Looking into the future: routine TDM for beta-lactams in ICU ?

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Brussels, Belgium

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

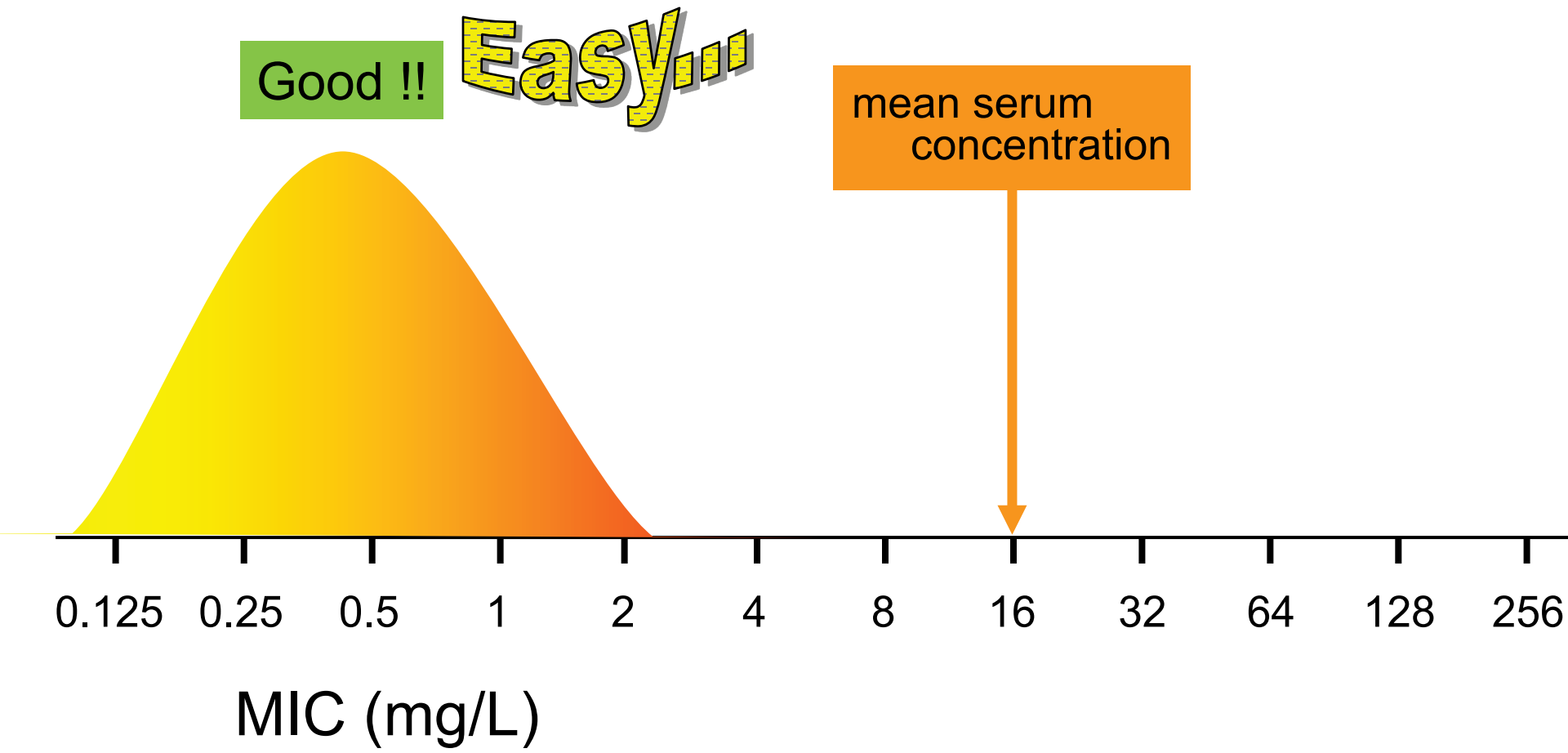
What is a "severe disease" ?

Problem ... #2 (of many)

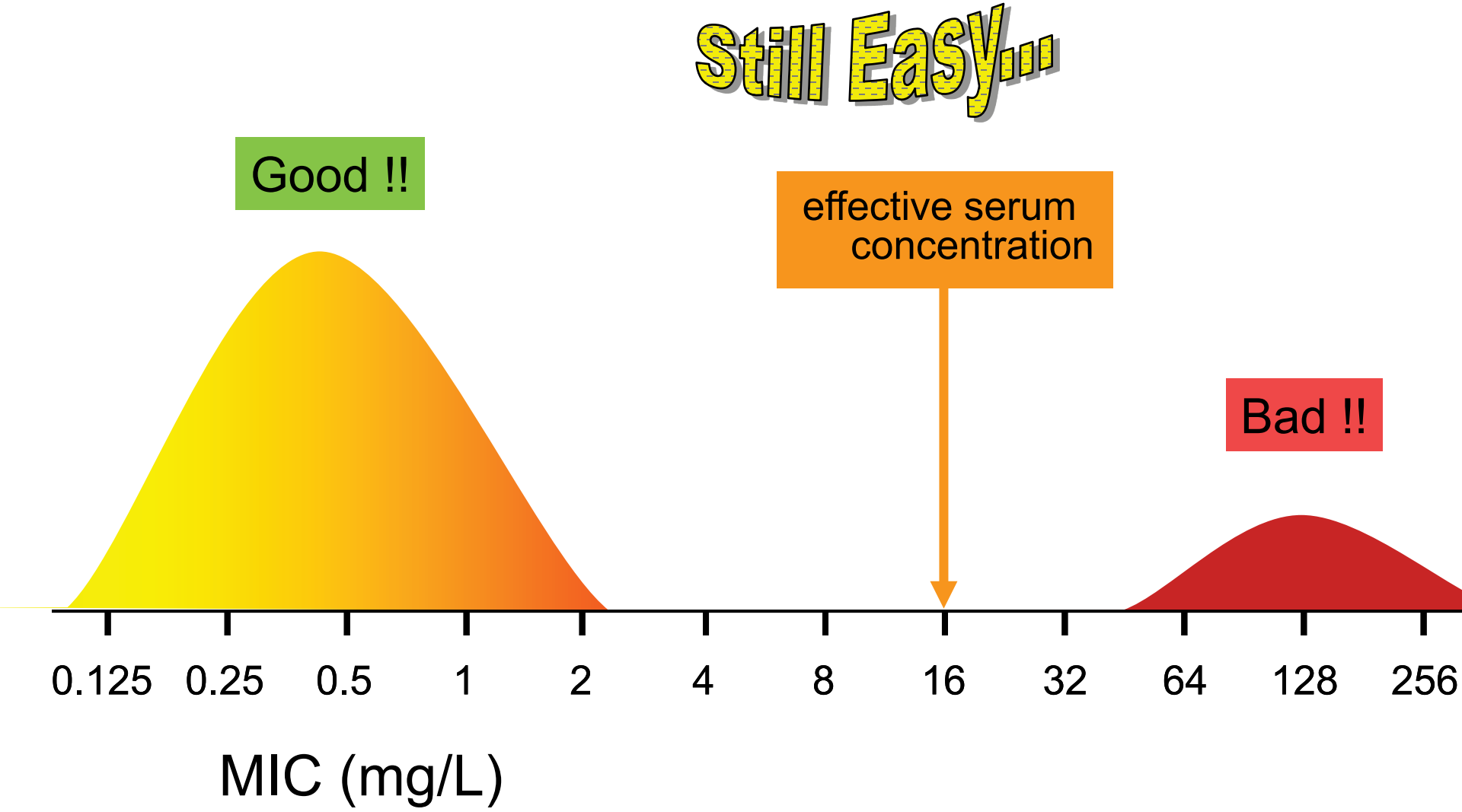
Clinicians tend to ask (and clinical microbiologists to provide only) "S – I – R" answers based on accepted breakpoints …

But, what is a breakpoint ?

