Why monitoring β-lactams on line ?

Paul M. Tulkens, MD, PhD
on behalf the
Louvain Drug Research Institute &
the **Louvain Toxicology and Applied Pharmacology**
Université catholique de Louvain,
Brussels, Belgium

MON4STRAT kick-off meeting
Liège, Belgium, 31 March 2014

The problem ... #1 of many …

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)

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

But, what is a breakpoint ?

EUCAST * breakpoints

Clinically Susceptible (S)

- level of antimicrobial activity associated with a high likelihood of therapeutic success

Clinically Intermediate (I)

- level of antimicrobial activity associated with indeterminate therapeutic effect

Clinically Resistant (R)

- level of antimicrobial activity associated with a high likelihood of therapeutic failure.

a microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system

Clinical breakpoints are presented as S≤ x mg/L ; I >x, ≤ y mg/L ; R >y mg/L

where mg/L is the Minimal Inhibitory Concentration (MIC) **in broth** (microdilution)

*** EUCAST**: European Committee for Antimicrobials Susceptibility Testing

EUCAST breakpoints

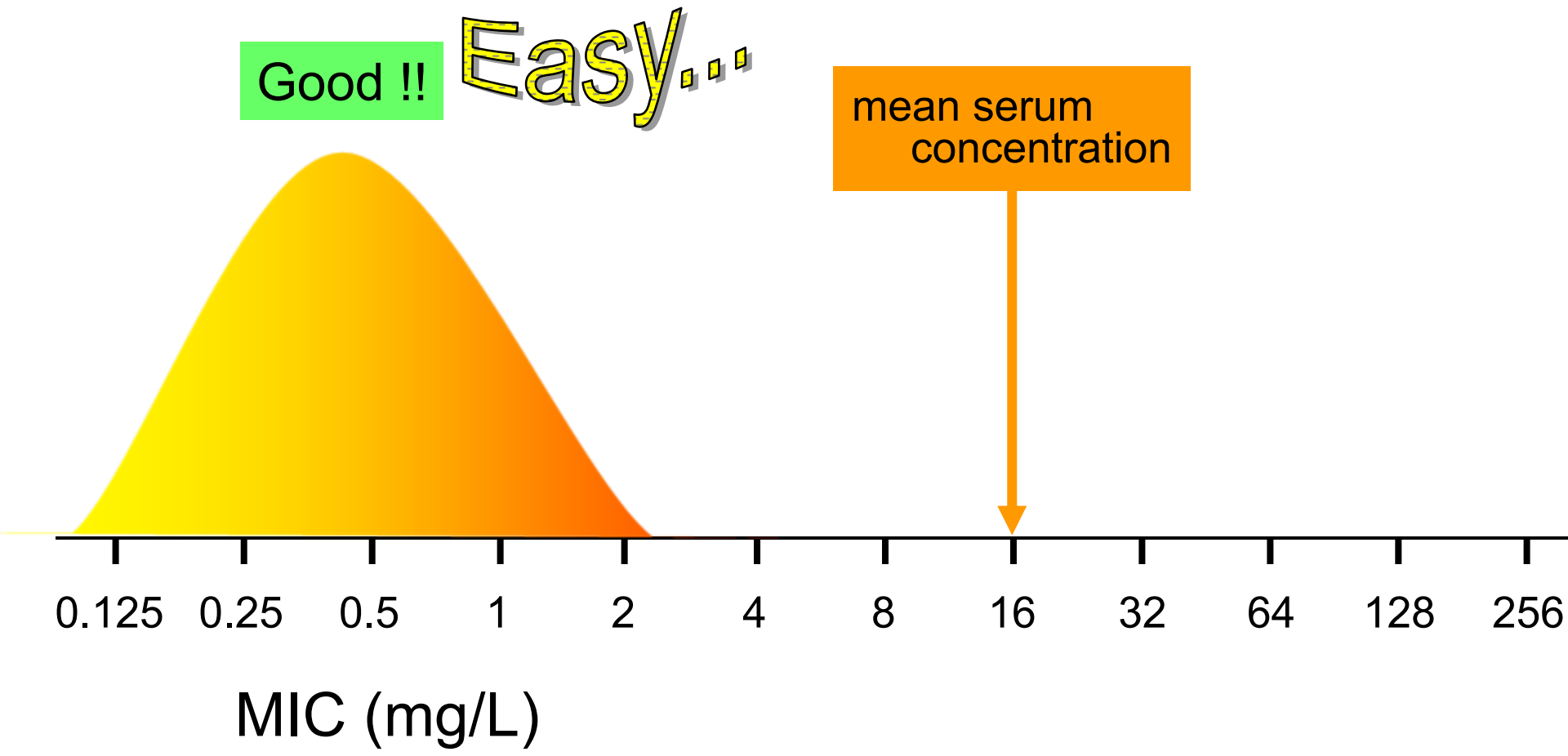
Enterobacteriaceae

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

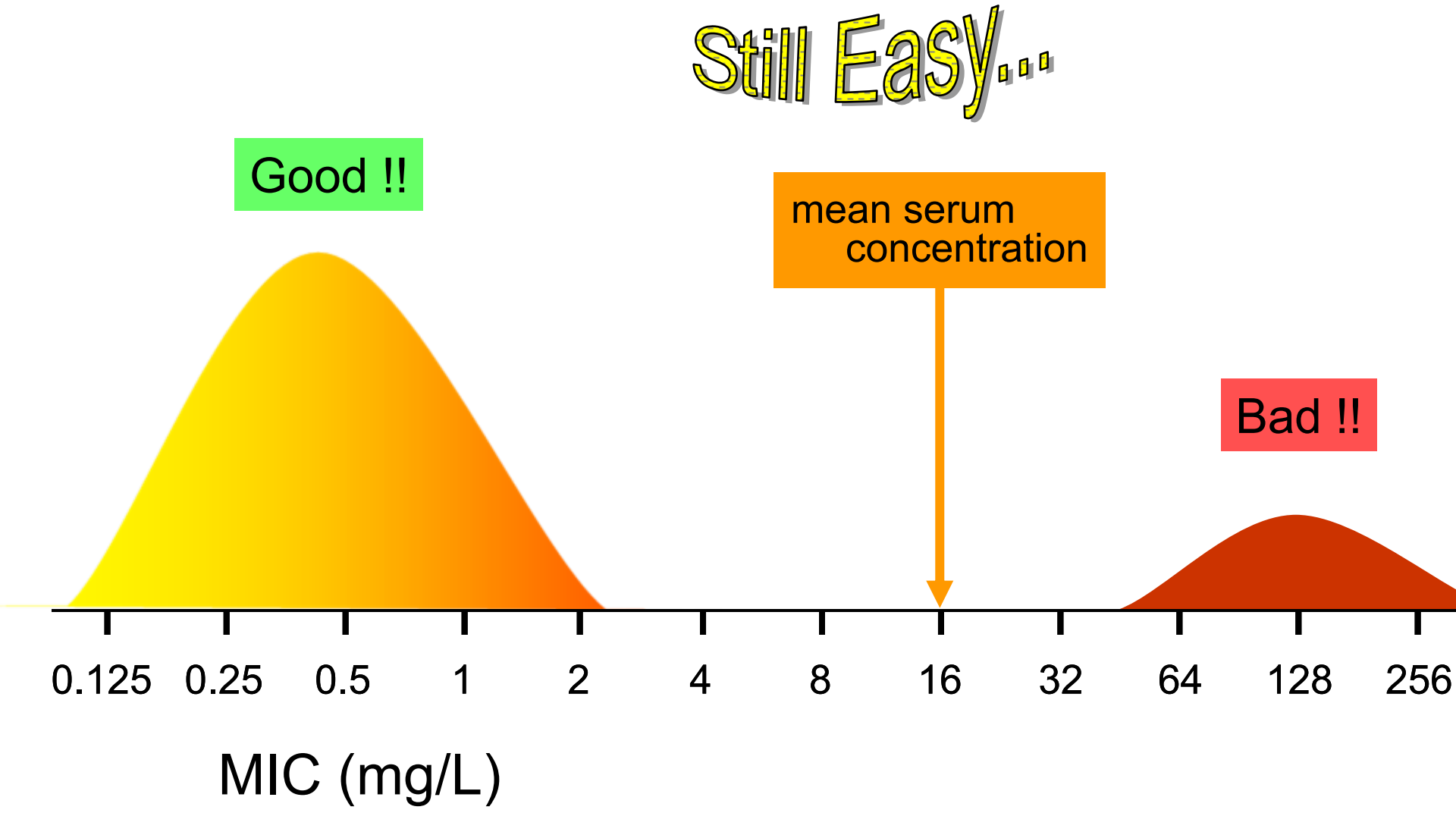
Cephalosporins[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Cefepime	1	4
Ceftazidime	1	4

