

Colistin

pharmacokinetics/pharmacodynamics

with an introduction and comments about
reasonable uses

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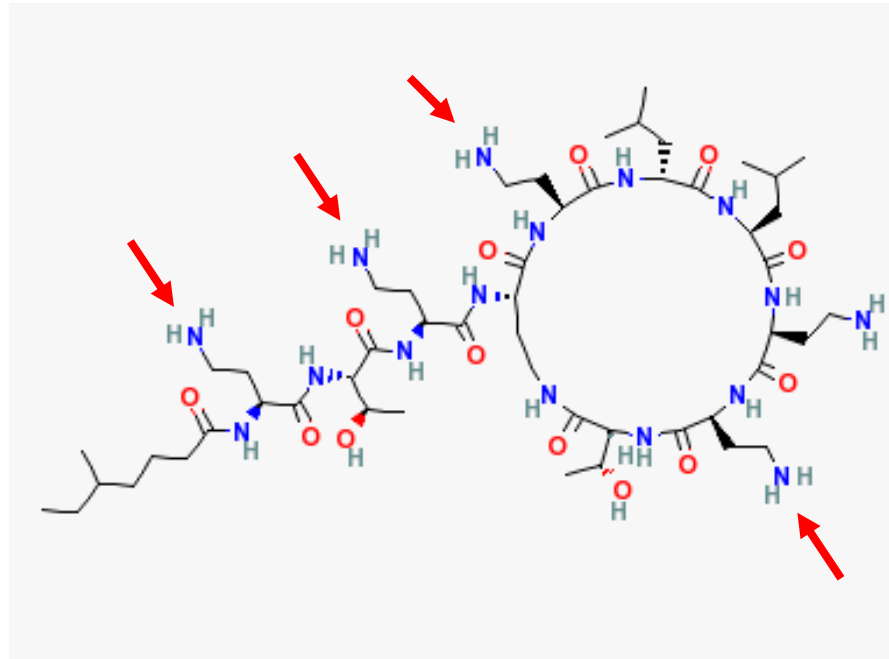


Contents of the presentation

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

as you can see, many " ? "

What is (exactly) colistin in its active form ?



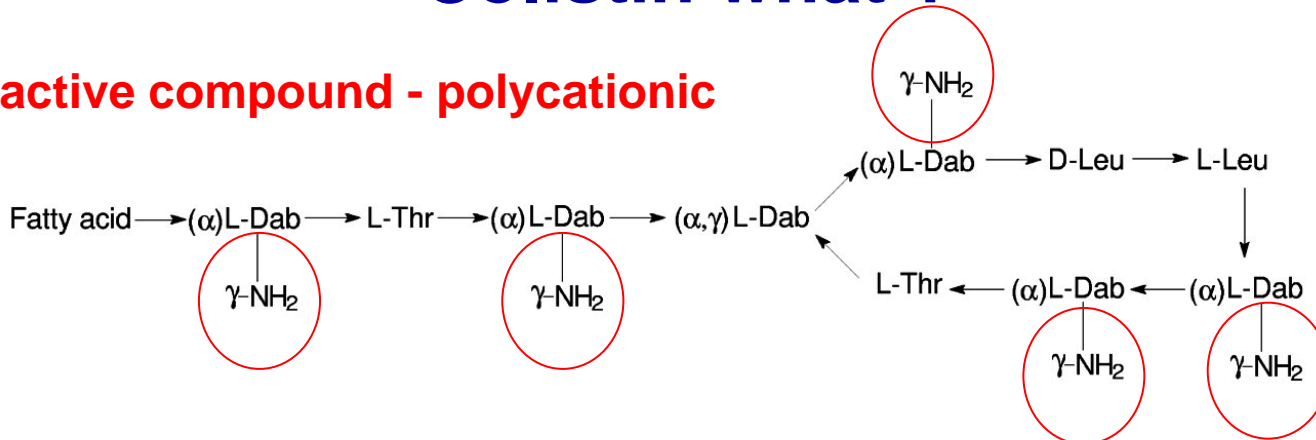
- A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain
- which **interacts with the lipopolysaccharide (LPS)** of the outer membrane of Gram-negative bacteria, triggering a "self-promoted uptake" process
- and **displaces Ca^{++} and Mg^{++}** , which further destabilizes microbial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

Colistin History

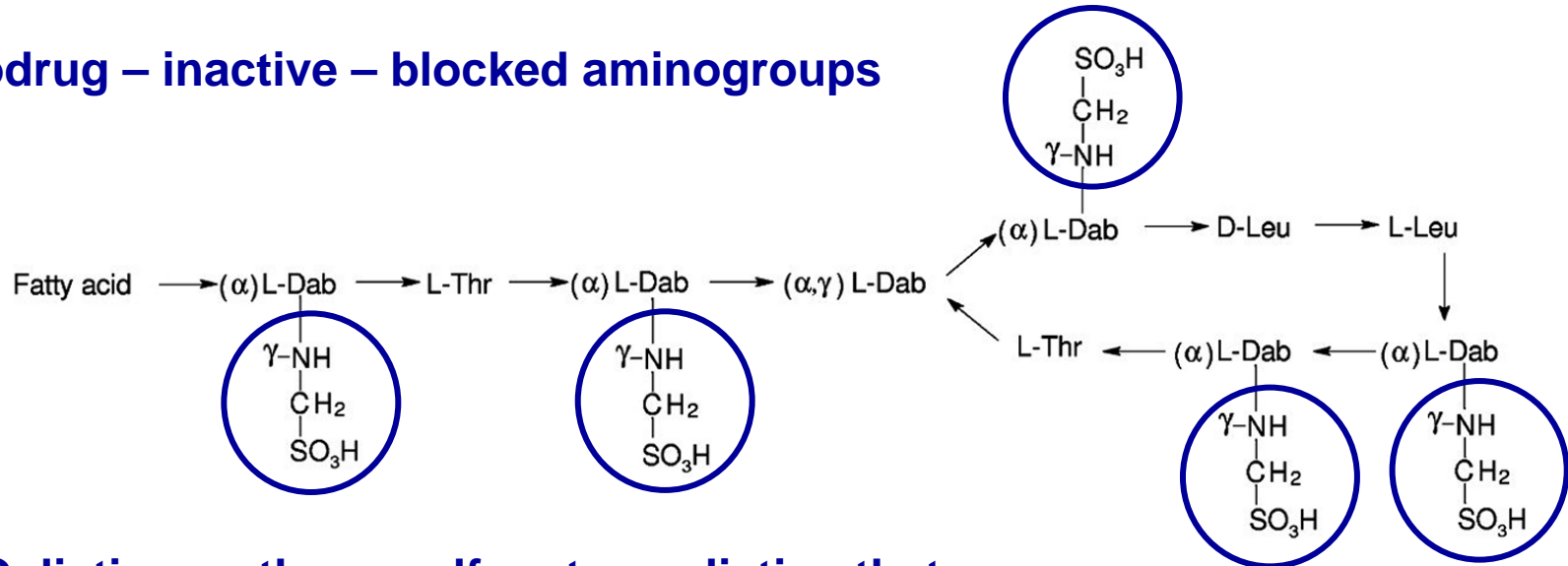
- Isolated in Japan in 1949 from *Bacillus polymyxa* var. *colistinus* and indentified as **polymyxin E** (discovered in 1947 among polymyxins (A to E)).
- Differs from polymyxin B by only one aminoacid (D-Phe replaced by D-Leu)
- Exists under at least 2 components (E1 and E2, also called colistin A and colistin B) differering 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 disposition

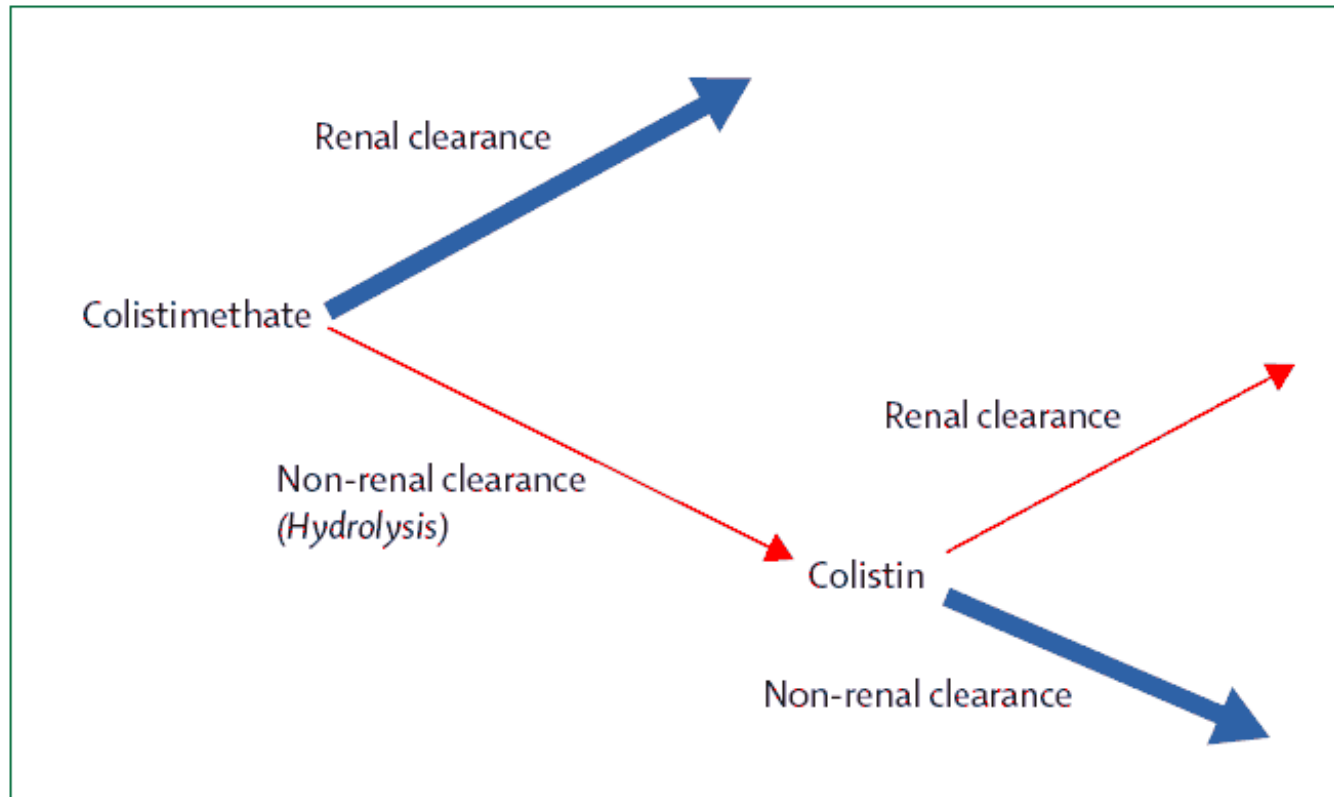


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

Colistin: mg and units ...

