Bad Bugs ! Bad Drugs ?

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Contents of the presentation

- Bad bugs !
  - which ones ?
  - why ?
- Bad drugs ?
  - optimizing good drugs
  - rediscovering old drugs
  - what you can (or must) do in despaired situations
  - how to avoid despaired situations ?

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Bad bugs in Asia ?

International Journal of Antimicrobial Agents 37 (2011) 291–295

Review

High burden of antimicrobial resistance in Asia

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Gram-positive

- → ***Staphylococcus aureus***
- → ***Streptococcus pneumoniae***
- – ***Enterococci***

Gram-negative

- → **Extended-spectrum β-lactamase-producing and carbapenem-resistant *Enterobactriaceae***
- → ***Acinetobacter baumanii***
- – ***Pseudomonas aeruginosa***

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Bad bug #1: *S. aureus*

- ubiquitous organism but found mainly in skin, nostrils, perineal region…
  - presence and persistence in affected patients (carriers) enven in absence of lesions
- easily transmitted because of natural resistance to environment
  - hygienic measures are a must (hand washing, clean dressing, …)
- large genome that easily integrates and transmits cassettes carrying several resistance mechanisms
  - horizontal transfer of resistance
- clonal dispersion (with variations over time and regions)

S. aureus: the path to resistance

- **early 1940's**: selection of strains producing penicillinase … even before penicillin was ever employed at any large scale…

penicillin-binding proteins (PBSs) and penicillinases are closely-related enzymes probably deriving from a common ancestor

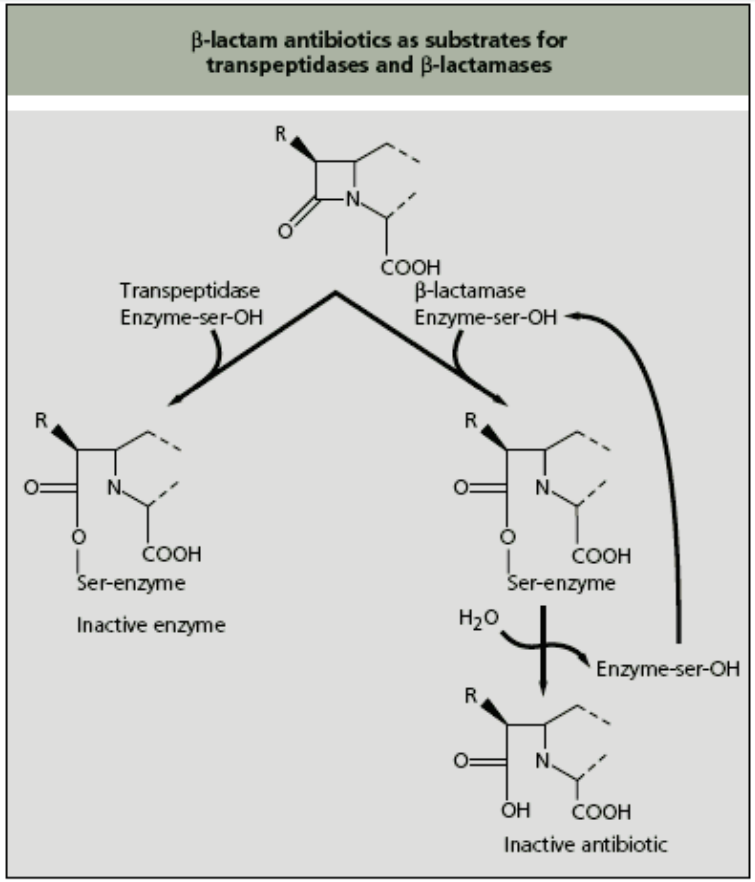


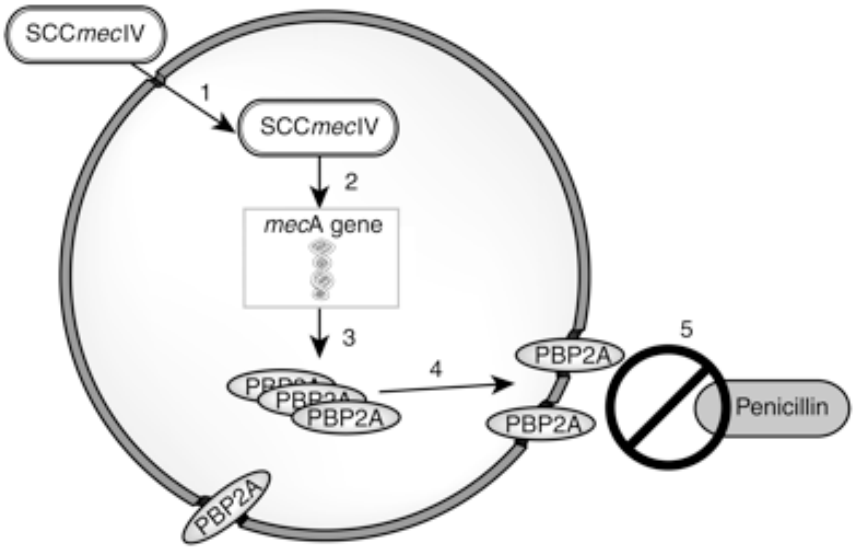
Fig. 130.3 β-Lactam antibiotics as substrates for transpeptidases and β-lactamases. The left part of the illustration shows how a β-lactam covalently binds to the transpeptidases. Hydrolysis of this acylated enzyme is very slow (one β-lactam per hour), making the enzyme inactive. The right part of the illustration shows that the same reaction occurs in the case of a β-lactamase. Hydrolysis of the acylated enzyme is, however, very rapid (1000 β-lactams per second), making the antibiotic inactive and regenerating the enzyme for a new cycle of hydrolysis.

Van Bambeke et al. *In:* Infectious Diseases, 3rd Edition, Eds: Cohen, Powderly & Opal - http://www.expertconsultbook.com

S. aureus: the path to resistance

- **mid 80's**: the rise of the MRSA…

Acquisition of a cassette a gene encoding for a a modified PBP (PBP 2a) that still works to form the peptidoglycan but is insensitive to all conventional β-lactams



Marcotte & A. Trzeciak 2008. J Am Acad Orthop Surg 16:98-106.

This cassette may carry other genes for resistance to other antibiotics → multiresistance

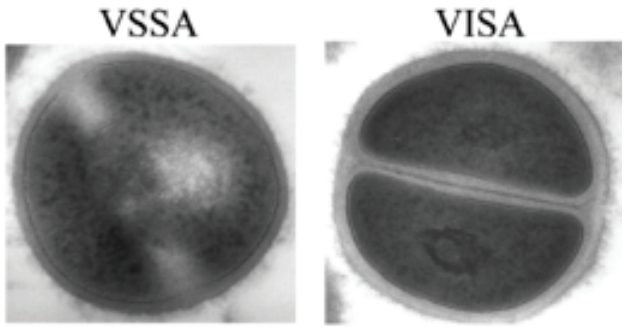
S. aureus: the path to resistance

- **early 2000's**: the rise of the VISA …

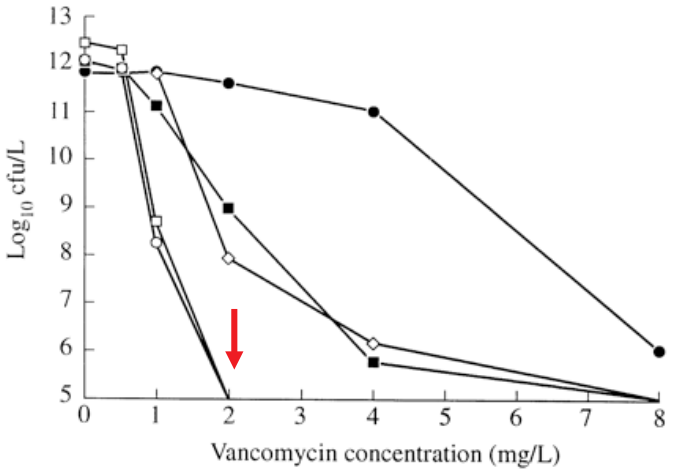
Thickening of the cell wall making vancomycin defeated by a too large abundance of its target (D-Ala-D-Ala)

Creates heteroresistance !

VISA is a misnamed acronym because these strains have MIC > 2 mg/L and should be considered as resistant (EUCAST) or to require high dosage of vancomycin (CLSI)



Howden B P et al. Clin. Microbiol. Rev. 2010;23:99-139

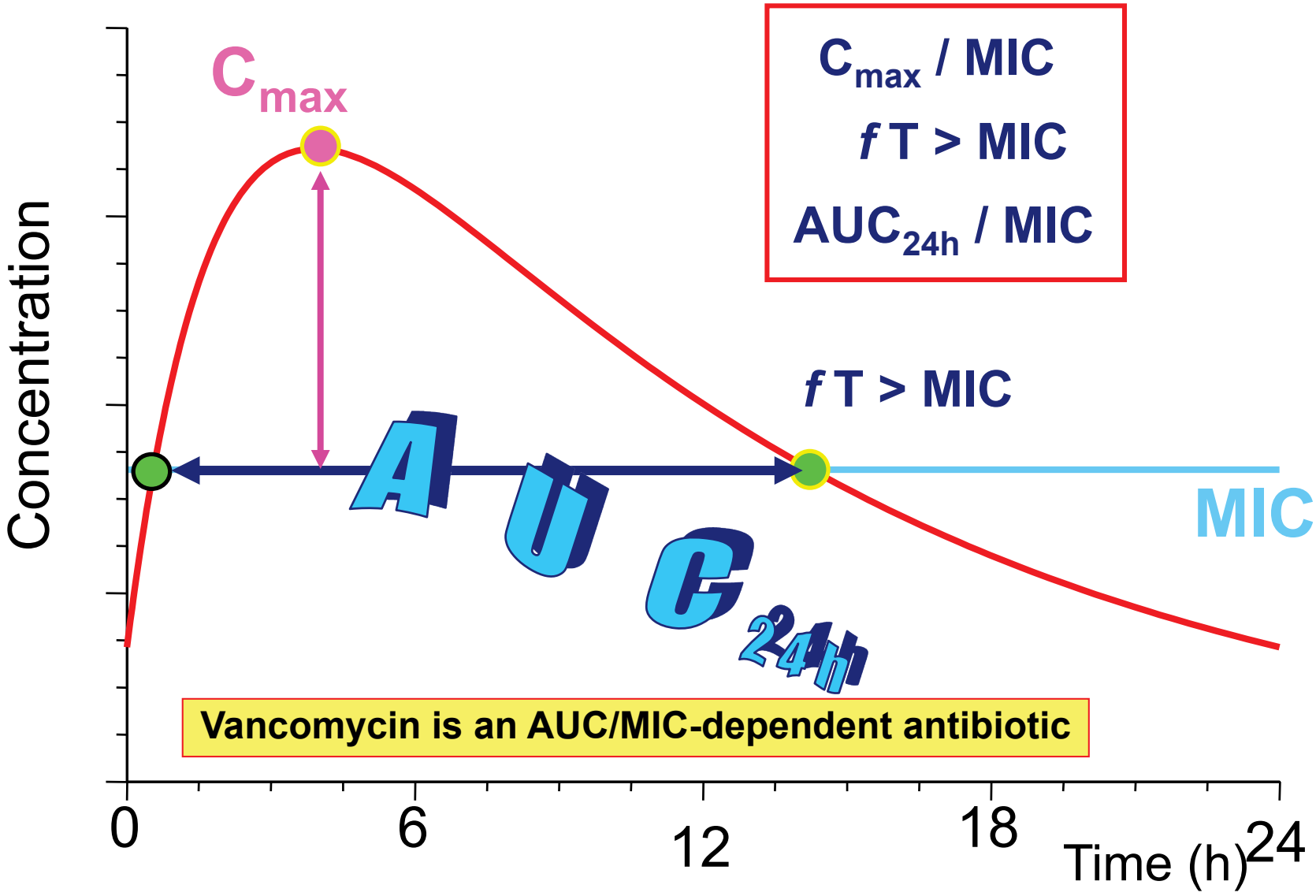


Howe et al. J. Antimicrob. Chemother. (2000) 45 (1): 130-131.

