Vancomycin, Carbapenems and Colistin: where and when do you really need to use them?

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Disclosures and slides availability

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  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*] (governance)
- **This presentation: *Wallonie-Bruxelles International***

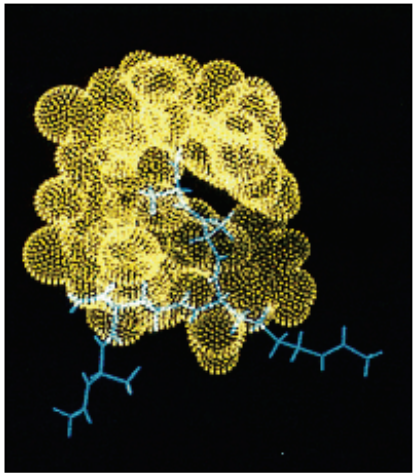
http://www.facm.ucl.ac.be/cooperation

Vancomycin

Contents of the presentation on vancomycin

- short summary of its history and general properties
- how to measure MICs and heteroresistance
- vancomycin PK/PD and minimal AUC_{24h}/MIC
- high doses in America ... and the risks
- continuous infusion of vancomycin:

Vancomycin History



binding of vancomycin
to D-Ala-D-Ala

- first isolated in 1953 by Edmund Kornfeld at Eli Lilly & Co.[1] from a soil sample collected in Borneo and produced by *Amycolatopsis orientalis*.
- remained for long a rarely used antibiotic because
  - poor oral bioavailability (must be given intravenously for most infections)
  - development of β-lactamase-resistant semi-synthetic penicillins (methicillin and derivatives) that solved the problem of β-lactamase-producing S. aureus
  - originally impure forms ("Mississippi mud") causing oto- and nephtotoxicity
- regained increasingly large usage from the mid-80's **ONLY** because of the **widespread emergence of MRSA** (methicillin-resistant *S. aureus*) that are resistant to all conventional β-lactams (incl. carbapenems)

[1] first company to mass-produce penicillin in in the 1940's

Vancomycin: spectrum and clinical resistance

- Broad activity against **Gram-positive microorganisms**.
  - Staphylococci (*S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. hominis, S. warneri,* and other coagulase-negative staphylococci)
  - most *Enterococcus faecalis* (variable for *E. faecium*)
  - *Streptococcus pneumoniae* and *S. pyogenes; S. agalactiae*, group C and group G streptococci,
  - *Listeria monocytogenes*
  - *Bacillus anthracis, B. cereus*, and other *Bacillus* spp.,
  - *Corynebacterium* spp.
  - anaerobes: *Peptostreptococcus* spp., *Actinomyces* spp., *Propionibacterium* spp., *Clostridium* spp. (including *Clostridium difficile* (not *Clostridium ramosum*)

- *Lactobacillus* spp., intrinsically vancomycin resistant.

- Clinically important resistance:
  - *S. aureus*: tickening of the cell wall (VISA): MICs increase from 2 to 8-16 mg/L (heteroresistance)
  - *Enterococci* (VRE): acquisition of gene(s) causing a change from D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser (usually high MICs)

But when do you really need vancomycin ?

- Do you have these Infections ?
  - Sepsis
  - Endocarditis
  - Skin and soft tissue infections
  - Osteomyelitis
  - Lower respiratory tract infections
  - Diarrhea associated with Clostridium difficile
  - Nosocomial intravascular catheter infections (prophylaxis and treatment)

- Are they caused by these organsisms ?
  - Staphylococci (*S. aureus, S. epidermidis)* resistant to β-lactasm (so called methicillin-resistant → MRSA / MRSE)
  - *Enterococcus faecalis*
  - *Clostridium difficile* (oral form)

But when do you really need vancomycin ?

- In
  - and

Do NOT use vancomycin without suspicion or evidence that these organisms cause these infection(s) !

- if caused by
  - Staphylococci (*S. aureus, S. epidermidis)* resistant to β-lactasm (so called methicillin-resistant → MRSA / MRSE)
  - *Enterococcus faecalis*
  - *Clostridium difficile* (oral form)

Empiric treatments with vancomycin ?

Sandford guide (2012-2013)

Skin infections, abscesses

Infection	Pathogen	Treatment
Arthritis, bursitis, osteomyelitis	**risk factors for MRSA**	vancomycin
Abscess, mastitis	**risk factors for MRSA**	vancomycin
Diabetic foot grade 4	**Recent exposure to AB**	Piperacillin-tazobactam or meropenem, + vancomycin if Gram(+)
Established burn wound infection	Staphylococci, Pseudomonas	vancomycin + (ceftazidime, cefepime or piperacillin-tazobactam)
Decubitus ulcer with sepsis	**Risk factor for MRSA**	vancomycin + pieracillin-tazobactam
Necrotizing soft tissue infection	**Risk factor for MRSA**	Vancomycin + clindamycin
Catheter related infections	**Severe or risk factors**	vancomycin + (ceftazidime, cefepime, piperacillin-tazobactam or meropenem)
	MRSA	vancomycin

Cardio-vascular infections

Infection	Pathogen	Treatment
Cardiovascular device related infection	**Staphylococci**	Vancomycin + rifampicin
endocarditis	**Risk factor for MRSA or coag. neg. Staph**	Vancomycin + gentamicin + rifampicin
Mediastinitis after cardiac surgery	Staphylococci, enterobacteriaceae	Vancomycin + (ceftazidime or cefepime)
Catheter related thrombophlebitis	Staphylococci, enterococci, enterobacteriaceae, Pseudomonas	Vancomycin + (ceftazidime or cefepime or piepracillin-tazobactam)
	Intracranial vein	Vancomycin + metronidazole +ceftriaxone

Respiratory tract infections

Infection	Pathogen/ population	Treatment
Pneumonia in immunocompetent neonates	Late onset in neonates > 7 days	Cefotaxime + vancomycin
HAP/VAP	**Risk of MRSA**	Amoxi-clav or cefuroxime + vancomycin

CNS infections

Infection	Pathogen/ population	Treatment
Brain abscess	**risk factors for MRSA**	cephalo III + vancomycin
Meningitis	neonate	vancomycin + (cefotaxime of ceftazidime)
	Child, postsurgery	vancomycin + (ceftazidime or meropenem)
	S. pneumoniae, MIC peni > 0.06	Vanco + cephalo III
Ventriculitis	**MRSA**	Vancomycin +/- rifampicin

Other type of infections

Infection	Pathogen	Treatment
colitis	**Clostridium difficile;** **- allergy to metronidazole** **- severe**	- Vancomycin PO - Vancomycin PO + metronidazole IV
Renal abscess	**risk factors for MRSA**	vancomycin
Toxic shock syndrome	**Risk factor for MRSA**	Vancomycin + clindamycin
Suppurative parotitis	**risk factors for MRSA**	vancomycin

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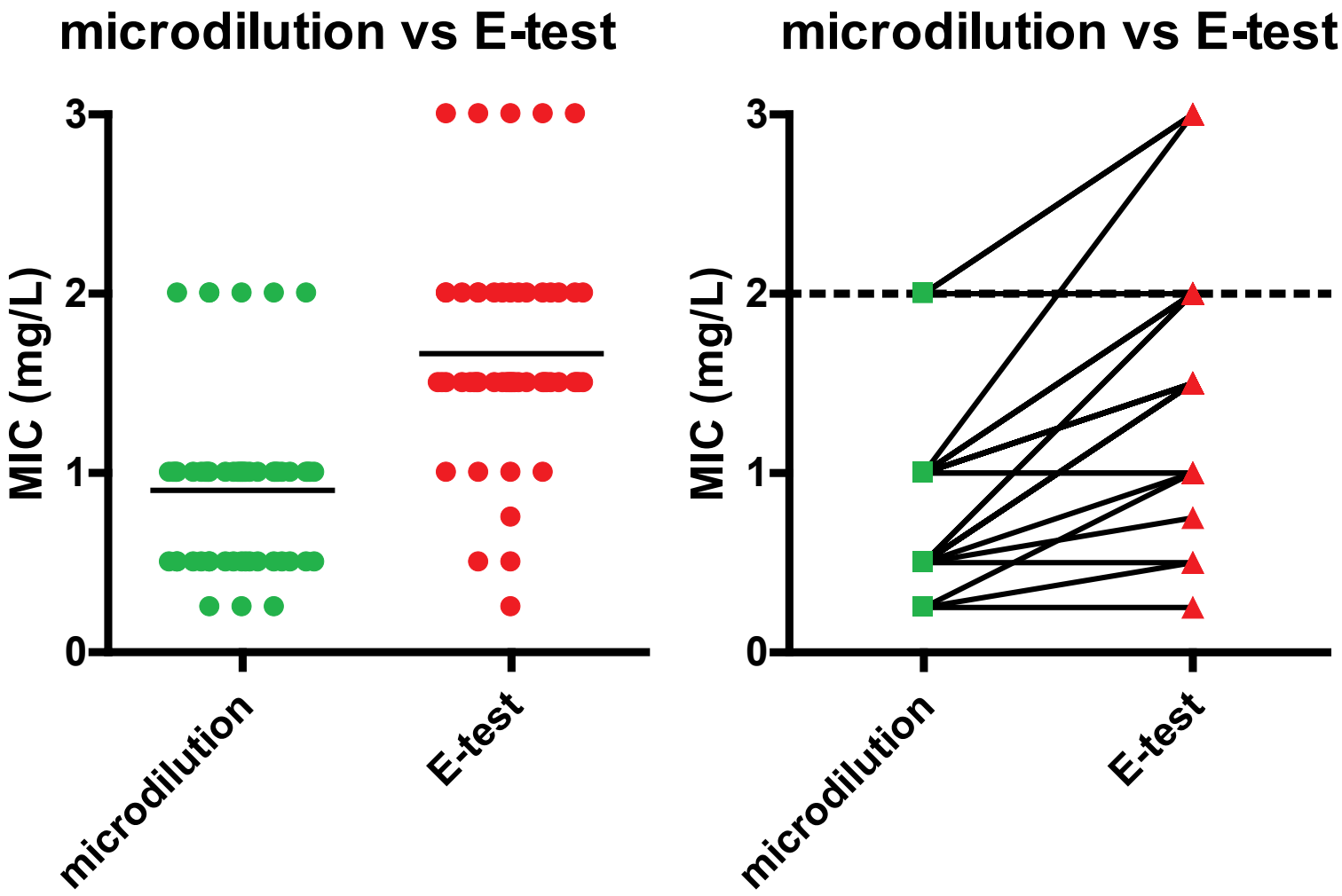
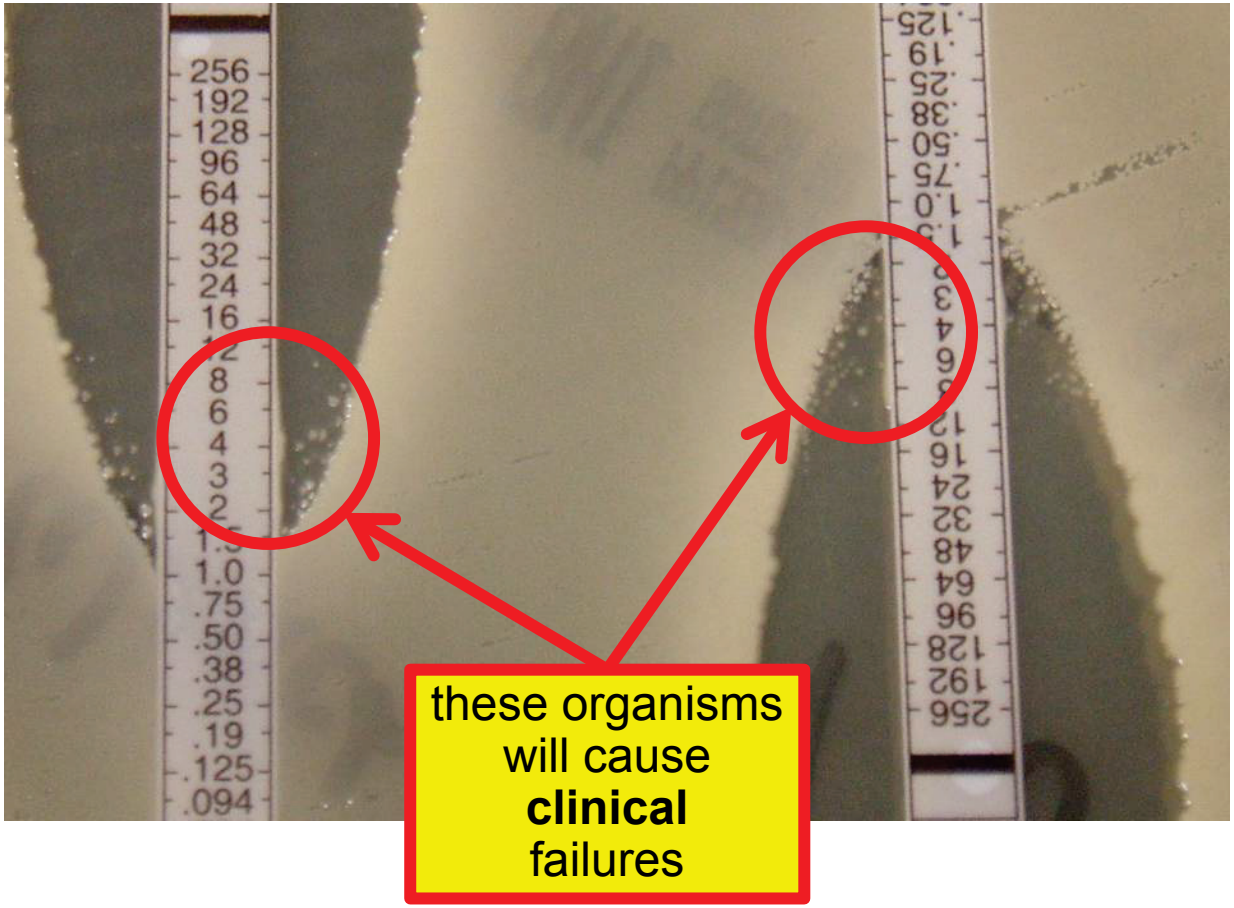
    - why ?
    - how we did it …
    - do the others do the same ?
  - unconventional uses of vancomycin (a few words)

You MUST get an MIC with the appropriate technique



54 strains (MSSA, MRSA and CNS) – Ampe et al. IJAA 2013 41(5):439-46 – Suppl. Mat.

Beware of hetero-resistance: how to see it …



This slide borrowed from Dr M. Dryden, Royal Hampshire Hospital, Winchester, UK

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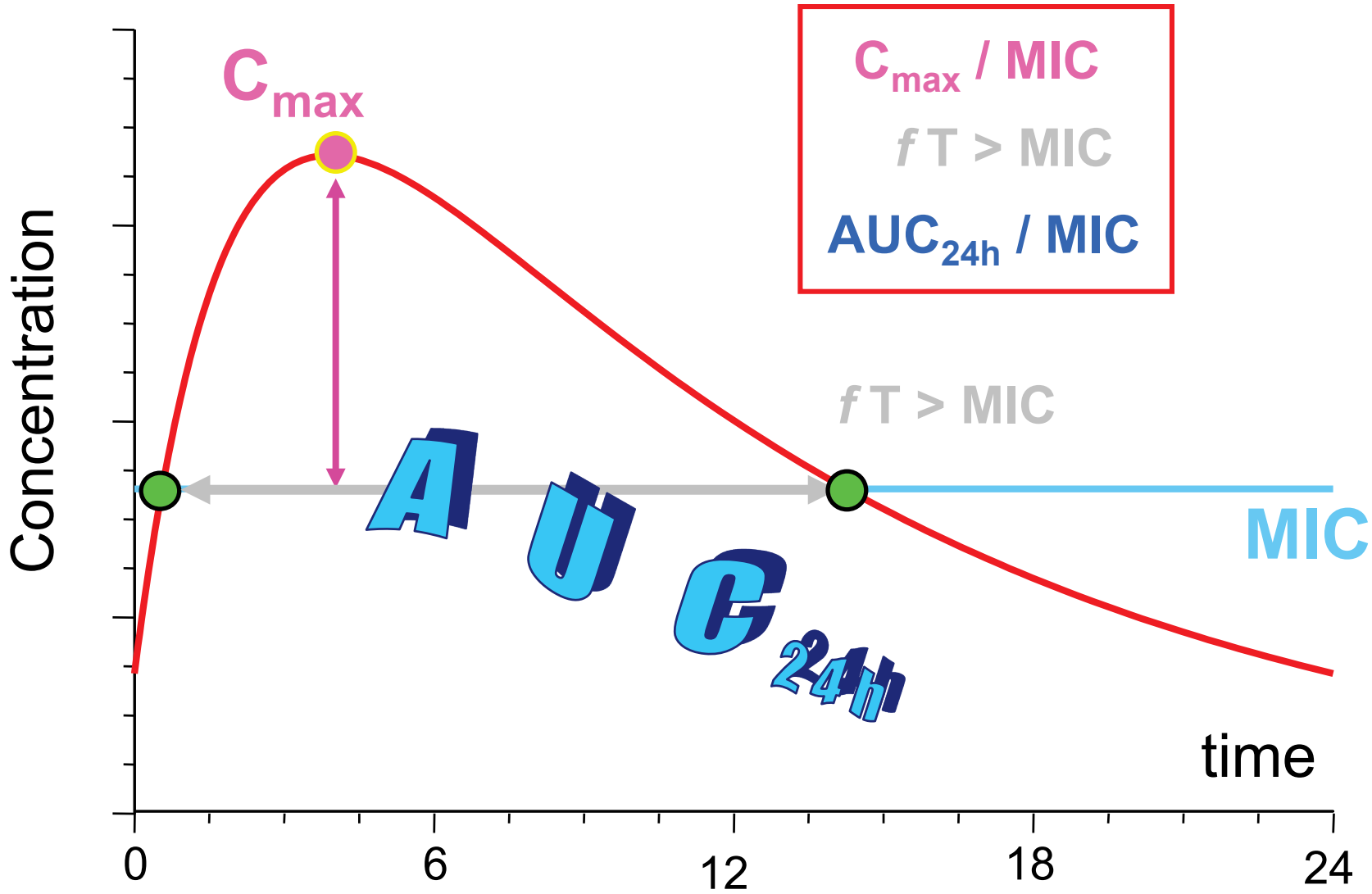
Vancomycin and Pharmacodynamics

- Vancomycin is an AUC_{24h}-MIC dependent antibiotic



Vancomycin – AUC_{24h} and efficacy

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2004; 43 (13): 925-942
0312-5963/04/0013-0925/$31.00/0

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Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections

Pamela A. Moise-Broder,[1] *Alan Forrest,*[1,2] *Mary C. Birmingham*[1] and *Jerome J. Schentag*[1,2]

1 CPL Associates, LLC, Amherst, New York, USA
2 University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, USA

Moise-Broder *et al.* Clin. Pharmacokinet. 2004; 43:925-942

Vancomycin – AUC_{24h} and efficacy

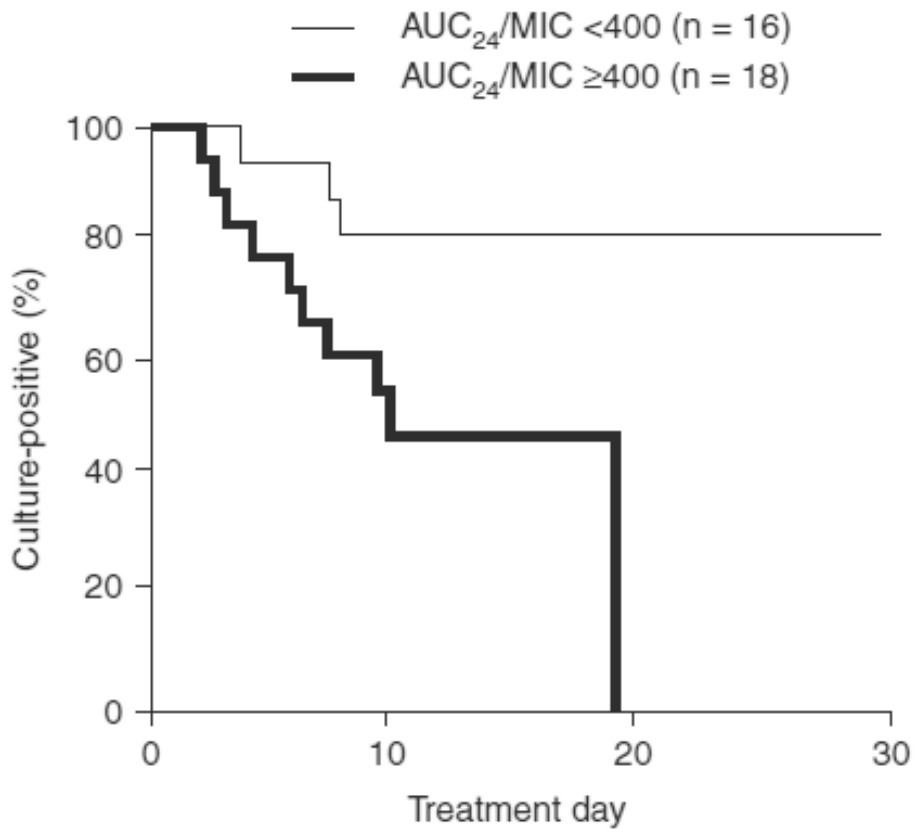


Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin AUC_{24}/MIC <400 and AUC_{24}/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC_{24}/MIC groups differed significantly ($p = 0.0402$). **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

Moise-Broder *et al.* Clin. Pharmacokinet. 2004; 43:925-942

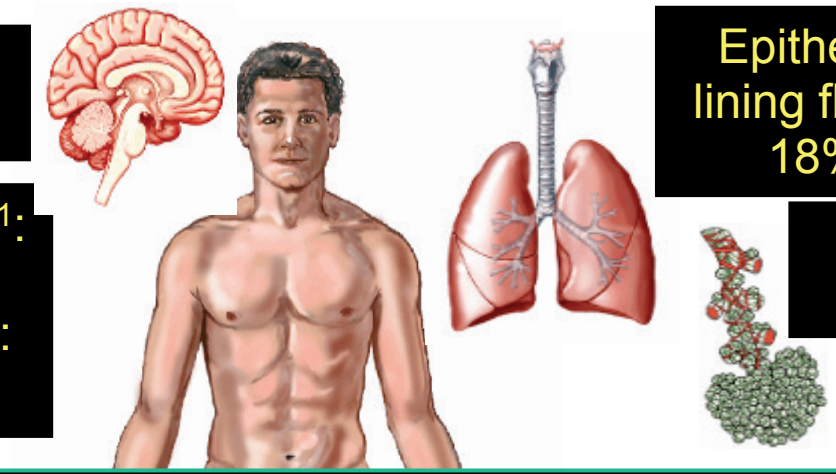
Why is a so large AUC_{24h}/MIC needed ?

