Vancomycin and Colistin: What is new (since 2011) ?

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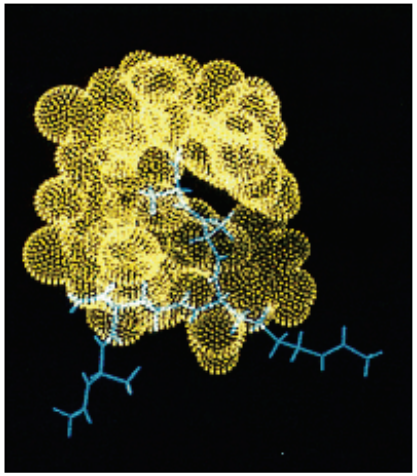
Contents of the presentation

- Vancomycin
  - short summary
  - high doses
  - continuous infusion of vancomycin: how to avoid mistakes
- Colistin
  - short summary
  - reminding dosage recommendations set in 2011
  - synergy: what's new
  - recent clinical overview…
  - resistance: it is coming …
  - at the end of the day … what can you expect ?

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

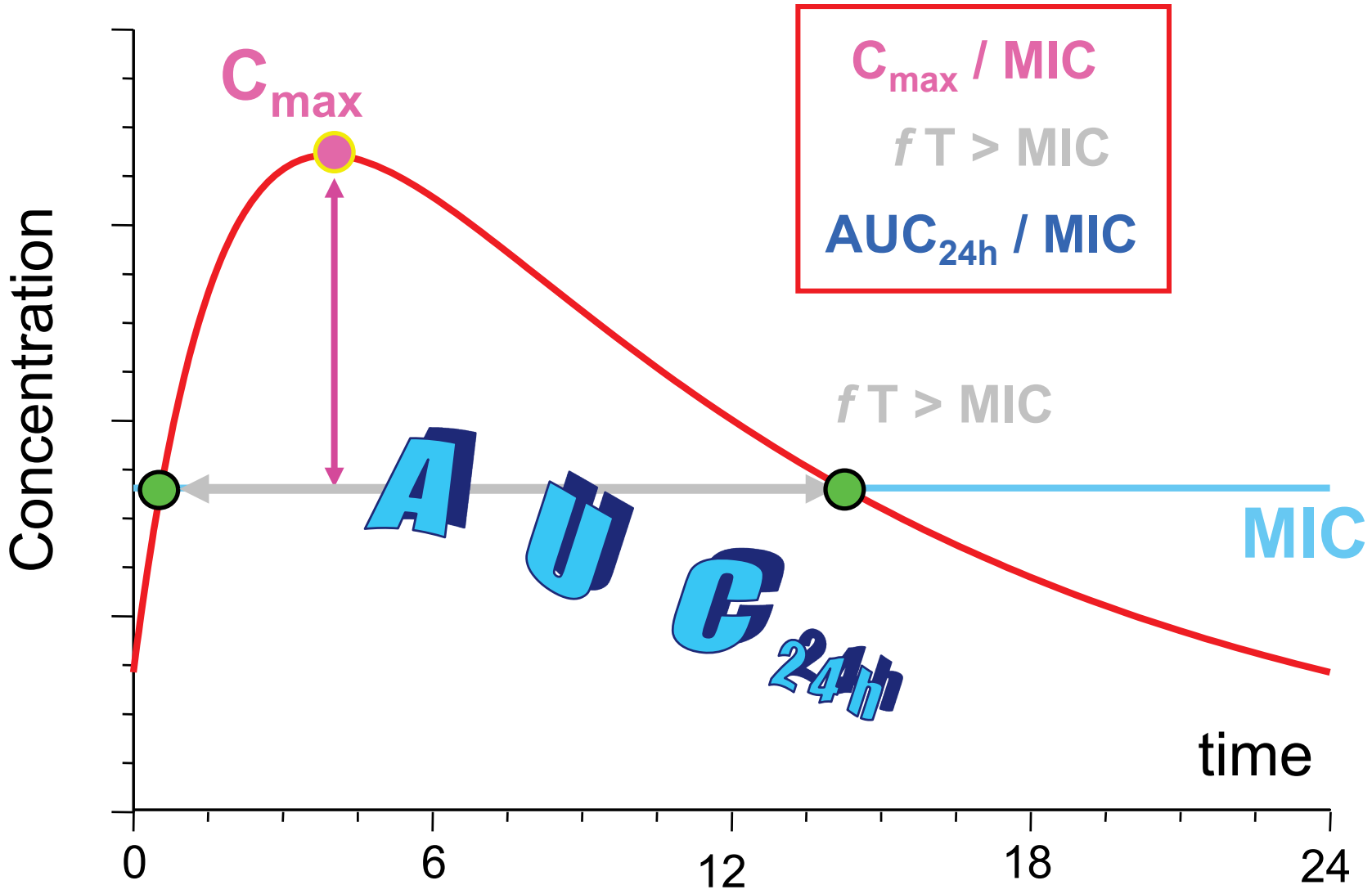
- Broad activity against Gram-positive microorganisms.
  - Staphylococci (*S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. hominis, S. warneri,* and other coagulase-negative staphylococci)
  - most *Enterococcus faecalis* (variable for *E. faecium*)
  - *Streptococcus pneumoniae* and *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 Pharmacodynamics

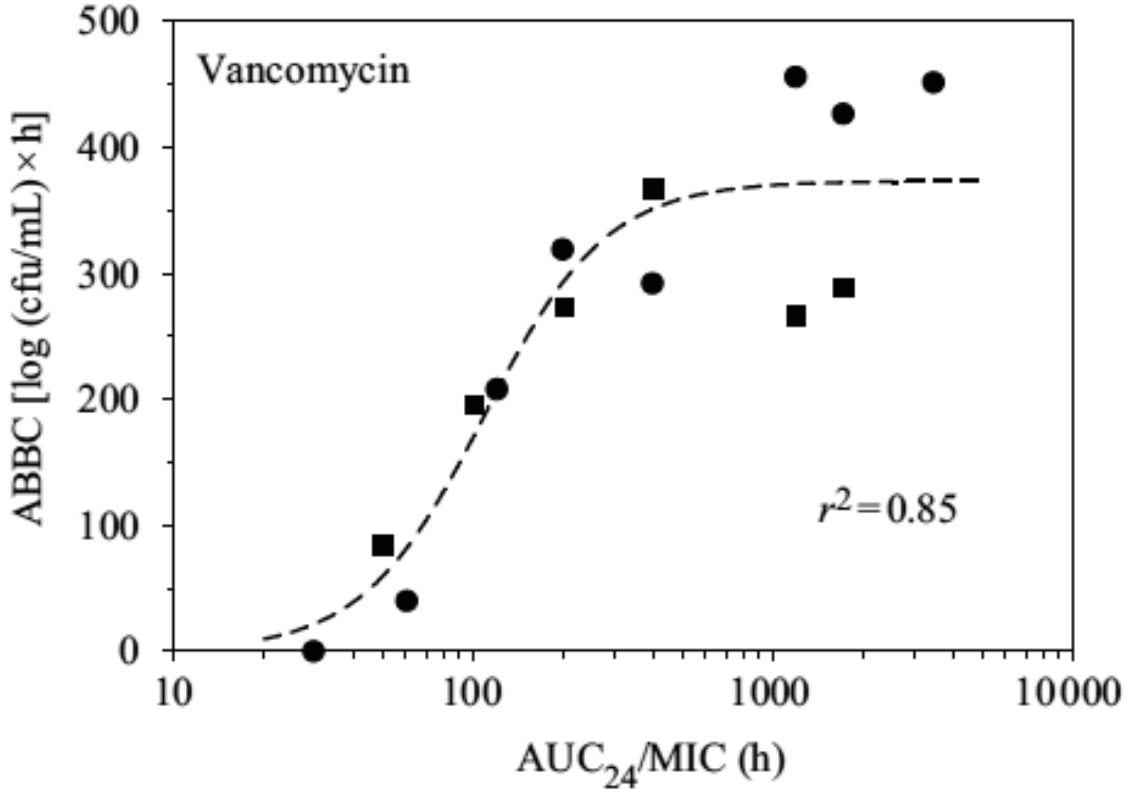
- Vancomycin is an AUC_{24h}-MIC dependent antibiotic



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} and efficacy

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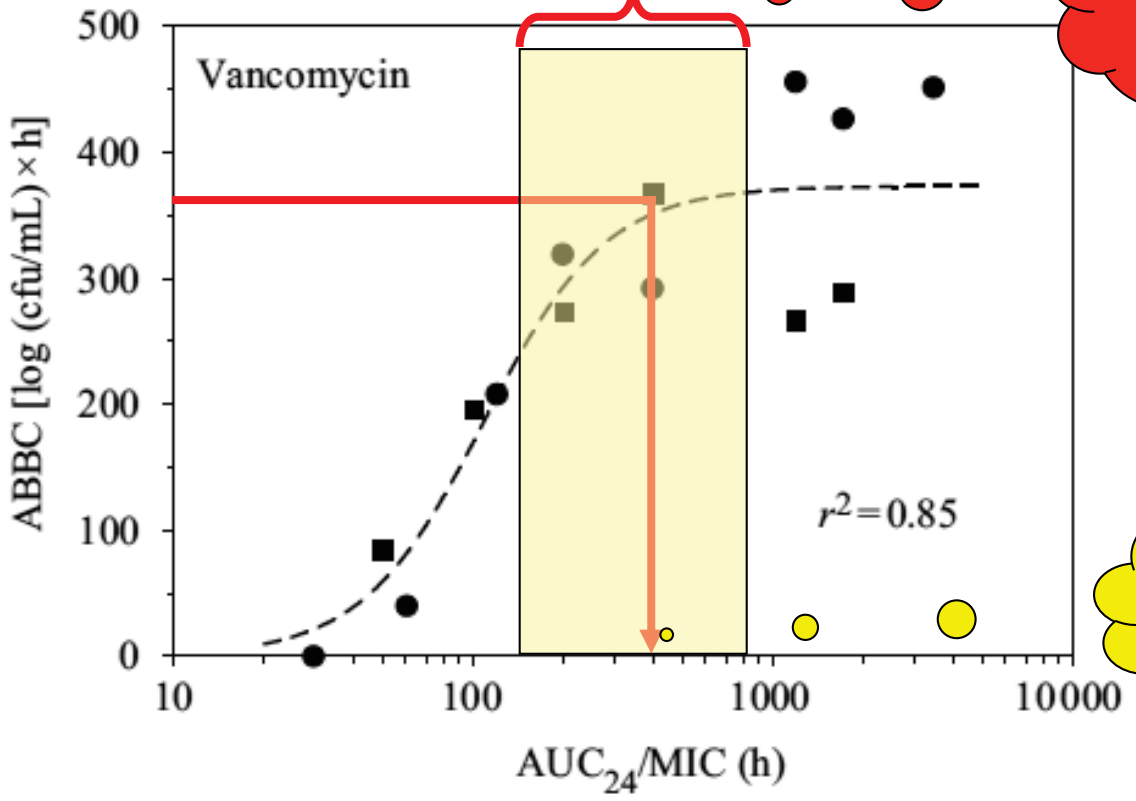


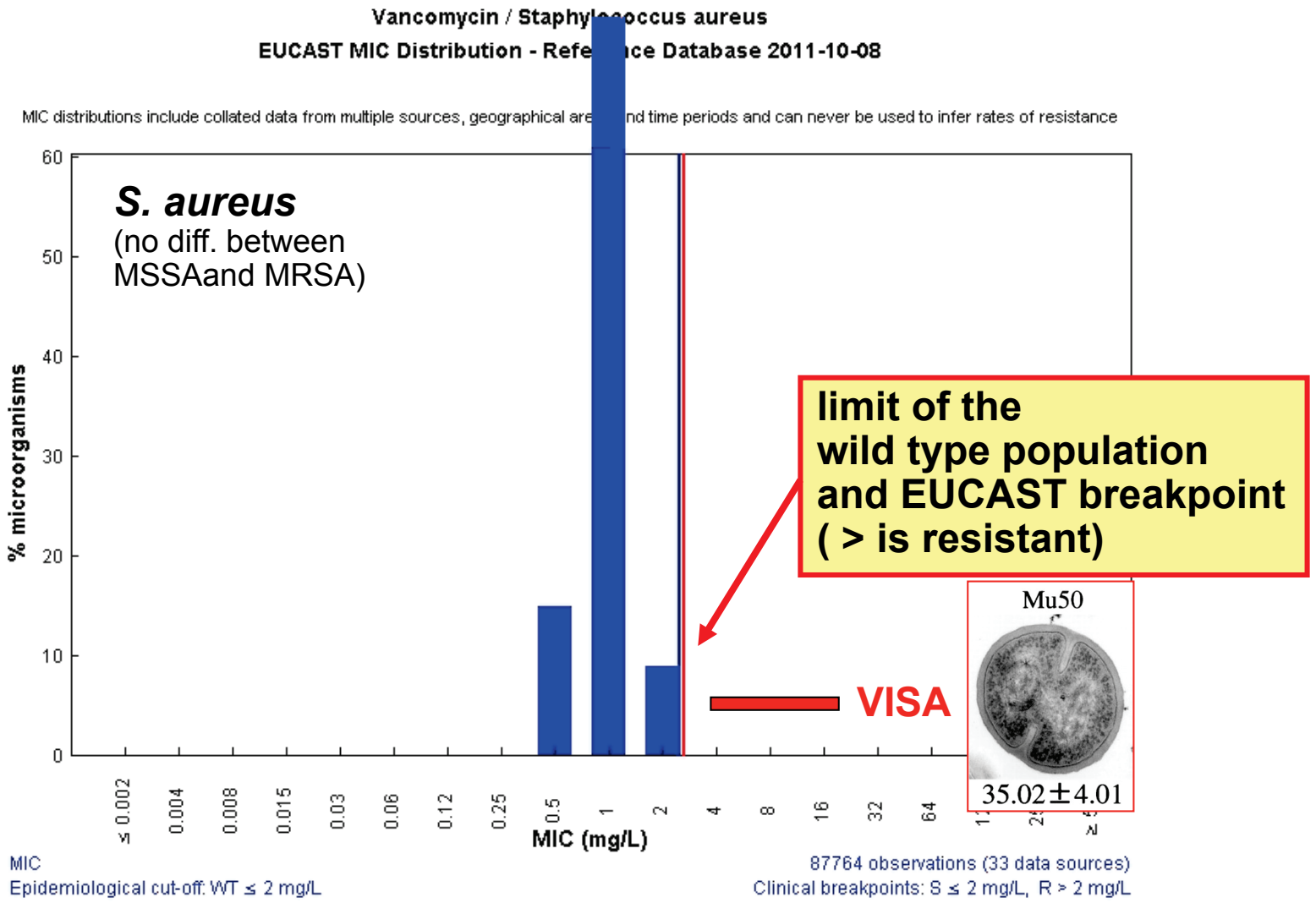
Typical range in patients

You need at least 400 !

