Vancomycin and Colistin: pharmacokinetics/pharmacodynamics

with comments about reasonable uses

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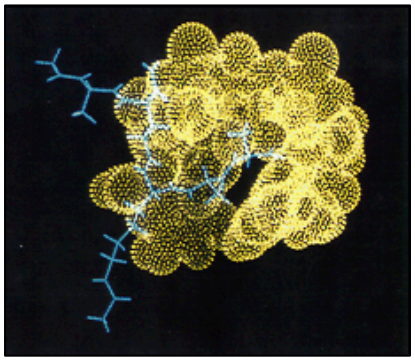
Contents of the presentation

- Vancomycin
  - origin and why has it been long neglected and then widely used
  - current breakpoints and PK-PD-based dosing recommendations
  - continuous infusion of vancomycin
- Colistin
  - origin and why has it neglected until recently but is now a last resource drug
  - antimicrobial activity, pharmacokinetics/pharmacodynamics
  - synergy
  - what can we expect ?

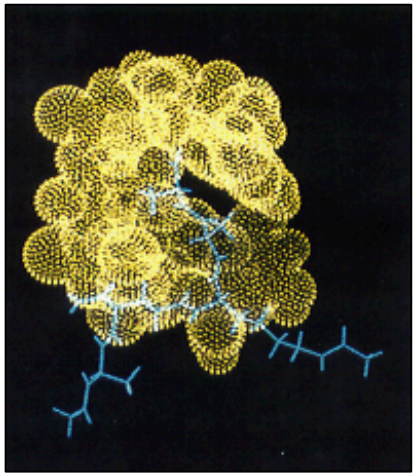

Bandar Seri Begawan
Brunei Darussalam
Borneo
Makassar Strait

Vancomycin




Mu50
35.02±4.01

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*.
- active against Gram-positive organisms only (size !) and most notably against penicillin-resistant *S. aureus* and *Enterococci* (naturally poorly susceptible to penicillins) by binding to the D-Ala-D-Ala motif in nascent peptidoglycan
- 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 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

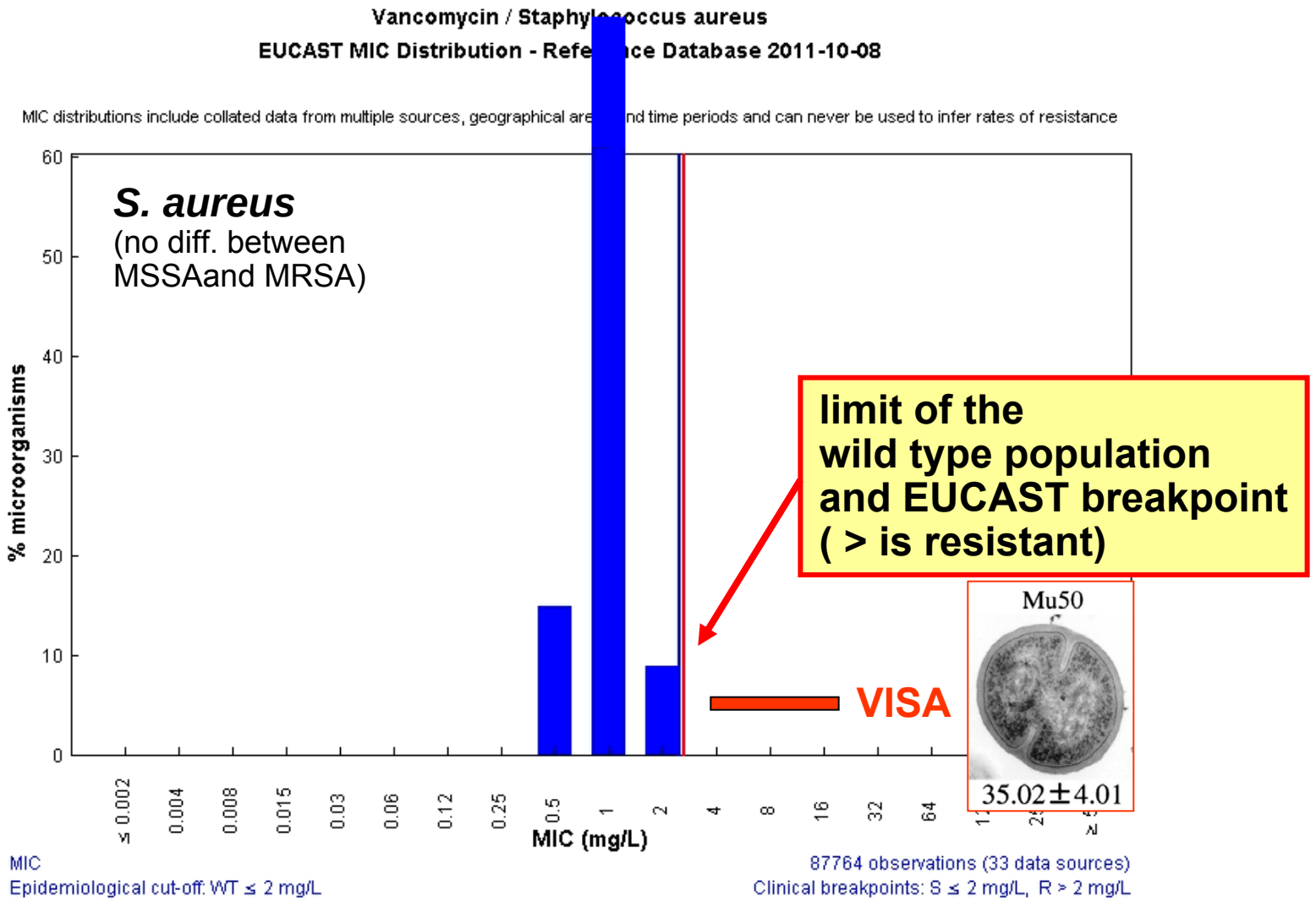
Vancomycin: spectrum and resistance

- 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)

Vancomycin and MIC (EUCAST distributions)



Vancomycin and Dosage

- Original proposals
  - patients with normal renal function [1]:
    - 15 mg/kg every 12 h
      (usually rounded up to 1 g / 12 h but … do you always weight 66.6 kg ?)
    - dilute in 100 to 250 mL of 5% glucose or 0.9% NaCl (≤ 5 mg/mL)
    - infuse at 15 mg/min max. (1 g in 60 min)
    - use antihistaminic agent to minimize the incidence of red-man (or red-neck) syndrome
  - patients with renal insuficiency
    - fixed interval (12h):
      Daily dose (mg/kg) = 15.4 x CrCl (mL/min) [2]
    - variable interval:
      Interval = 12 h x (0.86 / [0.689 x Cr Cl + 3.66]) [3]

[1] Murray & Nannini, Mandell's Principles and Practice of Infectious Diseases, 7th Ed. Chap. 31
[2] Moellering et al. Ann Intern Med 1981; 94:343-346 (based on 22 patients)
[3] Matzke et al. Antimicrob Agents Chemother 1984; 25:433-437.(based on 56 patients)

Vanco

- Original proposals
  - patients with normal
    - 15 mg/kg every
      (usually rounded up
    - dilute in 100 to 2
    - infuse at 15 mg/
    - use antihistamir
      (or red-neck) sy
  - patients with renal ir
    - fixed interval (12h):
      Daily dose (mg/kg) = 15.4 x CrCl (mL/min) [2]
    - variable interval:
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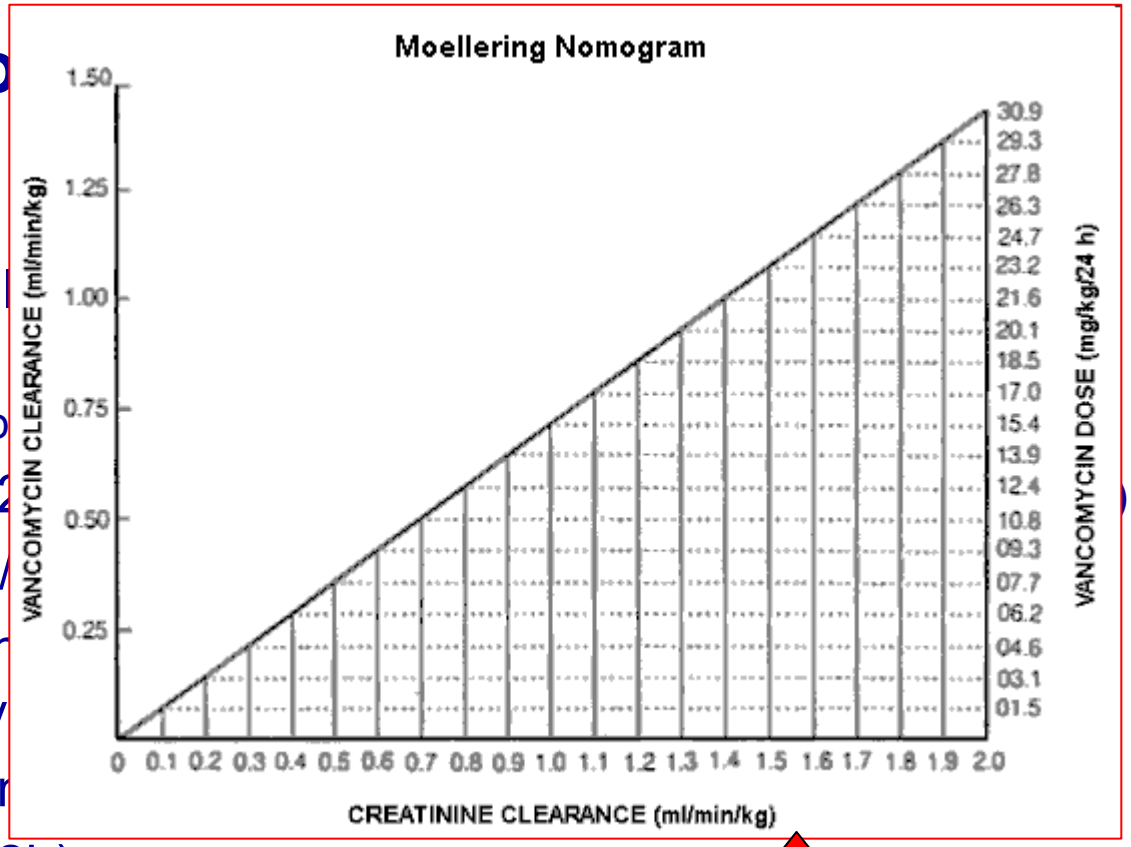

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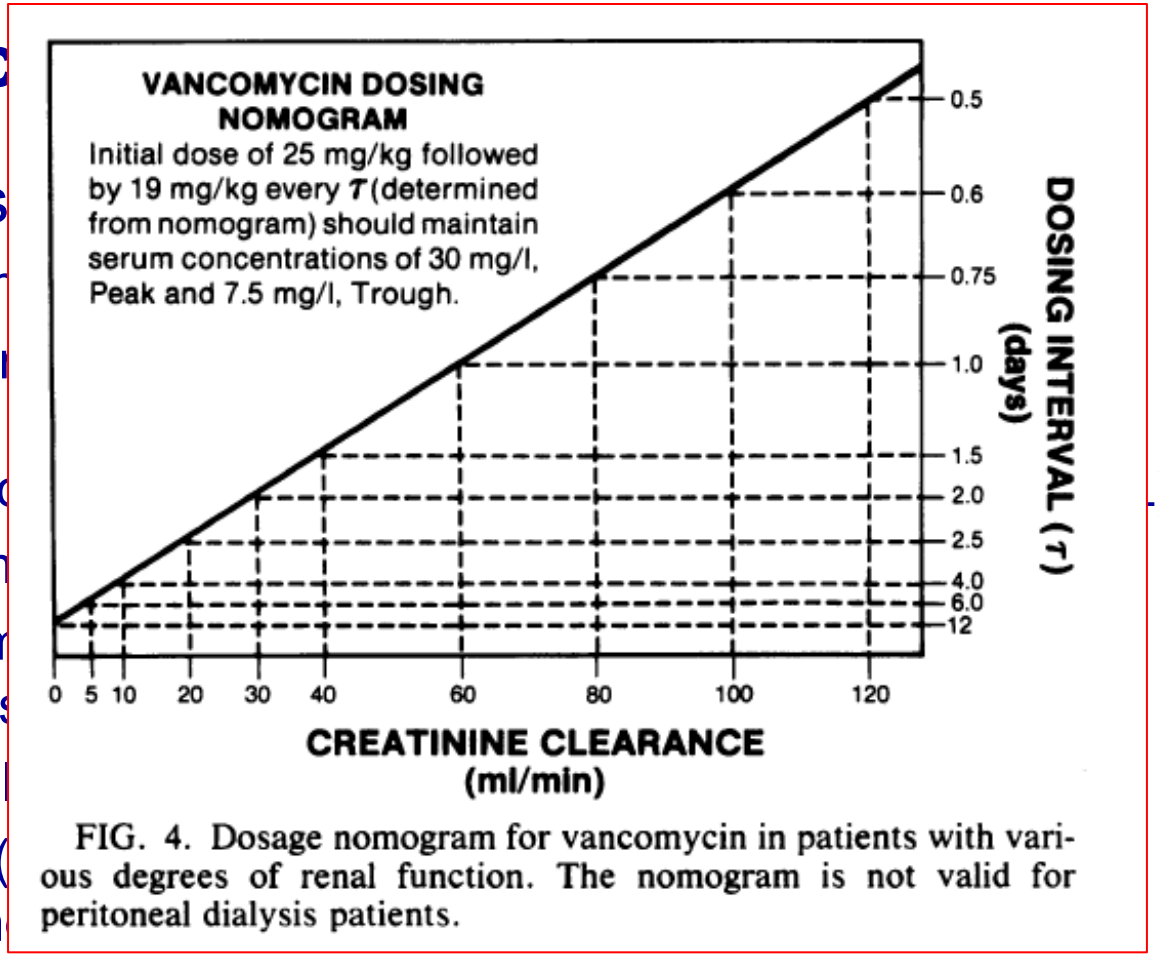

FIG. 4. Dosage nomogram for vancomycin in patients with various degrees of renal function. The nomogram is not valid for peritoneal dialysis patients.

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[2] Moellering et al. Ann Intern Med 1981; 94:343-346 (based on 22 patients)
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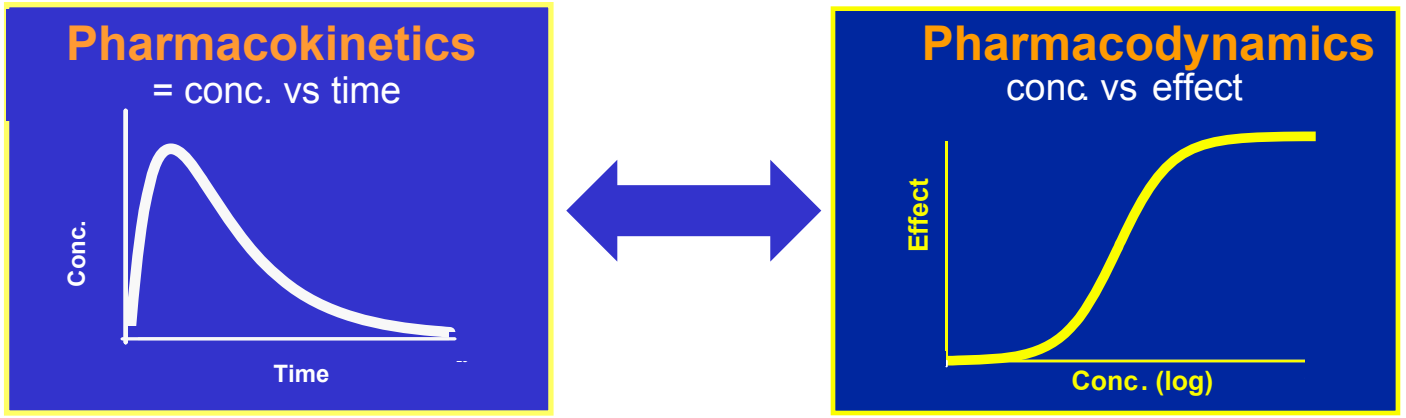
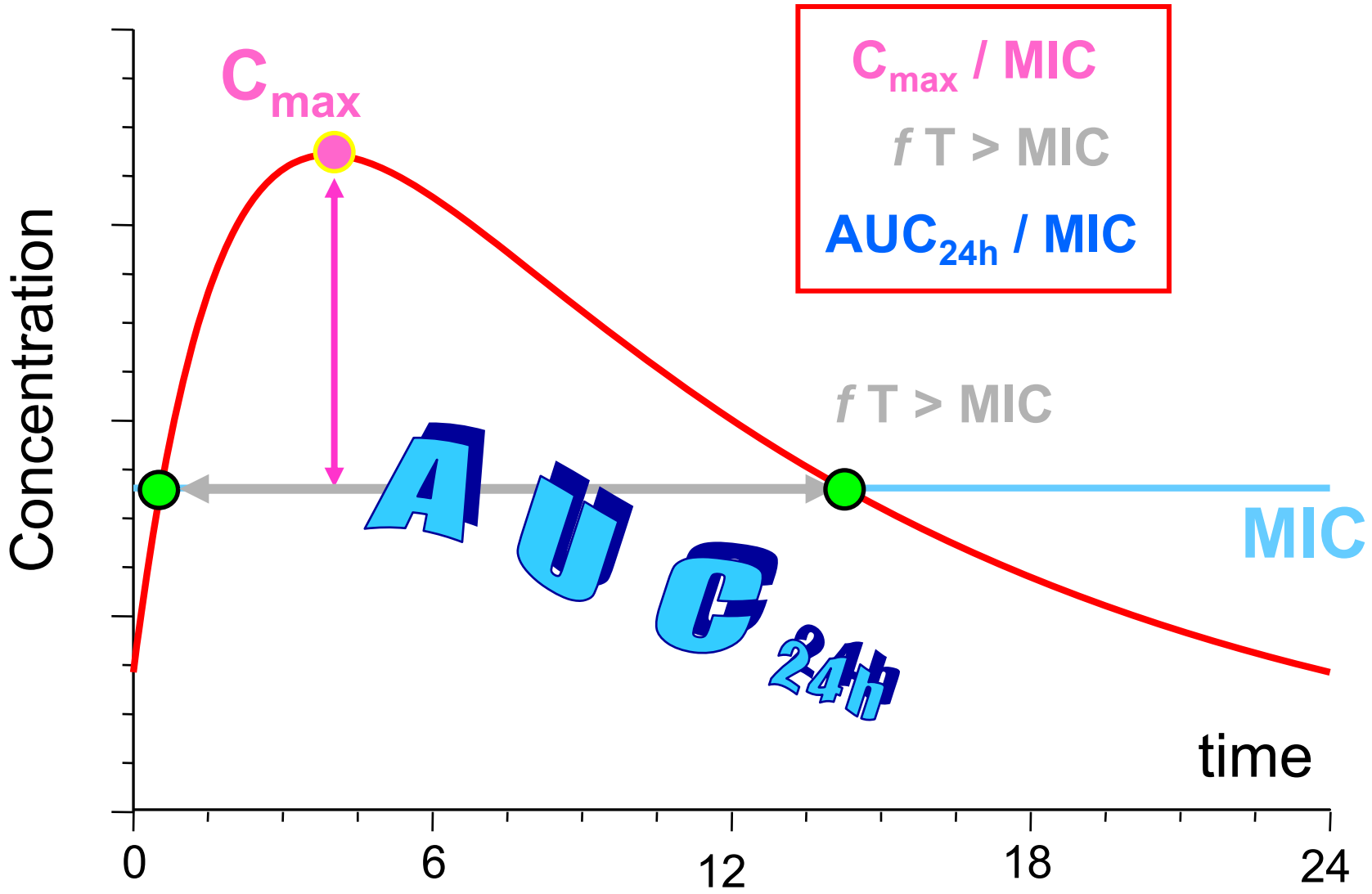
Vancomycin and Pharmacodynamics

- Questions:
  - do the "recommended" dosages allow you to obtain an optimized effect ?
  - in other words, are the concentrations large enough to fight bacteria that are reported as "susceptible" in microbiology testing (i.e. up to an MIC = 2 mg /L)
  - which concentration do we need to take care of ? (C_{max}, C_{trough}, other ?)



Vancomycin and Pharmacodynamics

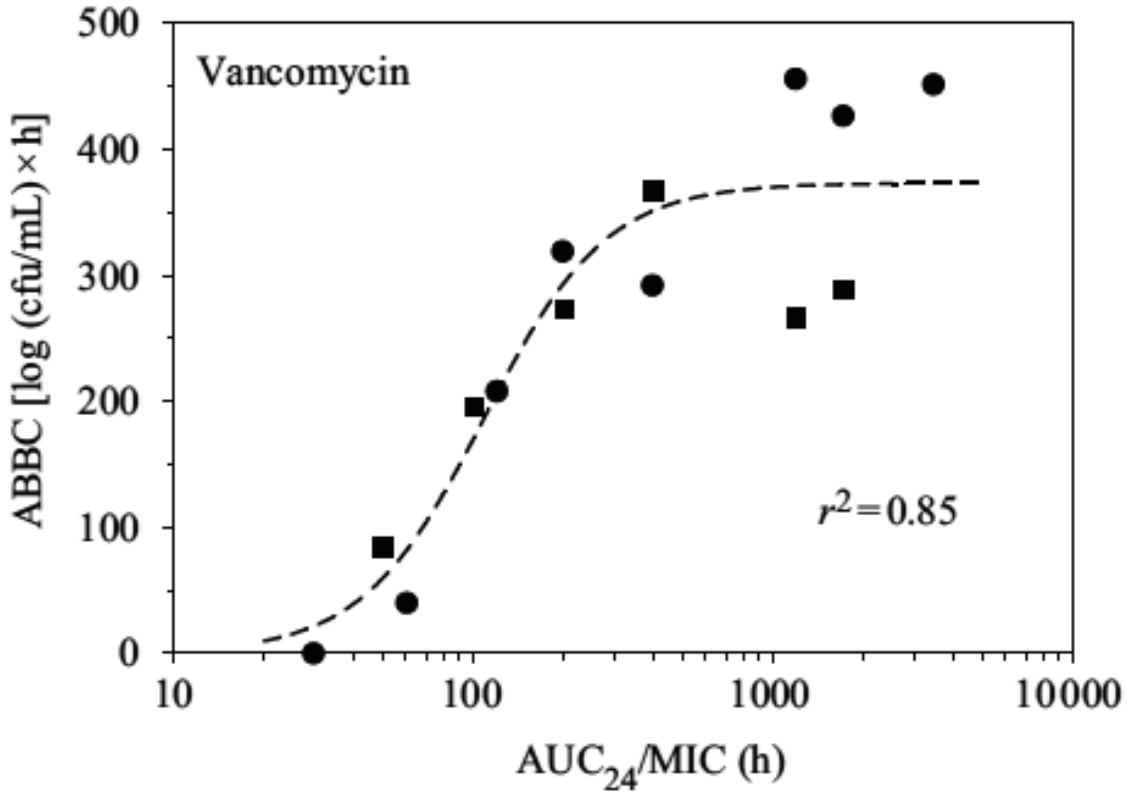
- Vancomycin is an AUC_{24h}-MIC dependent antibiotic



Vancomycin – AUC_{24h} and efficacy

1. In vitro model mimicking the human PK

efficacy

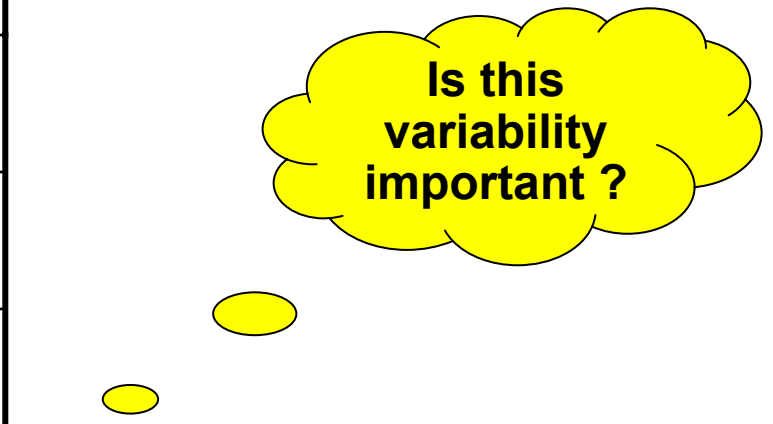


drug exposure

Lubenko et al. J Antimicrob Chemother. 2008; 62:1065-9.