S. aureus: What should we do ?

- Penicillin-sensitive: do not exist anymore except in collection or rare cases …
- MSSA: use flucloxacillin, nafcillin, oxacillin … (more active than cephalosporins…)
- MRSA: vancomycin … at appropriate dosage and with surveillance of the MIC and monitoring (peak and through if possible) or by continuous infusion

Vancomycin: PK/PD



An early study of vancomycin by continuous infusion

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

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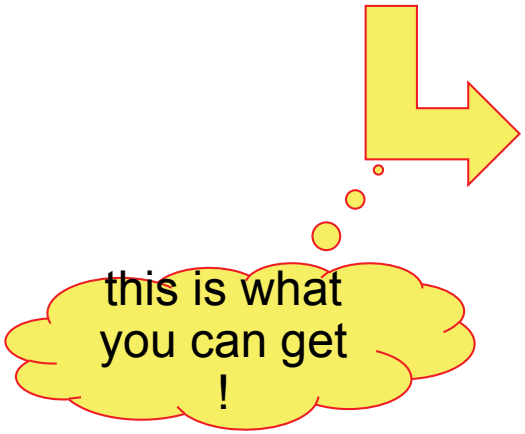
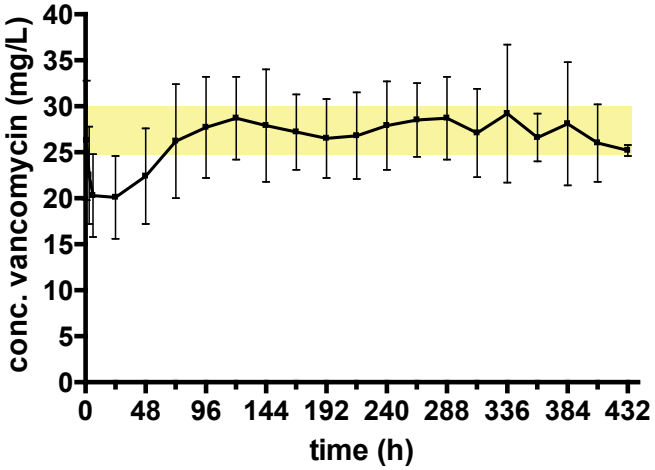
Received 28 June 2000/Returned for modification 2 January 2001/Accepted 5 June 2001

AAC 45:2460-2467, 2001

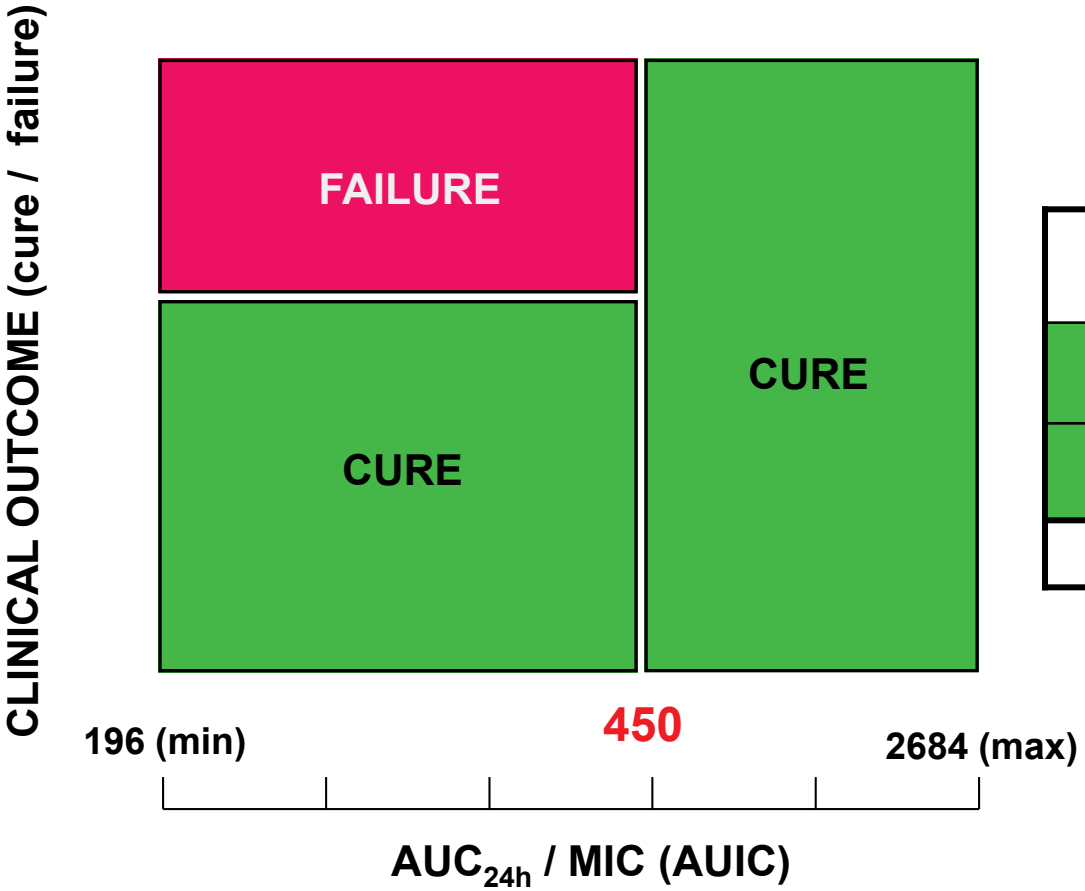




Ampe *et al.*, in preparation

And recent results …

Relation between AUC_{24h} / MIC (E-Test) and clinical efficacy (n=19)



AUIC < 450	
cure	failure
5/9	4/9
P < 0.05	

Ampe *et al.*, in preparation

S. aureus: when vancomycin fails ?

- VISA (and heterovisa):
  - useful drugs:
    - **linezolid:** effective but toxic > 10-14 days
    - **tigecycline:** effective so far …
      EUCAST breakpoint: S ≤0.5 – R > 0.5: close to the limit of the wild type population;
    - **ceftaroline** (FDA only so far; FDA break point: ≤ 1 mg/L [about 50 % strains with MIC > 1])

Tigecycline: MIC distributions, breakpoint and target attainment rate

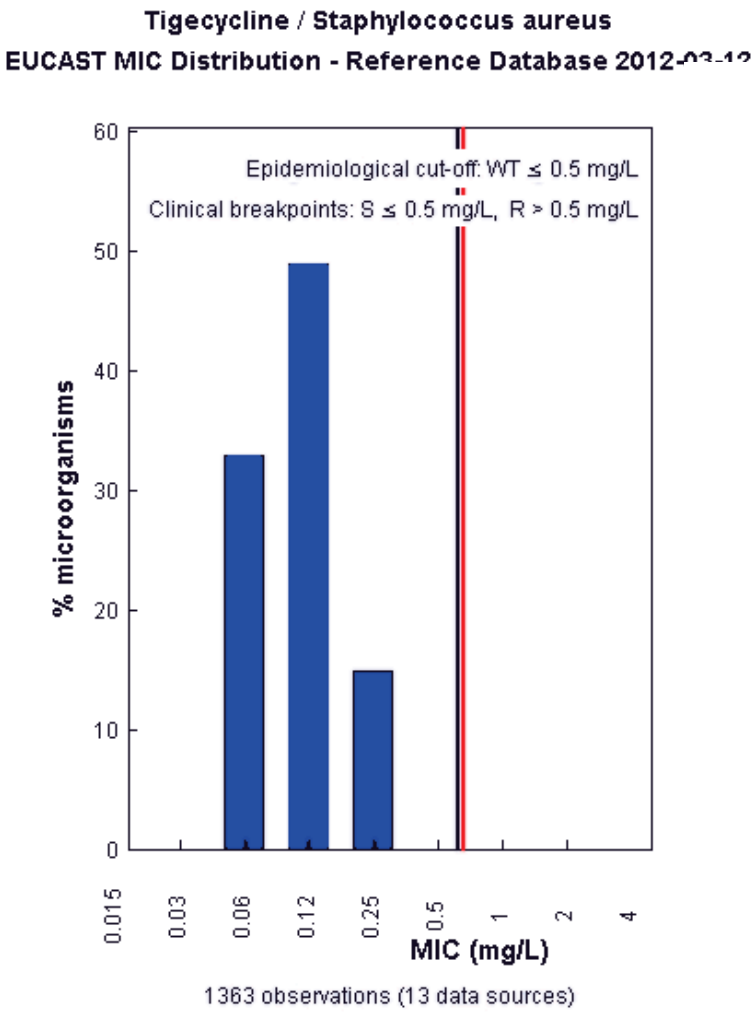
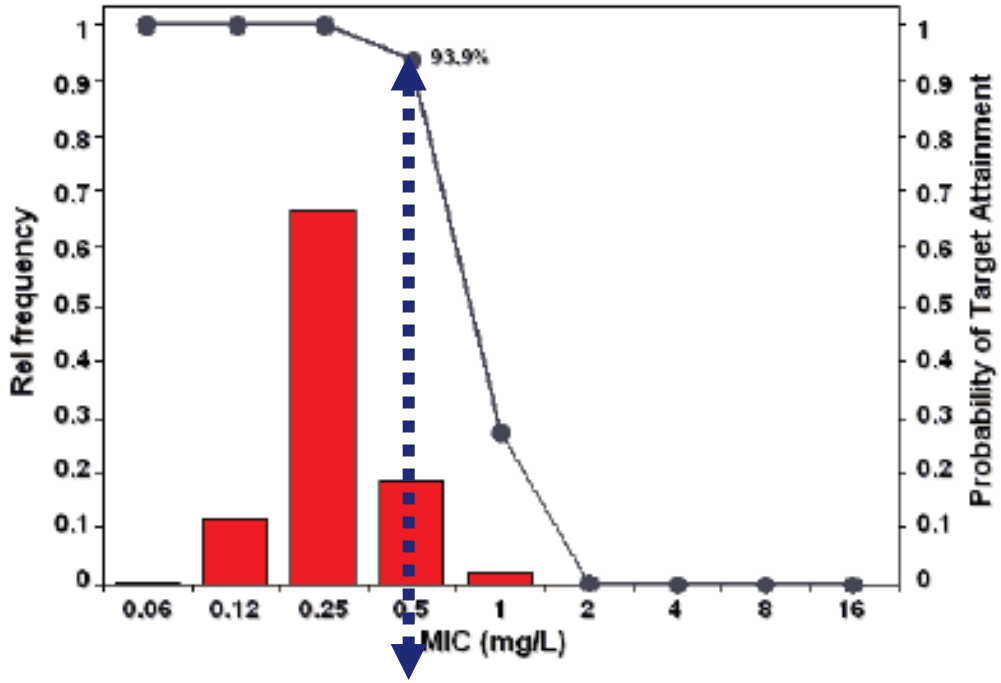


Figure 3. Probabilities of target attainment for tigecycline. Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file, Wyeth Inc.



an MIC = 0.5 is the limit for 90 % success !

EUCAST MIC distributions and rational documents: http://www.eucast.org

S. aureus: when vancomycin fails ?

- VISA (and heterovisa):
  - doubtful:
    - **daptomycin:** poor option (↗ MICs due to wall thickening)
      EUCAST breakpoints: S ≤ 1 / R > 1
      not for pneumonia (inactivation by surfactant)
    - **telavancin:** uncertain activity with VISA strains
      (in spite of a dual mode of action)
      EUCAST breakpoints: S ≤ 1 / R > 1
    - **quinuipristin/dalfopristin** (**SYNERCID®**)
      abandoned because of poor tolerance
      EUCAST breakpoints: S ≤ 1 / R > 2
      May be worthwhile to be revisited …

S. aureus: what is the pipeline ?

– abandoned, on hold, or under development

- oritavancin (did not pass the FDA; withdrawn from EMA)
- iclaprim (did not pass FDA; no future)
- ceftobiprole (passed neither FDA nor EMA; on hold)
- dalbavancin (abandoned by Pfizer; under development by Durata [phase III])
- fusidic acid (for USA): in development by Cempra
- radezolid / tedizolid: in development (Sanofi / Bayer)

Note about fluroquinolones

- **ciprofloxacin is not a real option against MRSA because of target mutations and efflux…**
- **moxifloxacin is active against MSSA but has no indication for MRSA (buts is active against strains with an MIC < 1**
- **several new anti-MRSA fluoro quinolones are under development**

Bad bug #2: *S. pneumoniae*

The rates of penicillin resistance amongst clinical *S. pneumoniae* strains are 71.4% in Vietnam, 68.8% in Thailand, 54.8% in Korea, 43.2% in Hong Kong and 38.6% in Taiwan [5,30].

