

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



AIM ACADEMY FOR
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MANAGEMENT
Improving outcomes through education

Delhi – 16 February 2011



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

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&

International Society of Antiinfective Pharmacology



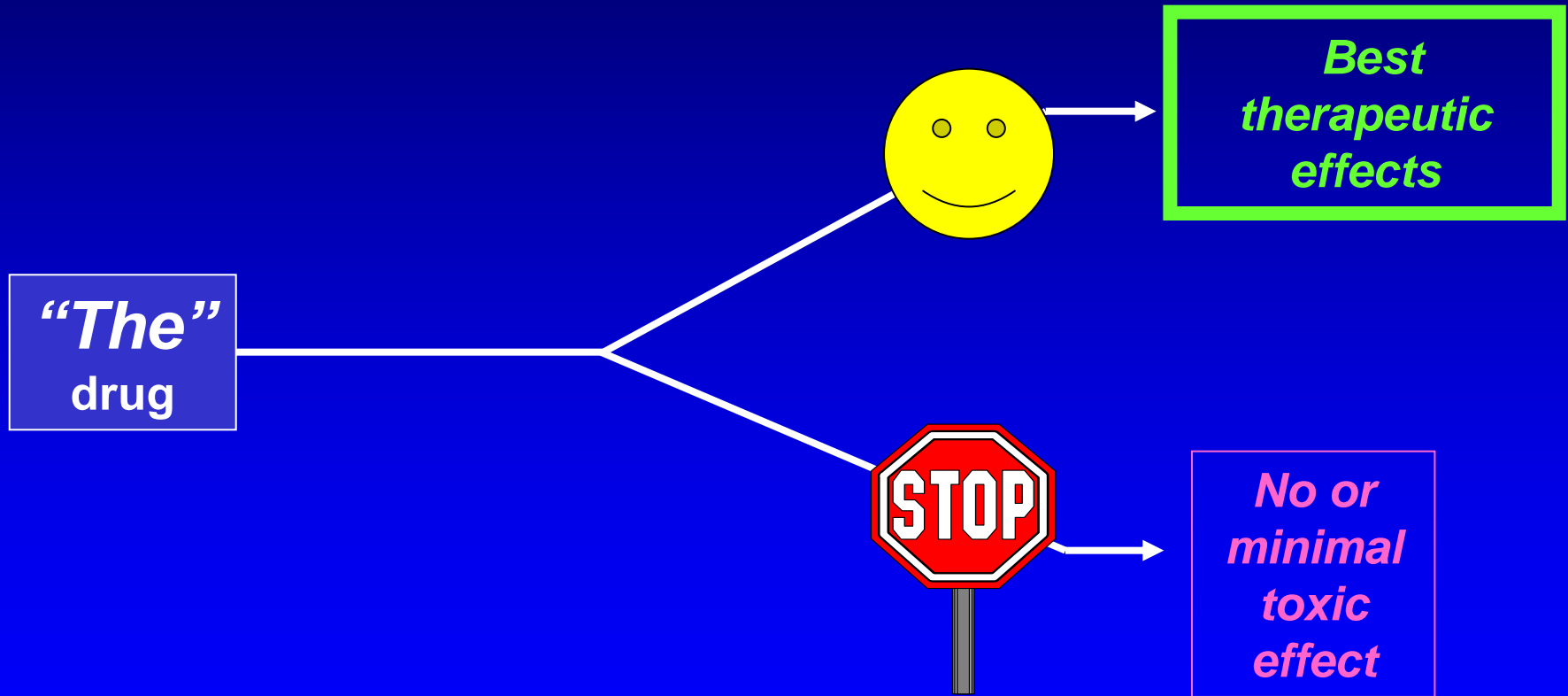
<http://www.facm.ucl.ac.be>



<http://www.isap.org>



Antibiotic treatment: Wat does the clinician want ?





The ideal antibiotic ...

the
molecule

brilliant
and
clear
solutions

ent's
cure

chemistry

microbiology

therapy





Is the molecule always ideal ?

the
ideal
molecule

brilliant
and
clear
solutions

patient's
cure

chemistry

microbiology

therapy



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

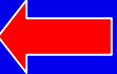
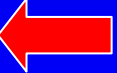
- **Patient related failures**

- 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

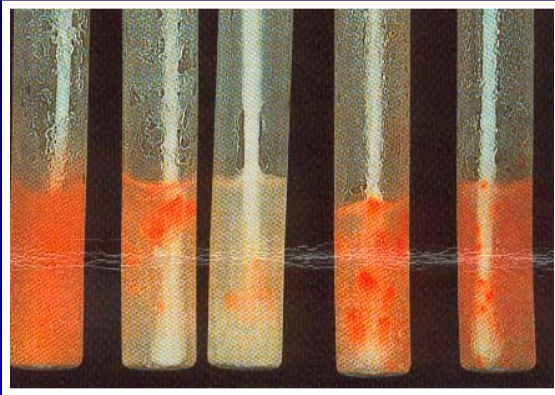


In a nutshell ... so far ...

- **Microbiology parameters: MIC !**
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams:
Time-above MIC
- The problems if you underdose
- Take home message



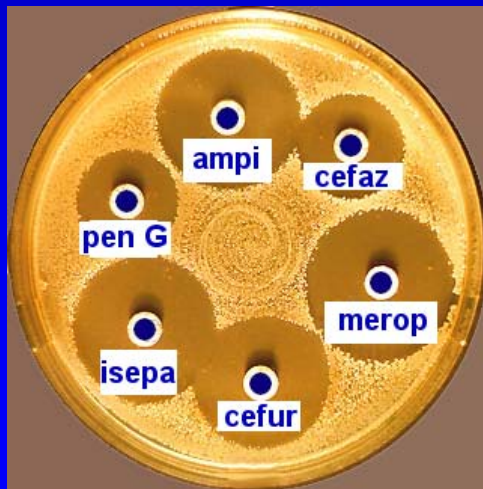
Microbiology



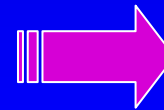
identification



susceptibility



by disc or
other
techniques



at which drug
concentration
do we inhibit
growth ?



What do I do in my country (in relation to microbiology) ?

- Survey the level of resistance of *P. aeruginosa* and *S. pneumoniae* from selected hospitals and relate it to therapy ¹
- Examine the mechanisms of resistance acquisition (with special reference to efflux pumps) ²

Assess new antibiotics and novel approaches
(immunotherapy) ³

- Examine the susceptibility to biocides ¹

Supported by

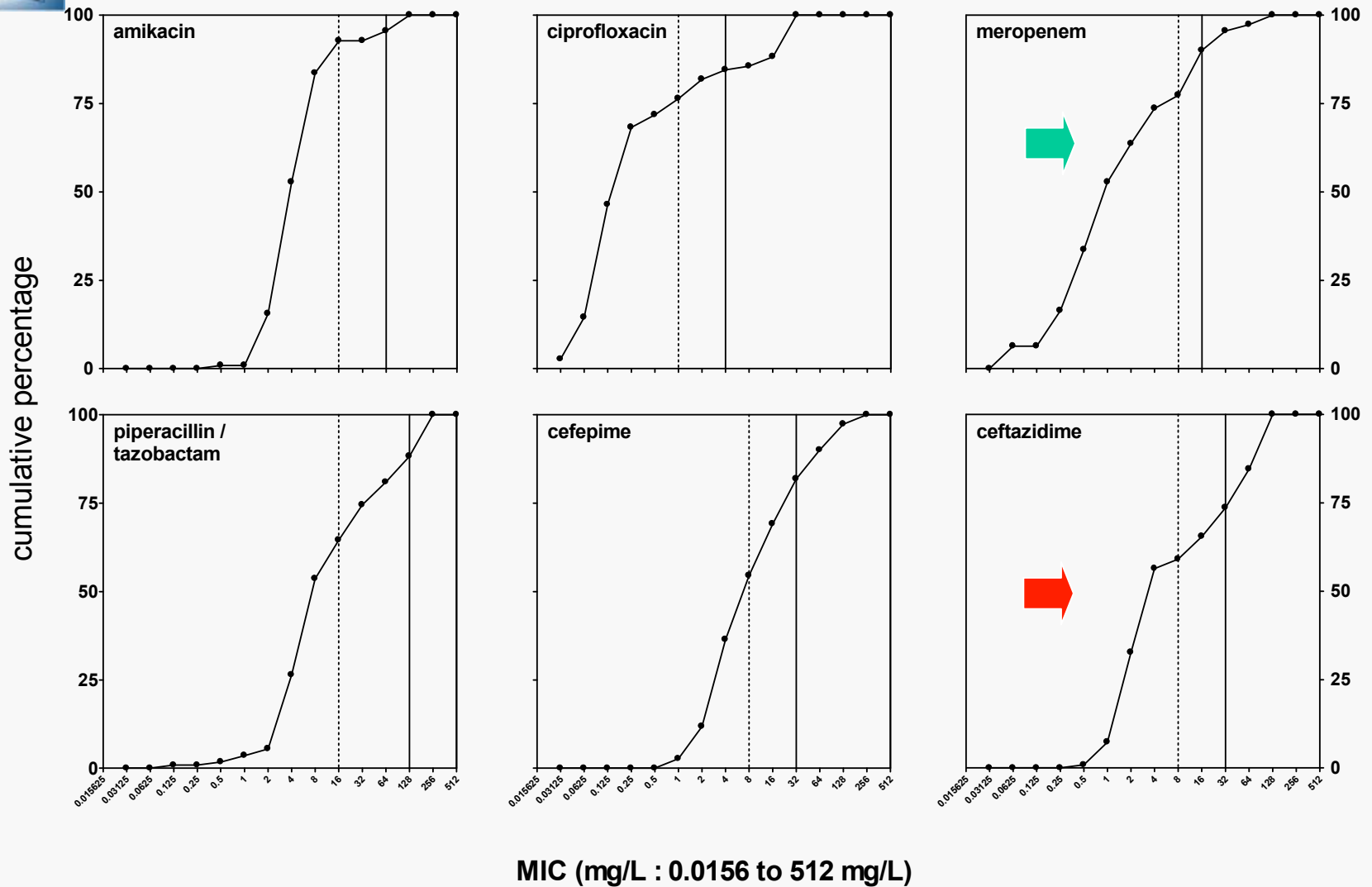
1 Regional authorities and the Fund for Industrial Research

2 Fund for Scientific and Medical Research

3 Pharmaceutical Industry and small/medium enterprises



What is the situation at day 0 with *P. aeruginosa* in HAP ?

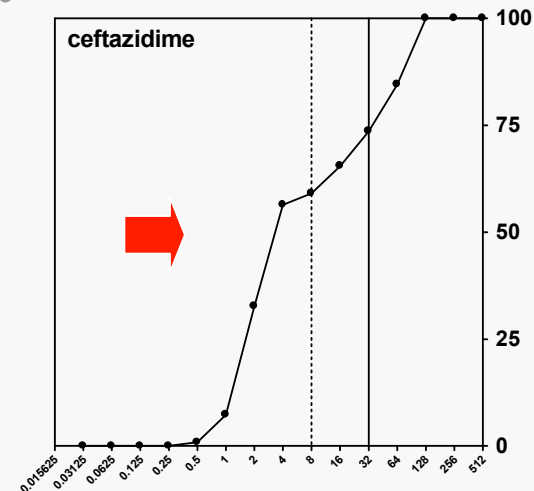
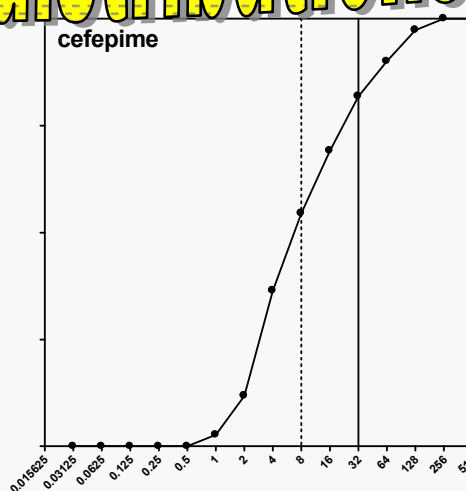
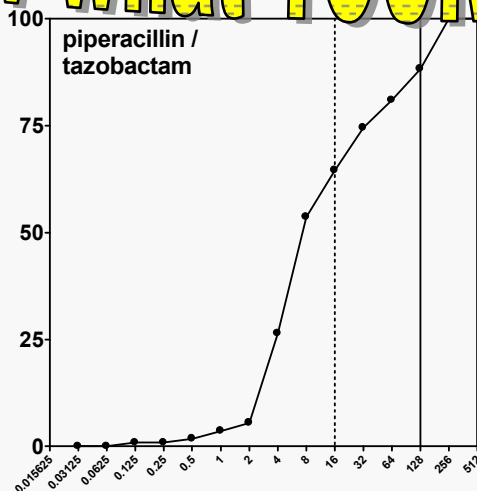
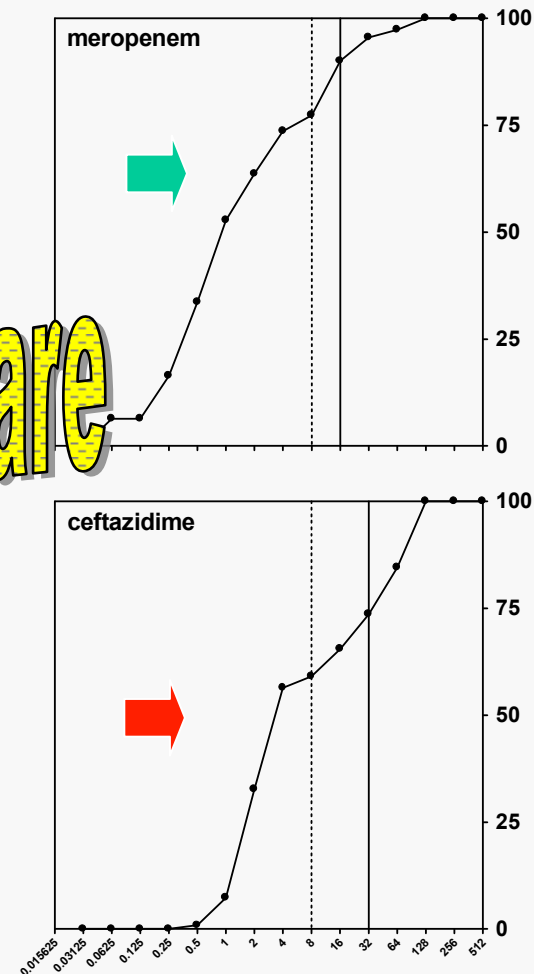
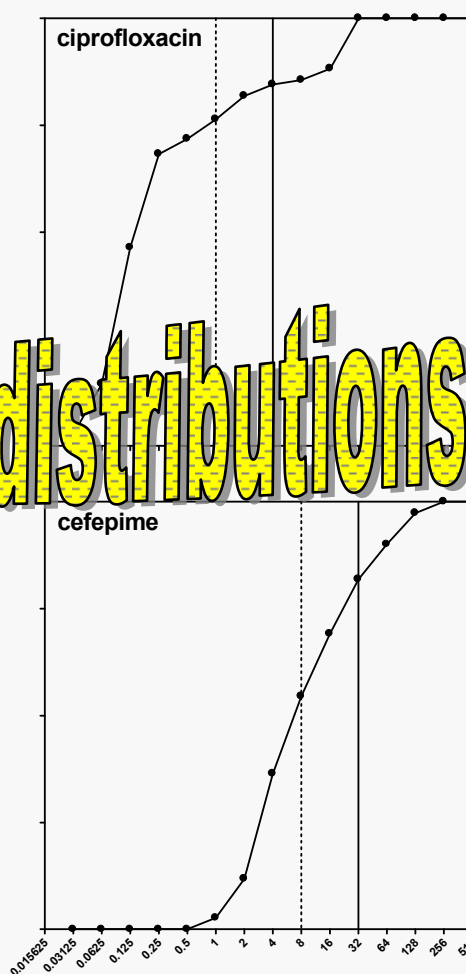
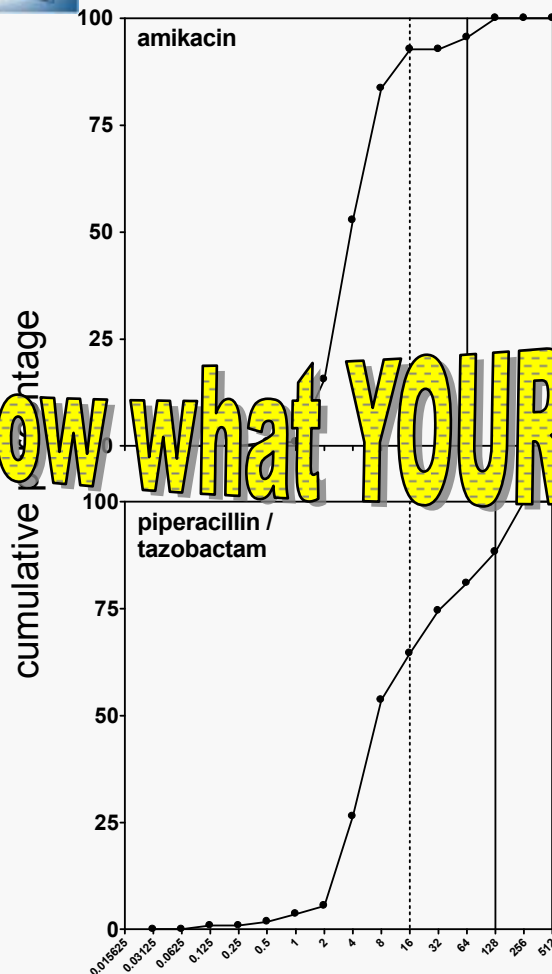


Riou et al. IJAA 2010; 36:513-522



What is the situation at day 0 with *P. aeruginosa* in HAP ?

