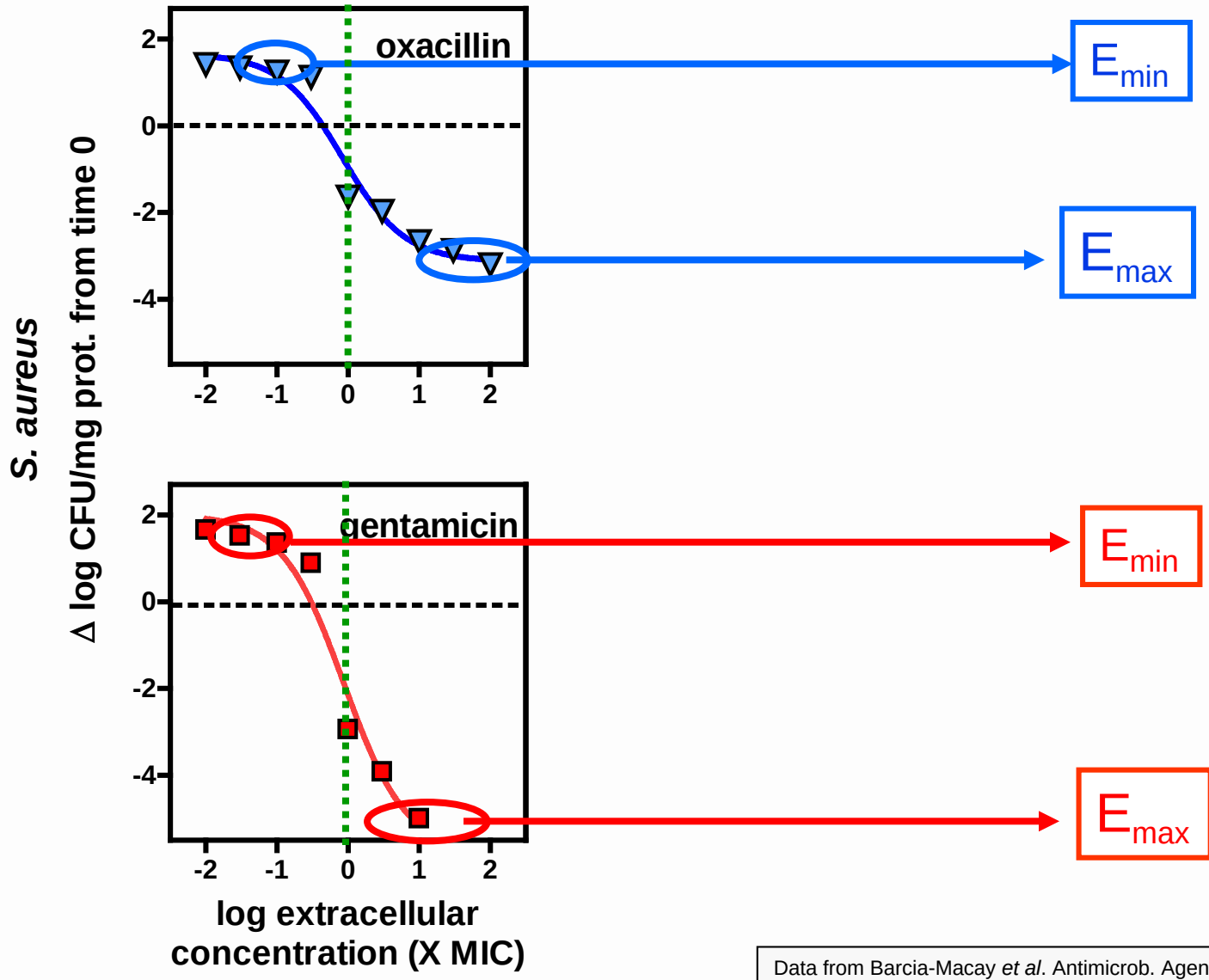
Beta-lactams …in a nutshell…

- 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)

What is the relationship between MIC and effect?



E_{min}

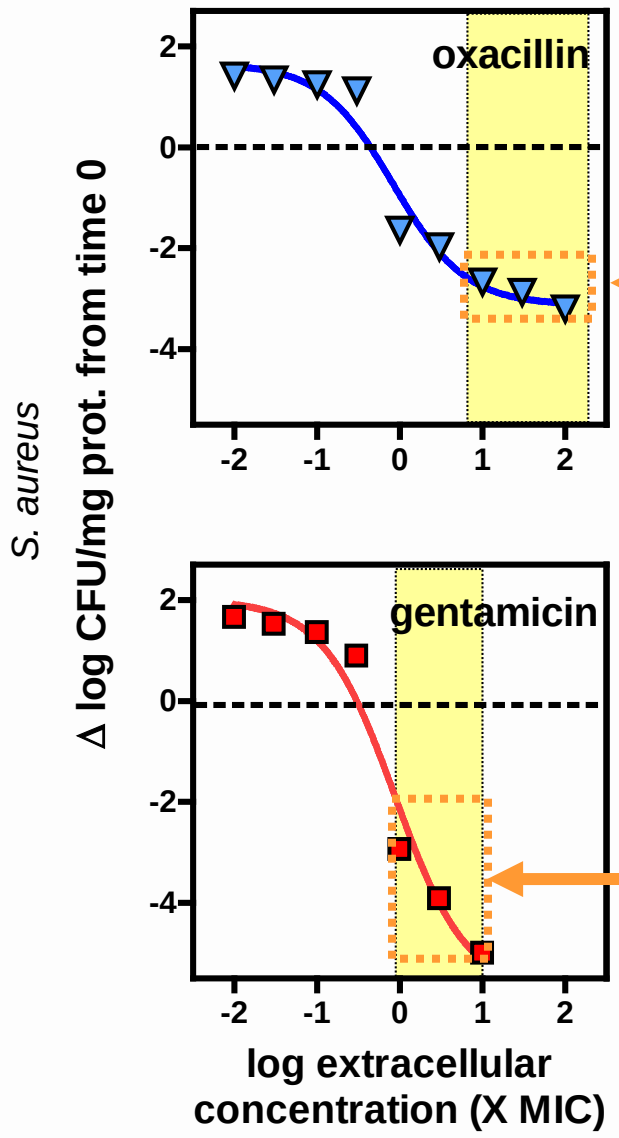
E_{max}

E_{min}

E_{max}

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

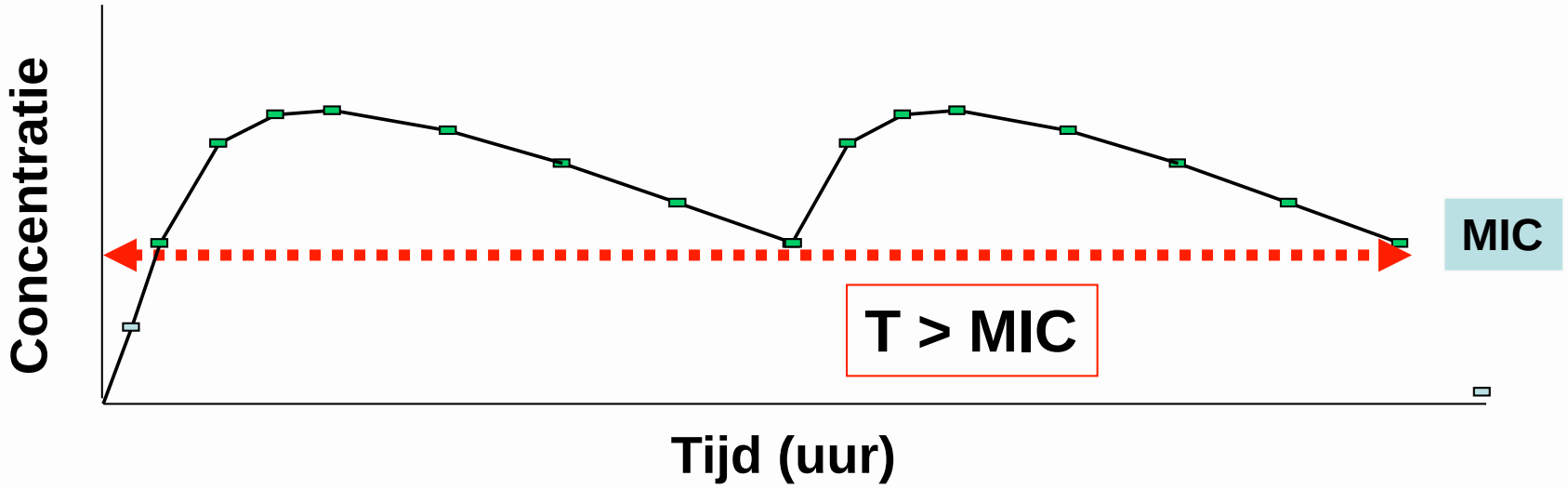
C_{min}–C_{max}

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

As a result ...

- Time above MIC becomes the main efficacy-driving parameter …
- β-lactams prefer to be administered several times a day rather once-daily



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

Continuous infusion …

Infusion will push music to its limits

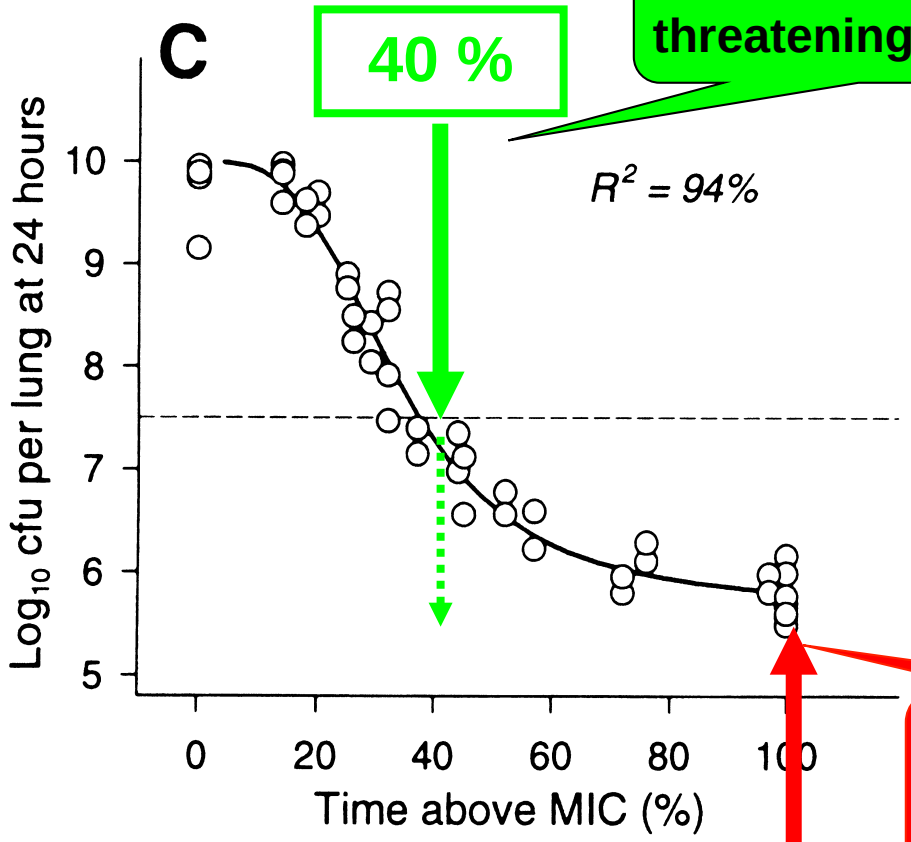
- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

- **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 ?