- Colistin: 10^6 units are
 - Colistin base: 33.3 mg
 - Colistin sulfate: 50 mg
 - Colistin methane sulfonate: 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

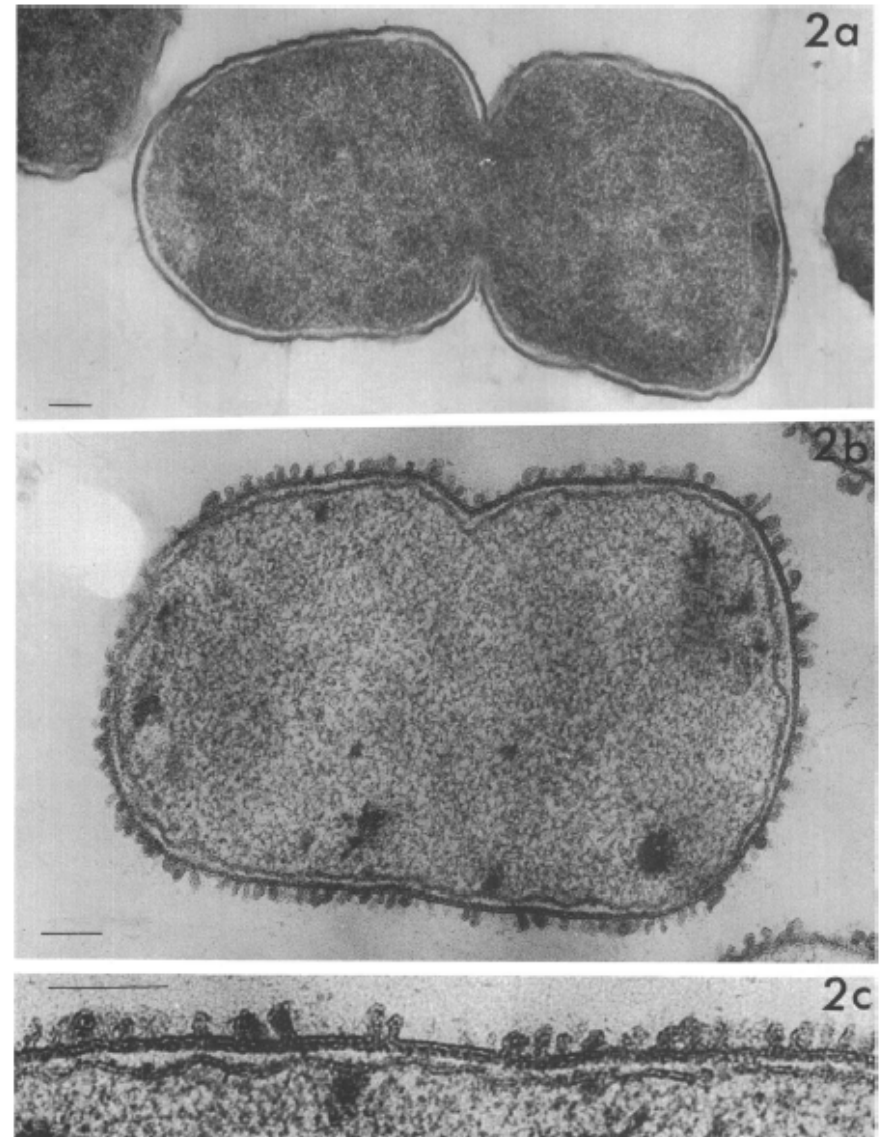
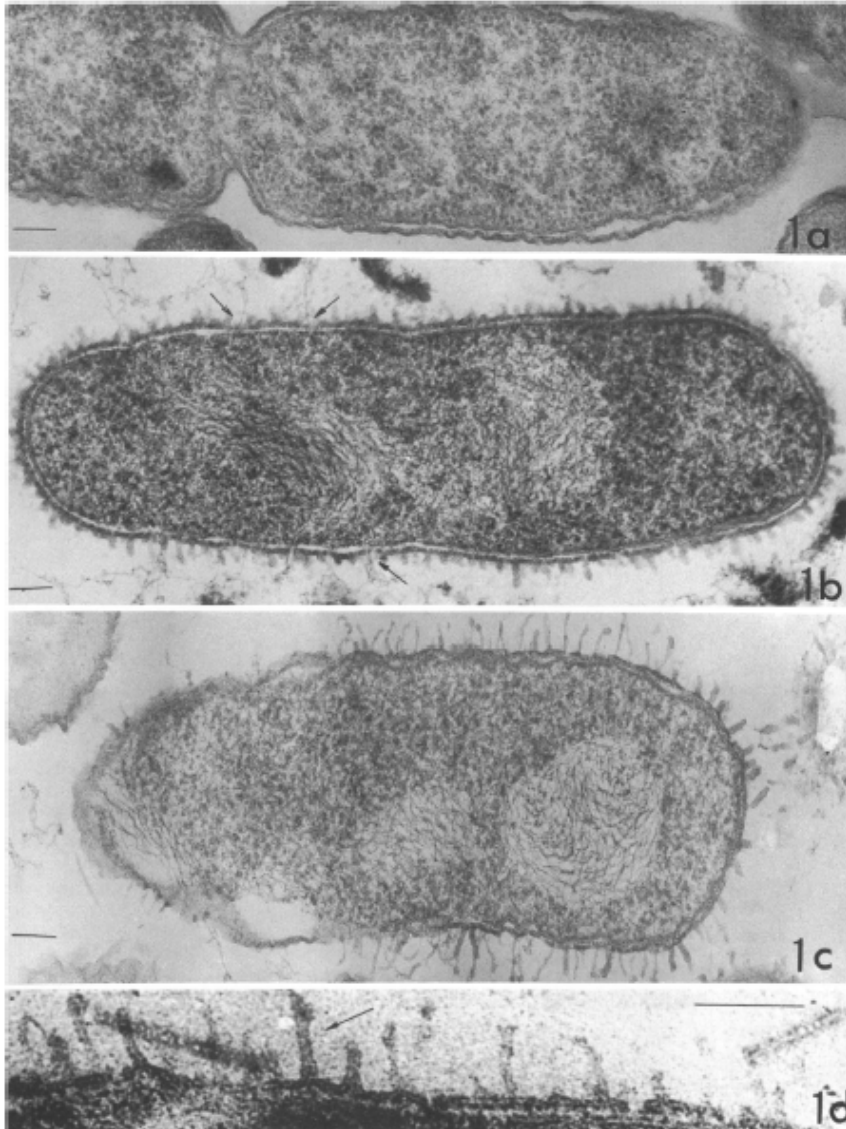
Colistin Microbiology

as defined in the late 1960's

- About 10 x more active against Gram-negative than Gram-positive bacteria
(but inactive against *Burkholderia cepacia*, *Serratia*, *Proteus*, *Bacteroides fragilis* ... and most Gram-negative cocci [inherent resistance]; synergism with sulfonamides may confer activity; synergy demonstrated with rifampin)
- 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)

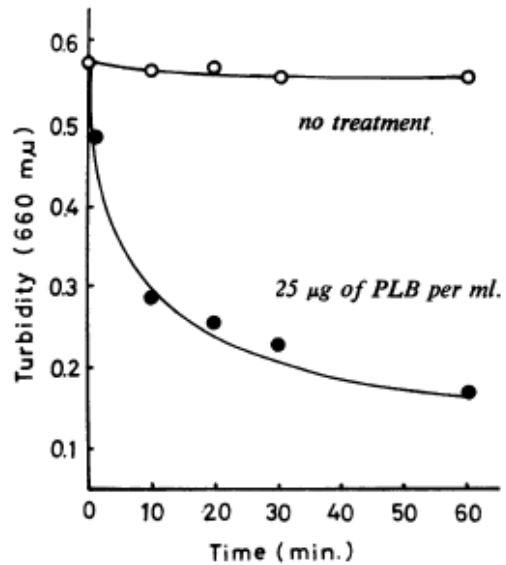
* current EUCAST breakpoint is 2/2 for all species with sufficient data (*P. aeruginosa*, *Enterobacteriaceae*, *Acinetobacter*)

