

Administration of beta-lactams by continuous infusion: when, how, and for which molecules ?

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SEPTEMBER 12-15, 2009

Meet-the-Experts – session 202.
Optimization of Beta-Lactams: Continuous and Prolonged Infusions versus Standard Regimens
Monday, September 14, 2009 5:30 - 6:45 PM

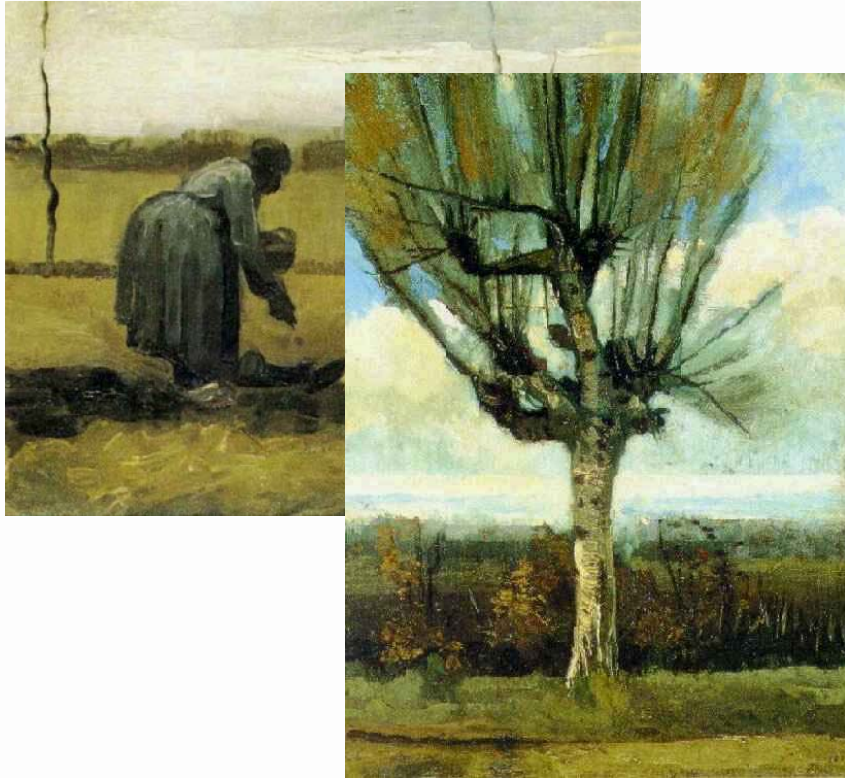
Is antimicrobial chemotherapy becoming crazy ?



They were discovered in the nature



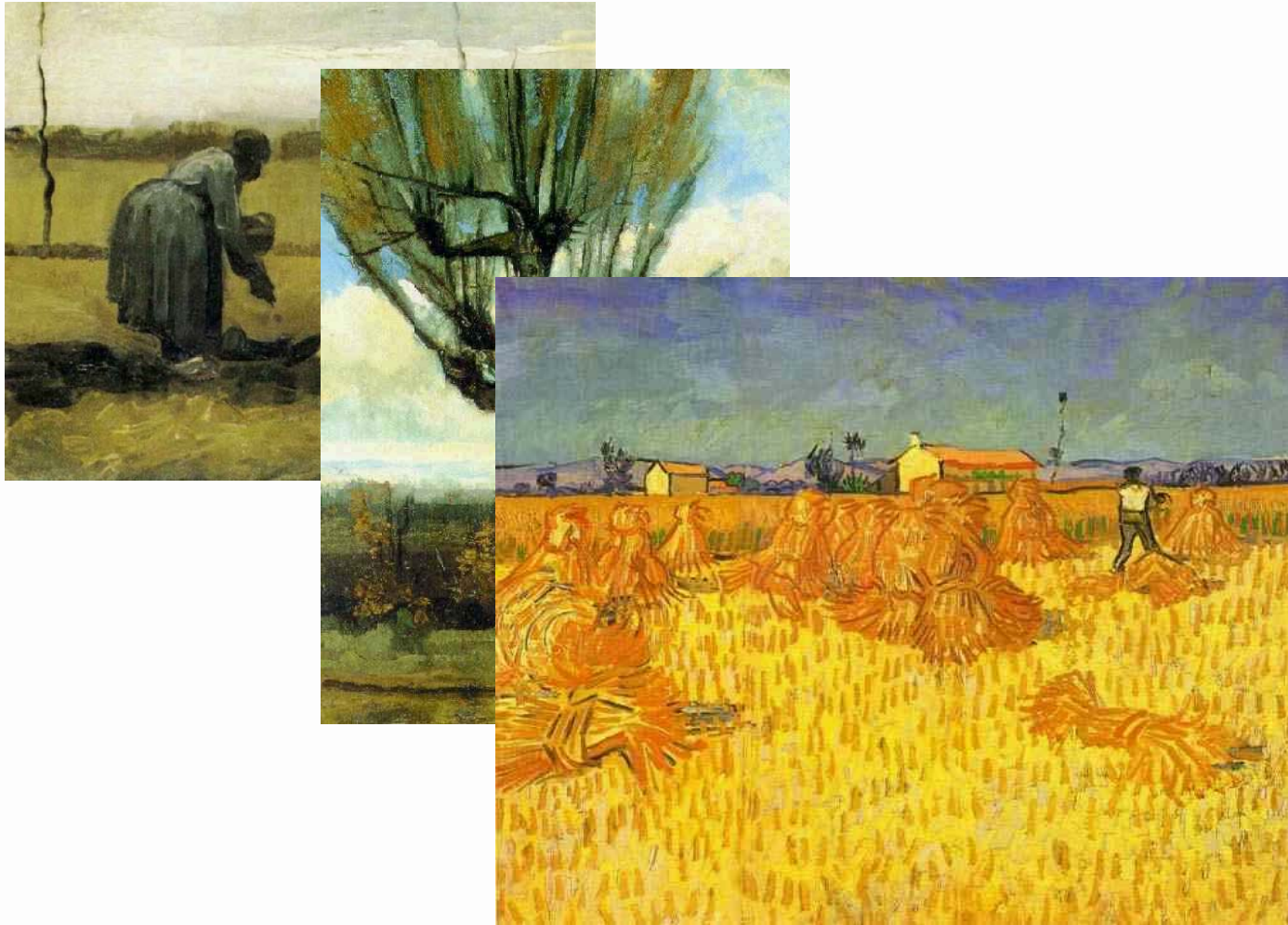
Is antimicrobial chemotherapy becoming crazy ?



... to give rise to a rich growth of new molecules, for almost every indication ...



Is antimicrobial chemotherapy becoming crazy ?



... and we thought that we
had succeeded ...

Is antimicrobial chemotherapy becoming crazy ?



But ...



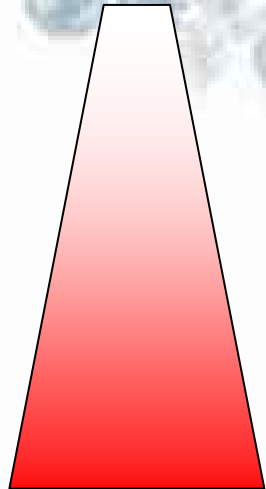
Optimization of antibiotic usage ...

Questions ...

- Did we use the antibiotics on a **rational** basis ?
- What do we need to do to reduce the **risk of resistance** ?
- Can we control **costs** ?

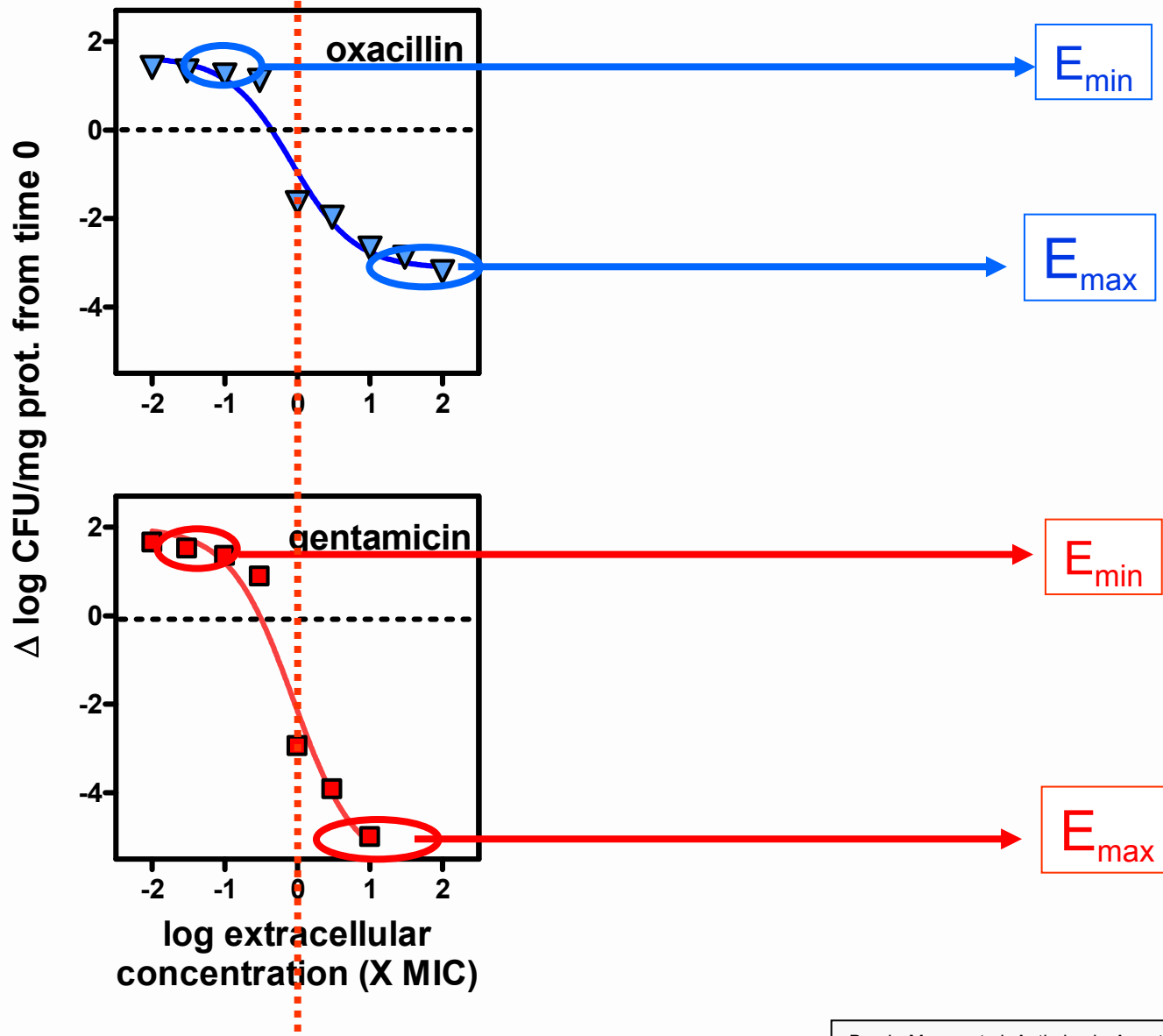
How can you improve ?