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

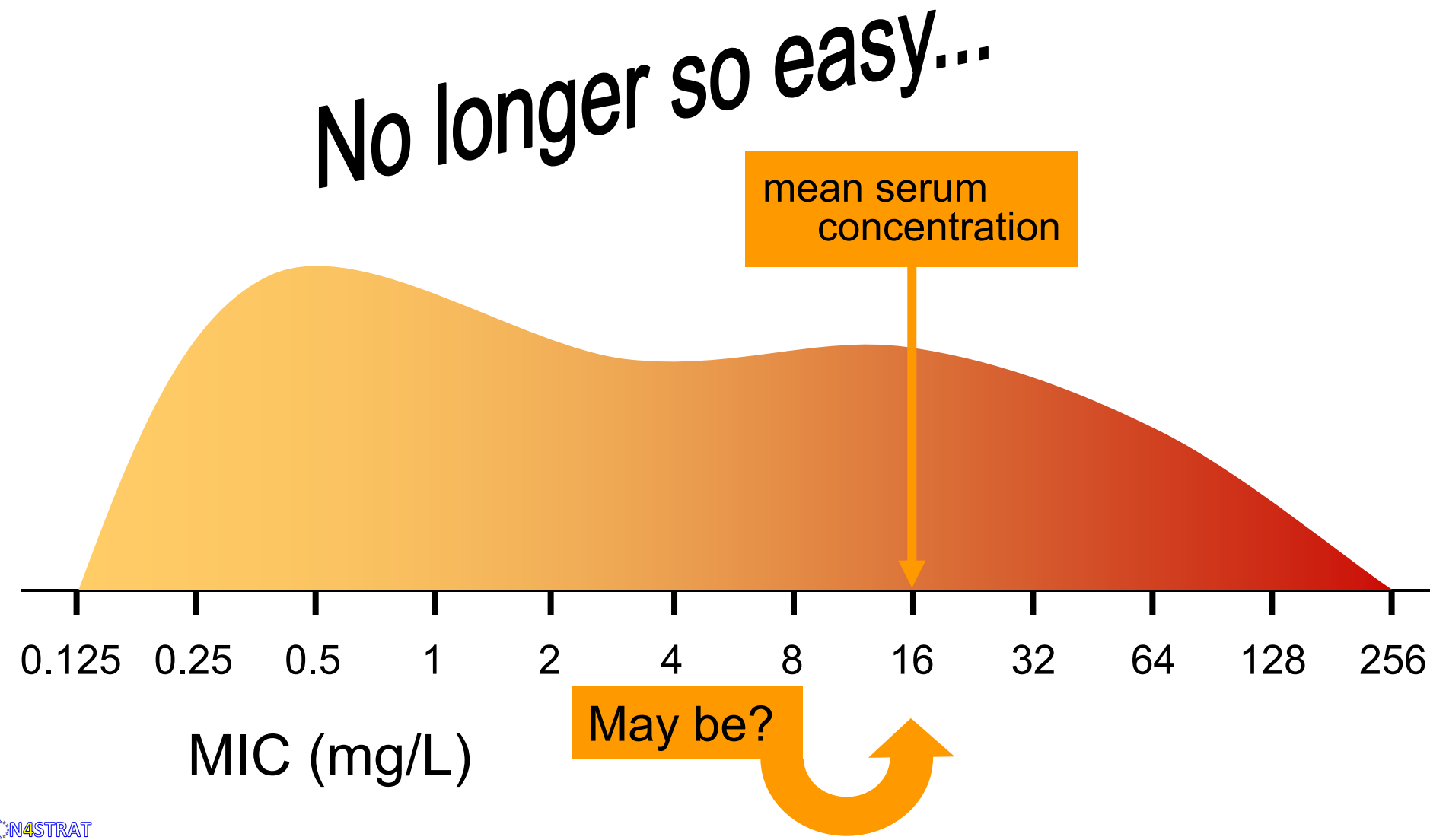
In the good old time…



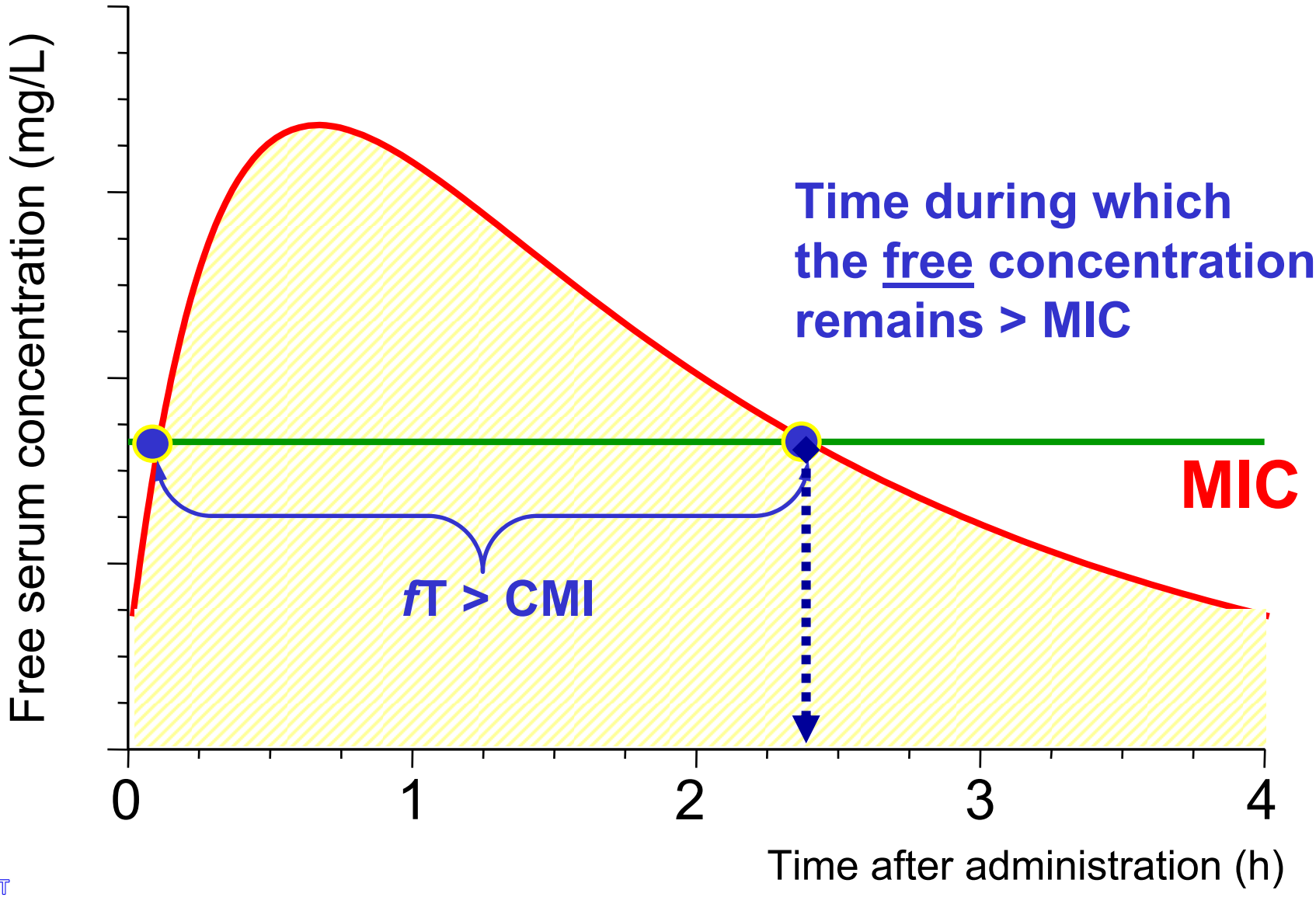
Still good old time ….



But now, what do you do with this ?



Which pharmacokinetic parameter drives the activity of β-lactams ?



