Updating and optimizing carbapenem use in critically ill patients

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology

Center for Clinical Pharmacy

Louvain Drug Research Institute

Université catholique de Louvain,

Brussels, Belgium

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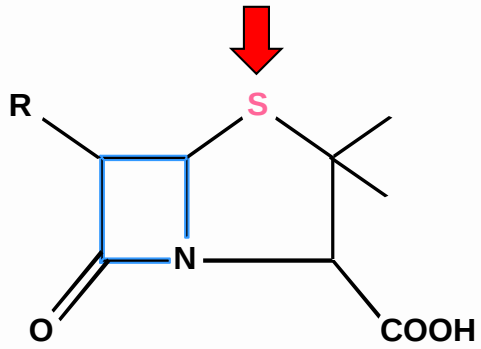
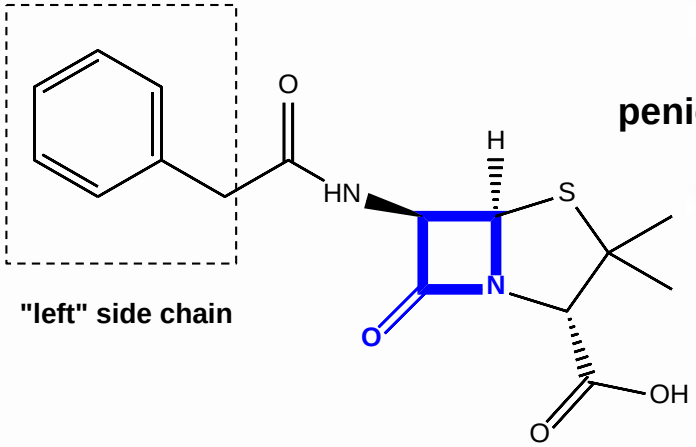
The slides are available for download from http://www.facm.ucl.ac.be → Lectures

You said "carbapenems" ?

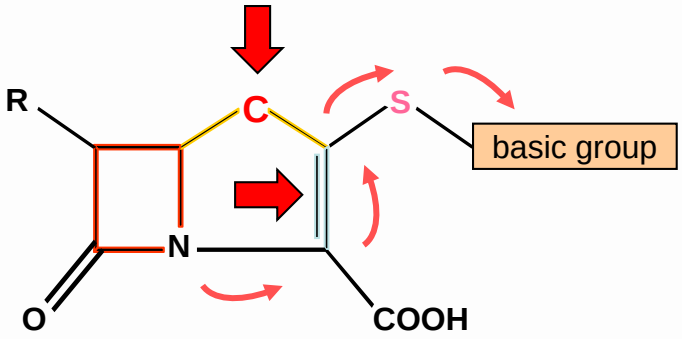


Penam

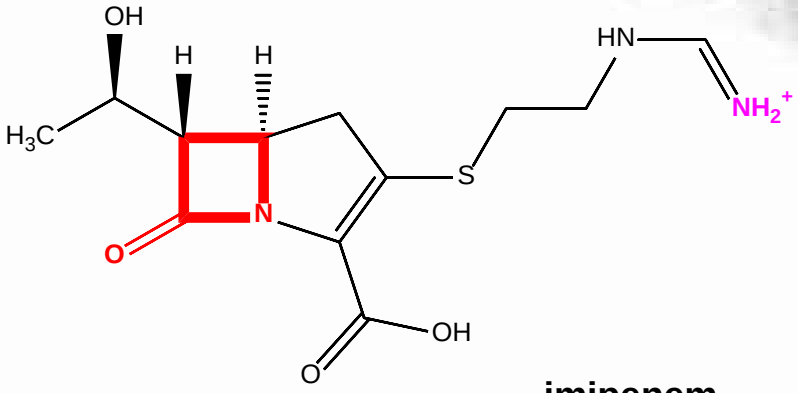


"left" side chain

penicillin G



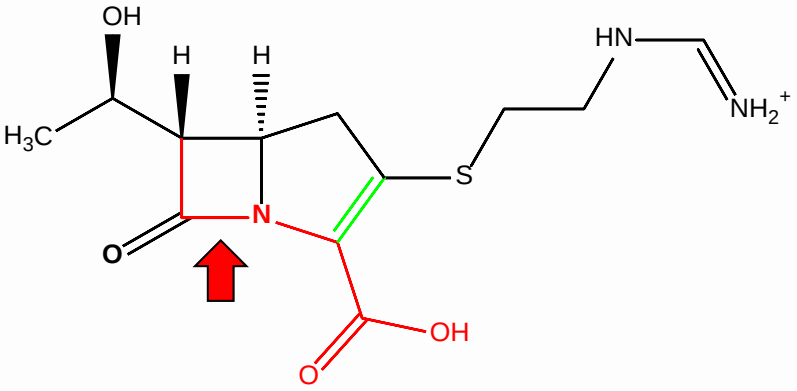
Carbapenem



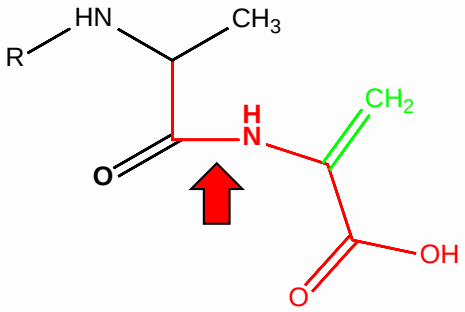
imipenem

- greater intrinsic activity due to larger instability of the β-lactam ring because of C1-C2 double bond and electrocapturing effect of the lateral basic group
- no need of a bulky "left" side chain…

But imipenem is degraded by a renal dehydropeptidase



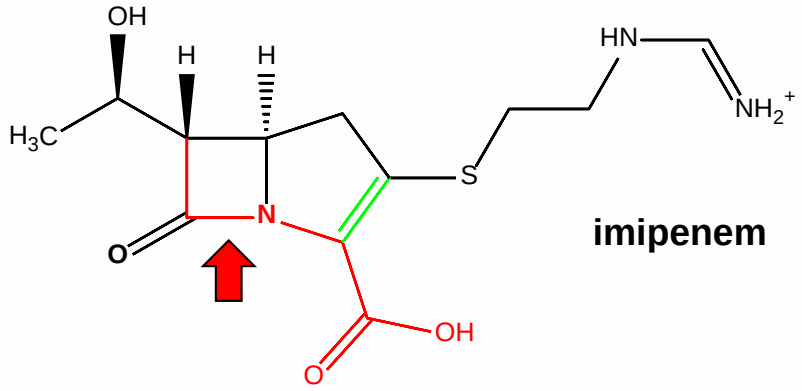
imipenem
Merck & Nippon-Merck-Banyu
1980



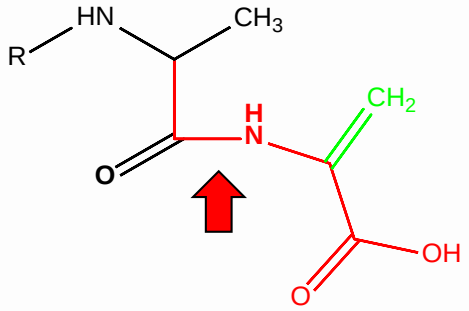
D-Ala-D-dehydro-Ala

Imipenem ($t_{½}$ 1 h) is inactivated by metabolism in the kidney by dehydropeptidase-1 (a brush border enzyme in the proximal renal tubules), producing an inactive metabolite that is nephrotoxic.

So, you DO need to co-administer an inhibitor (cilastatin)

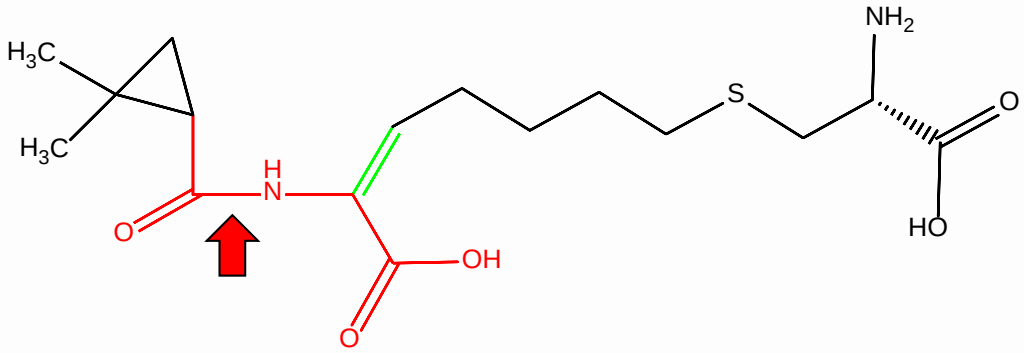


imipenem



D-Ala-D-dehydro-Ala

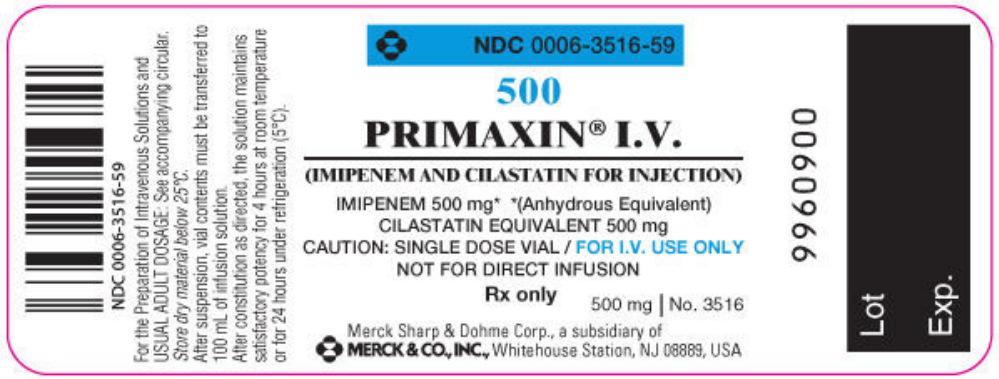
In order to prevent nephrotoxicity and maximize imipenem's antibacterial activity, imipenem is administered with cilastatin, an inhibitor of dehydropeptidase-1



cilastatin

Merck & Banyu, 1983

Imipenem is ALWAYS compounded with cilastatin



16 HOW SUPPLIED/STORAGE AND HANDLING

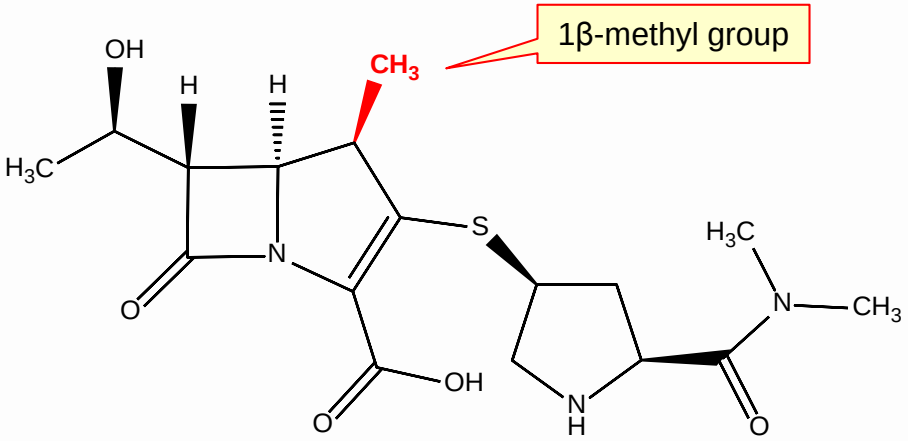
16.1 How Supplied

PRIMAXIN is supplied as a sterile powder mixture in single dose containers including vials containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

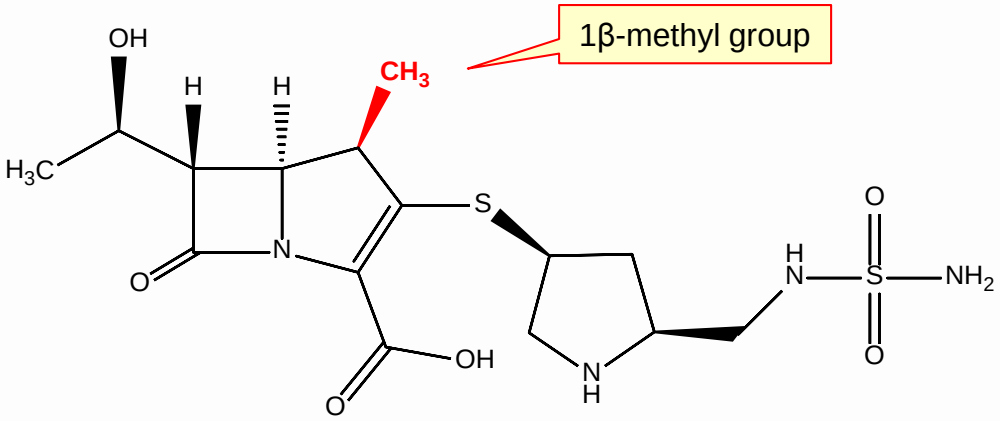
Each PRIMAXIN Package Contains:	National Drug Code (NDC) Number
A tray of 25 vials containing 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer.	(NDC 0006-3516-59)

https://www.merck.com/product/usa/pi_circulars/p/primaxin/primaxin_iv_pi.pdf - Last update: 2017 – Last visited: 13 Mar 2018

Meropenem and doripenem …

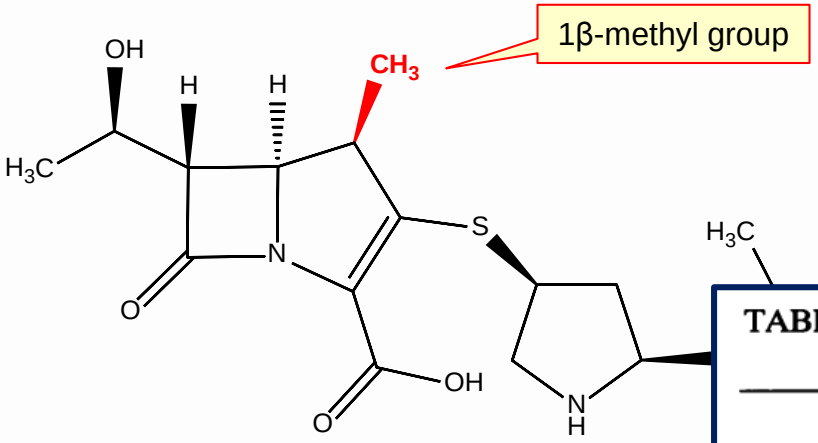


meropenem
Sumimoto,
1984



doripenem
Shionogi,
1993

Meropenem (and doripenem) is intrinsically resistant to human dehydropeptidase because of the 1β-methyl substitution…



meropenem

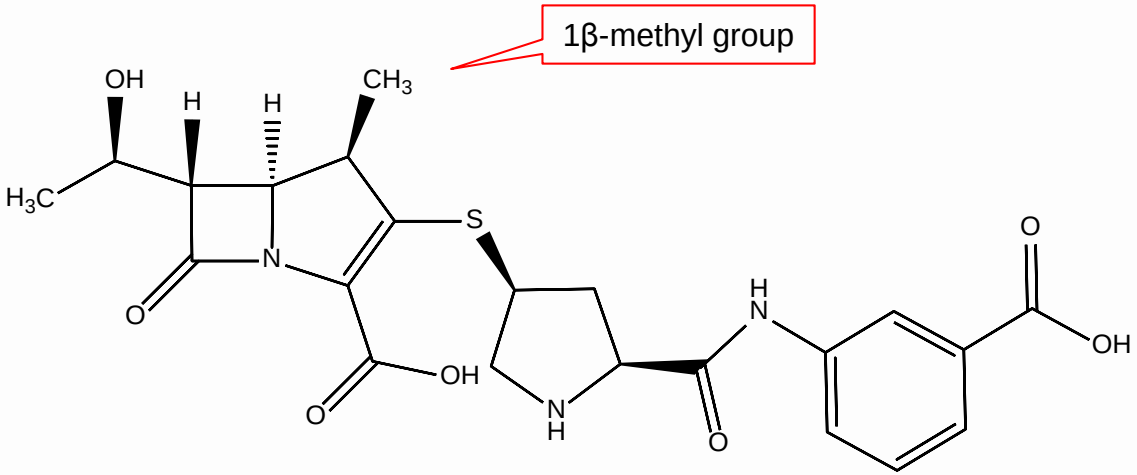
TABLE 1. Kinetic parameters of meropenem hydrolysis by renal DHP-Is from various animals

DHP-I source	Meropenem[a]			Imipenem[a]		
	K_m	V_{max}	V_{max}/K_m ratio	K_m	V_{max}	V_{max}/K_m ratio
Mouse	5.0	5.0	1.0	3.0	1.6	0.53
Rat	3.2	2.8	0.88	8.3	8.3	1.0
Guinea pig	8.3	0.91	0.11	13	14	1.1
Rabbit	1.9	5.7	3.0	2.8	2.5	0.89
Swine	8.3	1.0	0.12	11	11	1.0
Beagle dog	14	2.0	0.14	17	14	0.82
Rhesus monkey	10	56	1.7	4.8	2.9	0.43
Human	2.0	0.090	0.045	6.3	1.0	0.16

[a] K_m and V_{max} are expressed as millimolar and micromoles per minute per enzyme unit, respectively.

Fukasawa et al. Stability of meropenem and effect of 1 beta-methyl substitution on its stability in the presence of renal dehydropeptidase I. Antimicrob Agents Chemother. 1992 Jul;36(7):1577-9 - PMID: 1510457

Ertapenem



ertapenem
Zeneca,
1993

- loss of activity against *P. aeruginosa* (efflux)
- high protein binding

EU- and US-approved carbapenems[a]: similarities and differences

antibiotic	spectrum	half-life	resistance
imipenem [b]	Most Gram (+) • except if oxacillin-resistant (PBP2a) • low for Enterococci Most Gram (-) [c] Most anaerobes	~ 1 h (2-20 % protein binding)	• carbapenamases [e] • loss of porin (OprD) [f]
meropenem			• carbapenamases [e] • efflux (MexAB-OprM) [f]
doripenem			• carbapenemases [e] • efflux (MexAB-OprM) [f]
ertapenem	same except *P. aeruginosa* (MIC > 8) [d]	~ 4h (90% protein biding)	• carbapenemases [e,g] • efflux [f]

[a] panipenem, biapenem, and tebipenem are approved in Japan

[b] always with cilastatin

[c] *tenotrophomonas maltophilia* and *Elizabethkingia meningoseptica* are intrinsically resistant to carbapenems (class B β-lactamase)

[d] due to intrinsic efflux

[e] mostly class B (metallo-enzyme; no clinically-suable inhibitor), some class A (KPC) and some class D (*Acinetobacter*)

[f] *Pseudomonas aeruginosa*

[g] high affinity (can be used to protect another carbapenem)

S.

Pharmacokinetic properties

- Unstable in gastric acid → parenteral route
- Half-life : 1 hour for meropenem and imipenem and 4.5 hours for ertapenem (once daily administration)
- Protein binding: ~10%
  - Protein binding of DHP-I inhibitor cilastatine: 35%
- Distribution: most tissues and fluids, low concentrations occur in CSF
- Elimination: renal (7.%)
- Unstable in aqueous solution at room temperature
  - Degradation 10-20% in less than 3h for imipenem
- Liver failure: no dose adaptation; renal failure: lower doses

Main carbapenem resistance mechanisms

Pathogens	Mechanisms of resistance
Enterobacteriaceae	Cephalosporinase/ESBL + porin loss
	Carbapenemase
P. aeruginosa	Porin loss
	Up-regulated efflux
	Carbapenemase
Acinetobacter spp.	Cephalosporinase + porin loss
	Carbapenemase

Acquired carbapenemases

Class	Carbapenemase	Enterobacteriaceae	Non-fermenters
A (non-metallo)	**KPC**	**+++**	+
	IMI, NMC, SME	+	-
B (metallo)	**IMP*, VIM***	**+++**	**+++**
	NDM	**+++**	++
	AIM, DIM, SIM, SPM, TMB	-	++
D (non-metallo)	**OXA-48-like**	**+++**	-
	OXA-23, -40, -58, -143	+/-	**+++**

From Y. Glupczynski

Rapid evolving resistance in Enterobacteriaceae

Carbapenemases
(VIM, NDM, OXA-48, ..)

ESBLs
(CTX-M, TEM, SHV, ..

Penicillinase
(TEM-1, SHV-1)

Wild type

1940 1970 1990 2000

Variation of MIC in *Enterobacteriaceae* producing carbapenemases

Table 1. MIC range of carbapenems for *Enterobacteriaceae* that produce several types of carbapenemases*

	MIC, mg/L		
Carbapenemase	Imipenem	Meropenem	Ertapenem
KPC	0.5–>64	1–>64	0.5–>64
Metallo β-lactamases†	0.5–>64	0.25–>64	0.5–>64
OXA-48 type	1–>64	0.5–>64	0.25–>64

*KPC, *Klebsiella pneumoniae* carbapenemase; OXA-48, oxacillinase-48.
†Including New Delhi metallo-β-lactamase-1.

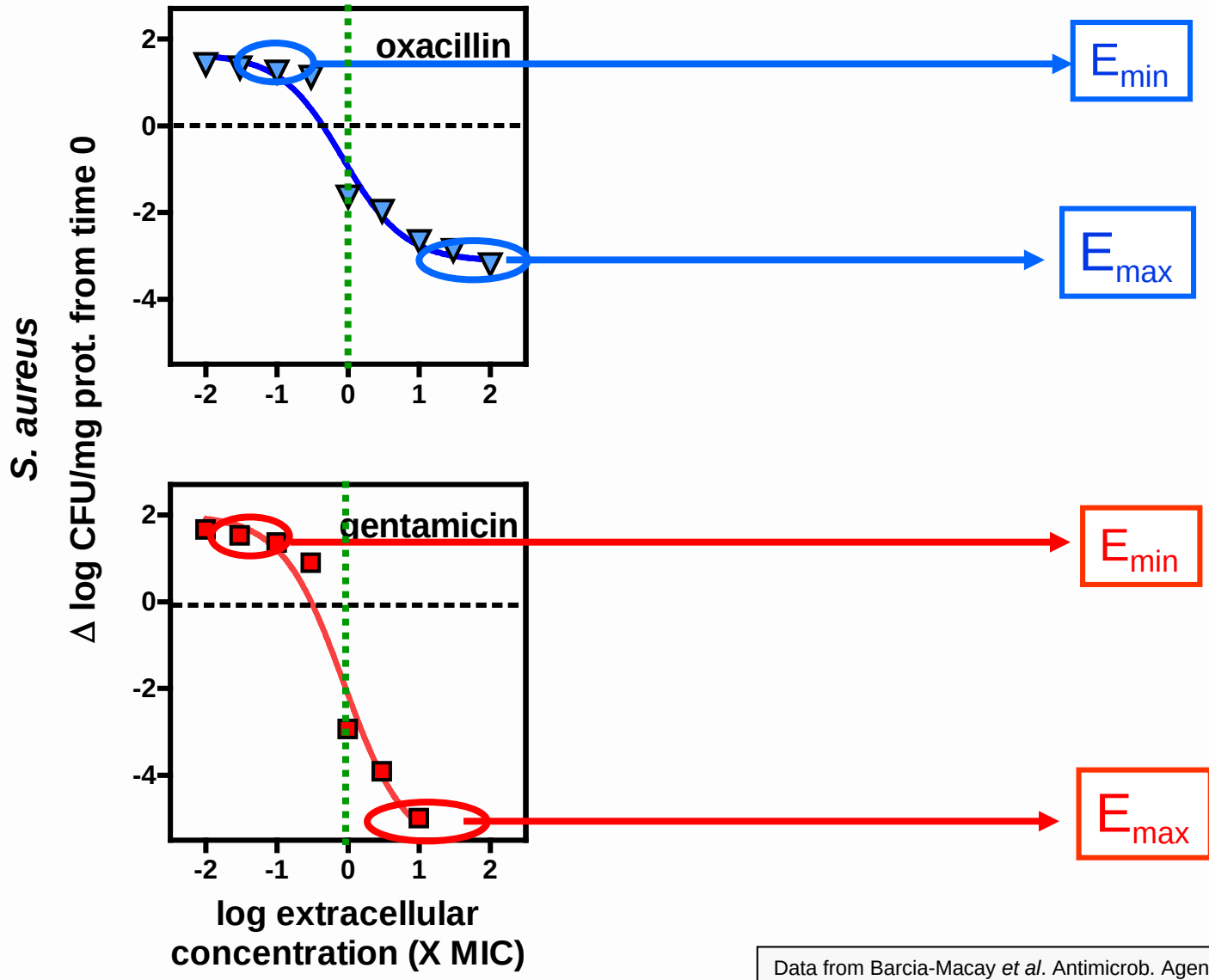
Nordmann P et al. EID 2011; 17:1791

PK-PD of β-lactams …in a nutshell…

- Every antibiotic is concentration-depedendent
  (simple pharmacological principle) …
- **BUT,** for β-lactams, activity if already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration… and bacteria with low MICs
- **AND**, having no post-antibiotic effect, β-lactams need to stay above the MIC (preferably 1 or even 4-fold…) for the maximum of time…

Medical controversies
by H. Daumier (1808-1879)

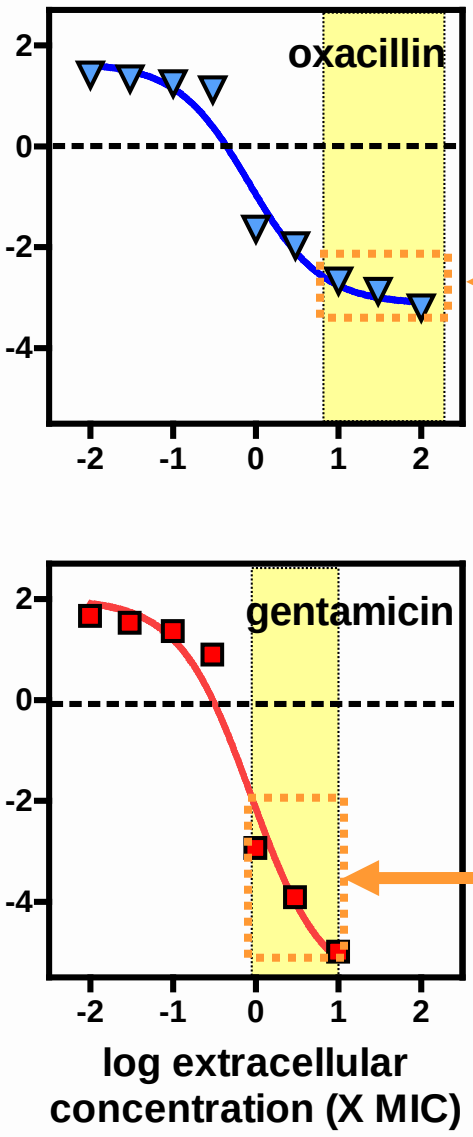
What is the relationship between MIC and effect?



It looks as if they are all concentration -dependent…

Data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851

But here comes pharmacokinetics …



Weak concentration-dependence (max. effect) over the C_{min}–C_{max} range

➔ TIME will emerge as the main parameter in vivo

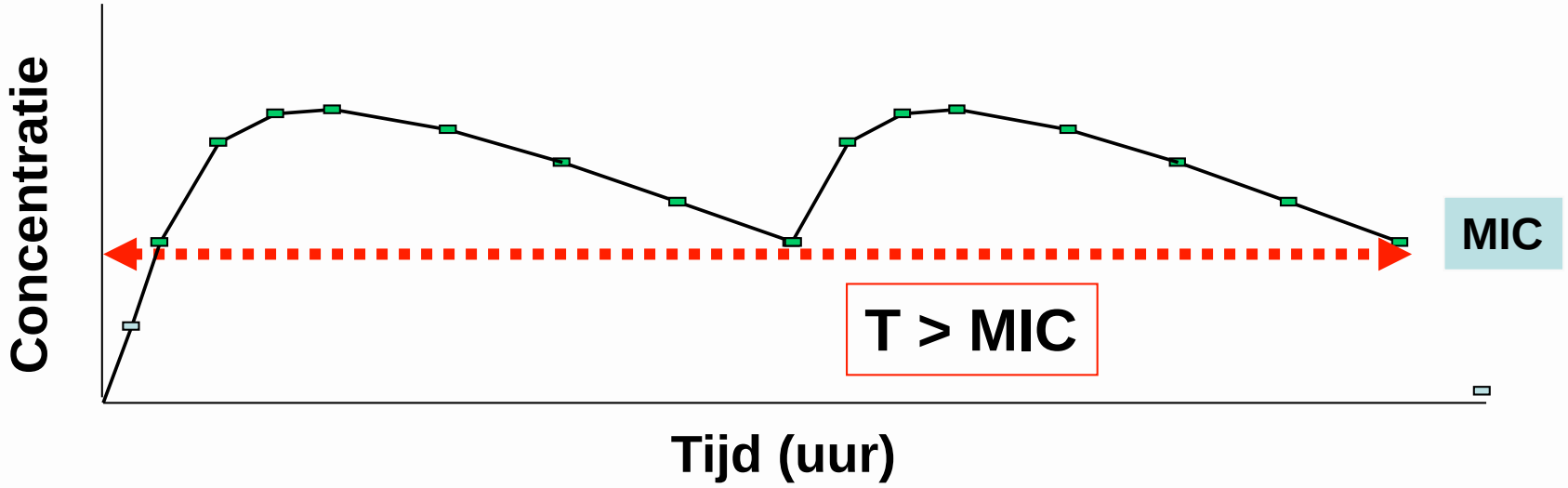
C_{min}–C_{max}

high concentration-dependence over the C_{min}-C_{max} range ➔ the time is less important than the actual concentration

- data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851
- C_{min}-Cmax: Principles and Practice of Infectious Diseases, 7th Ed. Mandell *et al*. eds.,Elsevier

As a result ...

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



2d example: β-lactams : T > MIC …

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 ?

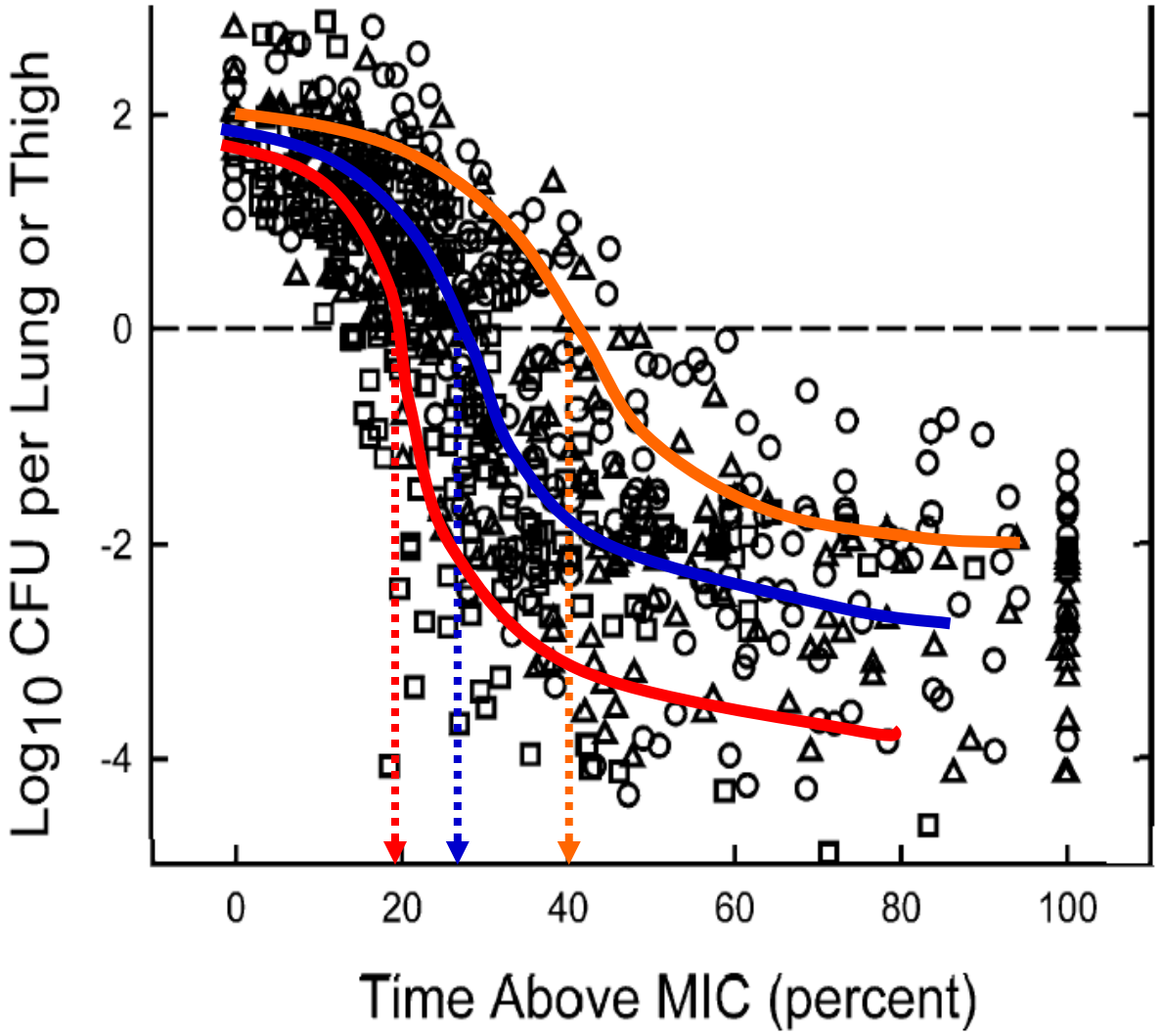
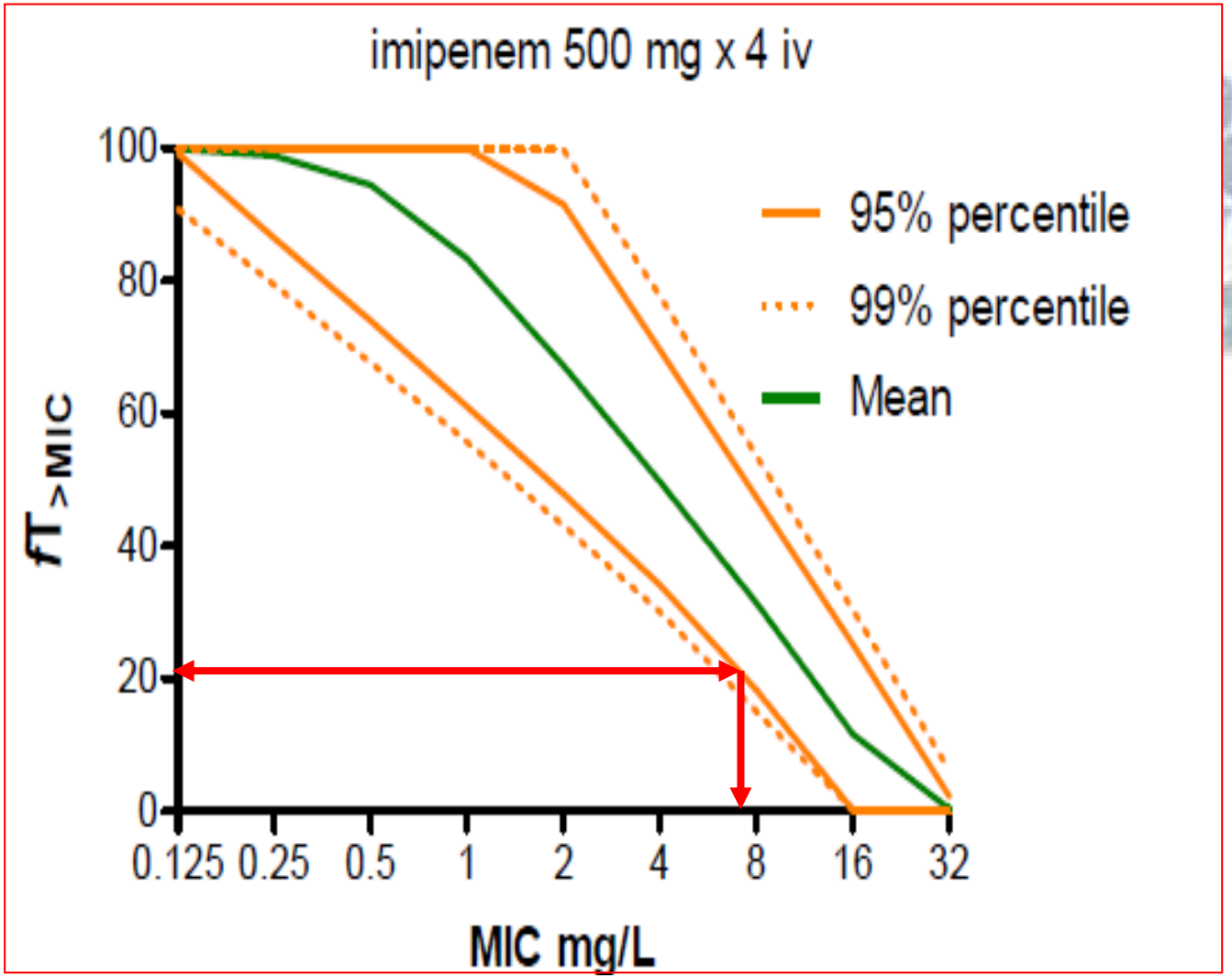


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

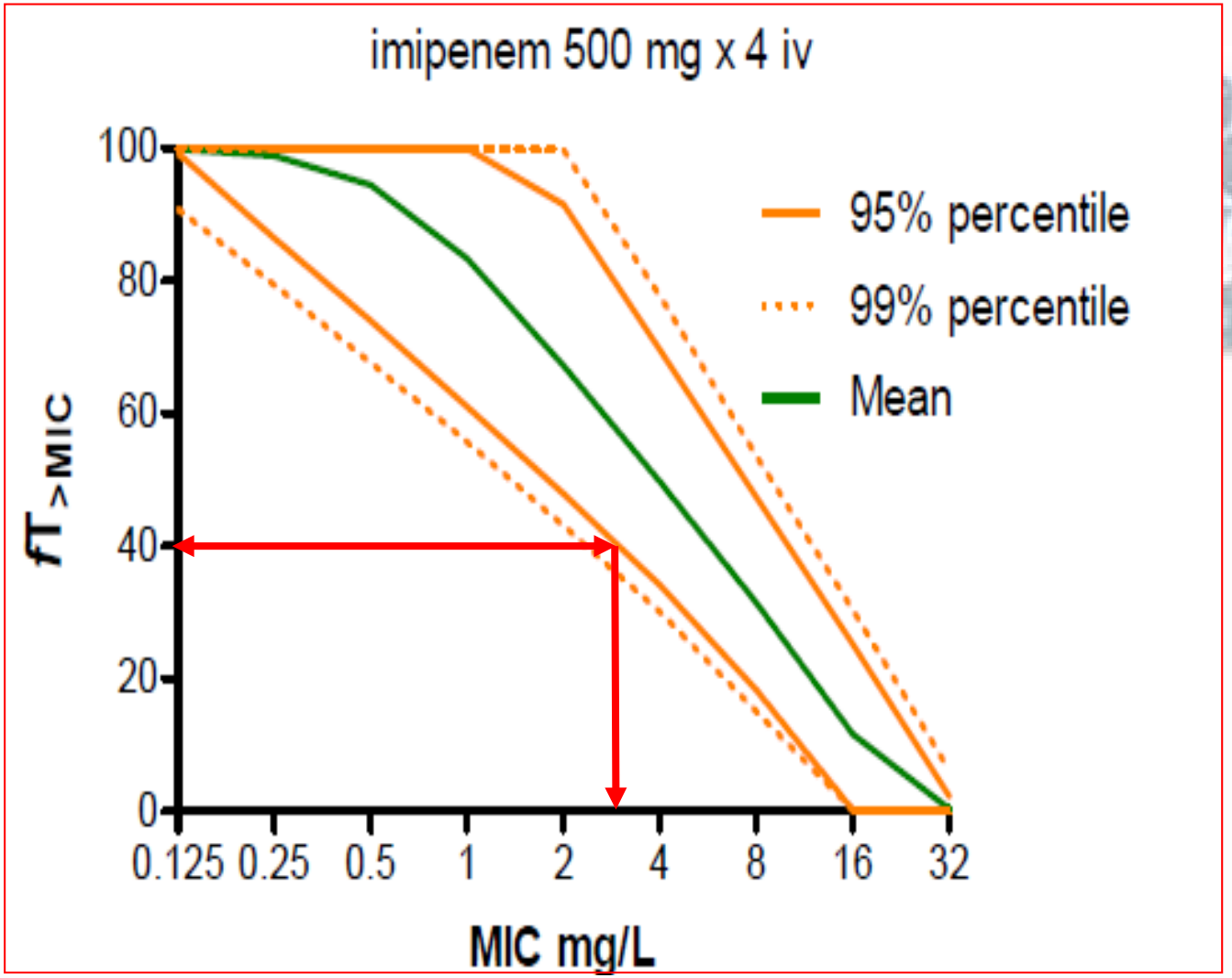
The same for all β-lactams ?

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

Calculation of a PK/PD breakpoint



Calculation of a PK/PD breakpoint



A question of breakpoints

Organism	Drug	CLSI 2018				EUCAST 2018		
		S	I	R	dosage	S	R	dosage
P. aeruginosa	imipenem	≤ 2	4	≥ 8	0.5g Q6h	≤ 4	> 8	high dose:1g Q6h
	meropenem	≤ 2	4	≥ 8	1g Q8h 0.5g Q6h	≤ 2	> 8	1-2g q8h
	doripenem	≤ 2	4	≥ 8	0.5g Q8h	≤ 1	> 2	high dose:1g Q8h 4h infus.
Enterobactriaceae	imipenem	≤ 1	2	≥ 4	0.5g Q6h 1g Q8h	≤ 2	> 8 *	0.5-1g Q6h
	meropenem	≤ 1	2	≥ 4	1g Q8h	≤ 2	> 8 *	1g Q8h
	doripenem	≤ 1	2	≥ 4	0.5g Q8h	≤ 1	> 2 *	0.5g Q8h
	ertapenem	≤ 0.5	1	≥ 2	1g Q24h	≤ 0.5	> 1 *	1g Q24h

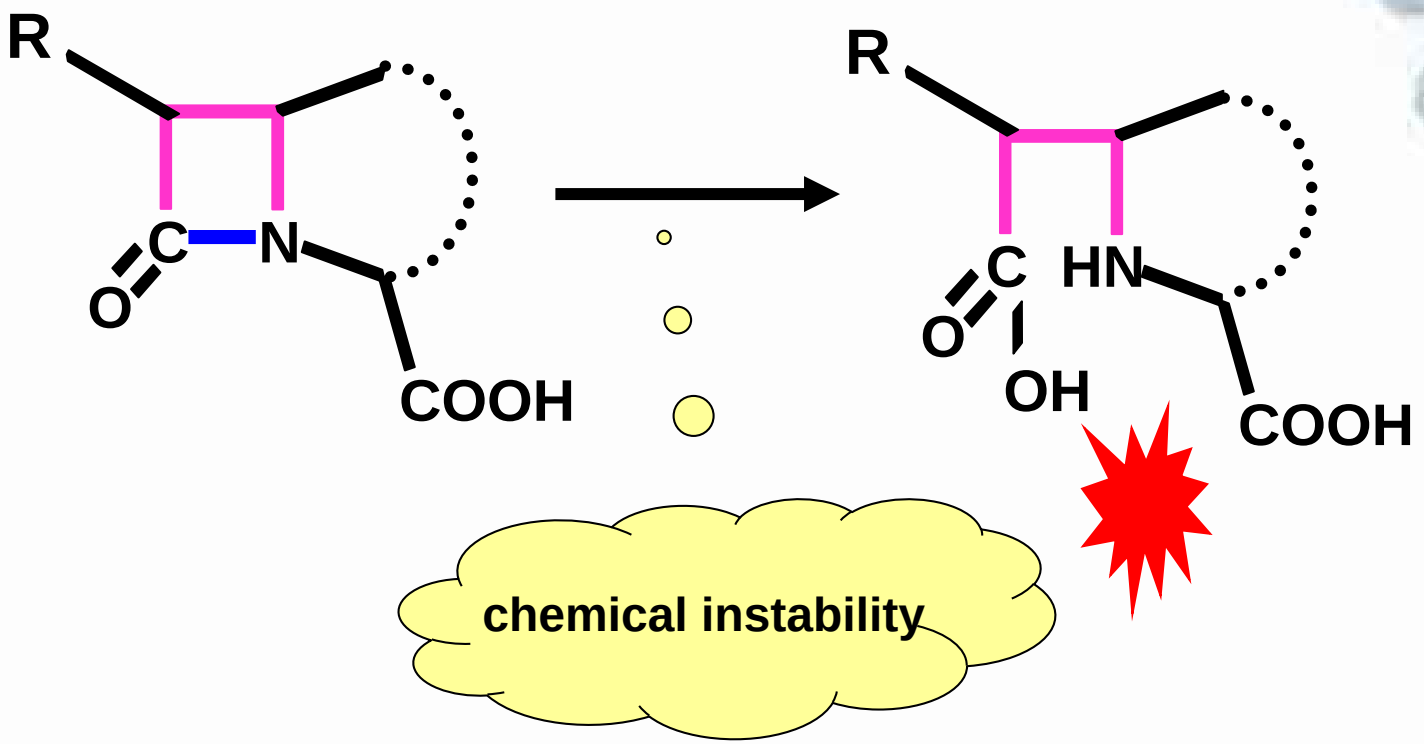
* The EUCAST carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases). Some isolates that produce carbapenemase are categorised as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorisation of susceptibility. Carbapenemase detection and characterisation are recommended for public health and infection control purposes.

Maximizing the utility of the carbapenems

- **High dose**
  - Specific population of patient with altered pharmacokinetics (severe sepsis) or infection with bacteria exhibiting higher MICs
    - Meropenem : good CNS tolerability and low incidence of nausea and vomiting
- **Increased frequency of administration**
  - Administer a smaller dose but more frequently
- **Extended infusion**
  - Extended infusion (over 3h)

Norrby et al. Scand J Infect Dis 1999;31:3-10.
Kotapati et al. Am J health Syst Pharm 2004;61:1264-70.
Roberts et al. Int J antimicrob Agents 2007;30:11-8.

Problem:
β-lactams are unstable molecules



What is the evidence of instability of carbapenems ?

- **chemical considerations**
- **experimental studies**

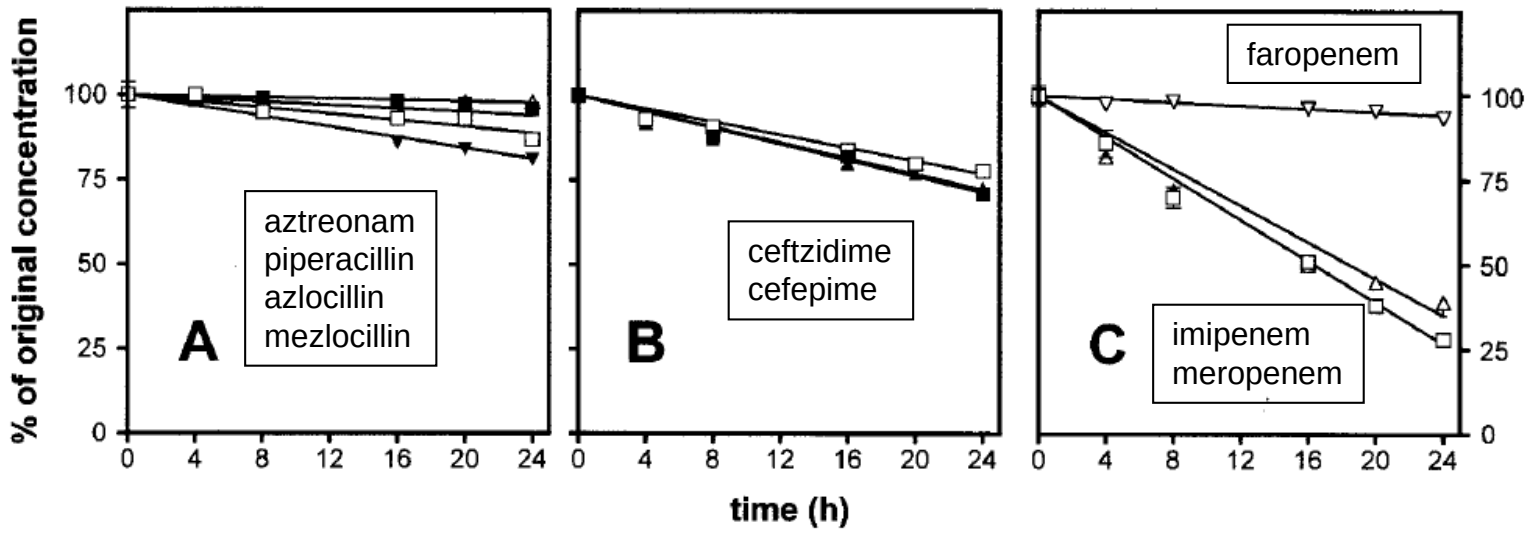


FIG. 1. Stability of the β-lactams in water at 37°C over time at the maximum concentration tested. (A) Symbols: △, 10% aztreonam; □, 12.8% piperacillin; ■, 12.8% piperacillin plus tazobactam (since the slope for 12.8% azocillin was almost identical to that for piperacillin-tazobactam, it was omitted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

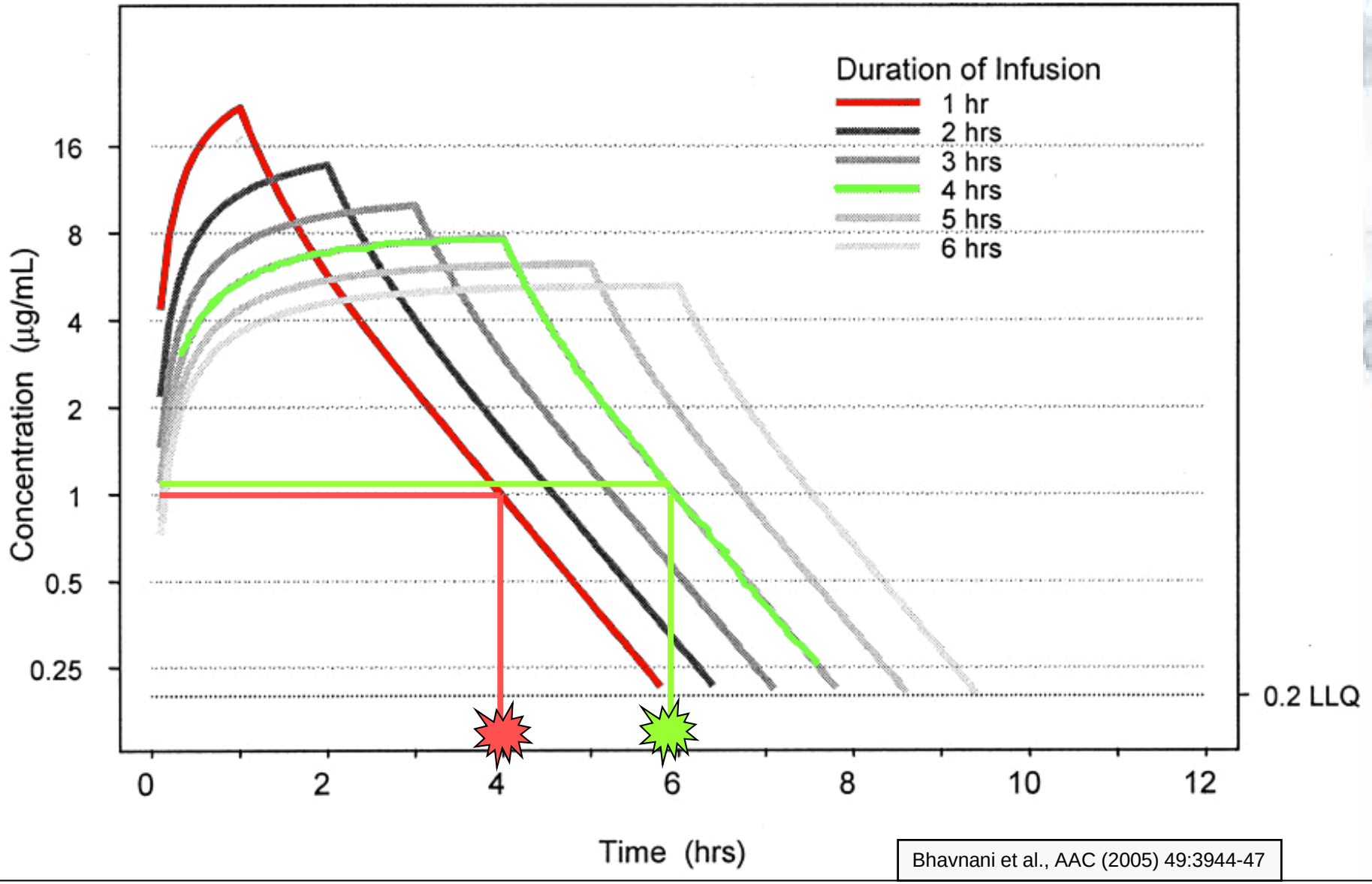
Viaene et al. Antimicrob. Agents Chemother. 2002; 46:2327–2332

Now, what about extended infusion ?

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

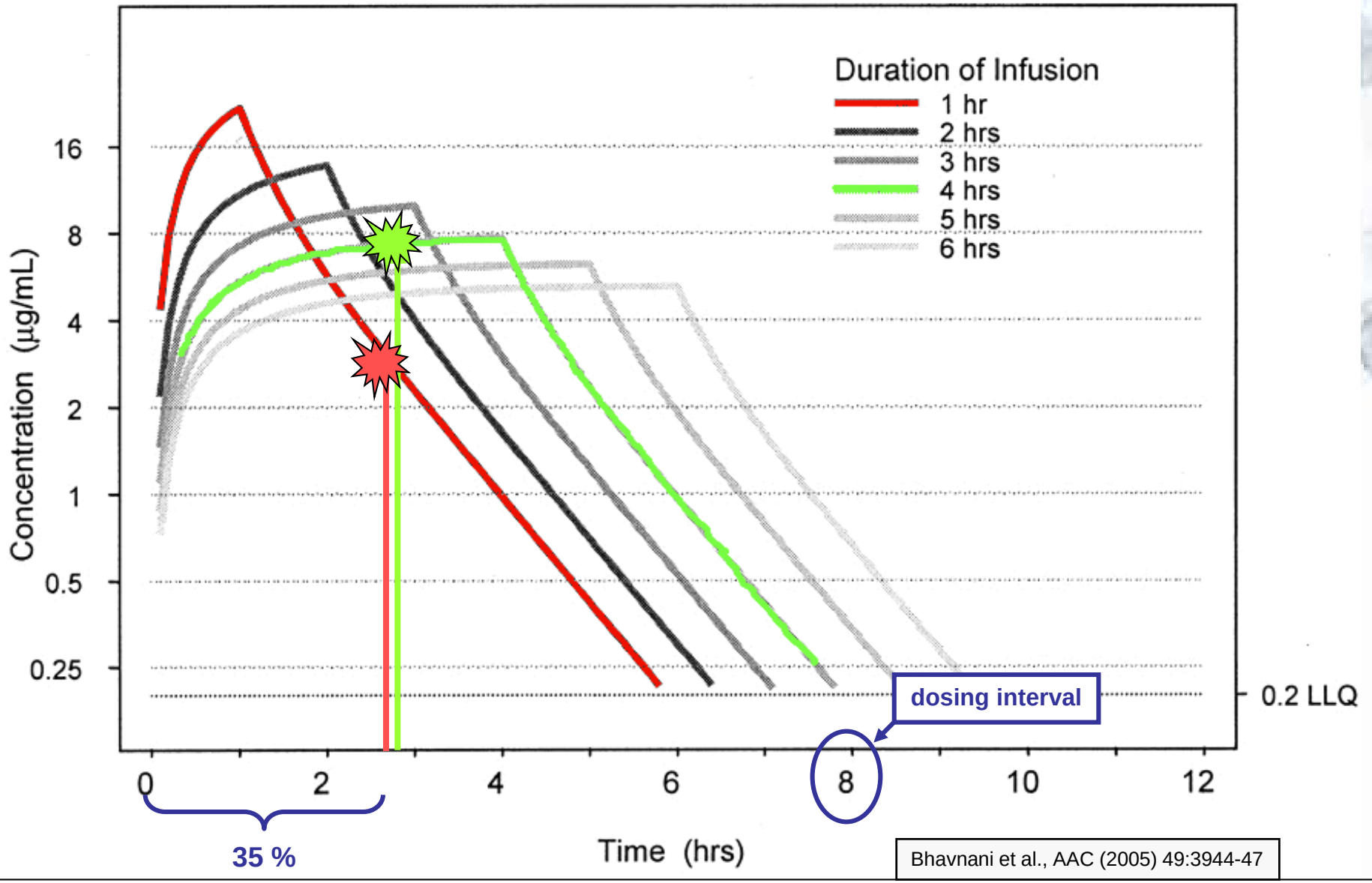
Extending the infusion time of Doribax to 4 hours maximizes the %T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response,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

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



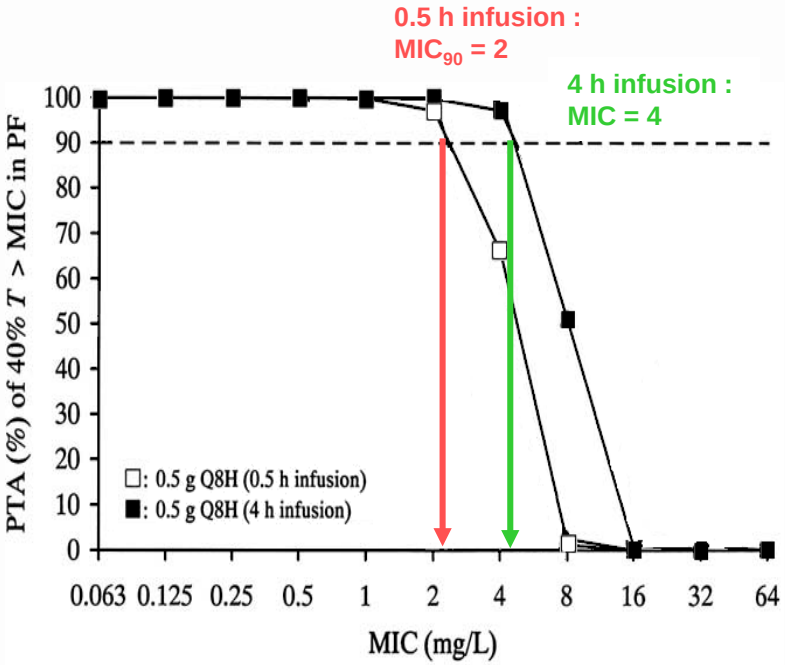
Bhavnani et al., AAC (2005) 49:3944-47

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



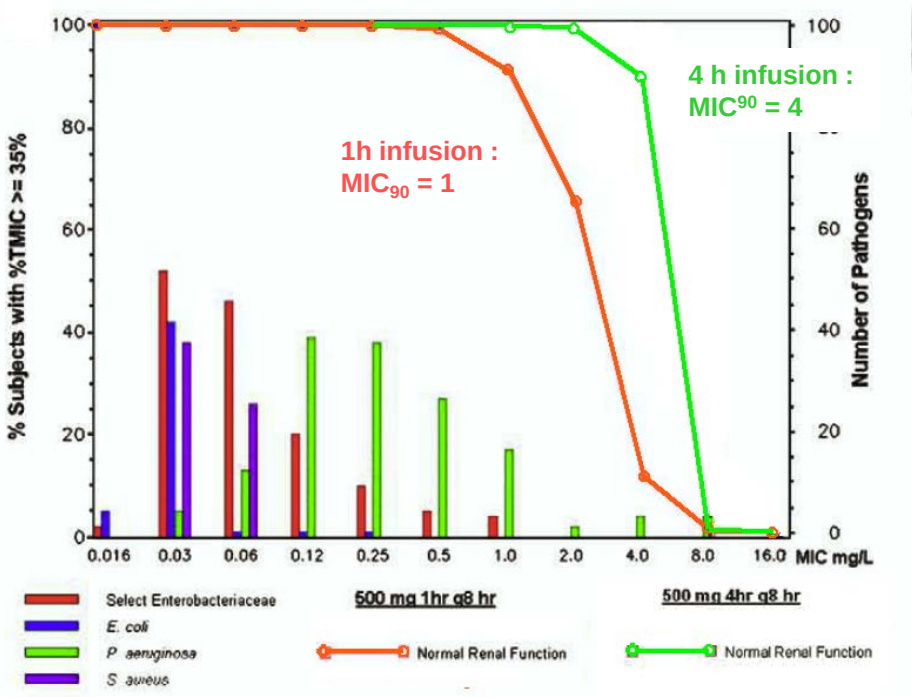
Bhavnani et al., AAC (2005) 49:3944-47

Doripenem: Target attainment rate after Monte-Carlo simulation



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

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

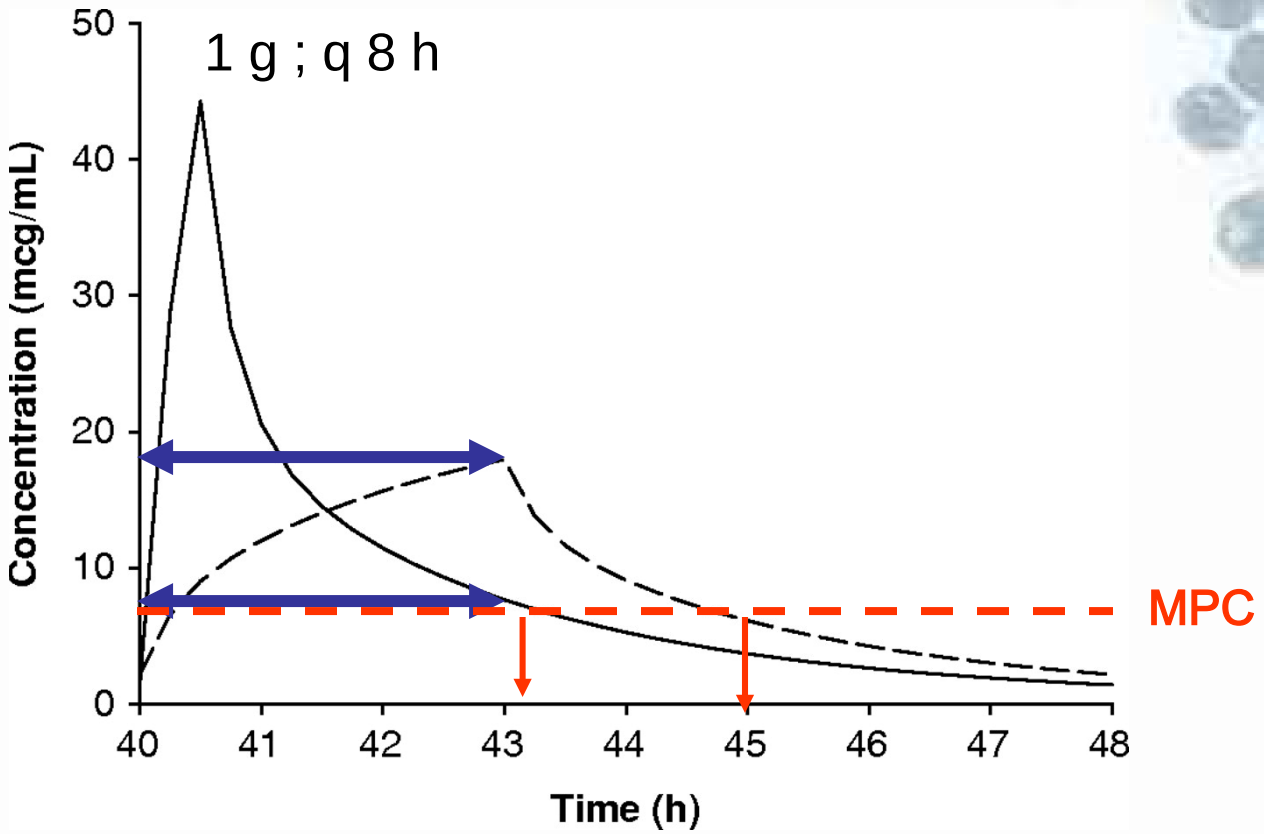


Meropenem: PK/PD modeling

PK/PD in support to dosing : t > MIC ~ 35 %

3 h infusion :
MIC = 18

0.5 h infusion :
MIC = 8



40 %

65 %

Li et al. J Clin Pharmacol. (2006) 46:1171-8

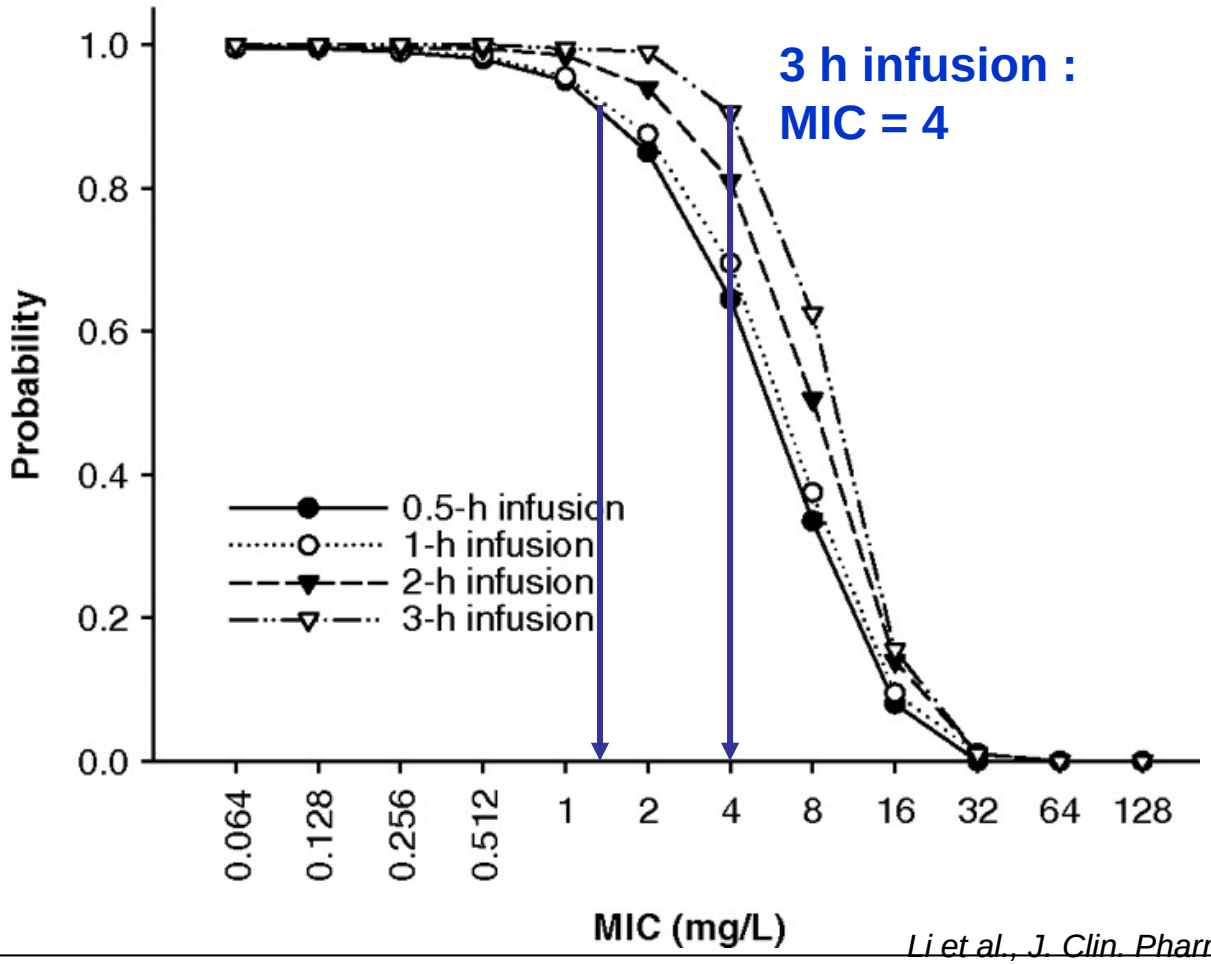
Meropenem : PK/PD modeling

Probability of target attainment rate based on Monte Carlo simulation

1 g ; q 8 h

0.5 h infusion :
MIC = 1.5

3 h infusion :
MIC = 4



Li et al., J. Clin. Pharmacol (2006) 46:1171-1178

Possible advantages and disadvantages of continuous/long infusion vs bolus

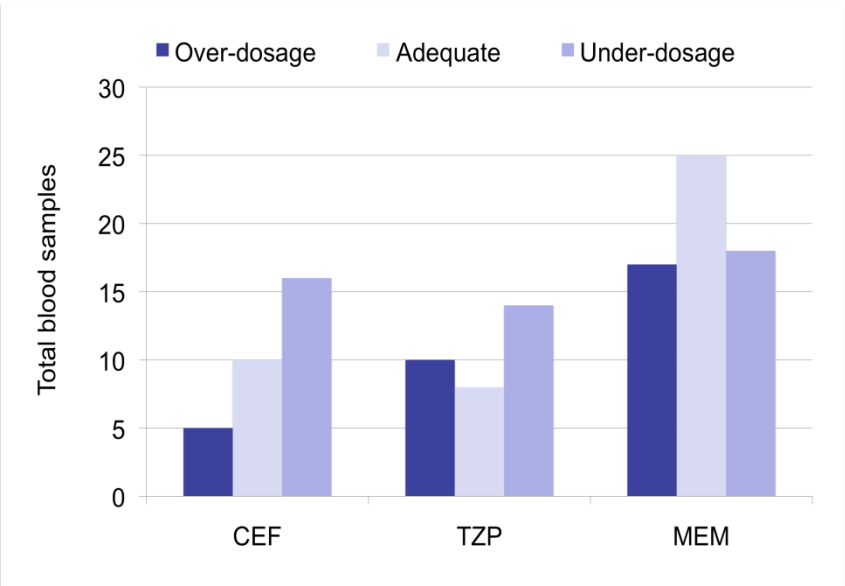
Administration method	Advantages	Disadvantages
Extended infusion	Predictable PK	Requires education
	Lower daily dose may be effective	Requires infusion pumps
	Less time consuming for nurses	Issues of stability
Bolus	Simple	Unpredictable PK
	Less likely failure/error	Neurological side-effects probably more common

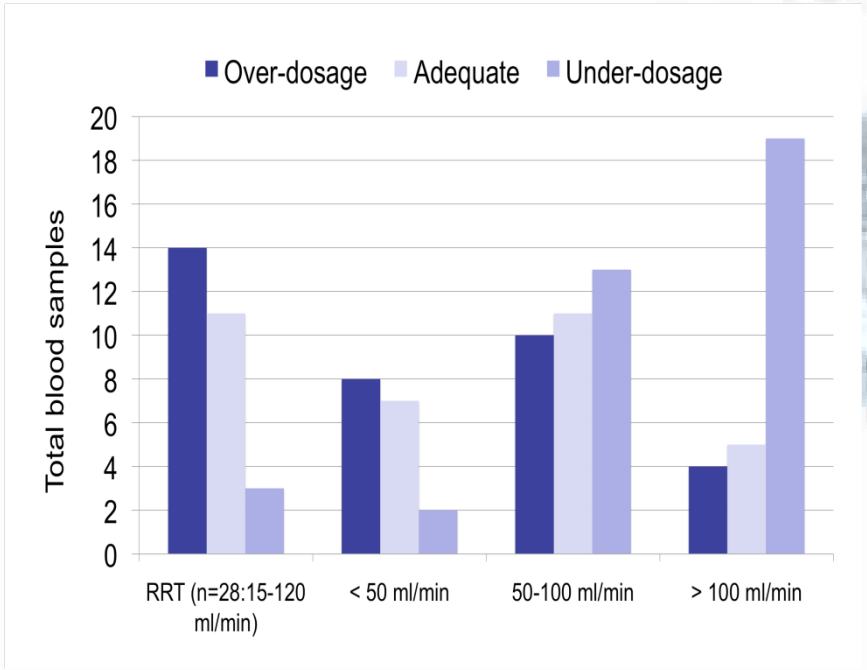
Modified from Abdul-Aziz MH Ann Intensive care 2012;2:37

Therapeutic drug monitoring

- Definition: analysis and subsequent interpretation of drug concentration in biological fluids
- Goals:
  - To maximize efficacy and minimize toxicity
  - To increase probability of success and to prevent the development of resistance
    → use the correct dose and frequency

Monitoring of β-lactams in ICU patients





Routine monitoring of broad-spectrum of β-lactams

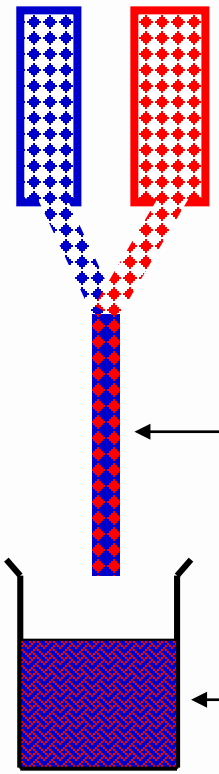
123 drugs levels

Adequat levels: between 4-8 times MIC of *P. aeuginosa* for recommended period of time (70% CEF, 50% TZP, 40% MEM)

Hites ICAAC 2012

Problem no. 2:
β-lactams may be incompatible with other drugs if administered through the same line

β-lactam
(typ. 8 g %)



Drug X

1st contact at high concentration (10 min)

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

direct examination (with viewer), HPLC, bioassay

Is extended infusion of carbapenems wih other drugs possible ?

Each molecule must

be <u>specifically</u>

looked at …

- Data (physical and chemical) published for **ceftazidime** (AAC 2001;45:2643-7), **cefepime** (JAC 2003;51:651-8) and **temocillin** (JAC 2008;61:382-8); also available for **vancomycine** (JAC 2013;68:1179-82)
- Colistin was found visually compatible (physical compatibility) with cefoperazone-sulbactam, ceftazidime, ertapenem, fosfomycin, **imipenem-cilastatin**, linezolid, **meropenem**, piperacillin-tazobactam, and vancomycin (AJHP 2017;74:1099-1102)

Critically ill patients: optimization of antibiotic therapy

- **ICU patients**
  - Increased volume of distribution
  - Modified antibiotic clearance (BOTH **decreased** and **increased**)
  - Modified protein binding protein caused by hypo-albuminemia
  - Modified tissue penetration

Implications for clinical efficacy and correct dosage of AB

→Potential underdosing → risk of development of resistance and/or therapeutic failure

- **Increase the drug dose**
  (to obtain at least 40% of 4 x MIC or 100% of 1 x MIC)
- **Prolong the infusion time**

TDM (Therapeutic Drug Monitoring)

Carbapenems: adverse drug effects

- Rash, nausea, diarrhea, thrombophlebitis
  - Imipenem: higher rate of nausea and vomiting (particularly after rapid infusion)
- Hypersensitivity reaction
  - ! Patient with history of penicillin allergy (cross-reactivity ~50%)
- Risk of developing pseudomembranous colitis, especially with prolonged therapy
- Seizure activity → **with imipenem**
  - If underlying CNS problems or decrease renal function
- Interaction with valproic acid: decreases its concentrations !!
  - patient with epilepsy may become undertreated … and show convulsions…

Imipenem approved indications and limitations

Approved indications (US)

- ✓ Lower respiratory tract infections
- ✓ Urinary tract infections
- ✓ Intra-abdominal infections
- ✓ Gynecologic infections
- ✓ Bacterial septicemia
- ✓ Bone and joint infections
- ✓ Skin and skin structure infections
- ✓ Endocarditis

Limitations (US)

- ❑ meningitis because (safety and efficacy not been established).
- ❑ pediatric patients with CNS (risk of seizures).
- ❑ pediatric patients < 30 kg and impaired renal function

Meropenem approved indications in US and EU

Approved indications (US)

- ✓ Complicated skin and skin structure infections (adult patients and pediatric patients > 3 months)
- ✓ Complicated intra-abdominal infections (adult and pediatric patients)
- ✓ **Bacterial meningitis** (pediatric patients > 3 months only)

Approved indications (EU)

- ✓ Severe pneumonia incl. HAP and VAP)
- ✓ Broncho-pulmonary infections in cystic fibrosis
- ✓ Complicated urinary tract infections
- ✓ Complicated intra-abdominal infections
- ✓ Intra- and post-partum infections
- ✓ Complicated skin and soft tissue infections
- ✓ **Acute bacterial meningitis**

Doripenem approved indications in US and EU

Approved indications (US)

- ✓ Complicated intra-abdominal infections
- ✓ Complicated urinary tract infections, including pyelonephritis

Approved indications (EU)

- ✓ Nosocomial pneumonia (including ventilator–associated pneumonia)
- ✓ Complicated intra-abdominal infections
- ✓ Complicated urinary tract infections

Note: The marketing authorization for doripenem (DORIBAX®) has been withdrawn in 2014 in Europe at the request of the marketing authorization holder.

Ref.:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000891/human_med_000744.jsp&mid=WC0b01ac058001d124

Ertapenem approved indications in US and EU

Approved indications (US)

- ✓ Complicated intra-abdominal infections
- ✓ Complicated skin and skin structure infections (include. diabetic foot infections)
- ✓ Community-acquired pneumonia
- ✓ Complicated urinary tract infections includ. pyelonephritis
- ✓ Acute pelvic infections (includ. endomyometritis, septic abortion and post surgical infections
- ✓ prophylaxis after elective colorectal surgery

Approved indications (EU)

- ✓ Intra-abdominal infections
- ✓ Community acquired pneumonia
- ✓ Acute gynaecological infections
- ✓ Diabetic foot infections of the skin and soft tissue
- ✓ prophylaxis after elective colorectal surgery

Carbapenems: our main clinical use

- Infections due to resistant pathogens
  - Regarded as first-line therapy for serious infections caused by Extended Spectrum β-Lactamase (ESBL)-producing organisms
  - Risk factors
    - Previous hospitalization or antibiotherapy
    - Colonization with MDR organism
    - Late nosocomial infection (> 5 days after administration)
    - Epidemic with MDR Gram-negative bacteria in the unit
- Infections with multiple organisms involved (e.g.: mixed, aerobic/anaerobic bacteria) when more than 1 antibiotic is required

Clinical use: warnings

- Empiric therapy for nosocomial infections must be initiated as soon as possible and needs to be broad enough
- BUT, **always reevaluate the clinical utility after 48 - 72 hours**
  - According to microbiological documentation

Towards a rational use of carbapenems…

- **Algorithm to limit excessive and inappropriate use of carbapenems**
  - 1. Appropriate indication for a carbapenem?
  - 2. Other alternatives?
    - Narrower spectrum or lower ecological impact on bacterial flora
  - 3. Duration of treatment appropriate?
  - 4. Adequate dose?

F. Jary at al. *Médecine et maladies infectieuses* 42(2012) 510-516

- 99 carbapenem prescriptions were evaluated
  - → 66.7% of all prescriptions were considered inappropriate
  - → An alternative was available in 16% of cases
  - → Need for guidelines and local best practices recommendations

Treatment of MDR bacteria

Combination therapy

- Monotherapy is associated with high mortality rates than combinaison

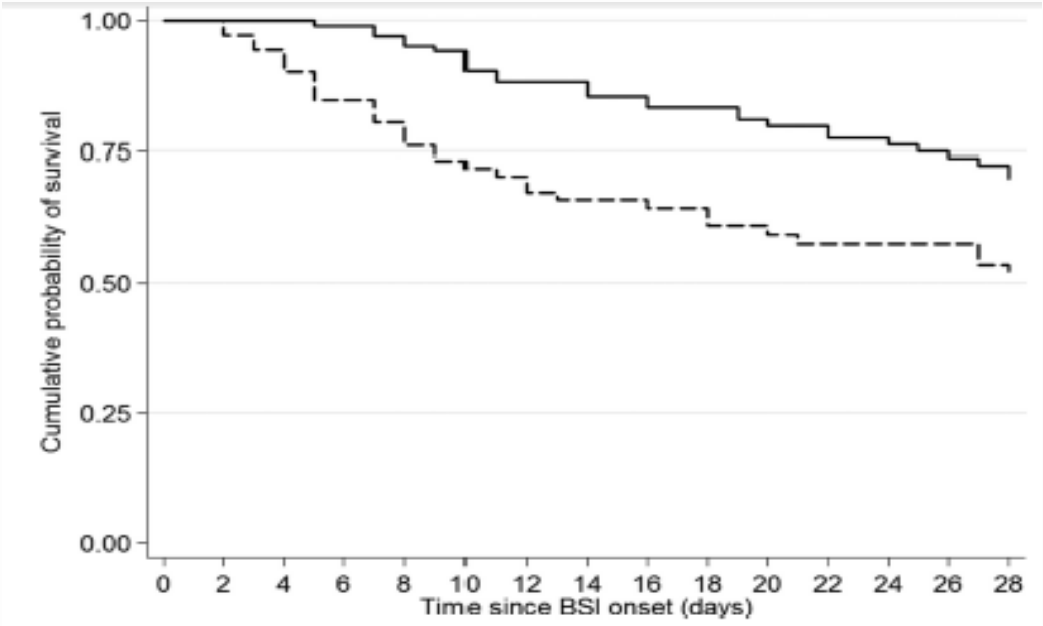


FIG 1 Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). $P = 0.003$ (log rank test).

Daikos et al Antimicrob. Agents Chemother 2014, 58 (4):2322

Combination therapy

- Aminoglycoside, ampicillin/sulbactam, carbapenem, colistin, rifampicin → *Acinetobacter* spp
- Aminoglycoside, ampicillin/sulbactam, carbapenem, colistin, rifampicin, tigecycline, fosfomycin → Enterobacteriacae
- Combination including carbapenem if MIC is ≤ 8 mg/L
  - Carbapenem-containing combinaisons resulted in significantly lower mortality rates (18.8%) than the carbapenem-sparing combinaisons (30,7%)
- Colistin: increases the permeability of other AB through the bacterial outer membrane by a detergent mechanism

Tängden T. Journal of Medical Sciences 2014;119:149-153
Tzouvelekis et al. Clin Microbiol Infect 2014;20:862-872

Conclusions (for discussion)

- **Specific rules for proper use:**
  - Prescription only in case of multidrug-resistant gram-negative bacilli in hospital
  - When there is no alternative
  - use at the appropriate dose (and adapted to the MIC if available) and, if needed, extended infusion…
  - If empirical treatment for 48 hours revaluation in order to de-escalate promoting therapeutic alternative

The slides are available for download from http://www.facm.ucl.ac.be → Lectures

Questions may flow …

https://www.pinterest.com/pin/464363411551511574/

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