Strategies to combat resistance:
Focus on pharmacokinetics/pharmacodynamics with applications to β-lactams and vancomycin

Paul M. Tulkens
Cellular & Molecular Pharmacology
Université catholique de Louvain,
Brussels, Belgium
&
International Society of Antiinfective Pharmacology

http://www.facm.ucl.ac.be

http://www.isap.org

ISCCM

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& International Critical Care Congress 2011
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In association with Ministry of Health & Family Welfare (Govt. of Delhi)

CRITICARE New Delhi, INDIA 2011

The ideal antibiotic ...

the molecule

brilliant and clear solutions

...ent's cure

chemistry **microbiology** **therapy**

Is the molecule always ideal ?

Main causes of antibiotic failures...

Adapted from Pechère J.C., 1988, 1993, 1998

- **False failures**
  - erroneous diagnosis
  - underlying disease uninfluenced by antibiotics
  - unjustified lack of patience
  - inactivation of the antibiotic
- **Patient related failures**
  - compliance failure (broadly speaking)
  - inappropriate administration route (broadly speaking)
  - immunodepressed hosts
- **Pharmacological failures**
  - **insufficient amount or drug inappropriately administered**
  - **no attention paid to pharmacodynamic parameters**
  - in situ inactivation or lack of drainage
- **Micro-organism related failures**
  - wrong pathogen
  - **resistance acquired during treatment**
  - **insufficient bactericidal activity**
  - inoculum effect

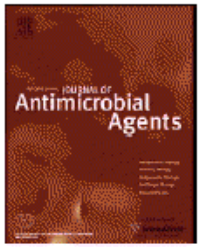
What was the situation in 2010 ?

International Journal of Antimicrobial Agents 36 (2010) 513–522

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag



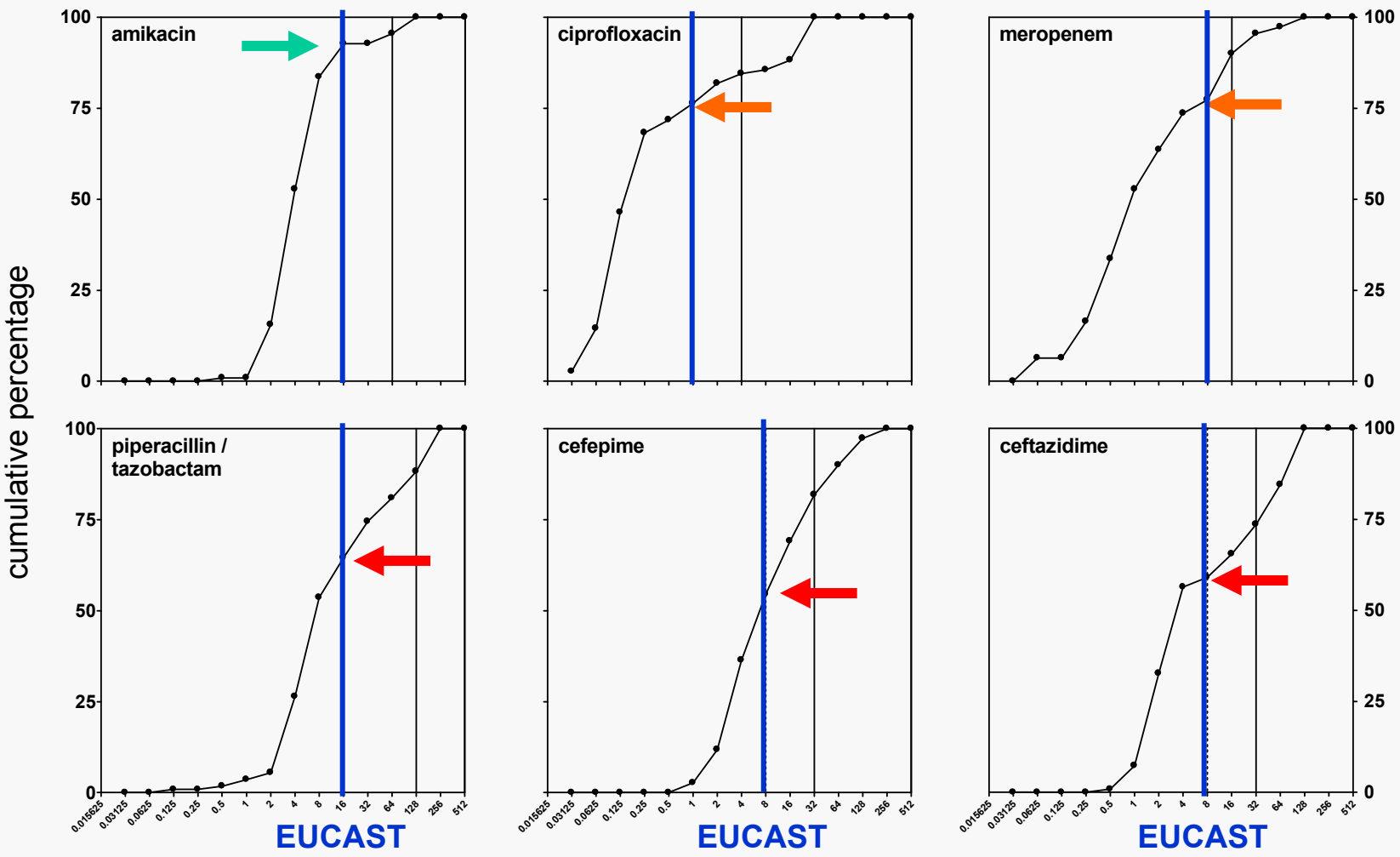
In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

[a] *Unité de Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
[b] *Coris BioConcept, Gembloux, Belgium*
[c] *Laboratory for Molecular & Cellular Technology, Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium*
[d] *Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium*
[e] *Laboratoire de Microbiologie, Cliniques Universitaires St-Luc, Brussels, Belgium*
[f] *Laboratorium voor Microbiologie, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[g] *Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium*
[h] *Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium*
[i] *Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium*