- through **increased efficacy**
- pharmacodynamics (PK/PD) ...
- optimization of administration...
- local evaluations for cost containment



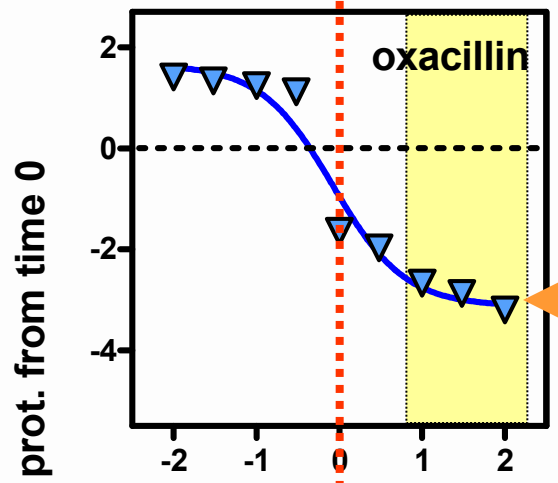
MIC

About efficacy ... and concentration effect relationships



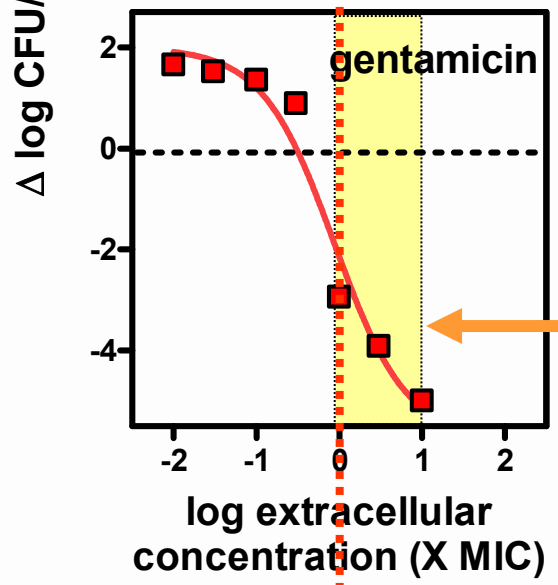
MIC

Introducing pharmacokinetics...



weak concentration dependence

$C_{\min} - C_{\max}$



strong concentration-dependence

First conclusions (and discussion)....

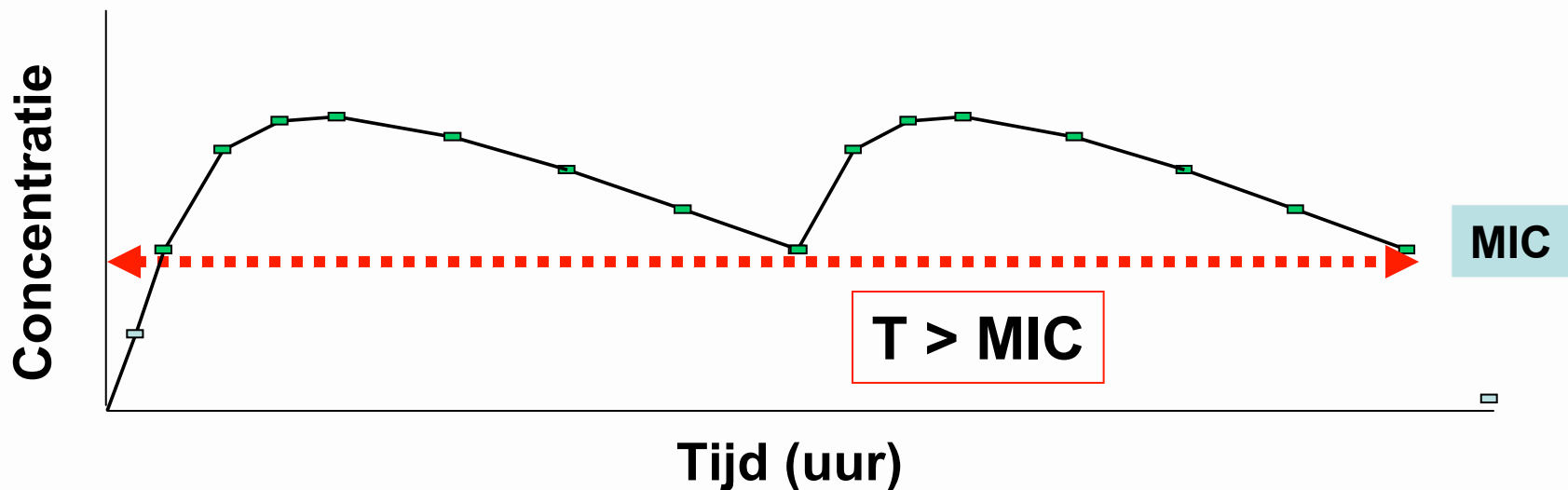
- Every antibiotic is concentration-dependent
(simple pharmacological principle) ...
- **BUT**, for β -lactams, activity is already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration... and bacteria with low MICs
- **AND**, having 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)

First conclusions (and discussion)....

- 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

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

No!

- aminoglycosides
- fluoroquinolones (**)



important

limited



- Concentrations **are important**
- The time of exposure is less important

** 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...

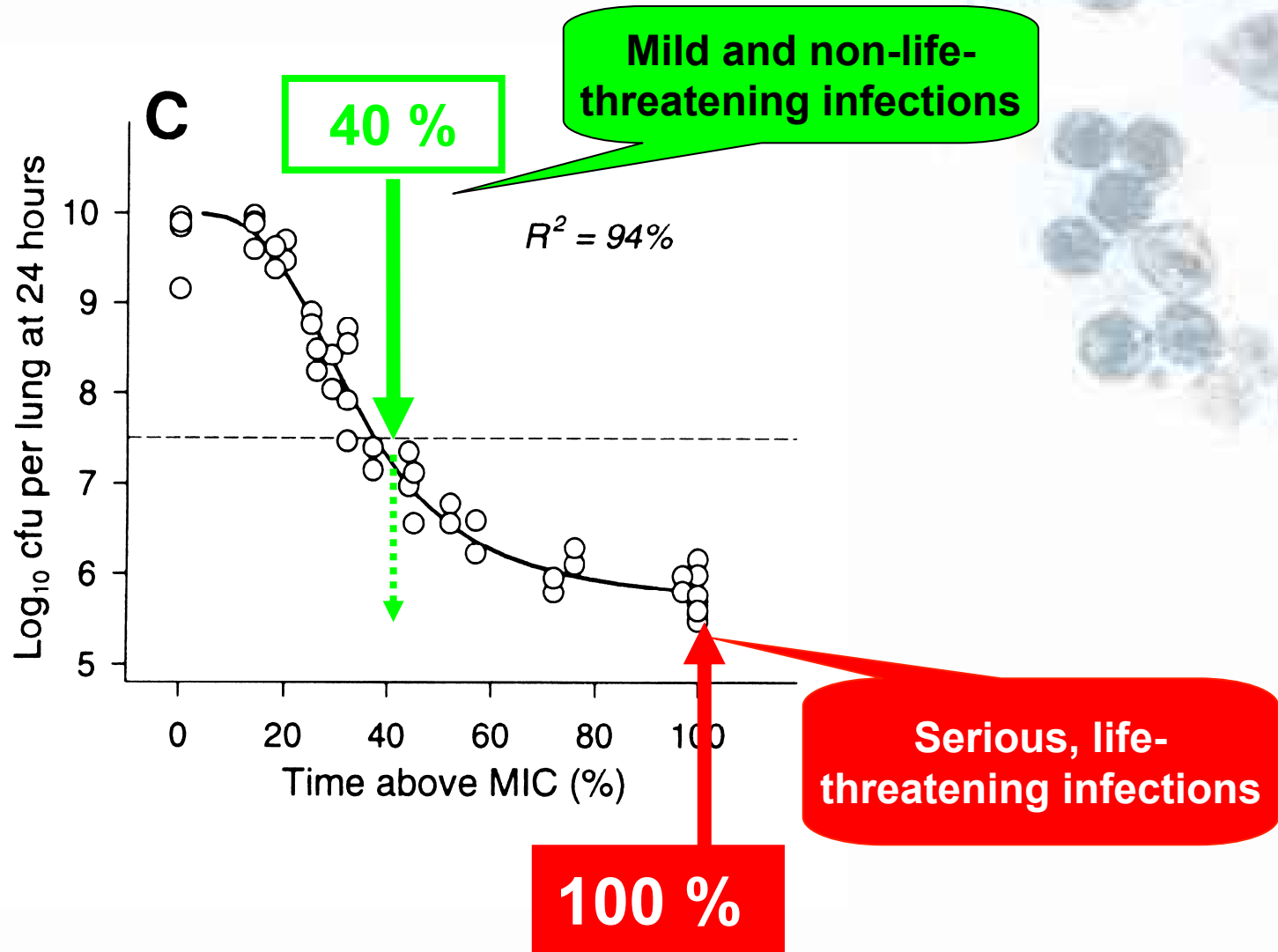
- **What do we need to do in terms of PK/PD ?**
- What is the clinical evidence ?
- What are the problems ?
- How you do this in practice ?
- Do you need to monitor blood levels ?