drug exposure

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

Vancomycin and MIC (EUCAST distributions)



Vancomycin – AUC_{24h} and efficacy

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

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

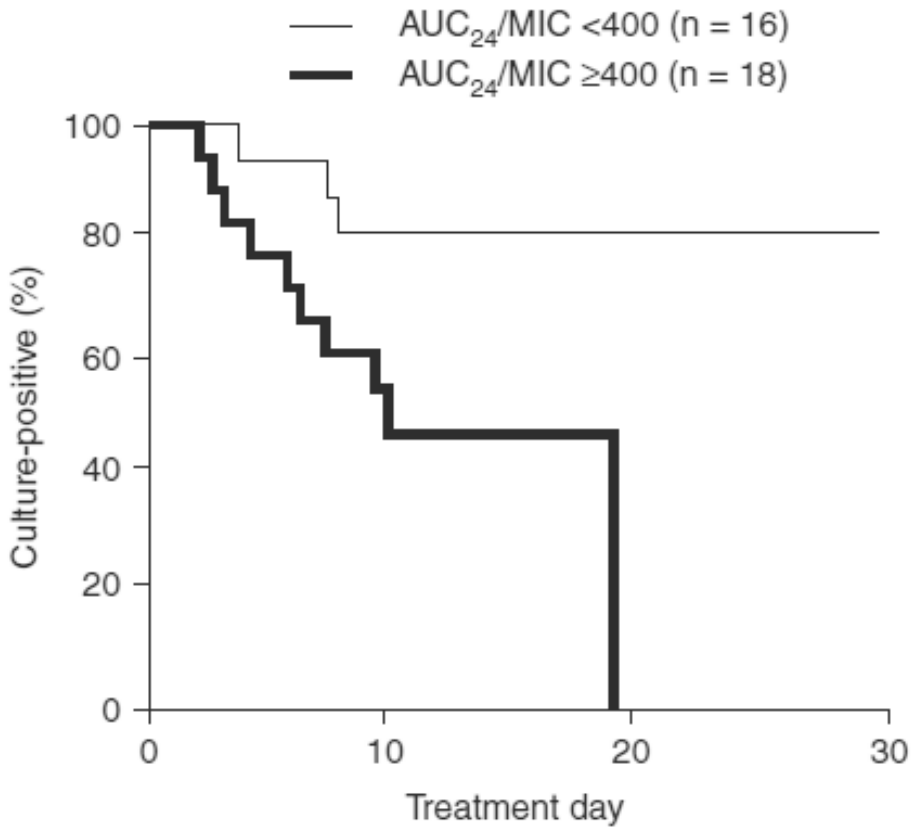
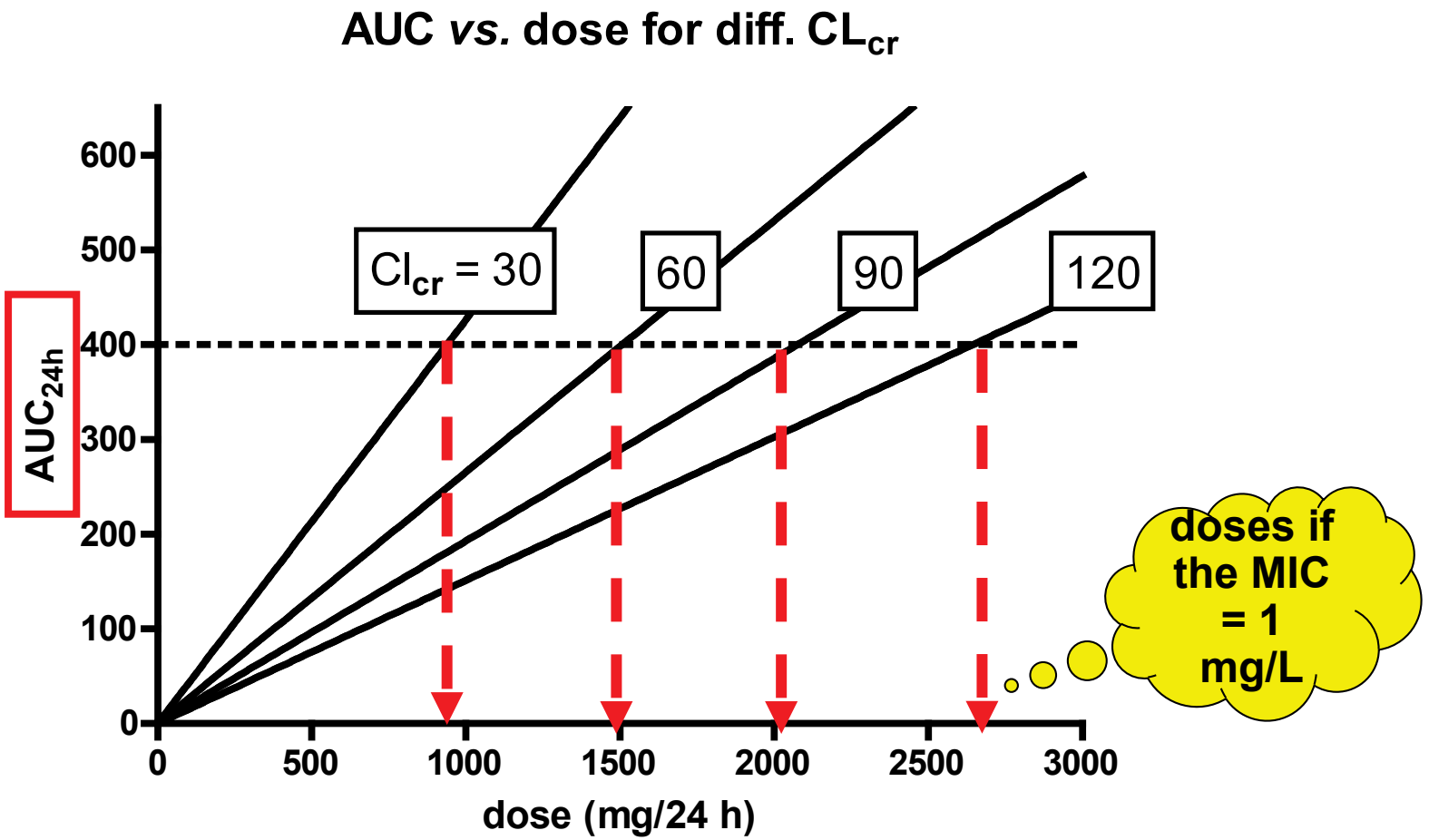


Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin AUC_{24}/MIC <400 and AUC_{24}/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC_{24}/MIC groups differed significantly (p = 0.0402).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

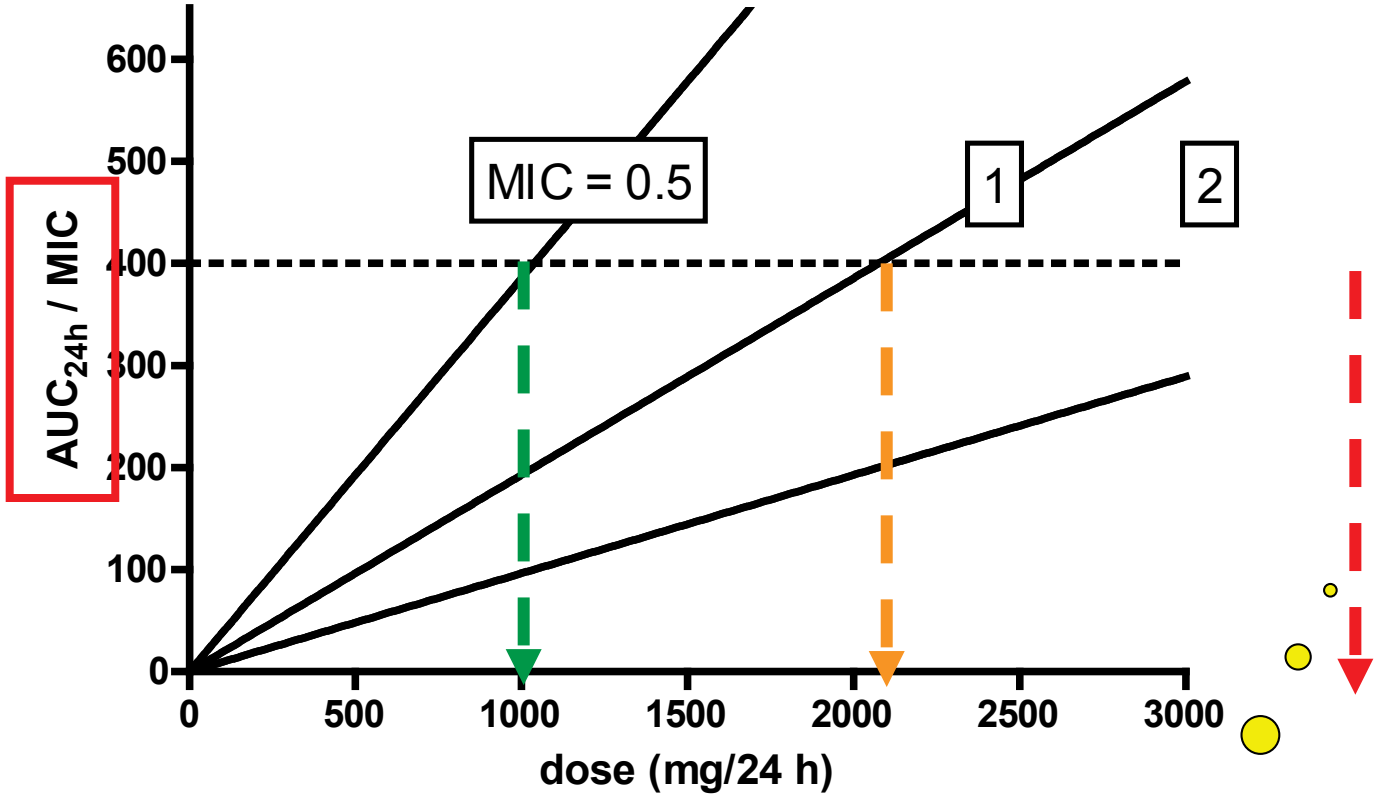


$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

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

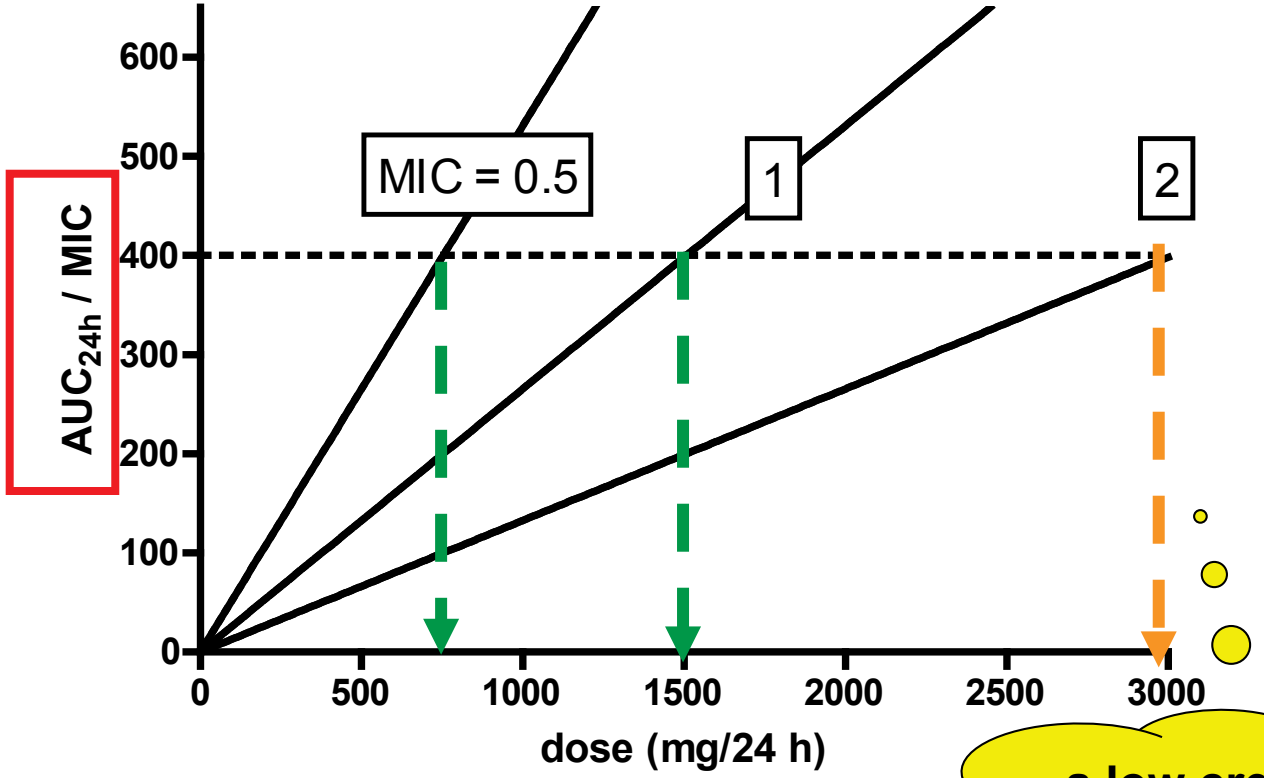


if the MIC reaches 2, you may have problems

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

A recent paper…

Pharmacotherapy. 2012 Jan 31. doi: 10.1002/PHAR.1017. [Epub ahead of print]

Effects of Targeting Higher Vancomycin Trough Levels on Clinical Outcomes and Costs in a Matched Patient Cohort.