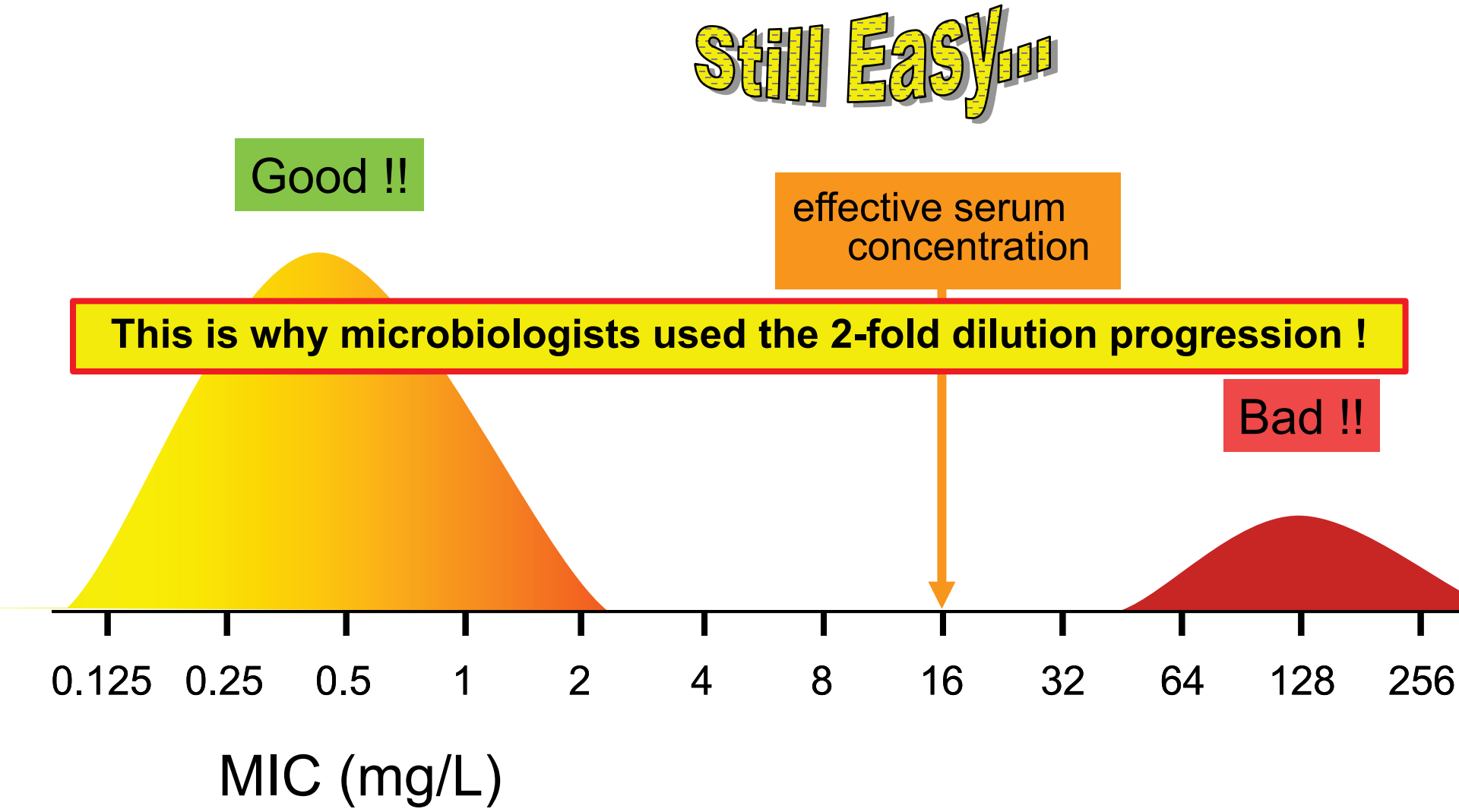
In the good old time…



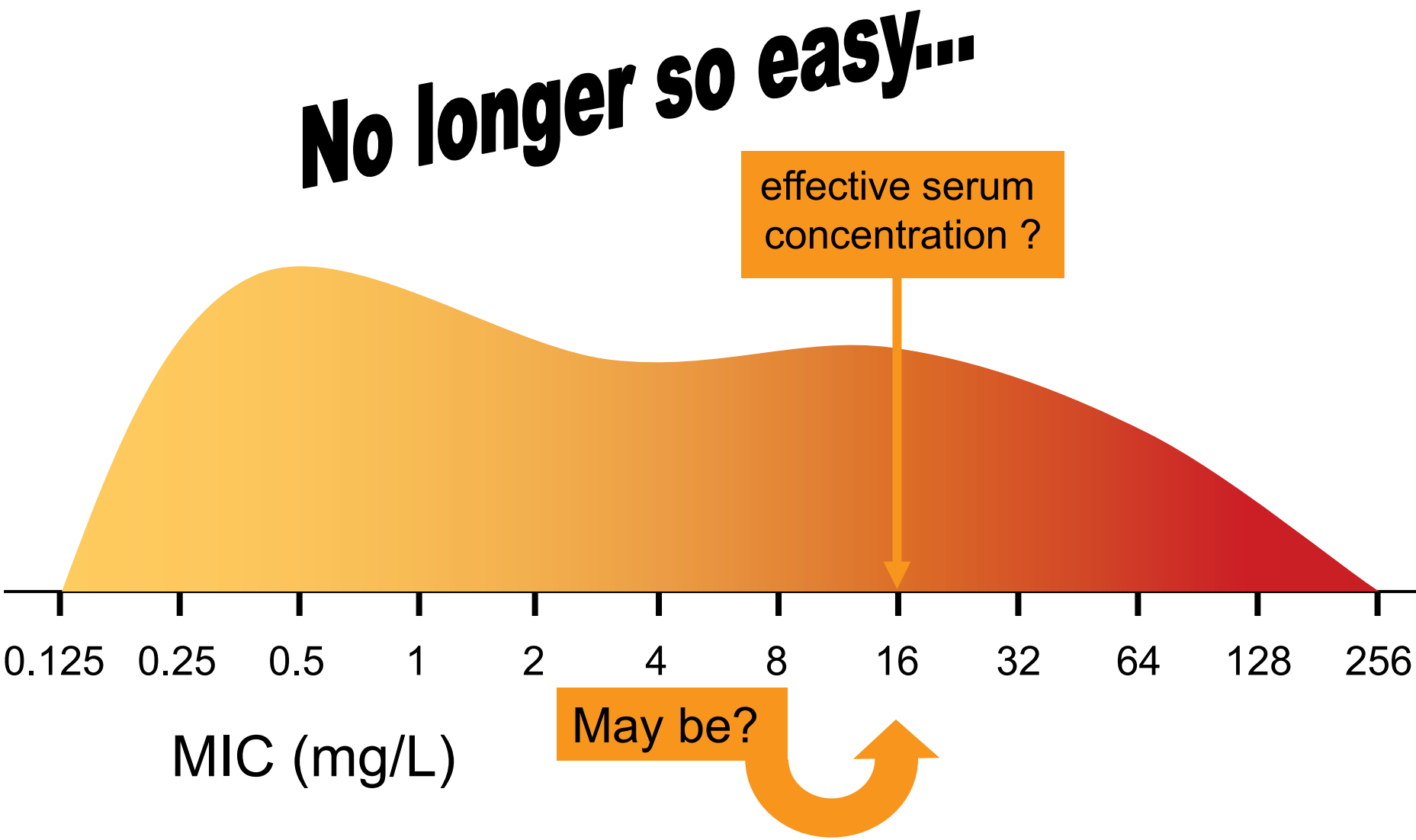
No so old but still good time ….



Still good old time ….



But now, what do you do with this ?



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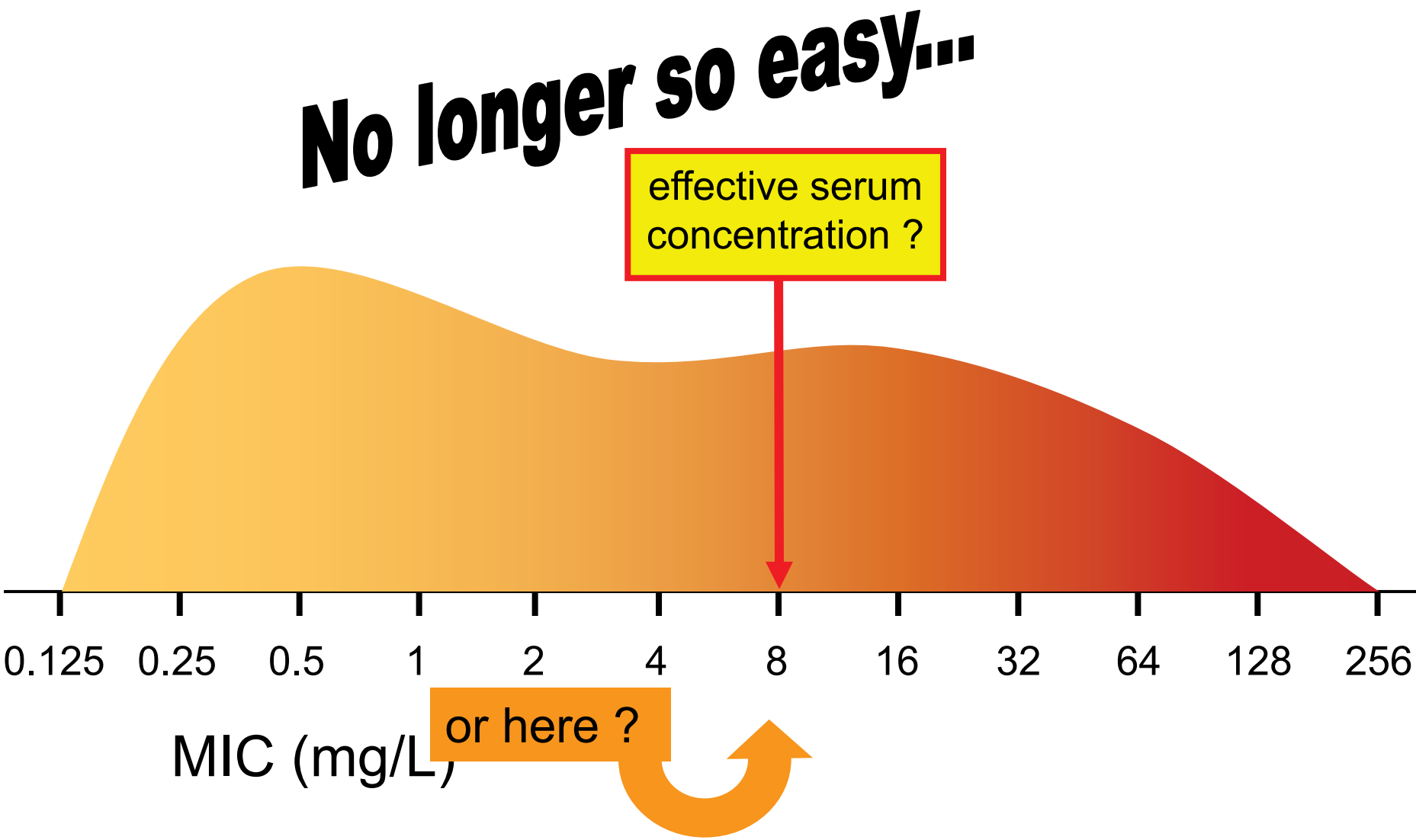