Continuous infusion with β -lactams: PK/PD aspects

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



How long above the MIC in discontinuous administration



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

How much
above MIC ?

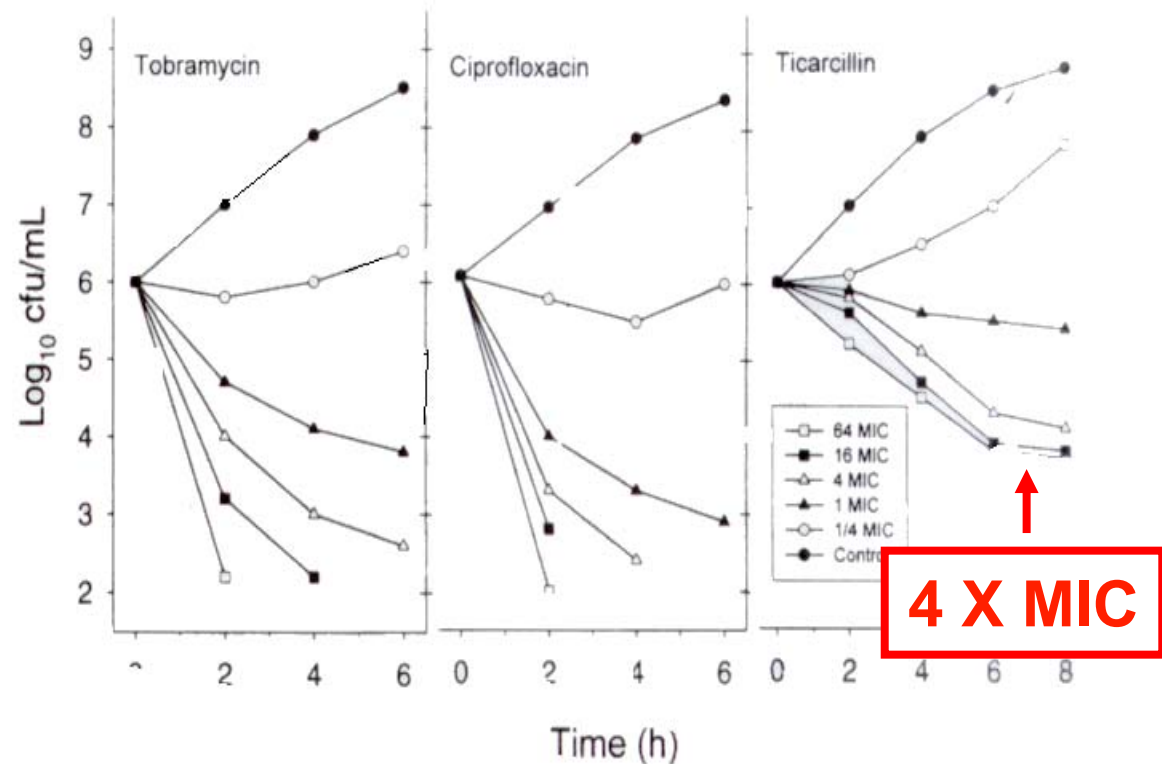
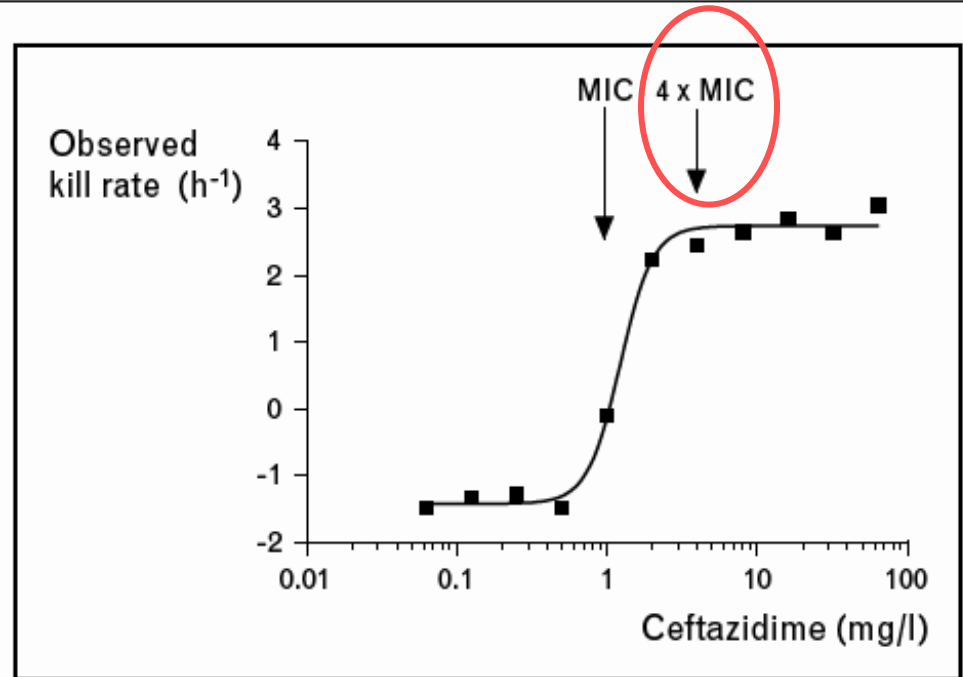


Figure 2. Time-kill curves for *Pseudomonas aeruginosa* ATCC (American Type Culture Collection) 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one-fourth to 64 times the MIC. Reprinted with permission from *Scandinavian Journal of Infectious Diseases* [3].

More recent confirmation for ceftazidime

Figure 2 Relationship between concentration of ceftazidime and kill rate



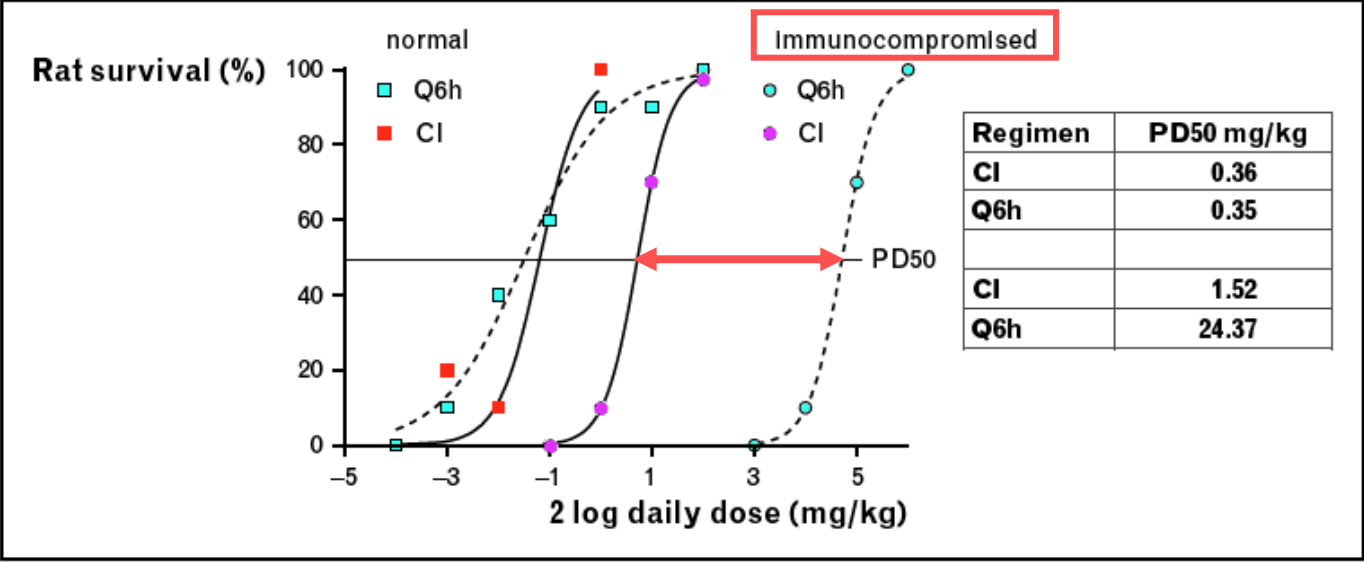
How much ?