CNS: <10%

Sternal bone[1]: 57%
Heart valve[4]: 12%

Epithelial lining fluid[3]: 18%

Lung tissue[2]: 17%–24%



Vancomycin Tissular Penetration is poor

Bone[5]: 7%–13%

Fat[4]: 14%
Muscle[4]: 9%

1. Massias L et al. *Antimicrob Agents Chemother*. 1992;36:2539-2541. 2. Cruciani M et al. *J Antimicrob Chemother.* 1996;38:865-869. 3. Lamer C et al. *Antimicrob Agents Chemother.* 1993;37:281-286. 4. Daschner FD et al. *J Antimicrob Chemother*. 1987;19:359-362. 5. Graziani AL et al. *Antimicrob Agents Chemother*. 1988;32:1320-1322.

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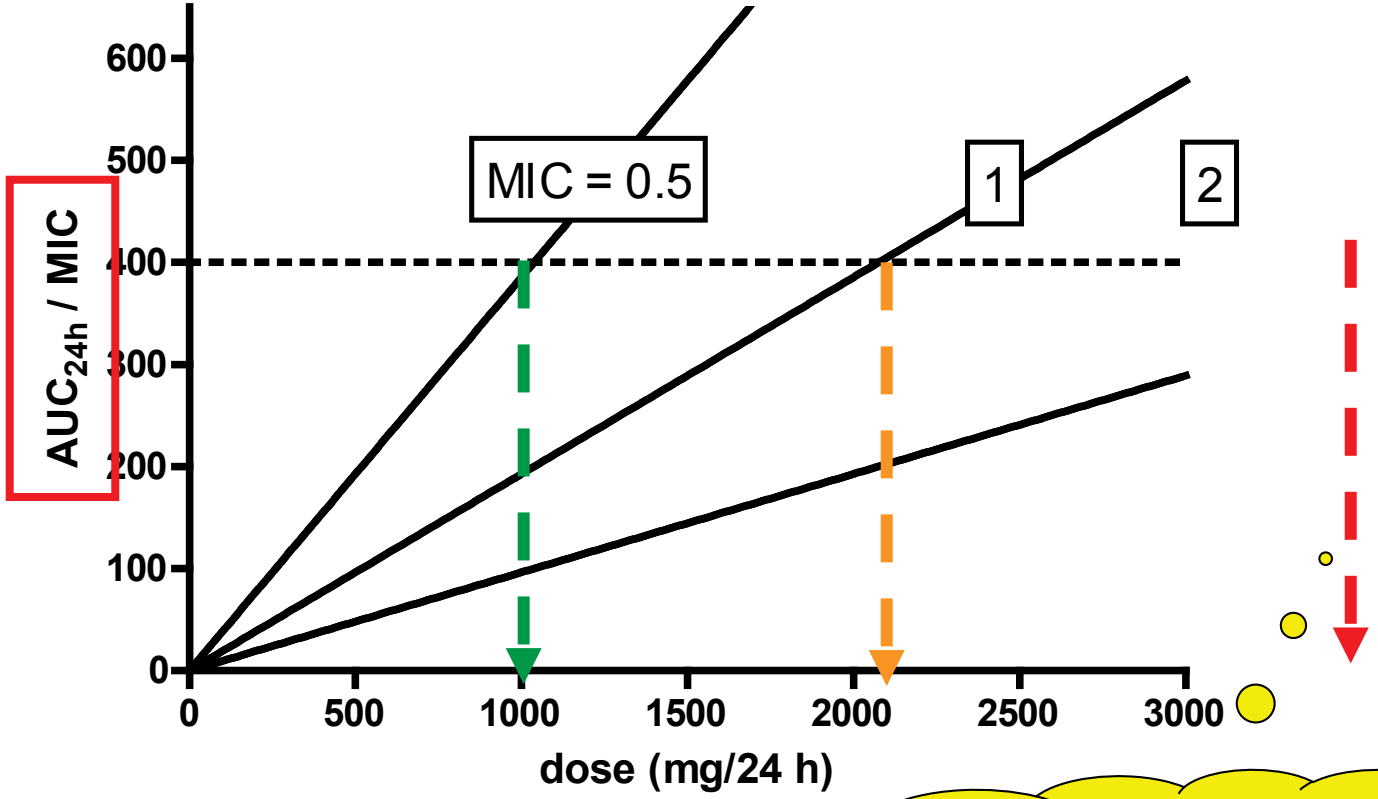
How to calculate the AUC_{24h} with the conventional BID schedule ?

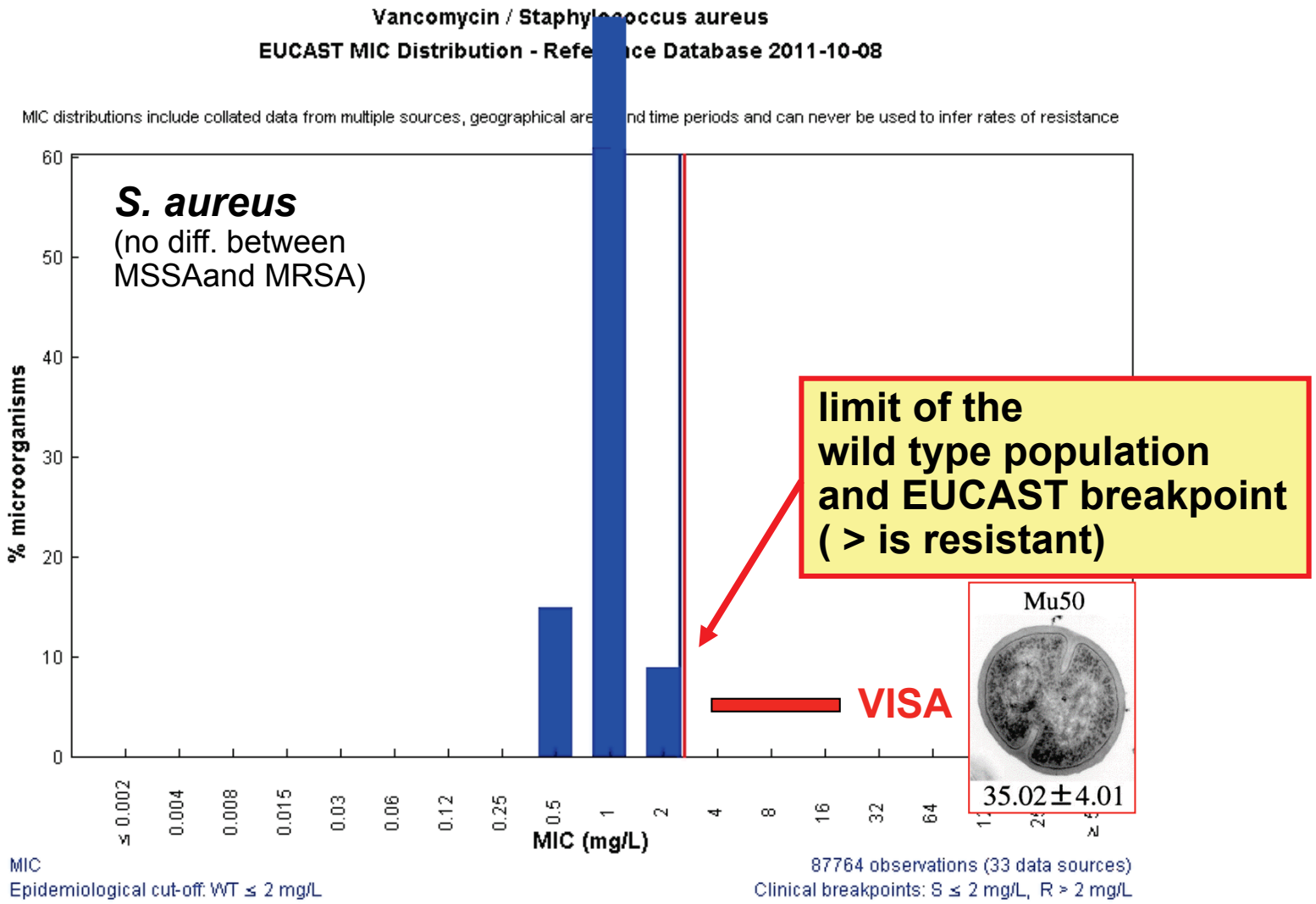
AUC_{24h} / MIC *vs.* dose for diff. MIC and CL_{cr}=90 mL/min



if the MIC is 2, you may fail <u>clinically</u>

Moise-Broder *et al.* Clin. Pharmacokinet. 2004; 43:925-942

Vancomycin and MIC (EUCAST distributions)



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IDSA guidelines in 2011

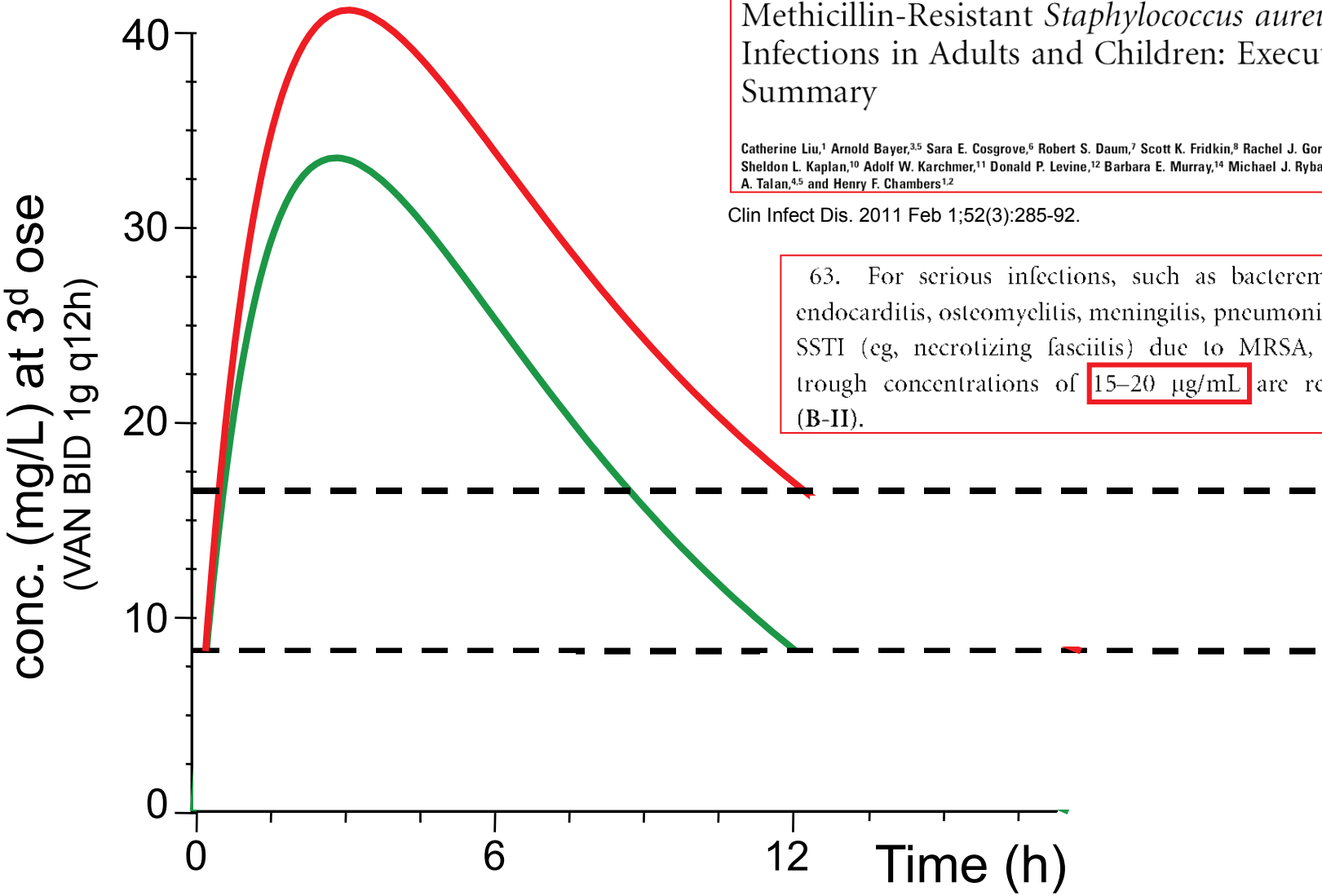
IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Clin Infect Dis. 2011 Feb 1;52(3):285-92.

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (B-II).



But risks in 2013 ...

Hall *et al. BMC Pharmacology and Toxicology* 2013, **14**:12
http://www.biomedcentral.com/2050-6511/14/12

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

Ronald G Hall II[1,2*], Kathleen A Hazlewood[1,7], Sara D Brouse[1,8], Christopher A Giuliano[3,9], Krystal K Haase[3], Chistopher R Frei[4], Nicolas A Forcade[4,10], Todd Bell[5], Roger J Bedimo[6] and Carlos A Alvarez[1,2]

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Nephrotoxicity occurred in 78 patients (23%), occurring in 56%, 11%, and 33% of patients at Hospitals A, B, and C, respectively. The median (interquartile range) increase from baseline to peak serum creatinine was 0.0 mg/dL (0.0, 0.2) for patients who did not develop nephrotoxicity versus 1.0 mg/dL (0.6, 2.1) for patients who developed nephrotoxicity. Fifteen percent of patients had a vancomycin trough concentration greater than 20 mcg/ml. Concurrent nephrotoxins included contrast dye (34%), aminoglycosides (19%), and vasopressors (12%). Concomitant antimicrobials active against MRSA were used in 23% of patients.

But be aware of the risk of underdosing

- Patients in continuous infusion and with increased renal clearance

ELSEVIER

International Journal of Antimicrobial Agents

Available online 3 March 2012

In Press, Corrected Proof — Note to users

Augmented renal clearance in septic patients and implications for vancomycin optimisation

João Pedro Baptista, Eduardo Sousa, Paulo J. Martins, Jorge M. Pimentel

Serviço de Medicina Intensiva, Hospitais da Universidade de Coimbra, Praceta Professor Mota Pinto 3000-075, Coimbra, Portugal

Dosing adjustment…

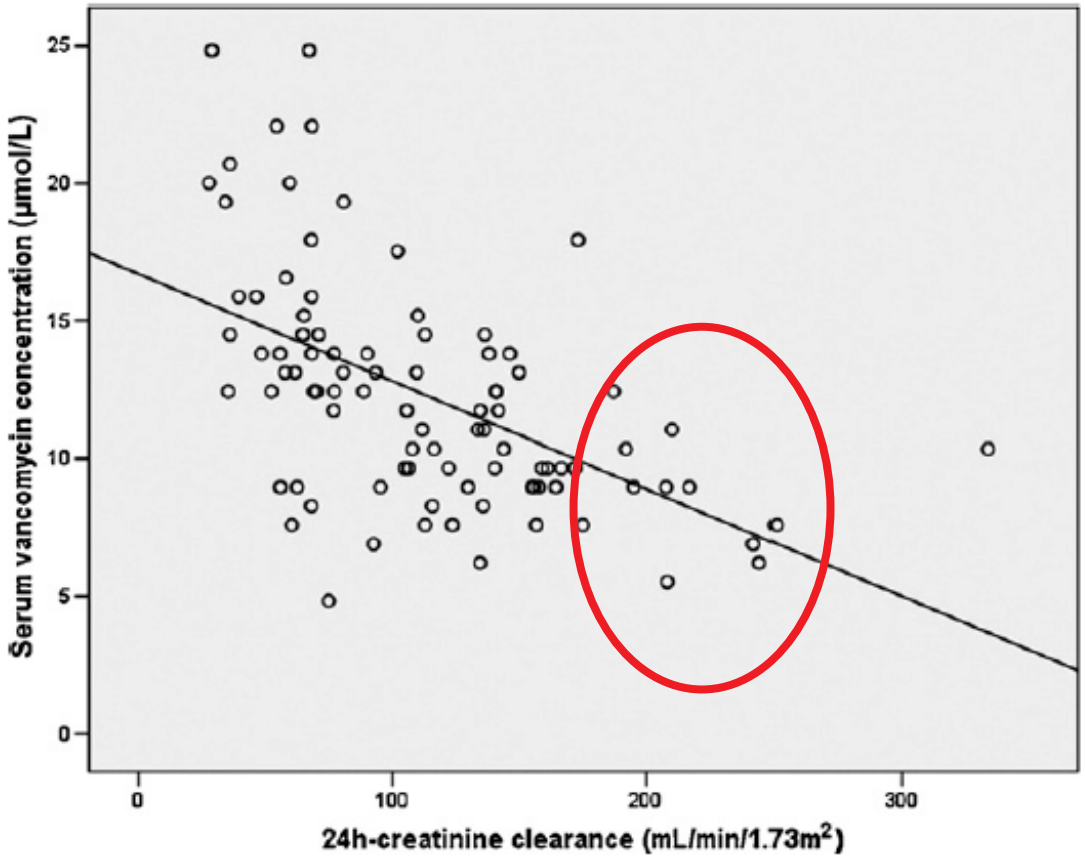

Fig. 2. Linear correlation between 24-h creatinine clearance (CL_{Cr}) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with CL_{Cr} in 93 septic critically ill patients ($rS = -0.57$; $P < 0.01$).

Patients with high clearance will have too low through levels !

Vancomycin: provisional conlusions

1. an old drug put back into service
2. will work for organisms with an MIC of maximum 2 mg/L and not higher (beware of CLSI ! – use EUCAST breakpoints)
3. You must
   - use a loading dose
   - optimize the maintenance dose
   - monitor blood levels (trough of at least 15 mg/L) at days 1, 3, 6 and later ….
4. use combined therapy for organisms with MIC > 2 mg/L
5. do not forget to detect heteroresistance… (use E-test)

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Vancomycin: continuous infusion

ELSEVIER

International Journal of Antimicrobial Agents 41 (2013) 439–446

International Journal of Antimicrobial Agents

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

ISC

Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic and toxicological aspects

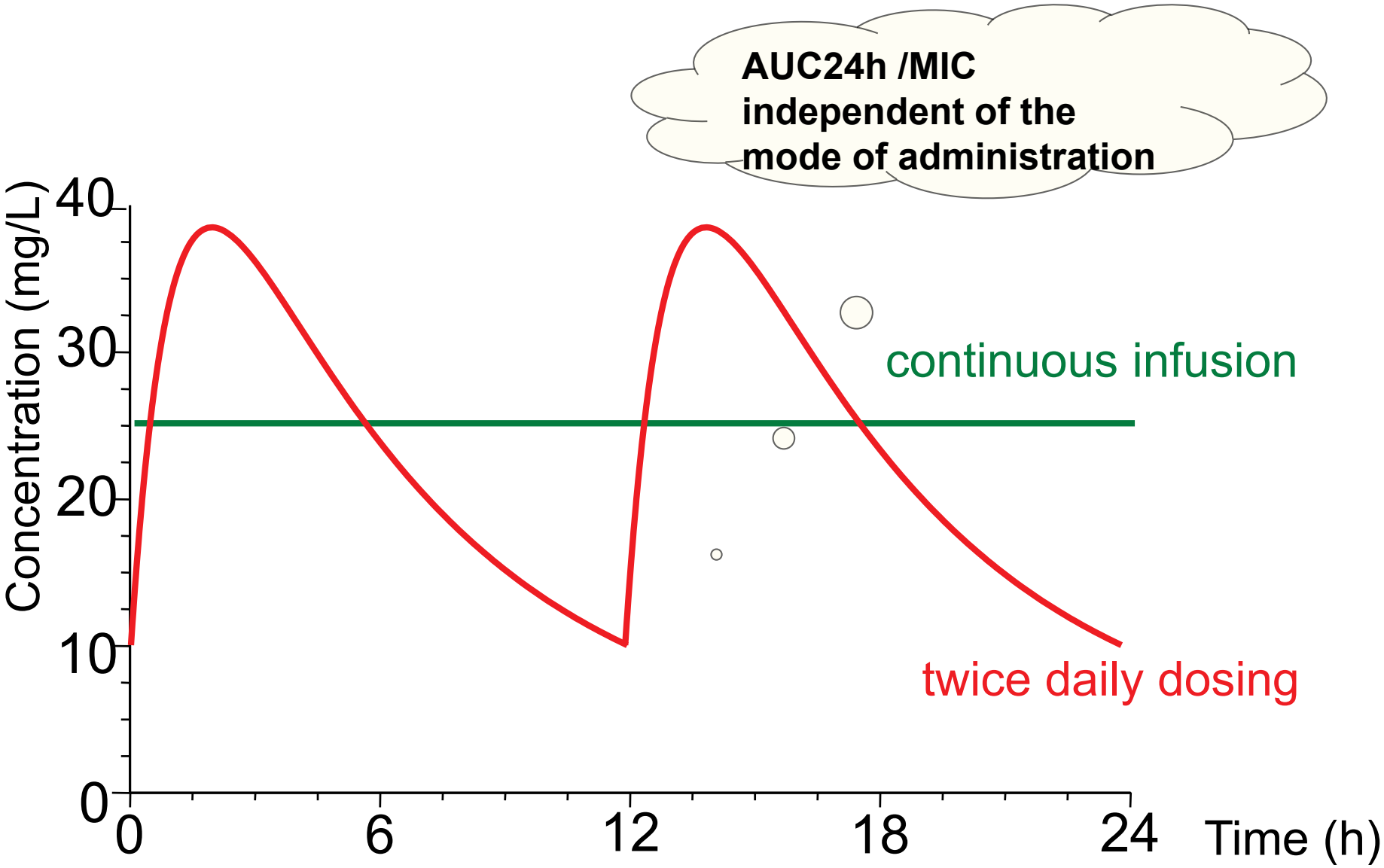
CrossMark

Els Ampe[a,b,1], Bénédicte Delaere[b], Jean-Daniel Hecq[b], Paul M. Tulkens[a,*], Youri Glupczynski[b]

