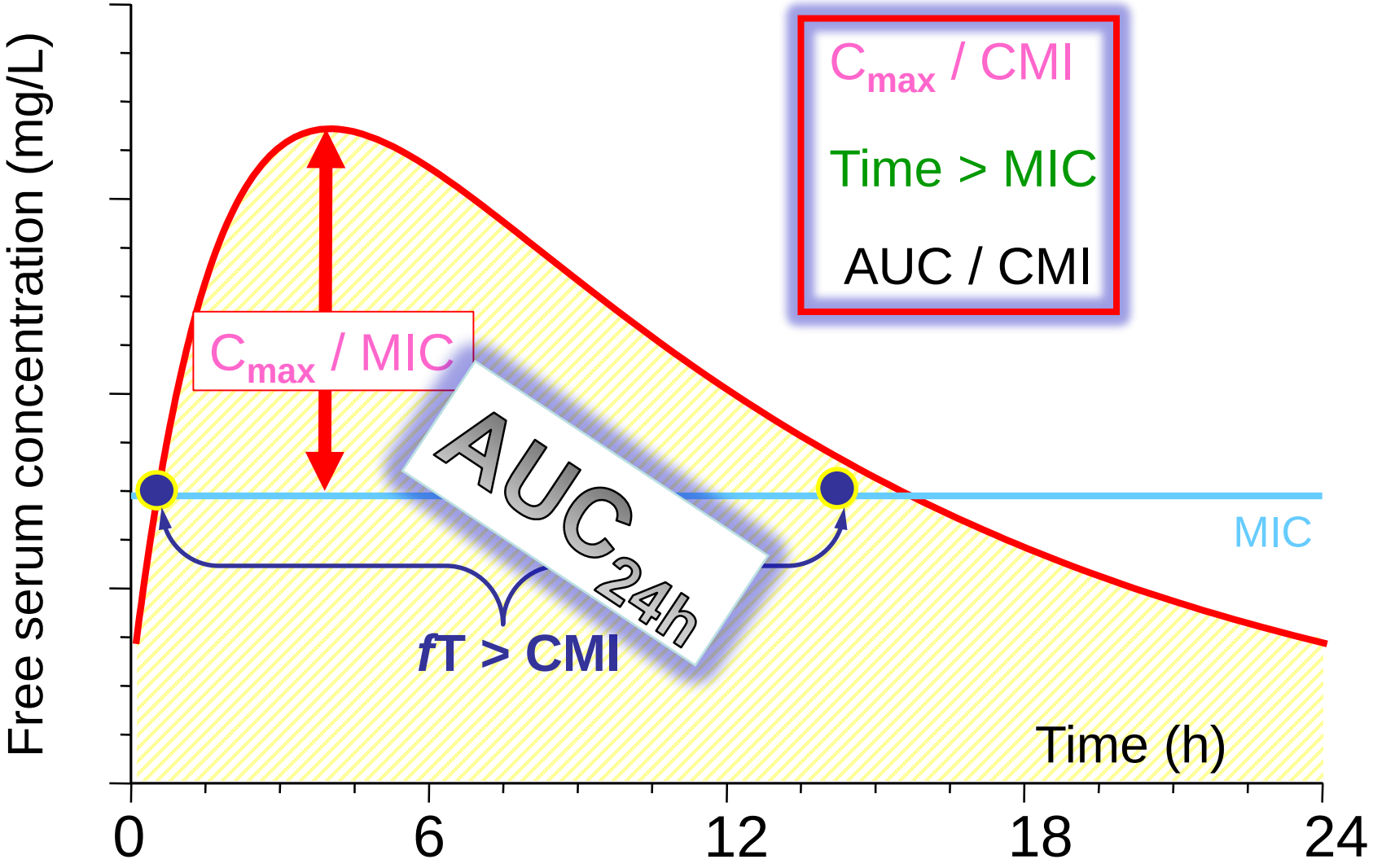


A few simple rules …

Pharmacological class	Parameter	Clinical consequence
β-lactams	time > MIC	• favor frequent administration … • continuous infusion
aminoglycosides fluoroquinolones	C_{max}/MIC (AUC/MIC)	• favor high peaks (aminoglycosides) • favor peak and total daily dose (fluoroquinolones)
most other antibiotics	AUC/MIC	• favor total daily dose • some may be eligible for continuous infusion

IV drugs

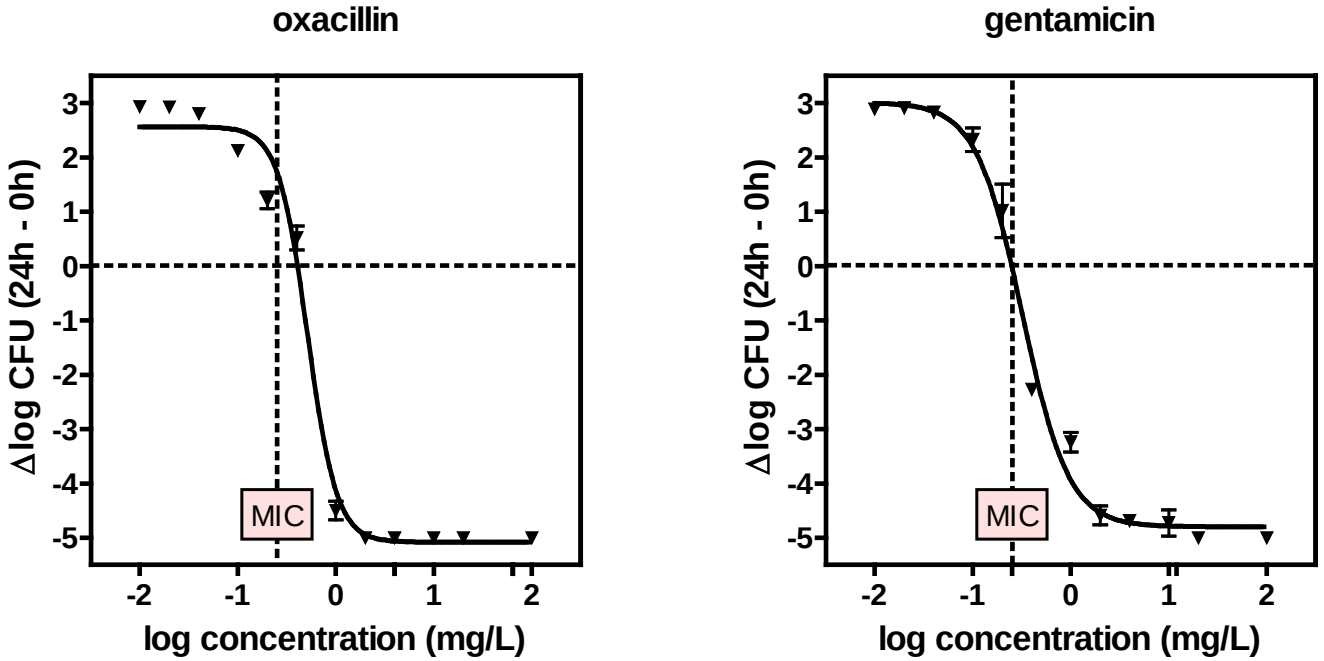
C_{max}: maximal serum concentration (typically after intermittent administration – C_{max} = dose/volume of distribution

AUC: area under the curve (most often over 24h) – AUC_{24h} = total daily dose/clearance

Why are β-lactams time-dependent and aminoglycosides concentration-dependent ?

- Simple experiments…

full susceptible MSSA



phamacodynamic model of antibiotic response
24 incubation at fixed concentrations

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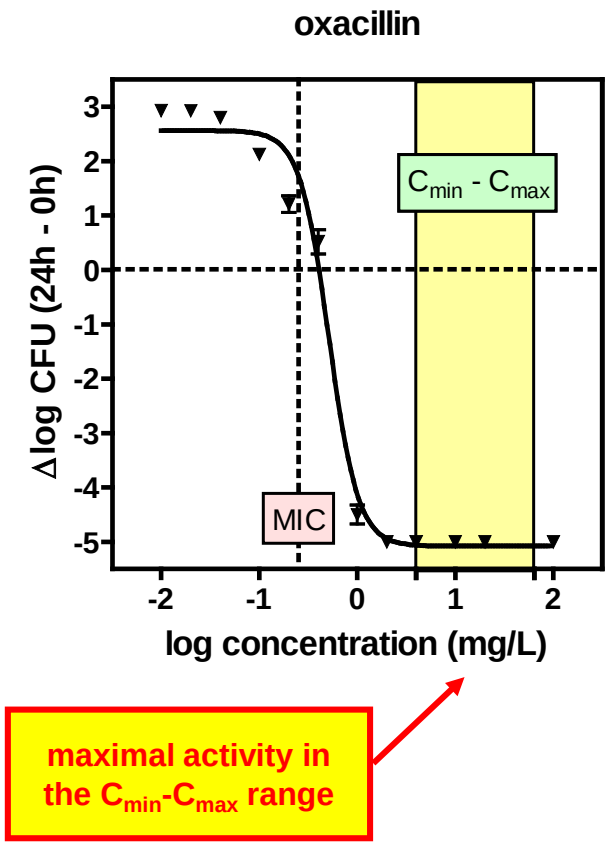
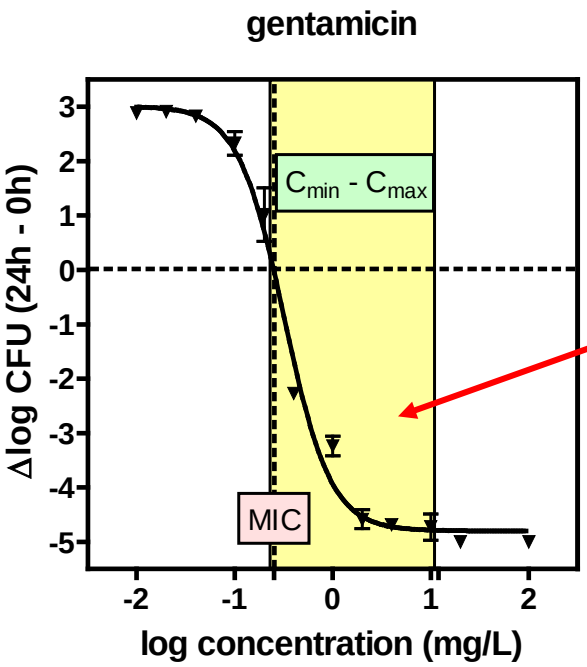




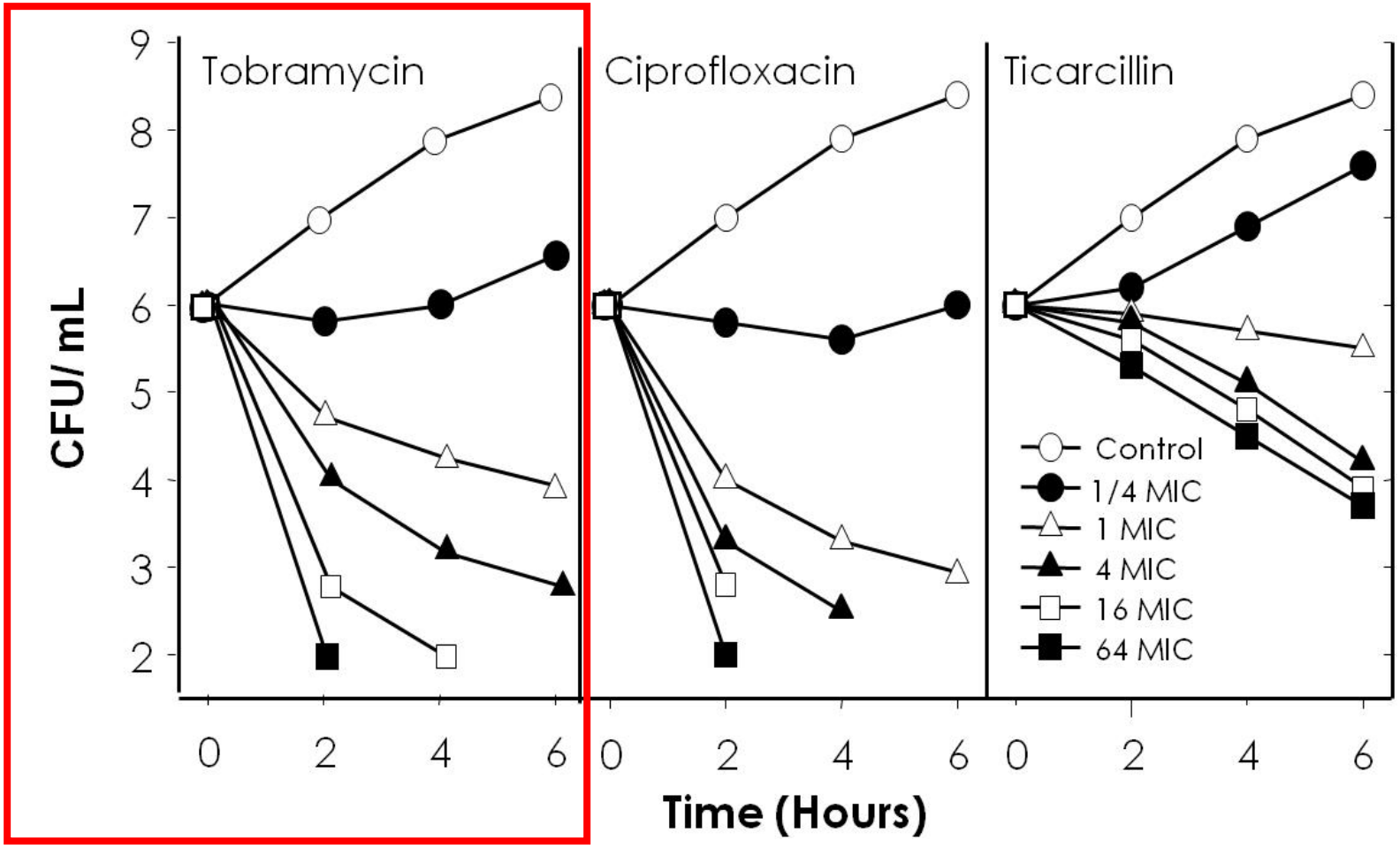
maximal activity in the C_{min}-C_{max} range

activity is concentration-dependent in the C_{min}-C_{max} range

phamacodynamic model of antibiotic response
24 incubation at fixed concentrations