Continuous infusion with β-lactams: PK/PD aspects

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

How long above the MIC in discontinous administration



How much above MIC ?

Original data from W. Craig *et al.* with ticarcilline

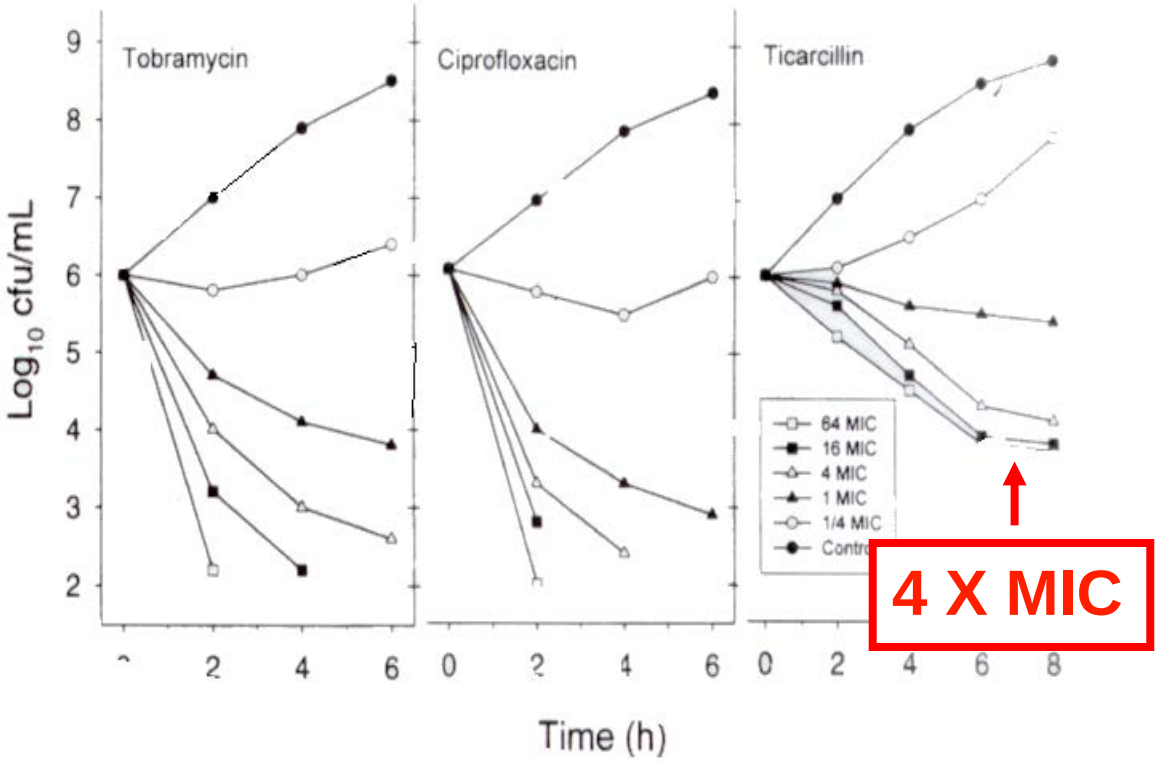
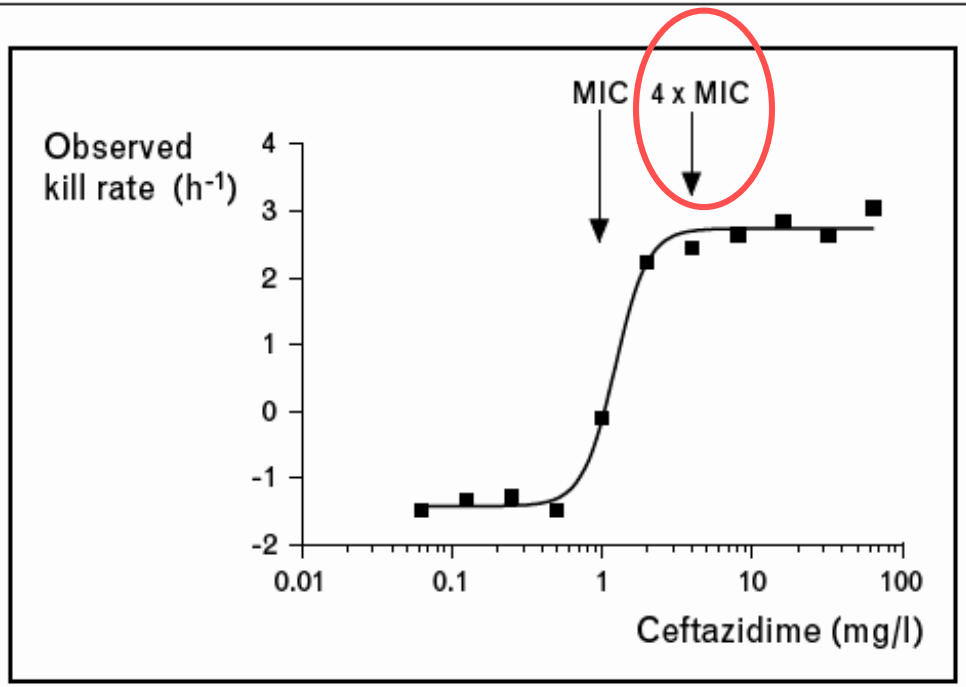


Figure 2. Time-kill curves for *Pseudomonas aeruginosa* ATCC (American Type Culture Collection) 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one-fourth to 64 times the MIC. Reprinted with permission from *Scandinavian Journal of Infectious Diseases* [3].

More recent confirmation for ceftazidime

How much ?

Figure 2 Relationship between concentration of ceftazidime and kill rate

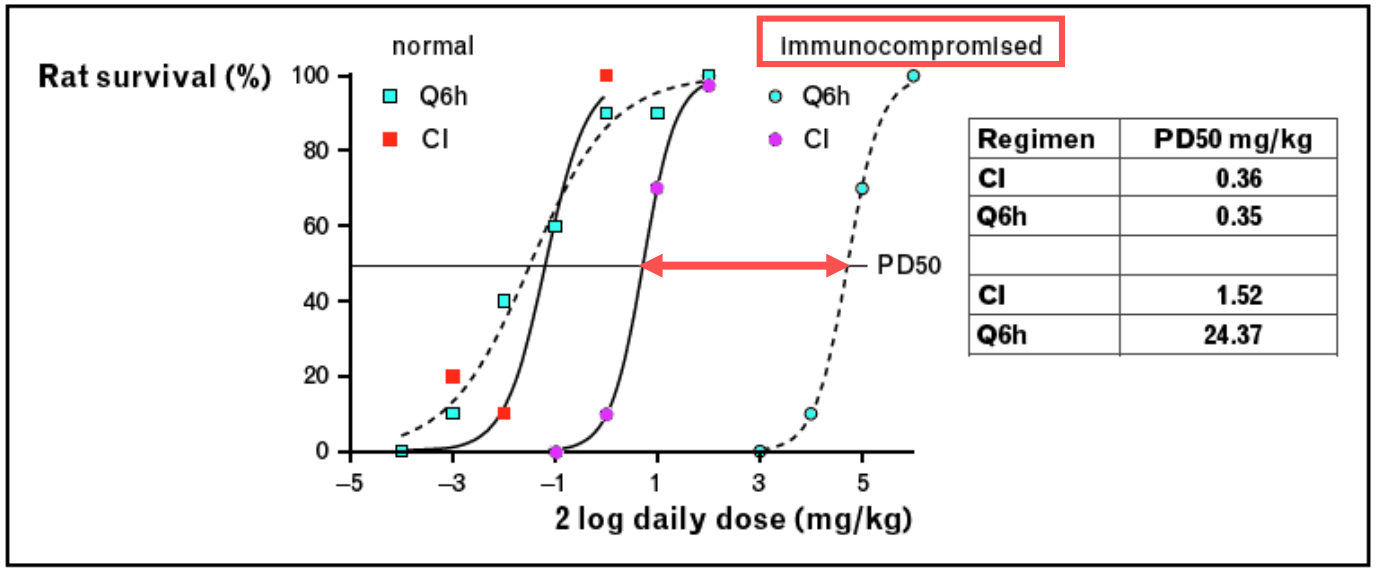


The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration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

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

The importance of the concentration/MIC ratio is dependent upon the immune status (animal data)

Figure 3 Relationship between daily dose and mortality in a pulmonary infection models in rats



Regimen	PD50 mg/kg
CI	0.36
Q6h	0.35
CI	1.52
Q6h	24.37

The daily dose needed to protect 50% of the animals from mortality (PD50) for two different dosing regimens in immunocompetent as well as immunodeficient animals is also displayed. Efficacy of continuous infusion (CI) is higher than intermittent infusion in immunodeficient animals. Q6h, every 6 h.

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

Second set of conclusions and discussions

- ***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
  - ➔ 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 !

