Update on PK/PD of antibiotics applied to critically ill patients: Focus on β-lactams and vancomycin

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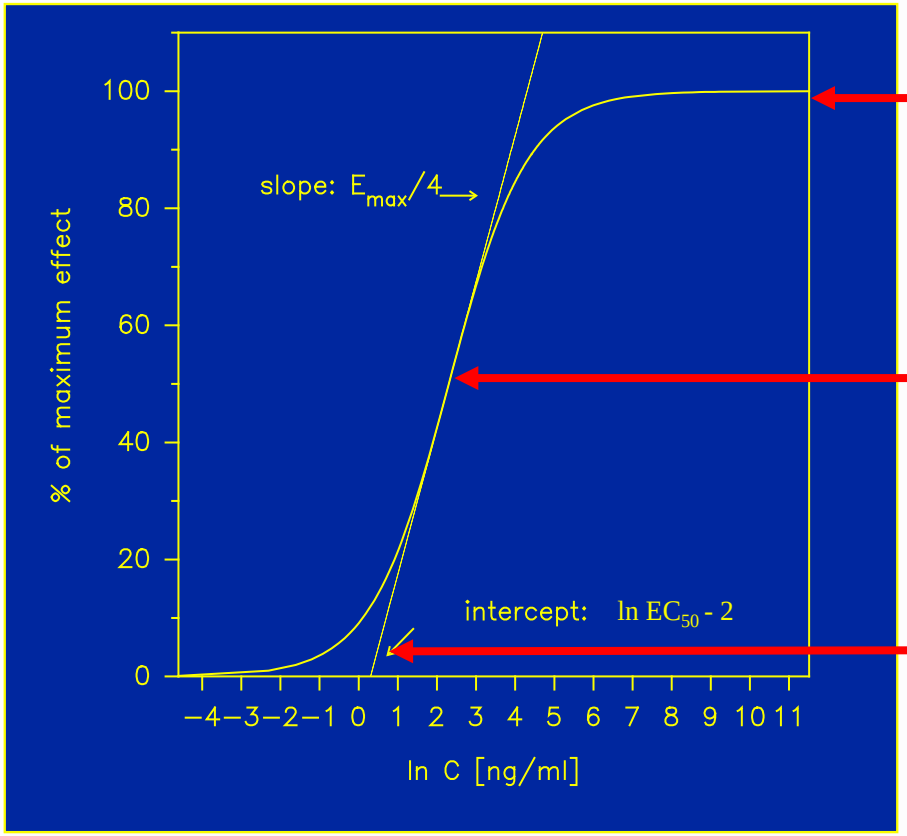
Đà Lạt, Lâm Đồng Province, Việt Nam

The slides are available for download from http://www.facm.ucl.ac.be → Lectures

A quick reminder of drug pharmacodynamics…



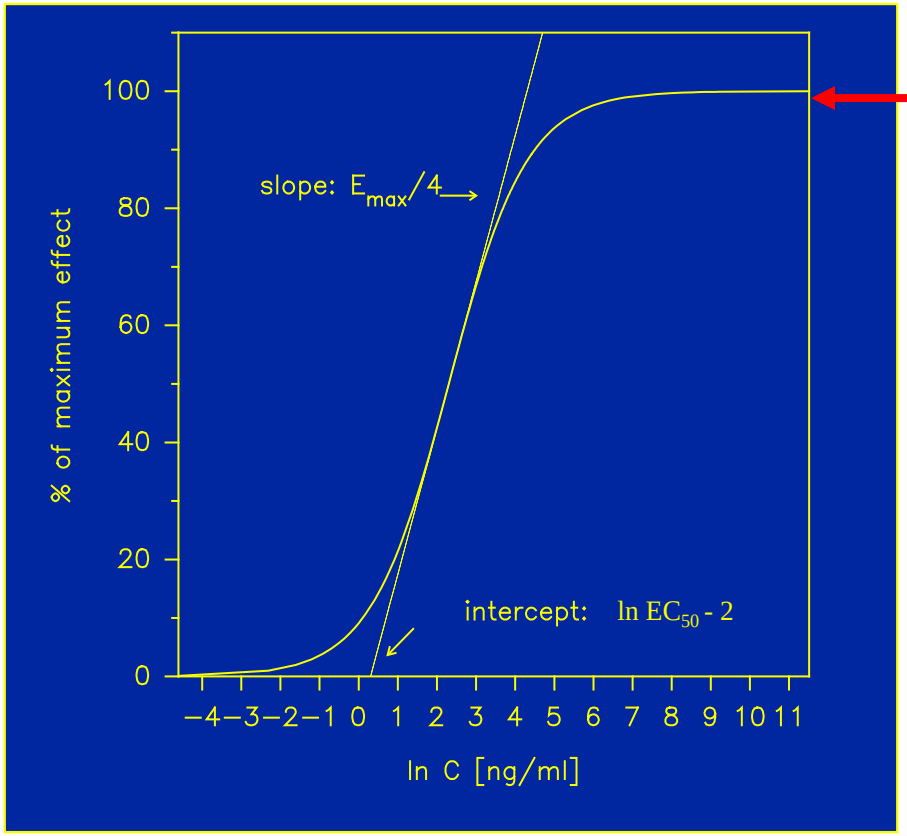
concentration

E_{max} — **Maximal effect**

$E_{50\%}$ — **Intermediate effect**

E_{min} — **Minimal effect**

In chemotherapy, aim for a maximal effect !



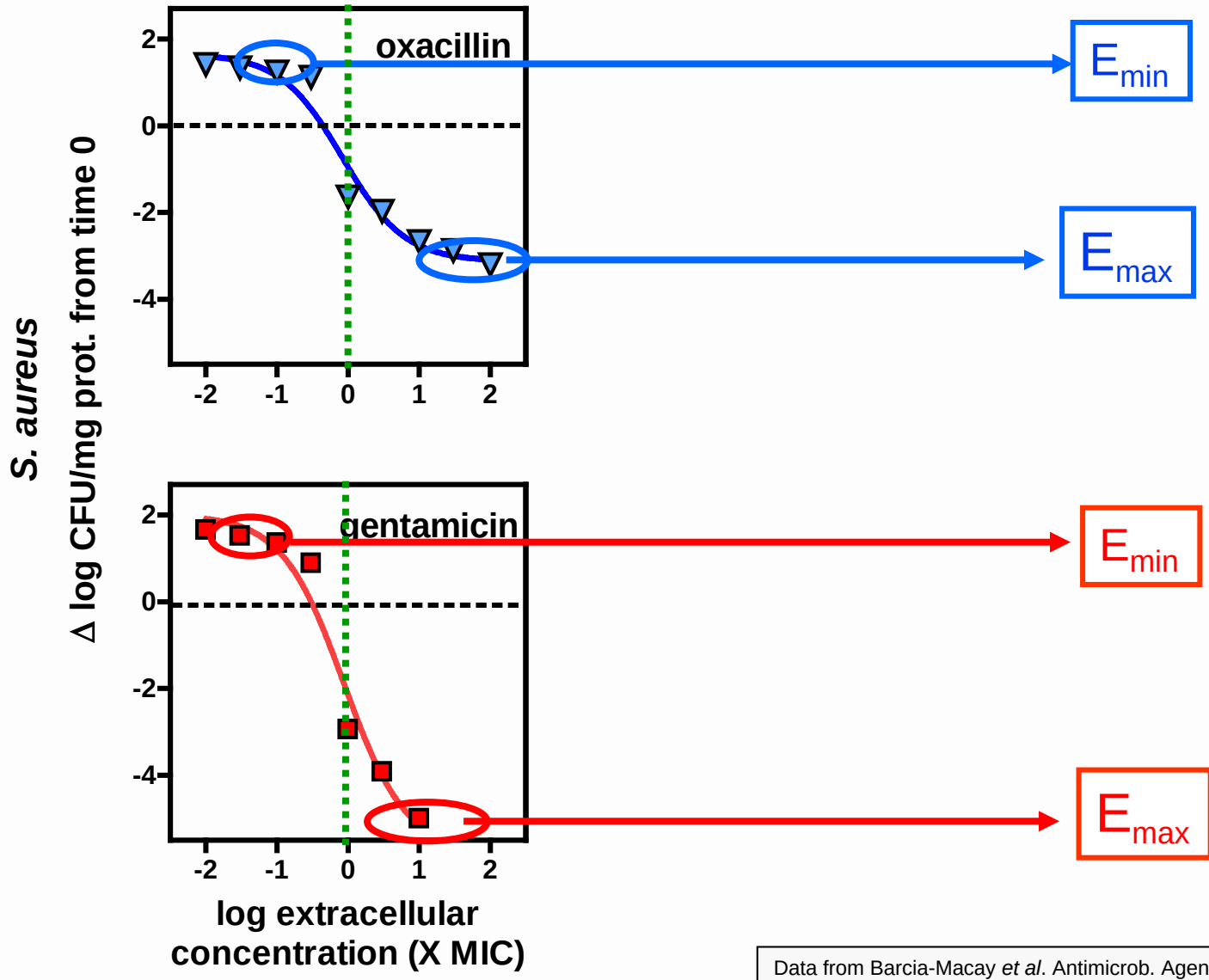
concentration

E_{max}

Maximal effect

This is what you should aim for in chemotherapy

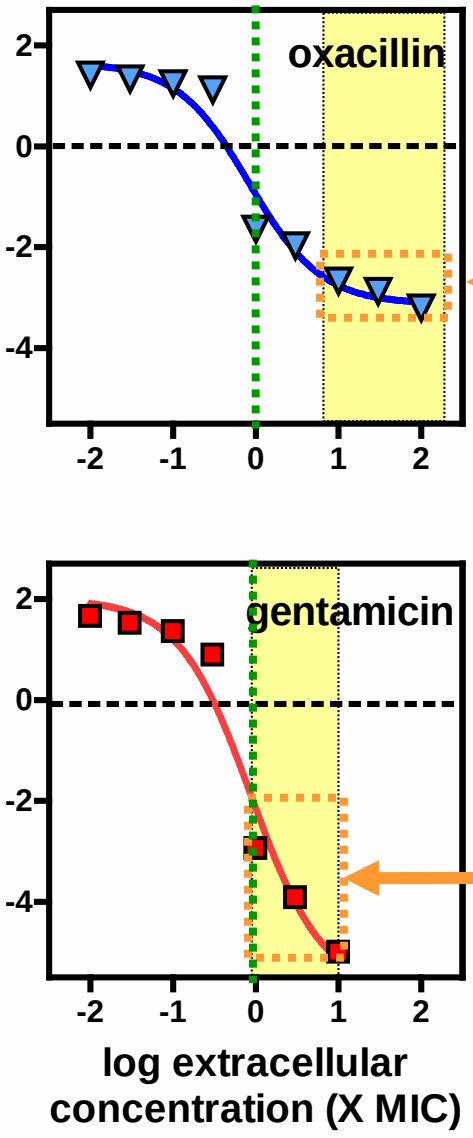
Pharmacodynamics of antibiotics…



It looks as if they are all concentration -dependent…

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

But here comes pharmacokinetics …



Weak concentration-dependence (max. effect over the C_{min}–C_{max} range)

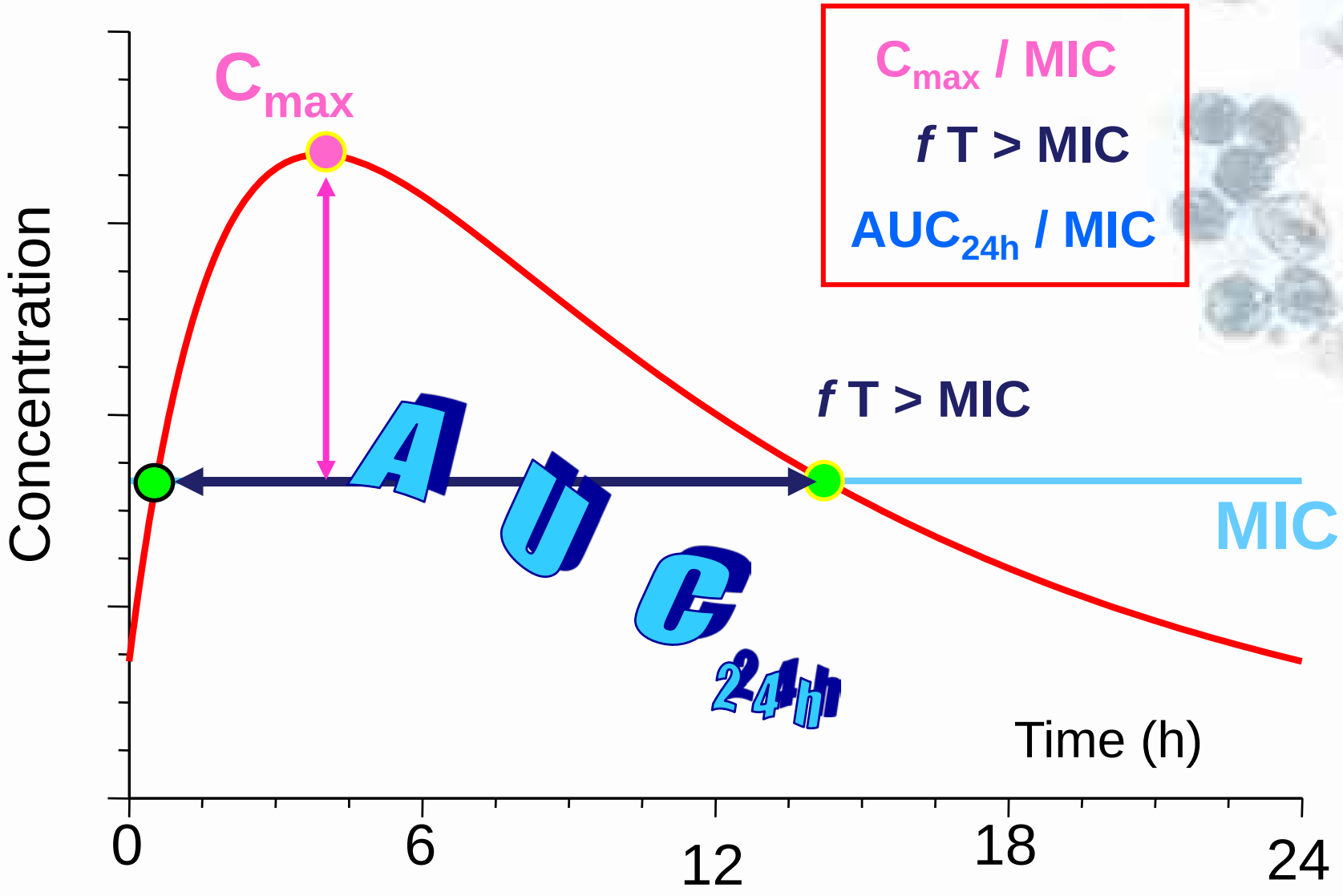
➔ TIME will emerge as the main parameter in vivo