Colistin Microbiology: morphological aspects

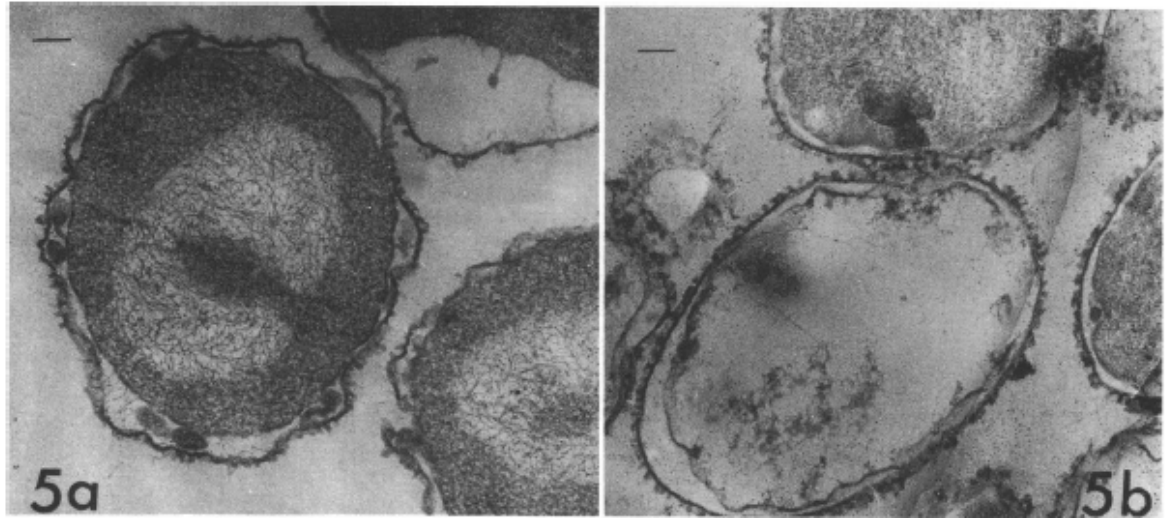


Koike et al. J. Bacteriol. 1969; 97:448-452

Colistin Microbiology: lysis of bacteria



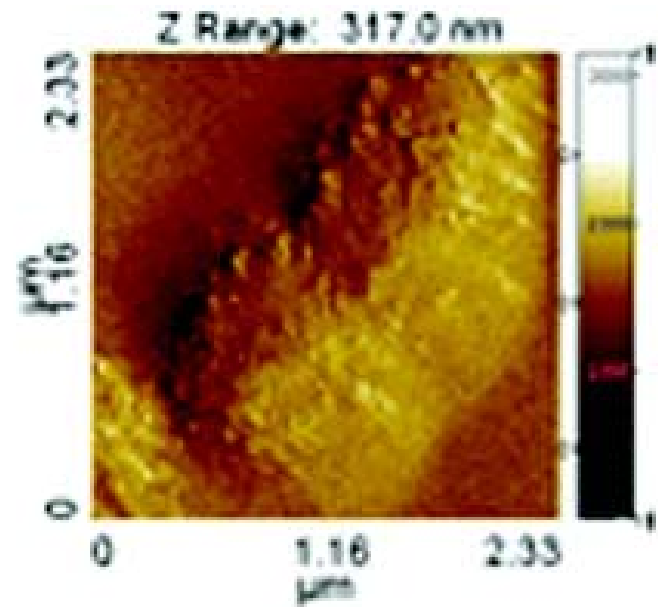
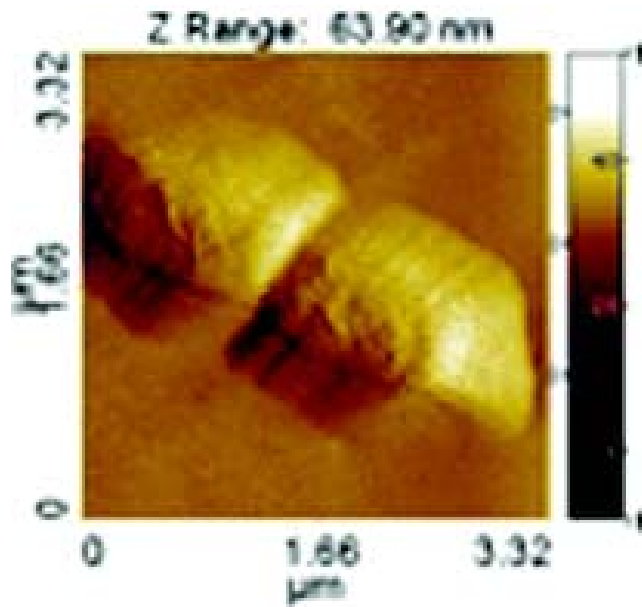
Lysis of the spheroplast of E. coli B



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

Colistin Microbiology: a modern view

Change in surface properties of *P. aeruginosa* upon colistin exposure as seen in atomic force microscopy studies



Colistin gross toxicology

- Colistin methanesulfonate is about 50 to 100 X less toxic in LD₅₀ 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 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)

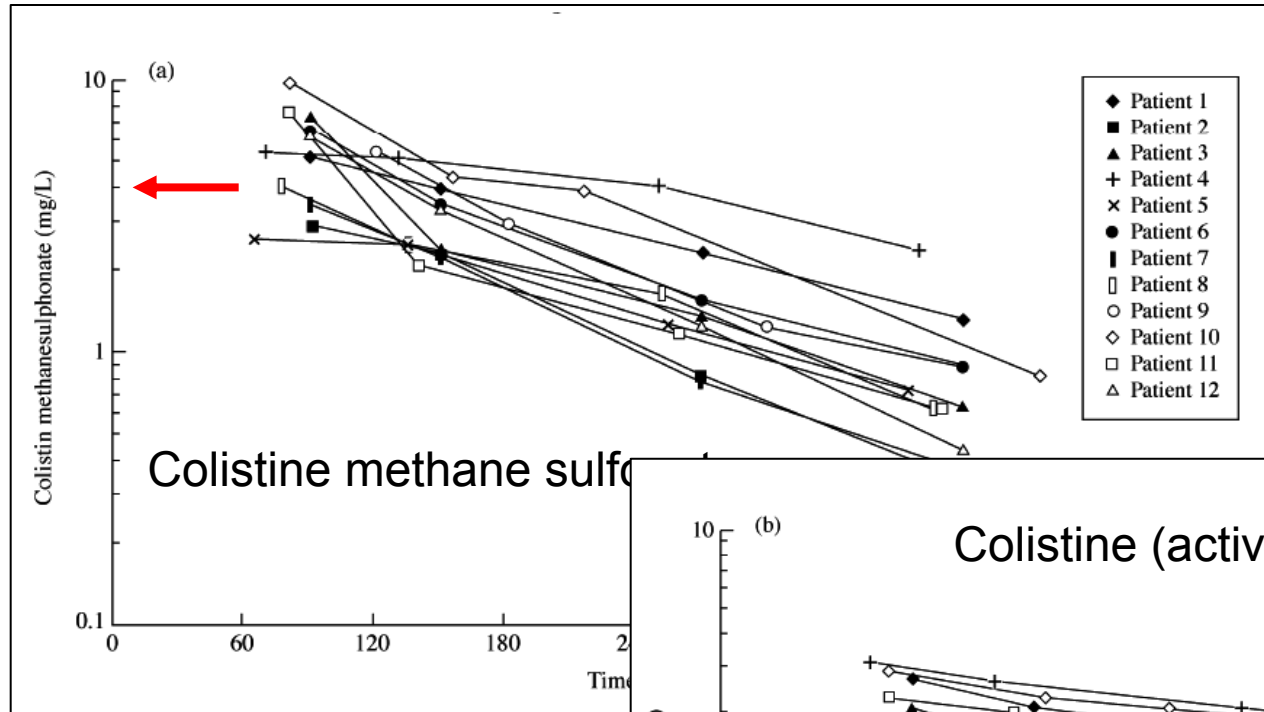
Colistin general pharmacokinetics as published in the late 60's

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 **

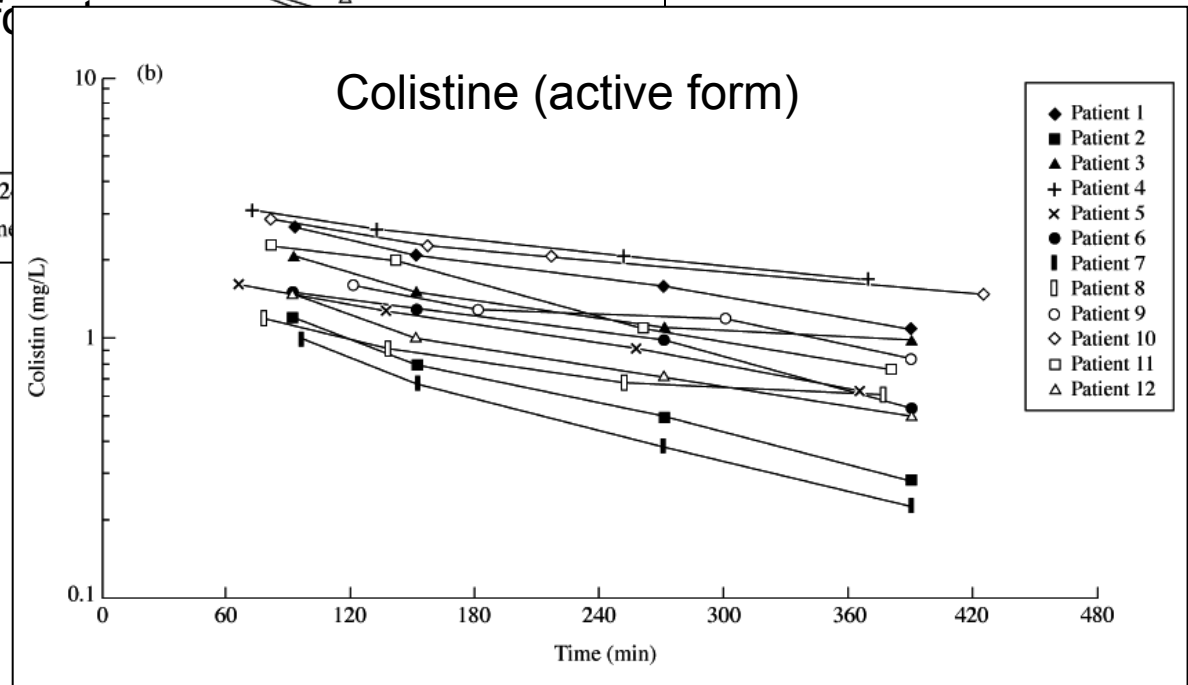
* 25-31,500 Units/kg or ~ 2 x 10⁶ UI

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

Colistin pharmacokinetics in CF patients after treatment with colistin methane sulfonate