Kullar R, Davis SL, Taylor TN, Kaye KS, Rybak MJ.

Anti-Infective Research Laboratory.

- STUDY OBJECTIVE: To compare clinical outcomes and costs in patients treated with the new vancomycin guidelines recommending goal serum trough concentrations of 15-20 mg/L versus patients treated with vancomycin doses targeting trough concentrations 5-20 mg/L prior to the new guidelines.

- PATIENTS: 200 with confirmed, complicated methicillin-resistant Staphylococcus aureus (MRSA) bacteremia
  - 100 before implementation (preperiod)
  - 100 after implementation (postperiod)
  - matched for diagnosis, any concomitant nephrotoxic agents (e.g., aminoglycosides, colistin, acyclovir), and age ± 5 years.

A recent paper…

- MEASUREMENTS AND MAIN RESULTS :
- Patients in the post-period
  - higher success rates (60% vs 45%, p=0.034).
  - similar length of stay (13.5 days vs 15 days; p=0.28)
  - shorter median treatment (8.5 days vs 13 days; p<0.001).
  - no difference was in total hospital costs ($ 27,709 vs $ 32,754 p=0.147)
  - higher drug and monitoring costs
  - initial vancomycin trough levels were significantly higher (15.8 mg/L vs 12.3 mg/L, p=0.02).
  - higher rates of nephrotoxicity (18% vs 15%; p=0.85)
  - higher costs if developing nephrotoxicity.

Dosing adjustment…

- 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…

loading dose (1h):
- 1000 mg if ≤70 kg
- 1500 mg if >70 kg)

over 1 h

infusion: 30 mg/kg/day

this was the mistake !

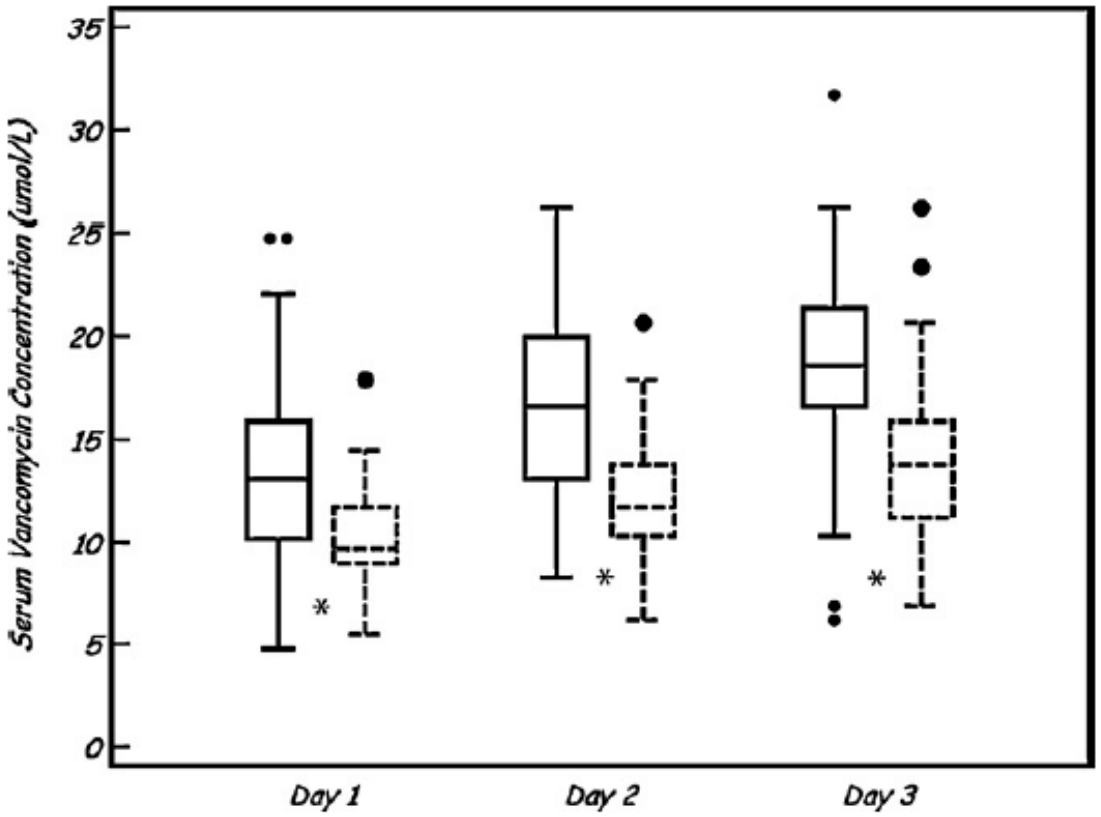


Fig. 1. Box and whisker plots showing the evolution of median (interquartile range) serum vancomycin concentrations on the studied days (Days 1–3) and comparison between Group A [control group without augmented renal clearance (ARC); continuous line] and Group B (study group with ARC; dashed line). * Indicates statistical significance for median differences ($P < 0.01$).

ARC was defined as CLCr > 130 mL/min/1.73 m^2

Dosing adjustment…

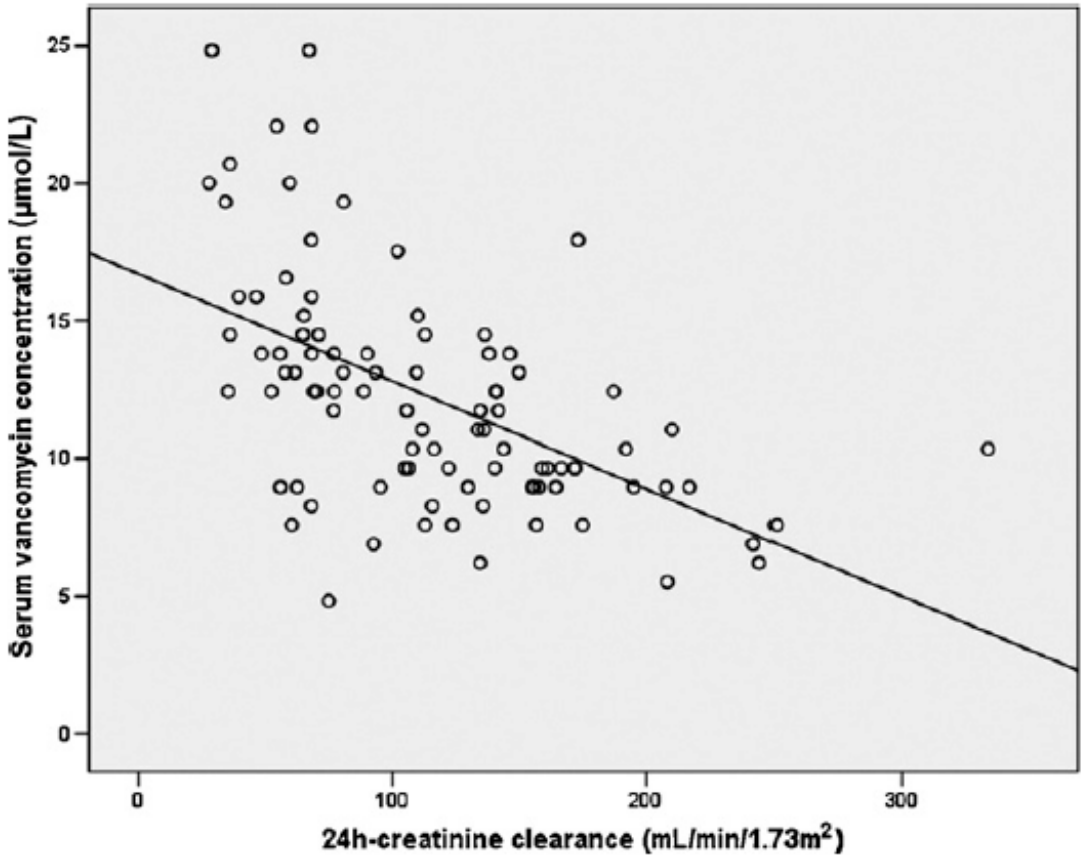


Fig. 2. Linear correlation between 24-h creatinine clearance (CL_{Cr}) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with CL_{Cr} in 93 septic critically ill patients ($rS = -0.57$; $P < 0.01$).

Vancomycin concentration in continuous infusion (at equilibrium) is dependent from its clearance

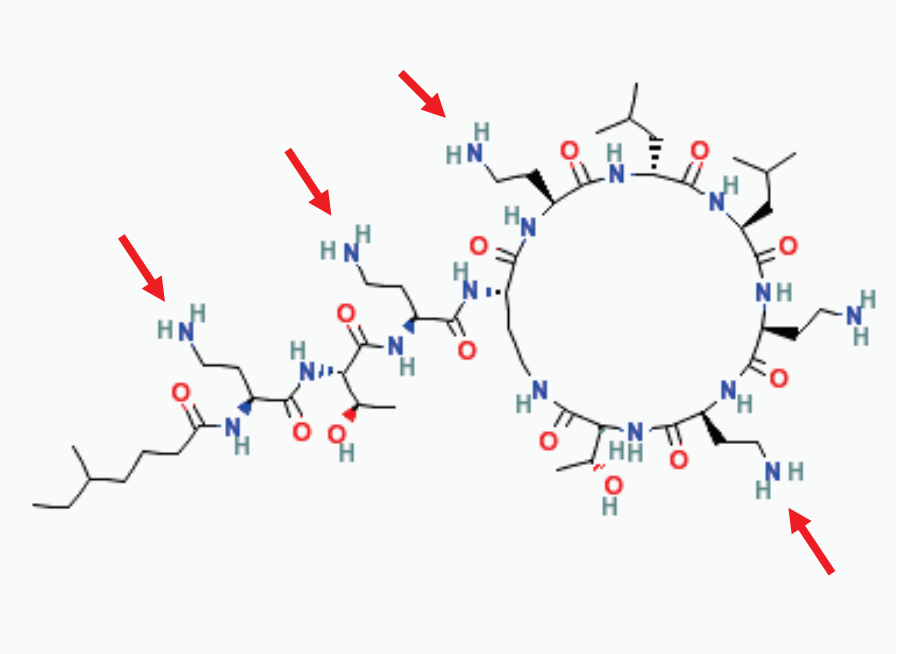
Vancomycin: conlusions

1. an old drug put back into service
2. will work for organisms with an MIC up to 2 mg/L but probably not higher (beware of CLSI !)
3. You must
   - use a loading dose
   - optimize the maintenance dose
   - if using continuous infusion, you MUST base your infusion rate on clearance, NOT body weight
   - 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… (use E-test)

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) 