Solution for β-lactams: *f*T > MIC…

You know it is "*free 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 ?)

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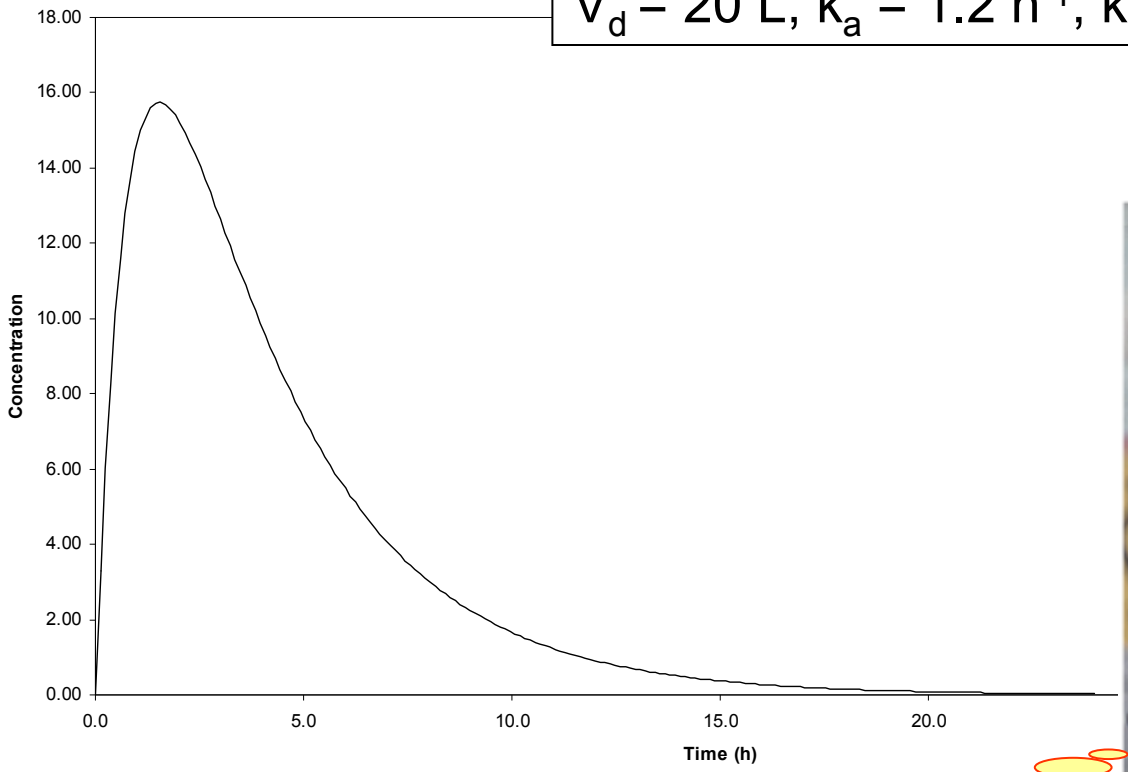
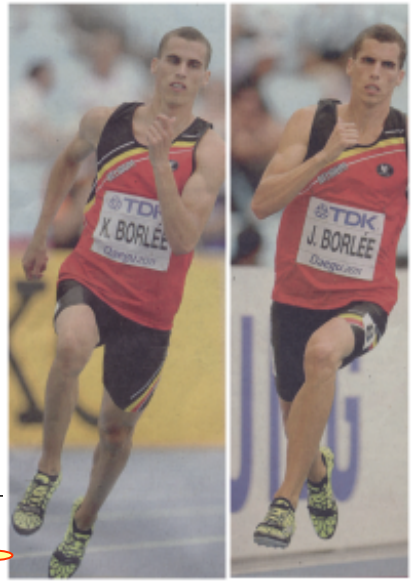
There are variations of PK in individuals...