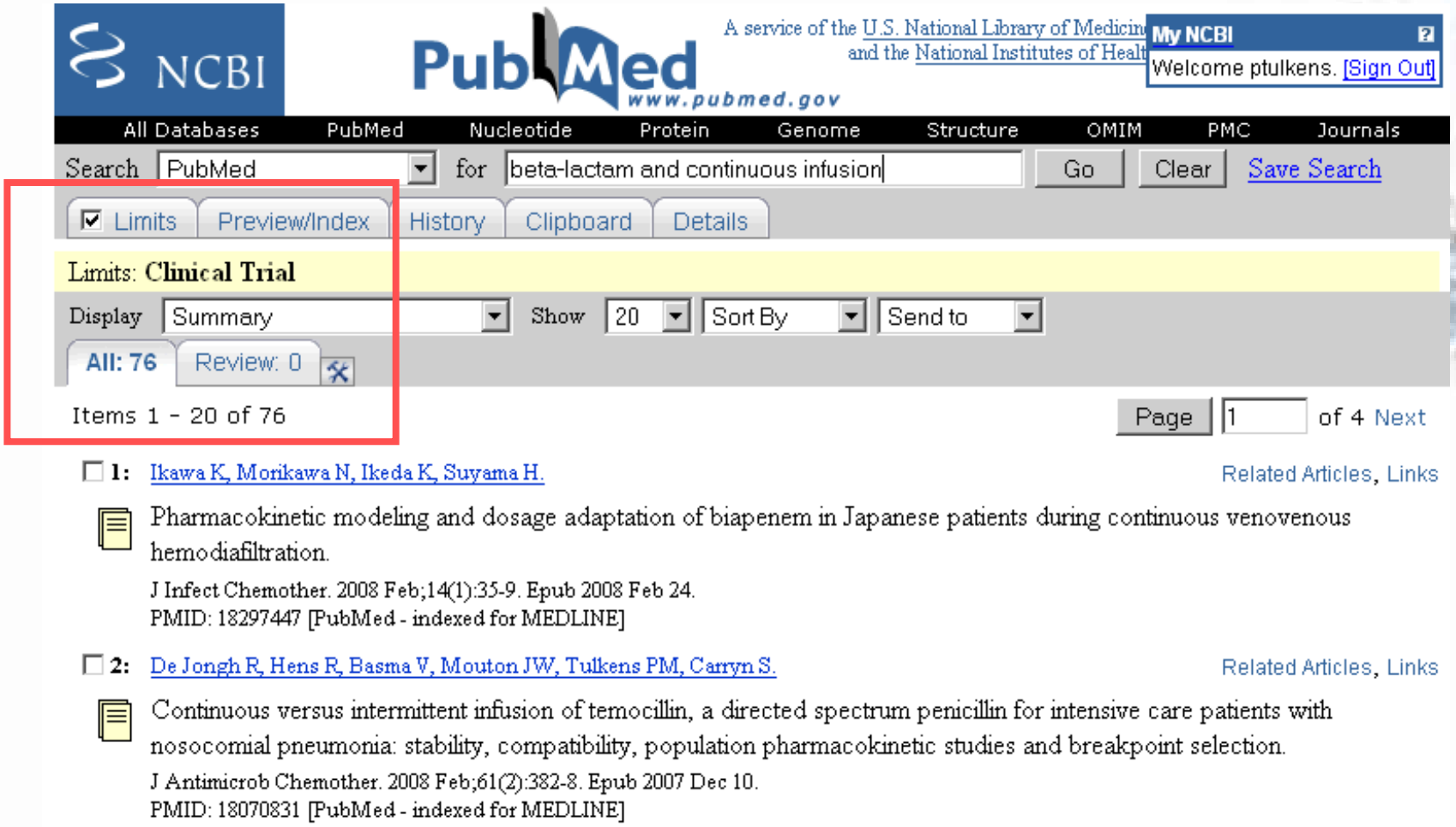
Continuous infusion …

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 ?

Continuous infusion of β-lactams in clinical practice



Continuous infusion of β-lactams in clinical practice: literature review *

drug	no. of studies	main indications	main conclusions
1. controlled studies with clinical end-point(s)			
piperacillin	5 [a]	cIAI / VAP / septicaemia / various infections	equivalence but superiority if ↗ MIC
ceftazidime	2 [b]	VAP / pneumonia/ melioidosis/ cystic fibrosis	superiority mainly with resistant isolates
cefriaxone	1 [c]	sepsis	superiority
meropenem	1 [d]	VAP	superiority

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

a Grant 2002; Buck 2005; Lau 2006; Rafati 2006; Lorente 2009

b Rappaz 2000; Angus 2000; Nicolau 2001; Lorente 2007; Hubert 2009

d Lorente 2006 (Note: meropenem is unstable and may, therefore, not be recommended for continuous infusion without specific precautions)

Continuous infusion of β-lactams in clinical practice: literature review *

drug	no. of studies	main indications	main conclusions
2. non-controlled studies with clinical end-point(s)			
penicillin G	1 [a]	serious infections	favorable
oxacillin	1 [b]	burn wound cell.	faster cure
ampicillin	2 [c]	septicemia (infants)	equivalence or superiority (practical)
ceftazidime	3 [d]	neutropenic fever and infections	favorable (2) unfavorable (1)

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

[a] Walton 2007

[b] Schuster 2009

[c] Colding 1982; Colding 1982

[d] Daenen 1995; Vinks 1997; Marshall 2000

Continuous infusion of β-lactams in clinical practice: literature review *

drug	no. of studies	type of patients	main conclusions
3. PK/PD studies in humans (no clinical end-point)			
ampicillin	1 [a]	colorectal surgery	equivalence
piperacillin	1 [b]	VAP.	favorable
temocillin	1 [c]	non *Ps*. Gram (-)	pharmacokinetic super.
ceftazidime	5 [d]	ICU, cIAI, neutropenia, VAP	pharmacokinet. super.
cefepime	4 [e]	nosocom. pneum. and severe Gram(-) infect.	equivalence or superiority (practical)
imipenem	1 [f]	surgery (various indic.)	equivalence
meropenem	3 [g]	neutropenic fever and infections	favorable (2) – unfavorable (1)

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

[a] Martin 1998 -- [b] Boselli 2008 -- [c] De Jongh, 2008

[d] Lipman 1999; Buyck 2002; Dalle 2002; Cousson 2005; Mariat 2006

[e] Georges 1999; Jaruratanasirikul 2002; Boselli 2003; Roos 2006 (Note: cefepime solutions develop color upon storage and may not be suitable for human use)

[f] Sakka 2007; [g] Thalhammer 1999; Langgartner 2008; Roberts 2009 (Note:both imipenem and meropenem are unstable and may, therefore, not be recommended for continuous infusion without special precautions)

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*
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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

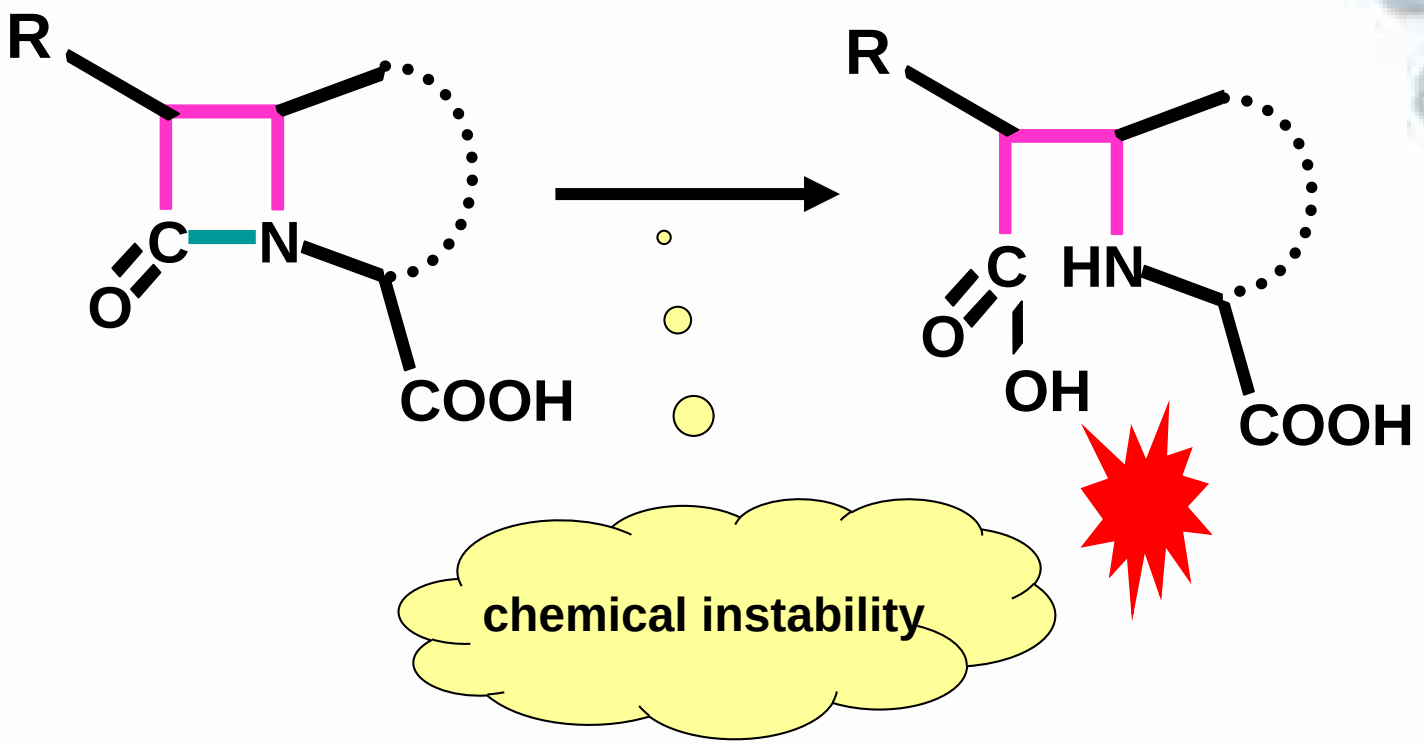
Continuous infusion …

Infusion will push music to its limits

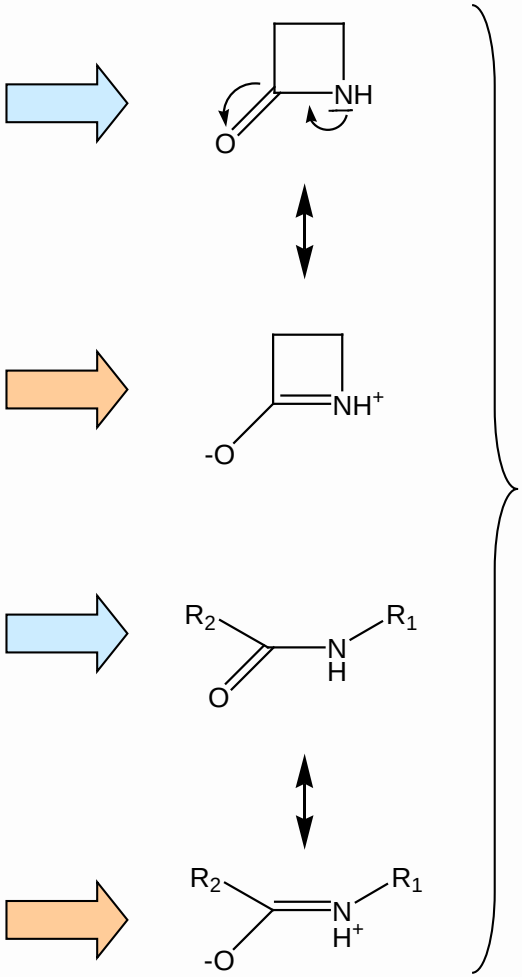
- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

- 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

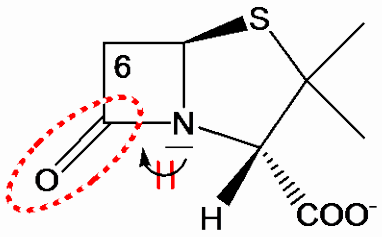


Why are β-lactams antibiotics **chemically** unstable ?