Know what YOUR distributions are



MIC (mg/L : 0.0156 to 512 mg/L)

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

Moving on ...

- Does your microbiologist discuss infection cases in ICU with you ?

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



Asking the question you always wanted to ask ...

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

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



Asking the question you always wanted to ask ...

- Does your microbiologist gives 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 the textbooks say about antibiotic dosages and schedules in the 70's ?

1. Stay above the MIC... but how much ?
2. Remain around for a while... but how long ?
3. Hope it works... against everything ?
4. Hope it is not toxic... can't do much ...

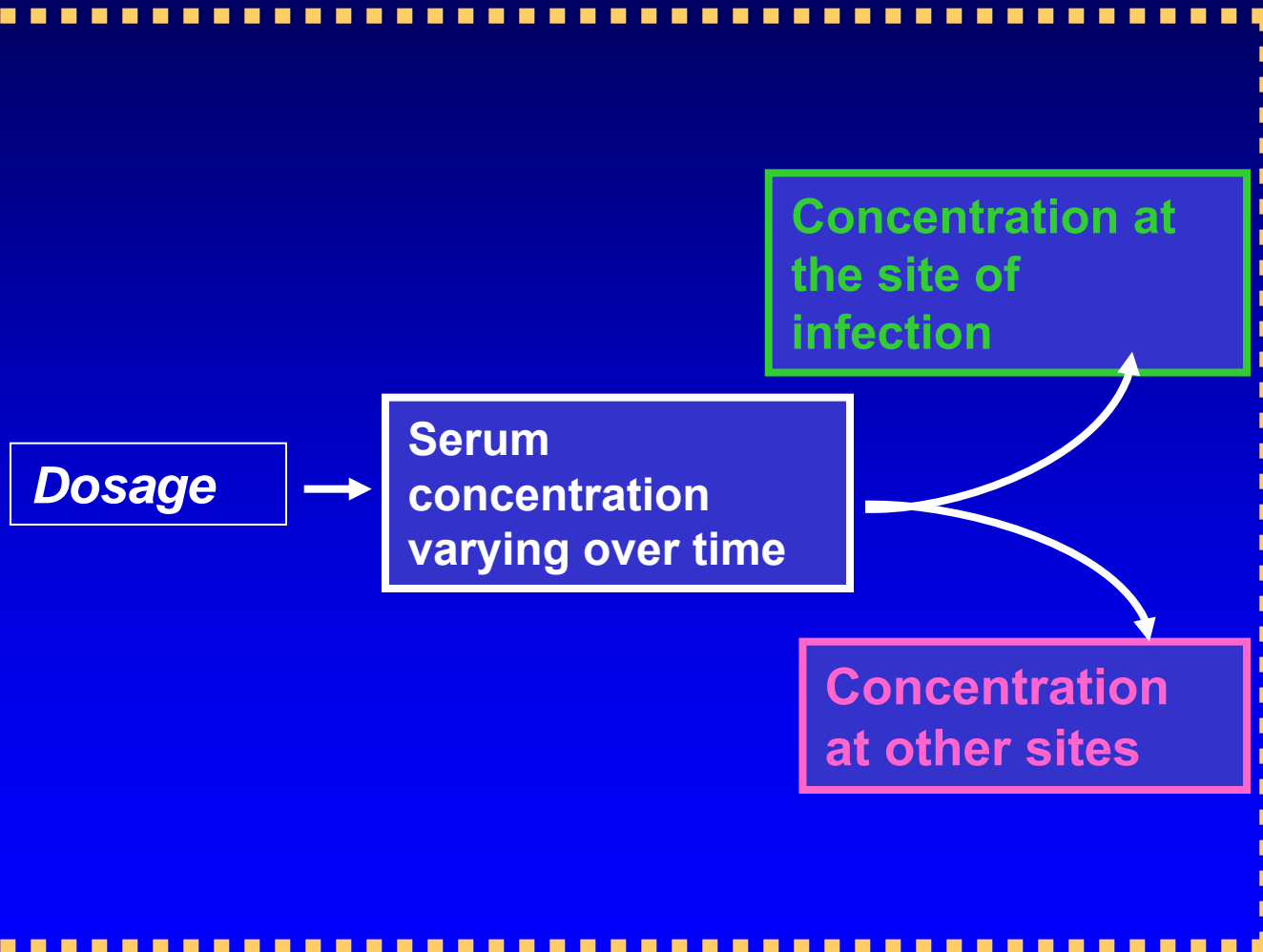


In a nutshell ... so far ...

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- **Pharmacodynamic parameters**
- PK/PD as applied to beta-lactams:
Time-above MIC
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- Take home message

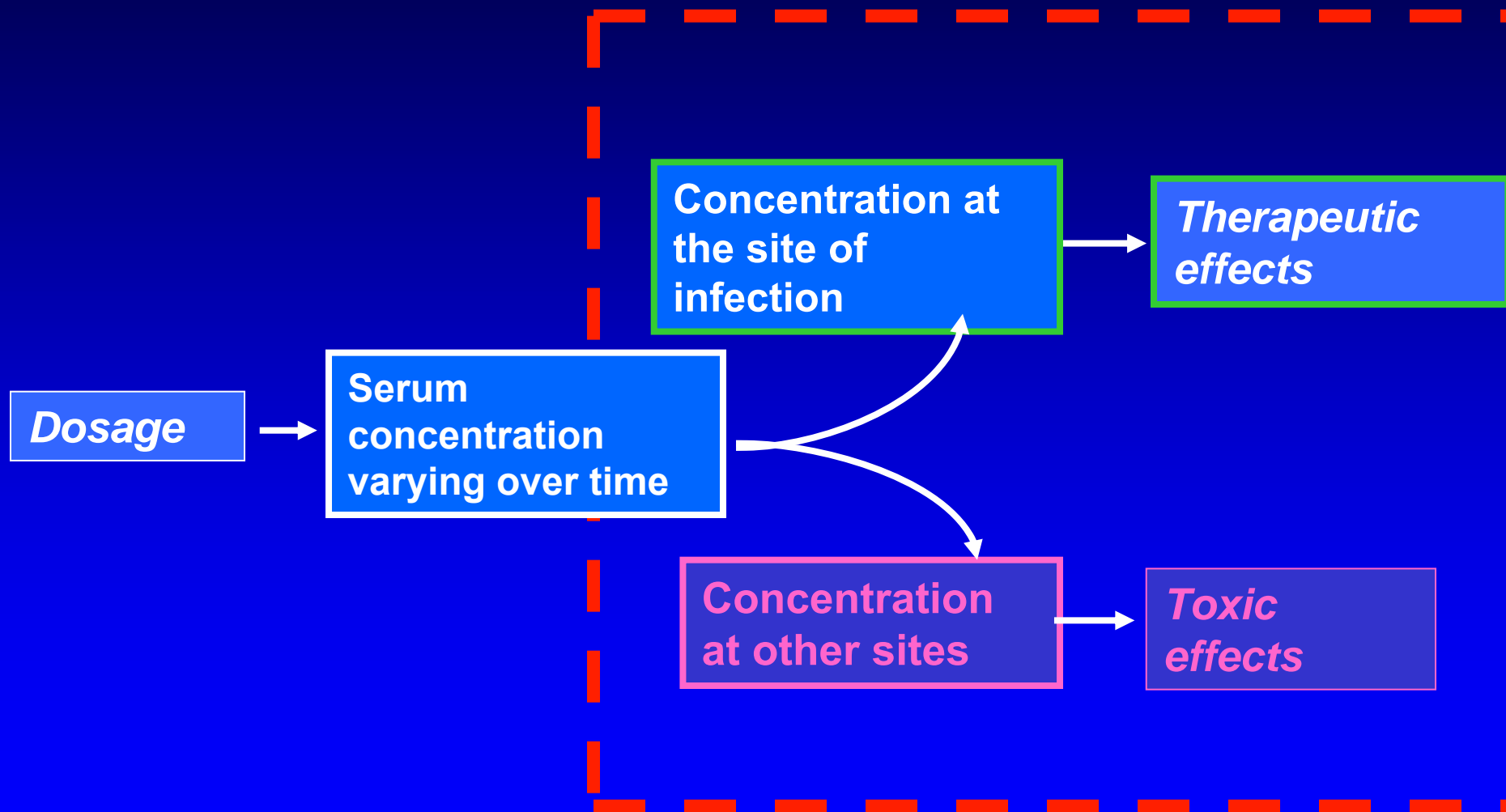


Pharmacokinetics





Pharmacodynamics

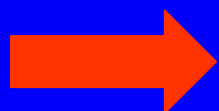




PK / PD : why does it improve the use of antibiotics ?

The basics:

- anti-infective drug usage has long been irrational or not scientifically based on a pharmacodynamic point of view
 - search for low doses for fear of toxicity
 - “errors” in drug dosages at registration
 - misunderstanding of “optimal schedules”
- pharmacokinetics was mostly used to establish “drug presence” rather than to correlate dosing with efficacy



pharmacodynamics of antiinfective drugs was largely “*terra incognita*” 20 years ago



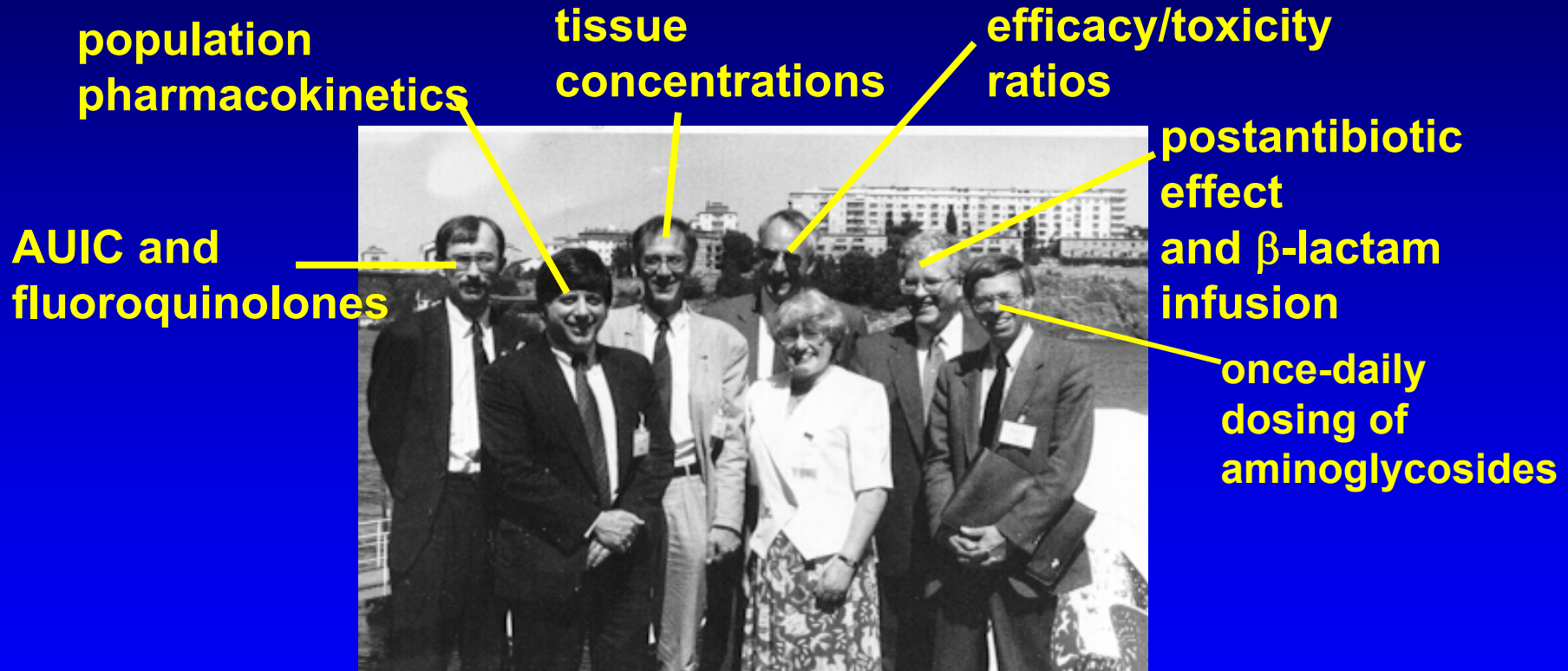
How did it start ?



met in Stockholm in 1989 ...

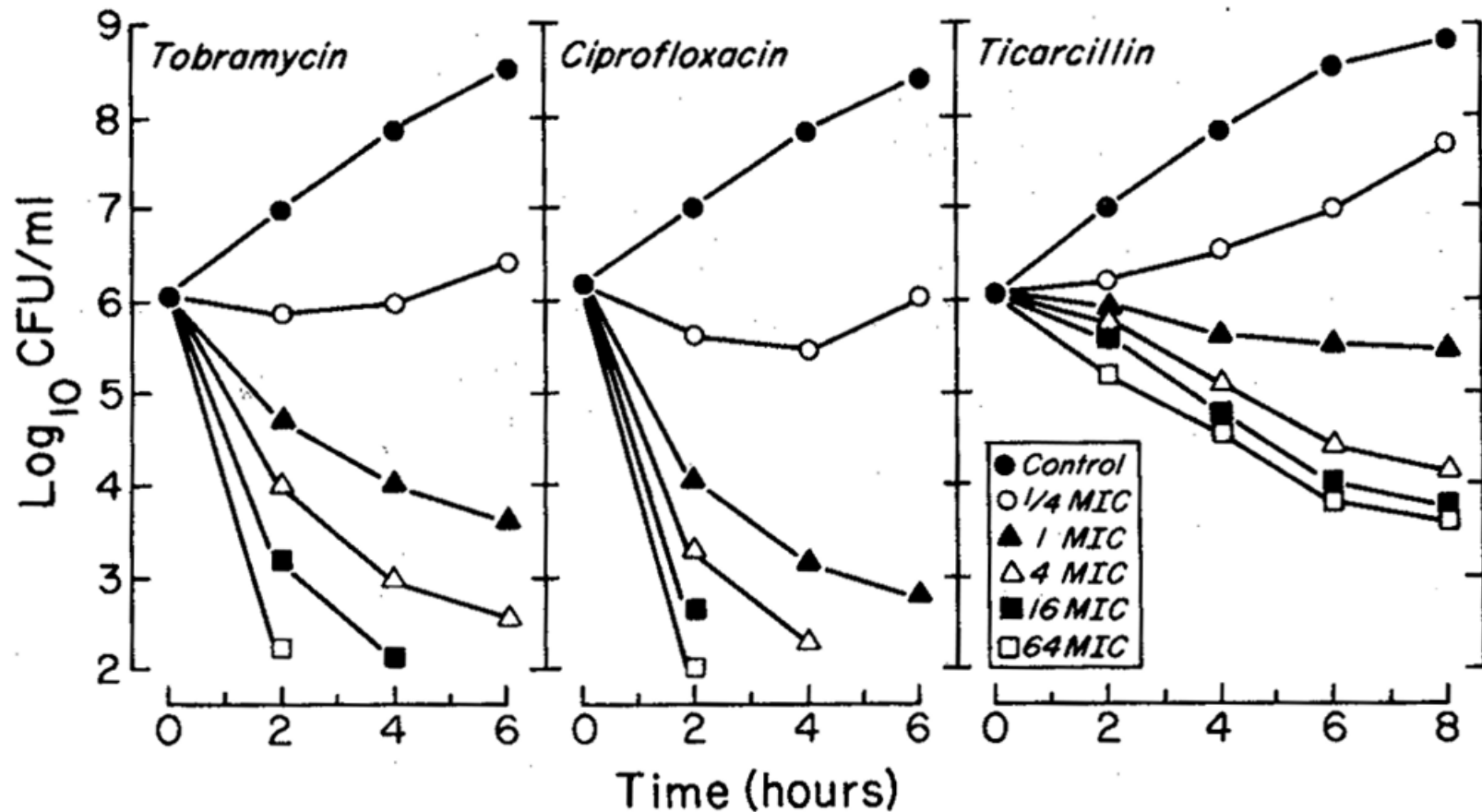


What did they think all about ?