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



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

- **$fT > MIC$** 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 severe 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

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Limits: **Clinical Trial**

Display Summary Show 20 Sort By Send to

All: 76 Review: 0

Items 1 - 20 of 76 Page 1 of 4 Next

1: [Ikawa K, Morikawa N, Ikeda K, Suyama H.](#) [Related Articles, Links](#)

Pharmacokinetic modeling and dosage adaptation of biapenem in Japanese patients during continuous venovenous hemodiafiltration.
J Infect Chemother. 2008 Feb;14(1):35-9. Epub 2008 Feb 24.
PMID: 18297447 [PubMed - indexed for MEDLINE]

2: [De Jongh R, Hens R, Basma V, Mouton JW, Tulkens PM, Carryn S.](#) [Related Articles, Links](#)

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.
J Antimicrob Chemother. 2008 Feb;61(2):382-8. Epub 2007 Dec 10.
PMID: 18070831 [PubMed - indexed for MEDLINE]

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 \uparrow MIC
ceftazidime	2 ^b	VAP / pneumonia/ melioidosis/ cystic fibrosis	superiority mainly with resistant isolates
ceftriaxone	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 <i>Ps.</i> 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*

^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 ...

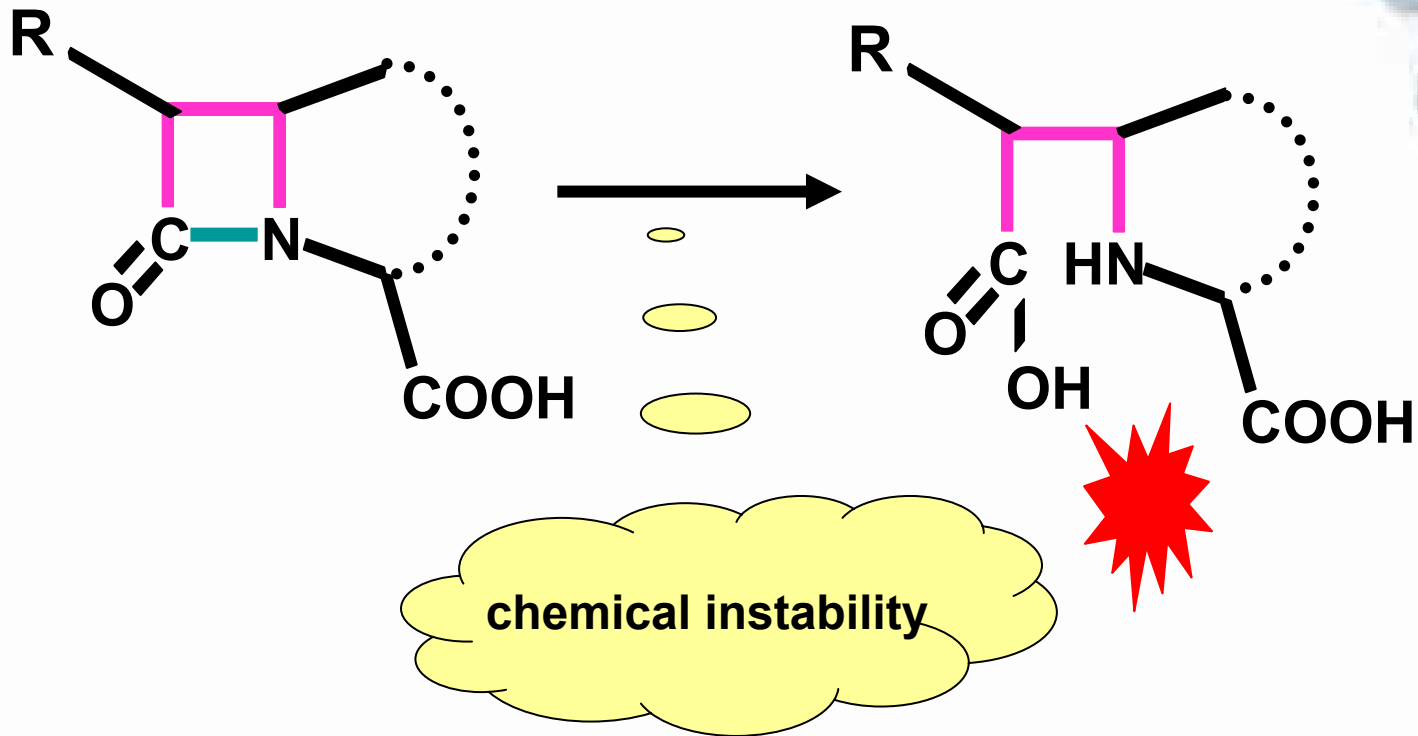


Infusion will push music to its limits

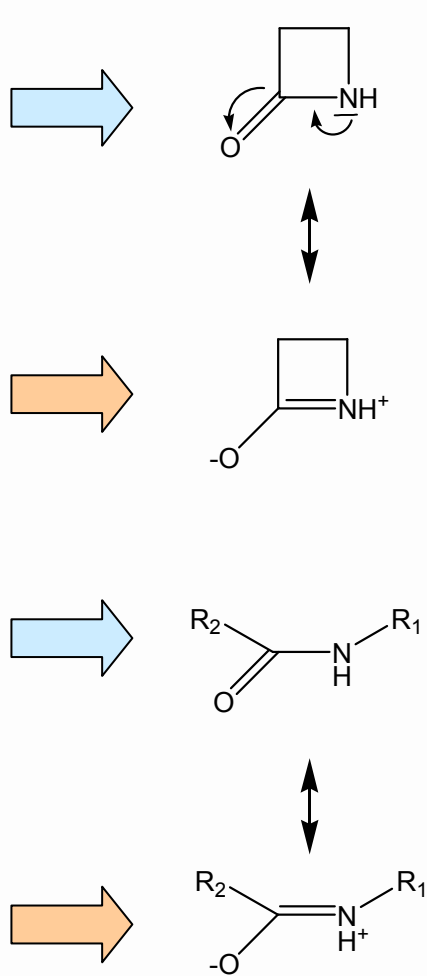
- Will push β -lactam efficacy to its maximum ...
- by staying above the MIC indefinitely...

- But what do we need to do in terms of PK/PD ?
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- **What are the problems ?**
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Problem no. 1: β -lactams are unstable molecules



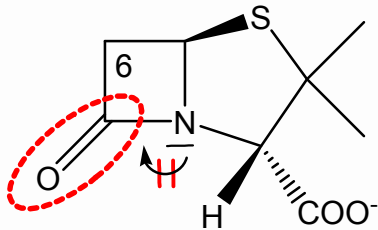
Why are β -lactams antibiotics **chemically** unstable ?



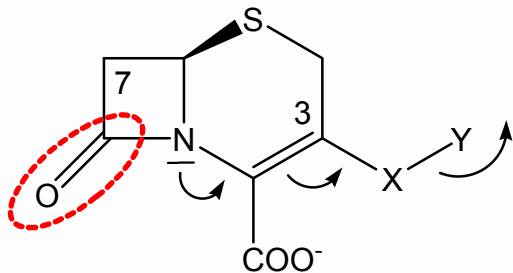
a β -lactam *per se* and without substituents is not necessarily unstable because it exists under **resonant forms** similar to what takes place for amides (which are very stable...)



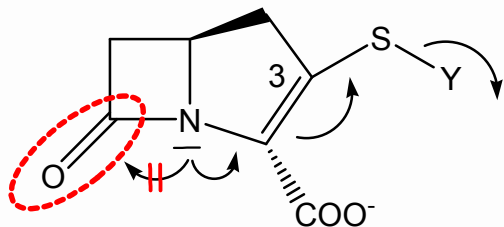
The problem is the substitutions...necessary for activity *



penems: 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=O becoming a true ketone *

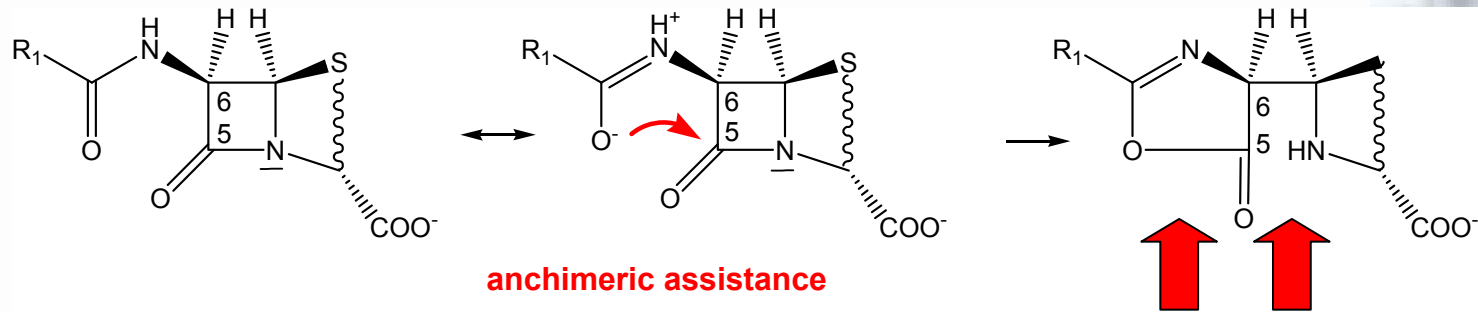


penems: combine the two above mechanisms, making the molecule very unstable

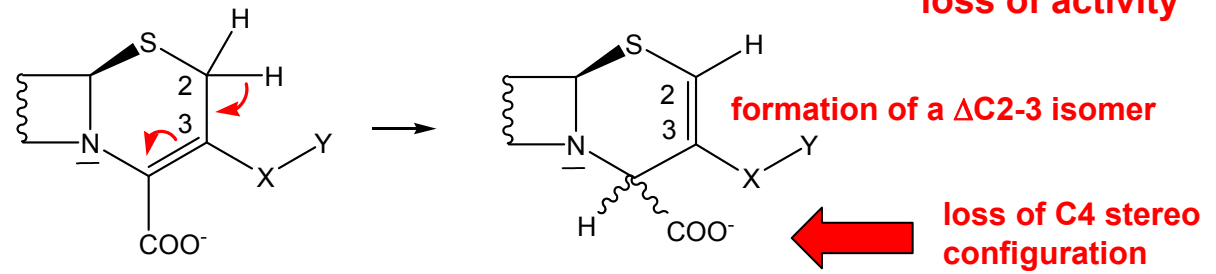
* essential for binding to the active serine in PBPs... and, therefore for activity