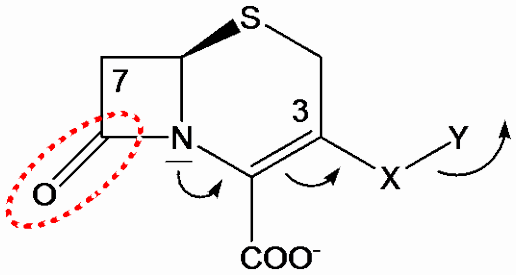


a β-lactam *per se* and without substituents is not necessarily unstable because it exists under **resonant forms** similar to what takes place for amides (which are very stable…)

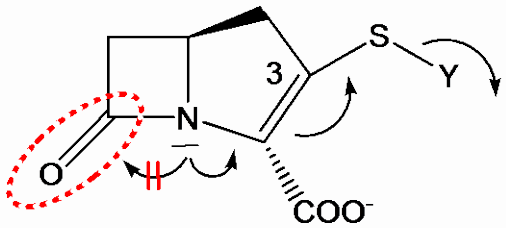
The problem is the substitutions…necessary for activity *



penams: the fused 5-membered S-containing cycle prevents electron migration within the β-lactam ring, making the C=O a true ketone *



cephems: the 6-membered S-containing ring cannot to block electron migration, but its C3 side chain attracts electrons from the N atom, resulting also in the C=0 becoming a true ketone *

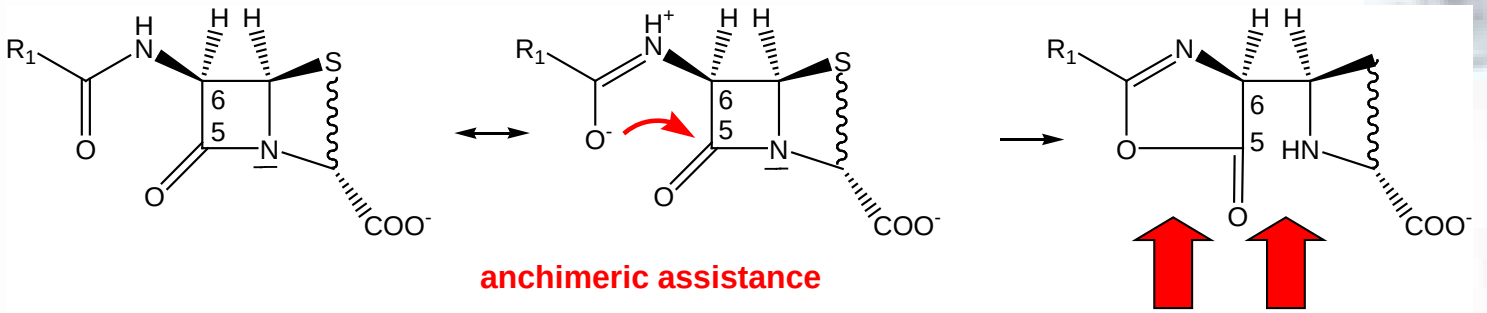


penems: combine the two above mechanisms, making the molecule very unstable

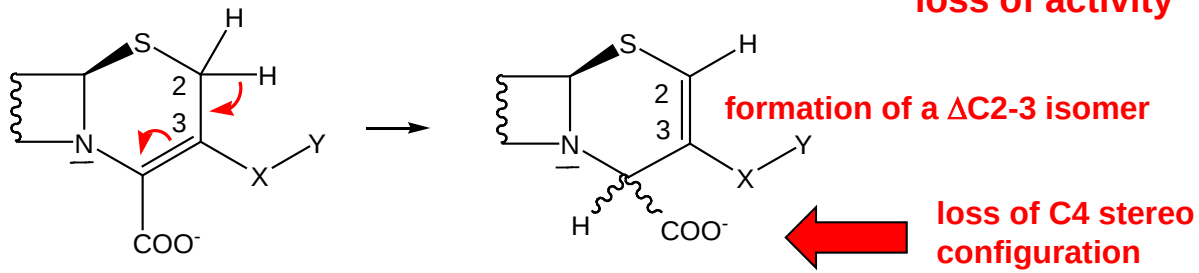
* essential for binding to the active serine in PBPs… and, therefore for activity

Mechanisms of chemical instability

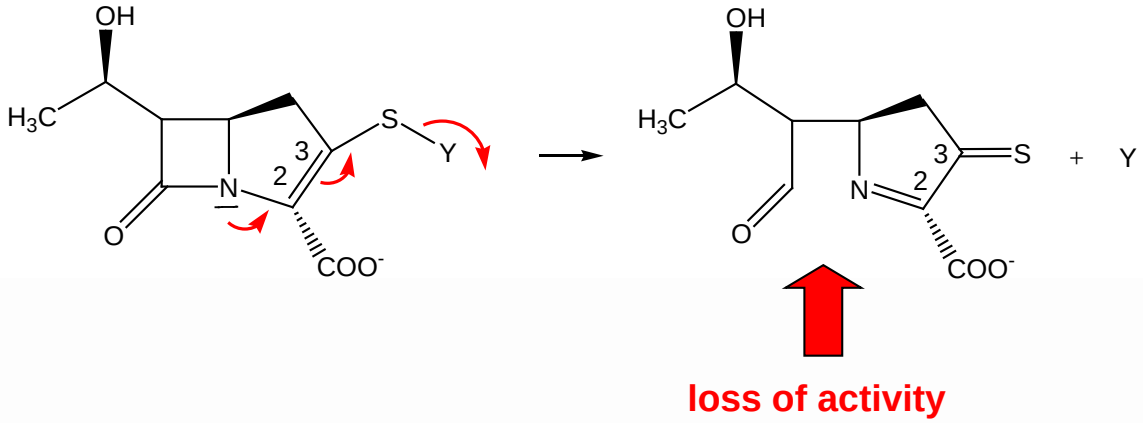
penams and cephems



additional mechanism for cephems



penems



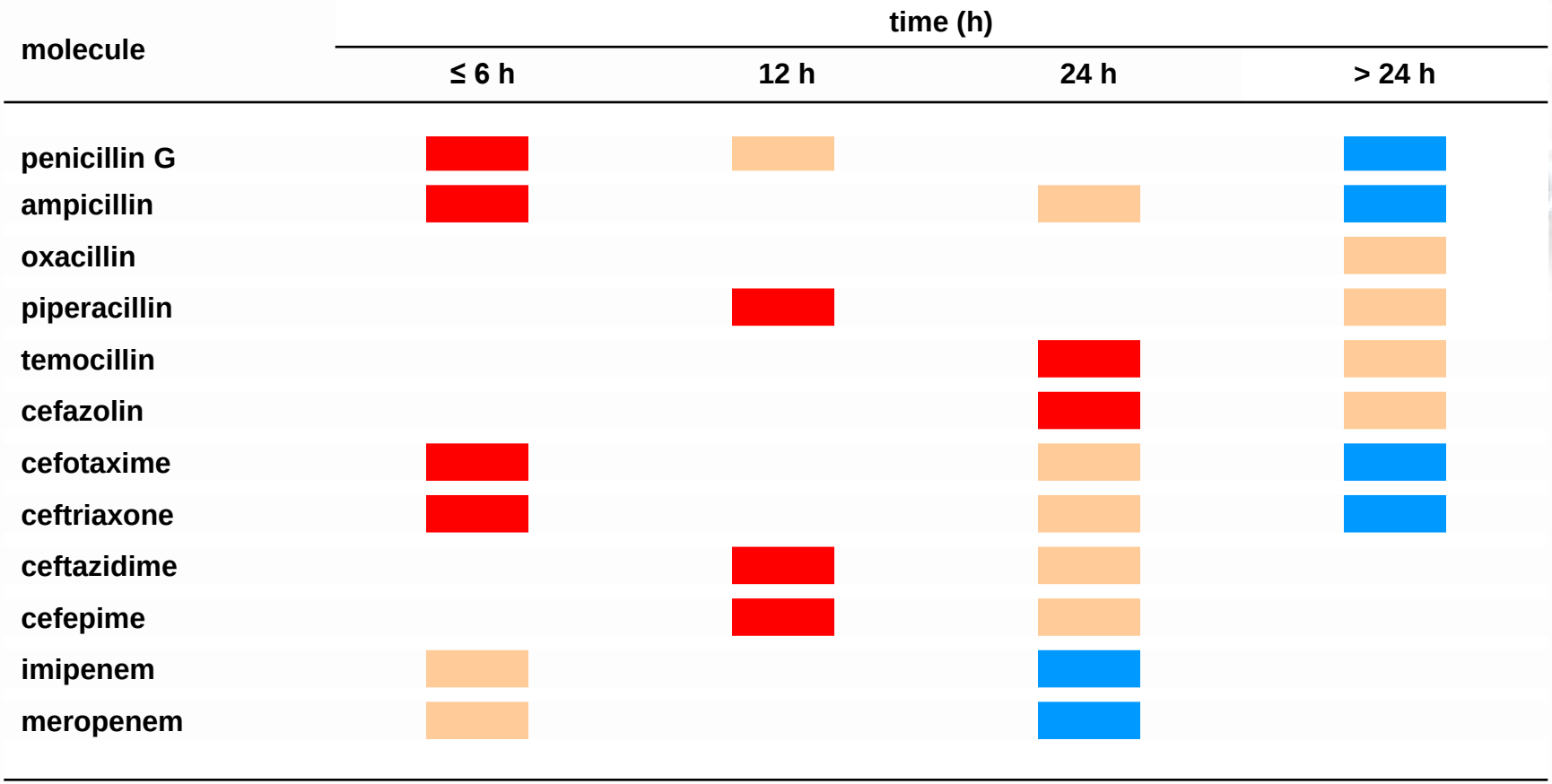
Can instability be modulated ?

- **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…

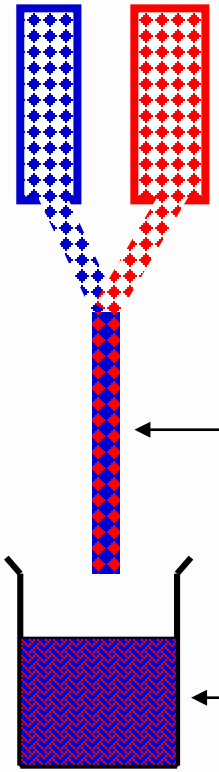
- **Definition: > 90% intact product (Pharmacopeia)**
- **Conditions: mimicking the total daily dose (commercial product) in 48 mL (motor operated syringe) water without pH adjustment and maintained at a fixed temperature (*)**
- **key:** **37°C** **25°C** **4°C**



* 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).

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

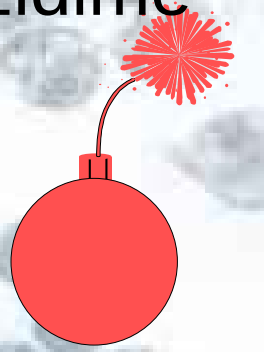
Drug compatibility studies: example for ceftazidime

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.

Is continuous infusion with β-lactams and other drugs possible ?

Each molecule must

be <u>specifically</u>

looked at …

* Data published for **ceftazidime** (AAC 2001;45:2643-7), **cefepime** (JAC 2003; 51:651-8) and **temocillin** (JAC 2008;61:382-8); also available for **vancomycine** (send me an e-mail)

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 ?

