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

EXCOLERE PROVENTUS PER DOCTRINAM

AIM ACADEMY FOR INFECTION MANAGEMENT

Improving outcomes through education

Chennai – 13 February 2011

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

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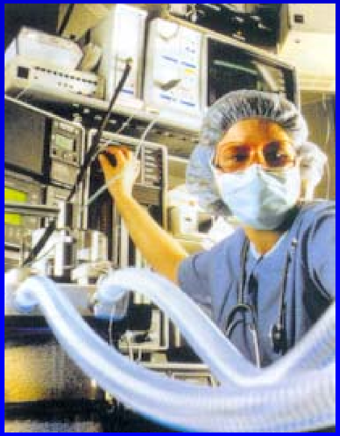
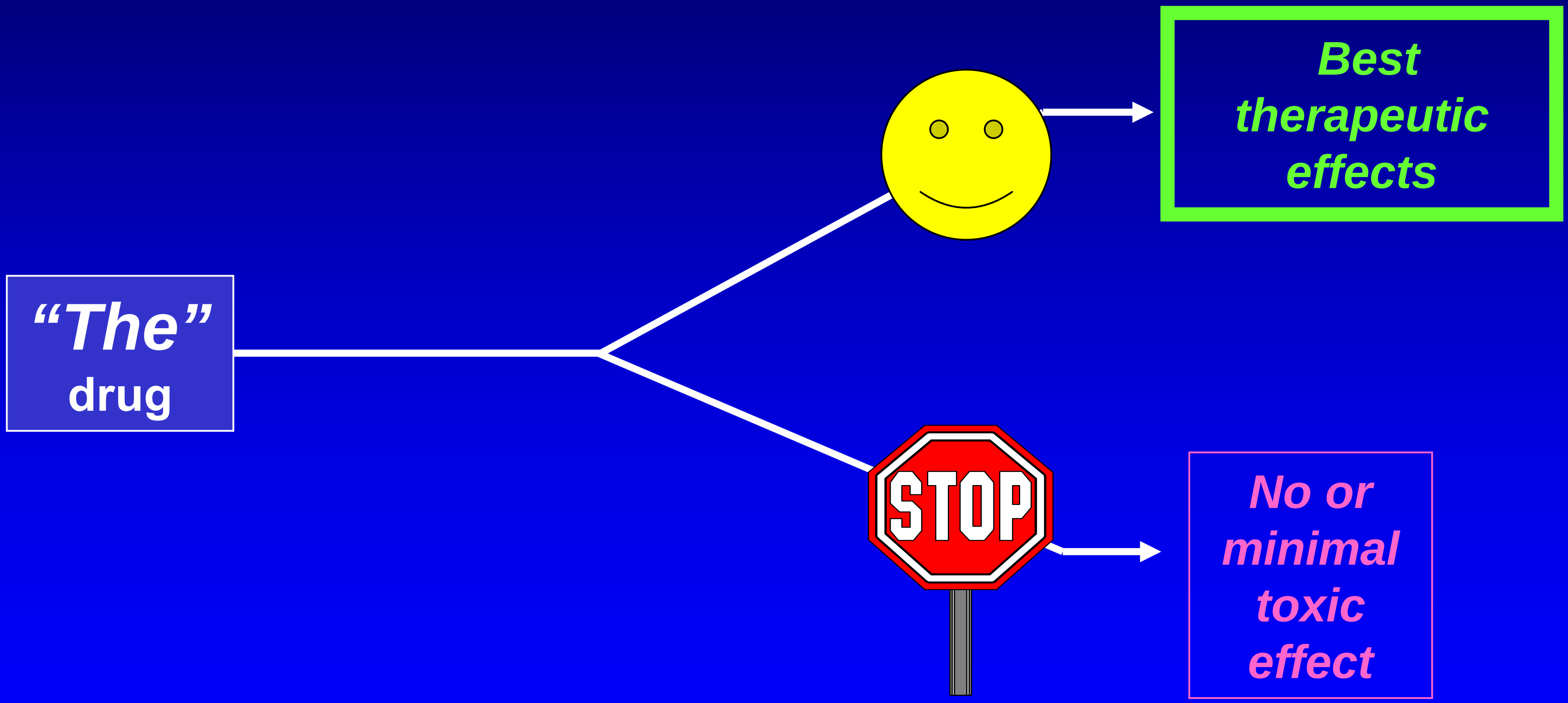
&
International Society of Antiinfective Pharmacology

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

nt’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

A time for questions …

- Where are the best French fries ?

1. In France

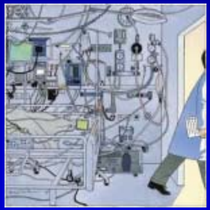
2. In Scotland ?

3. at the Mc Donald ?

4. in Belgium ?
5. none of the above ?

More questions ?

- What is you specialty



1. Intensivist
2. Microbiologist

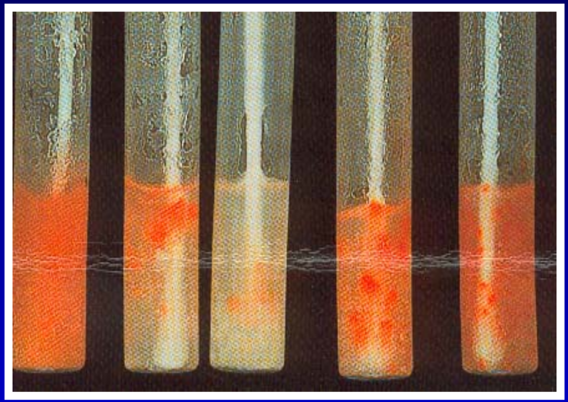
3. ID specialist
4. Surgeon

5. Others

In a nutshell ... so far …

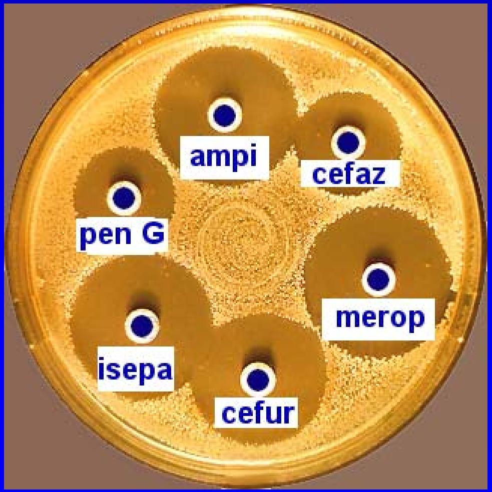
- **Microbiology parameters: MIC !**
- Pharmacodynamic parameters
- PK/PD as applied to beta-lactams: Time-above MIC
- The problems if you underdose
- Take home message

Microbiology



identification

susceptibility



by static techniques

drug concentration stays constant

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]

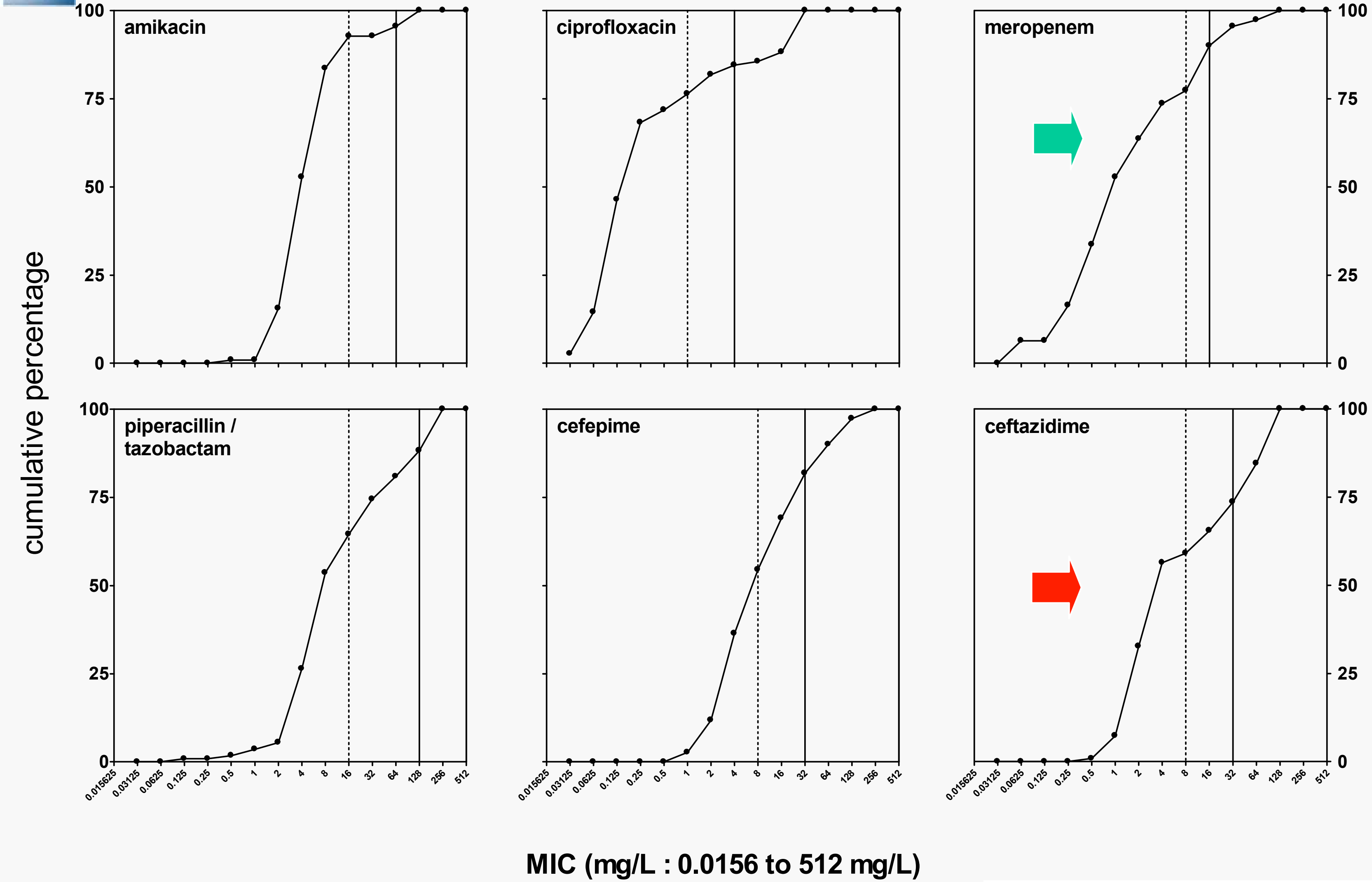
- Examine the mechanisms of resistance acquisition (with special reference to efflux pumps) [2]

Assess new antibiotics and novel approaches (immunotherapy) [3]

- Examine the susceptibility to biocides [1]

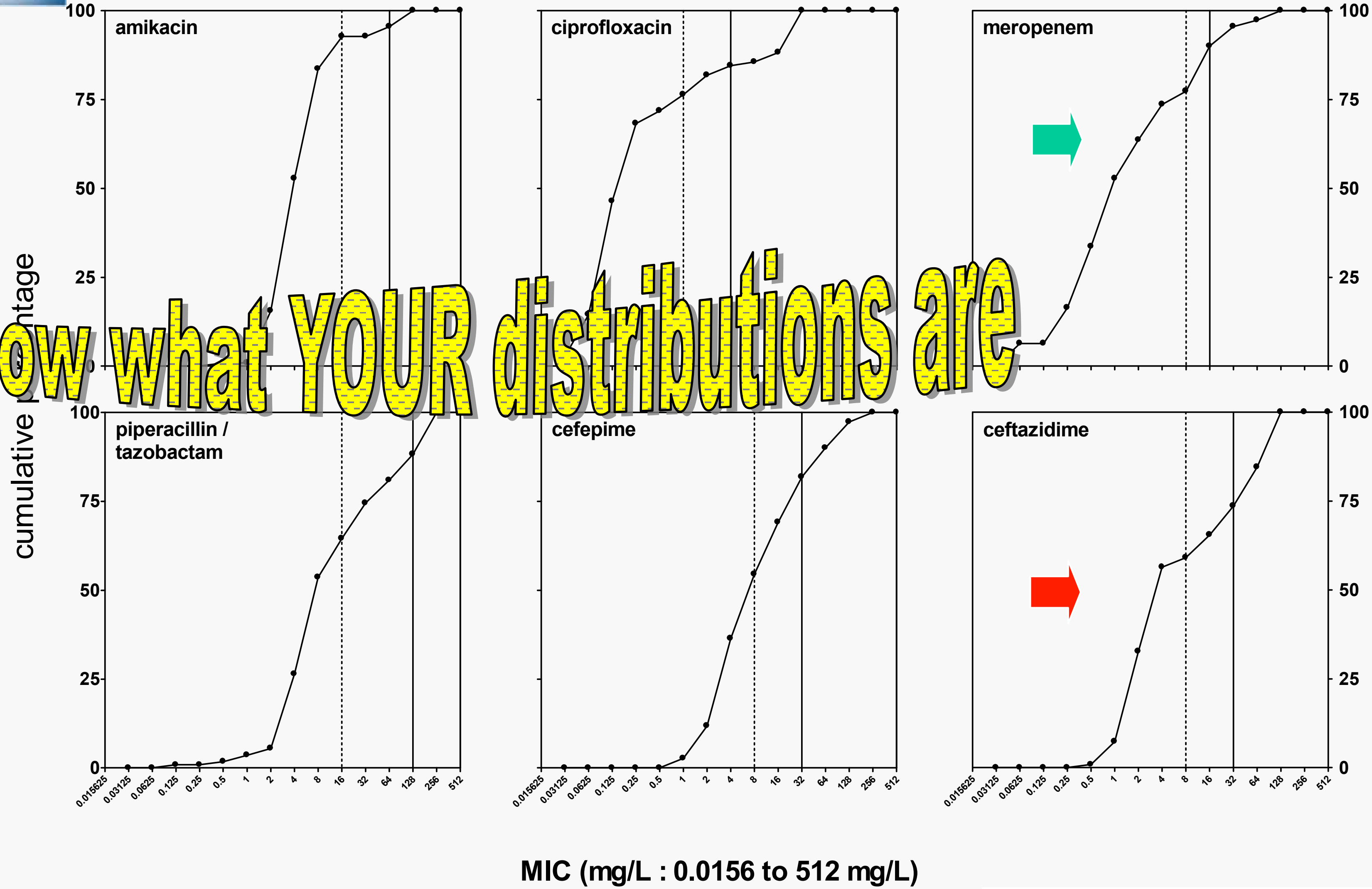
Supported by
1 Regional authorities and the Fund for Industrial Research
2 Fund for Scientific and Medical Research
3 Pharlmaceutical Industry and small/medium enterprizes

What is the situation at day 0 ?



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

What is the situation at day 0 ?