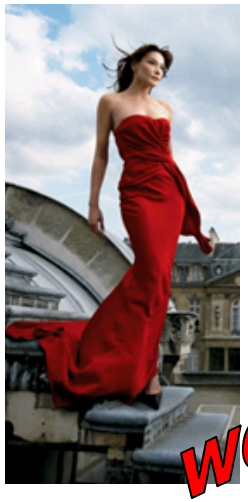
Concentration-time profile of a beta-lactam in volunteers
V_d = 20 L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}





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

What is, indeed, a standard patient ?



weight

age

physical condition

Kim Clijsters pose avec sa fille Jada. AFP

race

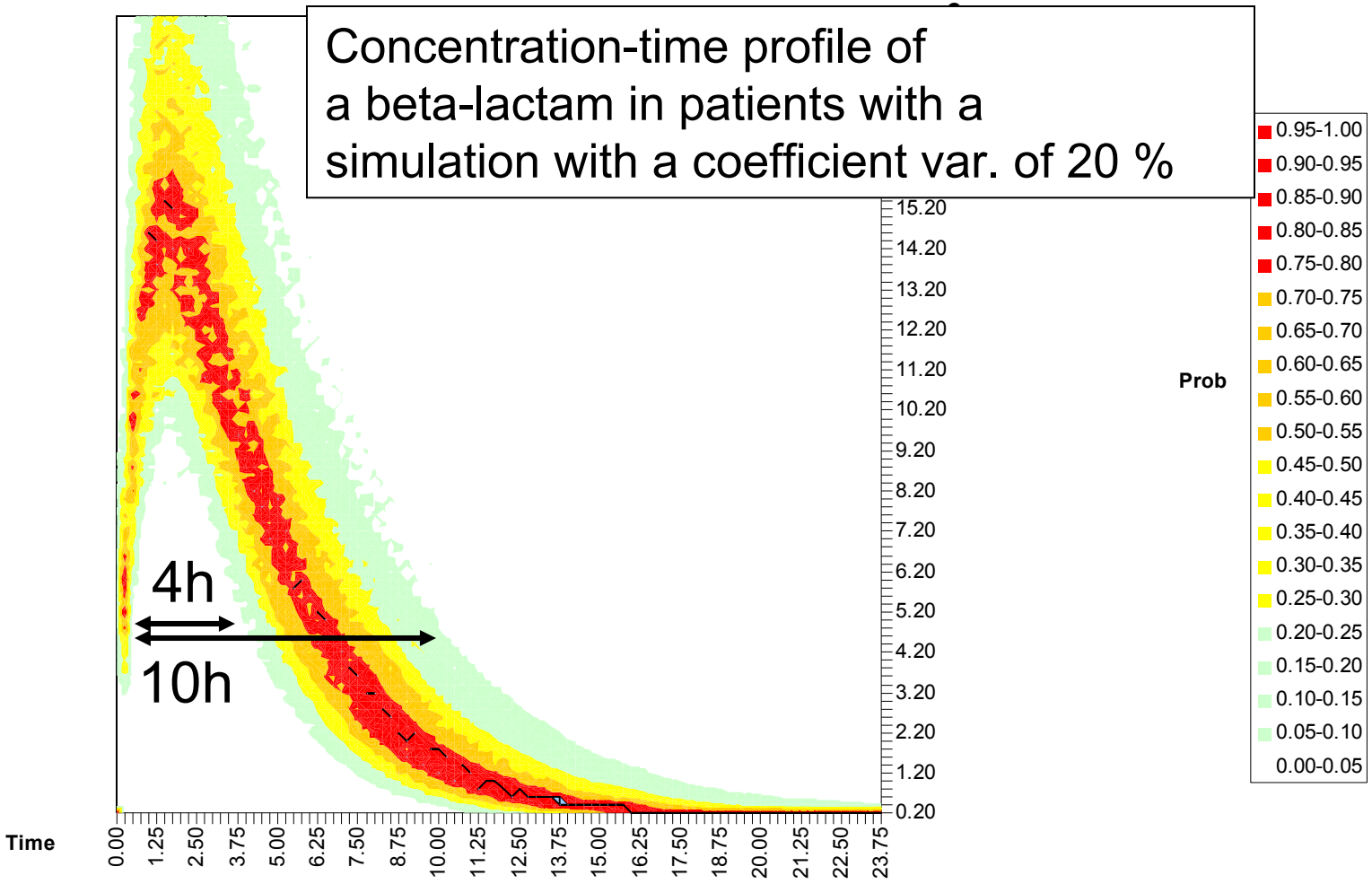
size

disease

elimionation functions

MON4STRAT

Variation of PK in individuals...