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)

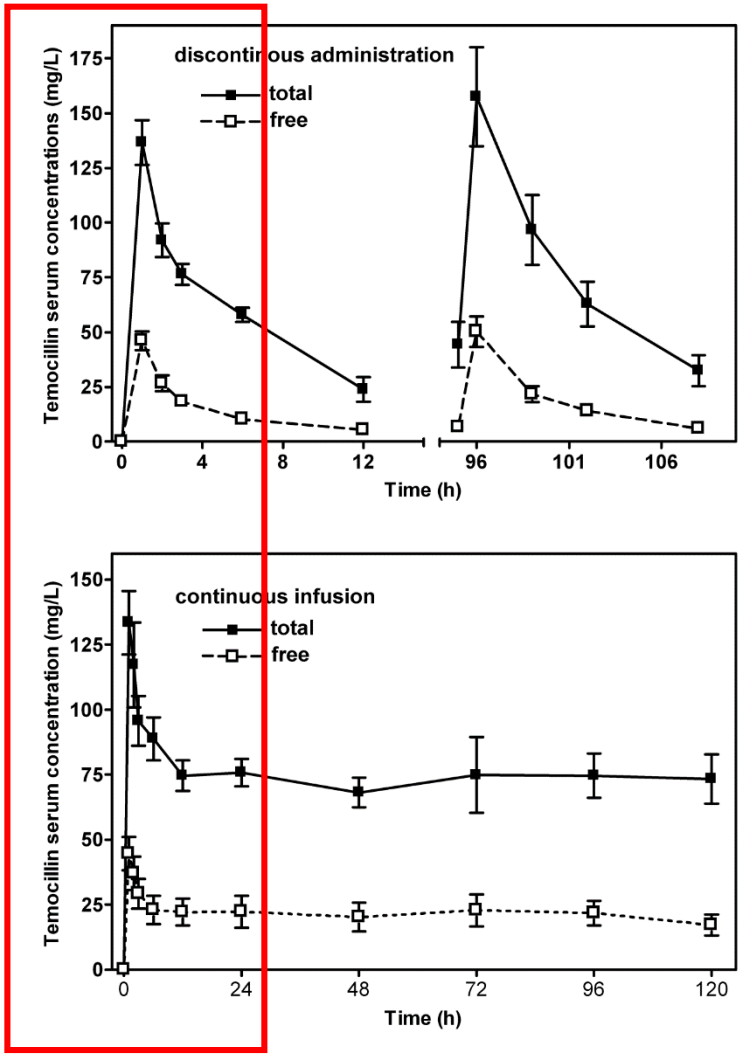
the loading dose is only dependent upon the volume of distribution and is directly influenced by the weight of the patient and his/her medical situation

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 *

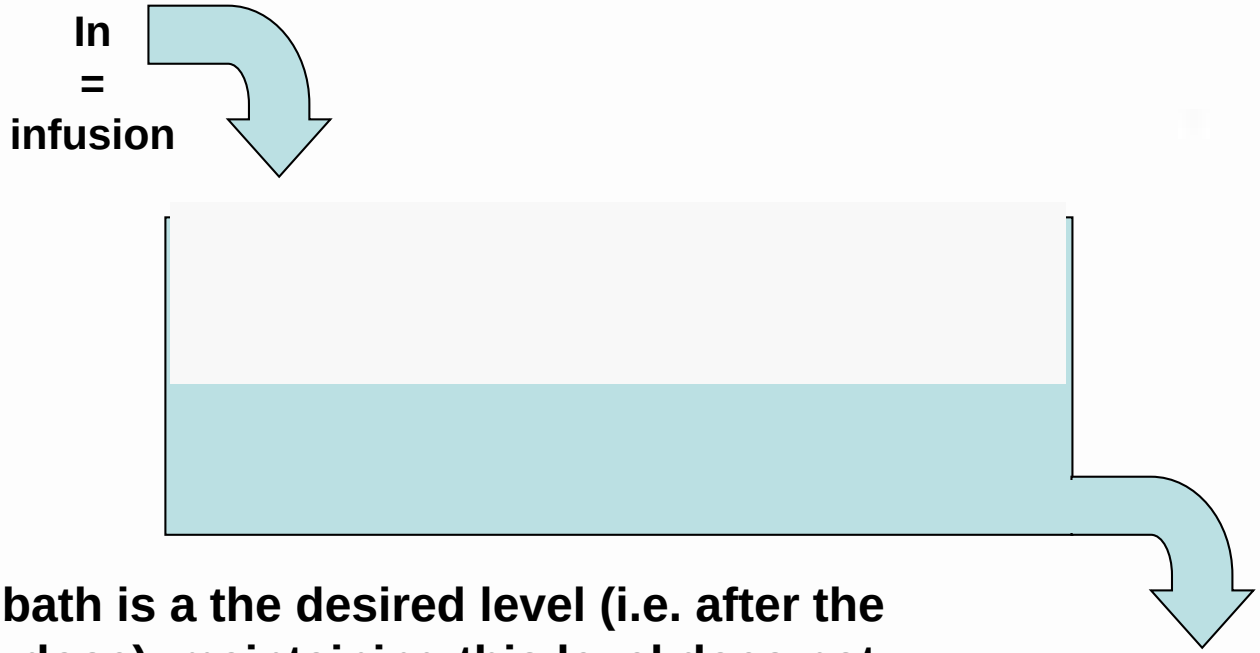
infusion rate

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 musts 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 of β-lactams: a practical example…

Journal of Antimicrobial Chemotherapy (2008) **61**, 382–388
doi:10.1093/jac/dkm467
Advance Access publication 10 December 2007

JAC

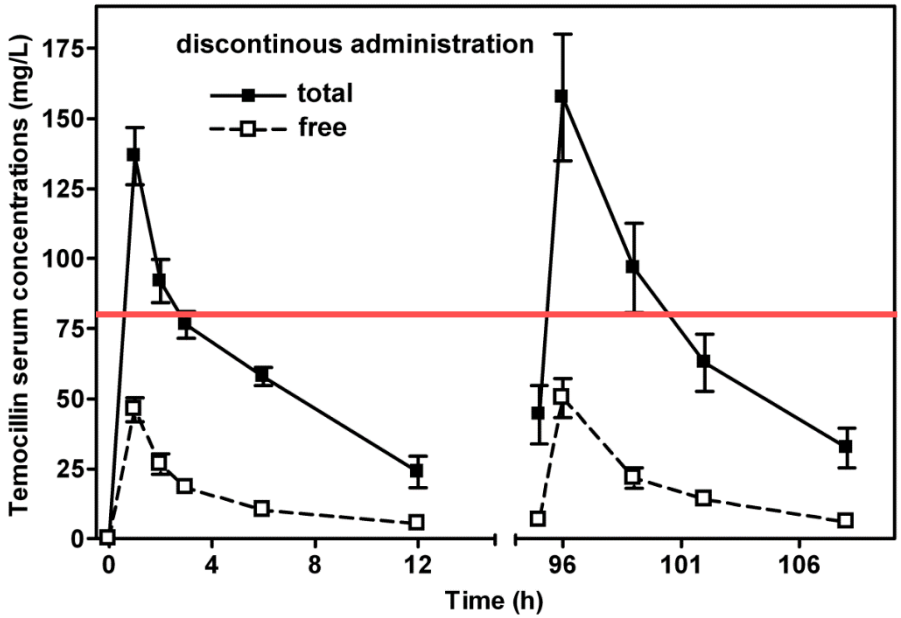
Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection

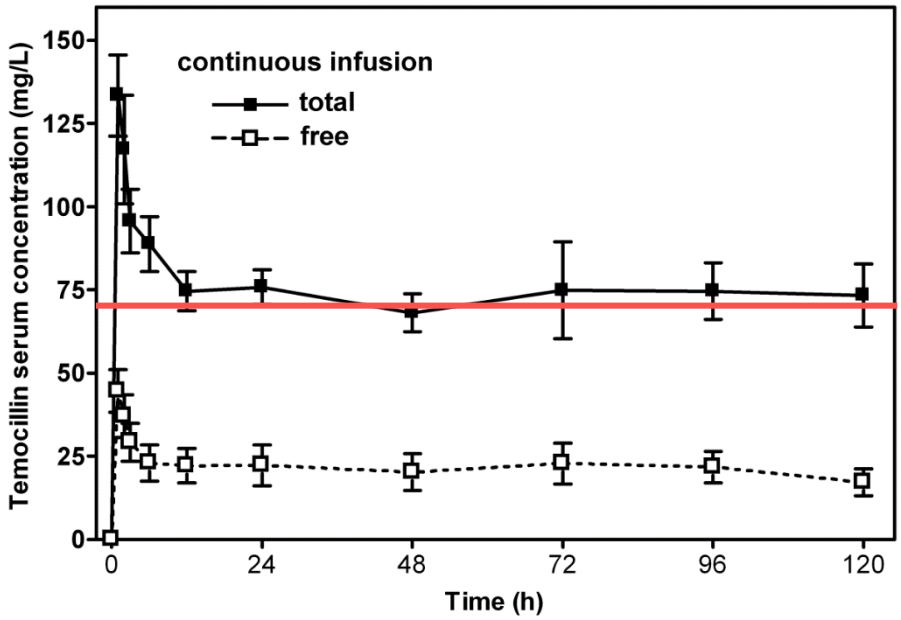
Raf De Jongh[1], Ria Hens[1], Violetta Basma[2], Johan W. Mouton[3], Paul M. Tulkens[2]* and Stéphane Carryn[2]

[1]Dienst Voor Intensieve Zorgen, Ziekenhuis Oost-Limburg, B-3600 Genk, Belgium; [2]Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, B-1200 Bruxelles, Belgium; [3]Afdeling Medische Microbiologie en Infectieziekten, Canisius Whilhemina Ziekenhuis, NL-6500 GS Nijmegen, The Netherlands

- target level: 64 mg/L
  (max. MIC: 16 mg/L; Belgian bkpt = 16 mg/L])
- loading dose: 2g
- infusion: 4 g/day (2.778 mg/min; assumed clearance: 40 ml/min)
  [drug diluted in 48 ml of water; infusion through motor-operated syringe at a rate of 2 ml/h; temperature 25°C or lower].