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

PK parameters governing the activity of antibiotics



The three main groups of antibiotics

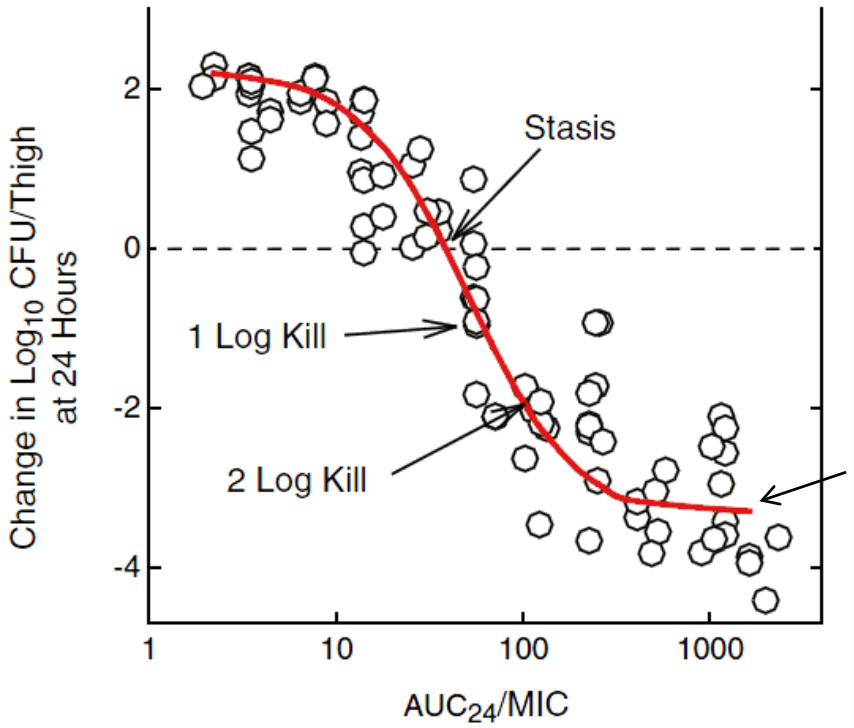
Class	Driving PK/PD parameter	Symbol	What to do ?
β-lactams	• time during which the free* concentration is > MIC	$fT>_{MIC}$	• frequent administrations • extended/continuous infusion
aminoglycosides and fluoroquinolones	• free* concentration > MIC → bactericidal rate • free* AUC/MIC ratio → global effect	fC_{max}/MIC $fAUC_{24h}$/MIC	• get a peak ! • total daily dose
most other antibiotics	• free* AUC/MIC	$fAUC_{24h}$/MIC	• total daily dose • schedule accord. to half-life • continuous infusion

* For most antibiotics, only the free fraction is active

Animal models: what can you measure…

2 In Vitro and Animal PK/PD Models 33

Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



Andes & Craig WA Int J Antimicrob Agents 2002;19:261–268

Beta-lactams …in a nutshell…

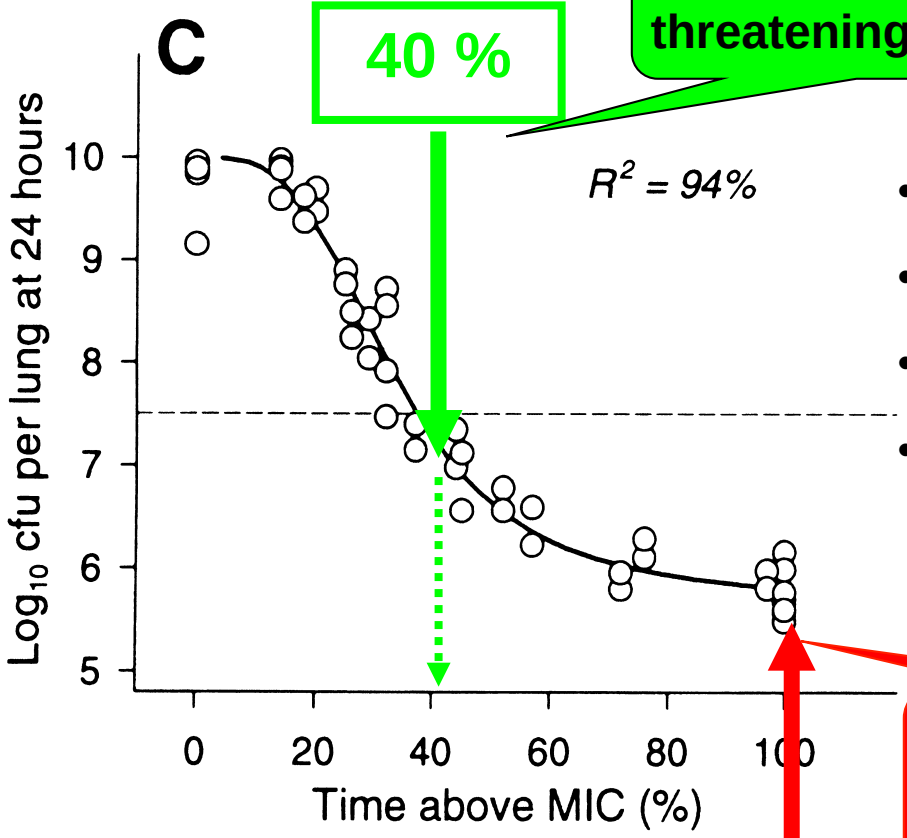
- Every antibiotic is concentration-depedendent
(simple pharmacological principle) …
- **BUT,** for β-lactams, activity if already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration… and bacteria with low MICs
- **AND**, having no post-antibiotic effect, β-lactams need to stay above the MIC (preferably 4-fold…) for the maximum time…

Medical controversies
by H. Daumier (1808-1879)

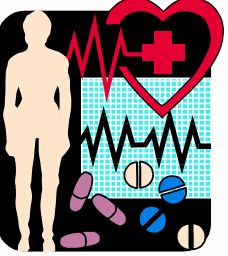
PK/PD questions about β-lactams: PK/PD aspects

- How long above the MIC ?
- How much above the MIC ?

How long above the MIC for a typical β-lactam ?



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



Typical pharmacokinetics of an IV β-lactam

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

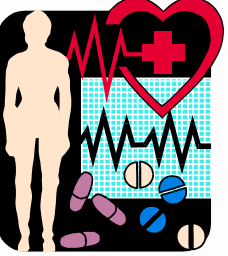
* Single administration; half-life 2h ; V_d = 0.2 l/kg

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**



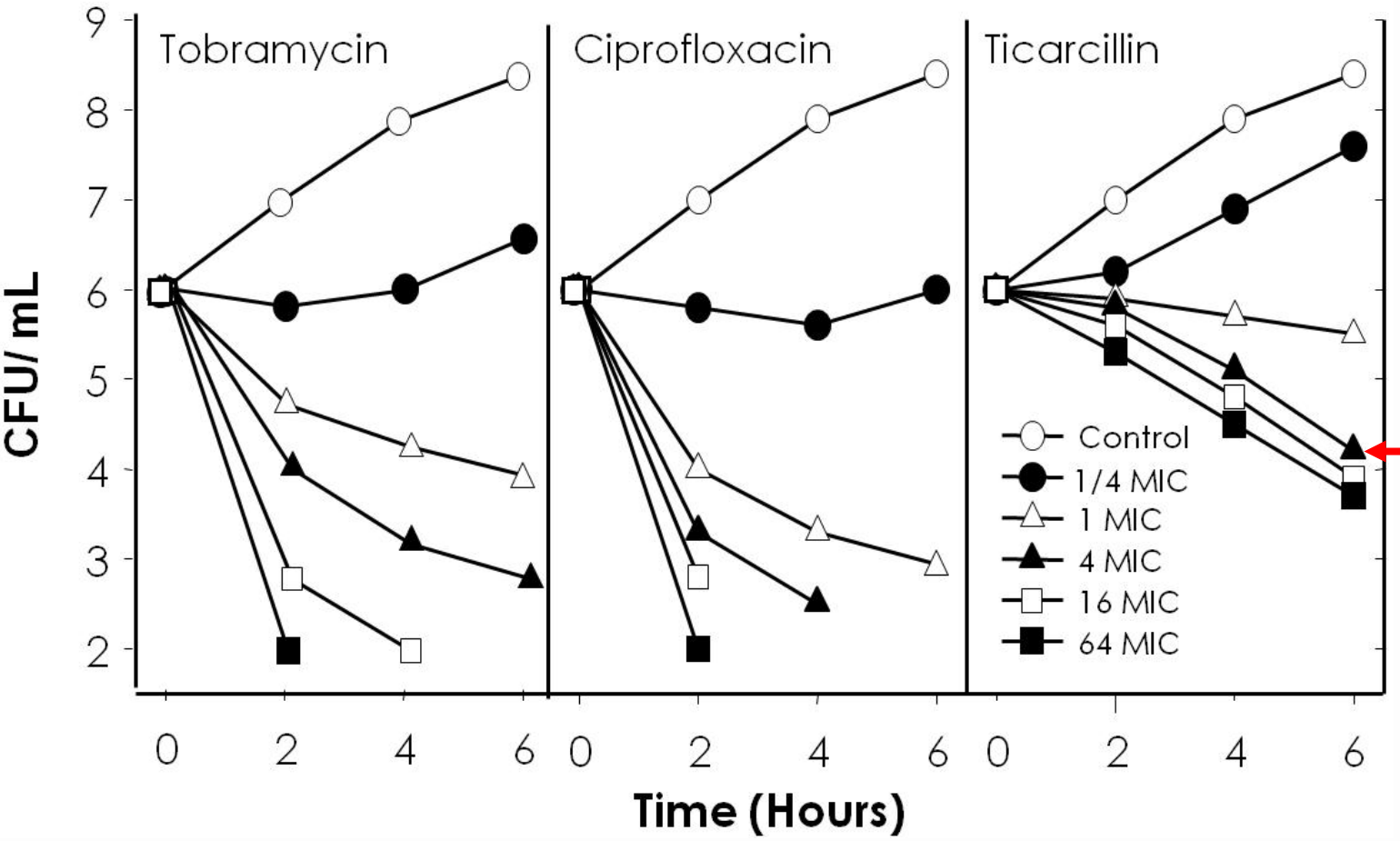
Where do you wish to be ?

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

this is what you may need…

* Single administration; half-life 2h ; V_d = 0.2 l/kg

But again, how much above MIC ?

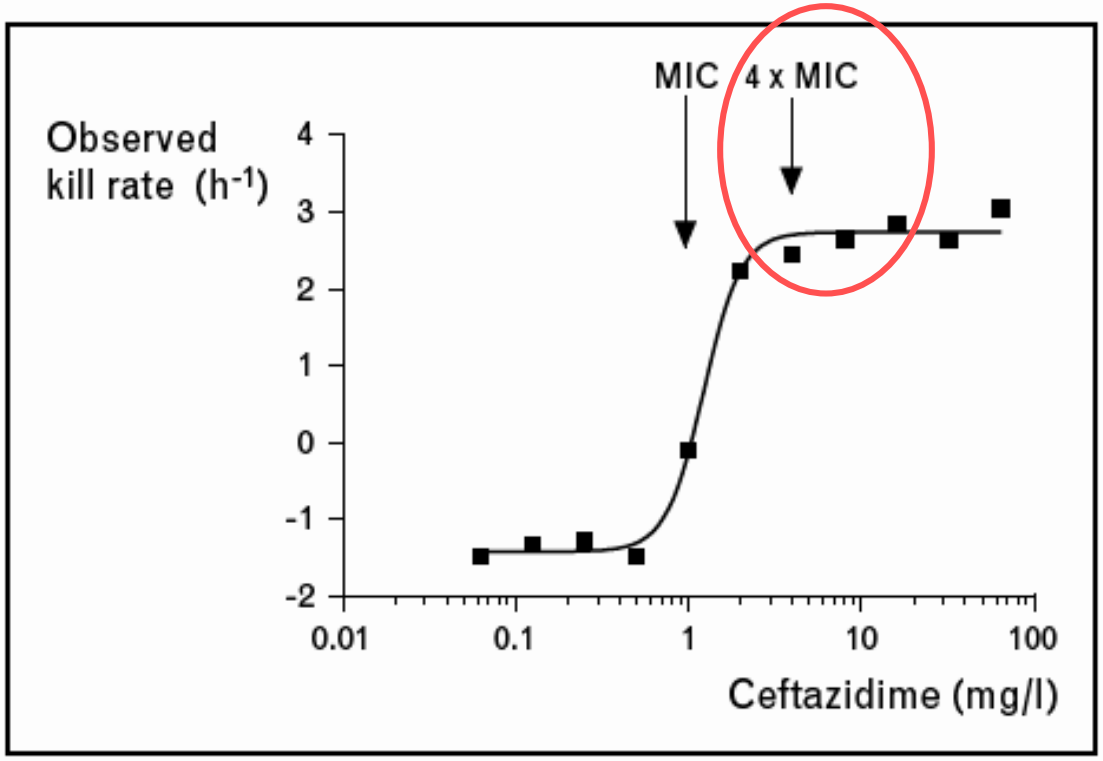


4 X MIC

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

How much ?

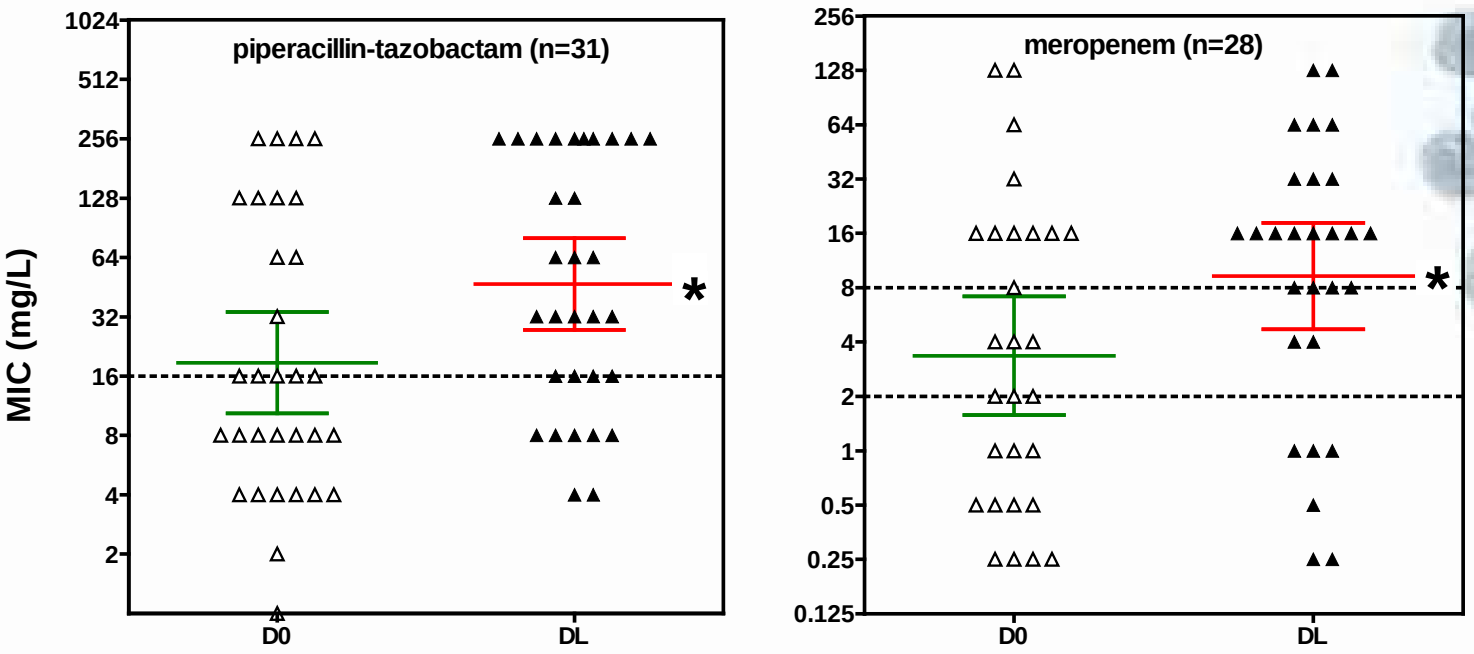
Figure 2 Relationship between concentration of ceftazidime and kill rate



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

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

But 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.