Aminoglycosides…

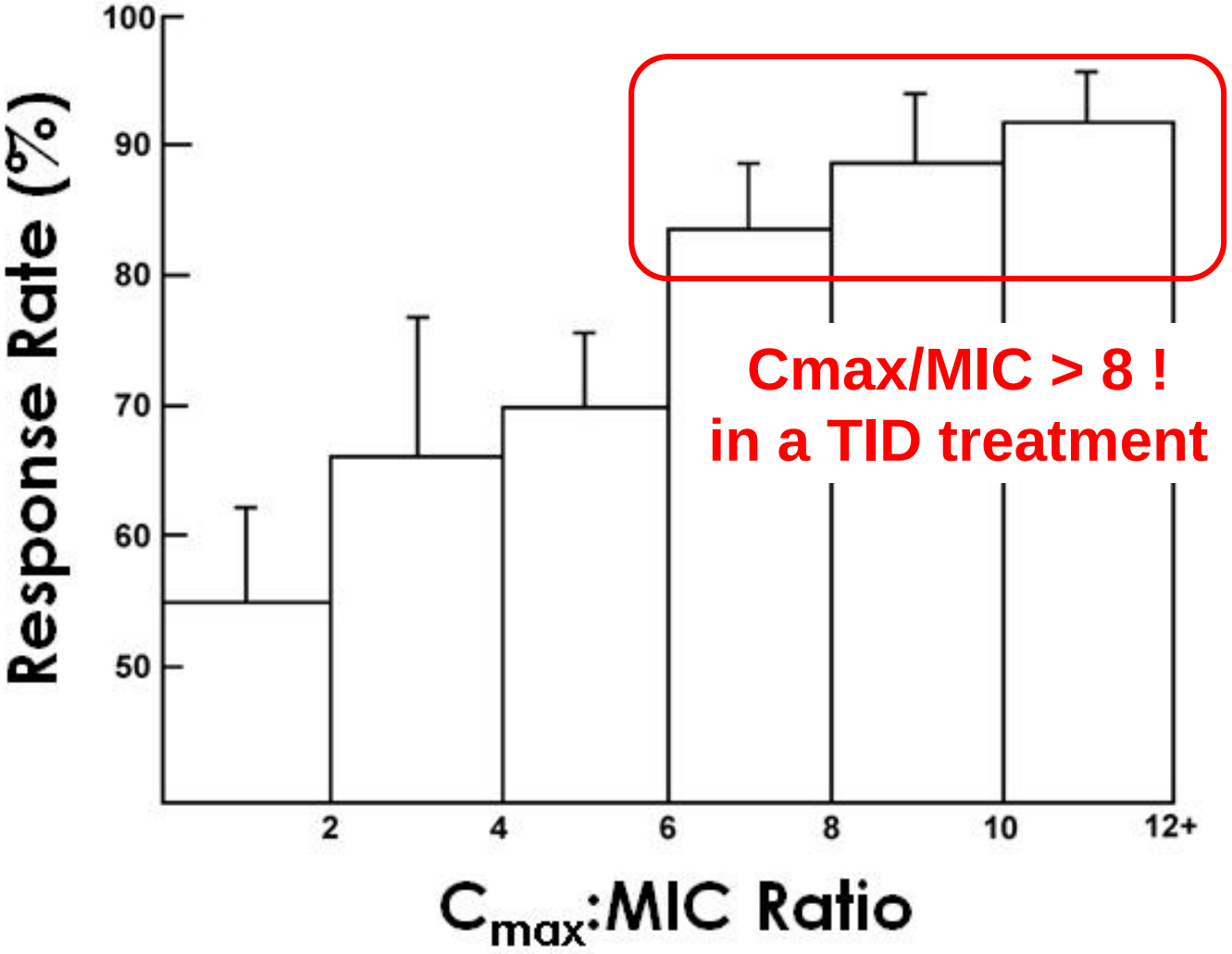
In vitro time-kill curves



Time and conc. – dependent killing

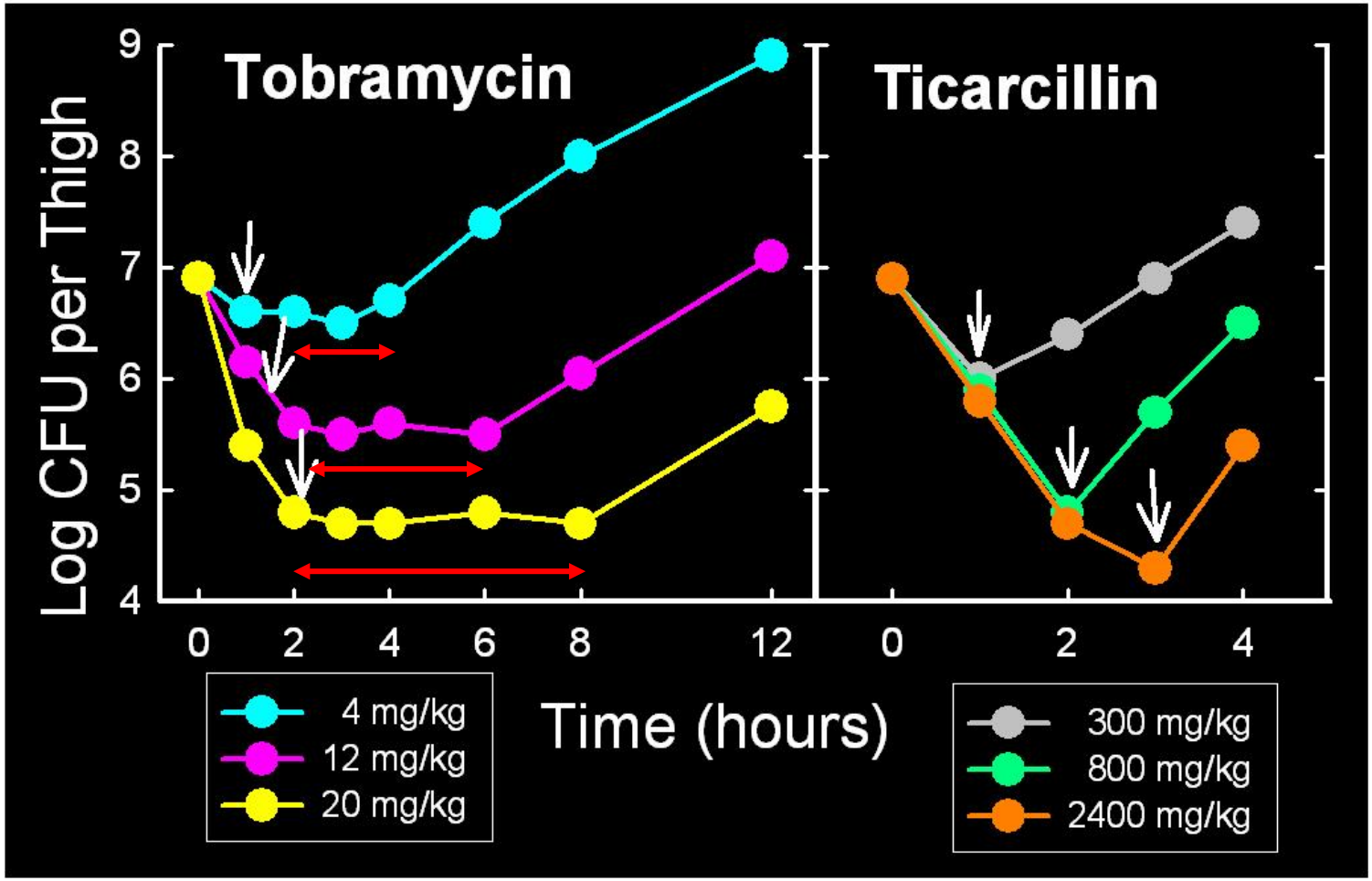
Craig WA, Ebert SC.. Scand J Infect Dis Suppl 1990; 74:63–70.

Concentration is important in patients also …



Moore RD, Lietman PS, Smith CR. JID 1987;155:93-99.

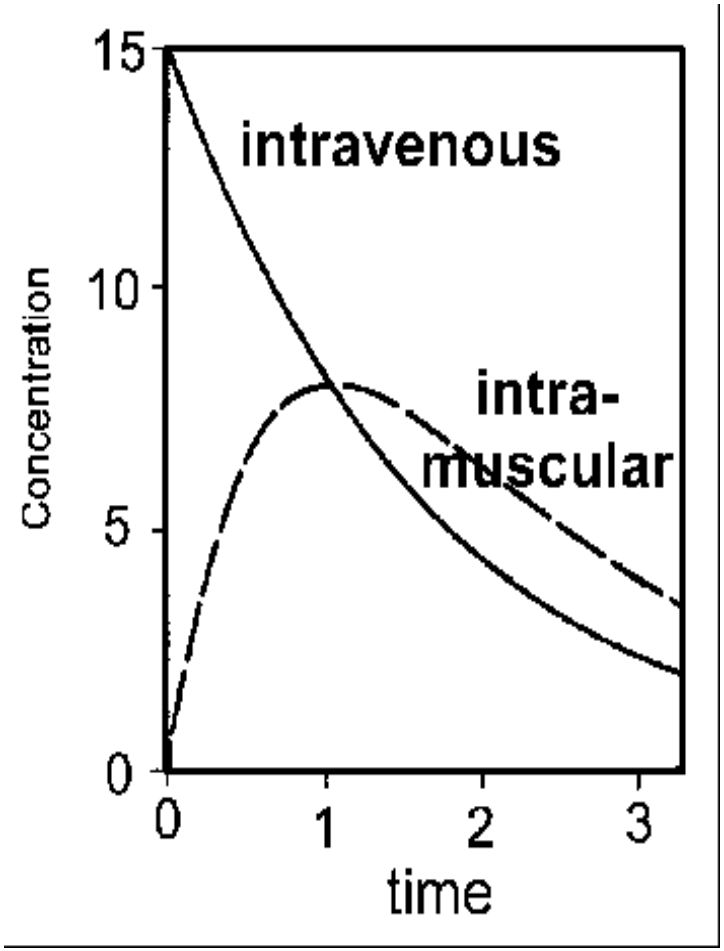
In vitro post-antibiotic effect



delay before regrowth

Vogelman et al. J Infect Dis. 1988 157:287–298

Aminoglycosides: get a peak !



1. Appropriate mode of administration

⇒ IV route

2. Calculation of the necessary peak value

⇒ minimal peak: = 8 x MIC

3. Calculation of the adequate dosis

⇒ peak = dose / V_d

⇒ dose = peak x V_d

⇒ dose = MIC x 8 x V_d

Aminoglycosides: which doses for which MIC ?

dose (mg/kg)	peak (mg/L) for V_d = 0.25 L/kg	peak/MIC for MIC = 4	2	1	0.5
1	4	1	2	4	**8**
2	8	2	4	**8**	**16**
3	12	3	6	**12**	**24**
4	16	4	**8**	**16**	**32**
6	24	6	**12**	**24**	**48**
8	32	**8**	**16**	**32**	**64**

Optimization of aminoglycoside usage: standard patients (Vd ~ 0.25 L/kg)

Do not try to treat with aminoglycosides bacteria with MIC

- > 2 µg/ml for molecules with maximal daily doses of 6 mg/kg
- > 4 µg/ml for molecules with maximal daily doses of 15 mg/kg

PK / PD breakpoints for AG

- Genta, Netil, Tobra (4 mg): 2 mg / L
- Amika / Isépa (15 mg): 8 mg / L

current EUCAST "S" breakpoints

≤ 2 mg/L

≤ 8 mg/L

Optimization of aminoglycoside usage: what if the VD is ↗

Anaesth Crit Care Pain Med 35 (2016) 331–335

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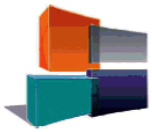

SFAR
Société Française d'Anesthésie et de Réanimation

Original Article

Assessment of the National French recommendations regarding the dosing regimen of 8 mg/kg of gentamicin in patients hospitalised in intensive care units

Nicolas Allou [a,*], Jérôme Allyn [a], Yaël Levy [a], Astrid Bouteau [b], Marie Caujolle [a], Benjamin Delmas [a], Dorothée Valance [a], Caroline Brulliard [a], Olivier Martinet [a], David Vandroux [a], Philippe Montravers [b], Pascal Augustin [b]

[a] *Réanimation polyvalente, CHU Felix-Guyon, allée des Topazes, 97405 Saint-Denis, France*
[b] *Département d'Anesthésie-Réanimation, AP–HP, CHU Bichat–Claude-Bernard, 46, rue Henri-Huchard, 75018 Paris, France*

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Anaesth Crit Care Pain Med 35 (2016) 331–335

Table 2
Sites of infection and isolated microorganisms.

	n
Sites of infection	34
Pulmonary	11
Catheter	9
Skin and soft tissue	6
Urinary tract	3
Other	2
Unknown	3
Bacteraemia	19
Isolated microorganisms	36
Cocci	18
Staphylococcus aureus	10
Other Staphylococci	4
Enterococcus faecalis	1
Streptococcus spp	3
Bacilli	18
Enterobacteriaceae	16
Escherichia coli	4
Enterobacter spp	6
Serratia marcescens	2
Klebsiella spp	4
Pseudomonas aeruginosa	2
None	5

Optimization of aminoglycoside usage: what if the VD is ↗

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[b] Département d'Anesthésie-Réanimation, AP-H

it should be 32 mg/L !

Table 3
Gentamicin pharmacokinetic/pharmacodynamic parameters.

Variable	$n = 34$
Dose (mg)	560 [510–610]
Dose (mg/kg of total body weight of the day)	8 [7.9–8.1]
Peak concentration (mg/L)	17.5 [15.4–20.7]
Patients with peak concentration > 30 mg/L	0
Patients with peak concentration > 16 mg/L	24 (71)
Patients with peak concentration > 8 mg/L	33 (97)
Trough concentration	1.6 [0.7–3.3]

Results are expressed as medians [25th–75th percentiles] or *n* (%).

V_d = dose/peak → 0.45 in this population (8/17.5)

Amikacin dosing in ICU: recent data from Leuven

Accepted Manuscript

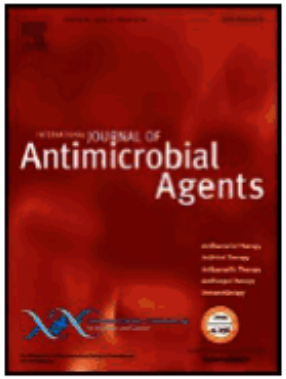
Title: Higher versus standard amikacin single dose in emergency department patients with severe sepsis and shock: a randomized controlled trial

Author: Sabrina De Winter, Joost Wauters, Wouter Meersseman, Jan Verhaegen, Eric Van Wijngaerden, Willy Peetermans, Pieter Annaert, Sandra Verelst, Isabel Spriet

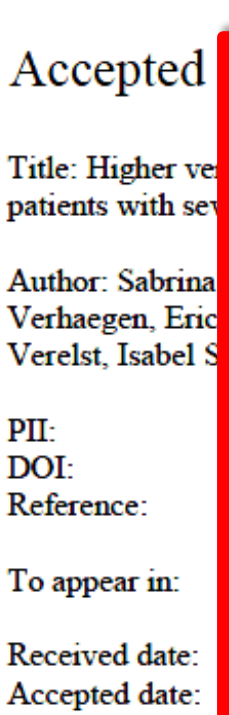
PII: S0924-8579(17)30426-0
DOI: https://doi.org/10.1016/j.ijantimicag.2017.11.009
Reference: ANTAGE 5301

To appear in: *International Journal of Antimicrobial Agents*

Received date: 28-2-2017
Accepted date: 18-11-2017



Amikacin dosing in ICU: recent data from Leuven


Accepted

Title: Higher ve
patients with se

Author: Sabrina
Verhaegen, Eric
Verelst, Isabel S

PII:
DOI:
Reference:

To appear in:

Received date:
Accepted date:

- Recent studies suggest that ICU patients treated with amikacin frequently do not attain the PK/PD target, i.e. a peak above minimal inhibitory concentration (MIC) ratio of at least 8, when a single dose of 15 mg/kg is used.
- 104 ED patients admitted with severe sepsis or septic shock were included and randomly treated with 25 vs. 15 mg/kg. Amikacin peak concentrations were collected.
- Primary outcome was target attainment defined as peak/MIC ≥ 8, using both **EUCAST susceptibility breakpoints** (8 mg/L) and **actually documented MIC** values as denominator.
- The **EUCAST based target (64 mg/L)** was attained in **76% *vs.* 40%** of patients assigned to the **25 *vs.*15 mg/kg** dose group (p<0.0001).
- Target attainment using **actual MIC values** (median of 2 mg/L, documented in 48 isolated gram-negative pathogens; **target = 16 mg/L**) was achieved in **95% *vs.* 94%** of patients in the **25 *vs.*15** mg/kg group (p=0.969).

Amikacin dosing in ICU: recent data from Leuven

Accepted Manuscript

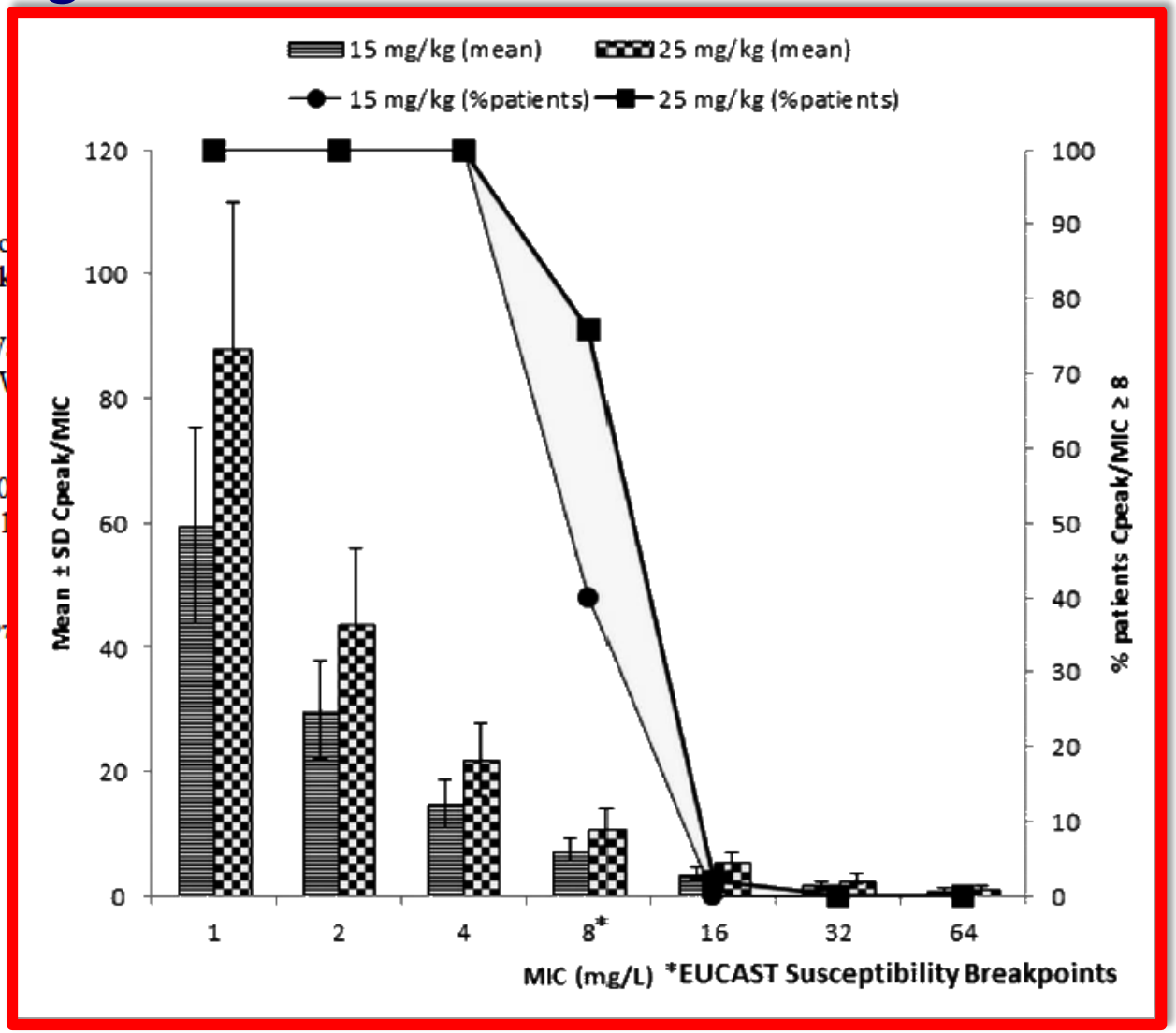
Title: Higher versus standard amikac
patients with severe sepsis and shock

Author: Sabrina De Winter, Joost W
Verhaegen, Eric Van Wijngaerden,
Verelst, Isabel Spriet

PII: S0924-8579(17)30
DOI: https://doi.org/10.1
Reference: ANTAGE 5301

To appear in: *International Jour*

Received date: 28-2-2017
Accepted date: 18-11-2017



PK/PD target attainment of critically ill ED patients in function of different MIC values

The vancomycin story: discontinuous or continuous infusion ?