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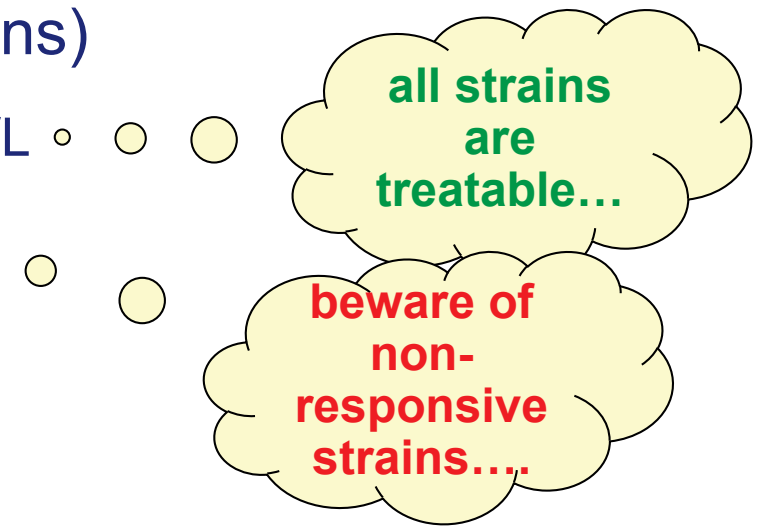
- Only found in humans … (reservoir: children…)
- No production of β-lactamases
- Was susceptible to β-lactams until the mid 70's
- Showed point mutations (mosaic gene) that made PBP's partially and progressively less susceptible to β-lactams
- Developed mutations for resistance (high level) to macrolides and poorly active fluroquinolones (ciprofloxacin)
- Developed efflux against macrolides (especially in North America) and fluroquinolones (ciprofloxacin)

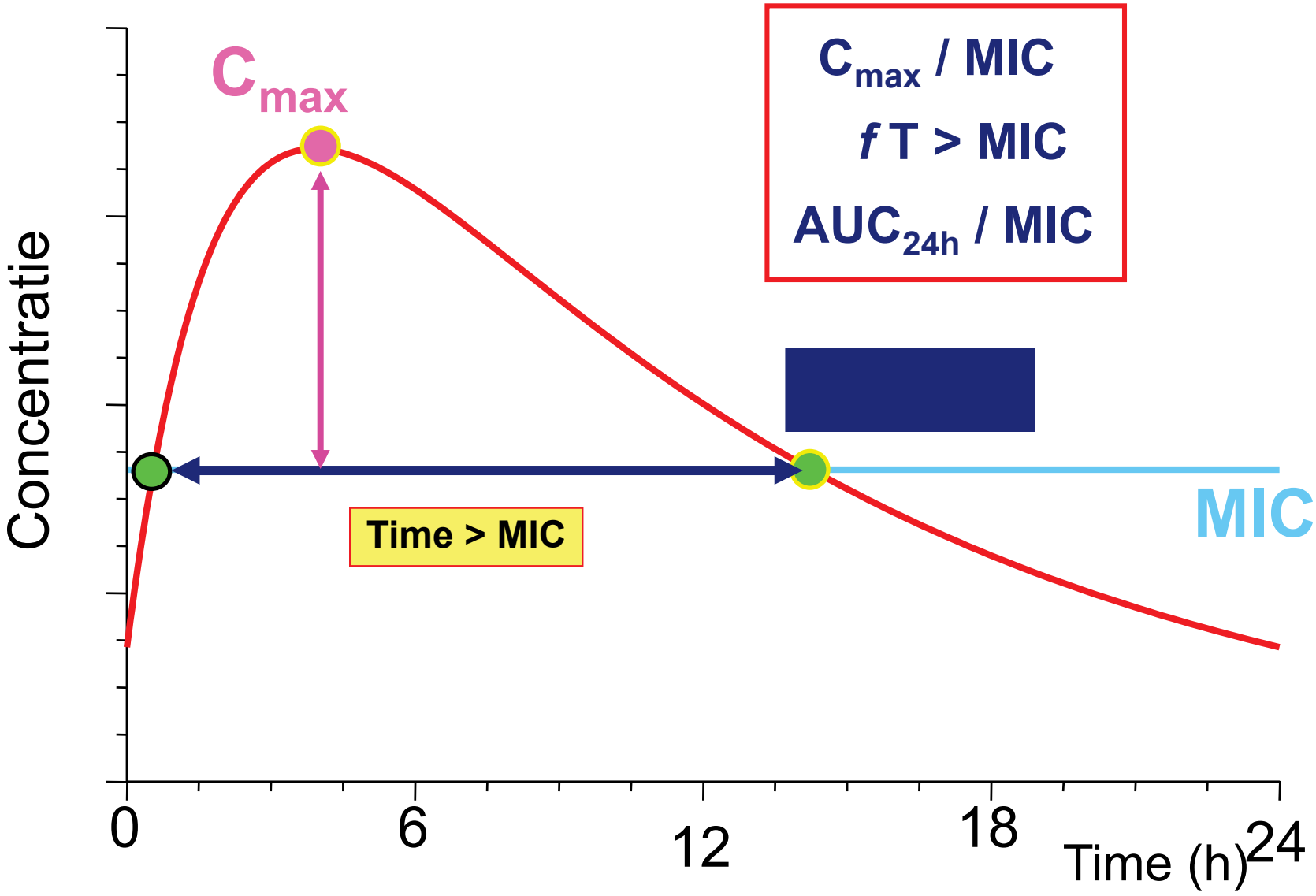
S. pneumoniae: experts' fights

- Resistance to penicillin:
  - "Mosaic gene"-related resistance has created strains
    - with reduced susceptibility (still "treatable" with high doses of pencillin
    - with "full resistance" (no more "treatable")

- CLSI and EUCAST diverge markedly on penicillin breakpoints (for systemic infections)
  - CSLI: S: ≤ 2 -- I: 4 to 8 – R: > 8 mg/L
  - EUCAST: S ≤ 0.06 - R > 2 mg/L



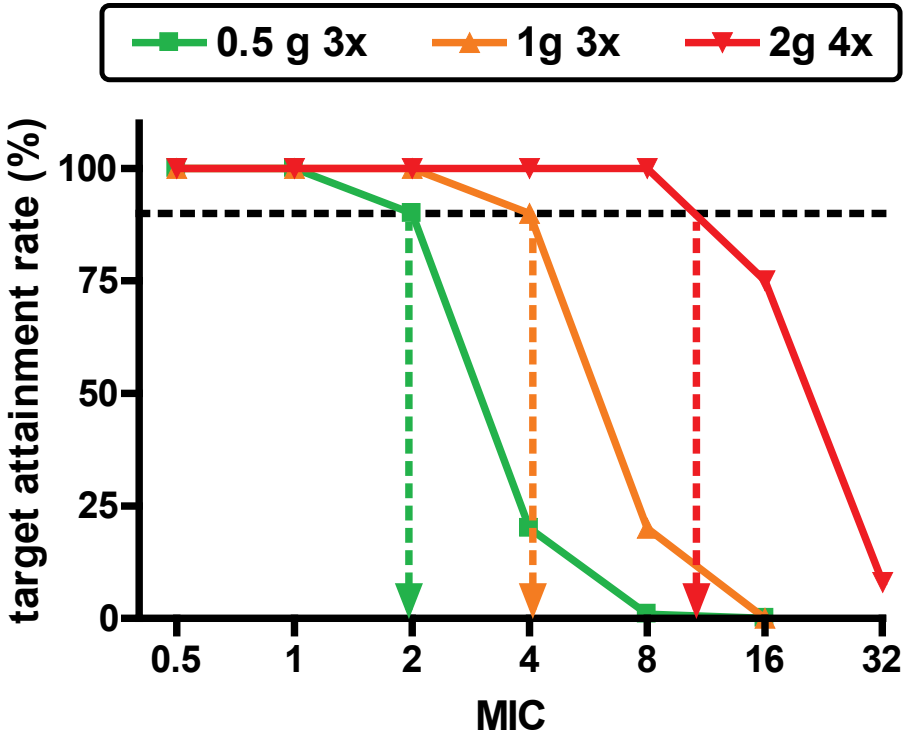
Penicillins PK/PD (all β-lactams)



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

EUCAST

Amoxicillin EUCAST rationale document: Target attainment rate*



* for *f* T >MIC = 40%

Depending on the dose and schedule, you may cover bacteria with MIC from 0.5 to 8 mg/L

Graph prepared from data in http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Amoxicillin_rationale_Nov2010_v_1.0.pdf

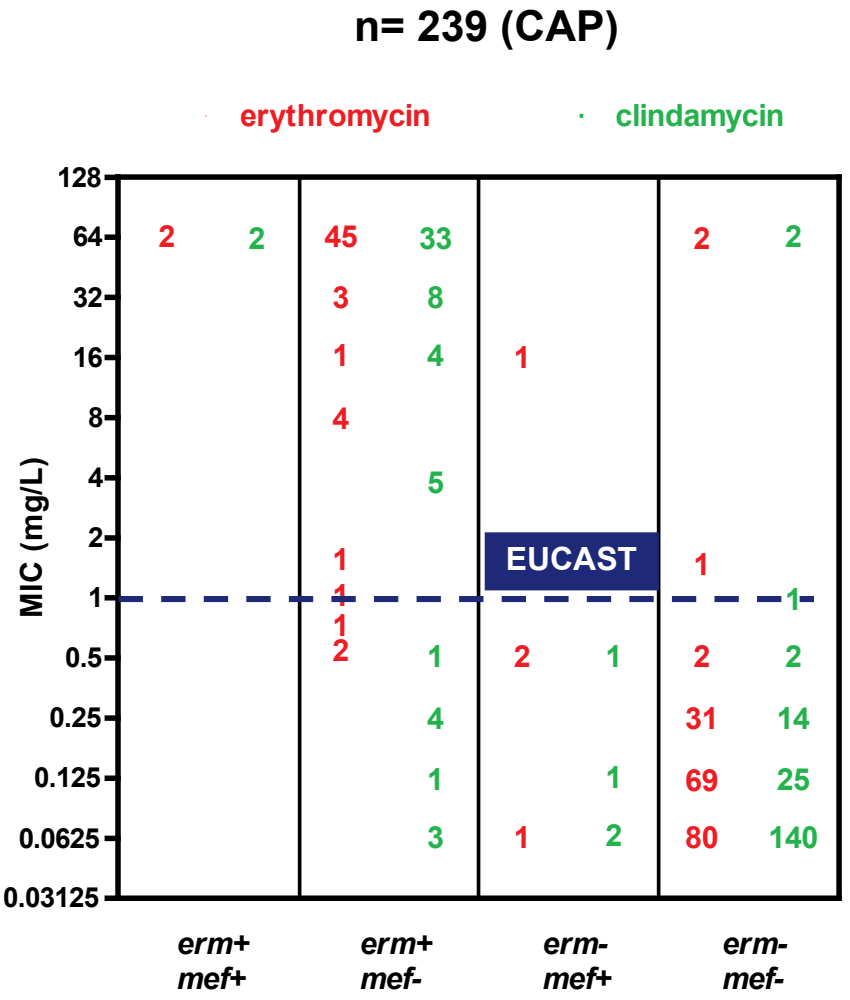
S. pneumoniae and macrolides

- North America and Europe diverge markedly on the use of macrolides…

➢ prevalent resistance mechanism is

  – efflux in NA
    → considered as still treatable because of high tissue accumulation
    (but EUCAST : R > 0.5-1 mg/L)

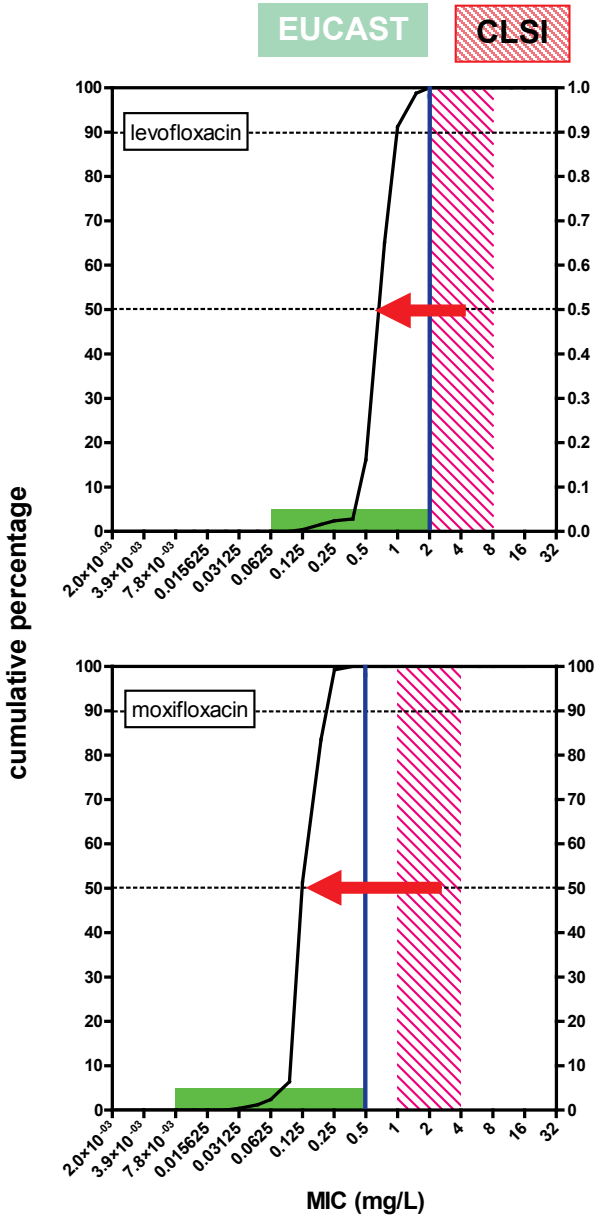
  – mutation in Europe: all strains with high MICs