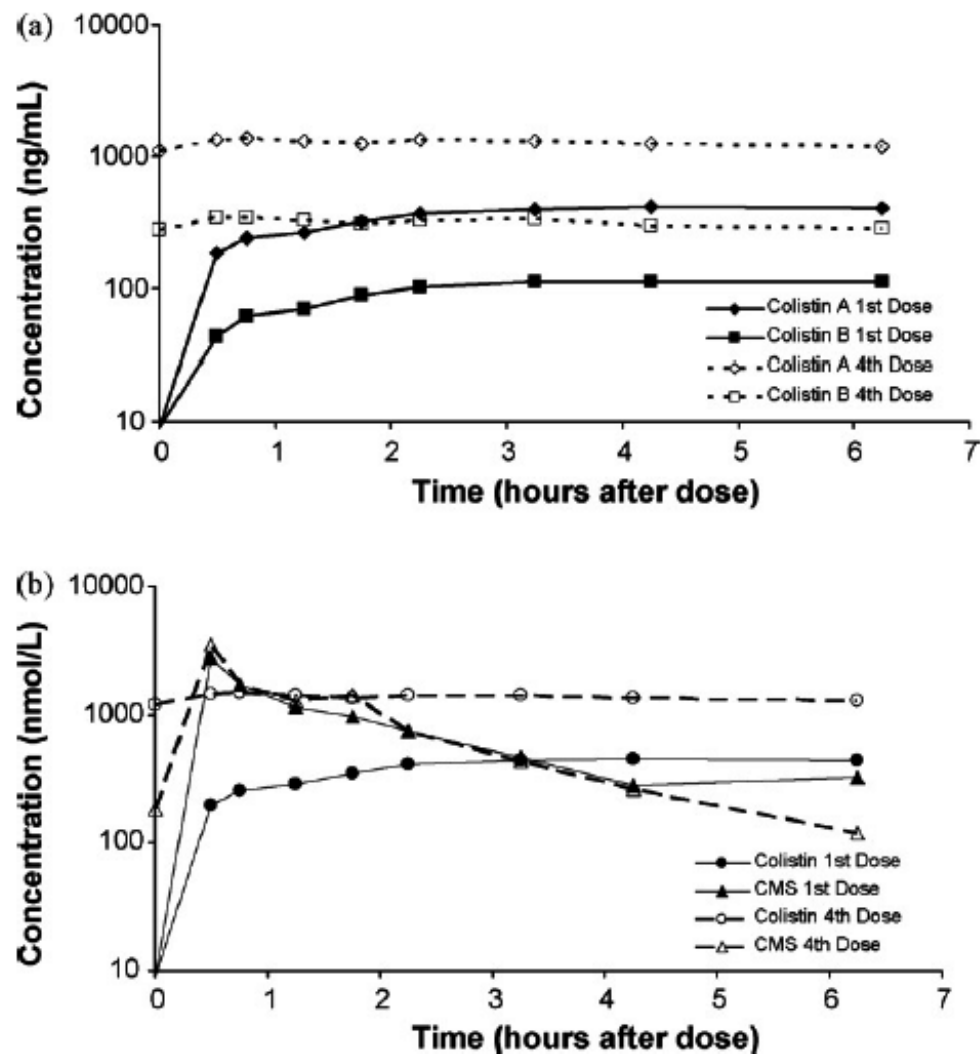


Patients with
160 mg TID
dor > 2 days



A recent progress in the assay of colistine

Differential measurement of colistine methane sulfonate and colistins A and B



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

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 every 8h

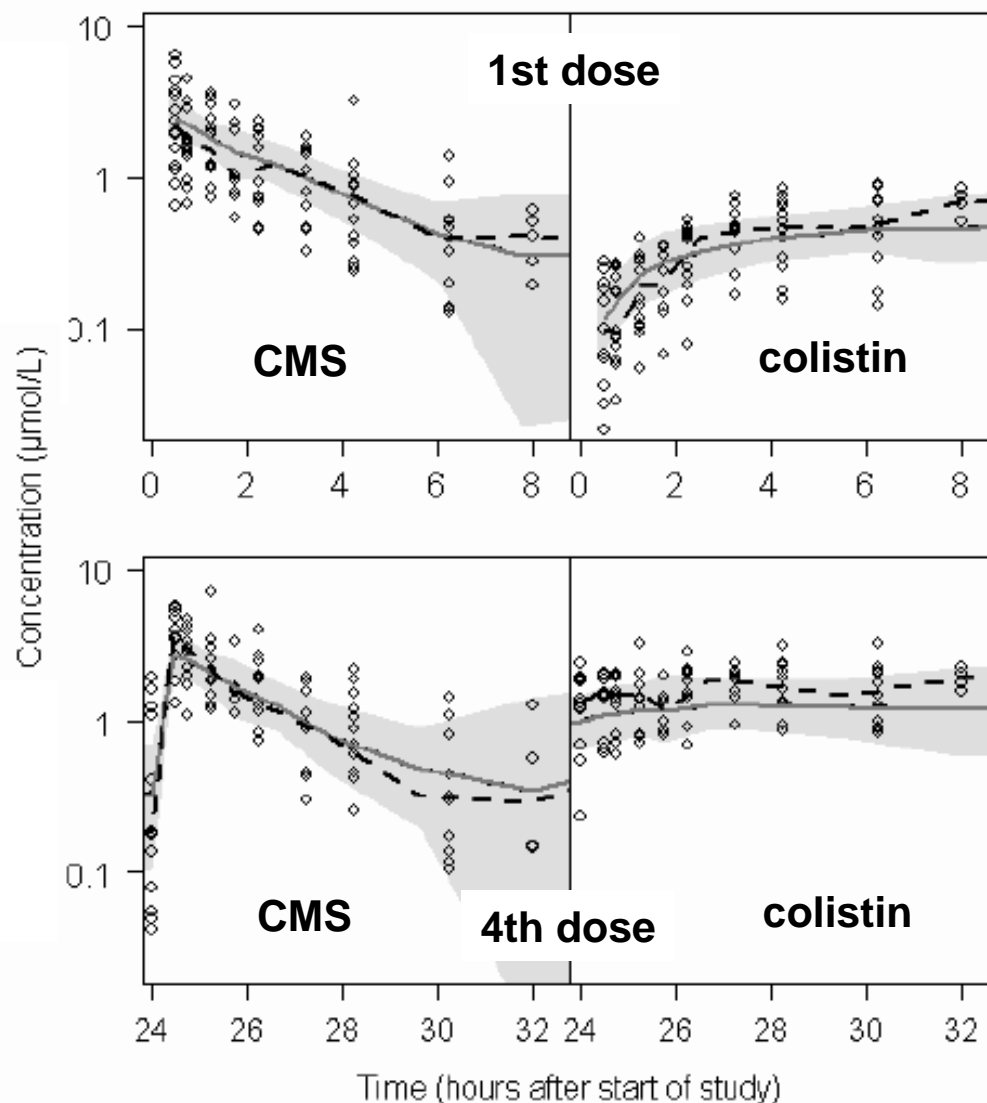
CMS

- $t_{1/2} \sim 2.3$ h,

Colistin:

- $t_{1/2} \sim 14.4$ h.
- C_{max} (pred.)
 - 1st dose: 0.60 mg/L
 - s.s.: 2.3 mg/L.

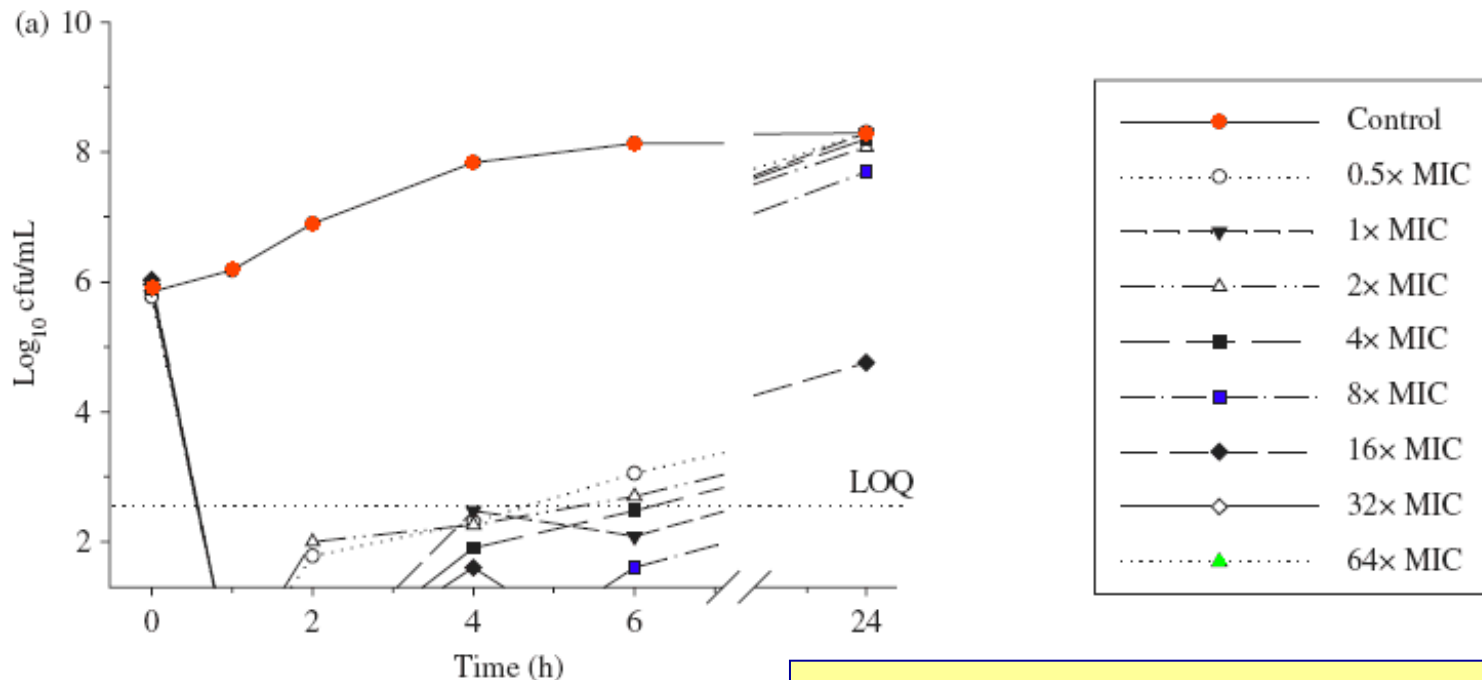
Conclusions: Colistin long half-life and insufficient plasma concentrations before steady state suggest using a loading dose ...