More optimization to prevent 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

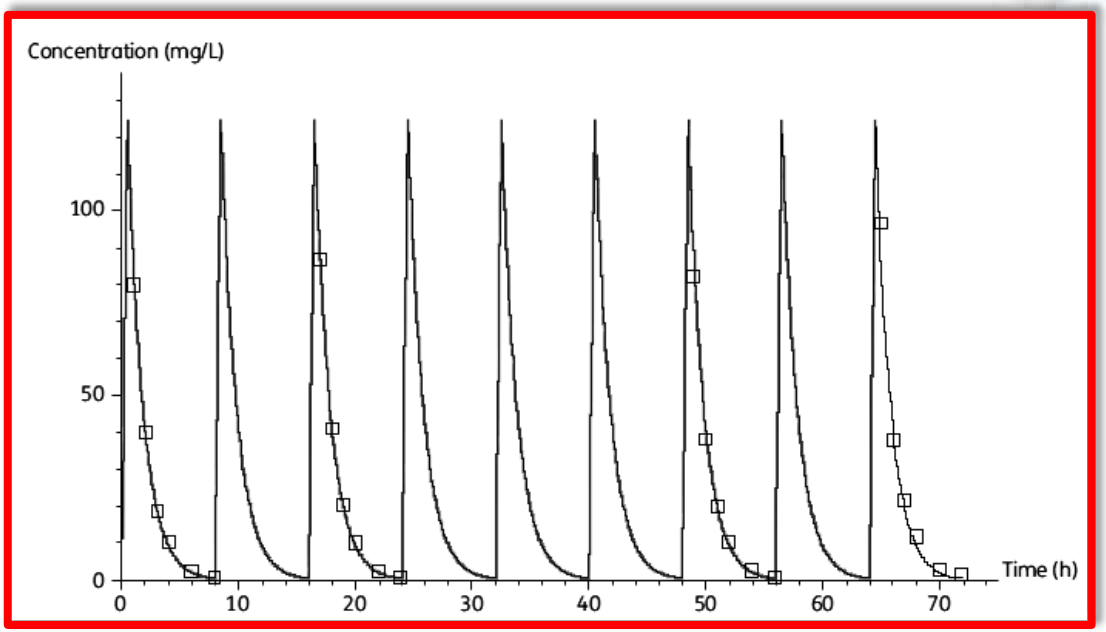
Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

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 serum concentration levels (hollow fivers model)



More optimization to prevent emergence of resistance

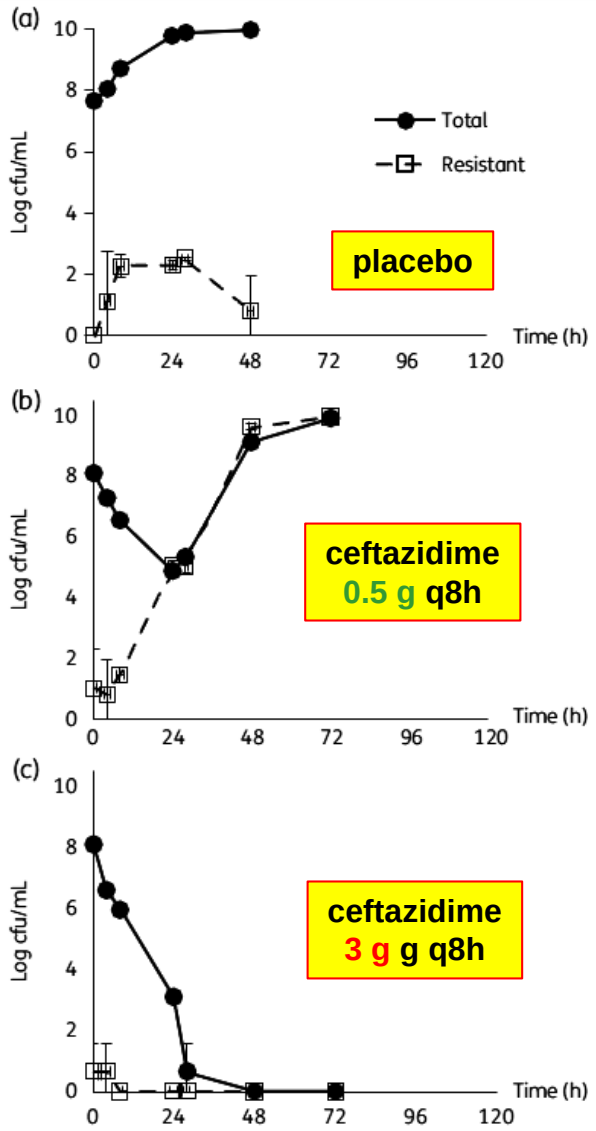


Figure 2. Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h (C_{min}/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h (C_{min}/MIC = 7.7) (c). Data are shown as mean ± SD.

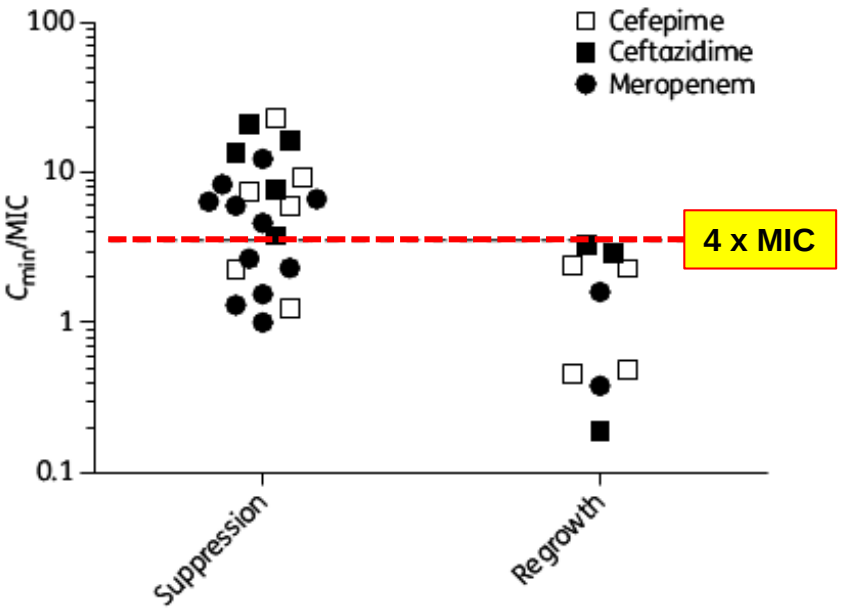


Figure 3. Drug exposures (C_{min}/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold (C_{min}/MIC ≥3.8) is depicted by the horizontal broken line.

To prevent emergence of resistance, C_{min} of β-lactams must stay > 4 x MIC (mean), which commands higher dosages…

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

Some discussion about β

- ***f* T > MIC** is the driving parameter, but what is needed may vary between **40 to 100 %** depending upon the severity of the infection…
  - ➔ providing a 100 % coverage may be particularly useful in servere infections (ICU, …) or β-lactams, activity if already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration… and bacteria with low MICs
- **4 x the MIC** provides optimal efficacy and prevention of resistance…
  - ➔ This is what you may like to aim at in severe, difficult-to-treat infections, but lower values may be effective (not lower than 1 x the MIC, however…

OK !

May be…

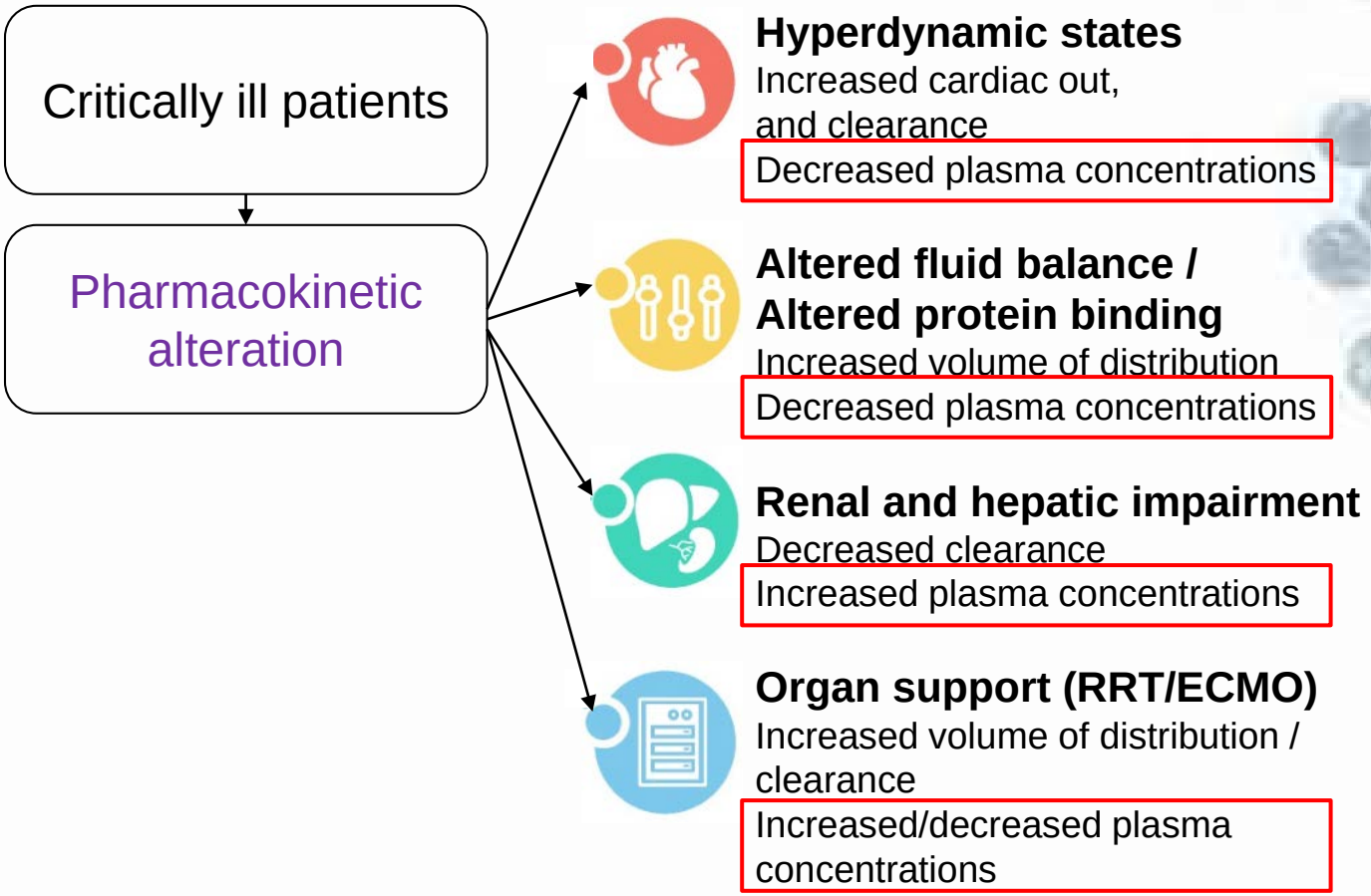
Oh no !

- There is growing evidence that standard antibiotic regimens may not provide adequate drug concentrations in ICU patients …

J.W. Mouton et al: Int J Antimicrob Agents. 2002 Apr;19(4):323-31.

Roberts *et al*, Br J Clin Pharmacol. 2012;73:27-36.

Critically-ill patients



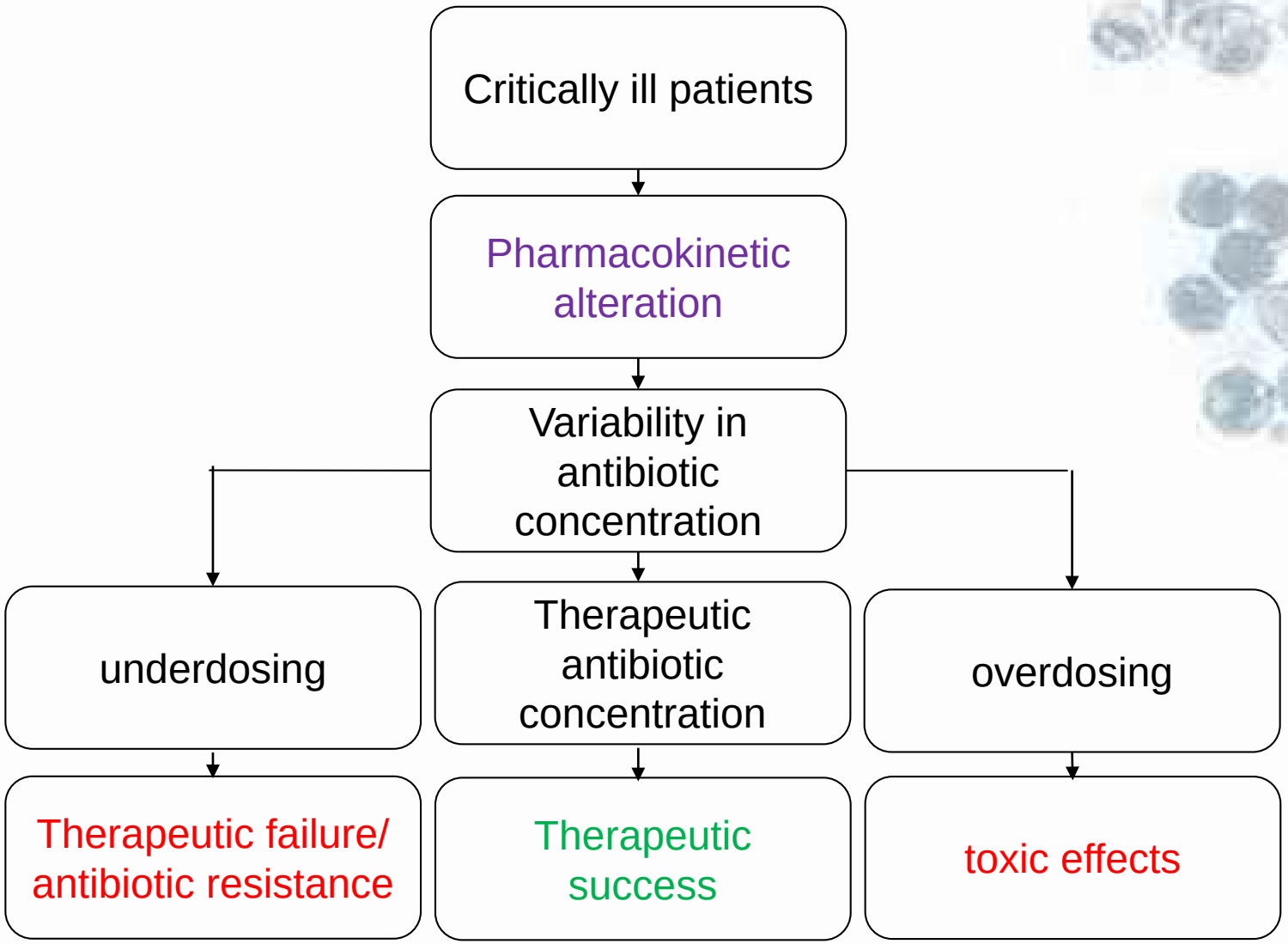
Roberts JA, Lipman J. Clin Pharmacokinetic 2006; 45 (8): 755-73