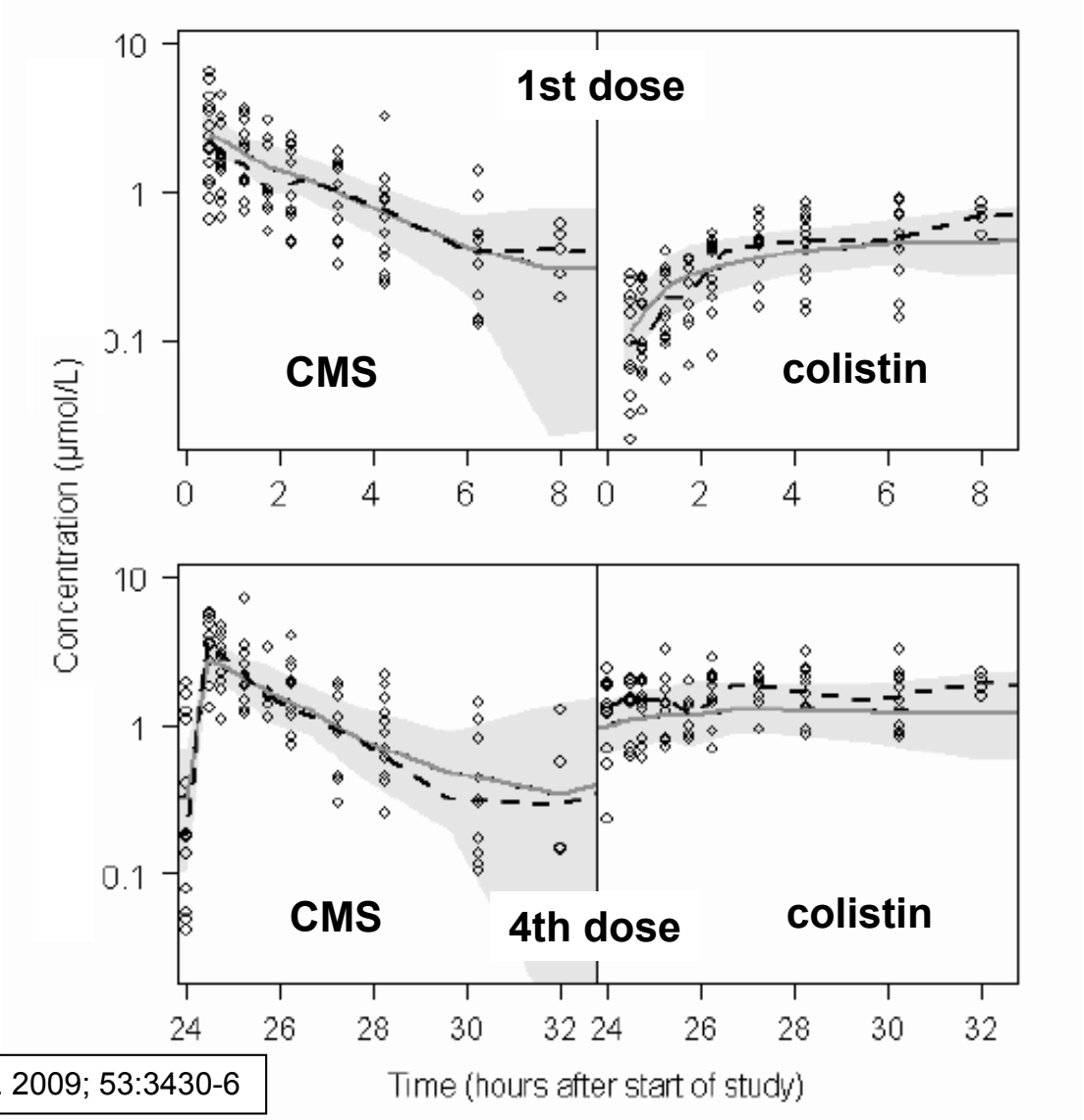
Population pharmacokinetics of colistin in critically-ill patients

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▽

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

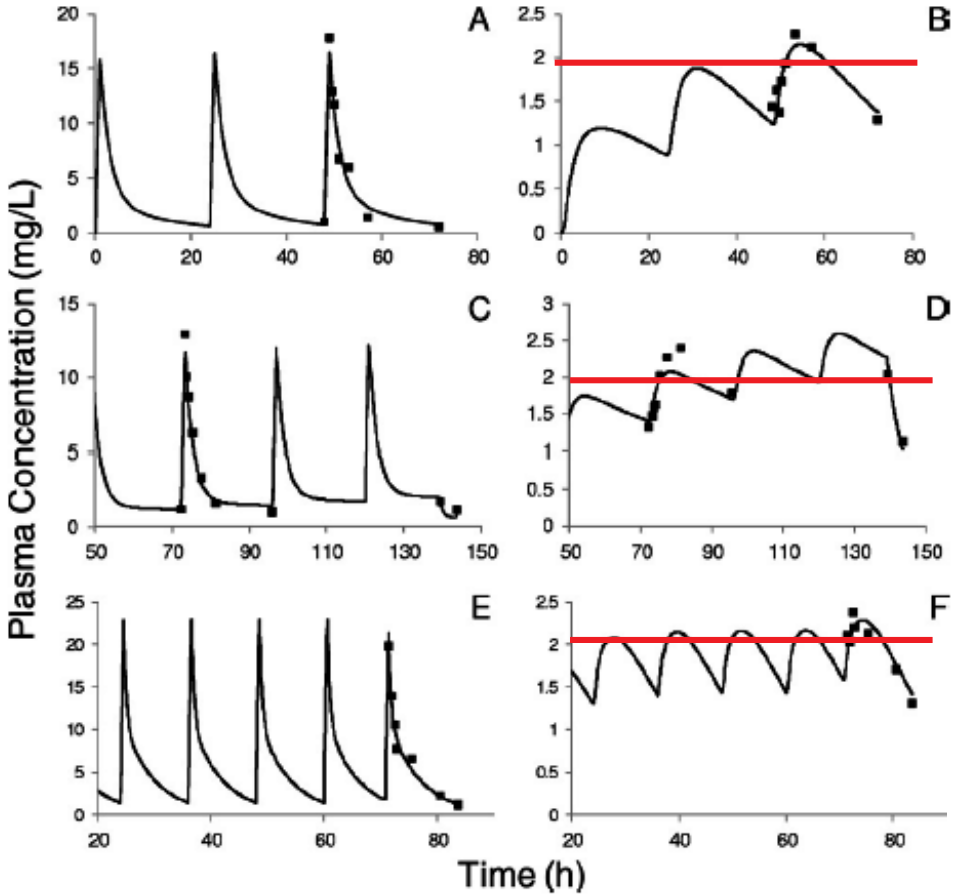
School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, New York[1]; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia[2]; Division of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

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

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

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

CMS



formed colistin

normal patient

hemodialysis

CCRT

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**

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* 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.

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* 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.**

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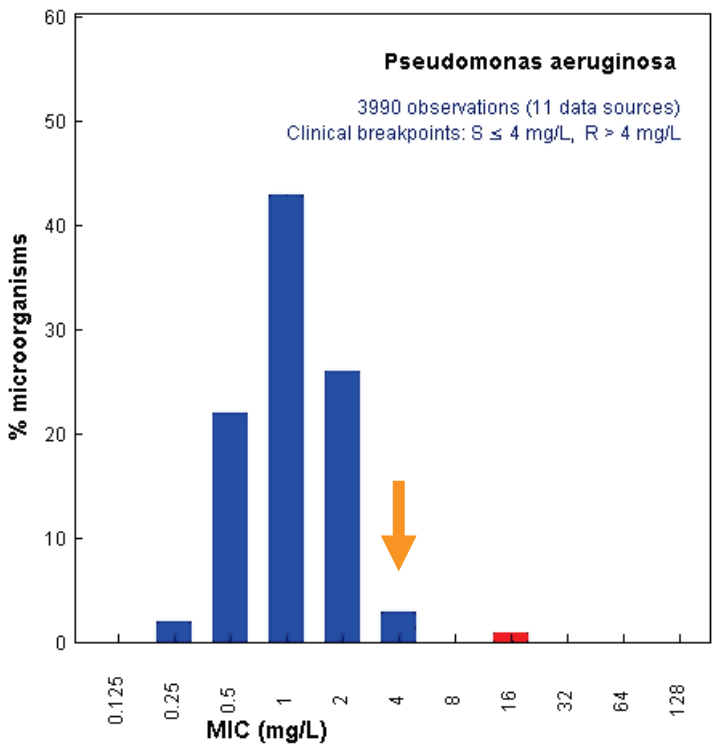
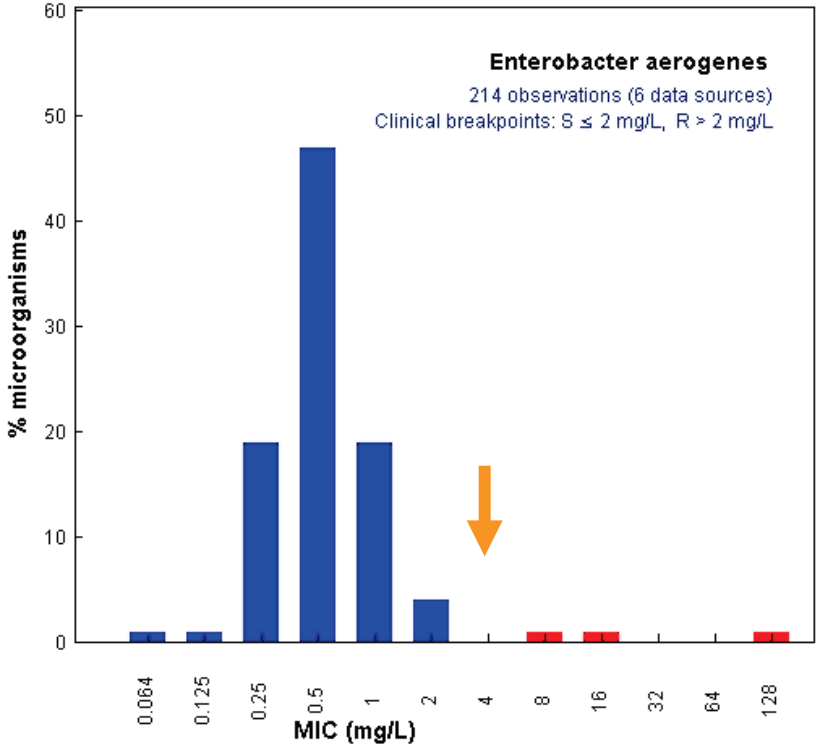
* after Garonzik et al. Antimicrob. Agents Chemother. (2011) 55:3284-3294

** 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



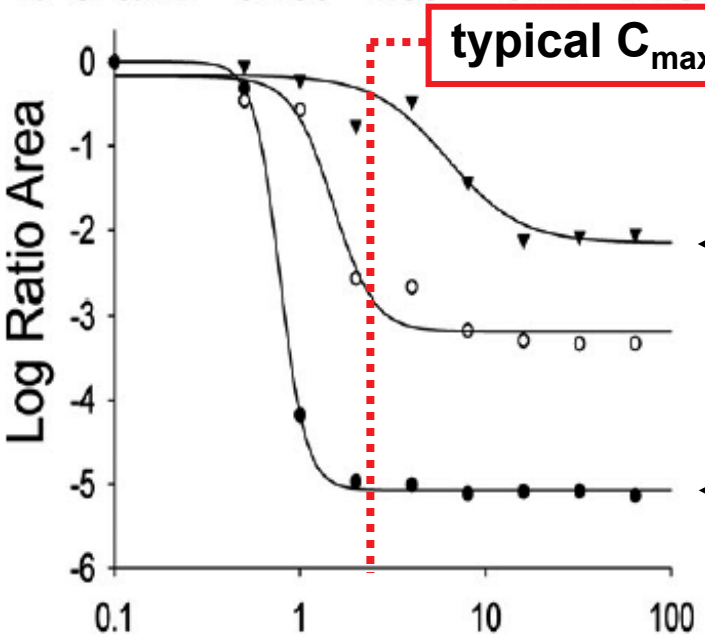


EUCAST and CLSI breakpoint is 4mg/L but the C_{max} is rarely > than 2 mg/L … Can you call this a true "susceptibility" breakpoint ?