Mechanisms of chemical instability

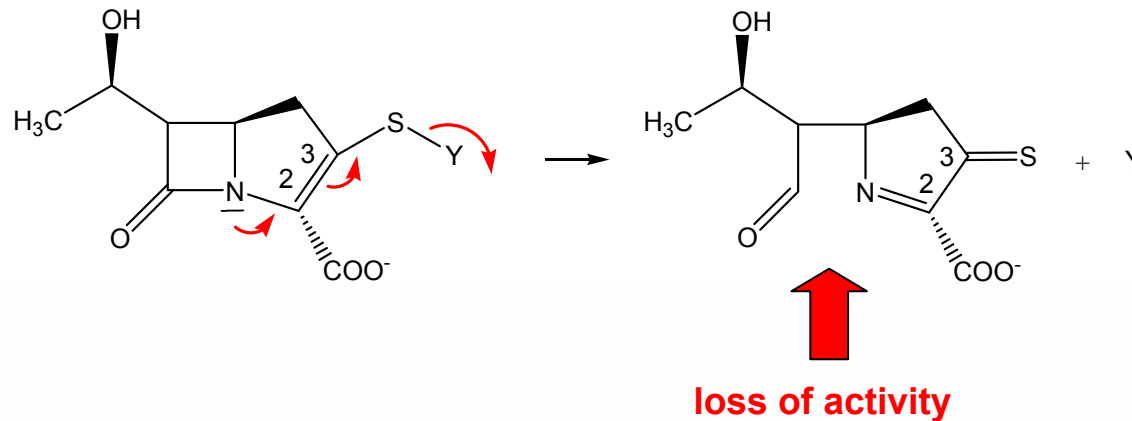
penams
and
cephems



additional
mechanism for
cephems



penems



Can instability be modulated ?

- **yes** for penams and cepheids, 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

molecule	time (h)			
	≤ 6 h	12 h	24 h	> 24 h
penicillin G				
ampicillin				
oxacillin				
piperacillin				
temocillin				
cefazolin				
cefotaxime				
ceftriaxone				
ceftazidime				
cefepime				
imipenem				
meropenem				

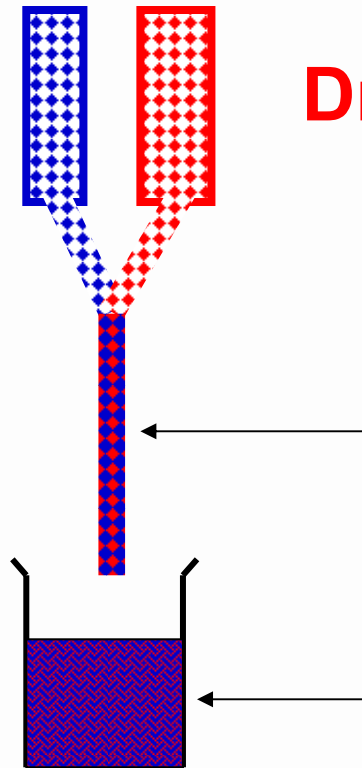
* Servais & Tulkens, AAC 200;45:2643-7 – Viaene et al. AAC 2002;46:2327-32 - Baririan et al. JAC 2003;51:651
other references for individual drugs in in Berthoin et al. (in preparation).

Problem no. 2:

β -lactams may be incompatible with other drugs if administered through the same line

β -lactam
(typ. 8 g %)

Drug X

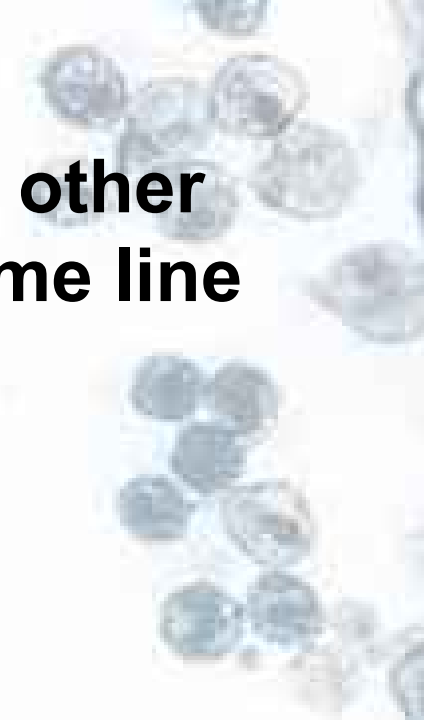


1st contact at high concentration (10 min)

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



direct examination (with viewer),
HPLC, bioassay



Drug compatibility studies: example for ceftazidime

Compatible:

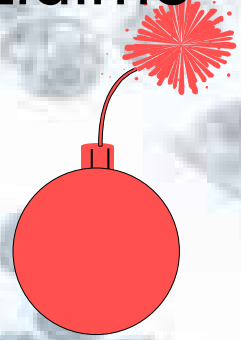
- **antiinfectives**
 - **aminoglycosides, macrolides** (diluted solutions), **fluconazole**
- **sedatives / anticonvulsivants**
 - **ketamine, valproic acid, sufentanil, remifentanil, morphine**
- **antihypertensives / diuretics**
 - **urapidil, furosemide**
- **varia**
 - **aminoacid solutions (VAMIN)**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

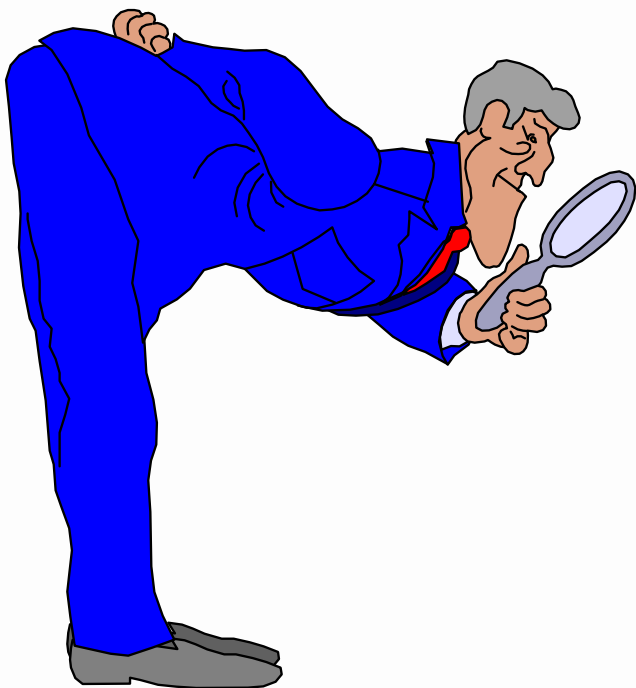
Non-compatible

- **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 specifically
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 ...