Hosthoff et al, Swiss Med Wkly. 2016;146:w14368

A. Abdulla et al: University Medical Center Rotterdam; eposter 069; ECCMID 2017

RRT: renal replacement therapy
ECMO: extra corporeal membrane oxygenation

Consequences of PK alteration



Roberts JA, Lipman J. Clin Pharmacokinetic 2006; 45 (8): 755-73
Hosthoff et al, Swiss Med Wkly. 2016;146:w14368
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Continuous infusion …

Infusion will push music to its limits

- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

- **What do we need to do in terms of PK/PD ?**
- What is the clinical evidence ?
- What are the problems ?
- How you do this in practice ?
- Do you need to monitor blood levels ?

Before we move further …..

antibiotic	dose-response	influence of time	clinical consequences
Yes • β-lactams • glycopeptides (*)	weak	critical	• Exposure to the drug **is** the important factor • Very high concentrations are unimportant
No ! • aminoglycosides • fluoroquinolones (**)	important	limited	• Concentrations **are** important • The time of exposure is less important

* AUC_{24h}/MIC dependent but weak post-antibiotic effect

** C_{max} is also important to prevent emergence of resistance

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Continuous infusion of β-lactams in clinical practice

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1. Pharmacokinetic and Pharmacodynamic Efficacies of **Continuous** versus Intermittent Administration of Meropenem in Patients with Severe Sepsis and Septic Shock: A Prospective Randomized Pilot Study.

Zhao HY, Gu J, Lyu J, Liu D, Wang YT, Liu F, Zhu FX, An YZ.

Chin Med J (Engl). 2017 May 20;130(10):1139-1145. doi: 10.4103/0366-6999.205859.

PMID: 28485312 **Free PMC Article**

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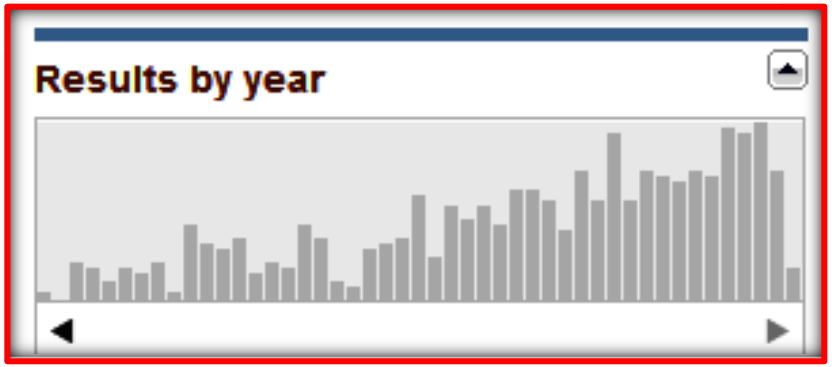


Continuous infusion of β-lactams: an overview…

International Journal of Antimicrobial Agents 30 (2007) 11–18

Review

Continuous infusion of β-lactam antibiotics in severe infections: a review of its role

Jason A. Roberts [a,b], Jennifer Paratz [a,b], Elizabeth Paratz [a], Wolfgang A. Krueger [c], Jeffrey Lipman [a,b,*]

[a] *Burns Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Australia*
[b] *Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia*
[c] *Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Tübingen, Germany*

Received 16 January 2007; accepted 23 January 2007

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
  - better attainment of pharmacodynamic targets for these drugs
  - More reliable pharmacokinetic parameters in seriously ill patients
  - when the MIC of the pathogen is ≥4 mg/L (empirical therapy where the susceptibility of the pathogen is unknown)
- Clinical data supporting continuous administration are less convincing, but
  - Some studies have shown improved clinical outcomes from continuous infusion
  - none have shown adverse outcomes.
  - clinical and bacteriological advantage are visible in seriously ill patients requiring at least 4 days of antibiotic therapy.
- **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., Intern. J. Antimicrob. Agents 30 (2007):11-18

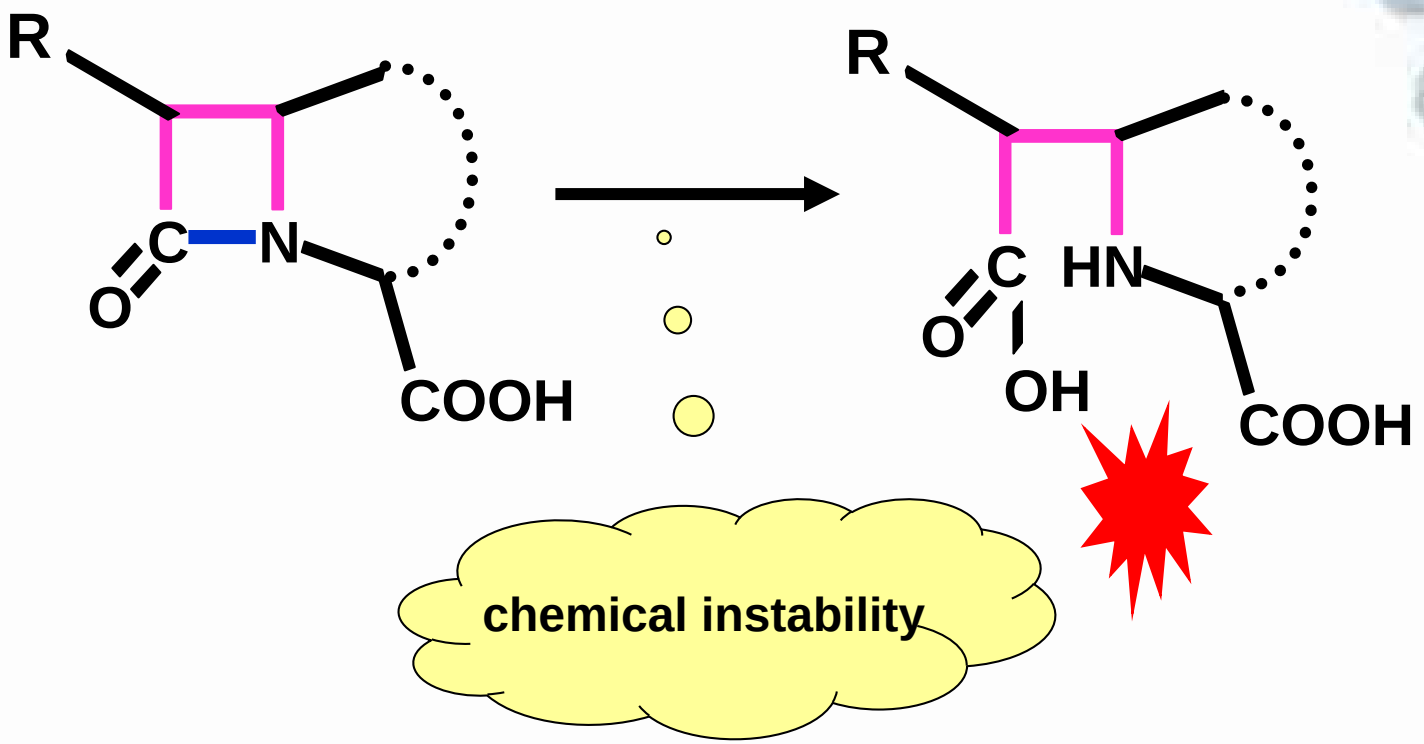
Continuous infusion …

Infusion will push music to its limits

- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

- But what do we need to do in terms of PK/PD ?
- What is the clinical evidence ?
- **What are the problems ?**
- How you do this in practice ?
- Do you need to monitor blood levels ?

Problem no. 1:
β-lactams are unstable molecules



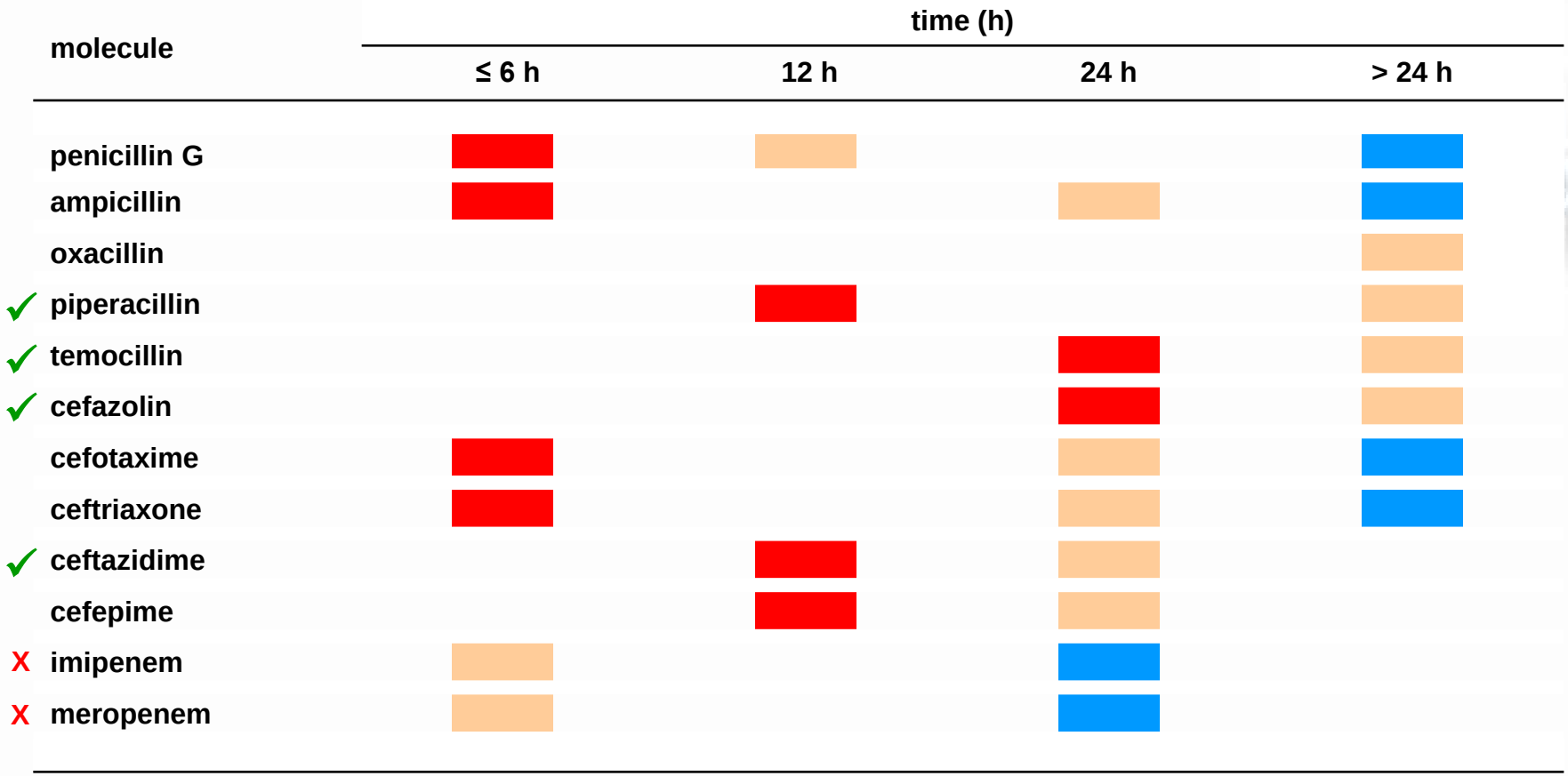
Can instability be modulated ?

- **yes** for penams and cephems, through
  - bulkiness and orientation of the C6/C7 substituent
    ↘ in anchimeric assistance
  - presence of a C6 methoxy (temocillin)
    ↘ in access of water
  - modulation of the C3 side-chain (cephems)
    ↘ in electroattracting properties

- **difficult** for carbapenems (imipenem, meropenem…)
  - strong tension in the β-lactam ring induced by the fused 5-membered ring;
  - strong electroattracting properties of the C3 side chain

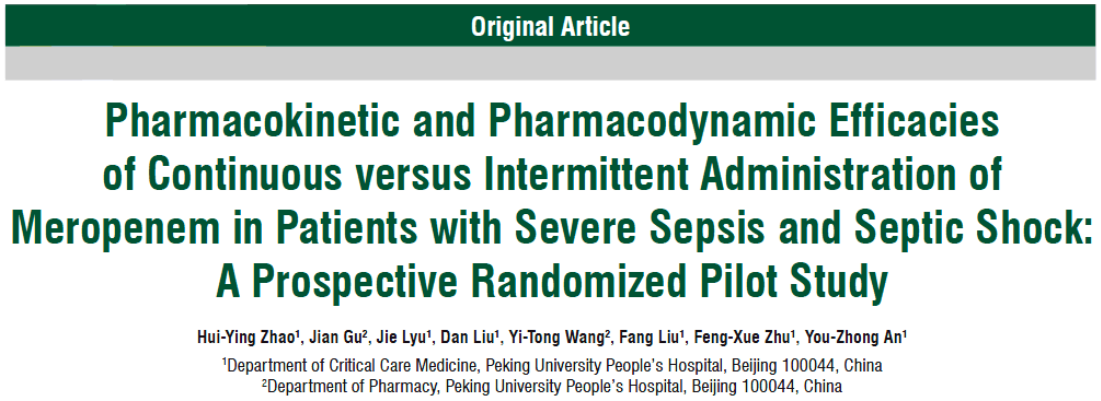
β-lactam stability in a nutshell…

- **Definition: > 90% intact product (Pharmacopeia)**
- **Conditions: mimicking the total daily dose (commercial product) in 48 mL (motor operated syringe) water without pH adjustment and maintained at a fixed temperature (*)**
- **key:** **37°C** **25°C** **4°C**



* Servais & Tulkens, AAC 2001;45:2643-7 – Viaene et al. AAC 2002;46:2327-32 - Baririan et al. JAC 2003;51:651 other references for indvual drugs in in Berthoin et al. (in preparation).