Colistin 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

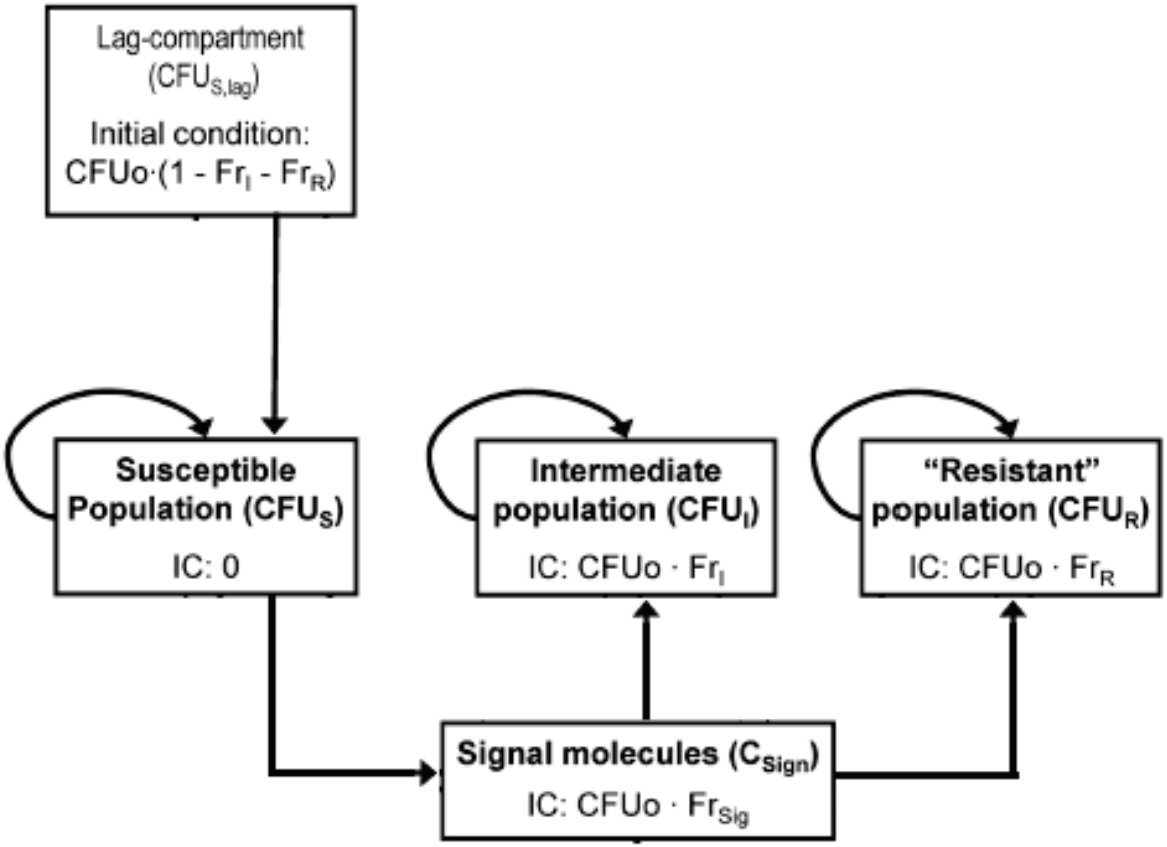


high inoculum (~ *in vivo*

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

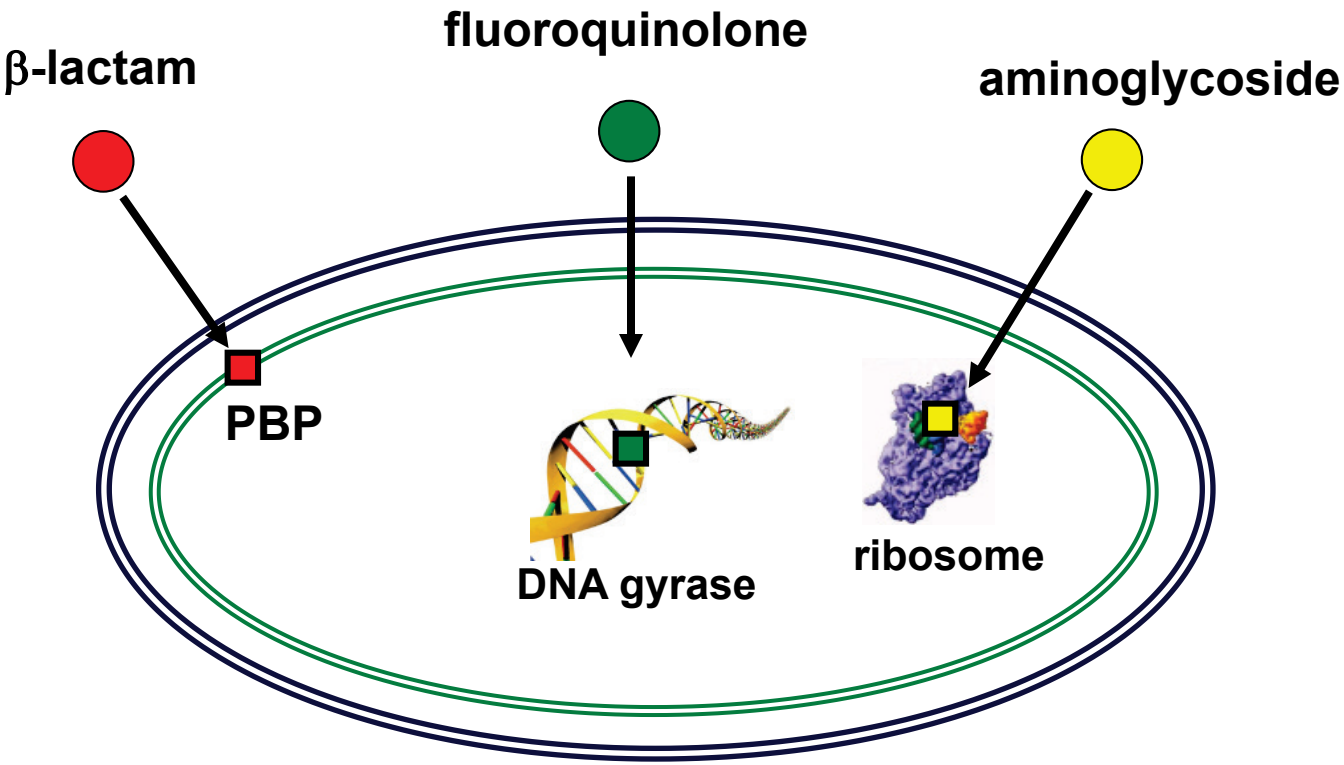
- Displays a **high and fast bactericidal effect** (named today: concentration-dependent antibiotic)

  ➔ **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**)

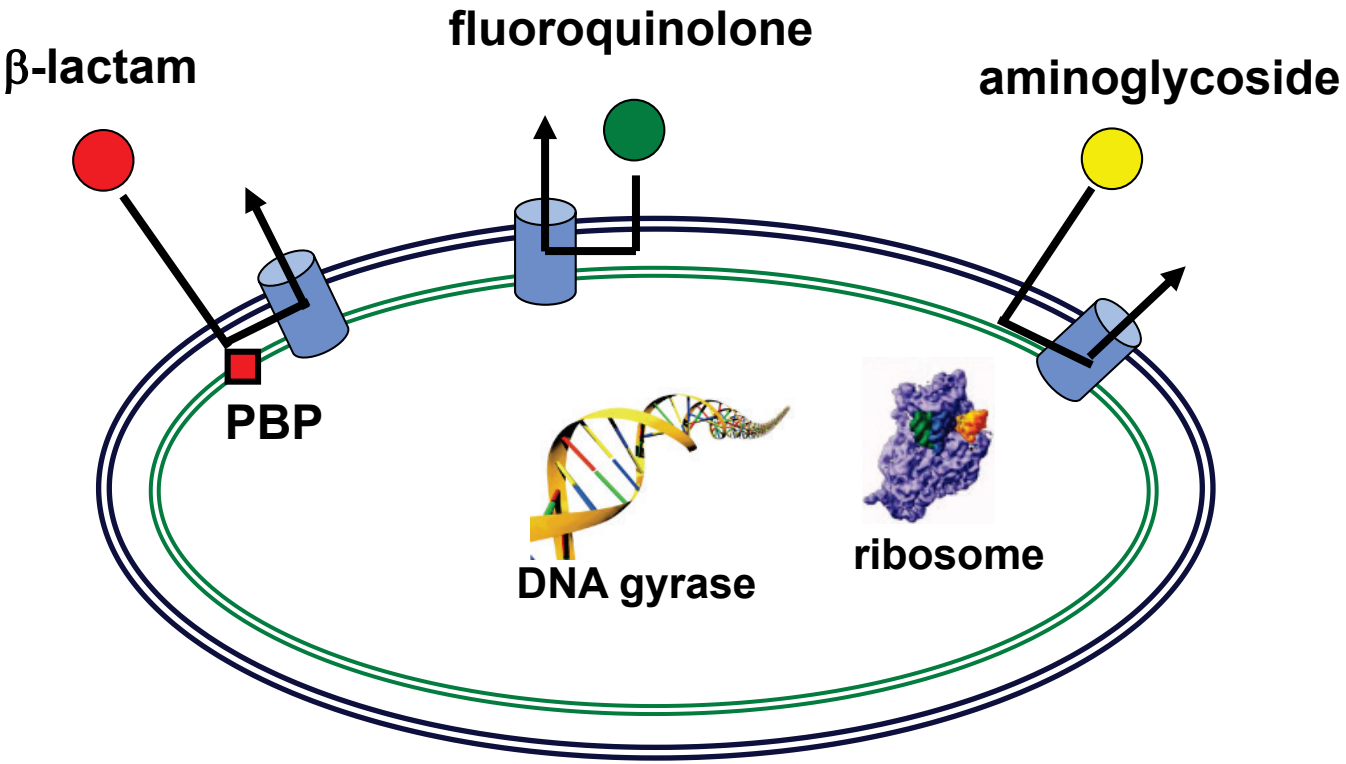
  ➔ colistin needs to be **administered several times a day to avoid regrowth**

Colistin synergy: the rationale (1 of 3)



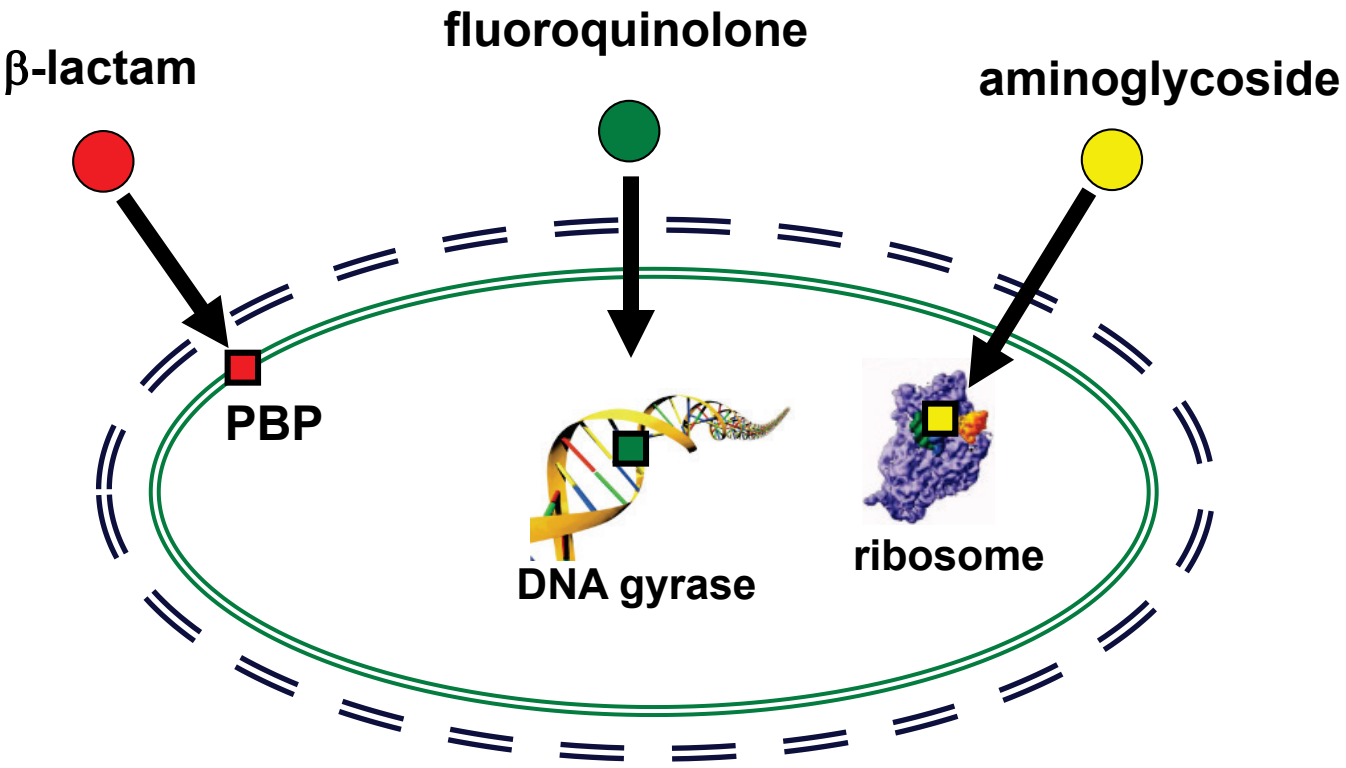
- Gram-negative bacteria have two membanes (OM and IM)
- Antibiotic targets are most often located in the IM or intracellularly
- Most antibiotics must at least pass across the OM to reach their target, which may represent a limiting step

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: an example of failure

Antimicrob Agents Chemother. 2012 Mar 5. [Epub ahead of print]

Bactericidal Activity of Multiple Combinations of Tigecycline and Colistin against NDM-1 producing Enterobacteriaceae.

Albur M, Noel A, Bowker K, Macgowan A.

Bristol Centre for Antimicrobial Research and Evaluation, Department of Medical Microbiology, North Bristol NHS Trust, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5ND, United Kingdom.

Abstract

The interaction between **colistin** and tigecycline against eight well-characterised NDM-1 producing Enterobacteriaceae was studied. Time-kill methodology was employed using a 4×4 exposure matrix with pharmacokinetically achievable free drug peak, trough and average 24hr serum concentrations. **Colistin** sulfate and methanesulfonate alone showed good early bactericidal activity often with subsequent grow back. Tigecycline alone had poor activity. Addition of tigecycline to **colistin** does not produce increased bacterial killing, instead it may cause antagonism at lower concentrations.

PMID: 22391543 [PubMed - as supplied by publisher]

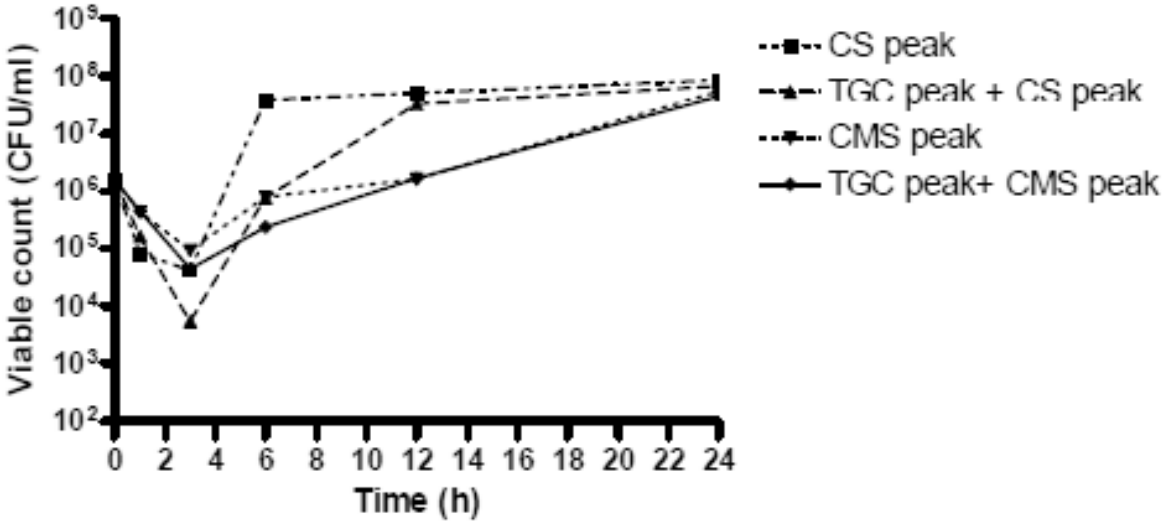
Colistin synergy: an example of failure

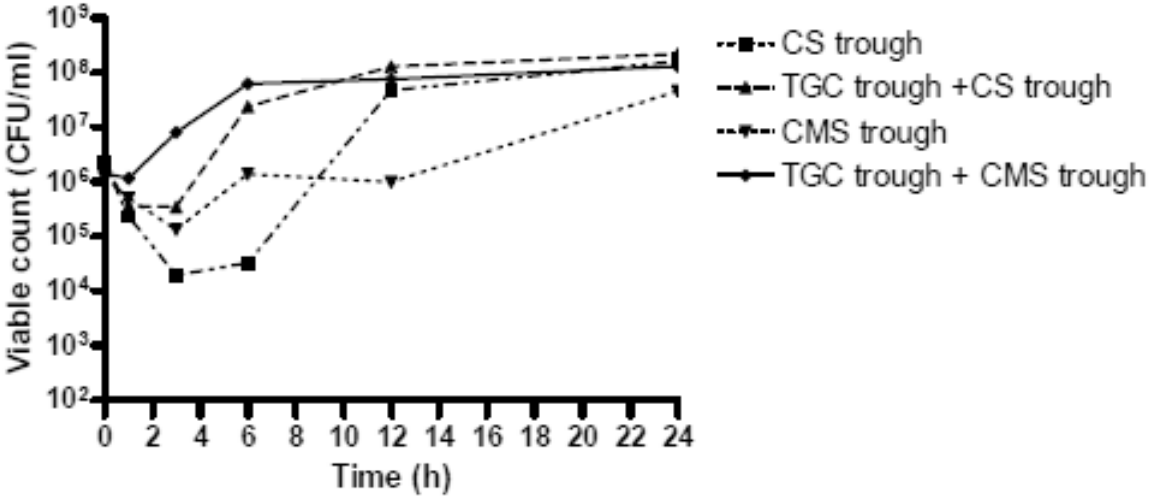
Concentrations used for testing

	TGC [1]	CS [2]	CMS [3]
C_{max}	0.17	0.29	8.5
24h C_{ss} (average)	0.04	0.16	2.7
C_{min}	0.025	0.1	2.1