Mouton, Int J Antimicrob Agents april 2002

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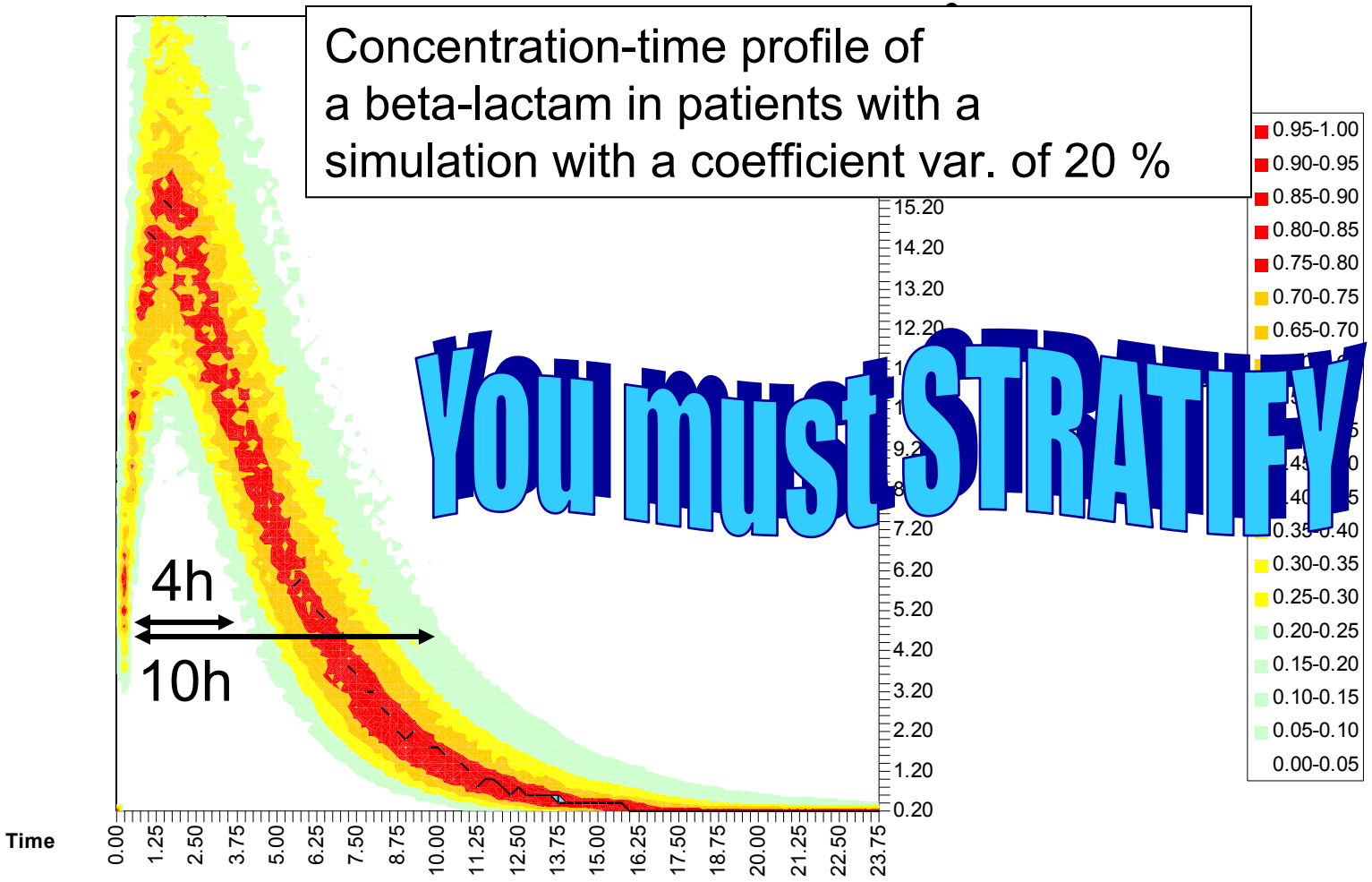

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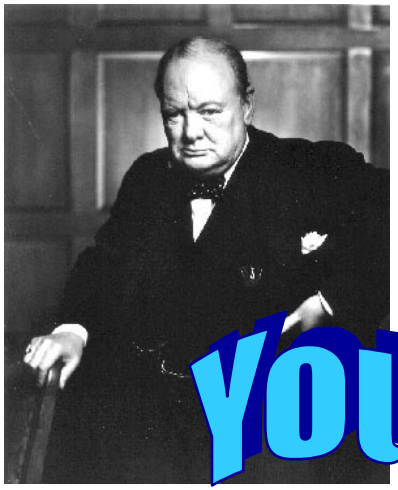
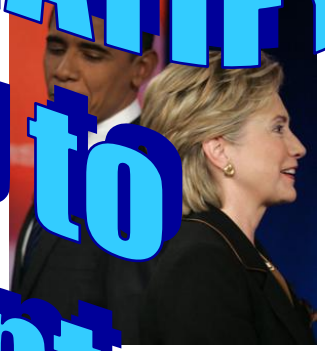


You must STRATIFY according to the patient



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

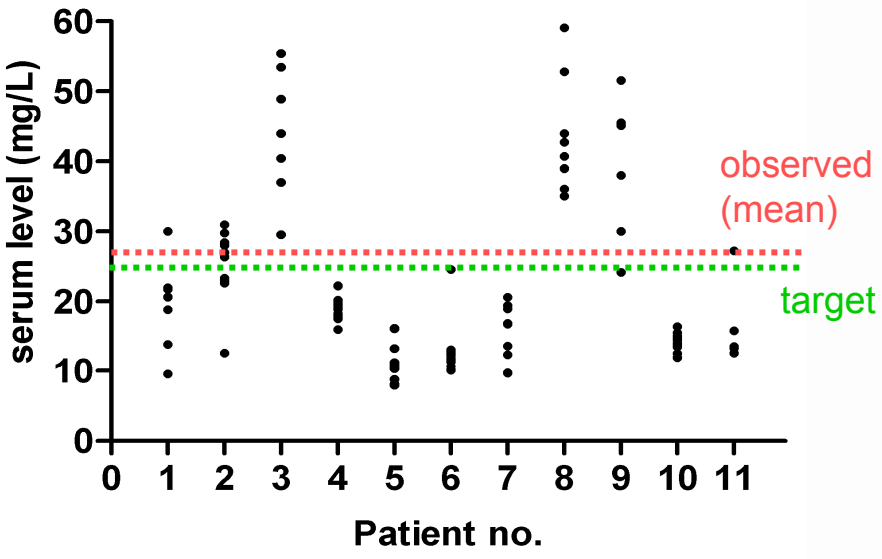
Continuous Infusion of Ceftazidime (4 g/day) vs Conventional Schedule and Dosis (3 X 2 g/day) for Treatment of Ventilator-associated Pneumonia in Intensive Care Units.