Know what YOUR distributions are

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 …

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

Pharmacokinetics

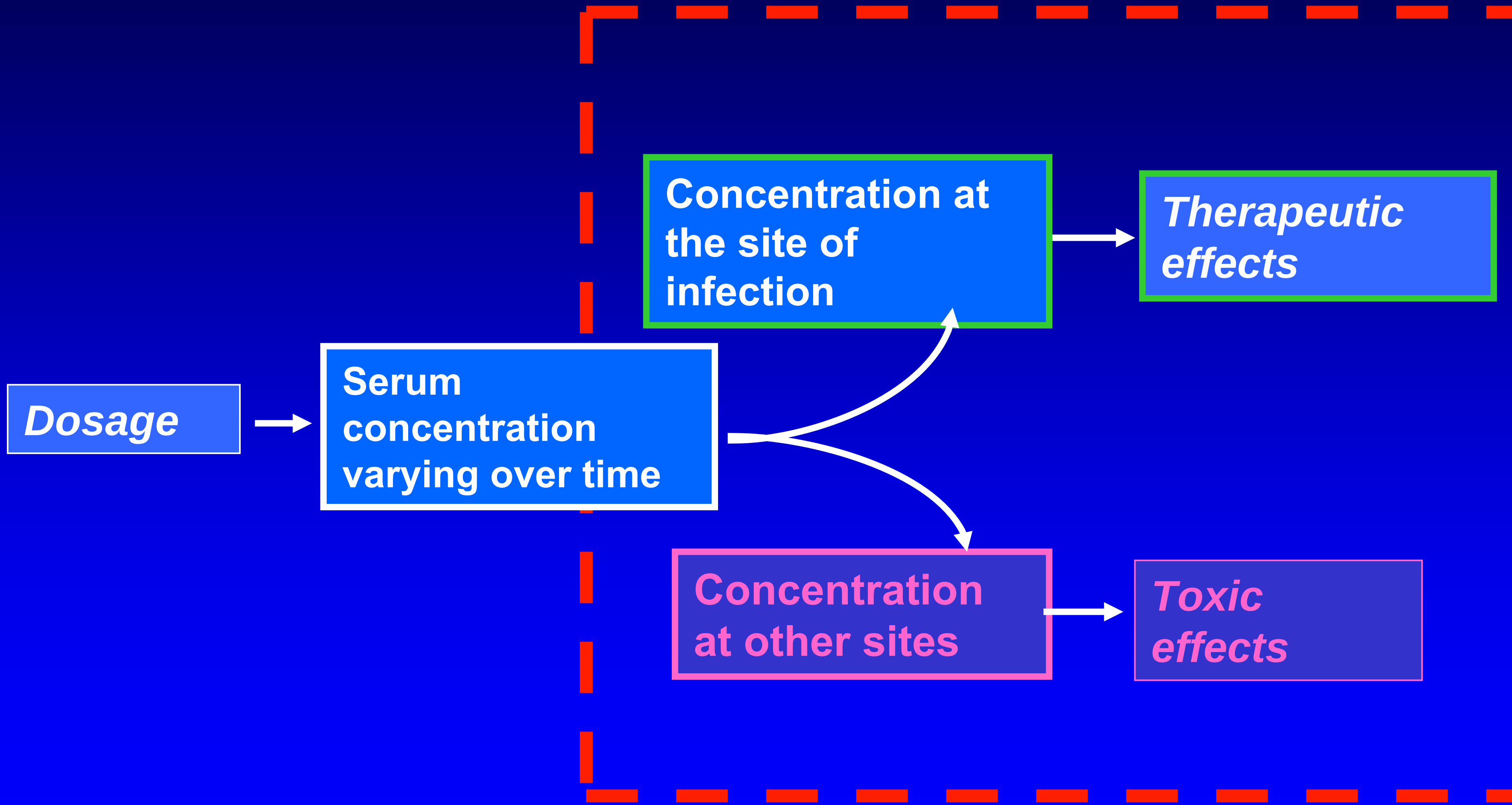
Dosage

Serum concentration varying over time

Concentration at the site of infection

Concentration at other sites

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 ?

A bunch of good guys met in Stockholm in 1989 ...

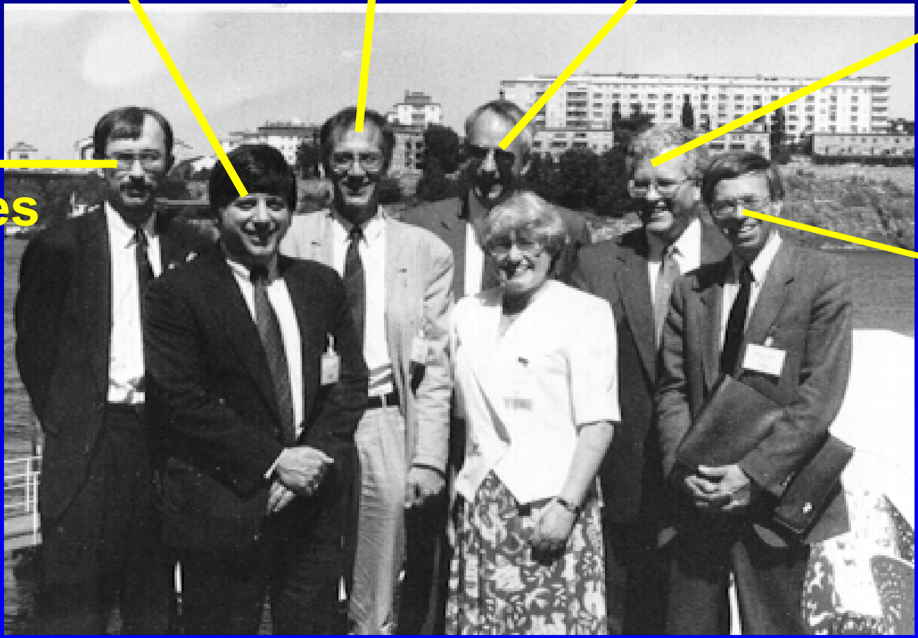
What did they think all about ?

population pharmacokinetics

tissue concentrations

efficacy/toxicity ratios

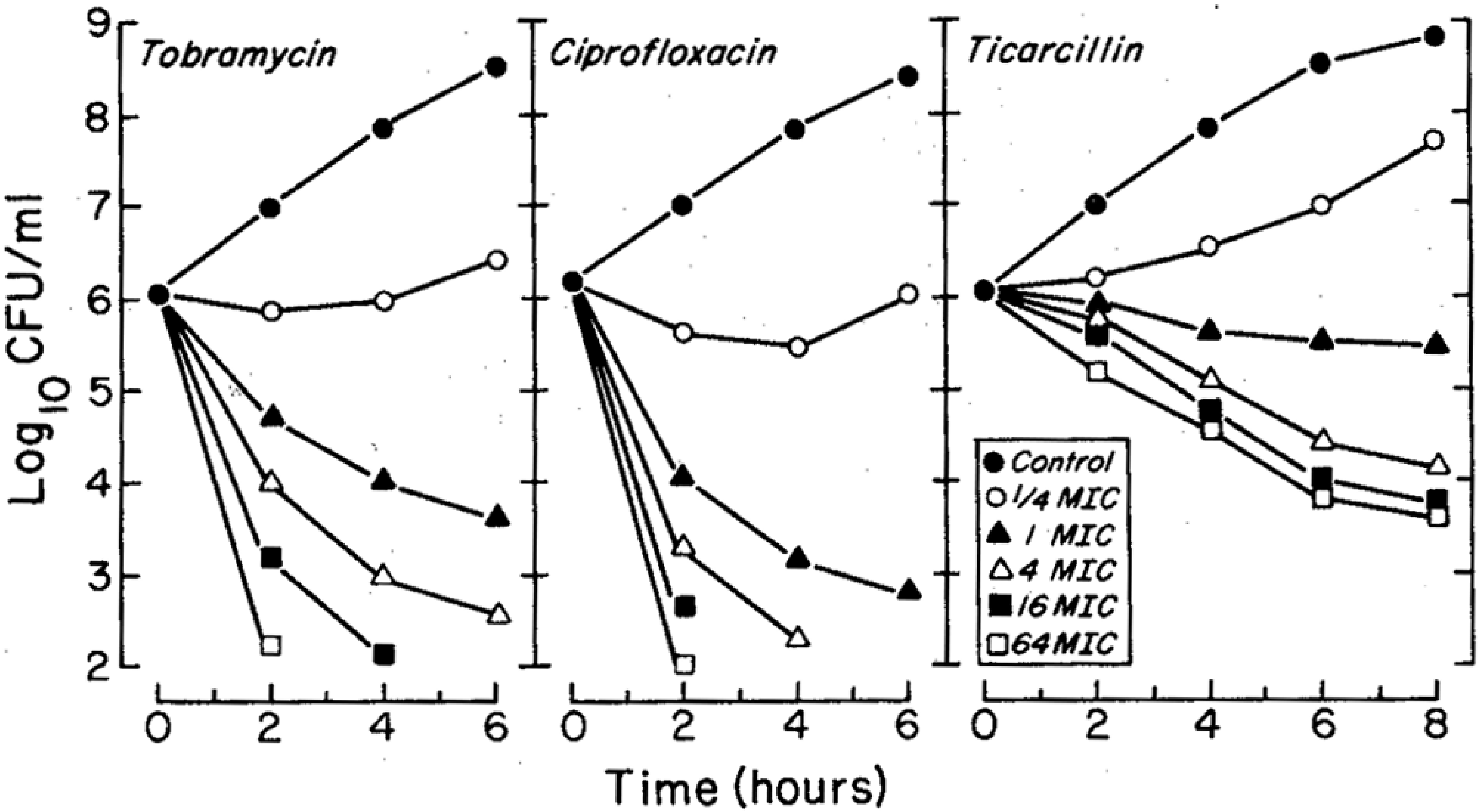
AUIC and fluoroquinolones



postantibiotic effect and β-lactam infusion

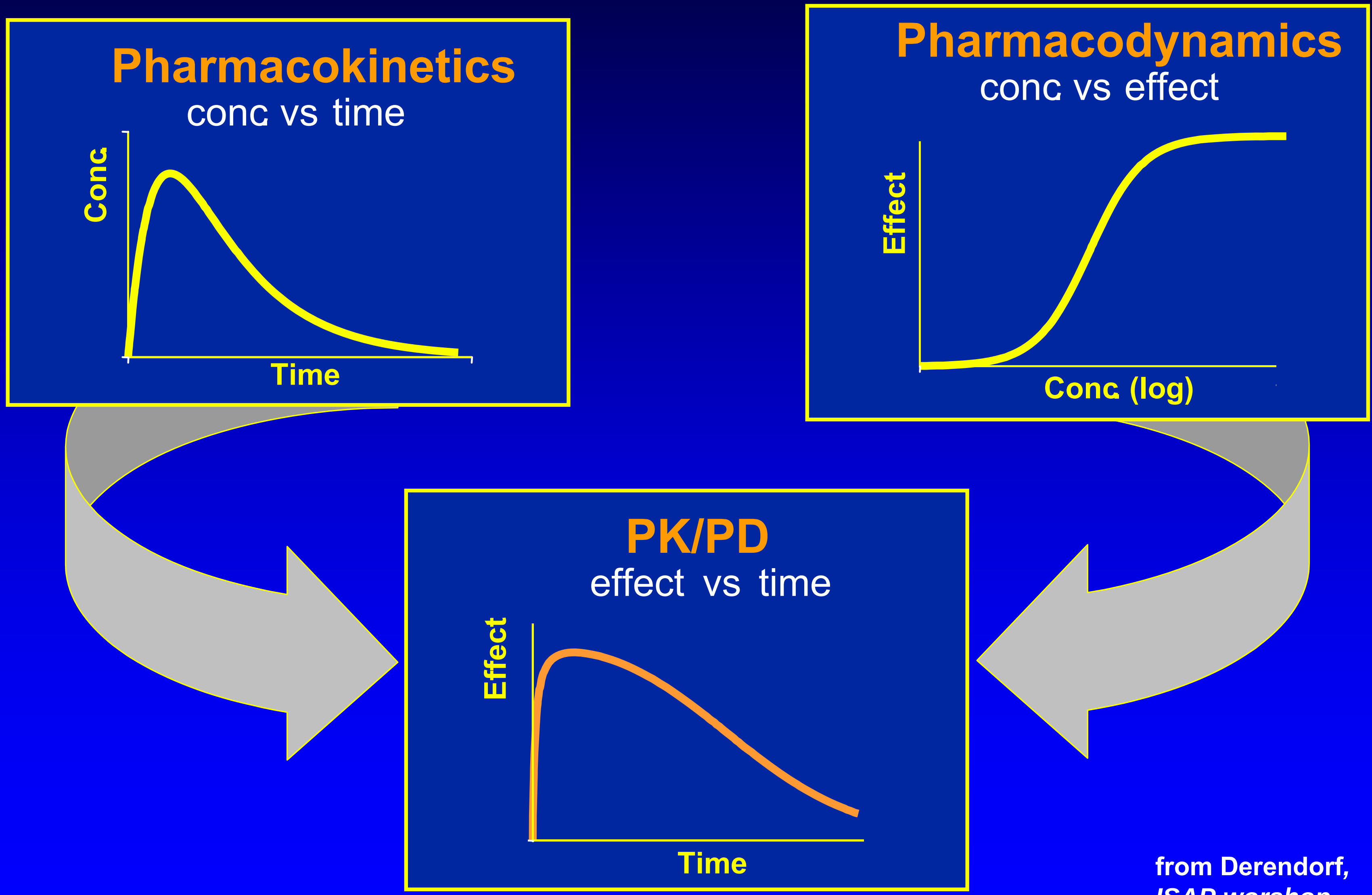
once-daily dosing of aminoglycosides

Pharmacodynamics : influence of time and concentration ...



Craig *et al.*

Pharmacokinetics - Pharmacodynamics



from Derendorf,
ISAP worshop

PK/PD since 1989 ...

1990 ... : organization of sessions on pharmacodynamics at the major international meetings (ICAAC, ECCMID, etc…)

1995 … : Introduction of PK/PD considerations in the <u>drug development and registration process ...</u> (FDA/EMEA)

2005 … : PK/PD considerations introduced in <u>clinical investigations and daily clinical activities</u> ...

now …. : PK/PD considerations begin to be used to define <u>optimal reimbursement schemes</u> in Europe …

PK /PD in action in the Regulatory in the USA

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 HIT FAST?