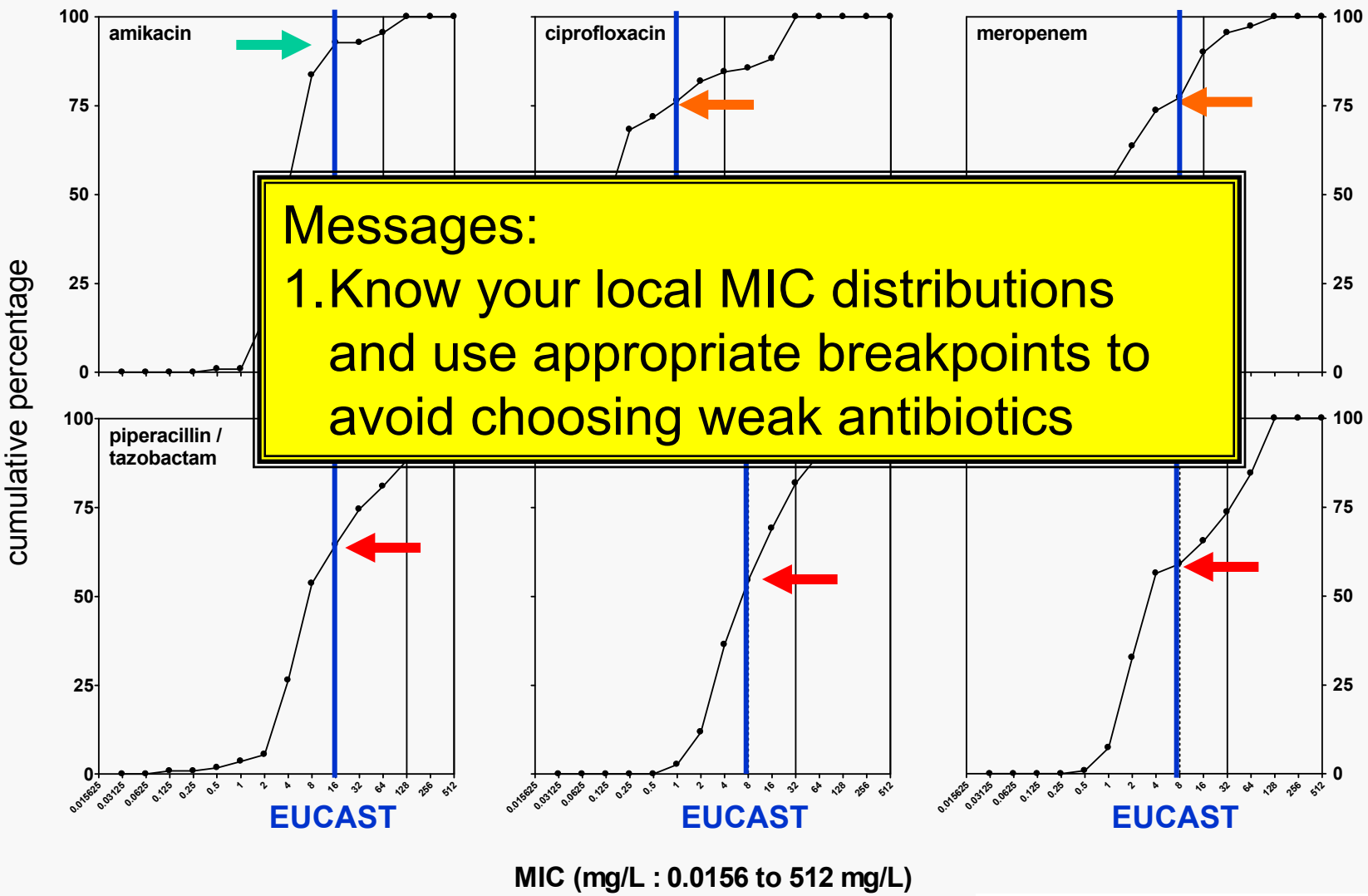
all in the Brussels Region

How was it at day 0 (*P. aeruginosa* in HAP) ?



Riou *et al.* IJAA 2010; 36:513-522

How was it at 0 (*P. aeruginosa* in HAP) ?



Messages:

1. Know your local MIC distributions and use appropriate breakpoints to avoid choosing weak antibiotics

Riou *et al.* IJAA 2010; 36:513-522

Asking the question you always wanted to ask ...

- Does your microbiologist give MIC of antibiotics apart from sensitivity in ICU infections ?

1. Each case
2. Few cases
3. upon asking
4. Never

No, MIC is not the acronym for "Minimal Interest to the Clinician" !

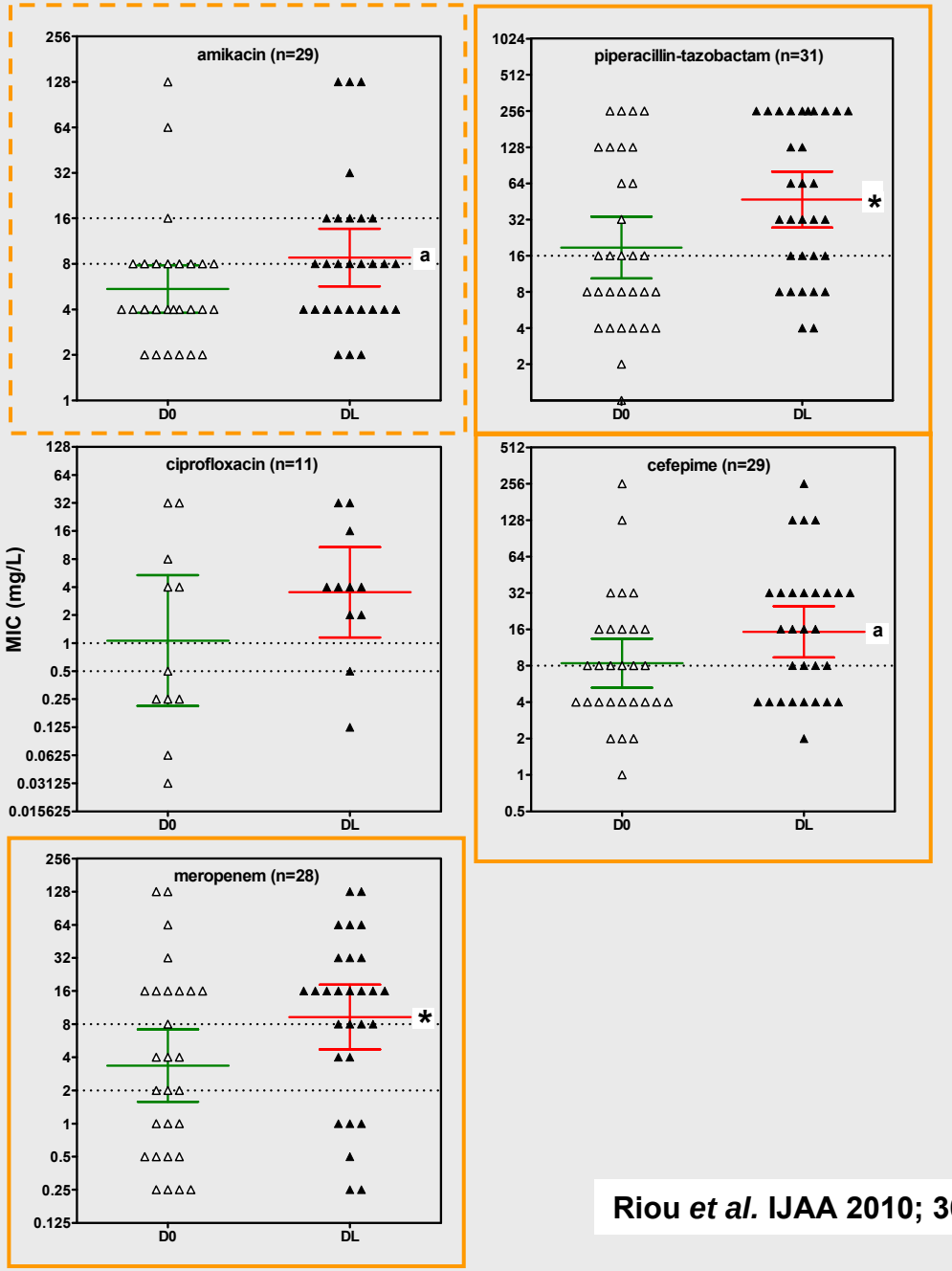
What did happen during treatment in case of no eradication?

- D0: initial isolate
  DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

[a] $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)



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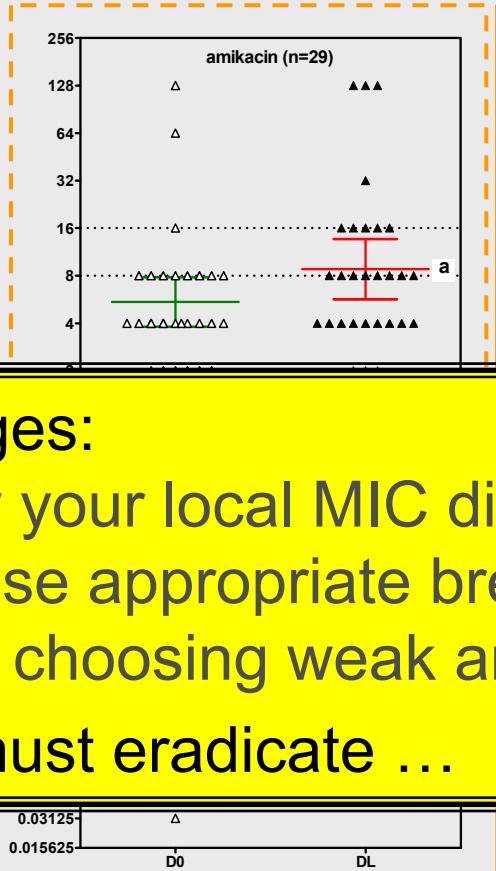
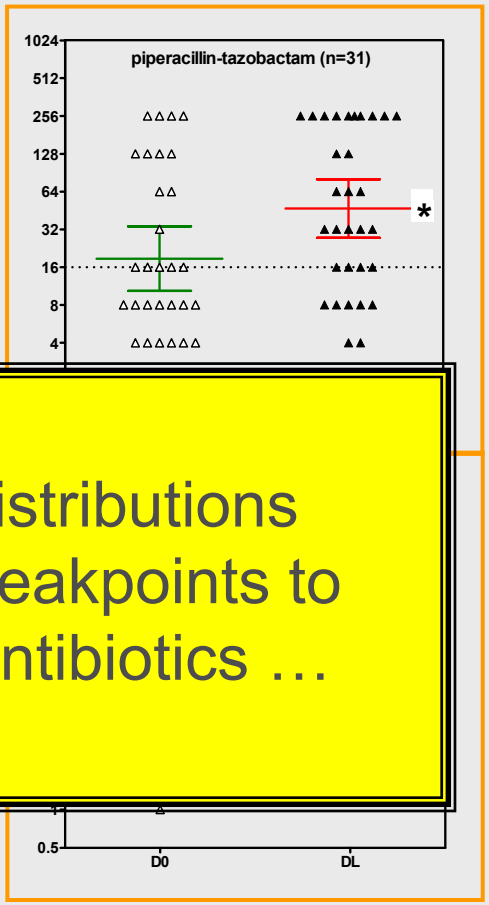
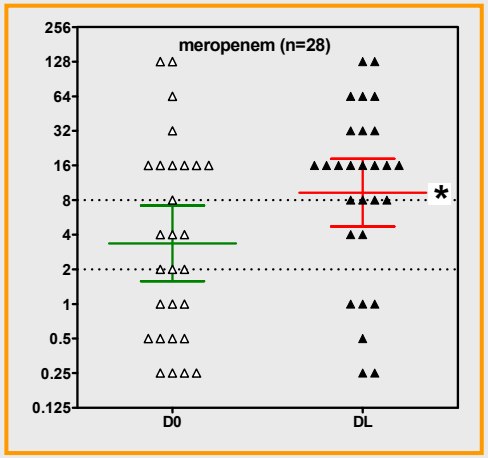