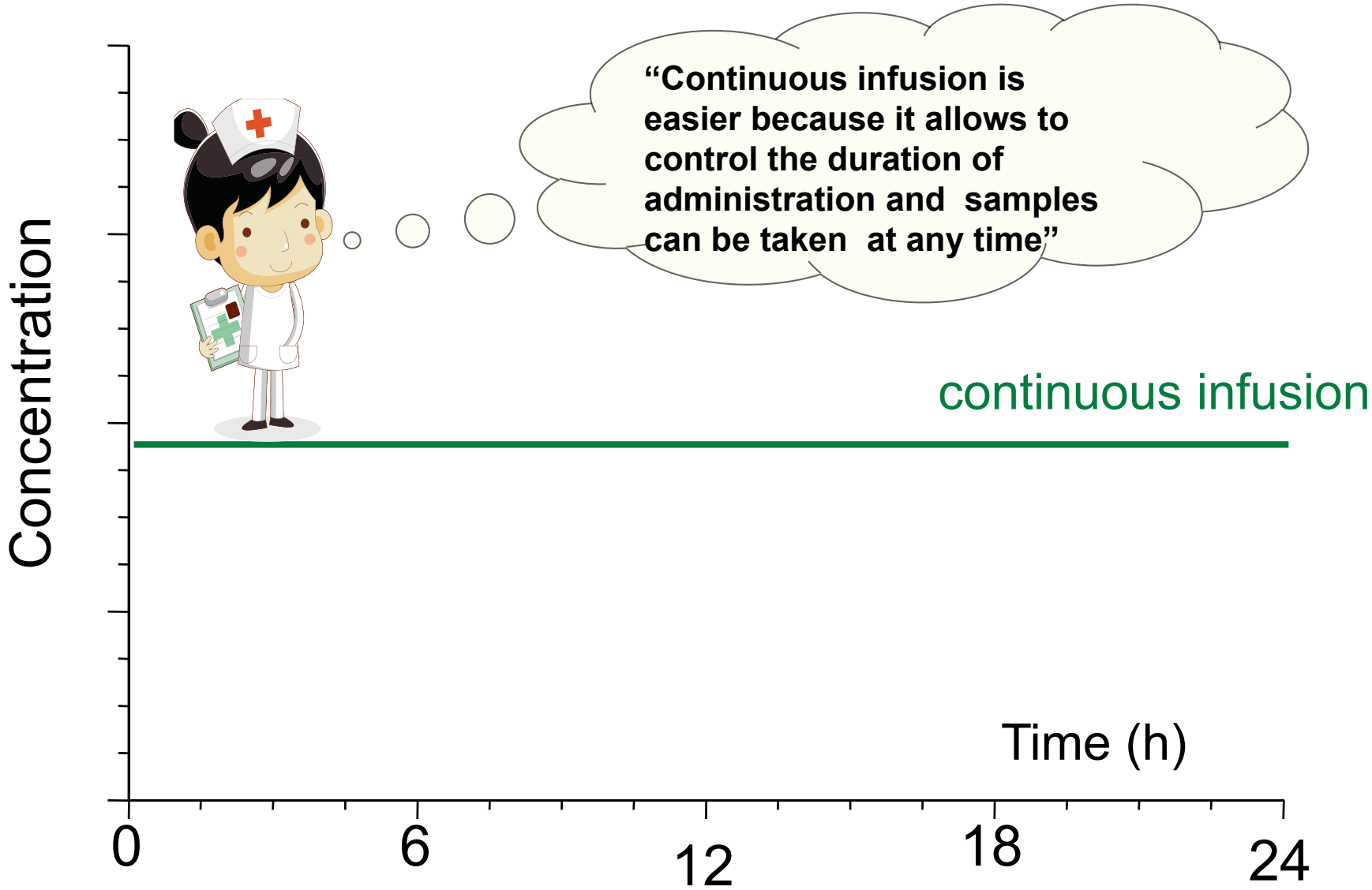
[a] *Pharmacologie cellulaire et moléculaire et Centre de pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*

[b] *Laboratoire de microbiologie, Service d'infectiologie et Département de pharmacie, CHU Mont-Godinne, Yvoir, Belgium*

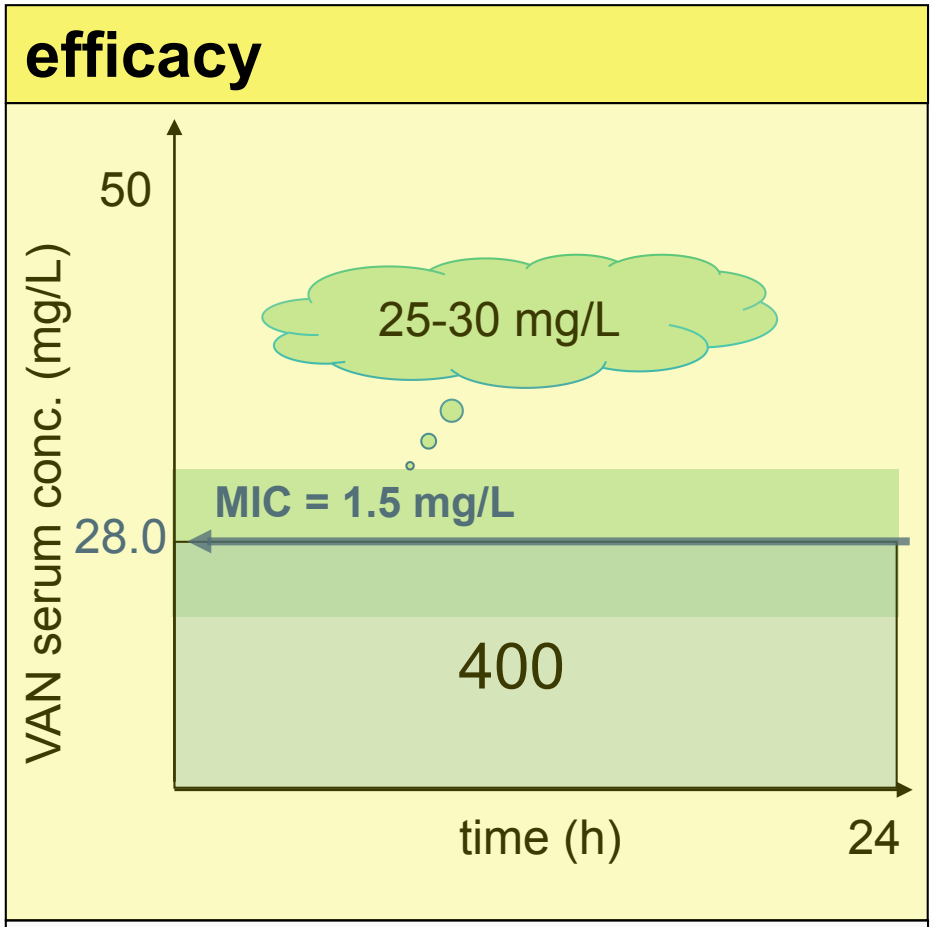
TDM of vancomycin by continuous infusion



how to optimize vancomycin treatment



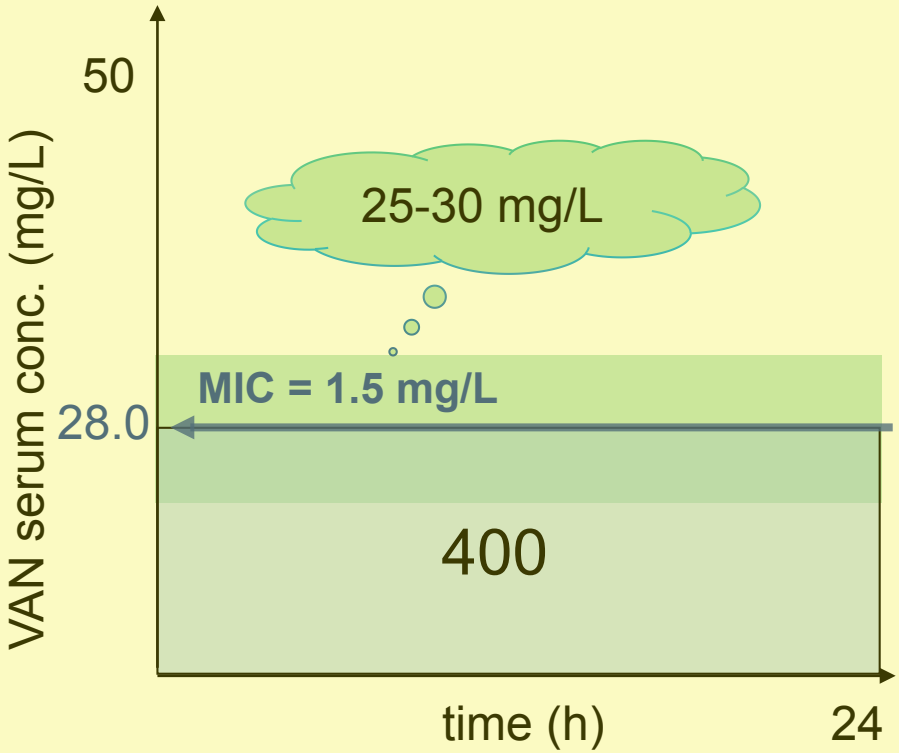
vancomycin CI: which serum concentration should we target?



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

vancomycin CI: which serum concentration should we target?

efficacy



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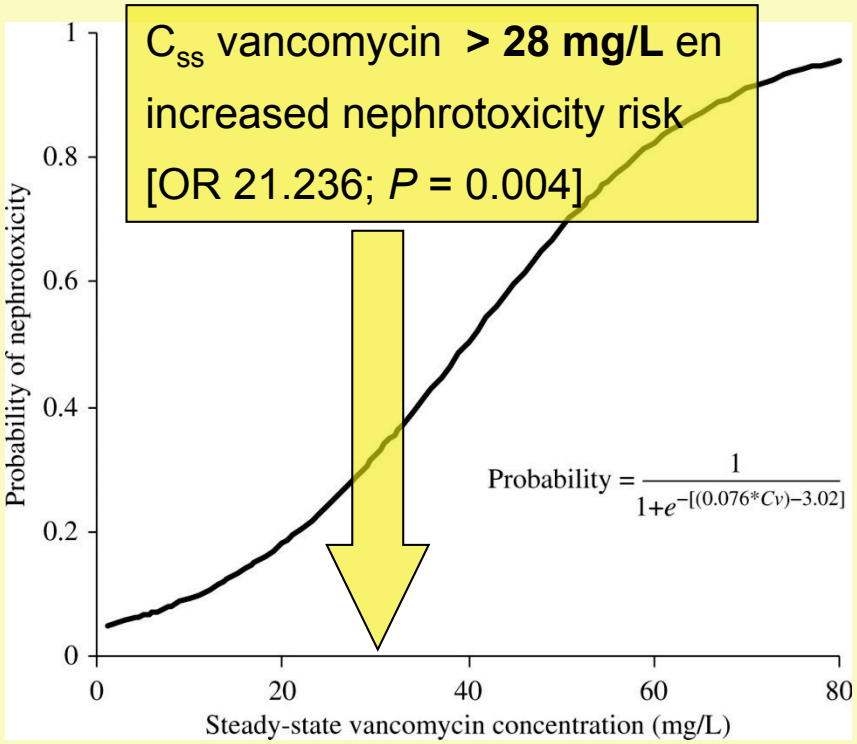
toxicity



Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

How to reach the serum target concentration target with CI?
1. loading dose: the correct scheme *

Target serum concentration

$$C_t = D_l / Vd$$

volume of distribution

loading dose

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

loading dose (in mg/kg) = **20 mg/kg** = **25** (mg/L) x **0.8** (L/kg)

* assuming linear pharmacokinetics

How to reach the serum target concentration target with CI? 2: infusion *

Target serum concentration

$$C_{ss} = K_o / Cl_V$$

infusion rate

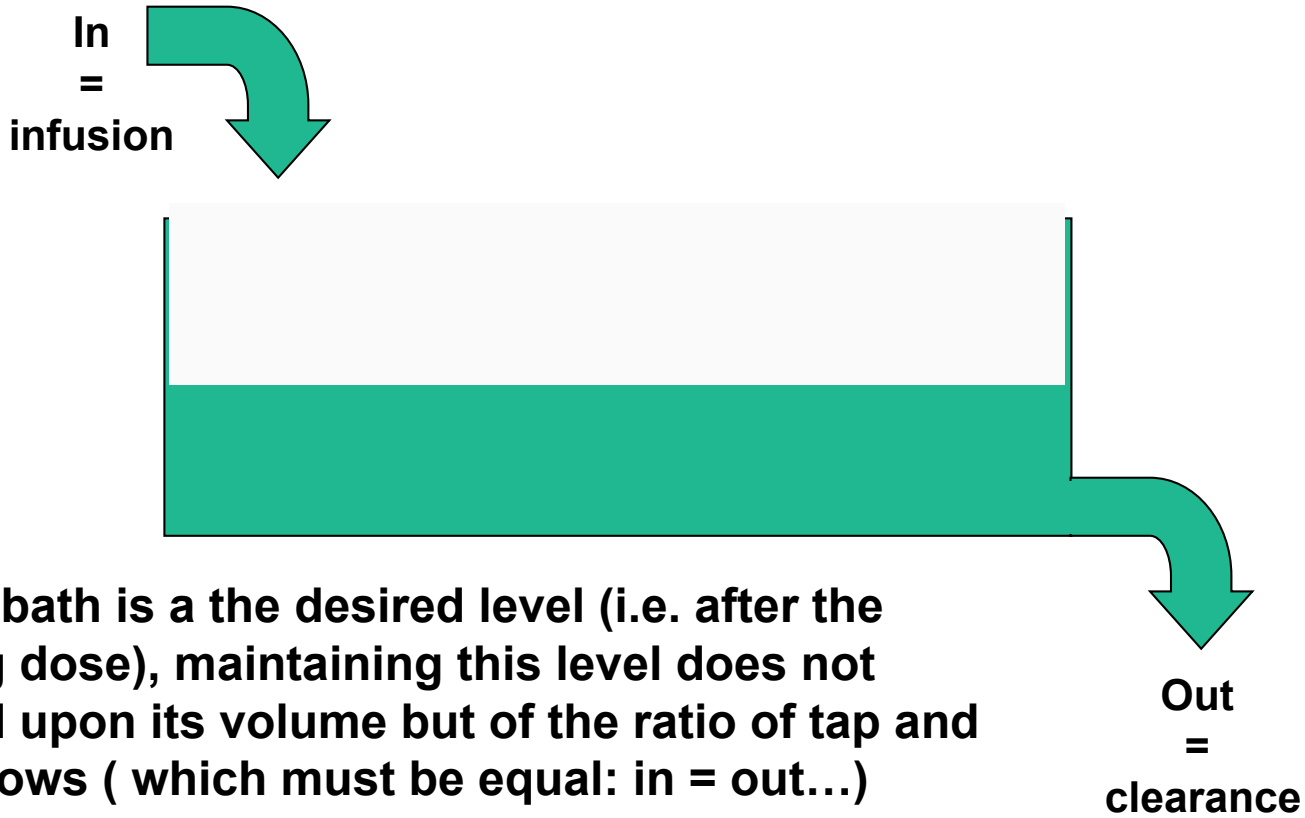
vancomycin clearance
(0.65 Creat. Cl.

daily dose for 27.5 mg/L = 2316 mg/24h for a CrCl=90mL/min)
(9.65 mL/h for a solution at 10g/L)

maintenance dose = the total daily dose corrected for the clearance

* assuming linear pharmacokinetics

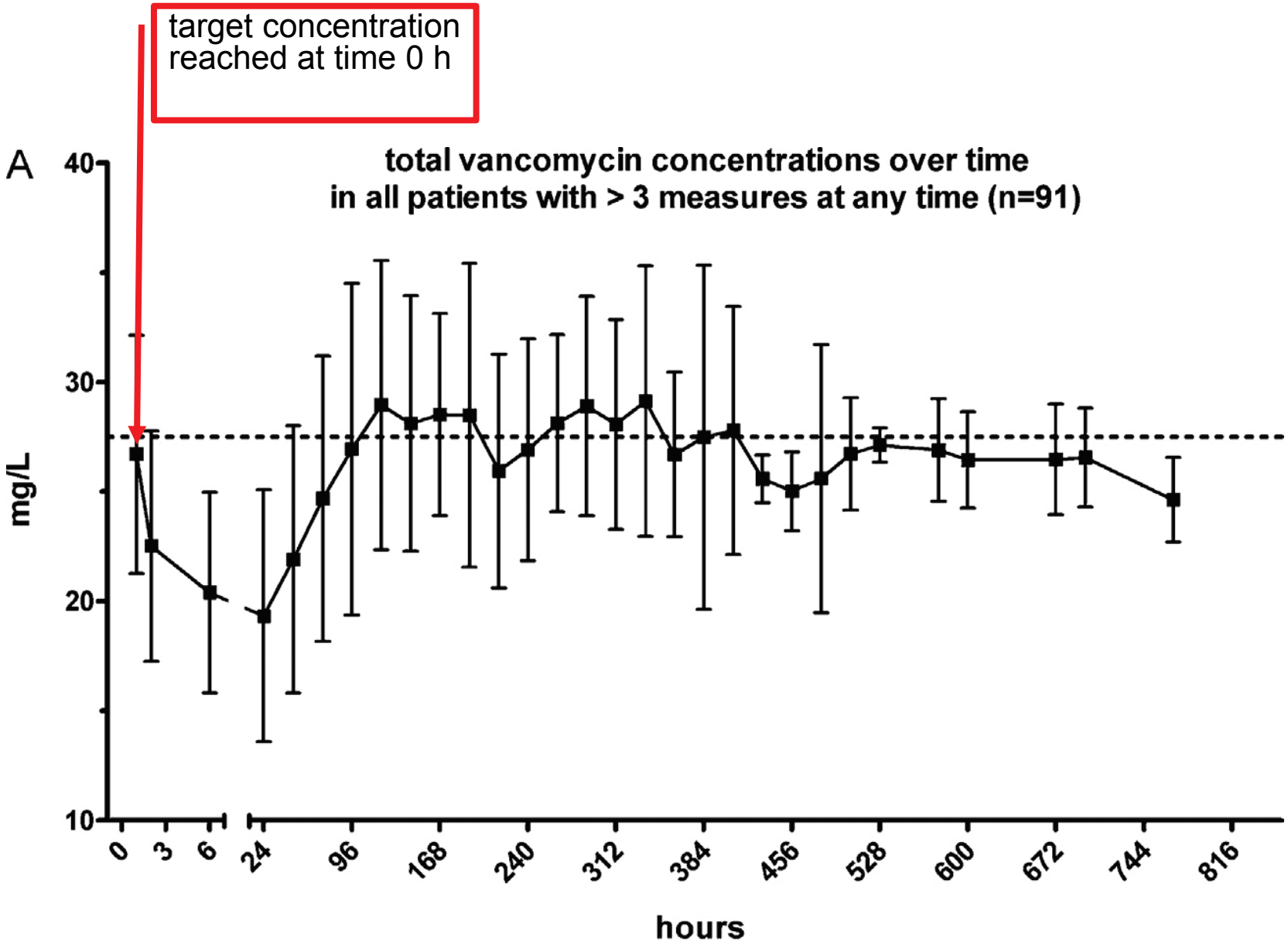
How to reach the serum target concentration target with CI?
2: infusion *



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 must be equal: in = out…)

*** during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance**

7. Total vancomycin serum concentrations



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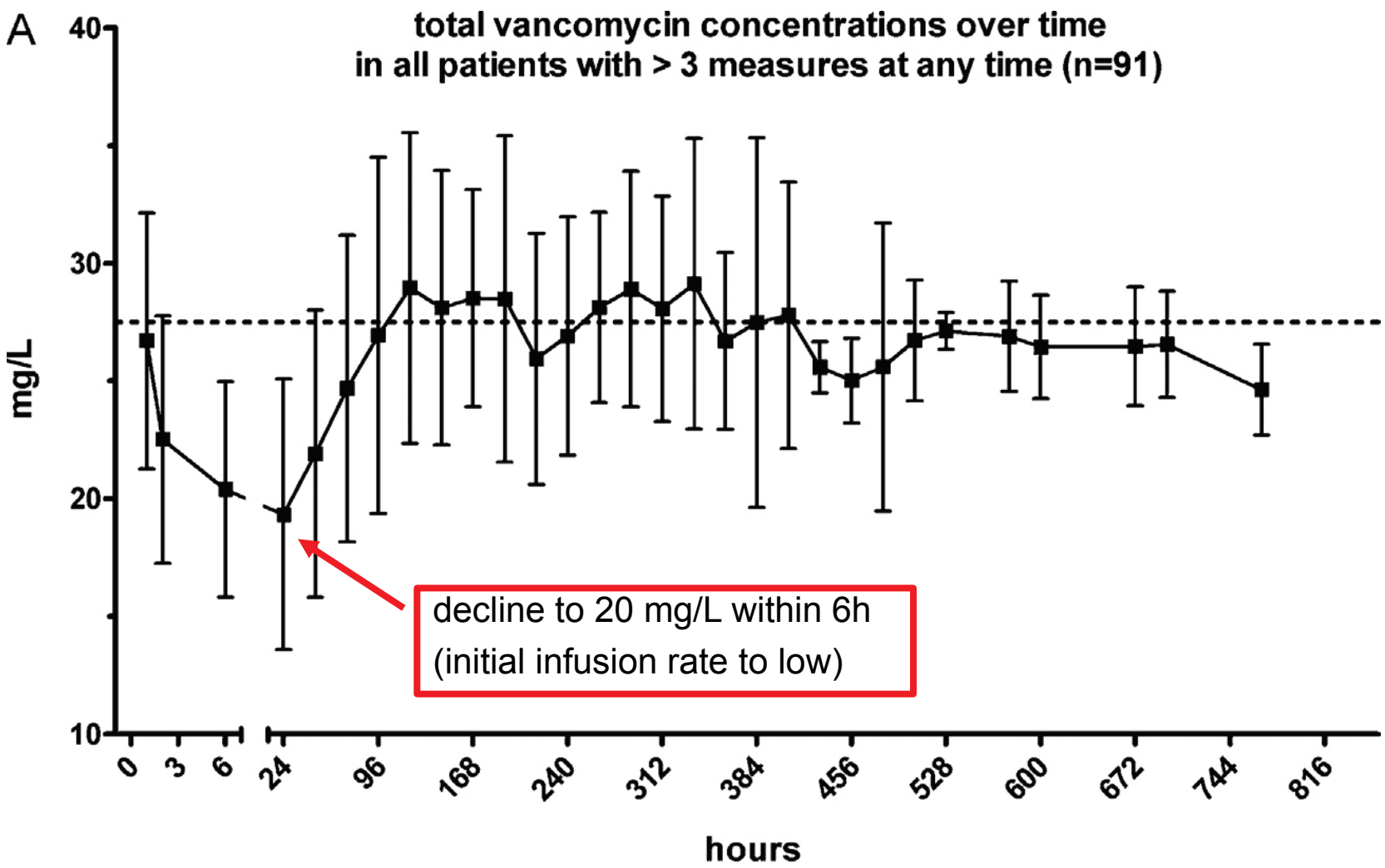