1. No
2. Yes

More questions …

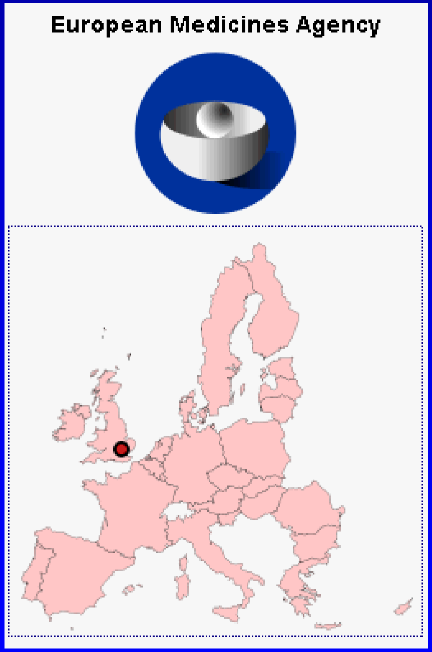
- Do you agree the benefit of HIT HARD HIT FAST?

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.



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… "

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* 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
EMEA/9880/99, Rev. 1

EMEA 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

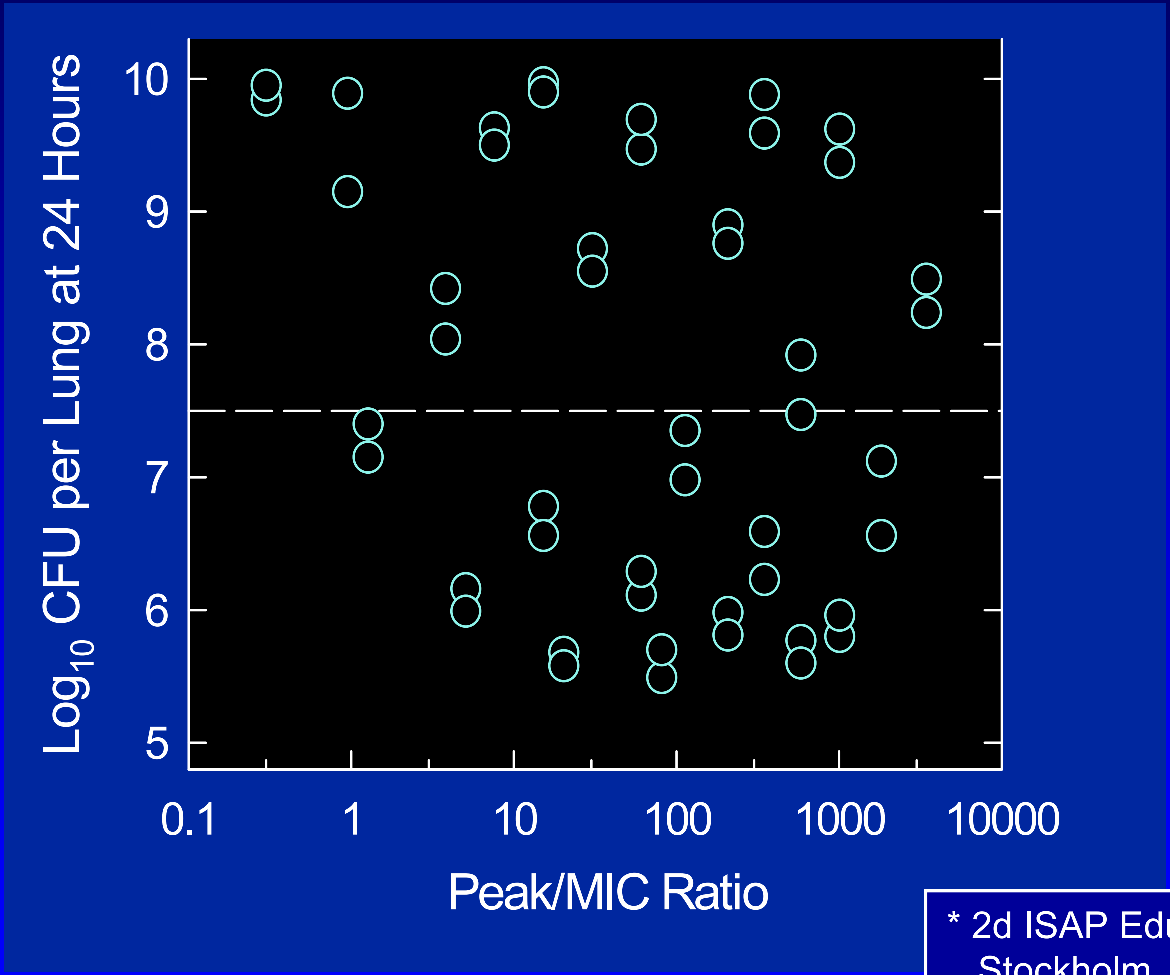
Most available antibiotics can be divided in 3 main groups with respect to PK/PD properties :

- Time-dependent (" T > MIC ")
  → β-lactams (all)

- Concentration-dependent (" Cmax / MIC")
  → aminoglycosides and, for eradication, fluroquinolones

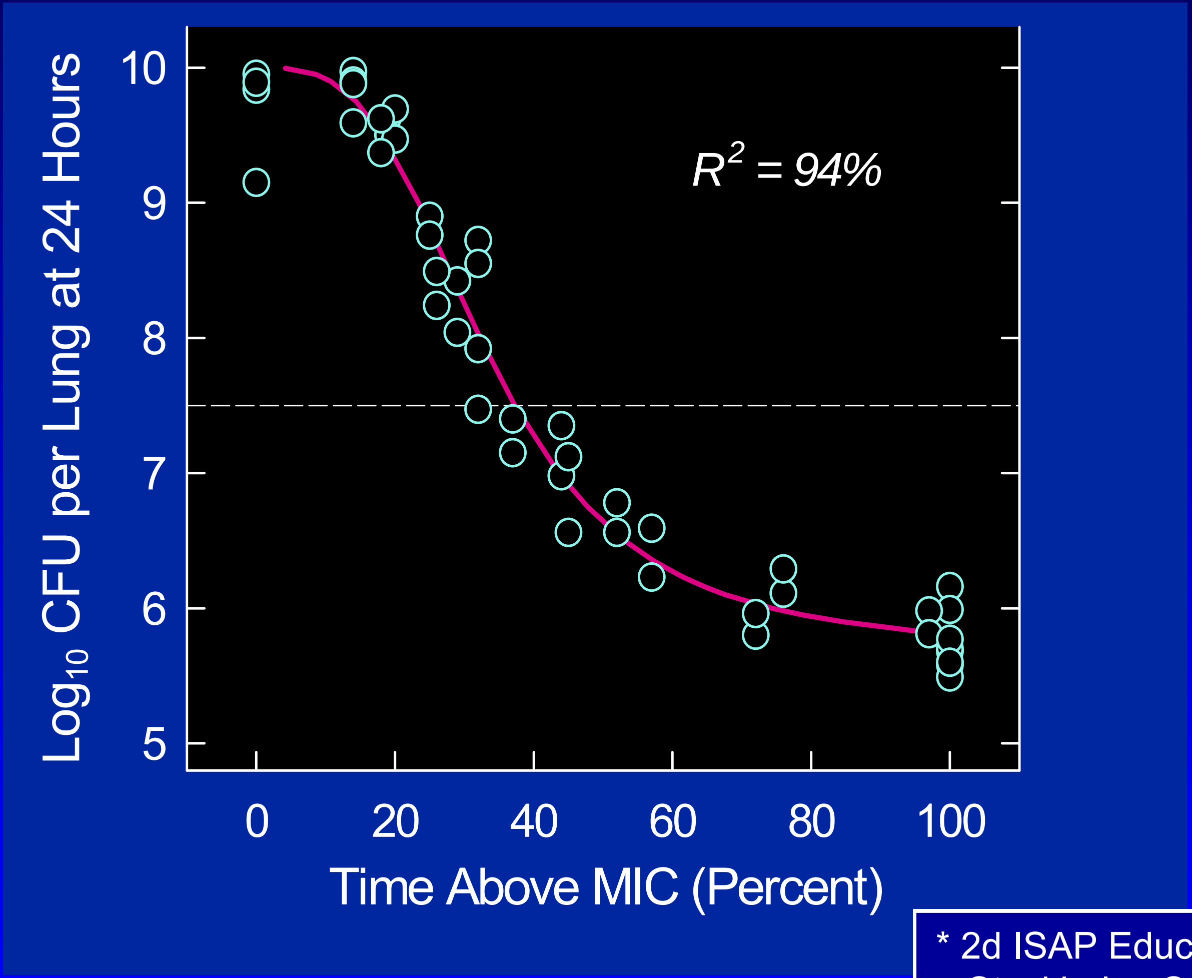
- Total daily dose-dependent (" AUC / MIC ")
  → fluroquinolones (for global efficacy) and all others

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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In a nutshell ... so far …

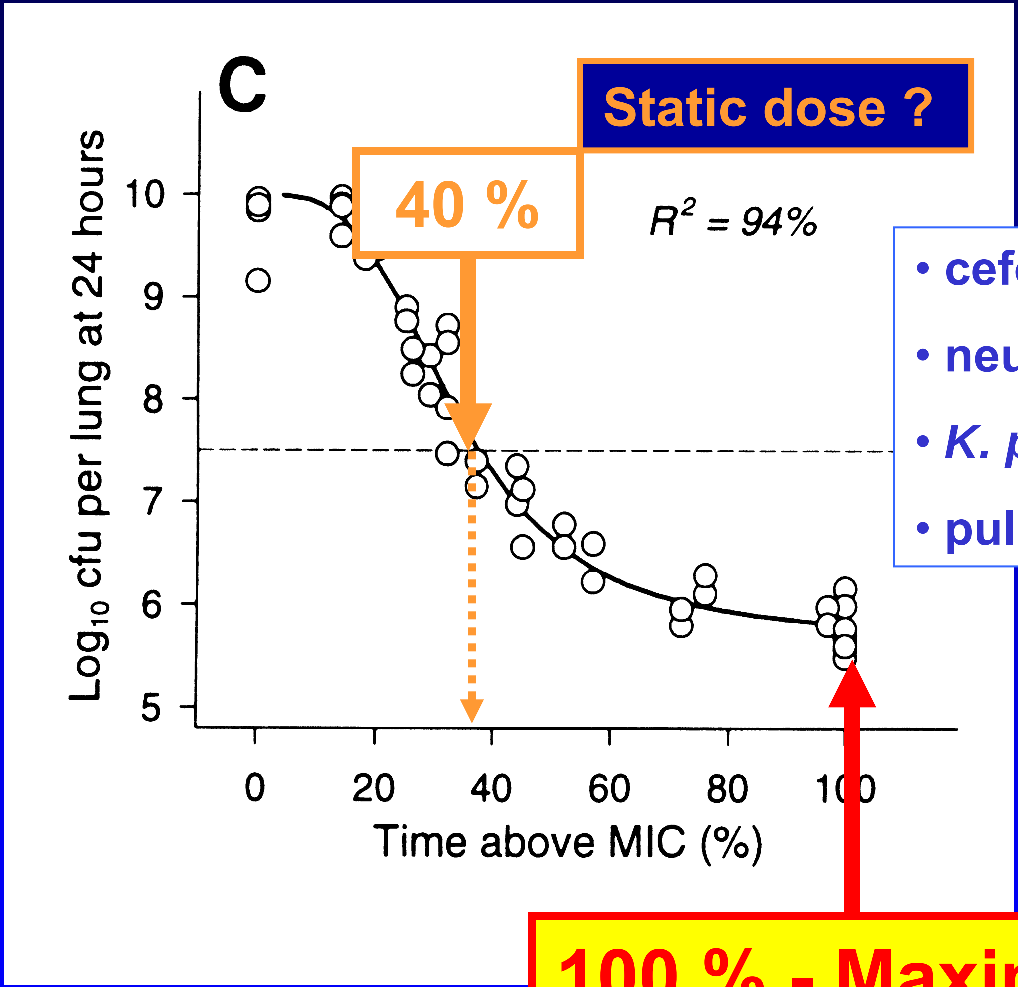
- Microbiology parameters: MIC !
- Pharmacodynamic parameters
- **PK/PD as applied to beta-lactams: Time-above MIC**
- The problems if you underdose
- Take home message

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 (*Fu*) ?)
- The same for all micro-organisms ?
- The same for all infections ?
- Can you apply to all patients ?

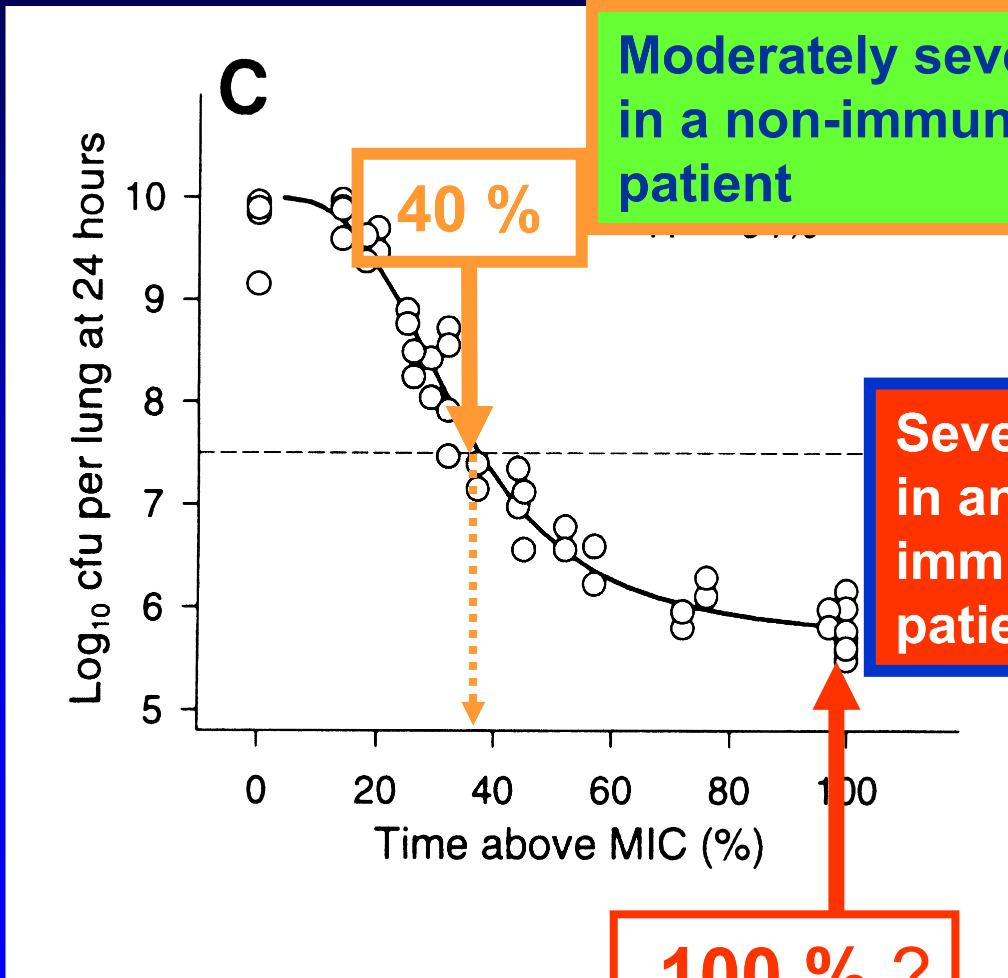
How much time above MIC ?