Messages:

1. Know your local MIC distributions and use appropriate breakpoints to avoid choosing weak antibiotics …
2. We must eradicate …

Riou *et al.* IJAA 2010; 36:513-522

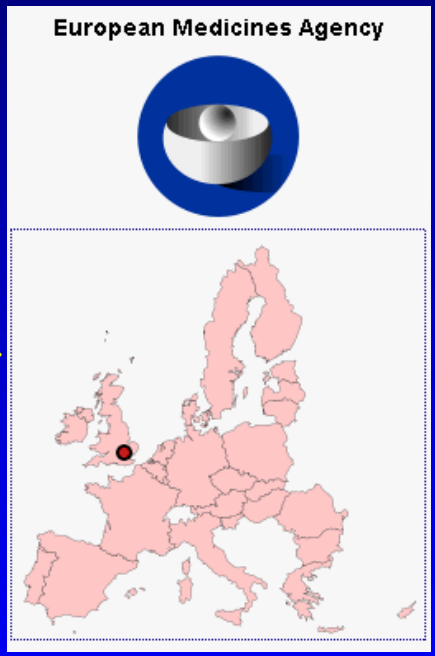
Eradication is already an old story …

Paul Ehrlich:

‚Frapper fort et frapper vite' (Hit hard and early) –

Address to the 17th International Congress of Medicine, 1913

Ehrlich P, Lancet 1913; 2:445–51.



PK /PD and resistance in Europe

" Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties… "

---

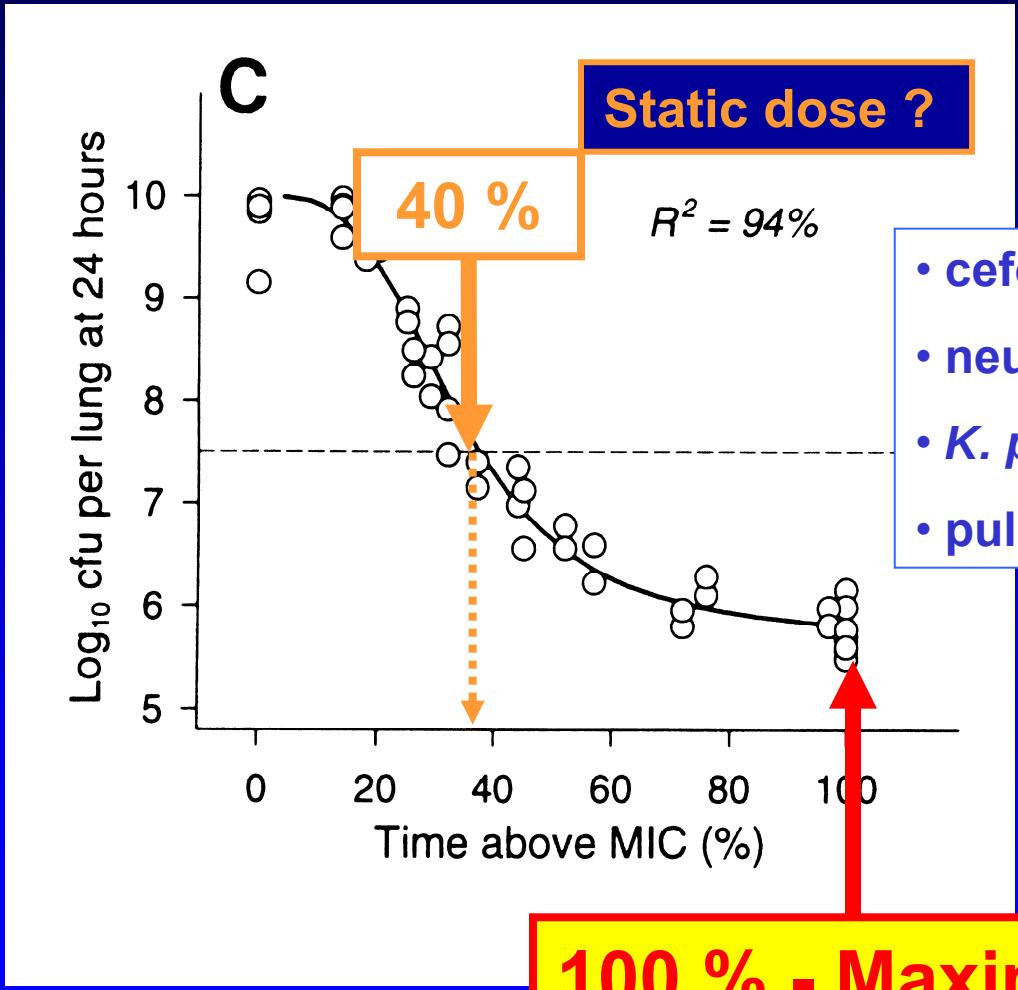
* Committee for Proprietary Medicinal Products – European Medicines Agency

PK-PD properties of antibiotics

Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties :

- **Time-dependent (" T > MIC ")**
  → β-lactams (all)
- **Concentration-dependent (" Cmax / MIC")**
  → aminoglycosides and, for eradication, fluroquinolones
- **Total daily dose-dependent (" AUC / MIC ")**
  → fluroquinolones (for global efficacy) and all others

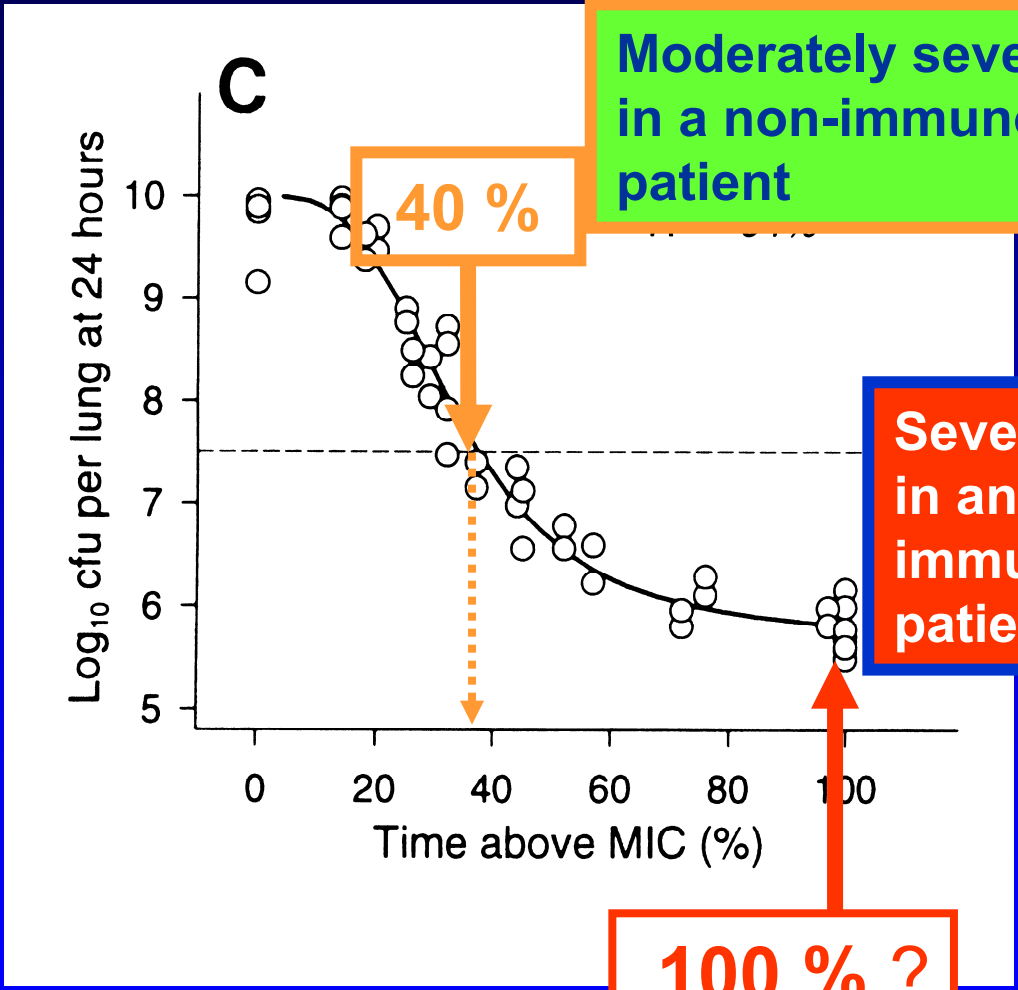
β-lactams: how much time above MIC ?