RESUME DES CARACTERISTIQUES DU PRODUIT - RCP

1 DÉNOMINATION DU MÉDICAMENT

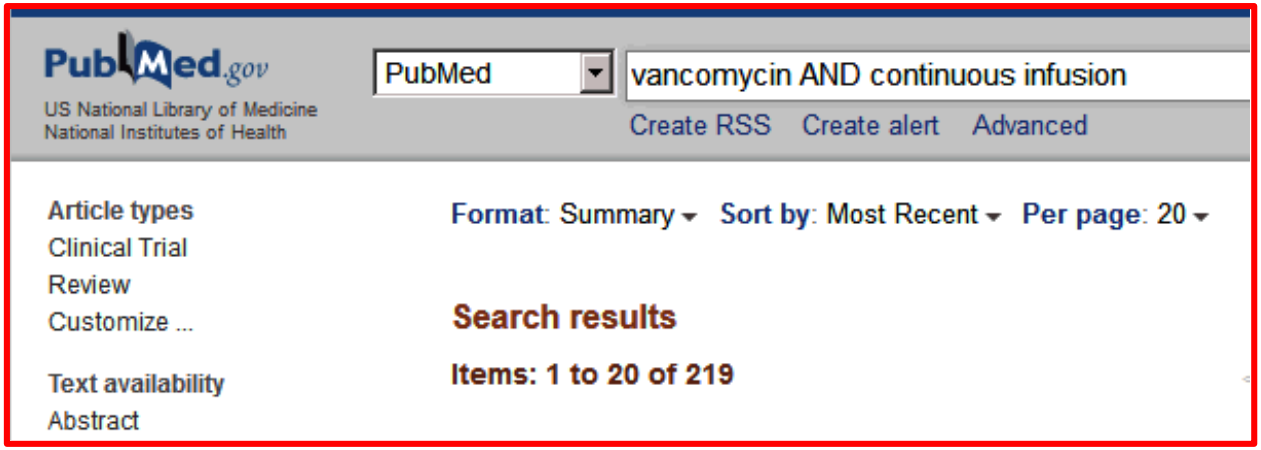
Vamysin 1000 mg, poudre pour solution à diluer pour solution pour perfusion.

4.2 Posologie et mode d'administration

Voie intraveineuse (perfusion) chez les patients présentant une fonction rénale normale :

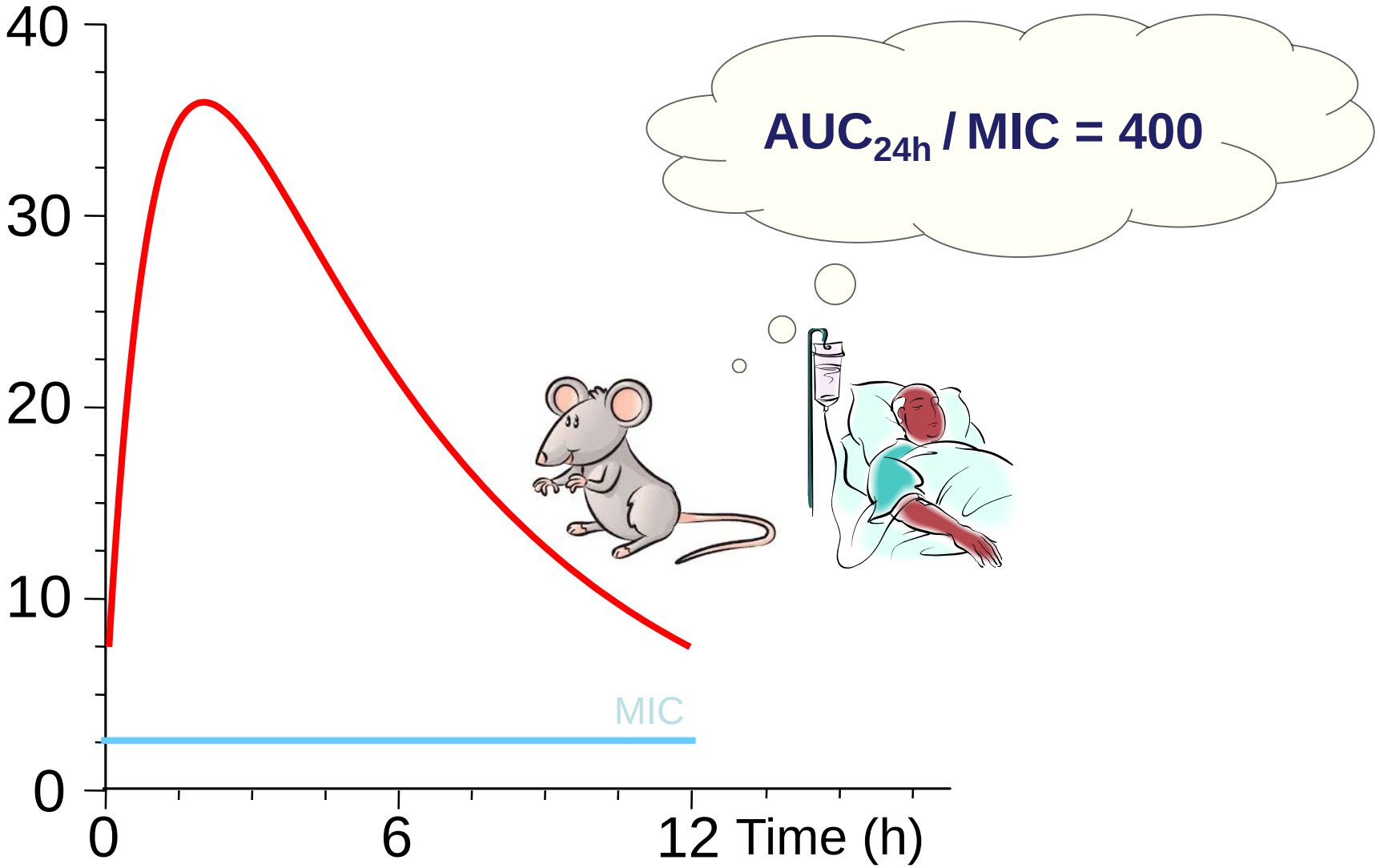
Adultes et adolescents âgés de plus de 12 ans :
La posologie intraveineuse quotidienne recommandée est de 2 000 mg, répartis en doses de 500 mg toutes les 6 heures ou de 1 000 mg toutes les 12 heures, ou 30 à 40 mg/kg/jour en 2 à 4 administrations quotidiennes.

http://bijsluiters.fagg-afmps.be/registrationSearchServlet?key=BE405291&leafletType=rcp
Last accessed: 18 Dec 2017

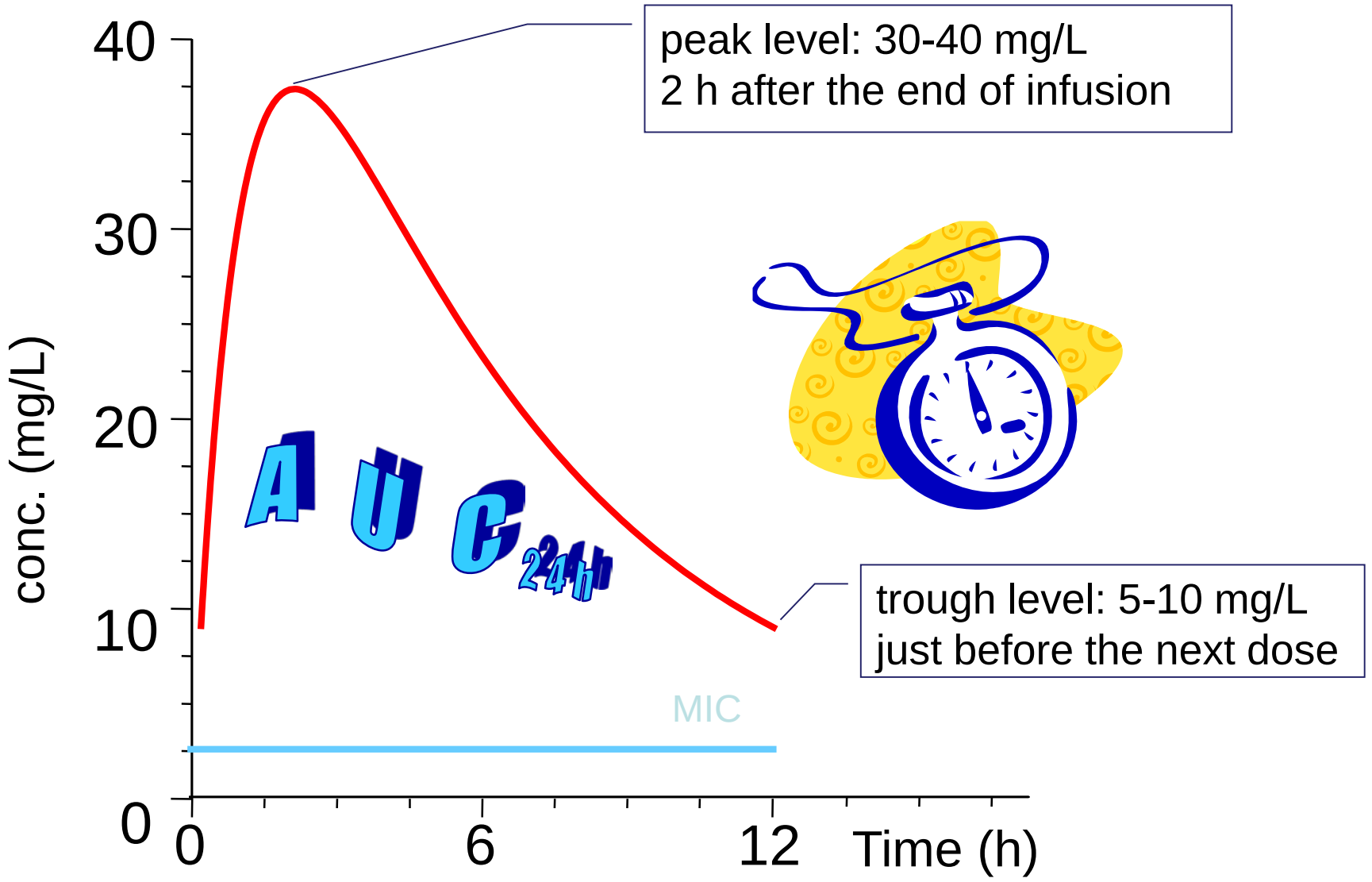


https://www.ncbi.nlm.nih.gov/pubmed/?term=vancomycin+AND+continuous+infusion
Last accessed: 18 Dec 2017

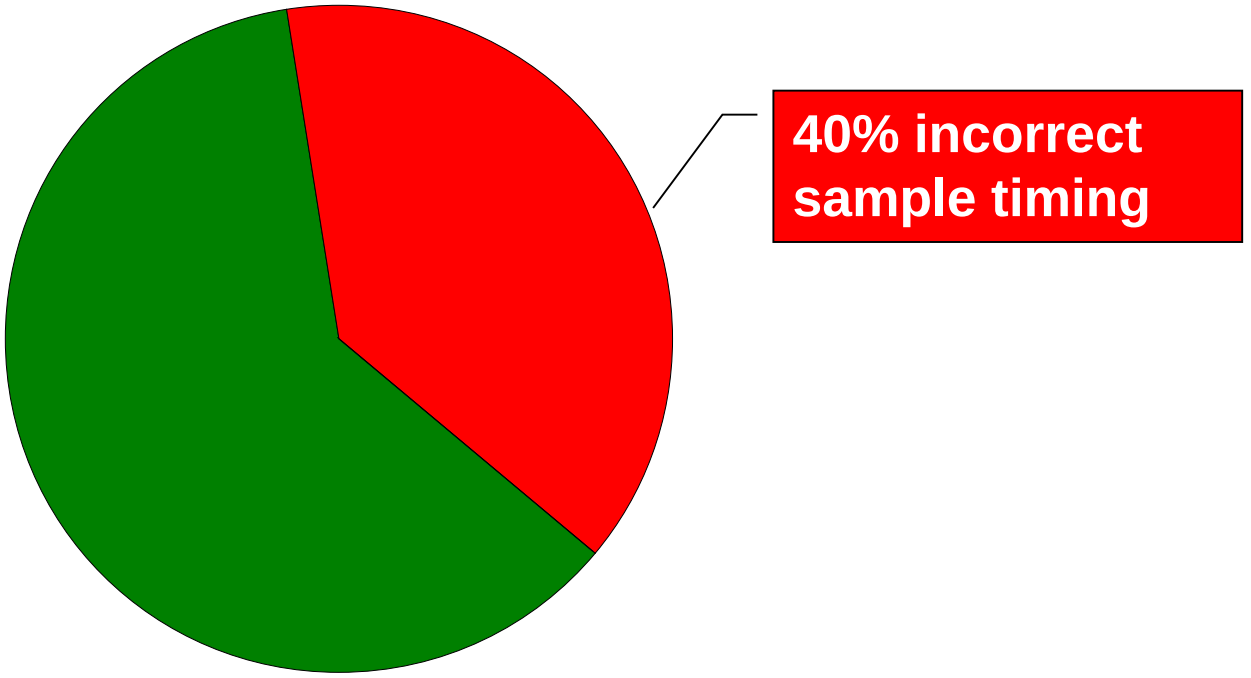
Vancomycin: how to optimize it ?



Vancomycin TDM at CHU Mont-Godinne at the start of the project



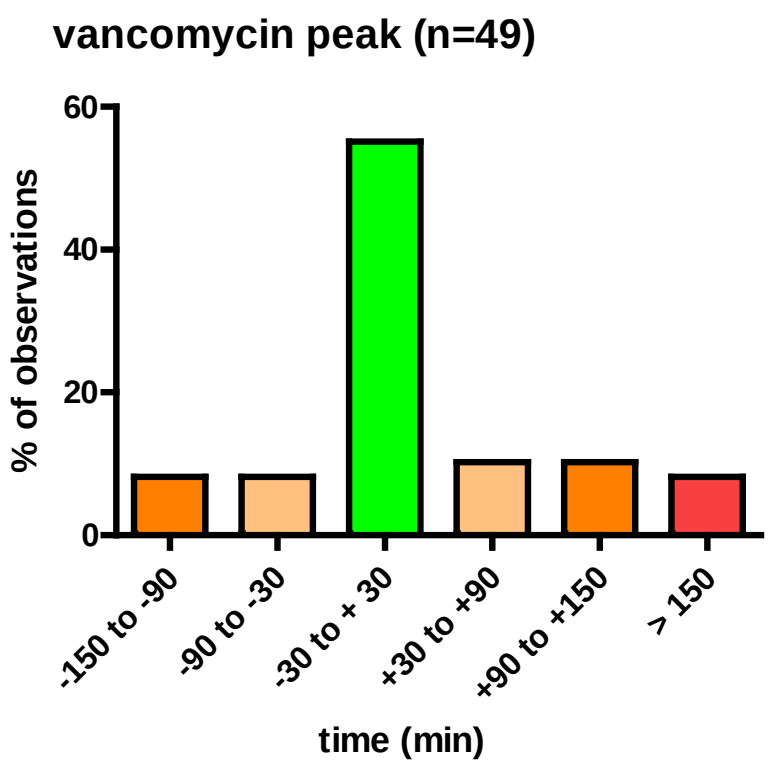
Observational study – results

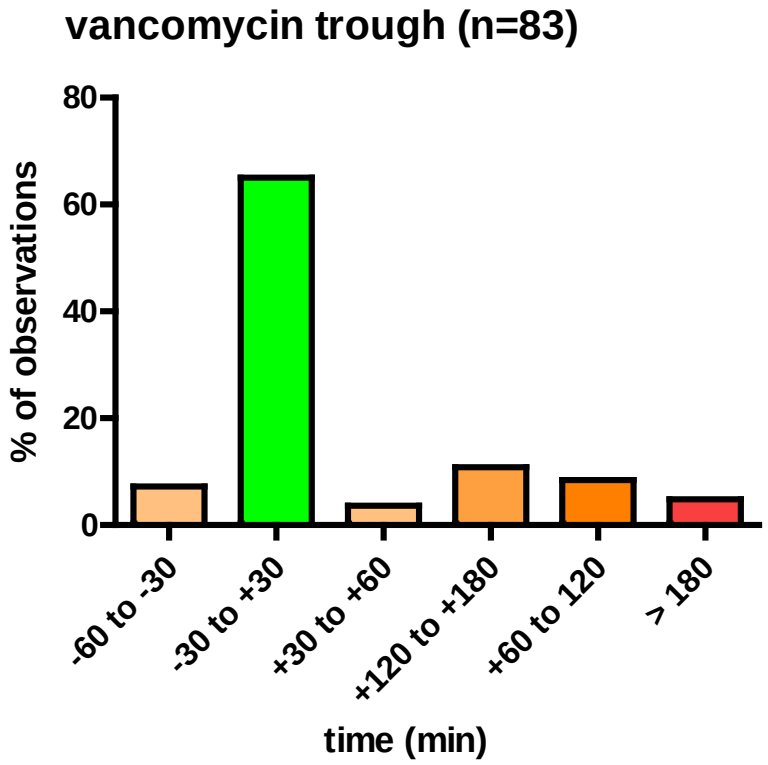


*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

Observational study – results

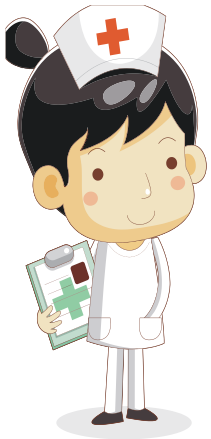
Observed deviations (in min) from recommended sampling times at baseline.