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

Solution for β-lactams: T > MIC…

You know it is "time above MIC", but…

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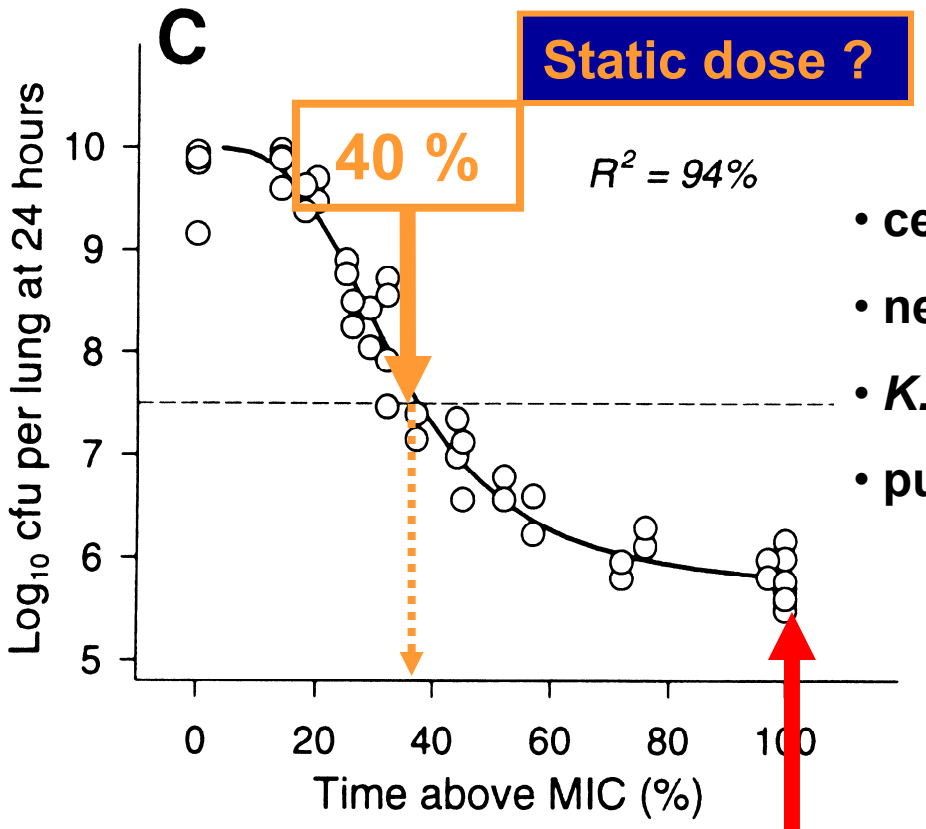
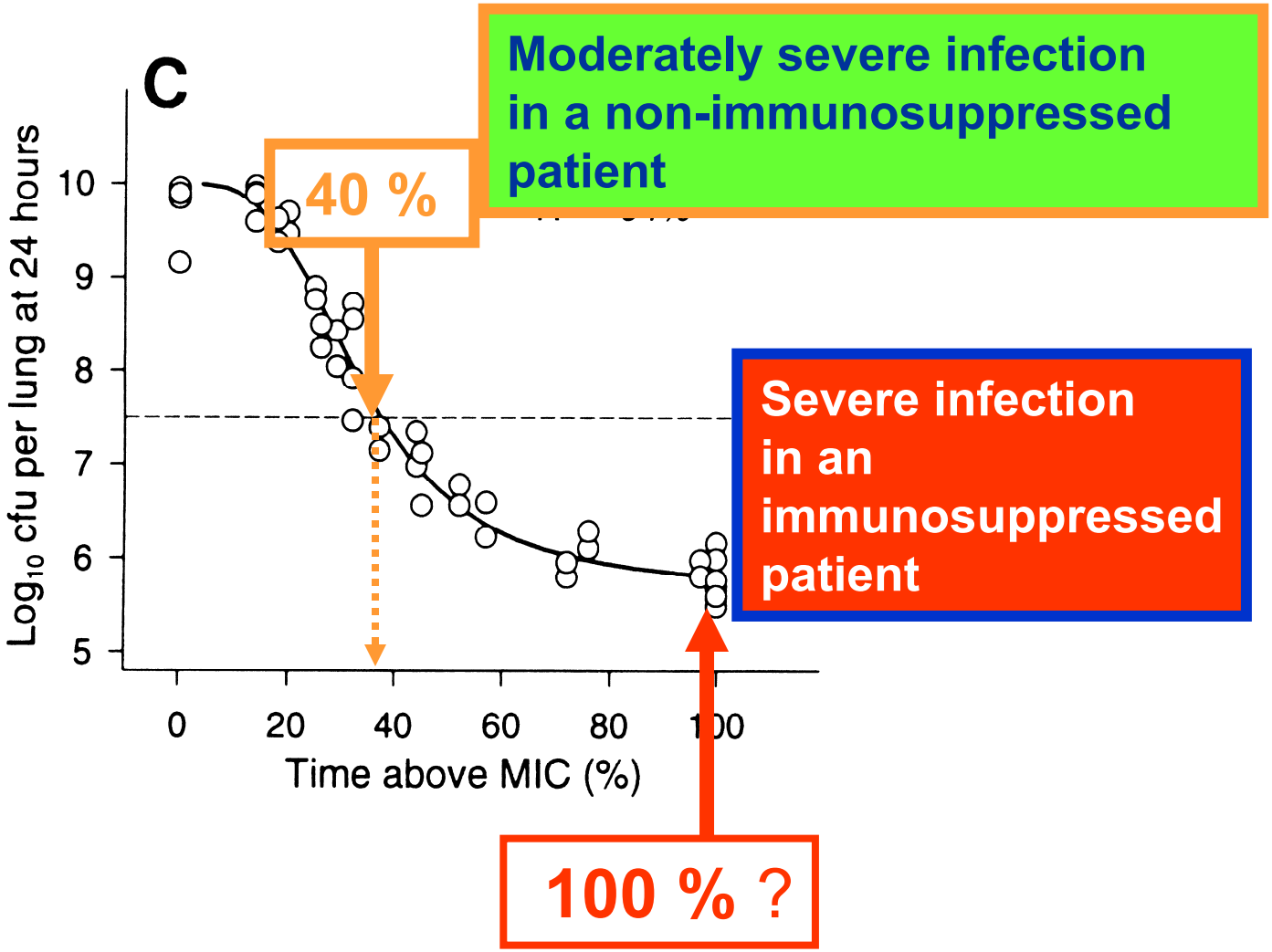
How much time above MIC ?



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

100 % - Maximal effect ?

It all depends on your patient !