Pharmacodynamics : influence of time and concentration ...

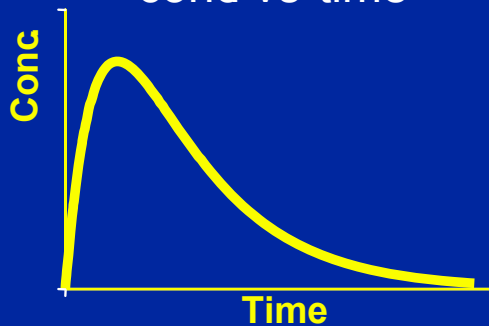


Craig et al.

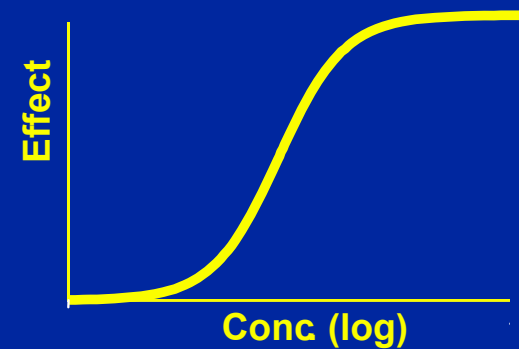


Pharmacokinetics - Pharmacodynamics

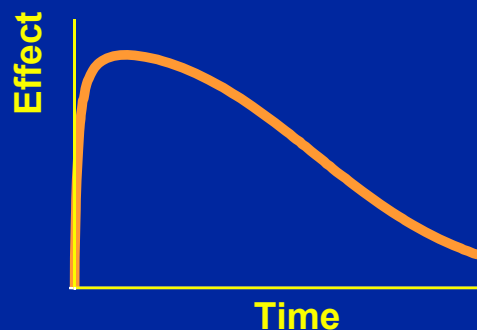
Pharmacokinetics conc vs time



Pharmacodynamics conc vs effect



PK/PD effect vs time



from Derendorf,
ISAP workshop



PK /PD in action in the Regulatory in the USA

PK/PD - Potential Benefits - Netscape

File Edit View Go Communicator Help

Bookmarks Location: www.fda.gov/cder/present/anti-infective798/biopharm/sld007.htm What's Related

PK/PD - Potential Benefits

- Facilitate Early Selection of Lead Drug Candidate (e.g., Pre-Clinical Screening)
- Select Appropriate Dosage Regimen (e.g., Phase 1/2)
- Better Understand Clinical / Microbiological Outcome (e.g., Phase 3)
- More Efficient Drug Development Program

July 1998 7

<http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm>

More questions ...

- Do you agree with the benefit of "HIT HARD and HIT FAST" ?



1.No

2.Yes

More questions ...

- Do you agree the benefit of "HIT HARD & HIT FAST ?"



Paul Ehrlich:

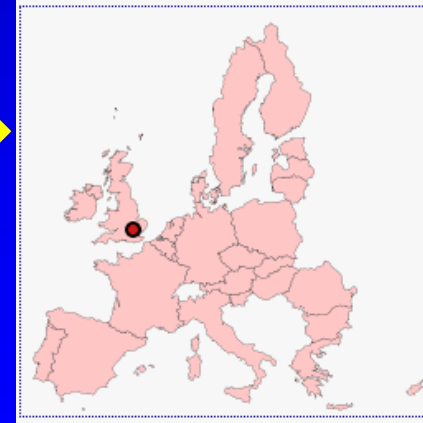
„Frapper fort et frapper vite“ (Hit hard and early) –

Address to the 17th International Congress of Medicine, 1913

Ehrlich P, Lancet 1913; 2:445–51.



European Medicines Agency





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





Publications of the EMA ...



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<http://www.ema.europa.eu>



The European Agency for the Evaluation of Medicinal Products

25 March 1999
EMA/9880/99, Rev. 1

EMA Discussion Paper on Antimicrobial Resistance

London, 27 July 2000
CPMP/EWP/2655/99

**POINTS TO CONSIDER ON PHARMACOKINETICS AND
PHARMACODYNAMICS IN THE DEVELOPMENT OF
ANTIBACTERIAL MEDICINAL PRODUCTS**



PK / PD in action for science and clinics

Some achievements:

- **once-daily dosing of aminoglycosides**
registration or reregistration in several countries
 - **amikacin, netilmicin (from bid to qd)**
 - **isepamicin (registered essentially for qd dosing)**
- **24h AUC / MIC and C_{\max} / MIC ratios used as guides**
for phase II / III trials, for treatment optimization
and for registration of new antimicrobials
 - **moxifloxacin**
 - **telithromycin**
- **Time above MIC as "gold standard" for β -lactams**



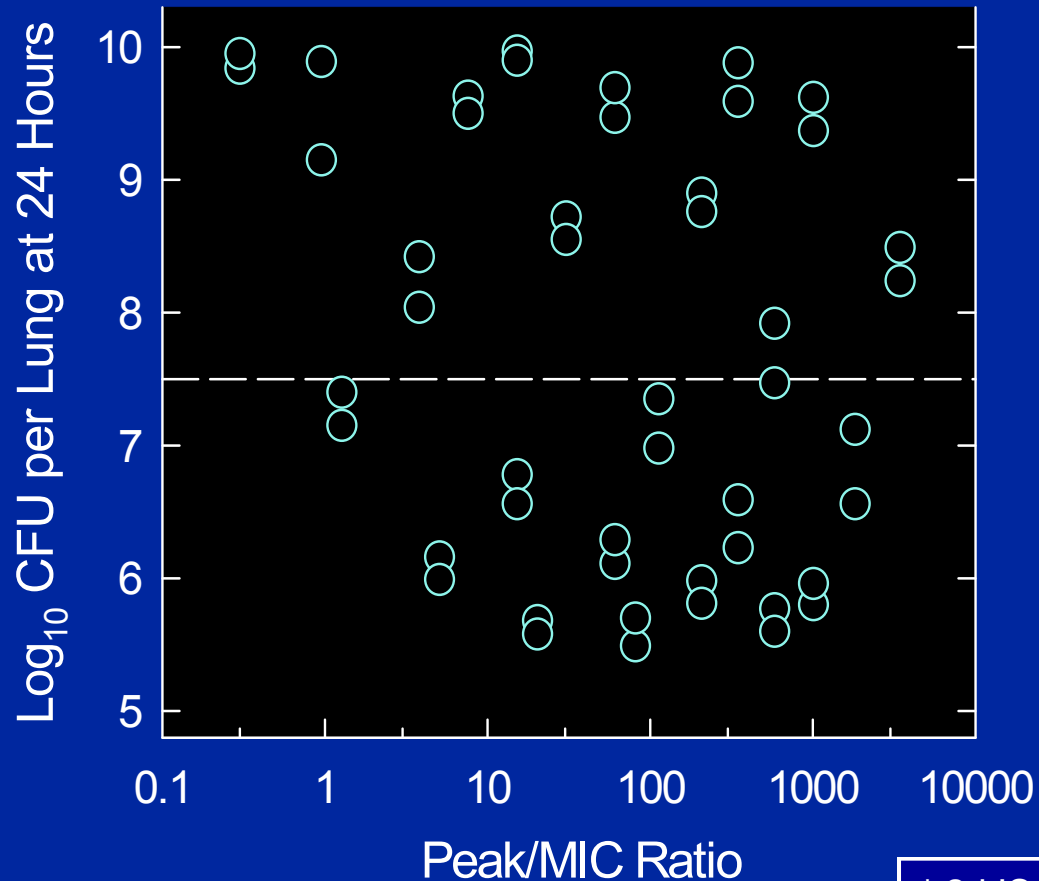
PK-PD properties of antibiotics

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 (" **C_{max} / MIC** ")
 - aminoglycosides and, for eradication, fluroquinolones
- Total daily dose-dependent (" **AUC / MIC** ")
 - fluroquinolones (for global efficacy) and all others



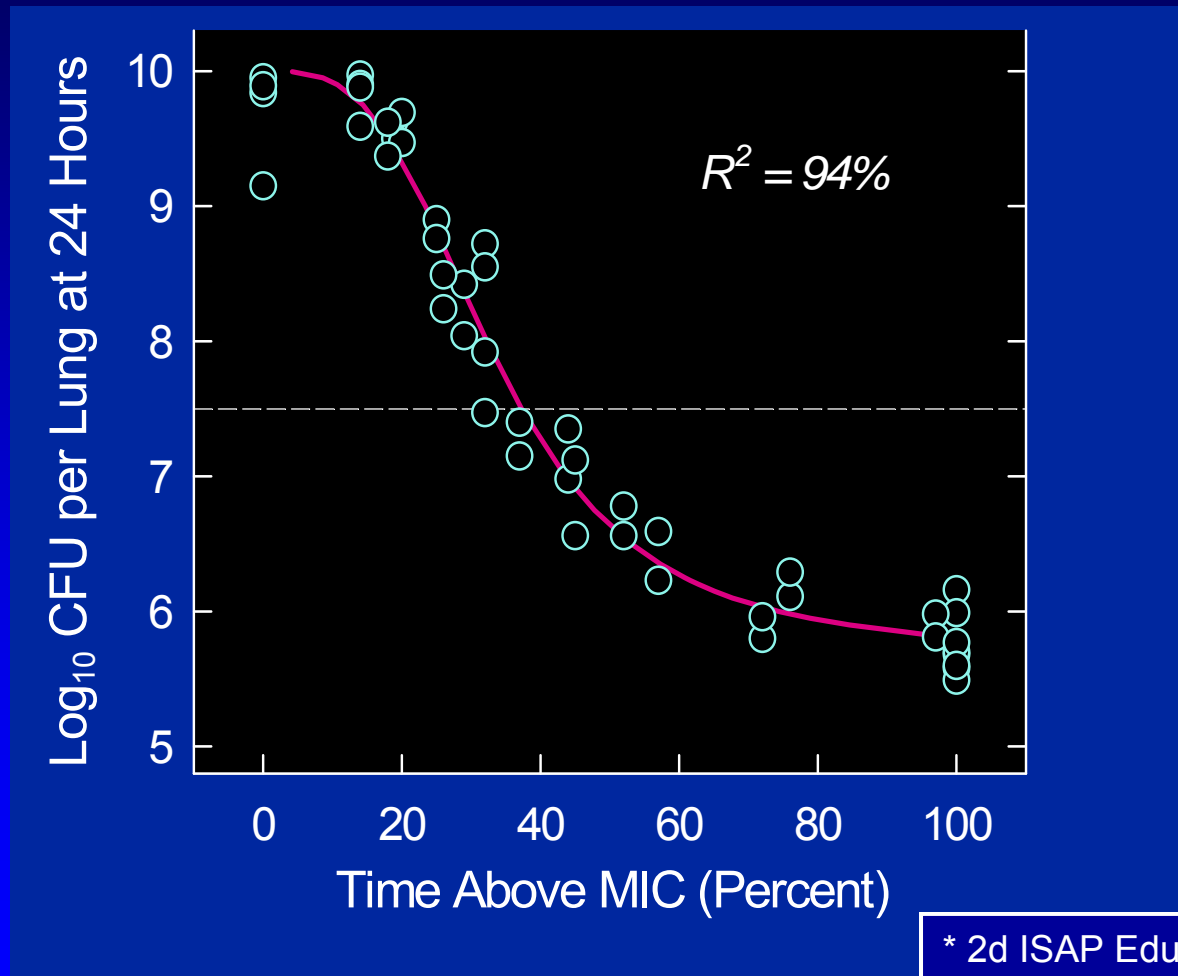
Relationship between peak/MIC and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000



Relationship between time above MIC (T>MIC) and efficacy of cefotaxime towards *Klebsiella pneumoniae* in murine pneumonia (after W.A. Craig *)





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Time-above MIC**
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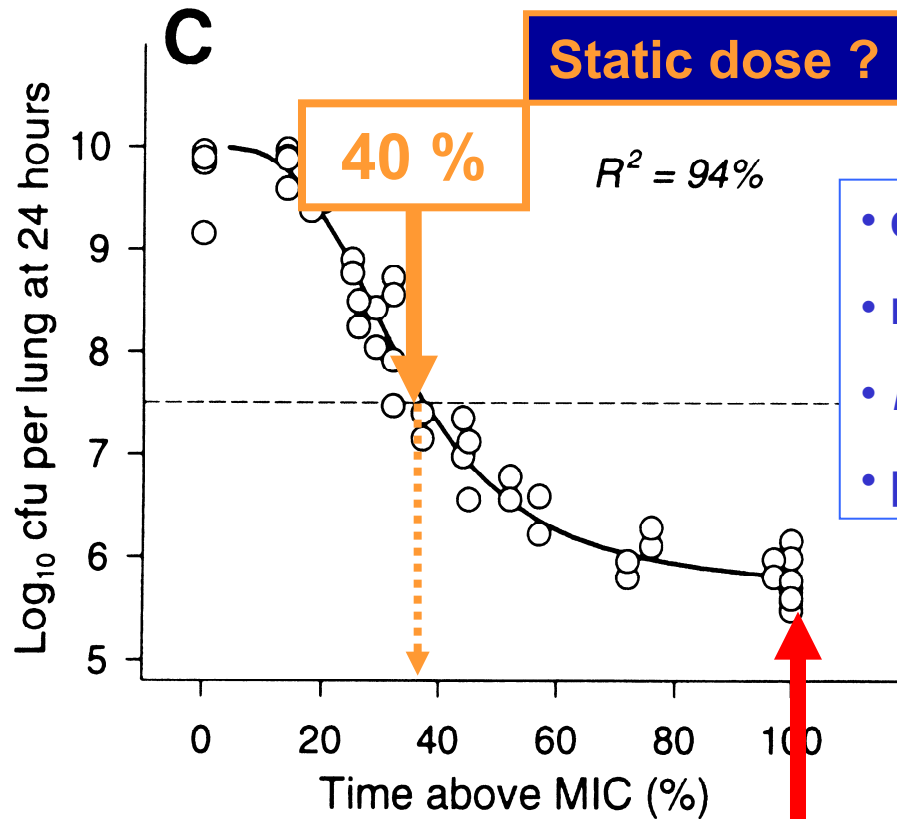
β -lactams : $T > MIC$... but ...

You know it is "time above MIC", but...

- How much / How frequent ?
(Static dose vs maximum effect ?)
- The same for all beta-lactams ?
(Free fractions of the drug (F_u) ?)
- The same for all micro-organisms ?
- The same for all infections ?
- Can you apply to all patients ?



How much time above MIC ?