Lismond et al. Intern. J. Antimicrob. Agents (2012) 39:208– 216

S. pneumonia and fluroquinolones

- North America and Europe diverge markedly on the use "respiratory" fluoroquinolones (levofloxacin / moxifloxacin)
  - North America: "use it when needed"
  - Europe: avoid because of risk of resistance but if you need them, use
    - levofloxacin at a high dose (2 x 500 mg)
    - moxifloxacin at its normal dose (1 x 400 mg)



Lismond et al. Intern. J. Antimicrob. Agents (2012) 39:208– 21

S. pneumoniae: what do you need to do ?

- Amoxicillin at large dose (3 x 2 g) will cover to MICs of 2-4 mg/L (non meningitis)
  MIC > 4 mg/L is definitely hazardous according to EUCAST
- Penicillin can be used up to 12 g (6 x 2 g) for organisms with an MIC = 8 according to CLSI …but is cumbersome
- Macrolides should only be used if epidemiology confirms susceptibility (< 20 % strains with MIC < 2 mg/L [EUCAST])
  … and keep an eye on failures
- Moxifloxacin: use 400 mg … and maintain epidemiological surveillance (no MIC increase in Europe, but …)

  Never use ciprofloxacin !!

  gemiflloxacin could be an alternative (no EU experience)

Van Bambeke F, Reinert RR, AppelbaumPC, Tulkens PM, Peetermans WE
Multidrug-Resistant Streptococcus pneumoniae infections: current and future therapeutic options.
Drugs (2007) 67:2355-2382

S. pneumoniae: when everything seems to fail ?

- **linezolid** (reference drug in some countries)
  MIC range: 1 – 4 mg/L
  EUCAST breakpoint: R > 4 mg/L
  600 mg 2 x /day
  toxicity > 10-14 days
- **carbapenems** (imipenem – meropenem – ertapenem – doripenem)
  MIC range: 0.008 – 0.12 … 0.5 …
  EUCAST breakpoints: 2/2 – 2/2 – 0.5/0.5 – 1/1
  Major risk of triggering resistance of Gram (-)

Table 1 Comparison of minimum inhibitory concentration (MIC) range, MIC_{50}, and MIC_{90} of meropenem, other β-lactams, aminoglycosides, and other antibiotics against five major species of respiratory pathogens isolated in 2007

Organism (no. tested)	Drugs[a]	MIC (μg/ml)		
		Range	50%	90%
Streptococcus pneumoniae (PSSP[a]) (29)	Meropenem	≤0.015–0.25	≤0.015	0.06
	Imipenem	≤0.015–0.06	≤0.015	0.03
	Panipenem	≤0.015–0.03	≤0.015	0.03
	Biapenem	≤0.015–0.12	≤0.015	0.03
	Doripenem	≤0.015–0.12	≤0.015	0.03

Gomi et al. J Infect Chemother. 2011 Apr;17(2):200-6

S. pneumoniae: be careful with carbapenems…

The limits of doripenem in France …

Table 1 Antimicrobial activity of doripenem against Gram-positive microorganisms (572 isolates)

Organism (no. tested)	MIC (mg/L)			
	50%	90%	Range	% susceptible[a]
Staphylococcus aureus (173)				–
OXA S (90)	0.03	0.25	≤0.008–0.5	
OXA R (83)	1	2	0.03–16	
Coagulase-negative staphylococci (104)				–
OXA S (50)	0.03	0.12	≤0.008–0.12	
OXA R (54)	2	8	0.25–64	
Enterococcus faecalis (63)	2	4	0.06–8	–
Enterococcus faecium (40)	128	>128	4–>128	–
Streptococcus pneumoniae (83)				83.0
PEN S (48)	≤0.008	0.03	≤0.008–0.25	
PEN I+R (35)	0.25	0.5	≤0.008–1	
Streptococci A, B, C, and G (60)	≤0.008	≤0.008	≤0.008–0.03	96.6
Other streptococci (49)	0.016	2	≤0.008–4	86.3

OXA: oxacillin; PEN: penicillin; S: susceptible; R: resistant; I + R: intermediate + resistant

[a] Determination of doripenem susceptibility according to EUCAST MIC breakpoints (not available for staphylococci and enterococci, ≤1 mg/L for streptococci)

Lascols et al. Eur J Clin Microbiol Infect Dis. 2011 Apr;30(4):475-82.

S. pneumoniae: the current pipeline…

- **ceftaroline:** very low MICs but approved only in the US so far (FDA breakpoint for CAPB: ≤ 0.25; for skin: ≤ 0.015)

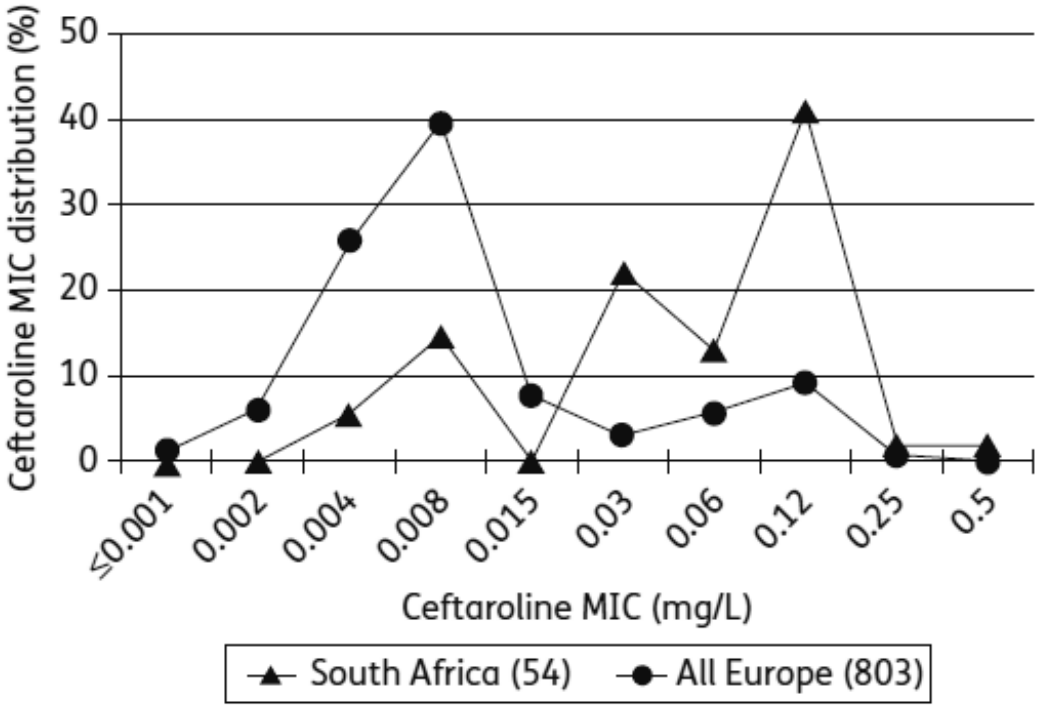


Figure 1. MIC distribution of ceftaroline for *S. pneumoniae* from combined European countries and South Africa.

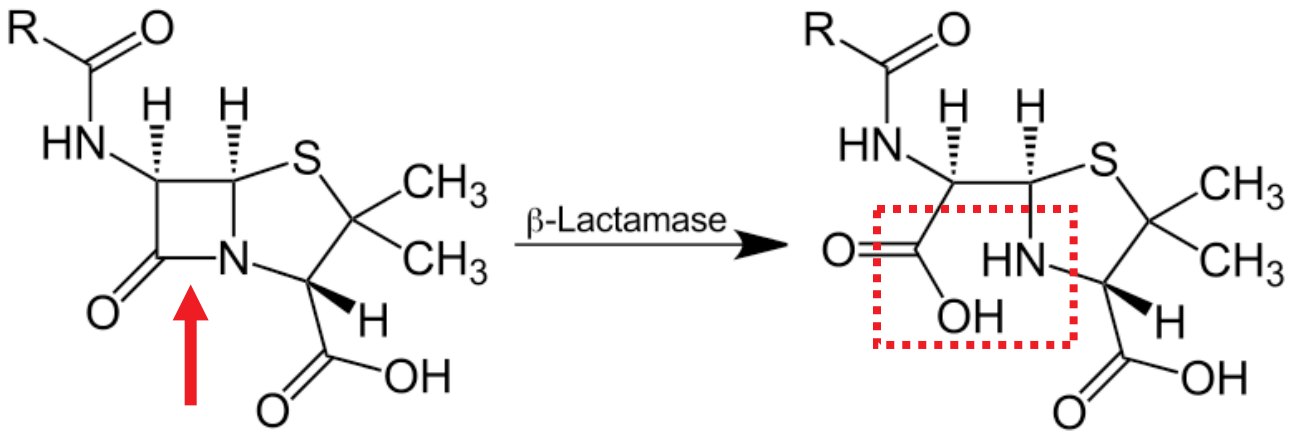
Morrissey & Leakey A. J Antimicrob Chemother. 2012 Feb 22.

Bad bug #3: *Enterobactereriaceae*

- Always pathogenic:
  Salmonella typhi, Shigella dysenteriae, Yersinia pestis …
- Opportunistic pathogens:
  Escherichia coli , *Klebsiella pneumoniae*…
- Naturally resistant to anti-Gram positive agents:
  Penicillin and several β-lactams (check !), macrolides, linezolid …
- Acquired resistance:
  - β-lactams → β-lactamases / enlarged spectrum β-lactamases / porins / efflux
  - aminoglycosides: enzymes / efflux
  - fluroquinolones: enzymes / efflux

β-lactams ?

- β-lactamases open the β-lactam ring of β-lactams and inactivate them …



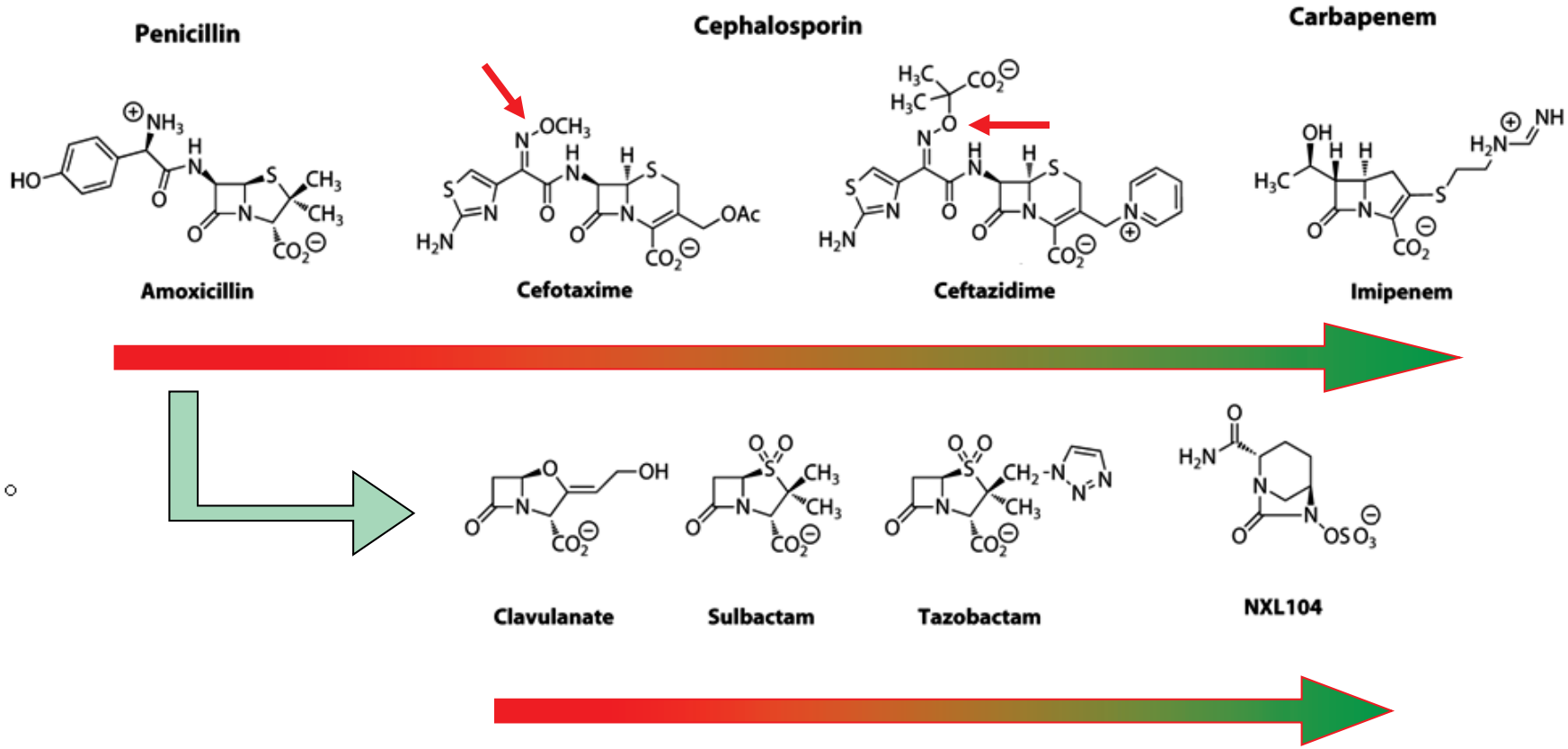
- **This potentially affects all penicillins, cephalosporins, and carbapenems if not built to resist to β-lactamases**
- **β-lactamases are related tp PBP's … explaining why they arose so quickly…**

ESBL ?