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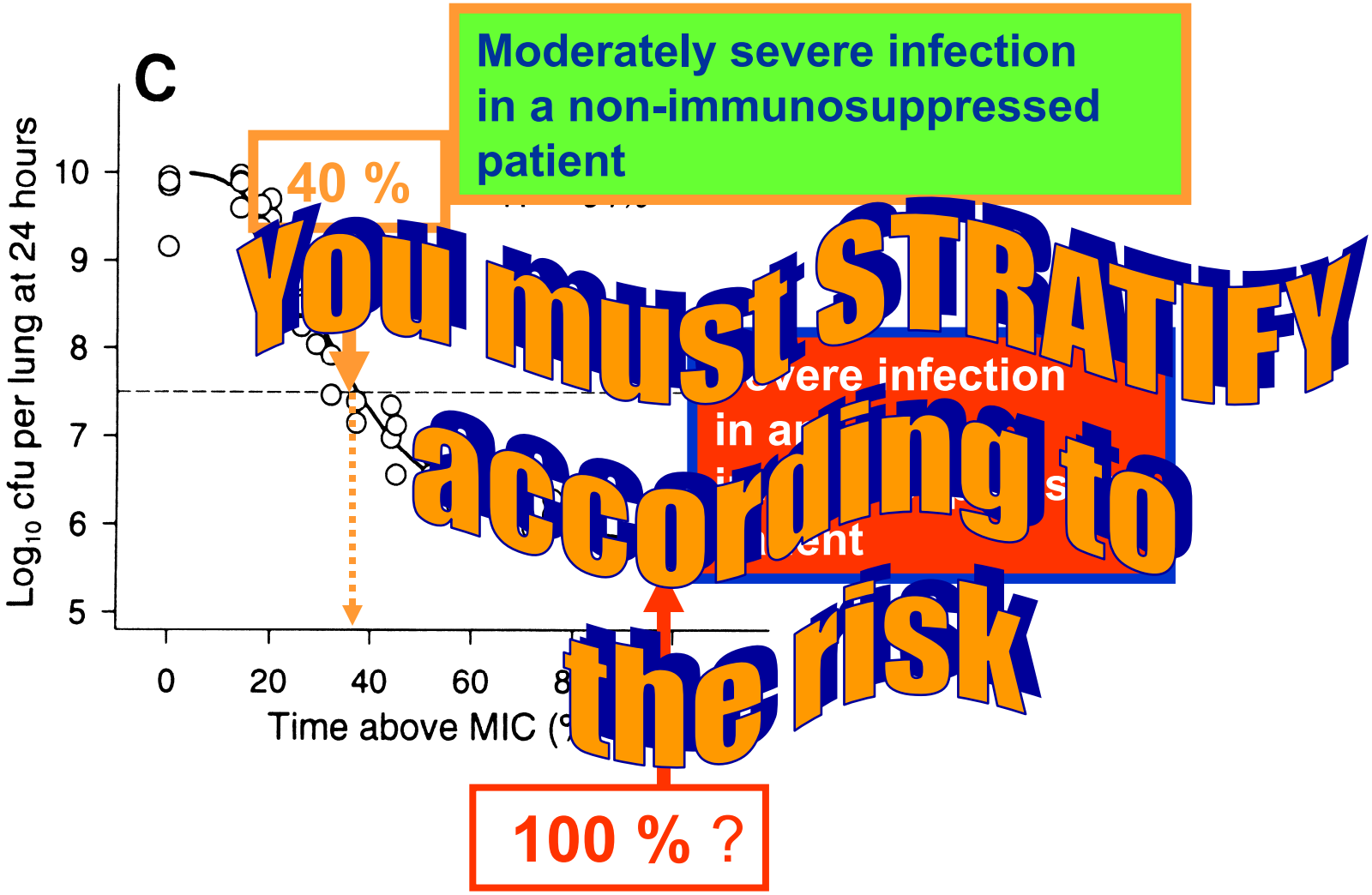
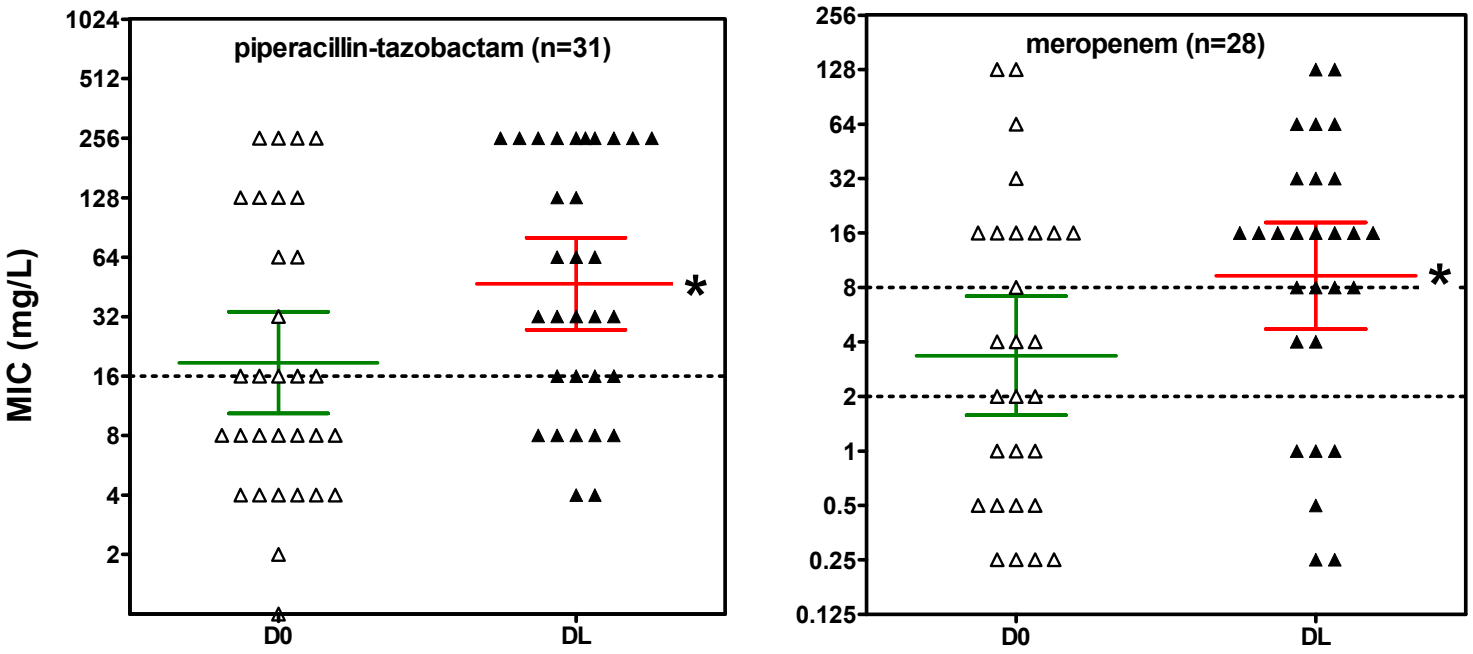


And do not forget about changes in MIC (low-level resistance) during treatment !



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 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.