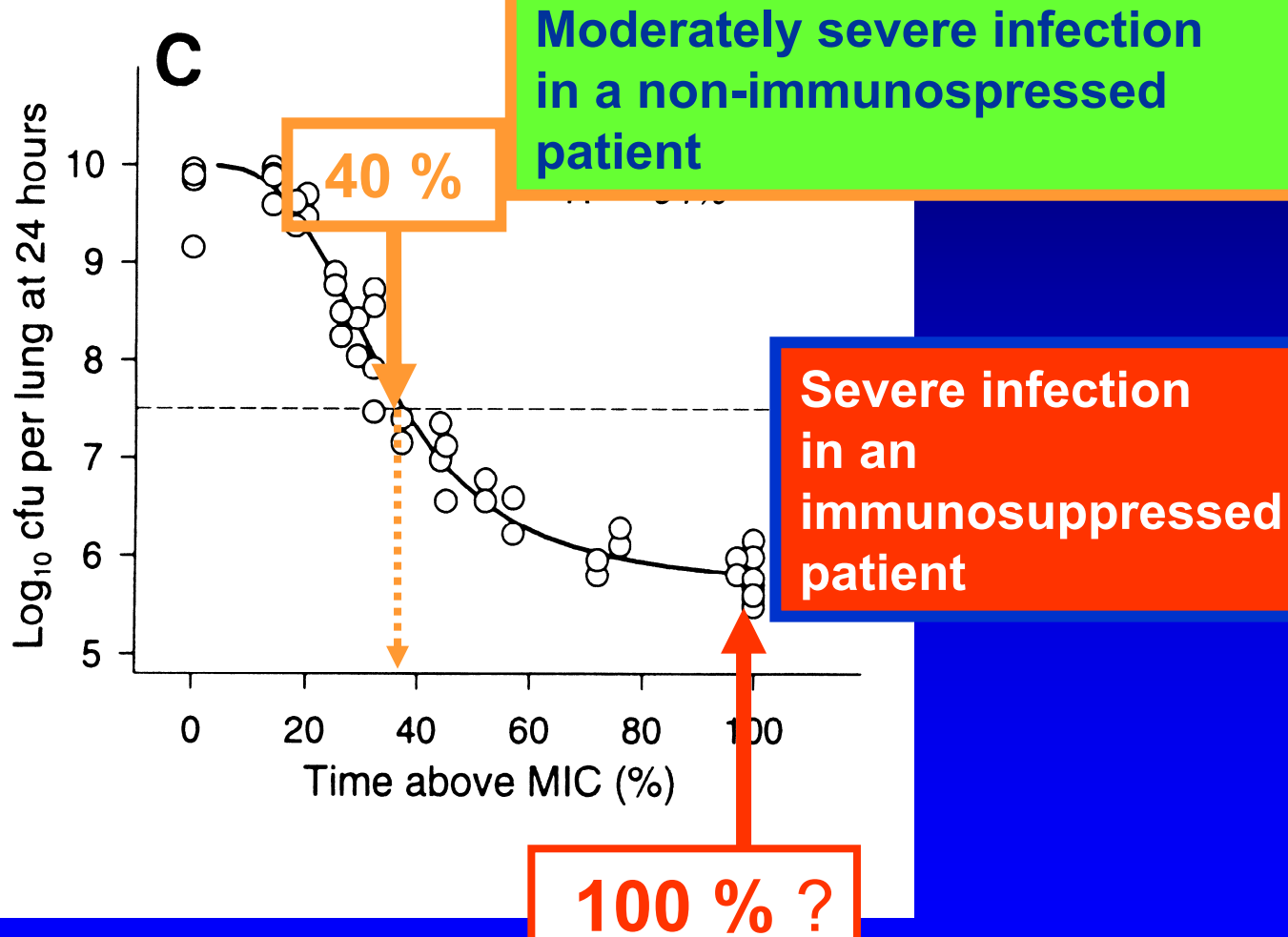


- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100 % - Maximal effect ?



Here is a proposal ...



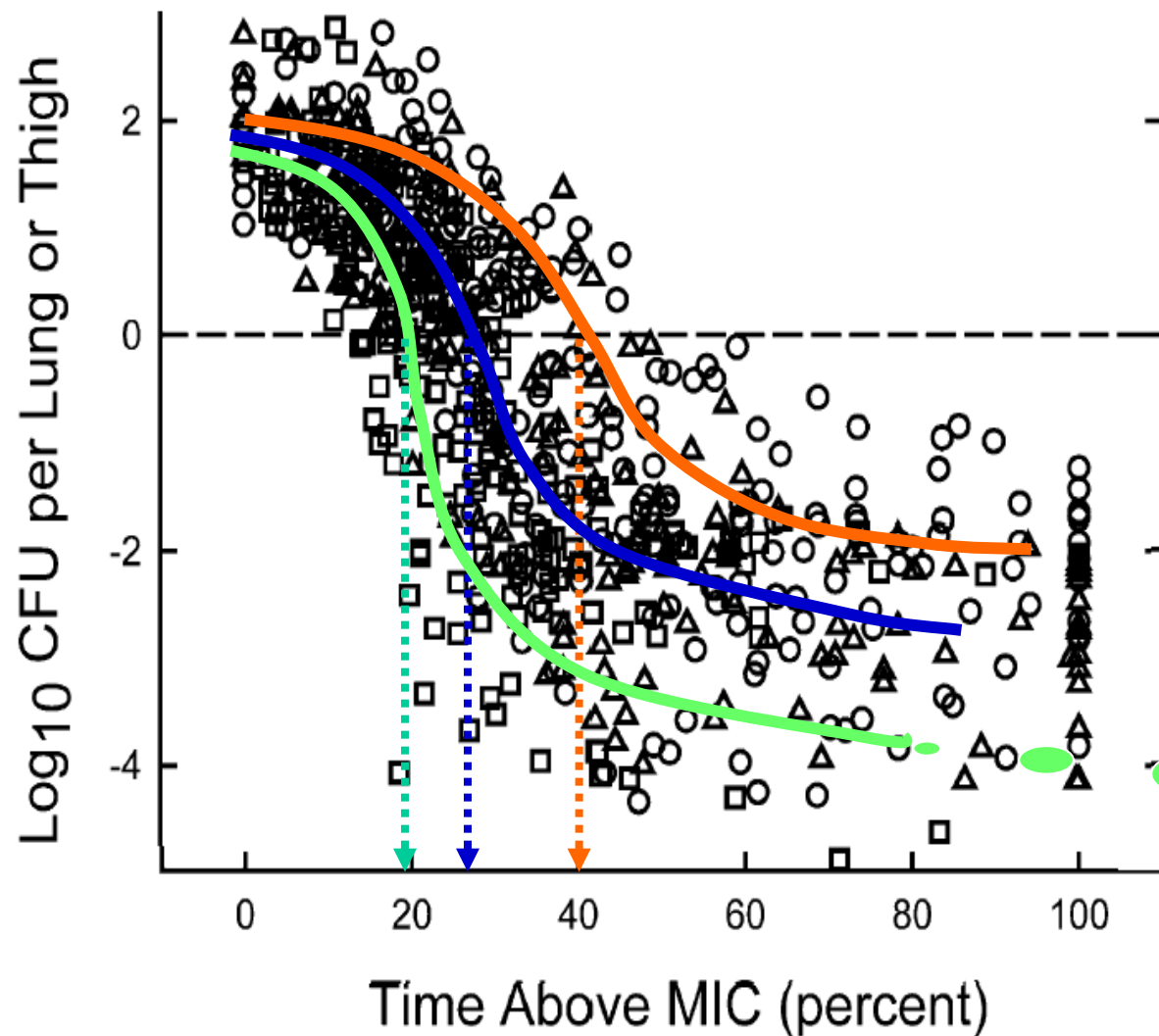


Fig. 7. Relationship between the change in log₁₀ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (Δ), cephalosporins (○) and carbapenems (□).

**The same
for all
β-lactams ?**

Carbapenems
tend to require
less time above
MIC

Andes & Craig Int.
J. Antimicrob. Agents
2002, 19: 261-268



The same for all microorganisms ?

T > MIC for static effect

Drug	Enterobacteriaceae	<i>S. pneumoniae</i>
Ceftriaxone (free)	38 (34-42)	39 (37-41)
Cefotaxime	38 (36-40)	38 (36-40)
Ceftazidime	36 (27-42)	39 (35-42)
Cefpirome	35 (29-40)	37 (33-39)
Meropenem	22 (18-28)	
Imipenem	24 (17-28)	

Craig *et al.*



How do you adjust the dose for a given "Time > MIC" ?

- Read the package insert and follow dosage recommendations
 - somewhat blind and simple but may be effective
- Run a simple calculation based on known pharmacokinetics
 - see example on next slide
- Monte-Carlo simulations and target attainment approaches
 - for the expert ... but regulatory authorities use it a lot



Calculation of concentration over time for a typical β -lactam

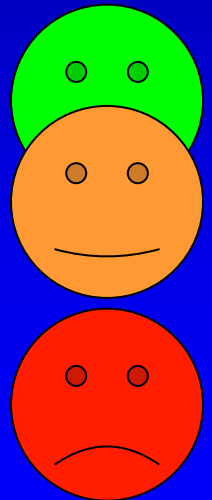
time (hours)	serum concentration for		
	0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

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



Reading the results against the MIC of the offending organism (100 % Time > MIC)

time (hours)	serum concentration for		
	0.5 g	1 g	2 g
2	25	Where would you like to be ?	
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



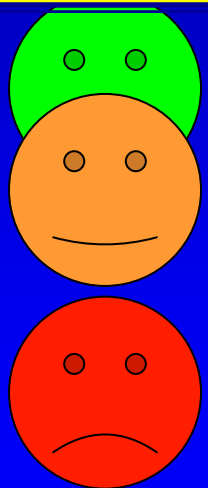
Reading the results against the MIC of the offending organism (100 % Time > MIC)

time (hours)	serum 0.5 g	2.5	50
2	25		
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

A calculator for different

- dosages
- half-life (clearance)
- volumes of distributions



will be available on our web site
(see address on last slide)



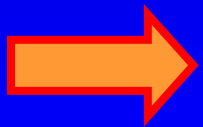
* Single administration unique; half-life 2h ; $V_d = 0.2$ l/kg



Simple optimisation of IV β -lactams for "difficult" organisms

- 2 g every 12 h  **$T > MIC = 100 \%$
if $MIC \leq 3 \text{ mg/L}$!**
- 2 g every 8 h  **$T > MIC = 100 \%$
if $MIC \leq 12 \text{ mg/L}$**

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 : $MIC = 8 \text{ } \mu\text{g/ml}$**

To be practical

In an environment where susceptibilities are compromised (MICs > 4 mg/L) but still "acceptable" (MIC < 16 mg/L) *

- cefepime: 2 g every 8 h
- ceftazidime: 2 g every 8 h
- meropeneme: 2 g every 8 h
- imipeneme: 1 g every 6 h

International labelling (SmPC)

Doses up to 2 g three times daily in adults ...may particularly be suited for treating nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter* spp.

* see discussion about breakpoints later on ...

To be practical

In an environment where susceptibilities are compromised (MICs > 4 mg/L) but still "acceptable" (MIC < 16 mg/L) *

- cefepime: 2 g every 8 h
- ceftazidime: 2 g every 8 h
- meropeneme: 2 g every 8 h
- imipeneme: 1 g every 6 h

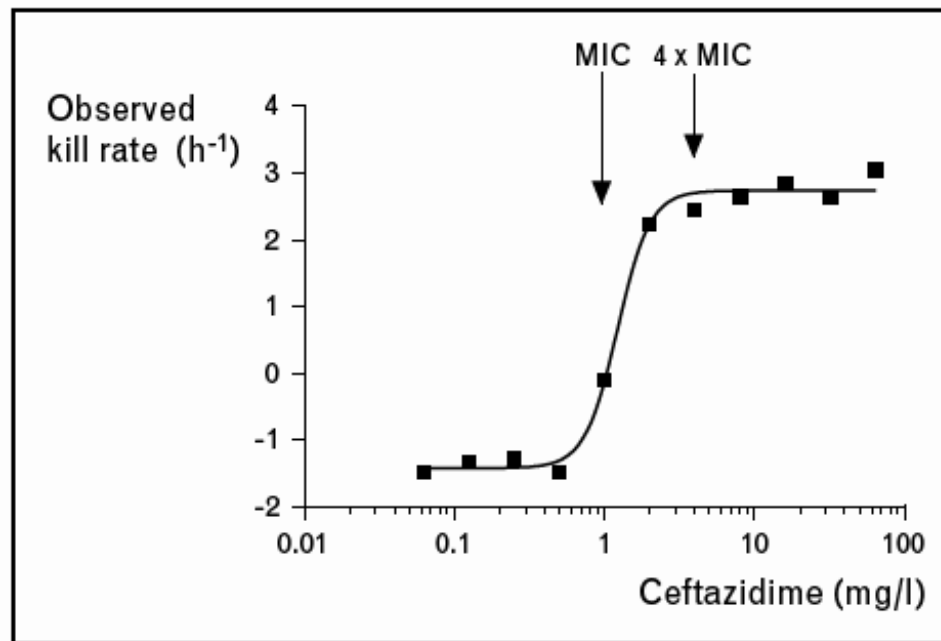
**The label of all EU countries
limit the dose of imipenem to
4 g/day !**

* see discussion about breakpoints later on ...



Target Concentration for β -lactams: continuous infusion

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.



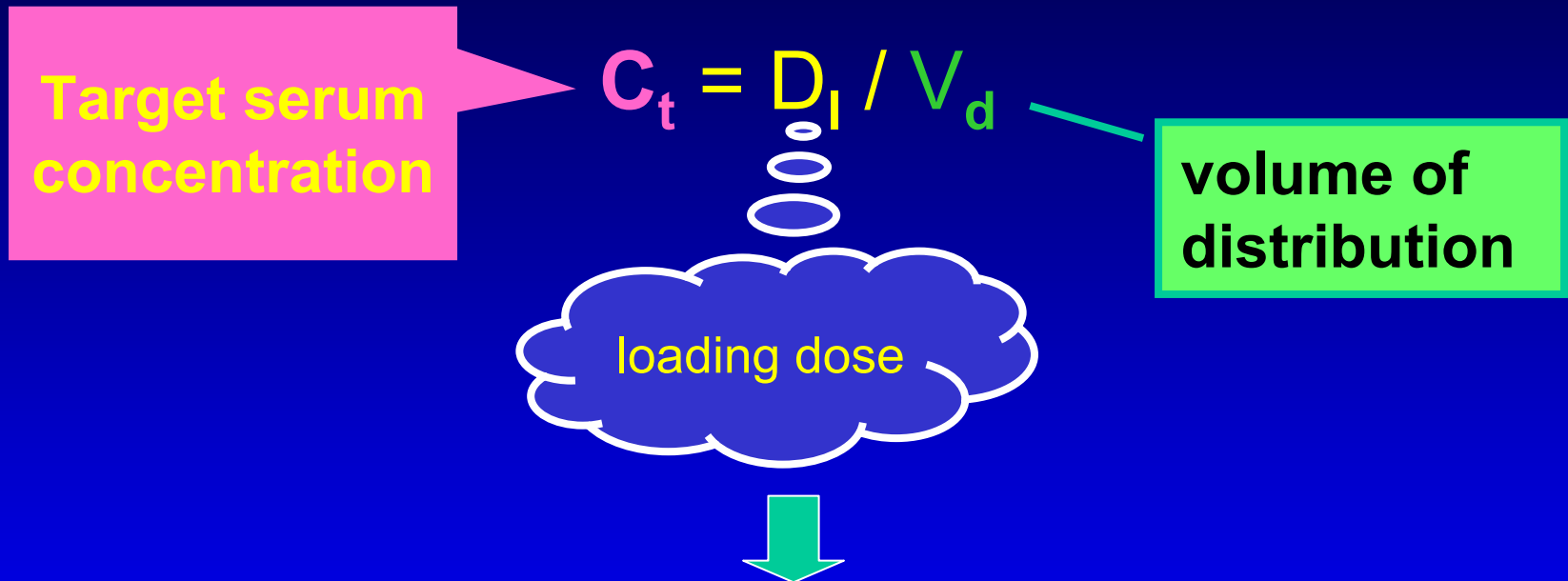
Continuous infusion of β -lactams: an overview...