Pharmacokinetics of temocillin 4 g/day: **total**



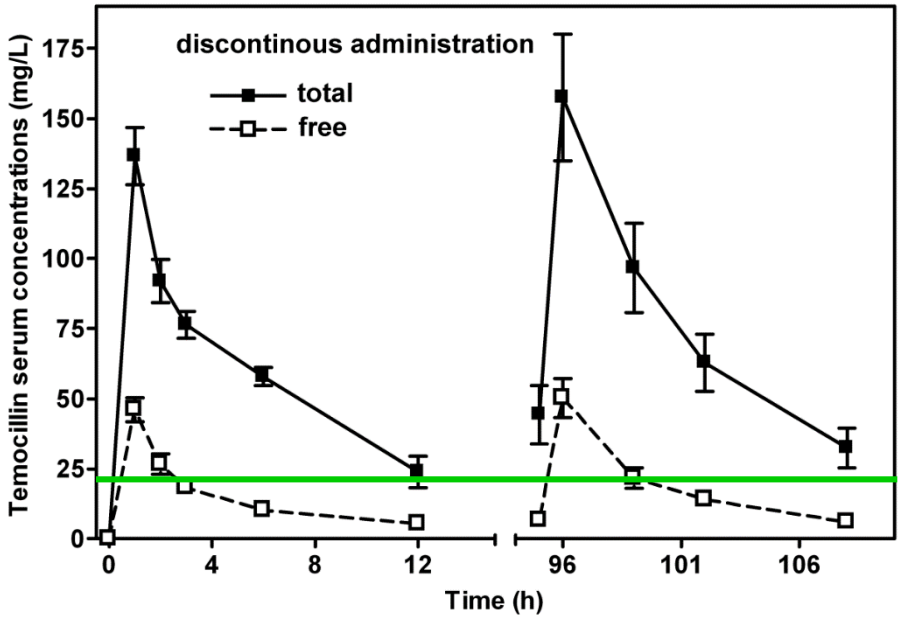


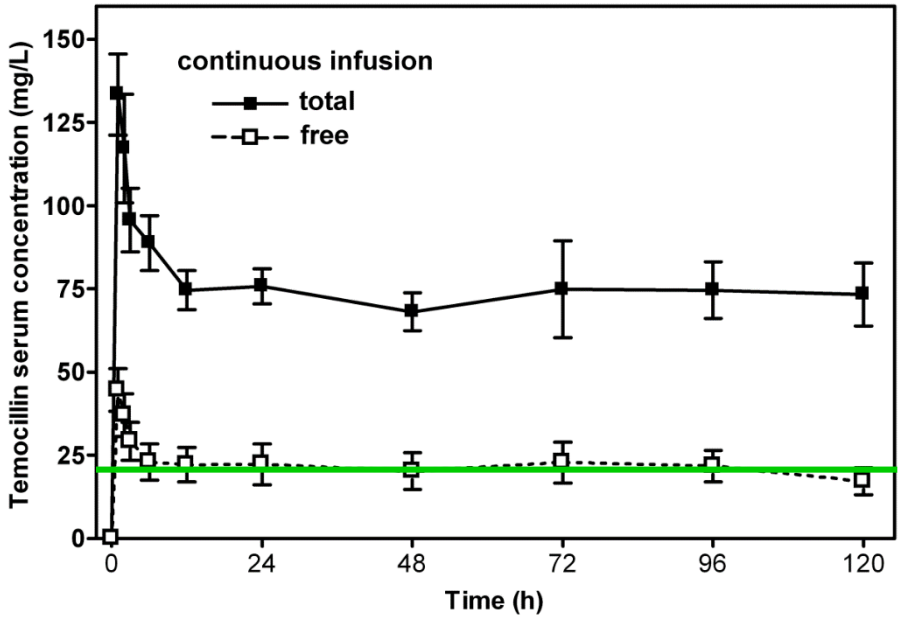
Concentration at equilibrium (total): 73 ± 3 (40 - 142)

J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

Pharmacokinetics of temocillin 4 g/day:

free





Concentration at equilibrium (free): 23 ± 2 (12 - 42)

J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

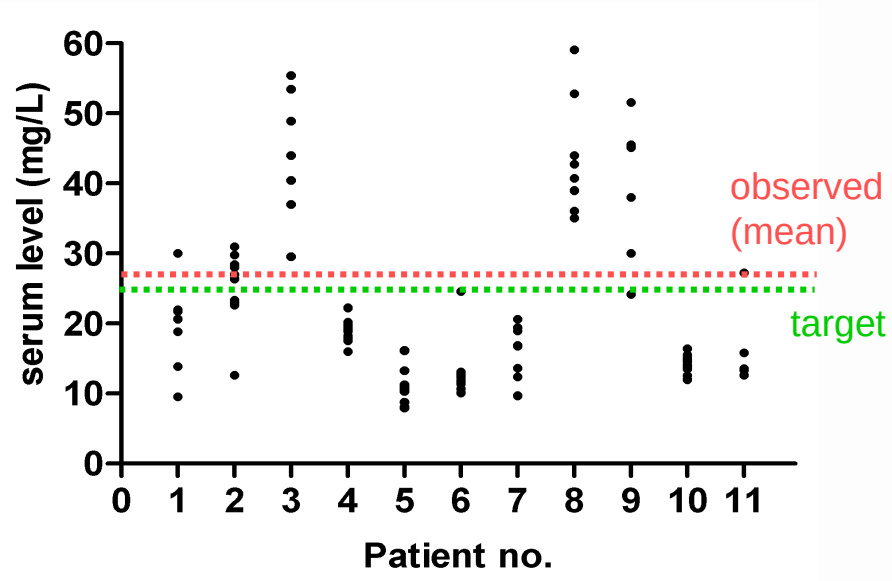
Continu infusion of β-lactams: a practical example

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.

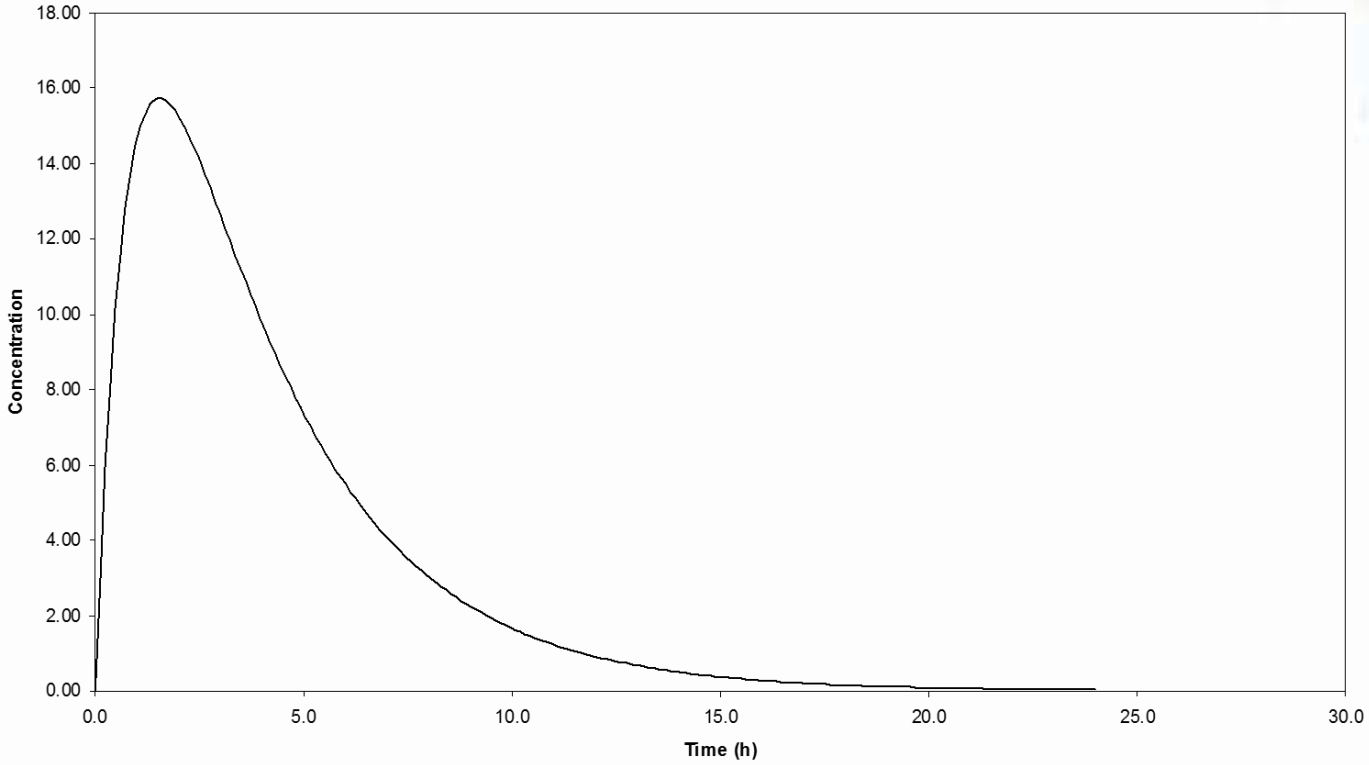
- target level: 24 mg/L
  (max. MIC: 6 mg/L [EUCAST bkpt = 8 mg/L])
- loading dose: 10.8 mg/kg
  (assumed Vd: 0.4 L/kg)
- infusion: 4 g/day
- assumed clearance: 102 ml/min (6.12 L/h)
- drug diluted in 48 ml of water
- infusion through motor-operated syringe at a rate of 2 ml/h;
- temperature 25°C or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



• ICAAC 2002 Poster no. A1 1402

Why are blood levels so variable ?

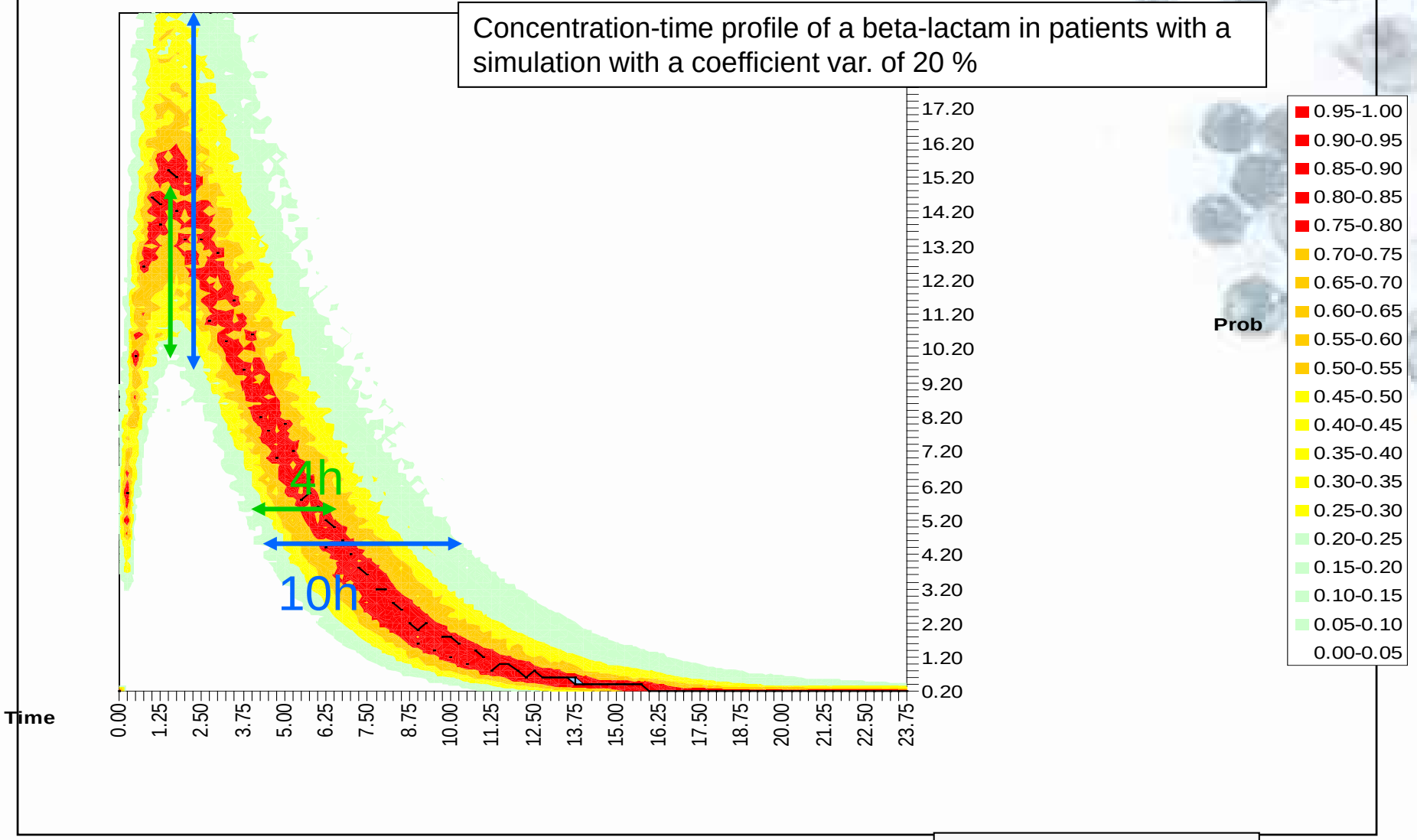
Concentration-time profile of a beta-lactam in volunteers
V_d = 20 L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}



vanaf J. Mouton, ISAP workshop

Why are blood levels so variable ?

