Carbapenems:
why, how and what are the risks ?

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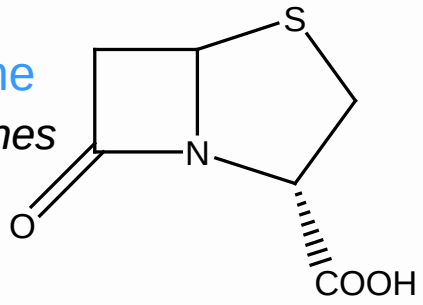
with many slides borrowed from
Françoise Van Bambeke and Magali Dodemont

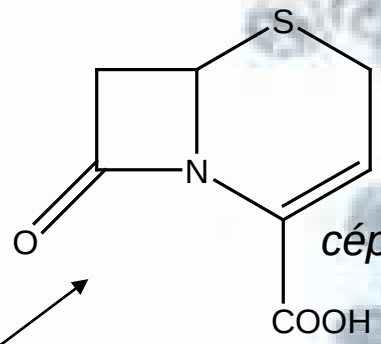
with the support of
Wallonie-Bruxelles International

β-lactames: pharmacochemistry

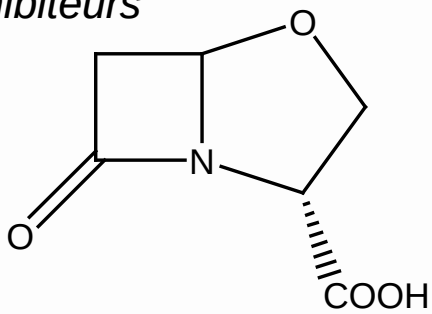
pénam
pénicillines

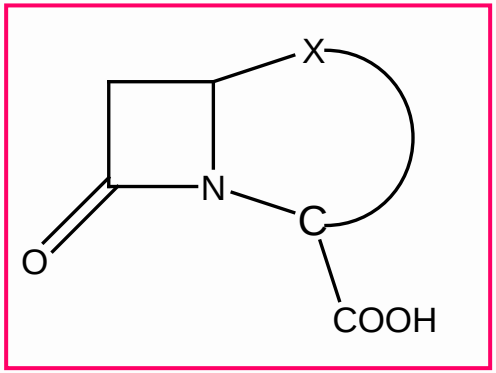


céphème
céphalosporines

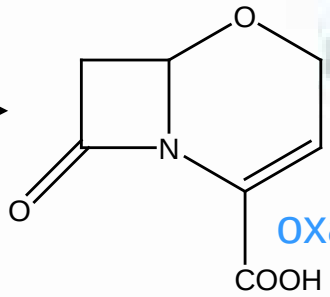


clavam
inhibiteurs

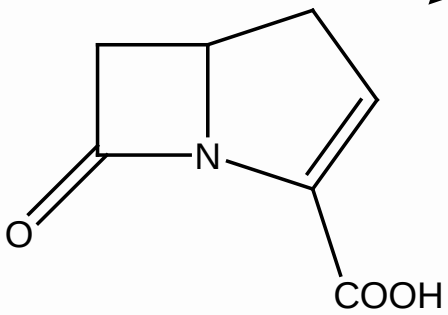




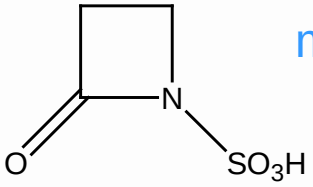
oxacéphème



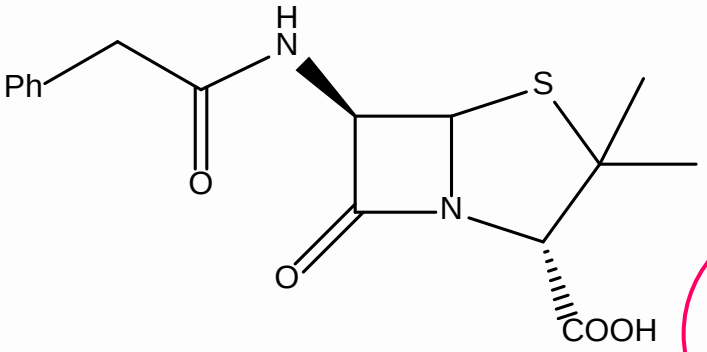
carbapénème

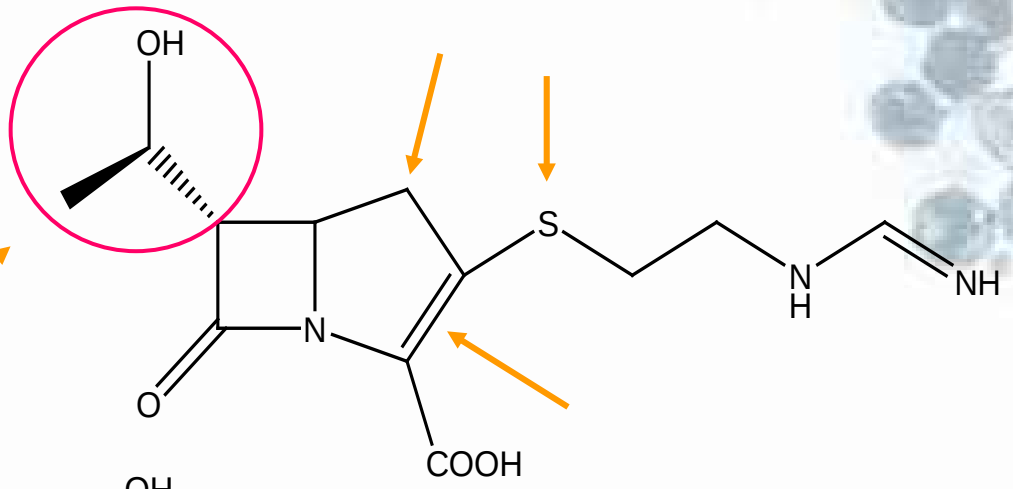


monobactame

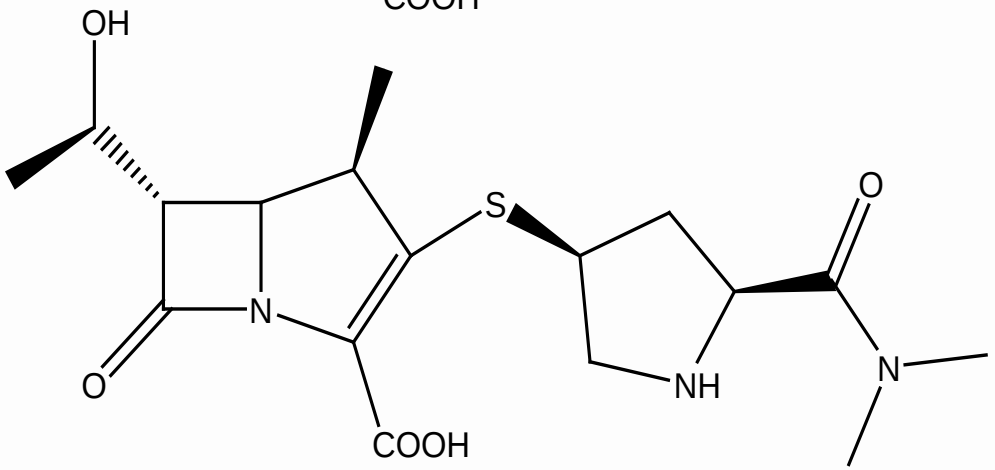


From penicillin to carbapenems





imipenem

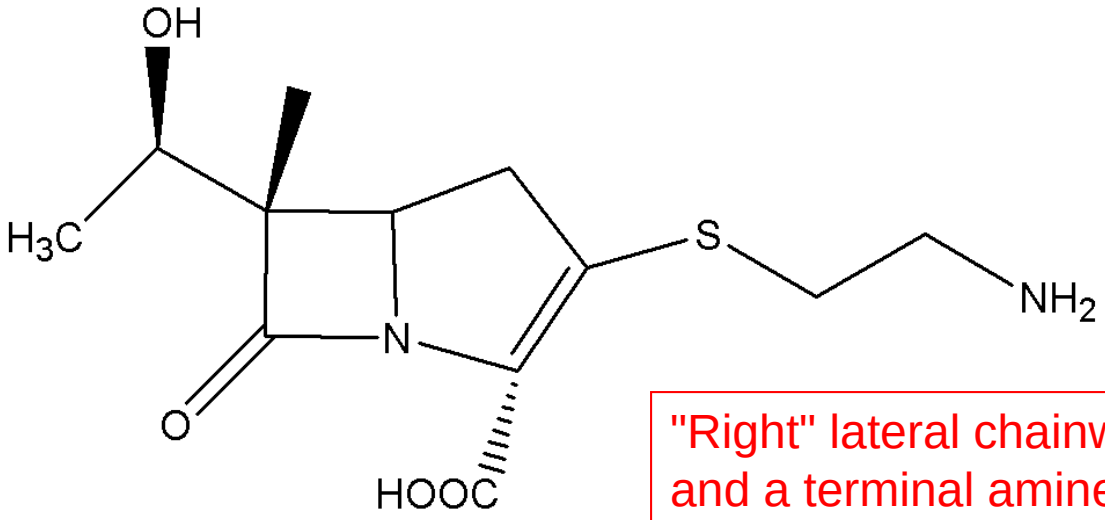


meropenem

Carbapenems: thienamycin

No "left" lateral chain
(but only a methyl)
➔ resist. to β-lactamases

No S atom in the cycle
➔ tight PBP binding
➔ VERY broad spectrum

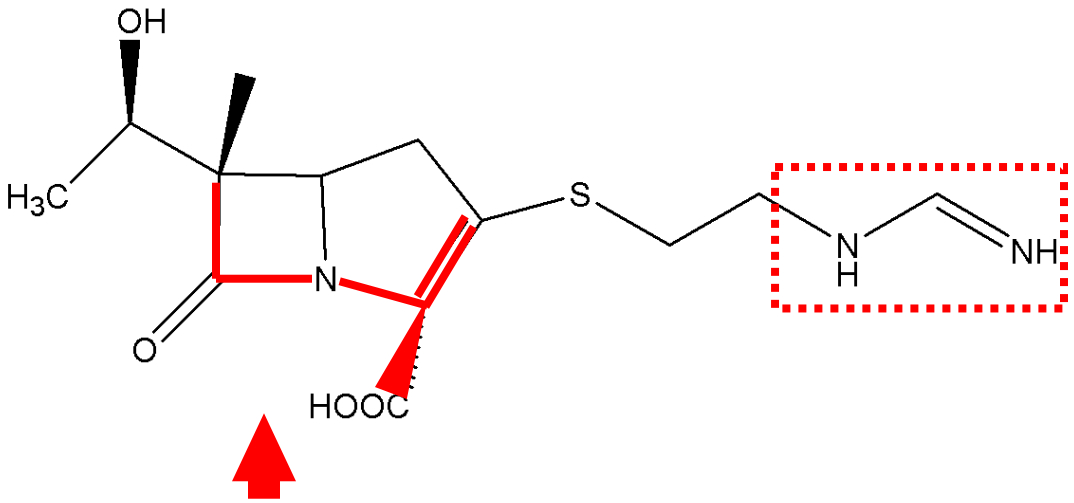


"classic"
pharmacophore

"Right" lateral chainwith a S atom
and a terminal amine
➔ tight binding to PBP
BUT
➔ intrinsic instability

Thienmycin is too unstable for clinical use

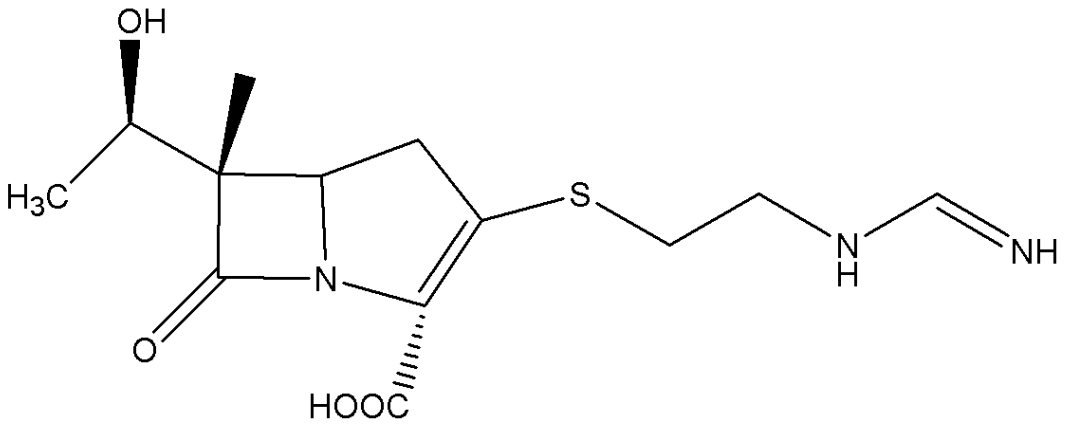
Carbapenems: from thienamycin to imipenem