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

100 % - Maximal effect ?

Here is a proposal ...



40 %

Moderately severe infection in a non-immunospressed patient

Severe infection in an immunosuppressed patient

100 % ?

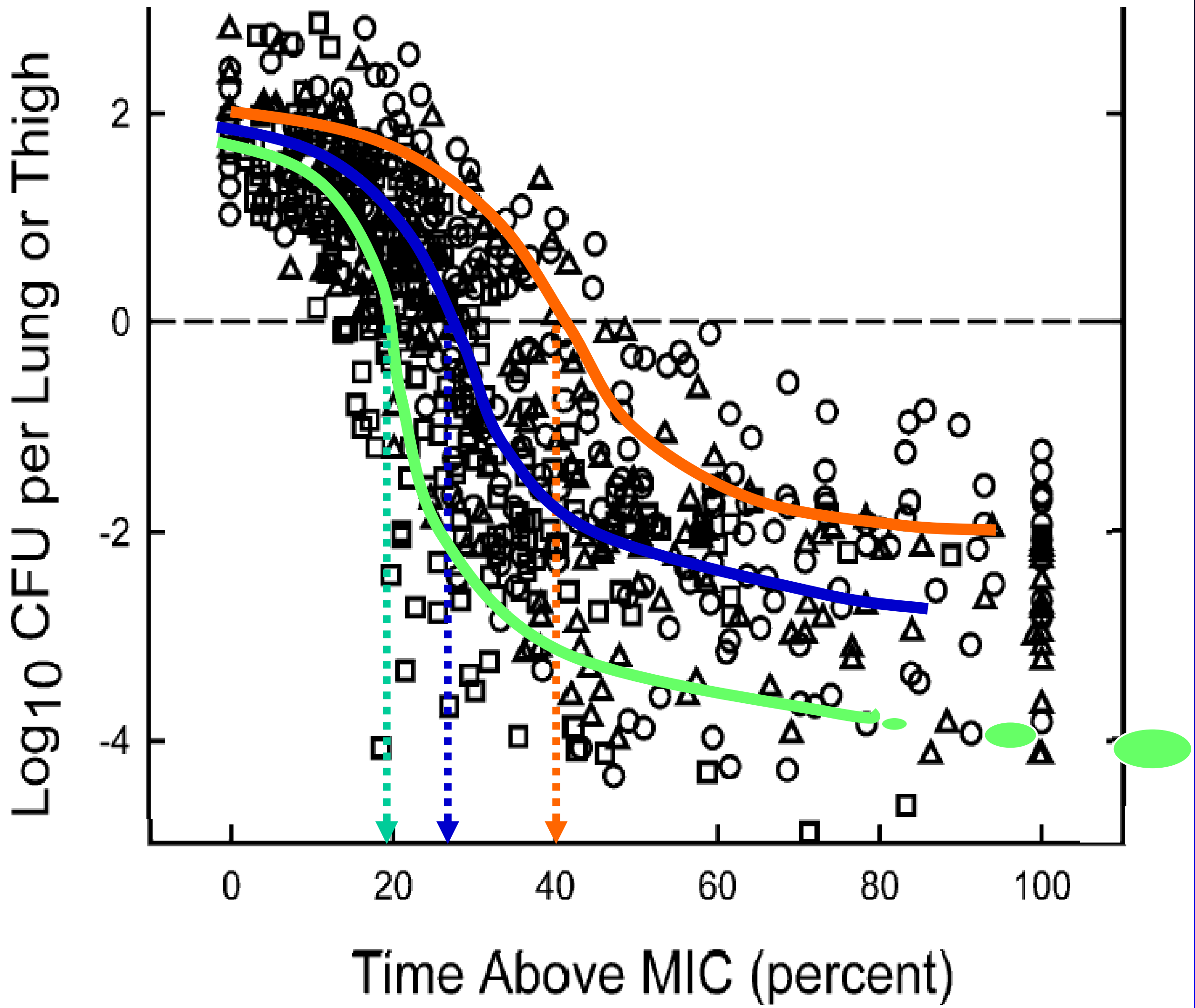


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

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 microorganims ?

T> MIC for static effect

Drug	Enterobacteriaceae	*S. pneumoniae*
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)	

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

- "out of the package insert" PK data
- Monte-Carlo simulations and target attainment approaches

Typical pharmacokinetics of an IV β-lactam

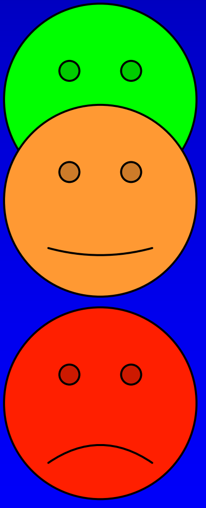
time (hours)	serum concentration for 0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

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

Reading the labeling (package insert)

time (hours)	serum concentration for 0.5 g	1 g	2 g
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

Where would you like to be ?



* 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 ≤ 3 mg/L !**
- 2 g every 8 h → **T > MIC = 100 % if MIC ≤ 12 mg/L**

More frequent administrations is the best way to increase the activity of β-lactams in difficult-to-treat infections...

→ **PK / PD breakpoint for IV β-lactams : MIC = 8 µg/ml**

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

Belgian labelling (SmPC)

Des doses allant jusqu'à 2 g trois fois par jour chez l'adulte ... peuvent être particulièrement adaptées au traitement ... des infections nosocomiales dues à *Pseudomonas aeruginosa* ou *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

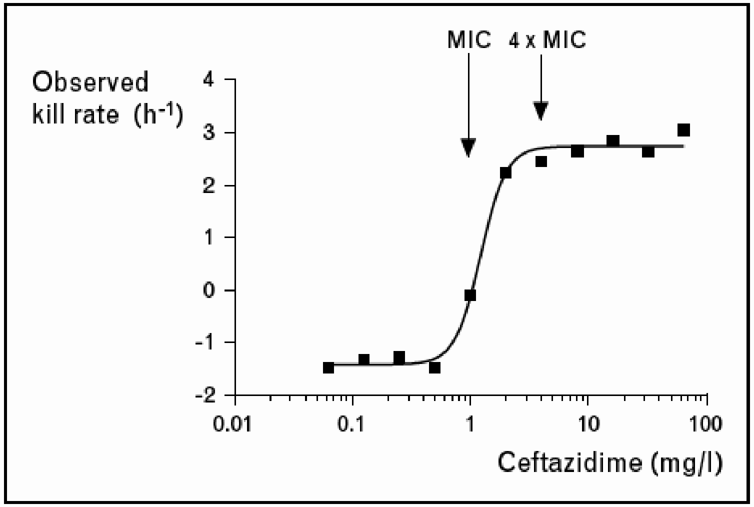
The label of all EU countries limit the dose of imipenem to 4 g/day !

*** see discussion about breakpoints later on ...**

Target Concentration for β-lactams: **continuous infusion**

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection

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 *

Target serum concentration

$C_t = D_l / V_d$

volume of distribution

loading dose

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

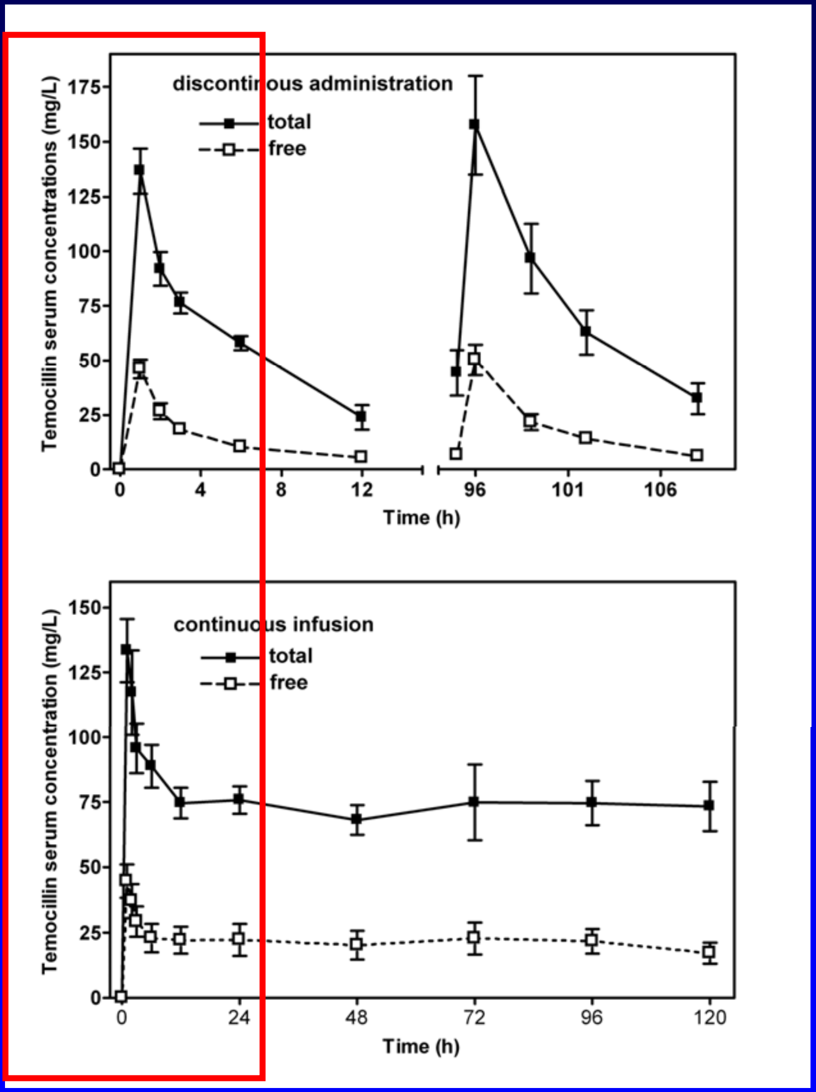
the loading dose is only dependent upon the volume of distribution and is directly influenced by the weight of the patient and his/her medical situation

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

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

Continuous infusion in practice
1. loading dose: a simplified (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 *

Target serum concentration

$C_{ss} = K_o / Cl$

Clearance *

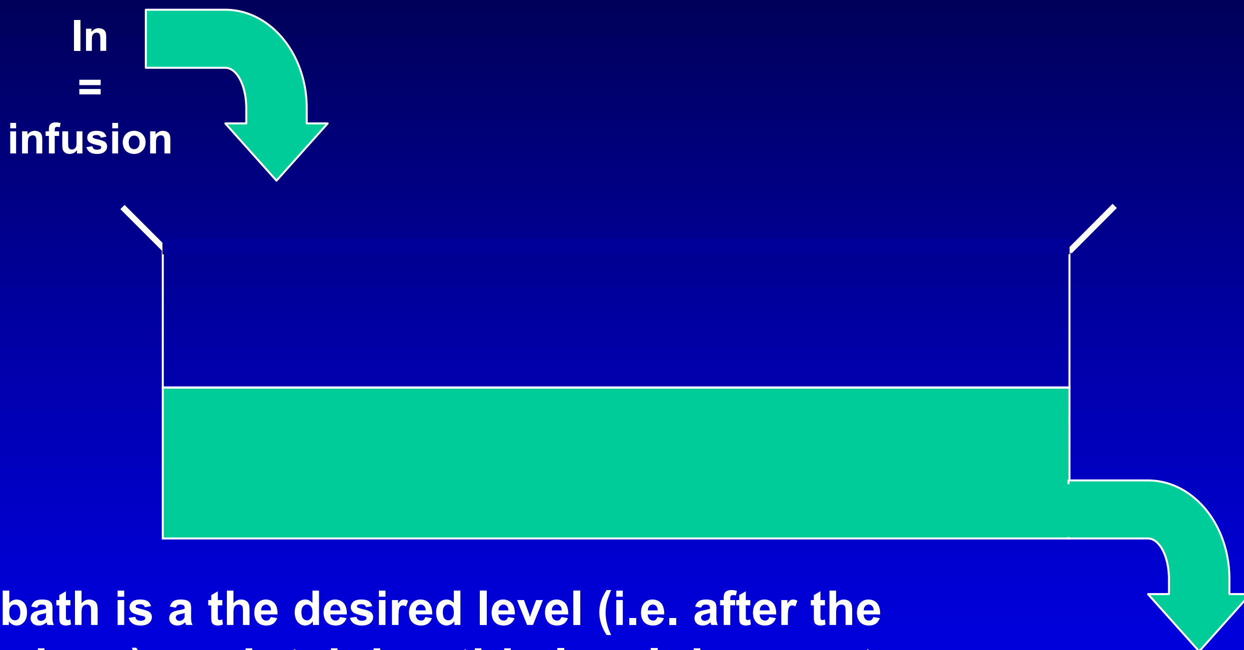
infusion rate

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

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

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

Continuous infusion in practice: why clearance only ?



once a bath is a the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which must be equal: in = out…)

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

Continuous infusion of β-lactams: a simplified practical scheme

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

JAC

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

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

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

- loading dose: **2 g**

the conventional unit dose

- 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].