- β-lactamases attacked penicillins …
- Chemists reacted by making / selecting
  - β-lactamase-resistant penicillins and cephalosporins
  - inhibitors of β-lactamases (clavulanic acid, sulbactam, tazobactam
- β-lactamases counter-attacked by small structure modifications allowing them
  - to destroy β-lactamase-resistant penicillins and cephalosporins
  - to resist β-lactamase inhibitors

→ **Extended spectrum β-lactamases**

The race for novel β-lactams and novel β-lactamase inhibitors …



Modified from Bush & Fisher, Annu. Rev. Microbiol. 2011. 65:455–78

Definition of an Extended-spectrum β-lactamase (ESBL)

- originally a β-lactamase that hydrolyzes oxyiminocephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) and monobactams (aztreonam) in addition to penicillins and early cephalosporins and that is inhibited by clavulanic acid or tazobactam
  - indicates that carbapenems are still active …
  - **BUT** does not guarantee that clavulanic acid or tazobactam will be effective (poor inhibition of many AmpC and of all class D enzymes)

- may now include carbapenemases …
  (proposed by EU investigators but may confuse the issues according to US investigators)…

Carbapenemases

Class A and class C
(serine β-lactamases)

1. emerged in 1990's and first identified in *Klebseille pneumoniae* in the northeastern United States (→ KPC)
2. Today, includes > 10 unique KPC amino acid sequences and 17 unique GES variants spread throughout the world in both fermentative and nonfermentative bacteria (*Enterobacteriaceae*, *Acinetobacter* spp., and *P. aeruginosa)*
3. Isolates treatable by only colistin/polymyxins, and possibly tigecycline.

Class of Metallo-β-Lactamases

1. thrive globally in the clinical environment, with outbreaks of VIM and IMP-producing pathogens reported throughout Europe and the Asia-Pacific region
2. include the famous NDM-1 (New Delhi metallo-β-lactamase)
3. Isolates treatable by only a very few antibiotics.

Increase in the number of β-lactamases

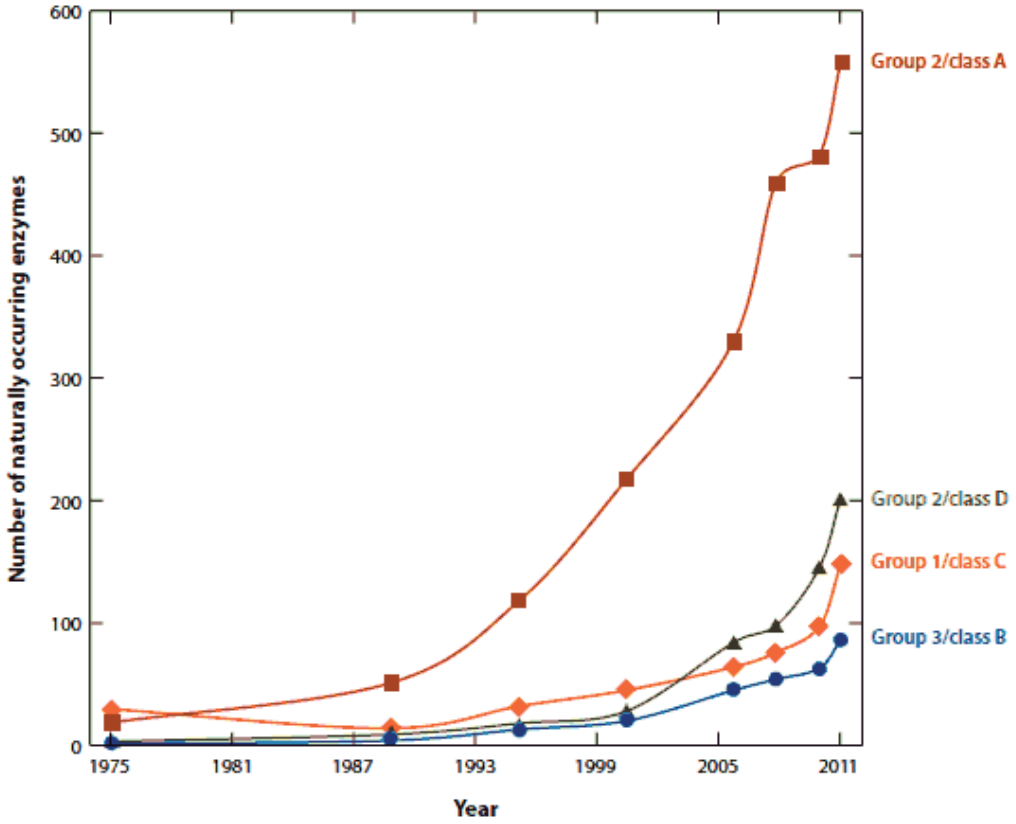


Figure 2

The number of naturally occurring β-lactamases identified from the main functional groups and molecular classes as indicated by the year in which the structures were provided to the curators of the β-lactamase Web site (46), or by the year in which the enzymes were reported in the literature (12), adapted with permission (copyright © American Society for Microbiology, 2010).

More than 1,000 naturally occurring β-lactamases have been identified, frequently as the result of the facile transfer of mobile elements from one Gram-negative organism to another

Most common (acquired):

- the AmpC cephalosporinases (CMY family),
- the ESBL CTX-M-14 and CTX-M-15 enzymes,
- the serine carbapenemases (KPCenzymes),
- the metallo-β-lactamases (NDM-1, VIM, and IMP families).

Bush & Fisher, Annu. Rev. Microbiol. 2011. 65:455–78

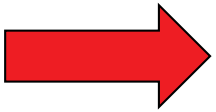
Why do β-lactamases also "cause" resistance to other antibiotics : a bacteria / doctor cooperation !

Bacteria:

The genetic elements that encode acquired β-lactamases are often associated with mobilizable resistance factors responsible for decreased susceptibility to other antibiotics (aminoglycosides, tetracyclines, and fluoroquinolones (c-resistance) …

Doctors:

Because physicians have relied heavily on cephalosporins, β-lactamase inhibitor combinations, and carbapenems, they selected strains with ESBL … and resistance to the other agents as well…



therapeutic vacuum ….

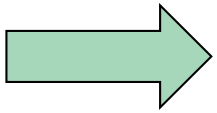
Where do ESBL come from ?

- β-Lactamase-producing organisms from other aquatic sources including rivers, lakes, and wastewater streams have been reported from Brazil and China
- In Italy, the novel IMP-22 MBL was identified from an isolate collected upstream from the city sewage treatment plant (96).
- The Seine River in Paris has provided a rich source of β-lactamases.

ESBL-Treatment bases: 1. finding inhibitors

- Effective therapy must include, if possible, agents that can treat organisms producing both serine and metallo-β-lactamases;
- Methodology relying upon synergistic activity between a key substrate and a selective inhibitor in broth dilution, disk diffusion, or commercial systems now exists to detect organisms with acquired β-lactamases, including AmpC, ESBLs, MBLs.

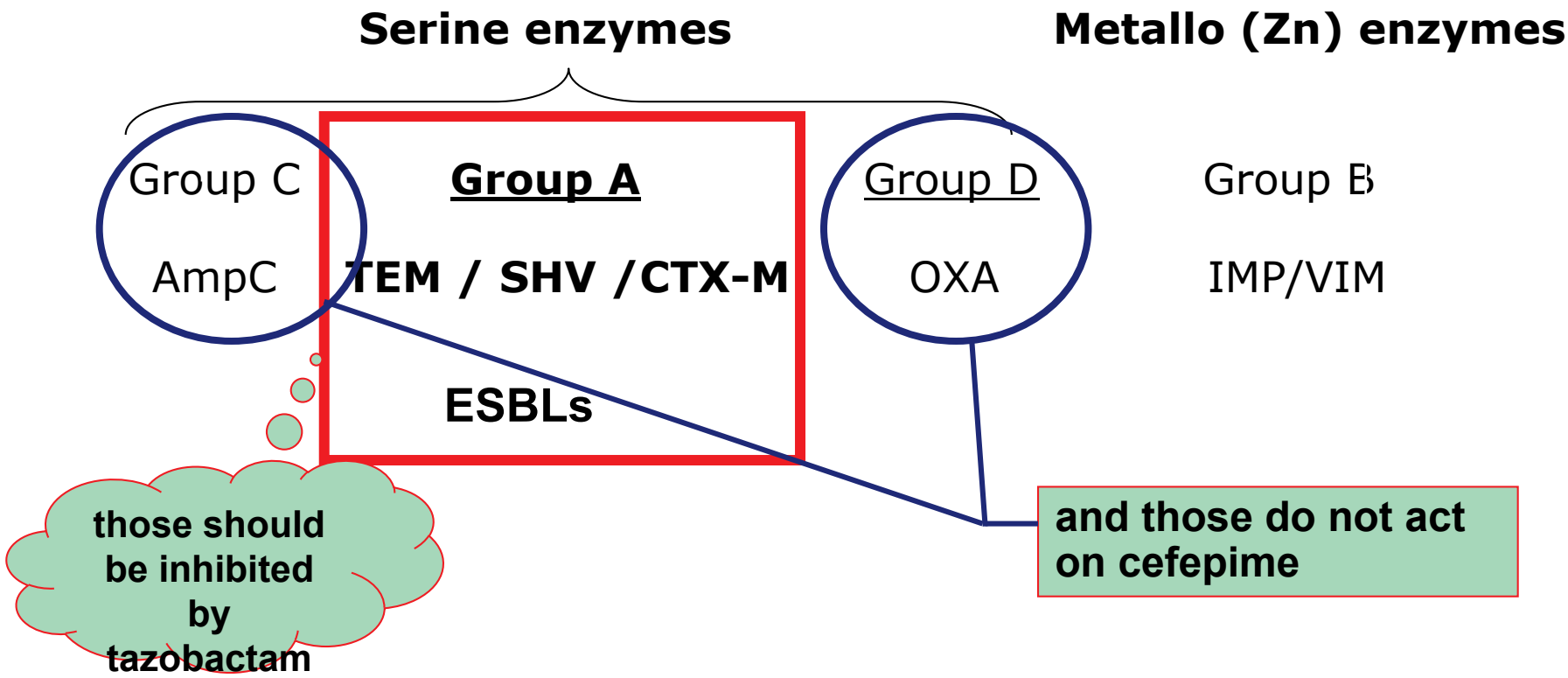
Many organisms now produce multiple β-lactamases from different functional groups…