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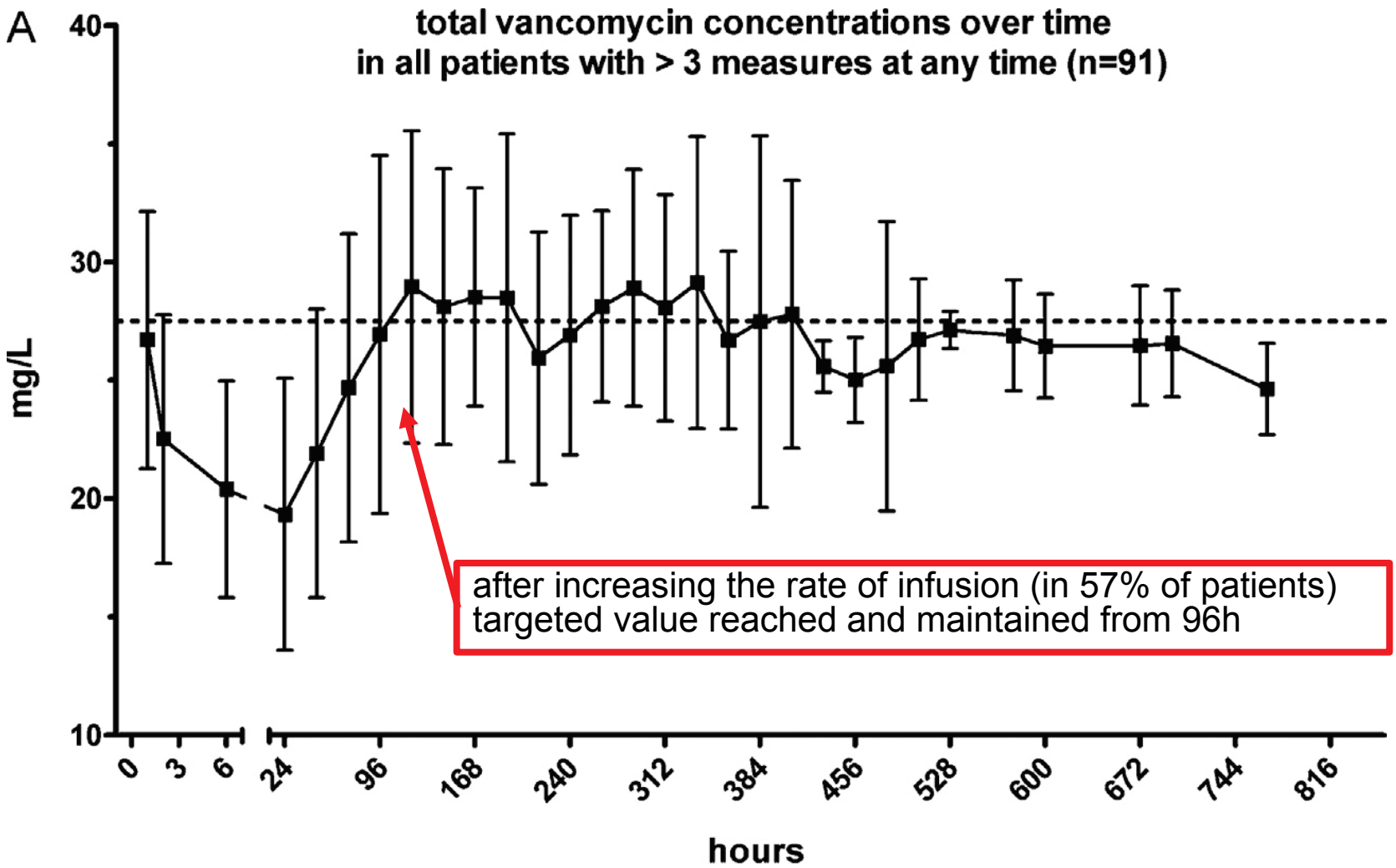

Vancomycin continuous infusion: how does it work

- Loading dose
  - 20 mg/kg (based on actual body weight and an estimated distribution volume of 0.7 L/kg [10-12]) administered over 1 h for doses < 2 g or over 2 h for larger doses.
- Infusion:
  - "bags" are prepared in the Central pharmacy at 10 g/L in 5% glucose solution for infusion and transferred to the wards
  - the preparation is infused with volumetric infusion pump at a rate of 9.5 mL/min
    (corrected for creatinine clearance < or > 90 ml/min)

Note: vancomycin is stable at 37°C for at least 3 days...

(Raverdy V, Ampe E, Hecq JD, Tulkens PM. Stability and compatibility of vancomycin for administration by continuous infusion. J Antimicrob Chemother. 2013 May;68(5):1179-82).

Continuous infusion in Mont-Godinne

- Hospital-wide implementation of CI is feasible and well accepted by health care professionals.
- Centralized preparation facilitated nursing and was perceived as contributing to the quality of care
- Clinical Pharmacists can play an important role in the development and implementation of transversal quality improvement strategies
- CI may help optimizing vancomycin usage in the absence of pharmacokinetic services and may improve the quality of these services if available

Vancomycin: continuous infusion

- **Do the others do the same ?**

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So, you asked about vancomycin…

- Vancomycin
  - short summary of its history and general properties
  - how to measure MICs and heteroresistance
  - vancomycin PK/PD and minimal AUC_{24h}/MIC
  - high doses in America ... and the risks
  - continuous infusion of vancomycin

an old drug and for specific indications: do you have MRSA ?

work with the microbiologist

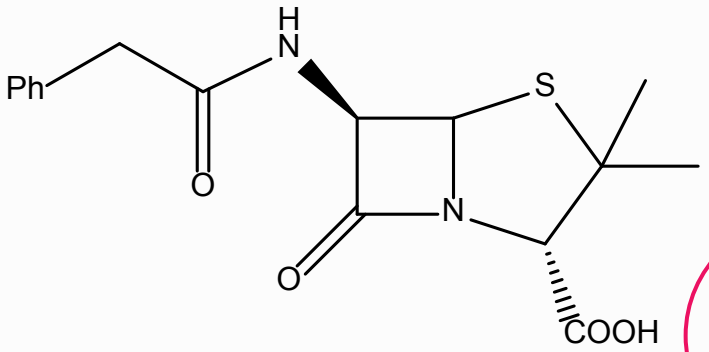
give a sufficient daily dose and monitor levels

be prepared for toxicity

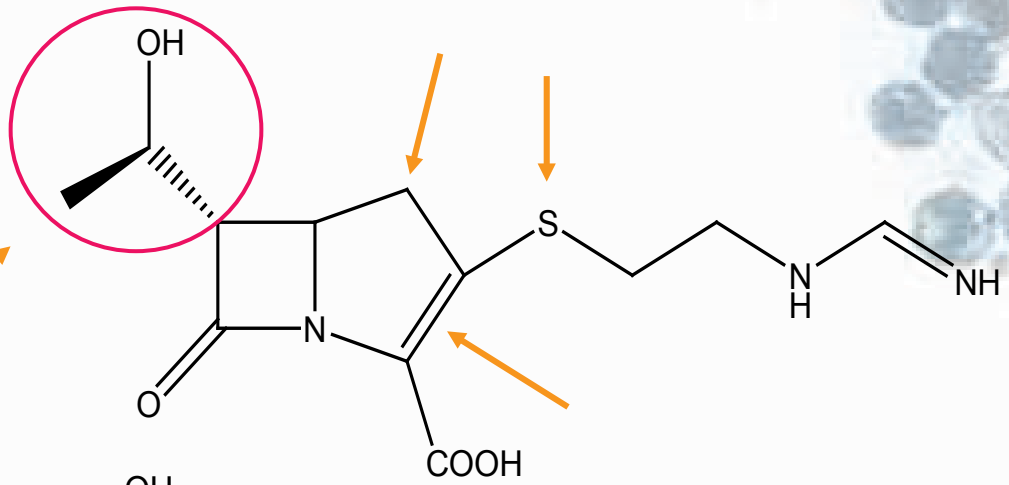
we use it !

Carbapenems

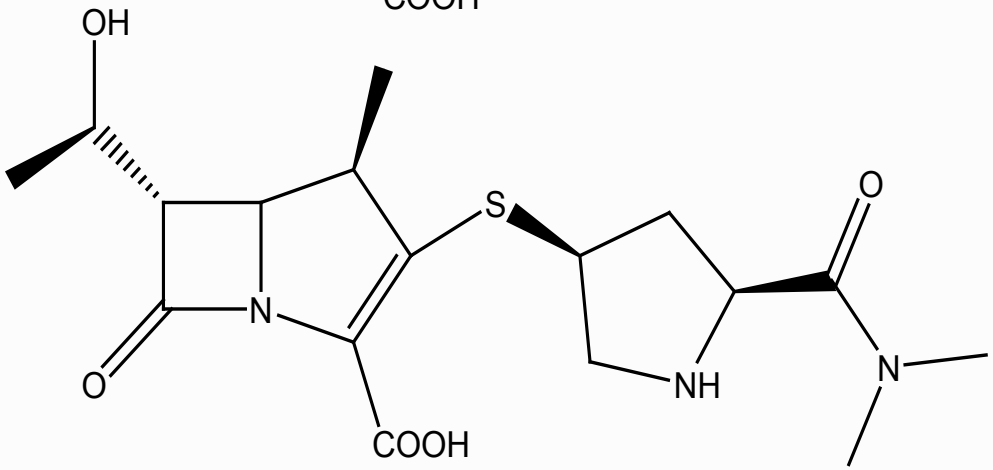
From penicillin to carbapenems



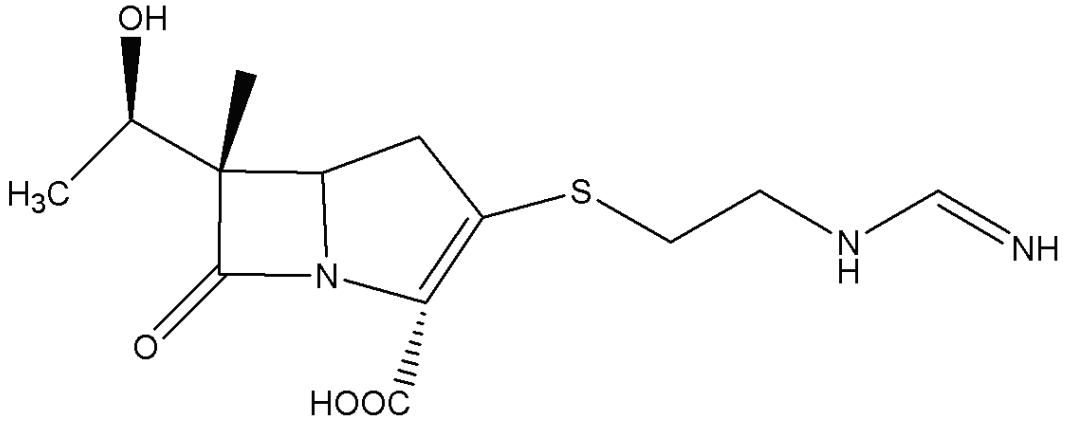
imipenem



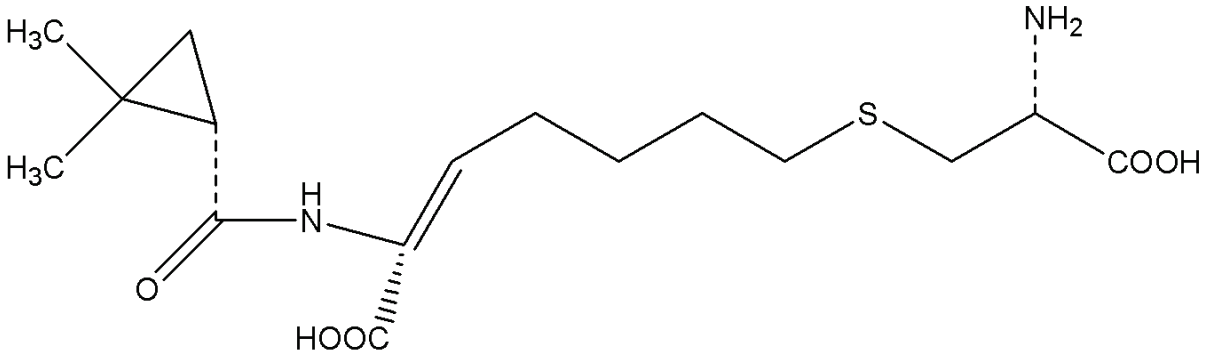
meropenem



Imipenem is ALWAYS with cilastatine



imipenem



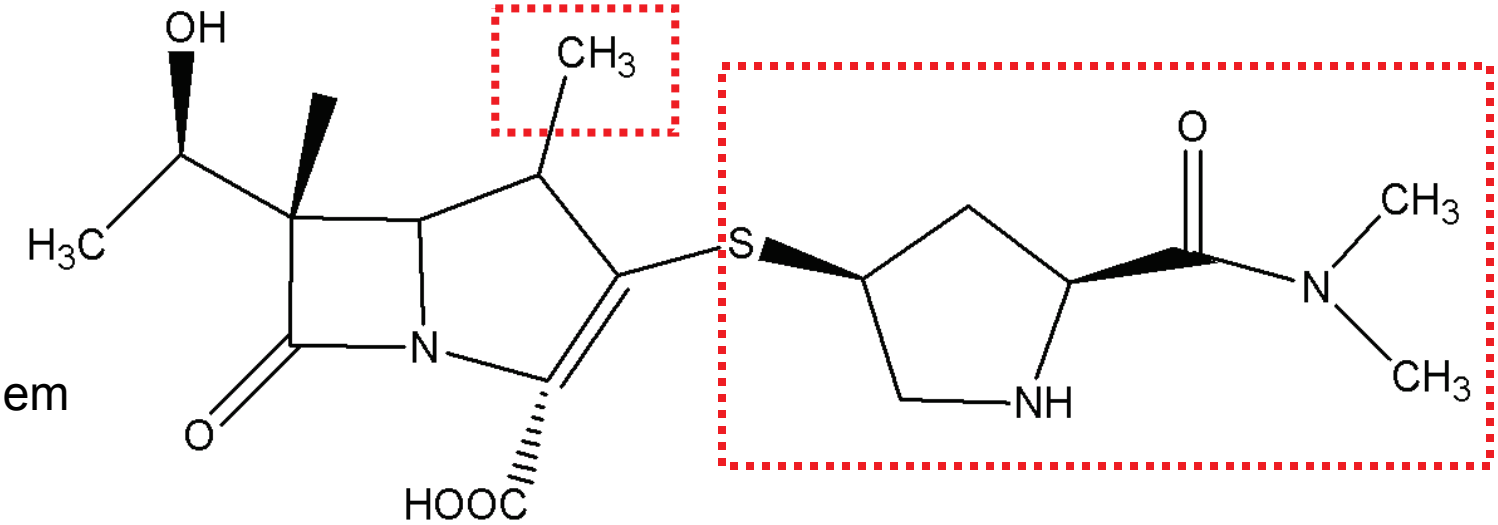
cilastatine

Inhibitor of the déhydropeptidase

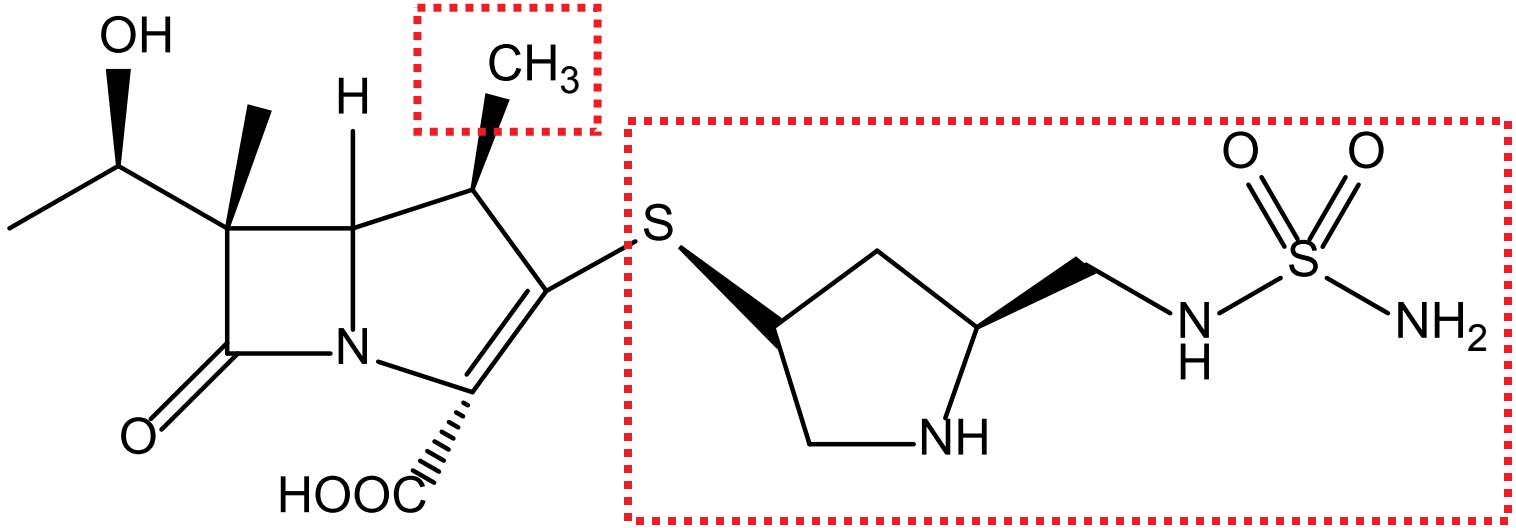
imipenem + cilastatine = **TIENAM ®**

Meropenem and doripenem are "solo" compounds

resistance to the dehydropeptidase through steric hindrance

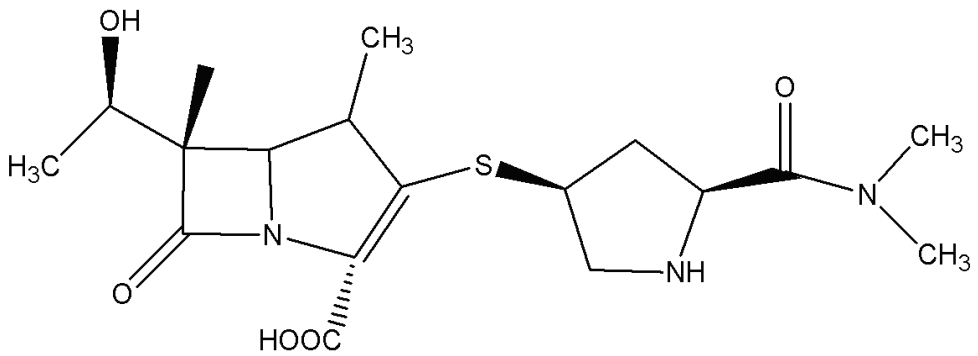


meropenem



doripenem

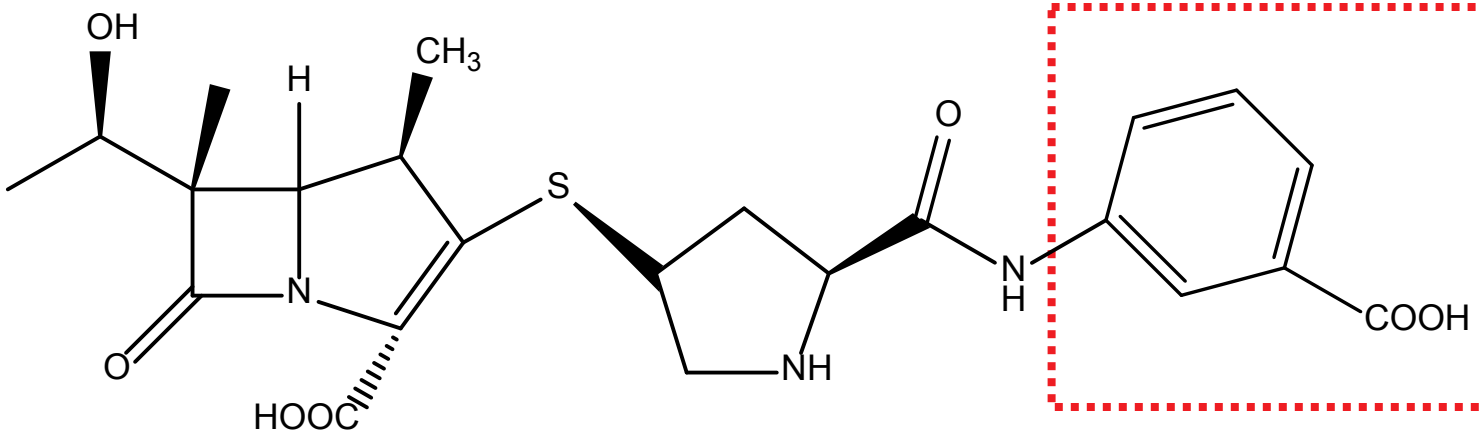
Ertapenem is NOT like other carbapenems



meropenem

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

ertapenem



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

---

* 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: 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**

Pharmacodynamics…

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

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

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

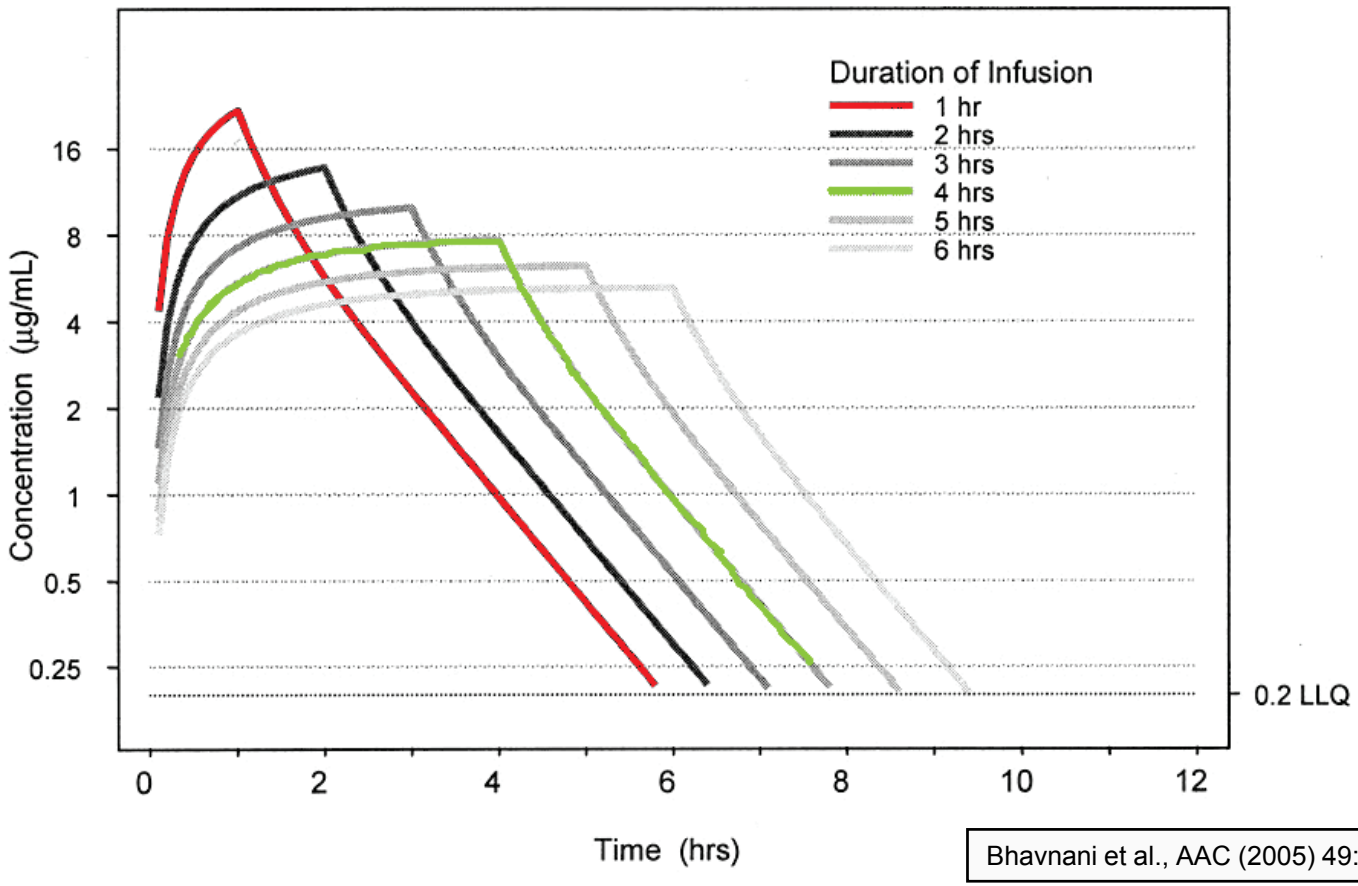
Maximising the utility of the carbapenems

- **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**

Mechanisms of resistance

Gram positive

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

All carbapenems are inactive against MRSA or MRSE ...

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

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

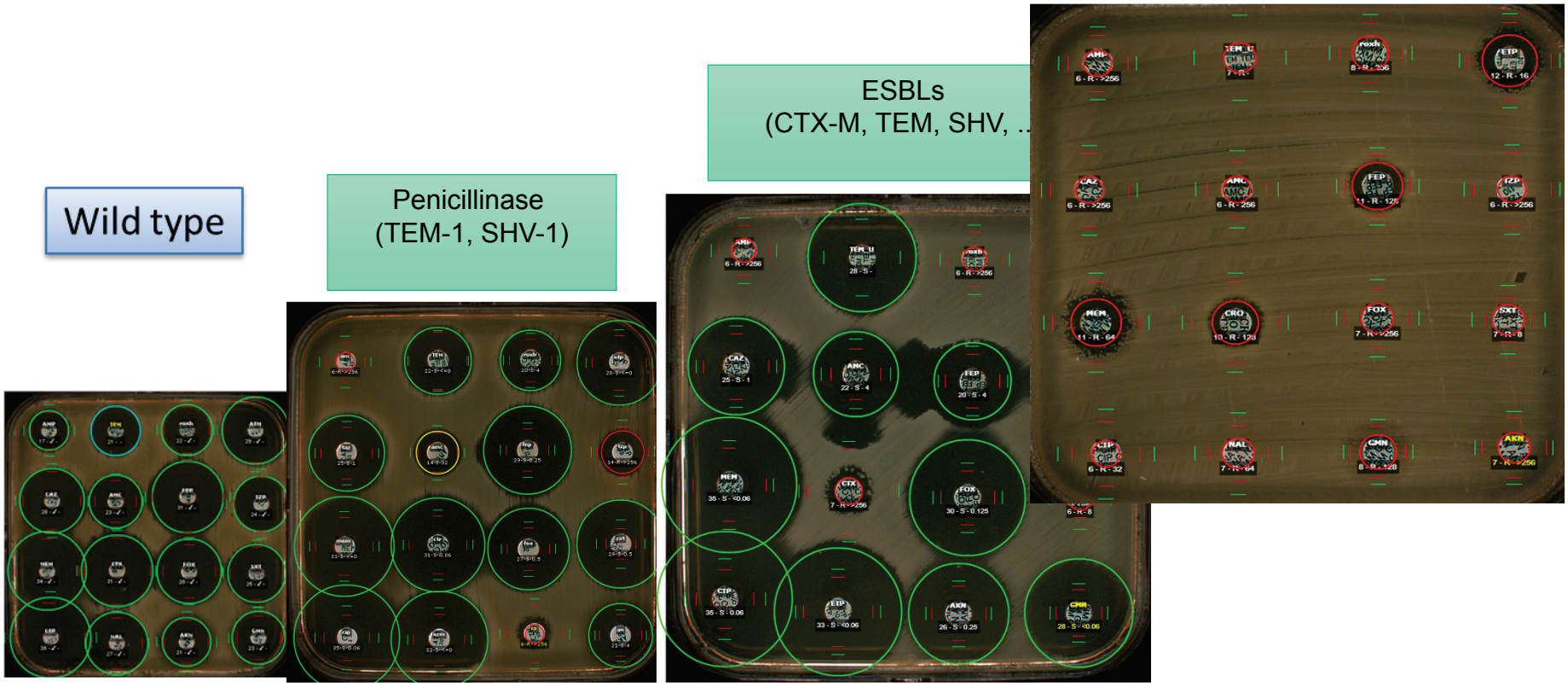
Rapid evolving resistance in Enterobacteriaceae

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

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

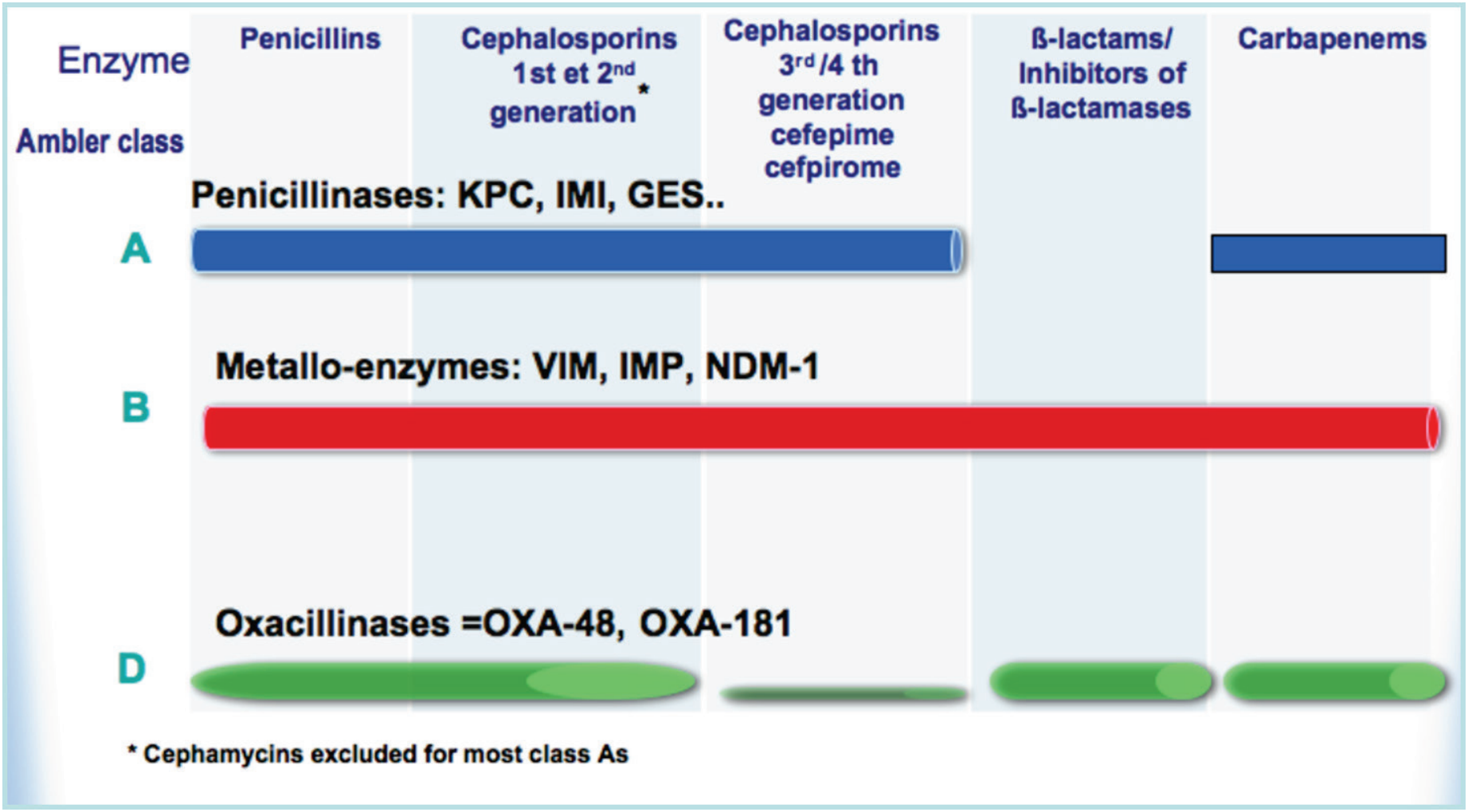
Wild type

Penicillinase
(TEM-1, SHV-1)



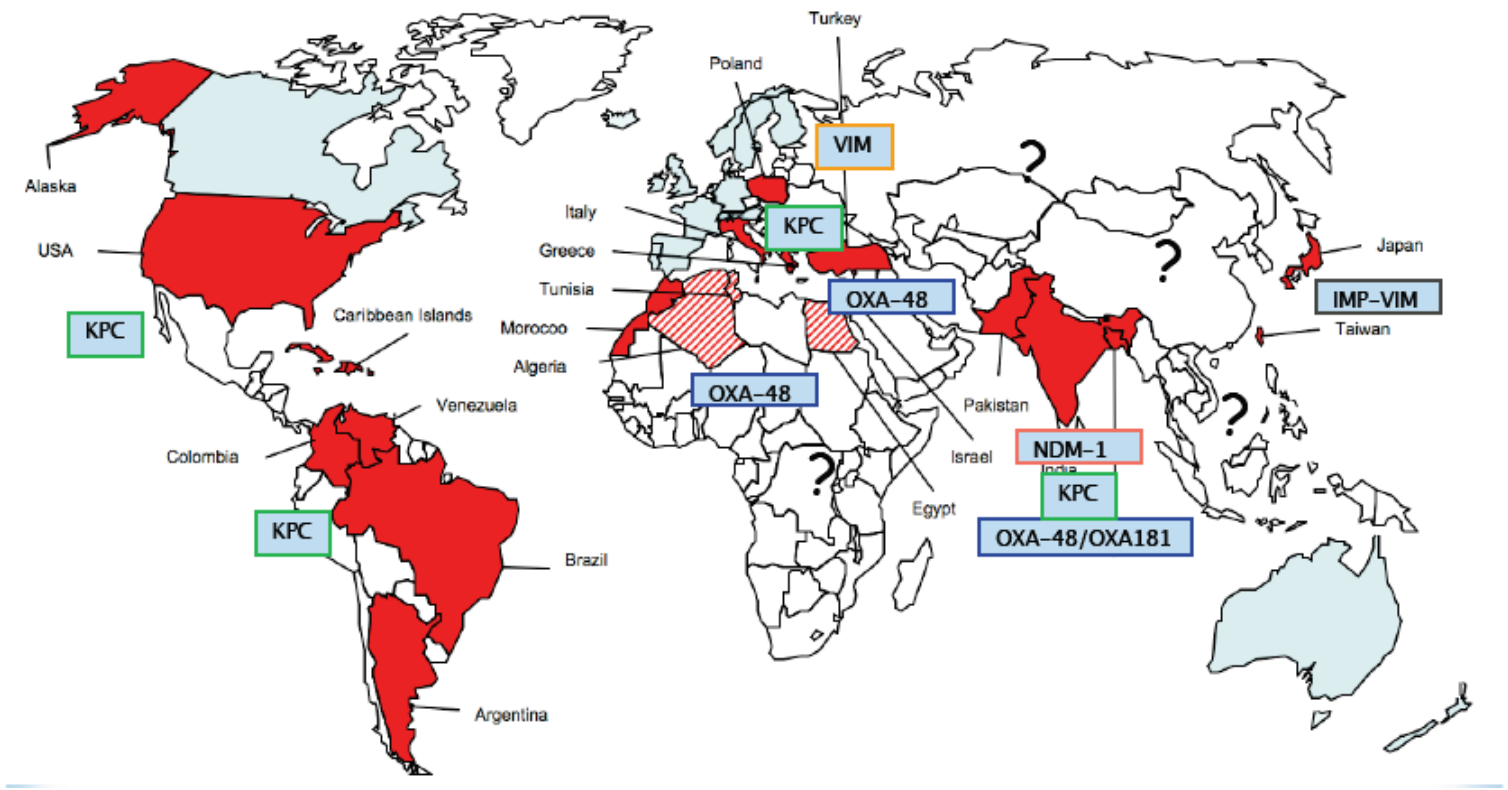
1940 **1970** **1990** **2010**

Classification of the different carbapenemases in *Enterobacteriaceae*



From P. Nordman

Carbapenemase producing- *Enterobacteriaceae*



From P. Nordman

NDM-producers…

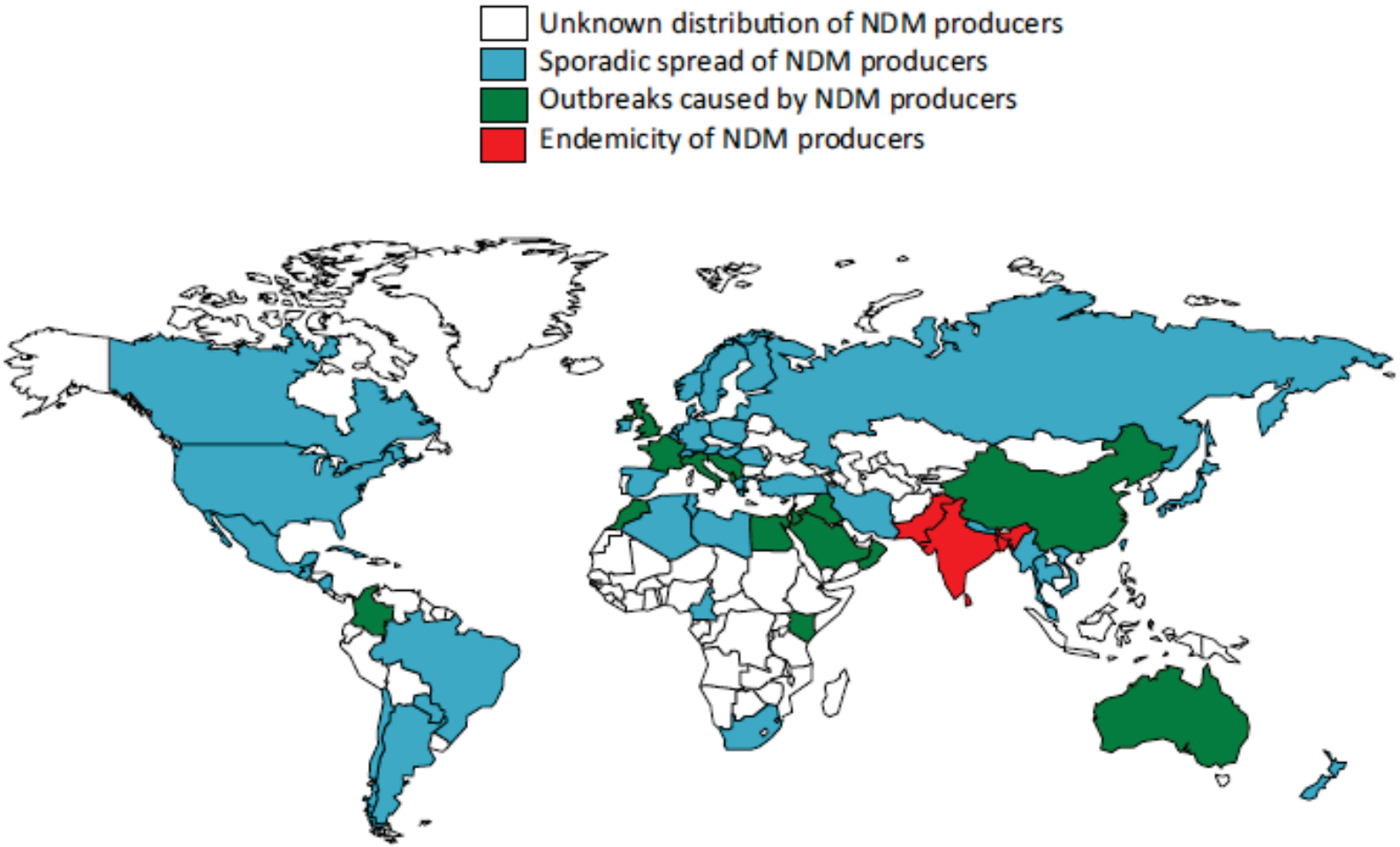


FIG. 2. Geographical distribution of NDM producers.

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

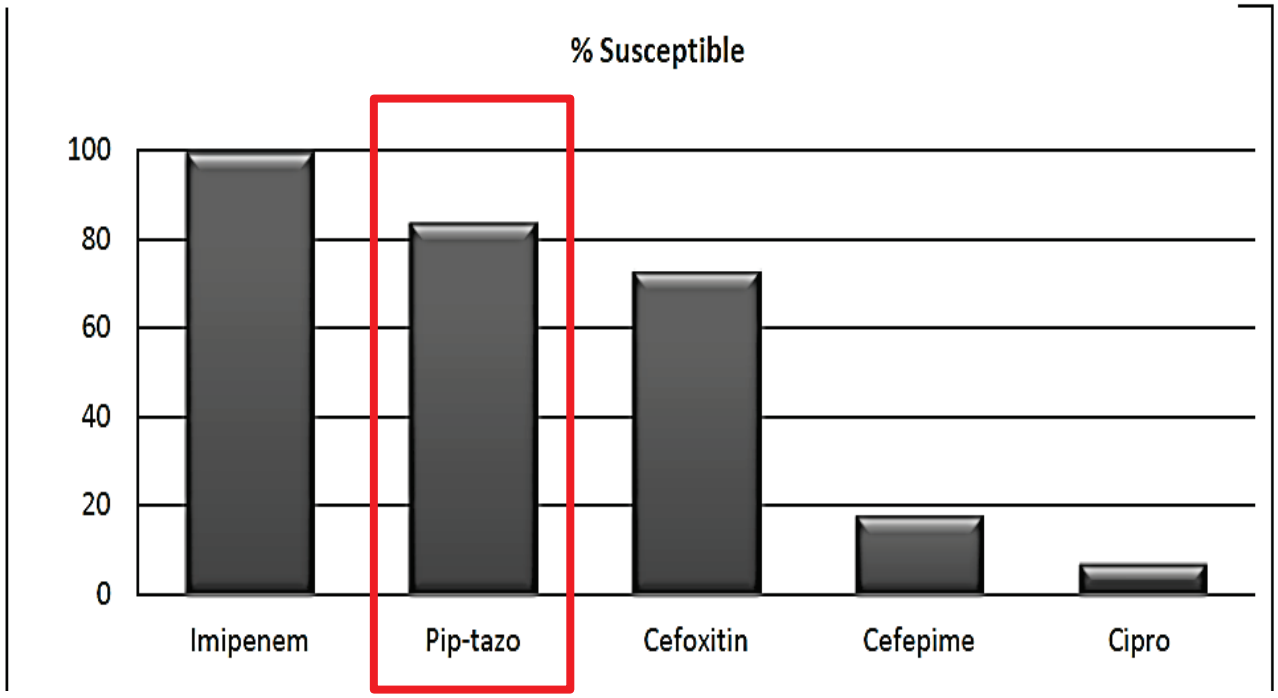
Resistance to carbapenems: why ?

- 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

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]



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]					
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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

Important message if you use 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. I
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 !

What could Bach Mai do ?