- 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: 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

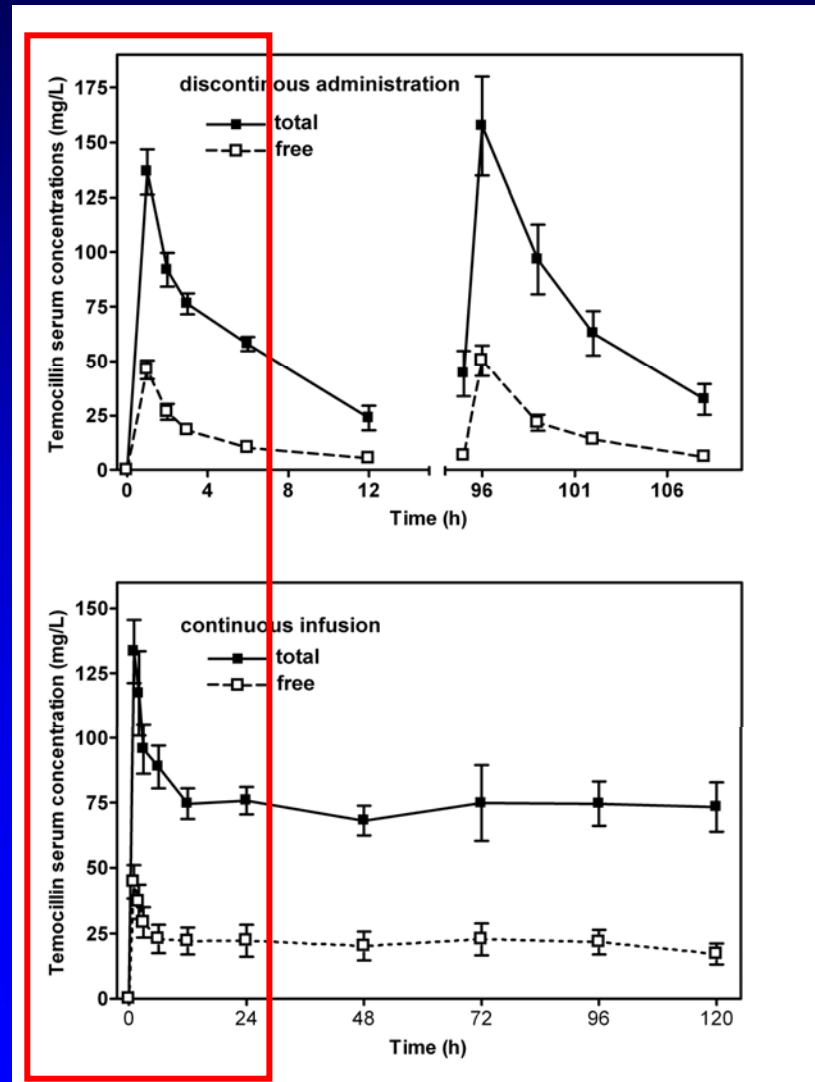
Typical volumes of distribution of a β -lactam are between 0.2 L/kg (volunteers) and 0.4-0.5 L/kg (Intensive Care and burned patients)

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

Continuous infusion in practice

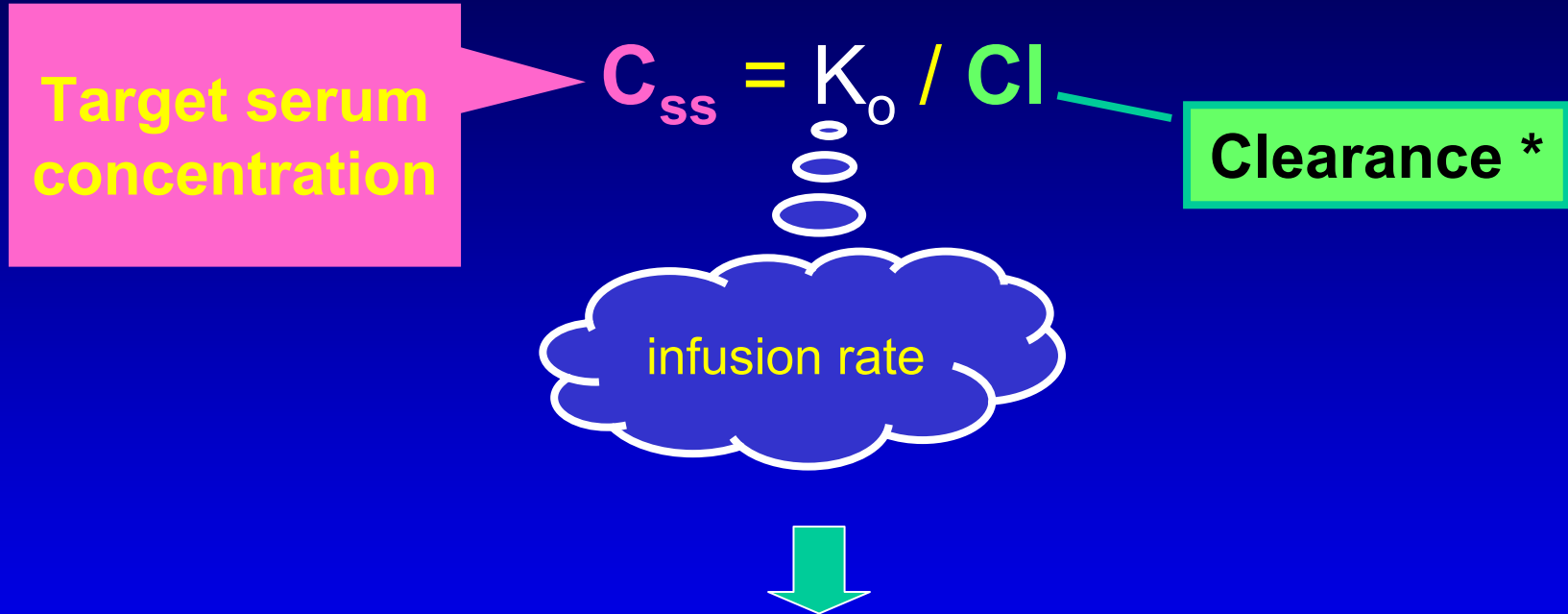
1. loading dose: a simplified (useful) scheme

- 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) ?



Continuous infusion in practice

2: infusion: the correct scheme *

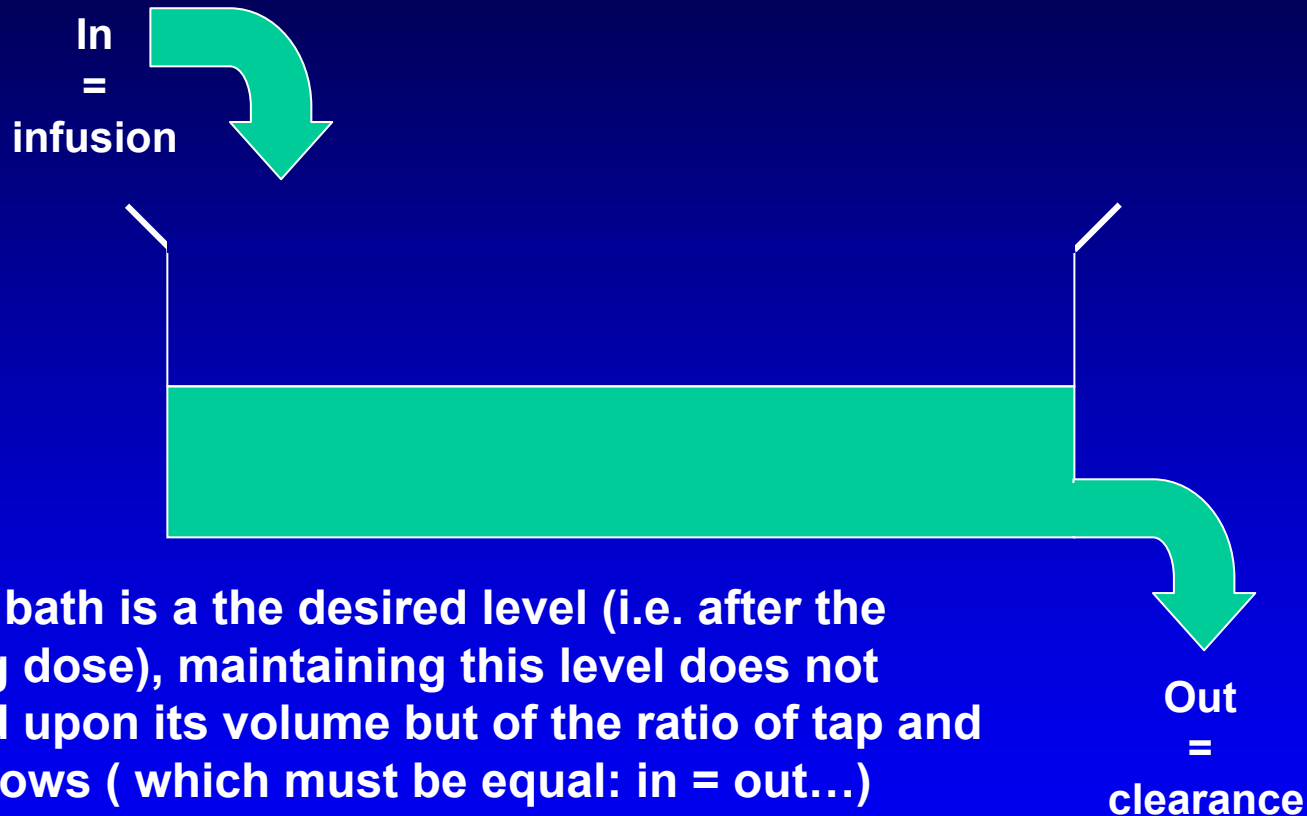


$$\text{daily dose (in mg)} = 24 \times \text{clearance (L/h)} \times C_{ss}$$

* 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: why clearance only ?



* 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 simplified practical scheme for patients with normal renal function

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

example of
 β -lactam

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

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

- loading dose: **2 g**
- 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].

the conventional
unit dose

Continuous infusion of β -lactams: a simplified practical scheme for patients with normal renal function

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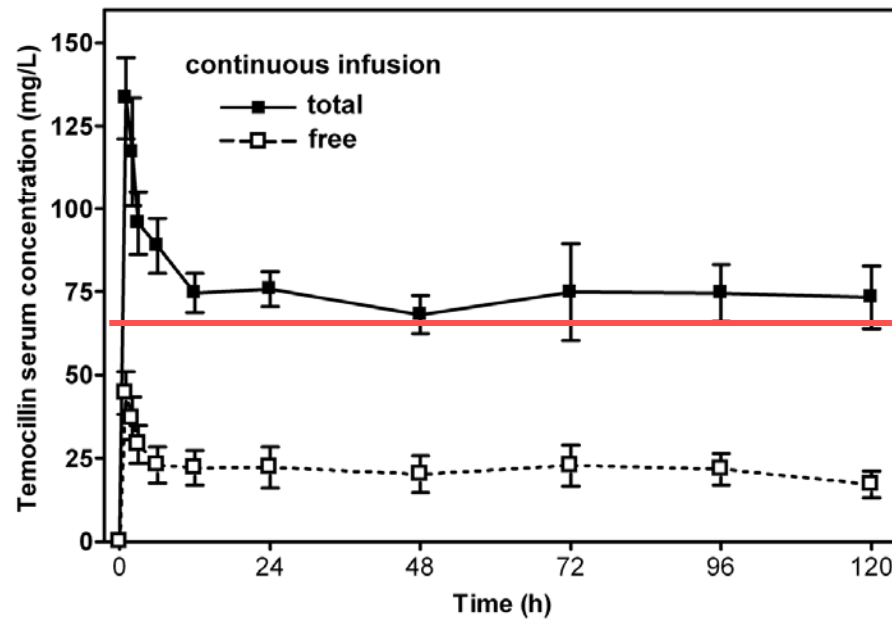
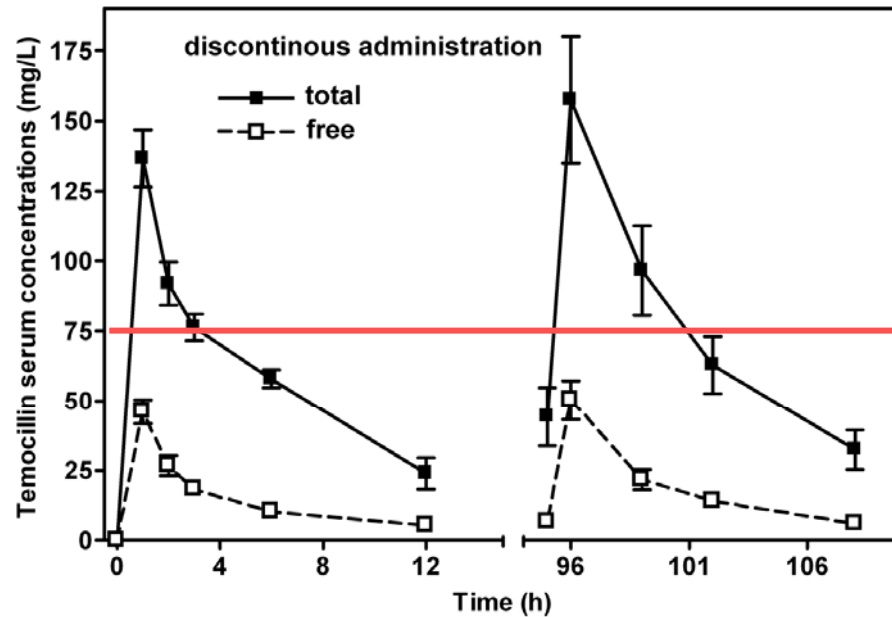
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- loading dose: **2 g**
- infusion: **4 g/day** (2 778 mg/min; assumed clearance: 40 ml/min)
[drug diluted in 48 ml of water, infusion through motor-operated syringe at a rate of 2 ml/h; temperature 25°C or lower].

the conventional daily dose

Pharmacokinetics of temocillin 4 g/day (as an example)

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

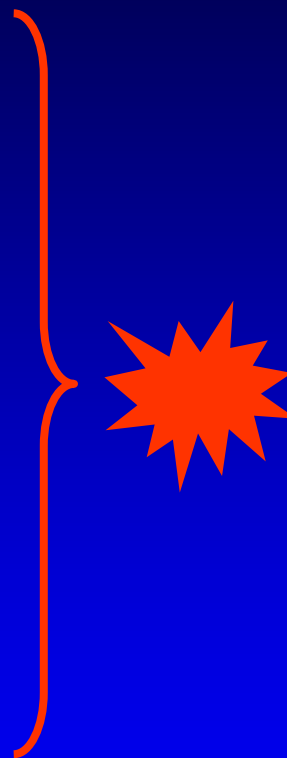


**data on
6 g/daily are
prepared
for
publication**



Problems with continuous infusion ...

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



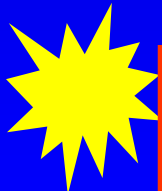


Problems with continuous infusion ...

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

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

- **drug instability**



!! carbapenems are unstable (3-4h max.)



Carbapenems stability

J Antimicrob Chemother (2010) 65:1073-1075

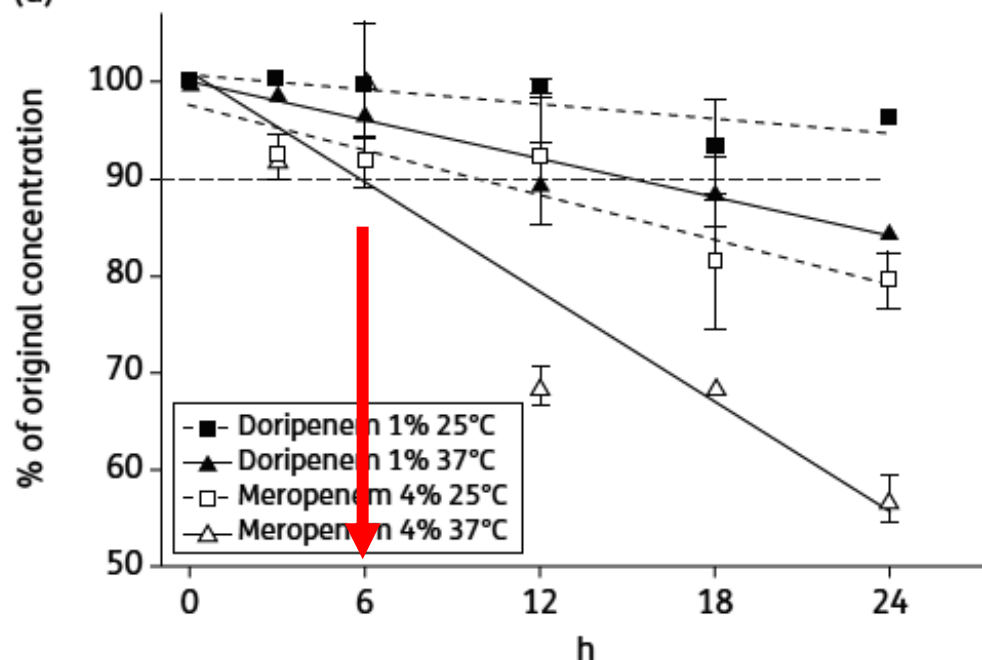
doi:10.1093/jac/dkq044

Advance publication 21 February 2010

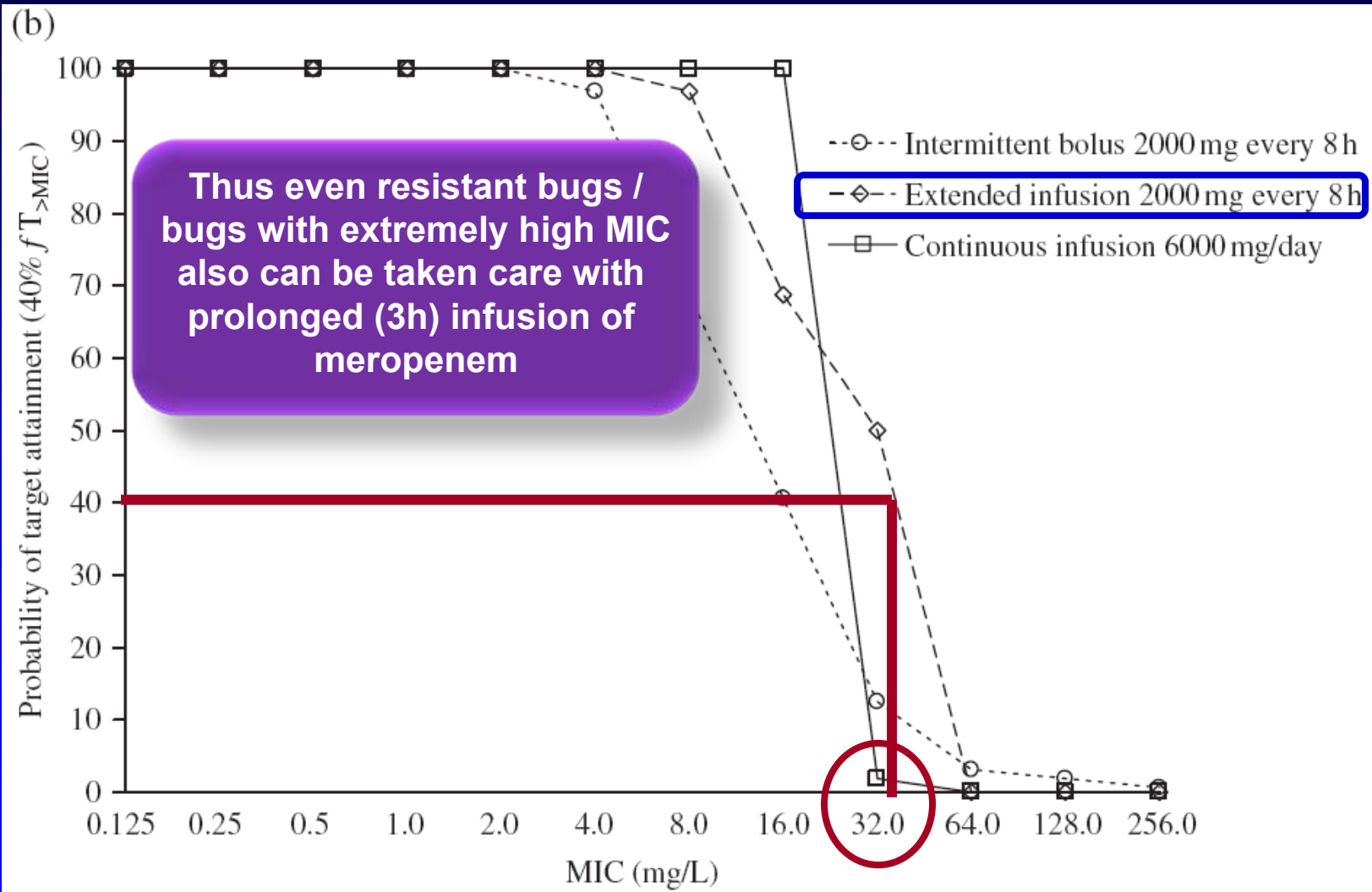
Stability of meropenem and doripenem solutions for administration by continuous infusion