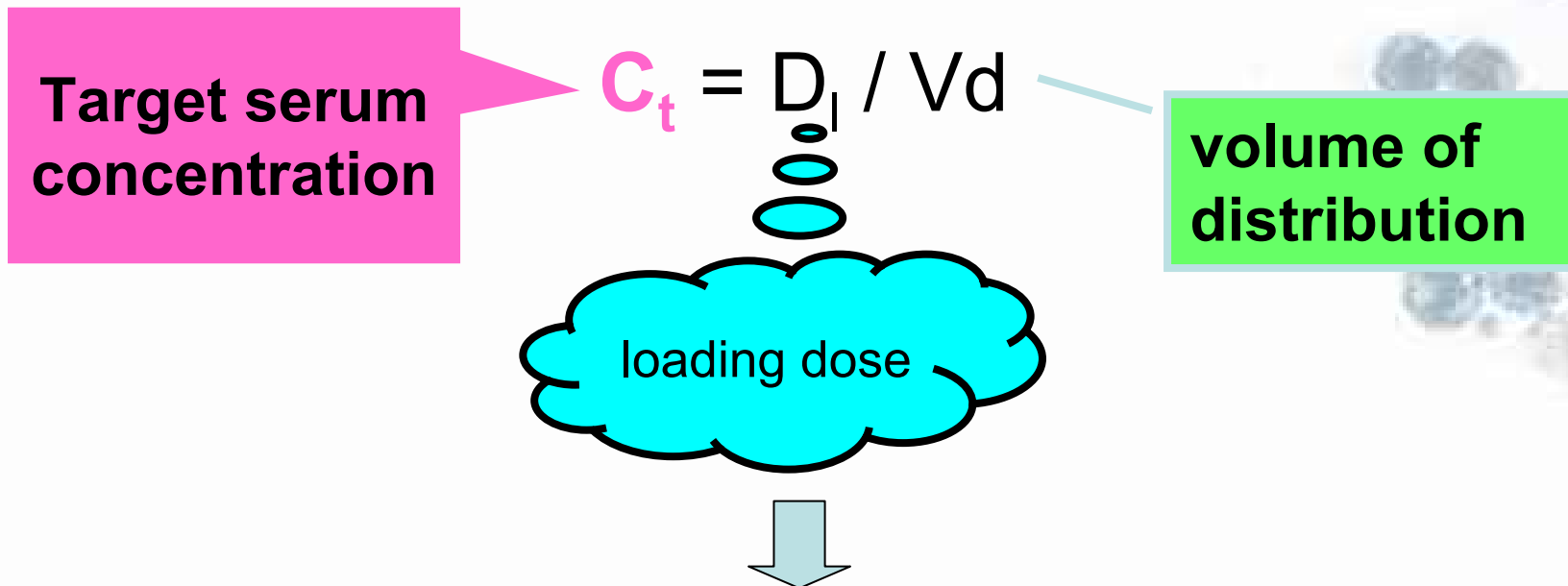
Infusion will push music to its limits

- 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 *



$$\text{loading dose (in mg)} = C_t \text{ (mg/L)} \times V_d \text{ (L)}$$

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

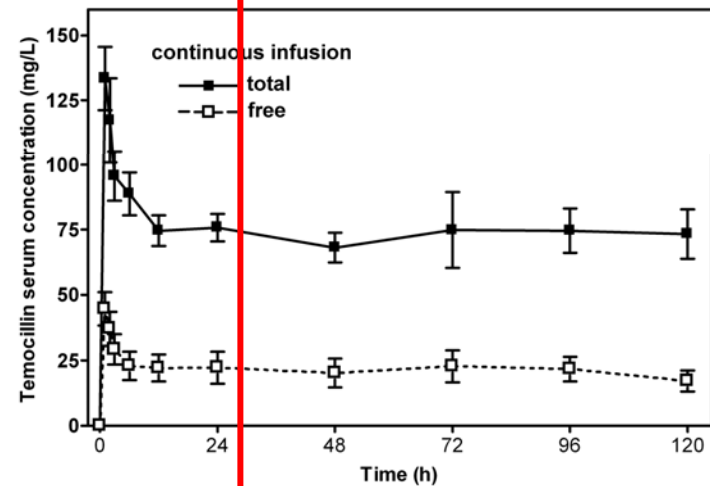
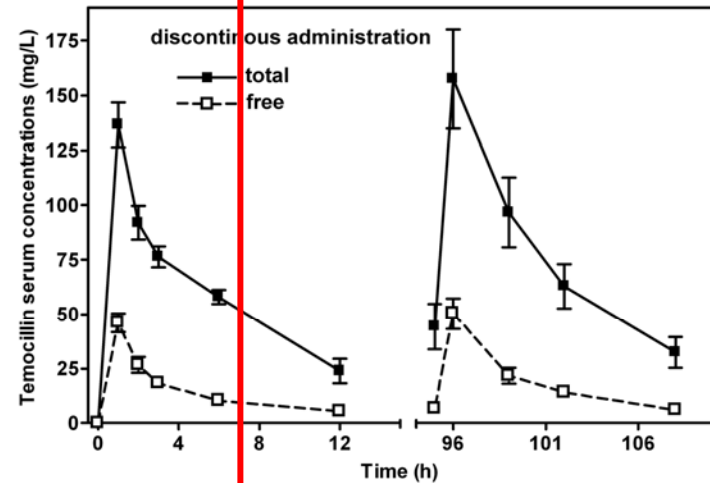
Typical volumes of distribution of a β -lactam are between 0.2 L/kg (volunteers) and 0.4-0.5 L/kg (Intensive Care and burned patients)

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

Continuous infusion in practice

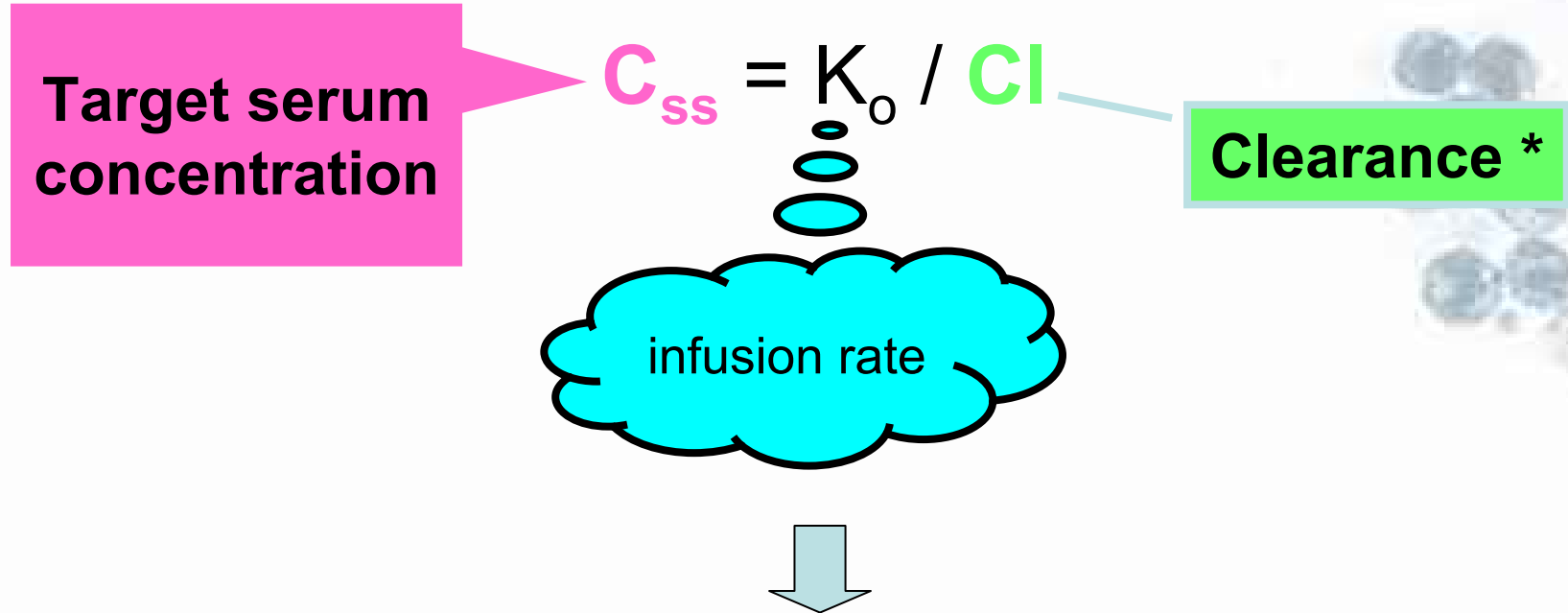
1. loading dose: a simplified scheme

- 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 *



$$\text{daily dose (in mg)} = 24 \times \text{clearance (L/h)} \times C_{ss}$$

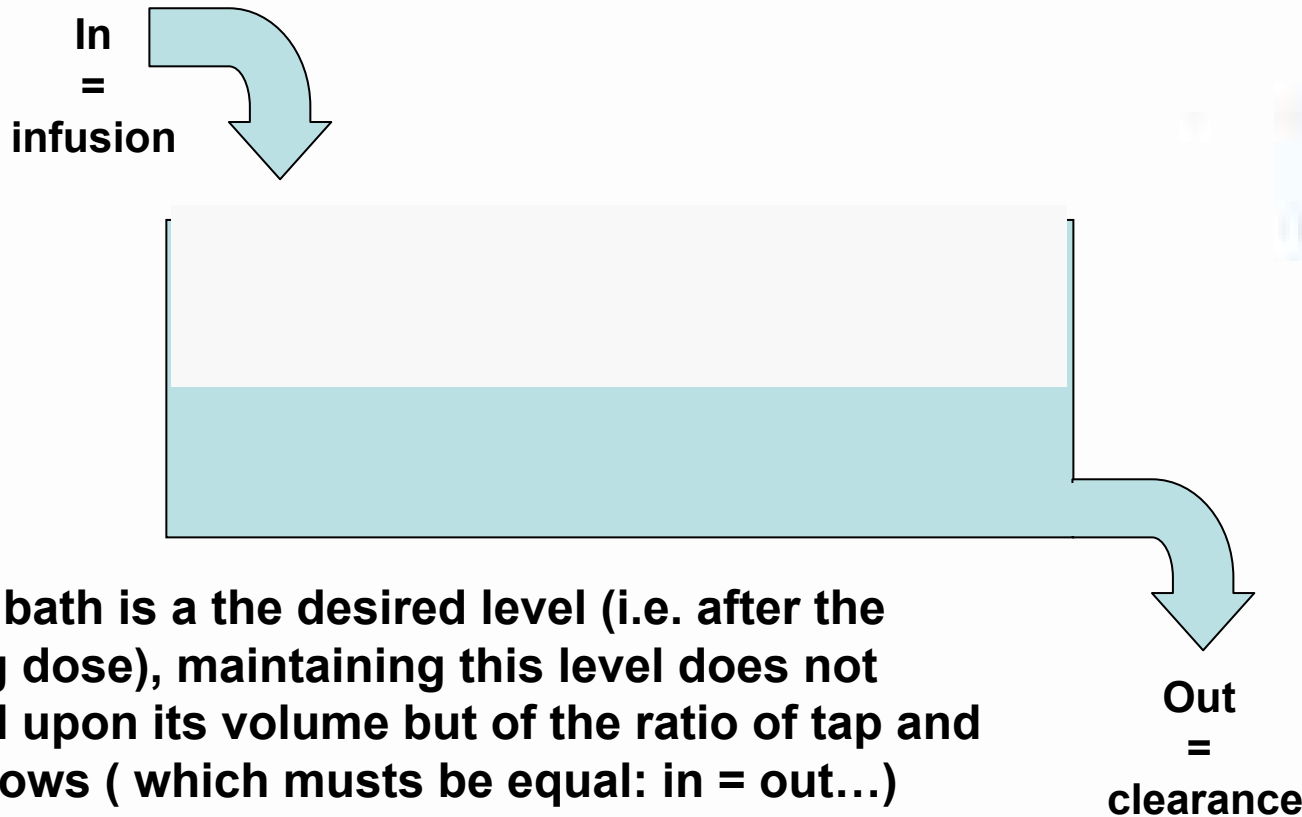
*** during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance and not the weight of the patient**

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

Continuous infusion in practice

2: infusion

In
=
infusion

A diagram of a rectangular tank. A light blue arrow points from the top left into the tank, labeled 'In = infusion'. The tank is partially filled with a light blue liquid. A light blue arrow points from the bottom right of the tank, labeled 'Out = clearance'.

once a bath is at 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...)