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 prev
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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

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**

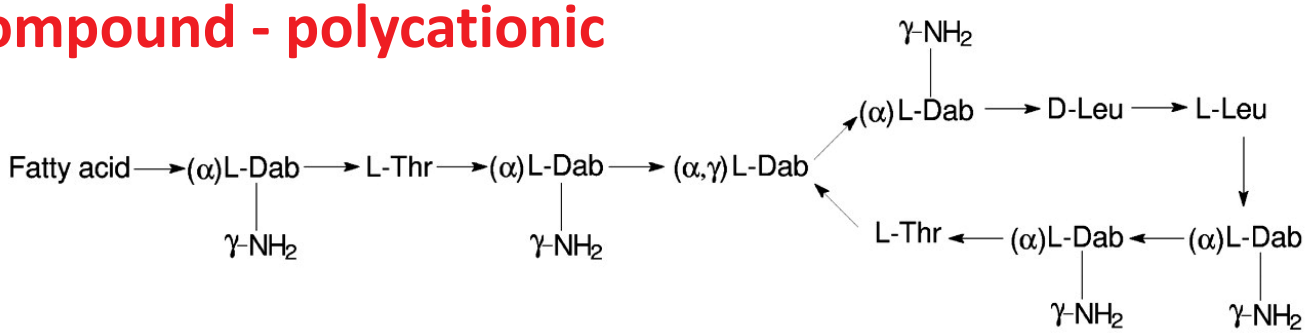
But why do you wish to use carbapenems ?

- 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 ?

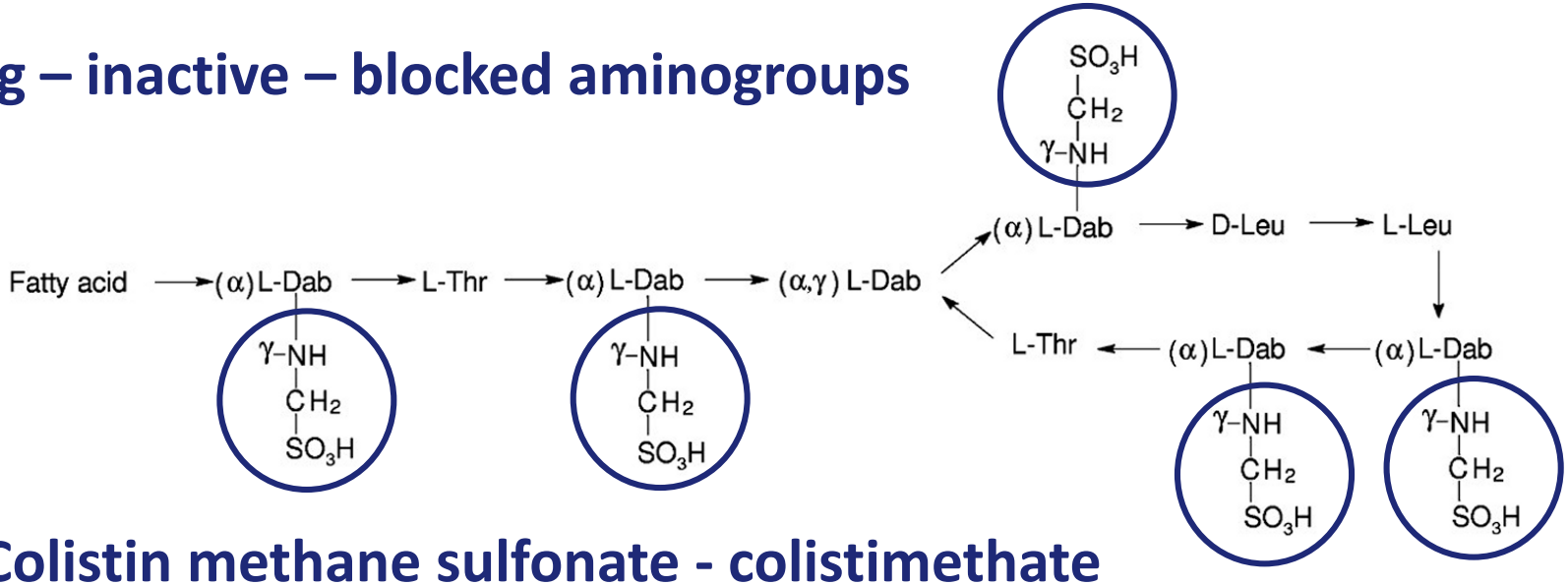
Colistin

Clinical form of colistin

Active compound - polycationic



Prodrug – inactive – blocked aminogroups



Colistin methane sulfonate - colistimethate

- **must be hydrolyzed to act -- has a lower toxicity and a faster elimination**
- **conversion is spontaneous in aqueous media … and complicates PK studies**

Li et al, AAC 2003; 47:1364-1370 – Bergen et al, AAC 2006; 1953-1958

Clinical form of colistin

Colistimethate sodium (IU)	Colistimethate sodium (mg)	Colistin-base activity (CBA) (mg)[1]
12 500	1	0.4
150 000	12	5
1 000 000	80	34
4 500 000	360	150
9 000 000	720	300

[1] Nominal potency of the drug substance = 12.500 IU/mg

European Medicines Agency completes review of polymyxin-based medicines
EMA/785229/2014

Li et al, AAC 2003; 47:1364-1370 – Bergen et al, AAC 2006; 1953-1958

Fate of the clinical form of colistin (colistimethate)

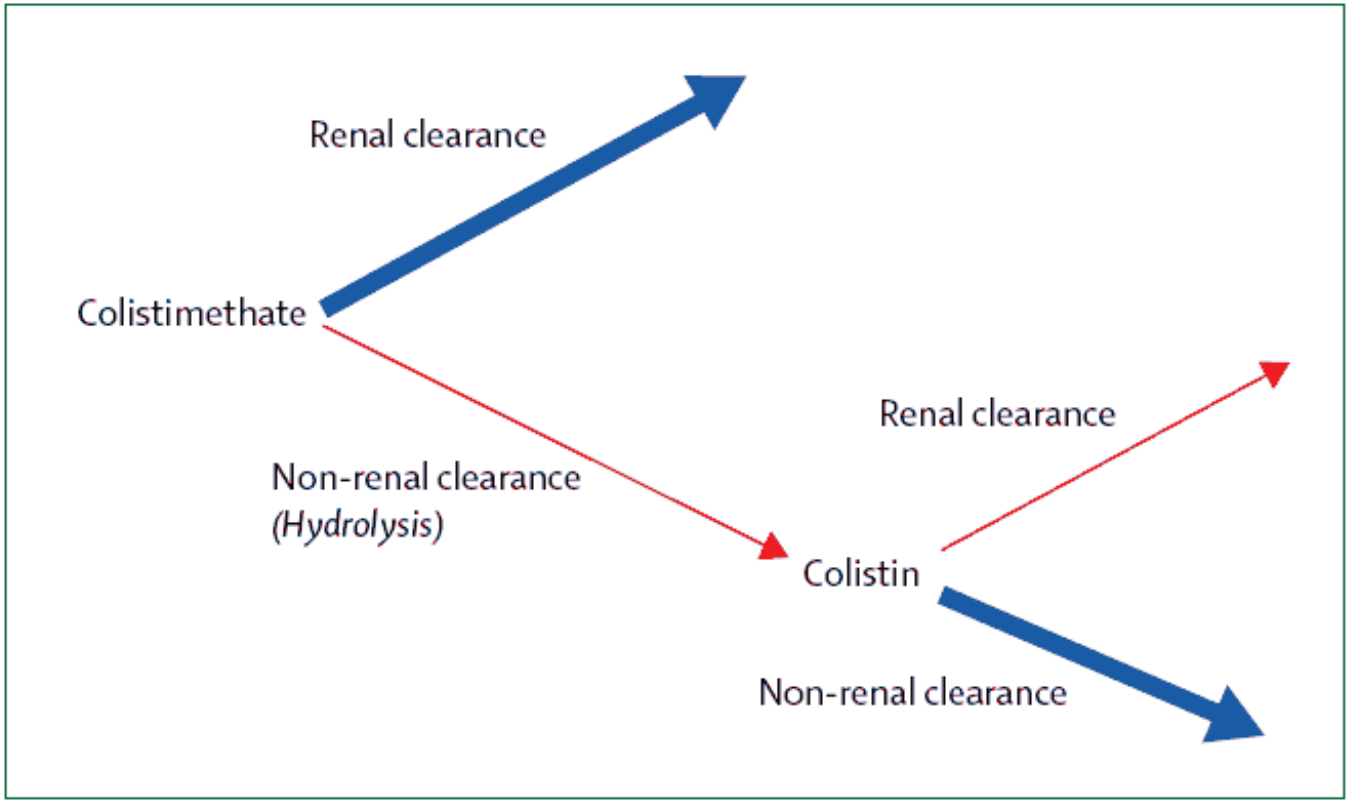
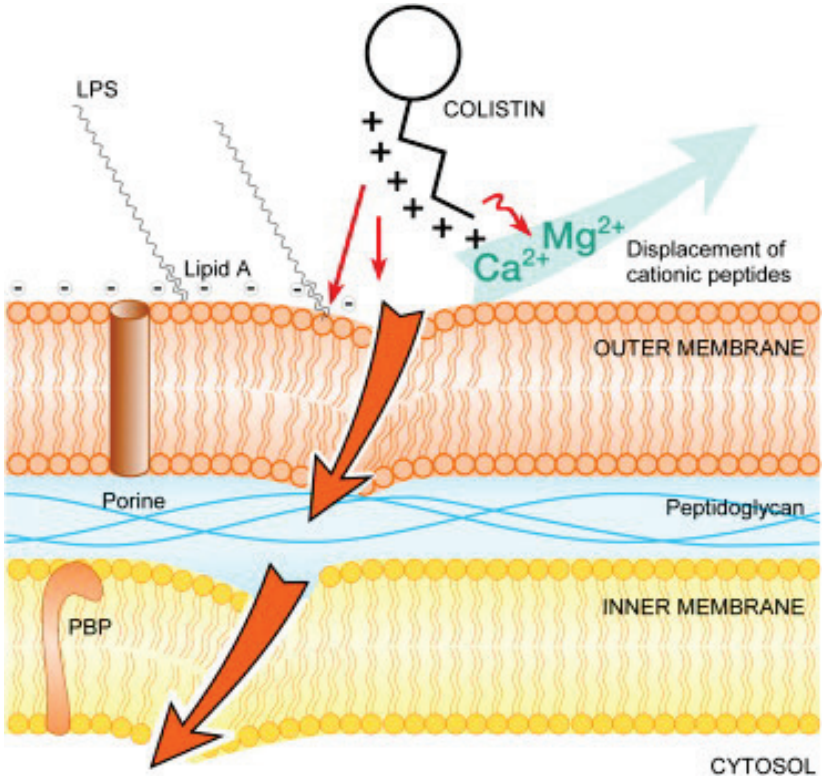


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

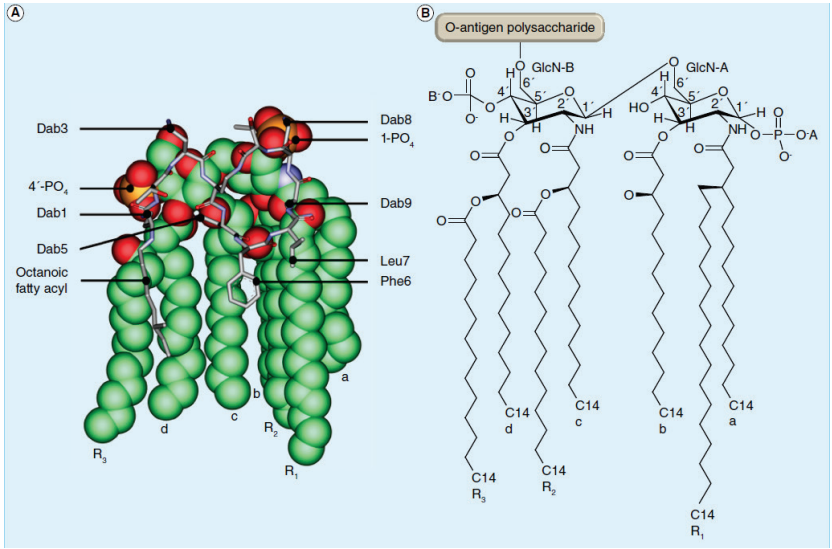
Li et al, Lancet Infect. Dis. 2006; 6:589-601

How do polymyxins work ?

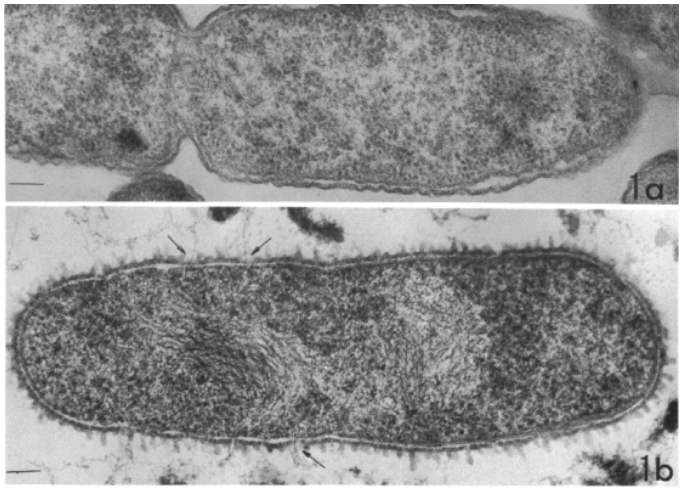
1. Interaction with LPS in the outer membrane



Martis et al, J. Infection 2014; 69:1-12



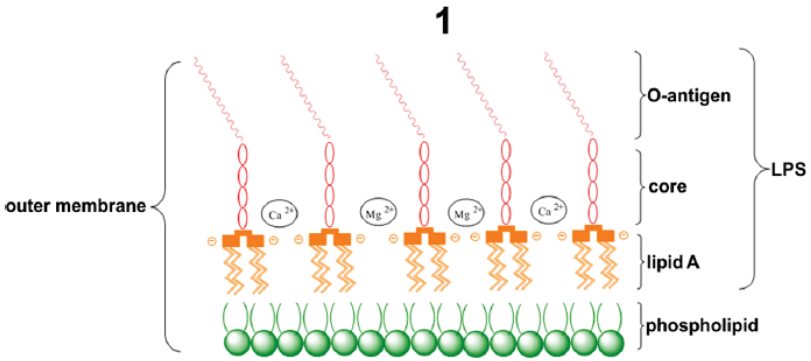
Velkov et al, Future Microbiol. 2013; 8:711–24

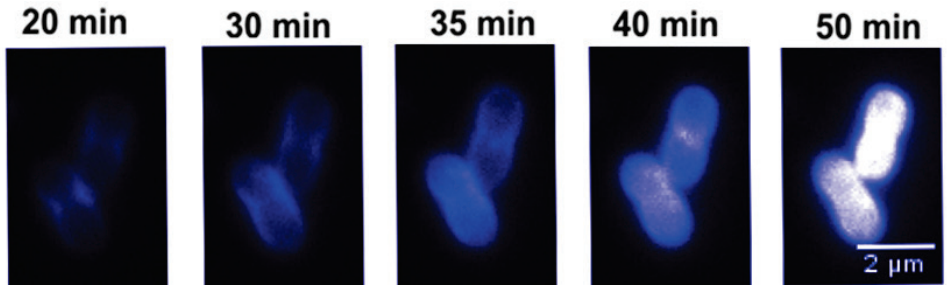


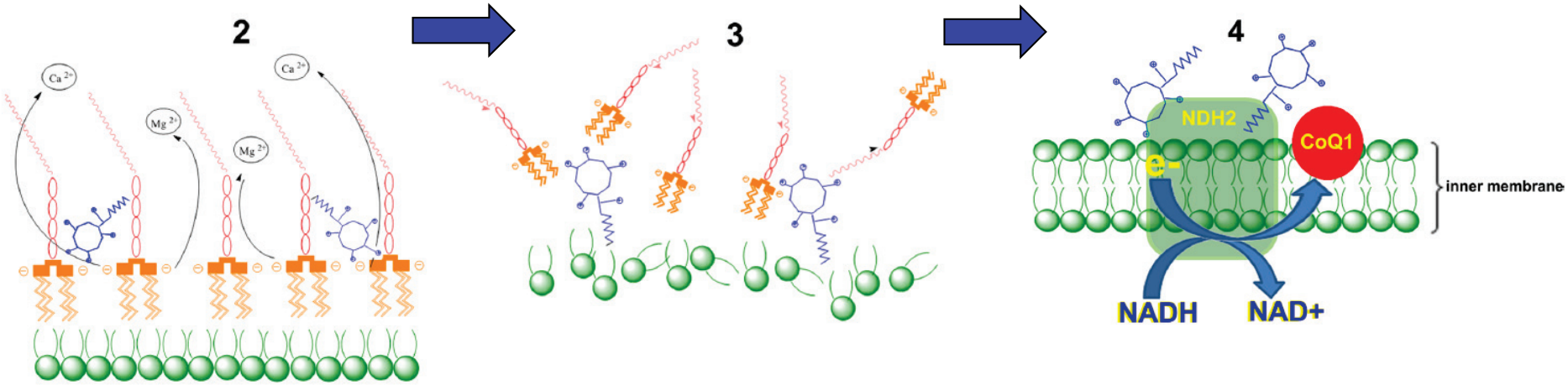
Koike et al, J. Bacteriol. 1969; 97:448-52

How do polymyxins work ?

2. Disruption of envelope integrity and access to bacterial cytosol







Deris et al, Bioconjugate Chem. 2014; 25:750−60; J Antibiot. 2014; 67:147–51

When can you use colistin ?

when you have MDR organisms only…

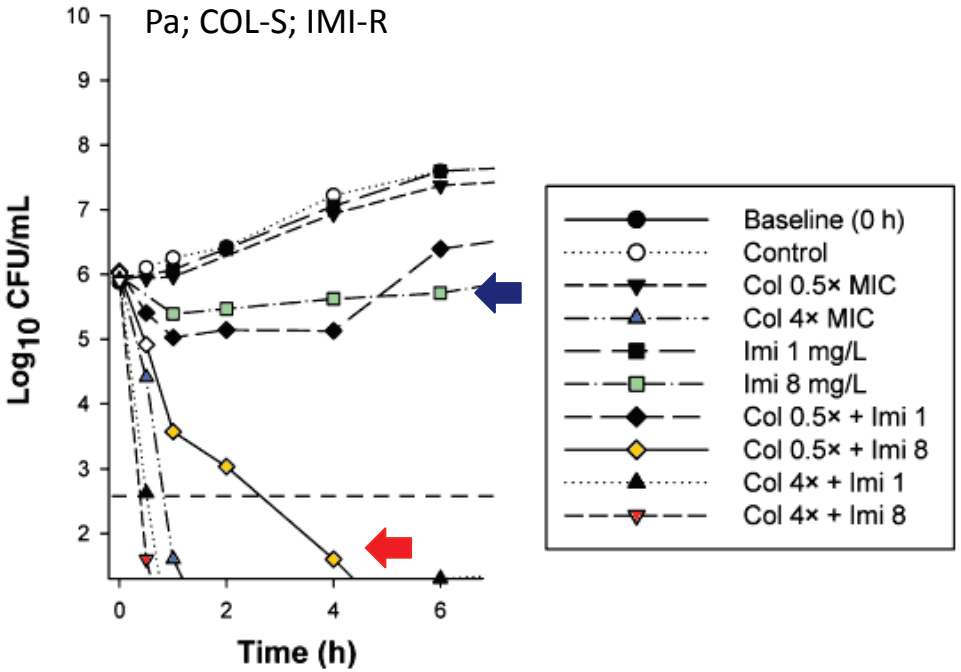
First choice	resistance	Combined with
Acinetobacter baumanii	R to pip-tazo, cephalo III, carbapenems, FQ, AG	+ gentamicin or rifampicin
Enterobacter	R to pip-tazo, cephalo III, carbapenems, FQ, AG	+ gentamicin or rifampicin
Enterobacteriaceae	carbapenemase	+ tigecycline or meropenem or iv fosfomycin or aminoglycoside, …
Pseudomonas aeruginosa	R to pip-tazo, cephalo III, carbapenems, FQ, AG	+ tigecycline or aztreonam or iv fosfomycin or rifampicin, or …

Clinical implications ?