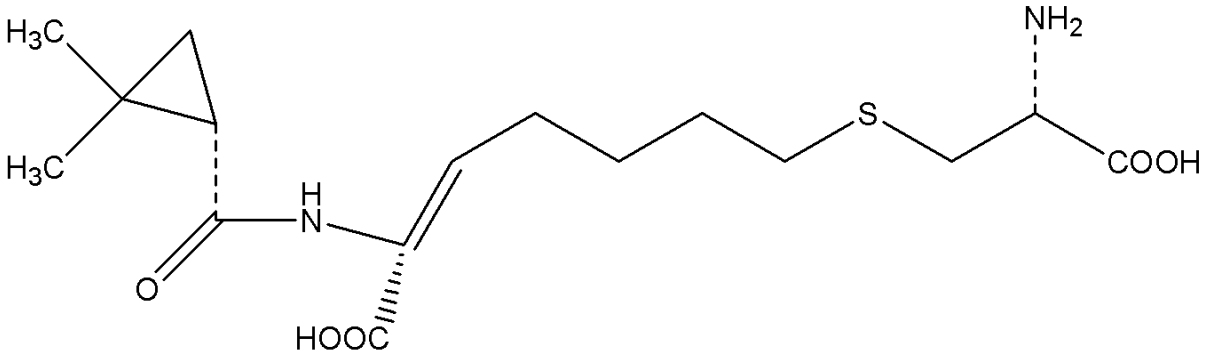
Addition of a formimidoyl (iminomethylamino)
➔ Improved stability

BUT imipenem is the substrate of a renal <u>DEHYDROPEPTIDASE</u>
- rapid degradation of the antibiotic…
- liberation of nephrotoxic reaction products…

Carbapenems: imipenem + cilastatine



imipenem



cilastatine

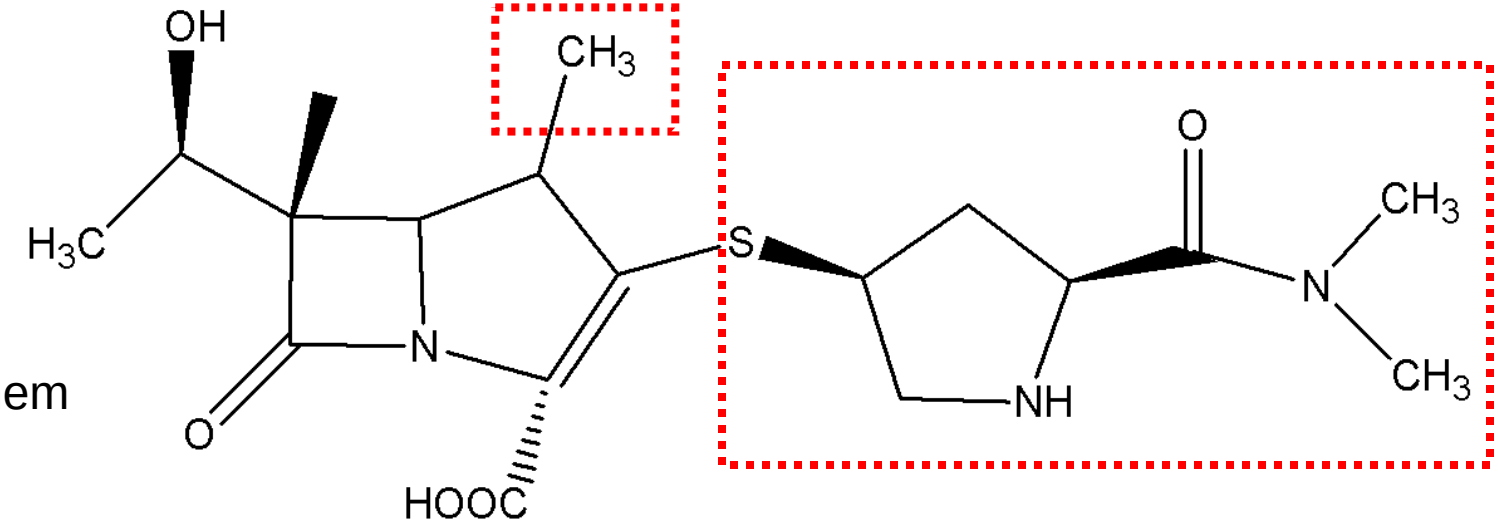
Inhibitor of the déhydropeptidase

imipenem + cilastatine = **TIENAM ®**

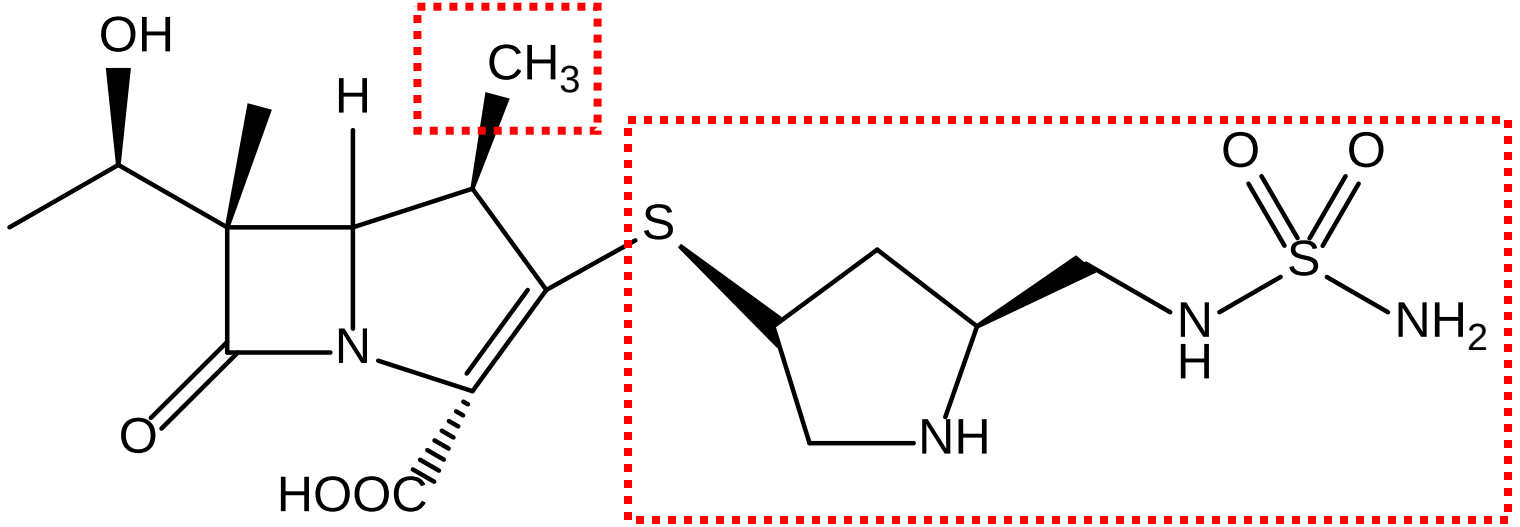
Carbapenems: from imipenem to meropenem

resistance to the dehydropeptidase through steric hindrance

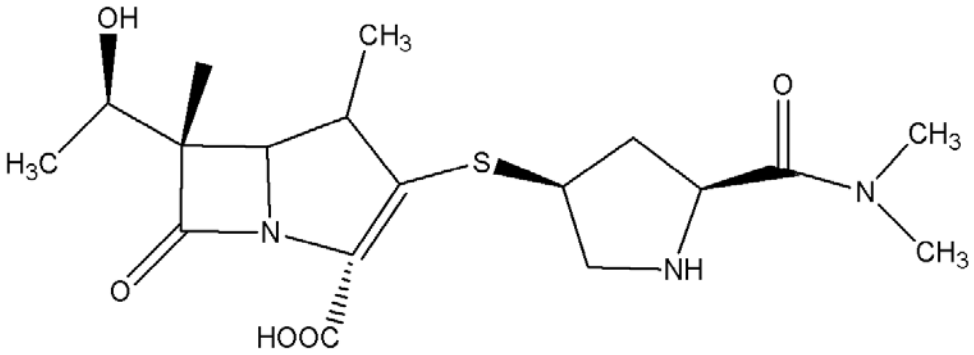
meropenem



doripenem

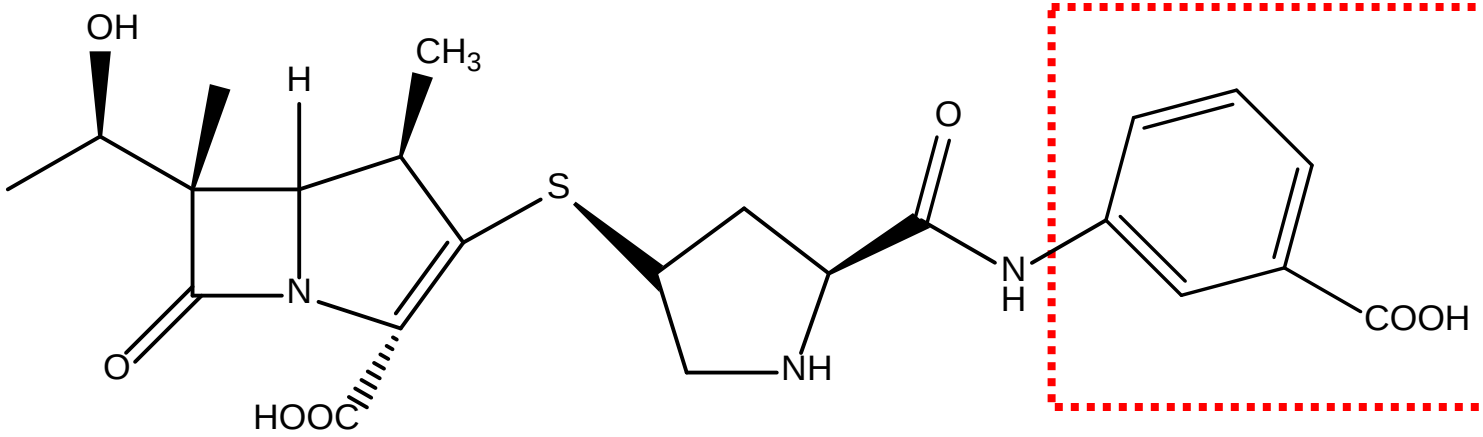


Carbapenems: from meropenem to ertapenem



meropenem

long half-life BUT
loss of useful activity
against
P. aeruginosa



ertapenem

Spectrum of activity

- Beta-lactams with the broadest antibacterial spectrum currently available
- Gram positive
  - *S. pneumoniae* (including penicillin-resistant), MSSA, *Streptococci*. *E. faecalis* are moderately susceptible.
- Gram negative: most of them (*)
- Anaerobes:
  - Very active, including *Bacteroides*, *Fusobacterium*, anaerobic gram-positive cocci