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

But, how could we improve ?



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

Concentration

continuous infusion

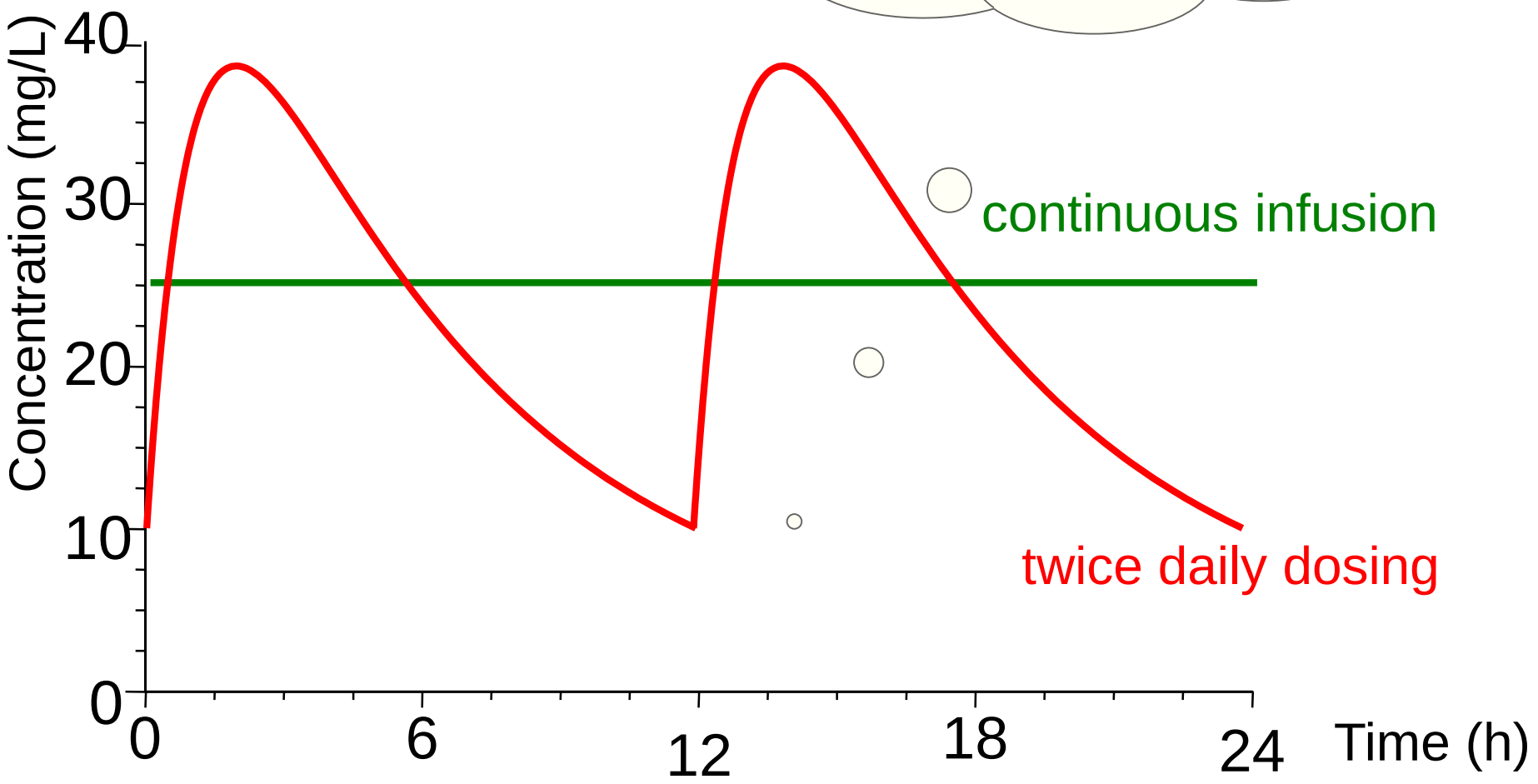
Time (h)

0 6 12 18 24

TDM of vancomycin by continuous infusion

AUC24h / MIC is independent of the mode of administration

of the same daily dose

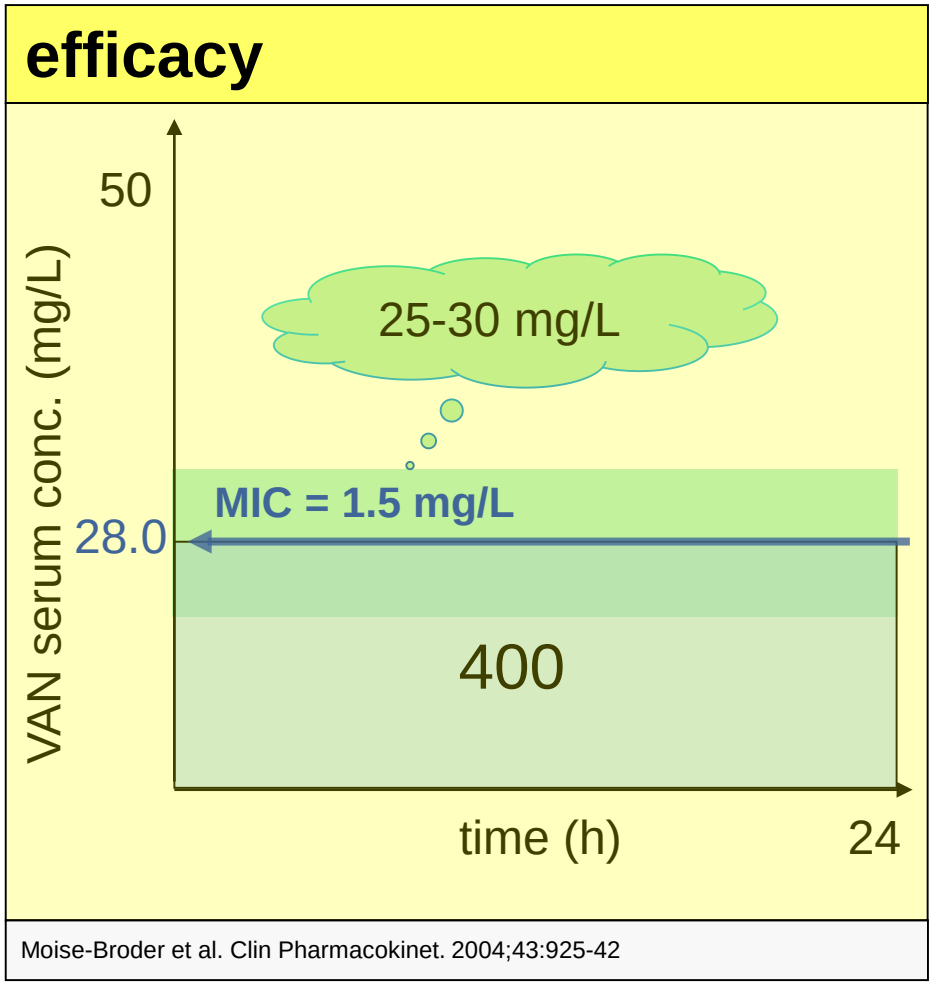


Vancomycin CI: which serum concentration should we target for continuous infusion?

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

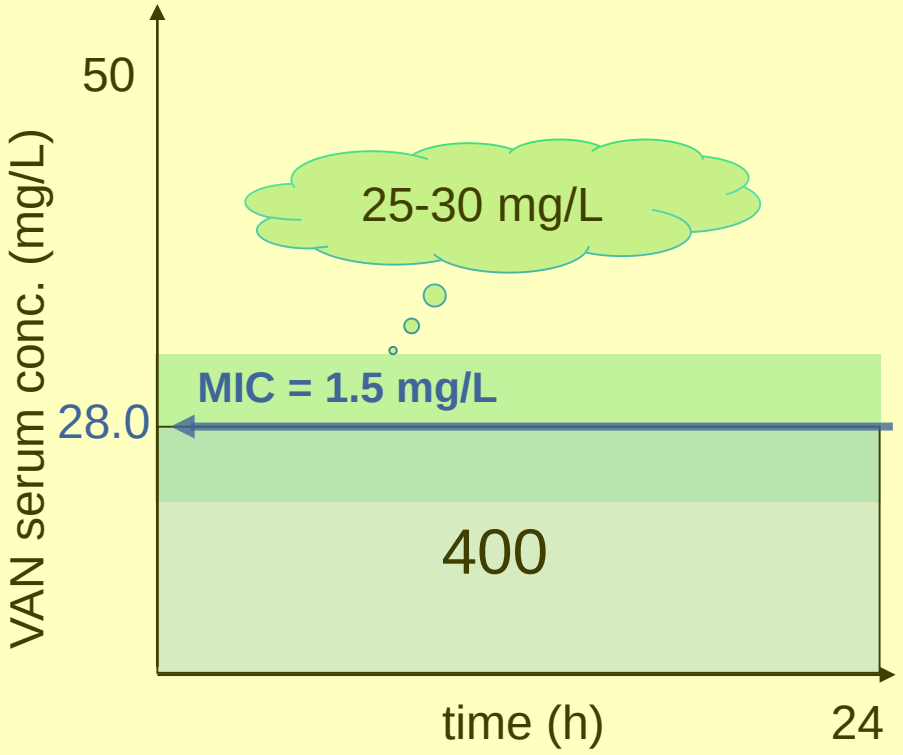
Vancomycin CI: Target for efficacy



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

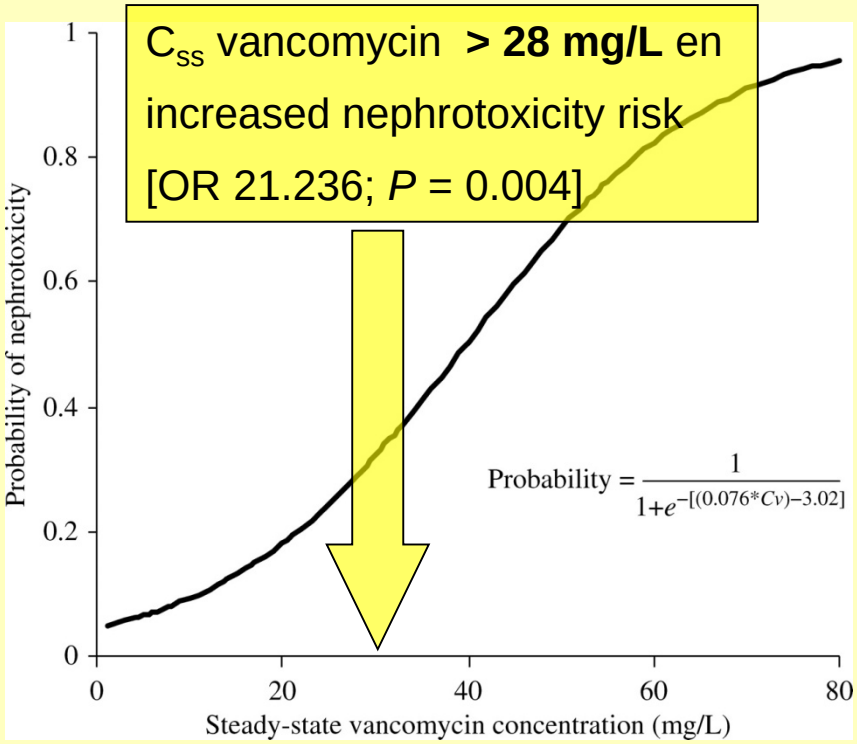
Vancomycin CI: efficacy vs toxicity …

efficacy



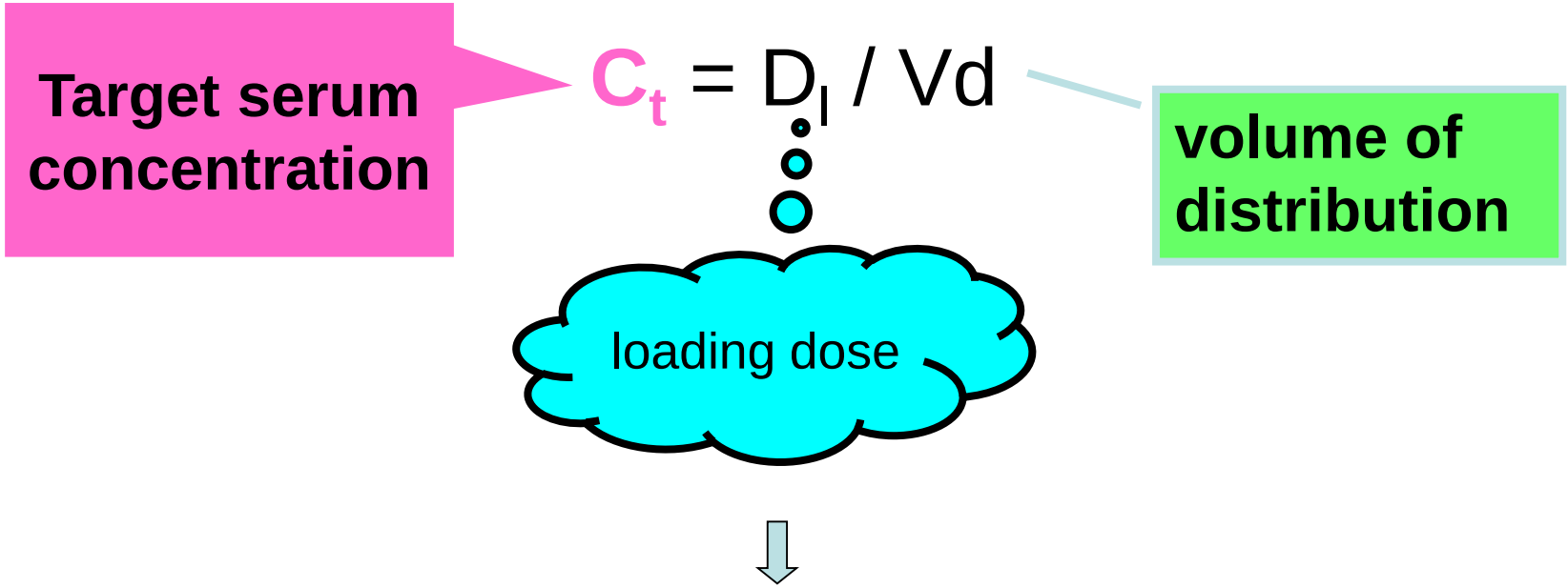
Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