Karine Berthoin¹, Cécile S. Le Duff²,
Jacqueline Marchand-Brynaert², Stéphane Carryn^{1,3}
and Paul M. Tulkens^{1*}

(a) Influence of time



Meropenem Infusion in the Critically-Ill



Roberts et al. J Antimicrob Chemother 2009; 64, 142–150.

Cefepime by prolonged (3 – 4h) infusion

International Journal of Antimicrobial Agents 37 (2011) 46–50



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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



Steady-state pharmacokinetics and pharmacodynamics of cefepime administered by prolonged infusion in hospitalised patients[☆]

S. Christian Cheatham^a, Katherine M. Shea^b, Daniel P. Healy^c, Melissa L. Humphrey^d, Megan R. Fleming^a, Matthew F. Wack^e, David W. Smith^f, Kevin M. Sowinski^d, Michael B. Kays^{d,*}

^a St Francis Hospital, Department of Pharmacy, Beech Grove, IN, USA

^b Seton Family of Hospitals, University Medical Center at Brackenridge, Austin, TX, USA

^c James L. Winkle College of Pharmacy, University of Cincinnati Academic Health Center, Cincinnati, OH, USA

^d Purdue University College of Pharmacy, Department of Pharmacy Practice, W7555 Myers Building, WHS, 1001 West Tenth Street, Indianapolis, IN 46202-2879, USA

^e Infectious Diseases of Indiana, Indianapolis, IN, USA

^f Clarian Health Partners, Inc., Methodist Hospital, Indianapolis, IN, USA

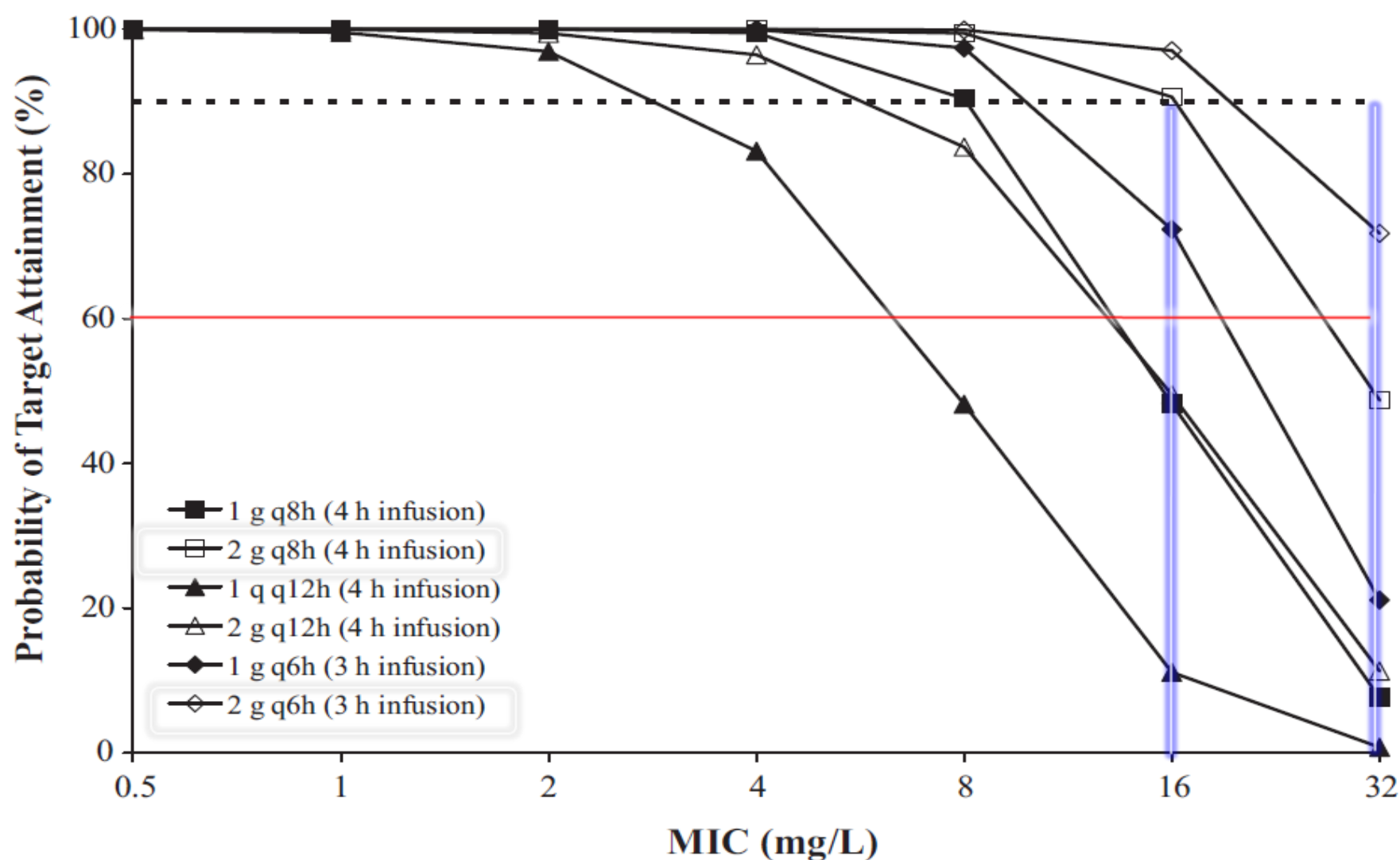


Fig. 2. Probability of target attainment (PTA) at 60% $fT > MIC$ for six prolonged infusion regimens of cefepime at specific minimum inhibitory concentrations (MICs). The dotted line indicates a $PTA \geq 90\%$. $fT > MIC$, time for which the free drug concentration remains above the MIC; q8h, every 8 h; q12h, every 12 h; q6h, every 6 h.

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.)



Breakpoints ...

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

But, what is a breakpoint ?



http://www.eucast.org/clinical_breakpoints/

points

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

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Organization

Clinical breakpoints

Expert rules

MIC - distributions and QC

Zone diameter distributions

EUCAST disk diffusion test

Frequently Asked Questions (FAQ)

Meetings

EUCAST Presentations

Documents

Information for industry

Links

Website changes

search term Search

Clinical breakpoints

Clinical breakpoints

Clinical breakpoints are for everyday use in the clinical laboratory to advise on patient therapy.

In EUCAST tables, the I-category is not listed. It is implied as the values between the S-breakpoint and the R-breakpoint.

For a breakpoint listed as $S \leq 1$ mg/L and $R \geq 8$ mg/L the intermediate category is 2 - 8 (technically $>1 - 8$) mg/L.

For a breakpoint listed as $S \geq 22$ mm and $R \leq 18$ mm the intermediate category is 18-21 mm.

clinical breakpoints - bacteria (v 1.1) - pdf-file for printing (April 27, 2010)

clinical breakpoints - bacteria (v 1.1) - Excelfile for screen (April 27, 2010)

clinical breakpoints - fungi (MIC breakpoints)

definitions of clinical breakpoints and epidemiological cut off values

procedure for harmonizing and defining breakpoints

Recommend page

<http://www.eucast.org>

http://www.eucast.org/clinical_breakpoints/

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Home Contact Sitemap

EUCAST procedure for setting breakpoints

Orga

Clinical breakpoints

Expert rules

MIC - distributions and QC

Zone diameter distributions

EUCAST disk diffusion

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search term Search

Clinical breakpoints

The next slides describe the EUCAST procedure for harmonizing European breakpoints and reach rational values.

<http://www.eucast.org>

1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted
2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined ($WT \leq X \text{ mg/L}$)
4. Pharmacokinetic / Pharmacodynamic data are collected and evaluated; . Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens
5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint
6. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type population

7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments.

When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:

- EUCAST general committee
- Expert committees (*Neisseria*, Anaerobes, others)
- pharmaceutical industry, AST device manufacturer
- others via EUCAST website

9 . Rationale document prepared and published on website

<http://www.eucast.org>

Enterobacteriaceae

Carbapenems ¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Doripenem	1	4	10	24	18
Ertapenem	0.5	1	10	25	22
Imipenem ²	2	8	10	21	15
Meropenem	2	8	10	22	16

- The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases).
- Some strains that produce carbapenemase are categorized as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorization of susceptibility.
- In many areas, carbapenemase detection and characterization is recommended or mandatory for infection control purposes.

EUCAST and cephalosporins

Cephalosporins ¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefepime	1	4	30	24	21
Ceftazidime	1	4	10	21	18
Ceftriaxone	1	2	30	23	20

[EUCAST_breakpoints_v1.1.pdf](#)

Why so low ?

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

To exclude
ESBL ..



What about ESBL ?

Beta-lactamases: Classification

Serine enzymes

Metallo (Zn) enzymes

Group C

Group A

Group D

Group B

AmpC

TEM / SHV / CTX-M

OXA

IMP/VIM

ESBLs



Class A and D of β -lactamases are poorly active on 3d generation cephalosporins

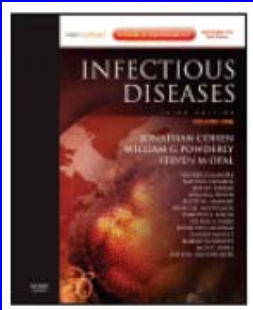
Table 130.1 Functional classification of β -lactamases

Group	Molecular class	Preferred substrates	Active β -lactams	Typical examples
Group 1: serine cephalosporinases not inhibited by clavulanic acid	C	Cephalosporins I and II (>> cephalosporins III, monobactams, penicillins)	Carbapenems Temocillin Cephalosporins III and IV (variable upon level of expression)	AmpC from gram-negatives; variable upon the species
2d: cloxacillin-hydrolyzing β -lactamases generally inhibited by clavulanic acid	D	Penicillins Cloxacillin Cephalosporins I and II	Carbapenems Cephalosporin III and IV Monobactams* Piperacillin + tazobactam	OXA-1 to -30, PSE-2 from Enterobacteriaceae and <i>P. aeruginosa</i> OXA-11 to -19, 28, 32, 45 are ESBLs in <i>P. aeruginosa</i> (R to Ceph 3) OXA-23, -24, -58 are carbapenemases in <i>Acinetobacter baumannii</i>

Van Bambeke F, Glupczynski, Y, Mingeot-Leclercq, MP, Tulkens PM

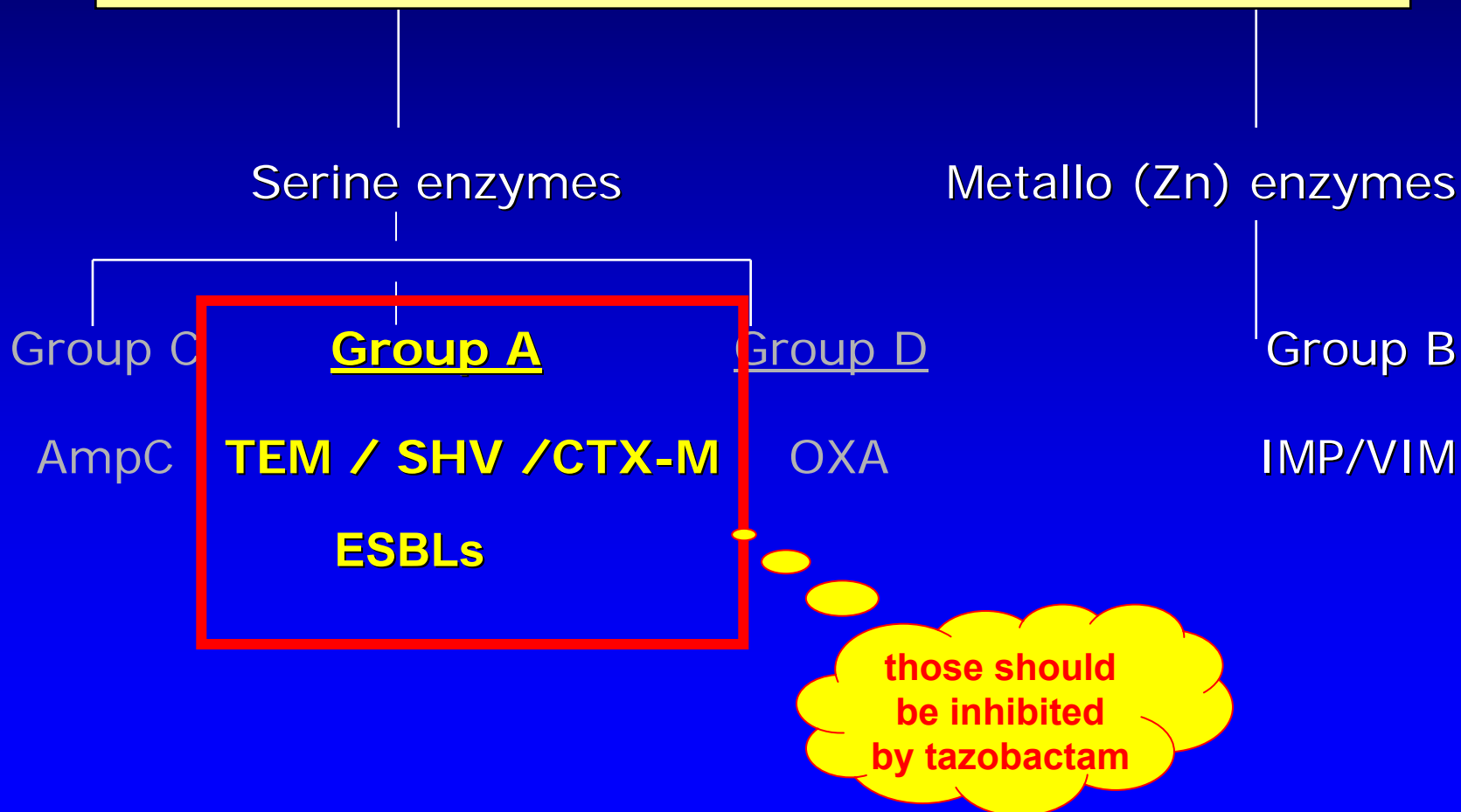
Mechanisms of Action.

In: Infectious Diseases (3d edition; J. Cohen, W. Powderly & S. Opal, eds), chapter 130, pp 1288-1307, Elsevier/Mosby, 2010



So, now you are left with the ESBL...

Beta-lactamases: Classification





An innovative approach for ESBL...