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

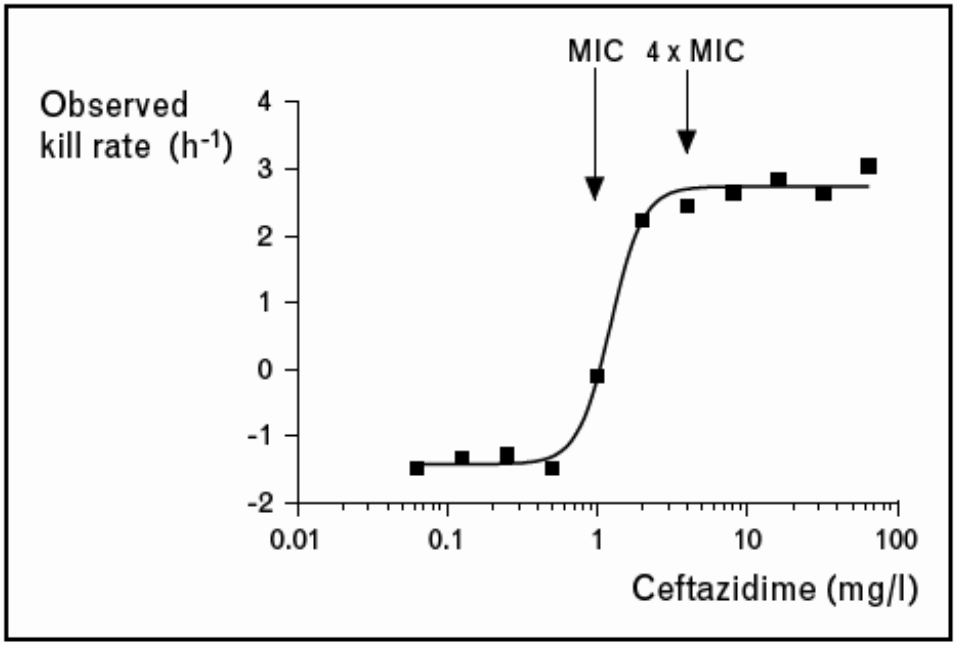
100 % - Maximal effect ?

Here is a proposal ...



But how much above the MIC ?

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.

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)

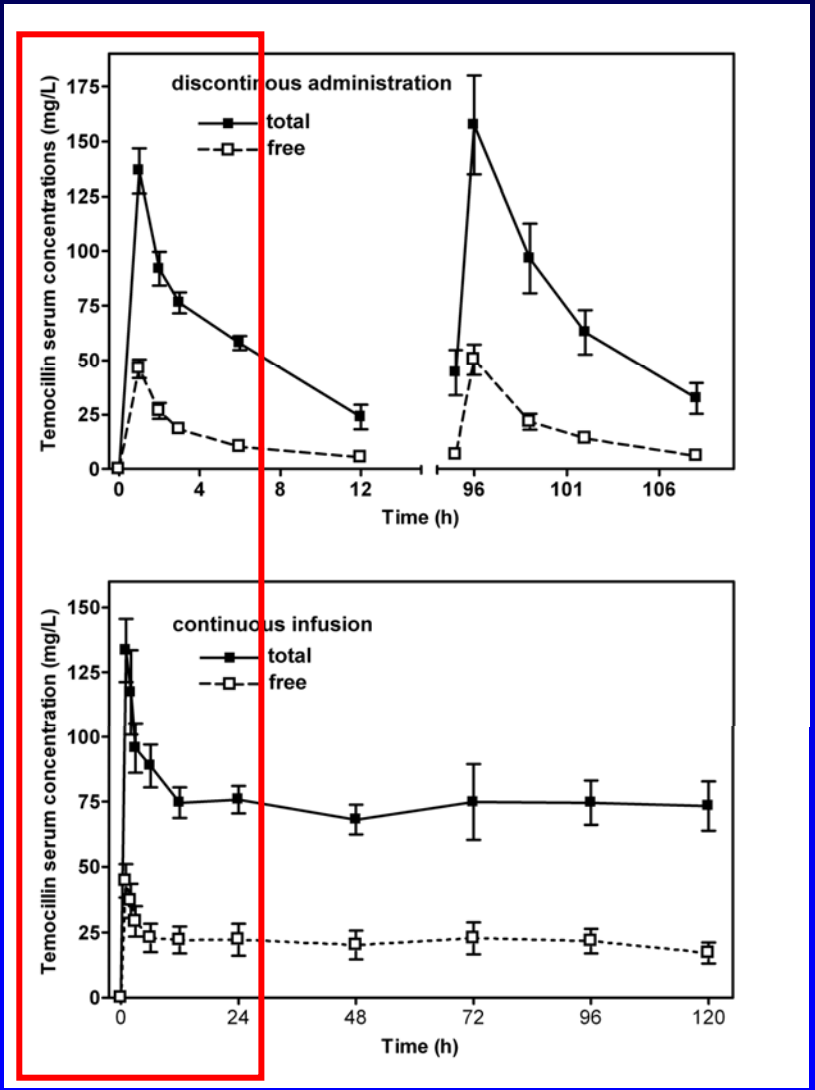
Continuous infusion of β-lactams: an overview…

- 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 in practice
1. loading dose: a simplified (useful) 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) ?