Vancomycin AUC_{24h} in patients

parameter	
Dosage (mg/kg)	15
Cmax (mg/L)	20-50
Cmin (mg/L) at 12h	5-12
AUC_{24h} (mg.h/L)	162-783
(%) prot. binding	55
T ½ (h) post-distrib.	3-9



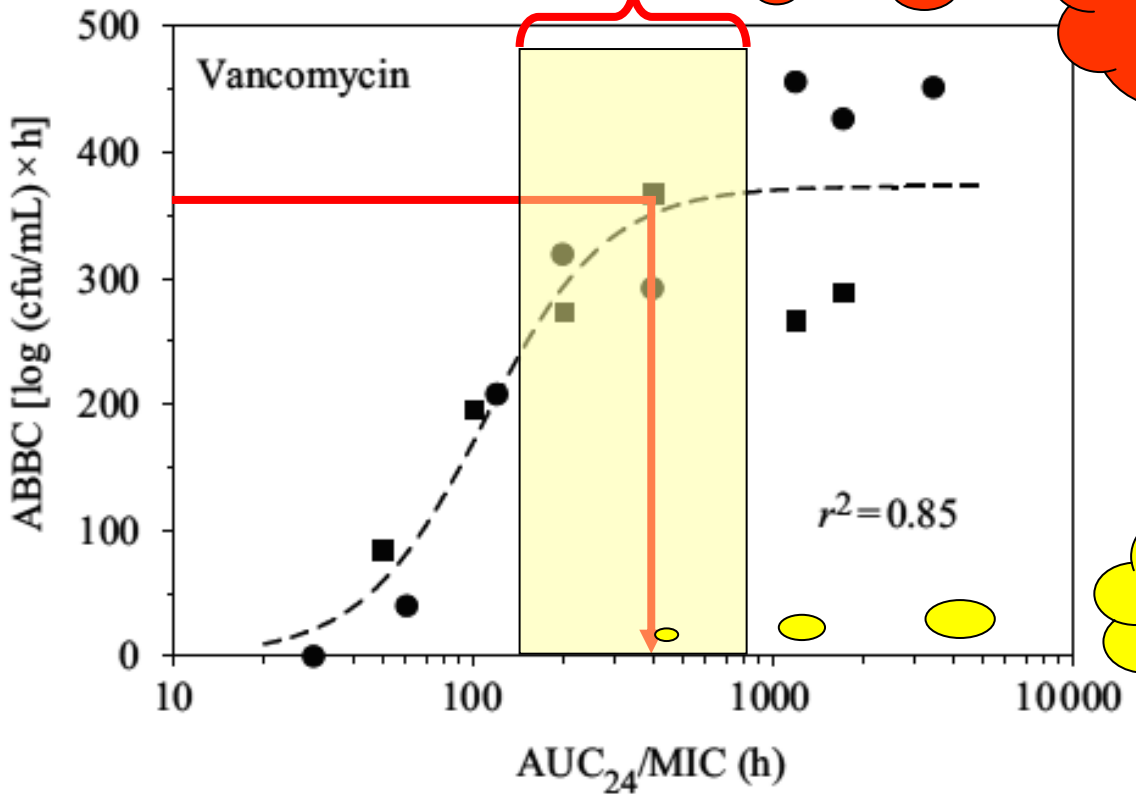
The answer is: What do YOU need ?

Harding & Sorgel (2000) J. Chemother. 12:15-20
modelling by P. Tulkens

Vancomycin – AUC_{24h} and efficacy

1. In vitro model mimicking the human PK

efficacy



But this is your range ! (160-783)

You need at least 400 !

drug exposure

Lubenko et al. J Antimicrob Chemother. 2008; 62:1065-9.

Vancomycin – AUC_{24h} and efficacy

2. In vivo (clinical study)

ORIGINAL RESEARCH ARTICLE

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

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

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

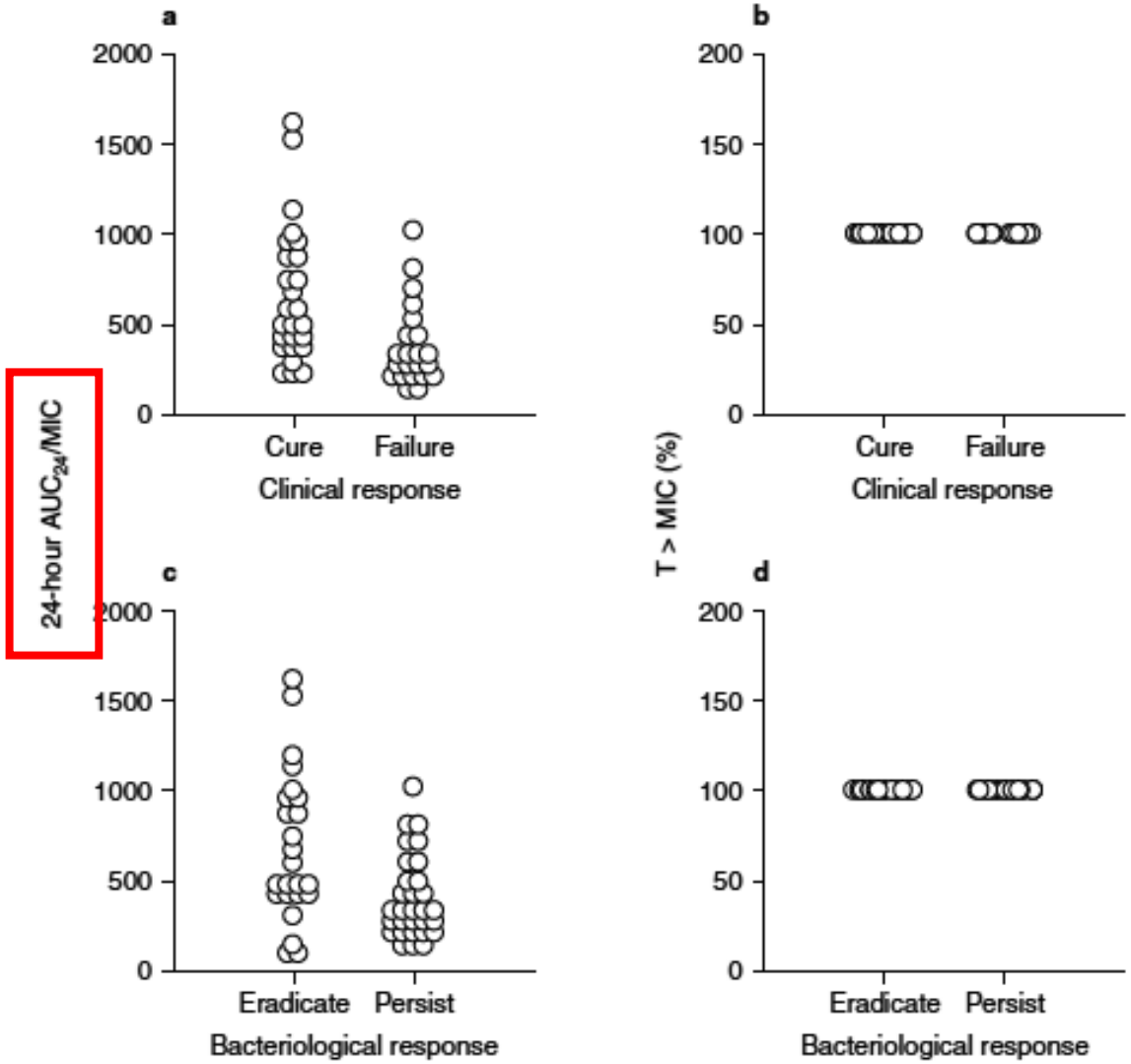


Fig. 3. Relationship between clinical and bacteriological responses and two pharmacodynamic indices: AUC_{24}/MIC and %T>MIC. Each point represents data for one patient. (**a**) Mean ± SD (median) vancomycin AUC_{24}/MIC values were 655 ± 374 (535) in patients whose infection outcomes were classified as vancomycin treatment successes (cure) and 378 ± 225 (306) in those whose infection outcomes were classified as treatment failures ($p = 0.0029$). (**b**) Vancomycin serum concentrations were above the MIC 100% of the time in all clinical treatment successes and failures. (**c**) AUC_{24}/MIC values for vancomycin-treated patients were 951 ± 1432 (593) when *S. aureus* was eradicated compared with 405 ± 224 (312) when the organism persisted ($p = 0.0046$). (**d**) %T>MIC was also 100% in all patients whose *S. aureus* was eradicated and in all patients who remained culture-positive. **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; **%T>MIC** = percentage of time that serum concentrations exceed the MIC.

Vancomycin – AUC_{24h} and efficacy

2. In vivo (clinical study) – clinical success

Table IV. Odds ratios for clinical success

Characteristic	Odds ratio	95% CI	p-Value
Vancomycin AUC_{24}/MIC value ≥350	7.19	1.91, 27.3	0.0036
MSSA as pathogen	3.88	1.10, 14.8	0.0359
Single lobe involvement	6.32	1.56, 25.6	0.0099
Baseline serum albumin (per 1 g/dL)	3.73	1.09, 12.8	0.0364
Baseline CL_{CR} (per 1 mL/min)	1.04	1.01, 1.07	0.0154

AUC_{24}/MIC = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; **CL_{CR}** = creatinine clearance; **MSSA** = methicillin-susceptible *Staphylococcus aureus*.

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

Vancomycin – AUC_{24h} and efficacy

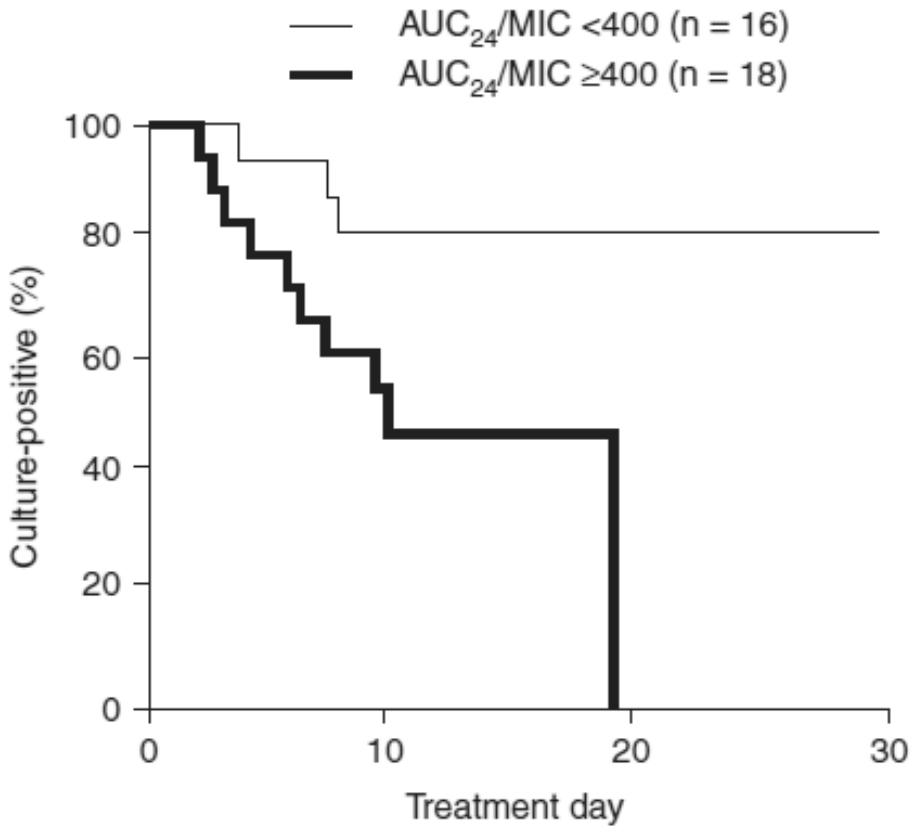
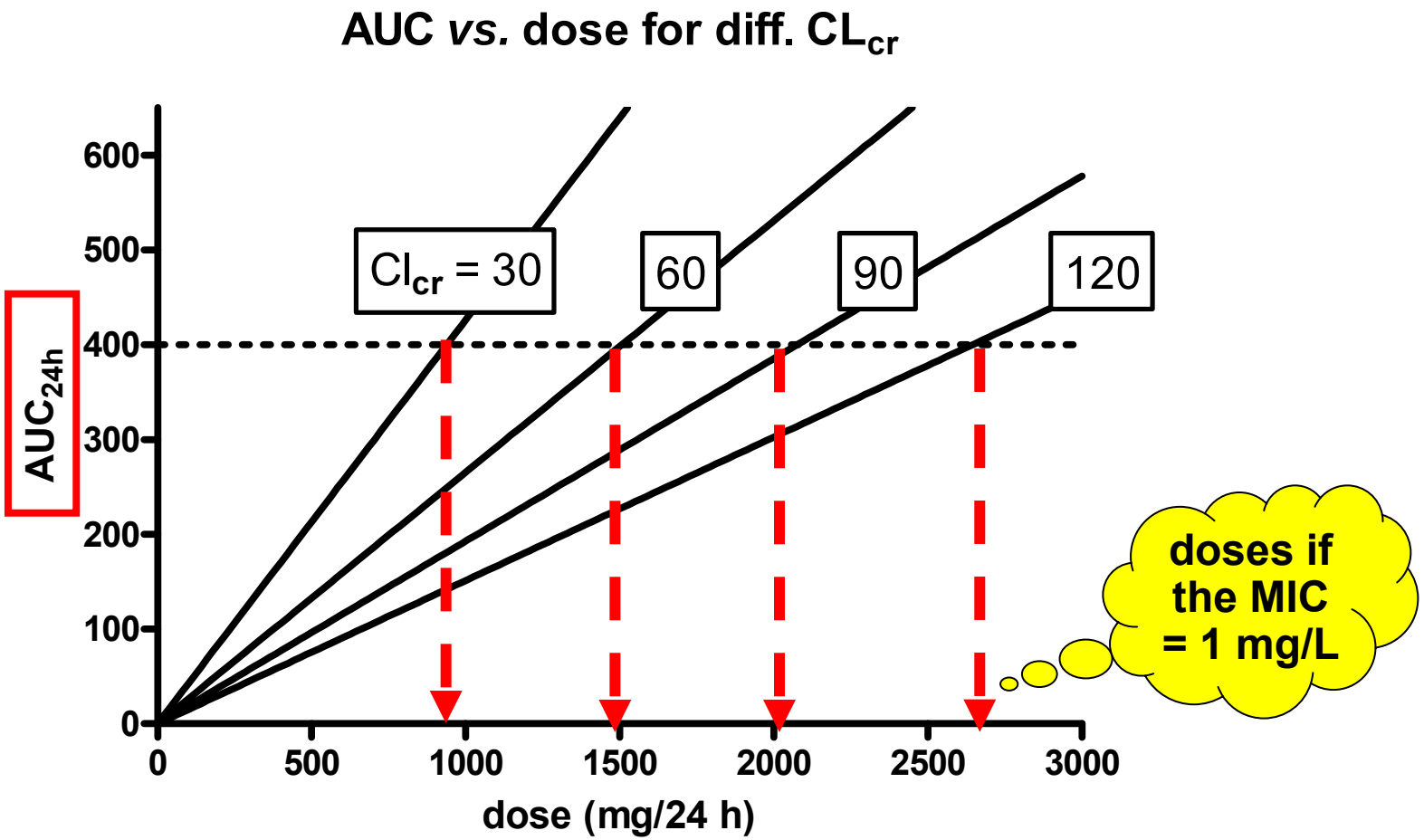


Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin AUC_{24}/MIC <400 and AUC_{24}/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC_{24}/MIC groups differed significantly (p = 0.0402).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

How to calculate the AUC_{24h} ?

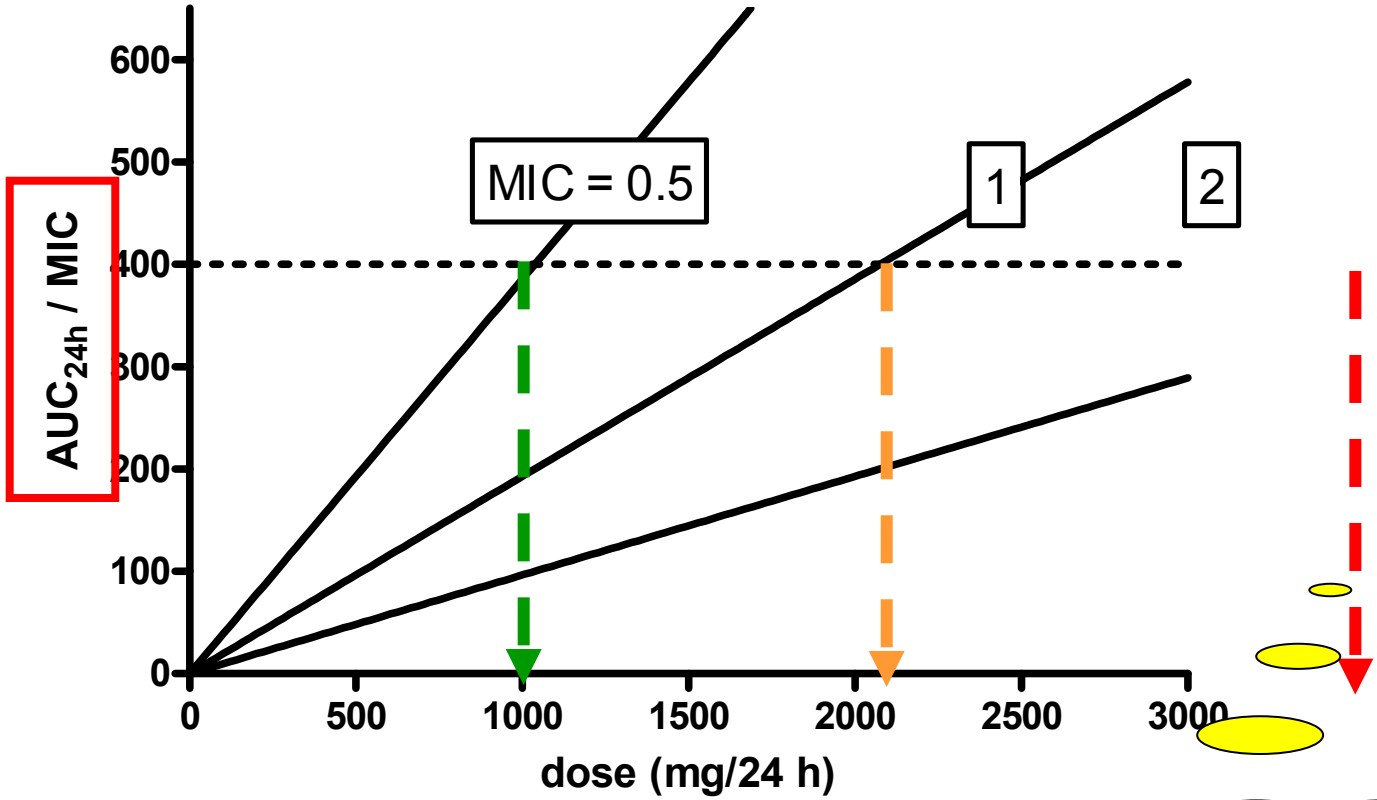


$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

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

How to calculate the AUC_{24h} ?

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

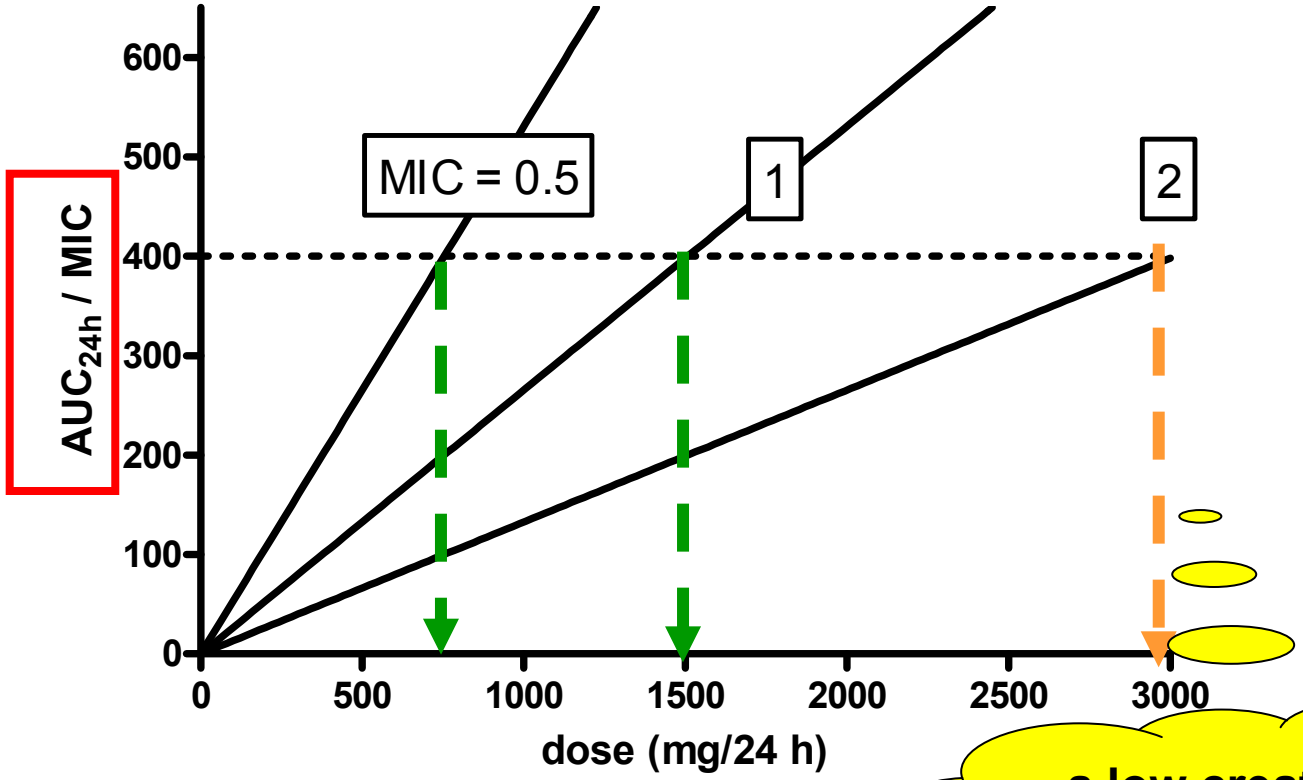


if the MIC reaches 2, you may have problems

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

How to calculate the AUC_{24h} ?