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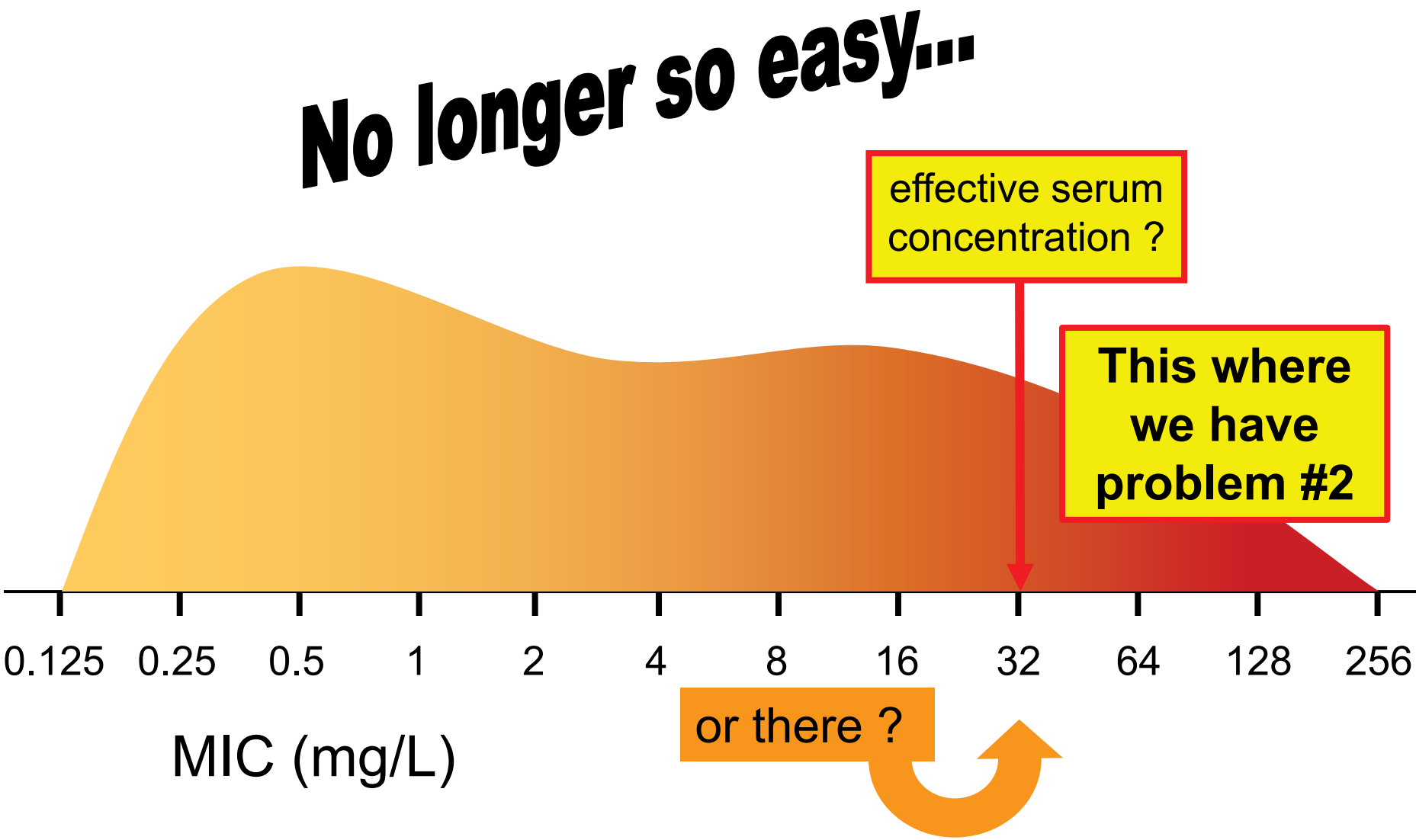


Breakpoints do not make things easy

Enterobacteriaceae

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

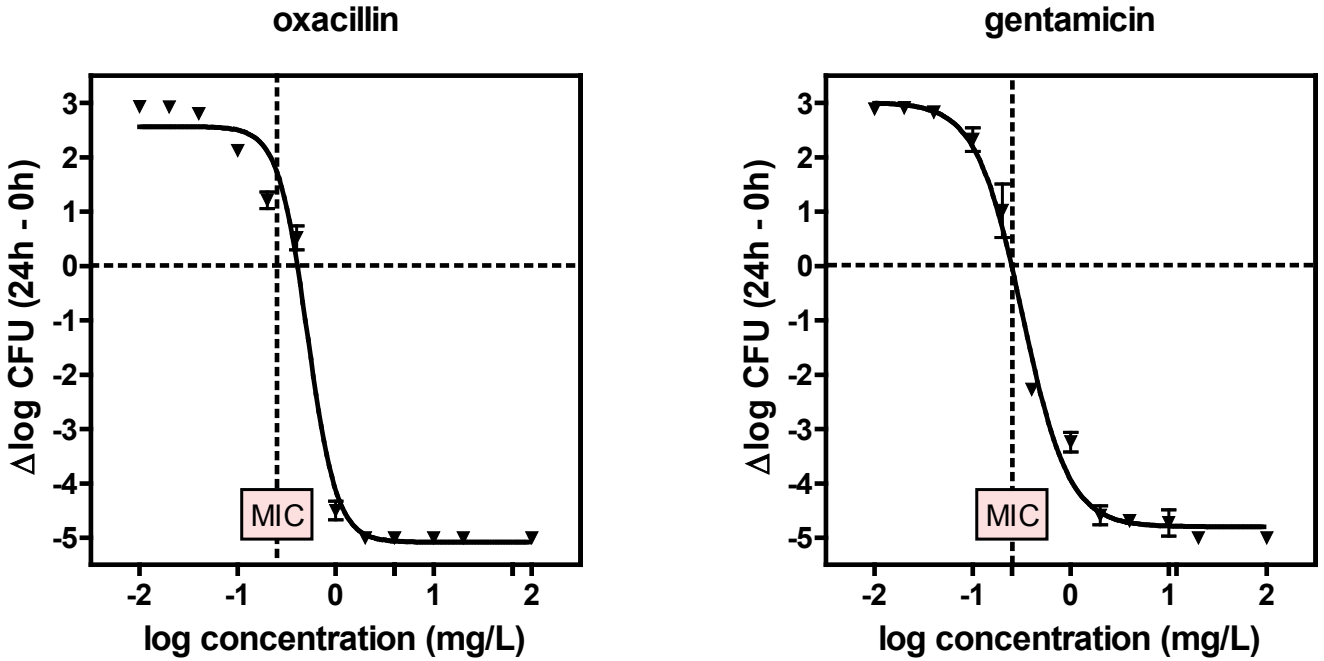
Cephalosporins[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Cefepime	1	4
Ceftazidime	1	4

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

Problem #3: which is the correct parameter to take into account ?

- Why are β-lactams time-dependent ?

full susceptible MSSA



phamacodynamic model of antibiotic response
24 incubation at fixed concentrations

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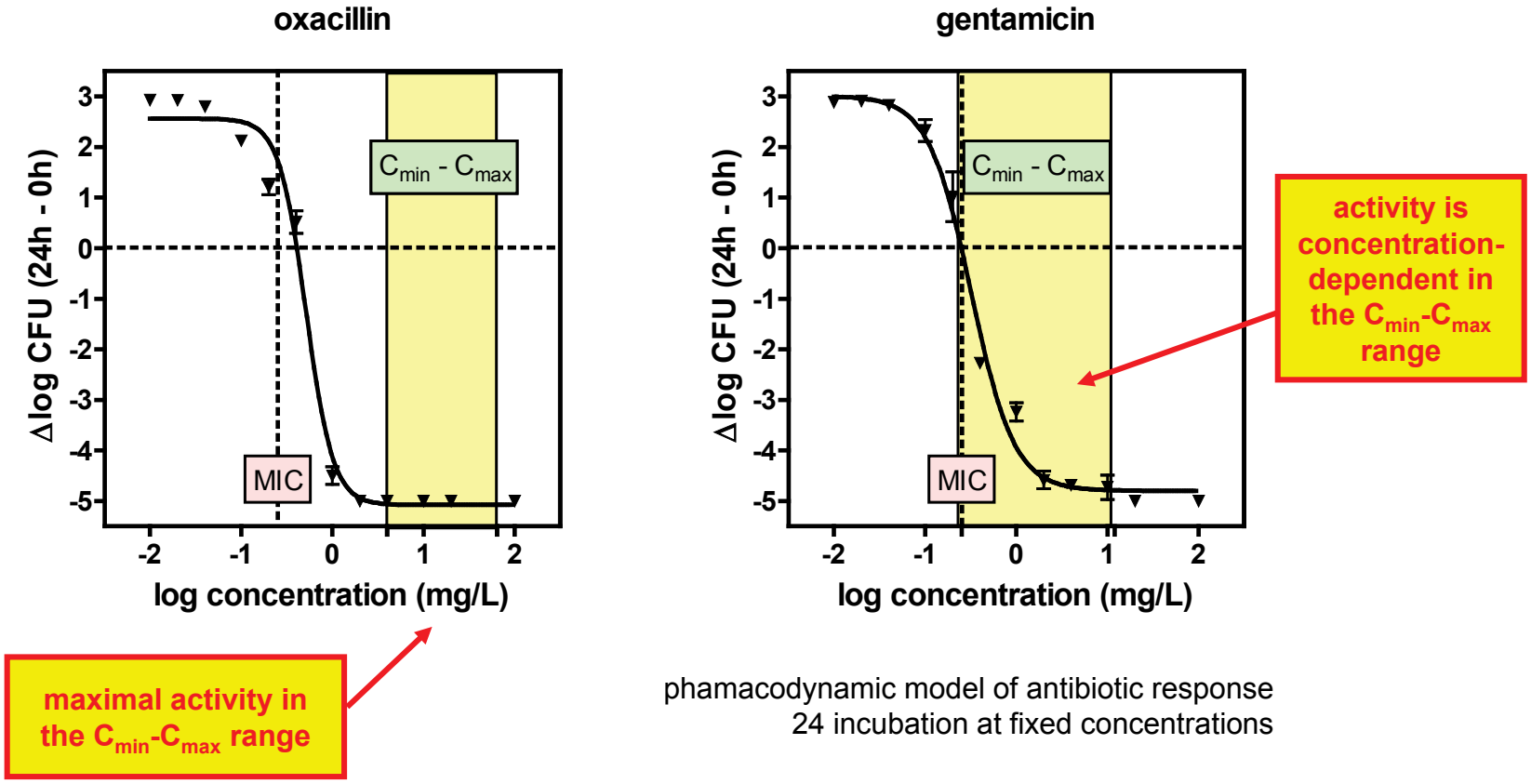