Continuous infusion of β-lactams: a simplified practical scheme

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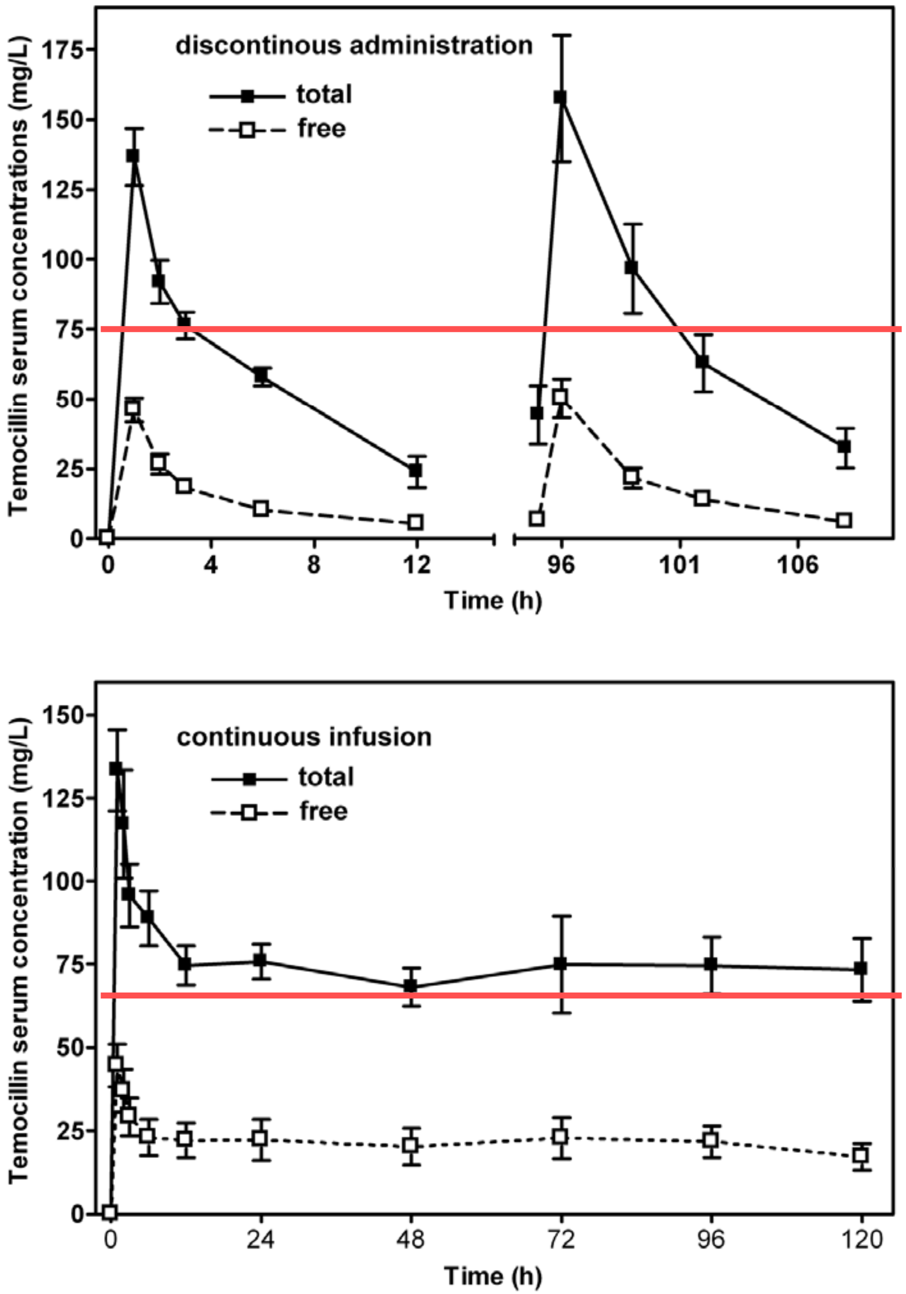
the conventional daily dose

Pharmacokinetics of temocillin 4 g/day:



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

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

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 $\geq$ 4
(also for discontinuous administration)

- **drug instability**

temocillin > piperacillin > ceftazidime > cefepime …

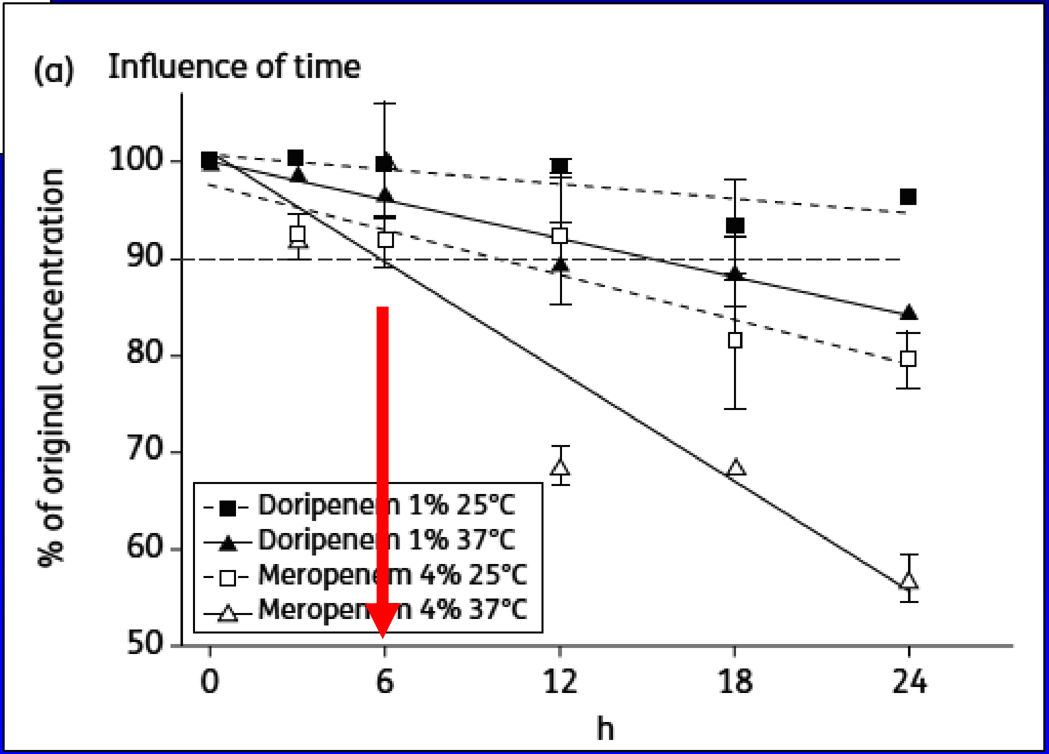
!! carbapenems are unstable (3-4h max.)

Carbapenems stability

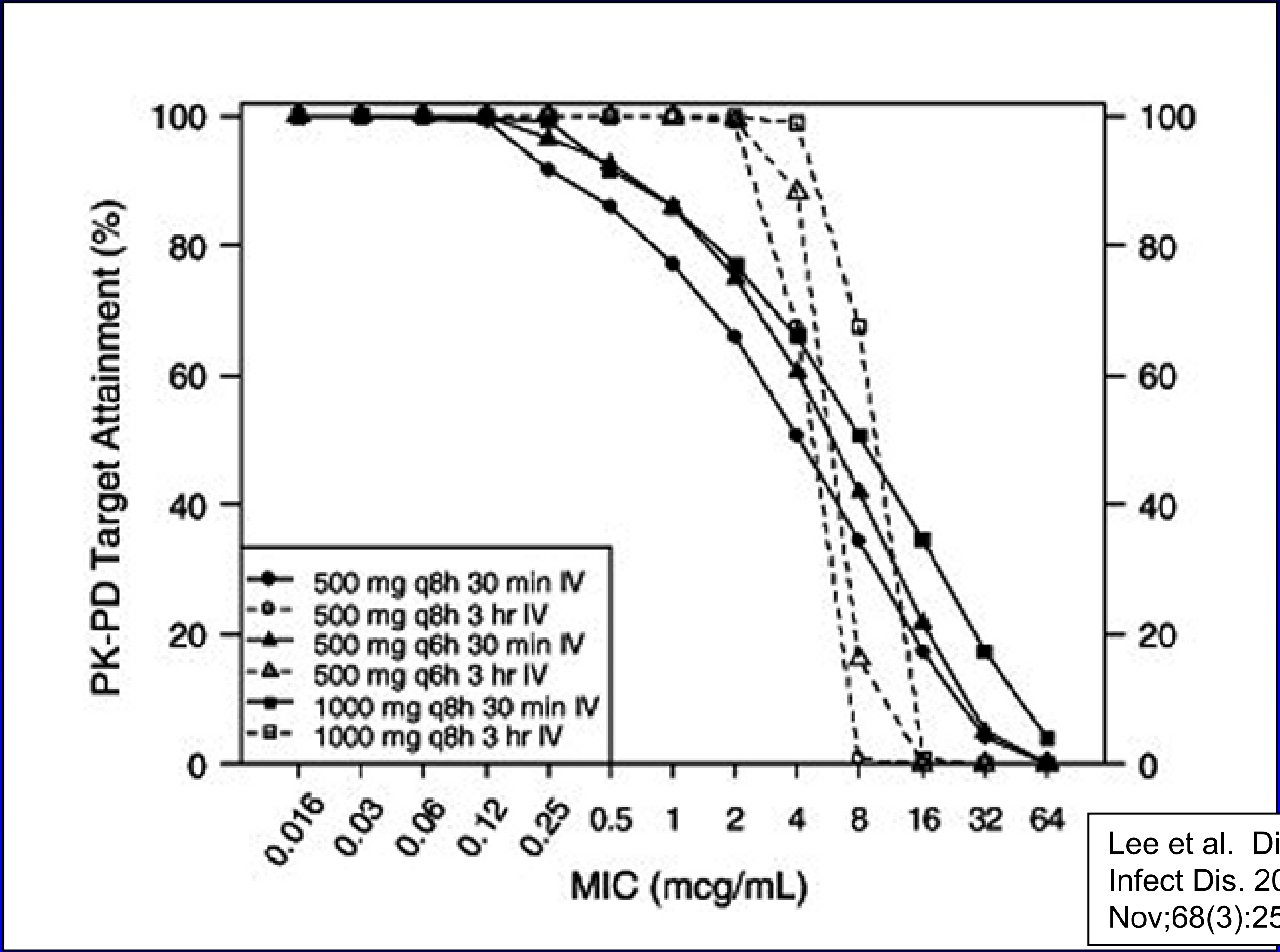
J Antimicrob Chemother (2010) 65:1073-1075
doi:10.1093/jac/dkq044
Advance publication 21 February 2010

Stability of meropenem and doripenem solutions for administration by continuous infusion

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



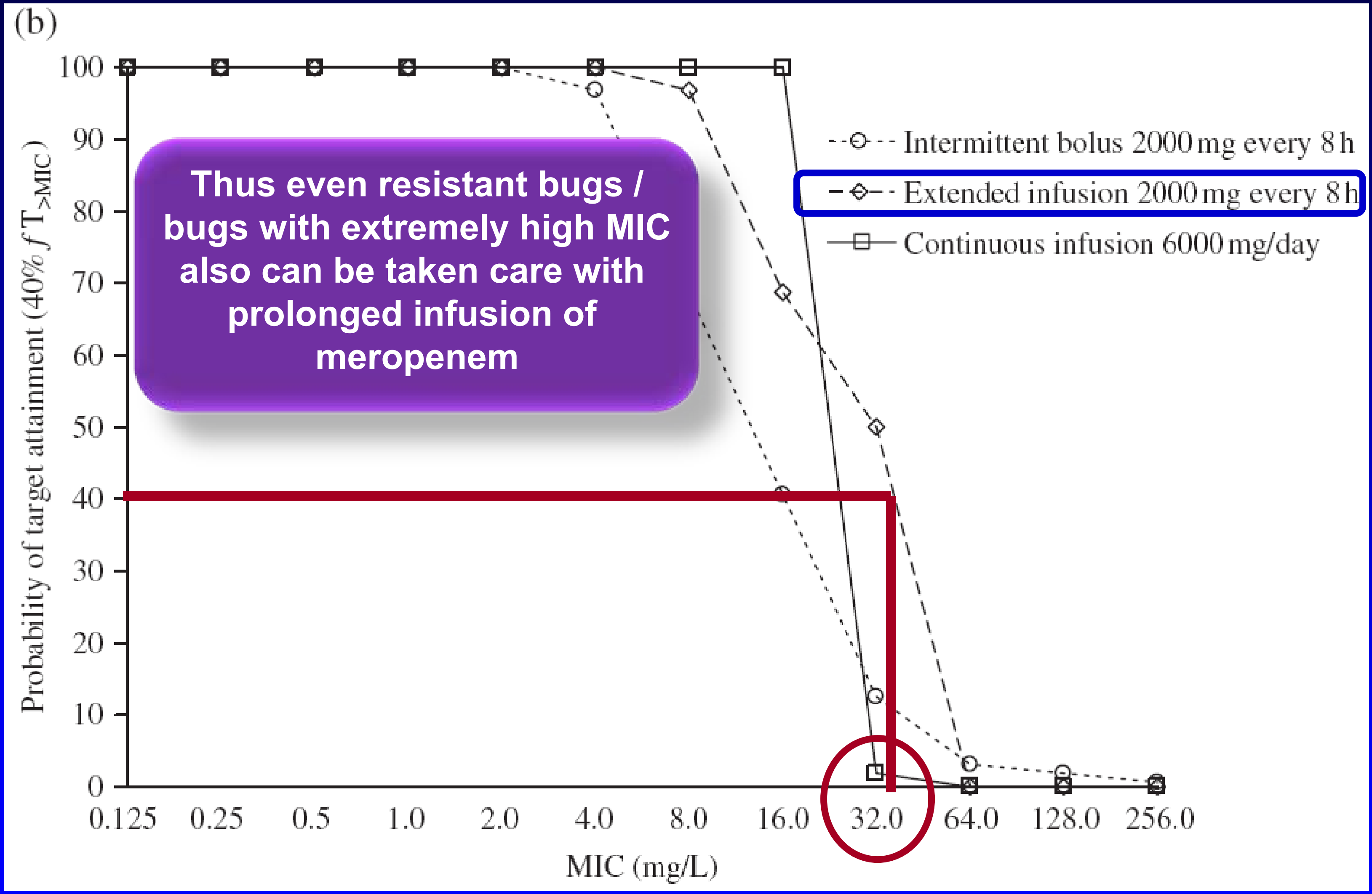
Carbapenems in 3h infusion: target attainment rate *



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

Meropenem Infusion in the Critically-Ill



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

Cefepime by continuous 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

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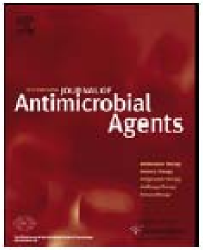


Steady-state pharmacokinetics and pharmacodynamics of cefepime administered by prolonged infusion in hospitalised patients☆