Out
=
clearance

*** 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

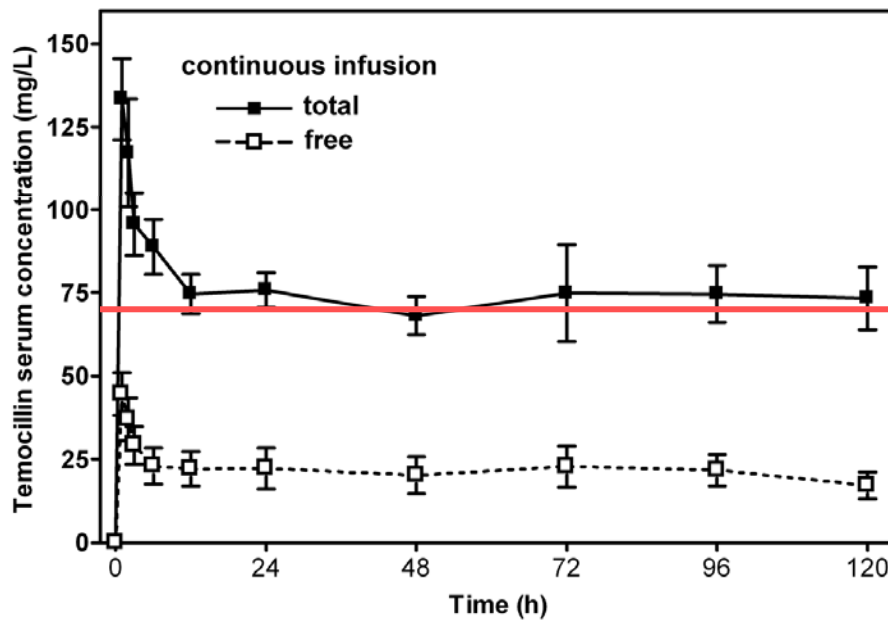
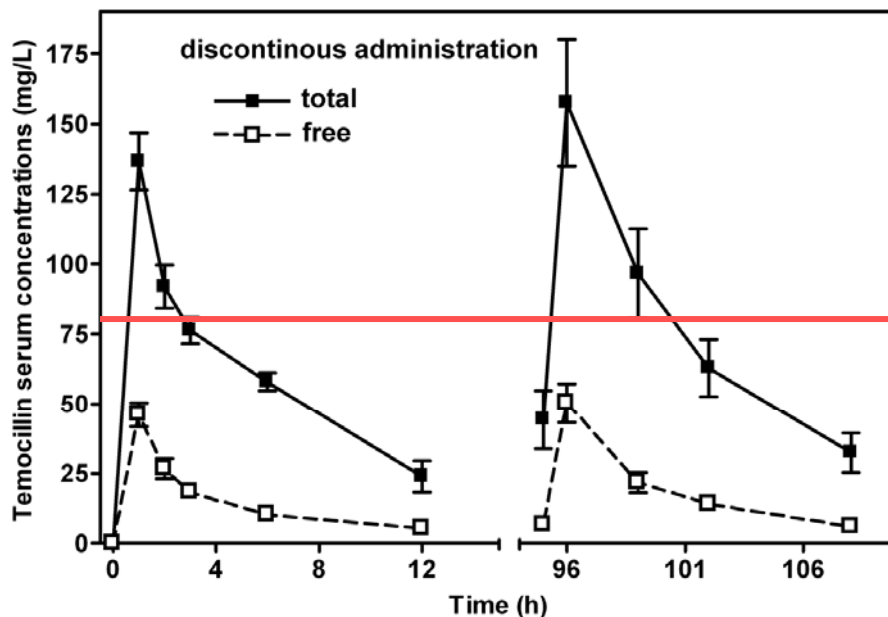
Raf De Jongh¹, Ria Hens¹, Violetta Basma², Johan W. Mouton³, Paul M. Tulkens^{2*}
and Stéphane Carryn²

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 Wilhelmina 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].

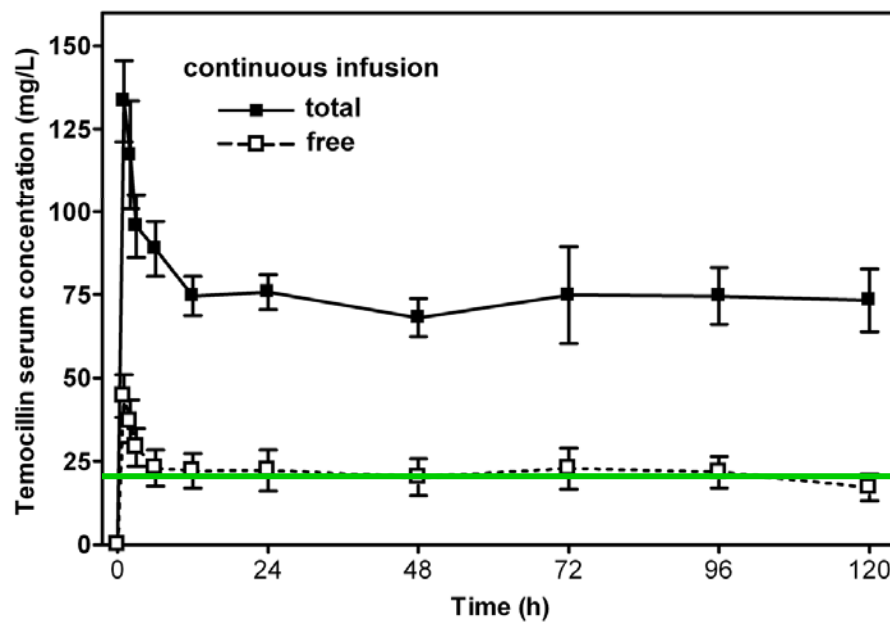
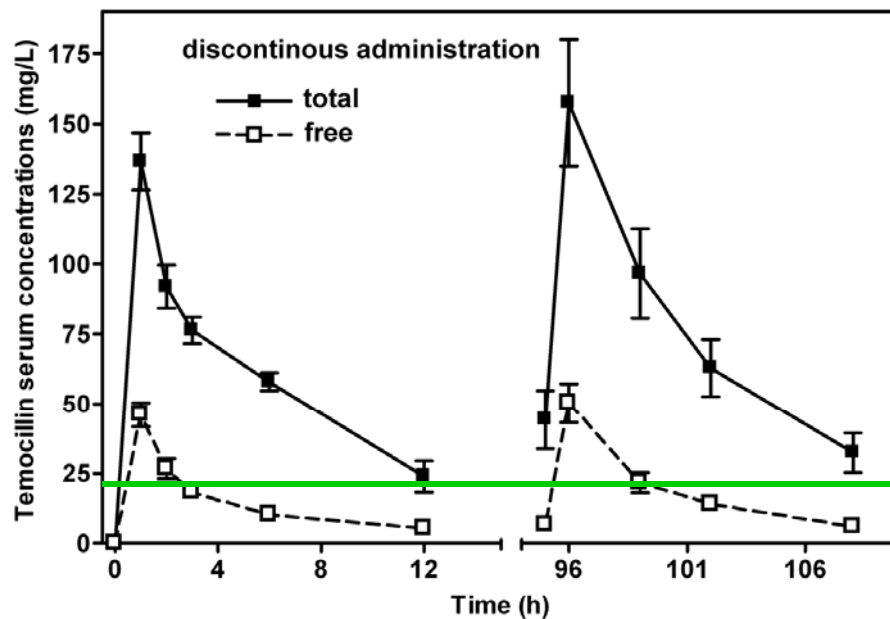
Pharmacokinetics of temocillin 4 g/day: **total**

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



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

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



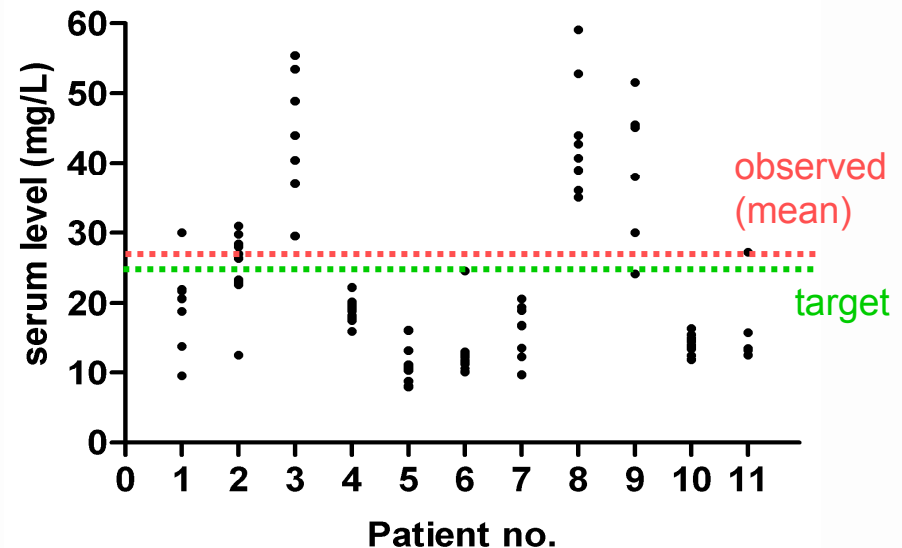
Continu infusion of β -lactams: a practical example



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.