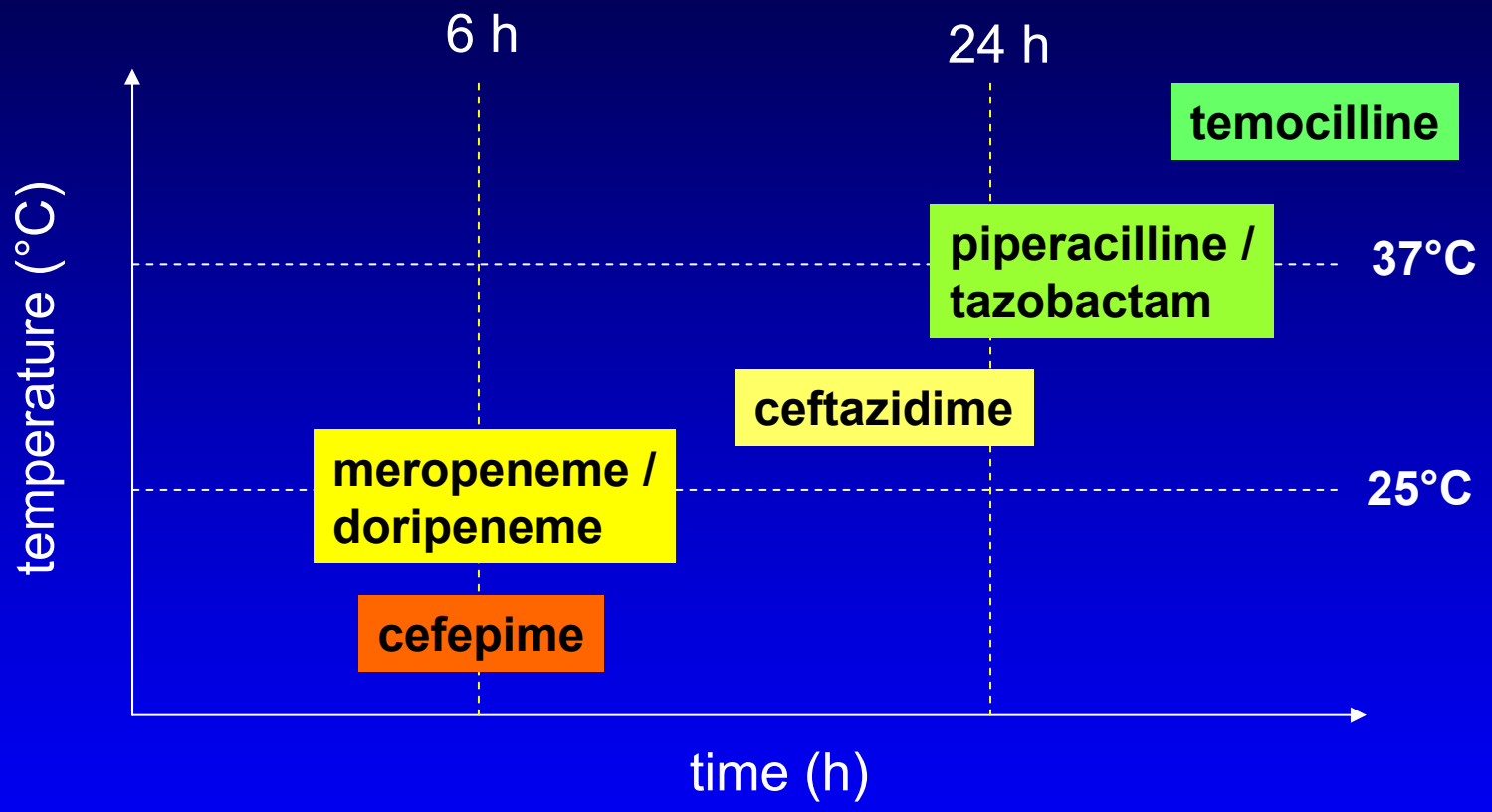


Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- **drug instability**

you may like to monitor the serum levels if MICs ≥ 4 (also for discontinuous administration)

β-lactam stability in a nutshell…



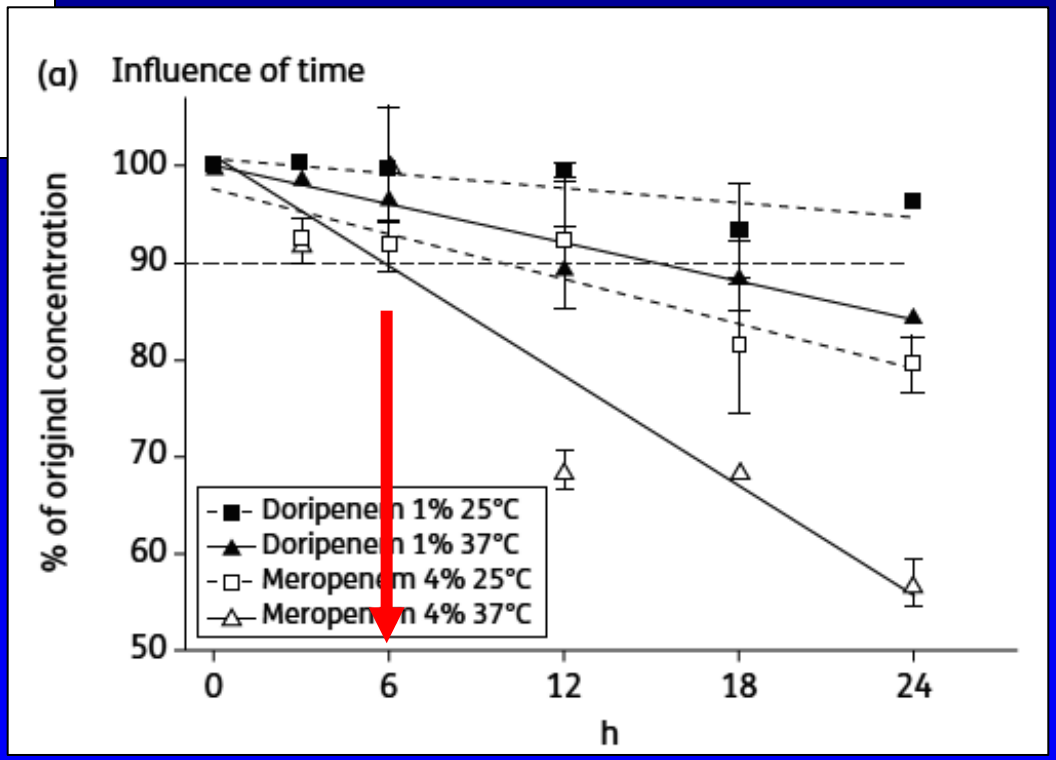
* Servais & Tulkens, AAC 200;45:2643-7 – Viaene et al. AAC 2002;46:2327-32 - Baririan et al. JAC 2003;51:651
other references for indivual drugs in in Berthoin et al. (in preparation).

Carbapenems stability

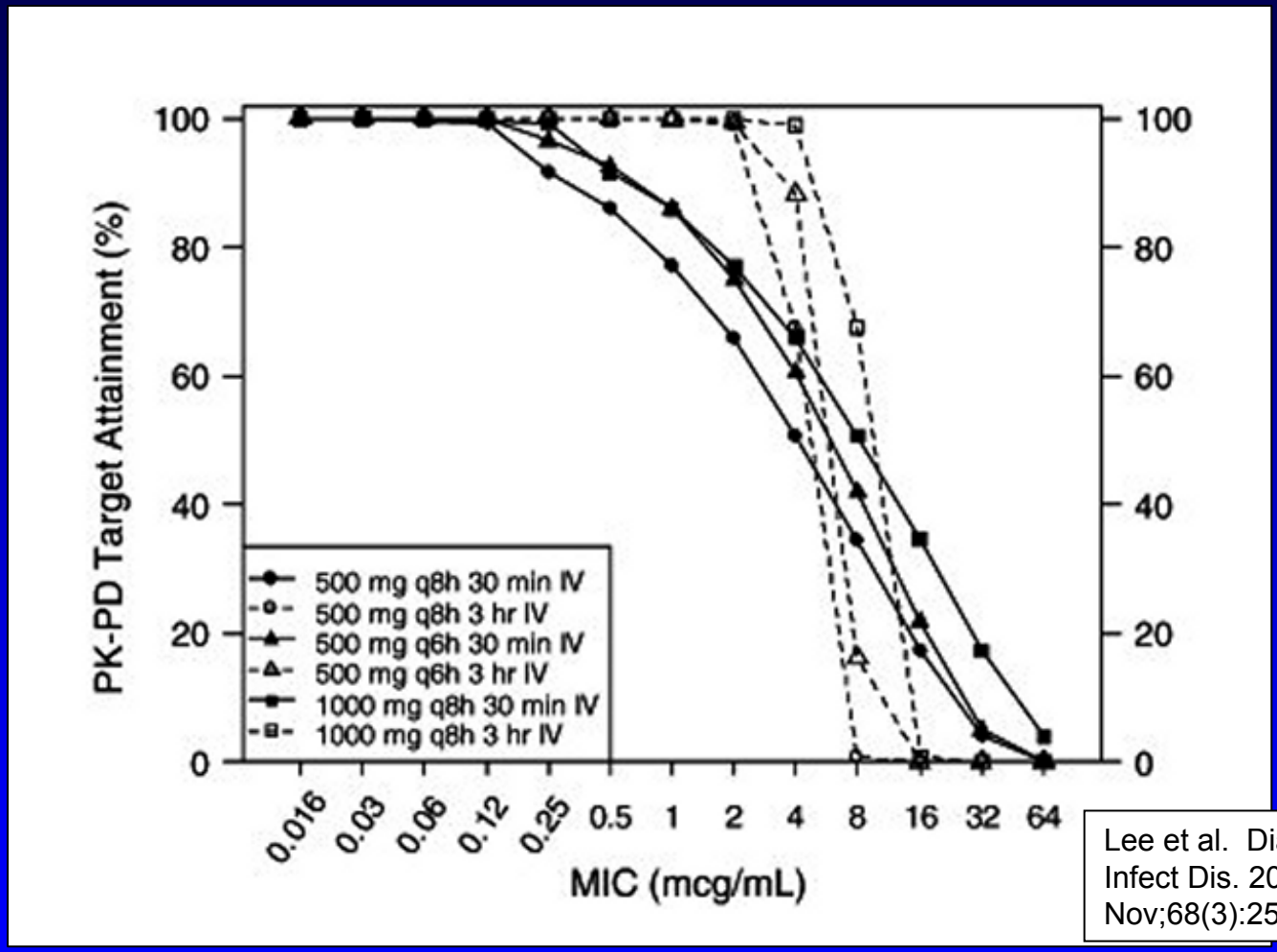
J Antimicrob Chemother ***(2010) 65:1073-1075***
doi:10.1093/jac/dkq044
Advance publication 21 February 2010

Stability of meropenem and doripenem solutions for administration by continuous infusion

Karine Berthoin[1], Cécile S. Le Duff[2], Jacqueline Marchand-Brynaert[2], Stéphane Carryn[1,3] and Paul M. Tulkens[1]*



Carbapenems in 3h infusion: target attainment rate *



Lee et al. Diagn Microbiol Infect Dis. 2010 Nov;68(3):251-8.