Plachouras et al. AAC 2009; E-pun 11 May

Colistin pharmacodynamics (1)

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



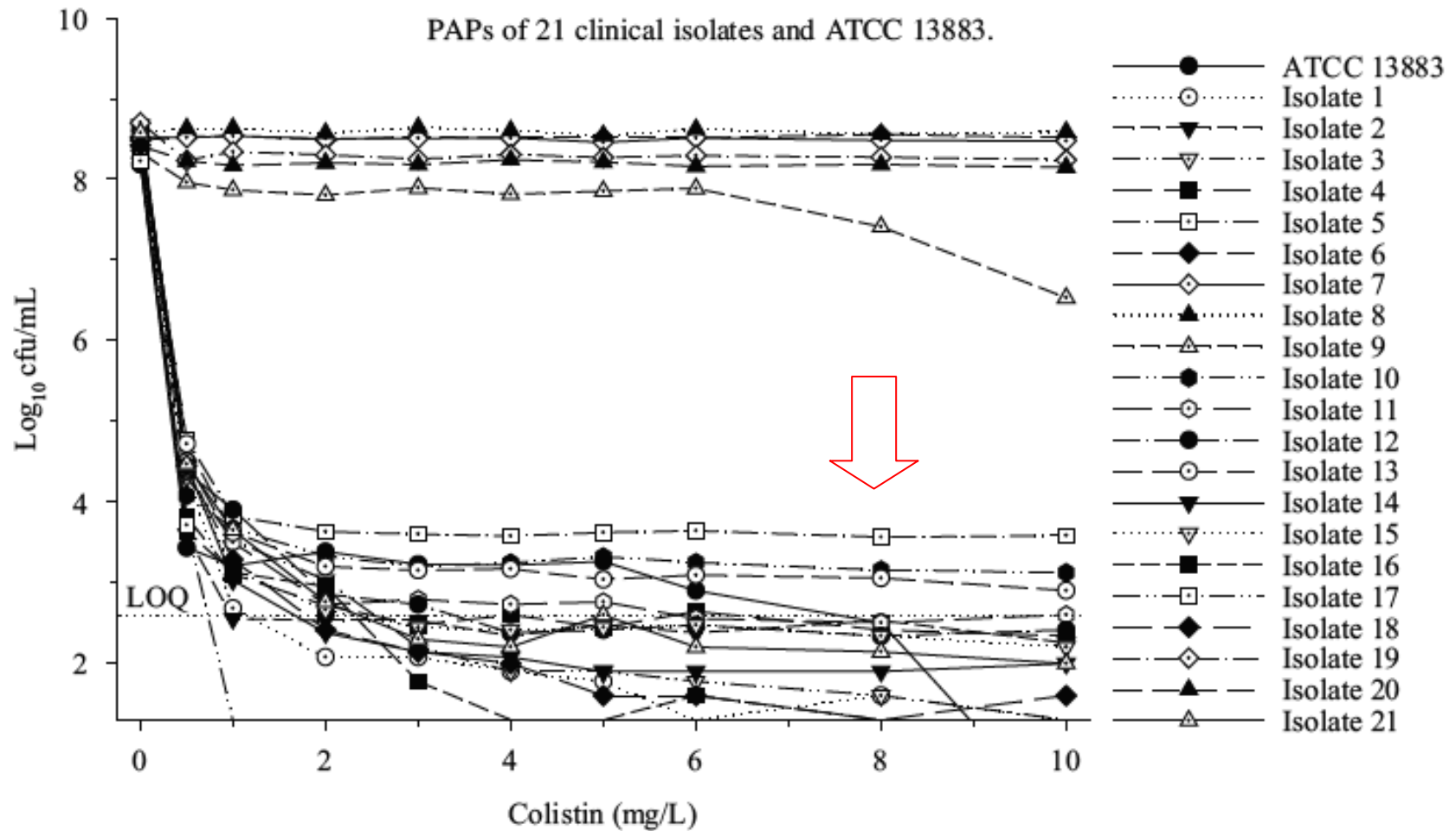
- excellent susceptibility at 2 h...
- **but** regrowth at 24h if conc. ≤ 16 MIC

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)

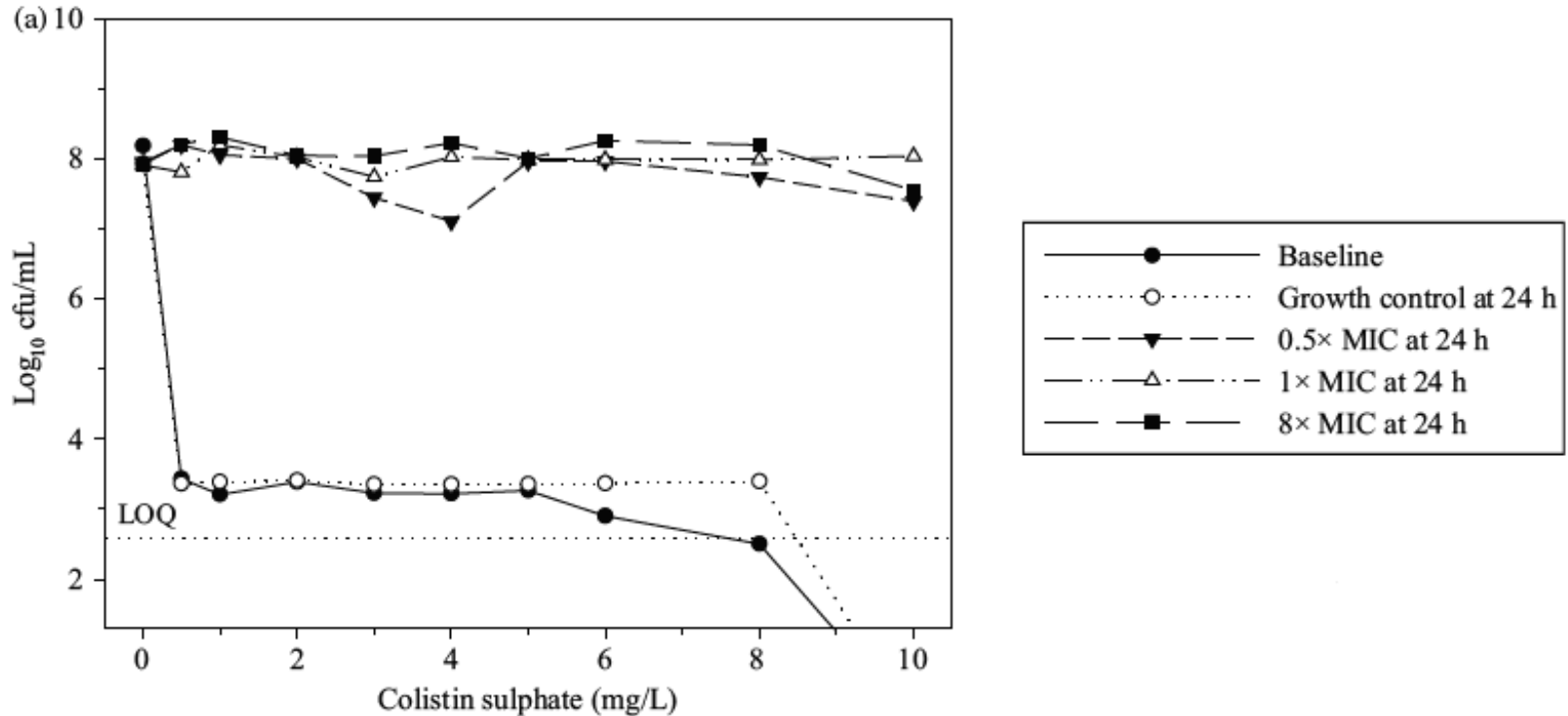
Population analysis profiles of *K. pneumoniae* isolates



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

Colistin pharmacodynamics (3)

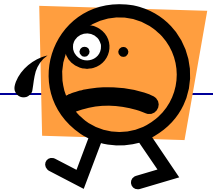
Loss of susceptibility of *K. pneumoniae* after single exposure



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

Colistin pharmacodynamics (4)

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 $64 \times \text{MIC}$ 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*.



Colistin pharmacodynamics and resistance (1)