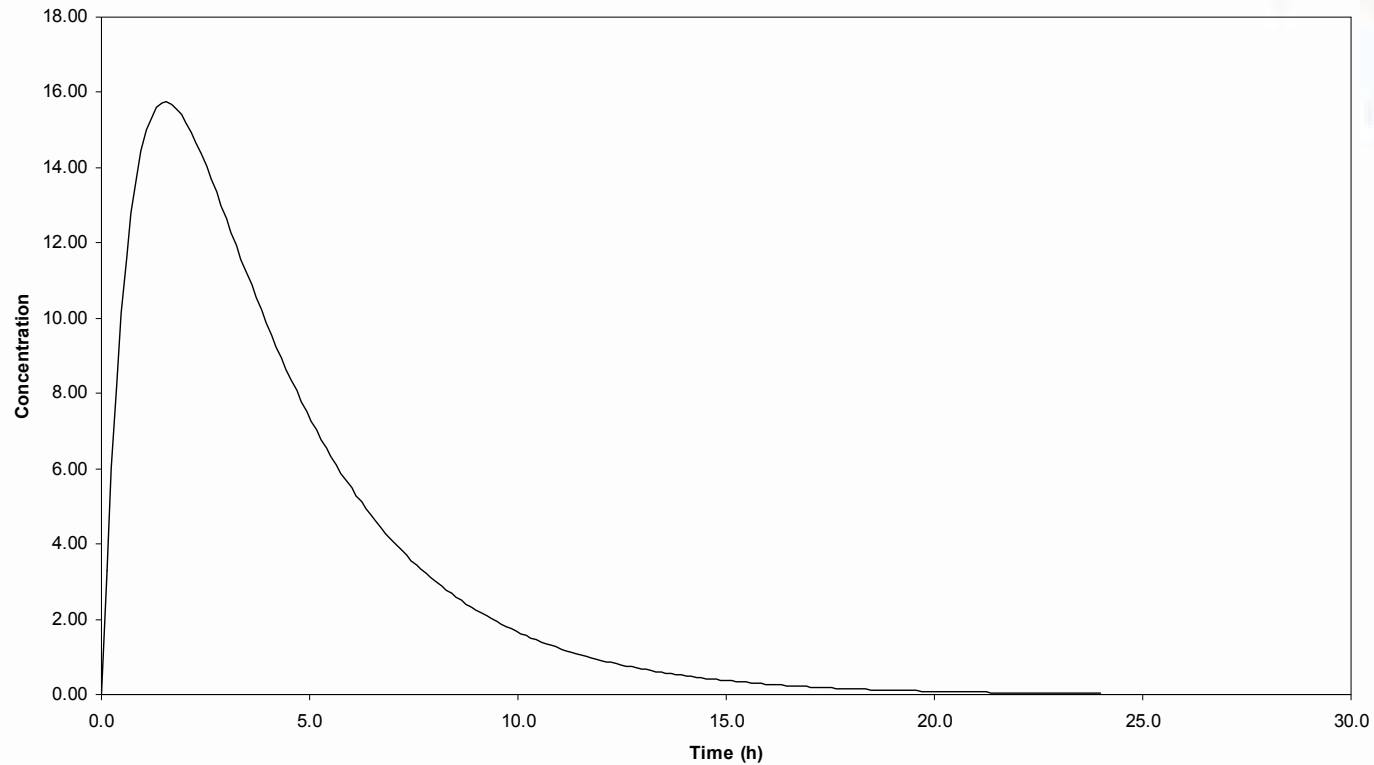
- target level: 24 mg/L
(max. MIC: 6 mg/L [EUCAST bkpt = 8 mg/L])
- loading dose: 10.8 mg/kg
(assumed Vd: 0.4 L/kg)
- infusion: 4 g/day
- assumed clearance: 102 ml/min (6.12 L/h)
- drug diluted in 48 ml of water
- infusion through motor-operated syringe at a rate of 2 ml/h;
- temperature 25°C or lower



• ICAAC 2002 Poster no. A1 1402

Why are blood levels so variable ?

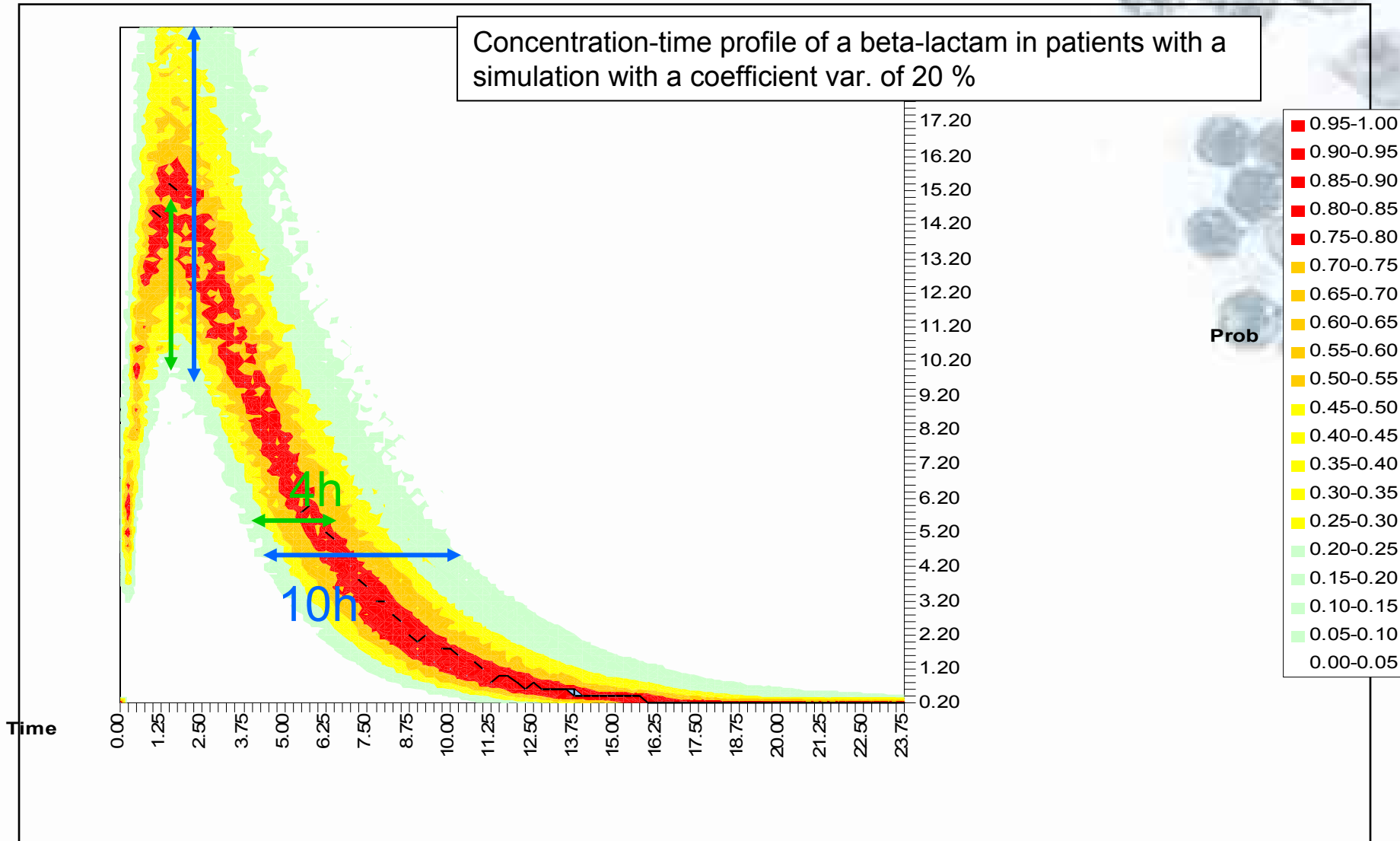
Concentration-time profile of a beta-lactam in volunteers
 $V_d = 20 \text{ L}$, $k_a = 1.2 \text{ h}^{-1}$, $k_e = 0.3 \text{ h}^{-1}$



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 %



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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 ?**

Yes!

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 continuous infusion



A BRILLIANT IDEA....



But do not forget the problems...

Belangenconflicten ... en dankbetuigingen

- Belangenconflicten
 - onderzoekstoelagen van het *Fonds de la Recherche Scientifique*, Bayer, Pfizer, Wyeth, GSK, ...en de Waalse en de Brusselse Gewesten
 - Vergoedingen voor voordrachten van AstraZeneca, Aventis, Bayer, Lilly ...
 - Presentiegeld van RIZIV en FOD "Volksgezondheid"
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