Concentration-time profile of a beta-lactam in patients with a simulation with a coefficient var. of 20 %



vanaf J. Mouton, ISAP workshop

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 ?**

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…

Now, what about extended infusion ?

- **this is a 3-4 h infusion rather than a continuous infusion**
- **it started with carbapenems because those were too instable to be administred bycontinuous infusion for several hours**
- **it gained popularity whith meropenem (bit is still "off label" and with doripenem for which J&J asked for (and obtained registration in the EU) with 4 h infusion period…**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Extending the infusion time of Doribax to 4 hours maximizes the %T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response, a 4-hour infusion time may be more suitable when the MIC of doripenem for the known or suspected pathogen(s) has been shown or is expected to be > 0.5 mg/l, in order to reach a target attainment of 50% T>MIC in at least 95% of the patients (see section 4.2). Monte Carlo simulations supported the use of 500 mg 4-hour infusions every 8 hours in subjects with normal renal function for target pathogens with doripenem MICs ≤ 4 mg/l.

What is the evidence of instability of carbapenems ?

- **chemical considérations (see above)**
- **experimental studies**

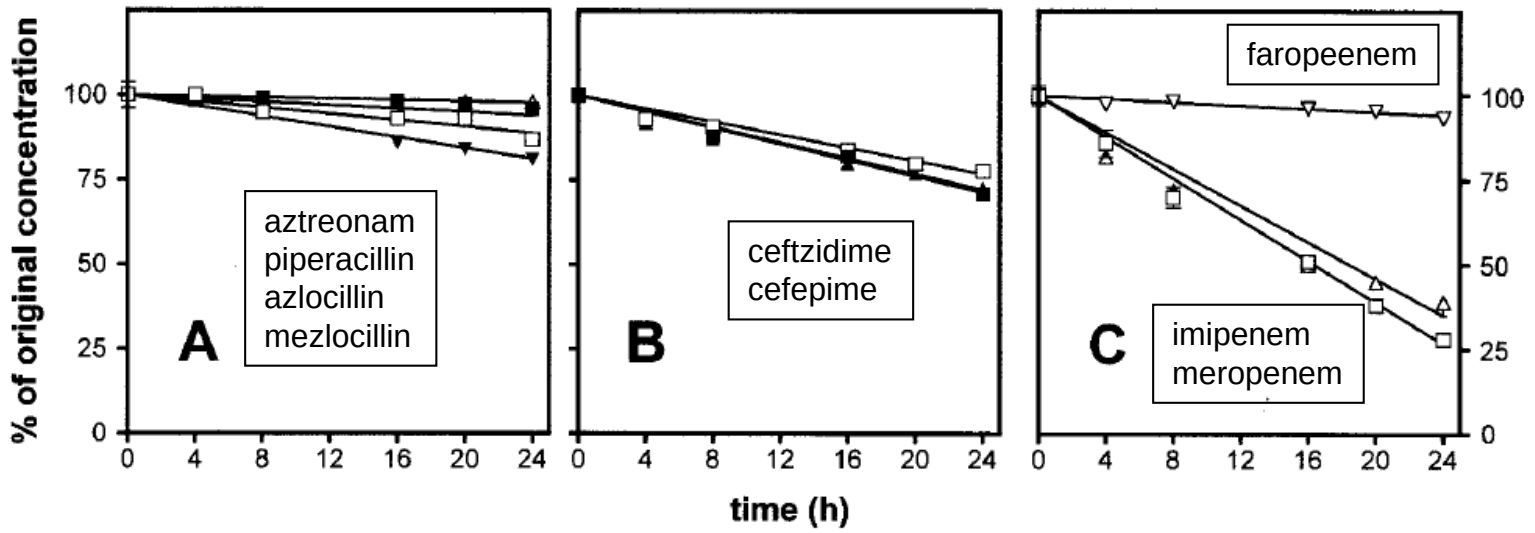
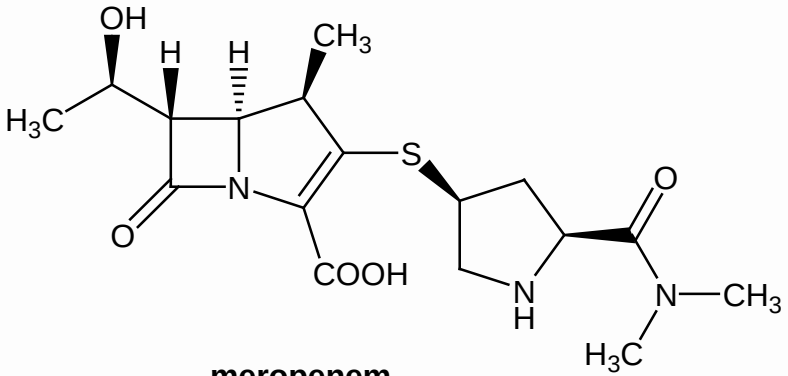


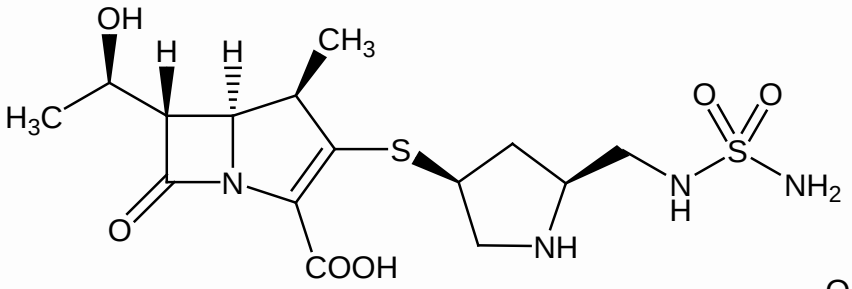
FIG. 1. Stability of the β-lactams in water at 37°C over time at the maximum concentration tested. (A) Symbols: △, 10% aztreonam; □, 12.8% piperacillin; ■, 12.8% piperacillin plus tazobactam (since the slope for 12.8% azocillin was almost identical to that for piperacillin-tazobactam, it was omitted for the sake of clarity); ▼ 12.8% mezlocillin. (B) Symbols: ■, 12% ceftazidime; □, 5% cefepime; ▲, 3.2% cefpirome. (C) Symbols: □, 0.8% imipenem plus cilastatin; △, 6.4% meropenem; ▽, 6.4% faropenem. All values are the means of three independent determinations ± the standard deviation (SD; symbols without bars indicate values for which the SD is smaller than the symbol size).