1. Preferential interaction with LPS → spectrum restricted to Gram-negative bacteria

2. Alteration of bacterial integrity → bactericidal activity

3. Facilitated penetration of other drugs inside bacteria
   → synergy in combination
   - Carbapenems, sulbactam
   - Rifampicin
   - Tigecycline, minocycline
   - Fosfomycin
   - Aminoglycosides
   - Fusidic acid
   - Glycopeptides
   - Daptomycin

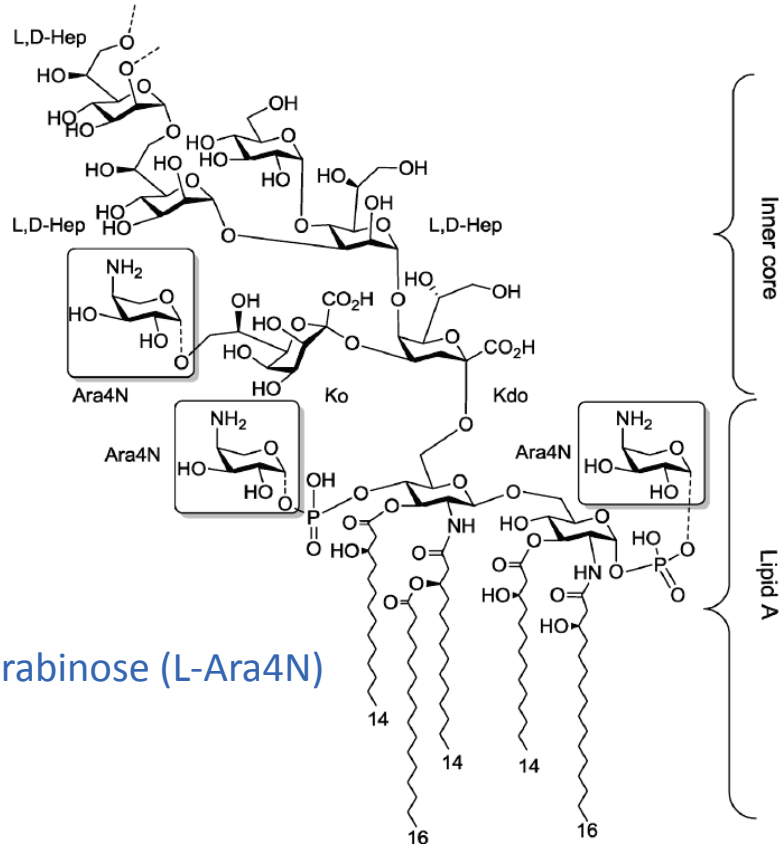


Bergen et al, Pharmacotherapy 2015; 35:34–42

Underlying mechanisms and clinical implications

1. **Intrinsic resistance in specific species (*P. mirabilis, B. cepacia*)**
   - **masking negative charges of LPS**
   - **reduction in sterol content of OM**
   - **production of periplasmic proteases**

→ **Limitation of the activity spectrum**



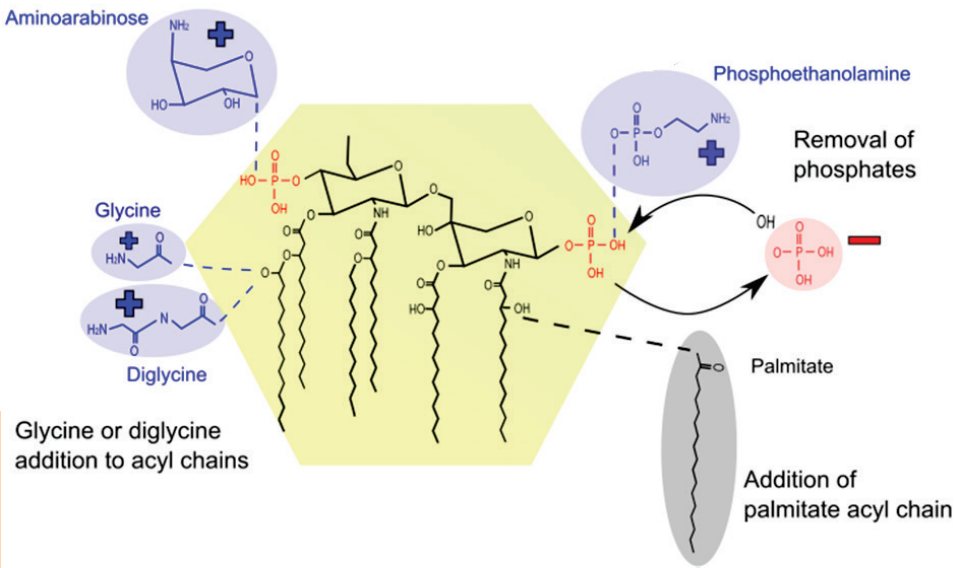
4-amino-4-deoxy-L-arabinose (L-Ara4N)

Loutet & Valvano, Front.Cell Infect.Microbiol. 2011; 1:6; Olaitan et al, Front Microbiol. 2014; 5:643
Velkov et al, Future Microbiol. 2013; 8:711–24

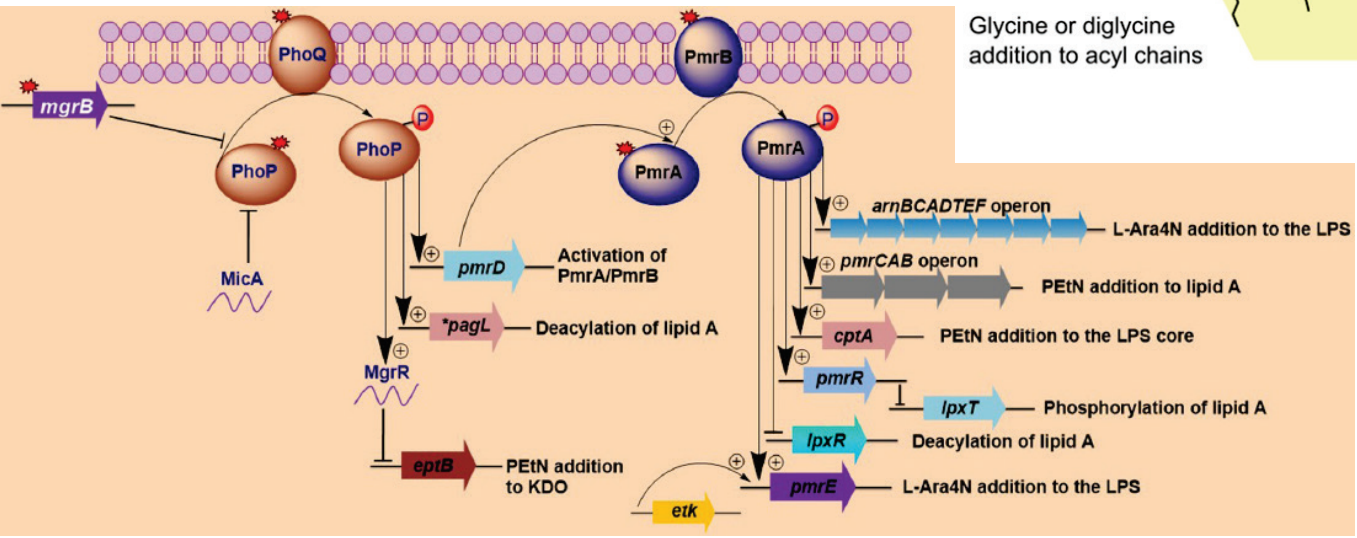
Underlying mechanisms and clinical implications

2. Acquired resistance (modifications of LPS; horizontal transfer possible)

→ Rational use
→ Dose optimization
→ Combinations



Up-regulation of 2-component regulatory systems

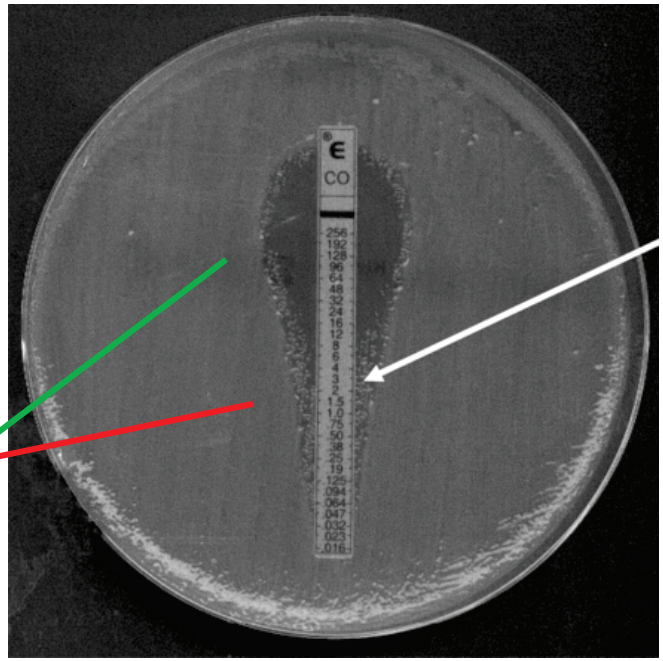


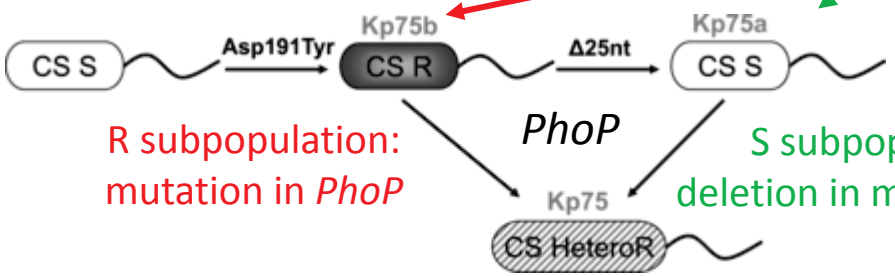
Olaitan et al, Front Microbiol. 2014; 5:643; Band & Weiss, Antibiotics 2015; 4:18-41

Underlying mechanisms and clinical implications

3. **Heteroresistance**
   - **mixture of S and R subpopulations**
   - **compensatory mutations**

→ visible on E-tests only





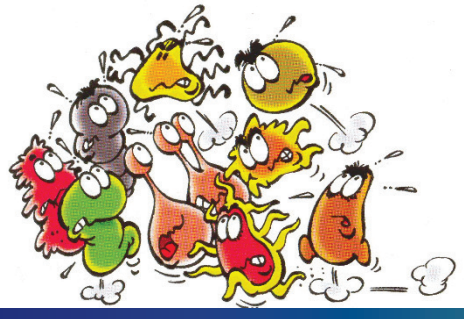
R subpopulation:
mutation in *PhoP*

S subpopulation:
deletion in mutated *PhoP*

Javol et al, AAC 2015; 59:2780-4

Current susceptibility breakpoints

species	EUCAST		FDA	
	S ≤	R >	S ≤	≥ R
Enterobacteriaceae	2	2	-	-
Acinetobacter	2	2	2	4
Pseudomonas	4	4	2	8
Non-enterobacteriaceae	-	-	2	8



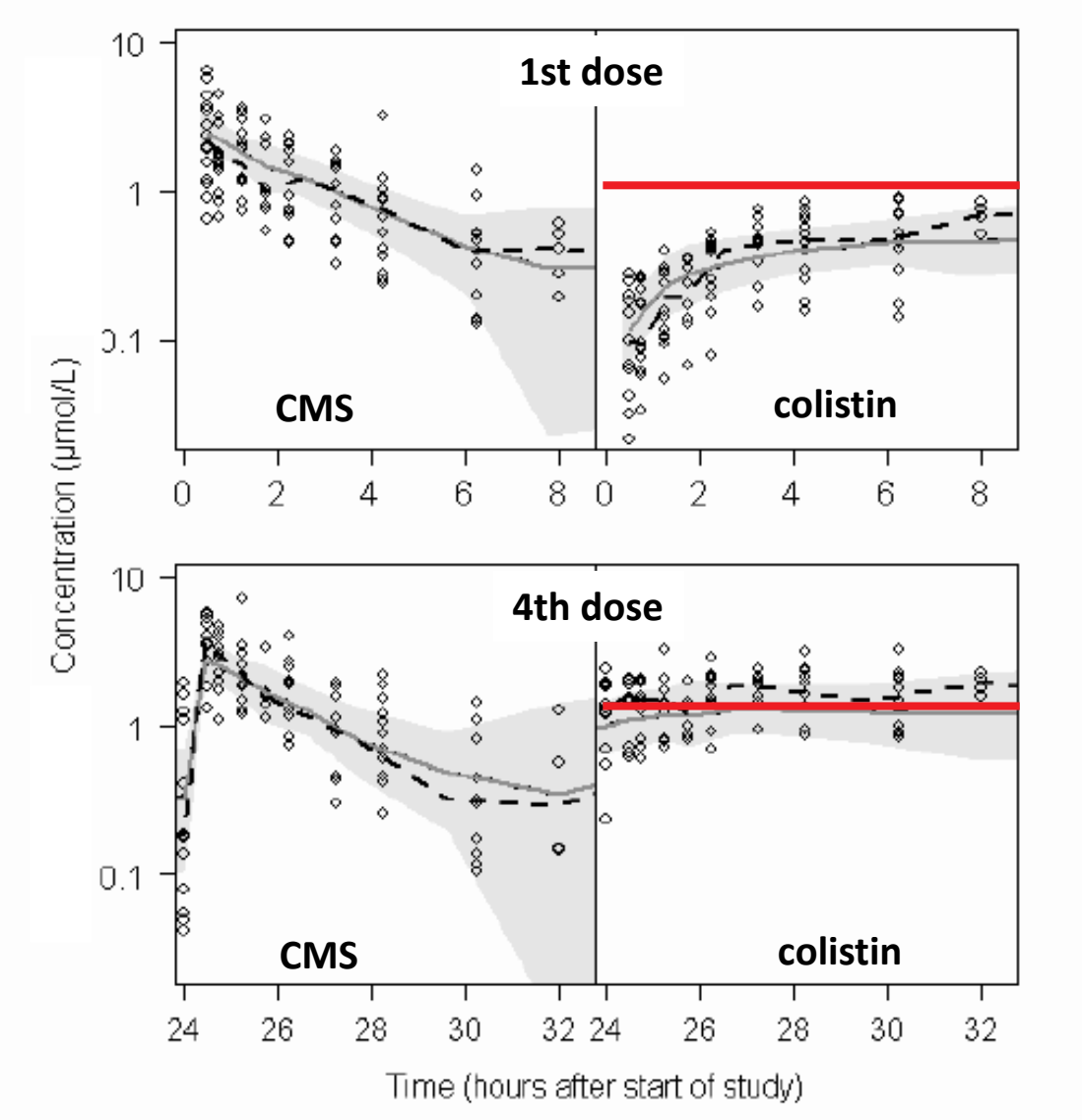
PK in critically-ill patients

Dosage (colistin methane sulfonate [CMS]): 240 mg (3 x 10^6 U) every 8h

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

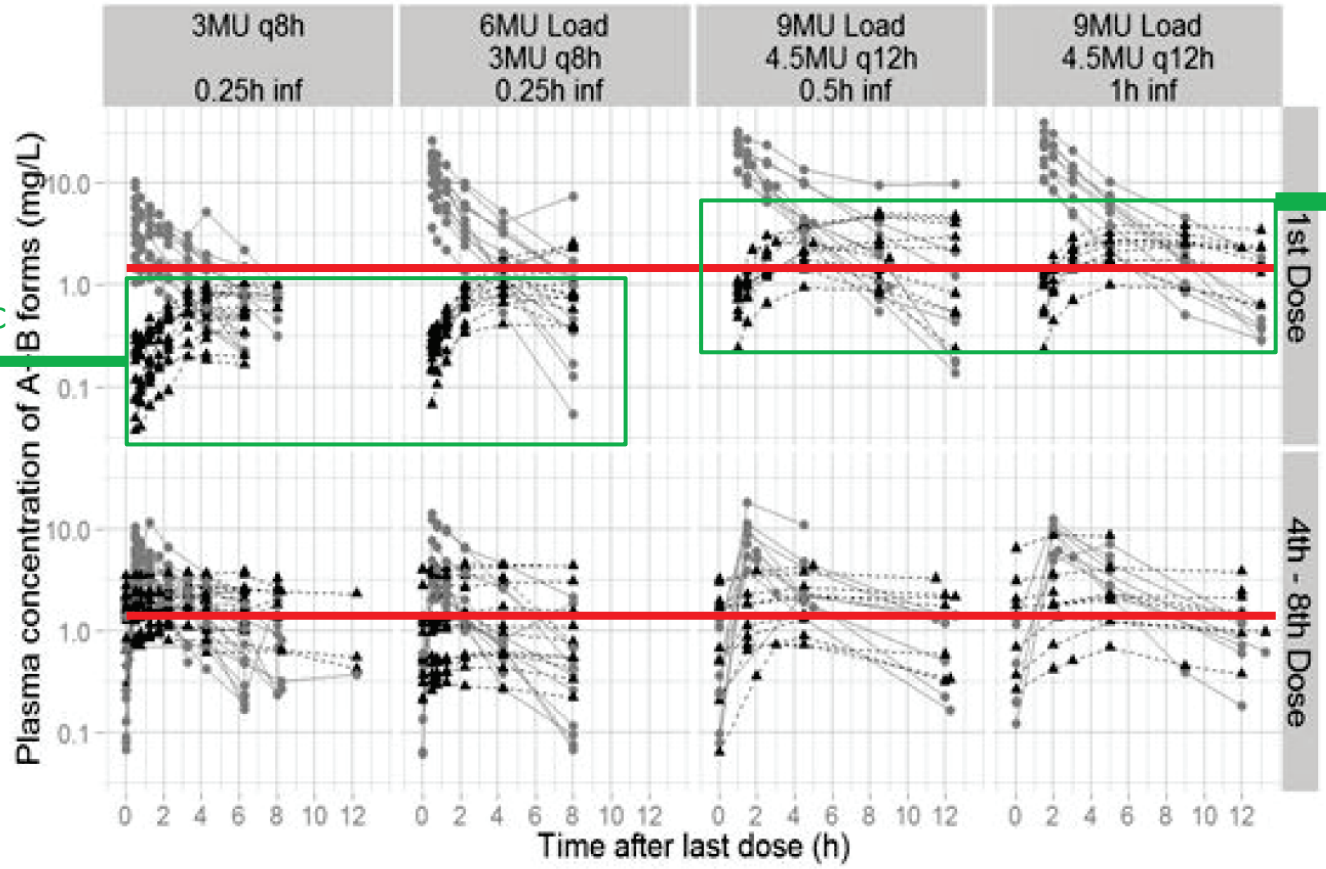
Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

Conclusions: Colistin long half-life and insufficient plasma concentrations before steady state suggest the necessity of a loading dose …



Plachouras et al, AAC 2009; 53:3430-6

Usefulness of a loading dose in critically-ill patients



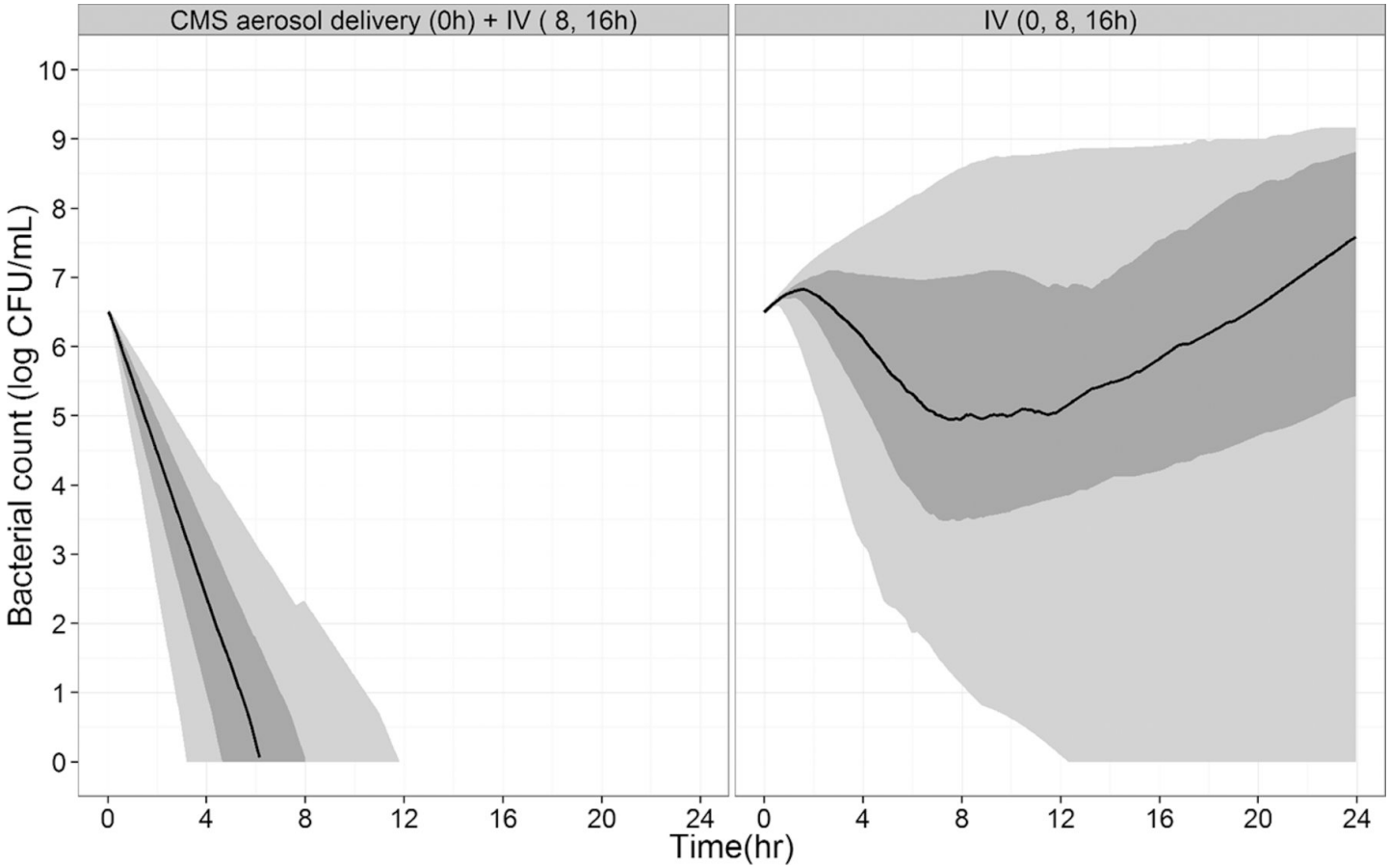
subtherapeutic levels

therapeutic levels in part of the population

Karaiskos et al, AAC 2015; epub [PMID: 26369974]

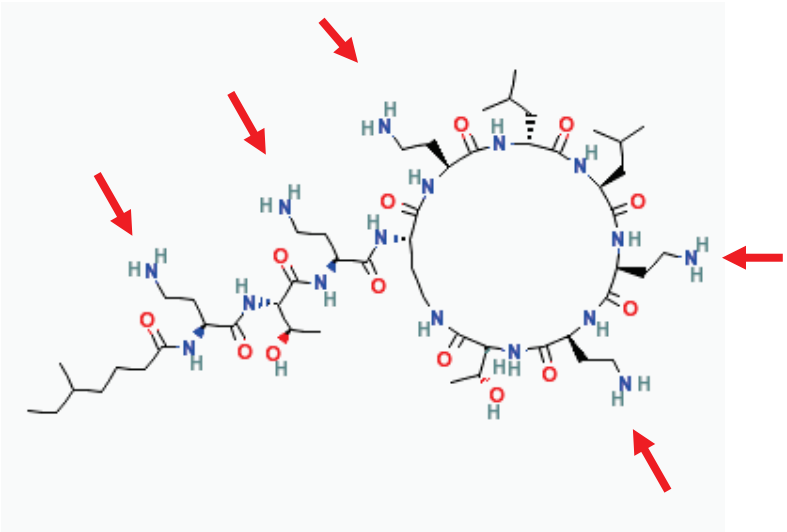
Pulmonary delivery: PK/PD rationale

Predicted bacterial count over time after CMS aerosol delivery (2 MIU followed by 2 MIU i.v. at 8 h and 16 h) or i.v. administration (2 MIU every 8 h).



Boisson et al, AAC 2014; 58:7331-9

A reminder: what is colistin ?