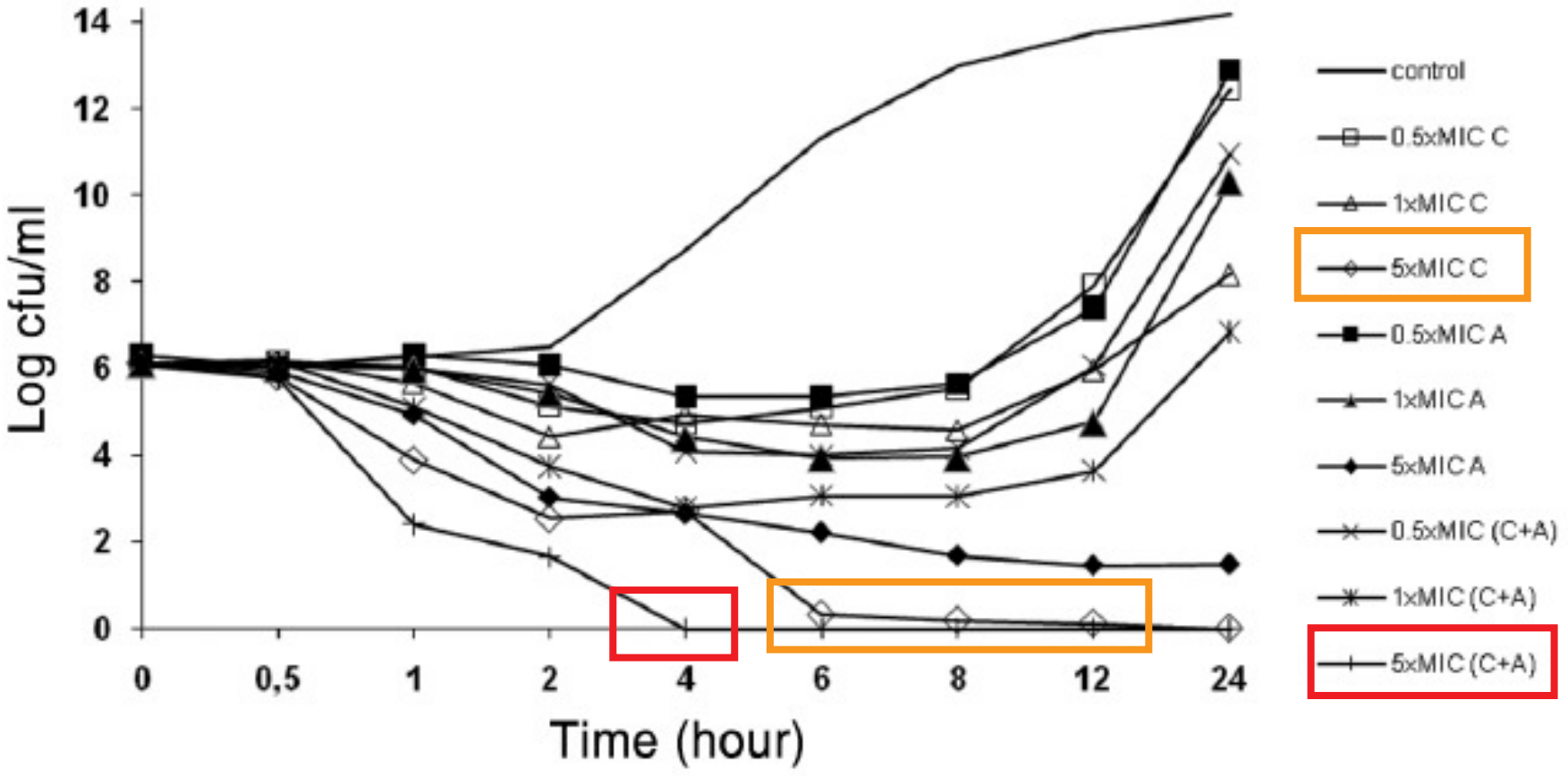
[1] Grayson et al. (2010). Kucers' The Use of 168 Antibiotics. 6th Edition p 885, Table 69.2.Publisher: Hodder Arnold
[2]. Dudhani et al. 2010. Antimicrob. Agents Chemother. 54:117 – 1124.
Markou et al. 2008. Clin Ther. 30(1): 143-51.
[3] Dollery C. (1999). Therapeutic Drugs, 2nd Edition, C326, Churchill-Livingstone publication.
Li et al. 2001. Antimicrob. Agents Chemother. 45:781 – 785
Li et al. 2003. J. Antimicrob. Chemother. 52: 987–992.

Colistin synergy: an example of failure





Colistin synergy: an example of success of the combination with amikacin, but …



Bozkurt-Guzel & Gerceker AA. *In vitro* pharmacodynamic properties of colistin methanesulfonate and amikacin against *Pseudomonas aeruginosa*. Indian J Med Microbiol 2012;30:34-8

MIC = 0.5 – 1 mg/L

Colistin synergy: a surprizing observation…

ELSEVIER

International Journal of Antimicrobial Agents

Volume 39, Issue 2, February 2012, Pages 180–181

Letter to the Editor

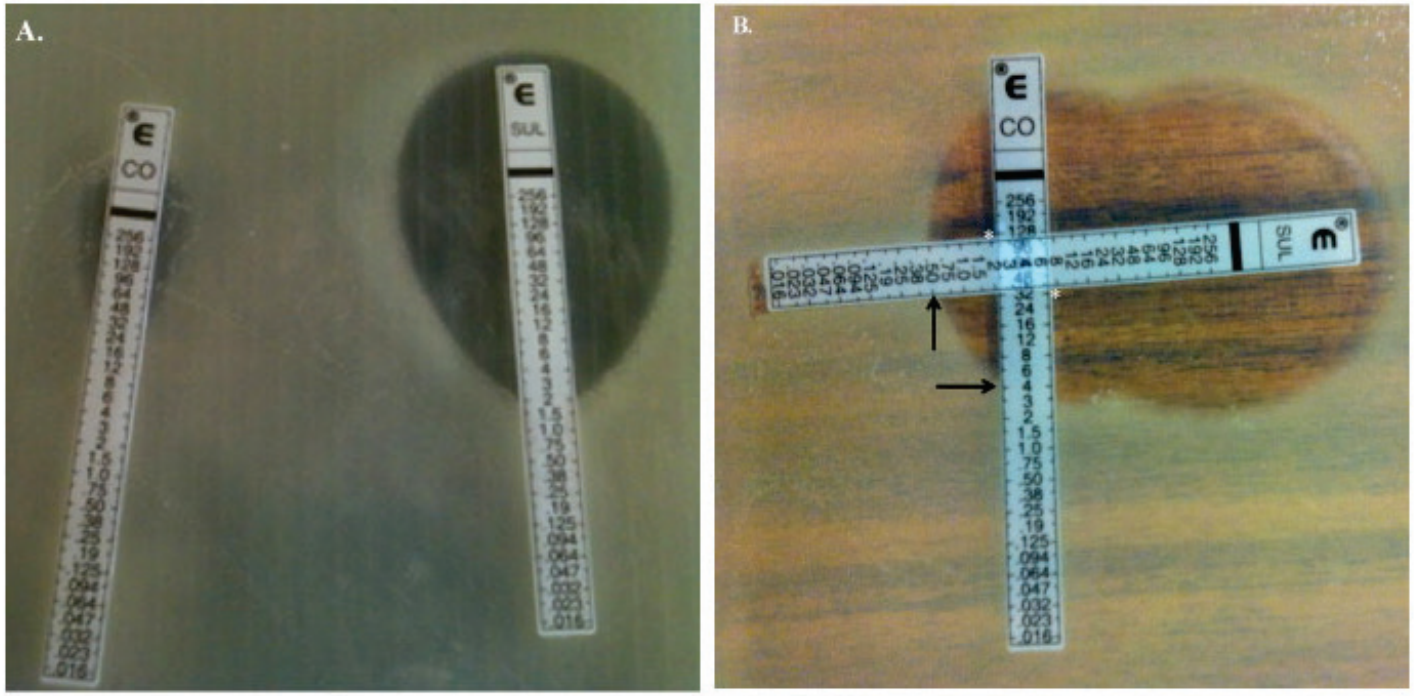
Synergistic activity of sulbactam combined with colistin against colistin-resistant *Acinetobacter baumannii*

Marie Kempf, Lamia Djouhri-Bouktab, Jean-Michel Brunel, Didier Raoult, Jean-Marc Rolain

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

Received 29 September 2011. Available online 17 November 2011.

Colistin synergy with sulbactam



Colistin and sulbactam minimal inhibitory concentrations (MICs) of the colistin-resistant *Acinetobacter baumannii* strain as determined by Etest: colistin, 32 mg/L; sulbactam, 2 mg/L. (B) Synergy as shown by Etest; the colistin MIC is decreased from 32 mg/L to 4 mg/L and the sulbactam MIC is decreased from 2 mg/L to 0.5 mg/L, as indicated by arrows (asterisks denote original MICs).

Colistin efficacy and safety in VAP ? …

Clin Infect Dis. 2012 Mar;54(5):670-80.

What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression.

Florescu DF, Qiu F, McCartan MA, Mindru C, Fey PD, Kalil AC.

Infectious Diseases Division.

CONCLUSION

Our data show that colistin can be a safe and effective alternative therapy for VAP caused by MDR gram-negative organisms. We do not suggest that colistin should be used as first-line therapy for VAP caused by MDR gram-negative organism; it should be considered as an alternative option once the susceptibility results are available. The 72% favorable clinical response rate and 34% in-hospital mortality rate with colistin therapy were within the range of clinical response and mortality rates reported in the literature.

Colistin efficacy and safety in VAP ? …

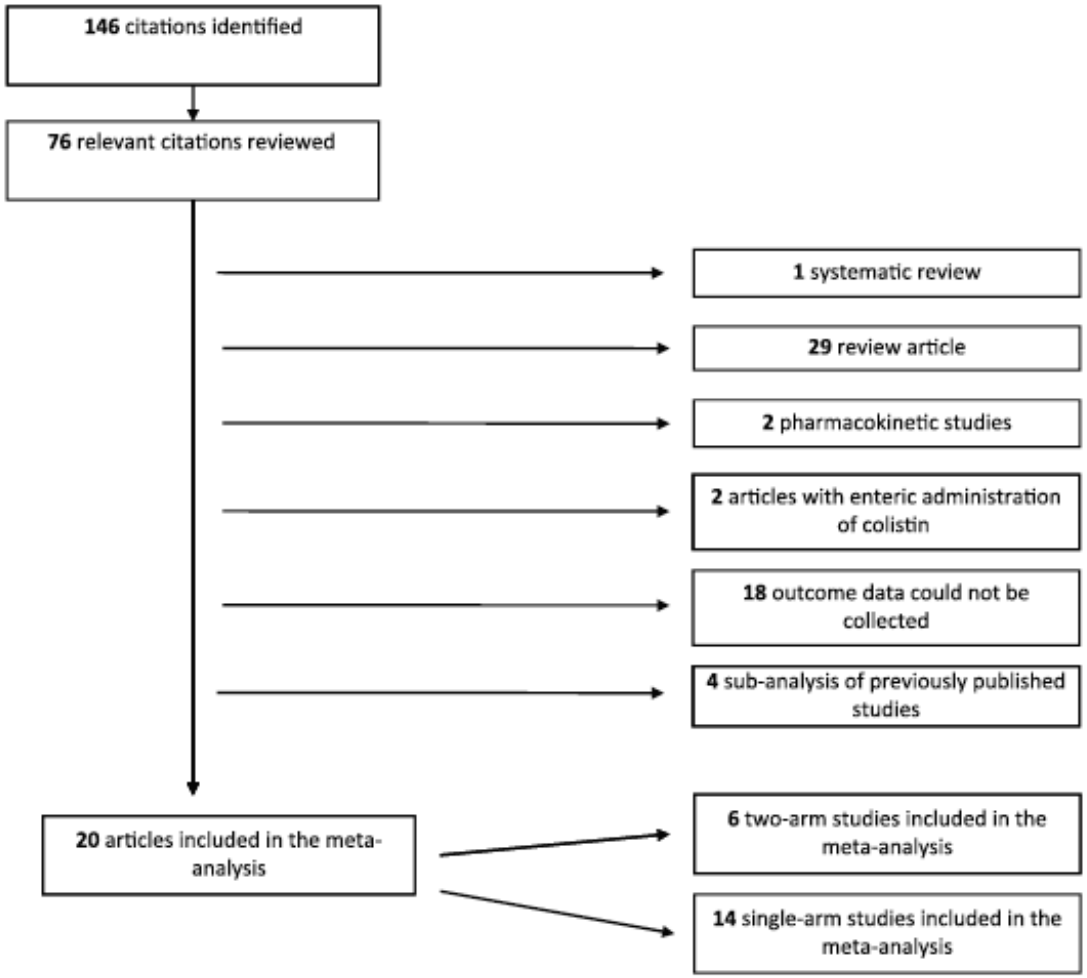


Figure 1. QUOROM trial flow.