- take a 4th generation cephalosporin (cefepime [PM])
 - should cover (partly AmpC) and resist to OXA
- add a β -lactamase inhibitor (tazobactam [TZ])
 - will take care of many ESBL

Mouton et al. ICAAC 2010

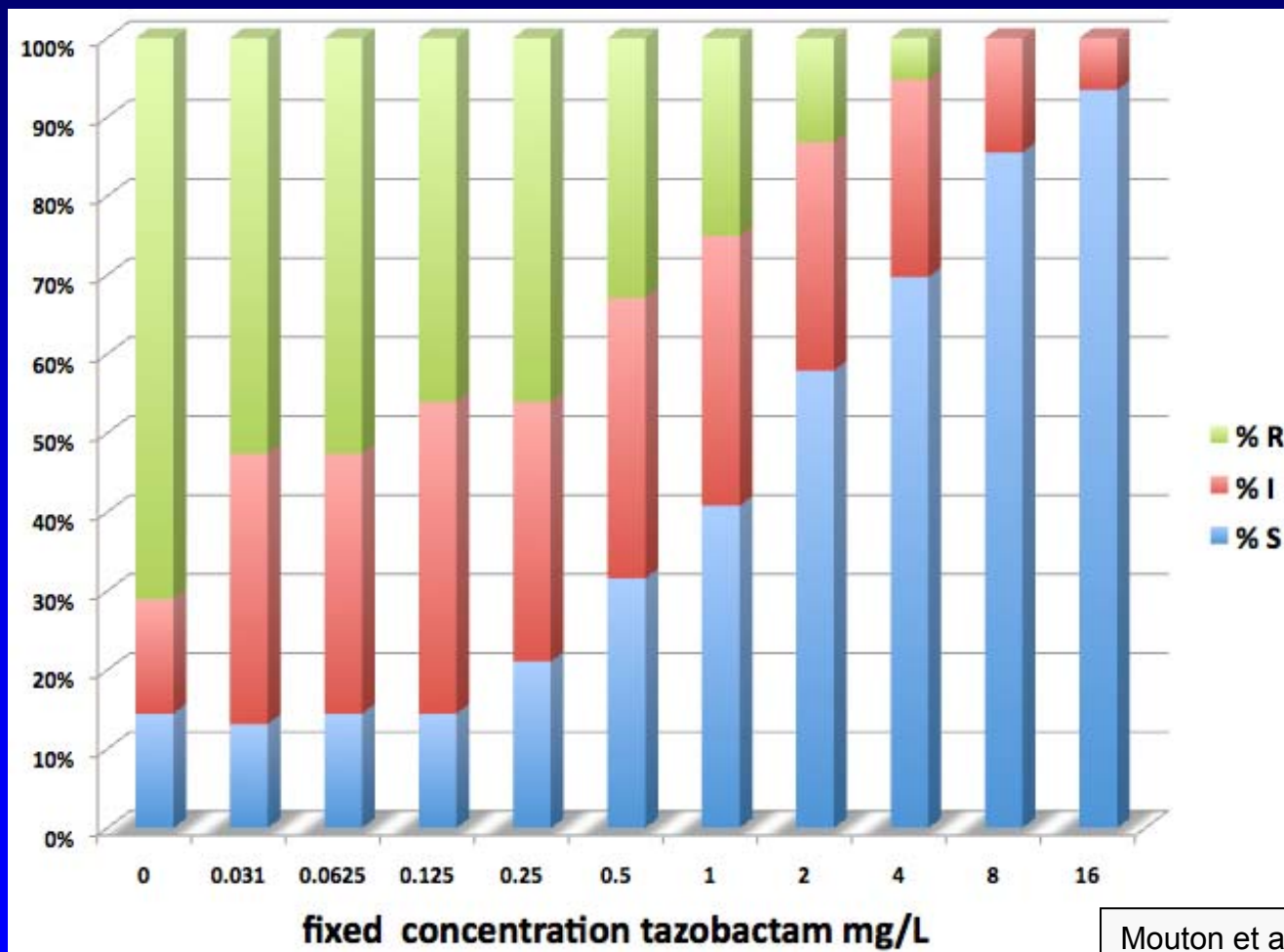
76 ESBL producing *Enterobacteriaceae* were selected from a variety of clinical specimens.

	%S	%I	%R	MIC50 (mg/L)	MIC90 (mg/L)
PM	15	14	71	>32	>32
PM/TZ 1mg/L	41	34	25	2	32
PM/TZ 4mg/L	70	25	5	0.5	4
PM/TZ 16mg/L	93	7	0	0,25	1



An innovative approach for ESBL...

Percentage **sensitive(S)**, **intermediate(I)** and **resistant(R)** cefepime (breakpoints EUCAST: ≤ 1 S – R > 8)



Mouton et al. ICAAC 2010




An innovative approach for ESBL...

Conclusions:

- The combination of cefepime and tazobactam may offer an alternative treatment option for ESBL harboring strains.
- If the same amount of tazobactam is used as current piperacillin/tazobactam regimens and breakpoint determinations, most strains would be categorized as susceptible.

Mouton et al. ICAAC 2010

In India, due to high ESBL: consider cefepime + tazobactam

- 
- **cefepime 3 x 2 g /day**
 - **tazobactam 3 x 0.25 g /day**

**or 3h
infusion**



In a nutshell ... so far ...

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



A simple experiment ...

Exposure of *E. aerogenes* to anti-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





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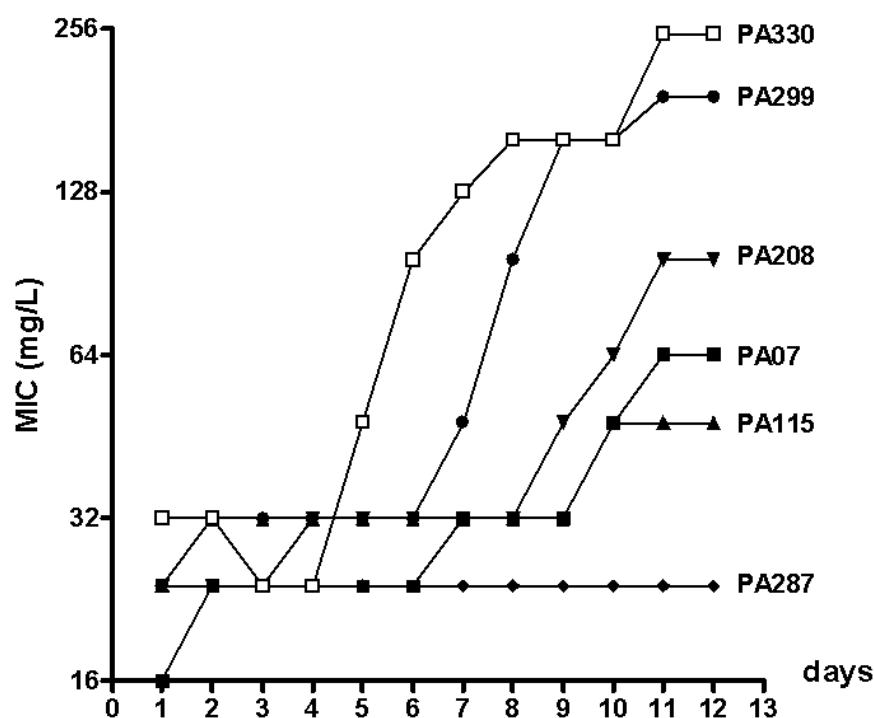
sub-MIC concentrations create resistance !



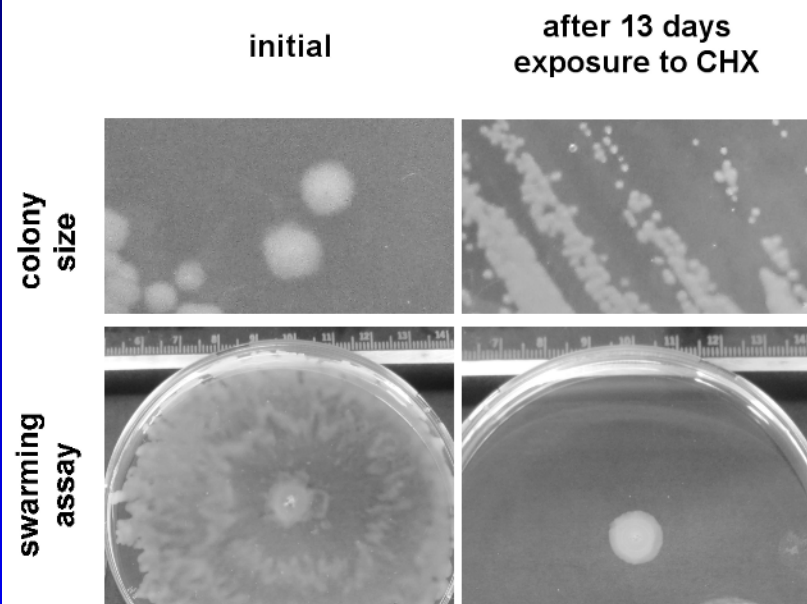


And this happens also with biocides

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 in the clinics ?

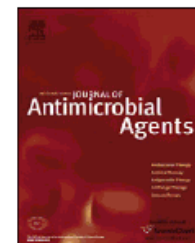
International Journal of Antimicrobial Agents 36 (2010) 513–522



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 Carboneille^{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 Glupczynskiⁱ



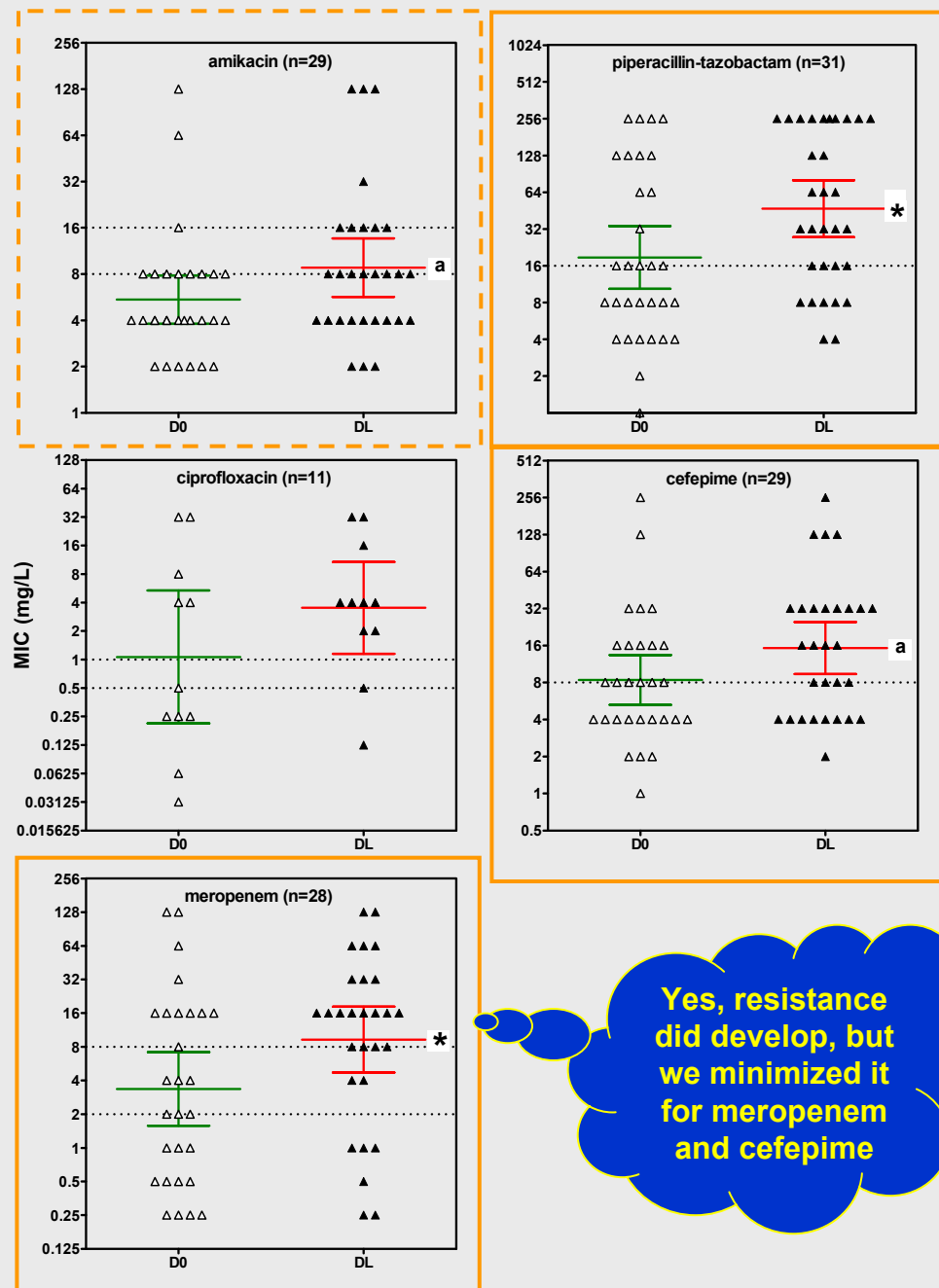
What happens during treatment ?

- 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)

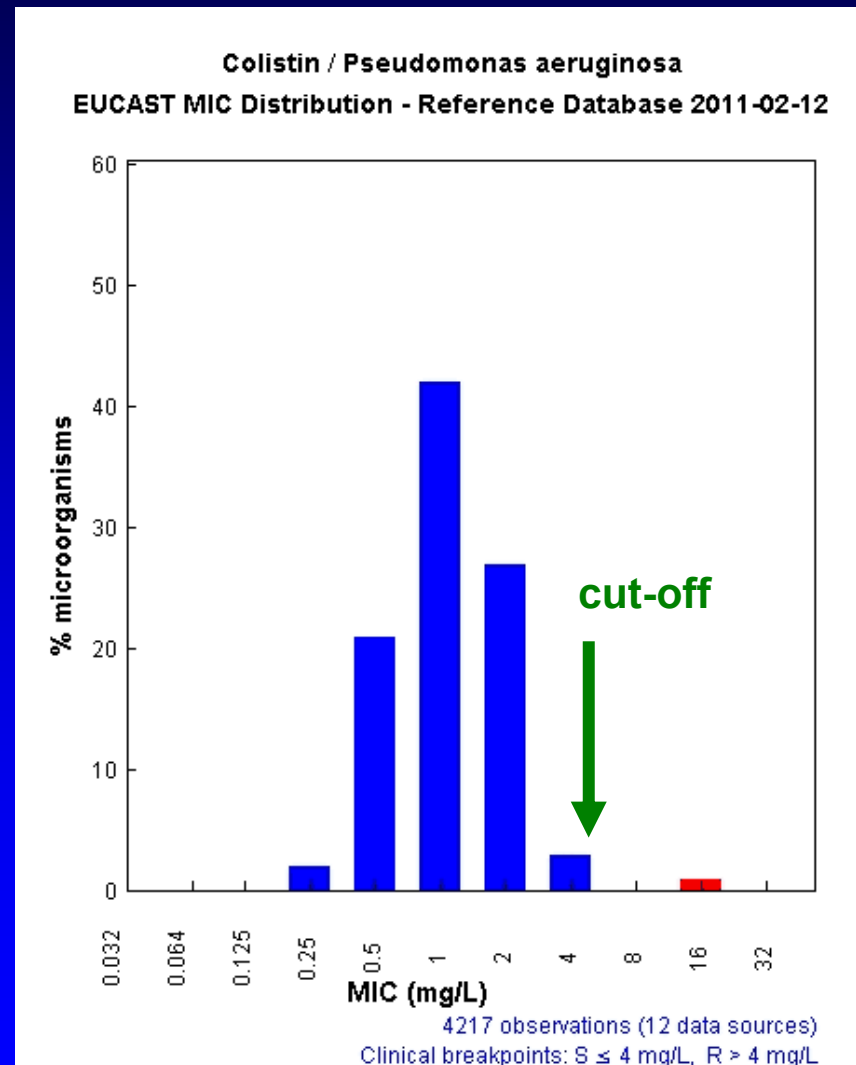


Yes, resistance did develop, but we minimized it for meropenem and cefepime

And what about colistin ?

You first need
to consider the
MIC
distribution.

Here are the
data of EUCAST
for
Pseudomonas



And what about colistin ?