toxicity



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

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 *

Target serum concentration

$C_{ss} = K_o / Cl$

Clearance *

infusion rate

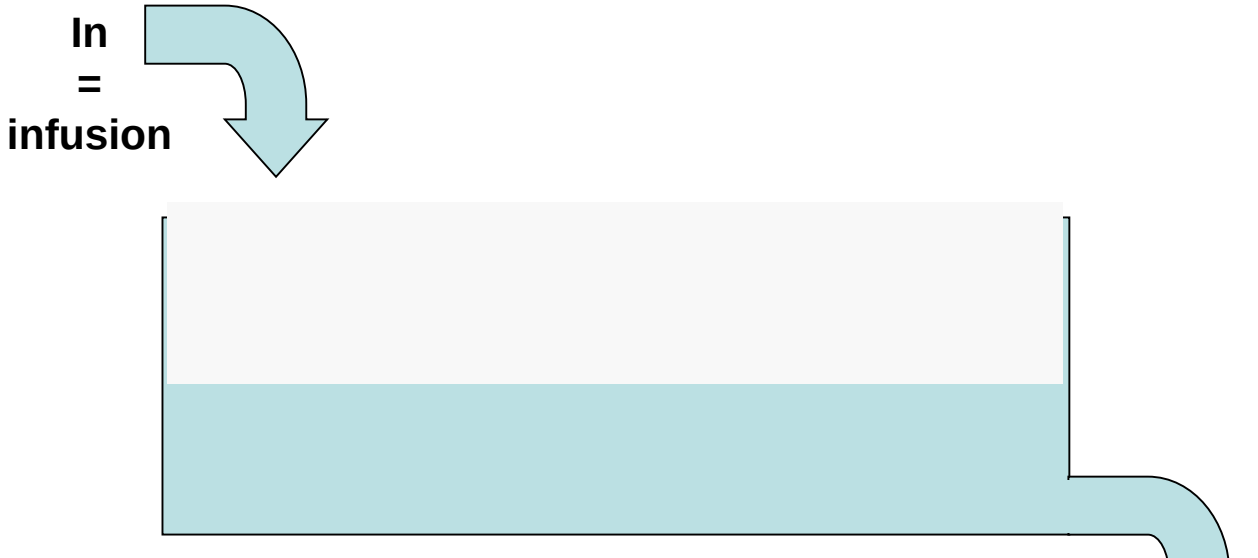
daily dose (in mg) = 24 x **VAN clearance** (L/h) x **Css**

daily dose (in mg) = 24 x 0.65 **creatinine clearance** (L/h) x **Css**

typically 2.5 g/day

* of vancomycin [assuming linear pharmacokinetics] = 0.65 creatinine clearance

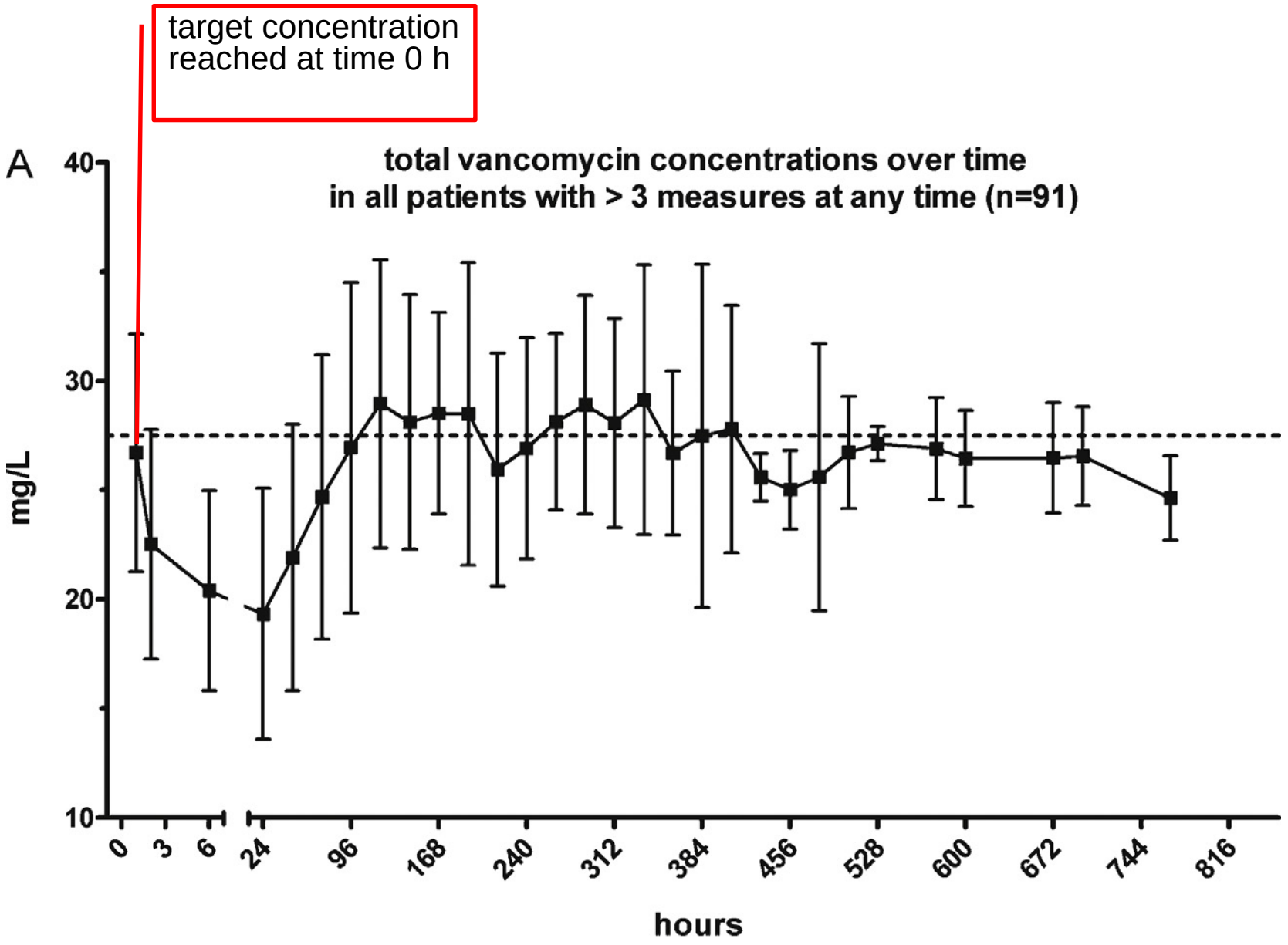
How to reach the serum target concentration target with CI? 2: infusion *



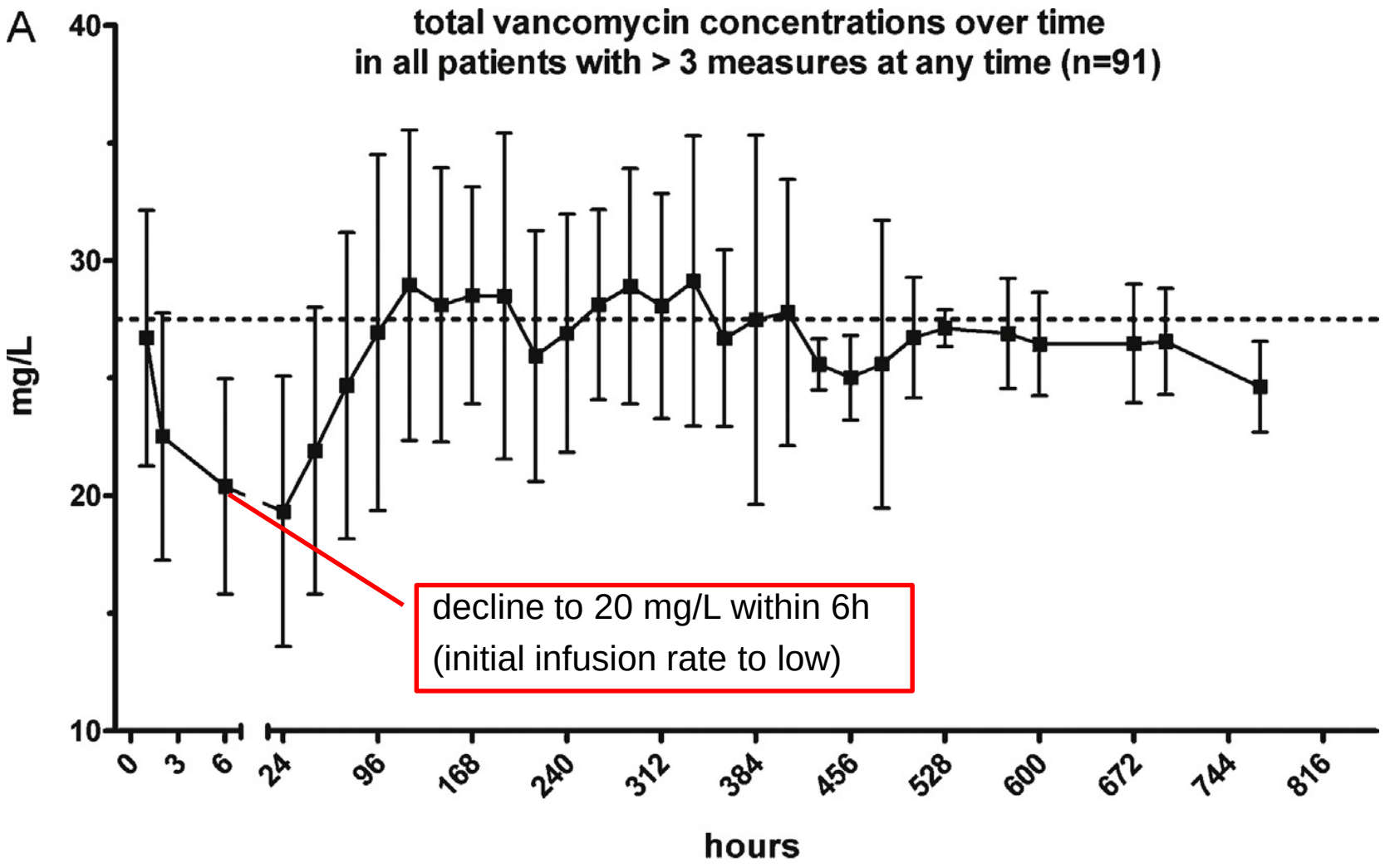
once a bath is a the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which musts be equal: in = out…)

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

7. Total vancomycin serum concentrations



7. Total vancomycin serum concentrations



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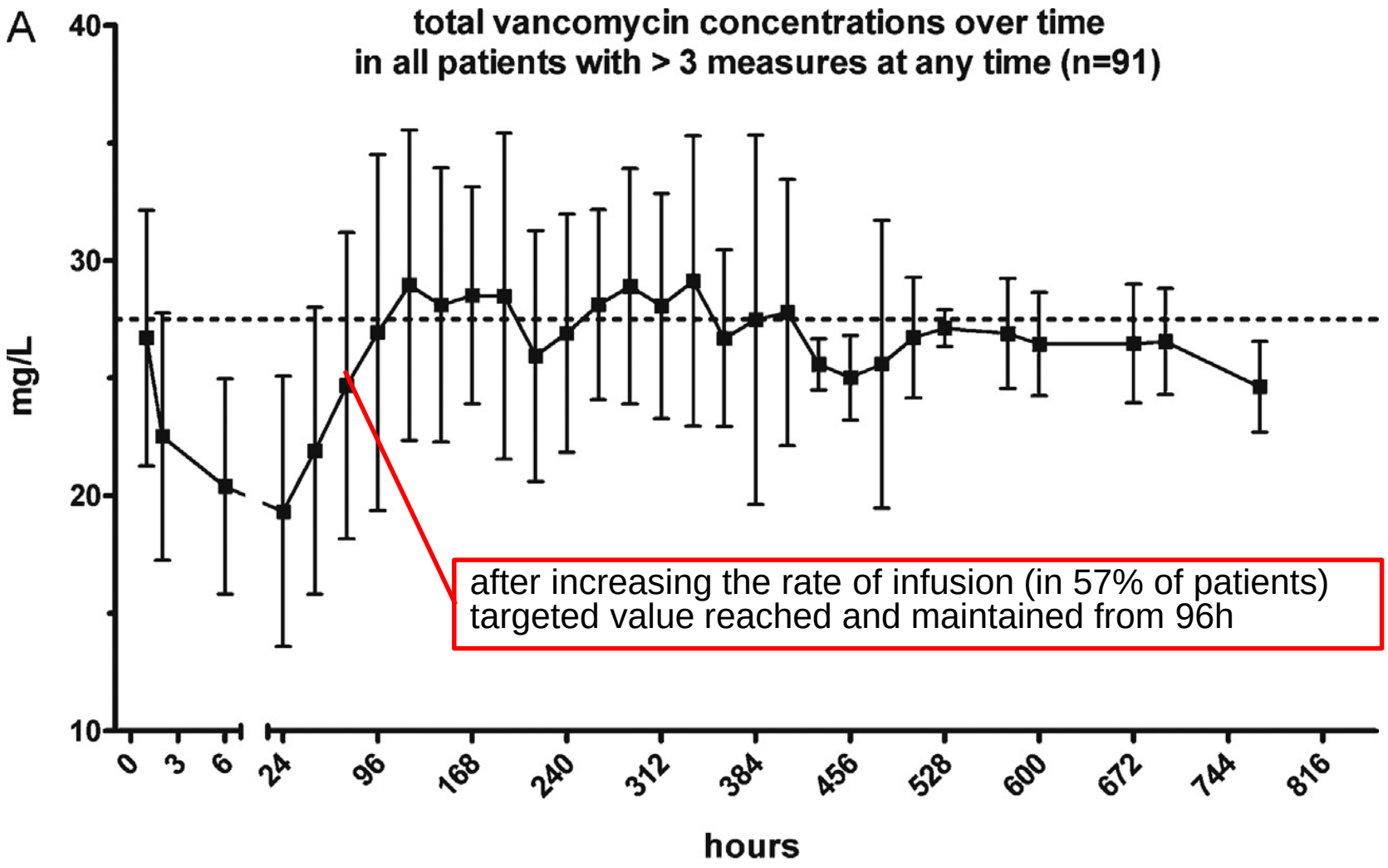

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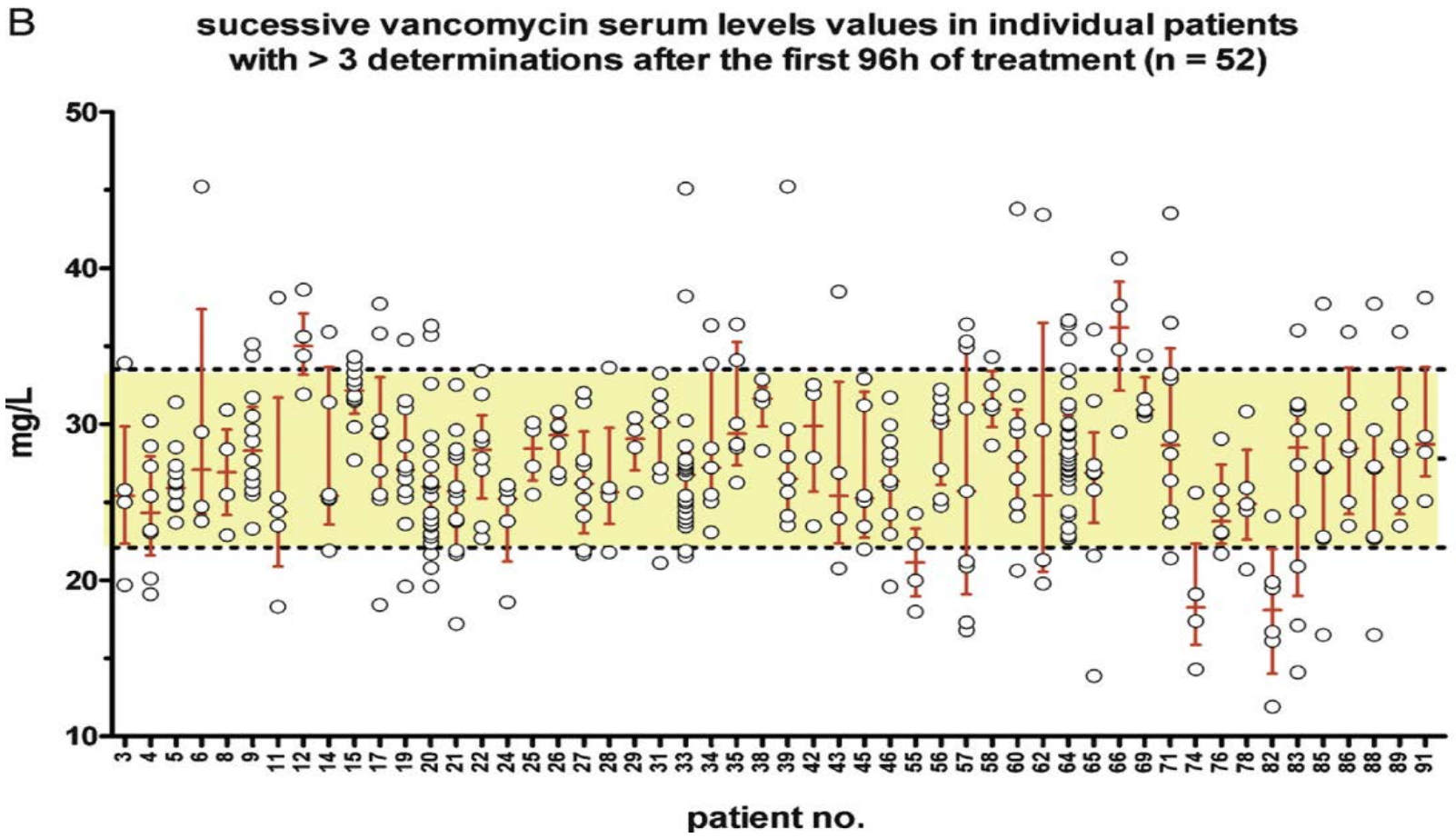
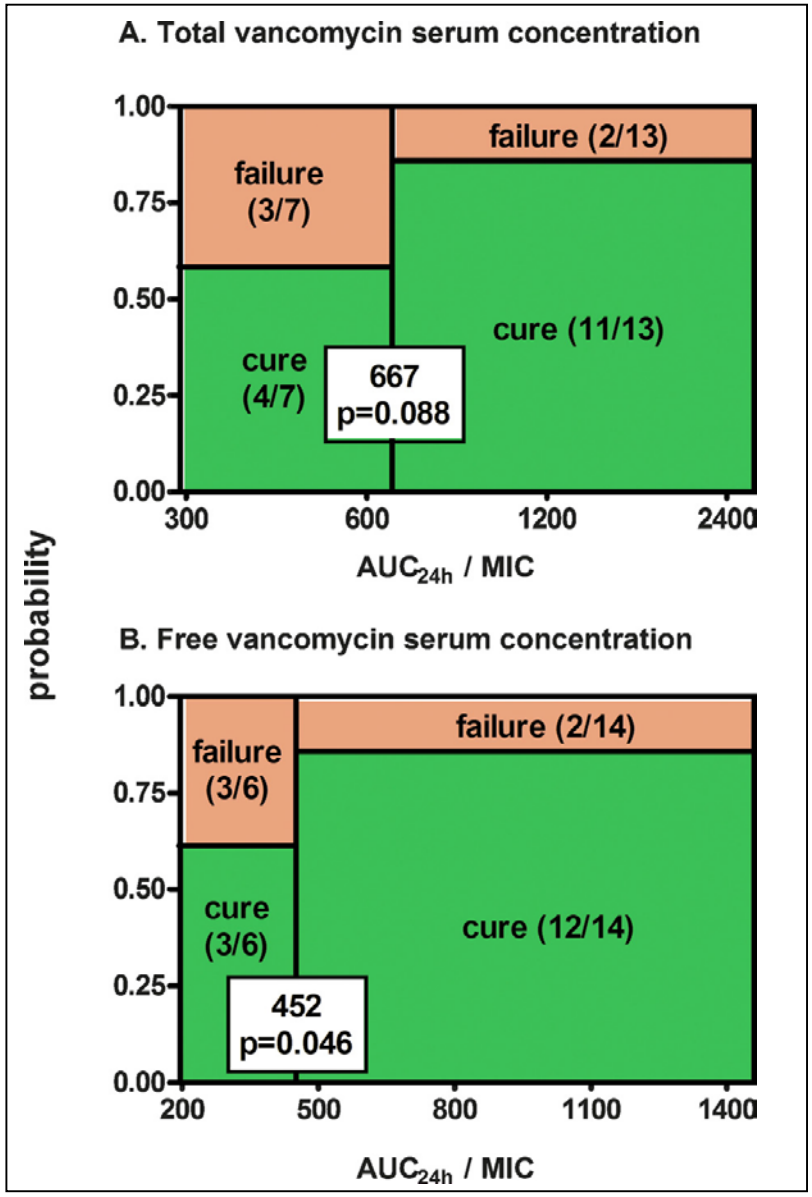