(*) !!! Bacteria resistant: MRSA, *E. faecium*, *Stenotrophomonas maltophilia*

Spectrum of activity

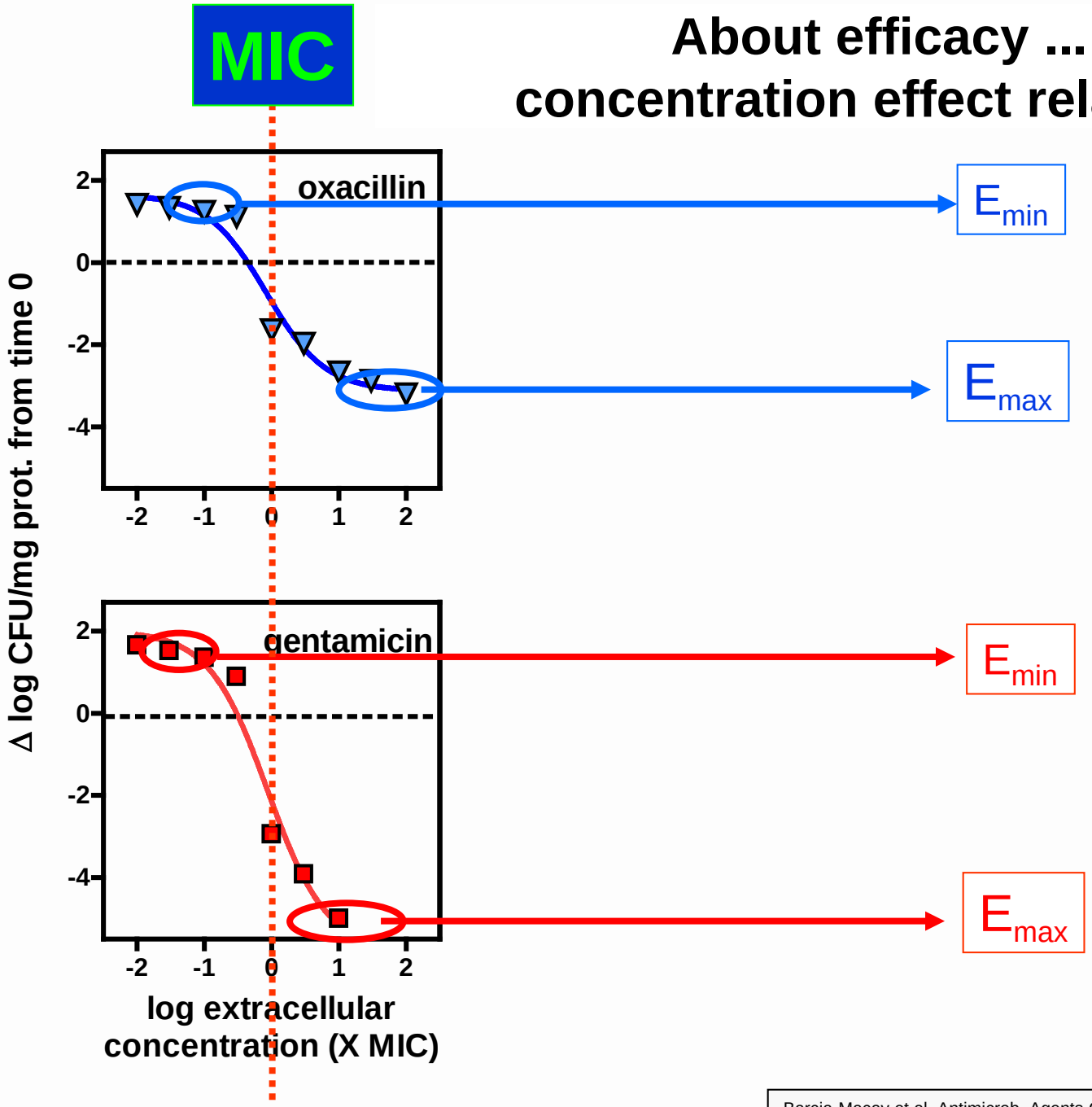
- Similar for all carbapenem **except ertapenem**
  - Ertapenem has no useful activity against *P. aeruginosa*
- **Little difference in the activities of individual agents**
  - **Imipenem:** slighter better activity against Gram-positive bacteria than meropenem
  - **Meropenem** is more active against Gram-negative bacteria than imipenem
  - **Doripenem:** slightly improved antipseudomonal activity
- Active against ESBL and AMPc producers

Pharmacokinetic properties

- Unstable in gastric acid → parenteral route
- Half-life : 1 hour for meropenem, imipenem and doripenem (frequent administration)
  BUT 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: essentially renal
- **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

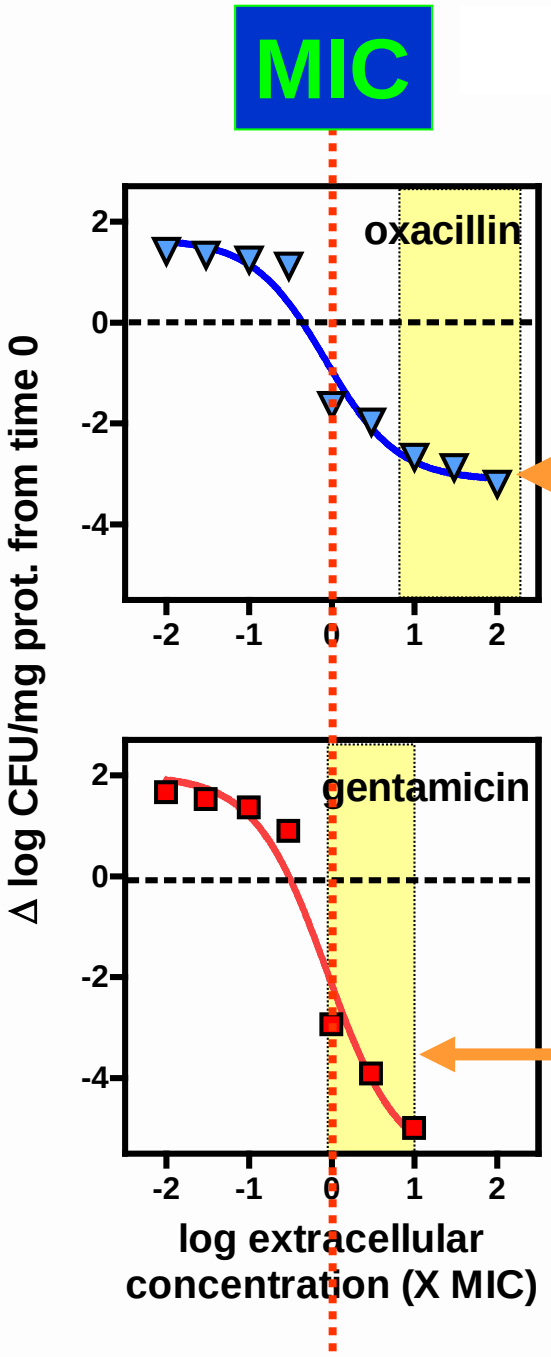
Pharmacodynamics…

About efficacy ... and concentration effect relationships



Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

Introducing pharmacokinetics…



weak concentration dependence

C_{min}-C_{max}

strong concentration-dependence

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

β-lactams are time-dependent…

but how long do you need them?

various β-lactams

various pathogens

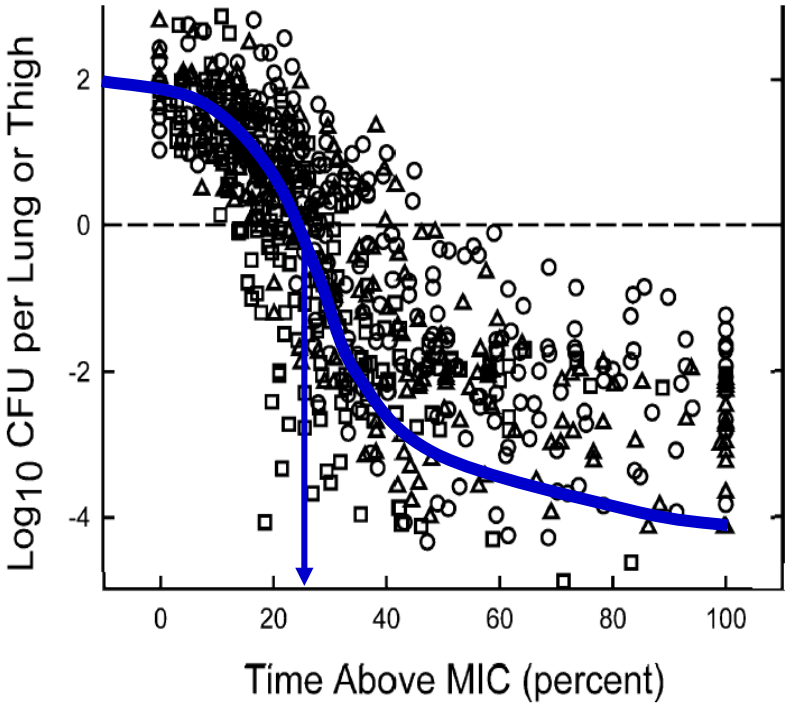


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

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

doripenem

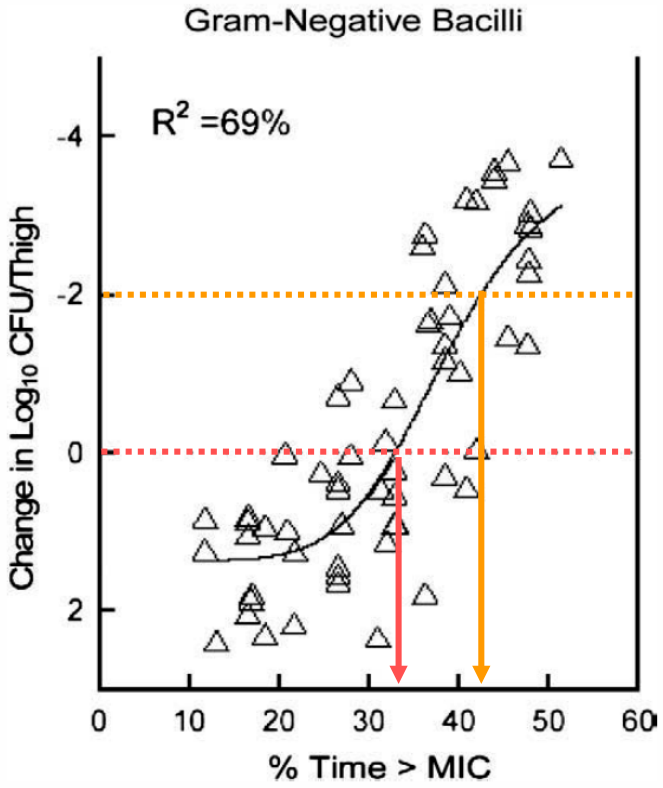


Fig. 4. Relationship between doripenem exposure, as measured by % Time > MIC, and response in a neutropenic murine-thigh infection model involving Gram-negative bacteria.

Van Wart et al., Diagn Microbiol Infect Dis. (2009) 63:409-414

First conclusions (and discussion)....

- 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 or little post-antibiotic effect, β-lactams need to stay above the MIC (preferably 4-fold…) for the maximum time…

Medical controversies
by H. Daumier (1808-1879)

First conclusions (and discussion)....

- The most important PK/PD parameter predicting bacteriological and clinical efficacy is **T>MIC**
- T>MIC of 20% →bacteriostatic effects
- T>MIC of 40% → bactericidal effects
- In severe critically ill septic patients, in impaired renal function patients and in neutropenic patients : imipenem has to exceed 66% of T>MIC to result in good clinical outcome (Mouton *et al.* Clin Pharmacokinet. 2000;39:185–201)
- Maximum killing effect is reached at concentration of 4 x MIC
- Some post-antibiotic effect against Gram-negative bacteria
  - Most marked with *P. aeruginosa*

Pharmacodynamics in the ICU …

- **ICU patients**
  - Increased volume of distribution
  - Modified antibiotic clearance
  - Modified protein binding protein caused by hypo-albuminaemia
  - Modified tissue penetration

Implications for clinical efficacy and correct dosage of AB

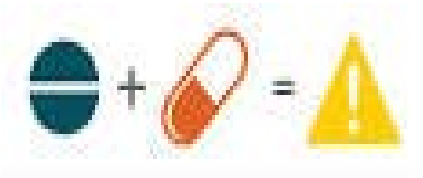
→ **Potential underdosing**
→ **Risk of development of resistance and/or therapeutic failure**

- **Increase the drug dose (to obtain at least 40% of 4xMIC)**
- **Prolong the infusion time**

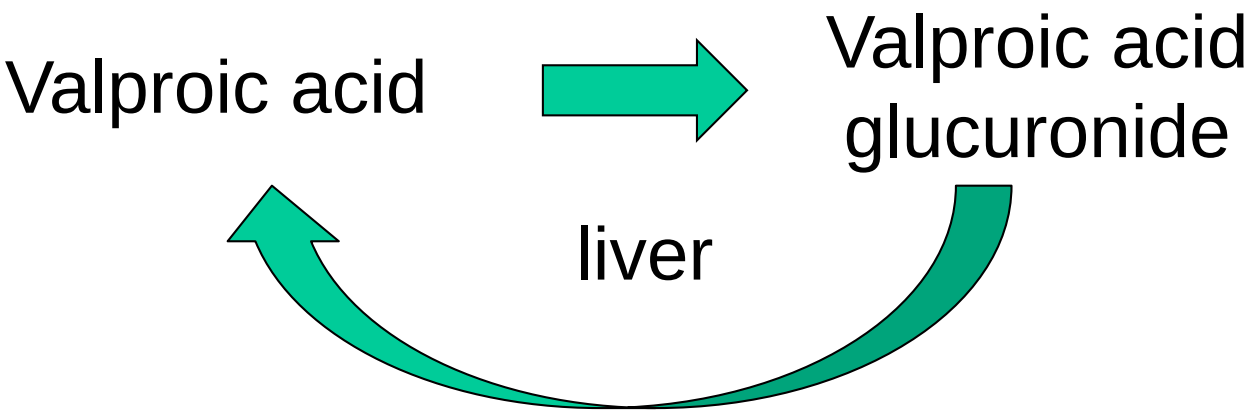
Adverse effects

- 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%)
- Seizure activity → with imipenem
  - If underlying CNS problems or decrease renal function
- Risk of developing pseudomembranous colitis, especially with prolonged therapy