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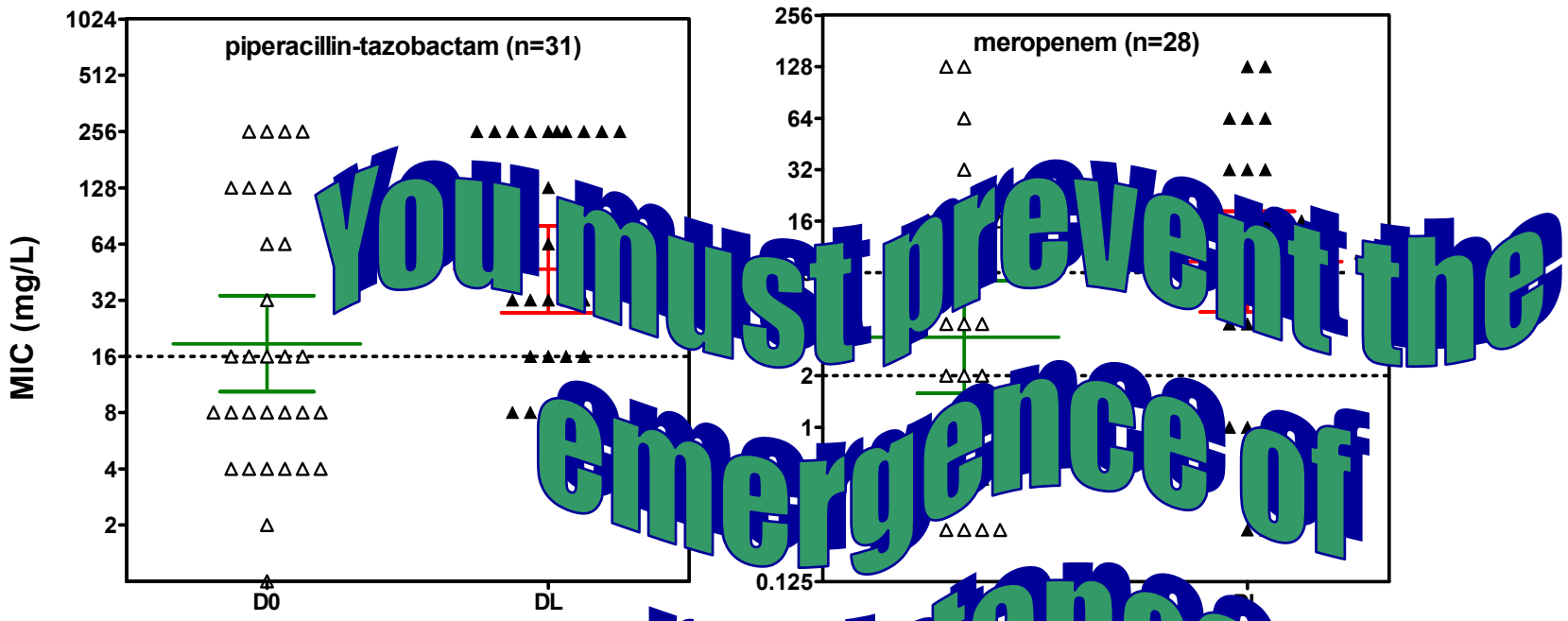

Change in MIC of antibiotics used in empiric ant[illegible] nosocomial pneum[illegible] intensive care units) towards the isolate identified before onset of therapy [illegible] isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using 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.

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

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

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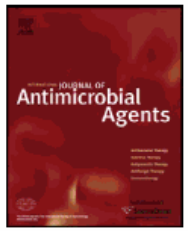

Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

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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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

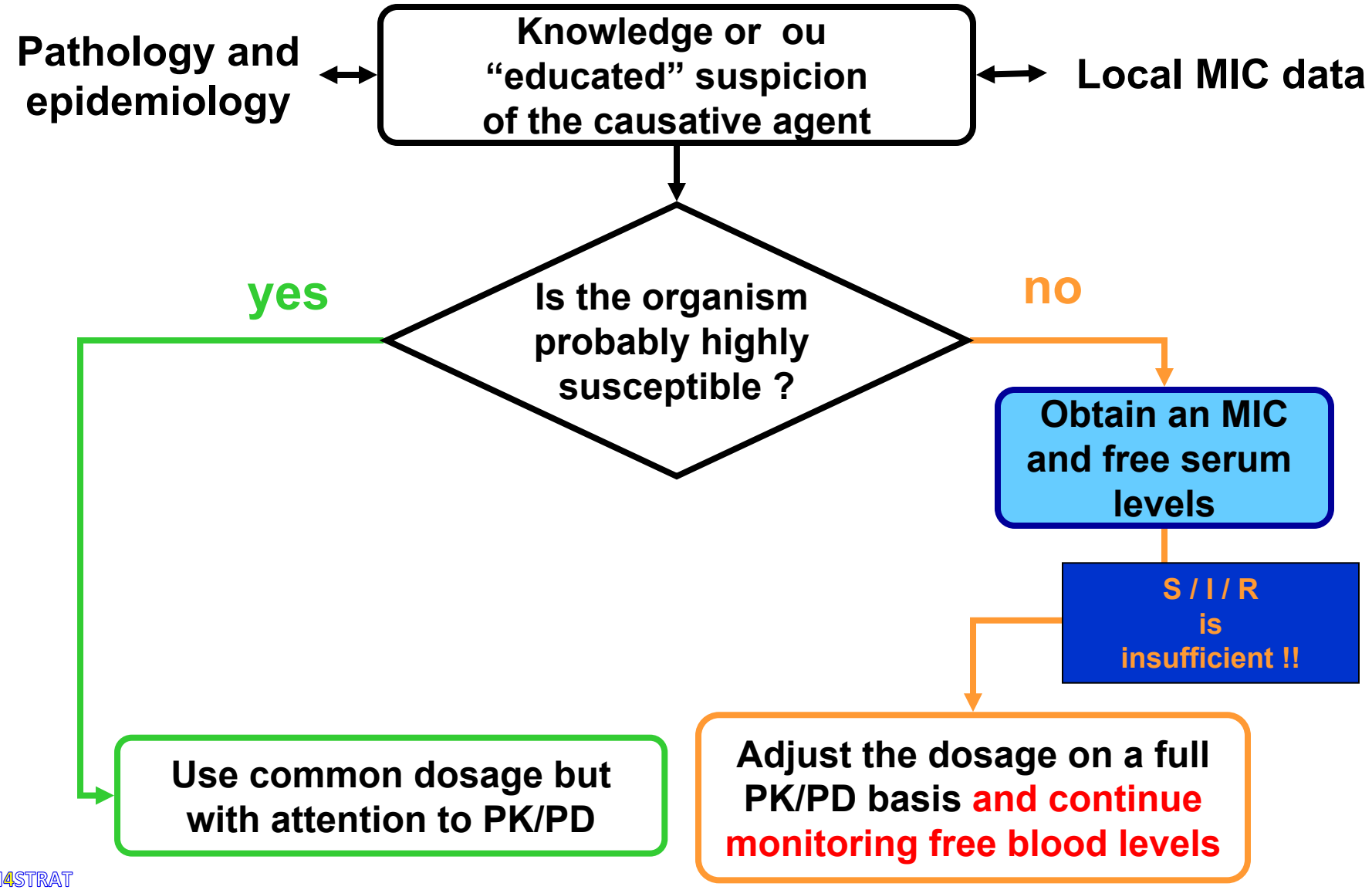
journal homepage: www.elsevier.com/locate/chromb

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...



Back-up

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