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

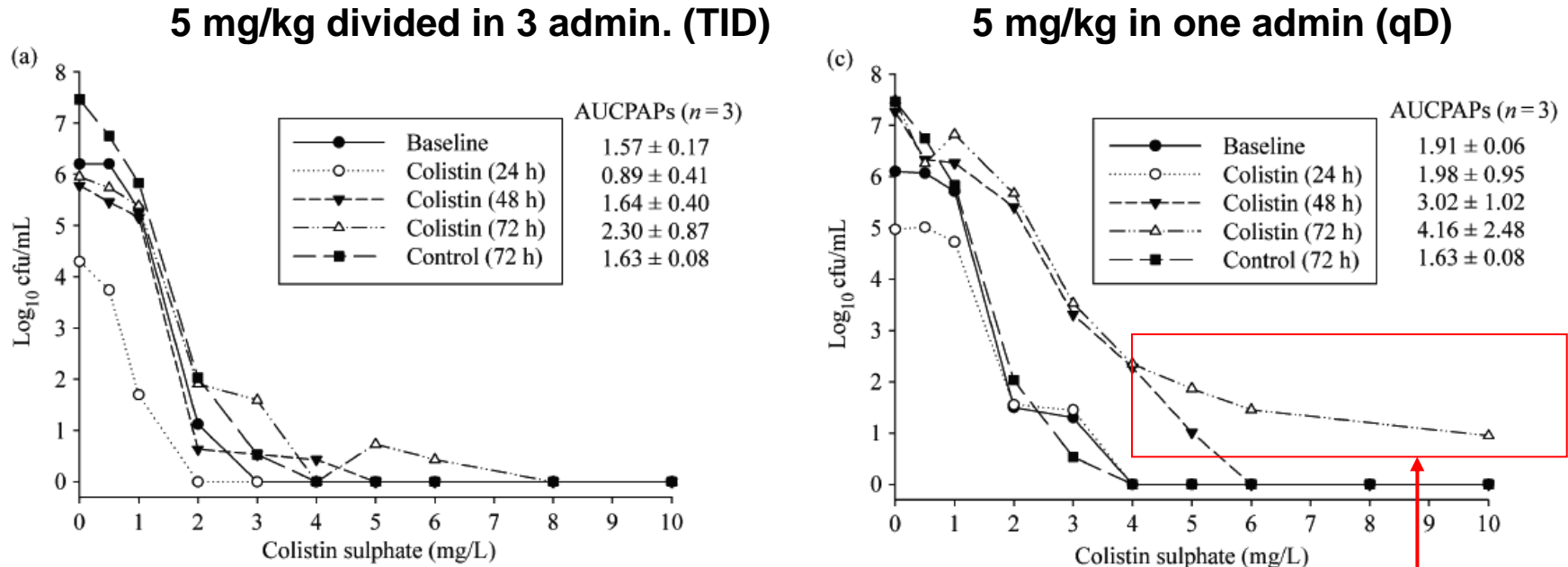


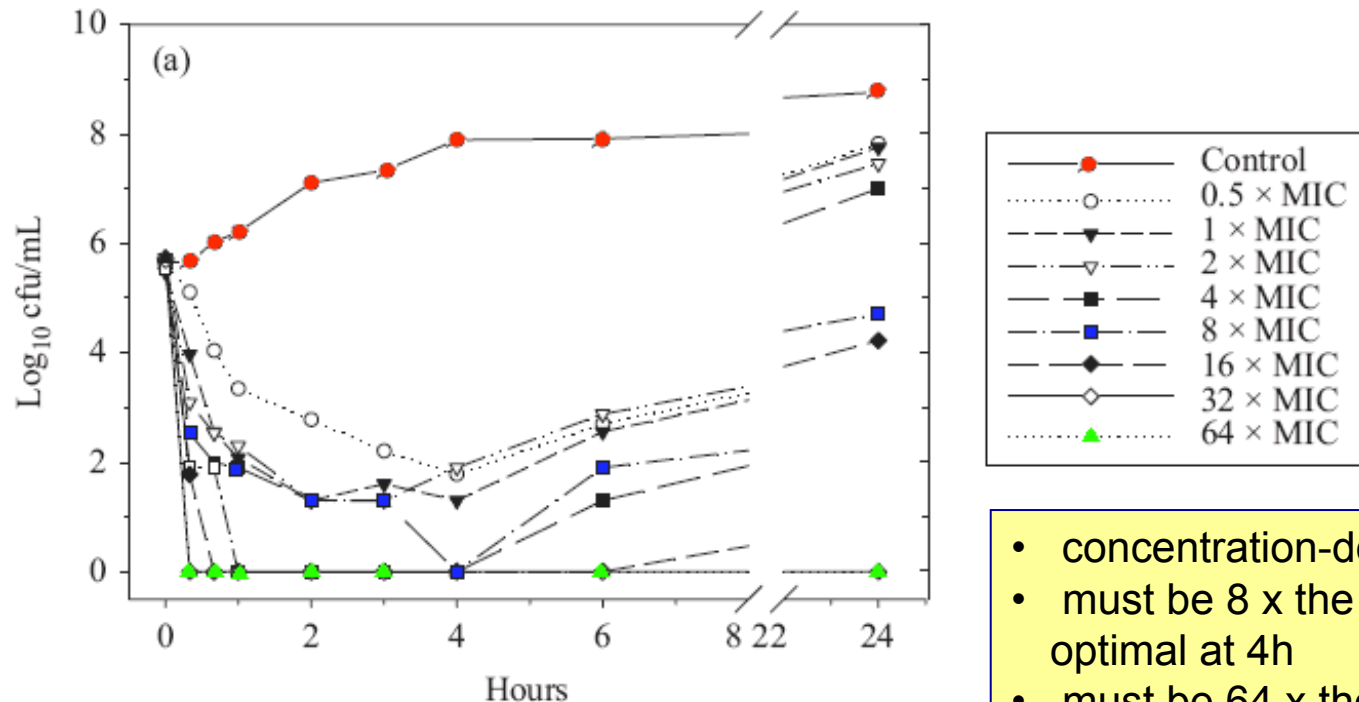
Figure 2. PAPs of ATCC 27853 in the *in vitro* PK/PD model: (a) 8 hourly (c) 24 hourly dosing.

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 (4)

Time kill curves against *A. baumannii*

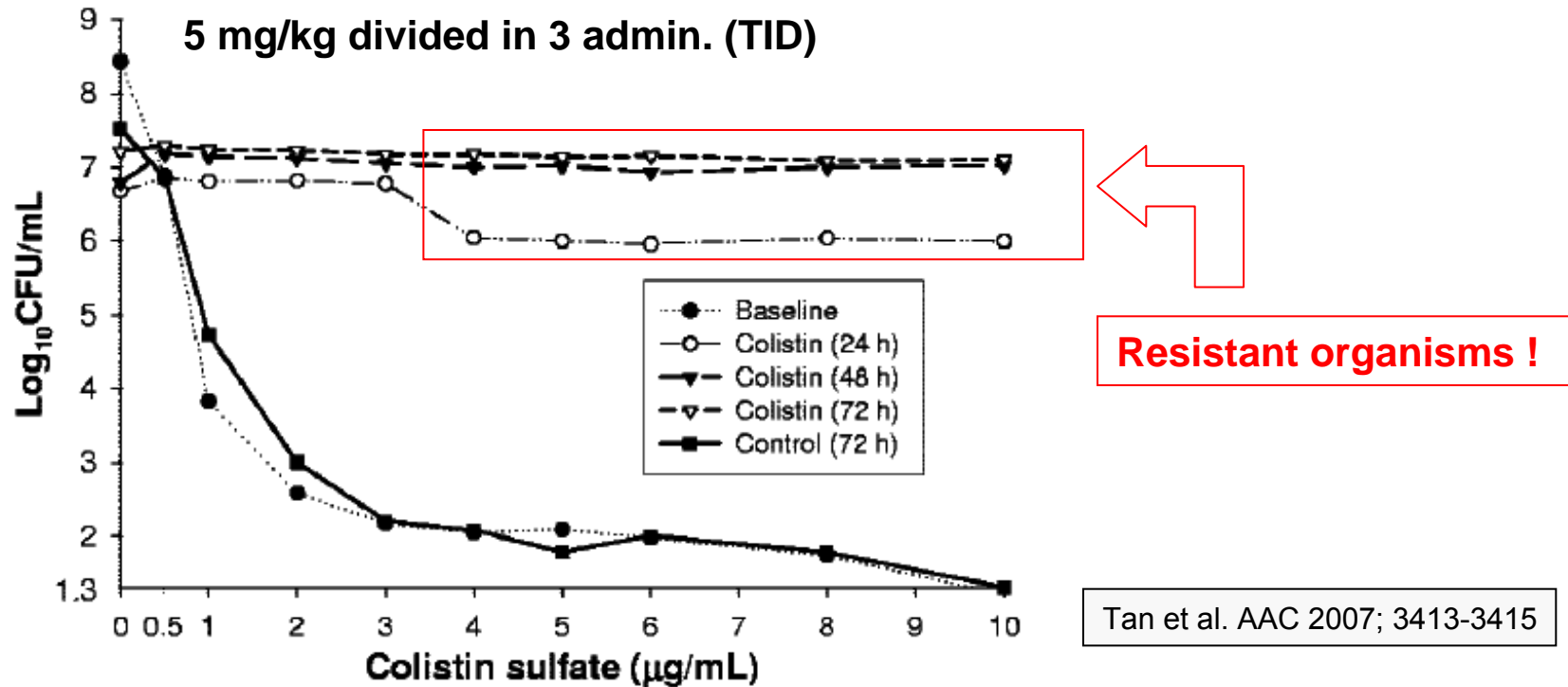


- concentration-dependence
- must be 8 x the MIC to become optimal at 4h
- must be 64 x the MIC to avoid regrowth
- modest post-antibiotic effect (see data in paper)

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*.

Colistin pharmacodynamics and resistance (2)

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



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 log₁₀ CFU/ml of growth control. Population analysis profiles revealed extensive emergence of resistant subpopulations regardless of the colistin regimen.

Colistin pharmacodynamics: conclusions

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

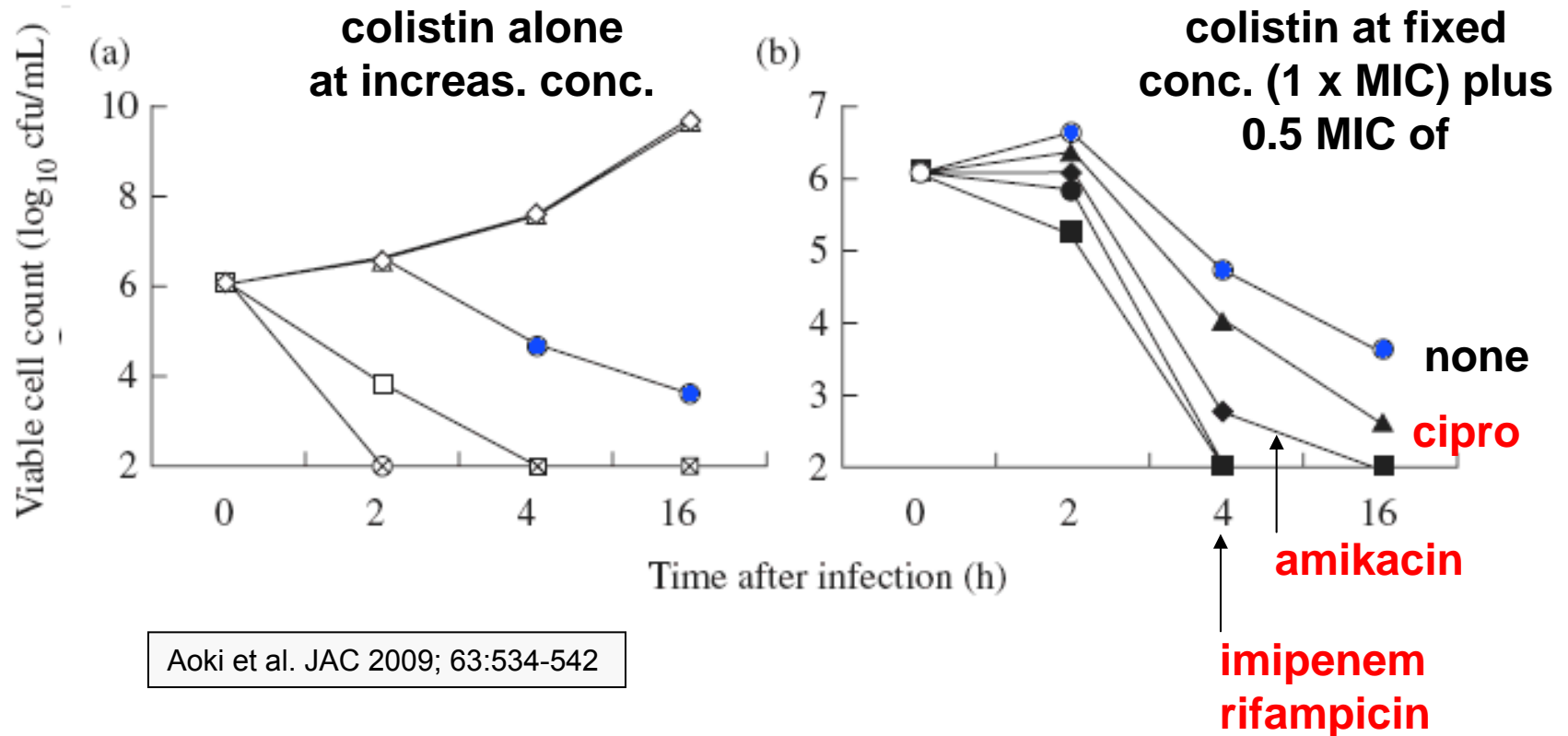
- Displays a **high and fast bactericidal effect** (named today: **concentration-dependent antibiotic**)
- But that its activity "**vanishes after even transient exposure**" (named today: **heteroresistance** and/or **persistence of less susceptible isolates, or adaptative resistance**)
- Needs to be **administered several times a day to avoid regrowth** (which, together with the concentration-dependent effect, will make this antibiotic a new mixture of "**C_{max}**-" and "**Time above x-fold MIC**"- dependent antibiotic)

Question: Could once-daily dosing be effective ?