- deviations of >10 mg/L according to the recommended range
  - ↘ if increased CCrCl (threshold at >104 mL/min)
  - ↗ if concomitant use of diuretics

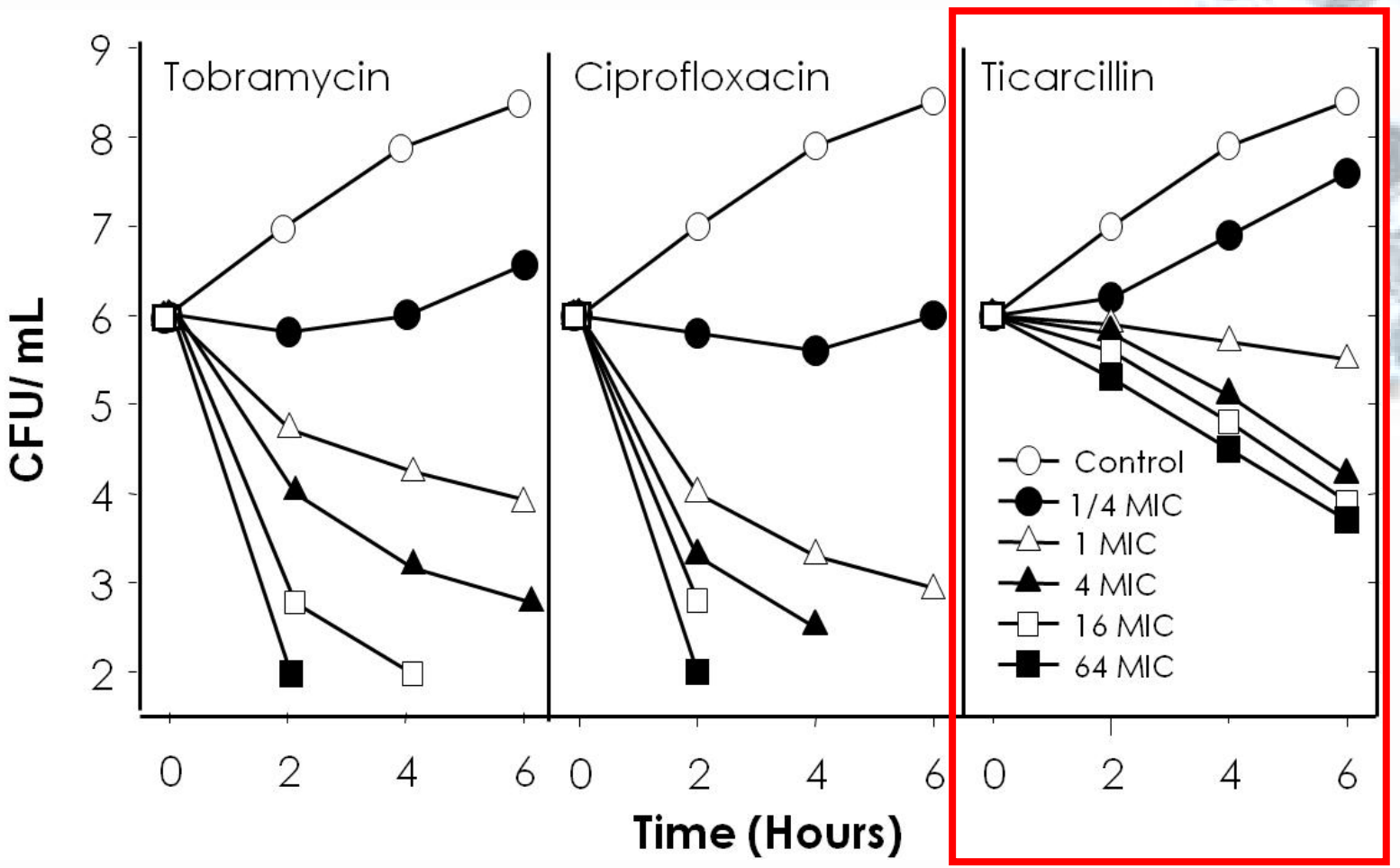
9. AUC_{24h}/MIC predictive of clinical success/failure (n=20)



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

β-lactams: T > MIC …

In vitro time-kill curves



Time dependent killing

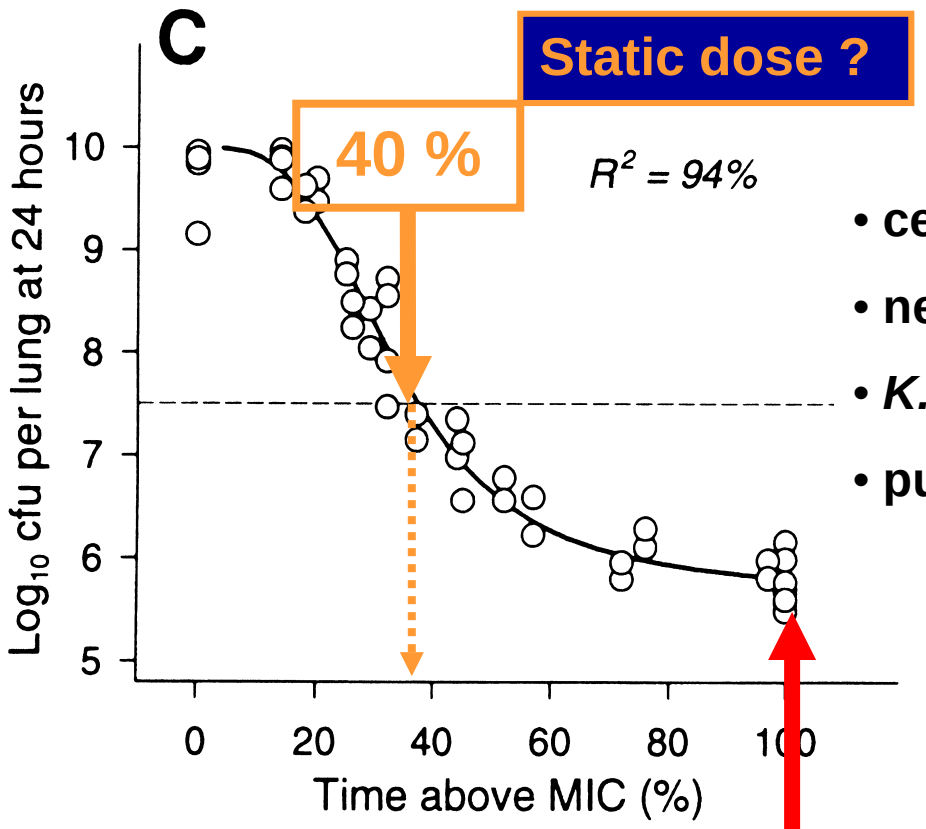
Craig WA, Ebert SC.. Scand J Infect Dis Suppl 1990; 74:63–70.

β-lactams: T > MIC…

You know it is "time above MIC", but…

- 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 / How frequent ?**
  (Static dose *vs* maximum effect ?)

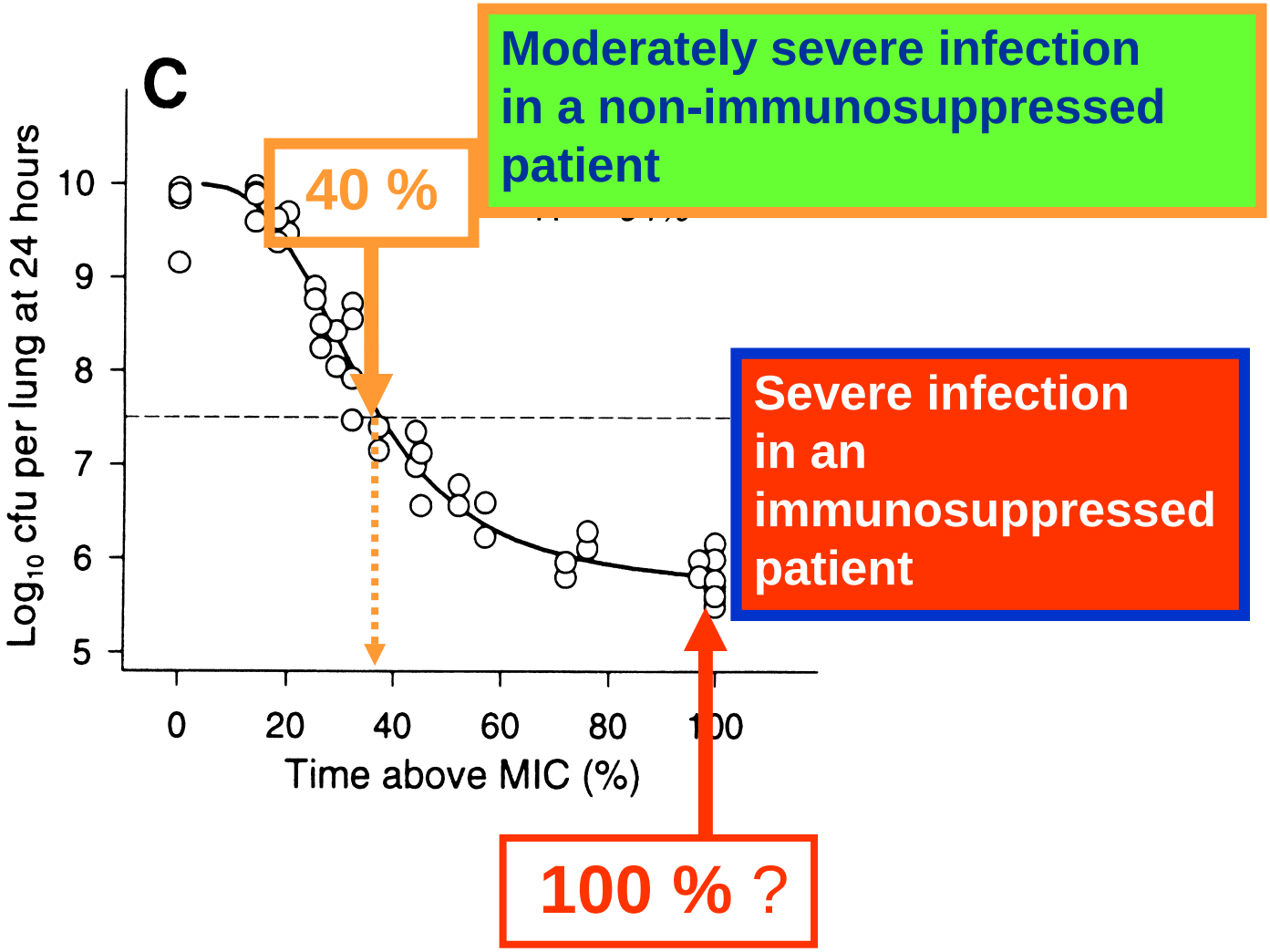
How much time above MIC ?



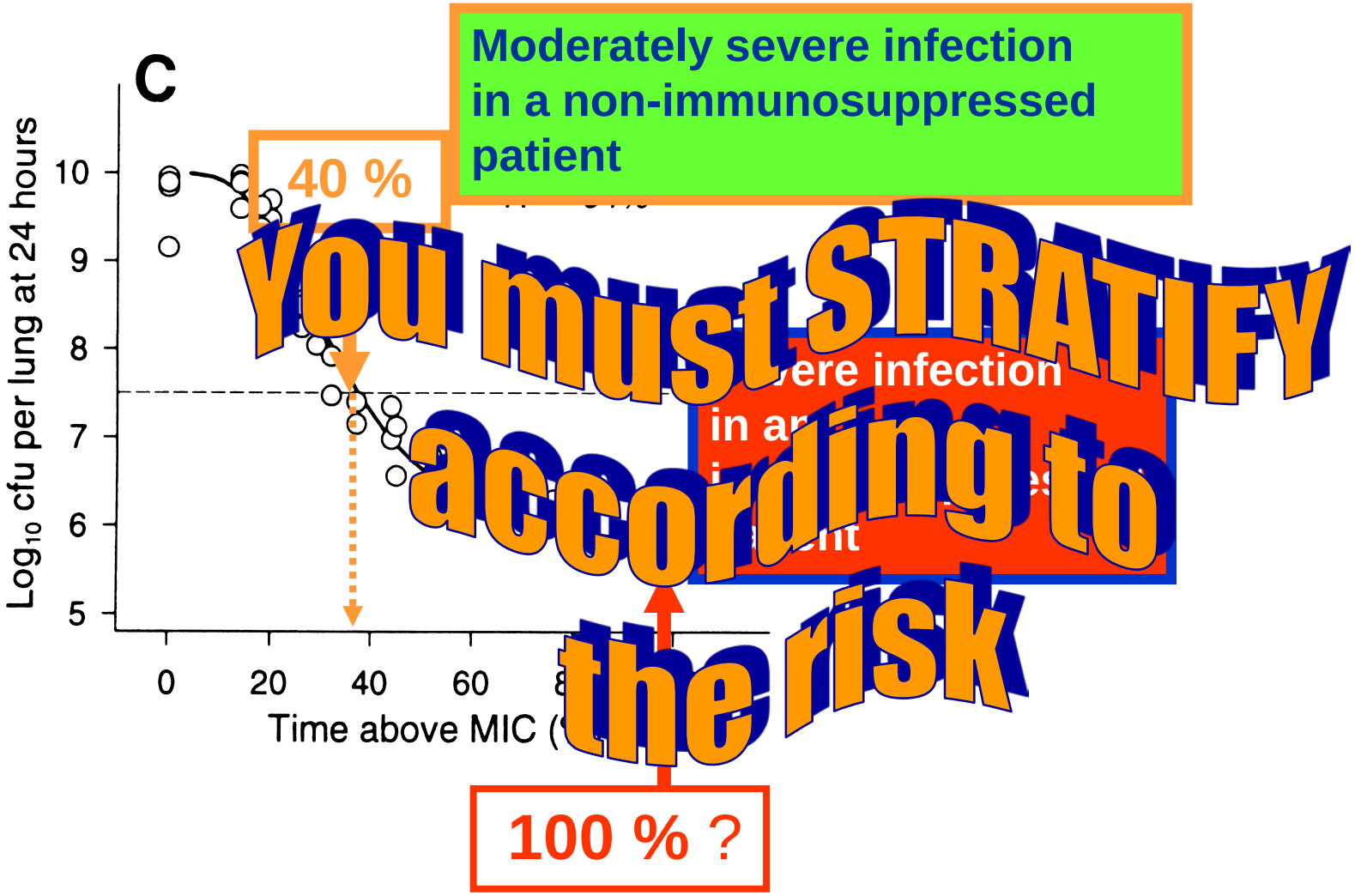
- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100 % - Maximal effect ?