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

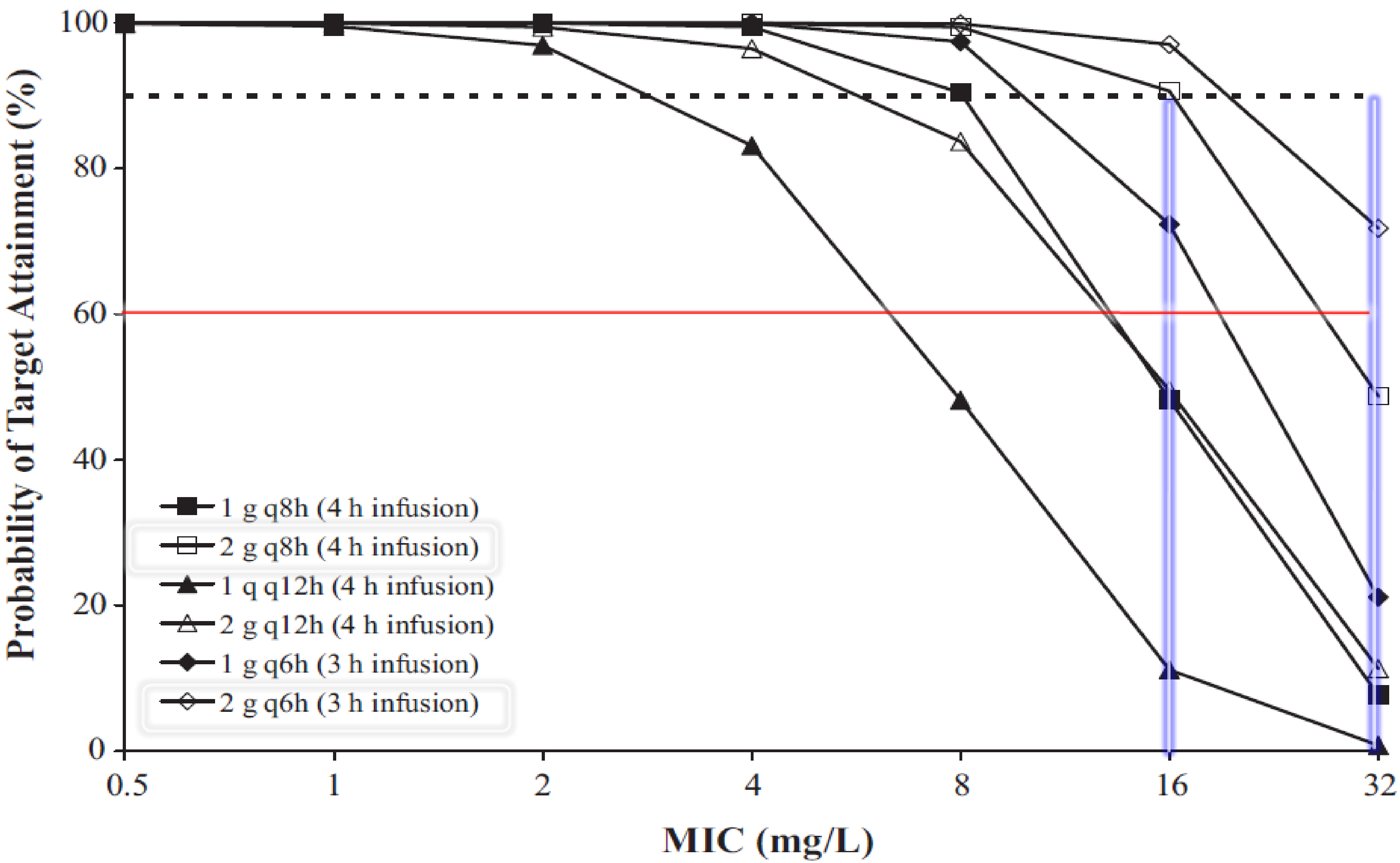


Fig. 2. Probability of target attainment (PTA) at 60% *f*T > MIC for six prolonged infusion regimens of cefepime at specific minimum inhibitory concentrations (MICs). The dotted line indicates a PTA ≥ 90%. *f*T > MIC, time for which the free drug concentration remains above the MIC; q8h, every 8 h; q12h,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

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

3 h infusion in (common) practice...
for patients with normal renal function

- 1st administration: loading dose in 30 min
  - 2 g (cefepime / meropenem)*
- followed immediately by an 3 h infusion of
  - 2 g (cefepime / meropenem)*
- Repeat step 2 every 8 h

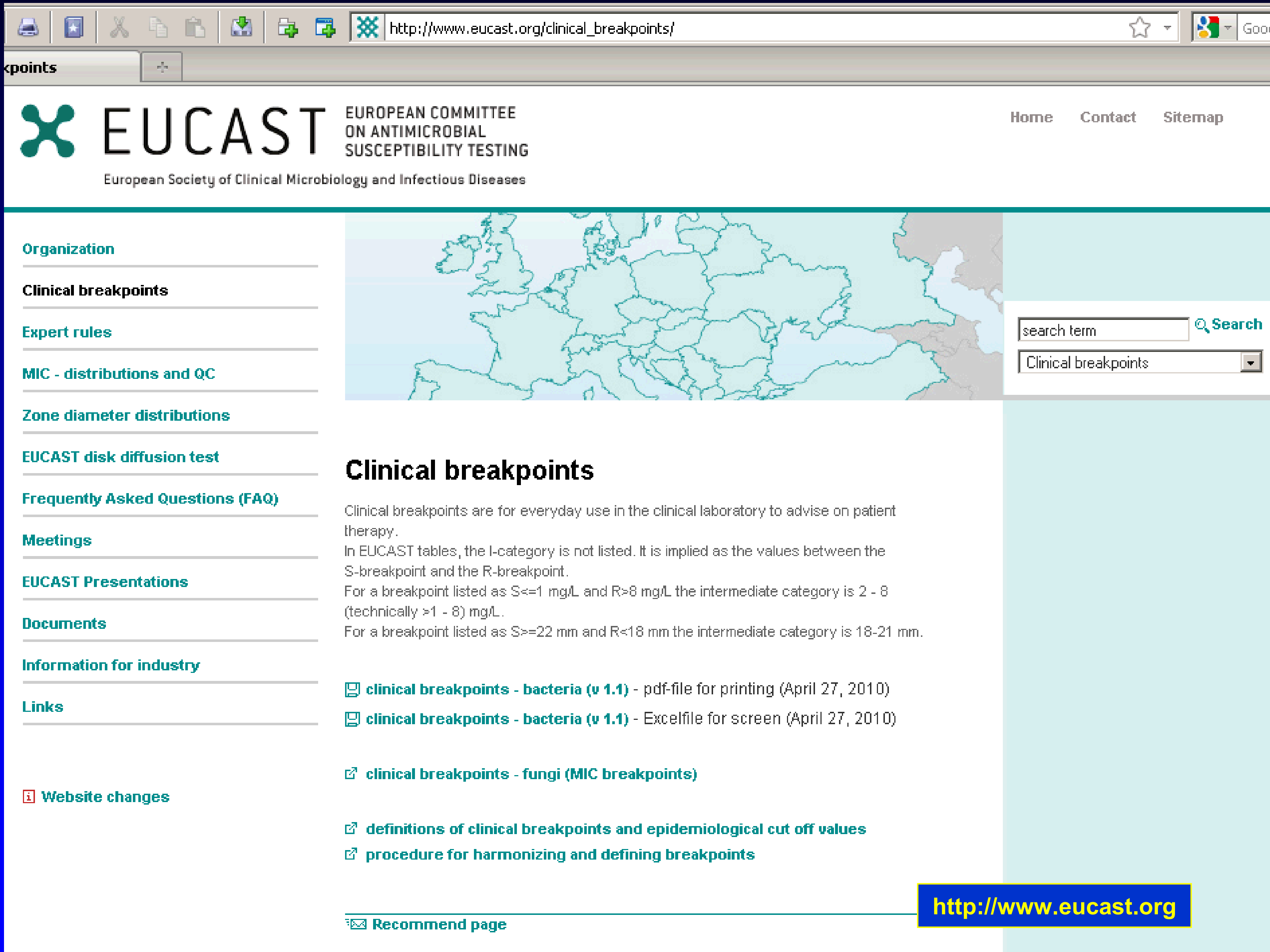
---

* 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

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/

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Home Contact Sitemap

- 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<=1 mg/L and R>8 mg/L the intermediate category is 2 - 8 (technically >1 - 8) mg/L.
For a breakpoint listed as S>=22 mm and R<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

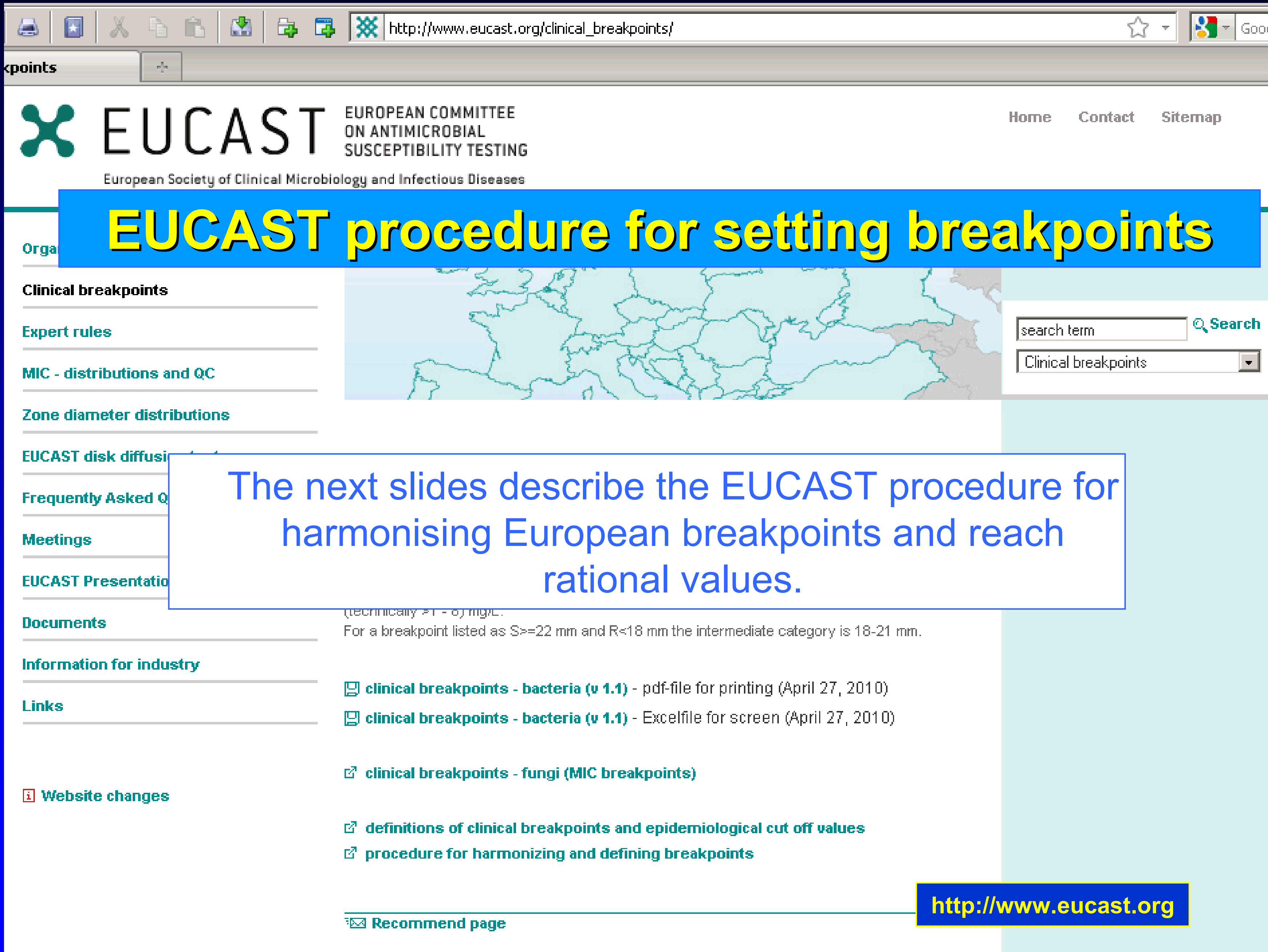
procedure for harmonizing and defining breakpoints

Recommend page

http://www.eucast.org

EUCAST procedure for setting breakpoints

The next slides describe the EUCAST procedure for harmonising 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 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. 6. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type population

http://www.eucast.org

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

EUCAST and carbapenems

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

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_breakpoints_v1.1.pdf

EUCAST and cephalosporins

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

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

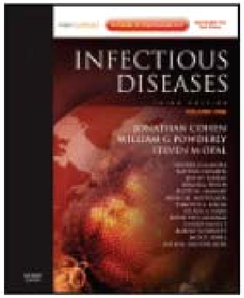
IMP/VIM

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 Monobactams* Piperacillin + tazobactam	OXA-1 to -30, PSE-2 from Enterobacteriaceae and *P. aeruginosa* OXA-11 to -19, 28, 32, 45 are ESBLs in *P. aeruginosa* (R to Ceph 3) OXA-23, -24, -58 are carbapenemases in *Acinetobacter baumannii*



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

Serine enzymes

Metallo (Zn) enzymes

Group C

Group A

Group D

Group B

AmpC

TEM / SHV / CTX-M

ESBLs

OXA

IMP/VIM

those should be inhibited by tazobactam

An innovative approach for ESBL...

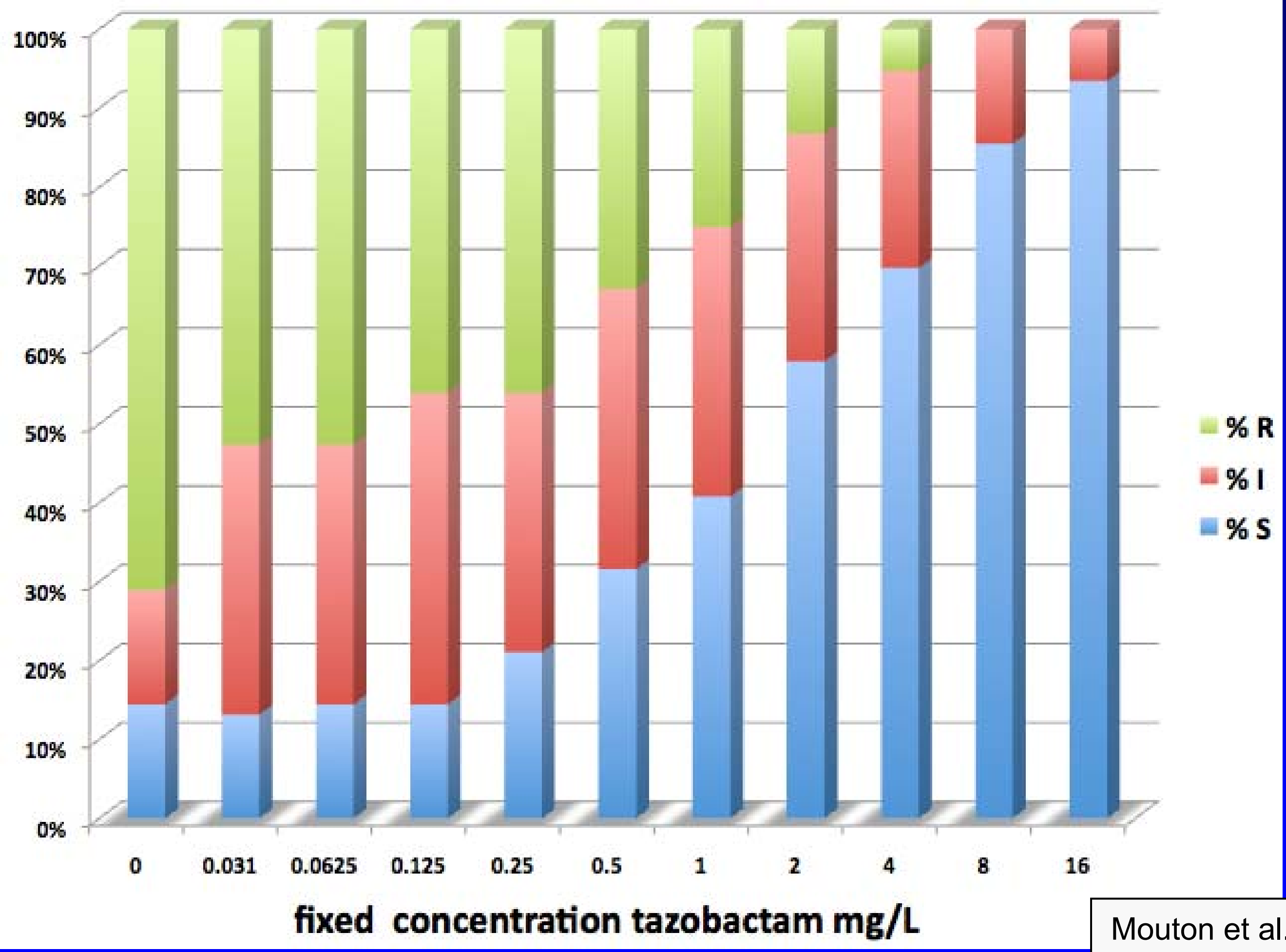
- take a 4th generation cephalosporin (cefepime [PM])
  - ➔ should cover (partly AmpC) and resist to OXA
- add a β-lactamase inhibitor (tazobactam [TZ])
  - ➔ will take care of many ESBL

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...