*** probability of attaining the target of 40% *T* > MIC by MIC for d meropenem as a 30-min and 3-h infusion at the simulated dosage regimens**

To be practical :
3 h infusion for "difficult" organisms and for patients with normal renal function

1. Loading dose (in 30 min)
   - 2 g (cefepime / meropenem)*
2. Followed immediately by an 3 h infusion
   - 2 g (cefepime / meropenem)*
3. Repeat step 2 every 8 h

---

* piperacillin/tazobactam: loading dose: 4.5 g; infusion: 4.5 g every 6 h
  imipenem: loading dose max. 1 g; infusion: 1 g every 6h (max.)

Continuous infusion with vancomycin ?

1. loading dose

C_t = Dosis / V_d

Dosis = C_t x V_d

target level: 27.5 mg/L

Vd (L/kg): **0.7 ***

dose (mg/kg): **19.25 mg/kg**

* 0.39 tot 0.97 L/kg
Matzke et al. Clin Pharmacokinet. 1986 Jul-Aug;11(4):257-82.

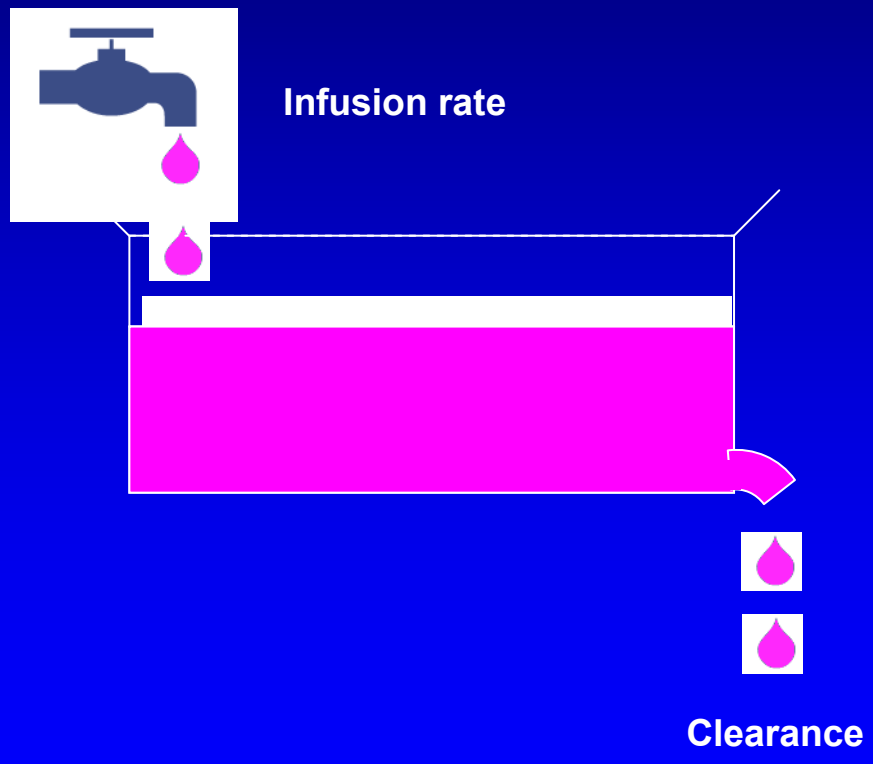
Continuous infusion of vancomycin …

2. infusion

C_{ss} = infus. rate / Cl_{van}

infus. rate = C_{ss} x Cl_{van}

make it stable …



target level: 27.5 mg/L

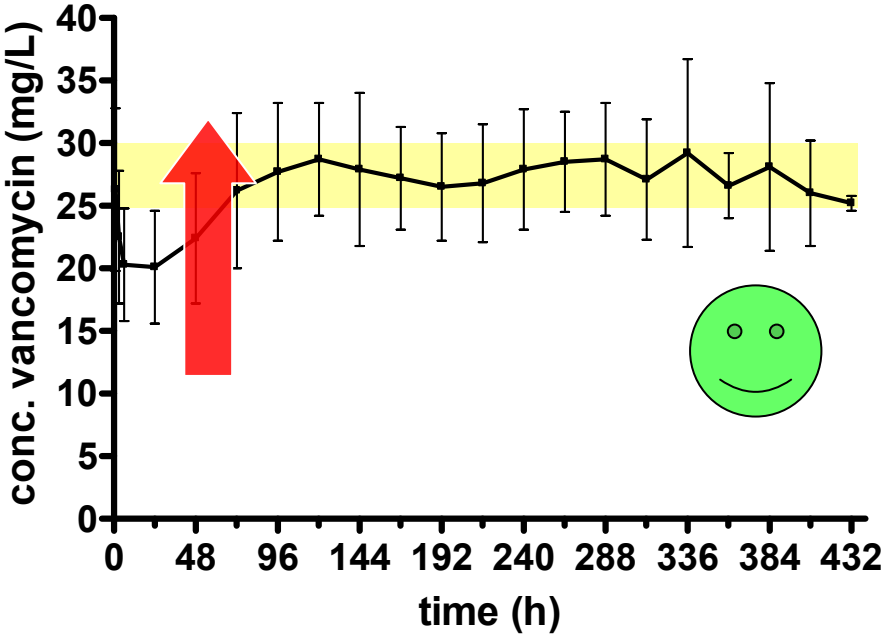
Cl_{van} : **0.65 x $Cl_{creatinin}$**

infus. rate: 1.78 mg x min^{-1}
(for Clcr = 0.1 L x min^{-1})

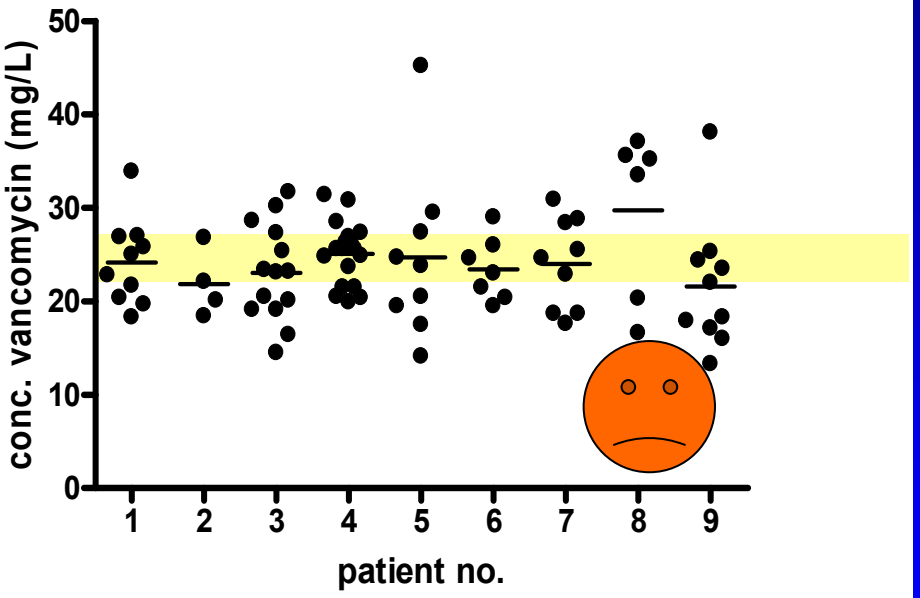
daily dose: **2.57 g**

Results

concentration of vancomycin as a function of the time in patients treated with continuous infusion



Variability of vancomycin concentration during continuous infusion (typical patients)



Ampe *et al.*, in preparation

"Pros" 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…

"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 vancomycin, levels > 28 mg/L have been associated with renal toxicity; for beta-lactams, levels > 80 mg/L have been associated with convulsions [cefepime]) *

* not addressed in this talk, but ask questions…

Continuous infusion of antibiotics ...

A brilliant idea....

But do not forget the problems...

In a nutshell ... so far …

- Microbiology parameters: MIC !
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams and vacomycin
- **The (hidden) problem if you underdose**
- Take home message

A simple experiment …

Exposure of *E. aerogenes* to anrti-Gram (-) penicillin (temocillin) to 0.25 MIC for 14 days with daily readjustment of the concentration based on MIC détermination

strains	Initial			TEM-exposed			Revertant		
	MIC (mg/L) [a]			MIC (mg/L)			MIC (mg/L)		
	TEM	FEP	MEM	TEM	FEP	MEM	TEM	FEP	MEM
2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
2502/4 [c]	8	2	0.125	**8192**	4	0.25	**4096**	1	0.125
3511/1 [c]	**32**	2	0.125	**4096**	**32**	0.125	**4096**	**8**	0.5
7102/10 [d]	**512**	**32**	1	**16384**	**> 128**	4 [e]	**8192**	**64**	1

[a] figures in bold indicate values > the R breakpoint for Enterobacteriaceae (EUCAST for MEM [8] and FEP [4]; BSAC and Belgium for TEM [16])
[b] dotblot applied with antiOmp36 antibody; signal quantified for grey value after subtraction of the signal of a porin-negative strain (ImageJ software); negative values indicate a signal lower than the background
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

Nguyen T *et al.* unpublished

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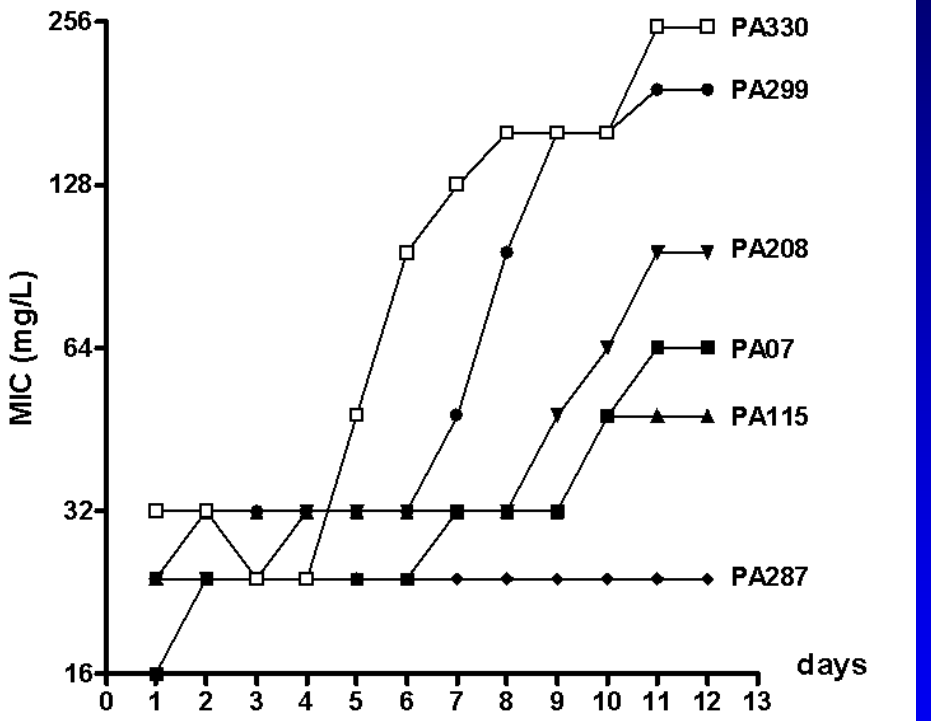
sub-MIC concentrations are associated with resistance !

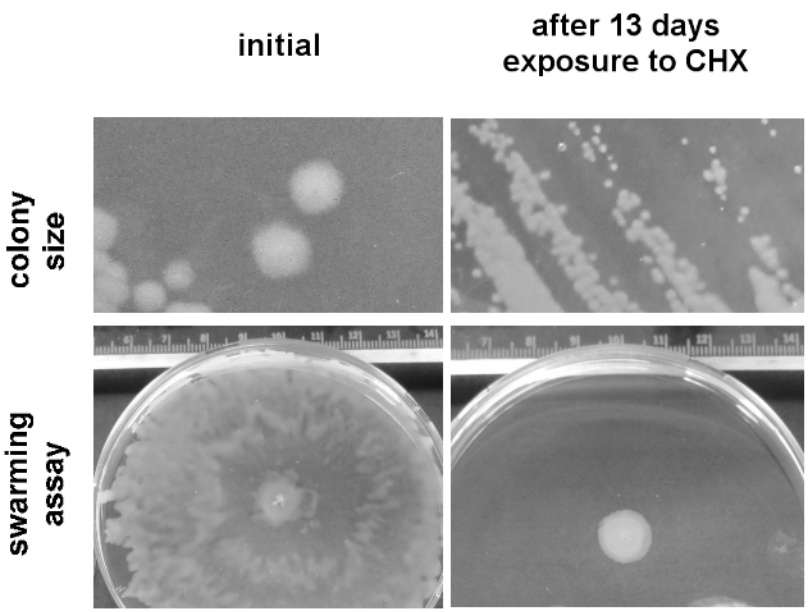
Nguyen T *et al.* unpublished

And this happens also with biocides

Exposure of *P. aeruginosa* to sub-MIC concentrations of chlorhexidine



Change in MIC of CHX during exposure to 0.5 MIC with daily concentration readjustment



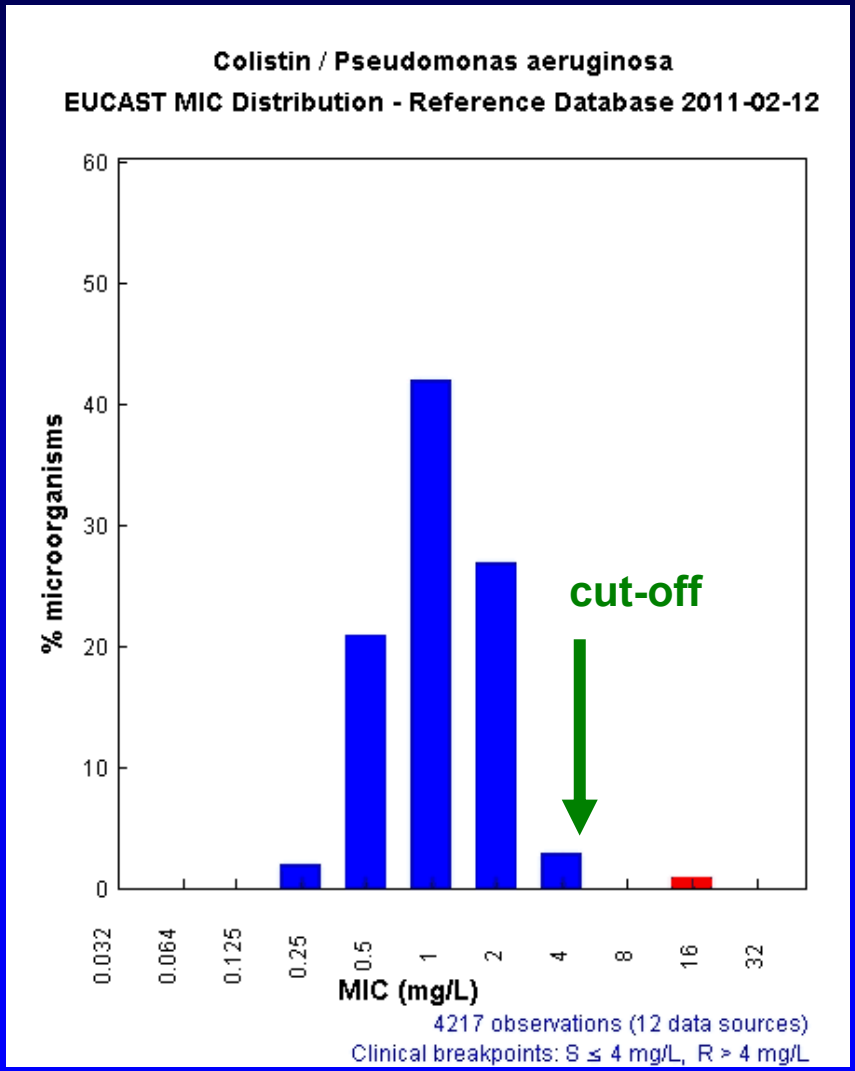
Typical change in colony size and swarming abilities after 13 days of exposure to 0.5 MIC

Tan *et al.* ECCMID 2011, in press

And what about colistin ?

You first need to consider the MIC distribution.

Here are the data of EUCAST for *Pseudomonas*



Do you ever reach the epidemiological cut-off ?