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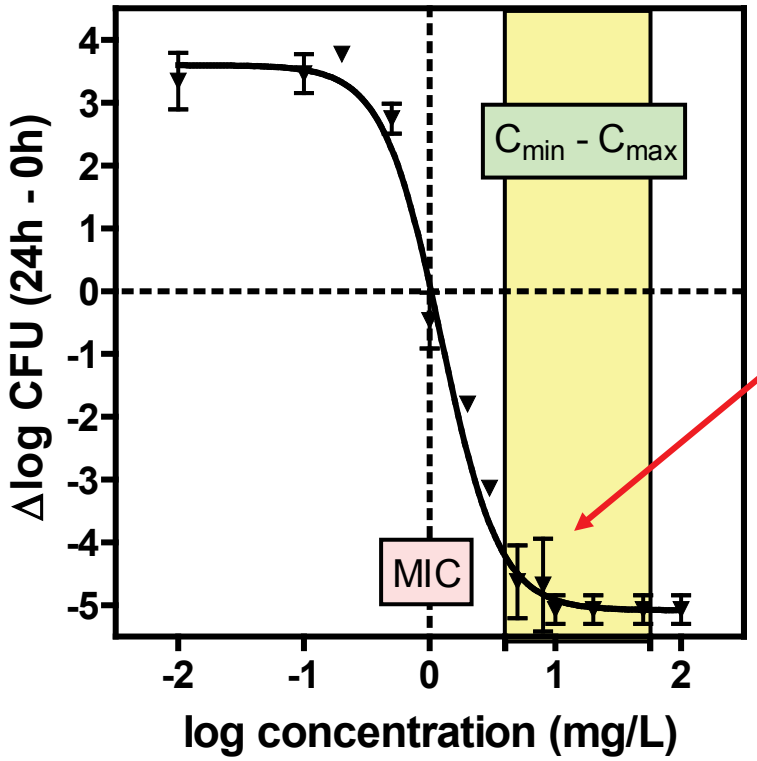
Clinical *P. aeruginosa*

meropenem



What do you do with this ?

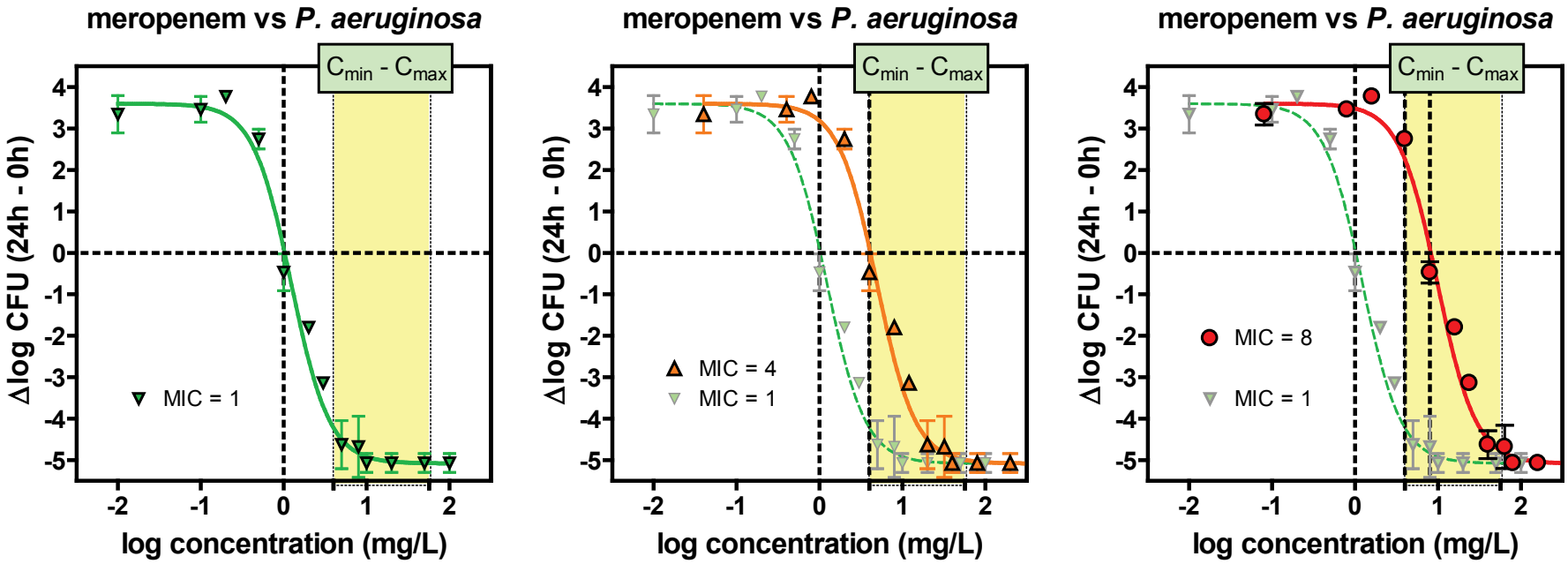
the C_{min}/MIC ratio becomes critical !

phamacodynamic model of antibiotic response
24 incubation at fixed concentrations

Problem #3: which is the correct parameter to take into account ?

- Are β-lactams really time-dependent ?

  Clinical *P. aeruginosa of increasing MIC*



phamacodynamic model of antibiotic response
24 incubation at fixed concentrations

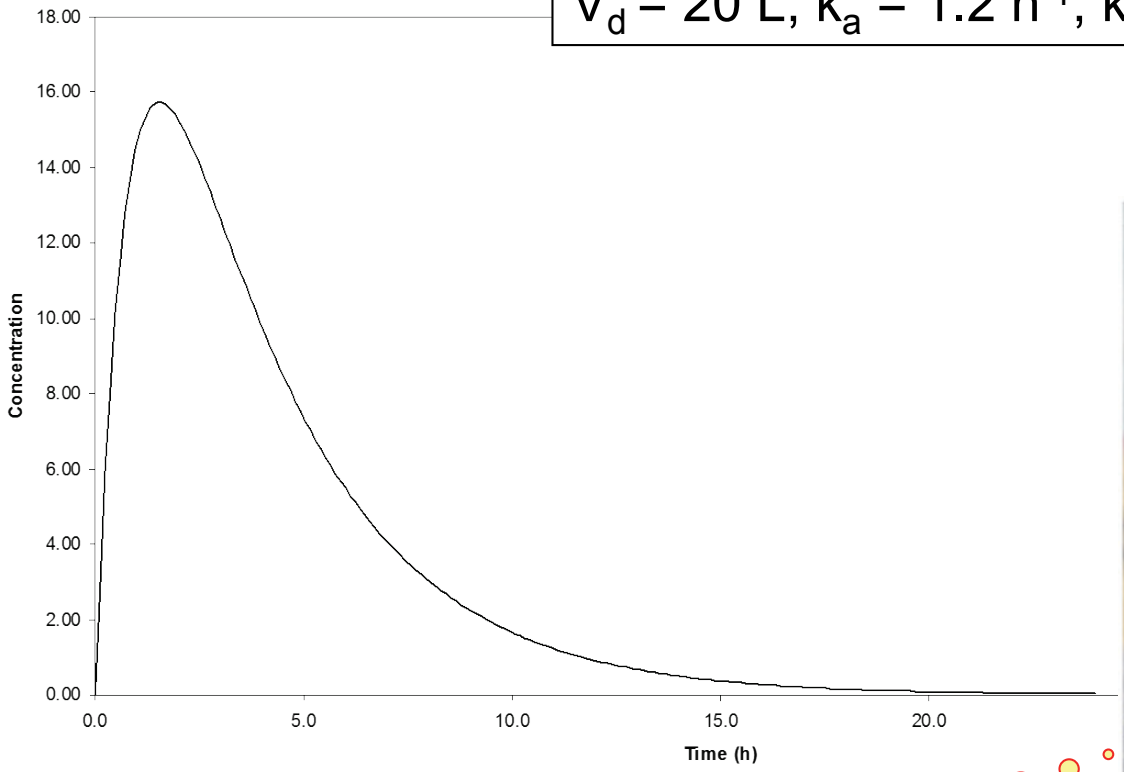
Solution for β-lactams: T > MIC…

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 ?)

There are 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

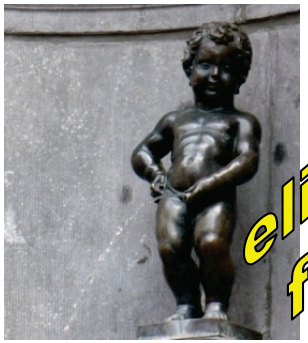
Kim Clijsters pose avec sa fille Jada. [illegible]/AFP