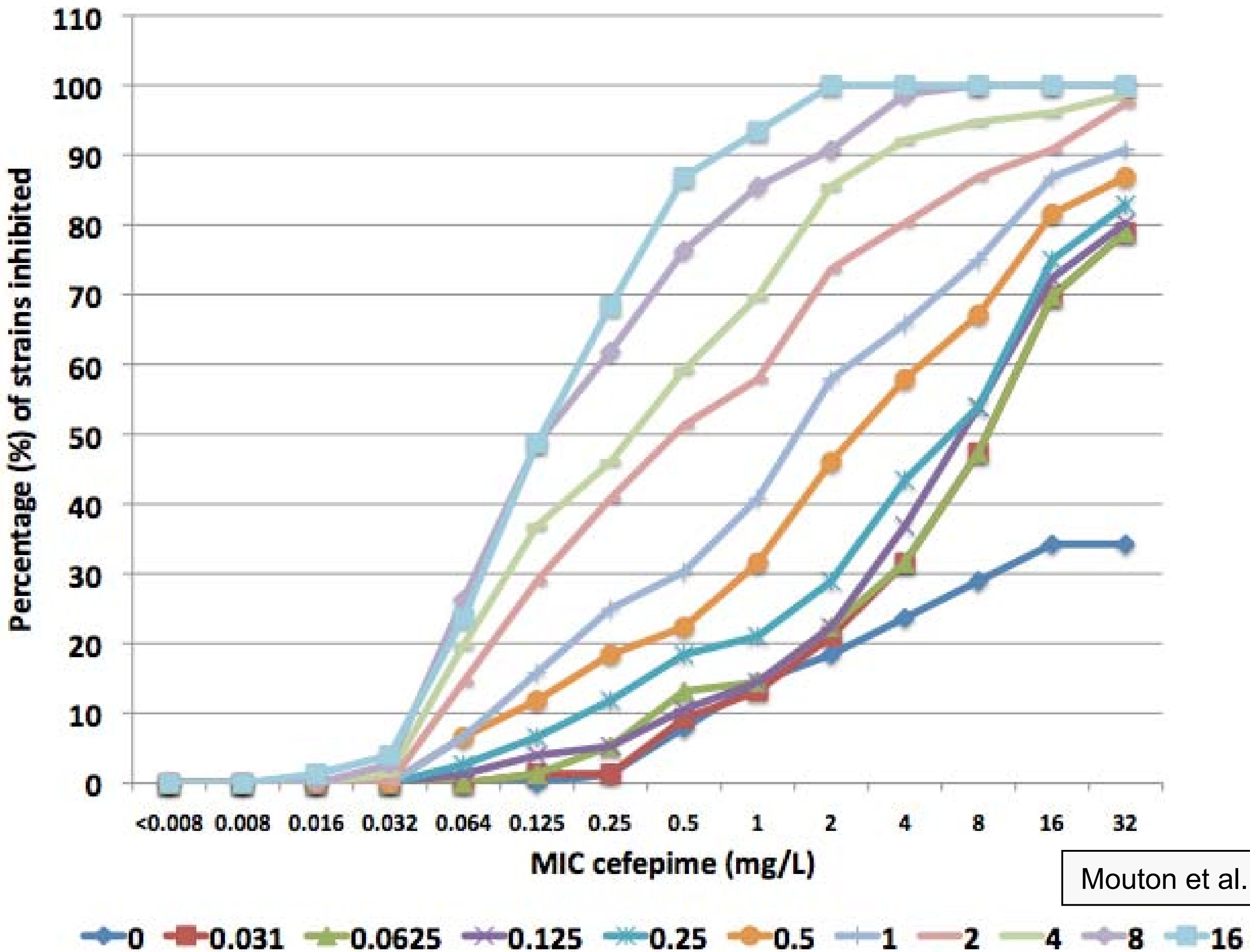
Percentage sensitive(S), intermediate(I) and resistant(R) cefepime (breakpoints EUCAST: ≤1 S – R >8)



Mouton et al. ICAAC 2010

An innovative approach for ESBL...

Cumulative % inhibition of strains with different fixed concentrations of tazobactam.



Mouton et al. ICCAC 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 problems 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 MIC (mg/L) [a]			TEM-exposed MIC (mg/L)			Revertant 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

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

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2114/2 [c]	8	2	0.25	**2048**	**> 128**	**16**	**32**	4	0.5
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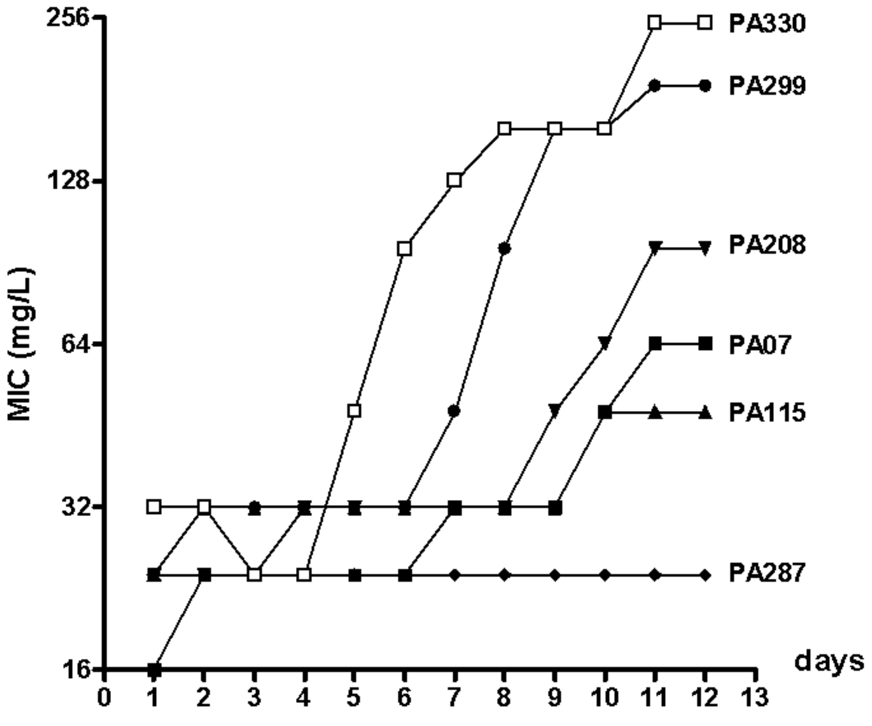
[c] ESBL TEM 24 (+) ; [d] ESBL (-) and AmpC (+) [high level] ; [e] Intermediate (I) according to EUCAST

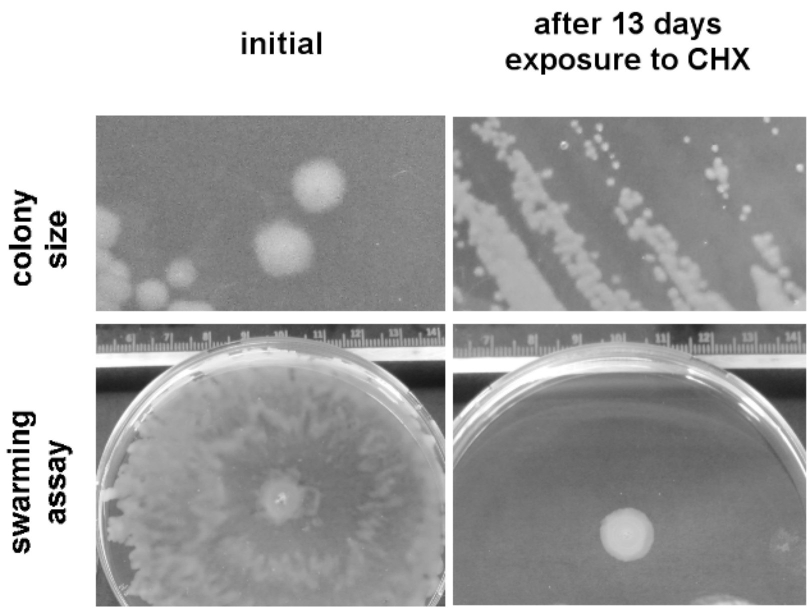
sub-MIC concentrations create resistance !

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

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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]

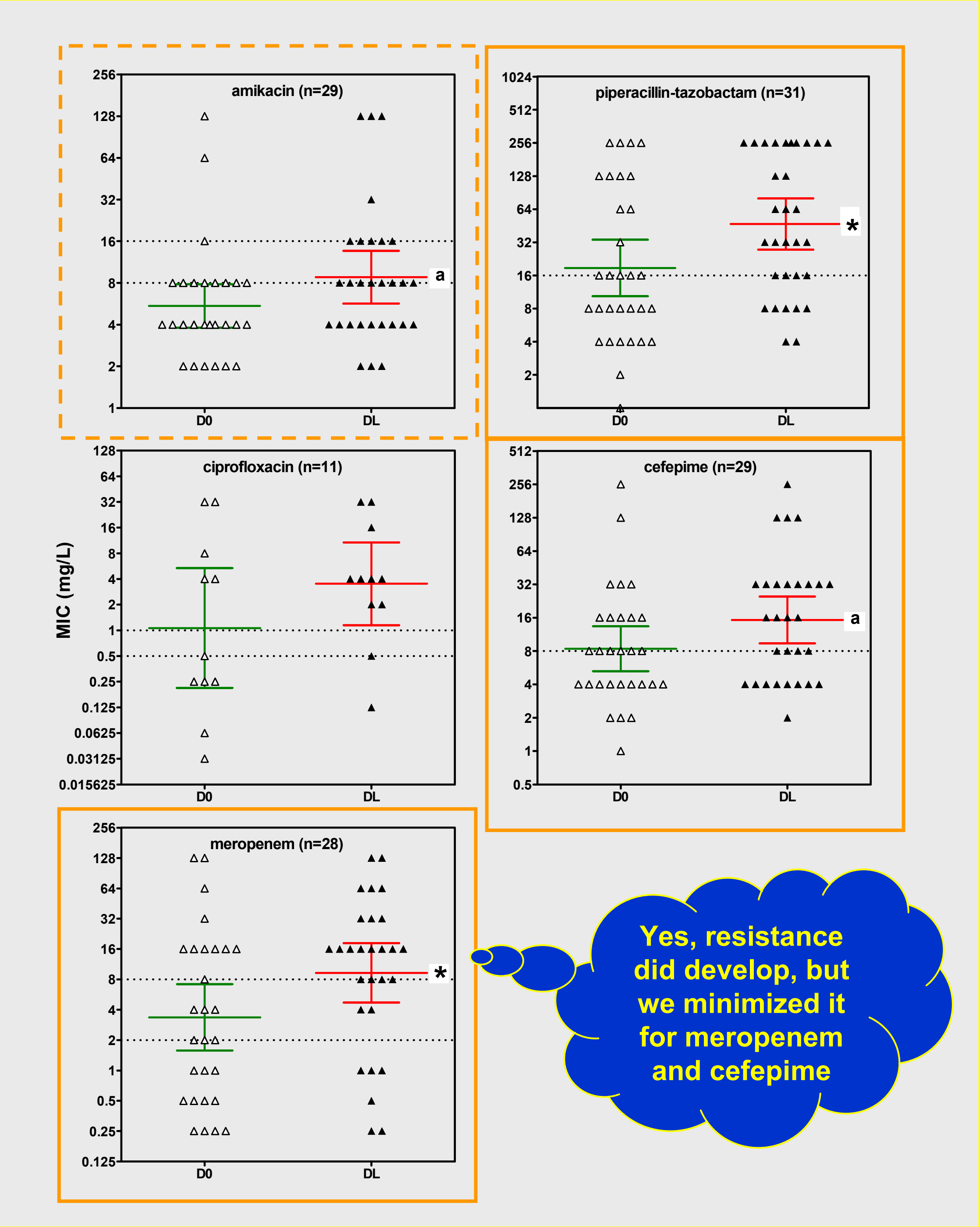
What happens during treatment ?

- 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

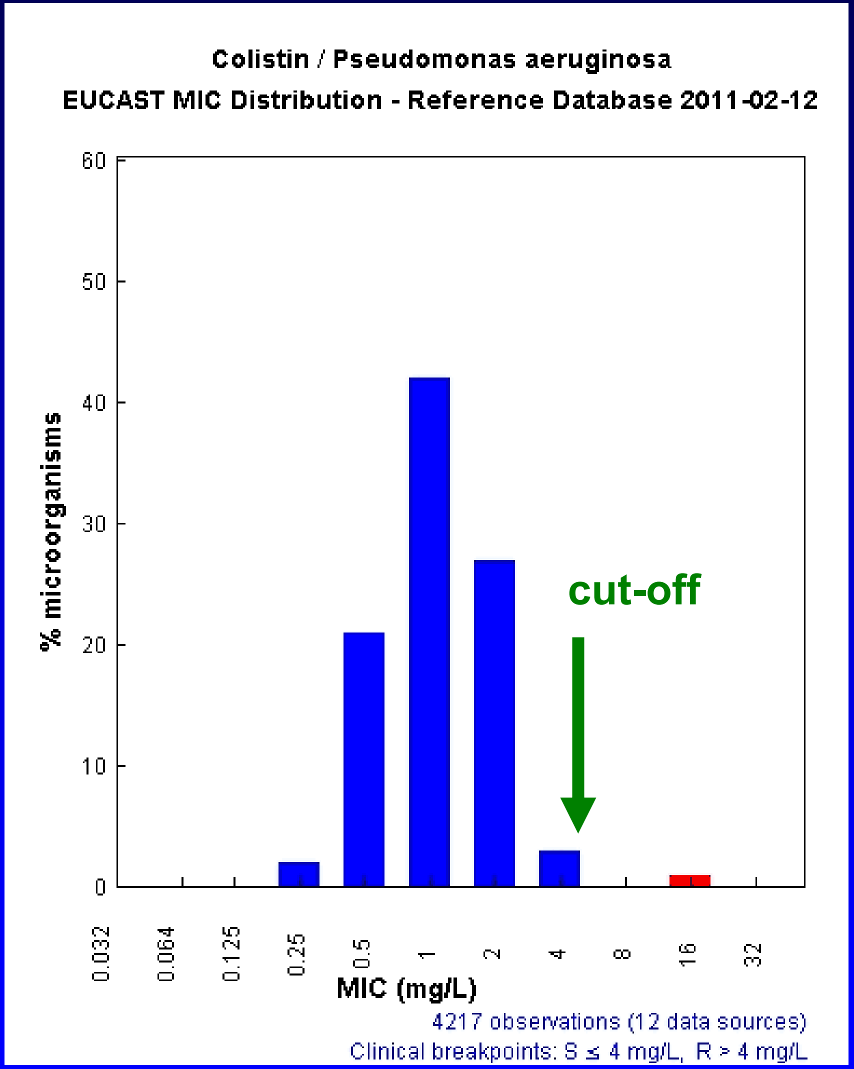
Note: stratification by time between D0 and DL gave no clue (too low numbers)



And what about colistin ?