Colistin efficacy (global)

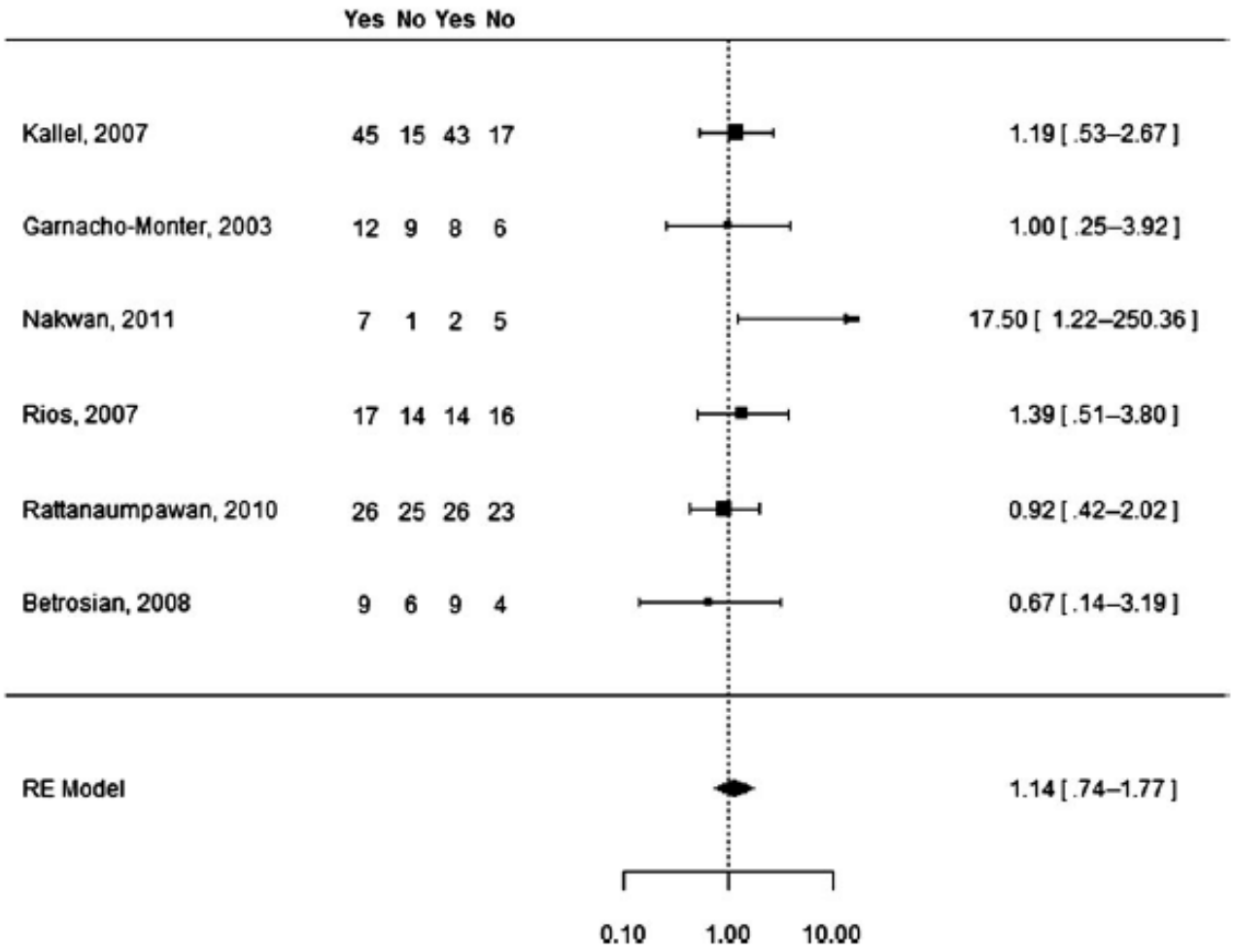


Figure 2. Clinical response with colistin compared with control antibiotics (6 2-arm studies; 359 patients) (odds ratio, 1.14 [95% confidence interval (CI), .74—1.77; $P = .56$]; $I^2 = 0\%$ [$P = .42$]) [18, 24, 25, 32, 33, 34]. Abbreviation: RE, random effect.

Colistin efficacy (by region)

Table 2. Subgroup Analysis of Clinical Response With Colistin Versus Control Antibiotics for Treatment of Ventilator-Associated Pneumonia in Controlled Studies

Variables	Studies, No. (Patients, No.)	Efficacy of Colistin Compared With Control OR (95% CI); *P*	Heterogeneity of Studies Included
Adult patients only	5 (344)	1.06 (.68–1.65); $P = .81$	$I^2 = 0\%$; $Q = 0.82$; $P = .96$
By route of administration			
Intravenous	4 (244)	1.13 (.66–1.93); $P = .66$	$I^2 = 0\%$; $Q = 0.64$; $P = .89$
Aerosolized	2 (115)	3.02 (.18–51.19); $P = .44$	$I^2 = 76.9\%$; $Q = 4.33$; $P = .04$
By study design			
Prospective	3 (163)	0.89 (.48–1.66); $P = .71$	$I^2 = 0\%$
Retrospective	3 (196)	1.45 (.79–2.68); $P = .23$	$I^2 = 0\%$
Randomized	2 (128)	0.86 (.43–1.74); $P = .68$	$I^2 = 0\%$
By geographic region			
Europe	3 (183)	1.04 (.55–1.96); $P = .91$	$I^2 = 0\%$; $Q = 0.41$; $P = .81$
Asia	2 (115)	3.02 (.18–51.19); $P = .44$	$I^2 = 76.9\%$; $Q = 4.33$; $P = .04$

Abbreviations: CI, confidence interval; OR, odds ratio.

Colistin safety (global)

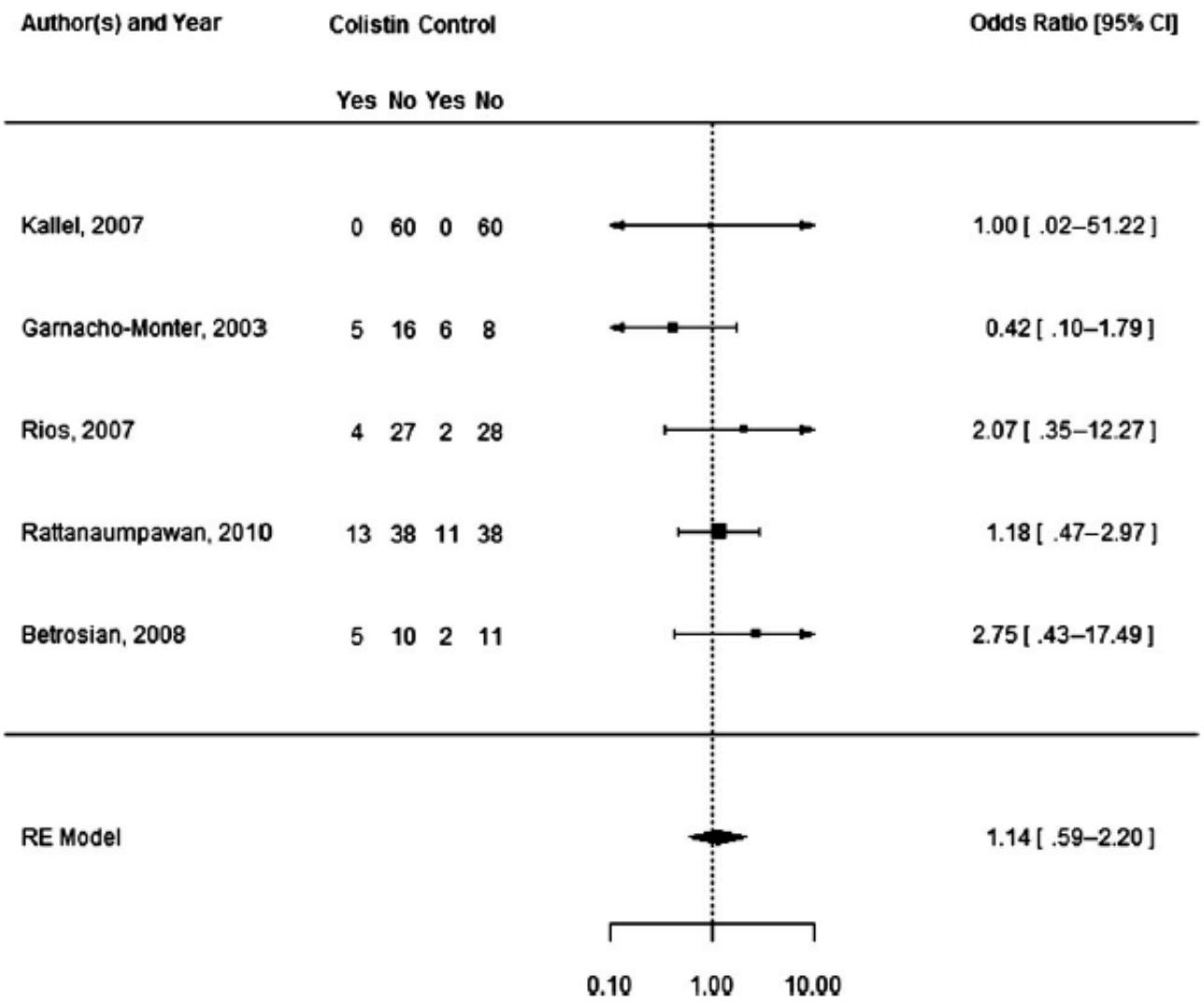


Figure 3. Risk of nephrotoxicity with colistin compared with control antibiotics (5 studies; 344 patients) (odds ratio, 1.14 [95% confidence interval (CI), .59—2.20; $P = .69$]; $I^2 = 0\%$ [$P = .53$]) [18, 24, 25, 32, 34]. Abbreviation: RE, random effect.

Colistin safety (by region)

Table 5. Nephrotoxicity With Colistin in Single-Arm Studies

Variables	Studies, No. (Patients, No.)	Nephrotoxicity of Colistin, % (95% CI)	Heterogeneity of Studies Included
Adult studies only	10 (259)	6 (.02–.09)	$Q = 21.26$; $P = .01$
By route of administration			
Intravenous	6 (98)	10 (.05–.16)	$Q = 4.22$; $P = .52$
Aerosolized	3 (121)	1 (0–.028)	$Q = 0.25$; $P = .88$
Intravenous + aerosolized	2 (51)	1.3 (0–.27)	$Q = 2.02$; $P = .16$
By definition of VAP			
Definition provided	9 (249)	5.7 (.02–.1)	$Q = 21.11$; $P = .007$
None provided	2 (21)	6.9 (0–.17)	$Q = 0.48$; $P = .49$
By study design			
Prospective	5 (109)	1 (0–.03)	$Q = 2.14$; $P = .71$
Retrospective	6 (161)	11 (.02–.20)	$Q = 18.56$; $P = .002$
By geographic region			
Europe	8 (206)	8 (.02–.14)	$Q = 20.35$; $P = .005$
Asia	3 (64)	1.5 (0–.044)	$Q = 1.74$; $P = .42$

Abbreviations: CI, confidence interval; VAP, ventilator-associated pneumonia.

Comparison between doripenem in 4h infusion and colistin (both with fosfomycin)

International Journal of Antimicrobial Agents

Volume 39, Issue 3, March 2012, Pages 271–272

Letter to the Editor

Carbapenem-resistant *Pseudomonas aeruginosa* pneumonia with intermediate minimum inhibitory concentrations to doripenem: combination therapy with high-dose, 4-h infusion of doripenem plus fosfomycin versus intravenous colistin plus fosfomycin

Anucha Apisarnthanarak

Division of Infectious Diseases, Thammasat University Hospital, Pratumthani 12120, Thailand

Linda M. Mundy

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Received 8 November 2011. Available online 9 January 2012.

Although interpretation of these findings is limited by the retrospective study design and small sample size, these data suggest an equivalency of regimens that contained high-dose, 4-h infusion of doripenem plus fosfomycin versus colistin plus fosfomycin for treatment of CRPA pneumonia with doripenem MICs of 4–8 mg/L. Both regimens were feasible, effective and well tolerated amongst patients with *P. aeruginosa* isolates of intermediate resistance to doripenem. Future clinical trial studies are needed to assess the efficacy and safety of these alternative treatment strategies that incorporate pharmacodynamic principles into the treatment of CRPA infections.