condition

race

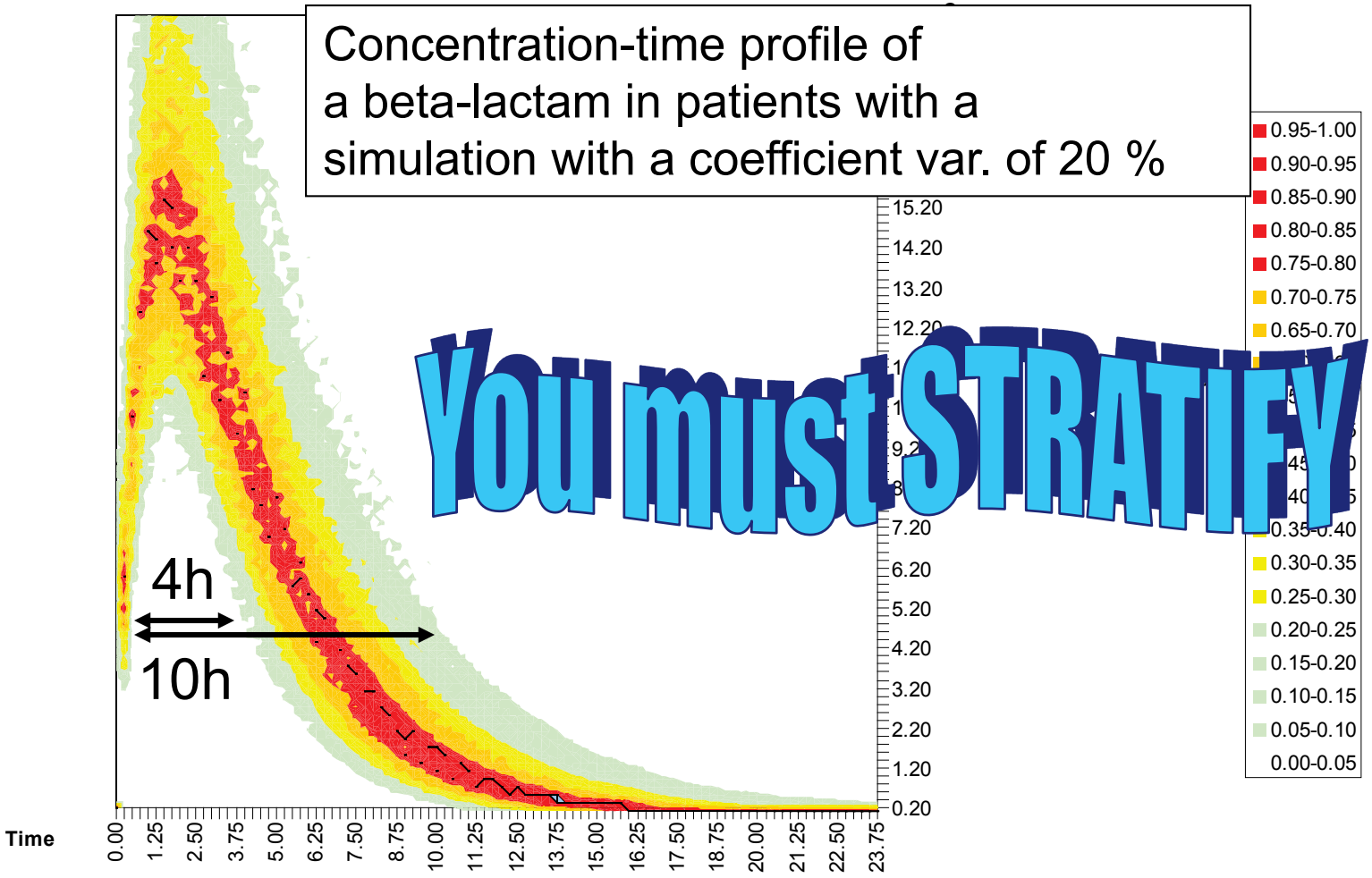
size

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

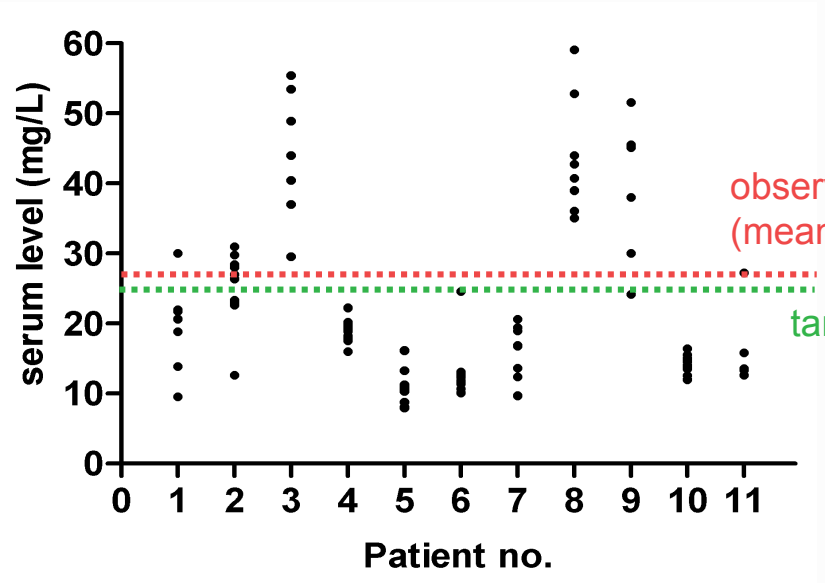
Continuous Infusion of Ceftazidime (4 g/day) vs Conventional Schedule and Dosis (3 X 2 g/day) for Treatment of Ventilator-associated Pneumonia in Intensive Care Units.

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.

patients with continous administration of ceftazidime

- 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



• ICAAC 2002 Poster no. A1 1402

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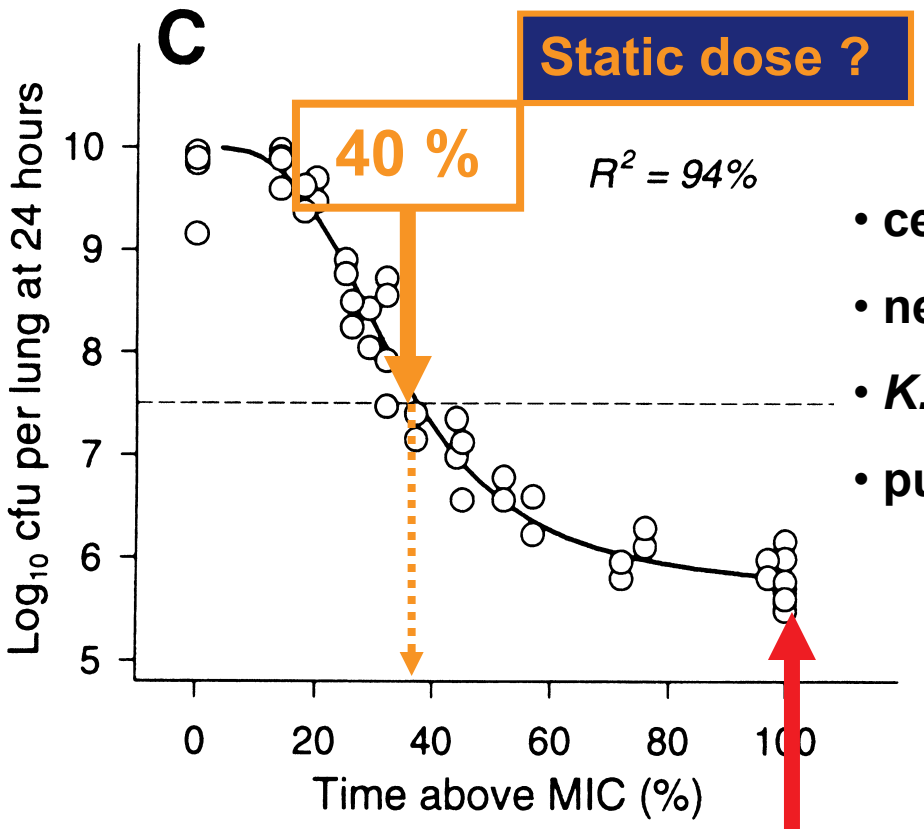
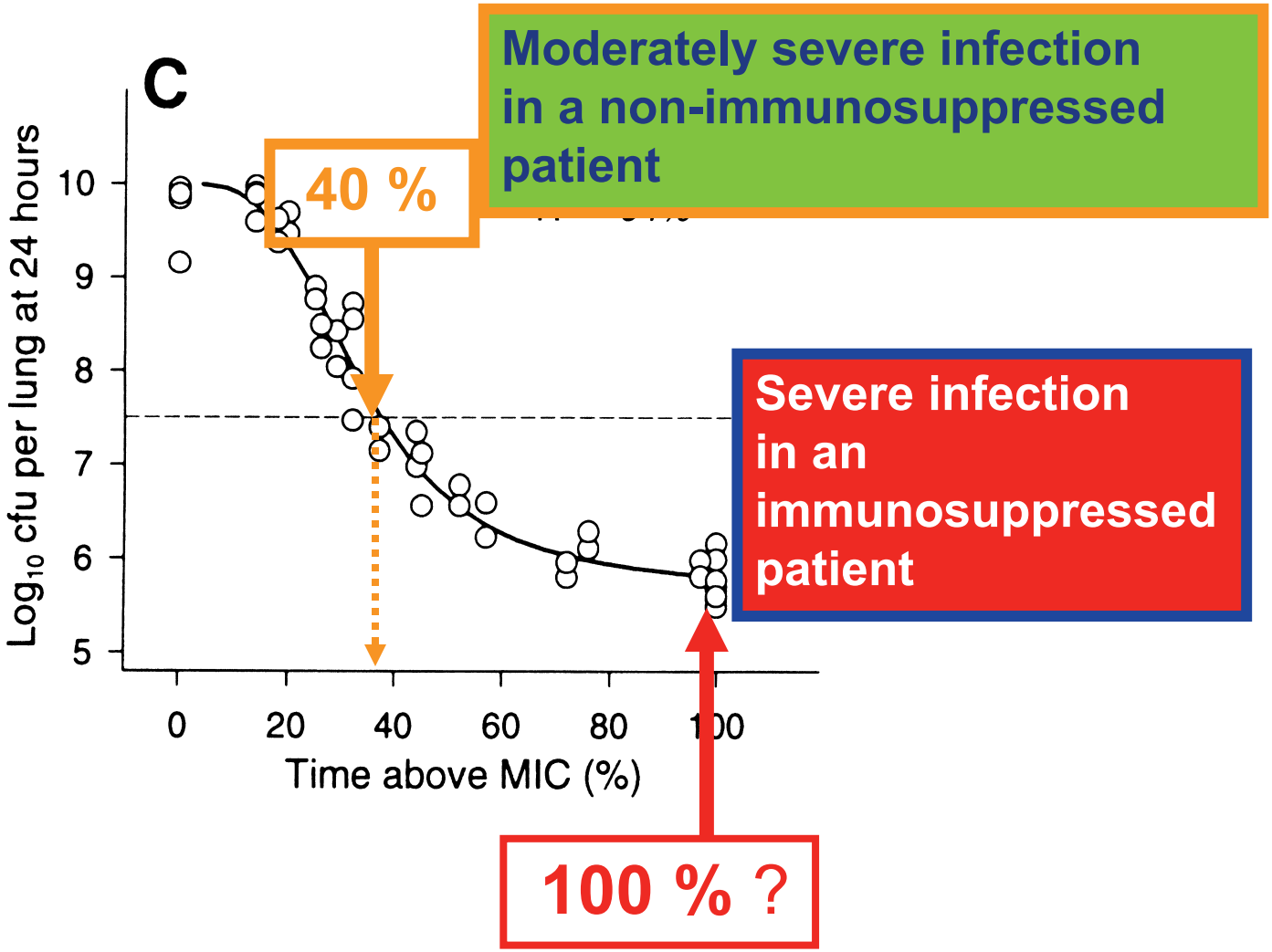
How much time above MIC ?



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

100 % - Maximal effect ?

It all depends on your patient !



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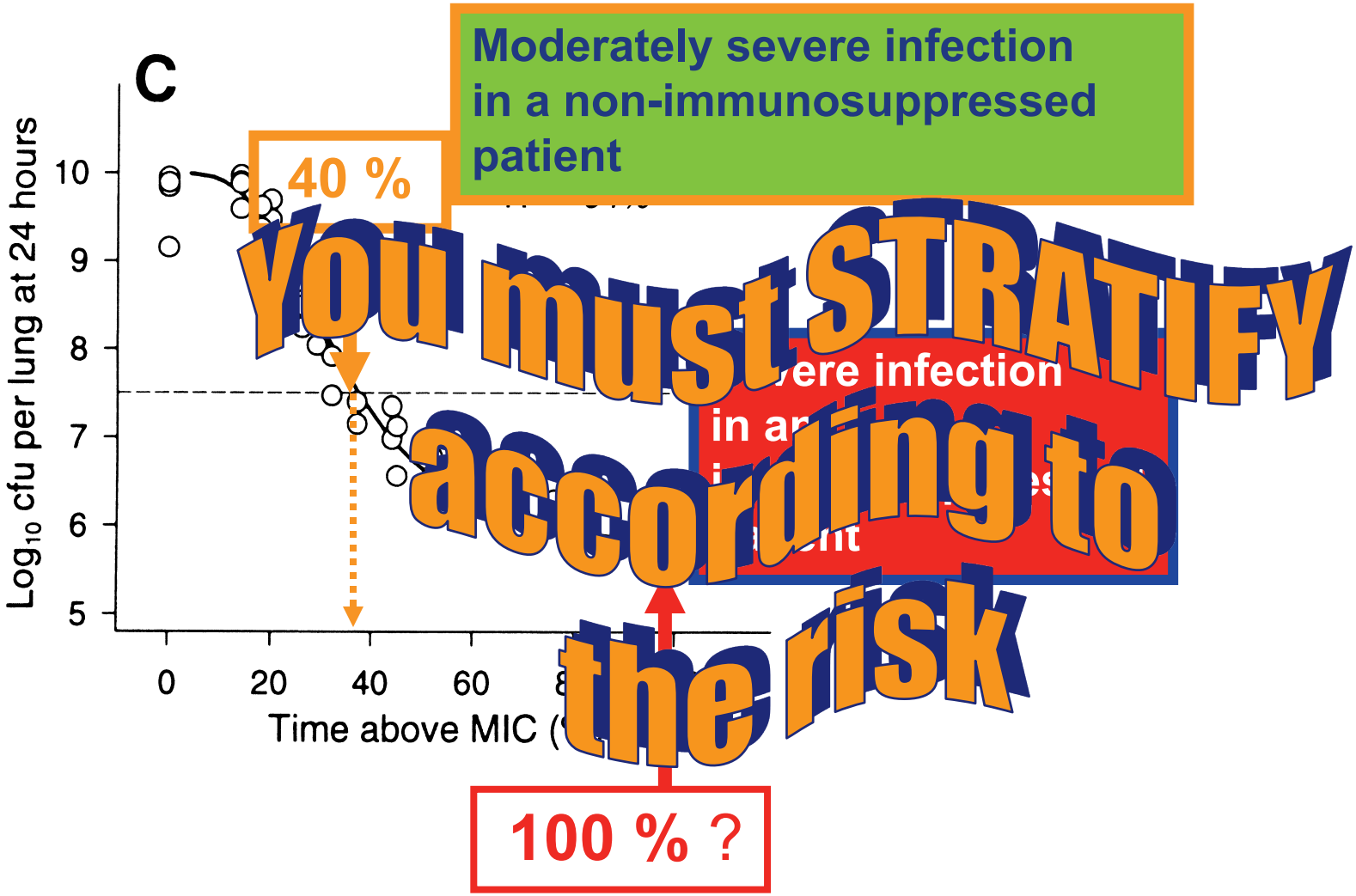


But back to MIC …!

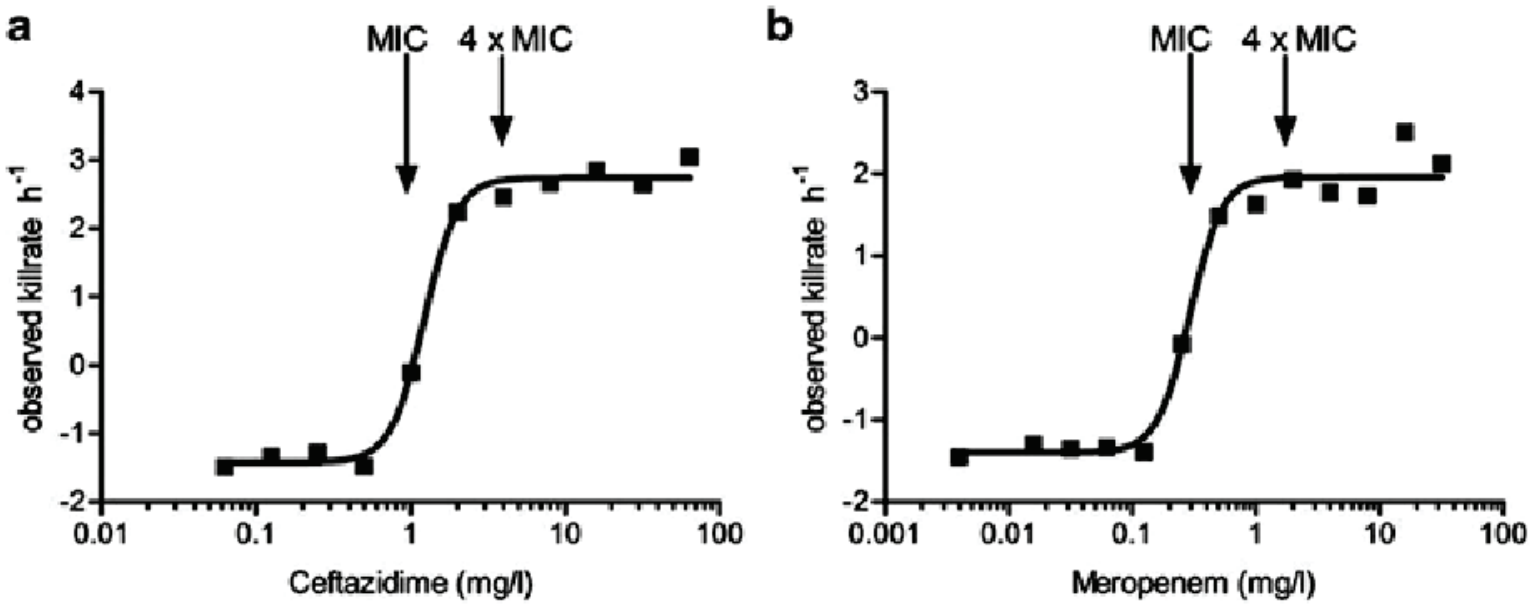
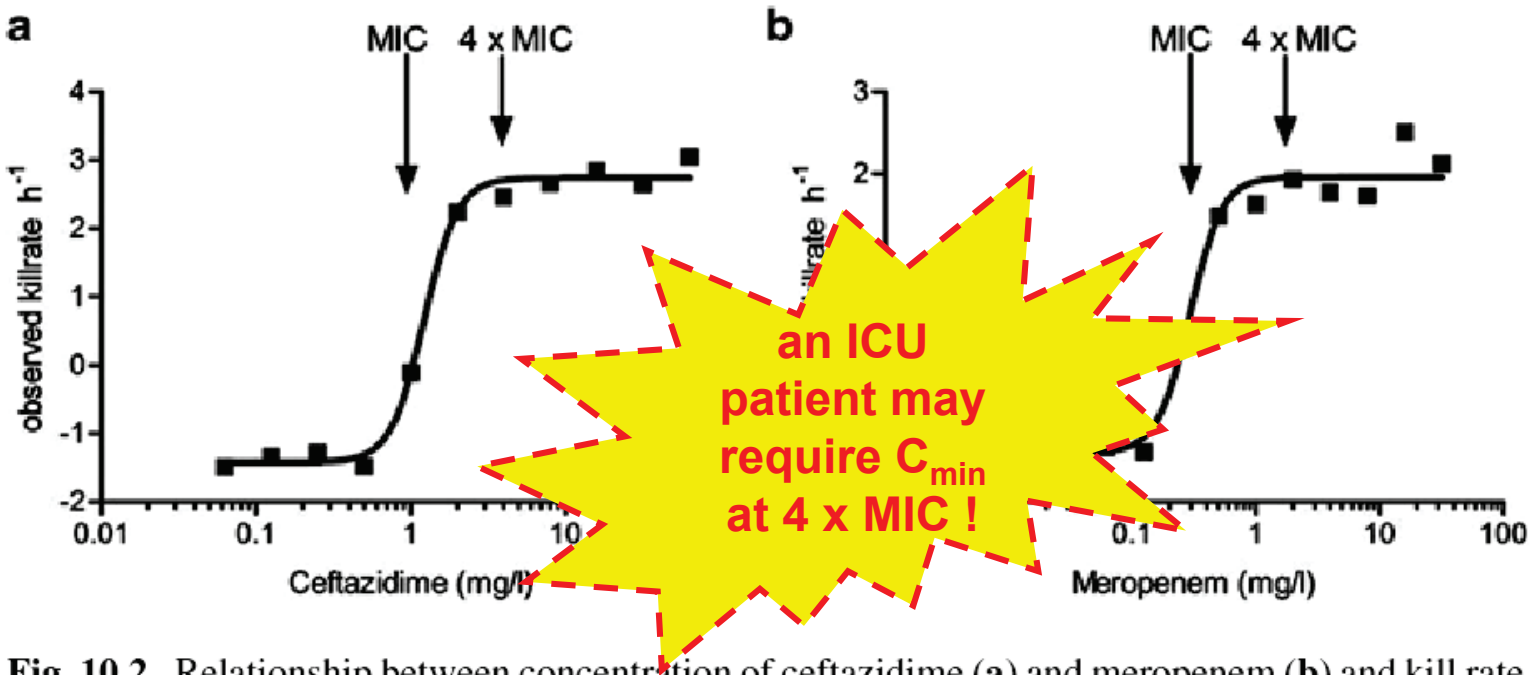