Drug-Drug Interactions



- Valproic acid → reduced serum concentrations of valproic acid



acylpeptide hydrolase (APEH)
acting as **valproic acid glucuronide (VPA-G) hydrolase**

Suzuki et al. Xenobiotica. 2015 Jun 15:1-6. [Epub ahead of print] PMID: 26075835

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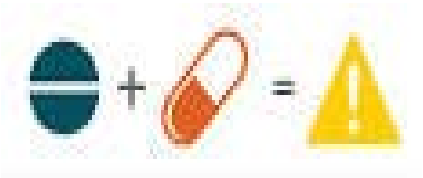

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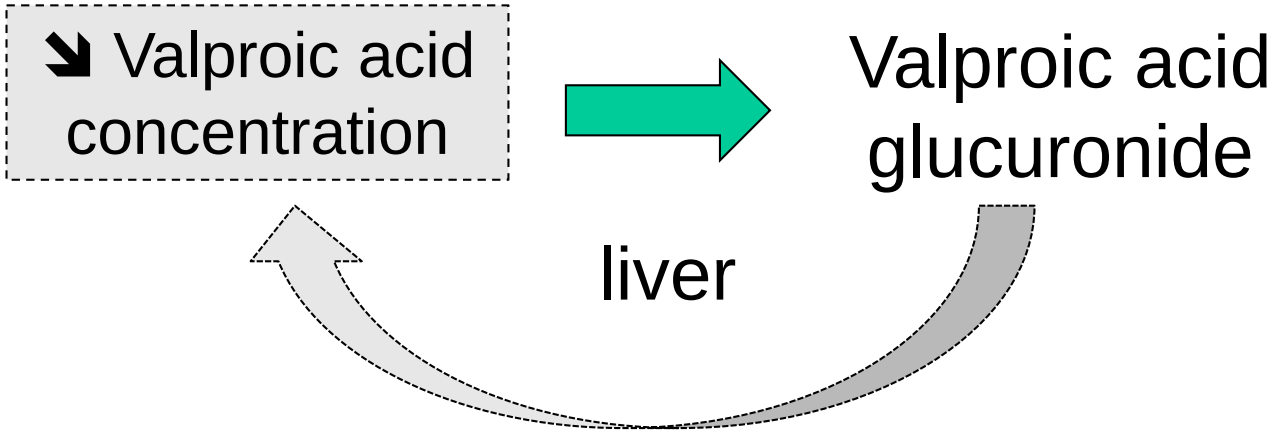

acylpeptide hydrolase (APEH)
acting as **valproic acid glucuronide (VPA-G) hydrolase**

INHIBITED BY CARBAPENEMS

Suzuki et al. Xenobiotica. 2015 Jun 15:1-6. [Epub ahead of print] PMID: 26075835

Clinical use: microbiological considerations (*)

- Infections due to resistant pathogens
  - Regarded as first-line therapy for serious infections caused by Extended Spectrum β-Lactamase (ESBL)-producing organisms
  - Especially in patients with risk factors of harbouring resistant pathogens
    - 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

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* imipenem and meropenem

MDR organisms that may require carbapenems (after documentation)

First choice	Comment	Combined with
Acinetobacter baumanii	R to pip-tazo, cephalo III, FQ, AG	
Enterobacter	R to pip-tazo, cephalo III, FQ, AG	
Enterobacteriaceae	ESBL	
Pseudomonas aeruginosa	R to pip-tazo and ceftazidime	+ ciprofloxacin or aminoglycoside
	R to pip-tazo, ceftazidime, aminoglycosides	+ ciprofloxacin

Empiric treatments with carbapenems ?

Sandford guide (2012-2013)

CNS infections

Infection	Pathogen/population	Treatment
Brain abscess	Pseudomonas suspected	(cefepime + metronidazole) or meropenem
ventriculitis	enterobacteriaceae	Meropenem or cephalo III
	Pseudomonas	Amikacin + (ceftazidime or meropenem)
Brain abscess or pulmonary infection or cutaneous infection in immunocompromised patient	Nocardia, disseminated	TMP-SMX + (meropenem or cefriaxone) + amikacin

Respiratory tract infections

Infection	Pathogen/population	Treatment
HAP/VAP	ESBL producer	meropenem (but see later !)
Pneumonia in immunocompromised patient		(Cephalo III or Pip-tazo or meropenem) +/- amikacin

Other infections

Infection	Pathogen/population	Treatment
mastoiditis	Often polymicrobial	Piperacillin-tazobactam or meropenem
Diabetic foot grade 4	Recent exposure to AB	Piperacillin-tazobactam or meropenem, + vancomycin if Gram(+)
Established wound infection with sepsis	Staphylococci, streptococci, enterobacteriaceae	(amoxi-clav + cipro or levo or amikacin) or meropenem
	Exposure to fresh water (Pseudomonas)	Ciprofloxacin or levofloxacin or meropemen
Sepsis in immunocompromised patients		(Ceftazidime or cefepime or Pip-tazo or meropenem) +/- amikacin
Catheter related infections	Severe or risk factors	vancomycin + (ceftazidime, cefepime, piperacillin-tazobactam or meropenem)
Hospital acquired pelvic or portal thrombophlebitis		Pip-tazo or meropenem or (cefepime or ceftazidime + metronidazole)

Clinical use: approved indications (*)

- Complicated intra abdominal infections
- Obstetric/gynecologic infections
- Respiratory tract infections (Hospital-acquired pneumonia)
- Bacteremia
- Serious skin and soft tissue infections
- Bone and joint
- Complicated UTI
- Febrile neutropenia
- Bronchial exacerbation in the cystic fibrosis patient
  - not in monotherapy → emergence of resistance
- Meningitis (meropenem only)

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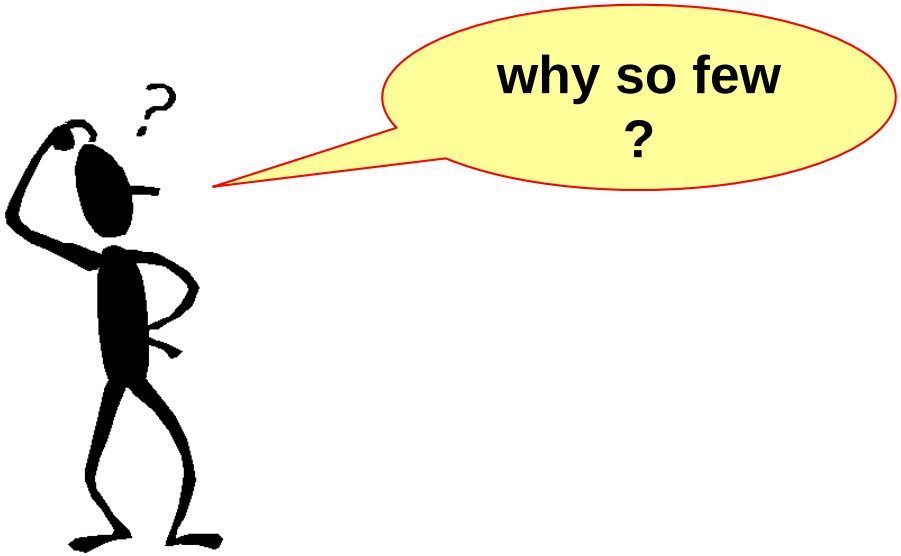
* imipenem and meropenem (imipenem: children ≥ 12 years only)

Clinical use: approved indications of doripenem

- Complicated intra abdominal infections
- Complicated UTI including pyelonephritis



Clinical use: approved indications of ertapenem

- Complicated Intra-Abdominal Infections
- Complicated Skin and Skin Structure Infections, Including Diabetic Foot Infections without Osteomyelitis
- Community Acquired Pneumonia
- Complicated Urinary Tract Infections Including Pyelonephritis
- Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post Surgical Gynecologic Infections
- Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery Complicated intra abdominal infection

Clinical use:
approved indications of ertapenem

- Complicated Intra-Abdominal Infections

- Complicated Skin and Skin Structure Infections, Including Diabetic Foot Infections without Osteomyelitis

- Community Acquired Pneumonia

- Complicated Urinary Tract Infections Including Pyelonephritis

- Acute Pelvic Infections Including Postpartum Endomyometritis, Septic Abortion and Post Surgical Gynecologic Infections

- Prophylaxis of Surgical Site Infection Following Elective Colorectal Surgery Complicated intra abdominal infection

You must exclude *P. aeruginosa*

Clinical use: general considerations

- 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**

Imipenem: details

- **Absorption**: poor oral absorption
- **Distribution**
  - Urine, sputum, synovial fluid, pleural fluid, bone
  - Variable penetration into the cerebral spinal fluid →3rd generation cephalosporins are the drugs of choice for meningitis
  - Imipenem not recommended for therapy of meningitidis because increase frequency of seizures due to higher doses necessary to achieve adequate CSF concentration of the drug
- **Elimination**
  - Primarily via the kidneys by glomerular filtration

    → specific dosage reductions for various degrees of renal dysfunction

Imipenem: details

Dosage

- EUCAST breakpoints apply to imipenem 500 mg x 4 daily administered intravenously over 30 minutes as the lowest dose. 1g x 4 daily was taken into consideration for severe infections and in setting the I/R breakpoint

- Pediatric dose: 20 to 50 mg/kg iv (q12h)
- Decreased dosage: renal failure (60 to 100 mg/kg) (div q6h)
- Increased dosage: pregnancy

Imipenem: dosage modifications

Renal impairment

- CrCl ≥71 mL/min/1.73 m²: 250 mg IV q6hr
- CrCl 41-70 mL/min/1.73m²: 250 mg IV q8hr
- CrCl 21-40 mL/min/1.73 m²: 125-250 mg IV q12hr
- CrCl ≤20 mL/min/1.73 m²: 125-250 mg IV q12hr
- CrCl <5 mL/min/1.73 m²: Use IV only if haemodialysis is instituted within 48 hours
- Haemodialysis: Give supplemental dose after each dialysis, then q12hr