It all depends on your patient !



It all depends on your patient !



But back to MIC …!

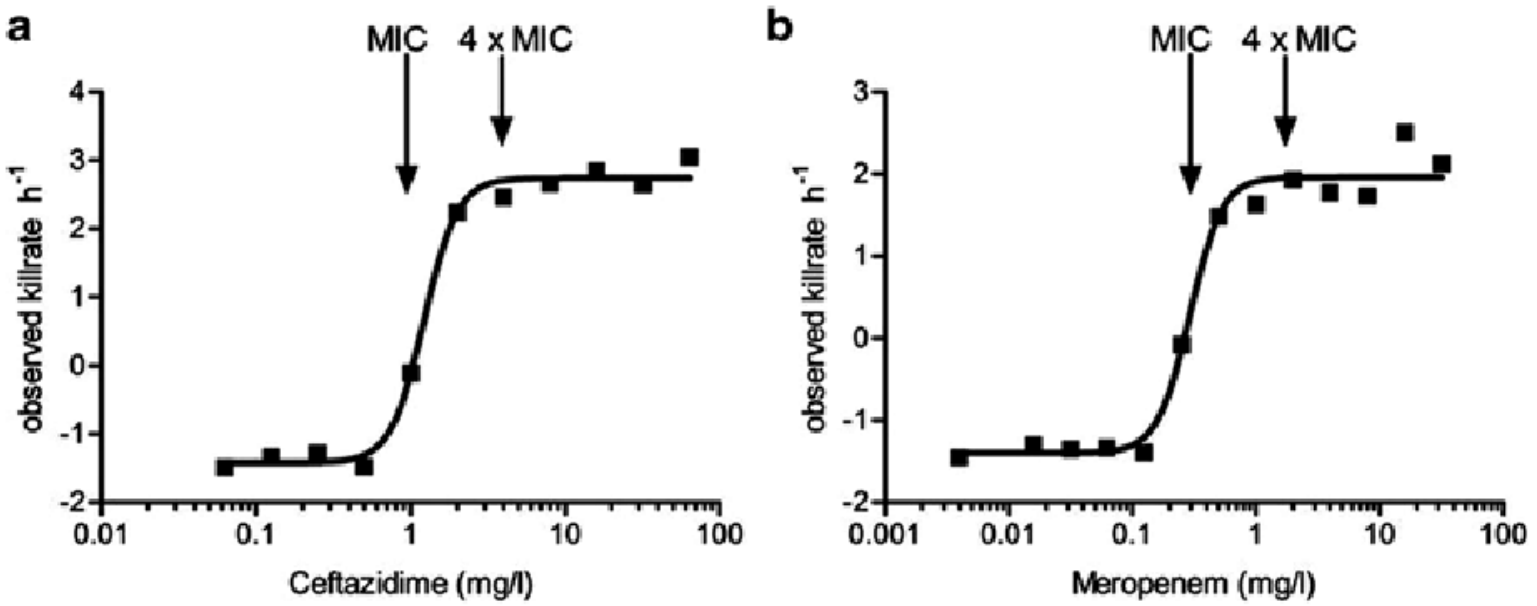
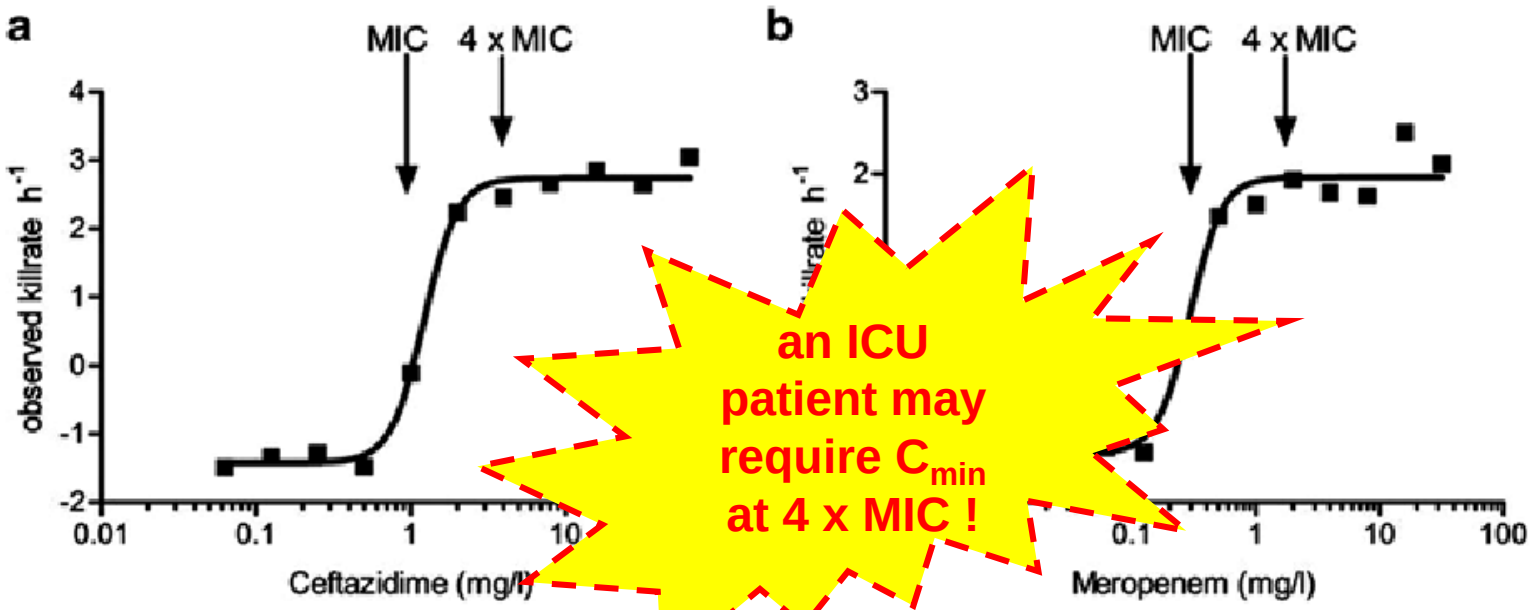


Fig. 10.2 Relationship between concentration of ceftazidime (**a**) and meropenem (**b**) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold dilutions. The maximum kill rate is attained at around 4× MIC. Figure modified from Mouton and Vinks (2005b, 2007). Reproduced from Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics: the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44(2):201–10 with permission from Adis (© Springer International Publishing AG [2005]. All rights reserved

But back to MIC …!



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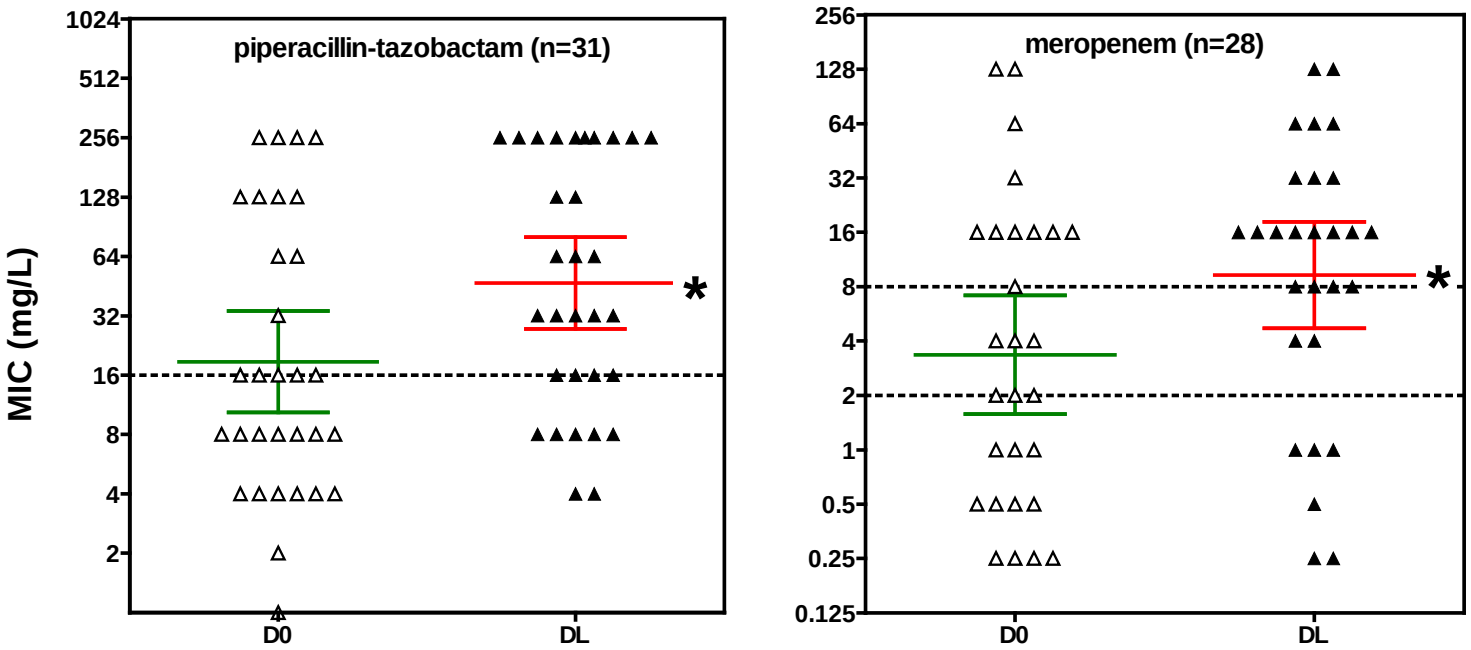
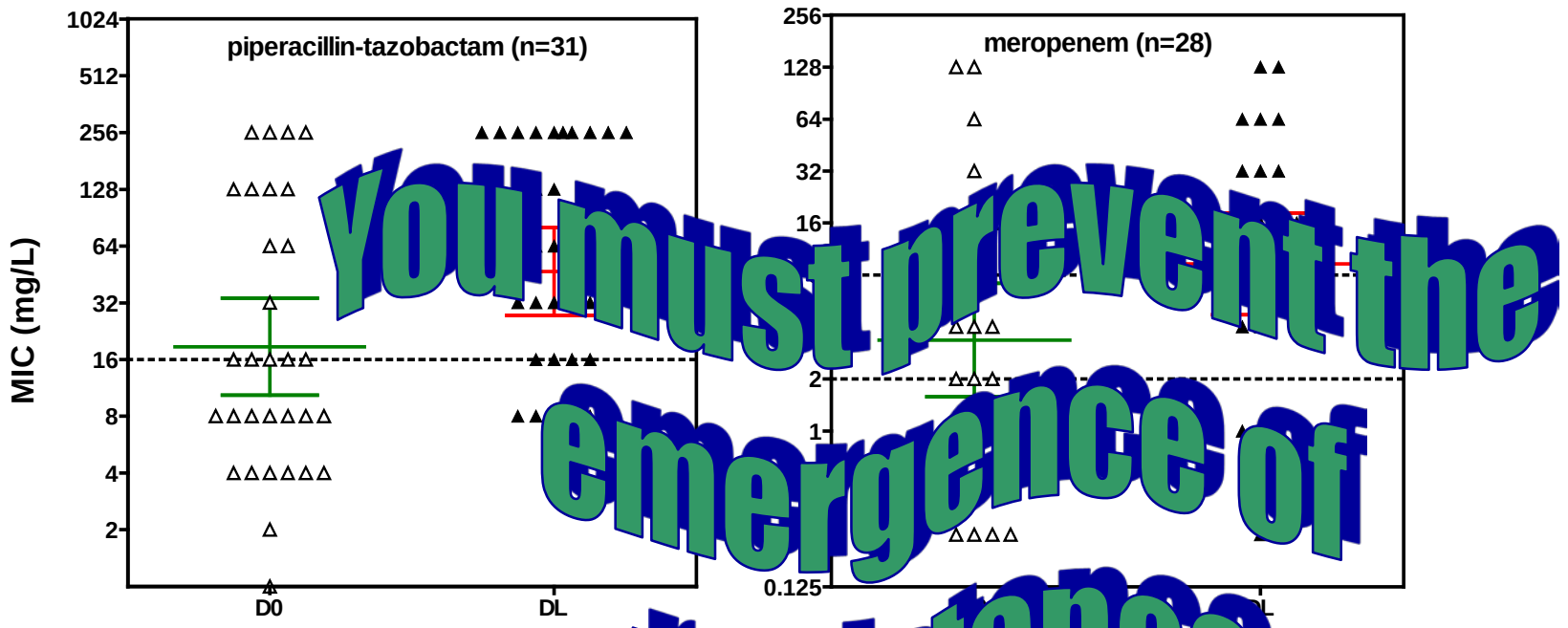
And do not forget about changes in MIC (low-level resistance) during treatment !



Change in MIC of antibiotics used in empiric antipseudomonal therapy (nosocomial pneumonia; intensive care units) towards the isolate identified before onset of therapy (D0) *vs*. the last isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and $\log_2$ transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

Riou et al. Int J Antimicrob Agents. 2010 Dec;36(6):513-22.

And do not forget about changes in MIC (low-level resistance) during treatment !



Change in MIC of antibiotics used in empiric ant[illegible]socomial pneu[illegible], intensive care units) towards the isolate identified before onset of therapy [illegible] isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and log2 transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

Riou et al. Int J Antimicrob Agents. 2010 Dec;36(6):513-22.

But how to prevent the emergence of resistance ?

J Antimicrob Chemother 2017; **72**: 1421–1428
doi:10.1093/jac/dkx001 Advance Access publication 31 January 2017

Journal of Antimicrobial Chemotherapy

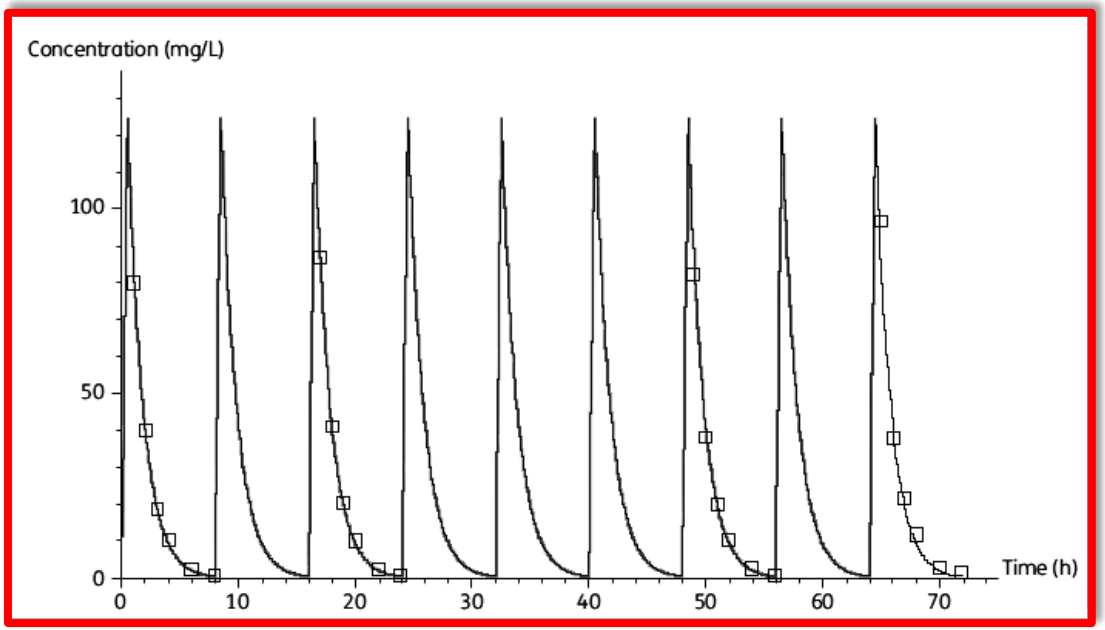
Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam[1]*, Kai-Tai Chang[1], Jian Zhou[1], Kimberly R. Ledesma[1], Kady Phe[1], Song Gao[1], Françoise Van Bambeke[2], Ana María Sánchez-Díaz[3], Laura Zamorano[4], Antonio Oliver[4] and Rafael Cantón[3]

[1]University of Houston, Houston, TX, USA; [2]Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; [3]Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [4]University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain

Tam *et al.* J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

Simulation of doses and drug exposure in an in vitro dynamic model of infection (ho*llow fiber*)



Prevention of resistance…

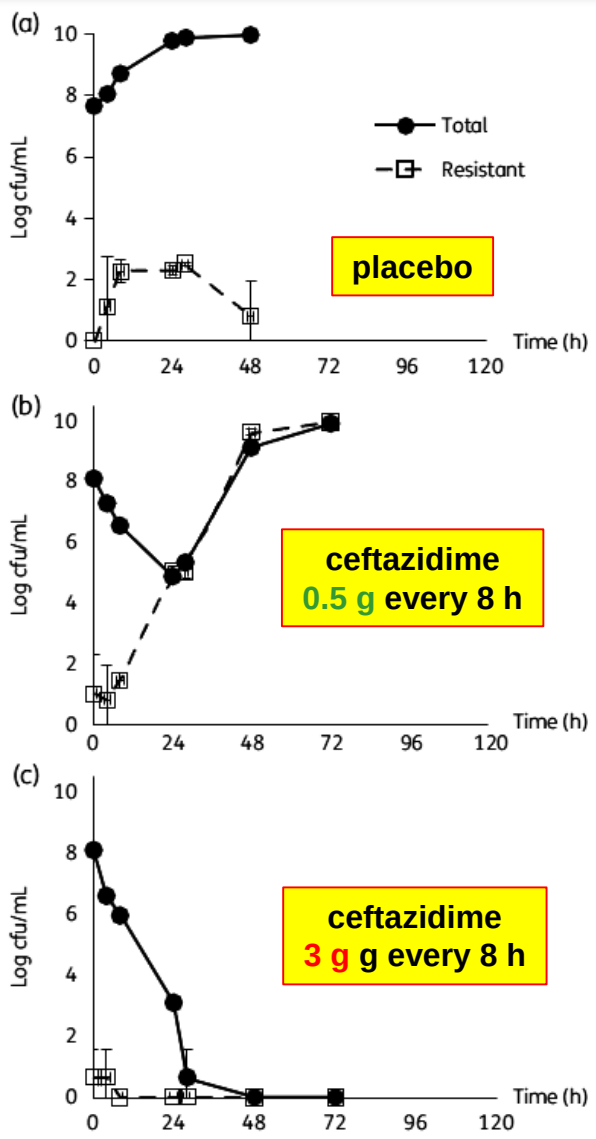


Figure 2. Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h (C_{min}/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h (C_{min}/MIC = 7.7) (c). Data are shown as mean ± SD.