Fig. 10.2 Relationship between concentration of ceftazidime (**a**) and meropenem (**b**) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold 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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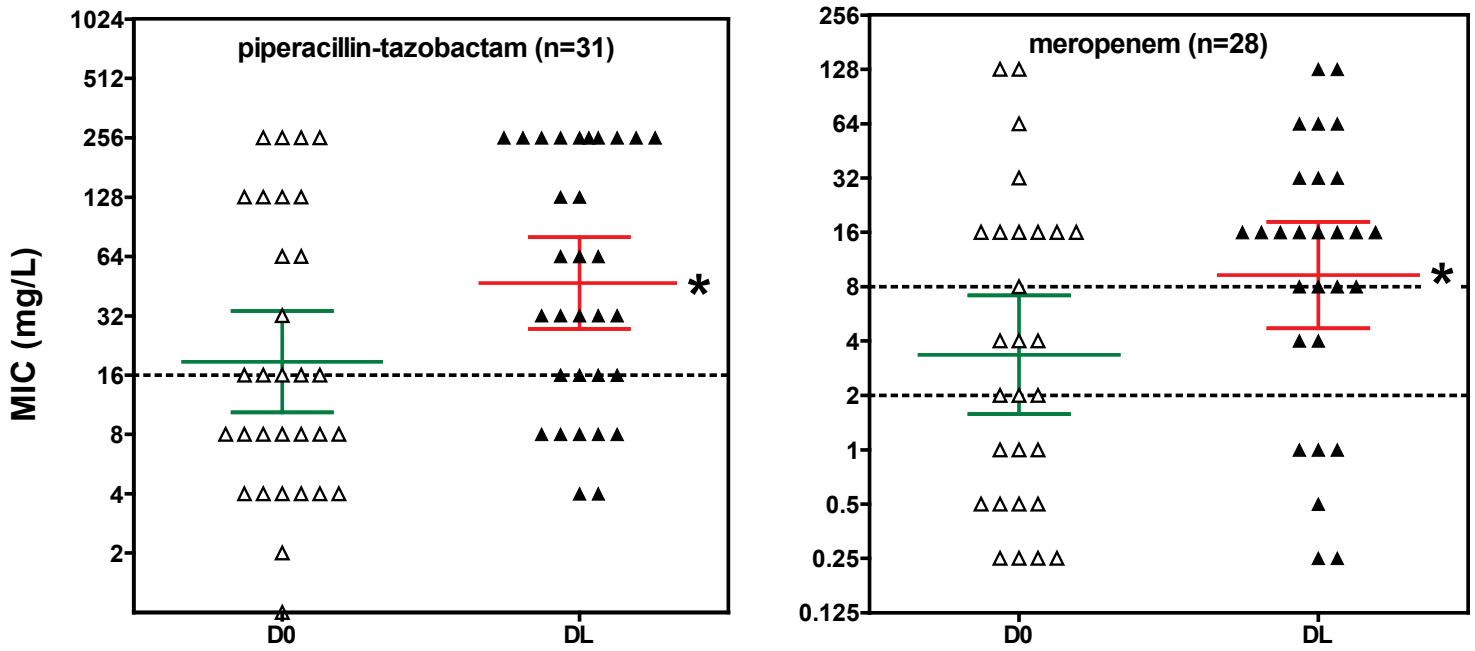
And do not forget about changes in MIC (low-level resistance) during treatment !



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.

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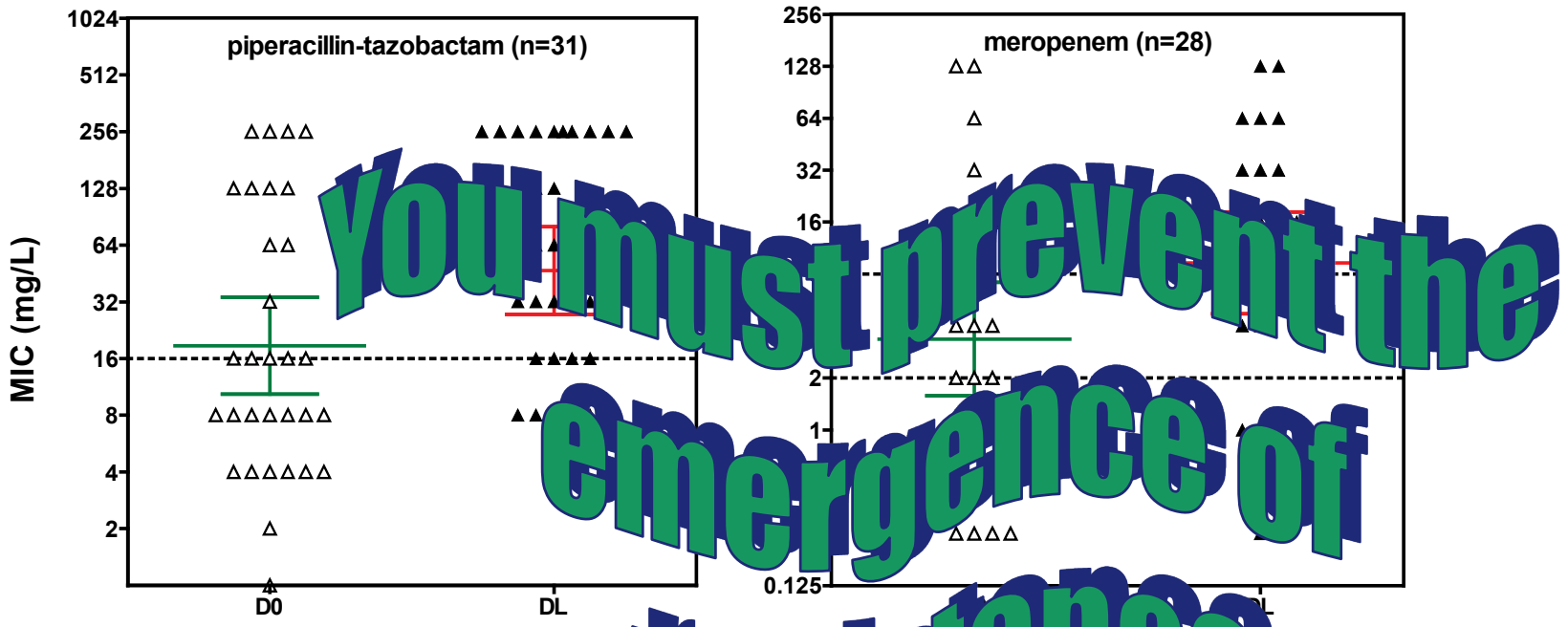

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Riou et al. Int J Antimicrob Agents. 2010 Dec;36(6):513-22.

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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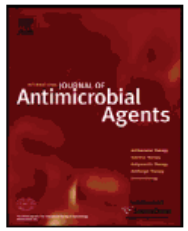

Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

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
[c] Department of Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia
[d] Critical Care Department, Vall d'Hebron University Hospital; Institut de Recerca Vall d'Hebron-Universitat Autònoma de Barcelona (UAB)-CIBER Enfermedades Respiratorias, Barcelona, Spain
[e] Therapeutics Research Unit, The University of Queensland, Brisbane, Australia
[f] School of Pharmacy, University of South Australia, Adelaide, Australia
[g] Department of Chemical Pathology, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia
[h] Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Brisbane, Australia
[i] University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Australia

But available methods are slow and complex, and do not measure the free concentration ...

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

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Journal of Pharmaceutical and Biomedical Analysis

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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,*]

[a] Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
[b] Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université catholique de Louvain,
[c] Center for Clinical Pharmacy, Université catholique de Louvain, Brussels, Belgium
[d] Department Nephrology and Infectious Diseases, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium

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

Contents lists available at ScienceDirect

Journal of Chromatography B

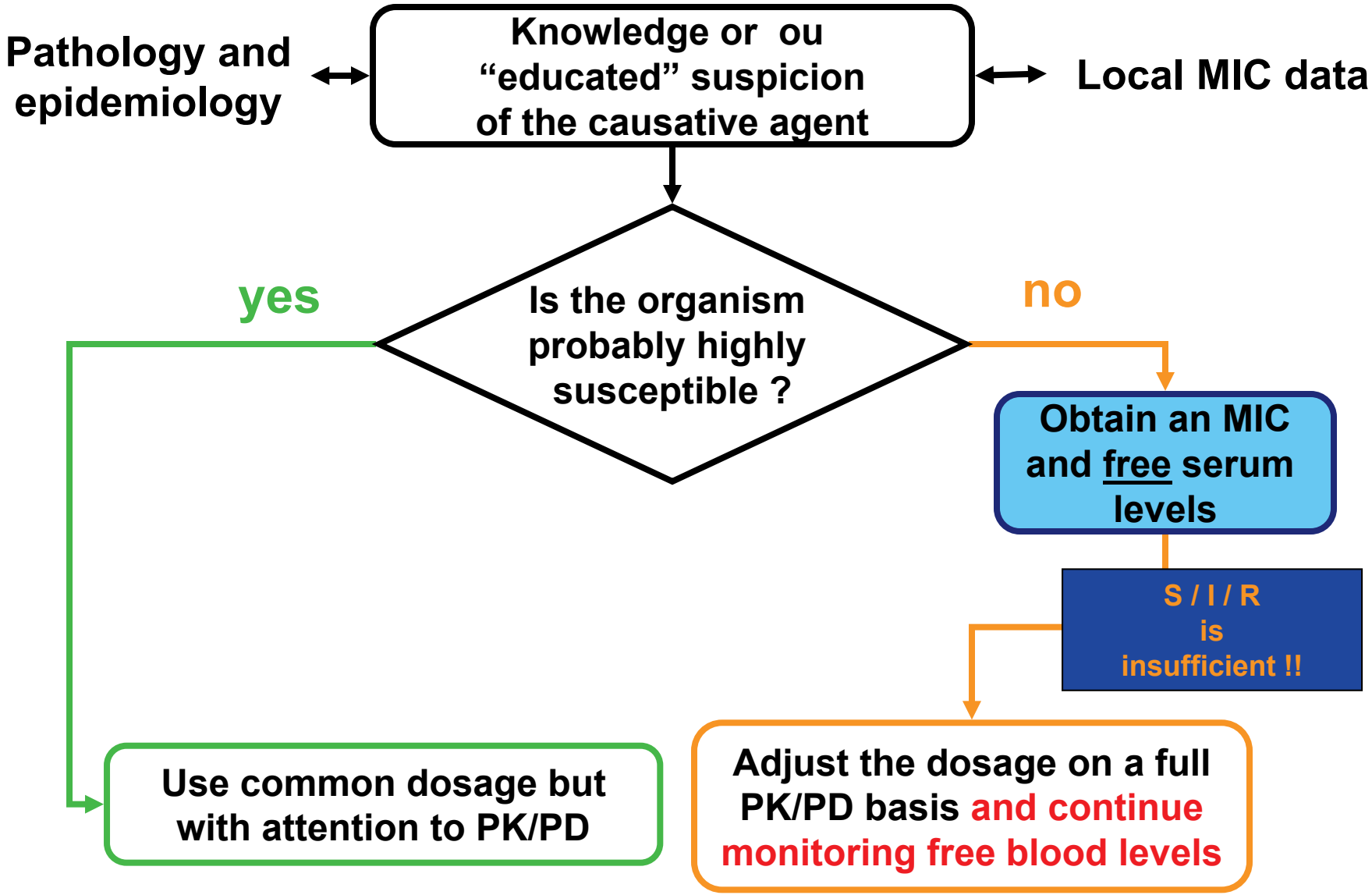
journal homepage: www.elsevier.com/locate/chromb