Dosage (colistine methane sulfonate [CMS]): 240 mg every 8h (= 3 x 10⁶ UI)

CMS

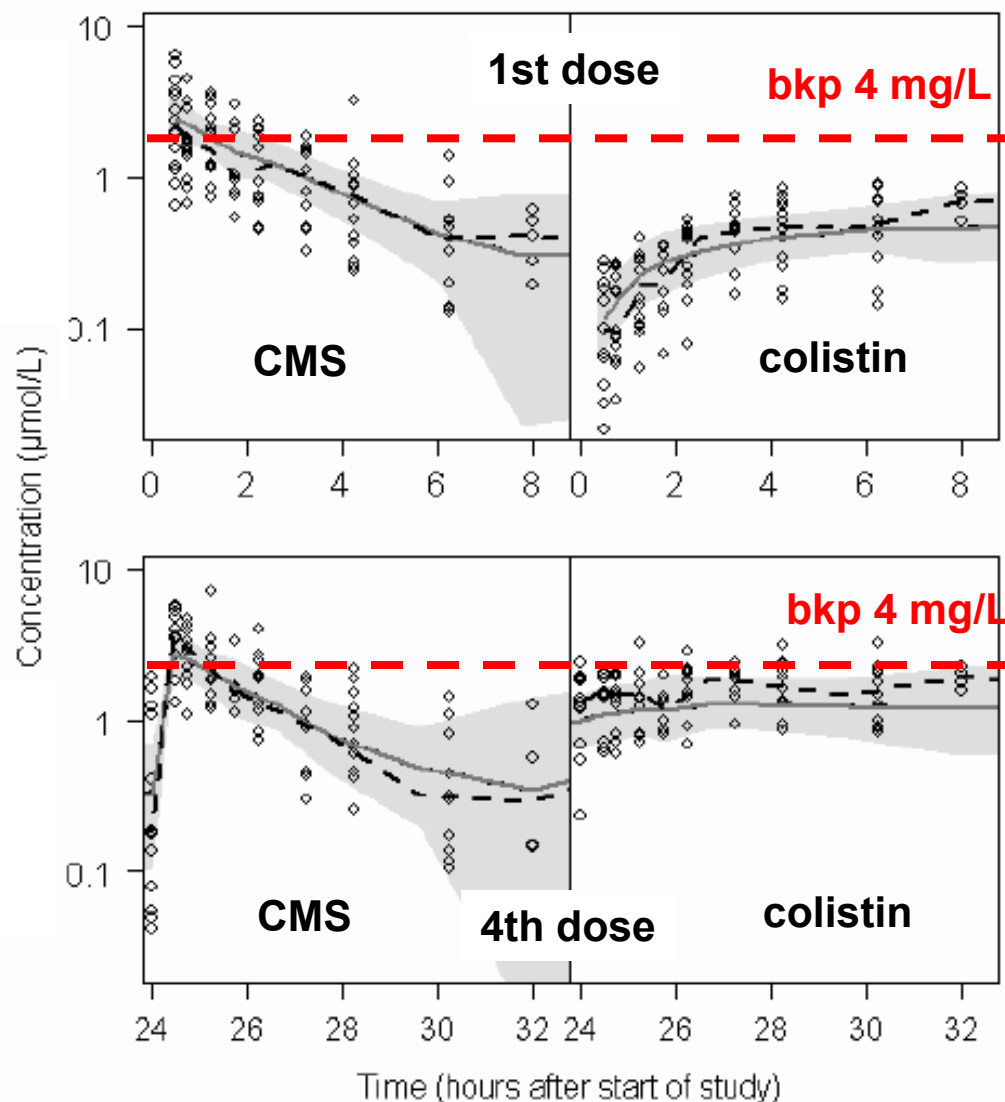
- $t_{1/2} \sim 2.3$ h,

Colistin:

- $t_{1/2} \sim 14.4$ h.
- C_{max} (pred.)
 - 1st dose: 0.60 mg/L
 - s.s.: 2.3 mg/L.

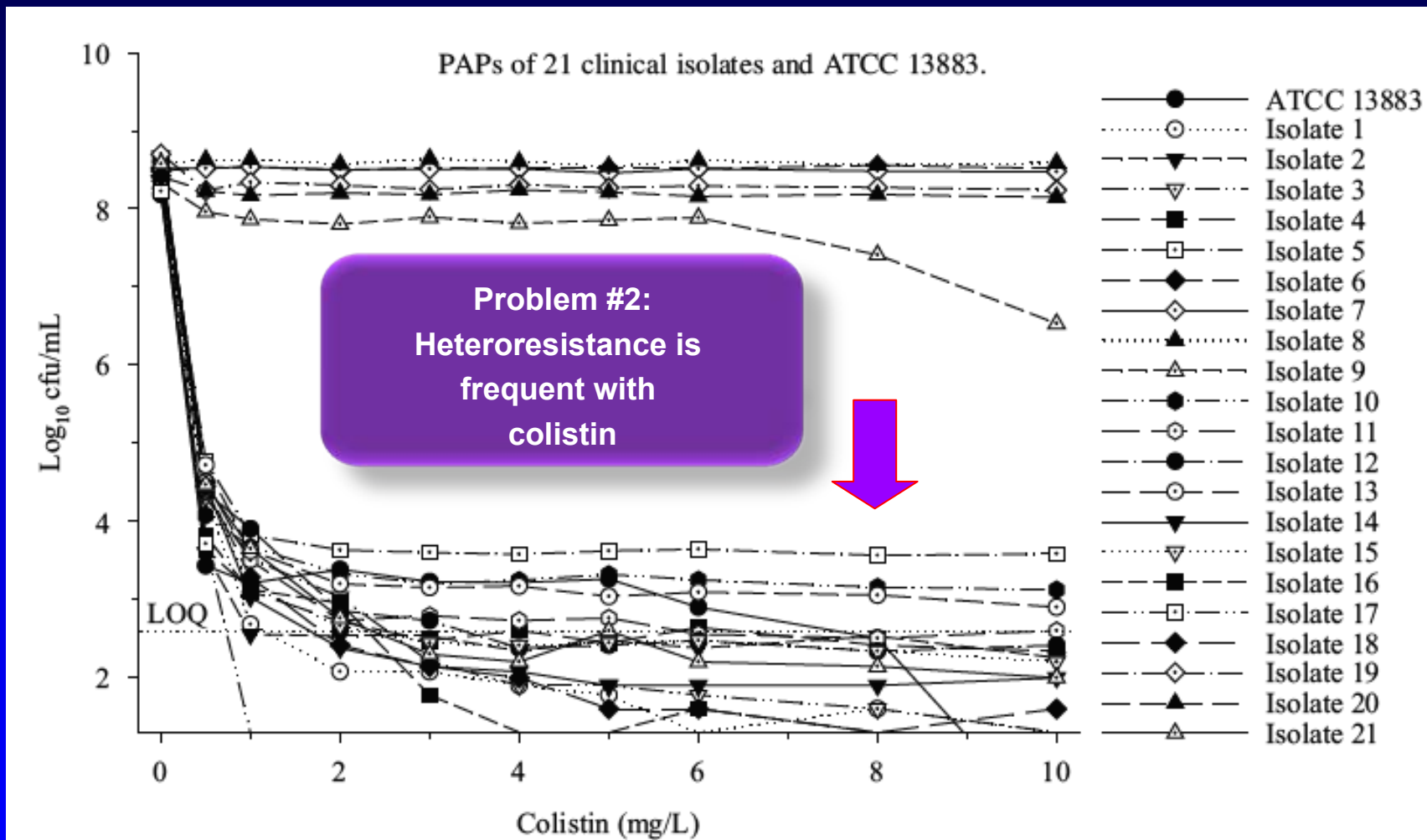
Problem #1:
Low initial blood levels
suggest the necessity
of a loading dose

Plachouras et al. AAC 2009; E-pub 11 May



And what about colistin ?

Population analysis profiles of *K. pneumoniae* isolates



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



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



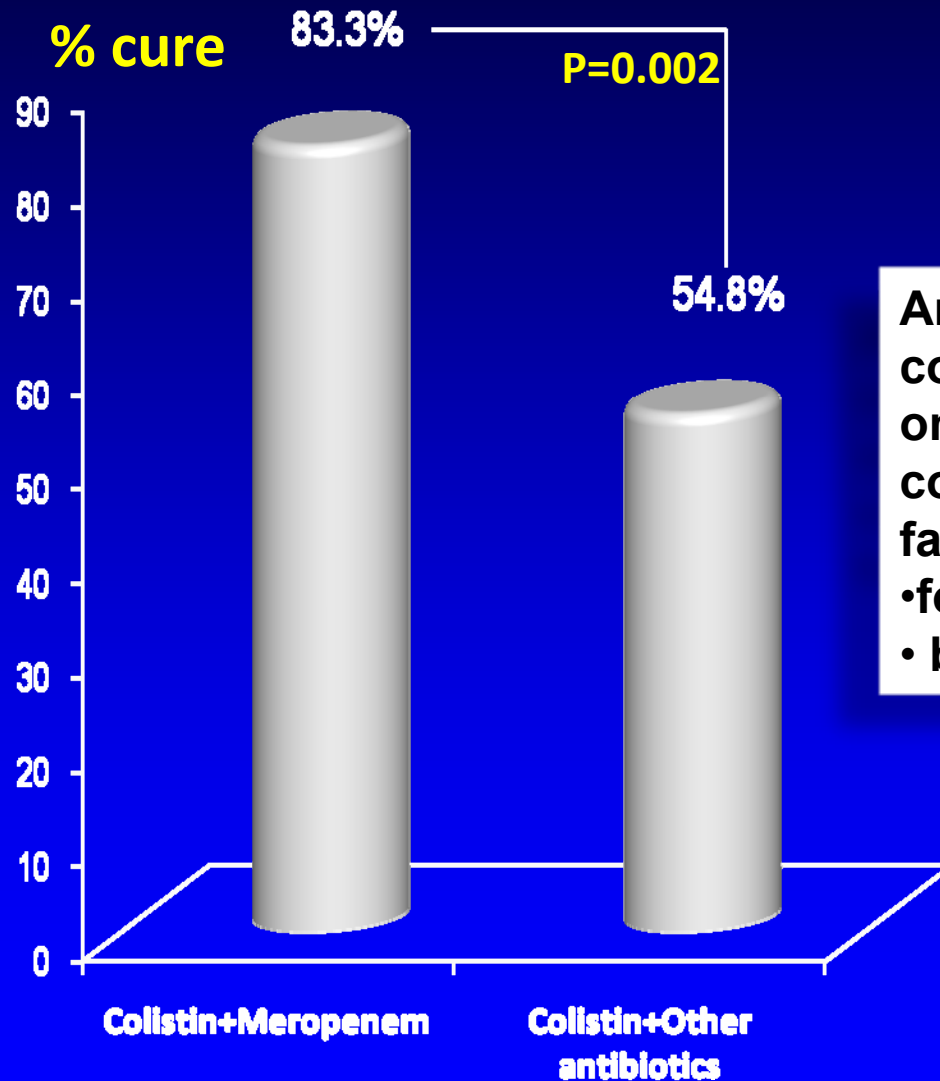
Short communication

Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients

Matthew E. Falagas^{a,b,c,*}, Petros I. Rafailidis^{a,b}, Elda Ioannidou^a, Vangelis G. Alexiou^a,
Dimitrios K. Matthaiou^a, Drosos E. Karageorgopoulos^a, Anastasios Kapaskelis^{a,b},
Dimitra Nikita^d, Argyris Michalopoulos^{a,e}

- Retrospective cohort clinical study of 258 patients
- 52.3% isolates were polymyxin–only-susceptible
- Remainder were susceptible to colistin & at least 1 other antibiotic

Patients with polymyxin-only-susceptible infections



Amongst the combinations of colistin with of other antibiotics , only Colistin+Meropenem combination was an independent factor ($P = 0.017$)

- for cure of infection &
- better infection outcome

Falagas ME et al. *International Journal of Antimicrobial Agents* 35 (2010) 194–199

- In how many patients are you implementing "once-daily dosing" of aminoglycosides?

1. 0%
2. 25%
3. 50%
4. 75%
5. 100%

Thank you !



Journal of Antimicrobial Chemotherapy (1991) 27, Suppl. C, 49–61

Pharmacokinetic and toxicological evaluation of a once-daily regimen versus conventional schedules of netilmicin and amikacin

Paul M. Tulkens

*Laboratoire de Chimie Physiologique, Université Catholique de Louvain, and
International Institute of Cellular and Molecular Pathology, Brussels, Belgium*

In conclusion, these very sensitive tests of nephro- and oto-toxicity suggest that
od dosing of amikacin or netilmicin is, if anything, safer than bd or tid dosing.

And what do we do now with toxicity ?

We work on polymyxins with the help of Debaditya Das ... from Kolkata !



Comparative analysis of the potential of polymyxin B and gentamicin to cause apoptosis and necrosis in cultured renal LLC-PK1 cells: concentration-dependent studies with incubated and electroporated cells
Oral presentation (Session: "Antimicrobial pharmacology: from bench to bedside" -- Saturday, 7 May 2011: 16:30)



“Take home” message

- dosage is key to success and protection against resistance...
- dosage should match bacterial susceptibility... and knowledge of MIC is essential
- for β -lactams, get TIME > MIC to reach maximal efficacy ... and dose appropriately...
 - ➔ 3h infusion of meropenem and cefepime may help
- Use of correct breakpoints will also help in avoiding the use of "weak antibiotics" ... or to decide dosage escalation to avoid emergence of resistance ...
- New combinations tailored to local needs (viz. cefepime + tazobactam) with 3h infusion) are useful ...



WHO statement 2000

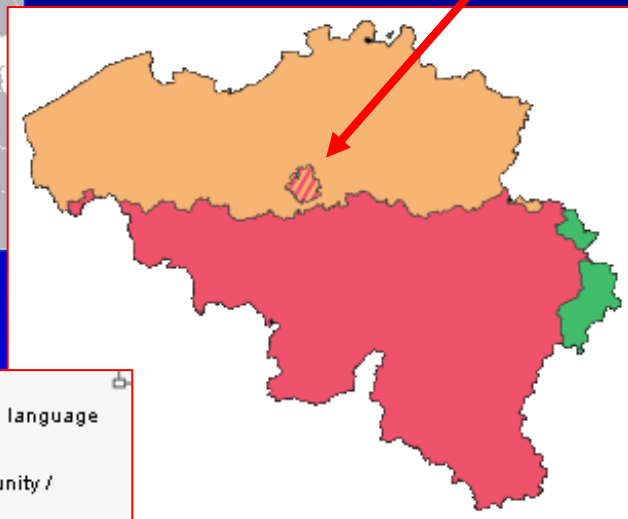
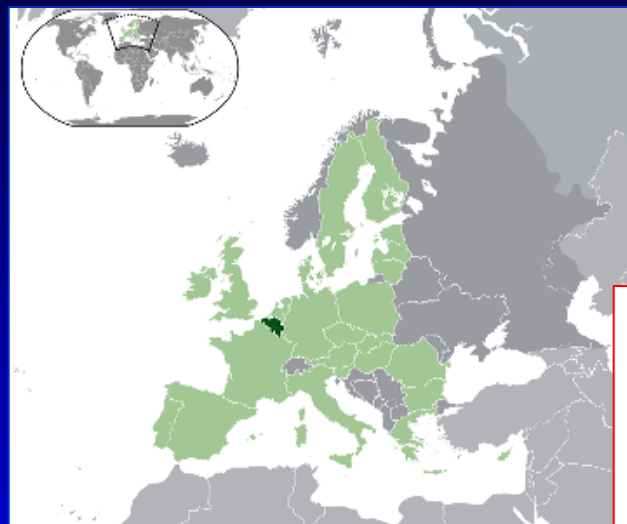
The most effective strategy against antibiotic resistance is:

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

WHO Overcoming Antimicrobial Resistance, 2000



And a few sights from Belgium...



Communities:

- Flemish Community / Dutch language area
- Flemish & French Community / bilingual language area
- French Community / French language area
- German-speaking Community / German language area

Brussels

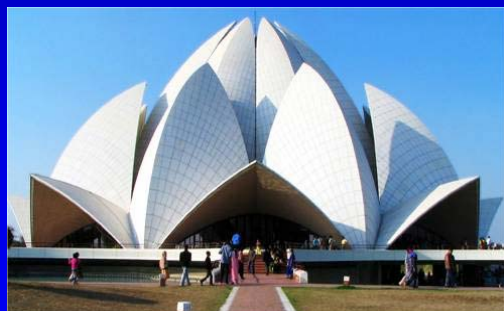
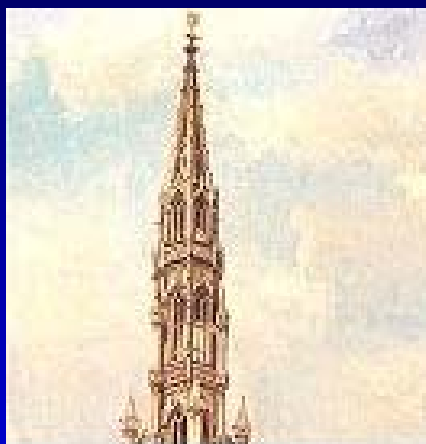




I hope the future will be fine with you...



<http://www.isap.org>



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

All slides are available from here