An example of how to cope with meropenem instability



Original Article

Pharmacokinetic and Pharmacodynamic Efficacies of Continuous versus Intermittent Administration of Meropenem in Patients with Severe Sepsis and Septic Shock: A Prospective Randomized Pilot Study

Hui-Ying Zhao[1], Jian Gu[2], Jie Lyu[1], Dan Liu[1], Yi-Tong Wang[2], Fang Liu[1], Feng-Xue Zhu[1], You-Zhong An[1]

[1]Department of Critical Care Medicine, Peking University People's Hospital, Beijing 100044, China
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Zhao et al. Chin Med J (Engl). 2017;130:1139-1145 - PMID: 28485312

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Patients in the continuous group:
- 0.5 g loading dose
- 3 g of meropenem over 24 h

[*To ensure*] meropenem stability, 0.5 g was infused over 4 h …
(thus 6 changes over 24h)

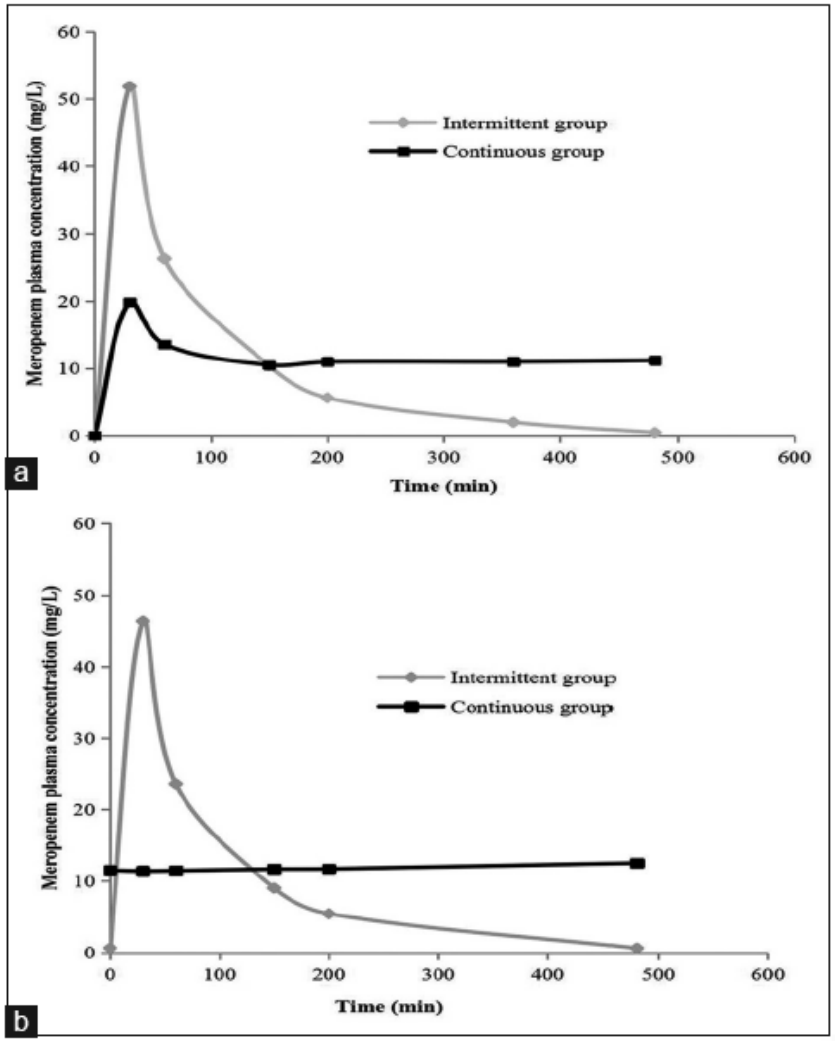
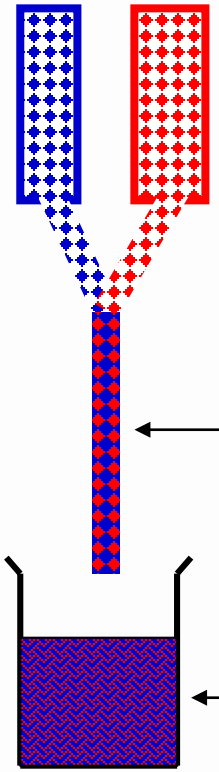


Figure 1: Plasma concentrations of meropenem administered to patients with severe sepsis or septic shock by intermittent infusion and continuous infusion for (a) the first dosing period and (b) third dosing period.

Problem no. 2:
β-lactams may be incompatible with other drugs if administered through the same line

β-lactam
(typ. 8 g %)



Drug X

1st contact at high concentration (10 min)

2d contact at 37°C at low concentration (1h)

direct examination (with viewer), HPLC, bioassay

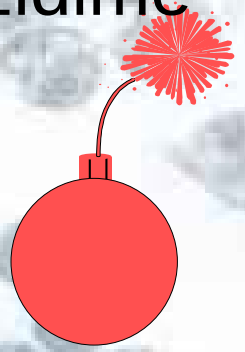
Drug compatibility studies: example for ceftazidime

Compatible:

- **antiinfectives**
  - **aminoglycosides**, **macrolides** (diluted solutions), **fluconazole**
- **sedatives / anticonvulsivants**
  - **ketamine, valproic acid, sufentanil, remifentanil, morphine**
- **antihypertensives / diuretics**
  - **urapidil, furosemide**
- **varia**
  - **aminoacid solutions (VAMIN)**
  - **insuline, methylprednisolone**
  - **isosorbide dinitrate**
  - **dopamine, adrenaline**

Servais & Tulkens, AAC, 2001 Sep; 45(9):2643-7.
Baririan et al., JAC, 2003 Mar; 51:651-8.

Drug compatibility studies: example with ceftazidime



Non-compatible

- **antibiotics**
  - **vancomycine** (precipitation); **macrolides** (if concentrated)
- **sedatives**
  - **propofol** (trapping in emulsion); **midazolam** (precipitation)
  - **piritramide** (precipitation), **phenytoïne** (precipitation)
- **antihypertensives**
  - **nicardipine** (precipitation)
- **varia**
  - **N-acetylcysteine** (chemical inactivation)
  - **dobutamine** (if concentrated)
  - **euphyllin** (chemical inactivation)

Servais & Tulkens, AAC, 2001 Sep; 45(9):2643-7.
Baririan et al., JAC, 2003 Mar; 51:651-8.

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Infusion will push music to its limits

- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

- What do we need to do in terms of PK/PD ?
- What is the clinical evidence ?
- What are the problems ?
- **How you do this in practice ?**
- Do you need to monitor blood levels ?

Continuous infusion in practice
1. loading dose: the correct scheme *

Target serum concentration

$C_t = D_l / Vd$

volume of distribution

loading dose

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

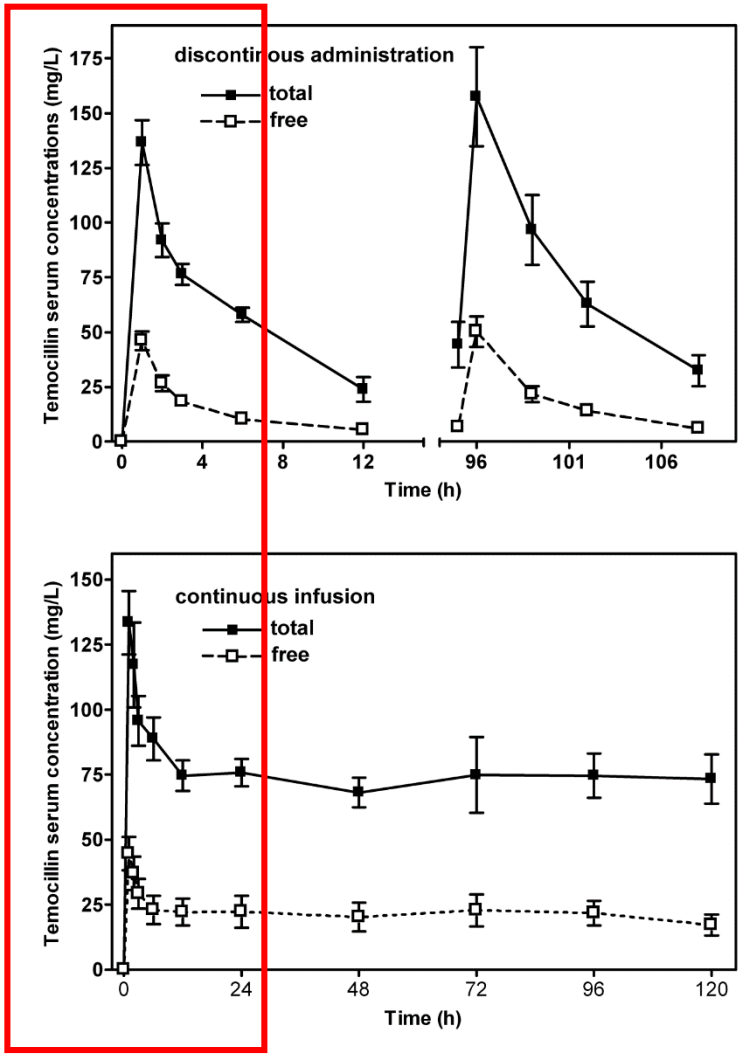
the loading dose is only dependent upon the volume of distribution and is directly influenced by the weight of the patient and his/her medical situation

Typical volumes of distribution of a β-lactam are between 0.2 L/kg (volunteers) and 0.4-0.5 L/kg (Intensive Care and burned patients)

* assuming linear pharmacokinetics (almost always the case for β-lactams)

Continuous infusion in practice
1. loading dose: a simplified scheme

- Because β-lactams have a low intrinsic toxicity, transient overshooting may not be a major problem…
- Conventional treatments (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) ?



Continuous infusion in practice 2: infusion *

Target serum concentration

$C_{ss} = K_o / Cl$

Clearance *

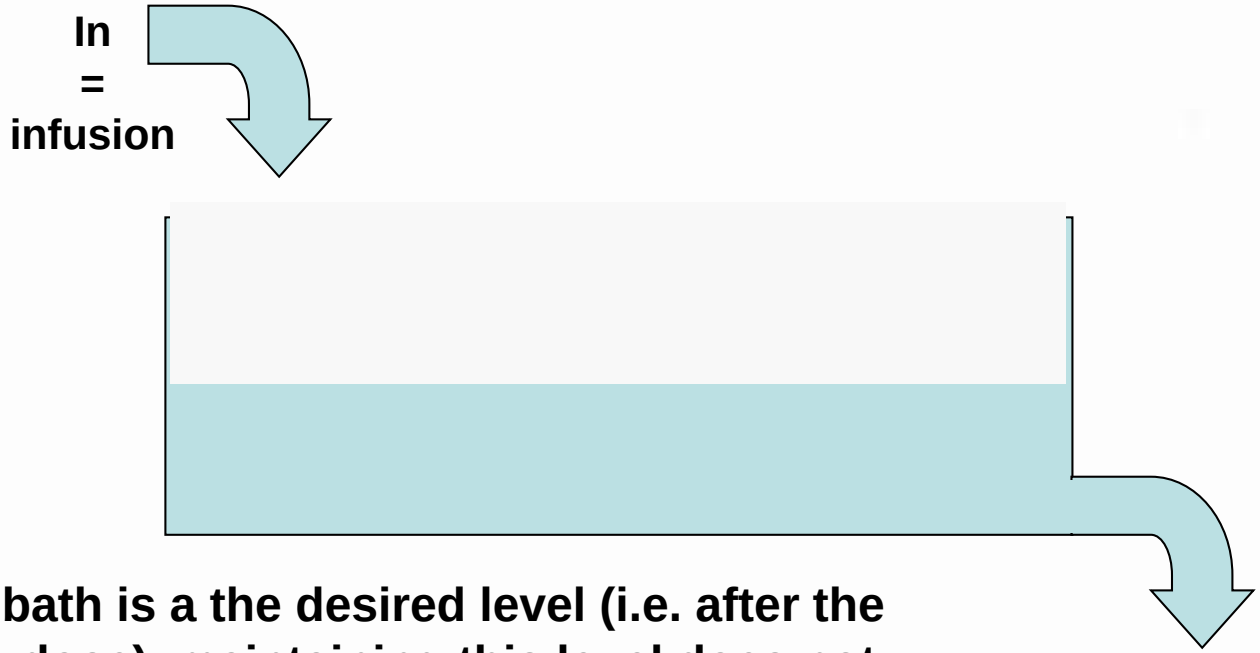
infusion rate

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

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

* assuming linear pharmacokinetics (almost always the case for β-lactams)

Continuous infusion in practice 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 must be equal: in = out…)

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

Continuous infusion …

Infusion will push music to its limits

- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

- What do we need to do in terms of PK/PD ?
- What is the clinical evidence ?
- What are the problems ?
- **How you do this in practice ?**
- **Do you need to monitor blood levels ?**

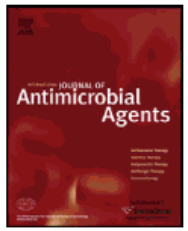
As a result, monitoring the serum levels of β-lactams has been proposed …

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

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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*
[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

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,*]

[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, Brussels, Belgium
[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