You may need to test for "local" combinations that may work in your environment

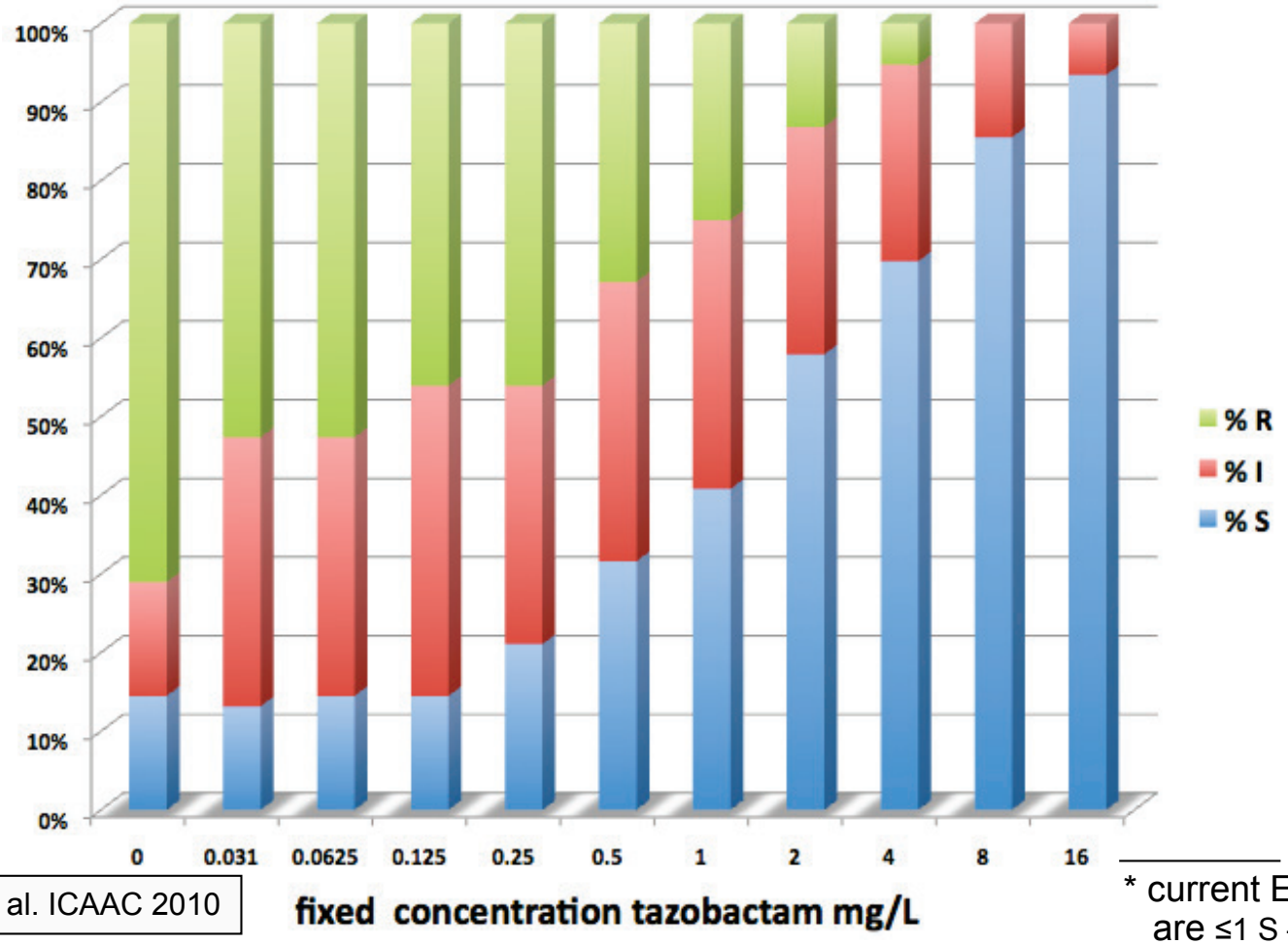
Customizing Inhibitors: an example from India

Beta-lactamases: Classification



Combining tazobactam with cefepime…

Percentage sensitive(S), intermediate(I) and resistant(R) ESBL + K. *pneumoniae* to cefepime (2010 EUCAST breakpoints : ≤1 S – R >8) *

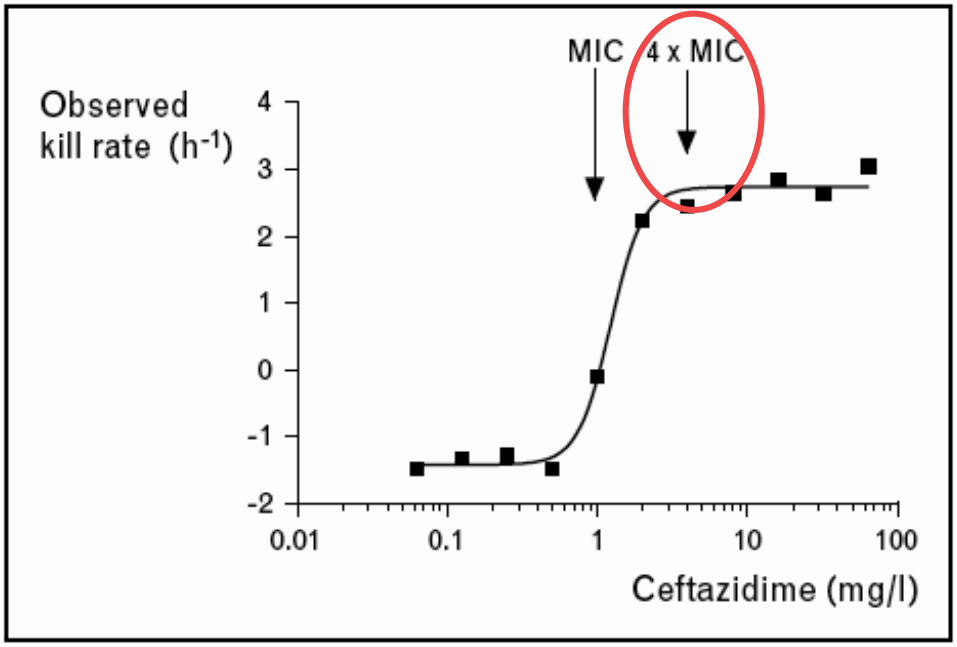


Mouton et al. ICAAC 2010

* current EUCAST bkpts are ≤1 S – R >4

ESBL-Treatment bases: 2: use high doses or even continuous infusion …

Figure 2 Relationship between concentration of ceftazidime and kill rate



The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

Mouton JW, Vinks AA. Curr Opin Crit Care. 2007 Oct;13(5):598-606.

Continuous infusion of β-lactams: an overview…

International Journal of Antimicrobial Agents 30 (2007) 11–18

Review

Continuous infusion of β-lactam antibiotics in severe infections: a review of its role

Jason A. Roberts [a,b], Jennifer Paratz [a,b], Elizabeth Paratz [a], Wolfgang A. Krueger [c], Jeffrey Lipman [a,b,*]

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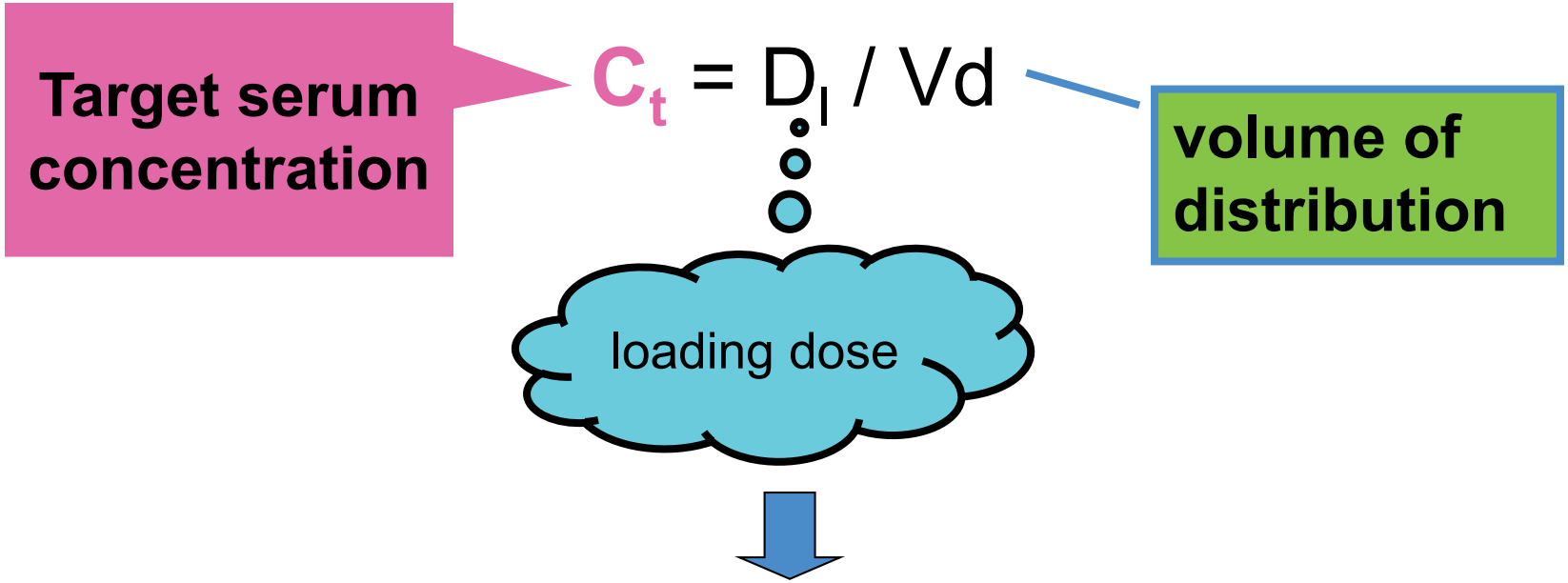
Received 16 January 2007; accepted 23 January 2007

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 *



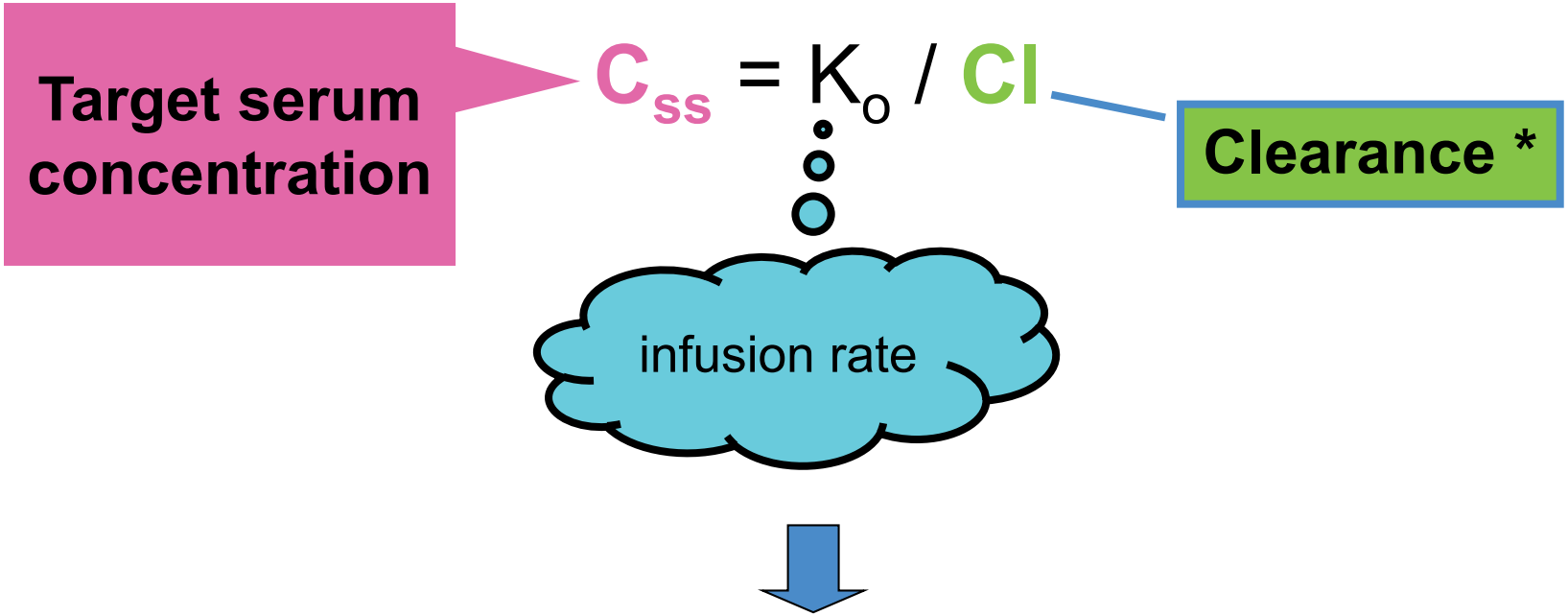
loading dose (in mg) = C_t (mg/L) x **Vd** (L)