You first need to consider the MIC distribution.

Here are the data of EUCAST for *Pseudomonas*



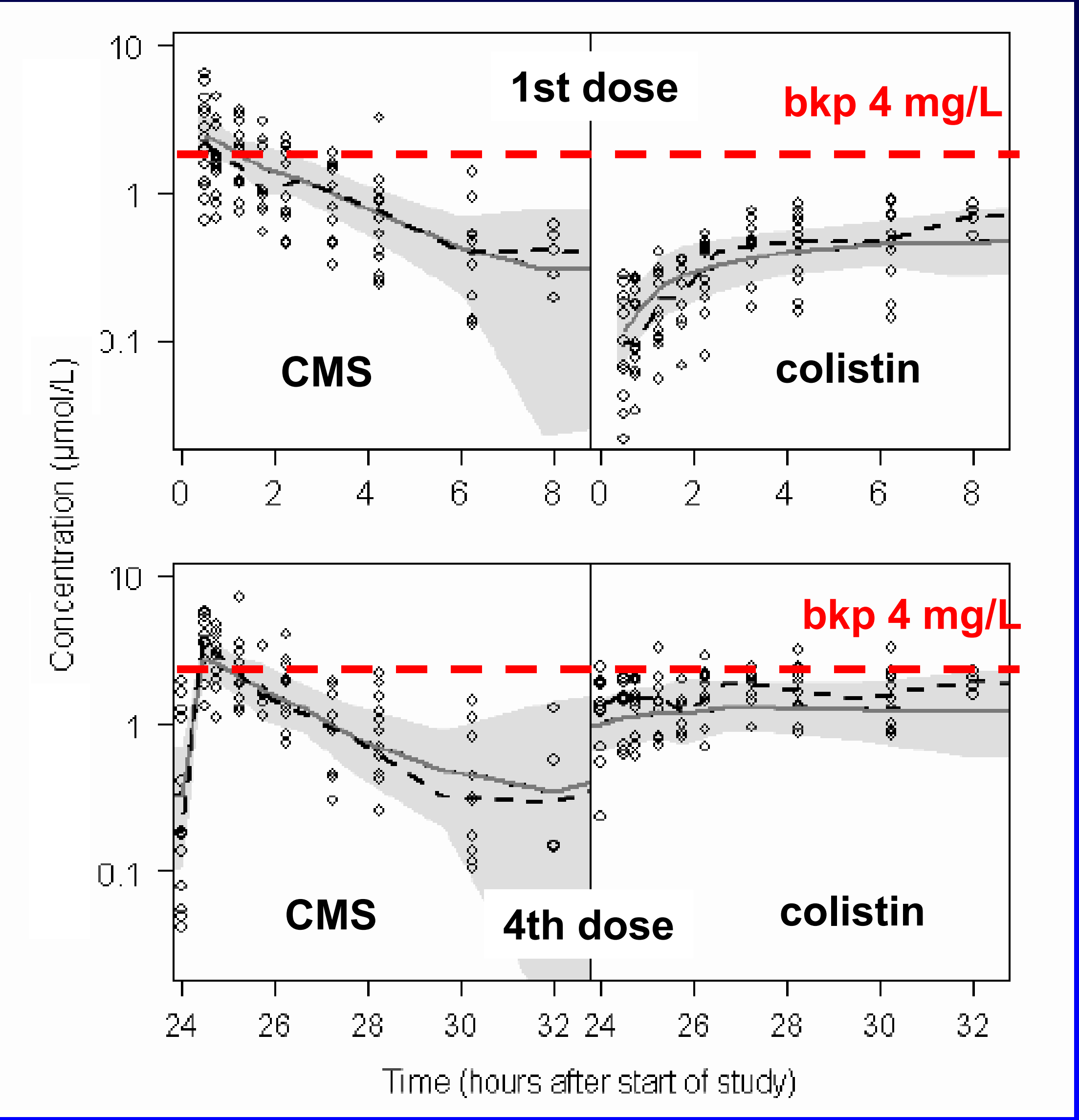
And what about colistin ?

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

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

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

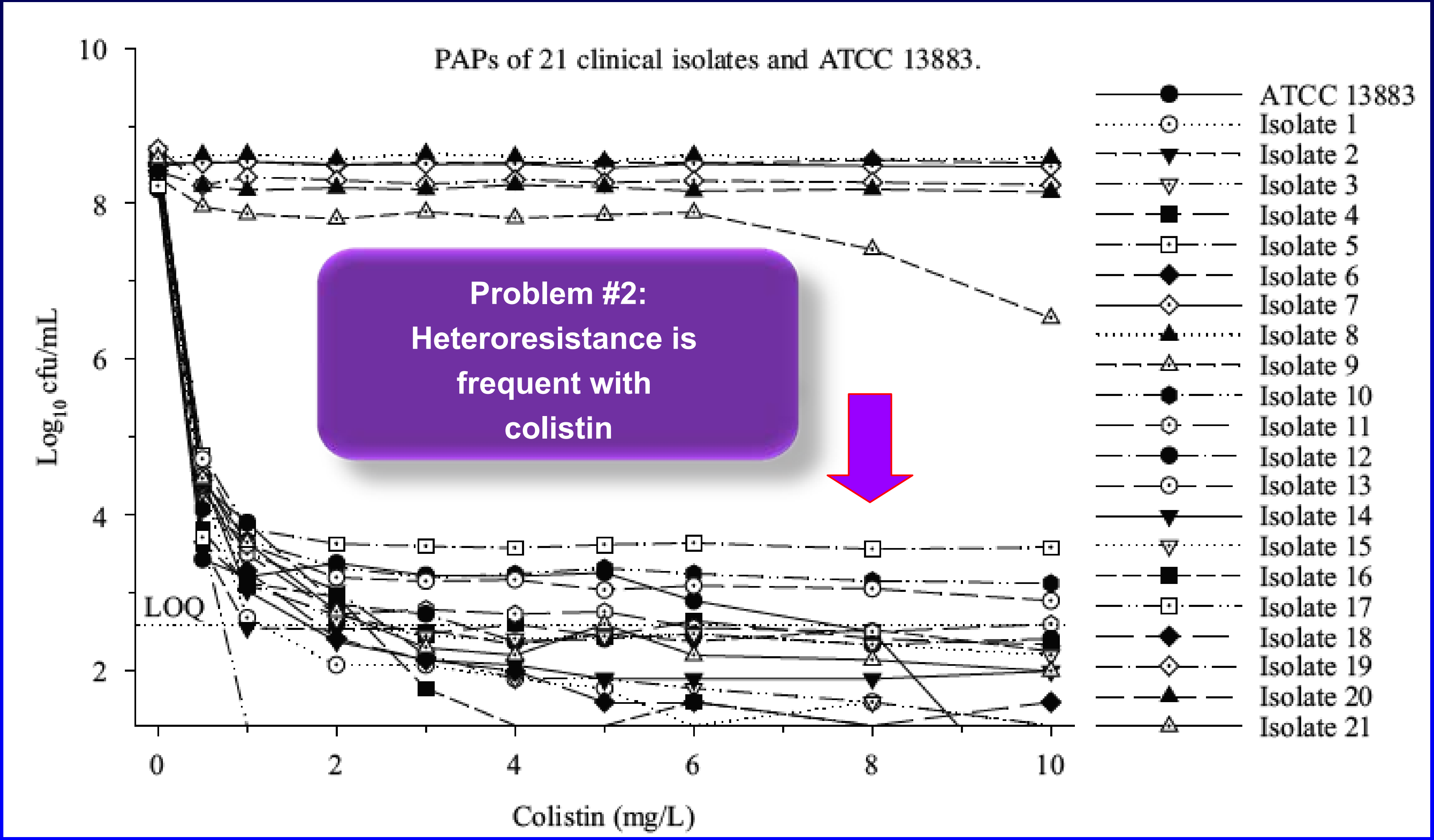
Problem #1:
Low initial blood levels suggest the necessity of a loading dose



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

International Journal of Antimicrobial Agents 35 (2010) 194–199

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

ELSEVIER

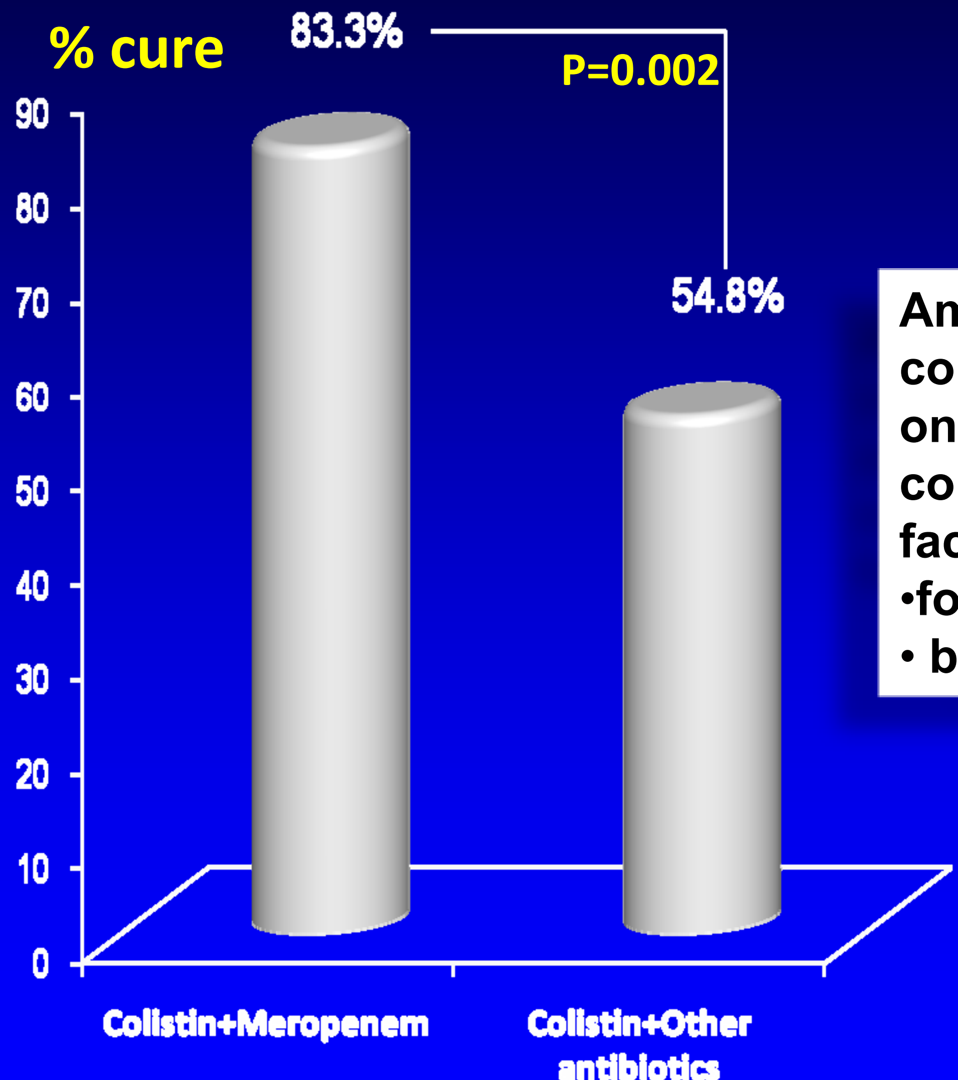
Short communication

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 you are 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.

“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 …

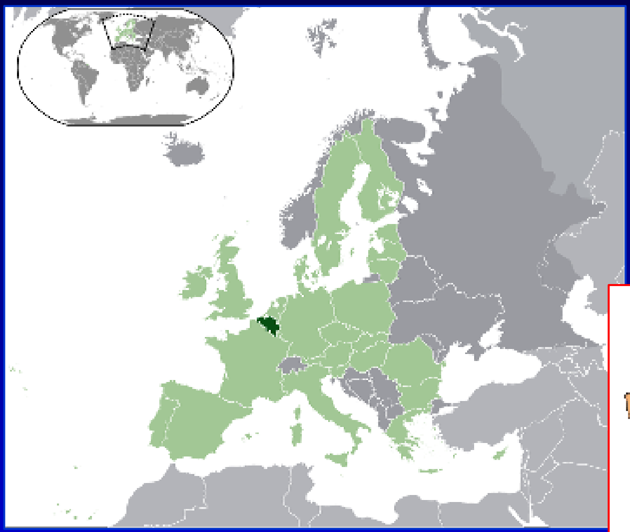
WHO statement 2000

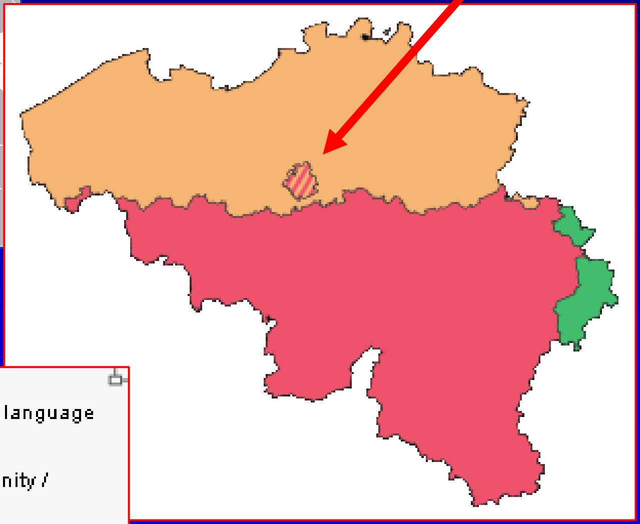
The most effective strategy against antibiotic resistance is:

- "to unequivocally destroy microbes"
- "thereby defeating resistance before it starts"

WHO Overcoming Antimicrobial Resistance, 2000

And a few sights from Belgium...





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