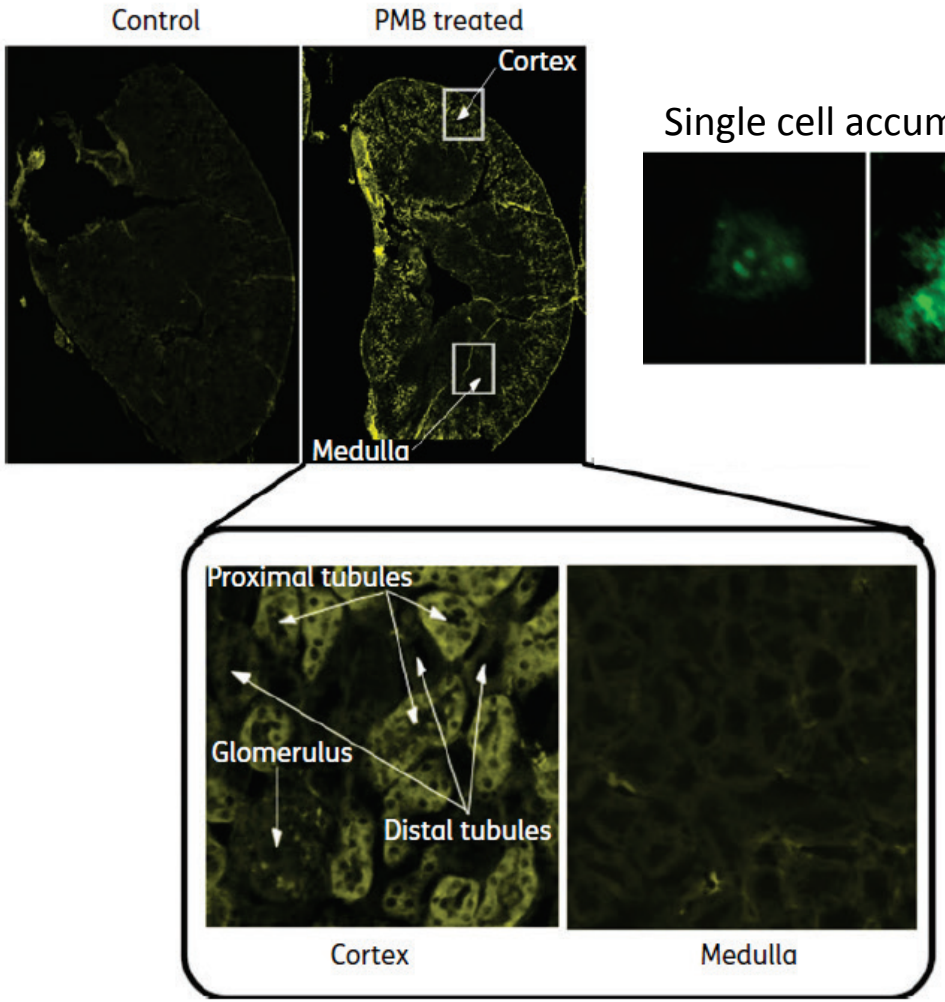
A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain

→ Interaction with eukaryotic cells ?

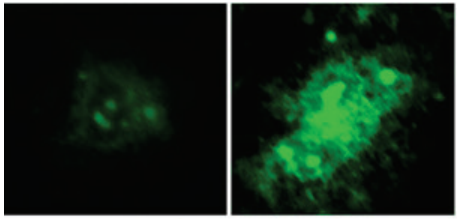
Toxicity:
the other flip of the coin

What about renal toxicity ?

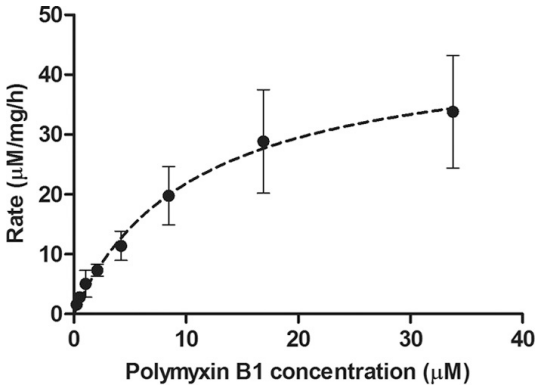
1. Polymyxins are reabsorbed by renal tubular cells and cause oxidative stress



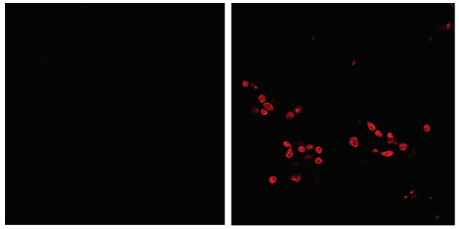
Single cell accumulation



Saturable process (megalin)



ROS production



Yun et al, JAC 2015; 70: 827–9; Abdelraouf et al, AAC 2014; 58:4200-2; Azad et al, Anal Chem 2015; 87:1590-5

Renal toxicity in clinical practice

Huge variability in prevalence among studies (33-61%)

- Limited number of patients included
- Severity of underlying renal disease variable
- Dose of colistin variable
- Definition of nephrotoxicity variable:

The impact of definition on an individual cohort

Definition	Incidence NTX (n=60)
AKIN	37 (62)
RIFLE	33 (55)
Increase Scr 0.5 or Decrease Clcr 50%	35 (58)
50% increase in Scr or RRT	33 (55)
Scr ≥ 2 or Decrease Clcr 50% or RRT	21 (35)
Doubling of Serum creatinine	16 (27)

Pogue JM et al ECCMID 2014

Risk factors for nephrotoxicity (1/2)

Cox Proportional Hazard Regression Model for Acute Kidney Injury Risk Based on Cumulative Colistin Dose

Variable[a]	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age	1.04 (1.01–1.06)	.003	1.03 (1.0–1.05)	.03
Baseline renal impairment	5.06 (2.4–10.6)	<.001	4.15 (1.9–9.2)	<.001
SOFA score	1.12 (1.01–1.24)	.03	1.09 (.9–1.3)	.19
Adjuvant ascorbic acid	0.26 (.12–.56)	<.001	0.27 (.13–.57)	<.001

Dalfino et al, CID 2015; doi 10.1093/cid/civ717

Risk factors for nephrotoxicity (2/2)

Multivariate analysis for independent risk factors for colistin-associated nephrotoxicity

End of treatment		
Variable	**Odds ratio (95% CI)**	**P**
Age	0.98 (0.93-1.03)	0.51
Charlson score	1.3 (1.01-1.57)	0.036
Albumin	0.59 (0.25-1.38)	0.22
CMS cumulative dose	0.99 (0.98-1)	0.38
CMS duration treatment	1.03 (0.98-1.08)	0.24
C_{min}	2.1 (1.33-3.42)	0.002
[3]NSAID use	5.09 (0.9-28.54)	0.64
Loop diuretic use	1.97 (0.61-6.38)	0.25
Co-administration of > 2 nephrotoxic drugs	2.61 (1–6.7)	0.049

[1]CMS:colistinmethanesulfonate sodium. [2]C_{min}: colistin trough plasma concentrations at steady state. [3]NSAID: non-steroidal anti-inflammatory drugs.

Incidence of AKI on day 7 and at the EOT related to quartiles of C_{min} values at steady state

	Cmin (mg/dL)			
	≤ 0.56	**0.57-1.04**	**1.05-2.2**	**> 2.2**
Nephrotoxicity on day 7	1 (4)	0 (0)	8 (32)	17 (65.4)
	Cmin (mg/dL)			
	≤ 0.56	**0.57-1.04**	**1.05-2.2**	**> 2.2**
Nephrotoxicity at the EOT	5 (20)	10 (38.5)	13 (52)	22 (84.6)

Data are n (%) of patients in each concentration category.

Sorli et al, BMC Infectious Diseases 2013, 13:380

Relationship between C_{min} and toxicity

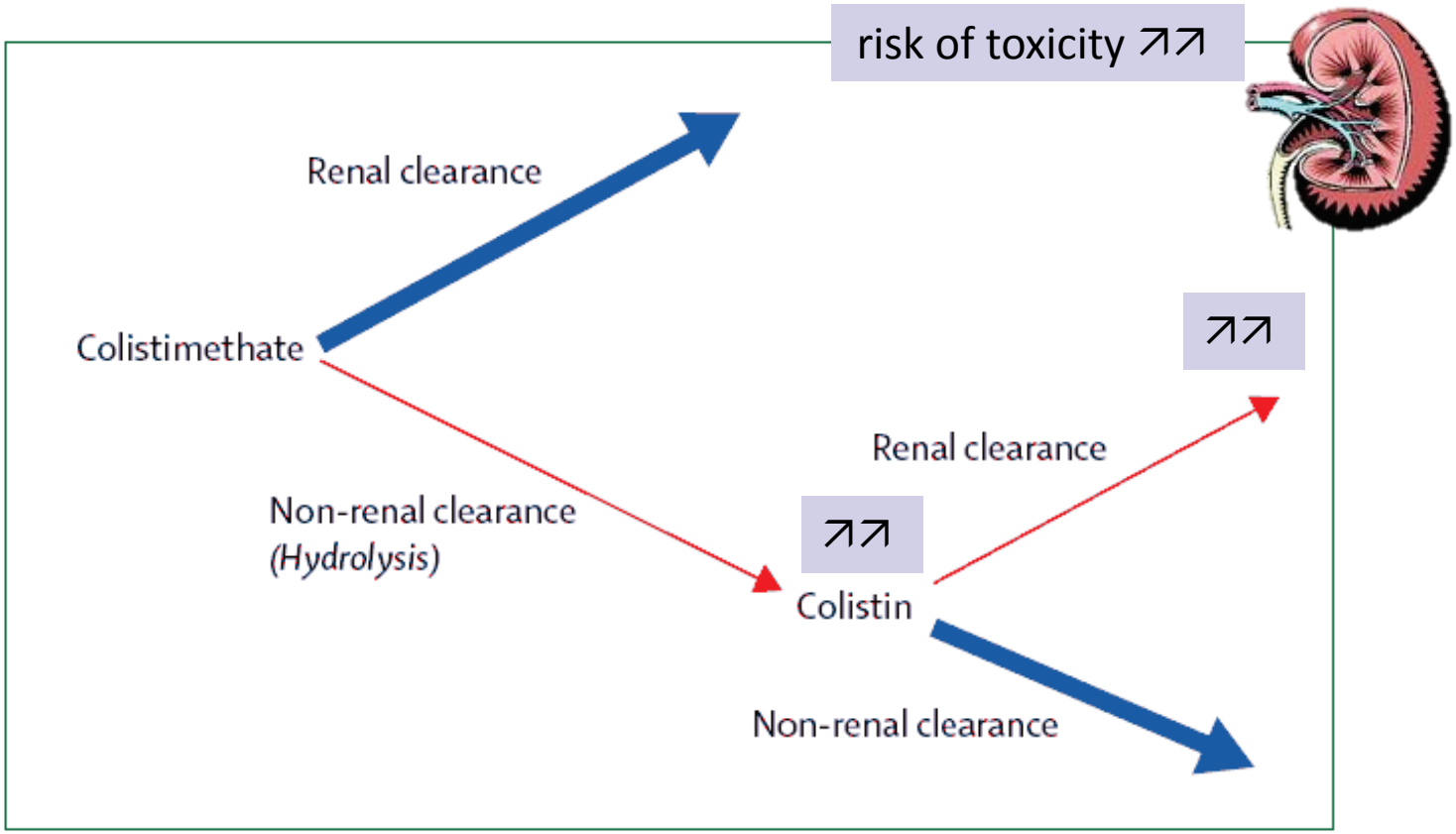
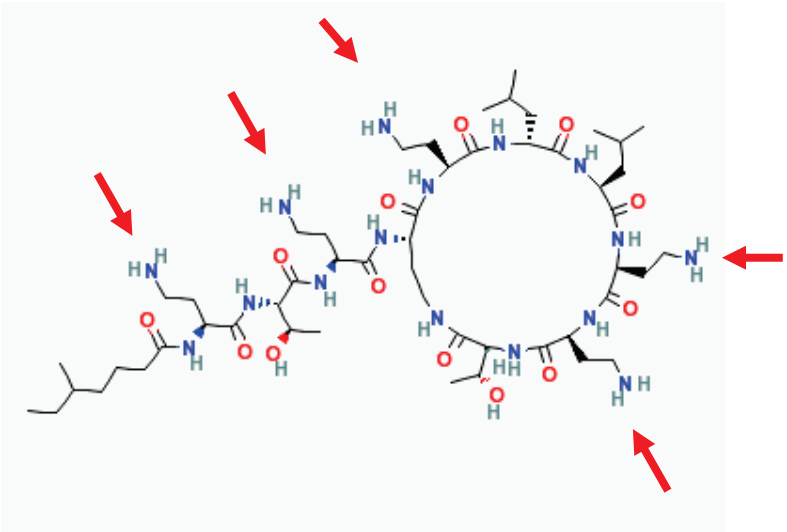


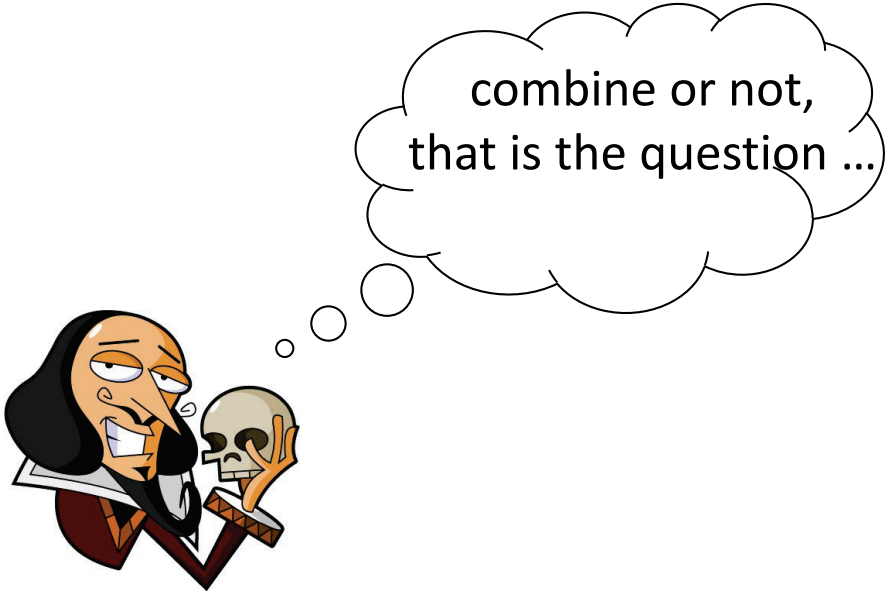
Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Li et al, Lancet Infect. Dis. 2006; 6:589-601

A reminder: what is colistin ?



Clinical experience:



from bench to bedside…

A. baumanii or *P. aeruginosa* in the ICU

Combinaison	Pathogen	N	Results
CST (2MU x 3/day) vs. CST+RIF[1] (randomized study)	*A. baumannii*	210	No difference (mortality, toxicity, length of stay)
CST (2 MU x 3/day) vs. CST+TGC or MEM/IMI[2] (observational, prospective study)	*A. baumannii*	101	No difference in 3-day mortality: 23 vs. 24%
CST vs CST+VAN/TEC[3] (retrospective study)	*A. baumannii*	68	Respiratory failure: 40% vs 58% VAP: 54% vs 71% MDR infection: 71% vs 52% G(+) coinfection: 41.2% vs 0% Nephrotoxicity: 12% vs 13% 30-day mortality: 34% vs 30%
CST vs. CST+MEM or CST+other[4] (retrospective study)	*P. aeruginosa* *A. baumannii*	258	Survival > if CST alone or +MEM vs others: 83% vs. 61-75%
CST vs. CST+other[5] (VAP) (systematic review ; 14 studies)	*P. aeruginosa* *A. baumannii*	1167	No difference in microbiological or clinical success and mortality

[1]Durante-Mangoni et al. CID 2013;57:349-58; [2]Lopés-Cortés et al. JAC 2014;69:3119-26
[3]Petrosillo et al. AAC 2014;58:851; [4]Falagas et al. IJAA 2010;35:194, [5]Wang-Jie & Gu IJAA 2014;44:477-85

K. pneumoniae infections (2/3 bloodstream)

treatment	Non survivors (N=225)	Survivors (N=436)	P value	OR (95 %CI)
CST monotherapy	45 (20.0 %)	76 (17.4)	0.41	1.18 (0.77-1.81)
Combination therapy	107 (47.6%)	247 (56.6%)	0.03	0.69 (0.49-0.97)
• 2 active drugs	38 (16.8%)	96 (22.2 %)	0.21	0.71 (0.46-1.10)
• 3 active drugs	67 (29.7%)	150 (34.4%)	0.23	0.81 (0.56-1.15)
• with carbapenem	54 (24.0%)	151 (34.6%)	0.005	0.59 (0.41-0.87)

Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

Tumbarello et al; JAC 2015;70:2133-43

Pulmonary infections : inhalation route

8 studies meta-analysed: IV vs (IV + inhaled) colistin
(but low to very low quality of evidence…

parameter	p	Odds ratio (95% CI)
Clinical response	0.006	1.57 (1.14-2.15)
Microbiological eradication	0.01	1.61 (1.11-2.35)
Infection-related mortality	0.04	0.58 (0.34-0.96)
Overall mortality	0.06	0.74 (0.54-1.01)
Nephrotoxicity	0.45	1.18 (0.76-1.83)

- Variability in delivered dose depending on nebulizers
- Never in monotherapy

Valachis et al, Crit Care Med. 2015;43:527-33

Current dosing recommendations

Target Css ≥ 2 mg/L
< 2.5 mg/L

→ If MIC ≥ 1 mg/L: think combinations
→ minimize risk of nephrotoxicity

- **very narrow therapeutic window**
- **way to optimal dosing difficult**

Landesdorfer et al, Semin Respir Crit Care Med 2015;36: 126–35; Nation, Polymyxins 2015 meeting

Current dosing recommendations: EMA 2014

Depending on renal function :

Creatinine clearance (mL/min)	Daily dose (Mio units)
≥ 80	9-12
50-80	9
30-50	5.5-7.5
10-30	4.5-5.5
<10	3.5

Limited experience; safety ???

Children ≤ 40kg
25.000-50.000 U/kg 3 X/day

in critically ill patients a loading dose of 9 million IU should be given.

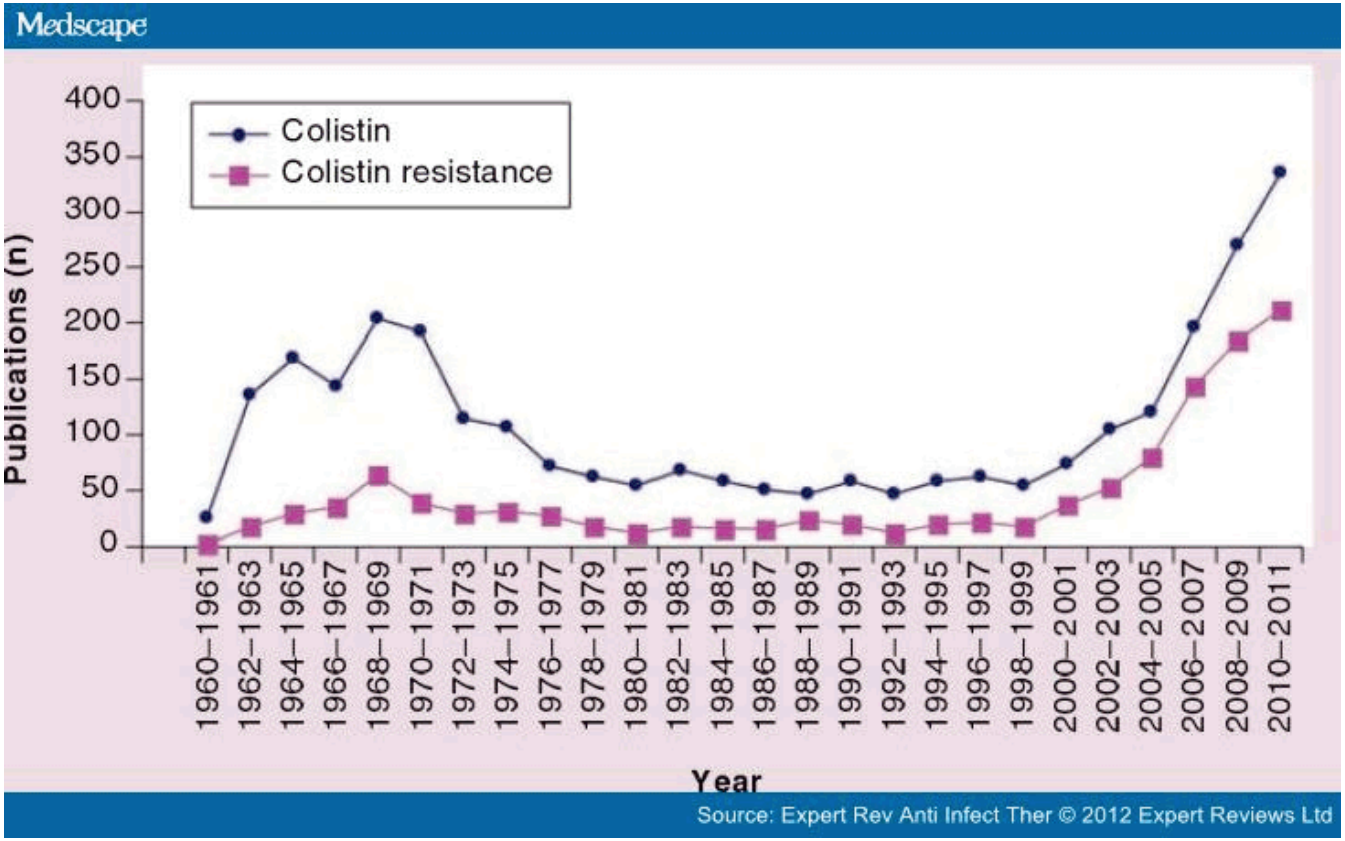
Current dosing recommendations: EMA 2014

In dialyzed patients:

Dialysis procedure	Daily dose (Mio units)
Intermittent hemodialysis	2.25 on non-dialysis days 3 after dialysis on dialysis days
CVVHF/CVVHDF	3 x /day as in patients with normal renal function

Still a lot f work ahead of us….

But beware of resistance …



http://www.micro-blog.info/2013/07/icpic-2013-conference-report/

This is the end (for the time being) !

But ask questions