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 2: infusion *

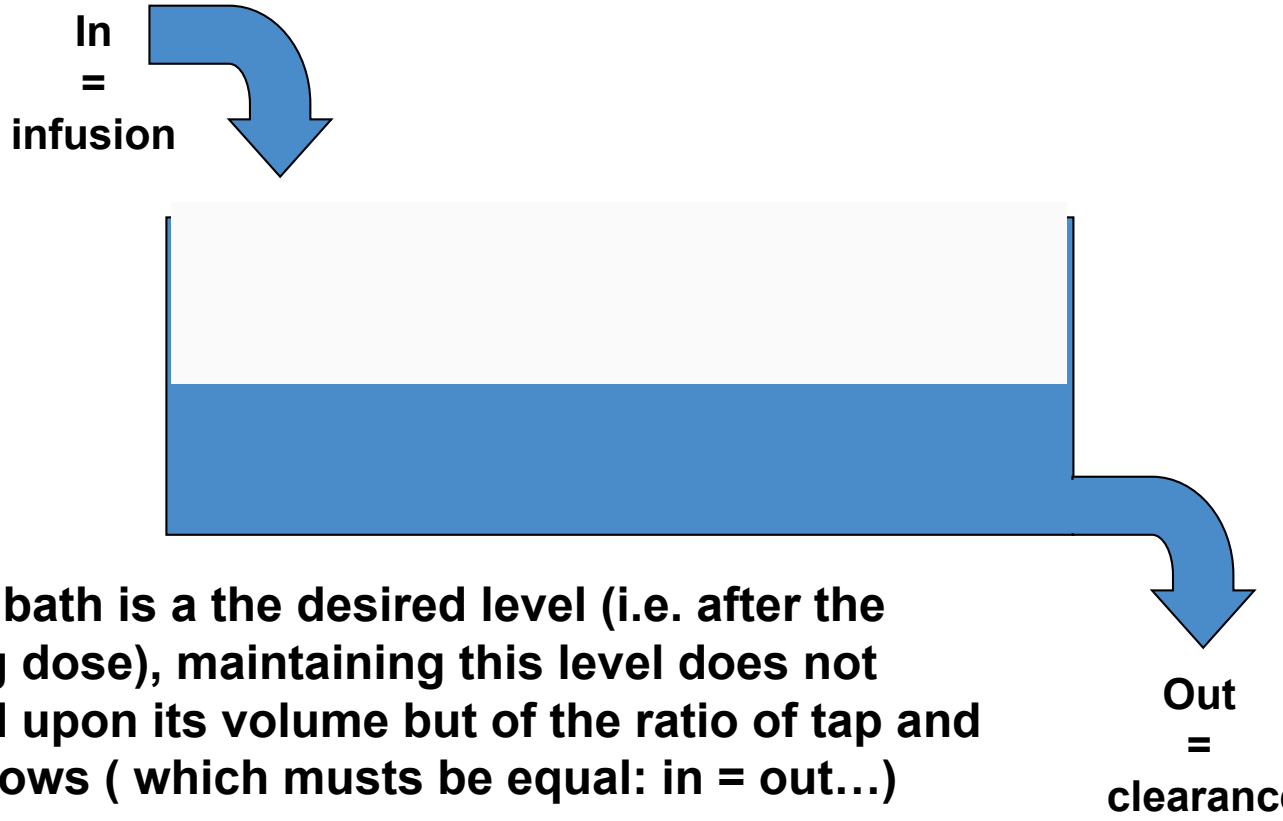


daily dose (in mg) = 24 x **clearance** (L/h) x **Css**

*** 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 2: infusion



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 musts be equal: in = out…)

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

ESBL-Treatment bases: 3. other antibiotics

- fluoroquinolones ? → often resistant (efflux / mutations)
- amikacin ? → inactivating enzymes and efflux
- fosfomycin ?
- colistin ?

Fosfomycin ?

- bactericidal antibiotic that interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase;
- must enter bacteria by transport uptake systems;
- very high breakpoints (EUCAST: R > 32 mg/L) → **high doses !** …
- good activity against *Enteriobacteriacaeae* … but poor against *A. baumanii* and *P. aeruginosa*;
- time-dependent killing → **frequent dosing !** …
- must be administered with another agent to prevent emergence of resistance…

→ **daily dose of 12 to 16 g administered in 2–4 infusions**

Fosfomycin clinical evidence

Table 1
Studies dealing with the curative use of fosfomycin in adult patients (intravenous administration)

Study	Patients (*n*)	Age, mean years	Pathogens	Infection	Combination therapy	Mortality (%)
Alvarez et al.[71]	1	-	*Serratia marcescens*	Endophthalmitis	Ceftriaxone + amikacin	0
Boulard et al.[72]	4	-	*Staphylococcus epidermidis*	CSF shunt infection	Aminoglycoside	0
Bureau-Chalot et al.[73]	1	-	*Stomatococcus mucilaginosus*	Spondylodiscitis	Cefotaxime	0
Florent et al.[70]	72	55	Multiple	Multiple	Multiple	13
Gillard et al.[74]	8	-	-	Pyogenic discitis	Quinolone[a]	0
Guerin et al.[75]	1	46	*Pseudomonas aeruginosa*	Prostatitis	Aztreonam	0
May et al.[76]	7	-	Multiple	Meningitis	Ceftriaxone	-
Meissner et al.[69]	60	37.4	Multiple	Chronic osteomyelitis	No combination therapy	26.4
Michalopoulos et al.[65]	11	67.5	MDR *Klebsiella pneumoniae*	ICU-acquired infection	Multiple	18.2
Mirakhur et al.[33]	15	23	*Pseudomonas aeruginosa*	Cystic fibrosis	Multiple	0
Nakayama et al.[77]	1	64	MRSA	Toxic shock syndrome	Vancomycin	0
Nissen et al.[78]	17	-	Multiple	Pneumonia	Ampicillin	6
Ortler et al.[79]	1	35	*Staphylococcus aureus*	Wound infection	Cefmenoxime	0
Portier et al.[80]	16	-	MRSA	Bacteremia; bone/ joint infection/meningitis	Cefotaxime	0
Roualdes et al.[81]	2	-	*Staphylococcus epidermidis*, *Staphylococcus capitis*, *Micrococcus varians*	CSF shunt infection	Vancomycin, rifampin	0
Silbermann et al.[82]	1	17	*Staphylococcus epidermidis*	Meningitis	Vancomycin	0
Ueda et al.[83]	65	-	Multiple	Multiple	0	46.1
Yamaguchi et al.[66]	1	64	MRSA	Pneumonia and sepsis	Arbekacin	0
Zink et al.[84]	1	81	*Staphylococcus albus*	Ventriculoatrial shunt meningitis	Gentamicin	0

[a] Eighteen patients received usually a fluoroquinolone with a beta-lactam or fosfomycin.

Michalopoulos et al. Int. J. Infect. Dis.15 (2011) e732–e739

Bad bug #4: *Acinetobacter baumanii*

CLINICAL MICROBIOLOGY REVIEWS, July 2008, p. 538–582 Vol. 21, No. 3
0893-8512/08/$08.00+0 doi:10.1128/CMR.00058-07

Acinetobacter baumannii: Emergence of a Successful Pathogen

Anton Y. Peleg,[1]* Harald Seifert,[2] and David L. Paterson[3,4,5]

Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts[1]; Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Goldenfelsstrasse 19-21, 50935 Cologne, Germany[2]; University of Queensland, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia[3]; Pathology Queensland, Brisbane, Queensland, Australia[4]; and Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania[5]

- A primary factor in the recent emergence of *Acinetobacter* spp. as a major Gram-negative pathogen is its expression of broad spectrum class D and class B β-lactamases (same situation as in *P. aeruginosa)*
- in addition, decreased porin permeability and efflux transporters allow to attain carbapenem resistance.

Acinetobacter baumanii: resistance mechanisms

TABLE 2. Mechanisms of resistance in *Acinetobacter baumannii*

Antimicrobial class and resistance mechanism	Enzyme(s)[a]	Reference(s)
β-Lactams		
β-Lactamases	TEM	148, 387
	SHV	248, 387
	ADCs	49, 249, 250, 427, 468
	VEB	71, 381, 382, 417, 442
	PER	250, 381, 385, 417, 439, 565, 611
	CTX-M	76, 386
	OXA	This study
	IMP	89, 104, 113, 179, 246, 265, 298, 316, 402, 471, 506, 530, 544, 618
	VIM	316, 335, 551, 606, 615
	SIM	320
OMPs	CarO (29 kDa)	336, 380, 511
	47-, 44-, and 37-kDa OMPs	446
	22- and 33-kDa OMPs	47
	HMP-AB	209
	33- to 36-kDa OMPs	94, 119
	43-kDa OMP	141
	OmpW	510
Efflux	AdeABC	232, 236, 347, 420
Altered penicillin-binding proteins	Altered penicillin-binding proteins	165, 188, 405, 510
Aminoglycosides		
Aminoglycoside-modifying enzymes	Acetyltransferases, nucleotidyltransferases, phosphotransferases	246, 250, 320, 395, 458, 503, 551, 556, 618
Ribosomal (16S rRNA) methylation		129, 314, 608
Efflux	AdeABC	347
	AdeM	525
Quinolones		
Modification to target binding site	GyrA, ParC	220, 236, 504, 581, 582
Efflux	AdeABC	236, 347
	AdeM	525
Tetracyclines and glycylcyclines		
Tetracycline-specific efflux	Tet(A), Tet(B)	217, 455, 457
Ribosomal protection	Tet(M)	457
Multidrug efflux	AdeABC	347, 420, 469

[a] ADCs, *Acinetobacter*-derived cephalosporinases; HMP-AB, heat-modifiable protein in *Acinetobacter baumannii*.

Peleg et al. Acinetobacter baumannii: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538–82.

Acinetobacter: a US overview (with EUCAST breakpoints)

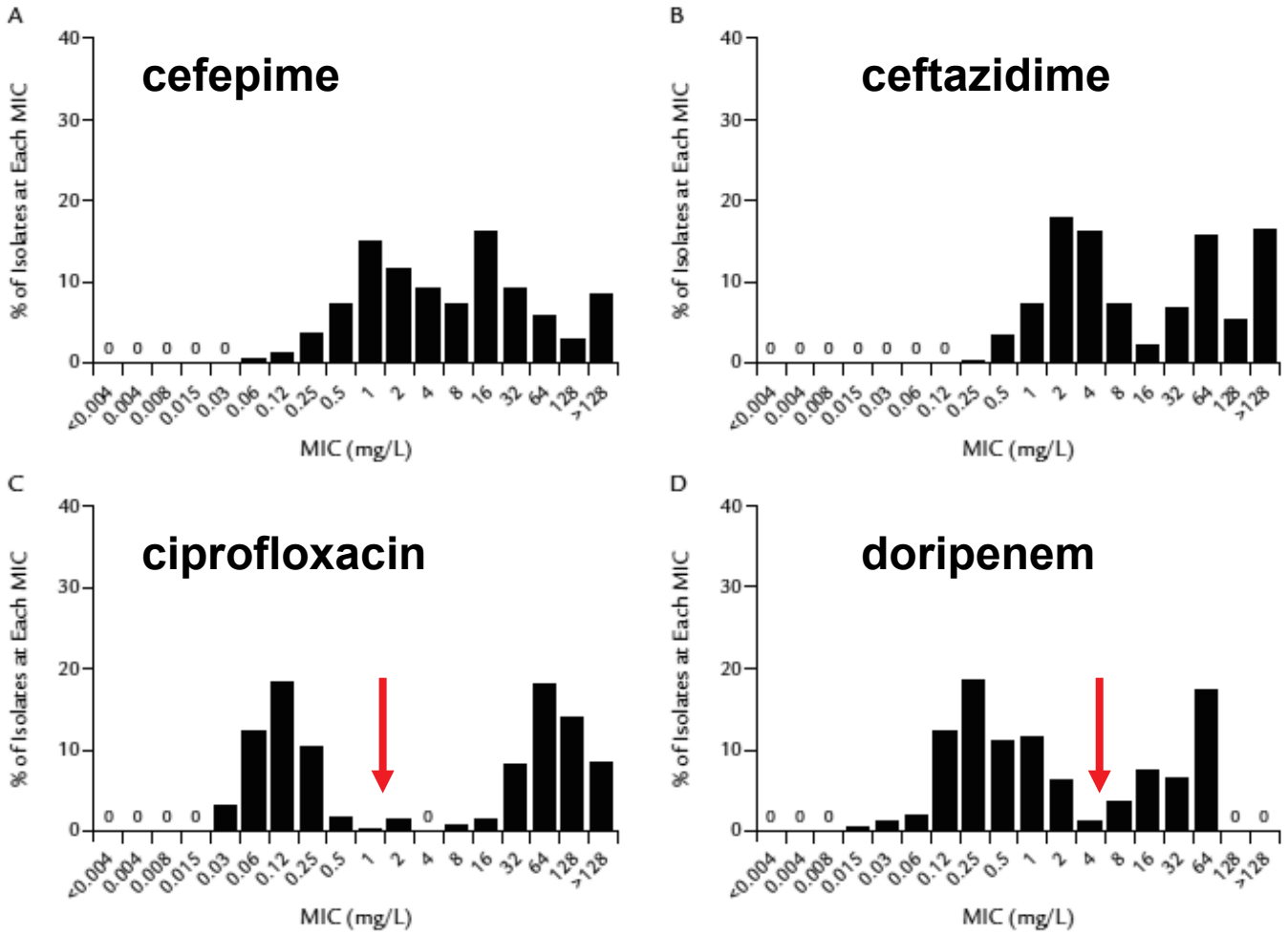


Figure 1. MIC distributions of antibiotics (A, cefepime; B, ceftazidime; C, ciprofloxacin; and D, doripenem) against 1533 *Acinetobacter baumannii* isolates used in simulations of the pharmacodynamics of intravenous antibiotics against gram-negative bacteria collected in the United States.