9 x 10⁶ units (720 mg) qD → 6 mg/L peak level ...

Skiada et al. ECCMID 2009 025

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 *A. baumannii*

Exposure to colistin alone *

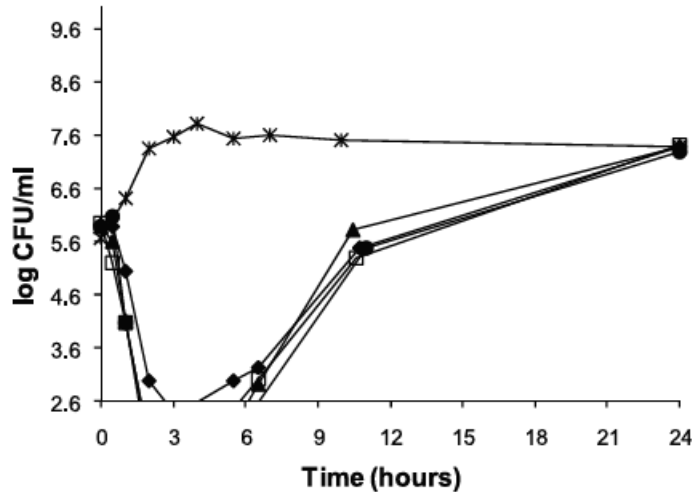


FIG. 1. Time-kill curves of CMS against *A. baumannii* at maximum serum drug concentrations of 3 µg/ml (◆), 6 µg/ml (●), 12 µg/ml (▲), and 24 µg/ml (□). The growth control (×) is also depicted.

* Initial MIC: 0.5 mg/L

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

Exposure to colistin ^a
and ceftazidime ^b

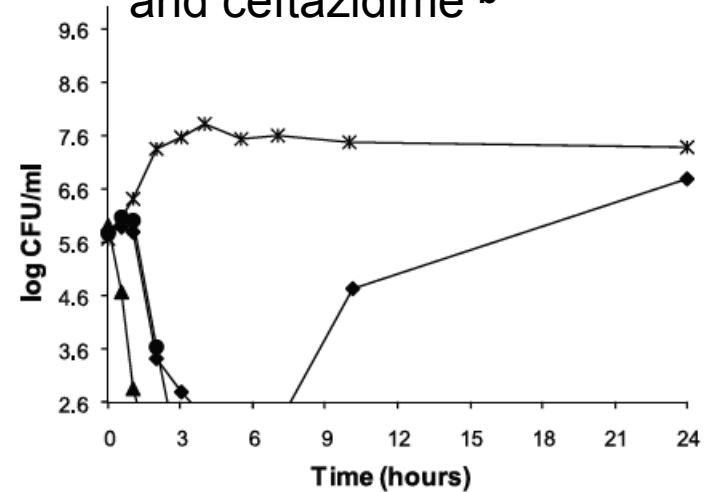


FIG. 2. Time-kill curves of CMS given at time zero plus the addition of continuous-infusion ceftazidime started at 2 h (▲) and continuous-infusion ceftazidime started at time zero plus a CMS bolus given at 2 h (●) against *A. baumannii*. Continuous-infusion ceftazidime given alone (◆) and the growth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

Colistin nephrotoxicity in the old days

- Nephrotoxicity is dose-dependent
(confirmed in 2005: Falagas et al. IJAA 2005; 26:504-507)
- Daily dose should not exceed 5 mg/kg per day...
- Dose / frequency must be decreased case of impaired renal function

	Normal	Mild	Moderate	Severe
Creatinine (mg %)	0.7-1.2	1.3-1.5	1.6-2.5	2.6-4.0
Unit dose	100-150	75-115	66-150	100-150
Frequency	4 - 2	2	2 - 1	every 36h
Total dose daily	300	150-230	133-150	100



Renal toxicity, considered as a major limitation, may be less than anticipated from the original trials (~ **20 %**) but was nevertheless (i) between **8** and **42 %** in the 5 studies summarized by Kasiakou *et al* (AAC 2005; 49:3136-3146) and published between 1999 and 2003; (ii) **30.8 %** in Koomanachai *et al.* (IJID 2007; 11:402-406); **10 %** in Bassetti *et al.* (JAC 2008; 61:417-420)

Colistin nephrotoxicity

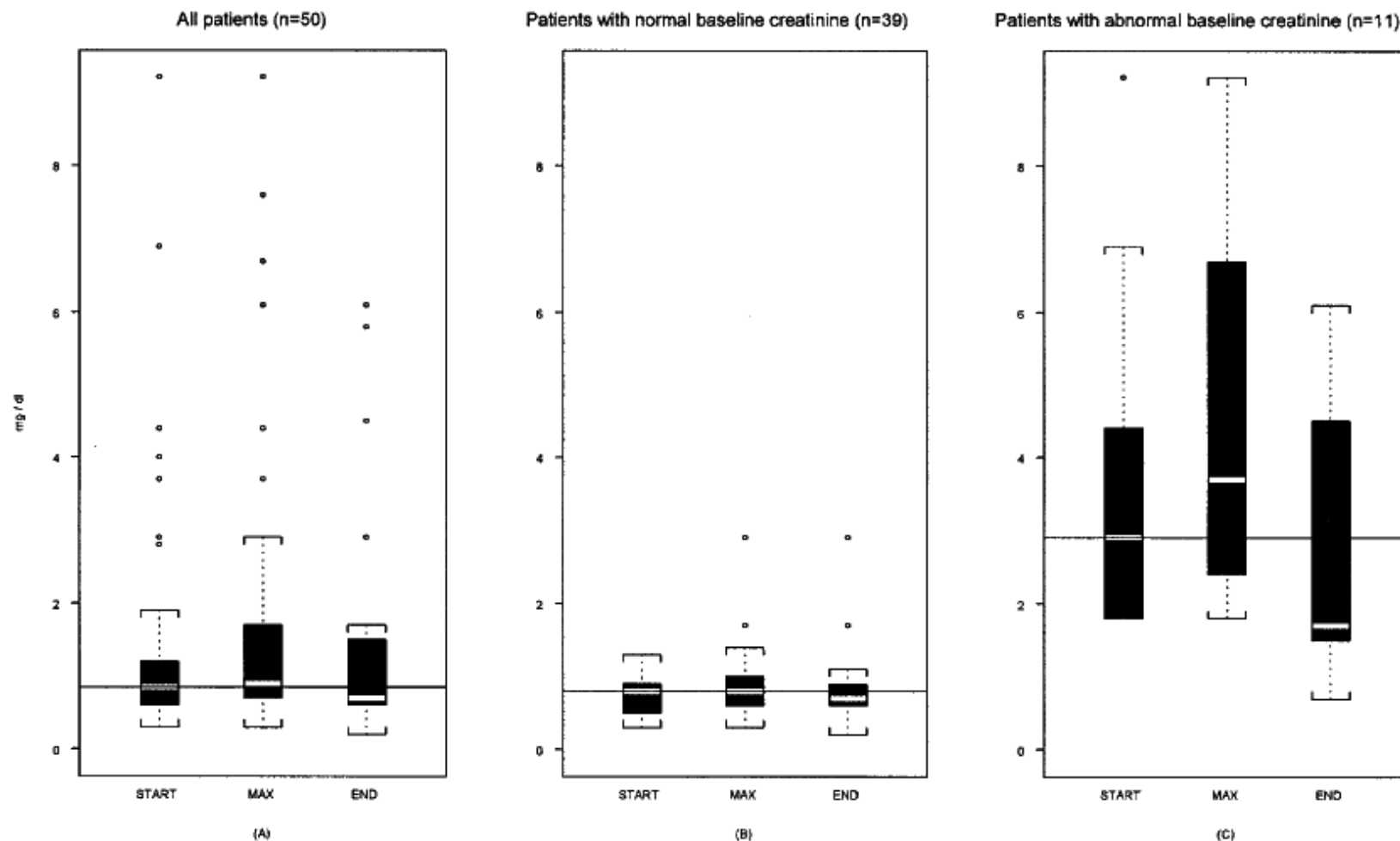
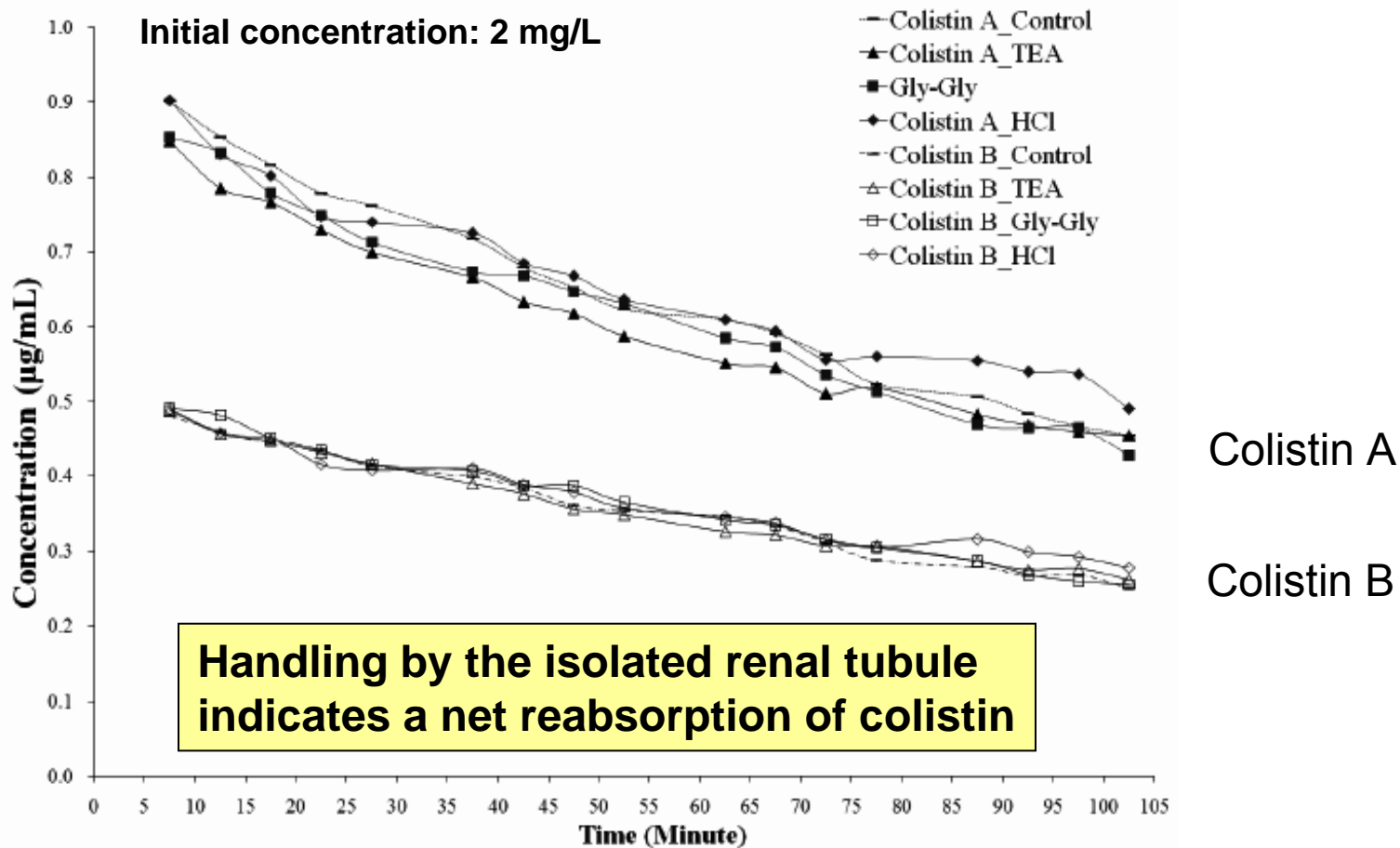