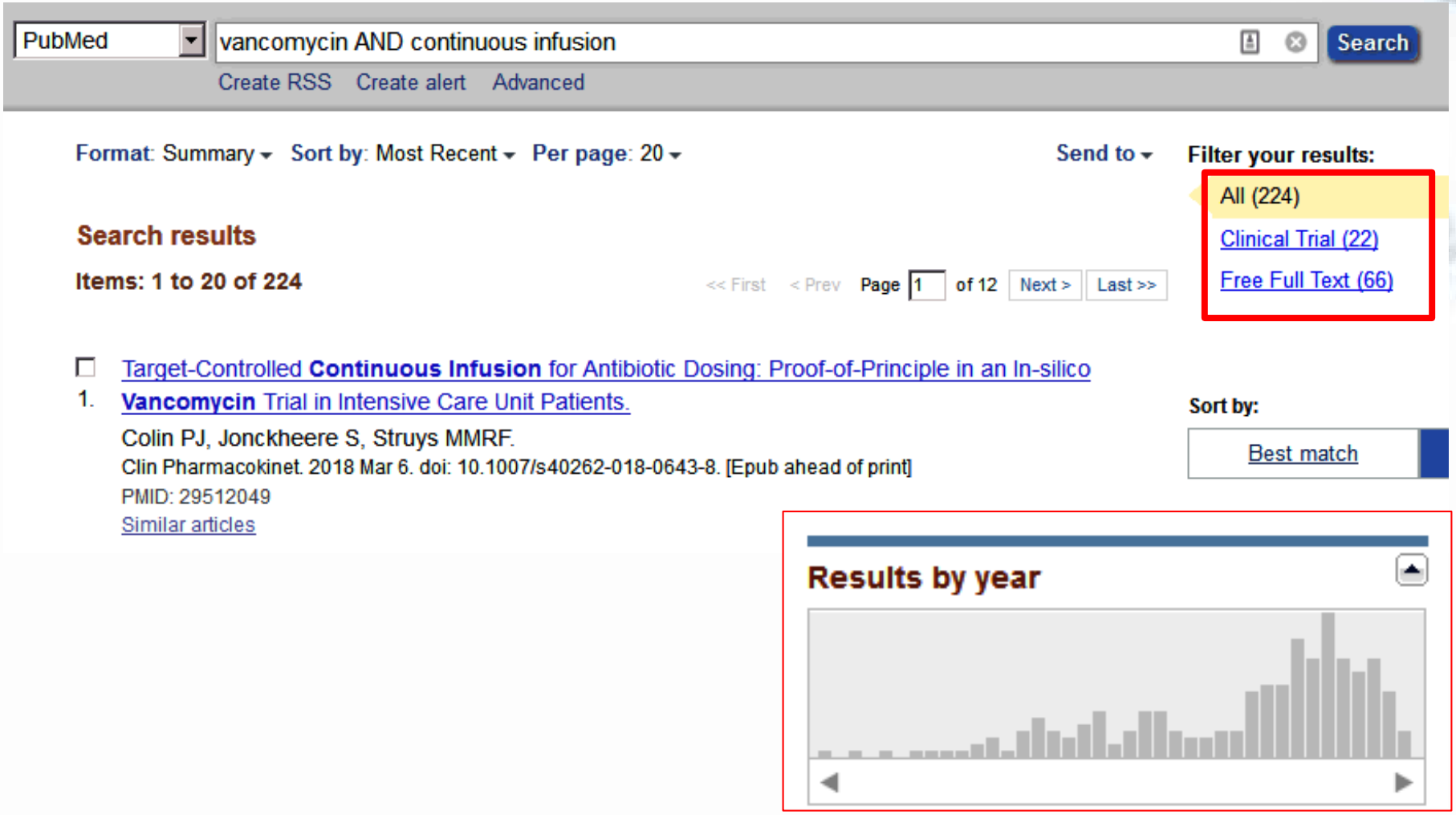
journal homepage: www.elsevier.com/locate/chromb

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]

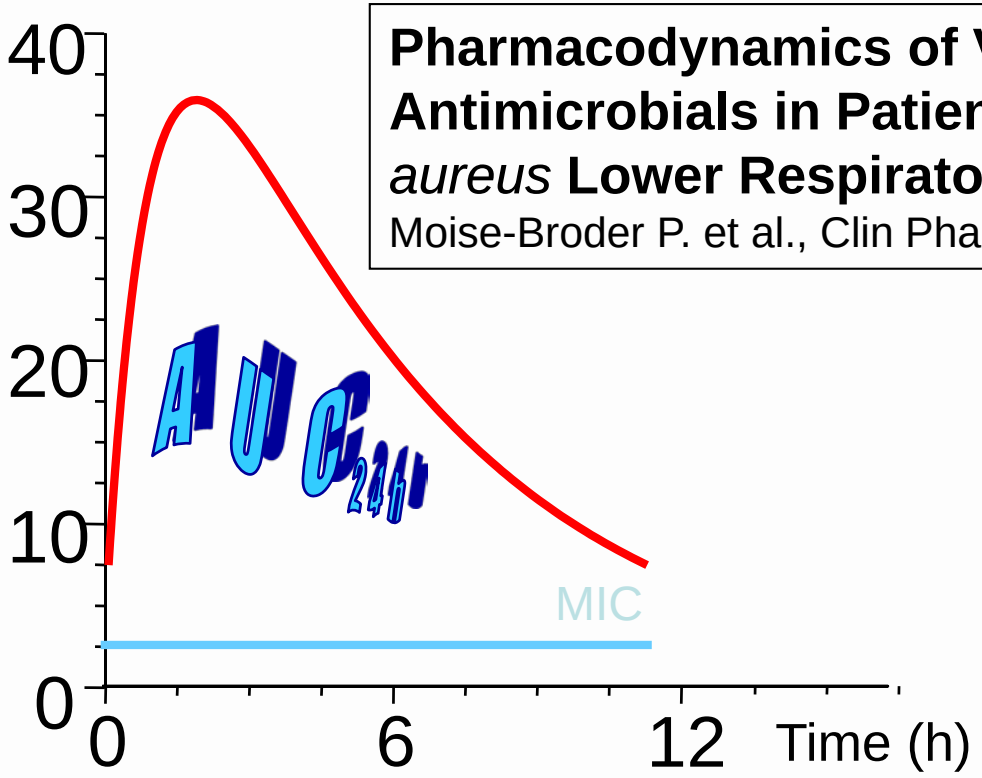
[a] Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan
[b] Department of Emergency and Disaster Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan

Continuous Infusion of vancomycin ?

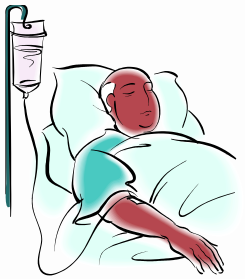


How to optimize vancomycin treatment: the classical way

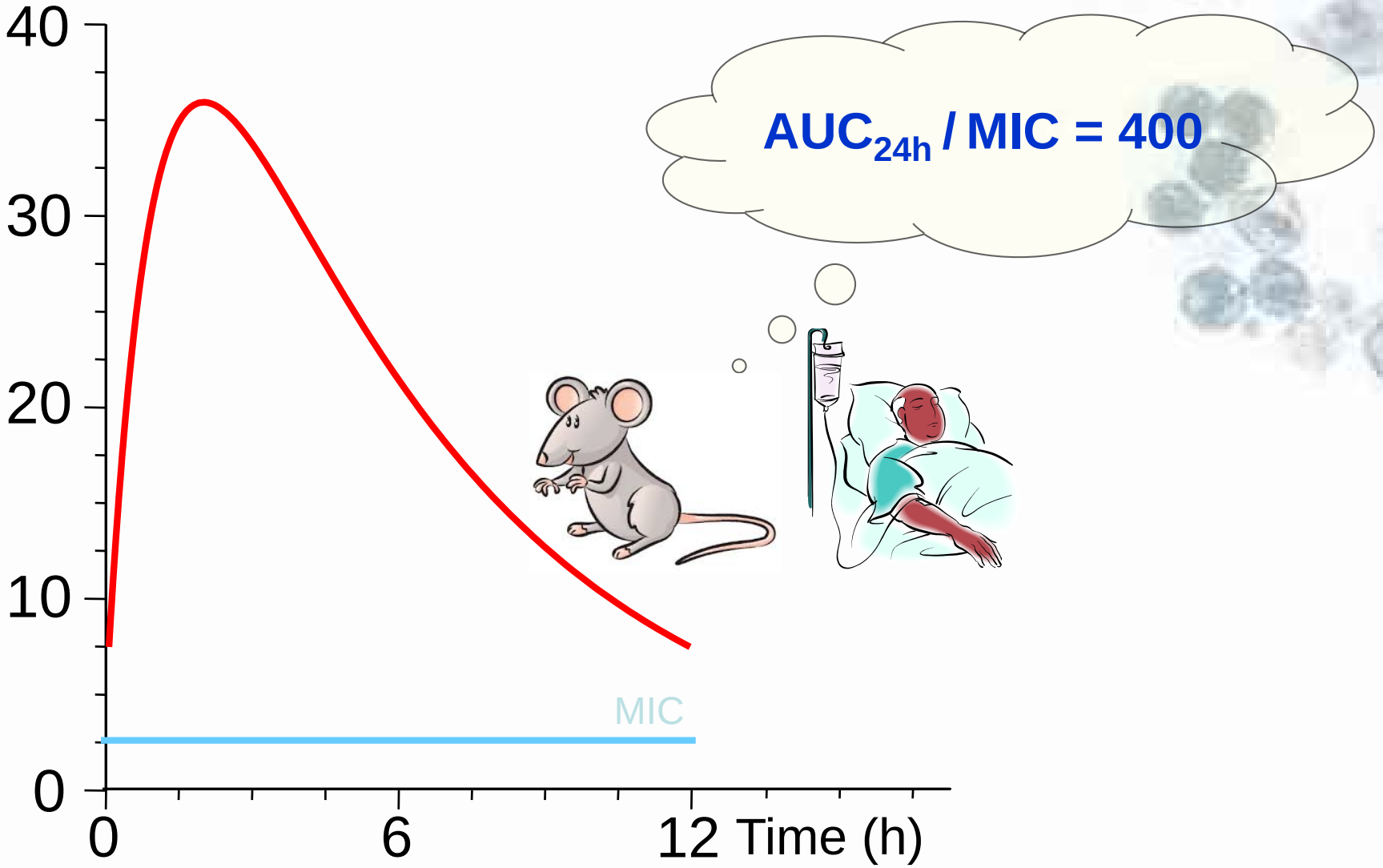
Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. Craig W. et al., Infect Dis Clin N Am 17 (2003)



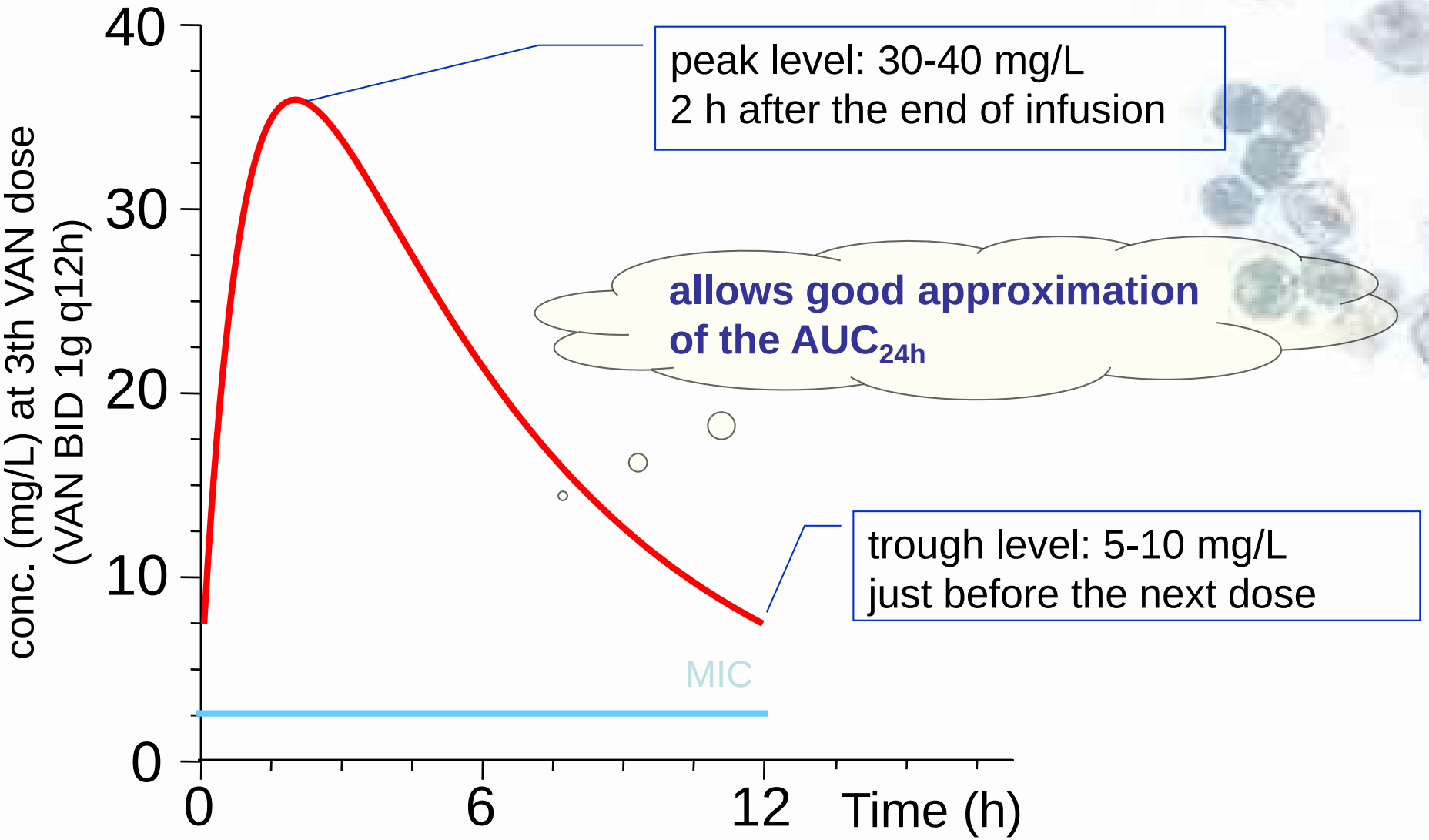
Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections
Moise-Broder P. et al., Clin Pharmacokinet 2004; 43 (13)



How to optimize vancomycin treatment: the classical way



Vancomycin TDM at CHU Mont-Godinne: how we did it…



But what about continuous infusion ?

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

Concentration

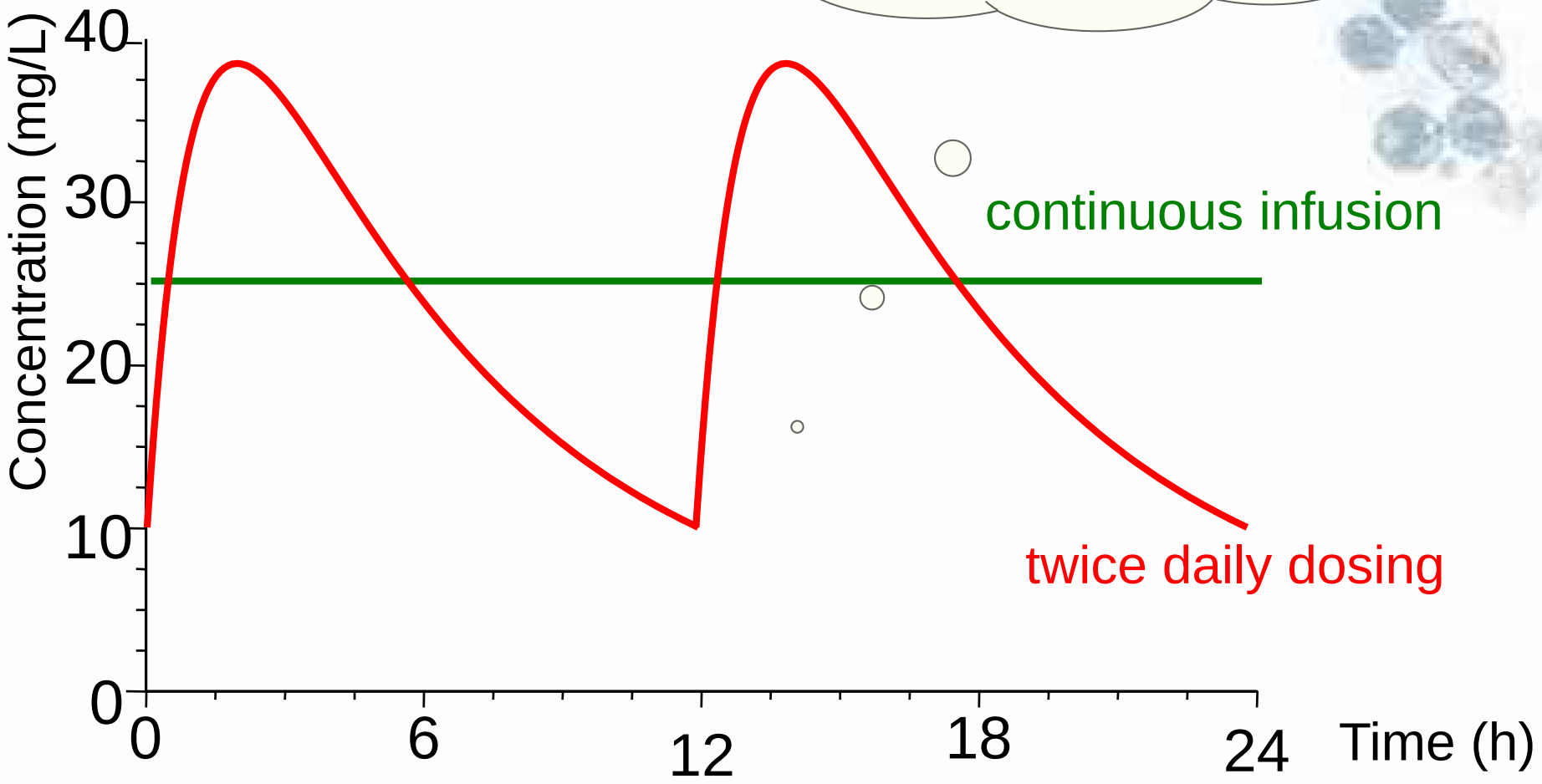
continuous infusion

Time (h)

0 6 12 18 24

TDM of vancomycin by continuous infusion

AUC_{24h} /MIC independent of the mode of administration



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

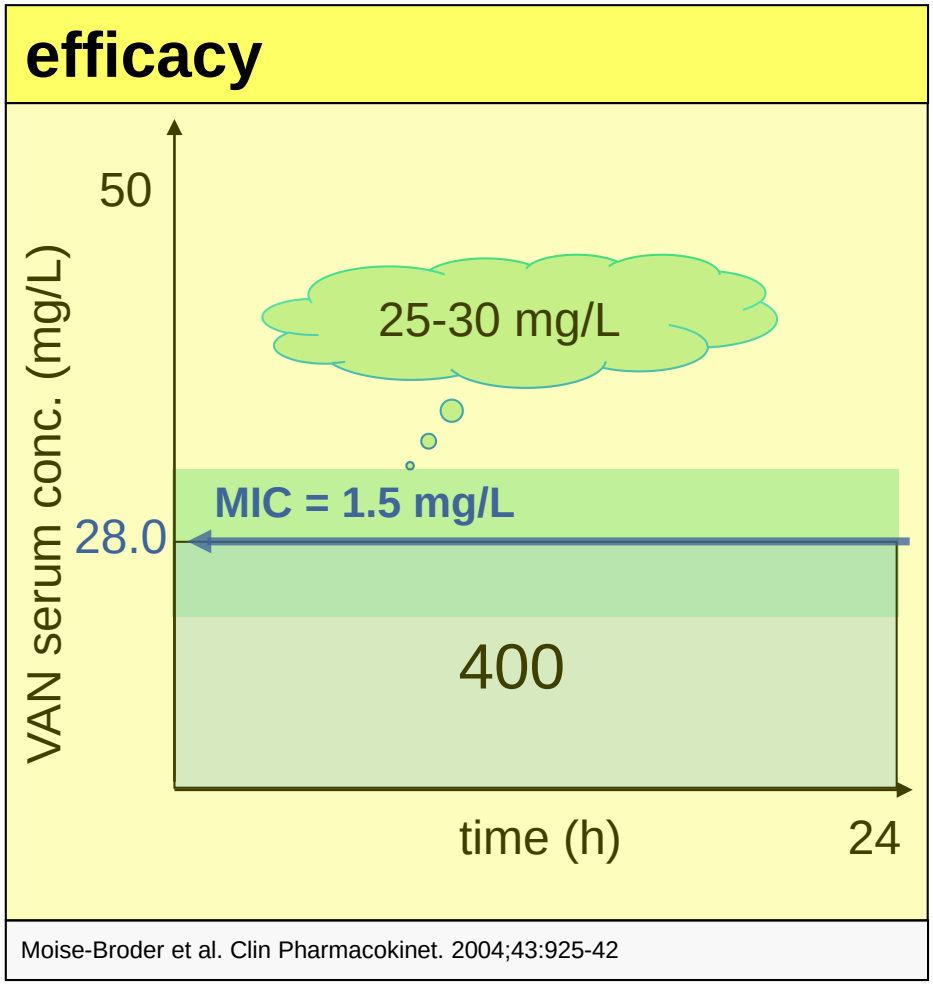
Int J Antimicrob Agents. 2013 May;41(5):439-46

Vancomycin CI: which serum concentration should we target?

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

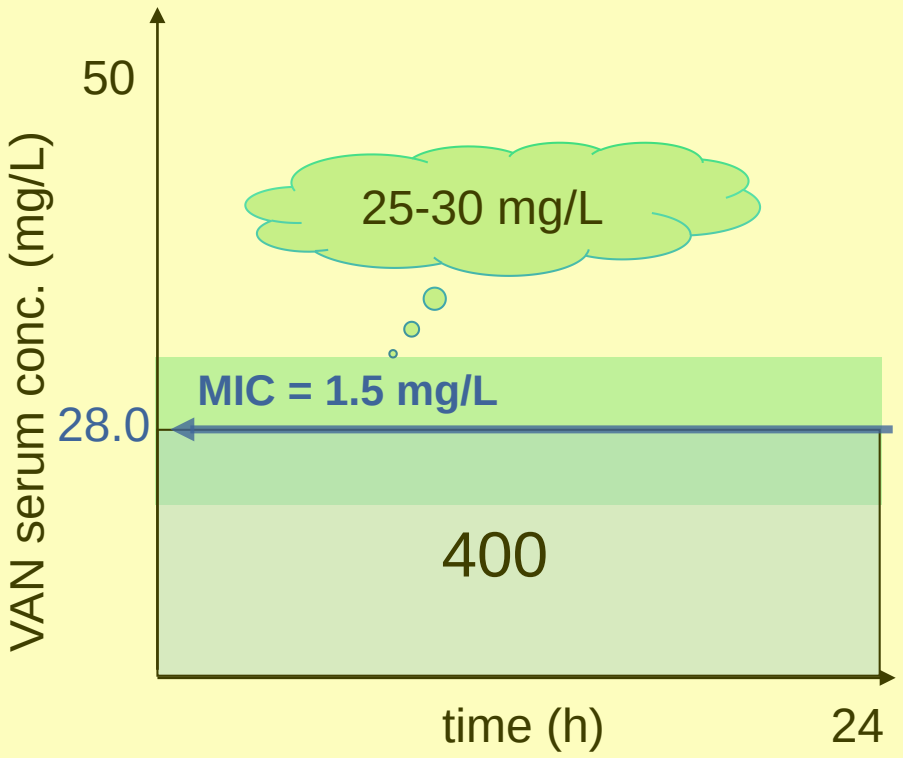
Vancomycin CI: which serum concentration should we target?



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

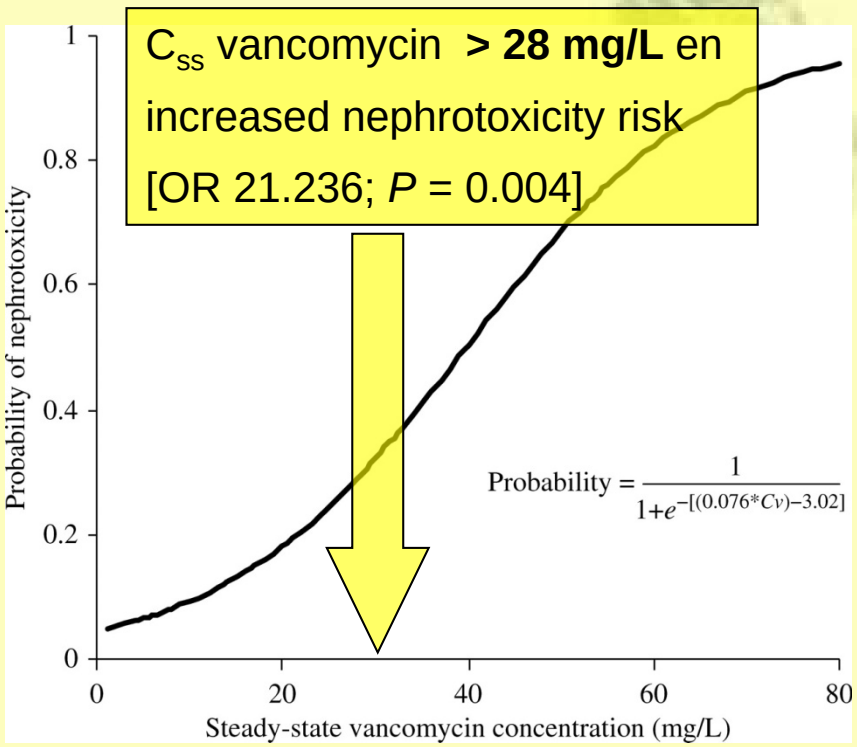
Vancomycin CI: which serum concentration should we target?

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 *

Target serum concentration

$C_t = D_l / Vd$

volume of distribution

loading dose

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 **clearance** (L/h) x **Css**

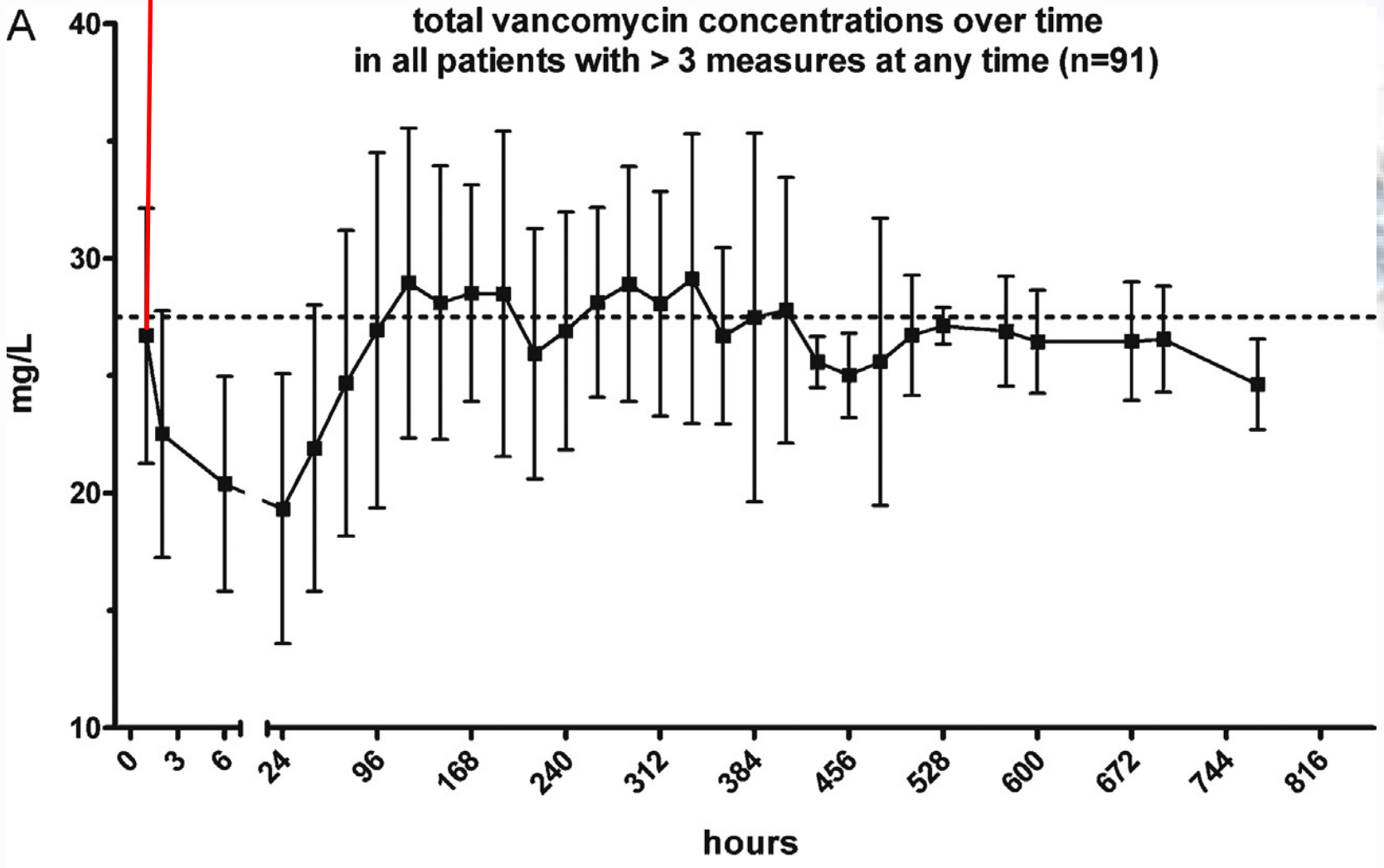
clearance of vancomycin = 0.65 calculated creatinine clearance (Cockroft-Gault)

daily dose = 2754 mg = 24 x (**0.65 x 6 L/h**) x **27.5 mg/L**

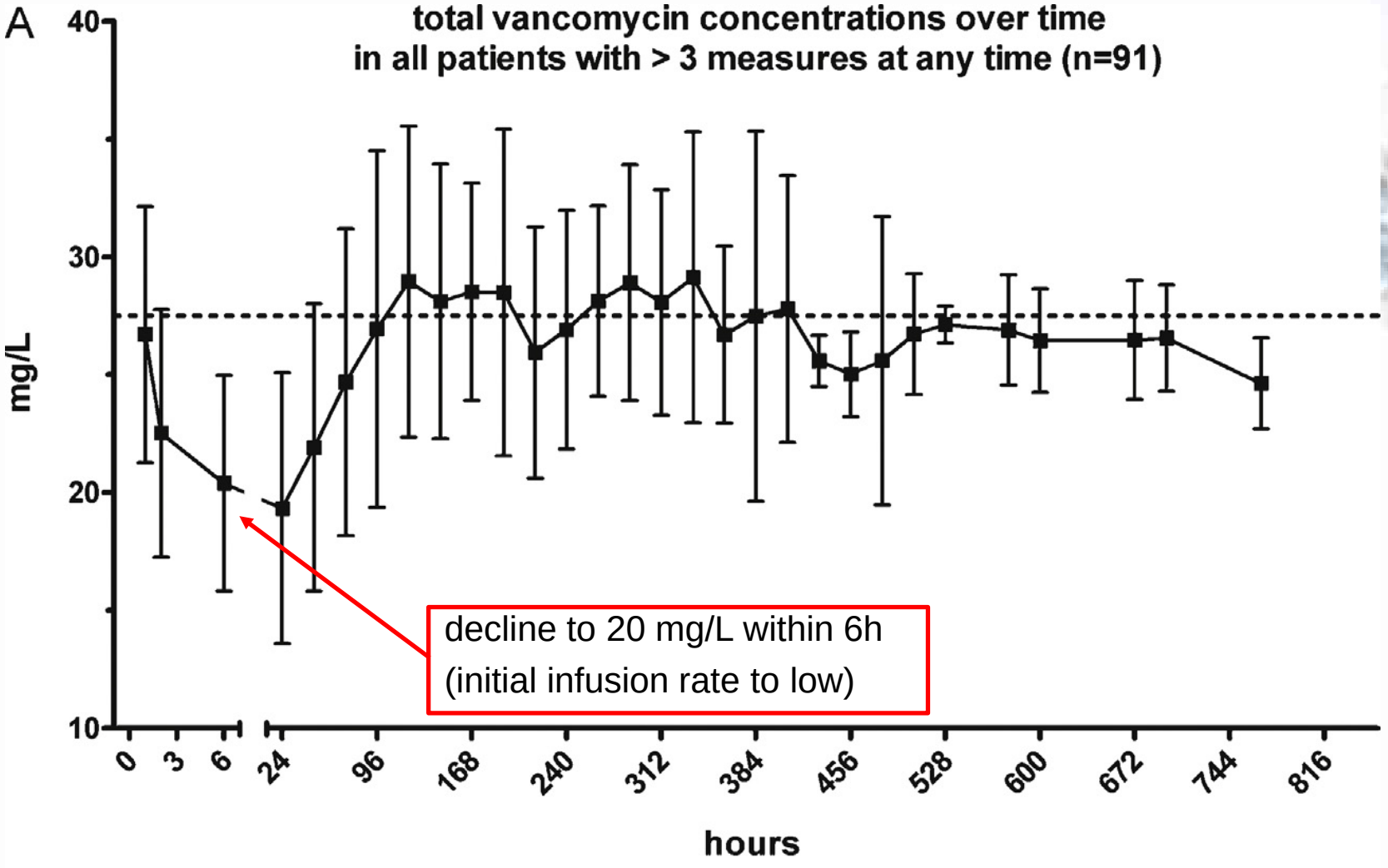
* assuming linear pharmacokinetics

Total vancomycin serum concentrations

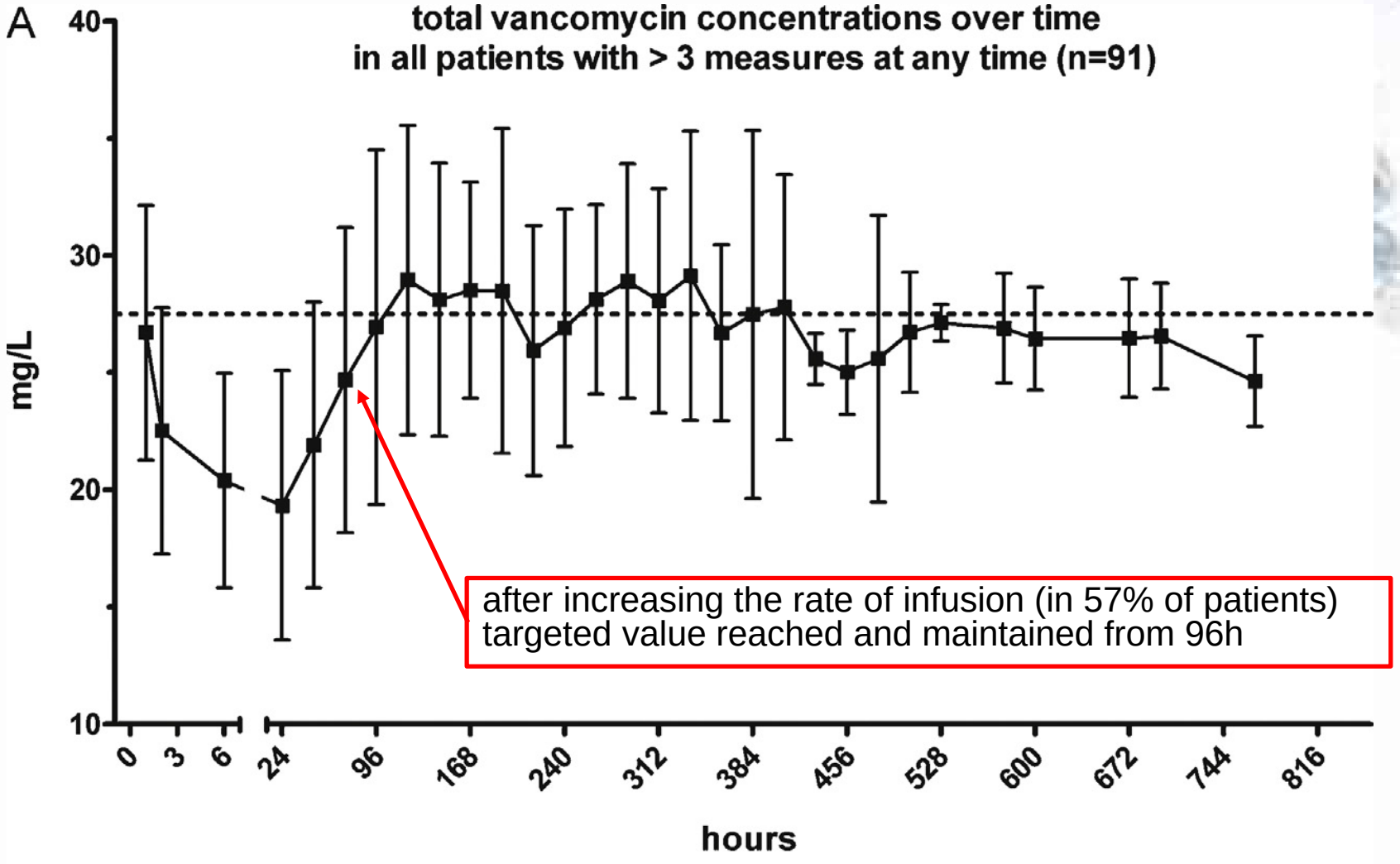
target concentration reached at time 0 h



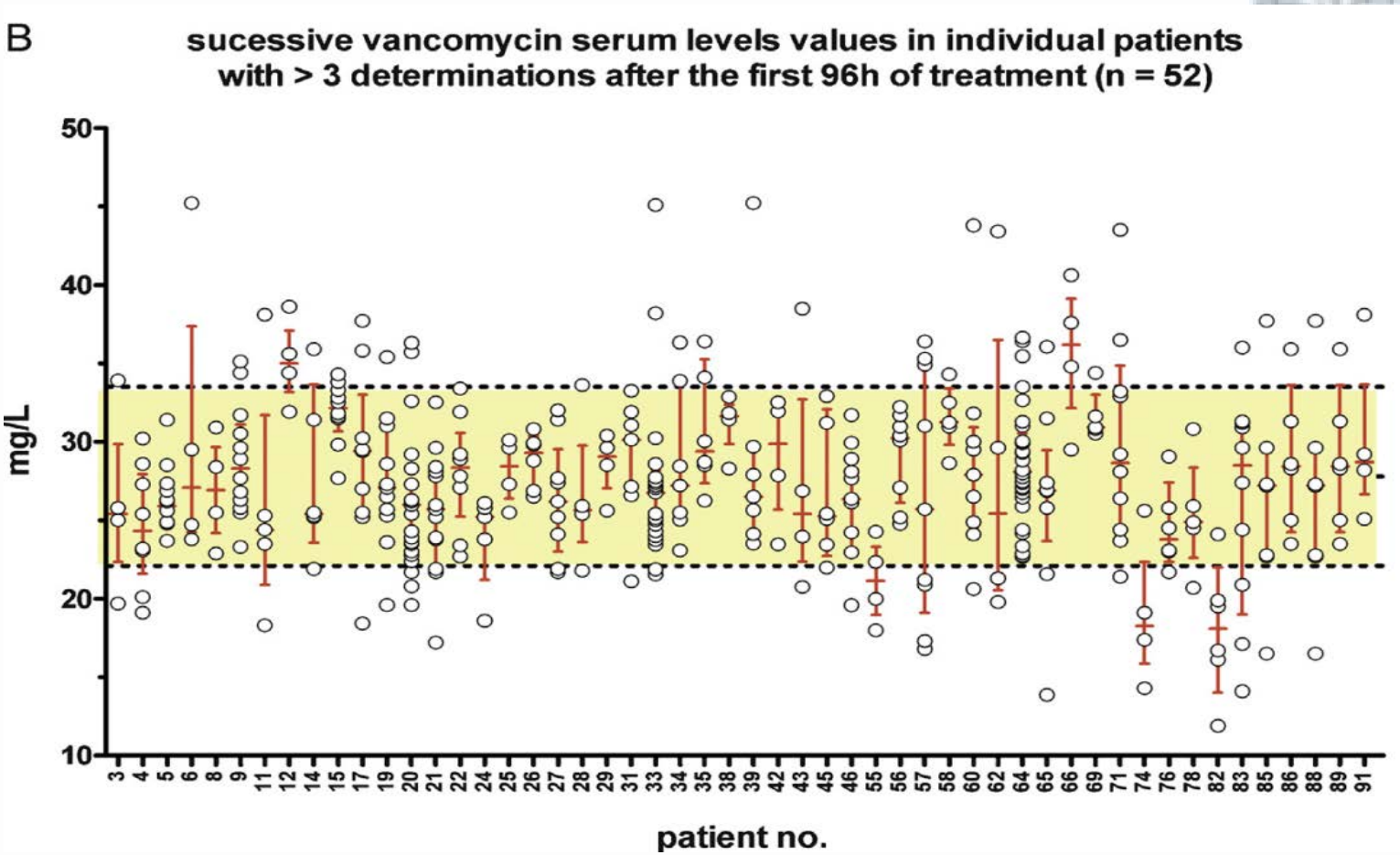
Total vancomycin serum concentrations



Total vancomycin serum concentrations



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

Pros / Cons of continuous infusion

(beta-lactams / vancomycine)

- A more rational way of administering beta-lactams (and also applicable to other antibiotics for which the impact of concentration [once above x-fold the MIC] is low)
- Can be easier to use in hospital setting
- "Monitoring made easy" and more reliable *
- Can help containing costs *

* not addressed in this talk, but ask questions…

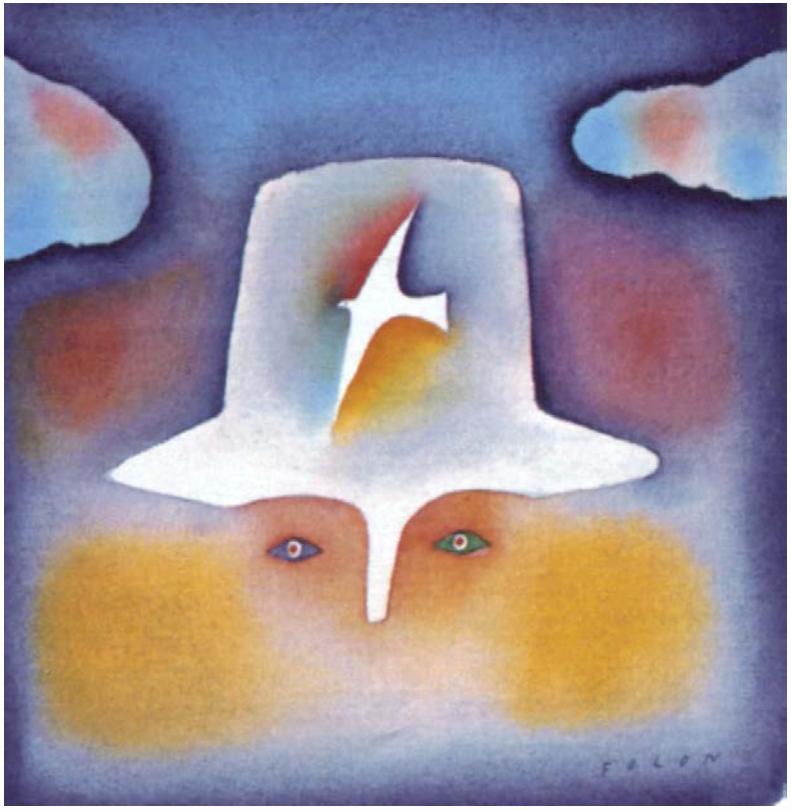
Pros / Cons of continuous infusion

(beta-lactams / vancomycine)

- The stability of each beta-lactam MUST be critically assessed under the conditions of practical use…
- Compatibility issues may make things quite complex unless a dedicated line is used
- use of motor-operated pumps (or pumps with similar reliability) is probably essential *
- High serum levels maintained for prolonged periods may be associated with toxicities (for vancomycine, levels > 28 mg/L have been associated with renal toxicity; for beta-lactams, levles > 80 mg/L have been associated with convulsions [cefepime]) *

* not addressed in this talk, but ask questions…

β- lactams and vancomycin continuous infusion



A BRILLIANT IDEA….

But do not forget the problems…

Our experience with 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 β-lactams and vancomycin usage in the absence of pharmacokinetic services and may improve the quality of these services if available

Perspectives

- application to other area's of pharmacotherapy?
  - from a 'quality of care' perspective:
    - factors underlying inappropriateness identified in other area's of drug therapy
    - intervention proved positive impact on quality of administration and TDM
  - from a PK/PD perspective:
    - special patient populations (hyperclearance, morbidly obese patients, patients infected with a certain type of organism…)
    - Other AUC or time-dependent drugs (e.g., antifungals…)
    - 'On line' monitoring
  - from a clinical/hospital pharmacist perspective:
    - standardization of drug preparation/administration
    - opportunities for clinical pharmacy services (TDM recommendations, drug incompatibilities…)
  - from a hospital administrator perspective
    - cost-effective?

Thank you for your attention!!

The slides are available for download from http://www.facm.ucl.ac.be → Lectures