Koomanachai et al. **Clinical Therapeutics (2010) 32:766-779**

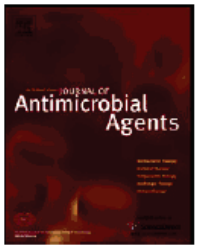
Acinetobacter: what can you do ?

International Journal of Antimicrobial Agents 39 (2012) 105–114

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

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



Review

Emergence of resistance to carbapenems in *Acinetobacter baumannii* in Europe: clinical impact and therapeutic options

Marie Kempf, Jean-Marc Rolain*

Aix-Marseille University, URMITE CNRS-IRD, UMR 6236, Faculté de Médecine et de Pharmacie, Université de la Méditerranée, 27 Bd. Jean Moulin, 13385 Marseille cedex 05, France

Acinetobacter: what can you do ?

- β-lactams by continuous/extended infusion…
  ➔ get an MIC and calculate dose for 4 x the MIC
  (EUCAST does not provide breakpoints [poor target])
- tigecyclin is active in vitro … but rapid emergence of resistance has been reported
- colistin … (see later)
- Sulbactam (in association with colistin) *
- Because of the serious problems of clonal dissemination of clinical MDR *A. baumannii* strains in Asian countries **strict adherence to infection control policies remains of utmost importance.**

---

* known as β-lactamase inhibitor, sulbactam has intrinsic activity against *A. baumanii* (see: Peleg *et al.* Clin Microbiol Rev 2008;21:538–82

Acinetobacter: detection of resistance

PLoS One. 2012;7(2):e31676. Epub 2012 Feb 16.

Rapid Detection of Carbapenem Resistance in Acinetobacter baumannii Using Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry.

Kempf M, Bakour S, Flaudrops C, Berrazeg M, Brunel JM, Drissi M, Mesli E, Touati A, **Rolain JM**.

Aix-Marseille-Université, Unité de Recherche sur les Maladies Infectieuses et Tropicales Émergentes (URMITE), CNRS-IRD-INSERM UMR 6236, Méditerranée Infection, Faculté de Médecine et de Pharmacie, Marseille, France.

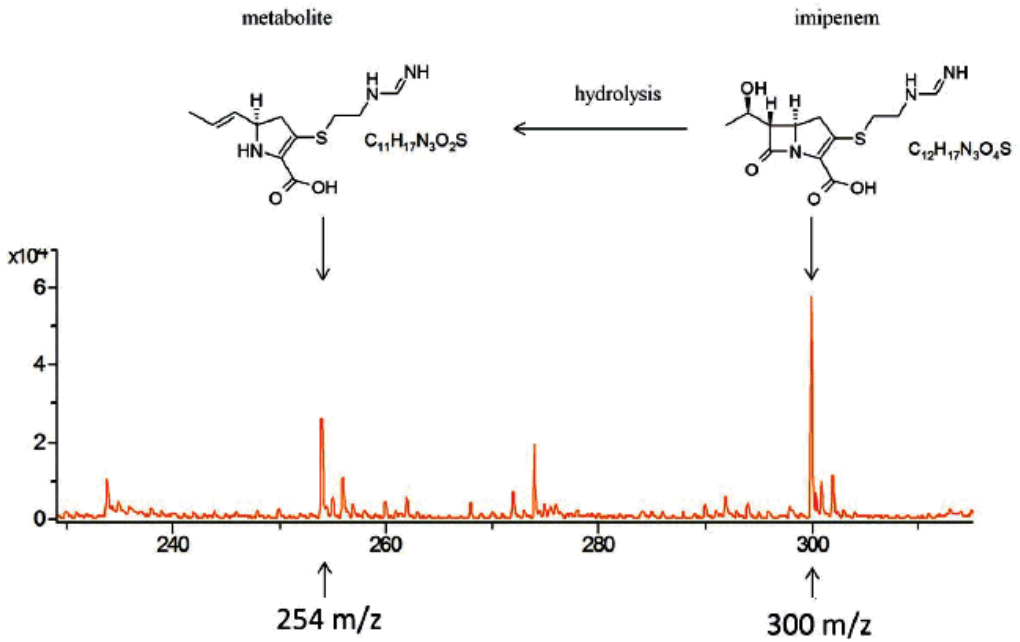


Figure 1. MALDI-TOF MS analysis of imipenem. (A) Imipenem and its natural degradation product. (B) Mass spectra of imipenem and its natural degradation product as determined using the Ultraflex mass spectrometer.

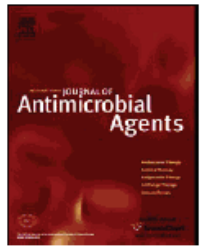
Pseudomonas aeruginosa: the hidden risk of therapy

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

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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



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

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

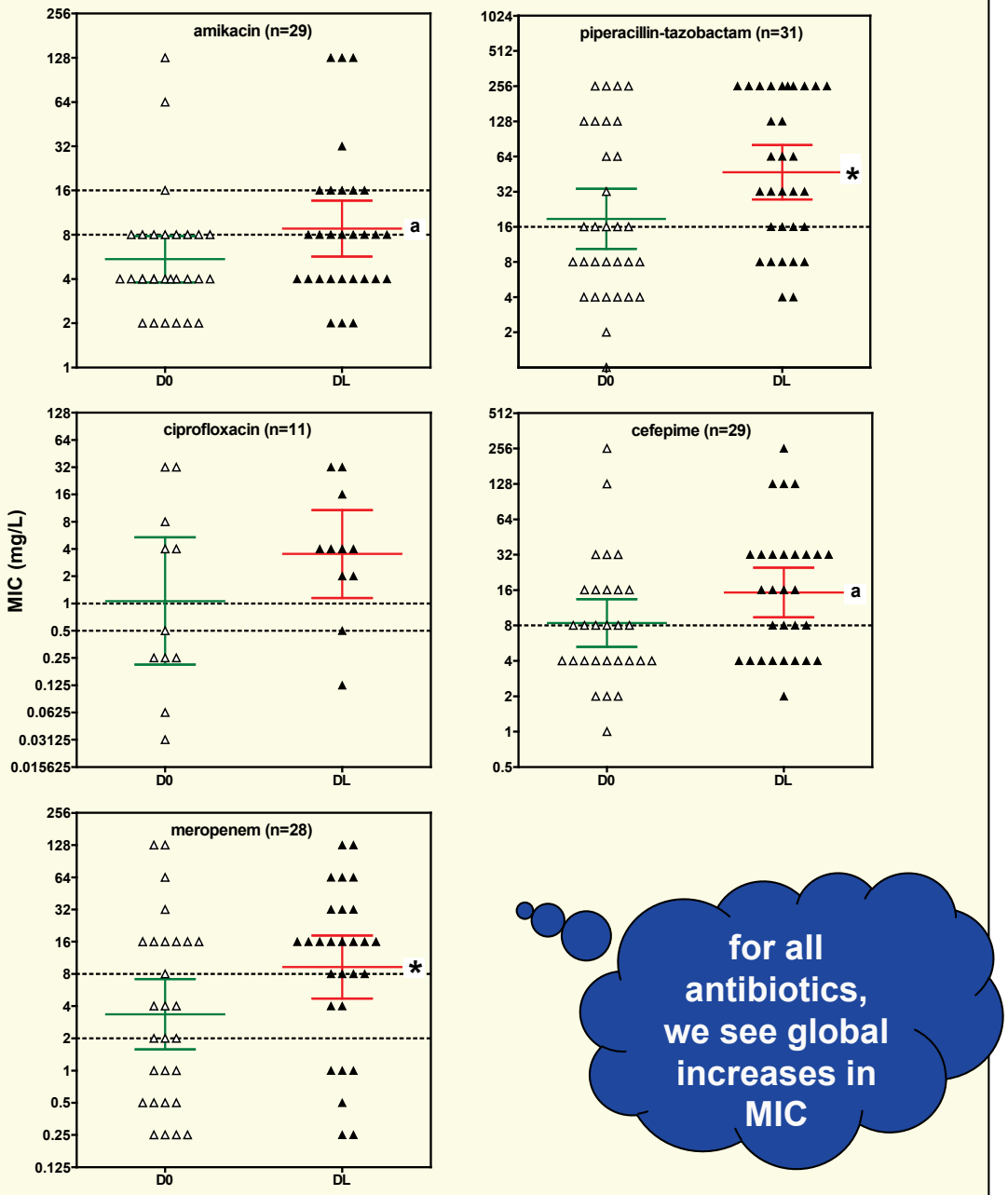
What happens during treatment ?

- 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)



for all antibiotics, we see global increases in MIC

Colistin pharmacokinetics/pharmacodynamics

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01733-10

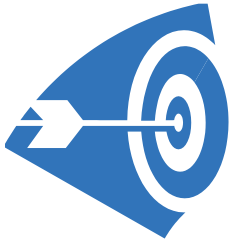
Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients▽

S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡

School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, New York[1]; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia[2]; Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand[3]; The University of Queensland Center for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, Australia[4]; Washington Hospital Center, MedStar Clinical Research Center, Washington, DC[5]; and Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania[6]

Received 13 December 2010/Returned for modification 13 March 2011/Accepted 28 April 2011

- **open-label population PK study (2 centers in US; 1 in Thailand)**
- **105 patients (February 2009 - July 2010)**
- **12 with HD, 4 with CRRT (3 CVV hemodialysis; 1 CVV hemofiltration)**
- **physician-selected doses: 75 to 410 mg/day colistin base (2.2 to 12.5 x 10^6 U)/day**
- **dosage intervals: 8 to 24 h,**



if colistin is your last option …

- a repeated dosage of 150 mg colistimethate (2 x 10^6 U or 66 mg colistin base) every 8h is probably the best option … but more may be needed …
- A loading dose (additional 4-6 x 10^6 U at first dose; total 6 to 8 x 10^6 is essential …
- We do NOT have good breakpoints → use MIC values !
- Never use it in monotherapy … (add meropenem, doripenem, … even if non-susceptible, BUT test the combination
- Test for susceptibility on a repeated fashion …
- Monitor the renal function and adjust by decreasing the dose and prolonging the interval …
- Remember that this is a last resource drug which should be put back on the shelf as soon as possible…

Pseudomonas: the end of the story (*)

Diagn Microbiol Infect Dis. 2012 Mar;72(3):267-71. Epub 2012 Jan 2.

Repeated isolation of Pseudomonas aeruginosa isolates resistant to both polymyxins and carbapenems from 1 patient.

Lee JY, Lim MH, Heo ST, Ko KS.

Department of Molecular Cell Biology, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon, South Korea.

Abstract

Emergence of polymyxin resistance in carbapenem-resistant isolates is a great concern in clinical settings because it may mean the end of treatment options against Gram-negative bacterial infections. Polymyxin-nonsusceptible and -susceptible Pseudomonas aeruginosa isolates resistant to carbapenems and harboring bla(IMP-6) were alternatively isolated from a patient. In vitro antimicrobial susceptibility testing, multilocus sequence typing, and pulsed-field gel electrophoresis were performed. Metallo-β-lactamase genes such as bla(IMP), bla(VIM), bla(SPM), bla(GIM), and bla(SIM) and bla(OXA-50) were detected by polymerase chain reaction. Sequences of 2-component systems, PmrAB and PhoPQ, were also determined. All showed ST235 and the same pulsotype. Amino acid substitutions were identified in PmrB and PhoP from polymyxin-nonsusceptible isolates. **Colistin** exposure might be associated with the recovery of polymyxin-nonsusceptible isolates in this patient.

*** both in time and geographic contexts…**

And …

Implementation of effective infection control policies is of paramount importance, especially for VISA, MDR *S.* Typhi and *S.* Choleraesuis, carbapenemase-producing Enterobacteriaceae, pandrug-resistant *A. baumannii* and *P. aeruginosa*, and XDR-TB in Asia. Periodic surveillance of resistance patterns, with linkage to associated mortality, is crucial to establish guidelines for the administration of appropriate antimicrobial agents in every Asian country.

International Journal of Antimicrobial Agents 37 (2011) 291–295

And …

The organization strongly recommends that governments focus control and prevention efforts in four main areas: (1) surveillance of antimicrobial resistance; (2) rational antibiotic use; (3) introduction or enforcement of legislation related to stopping the selling of antibiotics without prescription; and (4) strict adherence to infection prevention and control measures, including the use of hand-washing measures, particularly in healthcare facilities.

WHO. WHO urges countries to take measures to combat antimicrobial resistance, 2010. Available at: http://www.who.int/mediacentre/news/releases/2010/amr_201008

Disclosures and slides / publications availability

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- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics and for support to a PhD fellow (D. Das)
- the *Université catholique de Louvain* for support to E. Ampe (vancomycin studies)
- the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Research grant from Bophar Pharmaceuticals B.V., importer of colistimethate in Belgium (from Forest Pharmaceuticals UK)
- Wallonie-Bruxelles International for this presentation and my activities in Vietnam

slides and publications: http://www.facm.ucl.ac.be