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]

[a] Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan
[b] Department of Emergency and Disaster Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan

A clinical algorithm or a path to success...



A clinical algorithm or 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 ?**
- 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**

We can always dream …

difficult machinery

acrobatic algorithms

dead ends…

But at the end …

light at the end of the tunnel…

But at the end …

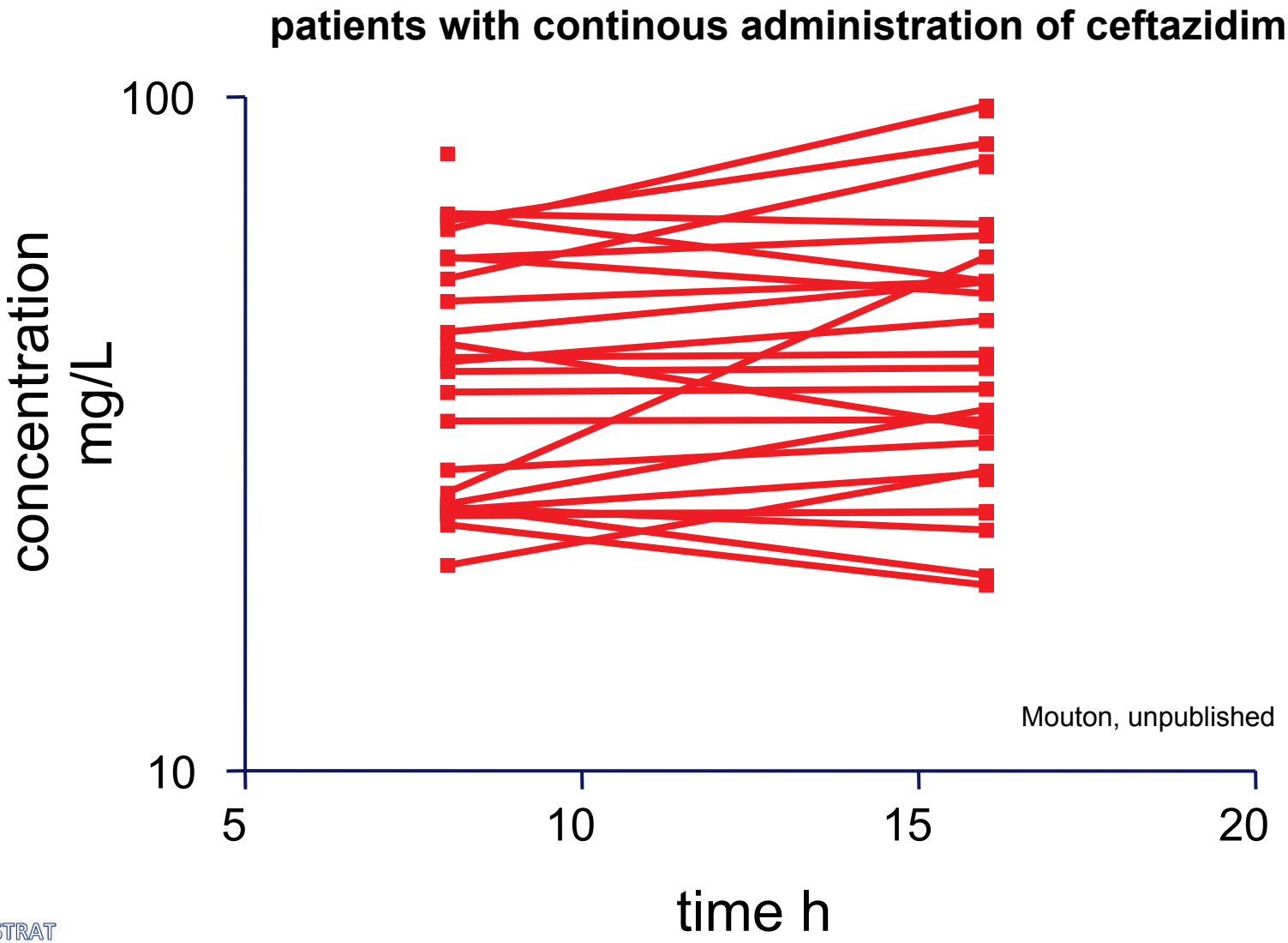
light at the end of th

http://www.spiegel.de/international/zeitgeist/peak-of-insanity-dutch-dream-of-building-artificial-mountain-a-784085.html
Last accessed: 13-10-2015

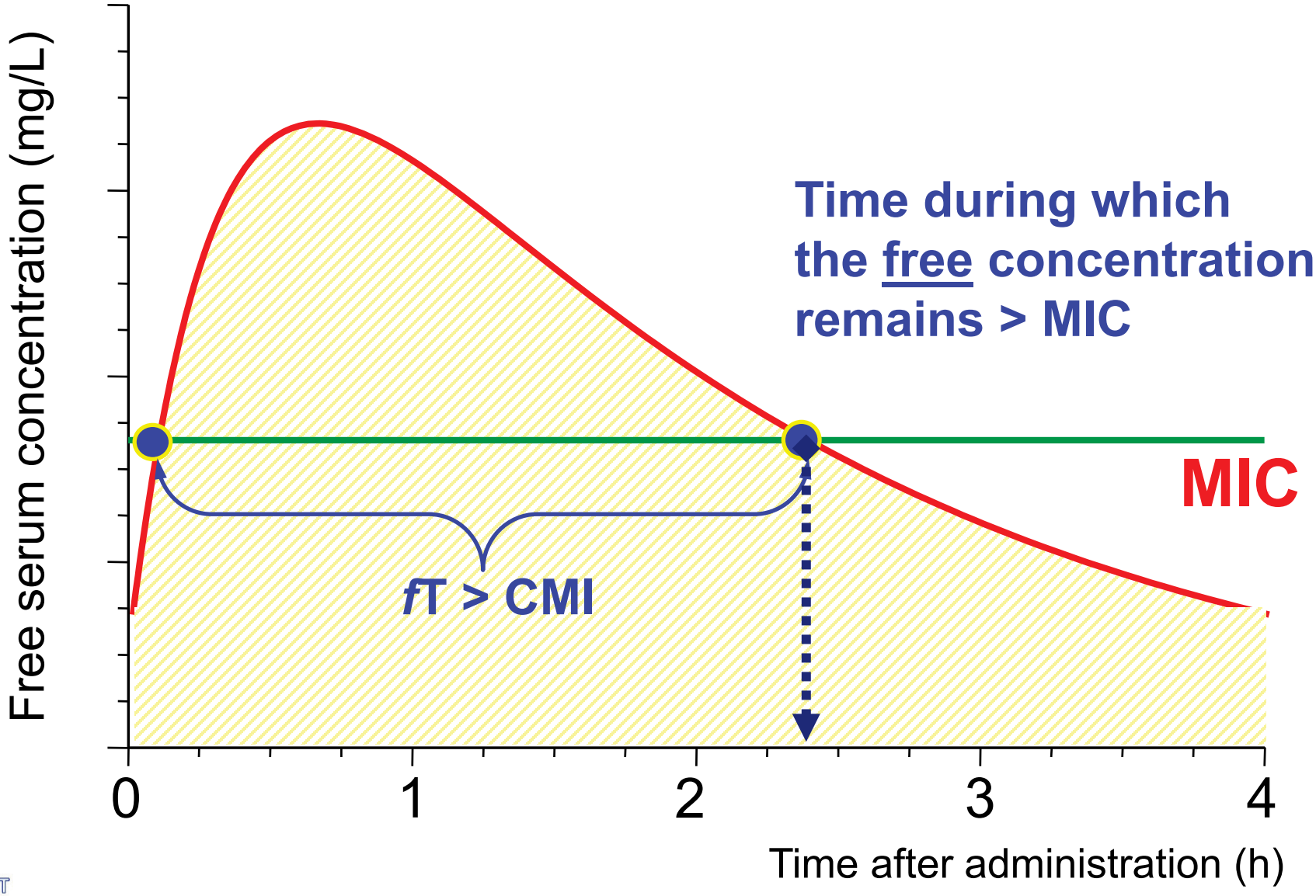
… and far above sea level

Back-up

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



Which pharmacokinetic parameter drives the activity of β-lactams ?



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