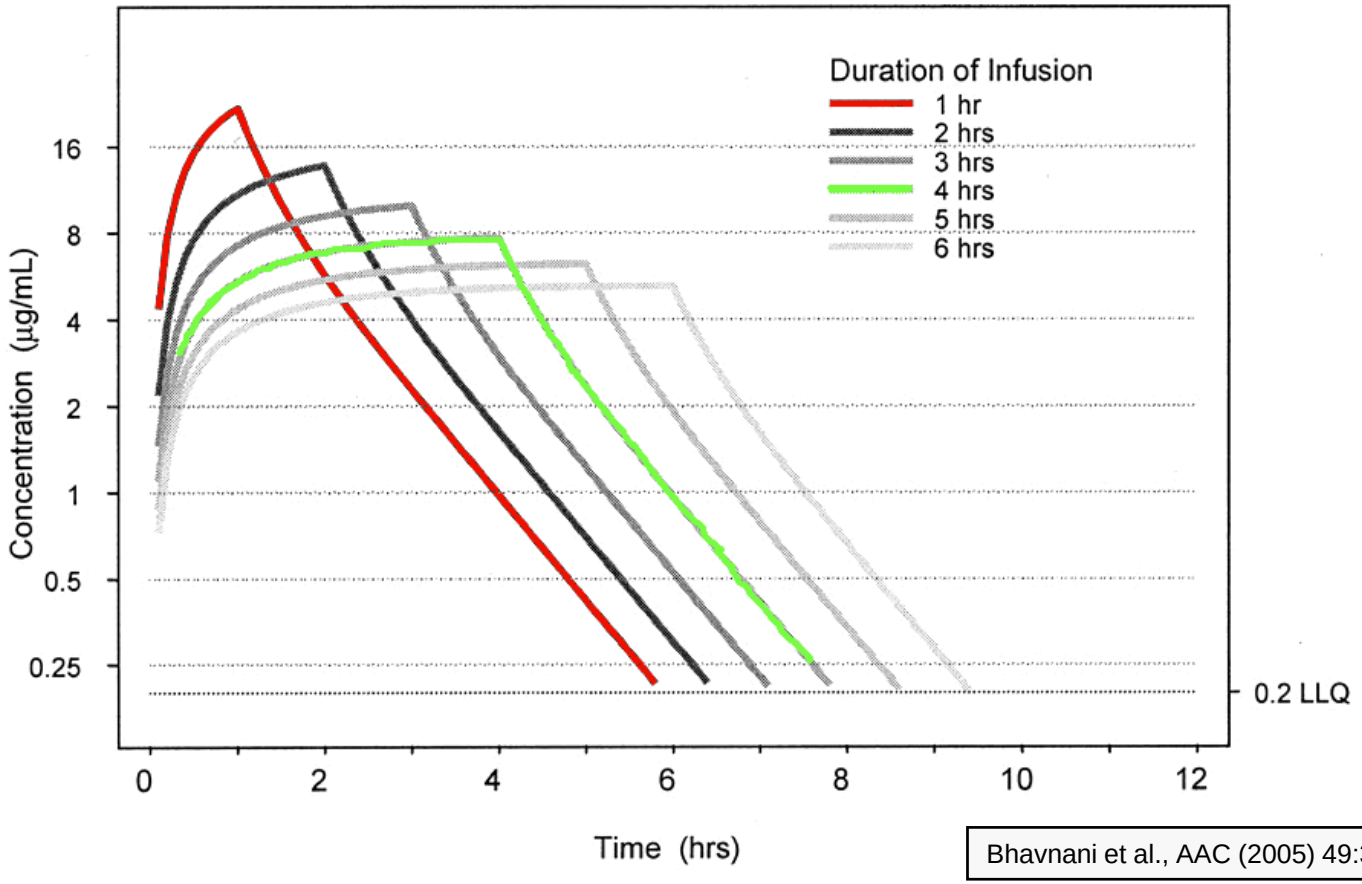
Maximising the utility of the carbapenems

- **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 **more frequently**
- **Extended infusion**
  - Extended infusion (3-5h)

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.

Mode of administration

- Standard regimen: intermittent short-term infusion
- Extended infusion may optimizing $T_{>MIC}$ particularly in critically ill patients.



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

Prolonged infusion

- useful to prolong the T > MIC
- can be the only solution for antibiotics that cannot be administered by continuous infusion (discussed later)
- the following slides are an example with doripenem that may also apply to meropenem
- **be careful for imipenem as it may be much less stable than the two other penems**

Comparative PK profile

Bolus vs Prolonged infusion

parameter	DOR (500 mg)		MEM (1g)	
	(Bol)	(Prol)	(Bol)	(Prol)
Cmax (mg/L)	23	8	112	30
AUC (mg.h/L) – 8 h	36	17	136	186
T > CMI 1	55	80	75	98
T > CMI 4	27.5	55	57	73
T > CMI 8	17.5	-	46	58

Kim et al., AAC (2008) 52:2497-2502
Jaruratanasirikul et al., AAC (2005) 49:1337-39

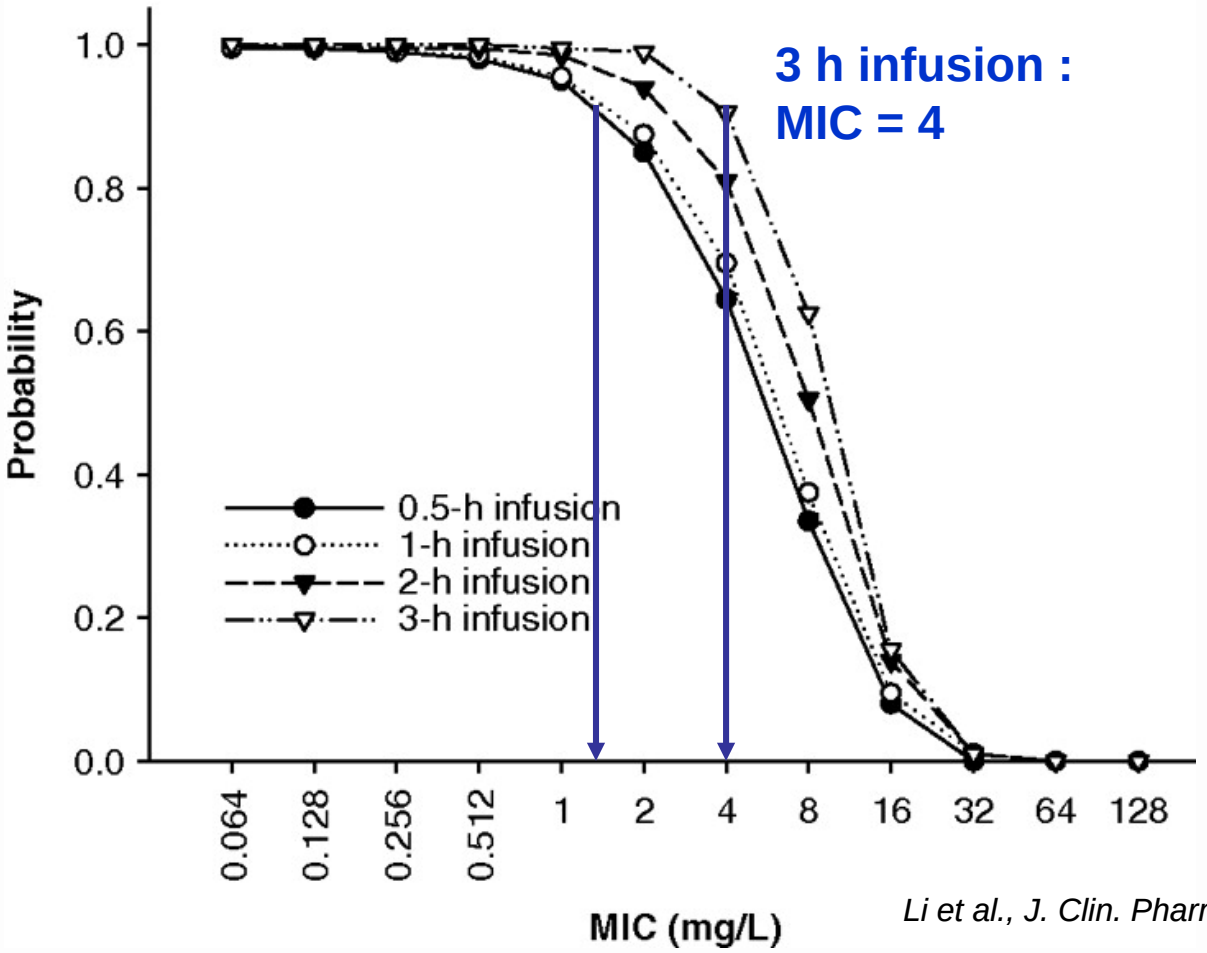
Meropenem : PK/PD modeling

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



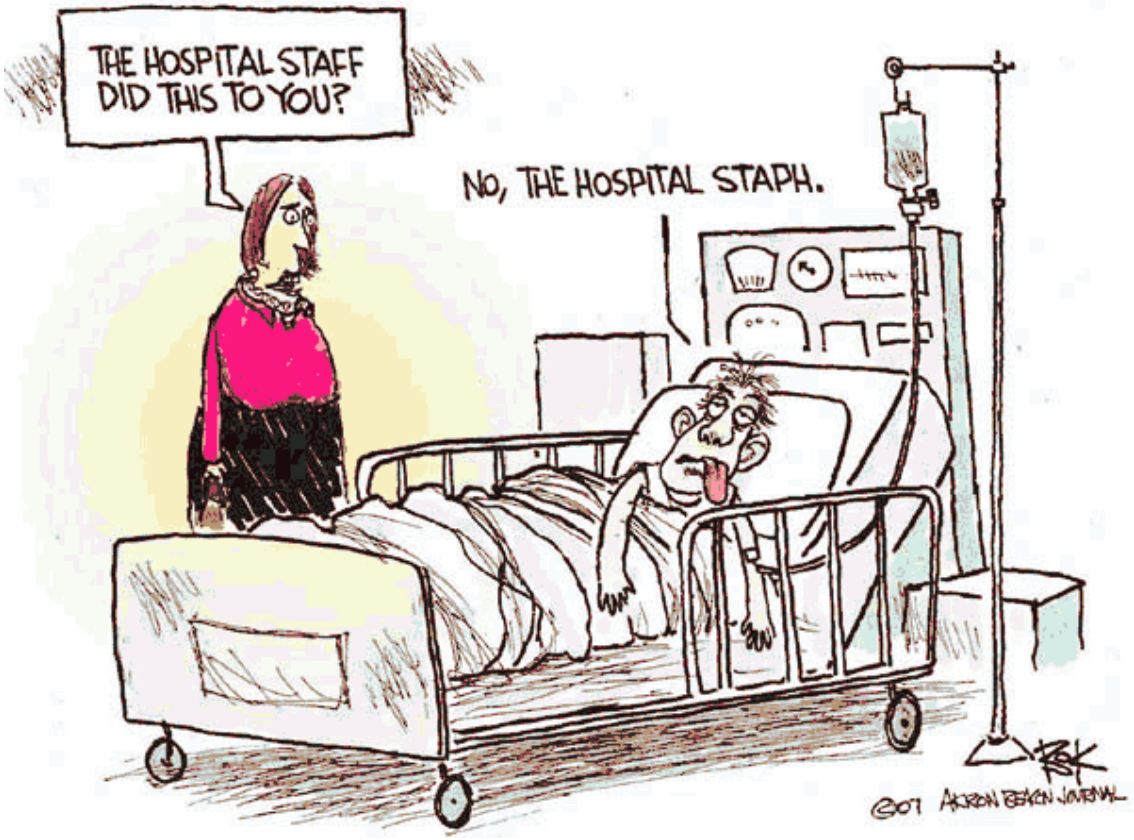
Li et al., J. Clin. Pharmacol (2006) 46:1171-1178

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

Resistance



Mechanisms of resistance

GRAM negative rods

- Membrane impermeability: Loss of an outer membrane protein (Opr D porin) which is necessary for imipenem to reach its PBP target site (*P. aeruginosa*)
- Efflux mechanisms: overexpression of the MexA-MexB-oprM pump system (P*. aeruginosa*)
- Destruction by beta-lactamases = **CARBAPENEMASE**
  - associated with mechanisms of resistance to other antibiotic classes -> highly multidrug resistant organisms

Mechanisms of resistance

Gram positive

- Mutation of PBPs
- Acquisition of a new carbapenem-resistant PBP

All carbapenems are inactive against MRSA or MRSE …

Escalating antimicrobial resistance to β-lactams

- **B-lactam agents**: have been used widely for treatment of infection caused by *Enterobacteriaceae* since the 70-80's
- **Worldwide emergence of community-acquire ESBL**+ strains since the early 2000's
- **Carbapenems**: **last resort antimicrobial agents** for the treatment of ESBL + infection
- **Since 1993**: emergence of first carbapenem-R isolates due to **production of carbapenemases**
- **Therapeutic dead-end** (almost no reserve/new drugs in the pipelines)

From Y. Glupczynski

Rapid evolving resistance in Enterobacteriaceae

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

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

Penicillinase
(TEM-1, SHV-1)

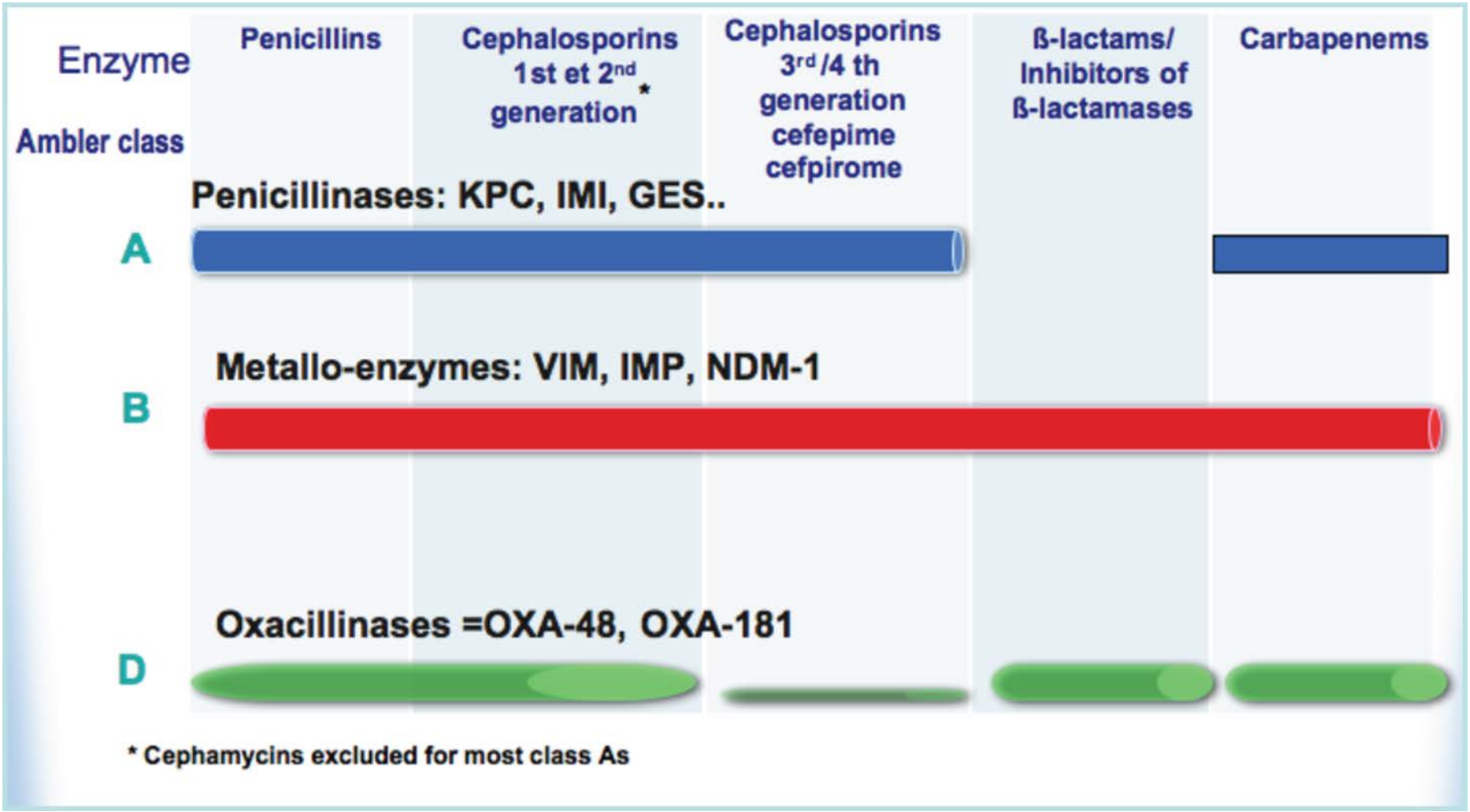
Wild type

1940 **1970** **1990** **2010**

Carbapenem resistance mechanisms

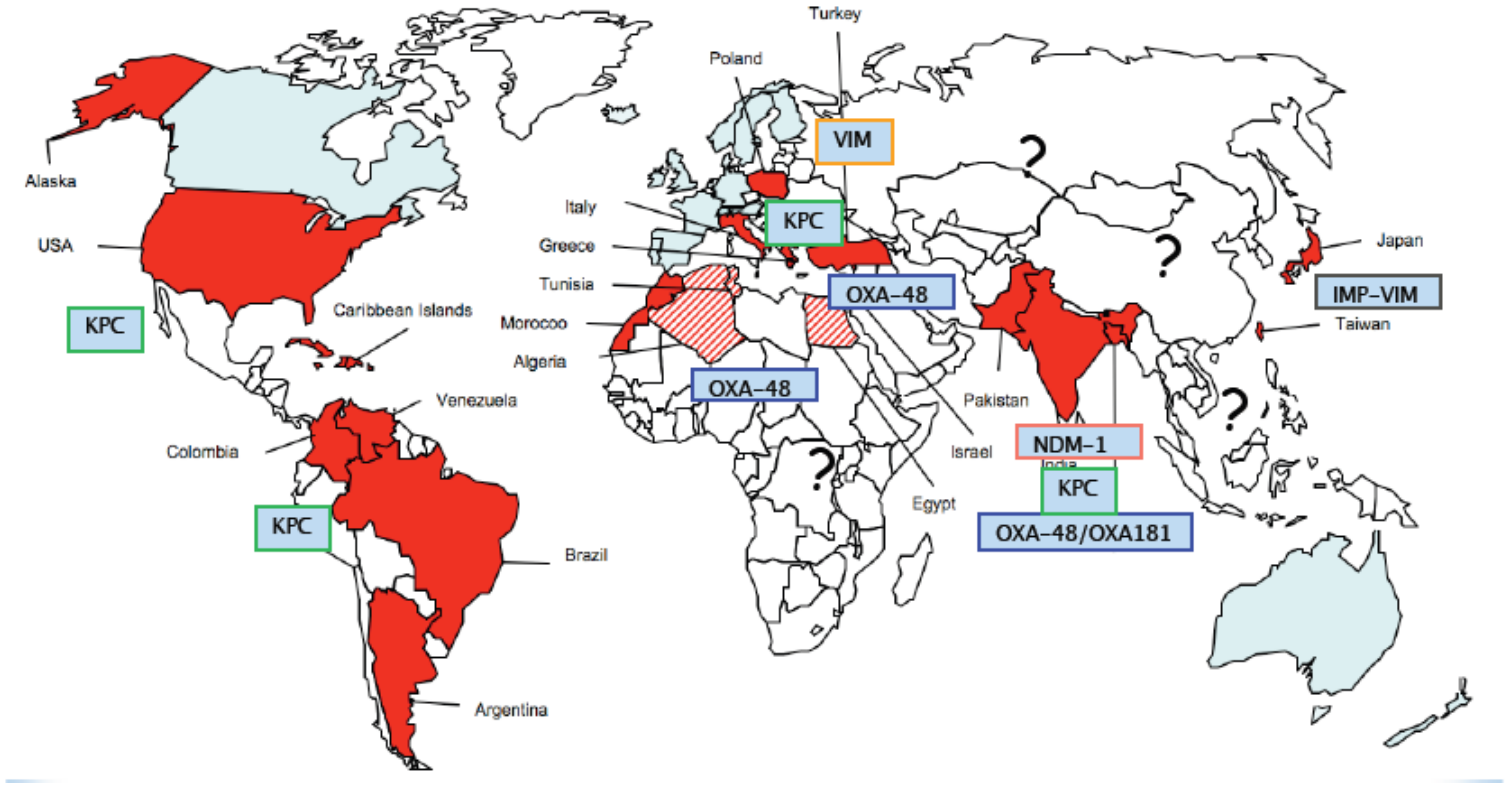
Pathogens	Mechanisms of resistance
Enterobacteriaceae	Cephalosporinase/ESBL + porin loss
	Carbapenemase
P. aeruginosa	Porin loss
	Up-regulated efflux
	Carbapenemase
Acinetobacter spp.	Cephalosporinase + porin loss
	Carbapenemase

Classification of the different carbapenemases in *Enterobacteriaceae*



From P. Nordman

Carbapenemase producing- *Enterobacteriaceae*



From P. Nordman

NDM-producers…

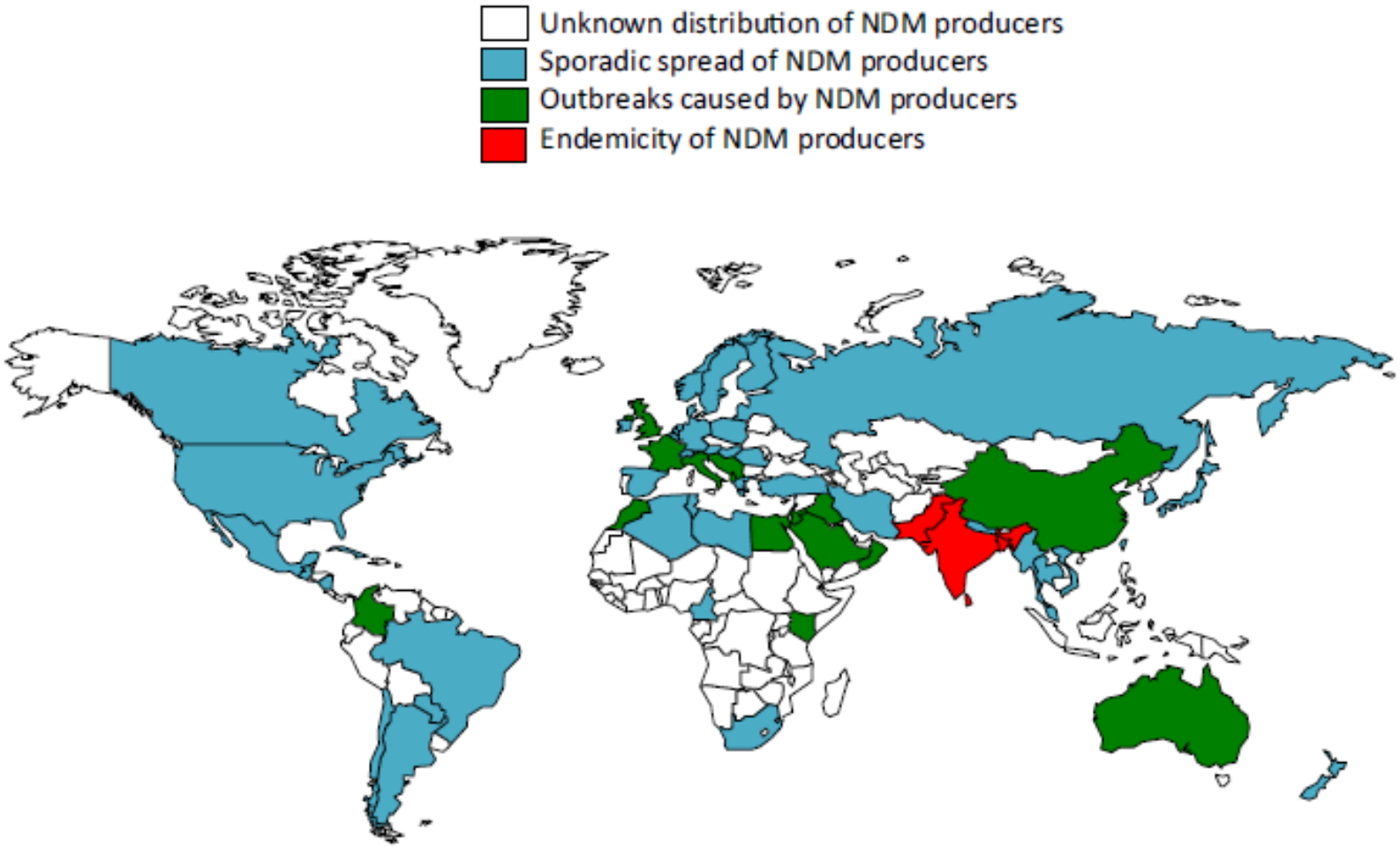


FIG. 2. Geographical distribution of NDM producers.

Clinical Microbiology and Infection ©2014 European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **20**, 821–830

Carbapenemase producing- *Enterobacteriaceae*

Table 1. Overview of Carbapenemase Enzyme Types in *Enterobacteriaceae*

Ambler Class (Active Site)	Example Enzymes	Host Organisms	Carbapenems	Inhibition by Currently Available β-Lactamase Inhibitors (Clavulanic Acid, Tazobactam, and Sulbactam)	Region Mostly Found In
A (serine)	KPC-2 to 22	Mainly found in *Klebsiella pneumoniae* (have been identified in other *Enterobacteriaceae* and nonfermenters)	Yes	Variable[a]	United States and worldwide
B (Zinc binding thiol –"MBLs")	NMD-1 IMP-I VIM-1	*Enterobacteriaceae* and nonfermenters	Yes	No	Southern Asia
D (serine)	OXA-48	*Enterobacteriaceae* (other types of OXA carbapenemases mainly found in *Acinetobacter* spp.)	Minimal Hydrolysis[b]	No	Southern Europe

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

[a] Some KPC enzyme types, such as KPC-2, can hydrolyze clavulanic acid, tazobactam, and sulbactam. However, this ability to hydrolyze these β-Lactamase Inhibitors is uncommon in Class A enzymes [8, 9].

[b] OXA-48 is weakly active against extended spectrum cephalosporins and hydrolyzes carbapenems only minimally [10].

Morrill et al. Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015;5:2, ofv050 (PMID: 26125030)

Resistance to carbapenems: why ?

- Carbapenems resistance is promoted by the widespread use of these antibiotics, creating a continuous selective pressure on bacteria
- Rational use of carbapenems is vital to control and prevent both the clinical impact and the development of resistance
  - Limit the duration of therapy (most infections: 5- 7 days)
  - Use of therapeutic alternatives for the treatment of infections caused by ESBL
    - β-lactam (amoxicillin) + inhibitor of β-lactamase (clavulanic acid)
    - Fosfomycin
    - Cotrimoxazole
    - Tigecycline
    - Piperacillin-tazobactam

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 carbapenme 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

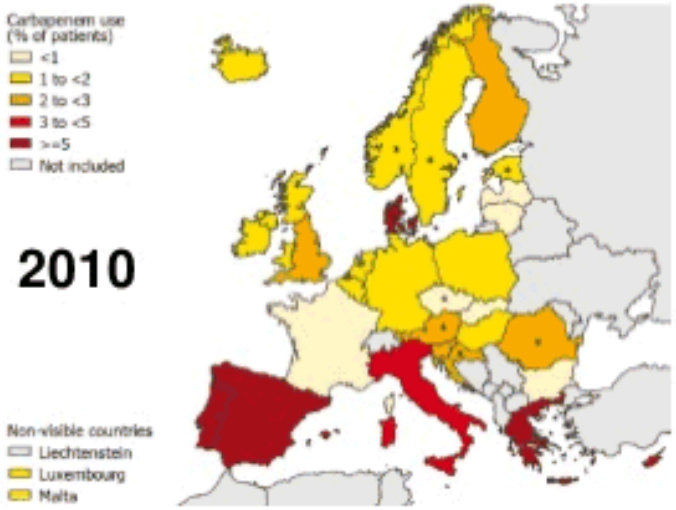
Can we avoid carbapenems ?

Some can do, others not …

High hospital consumption of carbapenems

DGS desde 1899 Direção-Geral da Saúde

Carbapenems



" In 2012, consumption of carbapenems varied by a factor of 14, from 0.01 (Bulgaria) to 0.14 DDD per 1 000 inhabitants and per day (Portugal)"

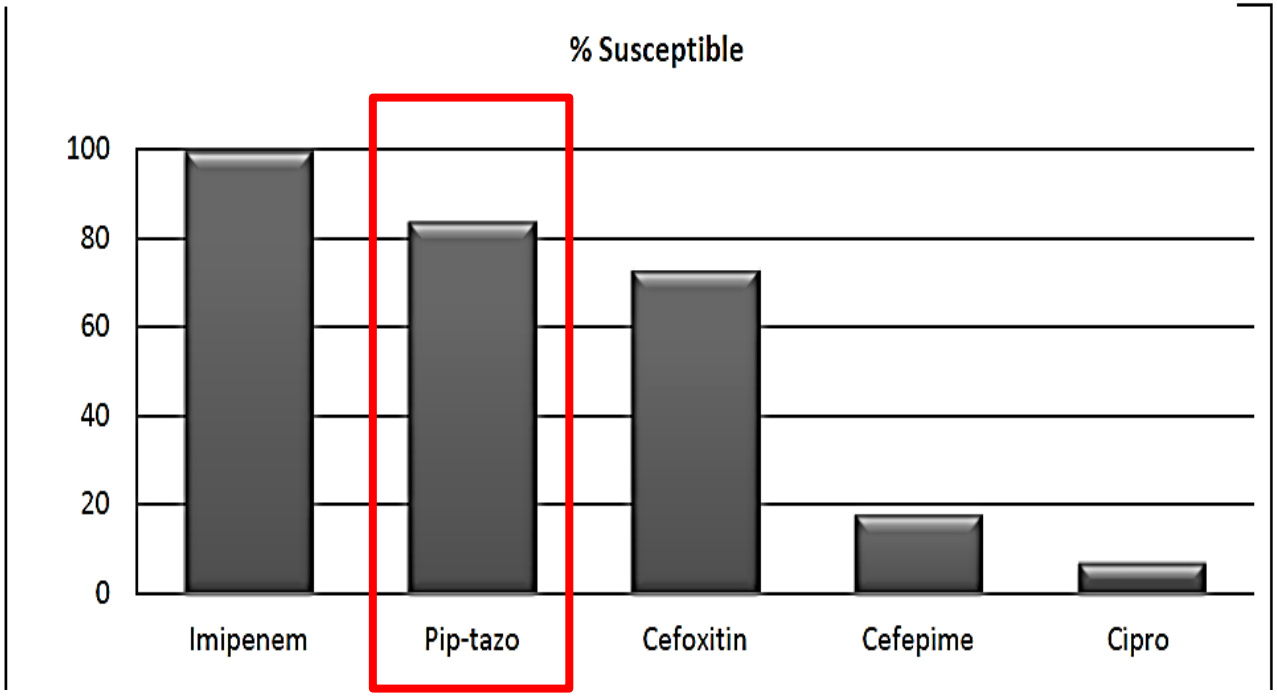
"The proportion of consumption of carbapenems out of antibacterials for systemic use ranged from 0.8% (Latvia) to 9.8% (Portugal) with an EU/EEA population-weighted mean of 2.9%."

ECDC; ESAC Net 2012

Non-Carbapenem Therapy for Bacteremia Caused by Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae*

- Presence of ESBL does not necessarily confer bacterial resistance to all β-lactams… (viz. piperacillin/tazobactam …)
- **MIC is a better predictor of outcome** than simple detection of enzyme (genomic) or mechanism-based categorization

Figure 4. In vitro susceptibility of *E. coli* in North America (2009-2010) using 2012 CLSI breakpoints[10]



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

Use of EUCAST breakpoints to predict outcome based on MIC determination

Enterobacteriaceae

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[A,B]	14[B]
Amoxicillin-clavulanic acid	8[1,3]	8[3]	20-10	19[A,B]	19[B]
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32[1,3]	32[3]	20-10	16[A,B]	16[B]
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17

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	22	19

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

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf

Use of EUCAST breakpoints to predict outcome based on MIC determination

Important message for the clinicians !

Enterobacteriac

Penicillins[1]					
Ampicillin-sulbactam					
Amoxicillin-clavulanic acid					
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Systematic review and meta-analysis of carbapenems vs alternatives in ESBL *Enterobacteriaceae*

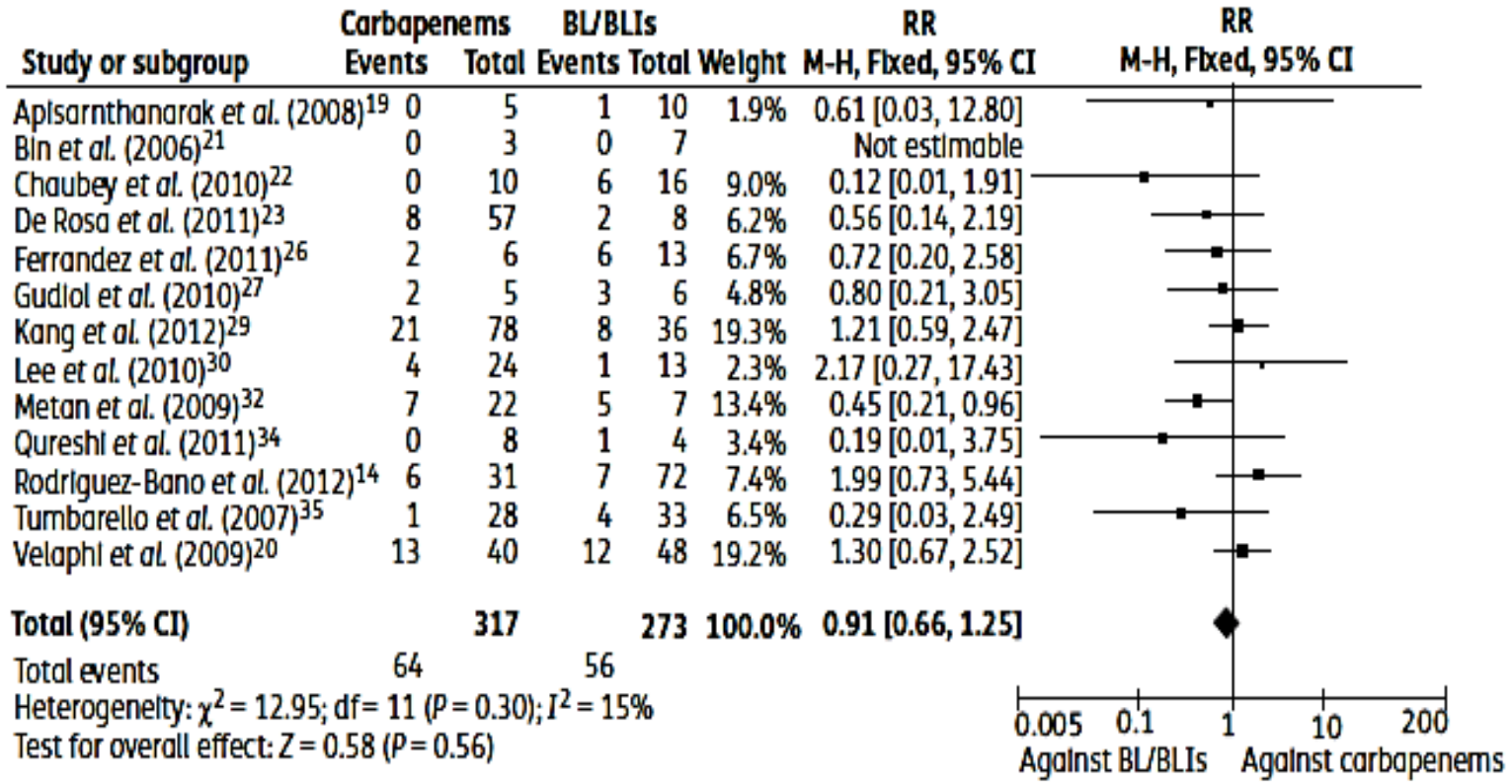

Figure 3. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated empirically with carbapenems versus BL/BLIs. Vertical line='no difference' point between the two regimens. Squares=RRs. Diamond=pooled RR for all studies. Horizontal lines=95% CIs.

Vardakas KZ et al. J Antimicrob Chemother 2012;67:2793

Systematic review and meta-analysis of carbapenems vs alternatives in ESBL *Enterobacteriaceae*