Viaene et al. Antimicrob. Agents Chemother. 2002; 46:2327–2332

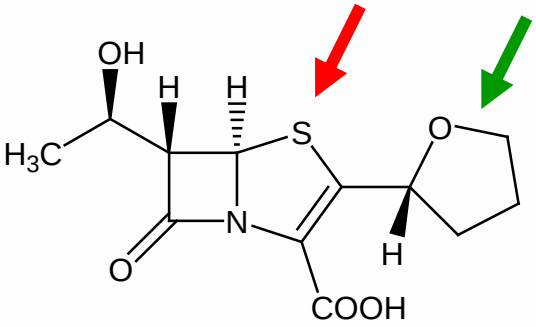
Penems are not penams…



meropenem

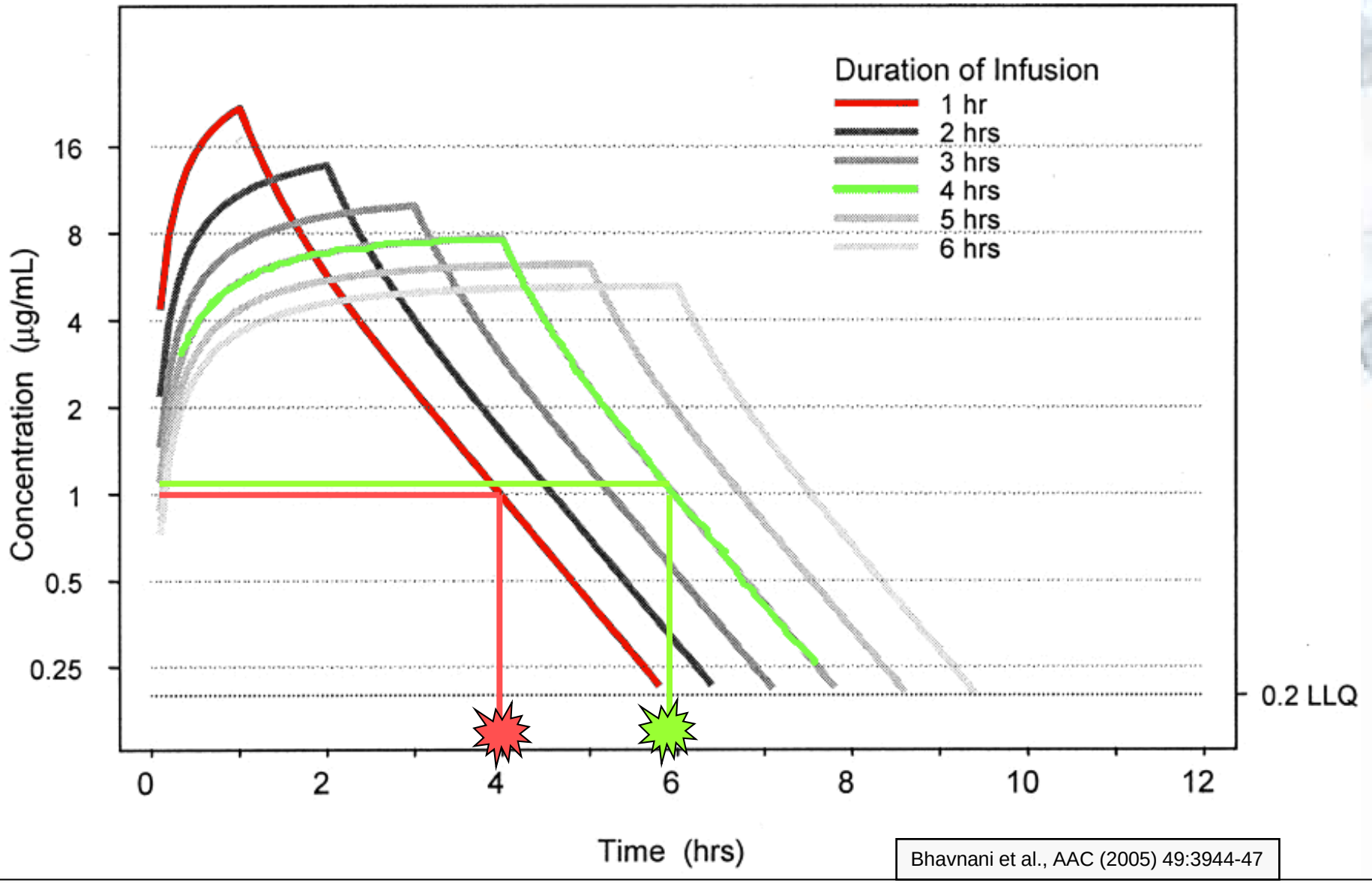


doripenem



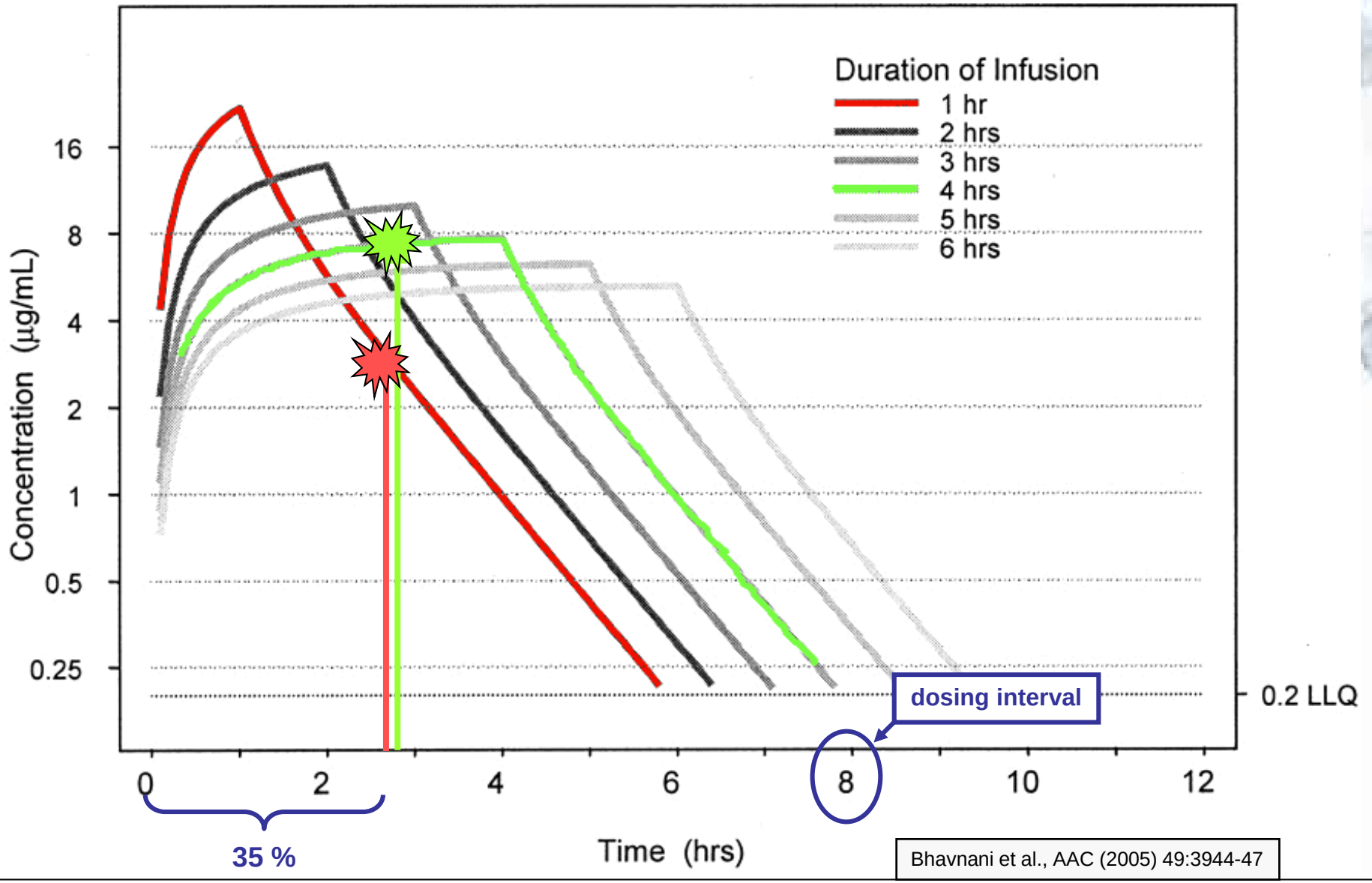
faropenem

Doripenem: improvement of *f* T > MIC by means of prolonged infusion



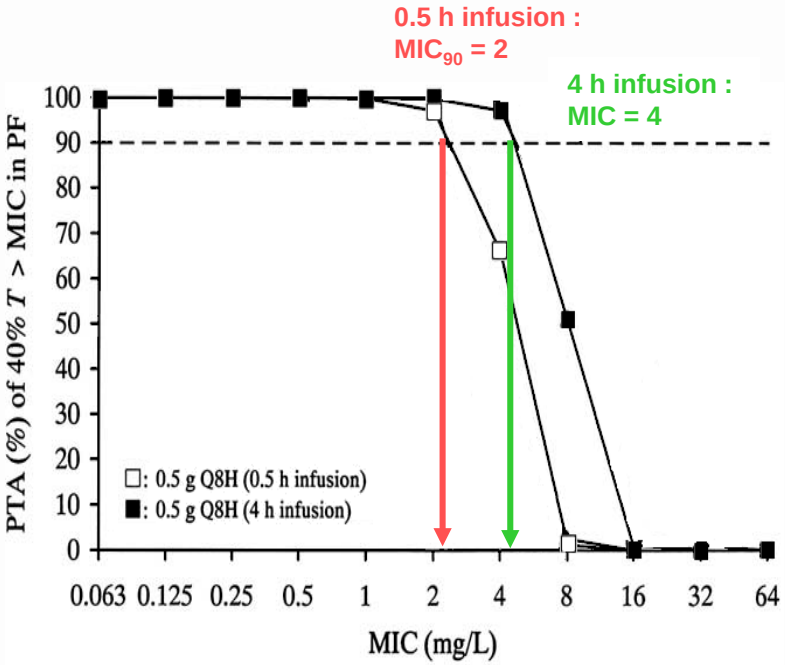
Bhavnani et al., AAC (2005) 49:3944-47

Doripenem: prolonged infusion allow to cover higher MICs for a *f* T > MIC of 35 %



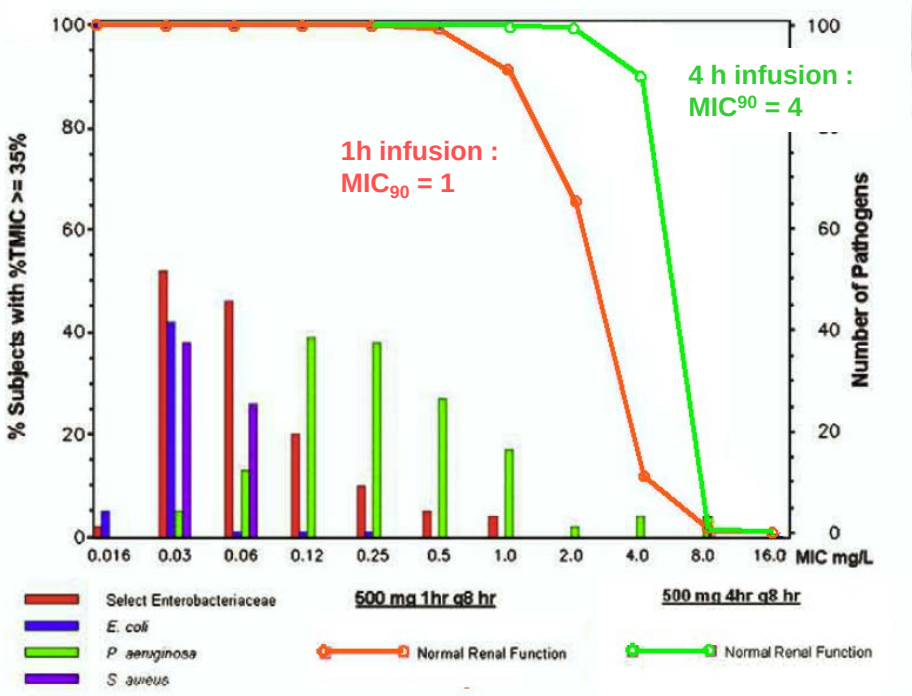
Bhavnani et al., AAC (2005) 49:3944-47

Doripenem: Target attainment rate after Monte-Carlo simulation

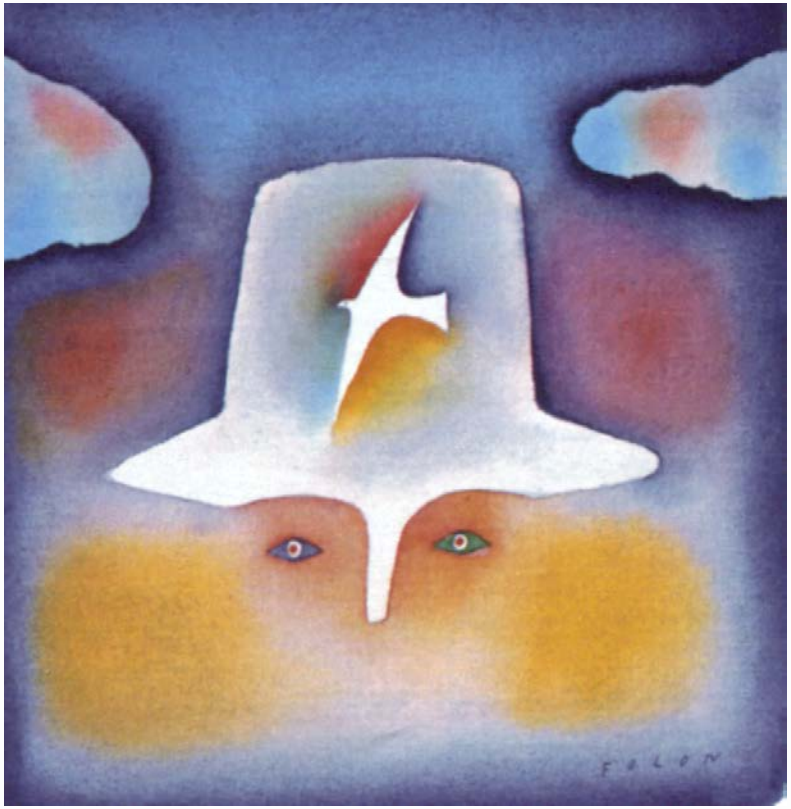


Ikawa et al., Diagn Microbiol Infect Dis. (2008) 62:292-7
Japanese patients after IA surgery…

Van Wart et al., Diagn Microbiol Infect Dis. (2009) 63:409-414
Patients from clinical trials …



β- lactams and continuous infusion



A BRILLIANT IDEA….

But do not forget the problems…