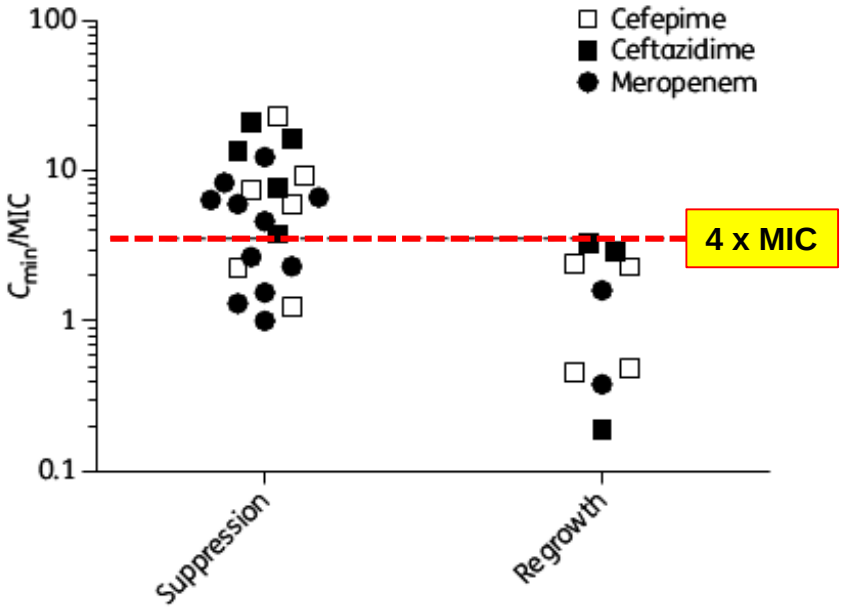


Figure 3. Drug exposures (C_{min}/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold (C_{min}/MIC ≥3.8) is depicted by the horizontal broken line.

To prevent the emergence of resistance in a closed system, the C_{min} of β-lactams should be ≥ 3.8 x MIC…

Tam et al. J Antimicrob Chemother 2017;72:1421-1428 - PMID: 28158470

But serum levels of β-lactams remain difficult to predict with accuracy…

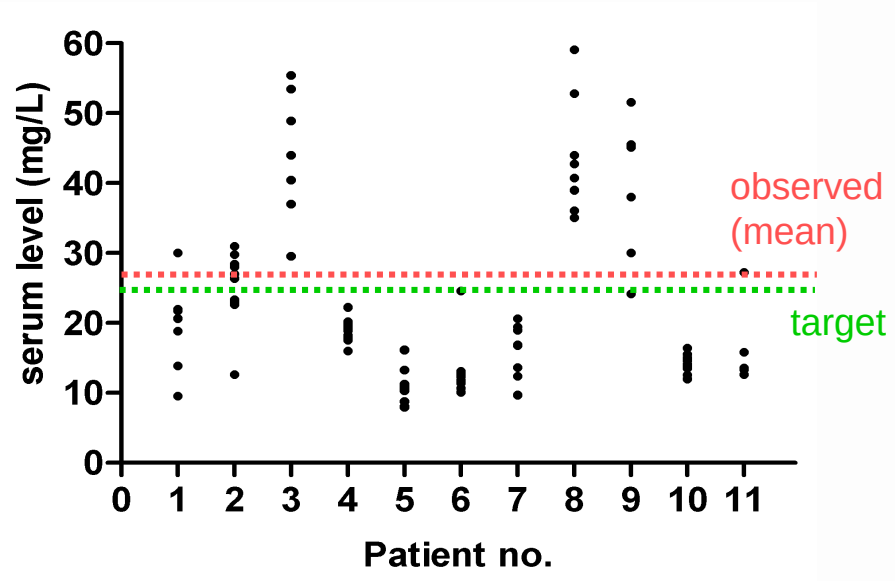
Continuous Infusion of Ceftazidime (4 g/day) vs Conventional Schedule and Dosis (3 X 2 g/day) for Treatment of Ventilator-associated Pneumonia in Intensive Care Units.

P.F. Laterre, N. Baririan, H. Spapen, T. Dugernier, M. Simon, D. Pierard, H. Servais, C. Seral and P.M. Tulkens

Cliniques universitaires St-Luc & Université catholique de Louvain, Brussels; Akademische Ziekenhuis, Vrije Universiteit Brussel, Brussels; Clinique St-Pierre, Ottignies; Clinique St Joseph, Arlon; Belgium.

- target level: 24 mg/L
  (max. MIC: 6 mg/L [EUCAST bkpt = 8 mg/L])
- loading dose: 10.8 mg/kg
  (assumed Vd: 0.4 L/kg)
- infusion: 4 g/day
- assumed clearance: 102 ml/min (6.12 L/h)
- drug diluted in 48 ml of water
- infusion through motor-operated syringe at a rate of 2 ml/h;
- temperature 25°C or lower

patients with continous administration of ceftazidime



• ICAAC 2002 Poster no. A1 1402

As a result, monitoring the serum levels of β-lactams has been proposed …

International Journal of Antimicrobial Agents 36 (2010) 332–339

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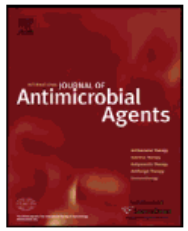
journal homepage: http://www.elsevier.com/locate/ijantimicag



Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

Jason A. Roberts[a,b,c,*], Marta Ulldemolins[a,d], Michael S. Roberts[e,f], Brett McWhinney[g], Jacobus Ungerer[g], David L. Paterson[h,i], Jeffrey Lipman[a,c]

[a] Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
[b] Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia
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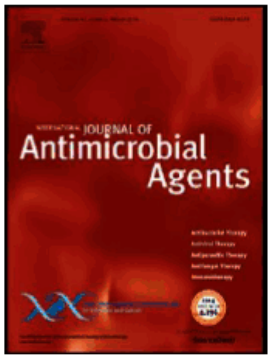
And monitoring β-lactams in ICU may be rewarding…

Accepted Manuscript



Title: Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β-lactams administered by continuous infusion. a prospective observational study

Author: Cedric Carrie, Laurent Petit, Nicolas D'houdain, Noemie Sauvage, Vincent Cottenceau, Melanie Lafitte, Cecile Foumenteze, Quentin Hisz, Deborah Menu, Rachel Legeron, Dominique Breilh, Francois Sztark

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And monitoring may be rewarding…

Accepted Manuscript

Title: Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β-lactams administered by continuous infusion. a prospective observational study

Author: Cedric C
Vincent Cottence
Deborah Menu, F

PII:
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To appear in:

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Accepted date:

Highlights

- In patients with augmented creatinine clearance (CrCL), desirable PK/PD targets may not be achieved by the use of high doses of β-lactam administered by continuous infusion.
- Mean values ≥ 170/min remain associated with higher rates of sub-exposure for β-lactams defined by at least one sample under 4 times the MIC of the known pathogen.
- Sub-exposure$_{< 4 \times MIC}$ is associated with higher rates of therapeutic failure in critically ill patients treated for a first microbiologically documented infection

Methods are being developed but are slow and complex, and do not measure the free concentration ...

Journal of Chromatography B, 879 (2011) 1038–1042

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Simultaneous determination of eight β-lactam antibiotics in human serum by liquid chromatography–tandem mass spectrometry

Tomofumi Ohmori[a,*], Akio Suzuki[a], Takashi Niwa[a], Hiroaki Ushikoshi[b], Kunihiro Shirai[b], Shozo Yoshida[b], Shinji Ogura[b], Yoshinori Itoh[a]

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Journal of Pharmaceutical and Biomedical Analysis 90 (2014) 192–197

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Development and validation of a high performance liquid chromatography assay for the determination of temocillin in serum of haemodialysis patients

Ana C. Miranda Bastos[a,b,c], Stefaan J. Vandecasteele[d], Paul M. Tulkens[a,c], Anne Spinewine[b,c], Françoise Van Bambeke[a,c,*]

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A clinical algorithm for β-lactams and a path to success...

Adjust the dosage on a full PK/PD basis and continue monitoring free blood levels

in ICU, the patient's situation changes rapidly !

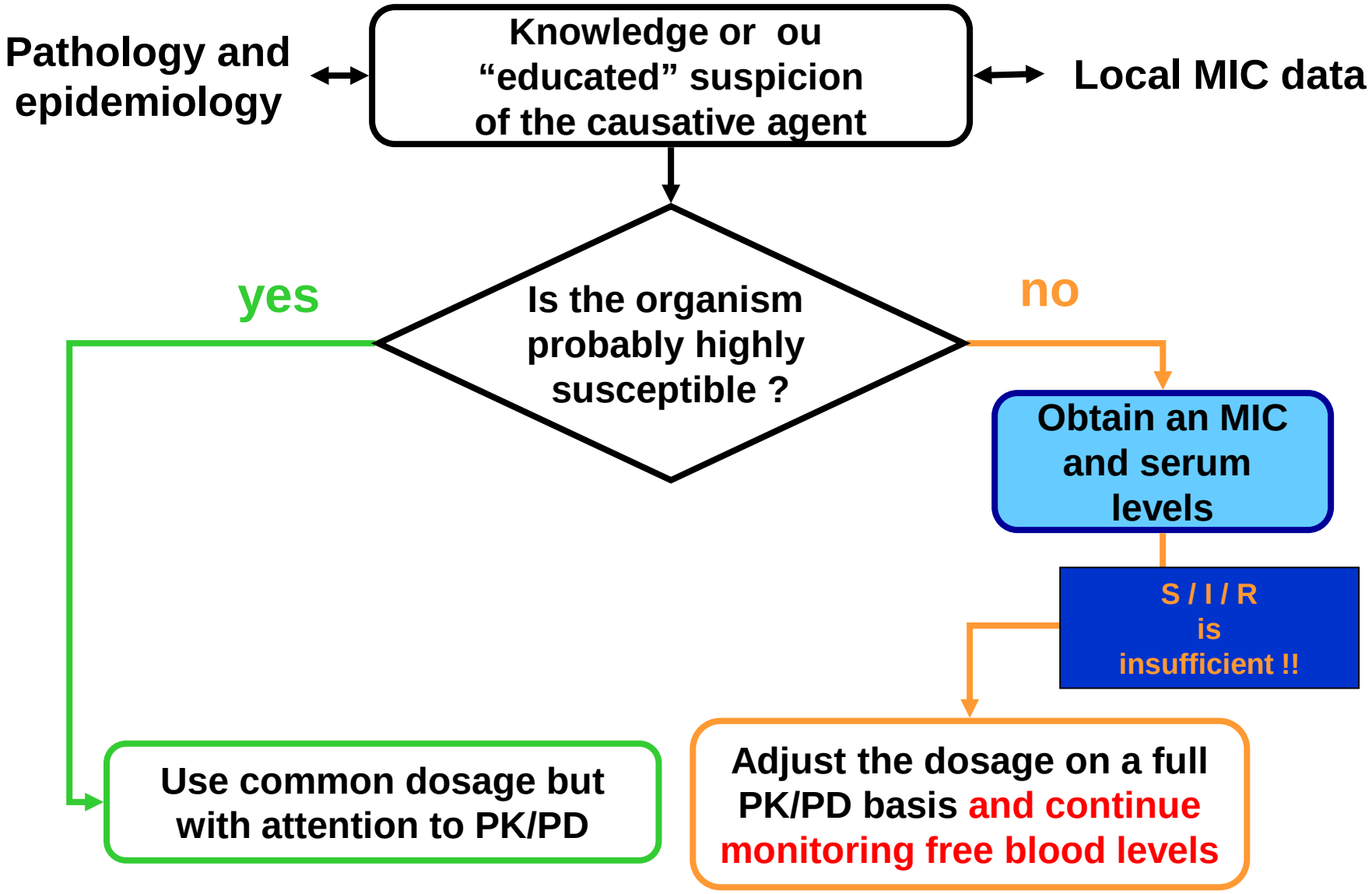
But what do we need ?

- a fast and reliable assay of the serum free fraction…
  → **results available within the period of the medical shift !**
- a clear definition of the desired target for efficacy … and prevention of emergence of resistance…
  → **C_{min} (or C_{ss}) at 4 x the MIC ?**

see discussion in Delattre *et al*. Expert Rev Anti Infect Ther. 2017;15:677-688 - PMID: 28571493

- a clear definition of the maximal doses without unacceptable toxicity (convulsions…) …
  → **C_{max} not exceed the value of an approved mode of administration ?**
- an algorithm that calculates the next dose based on population PK but also on real data from the previous administration…
  → **adaptive PK/PD modeling**

A clinical algorithm or a path to success...



The future: which other anti-infectives * ?

- **oxazolidinones** (linezolid, tedizolid, …)
  → C_{min} for prevention of toxicity

- **fluoroquinolones** (ciprofloxacin, levofloxacin, …)
  → C_{max} for prevention of resistance
  → AUC_{24h} for global antibacterial effect

- **azole antifungals** (fluconazole, voriconazole, …)
  → control of drug-drug interactions and inhibition of metabolism
  → AUC_{24h} for efficacy

- **anti-HIV drugs** (many …)
  → correction/prevention of HIGH variability in blood levels

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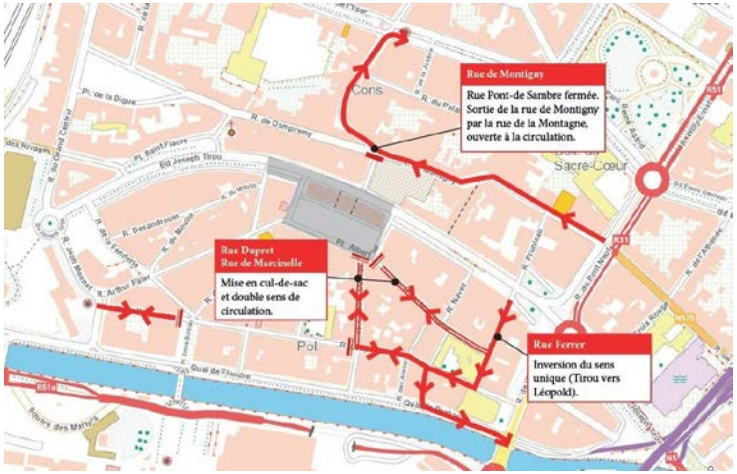
* many references… See, e.g.:

- Cattaneo et al. Drug monitoring and individual dose optimization of antimicrobial drugs: oxazolidinones. Expert Opin Drug Metab Toxicol. 2016;12:533-44 - PMID: 26982718.
- Nosseir et al. Therapeutic Drug Monitoring of antiinfectives in intensive care medicine. Dtsch Med Wochenschr. 2014;139:1889-94 - PMID: 25203549
- Stott & Hope. Therapeutic drug monitoring for invasive mould infections and disease: pharmacokinetic and pharmacodynamic considerations. J Antimicrob Chemother. 2017;72(suppl_1):i12-i18 - PMID: 28355463.
- Punyawudho et al. Therapeutic drug monitoring of antiretroviral drugs in HIV-infected patients. Expert Review of Clinical Pharmacology 2016;9:1583–1595 - PMID: 27626677

We can always dream …

difficult machinery

acrobatic algorithms



dead ends…

But at the end …

towards successes !

Back-up

But even then, serum levels remain are difficult to predict with accuracy…