FIG. 1. The distribution of serum creatinine levels on the first day of colistin treatment (START), at the peak value (MAX), and at the end of colistin treatment (END) in all studied patients (A), in the group of patients with normal baseline creatinine values (B), and in the group of patients with abnormal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

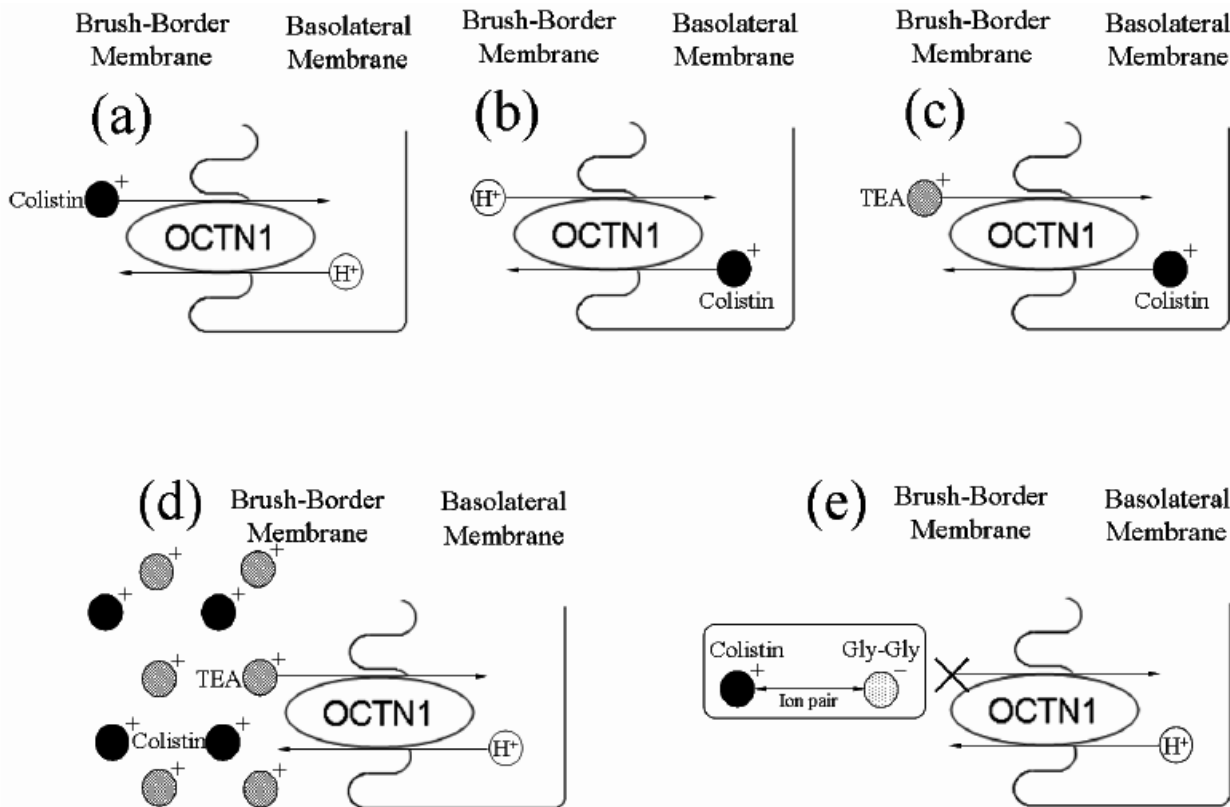
Kasiakou *et al.* AAC 2005; 49:3136-3146

Colistin nephrotoxicity: mechanism ...



AAC Accepts, published online ahead of print on 20 April 2009
Antimicrob. Agents Chemother. doi:10.1128/AAC.00030-09

Colistin toxicodynamics



Schematics of possible mechanisms for the renal tubular transport of colistin:

Notes:

- Uptake is very efficient (> 60 %)
 - Competition requires high doses
- little hope to reduce uptake by self-competition (like for aminoglycosides)
- The model is also compatible with a megalin-mediated uptake

Colistin pharmacokinetics in CF patients (inhaled form)

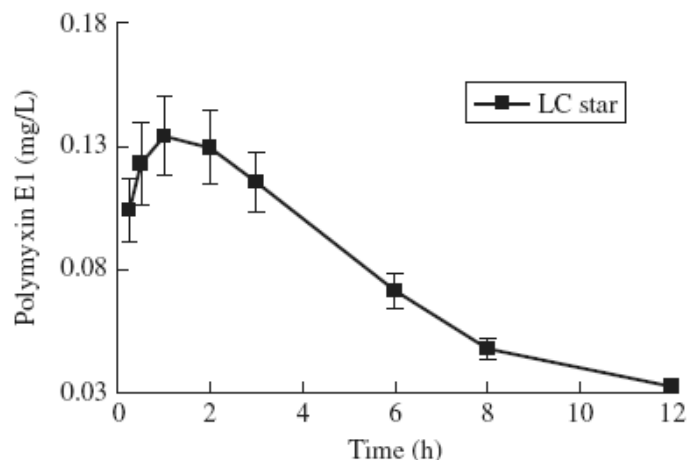


Figure 1. Serum concentrations of polymyxin E1 after a single dose of 2 million units of colistin (equal to 66 mg of colistin) administered with PARI LC Star jet nebulizer in 30 patients with cystic fibrosis. Data represent means \pm SEM.

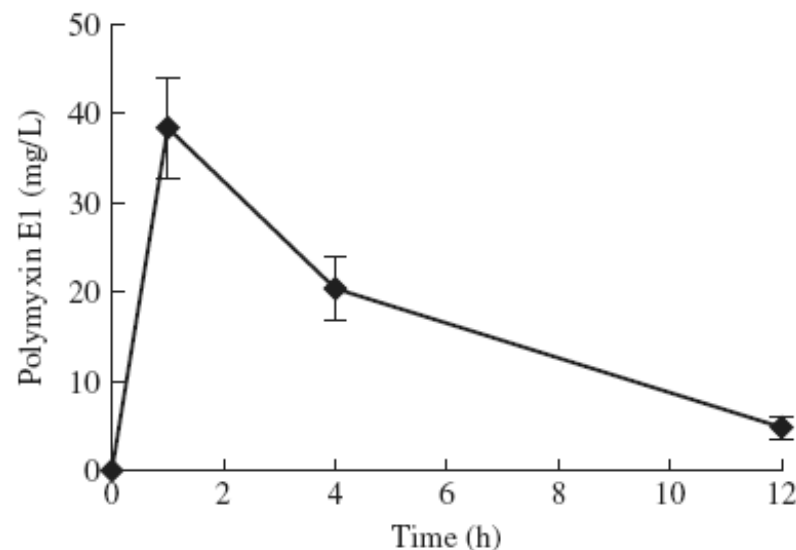


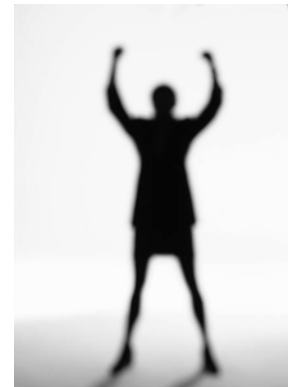
Figure 3. Sputum concentrations of polymyxin E1 after a single dose of 2 million units of colistin (equal to 66 mg of colistin) administered with a PARI LC Star jet nebulizer powered by a PARI Master compressor in patients with cystic fibrosis. Data represent means \pm SEM.

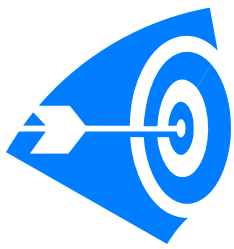
Conclusions: The low systemic and high local concentrations of colistin support the use of inhaled colistin in CF patients infected with *P. aeruginosa*.

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
- Clinical effectiveness:
 - incomplete clinical development





moving to the (perhaps)
real question... (as an MD)

...

Even if colistin was (reasonably) safe, what can we do with it ?

- Use it only if absolutely needed ...
- At this point, a repeated dosage of 150 mg every 8h is probably the maximum and safest option ... pending for more definitive information on PK/PD parameters and loss of susceptibility mechanisms... A loading dose is probably useful
- Never use it in monotherapy ...
- 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

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
- the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice