Colistin: from structure to clinical use via microbiology, PK/PD and toxicology

Paul M. Tulkens, MD, PhD *

Cellular and Molecular Pharmacology &
Centre for Clinical Pharmacy
Louvain Drug Research Institute
Université catholique de Louvain, Brussels, Belgium

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

With the support of *Wallonie-Bruxelles-International*

Contents of the presentation

- What is (exactly) colistin ?
- What do we know about its antimicrobial activity ?
- And its pharmacokinetics/pharmacodynamics ?
- And its toxicodynamics ?
- What can we do today with colistin ?

as you can see, many " ? "

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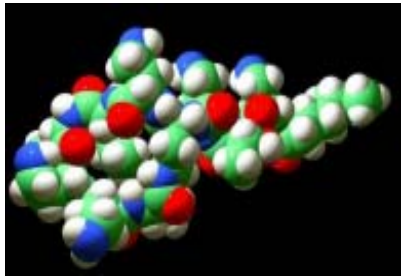
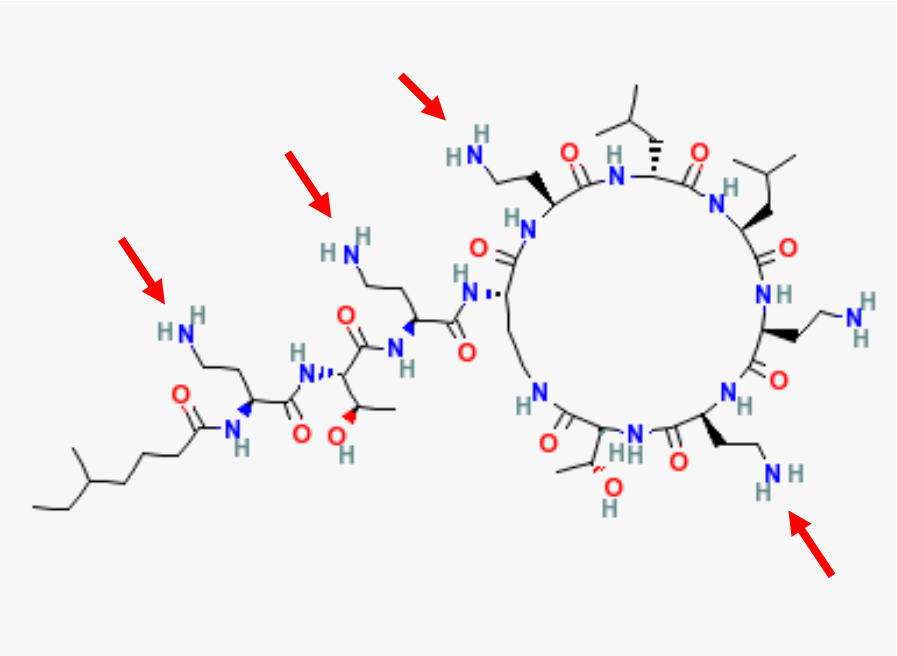


Credit: DR TIM EVANS/SCIENCE PHOTO LIBRARY

or

?

What is (exactly) colistin in its active form ?



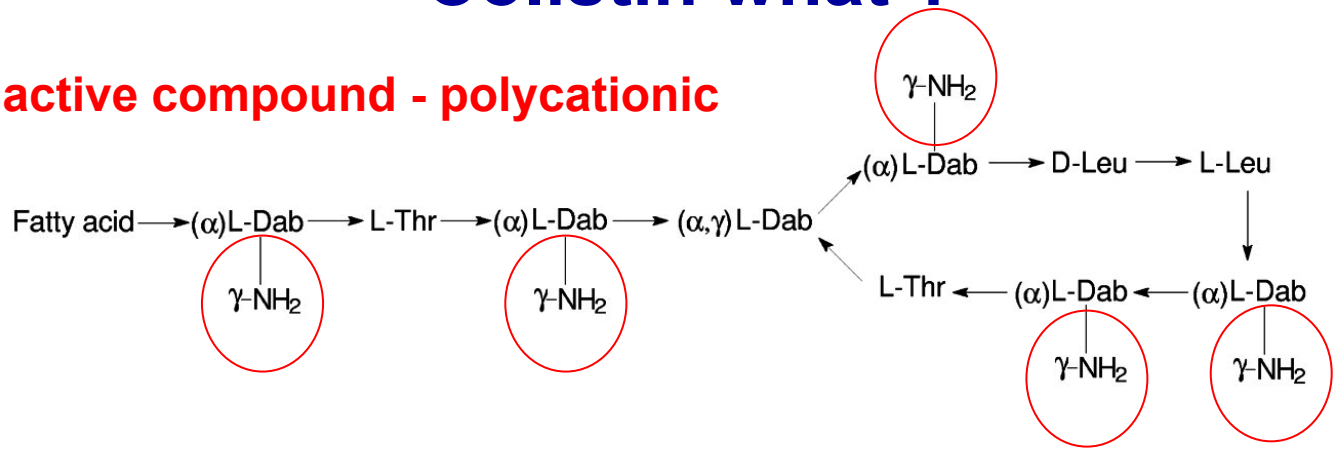
- A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain
- which **interacts with the lipopolysaccharide (LPS)** of the outer membrane of Gram-negative bacteria, triggering a "self-promoted uptake" process
- and **displaces Ca^{++} and Mg^{++}**, which further destabilizes microbial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

Colistin History

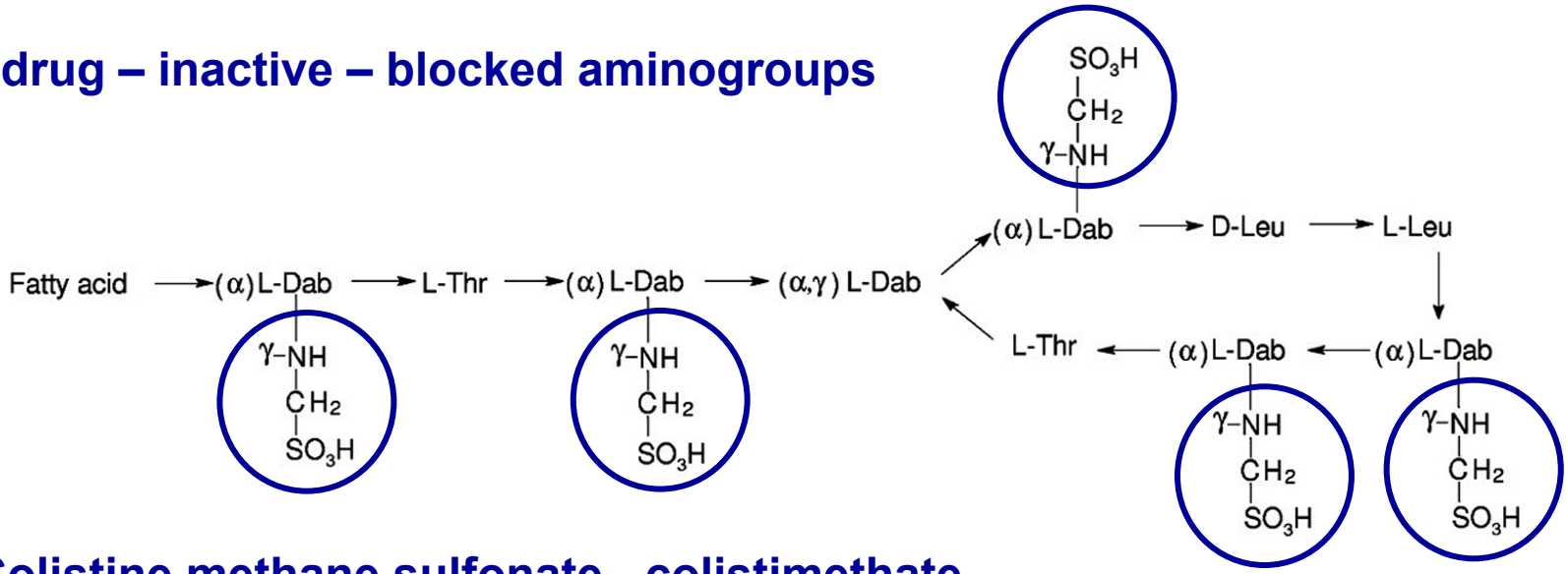
- Isolated in Japan in 1949 from *Bacillus polymyxa* var. *colistinus* and indentified as **polymyxin E**
  (discovered in 1947 among polymyxins A to E).
- Differs from **polymyxin B** by only one aminoacid (D-Phe replaced by D-Leu)
- Exists under at least 2 components (**E1** and **E2**, also called colistin A and colistin B) differ ring by the length of the fatty acid chain
- Supplied as the
  - methylsulfonate derivative (often called methane sulfonate and also known as **colistimethate sodium**), which is a **prodrug**
  - sulfate (**colistine sulfate**)

Colistin what ?

active compound - polycationic



Prodrug – inactive – blocked aminogroups



Colistine methane sulfonate - colistimethate

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

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

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

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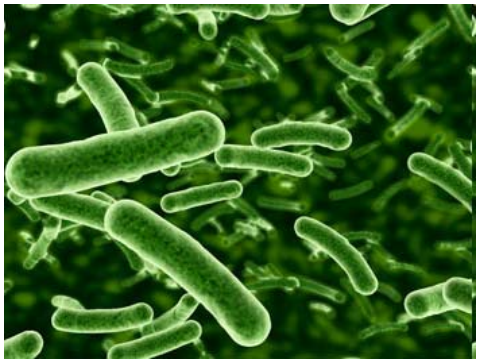

The absence of new antibiotics has led to a growing reliance on older, more toxic drugs such as colistin, but resistance to these is already arising. ChiroACCESS Mini-review, 27 April 2011; http://www.chiroaccess.com

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 
- Breakpoints variable between countries (2 mg/L in France [CA-SFM]) and 4-8 in UK [BSAC]) *
- MIC values highly dependent upon technique used (poor diffusion through agar; microdilution is preferred but influence by the inoculum) 

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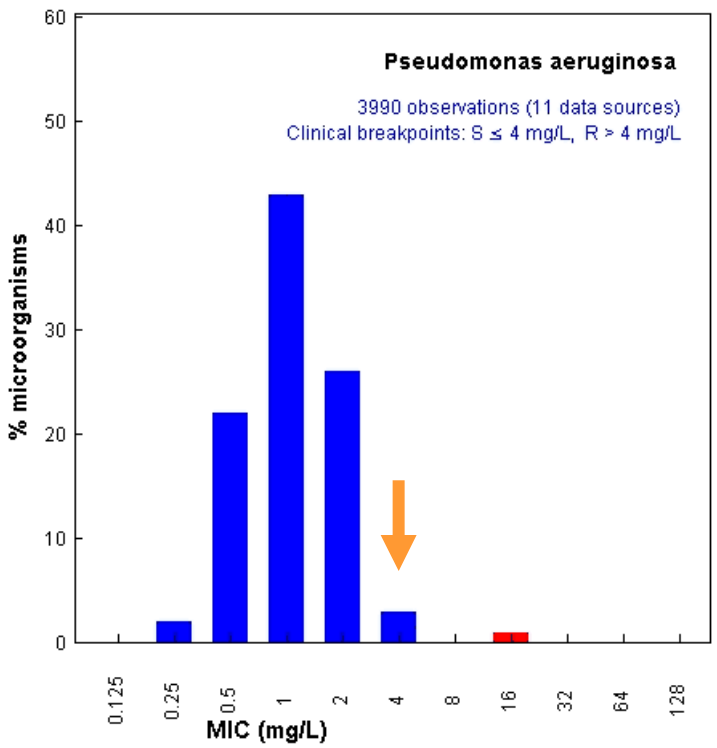
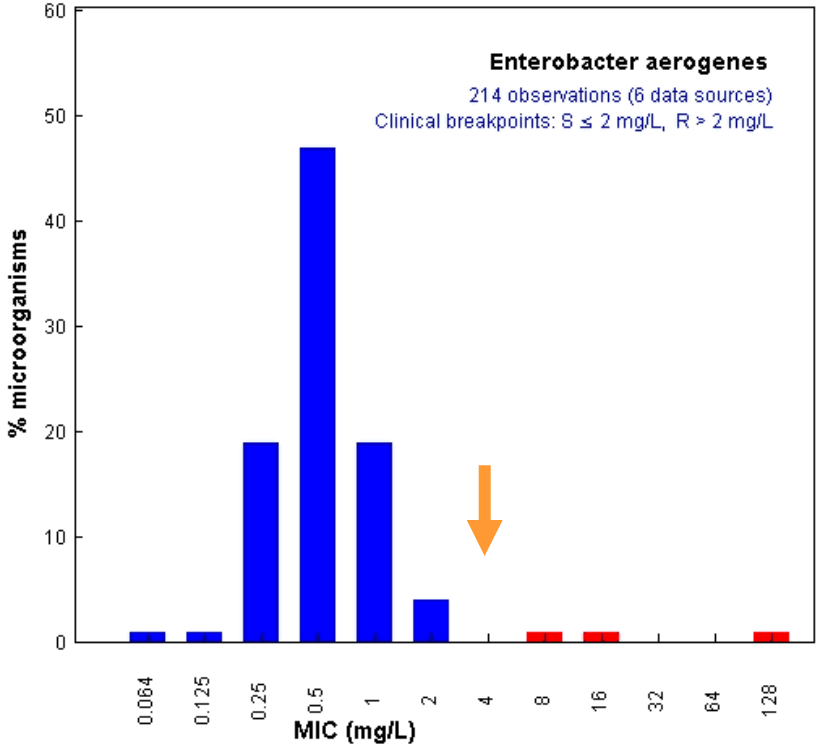
* current EUCAST breakpoint is 4/4 for all species with sufficient data (*P. aeruginosa*, *Enterobacteriaceae*, *Acinetobacter*) **to cover the wild type population**

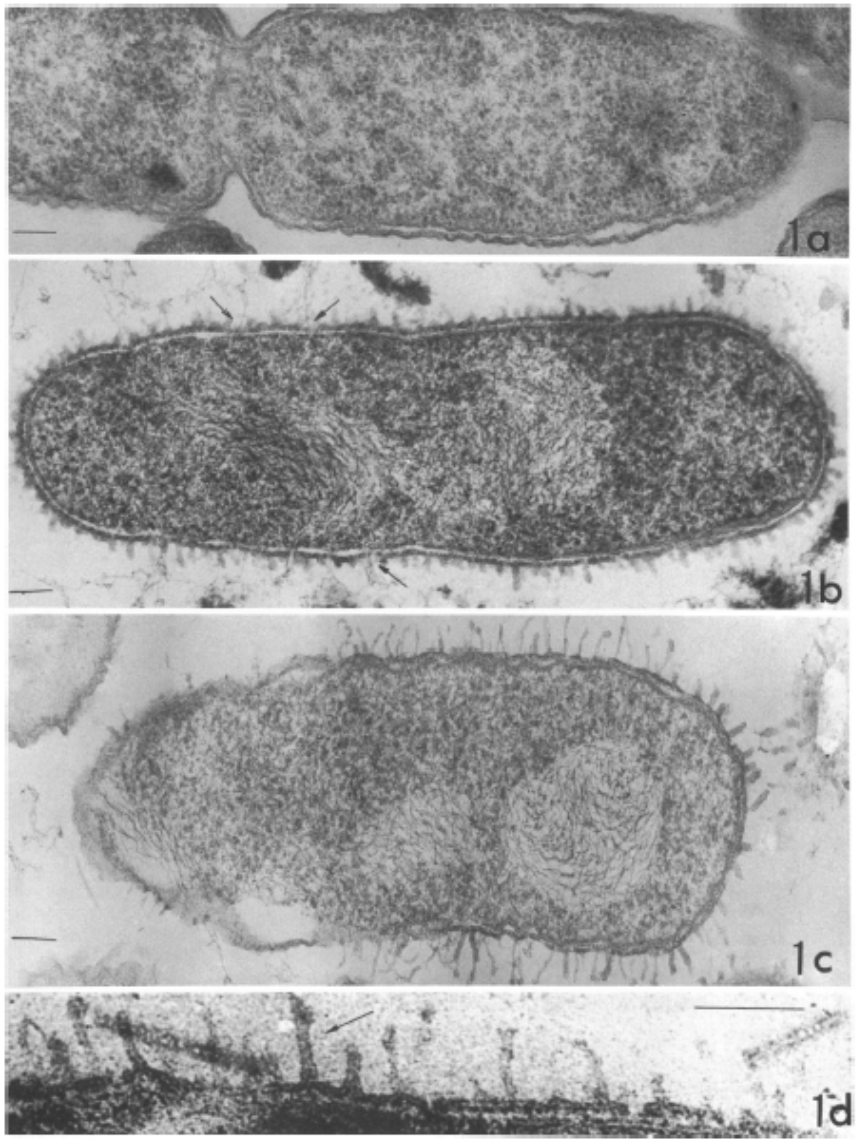
Two typical EUCAST MIC distributions for colistin

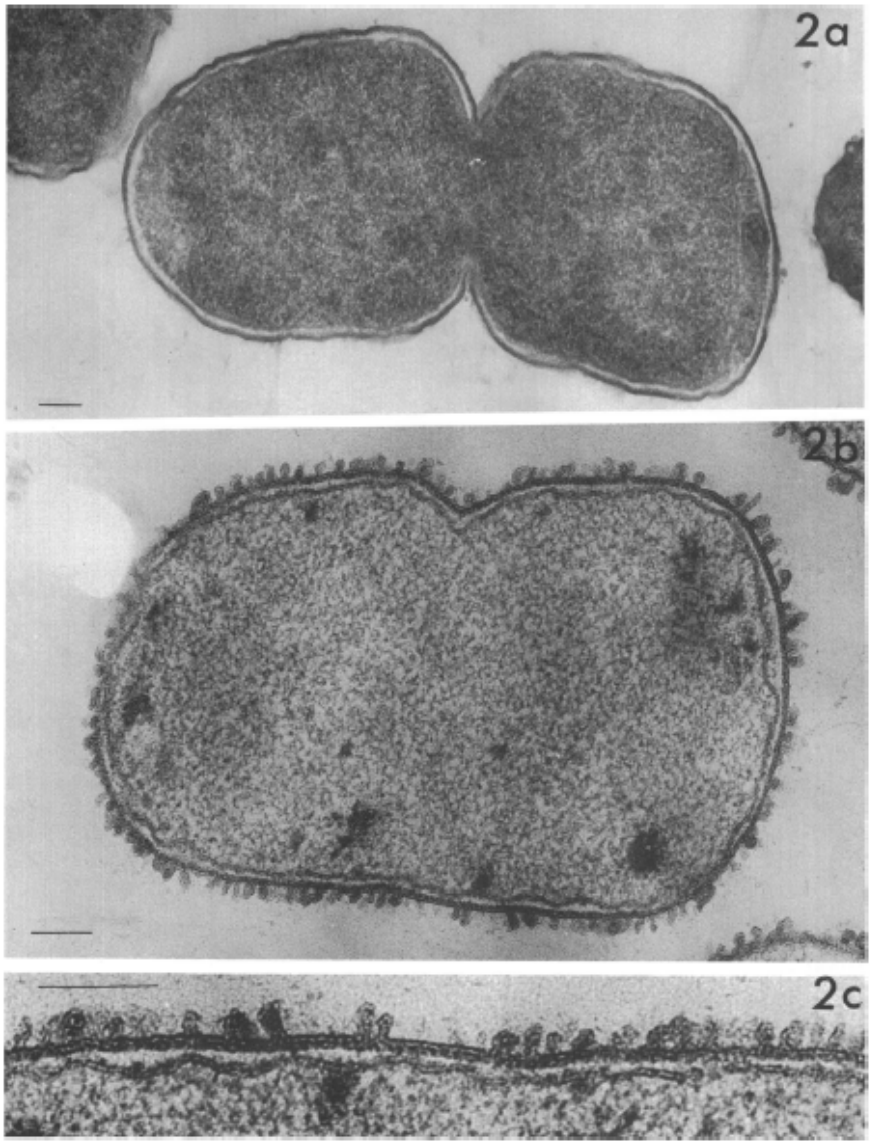




With a breakpoint of 4mg/L, almost all isolates are susceptible… but is this true ?

Colistin Microbiology: morphological aspects

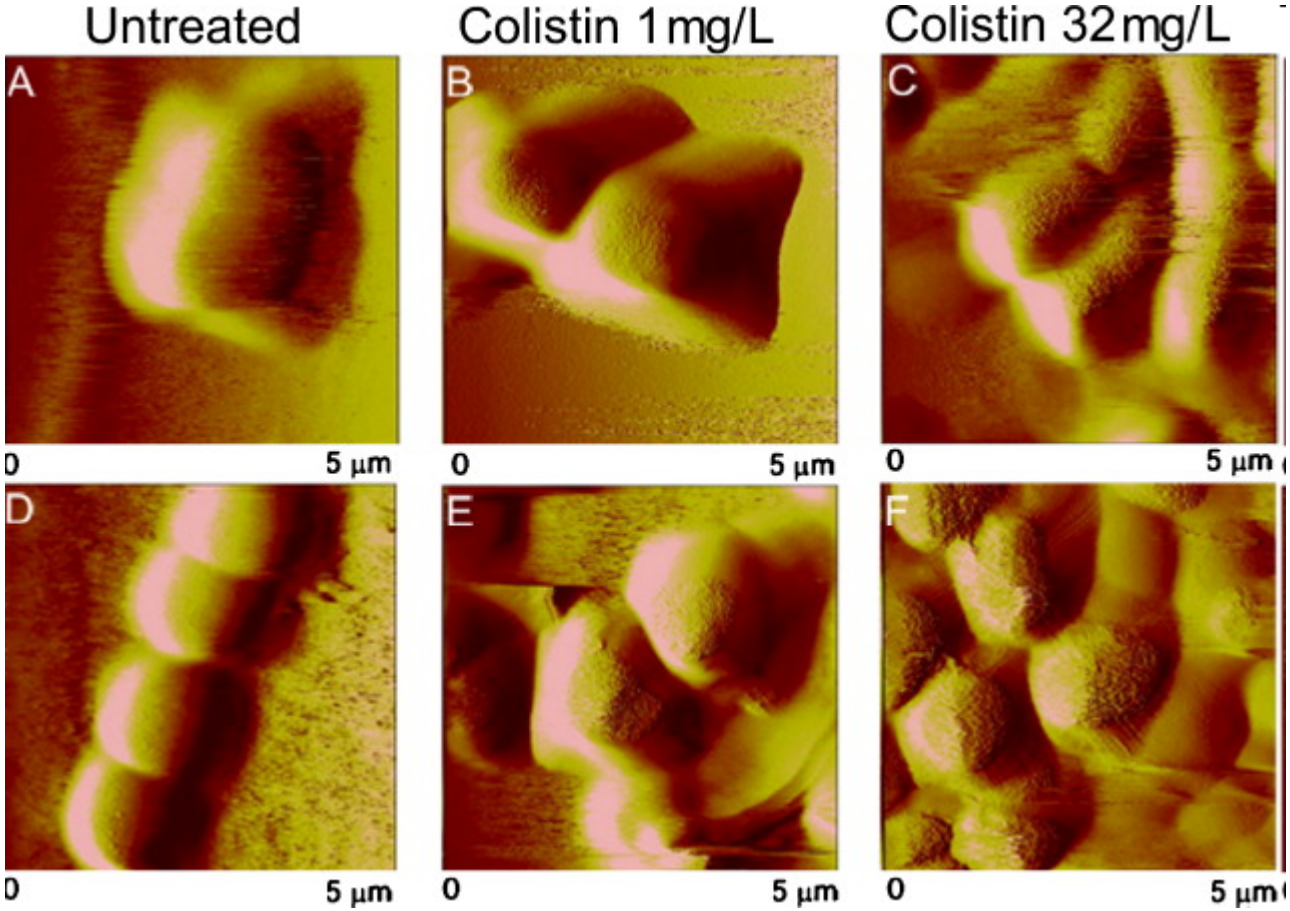




Koike et al. J. Bacteriol. 1969; 97:448-452

Colistin Microbiology: morphological aspects

Live *Acinetobacter baumanii* as seen in Atomic Force Microscopy (AFM°

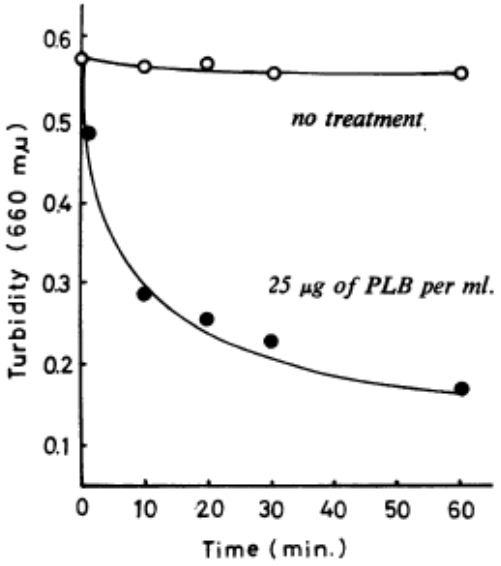


susceptible

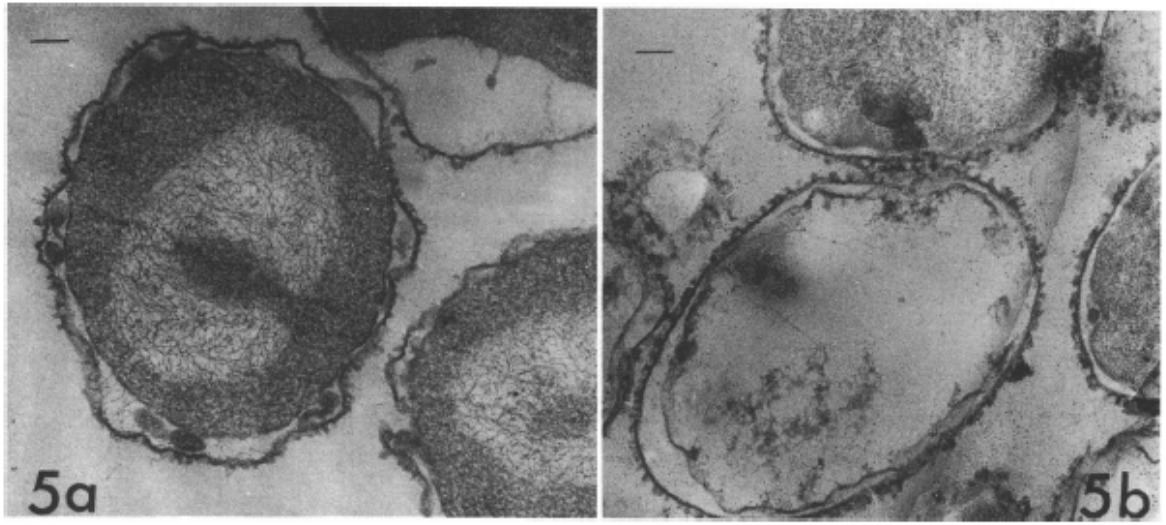
resistant

Soon et al. Int J Antimicrob Agents. 2011 Sep 16. [Epub ahead of print]

Colistin Microbiology: lysis of bacteria



Lysis of the spheroplast of E. coli B



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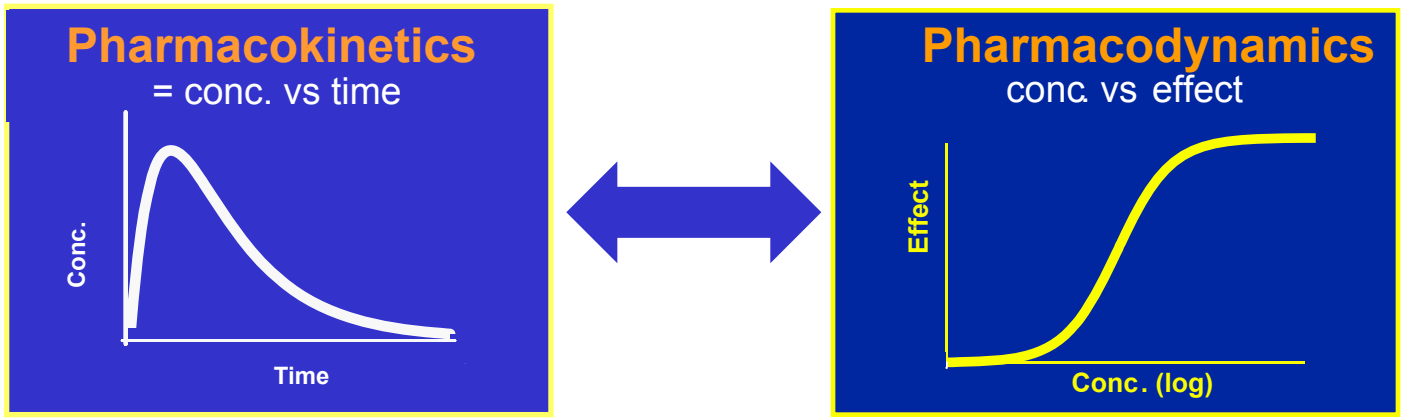


Colistin general mode of administration and dosage as proposed in the late 60's

- Sulfate: 2.5 – 3 mg/kg (25-30000 units) per day divided in 4 to 6 administrations (60-90 min infusion to avoid neuromuscular blockade)
- Methane sulfonate: 2.5-5 mg/kg per day divided in 2 to 4 administrations (20-30 min infusion)
- Adjustment necessary in renal failure
  - Increased interval
  - Reduce dosage
  - Both (combined approach)

Colistin general pharmacokinetics as published in the late 60's

preparation	Dose (adults)	C_{max}	$t_{1/2}$	Renal excretion
sulfate	50 mg	1-8 mg/L	~ 6 h	60 %
Methane sulfonate	2-2.5 mg/kg* (~150 mg)	6-15 mg/L	1.6-2.7 h	40 % in 8h **

* 25-31,500 Units/kg or ~ 2 x 10^6 UI

** 270 (2h) to 15 (8h) mg/L in urine

but was this colistin ?

Colistin disposition

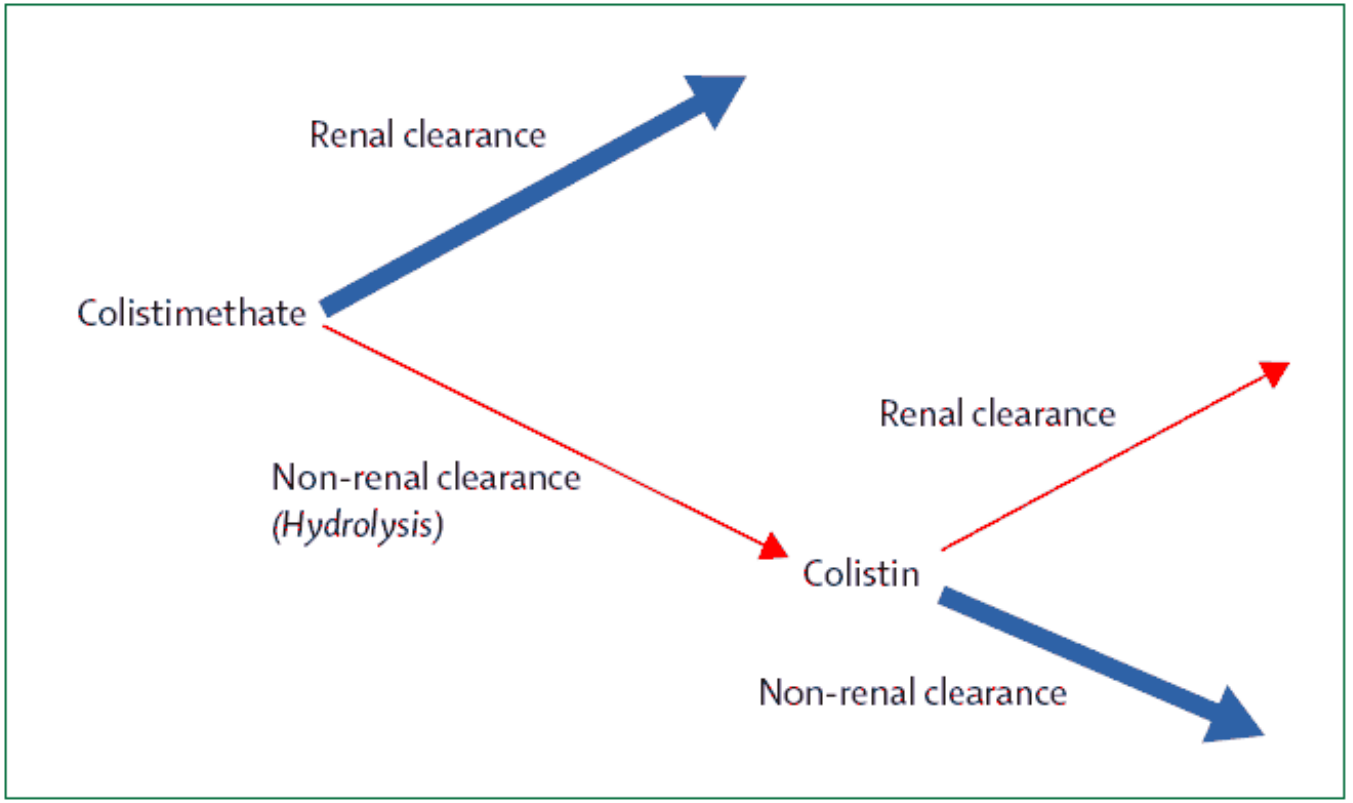
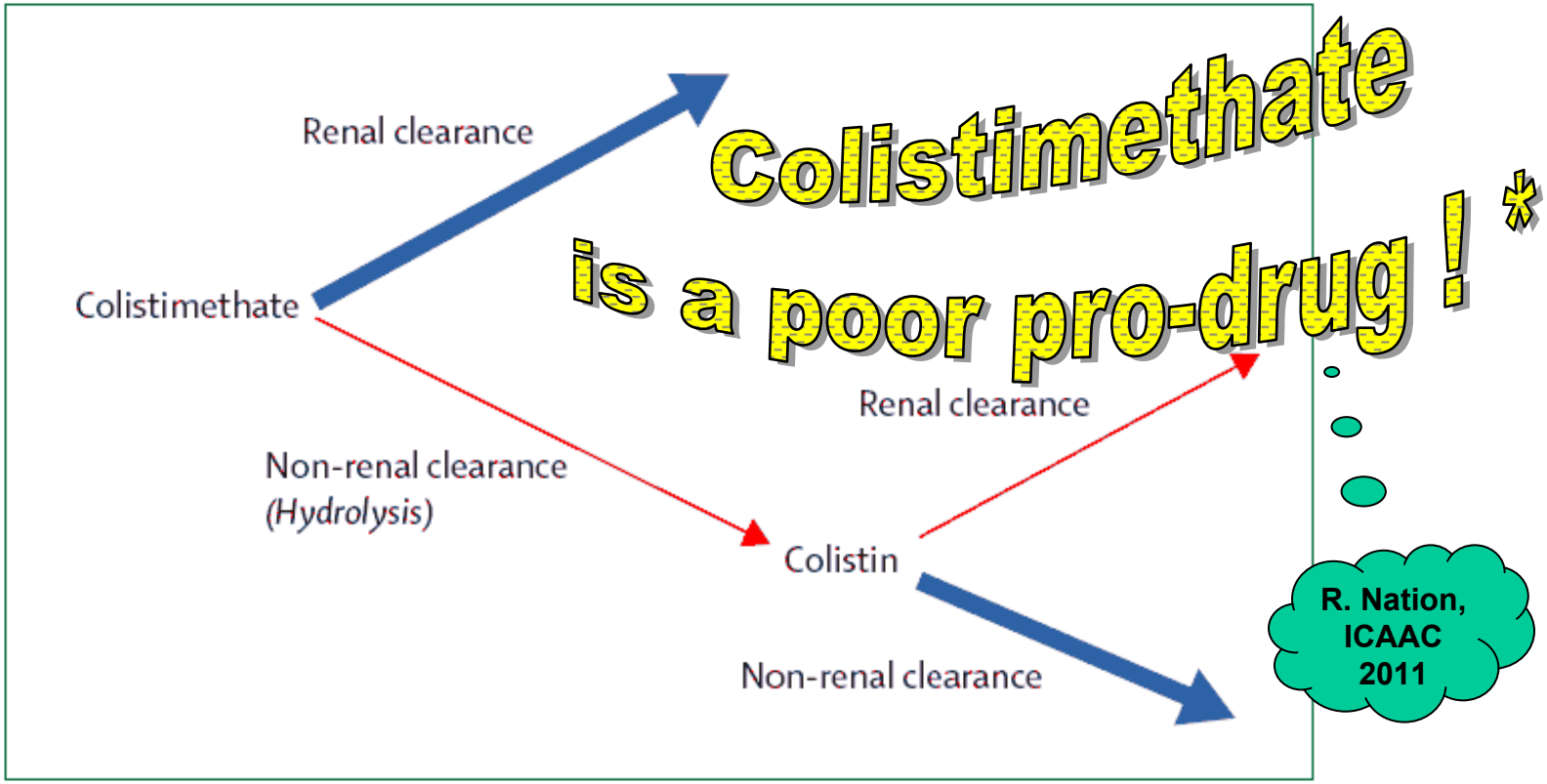


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

Colistin disposition



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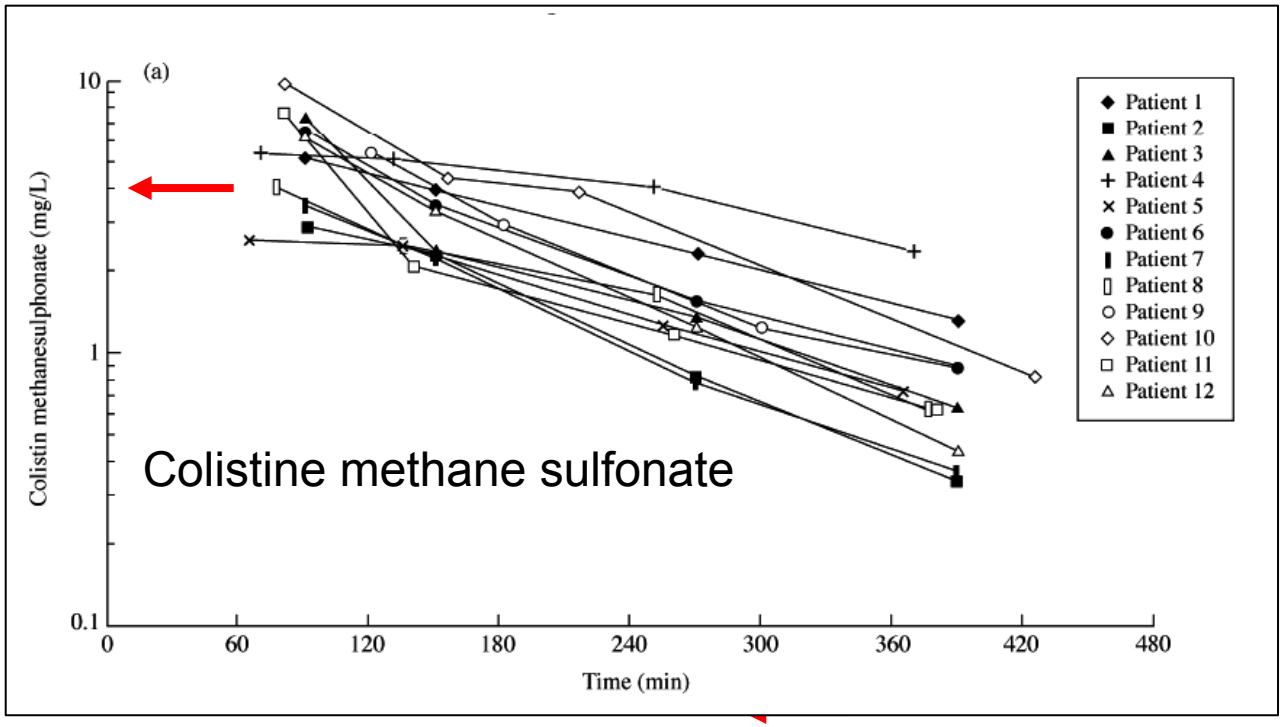
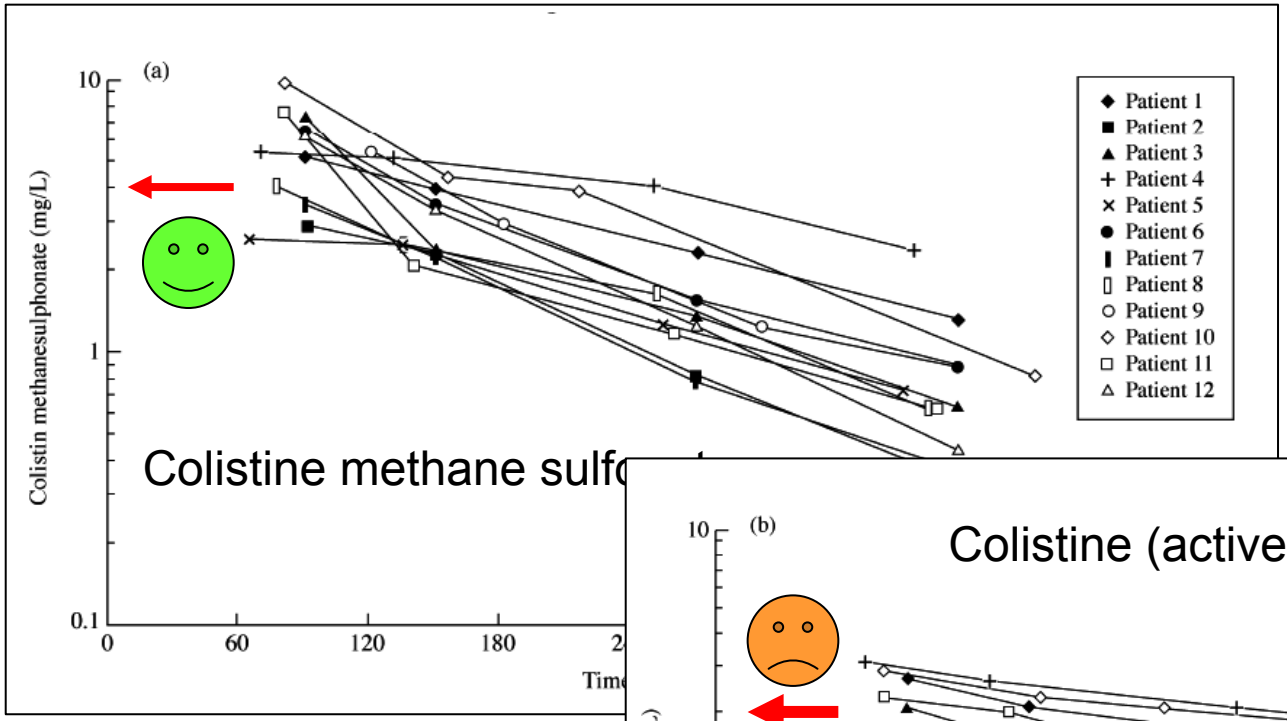
Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate



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

Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate



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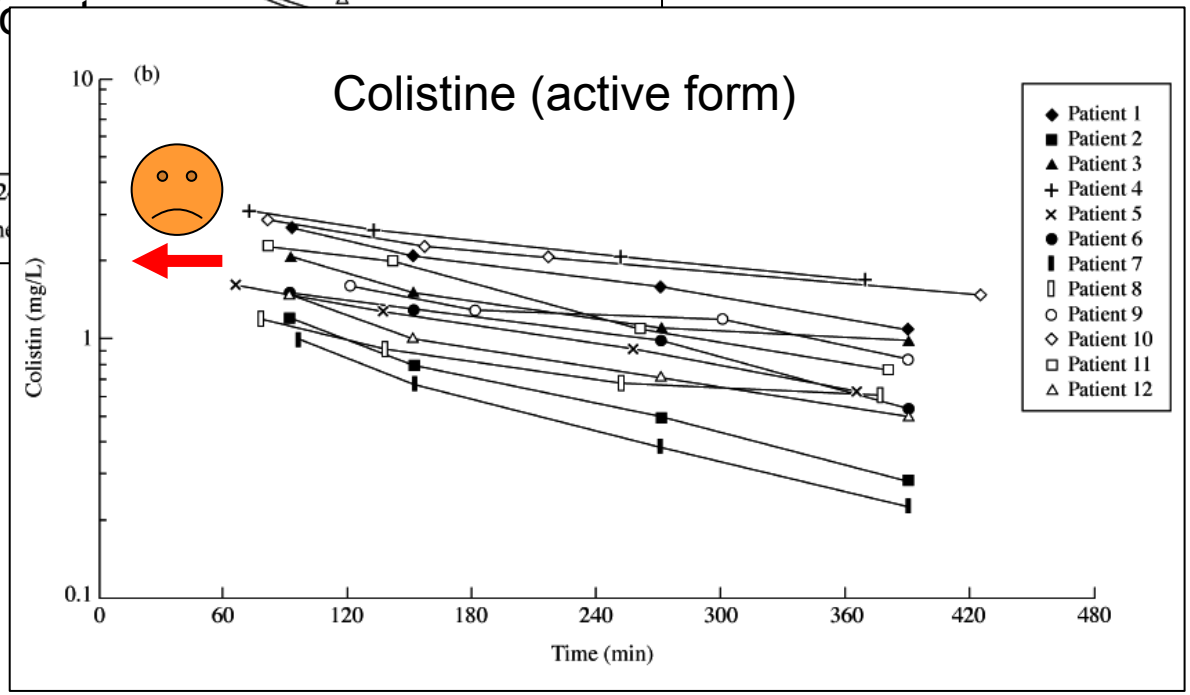


A recent progress in the assay of colistine

total colistin serum concentration is only ~ 1 mg/L

Jansson et al. Journal of Pharmaceutical and Biomedical Analysis 2009; 49:760–767

Differential measurement of colistine methane sulfonate and colistins A and B

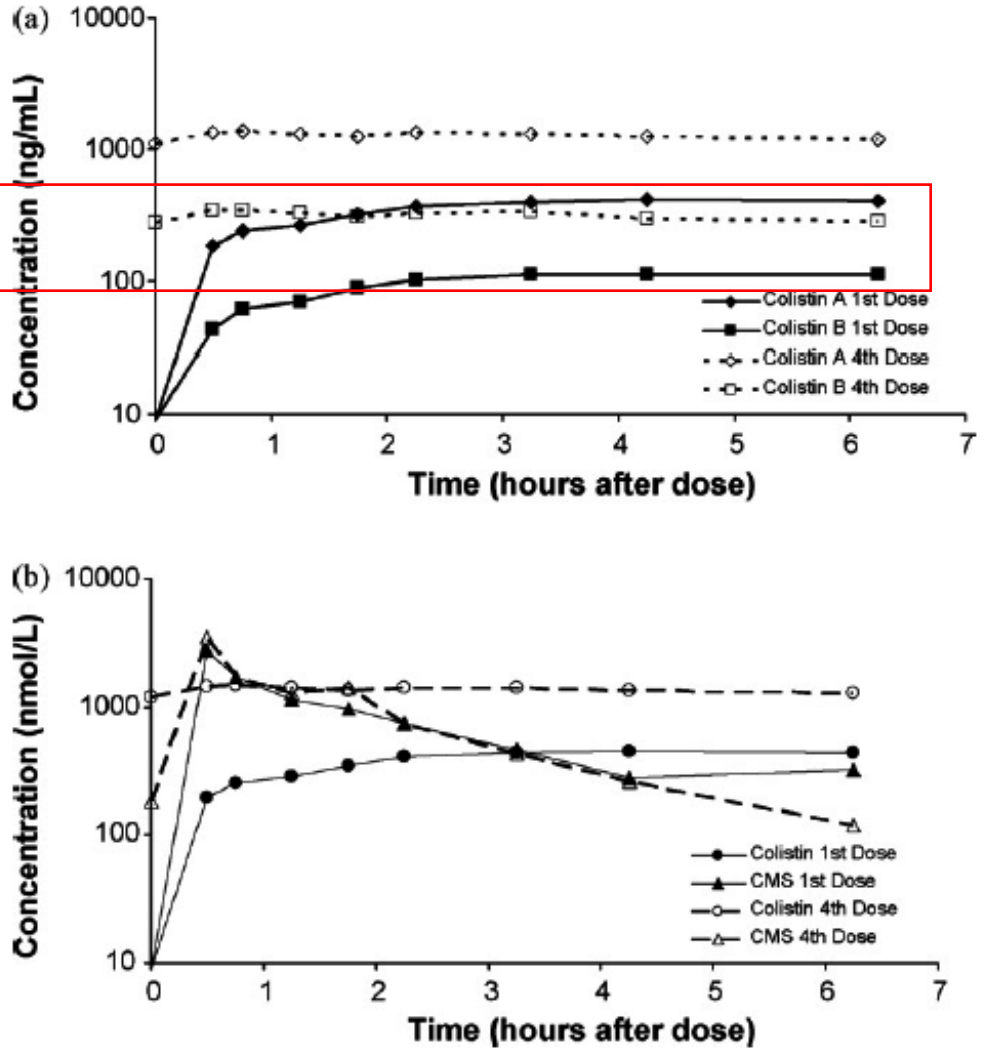


Fig. 6. Measured colistin A and colistin B concentrations versus time after the 1st and 4th dose (a) and measured total colistin and total CMS after the 1st and 4th dose (b) for a typical patient.

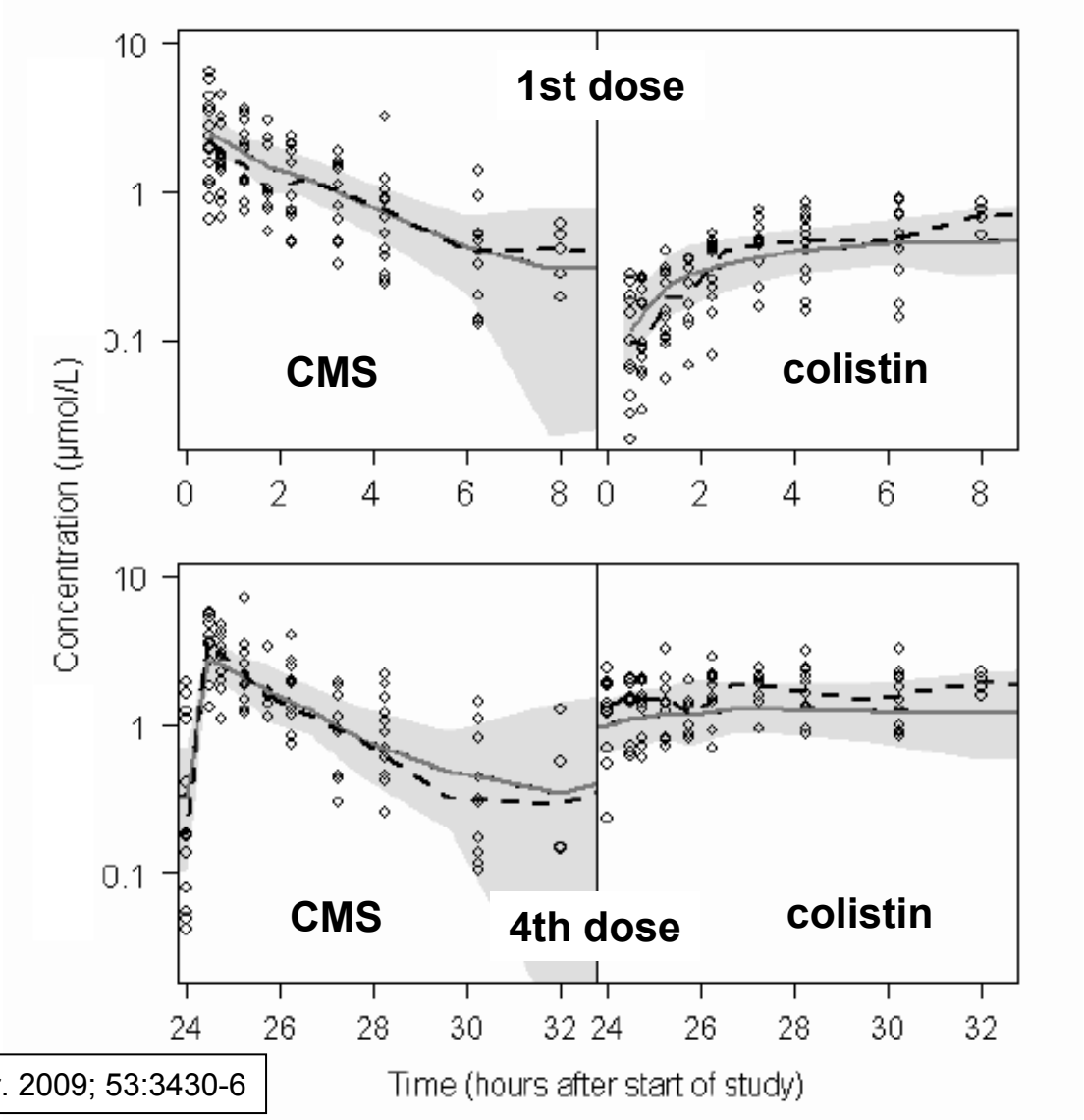
Population pharmacokinetics of colistin in critically-ill patients

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]*‡

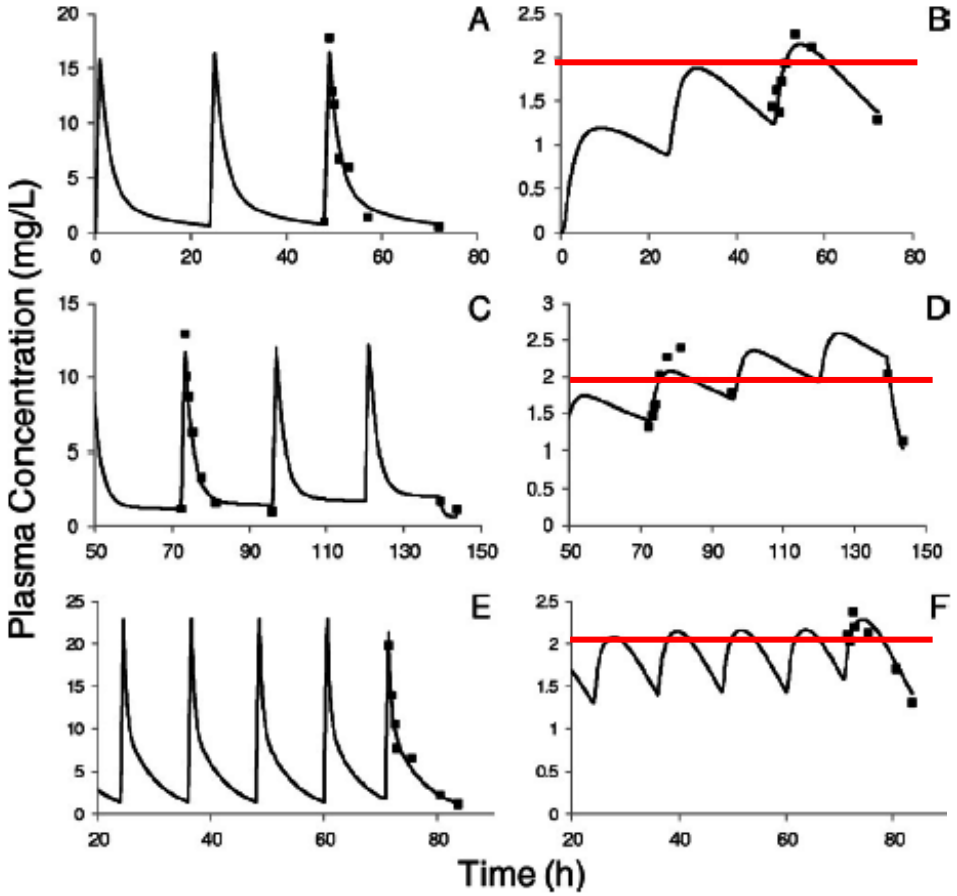
School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, New York[1]; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia[2]; Division of 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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** 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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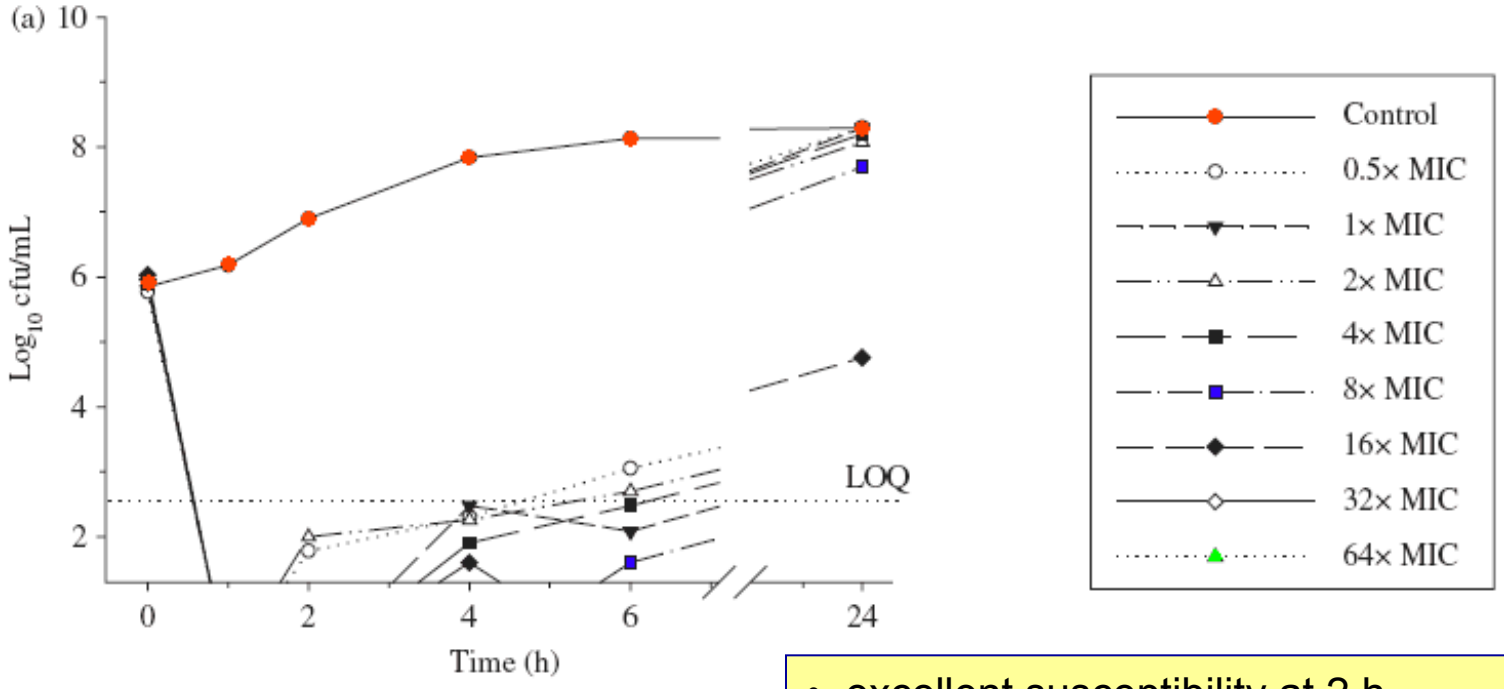
*** 275 mg CBA for loading dose = 8.3 x 10^6 U

Colistin pharmacodynamics (1)

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



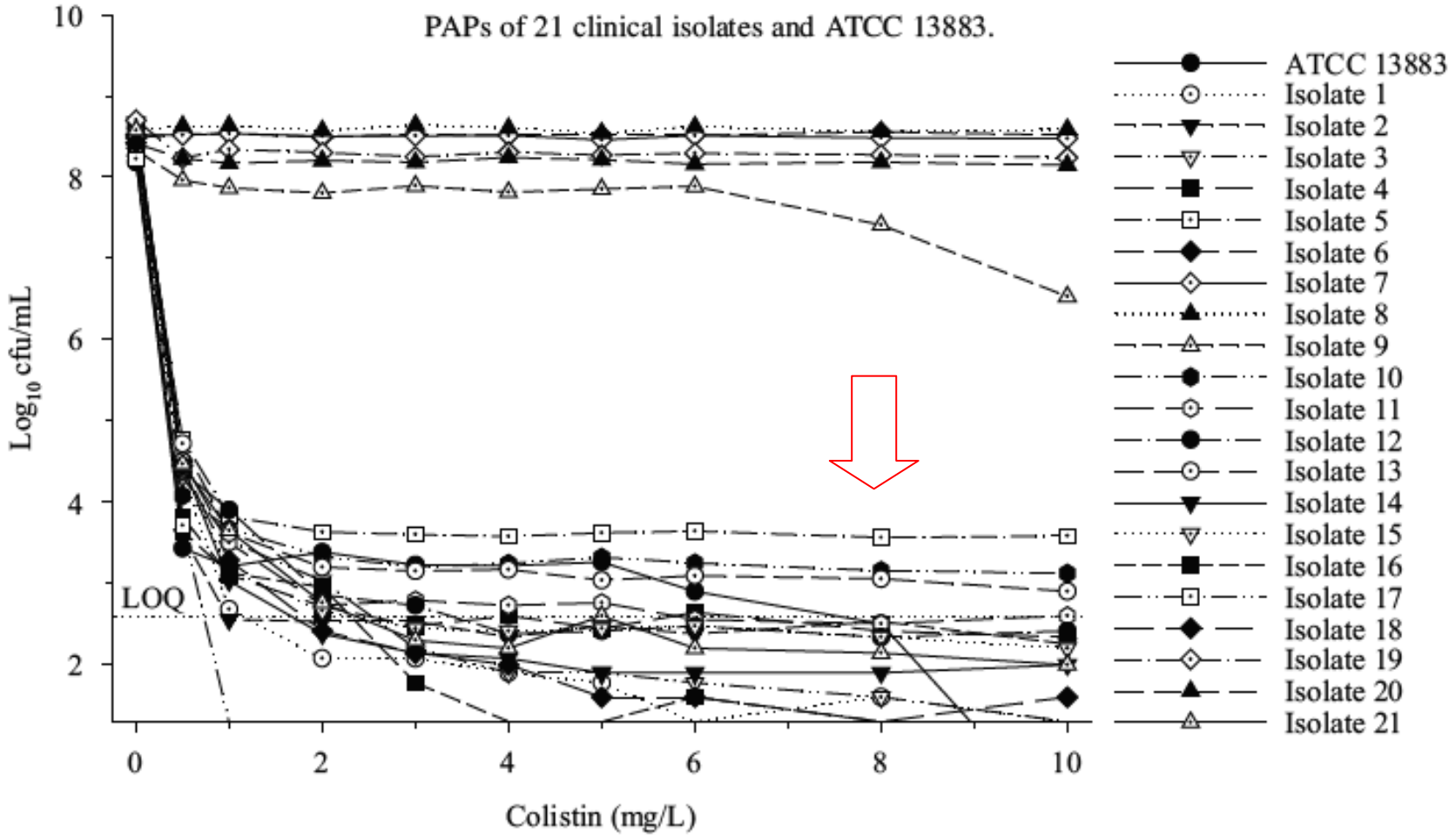
- excellent susceptibility at 2 h…
- **but** regrowth at 24h if conc. ≤ 16 MIC

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)

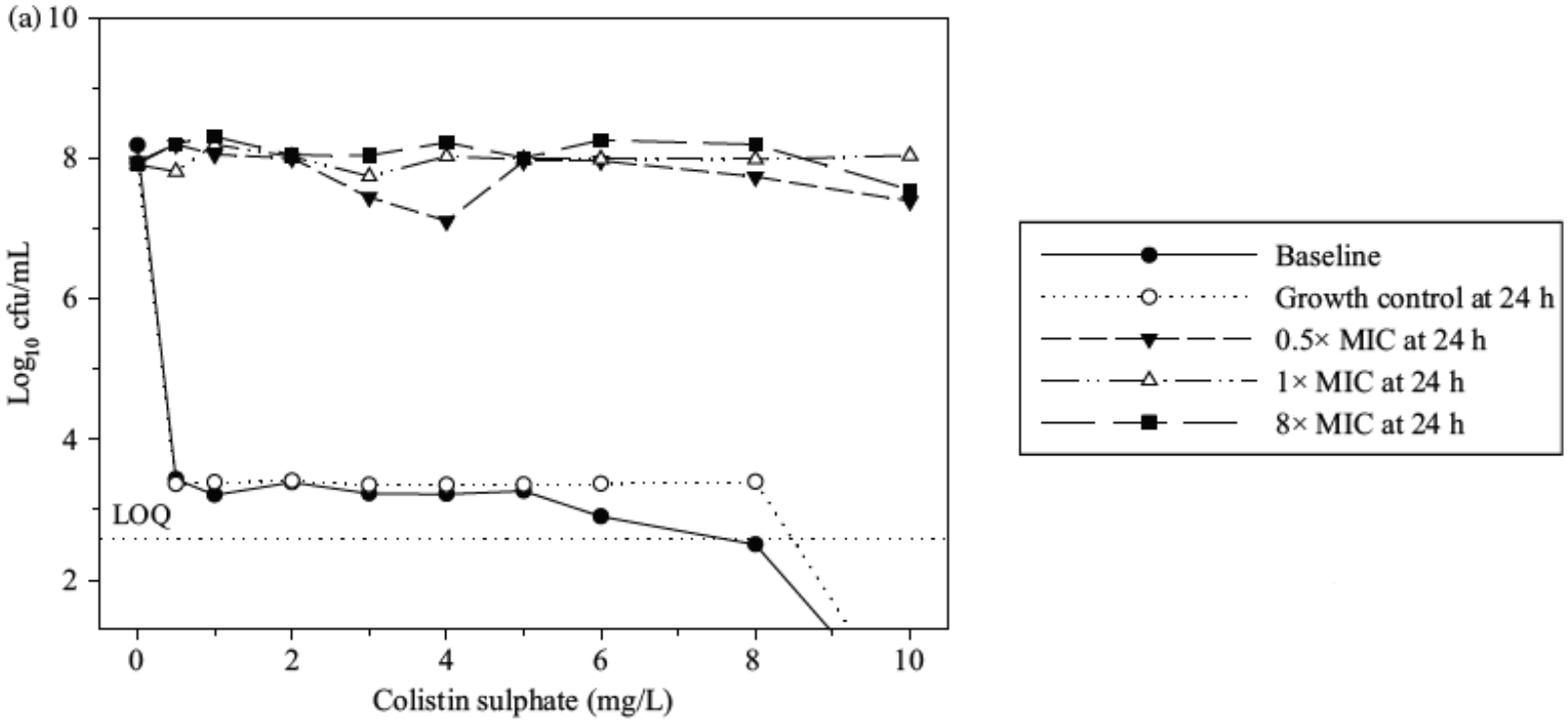
Population analysis profiles of *K. pneumoniae* isolates



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

Colistin pharmacodynamics (3)

Loss of susceptibility of *K. pneumoniae* after single exposure

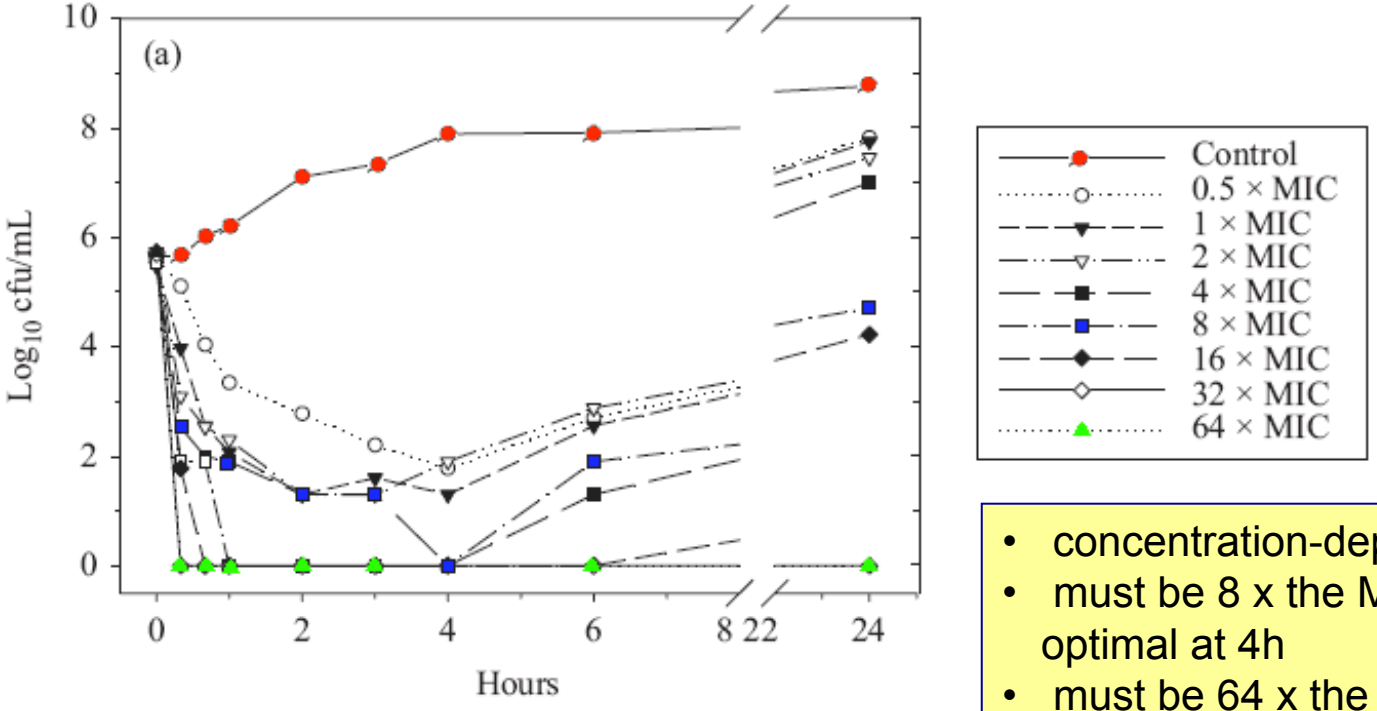


Changes in PAPs of ATCC 13883 after exposure to selected colistin concentrations (0, 0.5×, 1× and 8× MIC) for 24 h.

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

Colistin pharmacodynamics (4)

Time kill curves against *A. baumanii*



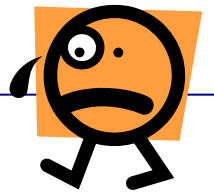
- concentration-dependence
- must be 8 x the MIC to become optimal at 4h
- must be 64 x the MIC to avoid regrowth
- modest post-antibiotic effect (see data in paper)

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*.



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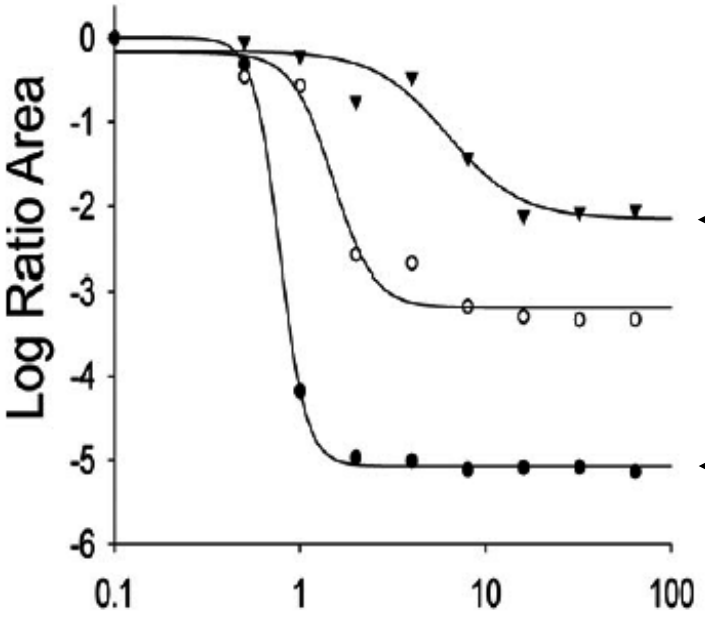
Colistin and inoculum effect

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*

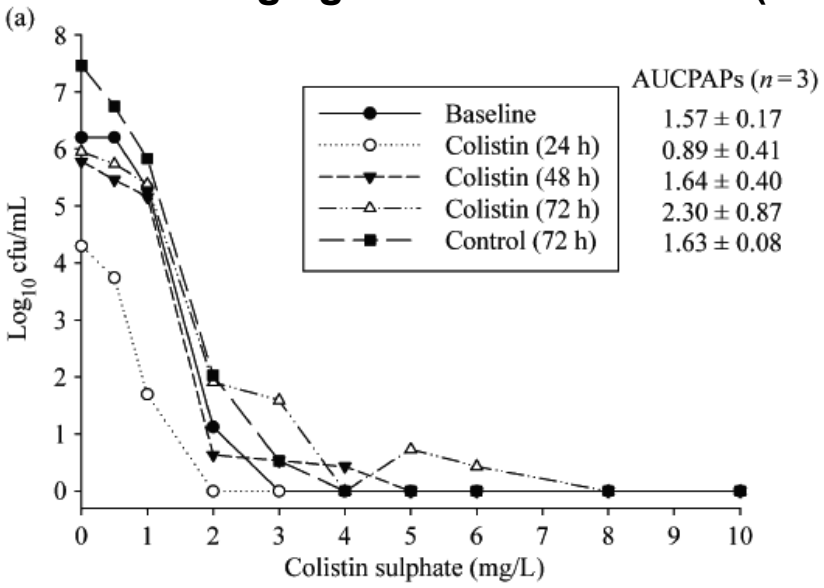
low inoculum (~ *in vitro* testing)

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 (1)

Population analysis of *P. aeruginosa* after exposure to colistin modeling:

5 mg/kg divided in 3 admin. (TID)



5 mg/kg in one admin (qD)

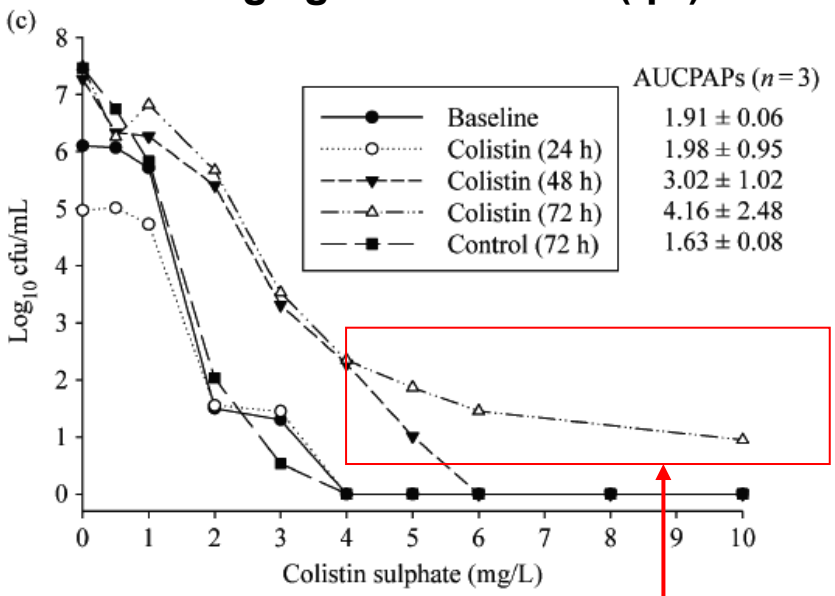


Figure 2. PAPs of ATCC 27853 in the *in vitro* PK/PD model: (a) 8 hourly (c) 24 hourly dosing.

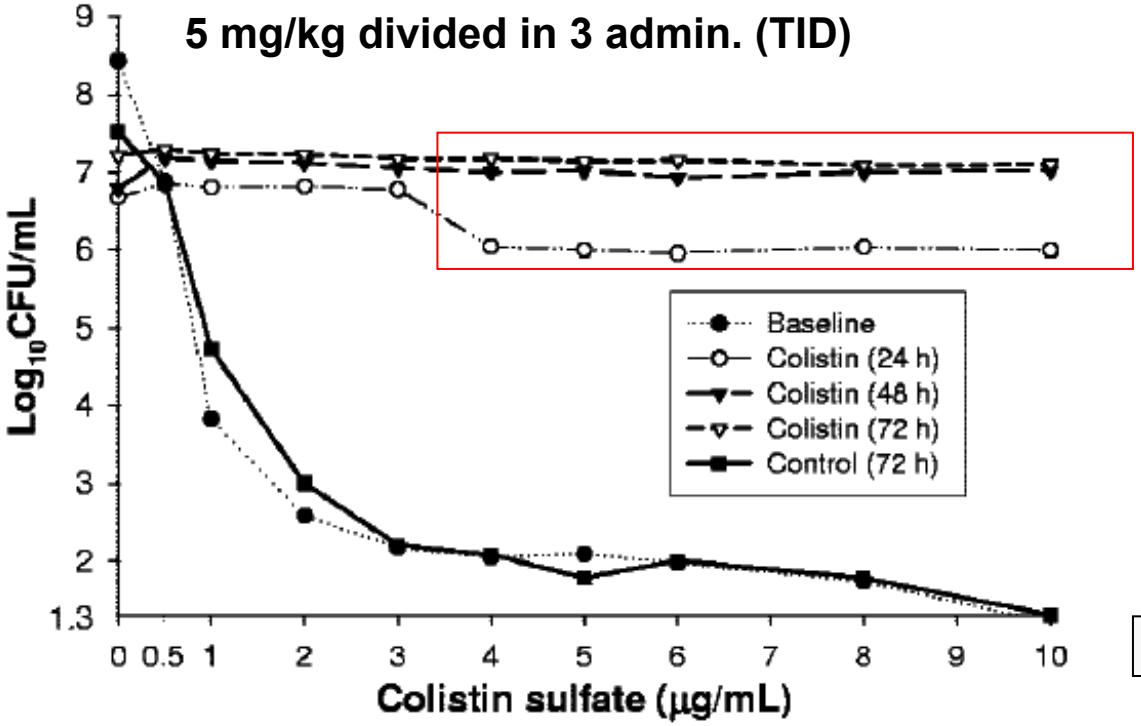
less-susceptible organisms

Bergen et al. JAC 2008; 61:636-642

***Conclusions*: No difference in overall bacterial kill was observed when the recommended maximum daily dose was administered at 8, 12 or 24 h intervals. However, the 8 hourly regimen appeared most effective at minimizing emergence of resistance.**

Colistin pharmacodynamics and resistance (2)

Population analysis of *A. baumanii* after exposure to colistin modeling:

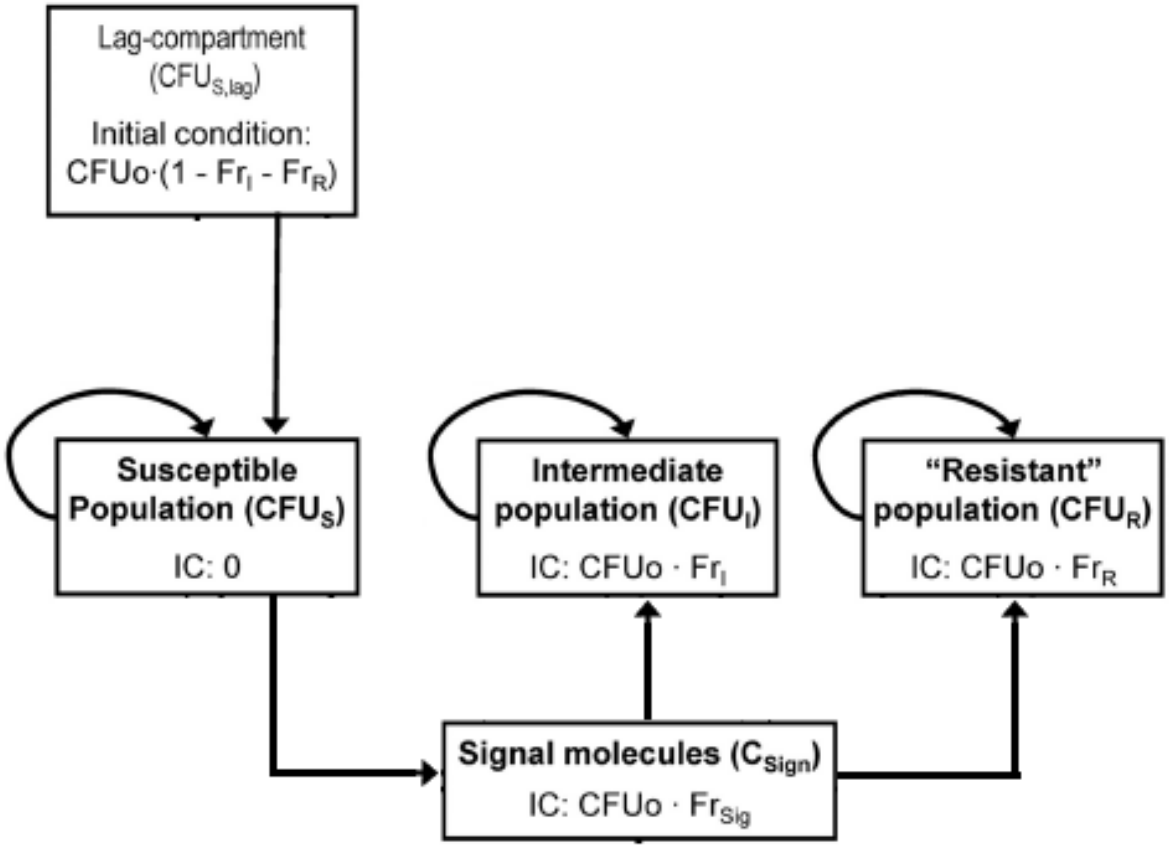


Resistant organisms !

Tan et al. AAC 2007; 3413-3415

Three clinically relevant intermittent regimens, and a continuous infusion, of colistin were simulated in an in vitro pharmacokinetic/pharmacodynamic model against two colistin-heteroresistant strains of *Acinetobacter baumannii*. Extensive initial killing was followed by regrowth as early as 6 h later; bacterial density in the 24- to 72-h period was within 1 $\log_{10}$ CFU/ml of growth control. Population analysis profiles revealed extensive emergence of resistant subpopulations regardless of the colistin regimen.

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

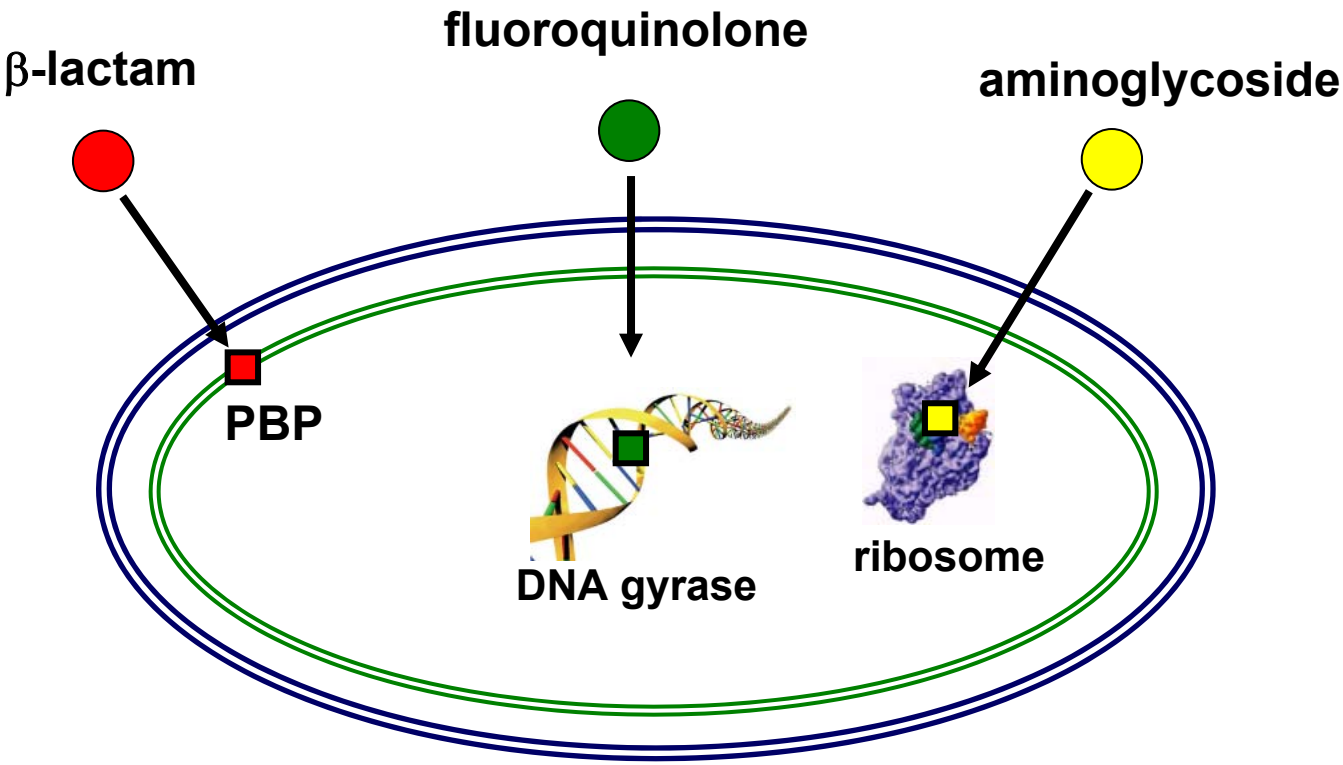
- Displays a **high and fast bactericidal effect** (named today: concentration-dependent antibiotic)

  ➔ **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**)

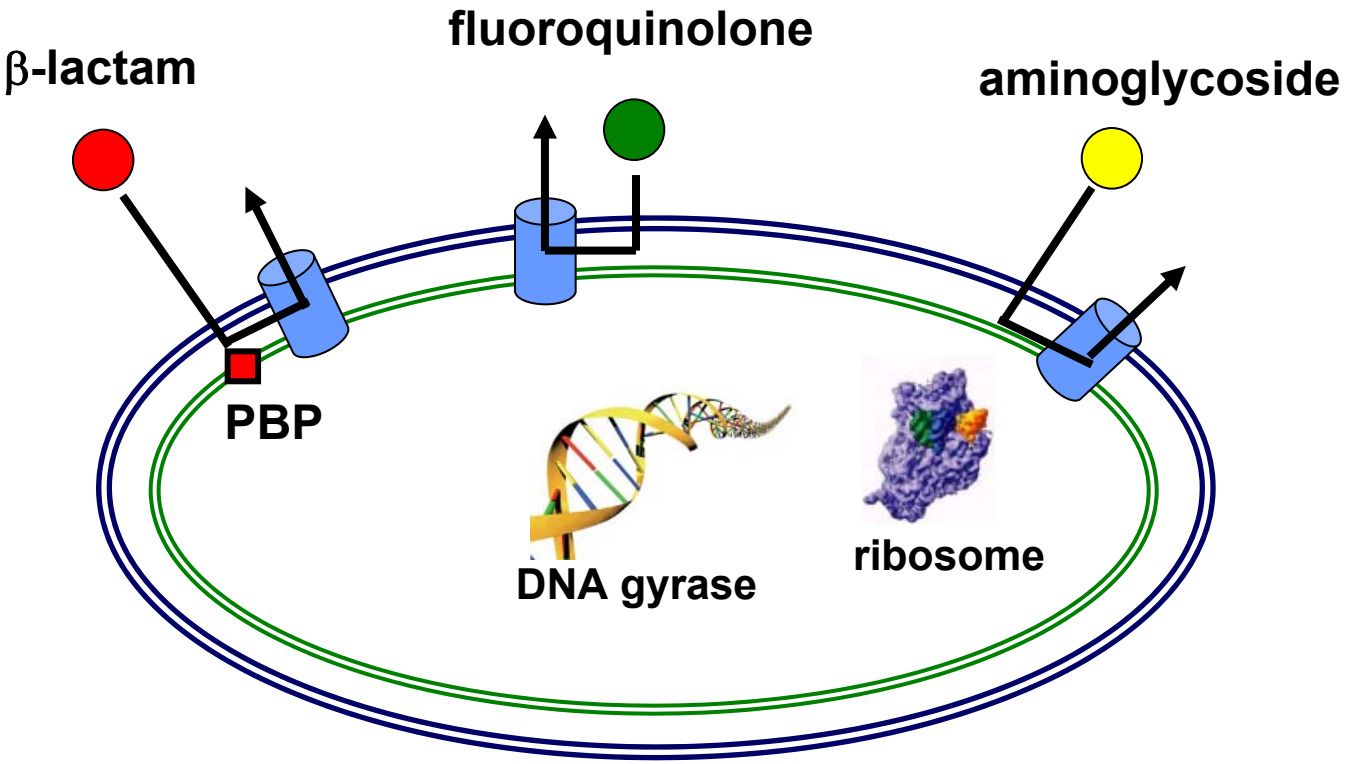
  ➔ colistin needs to be **administered several times a day to avoid regrowth**

Colistin synergy: the rationale (1 of 3)



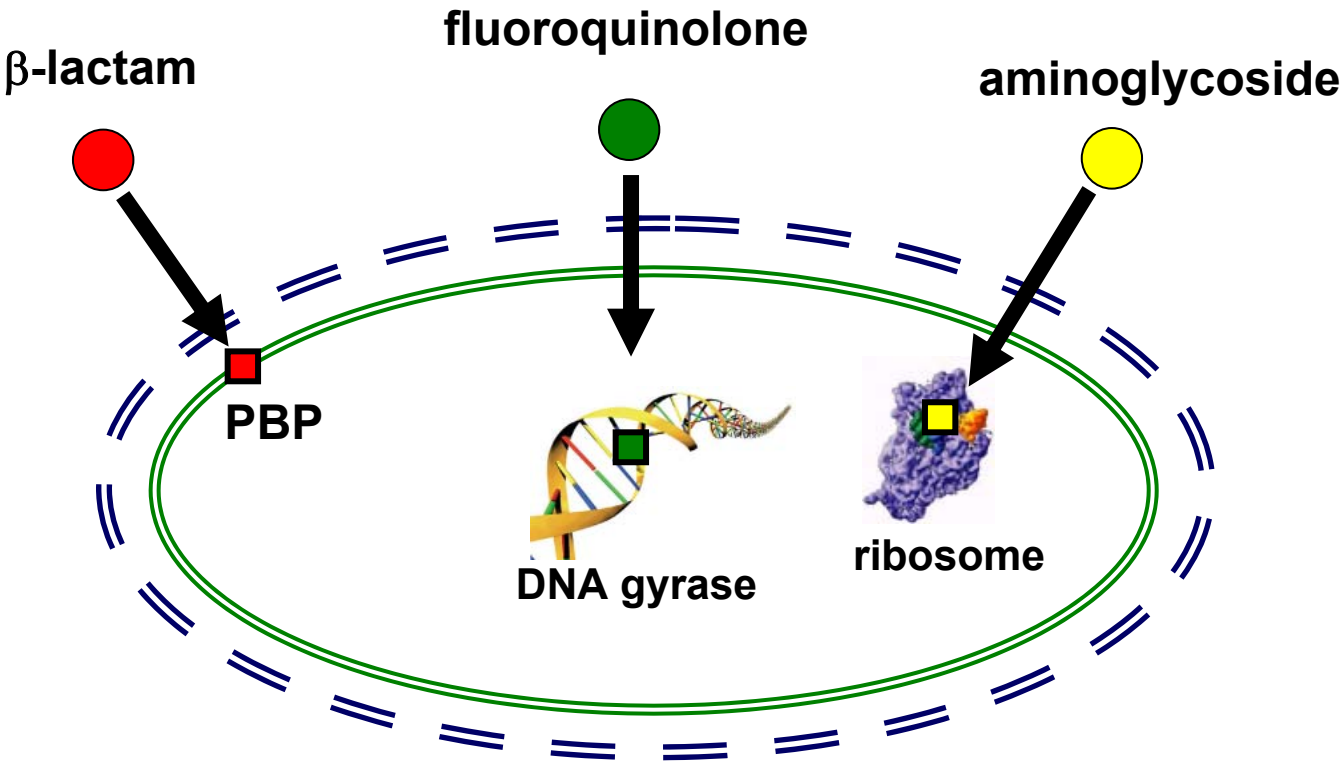
- Gram-negative bacteria have two membanes (OM and IM)
- Antibiotic targets are most often located in the IM or intracellularly
- Most antibiotics must at least pass across the OM to reach their target, which may represent a limiting step

Colistin synergy: the rationale (2 of 3)



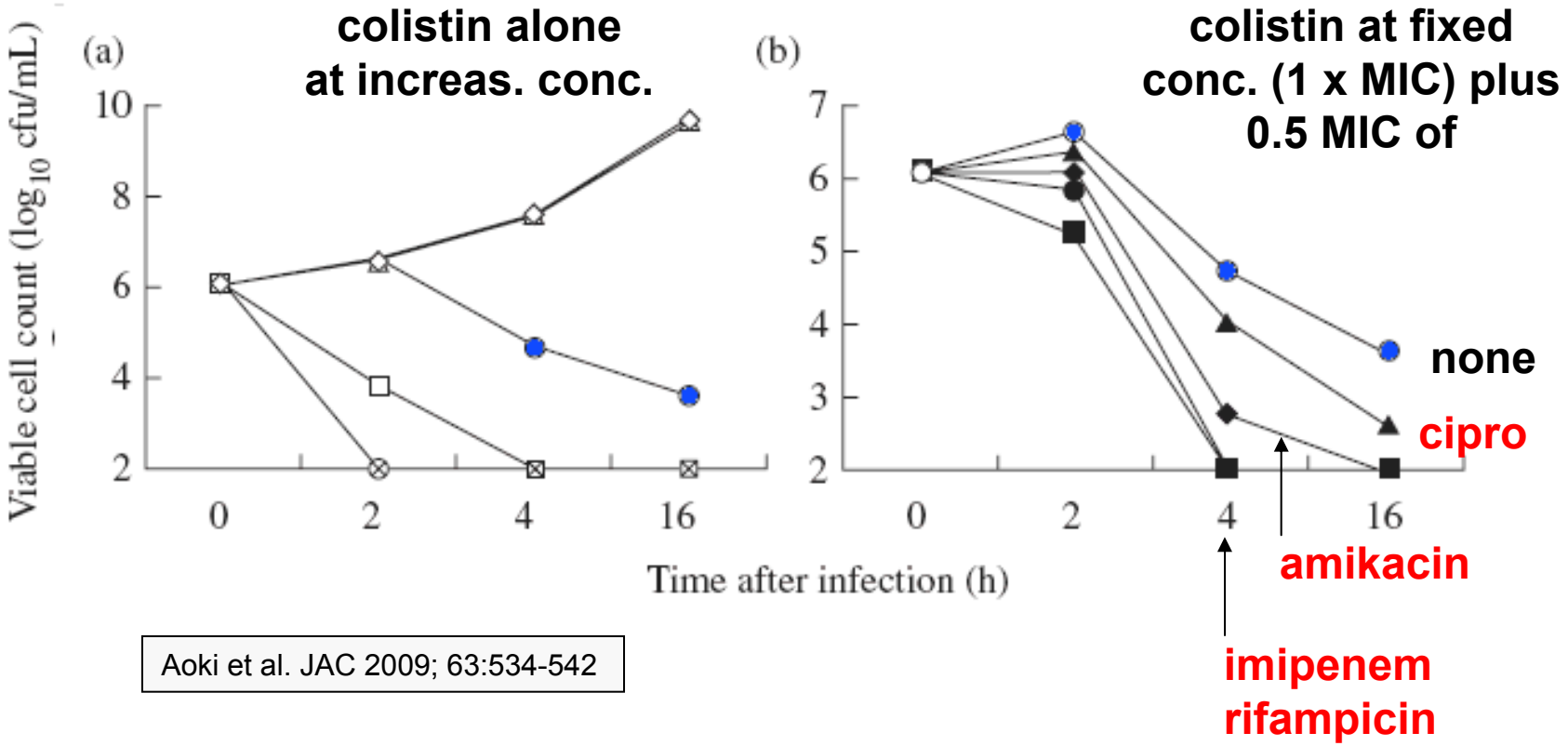
- Gram-negative bacteria have also efflux systems defeating the passage of drugs across the OM and explaining the low activity of many antibiotics (intrinsic resistance) and the so-called "adaptative" resistance (aminglycosides)

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

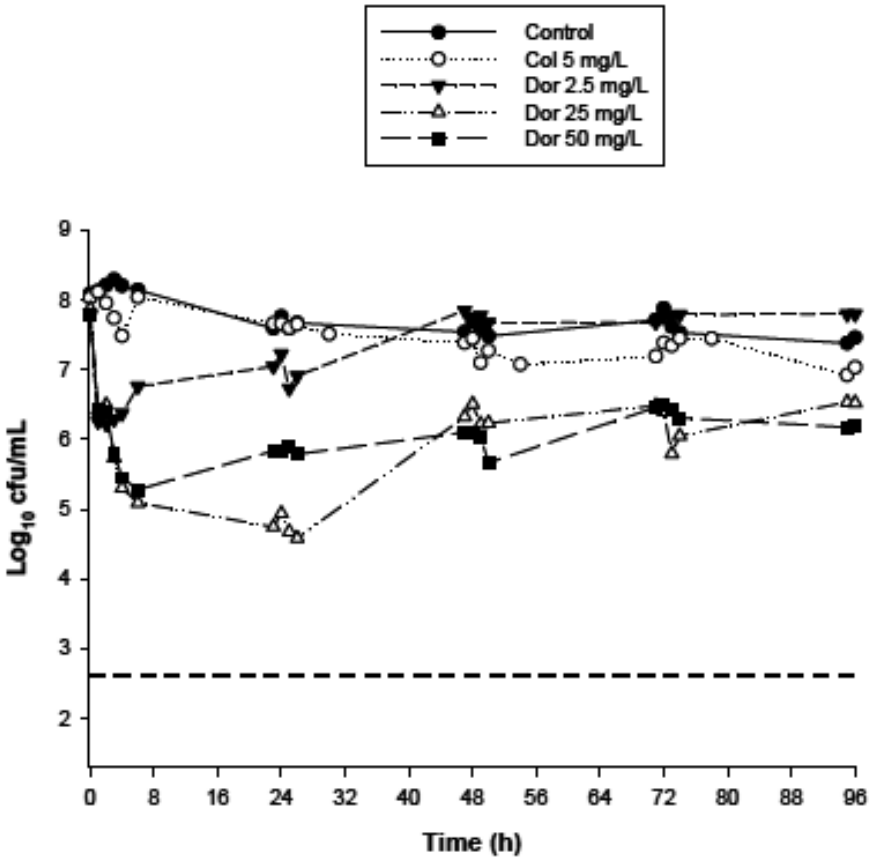
Souli et al. AAC 2009; 2133-2135:

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

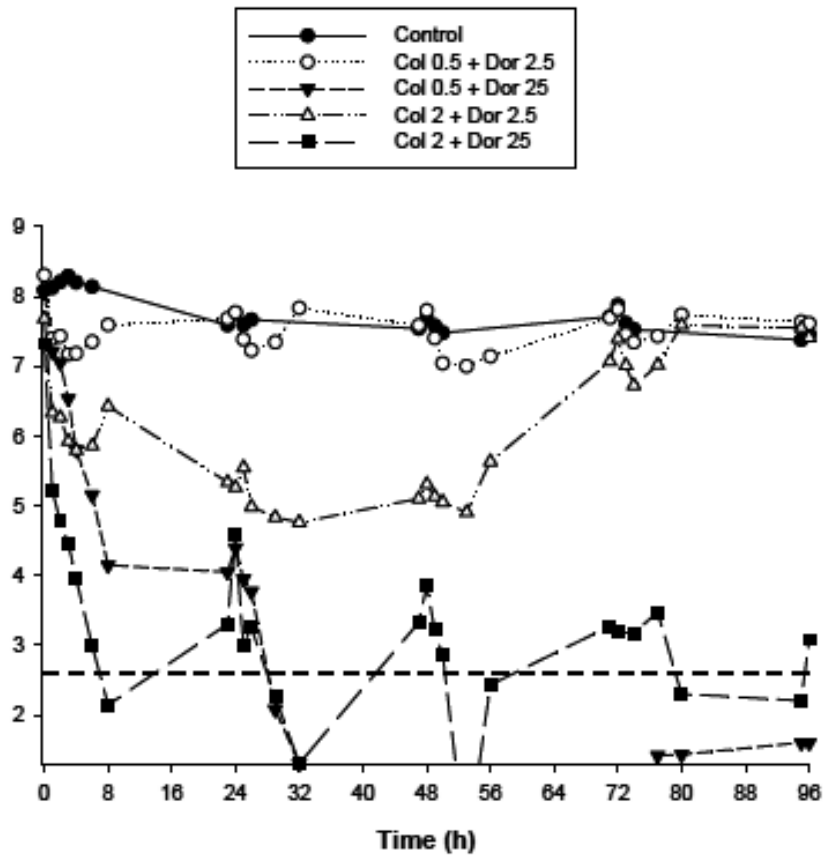
Colistin synergy *in vitro* and *P. aeruginosa*

synergy with doripenem at high inoculum concentration

drugs alone



combination



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

Colistin synergy *in vitro and A. baumannii*

Exposure to colistin alone *

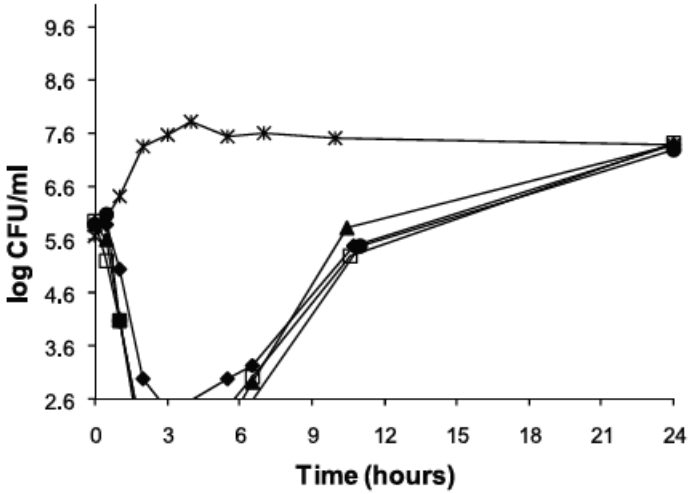


FIG. 1. Time-kill curves of CMS against *A. baumannii* at maximum serum drug concentrations of 3 μg/ml (◆), 6 μg/ml (●), 12 μg/ml (▲), and 24 μg/ml (□). The growth control (×) is also depicted.

* Initial MIC: 0.5 mg/L

Kroeger et al. AAC 2007; 51:3431-3433

Exposure to colistin [a] and ceftazidime [b]

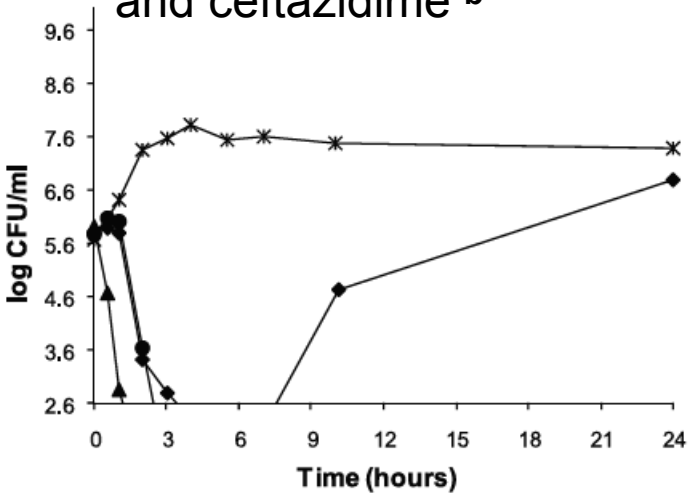


FIG. 2. Time-kill curves of CMS given at time zero plus the addition of continuous-infusion ceftazidime started at 2 h (▲) and continuous-infusion ceftazidime started at time zero plus a CMS bolus given at 2 h (●) against *A. baumannii*. Continuous-infusion ceftazidime given alone (◆) and the growth control (×) are also depicted.

[a] at 24 mg/L

[b] at 50 mg/L

MIC: 32-64 mg/L

Using an in vitro pharmacodynamic model, a multidrug-resistant strain of *Acinetobacter baumannii* was exposed to colistin methanesulfonate alone and in combination with ceftazidime. Pre- and postexposure colistin sulfate MICs were determined. A single daily dose of colistin methanesulfonate combined with continuous-infusion ceftazidime prevented regrowth and postexposure MIC increases.

Contents of the presentation

- What is (exactly) colistin ?
- What do we know about its antimicrobial activity ?
- And its pharmacokinetics/pharmacodynamics ?
- **And its toxicodynamics ?**
- What can we do today with colistin ?

??

Colistin gross toxicology

- Colistin methanesulfonate is about 50 to 100 X less toxic in LD_{50} evaluations than colistine sulfate
- Renal toxicity (polymyxin B << other polymyxins)
  - Up to 20 % of patients in early trials
  - Occurs after 4 days of treatment
  - Acute tubular necrosis (can progress after drug discontinuation)
  - Related to overdosage (obese ! Oliguric renal failure if if doses higher than recommended are used)
- Neurotoxicity:
  - Giddiness, numbness, paresthesia, peripheral neuropathy
  - Confusion, coma, psychosis at large doses
  - Neuromuscular blockade (paralysis) related to doses but other contributing factors

Colistin disposition and kidney

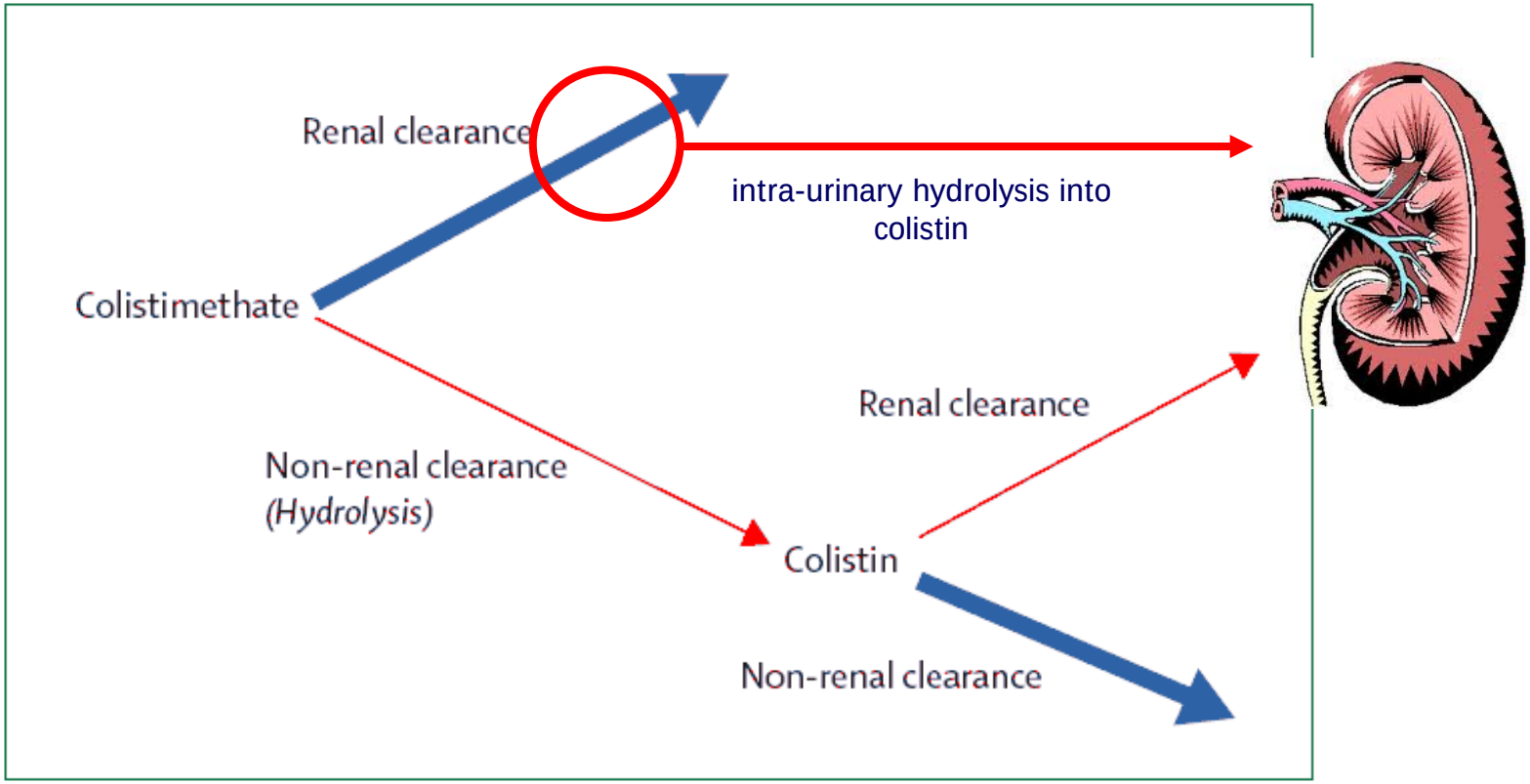
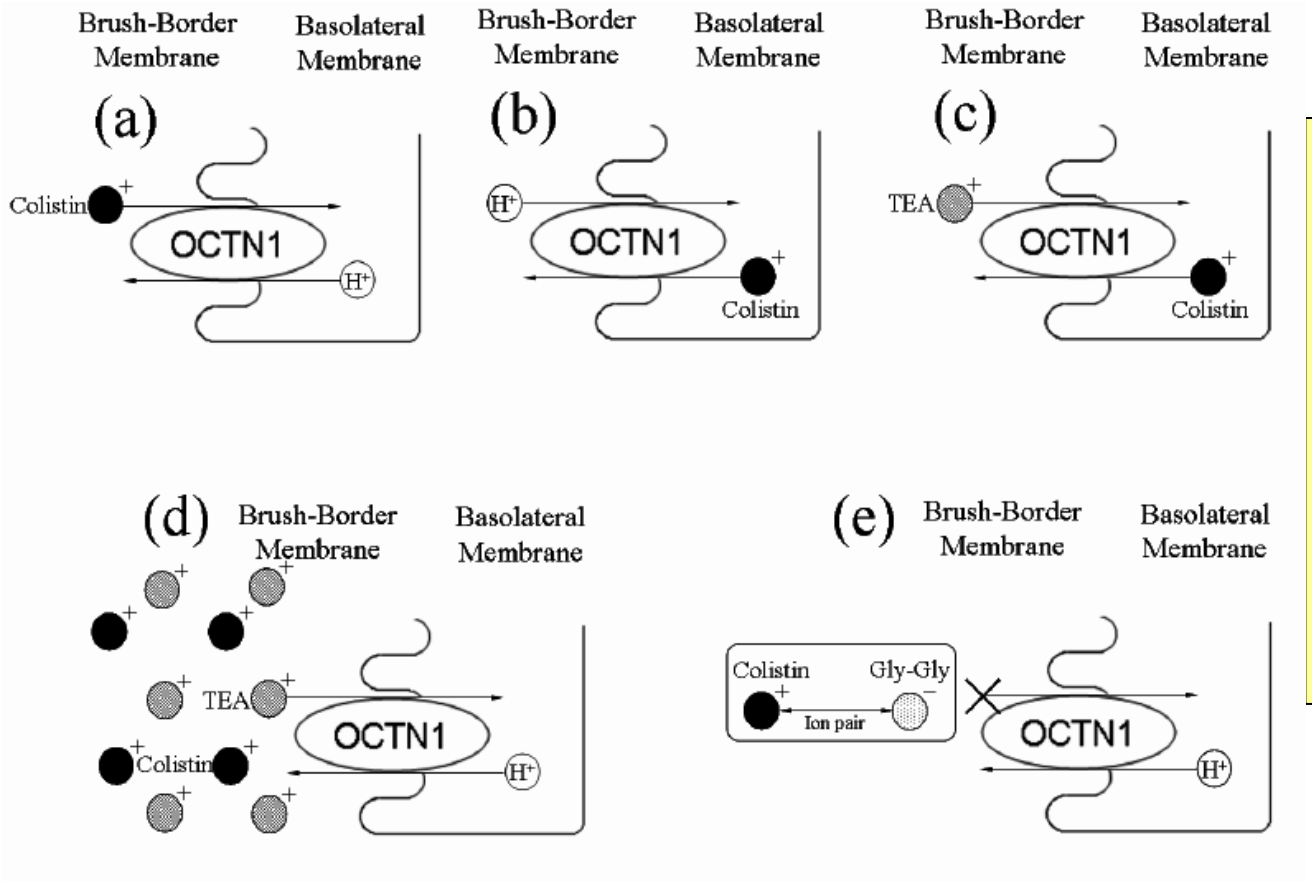


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

Colistin toxicodynamics



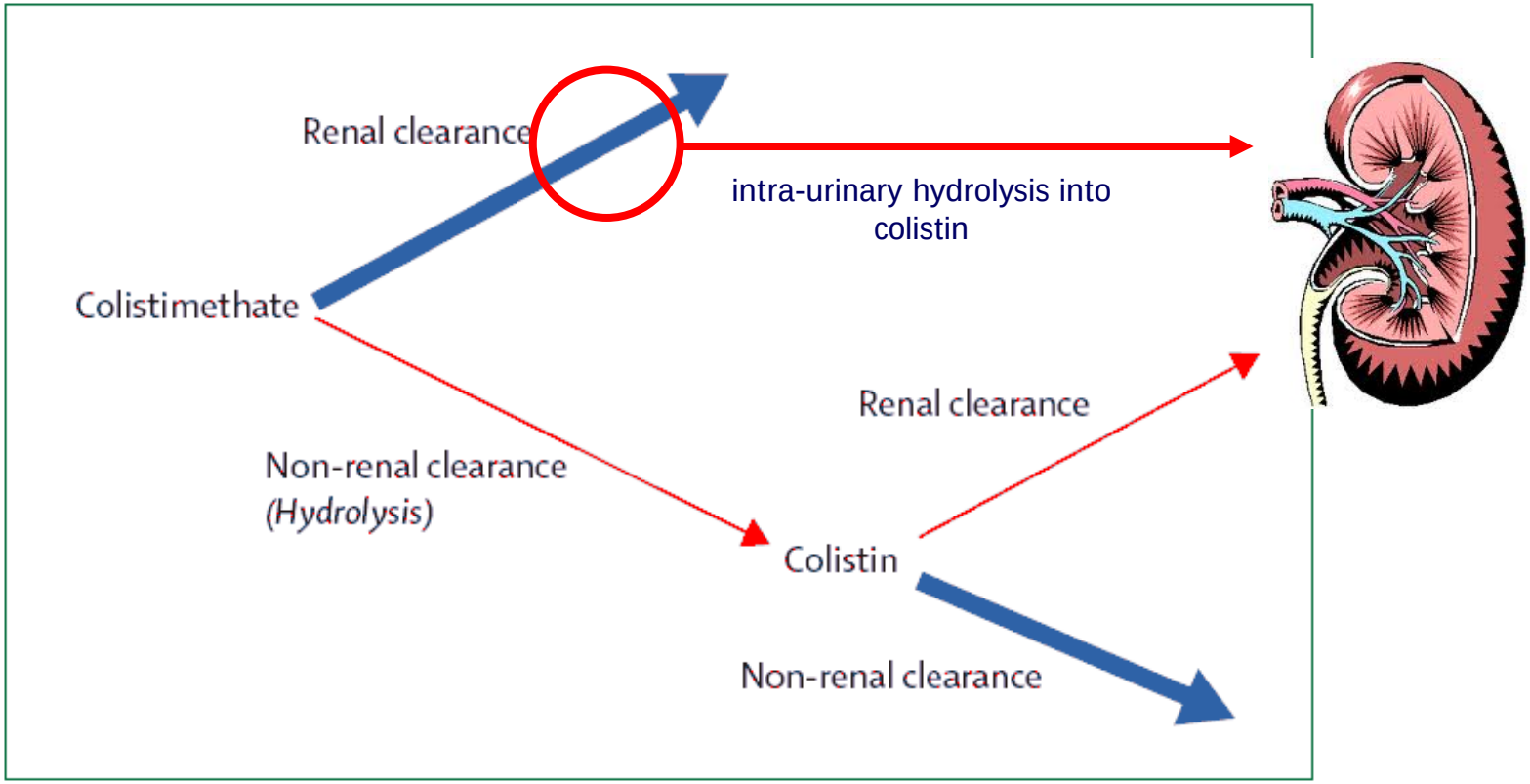
Schematics of possible mechanisms for the renal tubular transport of colistin

Notes:

- **Uptake is very efficient (> 60 %)**
- **Competition requires high doses**
- **The model is also compatible with a megalin-mediated uptake**

Zheng et al. Renal disposition of colistin in the isolated perfused rat kidney. Antimicrob. Agents Chemother. 2009; 53:2857-2864

Colistin nephrotoxicokinetic is complex…



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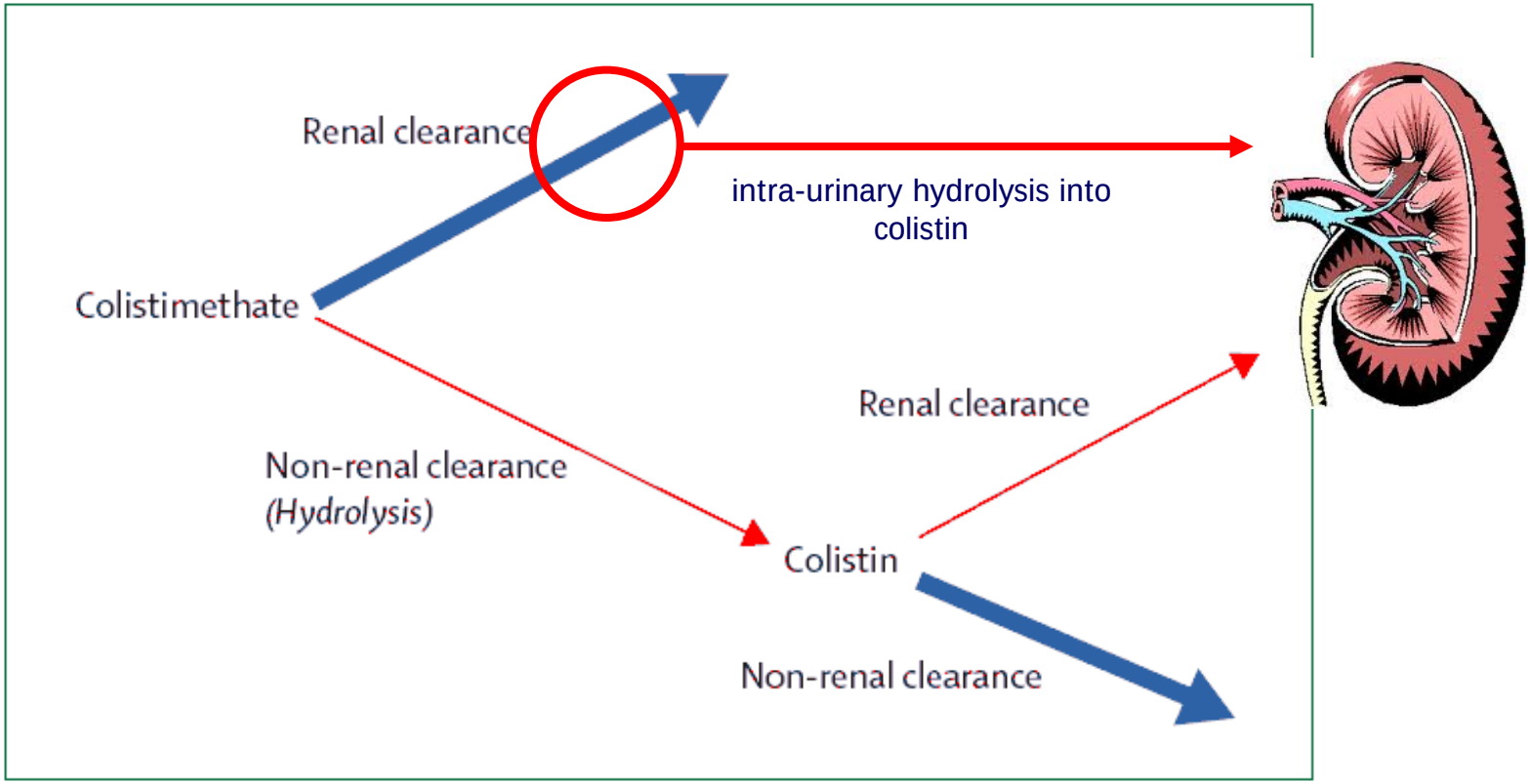

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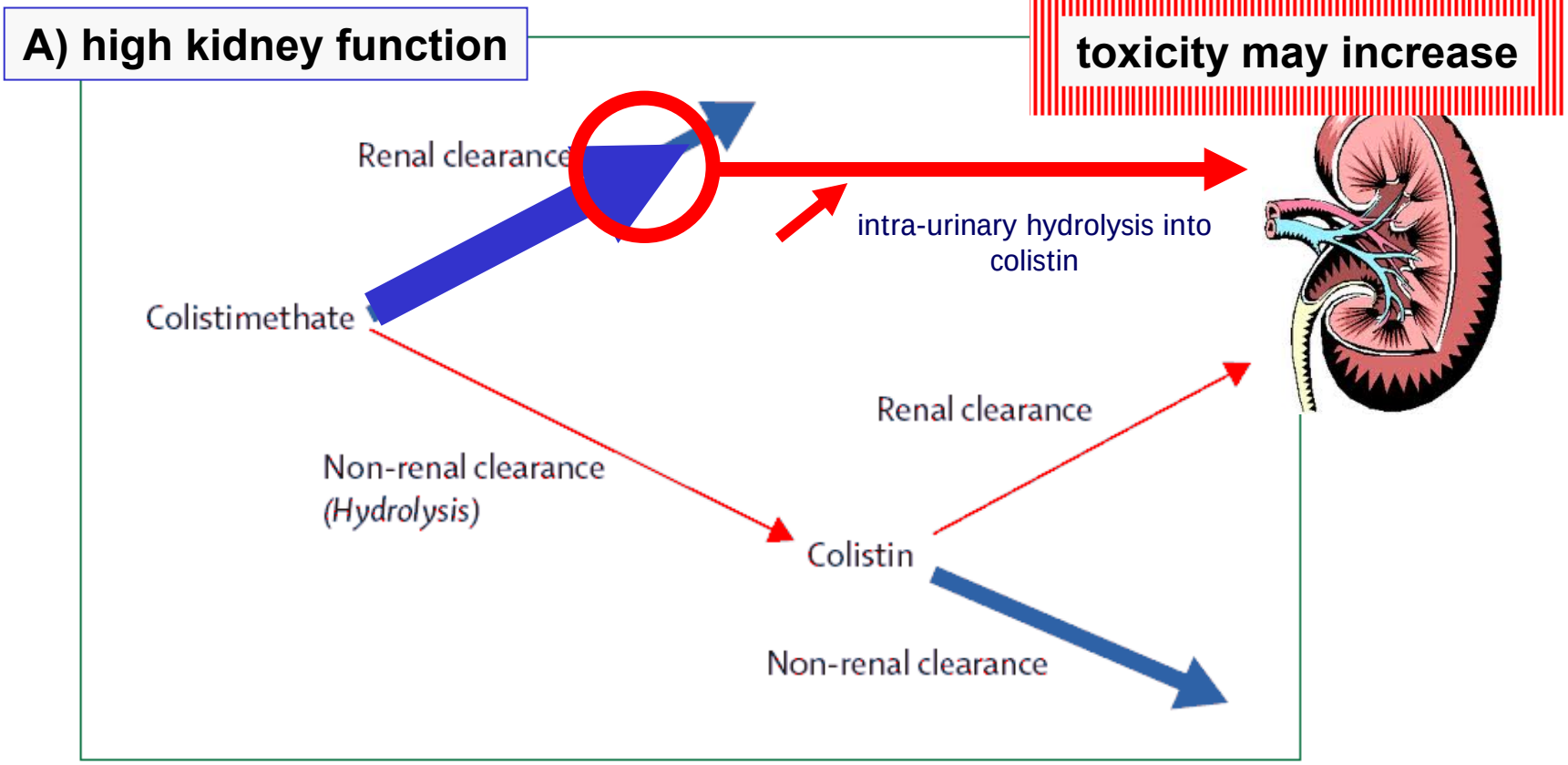

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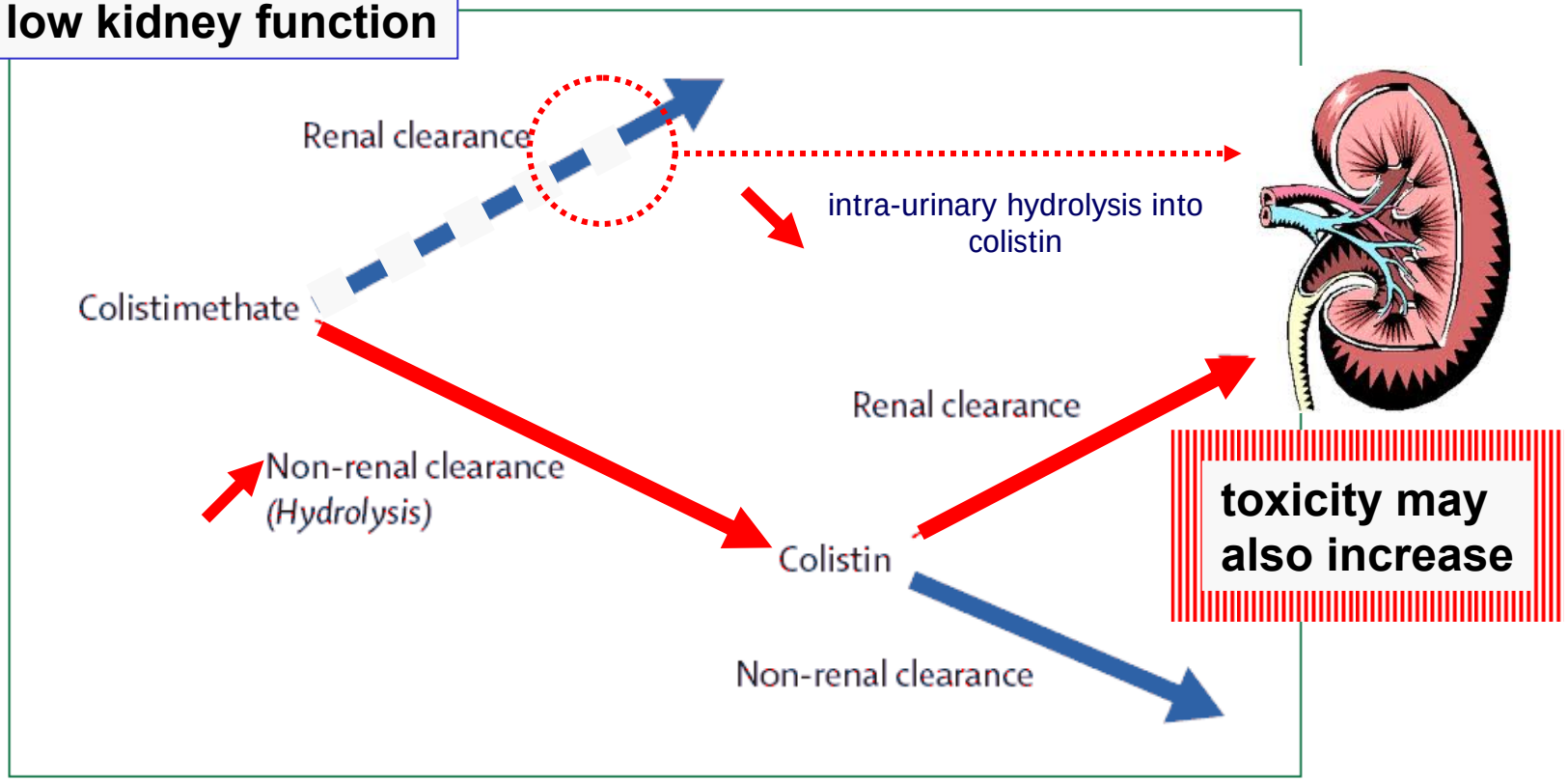
Li et al. Lancet Infect. Dis. 2006; 6:589-601 (modified)

Colistin nephrotoxicokinetic is complex…

B) low kidney function



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

Colistin nephrotoxicity

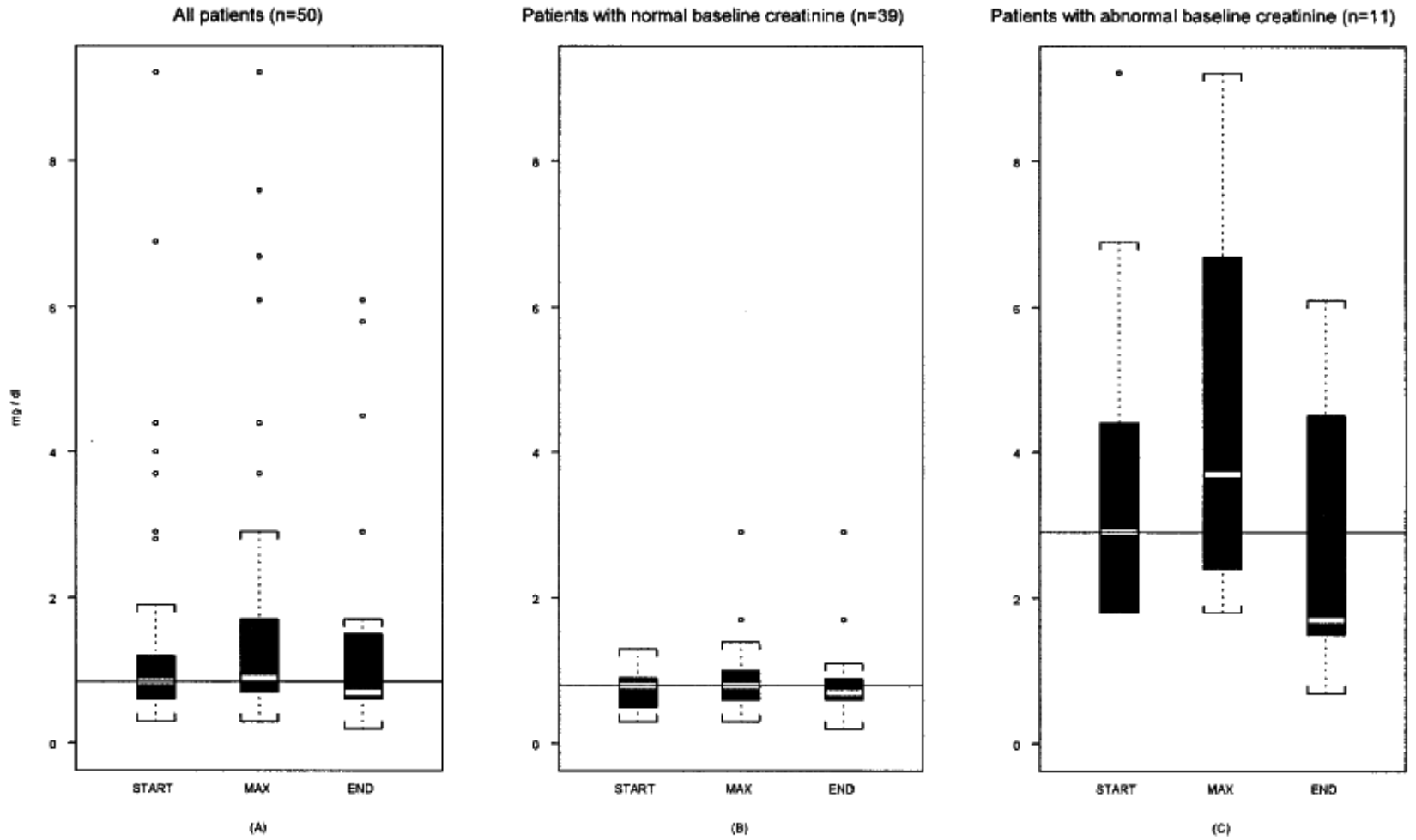

FIG. 1. The distribution of serum creatinine levels on the first day of colistin treatment (START), at the peak value (MAX), and at the end of colistin treatment (END) in all studied patients (A), in the group of patients with normal baseline creatinine values (B), and in the group of patients with abnormal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

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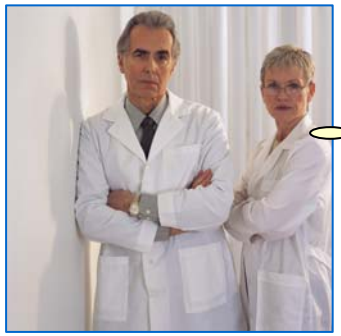


Is 4 mg/L really "susceptible" ?

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

*Corresponding author. Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petach Tikva, 49100, Israel. Tel: +972-3-9377512; Fax: +972-3-9377513; E-mail: paulm@post.tau.ac.il

Received 6 January 2010; returned 14 January 2010; revised 9 February 2010; accepted 12 February 2010

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

A recent prospective clinical study: efficacy

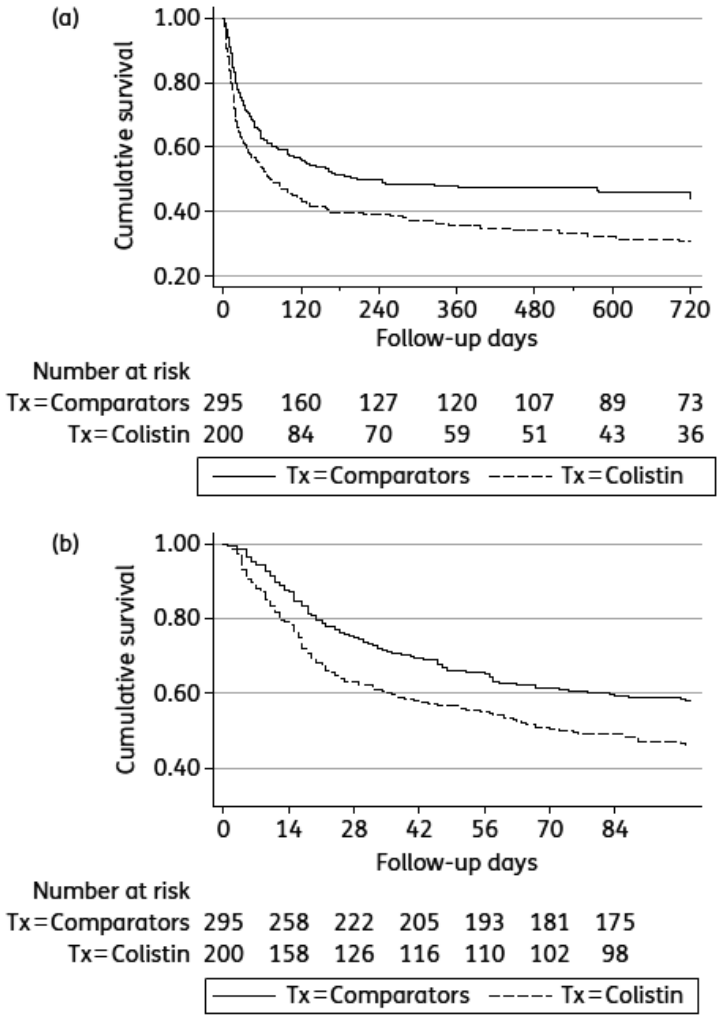


Figure 1. Kaplan–Meier survival analysis, by study arm. (a) Two years of follow-up. (b) Three months of follow-up.

Table 2. Unadjusted 30 day mortality, *n* (%)

	Colistin, *n*=200	Comparators, *n*=295	Unadjusted OR (95% CI)
All patients	78 (39)	85 (28.8)	1.58 (1.08–2.31)
Bacteraemia	45/92 (48.9)	47/128 (36.7)	1.65 (0.96–2.84)
No overlap	66/158 (41.8)	62/229 (27.1)	1.93 (1.26–2.97)
Main pathogen group			
Acinetobacter baumannii	39/107 (36.4)	53/178 (29.8)	1.35 (0.81–2.25)
Klebsiella pneumoniae	40/104 (38.5)	18/80 (22.5)	2.15 (1.12–4.15)

* Paul et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother. 2010 May;65(5):1019-27 PubMed PMID: 20299494.

A recent prospective clinical study: efficacy with adjustment for co-variables

Table 4. Adjusted survival analysis

	HR (95% CI)[a]	
Risk factor	all patients, $n=495$	bacteraemia, $n=220$
Colistin arm of the study	1.27 (1.01–1.60), $P=0.049$	1.65 (1.18–2.31), $P=0.004$
Age[b]	1.03 (1.02–1.04), $P<0.001$	1.02 (1.01–1.04), $P<0.001$
McCabe score		not significant
no fatal disease	0.53 (0.38–0.73), $P<0.001$	
ultimately fatal disease	0.65 (0.47–0.90), $P=0.001$	
rapidly fatal disease	reference	
Independent functional capacity on admission	0.80 (0.62–1.05), $P=0.104$	not significant
Hospitalization in medical ward at onset of infection	1.56 (1.19–2.05), $P=0.001$	2.37 (1.61–3.50), $P<0.001$
Mechanical ventilation at onset of infection	not significant	1.44 (0.95–2.18), $P=0.085$
Bacteraemia	1.37 (1.08–1.73), $P=0.008$	not relevant
SOFA score at onset of infection[b]	1.13 (1.09–1.18), $P<0.001$	1.12 (1.05–1.18), $P<0.001$
Albumin at onset of infection[b]	0.79 (0.62–0.99), $P=0.049$	not significant

[a]Cox backward regression survival analysis, forcing treatment arm into the final model, likelihood ratio test χ^2 206.0, df 9, $P<0.001$ for all patients. Variables included in the model and not retained in the final model included: trauma as the admission diagnosis; urinary tract infection or surgical site infection as the source of the index infection; presence of nasogastric tube; urinary catheter at infection onset; and those listed as not significant in the table.
[b]Continuous variable, increment of 1 year (age), 1 point (SOFA) and 1 g/dL (albumin).

* Paul et al. Effectiveness and safety of colistin: prospective comparative cohort study. J Antimicrob Chemother. 2010 May;65(5):1019-27

A recent prospective clinical study: undesired effects (*)

Table 5. Secondary outcomes

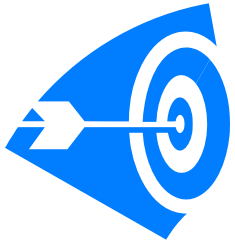
	Colistin	Comparators	*P* value
Development of septic shock, *n/N* (%)	71/200 (35.5)	62/295 (21)	<0.001
Renal failure[b], *n/N* (%)			
week 1	26/168 (15.5)	17/244 (7)	0.006
week 2	23/152 (15.1)	15/227 (6.6)	0.007
week 4	13/128 (10.2)	10/198 (5.1)	0.079
new need for haemodialysis after onset	12/200 (6)	15/295 (5.1)	0.660
Development of resistance[c], *n/N* (%)			
index bacteria, resistance to study drug at 3 months	16/158 (10.1)	48/229 (21)	0.005
any Gram-negative resistant to colistin at 3 months	42/158 (26.6)	36/229 (15.7)	0.009
Proteus spp. at 3 months	35/158 (22.2)	29/229 (12.7)	0.014

*** with p values ≤ 0.05**

If colistin had to be submitted for registration today …

A few problems…

- Pharmaceutical aspects:
  - uncertainties about the composition and strengths of the medicinal product offerings
- Microbiology:
  - High risk of failures by loss of bacterial susceptibility (regrowth and development of resistance)
- Preclinical safety:
  - Uncertain and incomplete animal safety testing
- Preclinical assessment of efficacy:
  - Incomplete and often unconvincing pharmacokinetics/pharmacodynamic parameters
- Clinical safety:
  - Uncertainties about the true human nephrotoxic potential and definite risk of emergence of resistance
- Clinical effectiveness:
  - incomplete clinical development



if colistin is your last option …

- a repeated dosage of 150 mg colistimethate (2 x 10^6 U or 66 mg colistin base) every 8h is probably the best option …
- A loading dose (additional 2 to 4 x 10^6 U at first dose) 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 it in the first place !

Disclosures

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 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.