Comparison between doripenem in 4h infusion and colistin (both with fosfomycin)

Table 1
Demographics, clinical characteristics and outcomes of patients with carbapenem-resistant *Pseudomonas aeruginosa* pneumonia treated with combination doripenem plus fosfomycin versus colistin plus fosfomycin therapy.

Characteristic	Doripenem/fosfomycin[a] (*N* = 25)	Colistin/fosfomycin[b] (*N* = 24)	*P*-value
Age (years) (median)	45	46	0.79
Sex (female) [*n* (%)]	10 (40)	11 (46)	0.69
Underlying diseases [*n* (%)]			
Diabetes	5 (20)	4 (17)	0.79
Hypertension	4 (16)	4 (17)	
COPD	6 (24)	8 (33)	
Cirrhosis	5 (20)	5 (21)	
Neurological diseases	5 (20)	6 (25)	
Type of nosocomial pneumonia [*n* (%)]			
VABP	15 (60)	14 (58)	0.93
HABP	10 (40)	10 (42)	
Receipt of empirical antibiotic [*n* (%)]	25 (100)	24 (100)	N/A
Time to receipt of combination therapy (days) [median (range)][c]	1 (1–2)	1 (1–2)	0.89
Outcomes [*n* (%)]			
Clinical cure	15 (60)	14 (58)	0.91
Microbiological cure	18 (72)	15 (63)	0.48
All-cause (28-day) mortality [*n* (%)]	10 (40)	10 (42)	0.90
Any serious adverse drug events [*n* (%)][d]	0 (0)	2 (8)	0.24

COPD, chronic obstructive pulmonary disease; VABP, ventilator-associated bacterial pneumonia; HABP, hospital-acquired bacterial pneumonia.

[a] One gram, 4-h infusion of doripenem in combination with fosfomycin for ≥2 days.

[b] Intravenous colistin (5 mg/kg/day in two divided doses) in combination with fosfomycin for ≥2 days.

[c] Time from report of *P. aeruginosa* susceptibility to receipt of combination regimen.

[d] Renal failure (defined as an increase in creatinine of >1.5× baseline creatinine), any neurological abnormality (e.g. paralysis, seizure) or drug rash; both patients in the colistin + fosfomycin group had evidence of reduced creatinine clearance of 25% of baseline creatinine clearance.

MIC range for doripenem: 4-8 mg/L (EUCAST breakpoints: S ≤ 1 – R > 4)

But (full) resistance is close … (*)

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

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

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

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

Abstract

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

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

And the mechanisms may be very effective …

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Journals.ASM.org

Colistin-Resistant, Lipopolysaccharide-Deficient *Acinetobacter baumannii* Responds to Lipopolysaccharide Loss through Increased Expression of Genes Involved in the Synthesis and Transport of Lipoproteins, Phospholipids, and Poly-β-1,6-*N*-Acetylglucosamine

Rebekah Henry,[a] Nuwan Vithanage,[a] Paul Harrison,[b] Torsten Seemann,[b] Scott Coutts,[a] Jennifer H. Moffatt,[a] Roger L. Nation,[c] Jian Li,[c] Marina Harper,[a,d] Ben Adler,[a,b,d] and John D. Boyce[a,b,d]

Department of Microbiology, Monash University, Clayton, Australia[a]; Victorian Bioinformatics Consortium, Monash University, Clayton, Australia[b]; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Australia[c]; and Australian Research Council Centre of Excellence in Structural and Functional Microbial Genomics, Monash University, Clayton, Australia[d]

We recently demonstrated that colistin resistance in *Acinetobacter baumannii* can result from mutational inactivation of genes essential for lipid A biosynthesis (Moffatt JH, et al., Antimicrob. Agents Chemother. 54:4971–4977). Consequently, strains harboring these mutations are unable to produce the major Gram-negative bacterial surface component, lipopolysaccharide (LPS). To understand how *A. baumannii* compensates for the lack of LPS, we compared the transcriptional profile of the *A. baumannii* type strain ATCC 19606 to that of an isogenic, LPS-deficient, *lpxA* mutant strain. The analysis of the expression profiles indicated that the LPS-deficient strain showed increased expression of many genes involved in cell envelope and membrane biogenesis. In particular, upregulated genes included those involved in the Lol lipoprotein transport system and the Mla-retrograde phospholipid transport system. In addition, genes involved in the synthesis and transport of poly-β-1,6-*N*-acetylglucosamine (PNAG) also were upregulated, and a corresponding increase in PNAG production was observed. The LPS-deficient strain also exhibited the reduced expression of genes predicted to encode the fimbrial subunit FimA and a type VI secretion system (T6SS). The reduced expression of genes involved in T6SS correlated with the detection of the T6SS-effector protein AssC in culture supernatants of the *A. baumannii* wild-type strain but not in the LPS-deficient strain. Taken together, these data show that, in response to total LPS loss, *A. baumannii* alters the expression of critical transport and biosynthesis systems associated with modulating the composition and structure of the bacterial surface.

Here they are (for *A. baumanii*)…

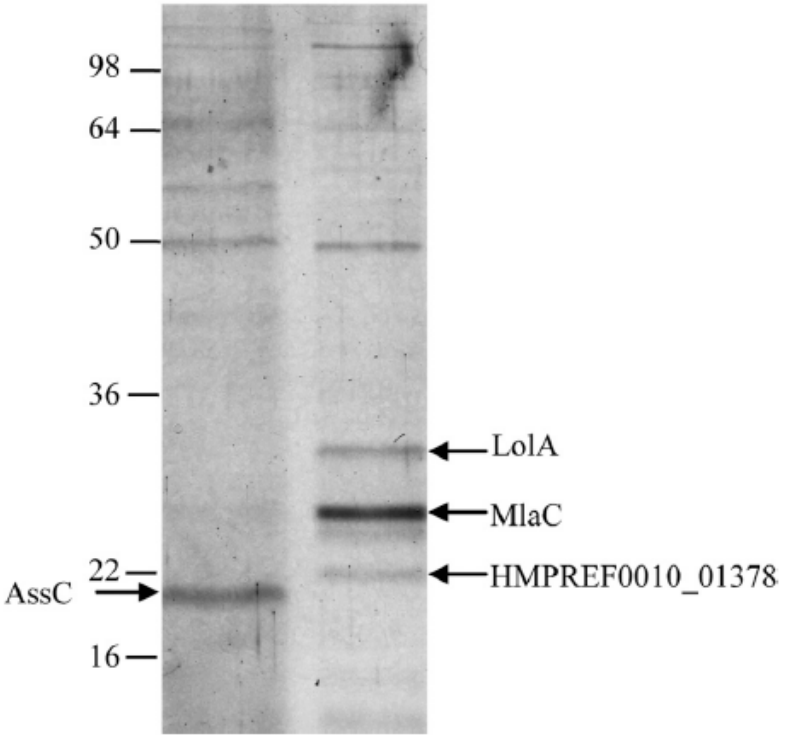


FIG 4 Differential expression of AssC, LolA, MlaC, and HMPREF0010_01378 in culture supernatants derived from the *A. baumannii* parent strain ATCC 19606 and the LPS-deficient strain 19606R. Proteins were identified using MALDI-TOF MS. Proteins with increased expression in the LPS-deficient strain 19606R were identified by MALDI-TOF MS as LolA, MlaC, and HMPREF0010_01378, as indicated by arrows on the right. The AssC protein was identified only in the ATCC 19606 supernatant samples and is indicated by the arrow at the left. The positions of molecular mass markers are indicated on the left (in kDa).

Antimicrob Agents Chemother. 2012 Jan;56(1):59-69. Epub 2011 Oct 24

To make a long story short …

Colistin: new lessons on an old antibiotic

D. Yahav[1,2], L. Farbman[1,2], L. Leibovici[1,2] and M. Paul[2,3]

1) Internal Medicine E, Rabin Medical Centre, Beilinson Hospital, Petah Tikva, 2) Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv and

3) Unit of Infectious Diseases, Rabin Medical Centre, Beilinson Hospital, Petah Tikva, Israel

Abstract

Colistin has been re-introduced into clinical practice for the treatment of carbapenem-resistant Gram-negative bacteria. Studies in the last decade attempted to reconstruct the path that present-day medications undergo prior to clinical use. In this review, we summarize the results of recent clinical studies. Colistin was associated with lower mortality than no effective treatment and higher unadjusted mortality than β-lactams in non-randomized clinical studies. However, it was administered to sicker patients with carabapenem-resistant bacteria. Overall, nephrotoxicity rates were not higher with colistin in these studies, and colistin-induced nephrotoxicity is reversible in most patients. The emergence of colistin resistance has been described in high-use settings. Synergy with carbapenem, rifampin and other antibiotics has been reported *in vitro*. Randomized controlled trials are ongoing or in planning to assess this and other aspects of colistin use in clinical practice.

Keywords: Colistin, multidrug-resistant bacteria, nephrotoxicity, polymyxins, ventilator-associated pneumonia
Article published online: 20 November 2011
Clin Microbiol Infect 2012; **18:** 18–29

At the end of the day…

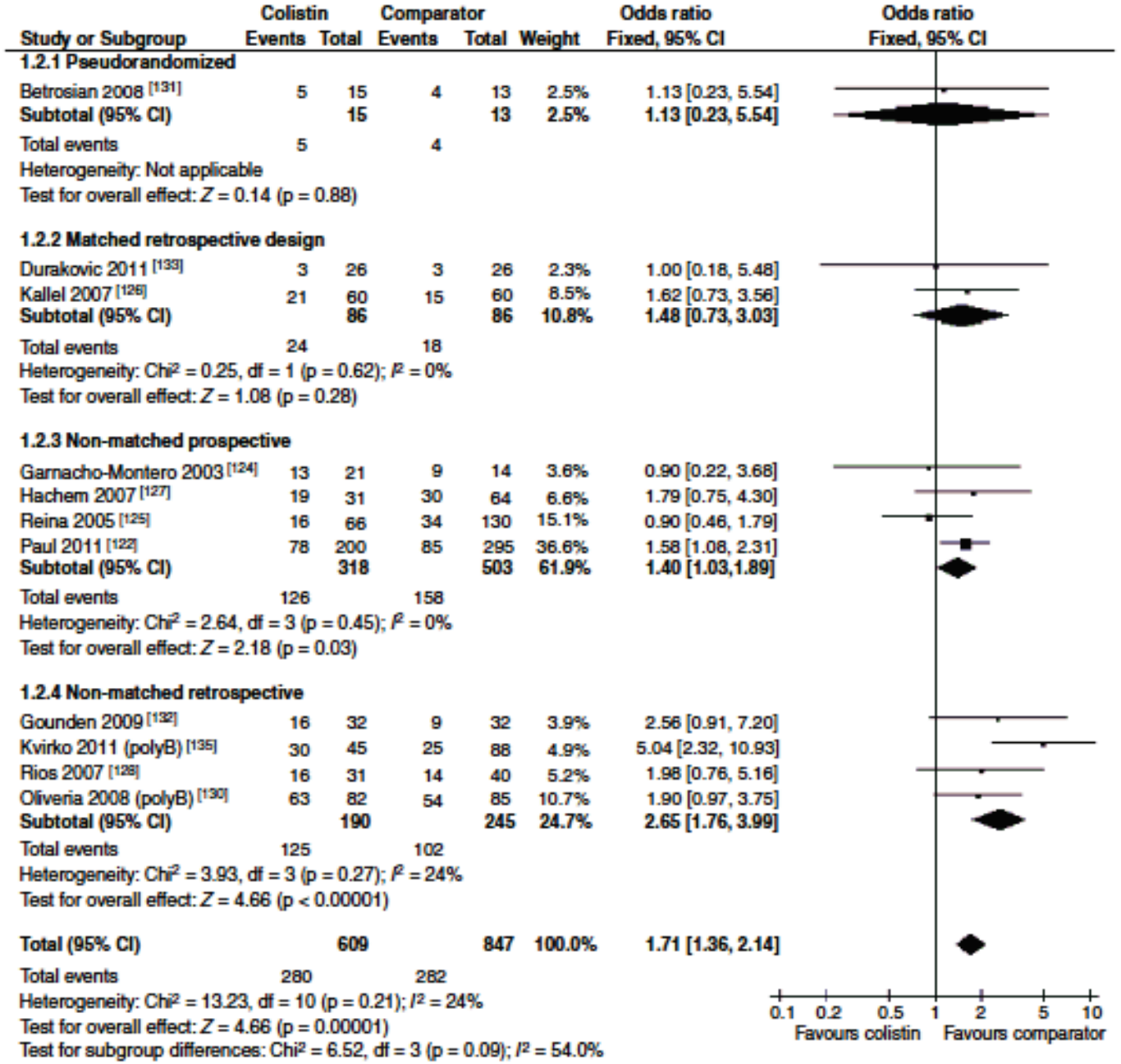
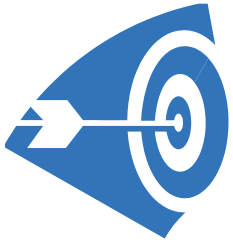


FIG. 1. All-cause mortality in studies comparing colistimethate sodium with other antibiotics. df., degrees of freedom.



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 …
- We do NOT have good breakpoints → use MIC values !
- Never use it in monotherapy … (meropenem, doripenem, … even if non-susceptible), BUT test the combination
- Test for susceptibility on a repeated fashion …
- Monitor the renal function and adjust by decreasing the dose and prolonging the interval …
- Remember that this is a last resource drug which should be put back on the shelf as soon as possible…

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)
- Wallonie-Bruxelles International for this presentation and my activities in Vietnam

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