AUC_{24h} / MIC *vs.* dose for diff. MIC and CL_{cr}=60 mL/min



a low creatinine clearance helps !

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

What if you do not know your MIC ?

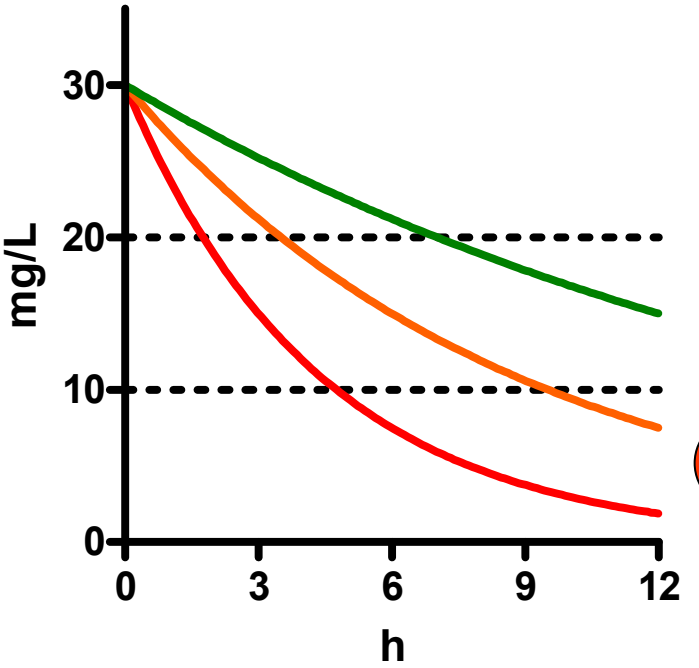
- assume a MIC of 2 mg/L (breakpoint) and check at the level of the population …
- monitor serum concentrations with
  - peak and trough (best to calculate AUC, but …see next slide)
  - through only (and ensure values of 15-20 mg/L !)
    ➔ this will (probably) ensure an AUC/MIC ~ 400
- use a loading dose (25-30 mg/kg)
  - obtain rapidly the peak and the necessary AUC/MIC
- organisms with an MIC ≥ 2 mg/L will be difficult …

See details in: Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.
Rybak et al. Am J Health-Syst Pharm. 2009; 66:82-98

Peak and through or through only ?

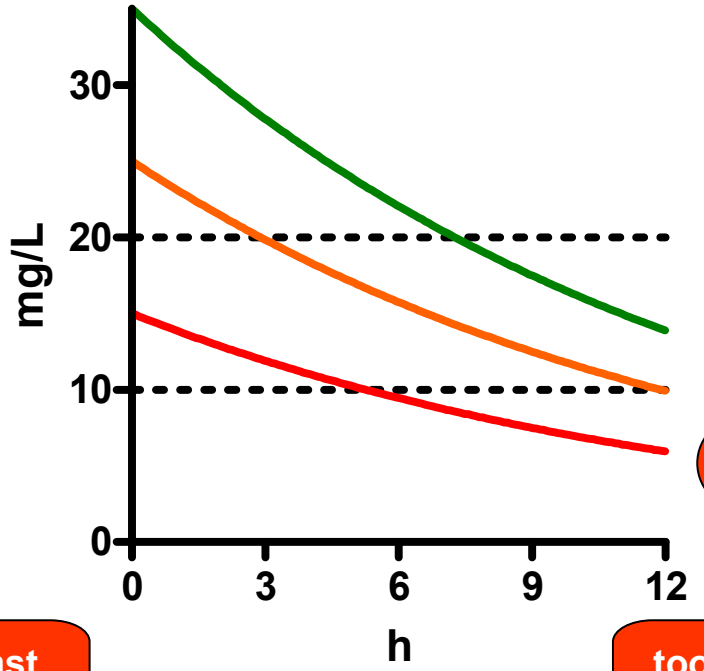
Against through only:
You do not distinguish between abnormal clearance and abnormal V_d

C_{max} = 30 mg/L
$t_{1/2}$ = 3 - 6 - 12 h



too fast clearance

C_{max} = 15 - 25 - 35 mg/L
$t_{1/2}$ = 9 h

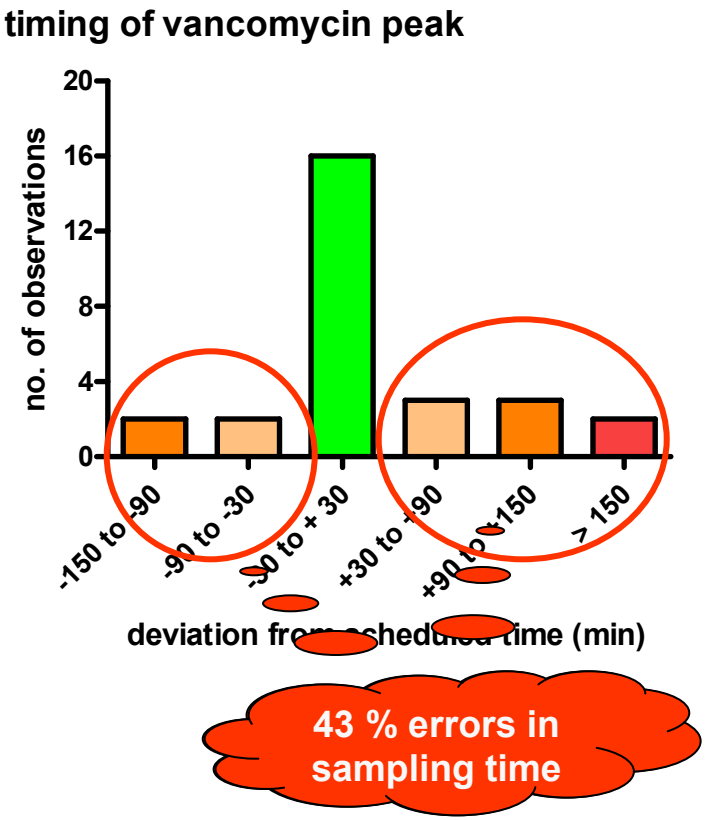


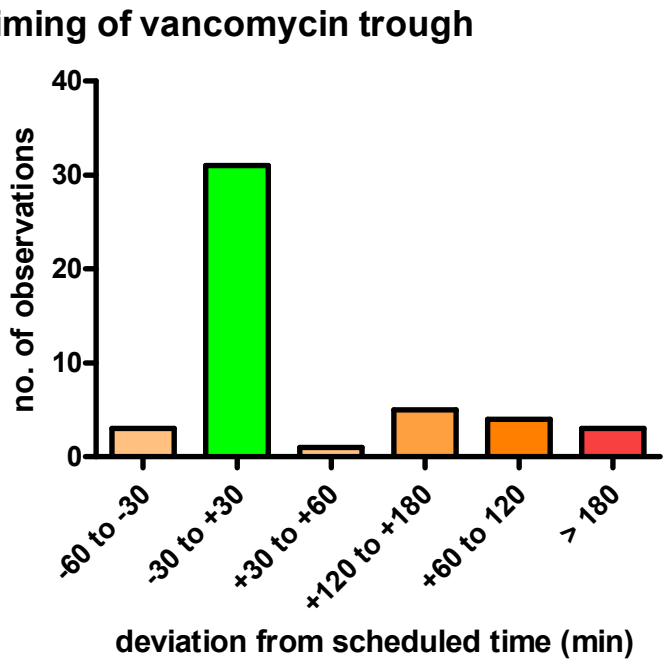
too large Vd

reminder: C_{max} = Dose / Vd -- $t_{1/2}$ = 0.693 x V_d / Cl

Peak and through or through only ?

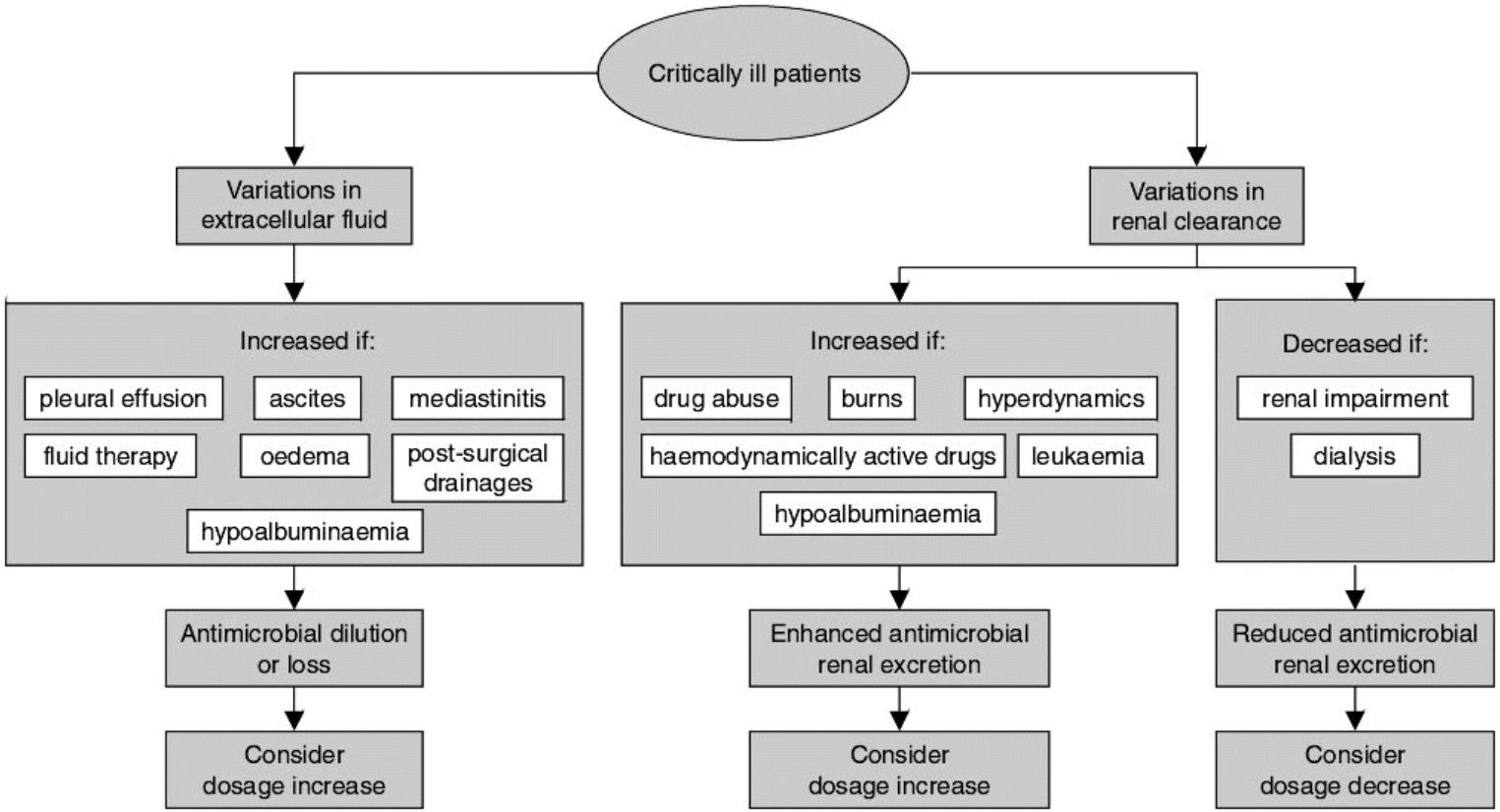
For through only:
Correct peaks are not easy to get…





Does "one size" fits all ?

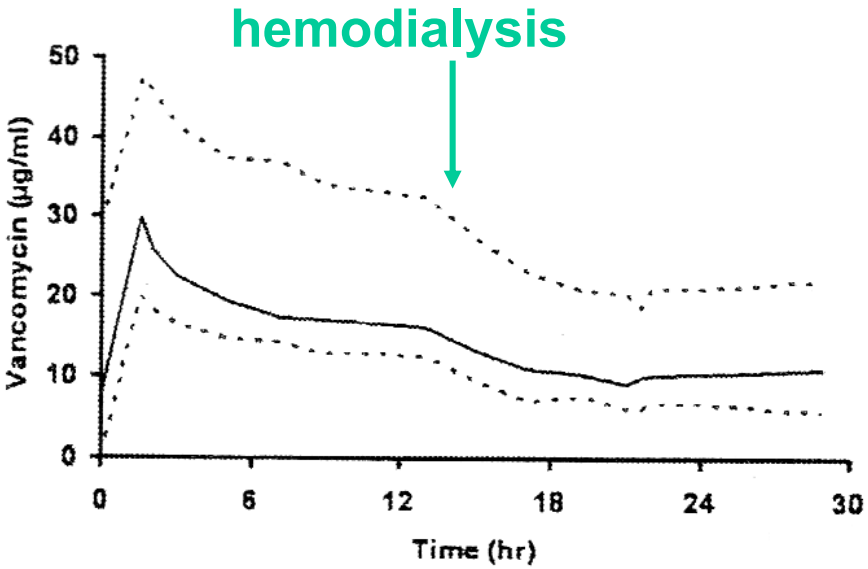
intensive care : variation in extracellular fluid and renal clearance



Pea *et al*. (2005) Clin. Pharmacokinet **44**:1009-34

Does one size fits all ?

- dialysis : removal of the drug (high flux membranes)
  Caution: vancomycin dialysis is poor …



dose adjusted according to:

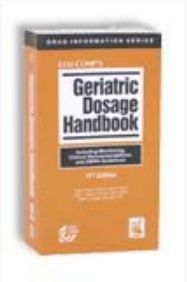
- trough level before intermittent dialysis
- plasma level at any time (continuous dialysis)
- 6 hours after the end of dialysis

Kielstein *et al*. (2006) Crit. Care Med. **34**:51-6

Vancomycin and elderly patients

- age: elderly patients: altered tissue distribution and renal function

↑ Vd ↓ clearance



dose (mg/kg/24 h) = $(0.227 \times Cl_{CR}) + 5.67$

Dosing intervals of vancomycin as a function of CL_{CR}

CL_{CR} (ml/min per 70 kg)	Dosage interval (h)
>65	8
40–65	12
20–39	24
10–19	48

adapt the dose and the interval as a function of Cl_{CR}

but this is where peak and trough may be important …

Rodvold *et al*. (1988) AAC **32**:848-52

Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

Journal of Antimicrobial Chemotherapy (2009) **63**, 1050–1057
doi:10.1093/jac/dkp085
Advance Access publication 19 March 2009

JAC

Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations

A. H. Thomson[1,2]*, C. E. Staatz[1,2]†, C. M. Tobin[3], M. Gall[4] and A. M. Lovering[3]

[1]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, UK; [2]Pharmacy Department, Western Infirmary, NHS Greater Glasgow and Clyde, Glasgow, Scotland, UK; [3]Bristol Centre for Antimicrobial Research and Evaluation, Department of Microbiology, Southmead Hospital, Bristol, UK; [4]Pharmacy Department, Southern General Hospital, NHS Greater Glasgow and Clyde, Glasgow, Scotland, UK

Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

Table 4. New vancomycin loading dose guidelines based on the final population model

	Weight (kg)		
	<60	60–90	>90
Loading dose (mg)	1000	1500	2000

Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

Table 4. New vancomycin loading dose guid
final population model

	We
	<60
Loading dose (mg)	1000

Table 5. New vancomycin maintenance dose guidelines based on the final population model

CL_{CR} (mL/min)	Dose (mg)	Interval (h)
<20	500	48
20–29	500	24
30–39	750	24
40–54	500	12
55–74	750	12
75–89	1000	12
90–110	1250	12
>110	1500	12

CL_{CR} estimate based on the Cockcroft–Gault equation.[24]
Higher troughs and lower peaks would be achieved by splitting the total daily dose into three or four equal portions, for example, 1000 mg 8 hourly instead of 1500 mg 12 hourly or 500 mg 6 hourly instead of 1000 mg 12 hourly.

Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   – based on population pharmacokinetic models

Table 4. New vancomycin loading dose guid
final population model

	We
	<60
Loading dose (mg)	1000

Table 5. New vancomycin maintenance dose guidelines based on the final population model

CL_{CR} (mL/min)	Dose (mg)	Interval (h)
<20	500	48
20–29	500	24
30–39	750	24
40–54	500	12

A preliminary evaluation of the guidelines indicated that 55% of trough concentrations should be within 10–15 mg/L and 71% within 10–20 mg/L over the first 4 days of therapy and that satisfactory AUC24/MIC ratios should be achieved in 87% of patients, assuming an MIC of 1 mg/L.

However, wide variability in the handling of vancomycin between and within patients indicates that monitoring of concentrations is required to ensure that dosage regimens are appropriate for individual patients.

Two ways to get better results…

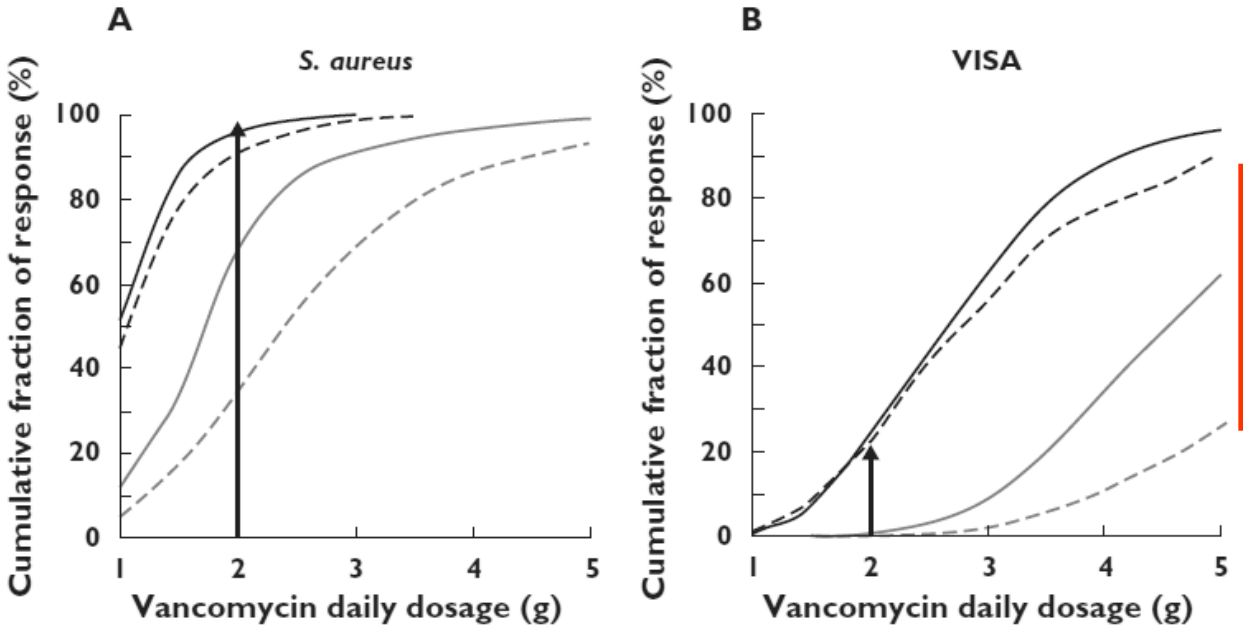
1. Use of more sophisticated algorithms for dose adjustment
   - based on population pharmacokinetic models
   - based on specific population analysis and Monte-Carlo simulations

Revilla et al. Br J Clin Pharmacol. 2010; 70:201–212

Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   - based on population pharmacokinetic models
   - based on specific population analysis and Monte-Carlo simulations

susceptible S. aureus (MIC = 2 mg/L max.)



bacteria with MIC above EUCAST bkpt (2 mg/L)

Figure 3

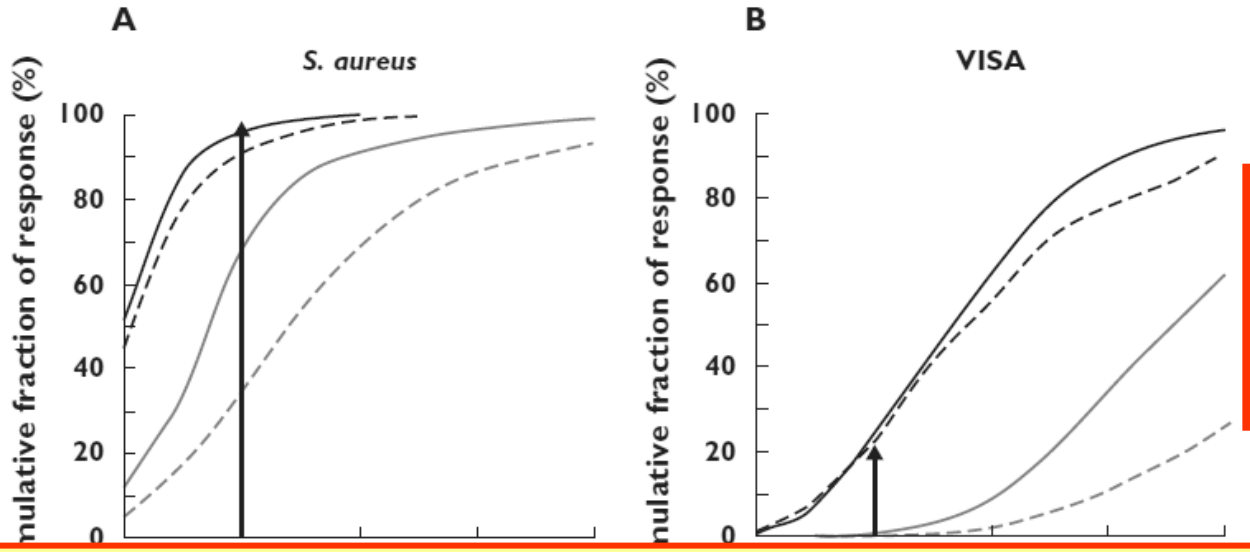
Cumulative fraction of response against *S. aureus* for several vancomycin daily doses in different ICU population subgroups: (A) For susceptible *S. aureus*; (B) For VISA strains. CL_{Cr}: Creatinine clearance measured in the ICU setting (ml min^{-1}). $CL_{Cr} \leq 60$ ml min^{-1} and Age > 65 years (——); $CL_{Cr} \leq 60$ ml min^{-1} and Age ≤ 65 years (– –); $CL_{Cr} > 60$ ml min^{-1} and Age > 65 years (——); $CL_{Cr} > 60$ ml min^{-1} and Age ≤ 65 years (– –)

Revilla et al. Br J Clin Pharmacol. 2010; 70:201–212

Two ways to get better results…

1. Use of more sophisticated algorithms for dose adjustment
   - based on population pharmacokinetic models
   - based on specific population analysis and Monte-Carlo simulations

susceptible S. aureus (MIC = 2 mg/L max.)



bacteria with MIC above EUCAST bkpt (2 mg/L)

Thus, for vancomycin-susceptible *S. aureus*, an initial 2000 mg day^{-1} dose of vancomycin must only be used for patients with CLCr < 60 ml min^{-1}. For better kidney function, the corresponding doses must be increased to 3000 and 3500 mg day^{-1} for aged (>65 years) or adult patients, respectively.

Figure 3
Cumulative fr… …eus; (B) For VISA strai… …nd Age ≤ 65 years (–…

Revilla et al. Br J Clin Pharmacol. 2010; 70:201–212

Two ways to get better results…

2. Use continuous infusion

- makes monitoring easier (sampling at any time)
- makes calculation of AUC very easy (C_{ss} x 24)

number of studies	indications	conclusion
controlled studies with clinical endpoint		
9 [a]	VAP, Gram + osteomyelitis, oter serious infections (ICU, open heart surgery)	equivalence (6) superiority (3)

a Wysocki 2001; Rello 2005; Hutschala 2009; James1996; Wysocki 1995; Kitzis 2006; Vuangnat 2004; Boffi 2004; Di Filippo 1998,

A typical example (from France)

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

MARC WYSOCKI,[1*] FREDERIQUE DELATOUR,[2] FRANÇOIS FAURISSON,[2] ALAIN RAUSS, YVES PEAN,[4] BENOIT MISSET,[5] FRANK THOMAS,[6] JEAN-FRANÇOIS TIMSIT,[7] THOMAS SIMILOWSKI,[8] HERVE MENTEC,[9] LAURENCE MIER,[10] DIDIER DREYFUSS,[10] AND THE STUDY GROUP†

Medico-Surgical Intensive Care Unit[1] and Microbiology,[4] Institut Mutualiste Montsouris, Medico-Surgical Intensive Care Unit, Hôpital Saint-Joseph,[5] Medico-Surgical Intensive Care Unit, Hôpital de Diaconesses,[6] INSERM U13[2] and Infectious Diseases Critical Care Unit,[7] Hôpital Bichat-Claude Bernard, and Respiratory Intensive Care Unit, Hôpital de la Pitié-Salpêtrière,[8] Paris, Medico-Surgical Intensive Care Unit, Hôpital V. Dupouy, Argenteuil,[9] and Medical Intensive Care Unit, Hôpital Louis Mourier, Colombes,[10] France

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

AAC 45:2460-2467, 2001

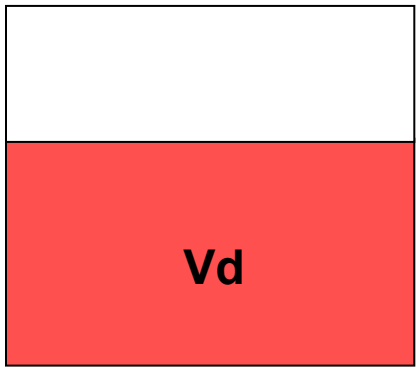
- 119 critically-ill patients with multi-resistant organisms (bacteriaemia, 35%; pneumonia, 45%).
- Microbiologic and clinical outcomes
- Evaluation of safety, pharmacokinetic parameters, ease of dose ajhustment, and cost
  - ➔ clinical outcomes and safety: equivalent
  - ➔ target concentrations (20-25 mg/L – AUC = 480 - 600) obtained more rapidly
  - ➔ less samples needed for surveillance of blood levels
  - ➔ less variability in AUC_{24h}
  - ➔ costs: 23% lower !

Continuous infusion in daily practice…

- loading dose

$C_t = Dose/V_d$

$Dose = C_t \times V_d$



Vancomycine: target concentration 25 µg/ml

V_d (L/kg):	0.5	0.6	**0.7 ***	0.8
dosis (mg/kg):	12.5	15.0	**17.5**	20.0

* The "steady-state" distribution volume (Vdss) of vancomycin varies between 0.39 and 0.97 L/kg

Matzke et al. Clin Pharmacokinet. 1986 Jul-Aug;11(4):257-82.

Continuous infusion in daily practice…

- maintenance dose : $\mathbf{K_o = C_{ss} \times 0.65 \times Cl_{CR}}$

  ➔ Ko = rate of infusion (mg/min

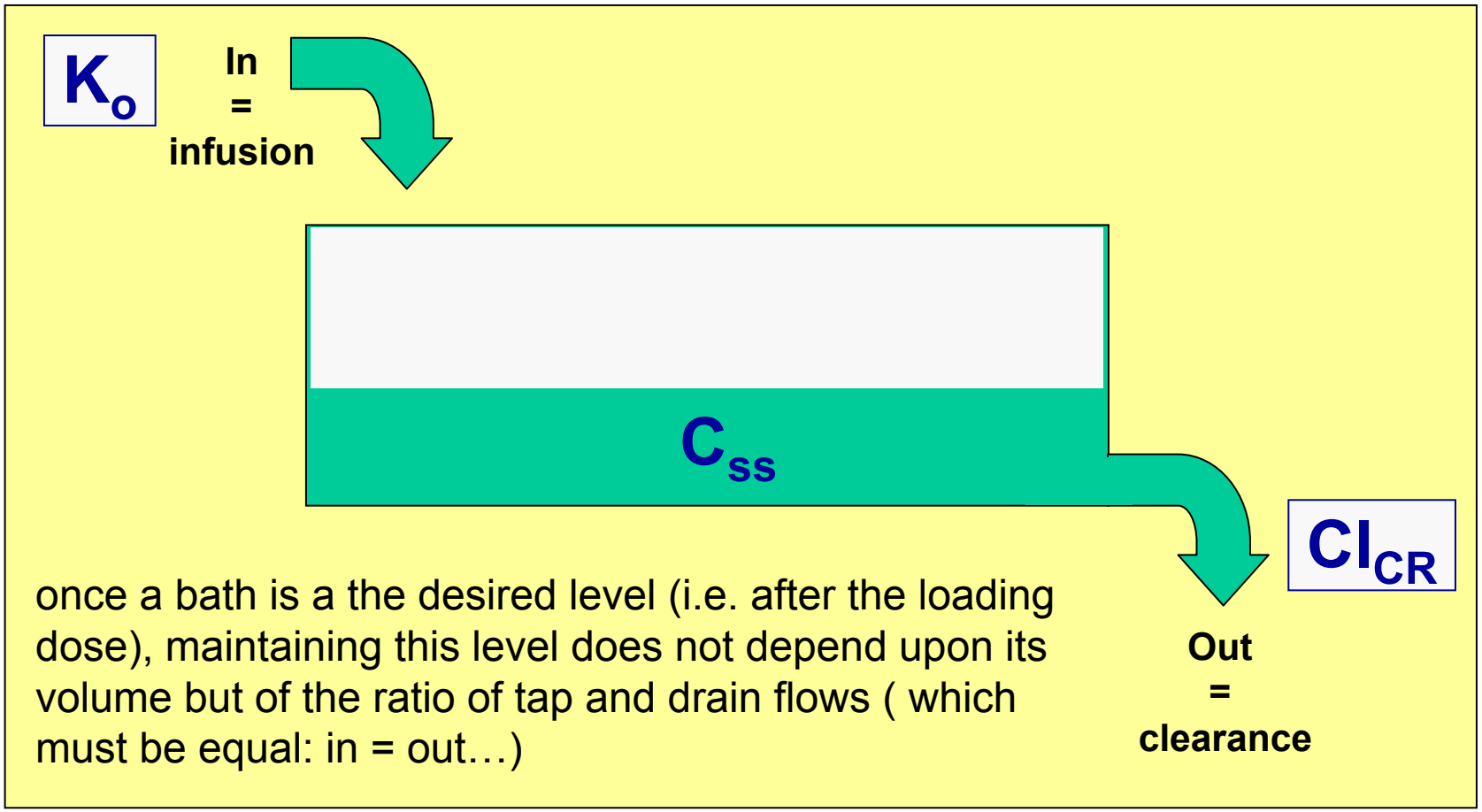
  ➔ Css (mg/L) serum target concentration at steady state

  ➔ ClCR = calculated creatinine clearance (in L/min, based on Cockroft and Gault formula [16])

  ➔ 0.65: correction factor for prediction of vancomycin clearance from calculated creatinine clearance

Continuous infusion in daily practice…

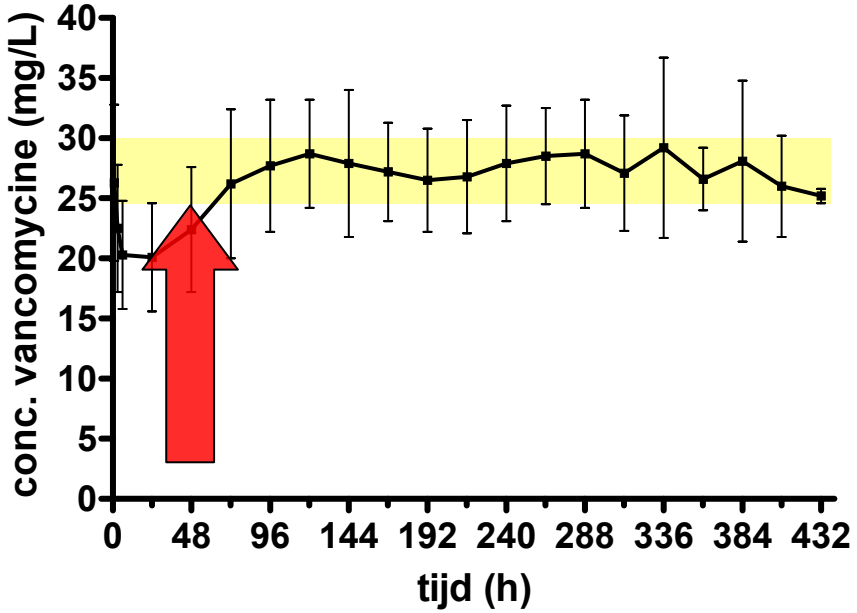
- maintenance dose : $K_o = C_{ss} \times 0.65 \times Cl_{CR}$



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…)

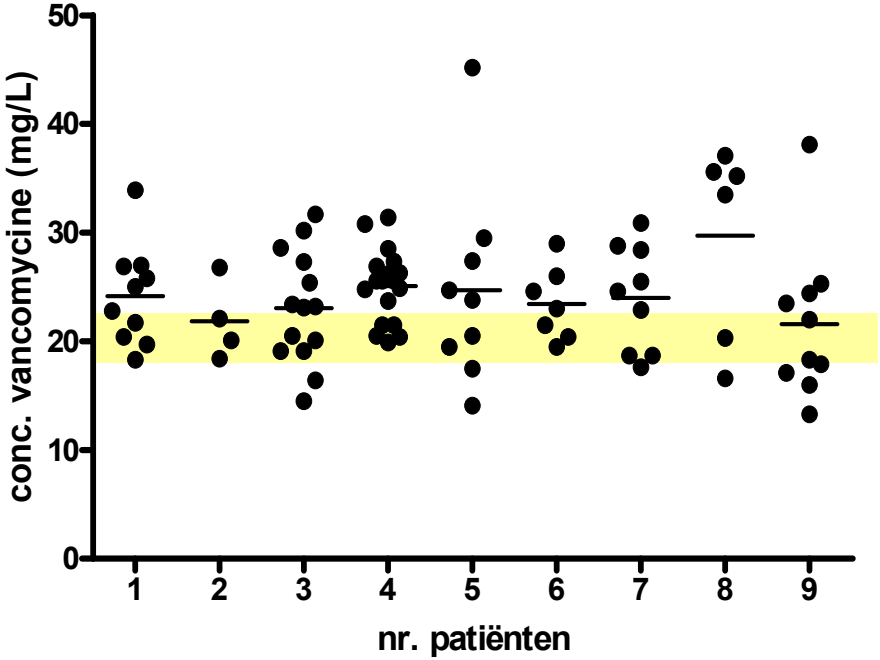
A few results

concentratie van vancomycine in functie van de tijd in patiënten behandeld met continu infuus



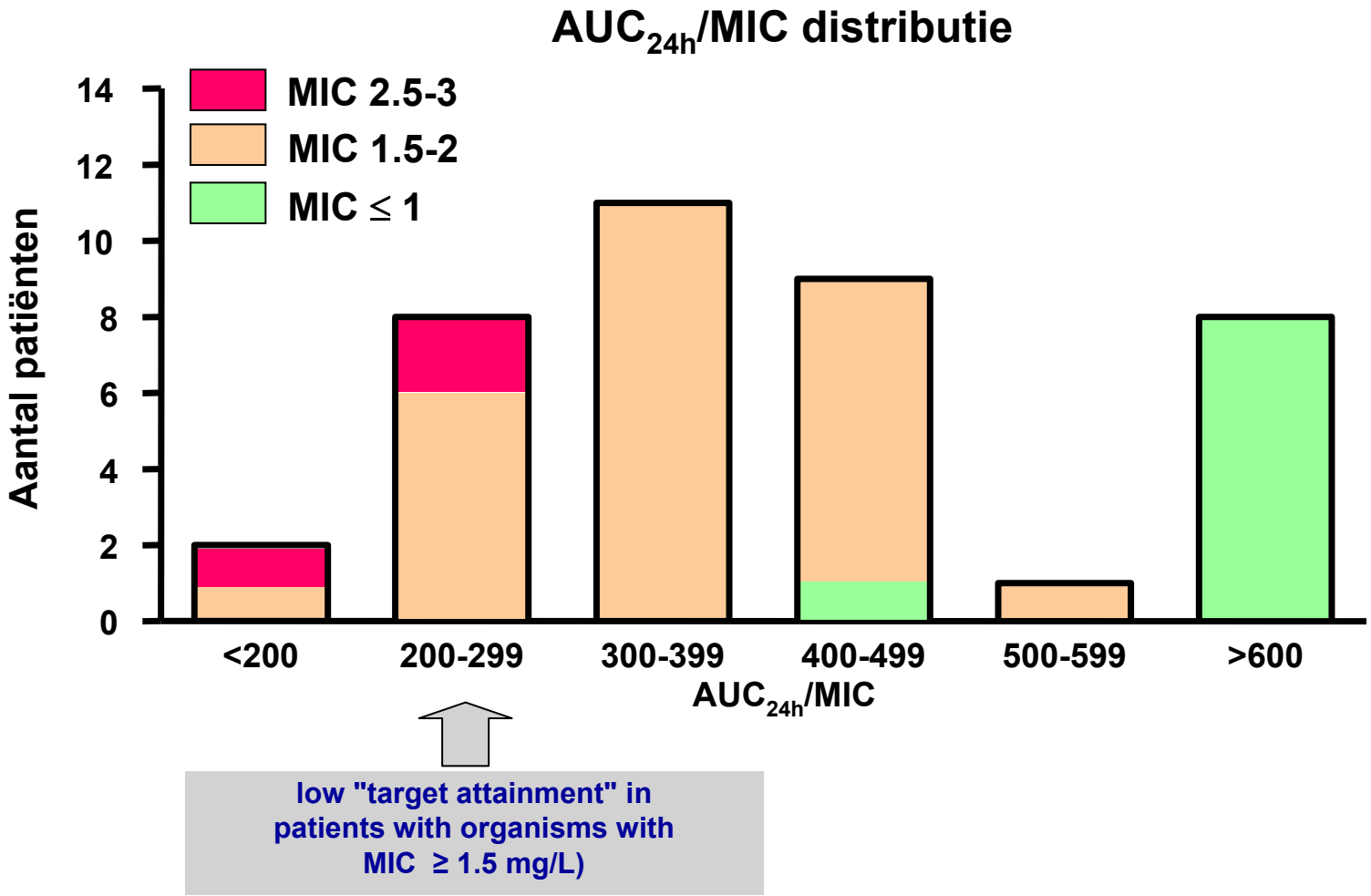
monitoring remains important

variabiliteit VAN concentraties tijdens continu infuus (voorbeelden van typische patiënten)



Ampe *et al.*, in preparation

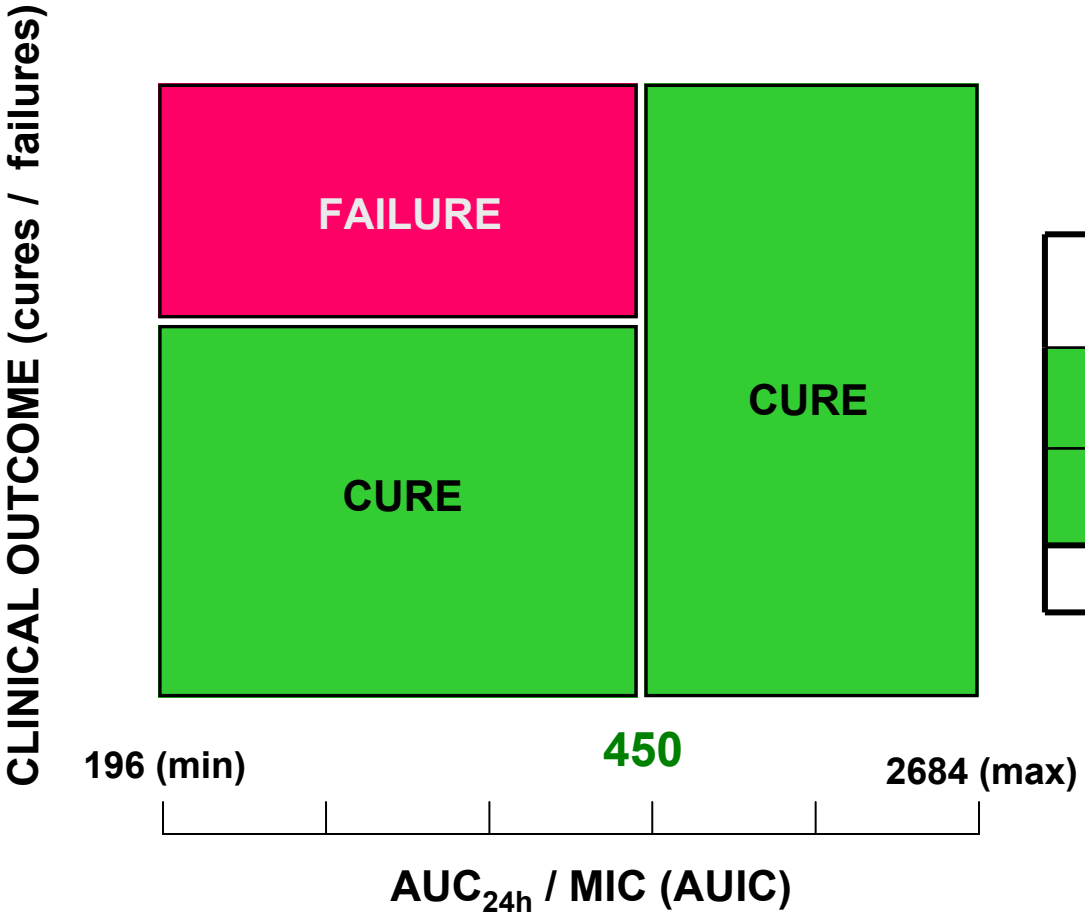
AUC / MIC distributions … and MICs



Ampe *et al.*, in preparation

AUC / MIC and success / failures

relation between AUC_{24h} / MIC (E-Test) and clinical efficacy in vancomycin monotherapy (n=19)



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

Ampe *et al.*, in preparation

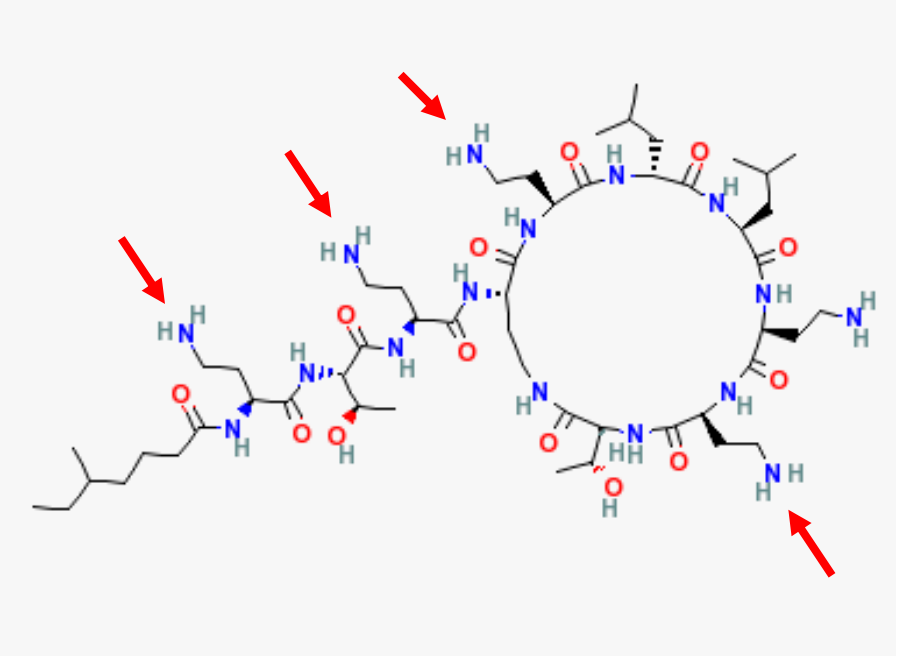
Vancomycin: conlusions

1. an old drug put back into service
2. will work for organisms with an MIC up to 2 mg/L
3. but you must
   - use a loading dose
   - optimize the maintenance dose
   - if possible, monitor blood levels AND compare with the MIC
4. use combined therapy for organisms with MIC > 2 mg/L
5. do not forget to detect heteroresistance…

Colistin

or

Colistin



- A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain
- which **interacts with the lipopolysaccharide (LPS)** of the outer membrane of Gram-negative bacteria, triggering a "self-promoted uptake" process
- and **displaces Ca^{++} and Mg^{++}**, which further destabilizes microbial outer membranes and helps conferring more specificity towards procaryotic cells

Colistin History

- Isolated in Japan in 1949 from *Bacillus polymyxa* var. *colistinus* and indentified as **polymyxin E**
  (discovered in 1947 among polymyxins A to E).
- Differs from **polymyxin B** by only one aminoacid (D-Phe replaced by D-Leu)
- Supplied as the
  - methylsulfonate derivative (often called methane sulfonate and also known as **colistimethate sodium**), which is a **prodrug** that gets spontaneously hydrolyzed into colistin
  - sulfate (**colistine sulfate**) which is more toxic and should no longe be used in the clinics.

Colistin: mg and units …

- Colistin: 10^6 units are
  - Colistin base: 33.3 mg
  - Colistin sulfate: 50 mg
  - Colistin methane sulfonate (colistimethate): 80 mg

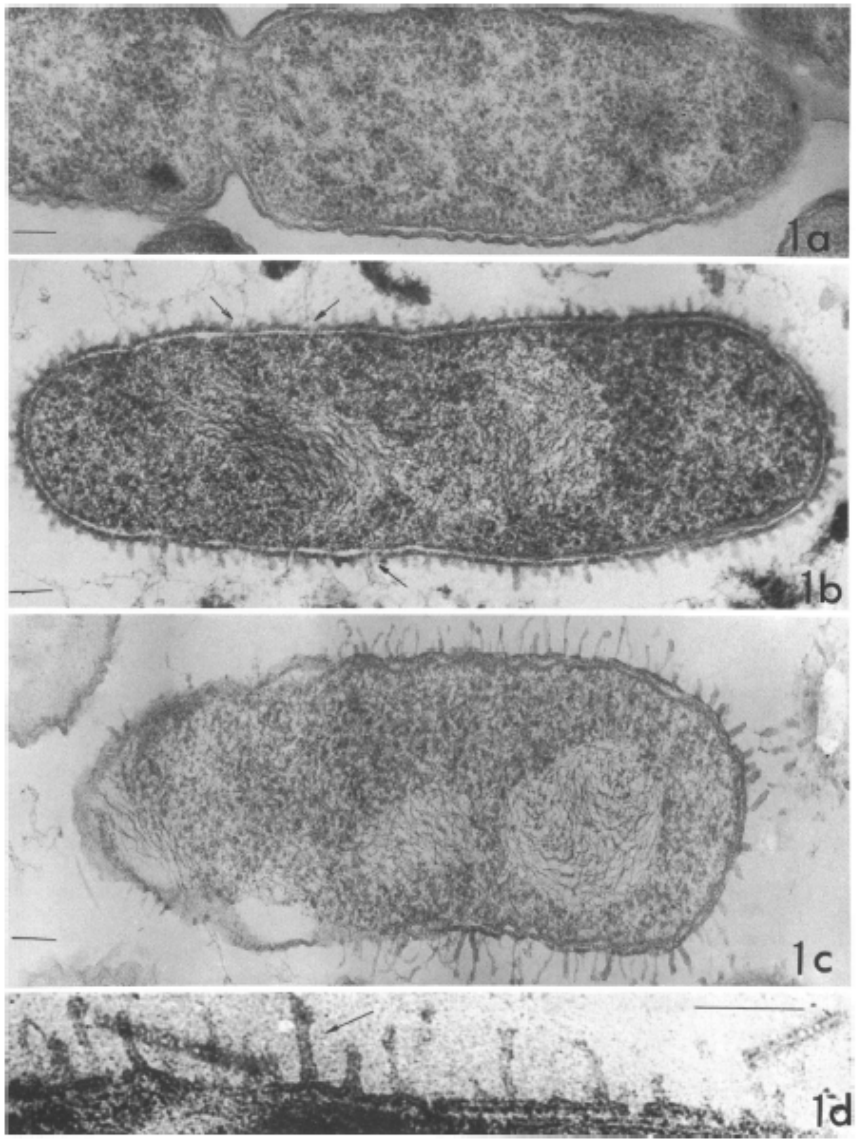
- Polymyxin B: 10^6 units are
  - Polymyxin base: 100 mg
  - Polymyxin sulfate: 119 mg (but often = 100 mg …)

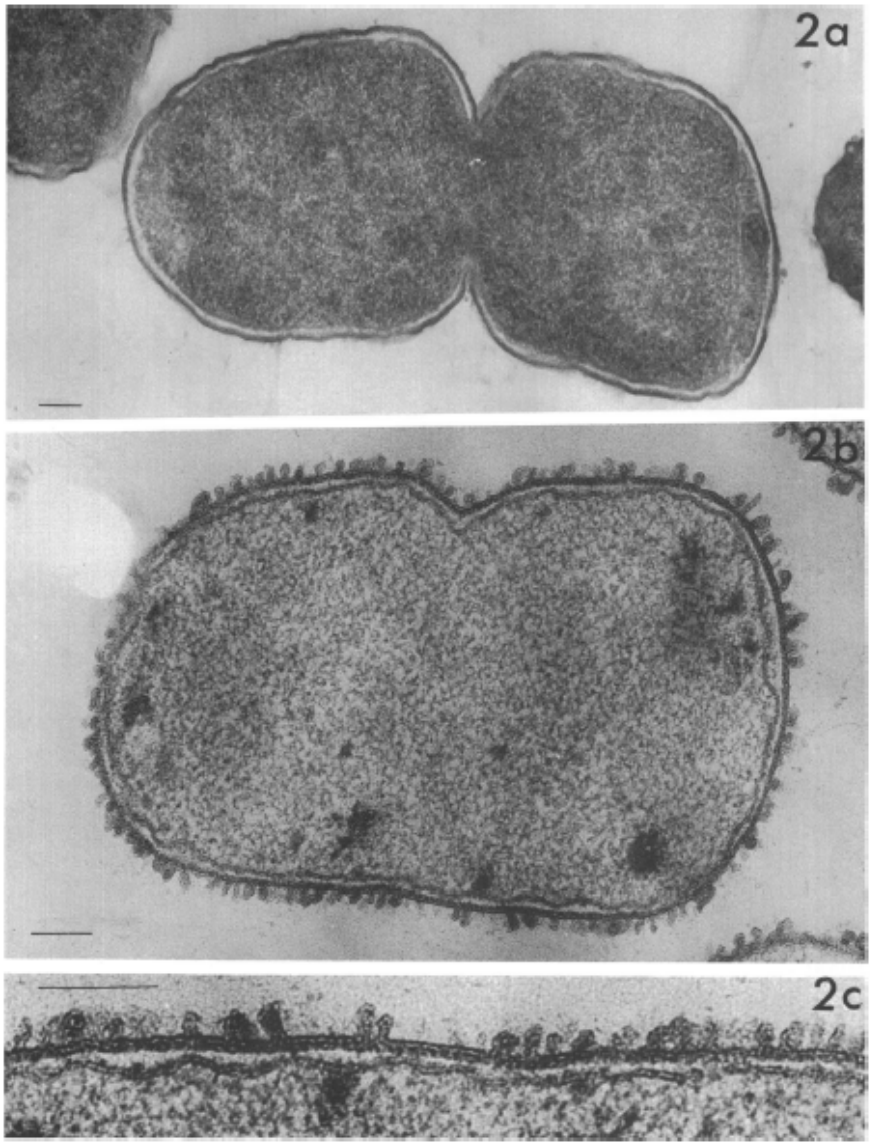
The true content of commercial preparations and the balance between the E1 and E2 components may vary

Colistin Microbiology
as defined in the late 1960's

- About 10 x more active against Gram-negative than Gram-positive bacteria
  - inactive against *Burkholderia cepacia*, *Serratia*, *Proteus, Bacteroides fragilis* … and most Gram-negative cocci [inherent resistance];
  - synergism with sulfonamides, rifampin (later: beta-lactams, fluroquinolones)
- Bactericidal 
- Marked inoculum effect 
- Loss of susceptibility of pre-exposed bacteria 
- MIC values highly dependent upon technique used (poor diffusion through agar; microdilution is preferred but influence by the inoculum) 

Colistin Microbiology: morphological aspects





Koike et al. J. Bacteriol. 1969; 97:448-452

Colistin disposition

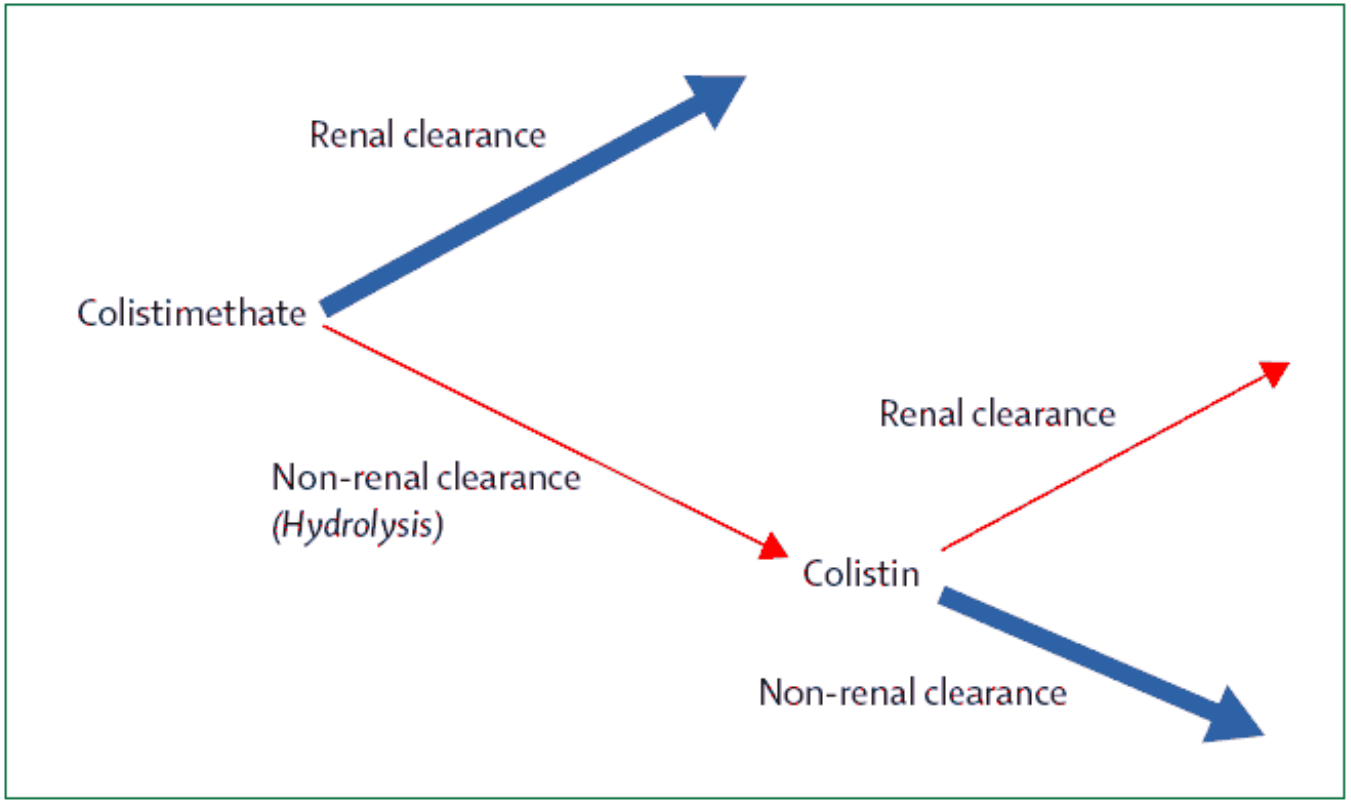


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

Colistin disposition

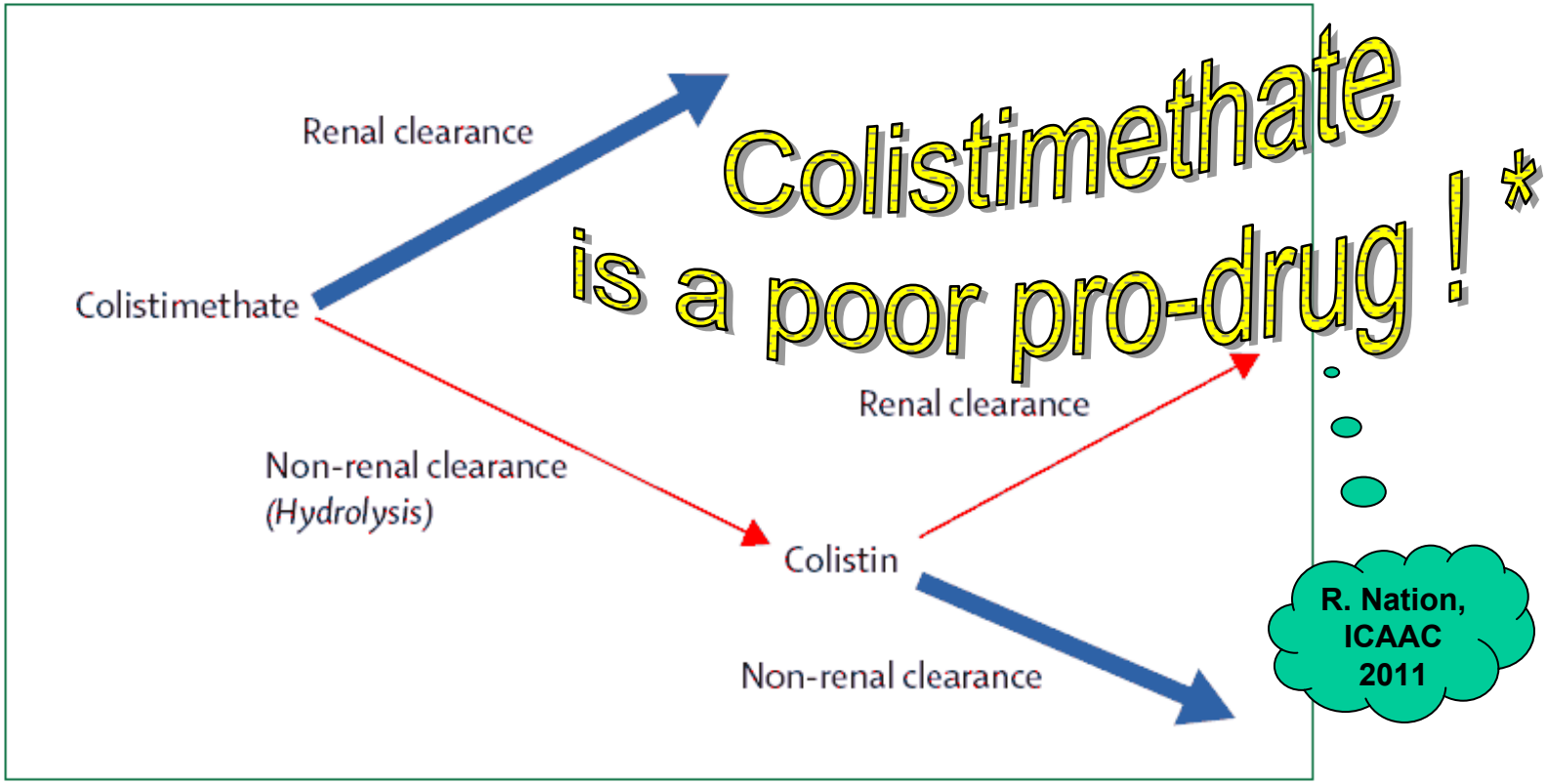
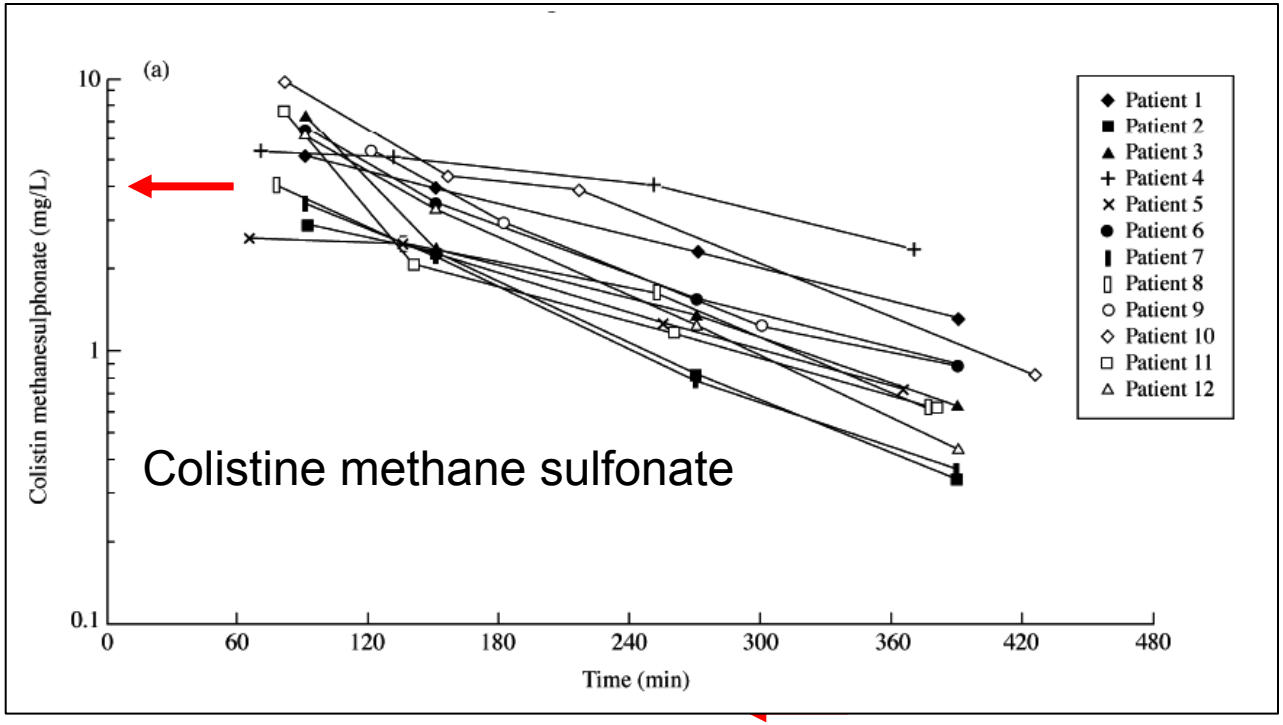


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

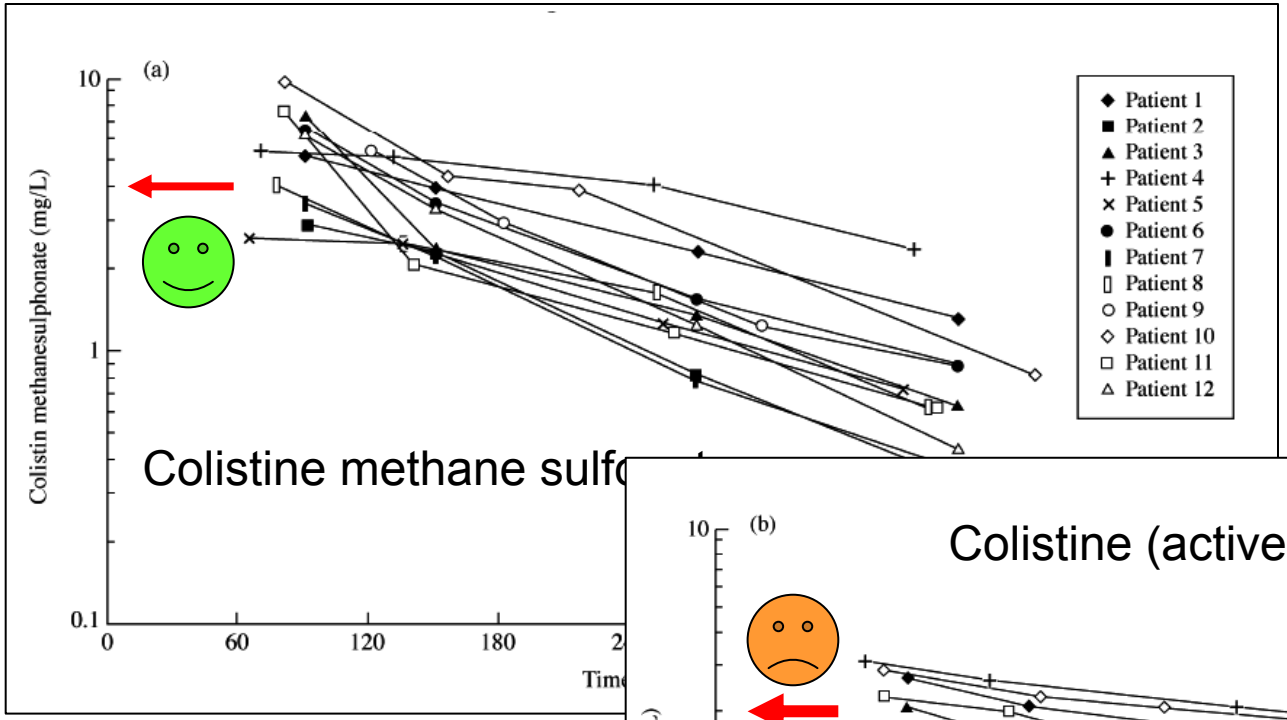
Li et al. Lancet Infect. Dis. 2006; 6:589-601

Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate

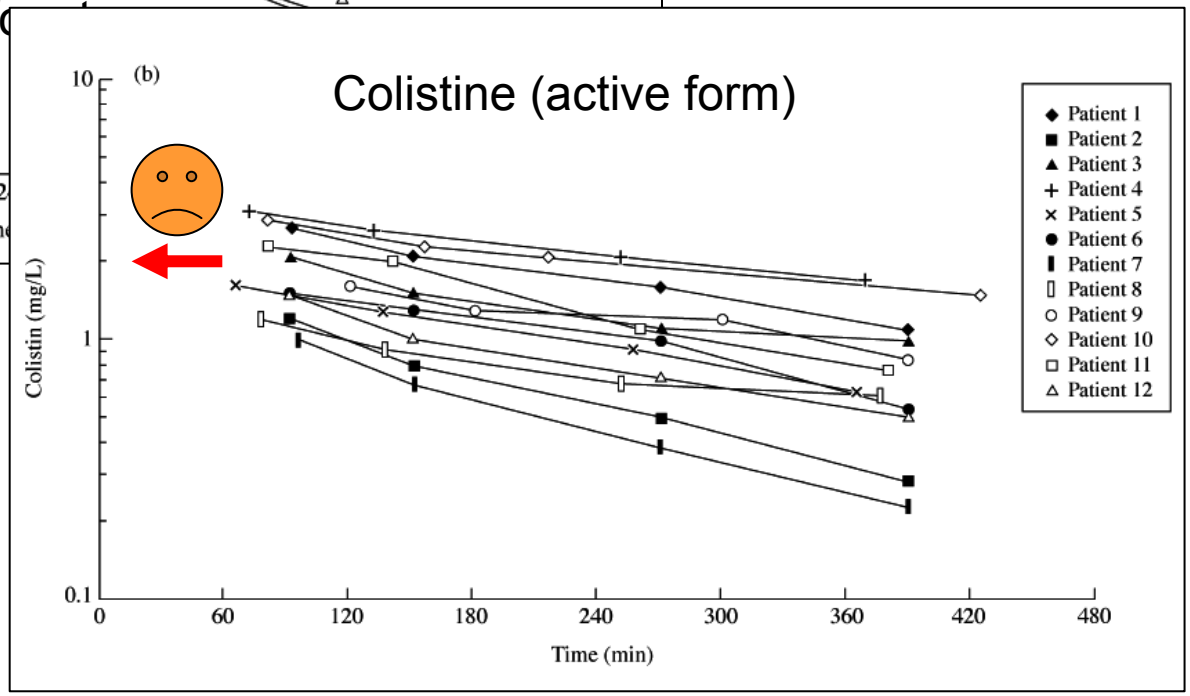


Patients with
160 mg TID
~ 2 x 10^6 Units)
for > 2 days

Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate



Patients with
160 mg TID
~ 2 x 10^6 Units)
for > 2 days



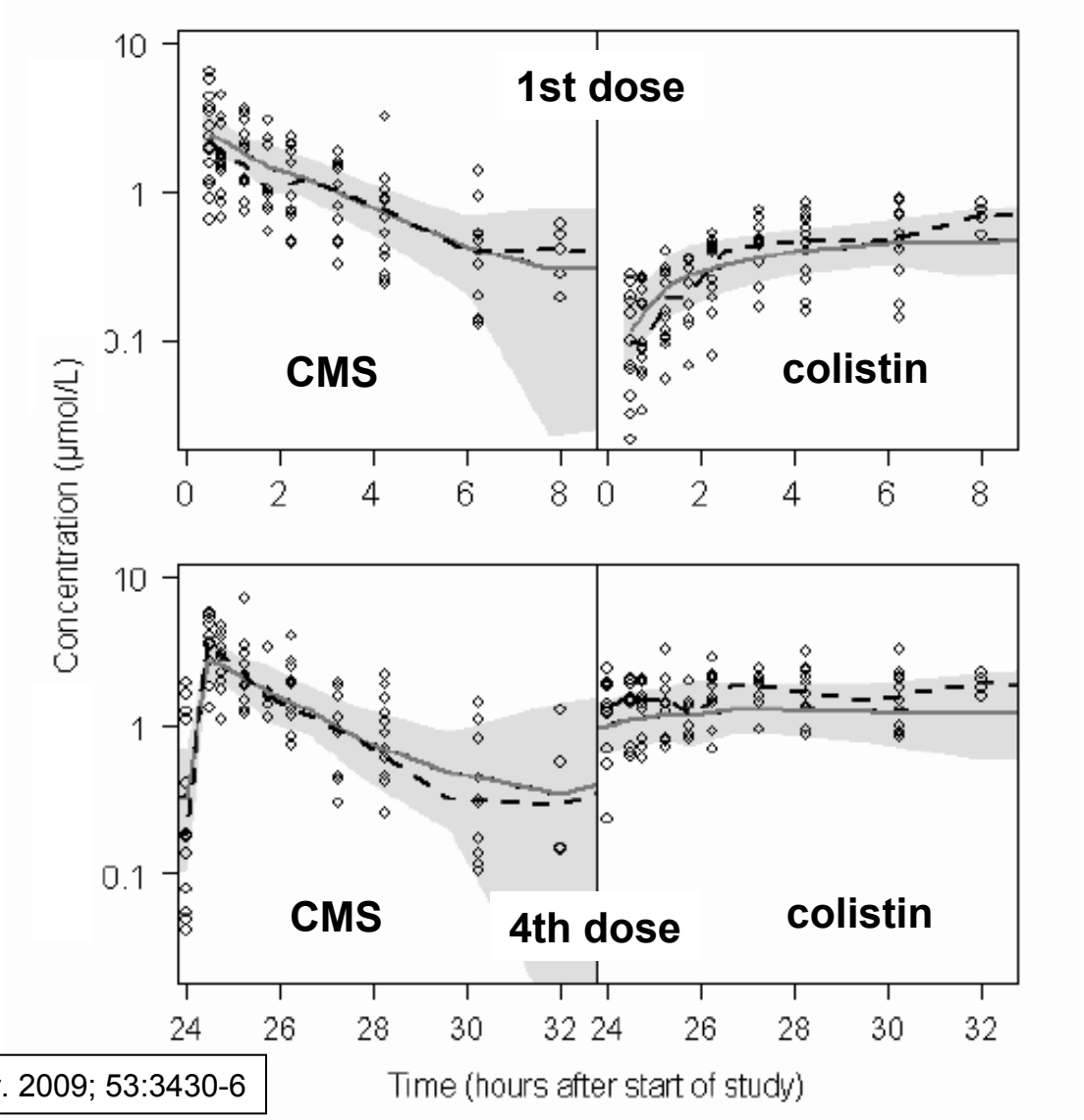
Population pharmacokinetics of colistin in critically-ill patients

Dosage (colistine 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 (pred.)
  - 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. Antimicrob Agents Chemother. 2009; 53:3430-6

Colistin pharmacodkinetics : current clinical data

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▽

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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,**

Population pharmacokinetics of CMS and colistin in normal, HD, and CCRT patients

CMS

formed colistin

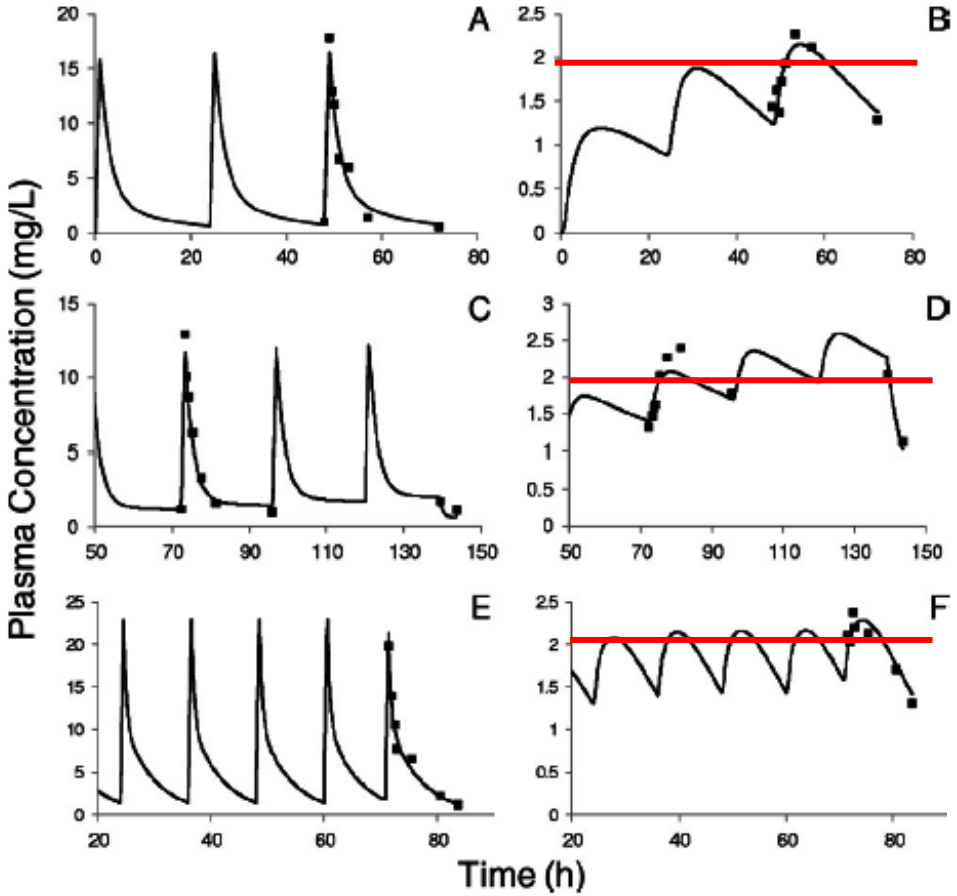


FIG. 3. Representative individual population PK model fits of CMS (A, C, and E) or formed colistin (B, D, and F) in critically ill patients. Panels A and B are representative of a subject not on renal replacement, C and D are representative of a subject on HD, and E and F are representative of a subject on CRRT.

Current dosing recommendations (*): 1 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.

a **Expressed as mg of colistin base (**) activity (CBA) for various categories of critically ill patients. The suggested maintenance daily dose would commence 24 h after administration of a CMS loading dose.**

Example: To target a colistin Css,avg of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m2 would receive a loading dose of 275 mg CBA (***) followed in 24 h by commencement of a maintenance regimen of 225 mg CBA/day in 2 to 3 equally divided doses.

b **Colistin Css,avg target is expressed in mg/liter. This target should be based on MIC, site, and severity of infection.**

c **Use the lower of ideal or actual body weight, expressed in kg. At this time, we suggest caution in the use of a loading dose greater than 300 mg CBA**

---

* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 33 mg colistine base = 80 mg colistimethate = 1 x 10^6 U

*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Current dosing recommendations (*): 2 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.

d **Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin Css,avg target expressed in mg/L.**

Creatinine clearance (CrCL) expressed in ml/min/1.73 m2. Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft and Gault equation) may be used to estimate CrCL which would then be normalized to a body surface area of 1.73 m2.

in patients with CrCL values 70 ml/min/1.73 m2 or when targeting a "high" colistin Css,avg, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.

---

* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 33 mg colistine base = 80 mg colistimethate = 1 x 10^6 U

*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Current dosing recommendations (*): 3 of 3

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Maintenance dose	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

***e* Based upon use of equation 10 and setting CrCL to zero.**

***f* Supplemental dose of CMS to achieve a similar colistin Css,avg on a HD day as occurs on a non-HD day. It is assumed that the hemodialysis session occurs toward the end of a CMS dosage interval.**

***g* Based on the population PK analysis for 4 critically ill patients receiving continuous renal replacement therapy.**

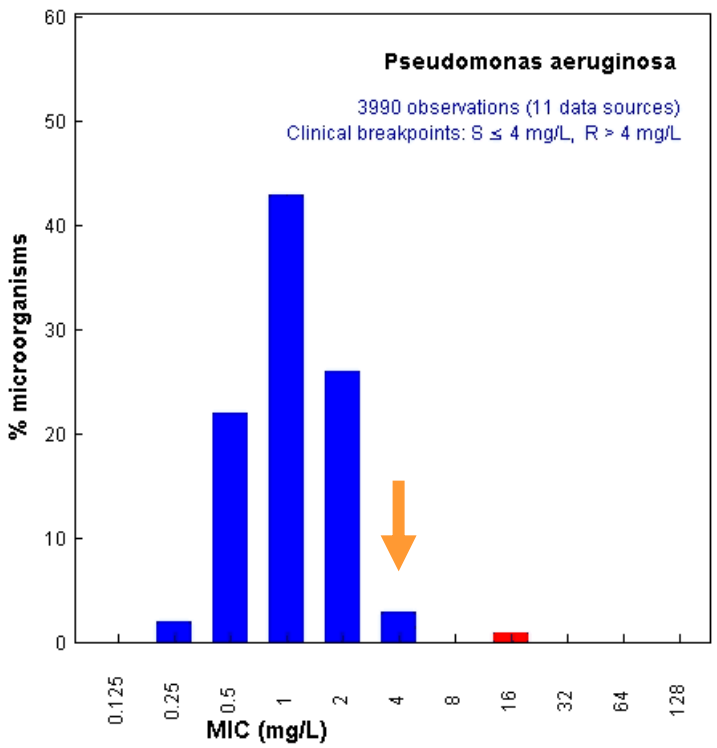
---

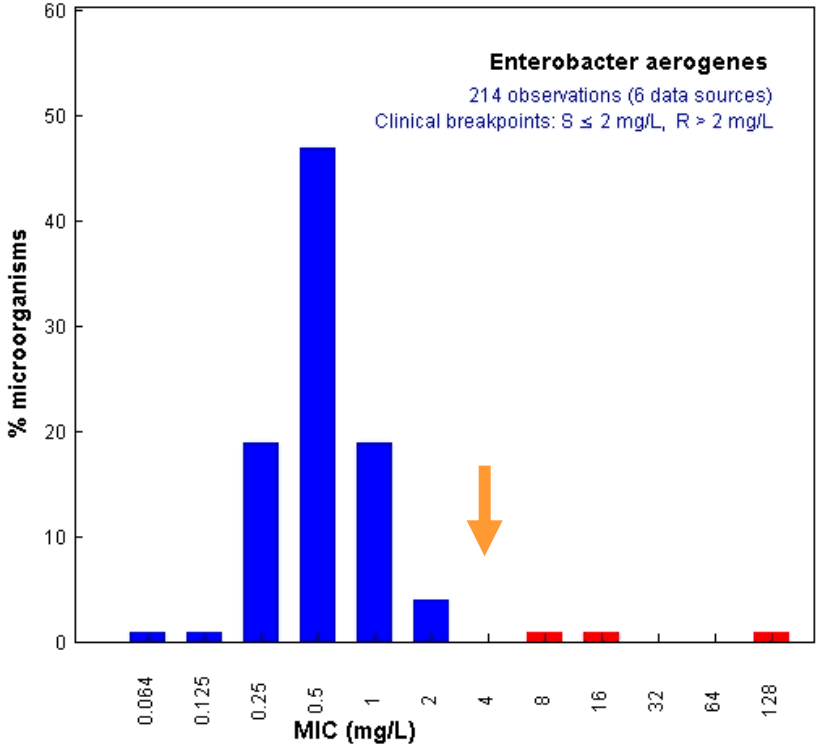
* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 33 mg colistine base = 80 mg colistimethate = 1 x 10^6 U

*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Two typical EUCAST MIC distributions for colistin

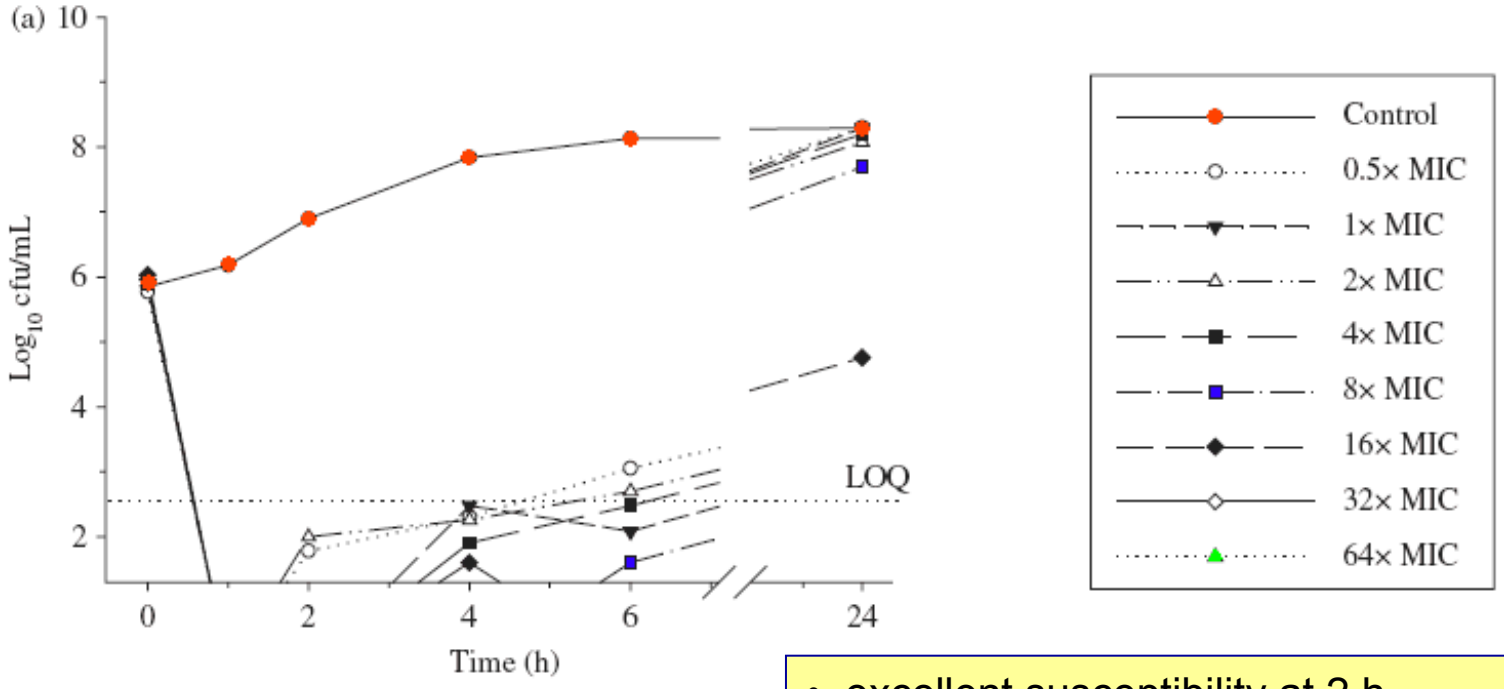




EUCAST and CLSI breakpoint is 4mg/L but the C_{max} is rarely > than 2 mg/L … Can you call this a true "susceptibility" breakpoint ?

Colistin pharmacodynamics (1)

Time kill curves against *K. pneumoniae* "single dose"



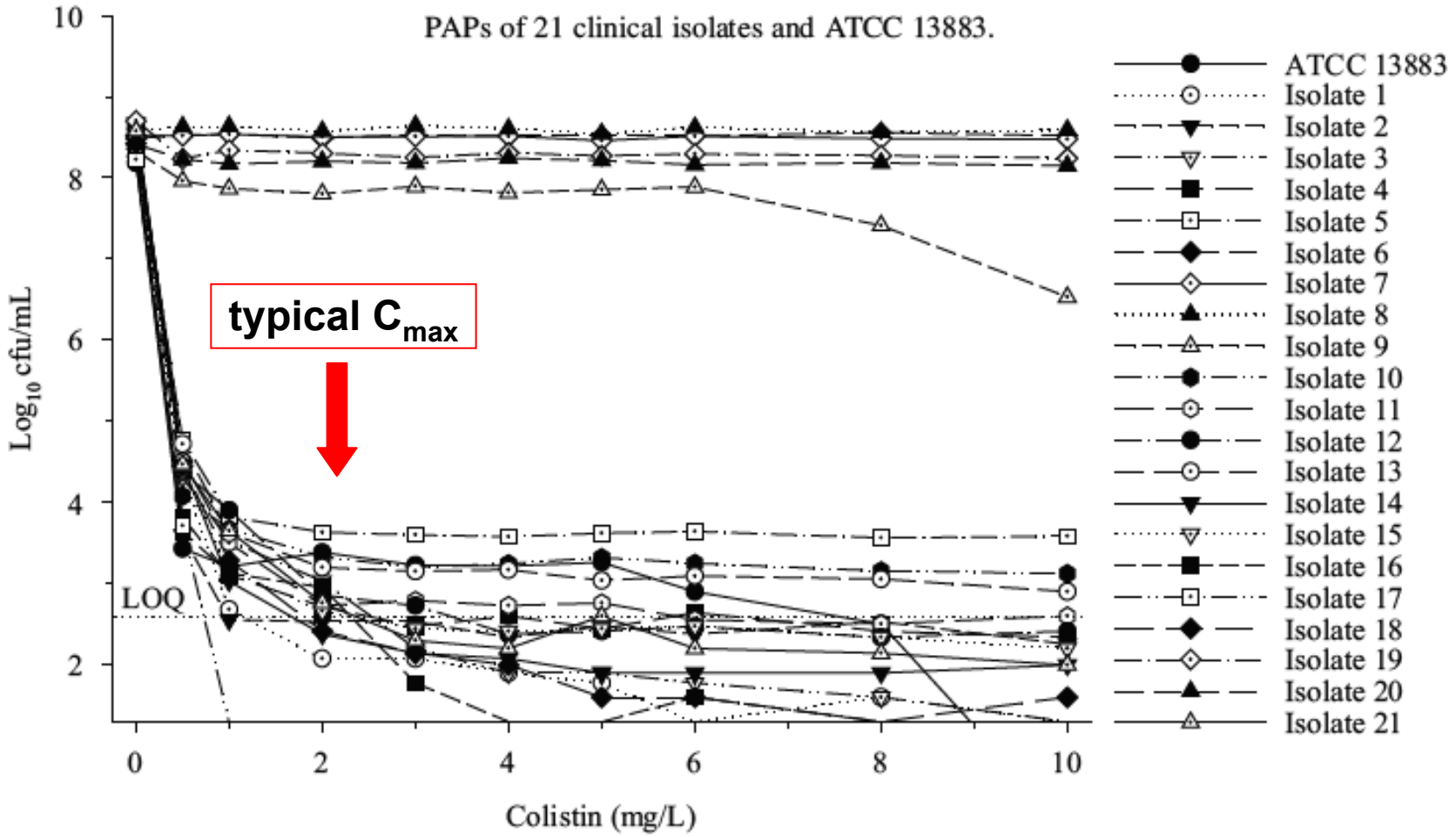
- excellent susceptibility at 2 h…
- **but** regrowth at 24h if conc. ≤ 16 MIC

Conclusions: **The data suggest that monotherapy with colistin methanesulfonate, the parenteral form of colistin, and long dosage intervals may be problematic for the treatment of infections caused by multidrug-resistant *K. pneumoniae*, particularly for colistin-heteroresistant strains. Further investigation on combination therapy of colistin with other antibiotics is warranted.**

Poudyal et al. JAC 2008; 62:1311-1318

Colistin pharmacodynamics (2)

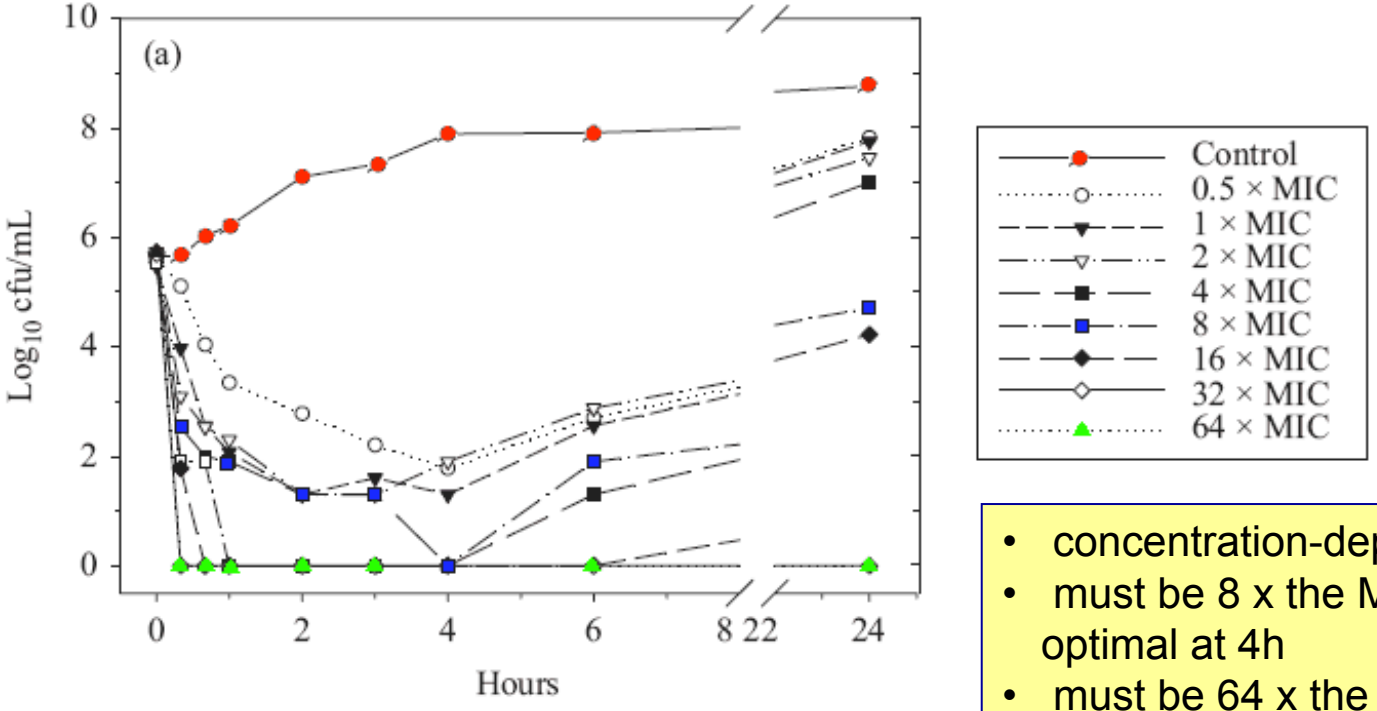
Population analysis profiles of *K. pneumoniae* isolates



Poudyal et al. JAC 2008; 62:1311-1318

Colistin pharmacodynamics (4)

Time kill curves against *A. baumanii*



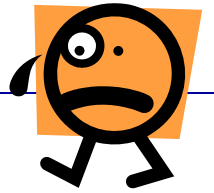
- concentration-dependence
- must be 8 x the MIC to become optimal at 4h
- must be 64 x the MIC to avoid regrowth
- modest post-antibiotic effect (see data in paper)

Conclusions: **These findings suggest that monotherapy with colistin methanesulphonate, the parenteral form of colistin, and long dosage intervals (e.g. 24 h) may be problematic for treatment of infections caused by colistin heteroresistant *A. baumannii*.**

Owen et al. JAC 2007; 59:473-477

Colistin pharmacodynamics (5)

In conclusion, the present study demonstrated initial rapid bacterial killing by colistin against susceptible *K. pneumoniae*. However, the concerning findings were a high frequency of colistin heteroresistance, the substantial regrowth within 24 h that occurred even at colistin concentrations up to 64× MIC and no significant colistin PAE. These findings suggest the potential risk that monotherapy with CMS and extended-interval dosage regimens may promote colistin resistance in multidrug-resistant *K. pneumoniae*.

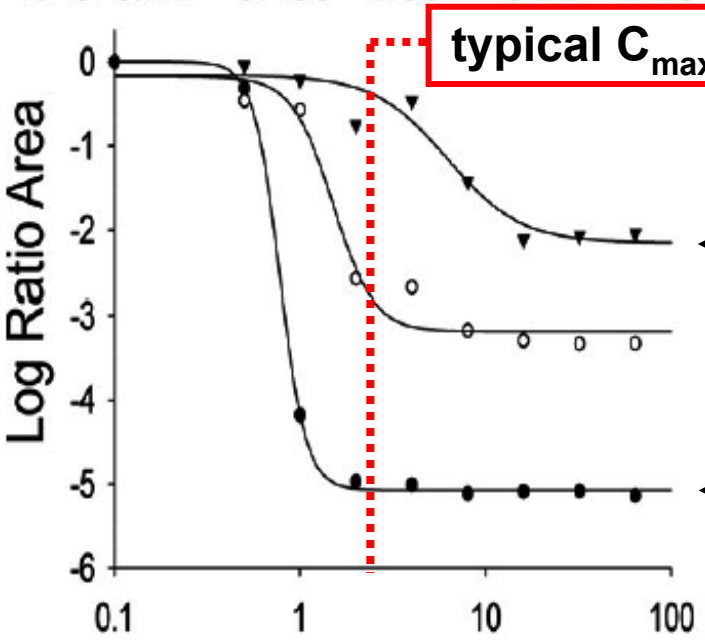


Poudyal et al. JAC 2008; 62:1311-1318

Colistin and inoculum effect

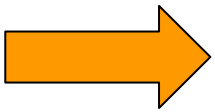
A)

Inoculum	E_0	Emax	EC_{50}	H
10^6 CFU/mL	-0.003	5.07	0.777	6.10
10^8 CFU/mL	-0.173	3.01	1.49	3.95
10^9 CFU/mL	-0.156	1.99	6.22	2.20



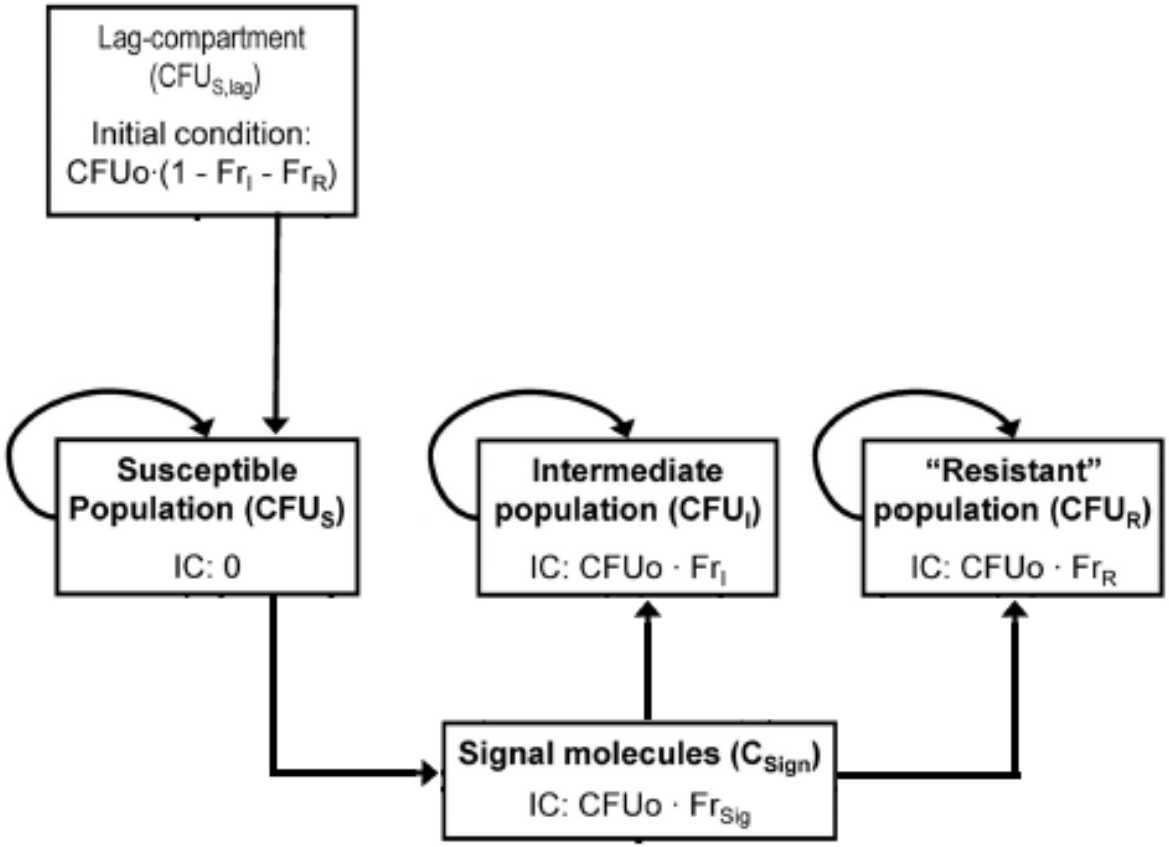
high inoculum (~ *in vivo*

low inoculum (~ *in vitro* testing)



The extent and rate of killing of *P. aeruginosa* by colistin were markedly decreased at high CFUo compared to those at low CFUo.
Bulita et al. Antimicrob. Agents Chemother. (2010) 54:2051-2062

Colistin pharmacodynamics and resistance (3)



Proposed model for mergence of less-suscpetible and resistant population of *P. aeruginosa* as deduced from an in vitro model.
(highly simplified from Bulita et al. Antimicrob. Agents Chemother. (2010) 54:2051-2062)

Colistin pharmacodynamics: conclusions

These recent elegant studies confirm what early investigators had already observed, namely that colistin

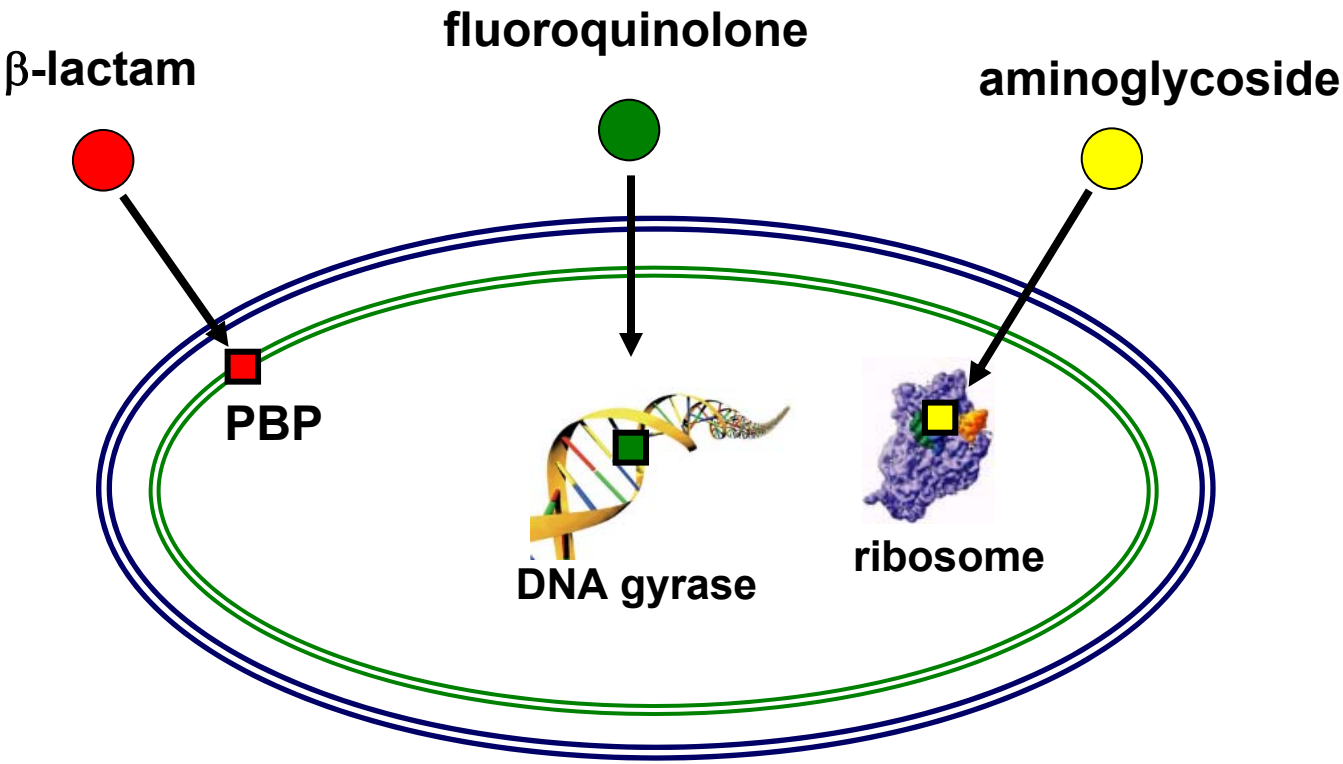
- Displays a **high and fast bactericidal effect** (named today: concentration-dependent antibiotic)

  ➔ **A loading dose to reach quickly max. bactericidal effect is essential**

- But that its activity **vanishes after even transient exposure** (named today: **heteroresistance** and/or **persistence of less susceptible** isolates, or **adaptative resistance**)

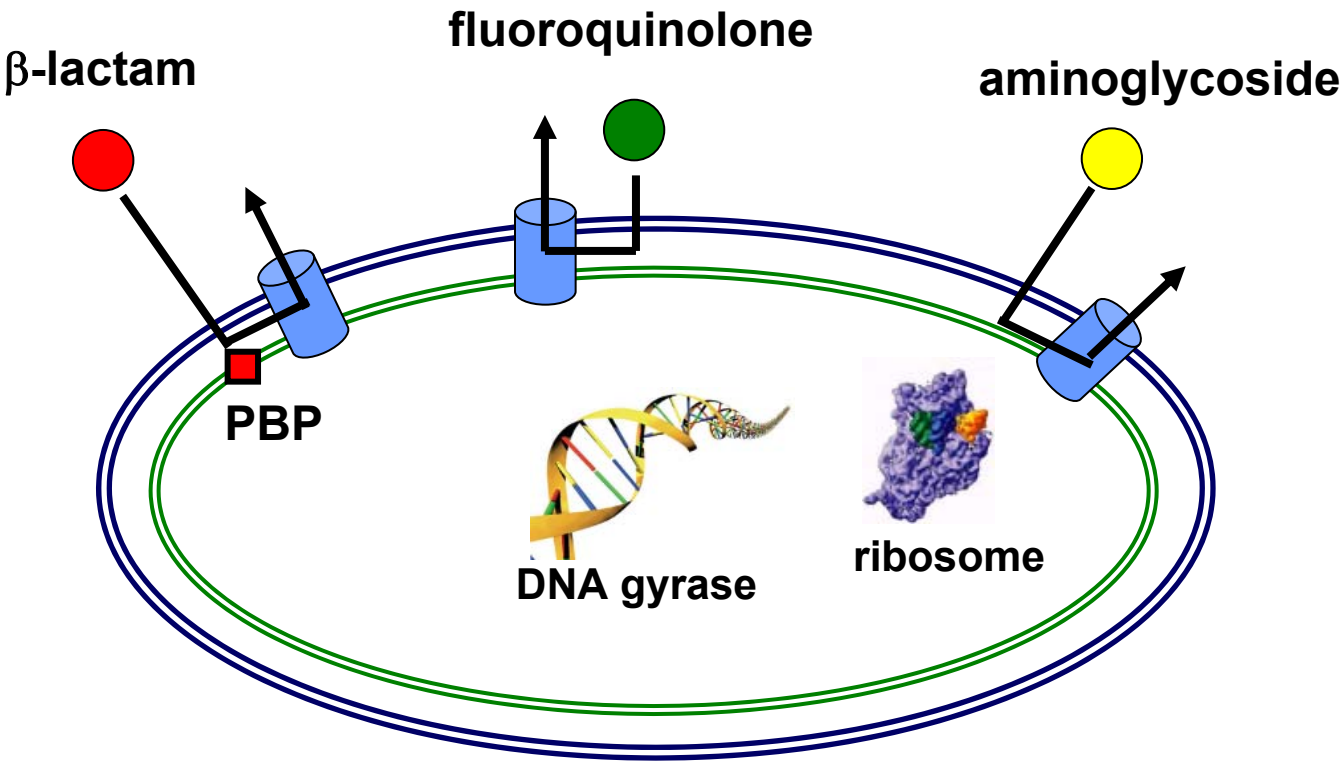
  ➔ colistin needs to be **administered several times a day to avoid regrowth**

Colistin synergy: the rationale (1 of 3)



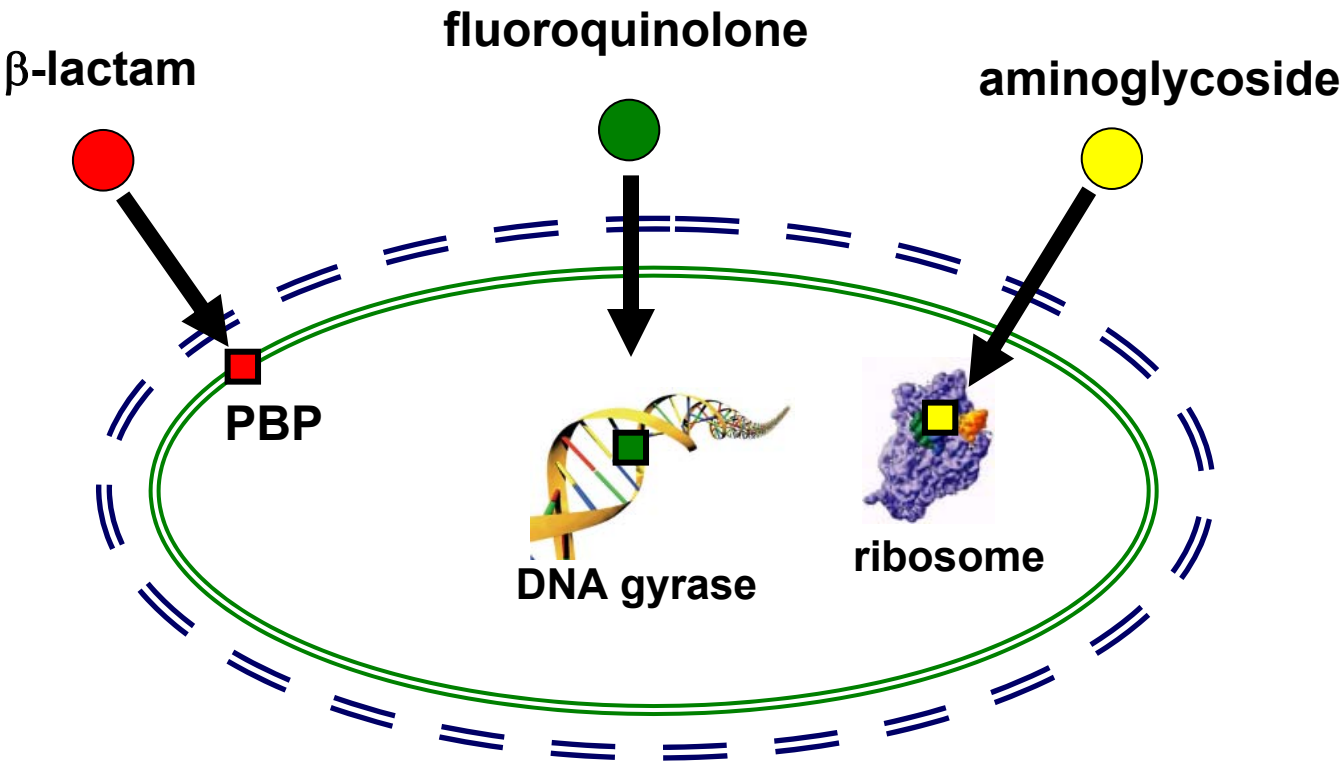
- Gram-negative bacteria have two membanes (OM and IM)
- Antibiotic targets are most often located in the IM or intracellularly
- Most antibiotics must at least pass across the OM to reach their target, which may represent a limiting step

Colistin synergy: the rationale (2 of 3)



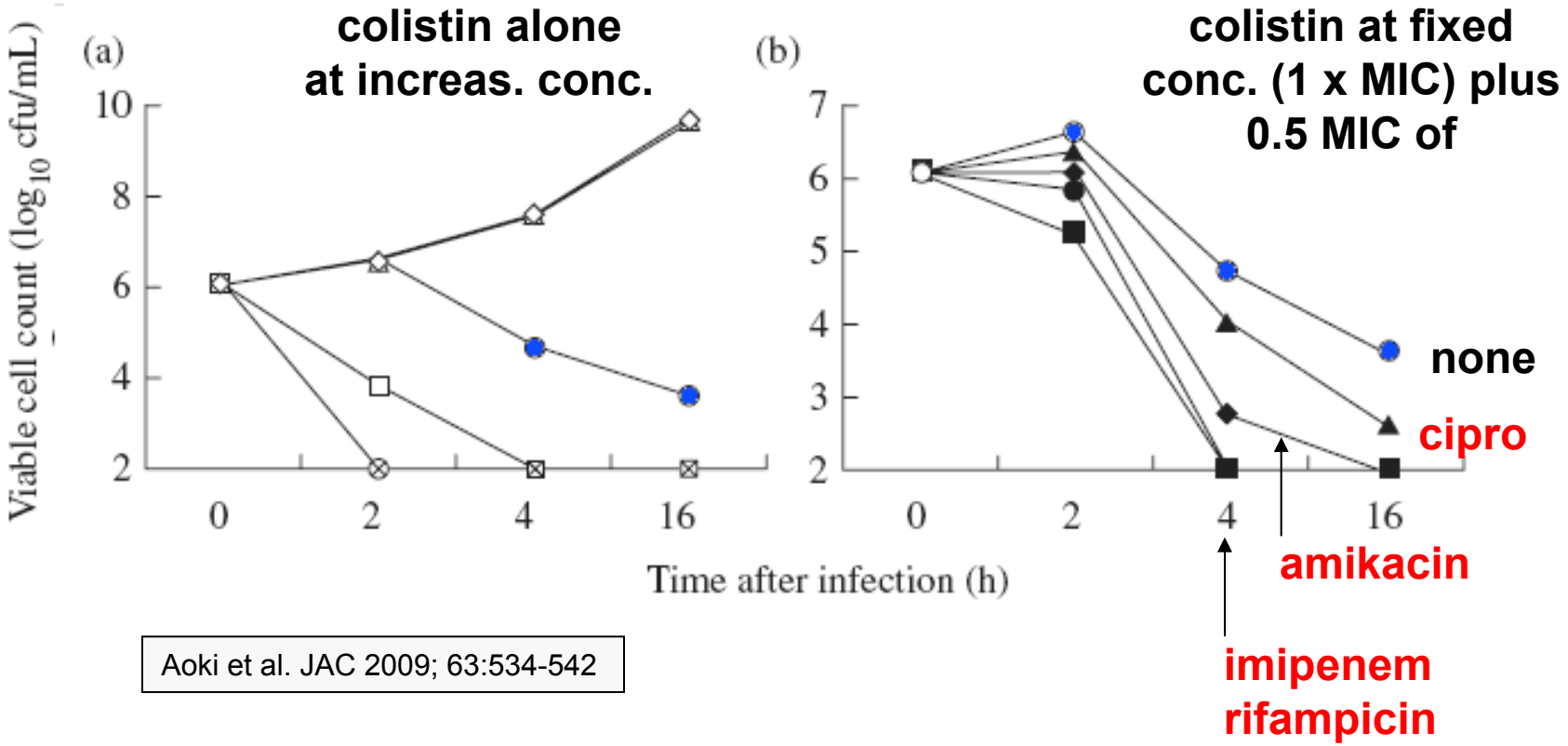
- Gram-negative bacteria have also efflux systems defeating the passage of drugs across the OM and explaining the low activity of many antibiotics (intrinsic resistance) and the so-called "adaptative" resistance (aminglycosides)

Colistin synergy: the rationale (1 of 3)



- **Disrupting the OM (as colistin does) will facilitate access of the other antibiotics to their targets**
- **This may apply EVEN to antibiotics for which the bateria are resistant (if due to OM impermeability/efflux phenomenon)**

Colistin synergy *in vitro* and *P. aeruginosa*



Aoki et al. JAC 2009; 63:534-542

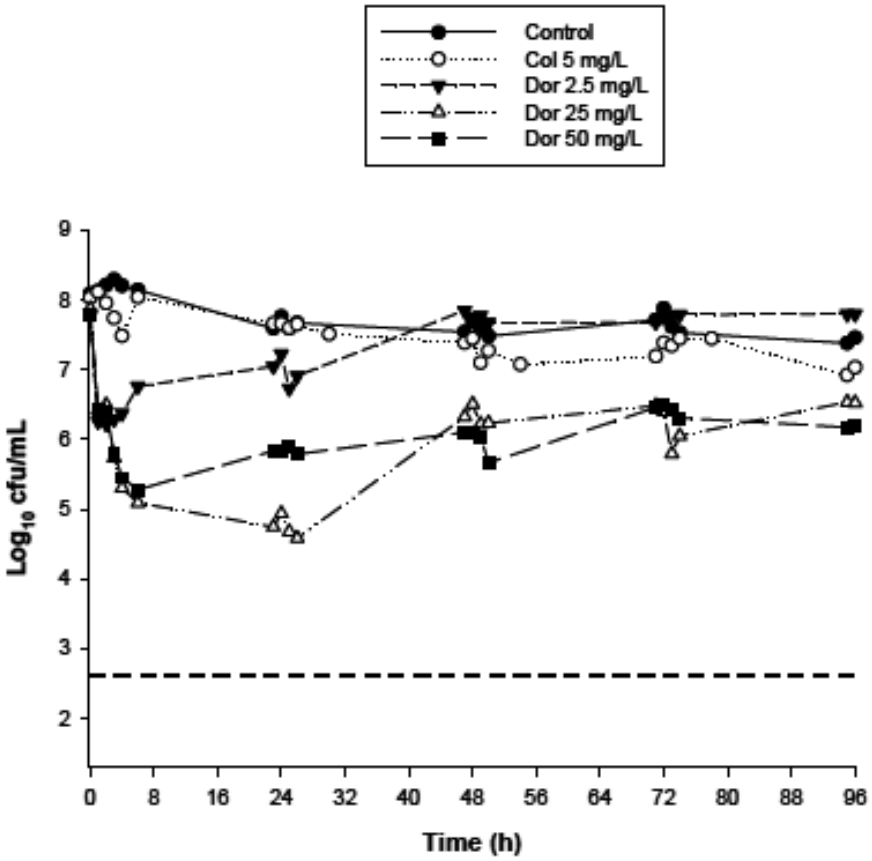
Souli et al. AAC 2009; 2133-2135:

- Synergy / Improved activity if susceptible to both agents or to colistin only
- **Antagonism frequent if colistin-insensitive**

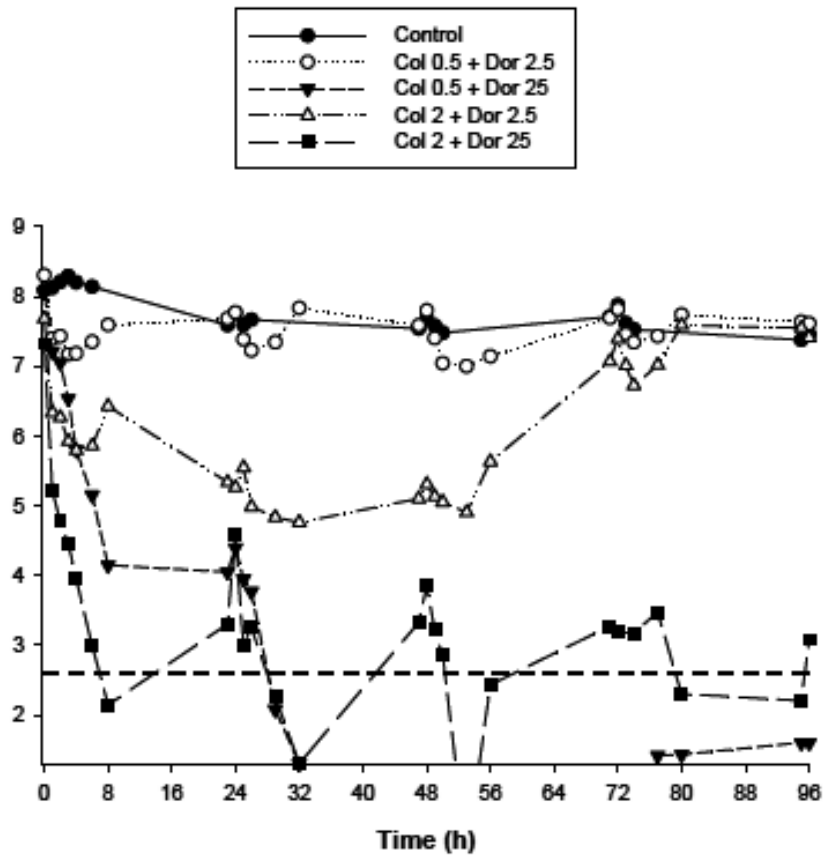
Colistin synergy *in vitro* and *P. aeruginosa*

synergy with doripenem at high inoculum concentration

drugs alone



combination



Bergen et al. AAC Accepts, online: 12 September 2011

Colistin nephrotoxicokinetic is complex…

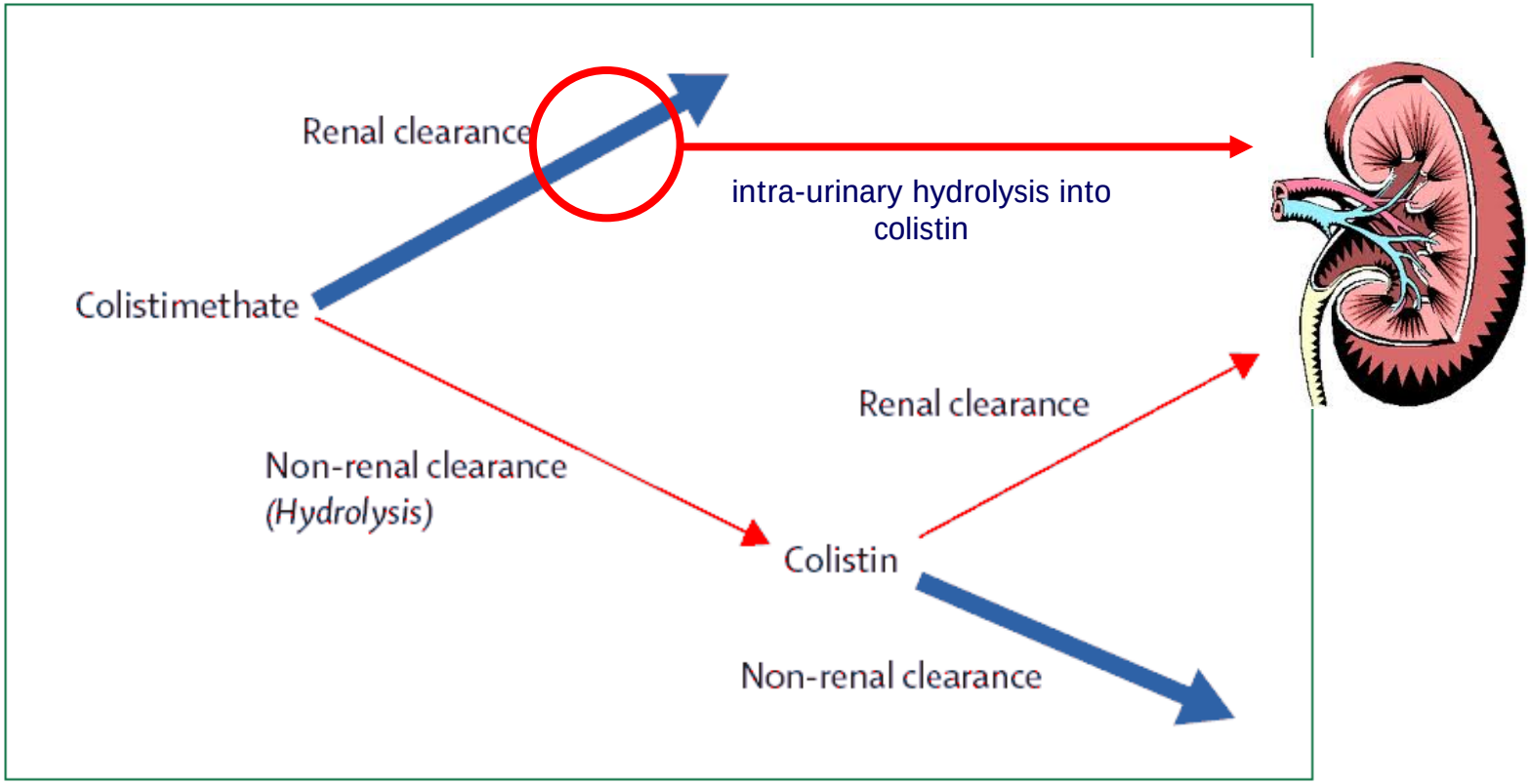
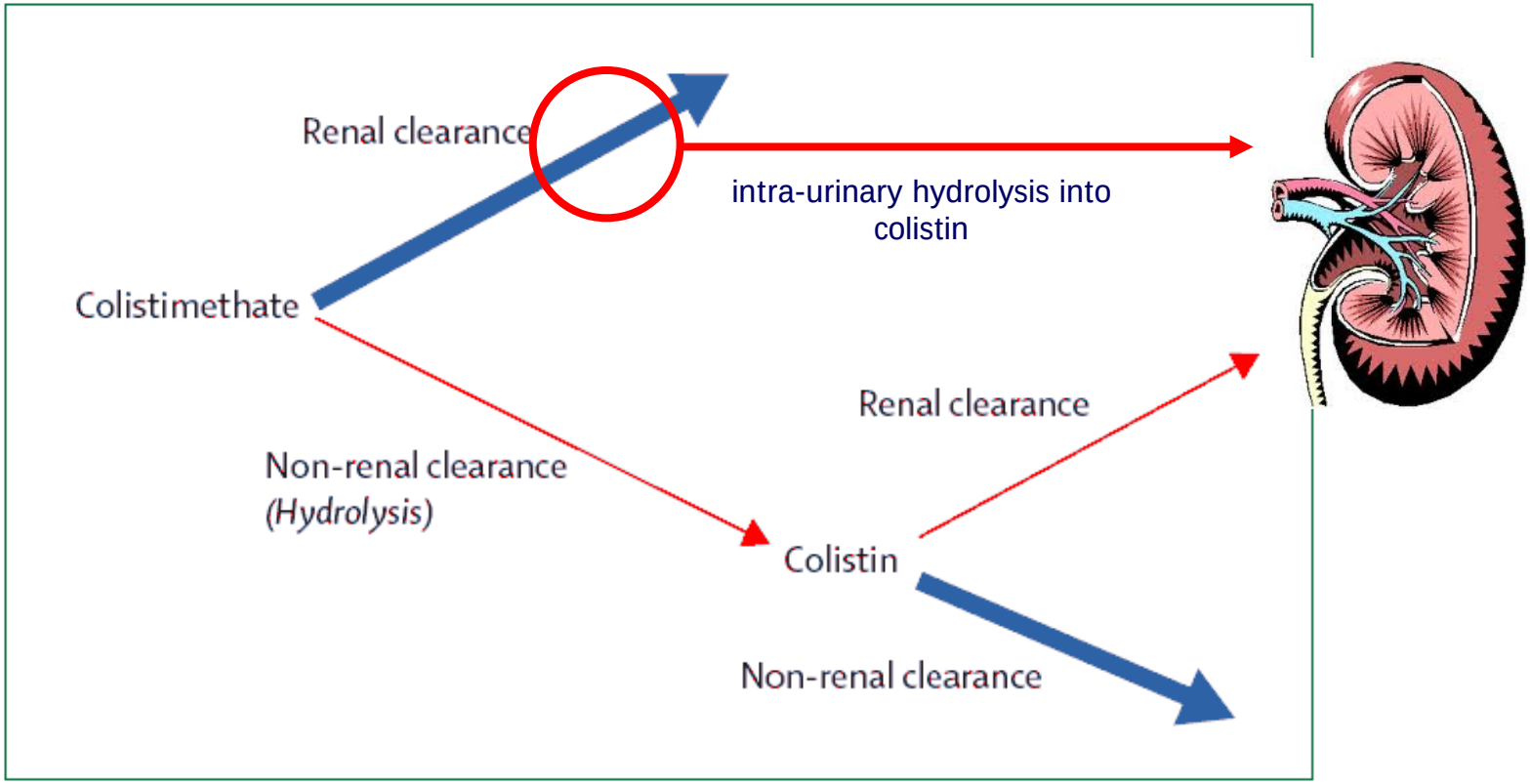


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Li et al. Lancet Infect. Dis. 2006; 6:589-601 (modified)

Colistin nephrotoxicokinetic is complex…



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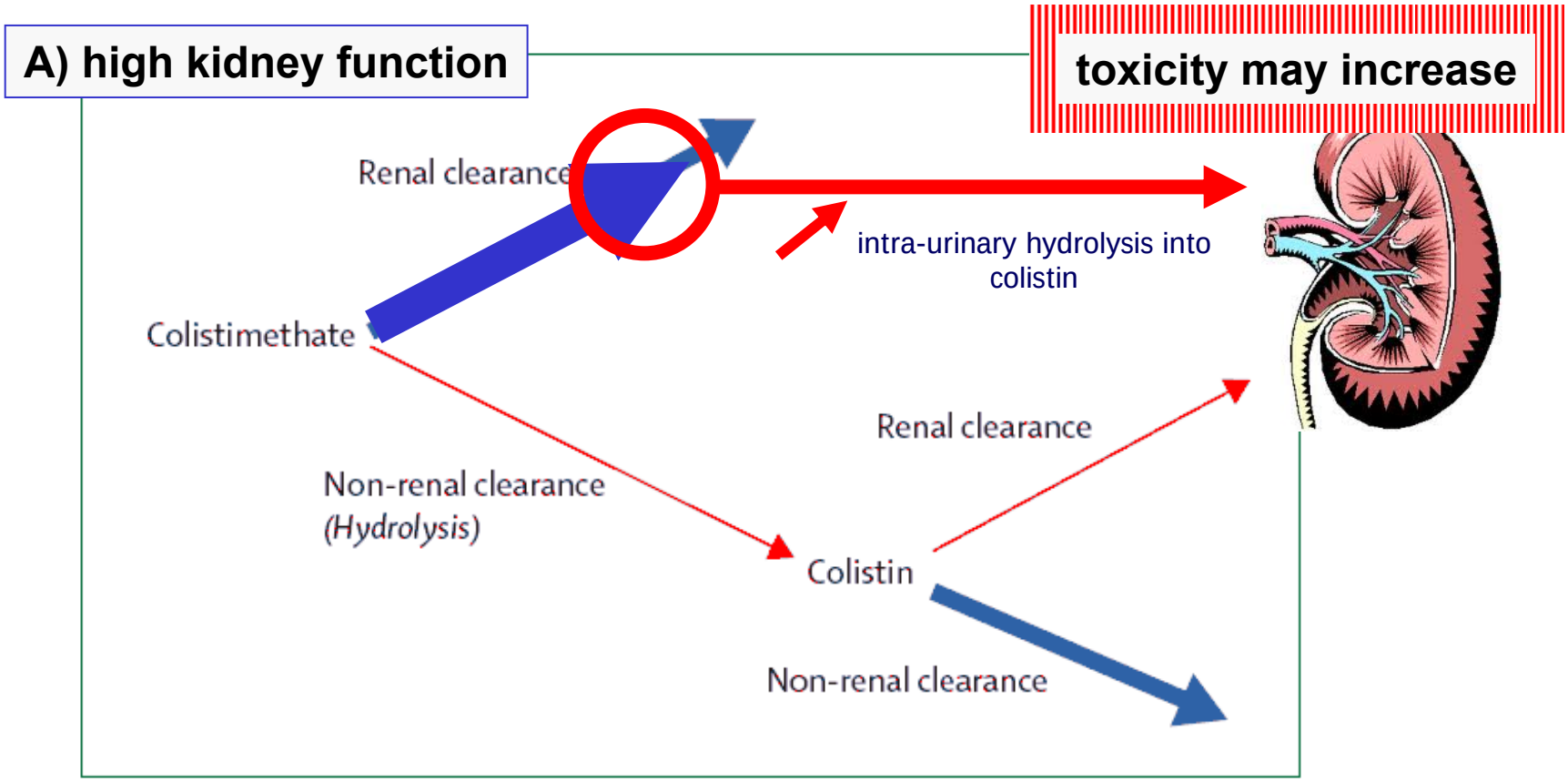

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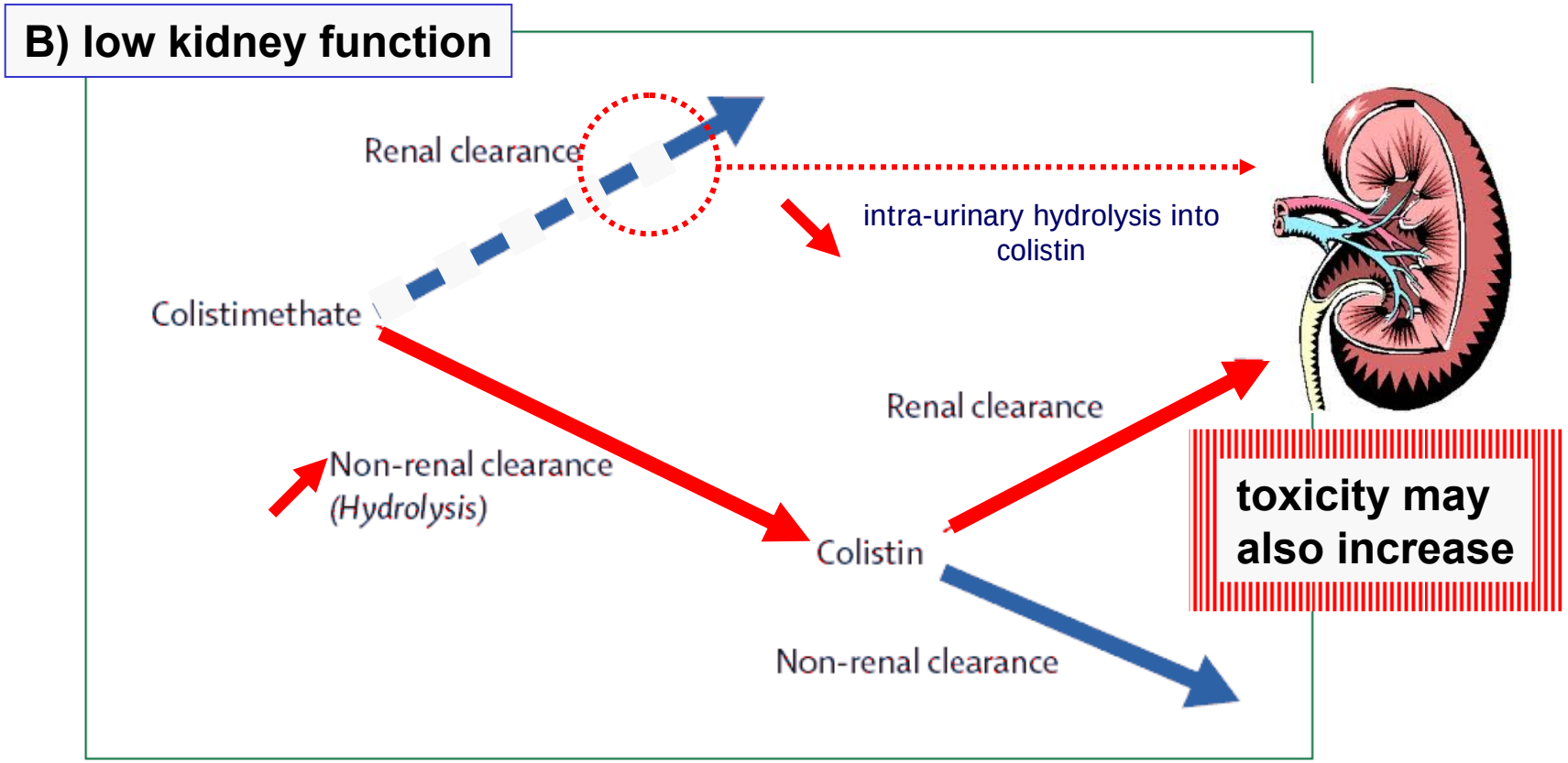

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Li et al. Lancet Infect. Dis. 2006; 6:589-601 (modified)

Colistin nephrotoxicity

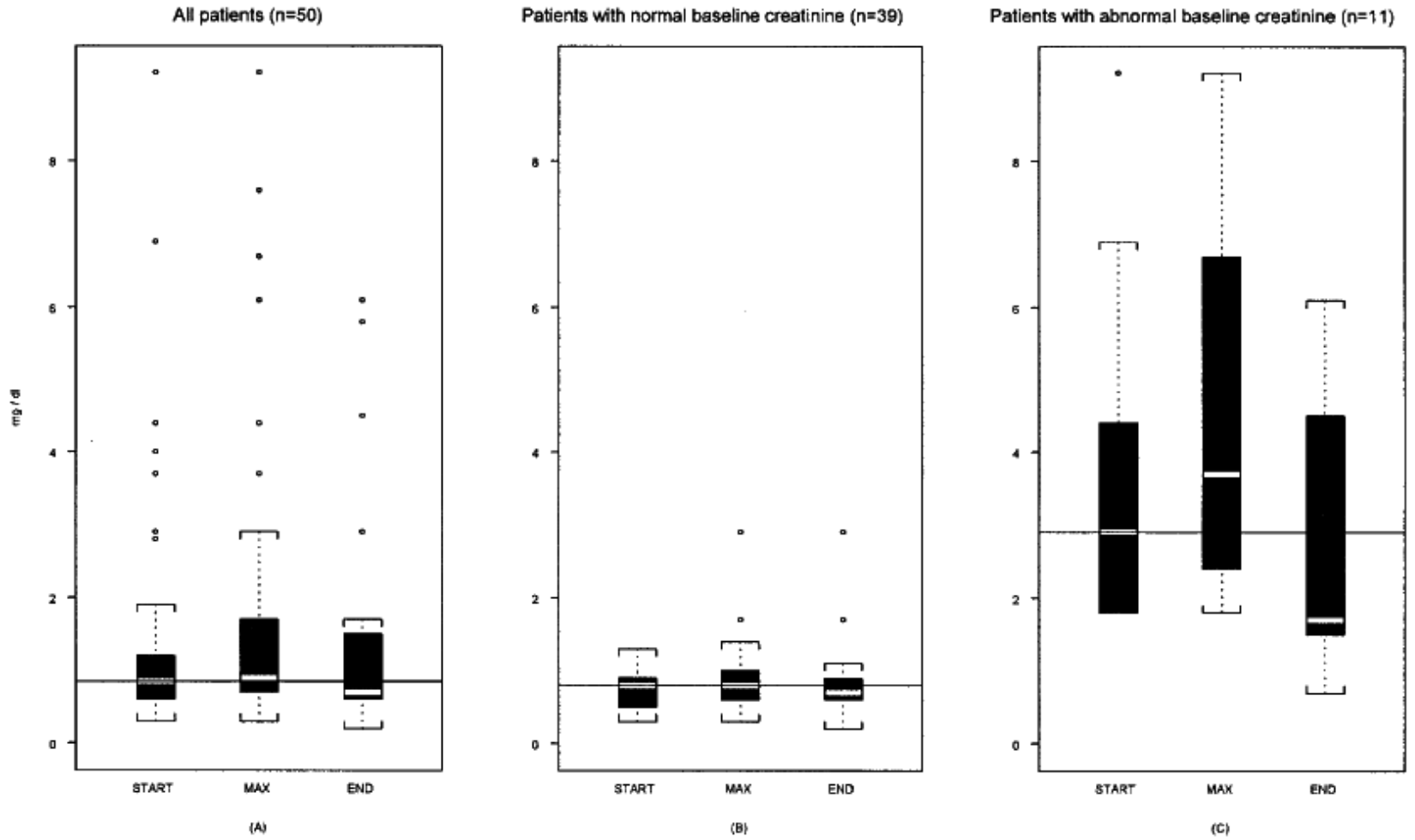

FIG. 1. The distribution of serum creatinine levels on the first day of colistin treatment (START), at the peak value (MAX), and at the end of colistin treatment (END) in all studied patients (A), in the group of patients with normal baseline creatinine values (B), and in the group of patients with abnormal baseline creatinine values (C). The horizontal lines within the boxes represent the median creatinine baseline value at the first day of colistin treatment.

Kasiakou *et al*. AAC 2005; 49:3136-3146

A recent prospective clinical study

Effectiveness and safety of colistin: prospective comparative cohort study

Mical Paul[1,2*], Jihad Bishara[1,2], Ariela Levcovich[1,2], Michal Chowers[2,3], Elad Goldberg[1,2], Pierre Singer[2,4], Shaul Lev[2,4], Perla Leon[5], Maria Raskin[1,2], Dafna Yahav[2,6] and Leonard Leibovici[2,6]

[1]Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [3]Unit of Infectious Diseases, Meir Medical Center, Kfar Saba, Israel; [4]Intensive Care Unit, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [5]Department of Anesthesiology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; [6]Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

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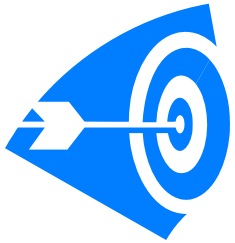
Background: Colistin has re-entered clinical use by necessity. We aimed to assess its effectiveness and safety compared with newer antibiotics.

colistimethate: 6–9 MU (million units) divided in 3 doses/day (if hemodialysis: 1–2 MU twice daily) if Gram (-) carbaoenem resistant *vs.* beta-lactams (if susceptible)

Conclusions: The need for colistin treatment is associated with poorer survival. Adjusted analyses suggest that colistin is less effective and more toxic than β-lactam antibiotics.

J Antimicrob Chemother 2010; **65**: 1019–1027
doi:10.1093/jac/dkq069 Advance publication 18 March 2010



if colistin is you 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 (see slide 58)…
- A loading dose (additional 2 to 4 x 10^6 U at first dose; total 4 to 6 x 10^6 U and perhaps up to 8-9 [see slide 57]) is essential …
- Never use it in monotherapy … (meropenem, doripenem, … even if non-susceptible)
- 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… and should not have left in the first place !

Disclosures and slides availability

Financial support from

- 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)

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