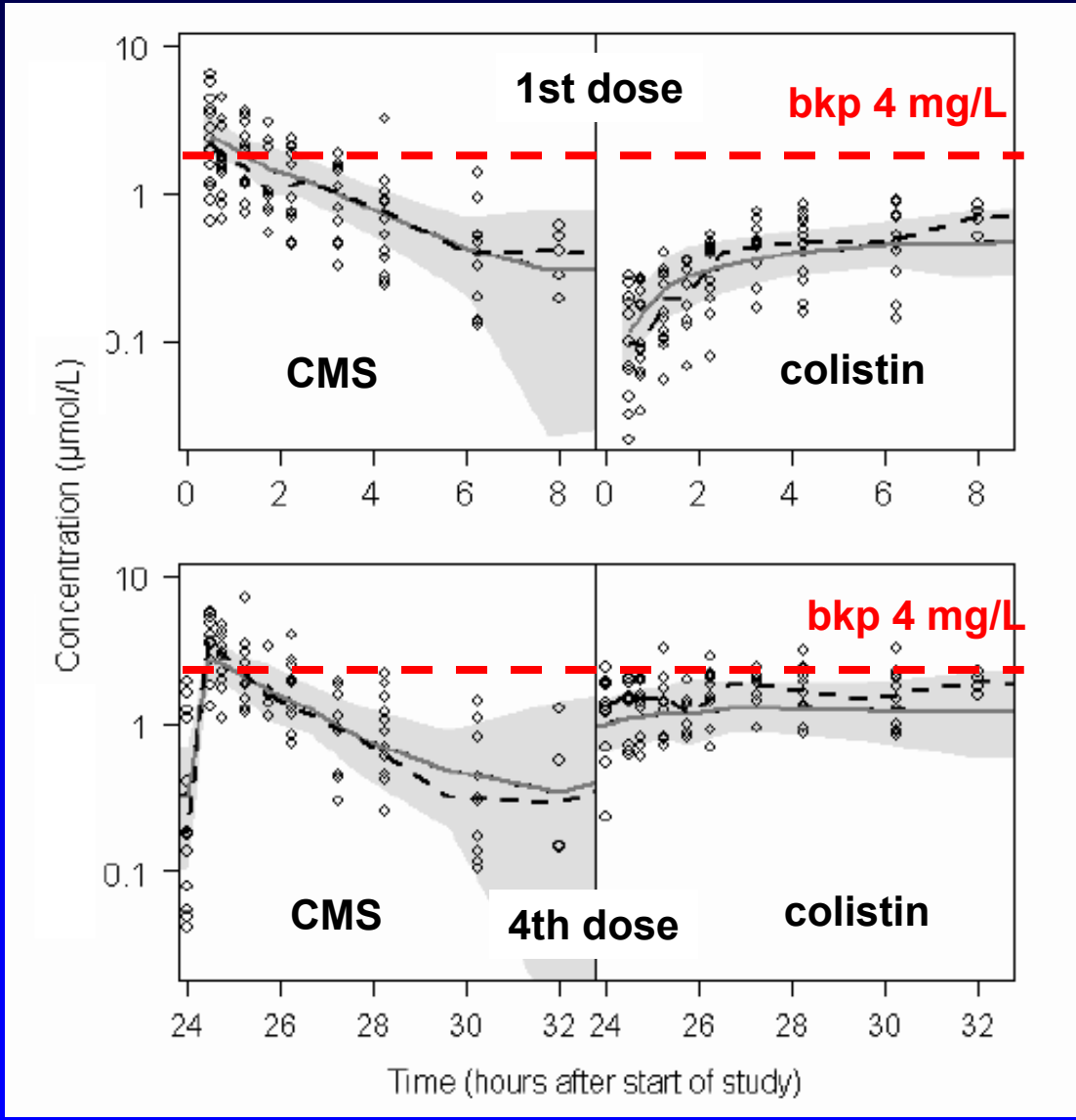
Dosage (colistine methane sulfonate [CMS]): 240 mg every 8h (= 3 x 10^6 UI)

CMS
- $t_{1/2}$ ~ 2.3 h,

Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax (pred.)
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

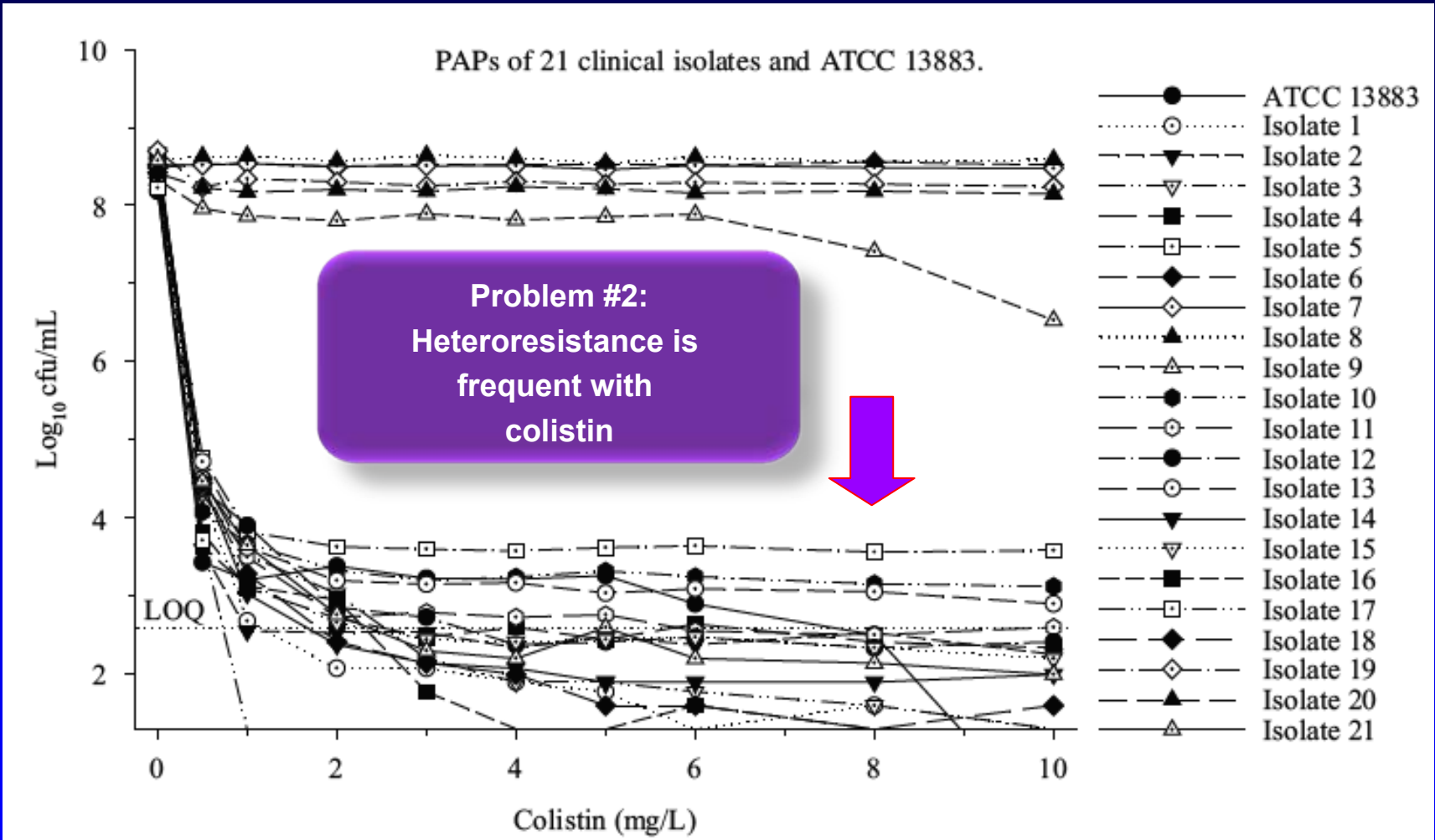
Problem #1:
Low initial blood levels suggest the necessity of a loading dose

Plachouras et al. AAC 2009; 53:3430-6



Do you hit all your inoculum ?

Population analysis profiles of K. pneumoniae isolates



Poudyal et al. JAC 2008; 62:1311-1318

WHO statement 2000

The most effective strategy against antibiotic resistance is:

- “to unequivocally destroy microbes”
- “thereby defeating resistance before it starts”

WHO Overcoming Antimicrobial Resistance, 2000

Slides are available from http://www.facm.ucl.ac.be