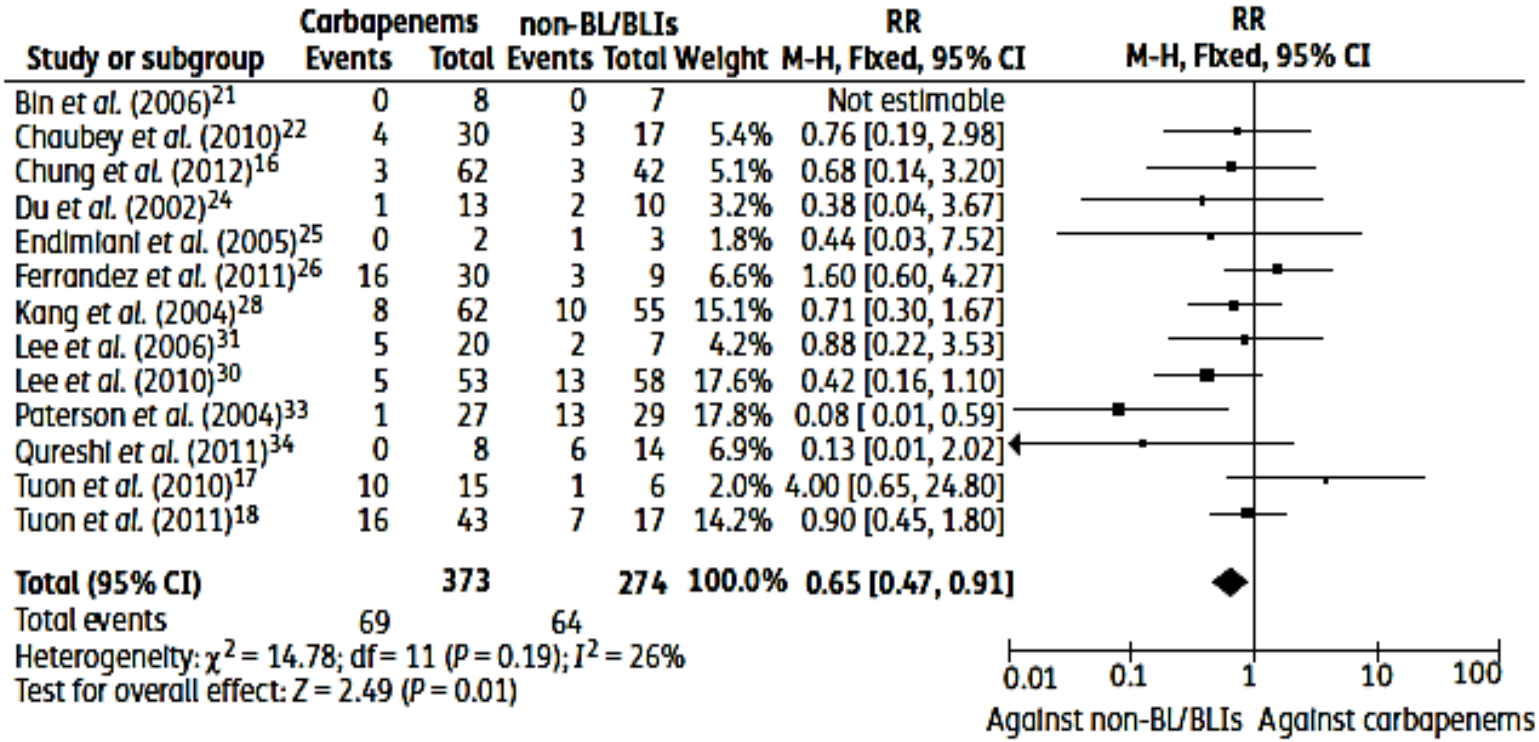

Figure 4. Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated definitively with carbapenems versus non-BL/BLIs. Vertical line='no difference' point between the two regimens. Squares=RRs. Diamond=pooled RR for all studies. Horizontal lines=95% CIs.

Vardakas KZ et al. J Antimicrob Chemother 2012;67:2793

Non-Carbapenem Therapy for Bacteremia Caused by Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae*

such as *K. pneumoniae*. Moreover, our data extend to AMC and PTZ but not to other BLBLIs. In conclusion, our results suggest that AMC or PTZ, if used at adequate dosages, are suitable options for the definitive therapy of susceptible ESBL-EC strains causing BSI, mainly in the urinary and biliary tracts, which could help prevent overuse of carbapenems.

Radriguez-Bano et al. CIS 2012:54

Treatment of MDR bacteria

Combination therapy

- Monotherapy is associated with higher mortality rates than combination in case of MDR

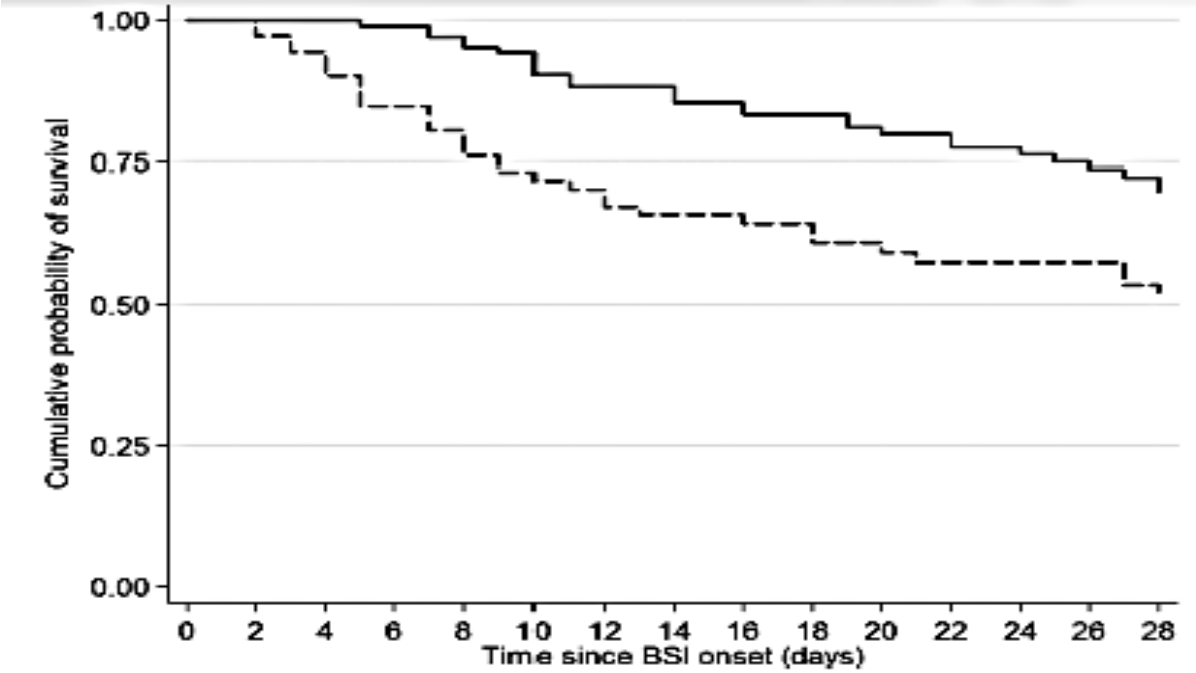

FIG 1 Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). $P = 0.003$ (log rank test).

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

Combination therapies

- Aminoglycoside, ampicillin/sulbactam, carbapenem, colistin, rifampicin → *Acinetobacter* spp
- Aminoglycosides, ampicillin/sulbactam, carbapenem, colistin, rifampicin, tigecycline, fosfomycin → Enterobacteriacae
- Combination including carbapenem if MIC is ≤ 8 mg/L
  - Carbapenem-containing combinations resulted in significantly lower mortality rates (18.8%) than the carbapenem-sparing combinations (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

In case of carbapenem-resistance: other options

Treatment Options for Carbapenem-Resistant *Enterobacteriaceae* Infections

Haley J. Morrill,[1,2] Jason M. Pogue,[3] Keith S. Kaye,[4] and Kerry L. LaPlante[1,2,5]

[1]Veterans Affairs Medical Center, Infectious Diseases Research Program, Providence, Rhode Island; [2]College of Pharmacy, Department of Pharmacy Practice, University of Rhode Island, Kingston; [3]Department of Pharmacy Services; [4]Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Michigan; and [5]Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, Rhode Island

This article provides a comprehensive review of currently available treatment options for infections due to carbapenem-resistant *Enterobacteriaceae* (CRE). Antimicrobial resistance in Gram-negative bacteria is an emerging and serious global public health threat. Carbapenems have been used as the "last-line" treatment for infections caused by resistant *Enterobacteriaceae*, including those producing extended spectrum ß-lactamases. However, *Enterobacteriaceae* that produce carbapenemases, which are enzymes that deactivate carbapenems and most other ß-lactam antibiotics, have emerged and are increasingly being reported worldwide. Despite this increasing burden, the most optimal treatment for CRE infections is largely unknown. For the few remaining available treatment options, there are limited efficacy data to support their role in therapy. Nevertheless, current treatment options include the use of older agents, such as polymyxins, fosfomycin, and aminoglycosides, which have been rarely used due to efficacy and/or toxicity concerns. Optimization of dosing regimens and combination therapy are additional treatment strategies being explored. Carbapenem-resistant *Enterobacteriaceae* infections are associated with poor outcomes and high mortality. Continued research is critically needed to determine the most appropriate treatment.

Keywords. carbapenemases; carbapenem-resistant *Enterobacteriaceae*; carbapenems; resistant infections; treatment.

Morrill et al. Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015;5:2, ofv050 (PMID: 26125030)

In case of carbapenem-resistance: other options

Table 2. Potential Treatment Algorithm for Carbapenem-Resistant KPC-Producing *Klebsiella pneumoniae**

Infection Source	Empiric Treatment: Core Drugs	Empiric Treatment: Possible Adjunct Drugs	Antimicrobial Susceptibility Directed Treatment Considerations
Bloodstream	• High-dose meropenem or doripenem • And polymyxin B	• Aminoglycoside • Tigecycline • Fosfomycin • Rifampin	Meropenem/doripenem: • MIC ≤16 µg/mL continue high-dose meropenem/ doripenem • MIC >16 µg/mL consider alternative in vitro active antimicrobial[a] Polymyxin B/colistin: • MIC ≤ 2 µg/mL continue polymyxin B/colistin[b,c] • MIC >2 µg/mL consider alternative in vitro active antimicrobial If both meropenem/doripenem MIC (>16 µg/mL) and polymyxin B/colistin MIC (>2 µg/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen[d,e] If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen[e] Tigecycline: • MIC ≤1 µg/mL consider tigecycline[d] • MIC >1 µg/mL consider alternative in vitro active antimicrobial Fosfomycin[f]: • MIC ≤32 µg/mL consider fosfomycin • MIC >32 µg/mL consider alternative in vitro active antimicrobial Amioglycoside: • MIC ≤2 µg/mL (Gentamicin/ Tobramycin) or ≤4 µg/mL (Amikacin) consider aminoglycoside • MIC >2 (Gentamicin/ Tobramycin) or >4 µg/mL (Amikacin) consider alternative in vitro active antimicrobial
Lung	• High-dose meropenem or doripenem • And polymyxin B	• Tigecycline • Aminoglycoside • Fosfomycin • Rifampin	
Gastrointestinal/ biliary tract	• High-dose meropenem or doripenem • And polymyxin B • And high-dose tigecycline	• Fosfomycin • Rifampin	
Urine	• High-dose meropenem or doripenem • And fosfomycin[g] • Or aminoglycoside[g]	• Colistin • Aminoglycoside	

General conclusion for combinations

- **The hospital MUST have specific rules for proper use:**
  - Prescription only in case of multidrug-resistant gram-negative bacilli in hospital
  - When there is no alternative
  - If empirical treatment for 48 hours revaluation in order to de-escalate promoting therapeutic alternative

First general conclusions for carbapenems: do NOT loose the battle !

REVIEW 10.1111/1469-0691.12748

Combating the spread of carbapenemases in *Enterobacteriaceae*: a battle that infection prevention should not lose

P. Savard[1,2] and T. M. Perl[3,4]

1) Department of Microbiology, Infectiology and Immunology, Université de Montréal, 2) Medical Microbiology and Infectious Diseases Department, Centre Hospitalier Universitaire de Montréal, Hôpital St-Luc, Montréal, QC, Canada, 3) Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine and 4) Epidemiology and Infection Prevention, The Johns Hopkins Health System and Johns Hopkins Medicine, Baltimore, MD, USA

Savard & Perl. Clin Microbiol Infect. 2014;20:854-61. PMID: 24980472.

First general conclusions for carbapenems: do NOT loose the battle !

REVIEW

Combating
that infecti

P. Savard[1,2] **and T.**
1) *Department of Micro*
Hospitalier Universitaire
University School of Medi

Savard & Perl. Clin Micro

TABLE 1. Infection prevention and antimicrobial stewardship recommendations published to prevent the spread of carbapenem-resistant *Enterobacteriaceae*

Required infection prevention measures

Implement a surveillance programme to identify potential carriers (screening)
Use contact isolation precautions for colonized and infected patients
Cohort colonized and infected patients
Enhance hand hygiene and support with audits
Increase the frequency of environmental cleaning
Limit the use of devices and remove unnecessary devices
Implement antimicrobial stewardship, including a programme
Educate healthcare workers about critical prevention measures

Suggested enhanced infection prevention measures

Limit patient transfers
One-to-one nursing
Decolonize patients with chlorhexidine gluconate baths

First general conclusions for carbapenems: do NOT loose the battle !

REVIEW

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TABLE 1. Infection preve
ship recommendations p
carbapenem-resistant *Ent*

What could Bach Mai do ?

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Suggested enhanced infection prevention measures

Limit patient transfers
One-to-one nursing
Decolonize patients with chlorhexidine gluconate baths

Second general conclusions for carbapenems: Use them appropriately

These antibiotics must be used only

- **under supervision of ID specialists**
- **maintained ONLY after adequate microbiological investigations**
- according to rules set forth by the **Antibiotic Management Team**
- and with surveillance from the **Infection control Team**

But why do you wish to use carbapenems ?

- Do you have **resistant organisms that you cannot "treat" with other antibiotics** ?
- Can you obtain **MICs** and provide **interpretation** ?
- If used empirically, do you have plans for **de–escalation** ?
- Do you have an **Infection Control Plan** working ?