COLISTIN:
news from an old drug

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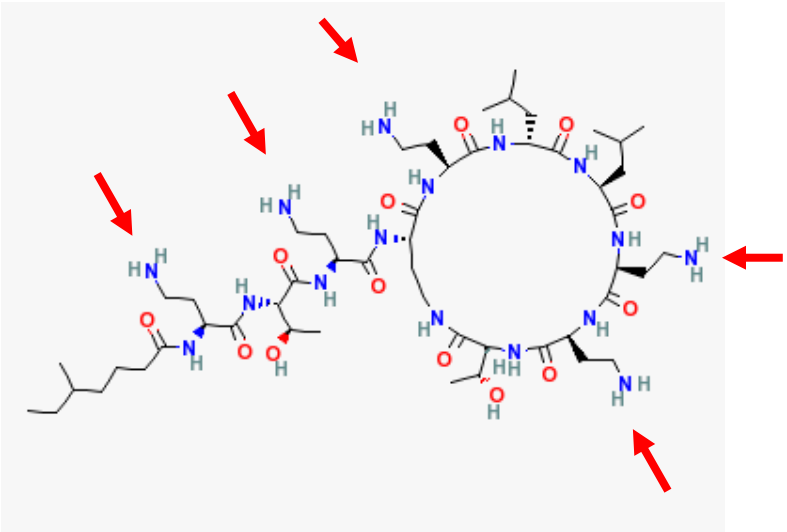
Brussels, Belgium

with the support of
Wallonie-Bruxelles International

A reminder: what is colistin ?

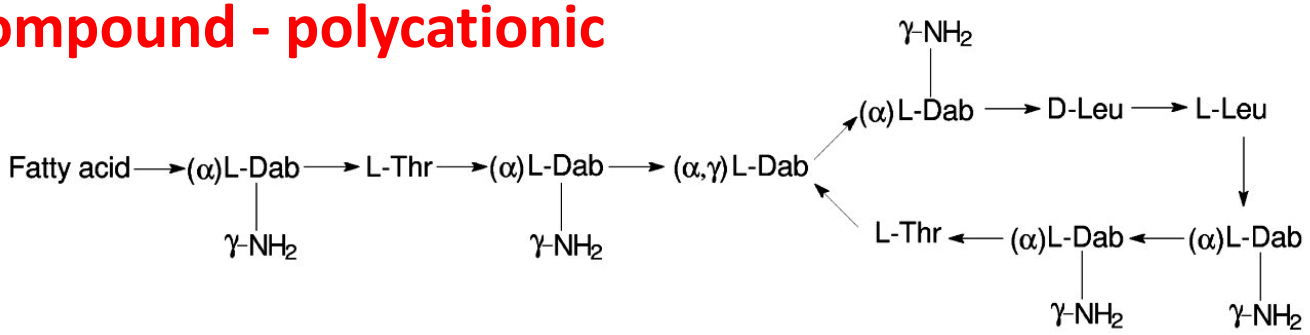


A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain administered as a prodrug …

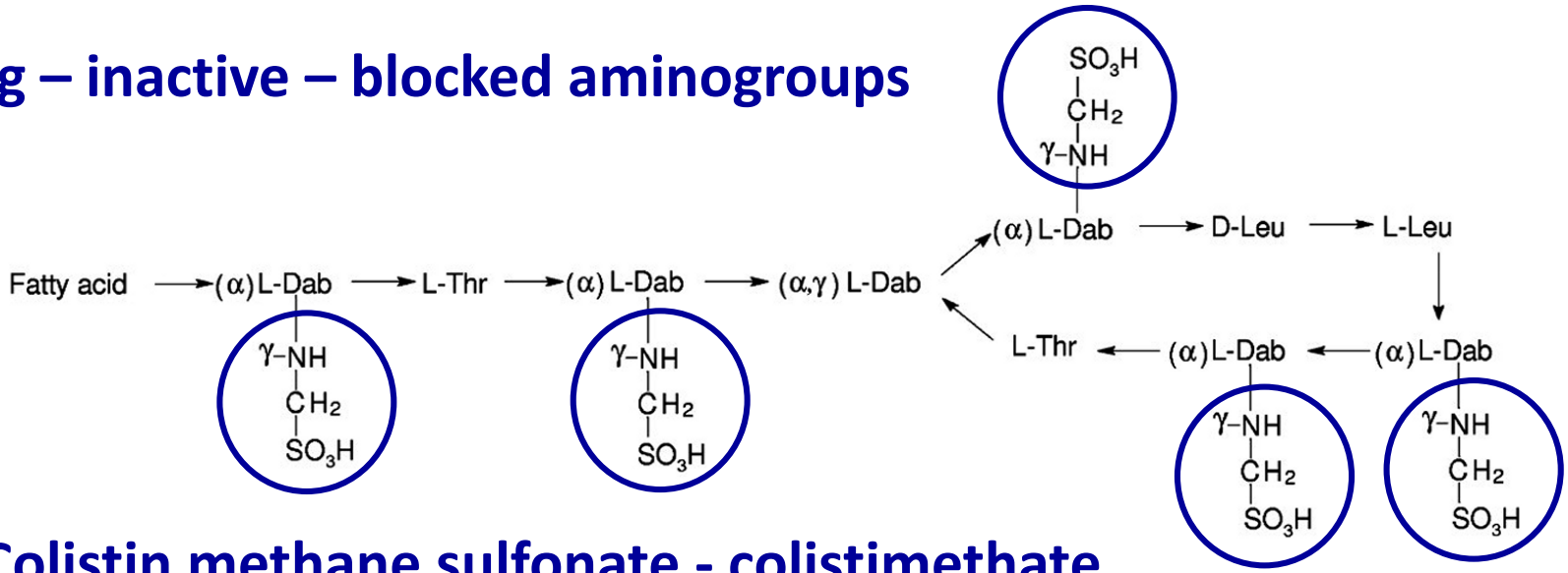
From the molecule to the drug …

Clinical form of colistin

Active compound - polycationic



Prodrug – inactive – blocked aminogroups



Colistin methane sulfonate - colistimethate

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

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

Fate of the clinical form of colistin (colistimethate)

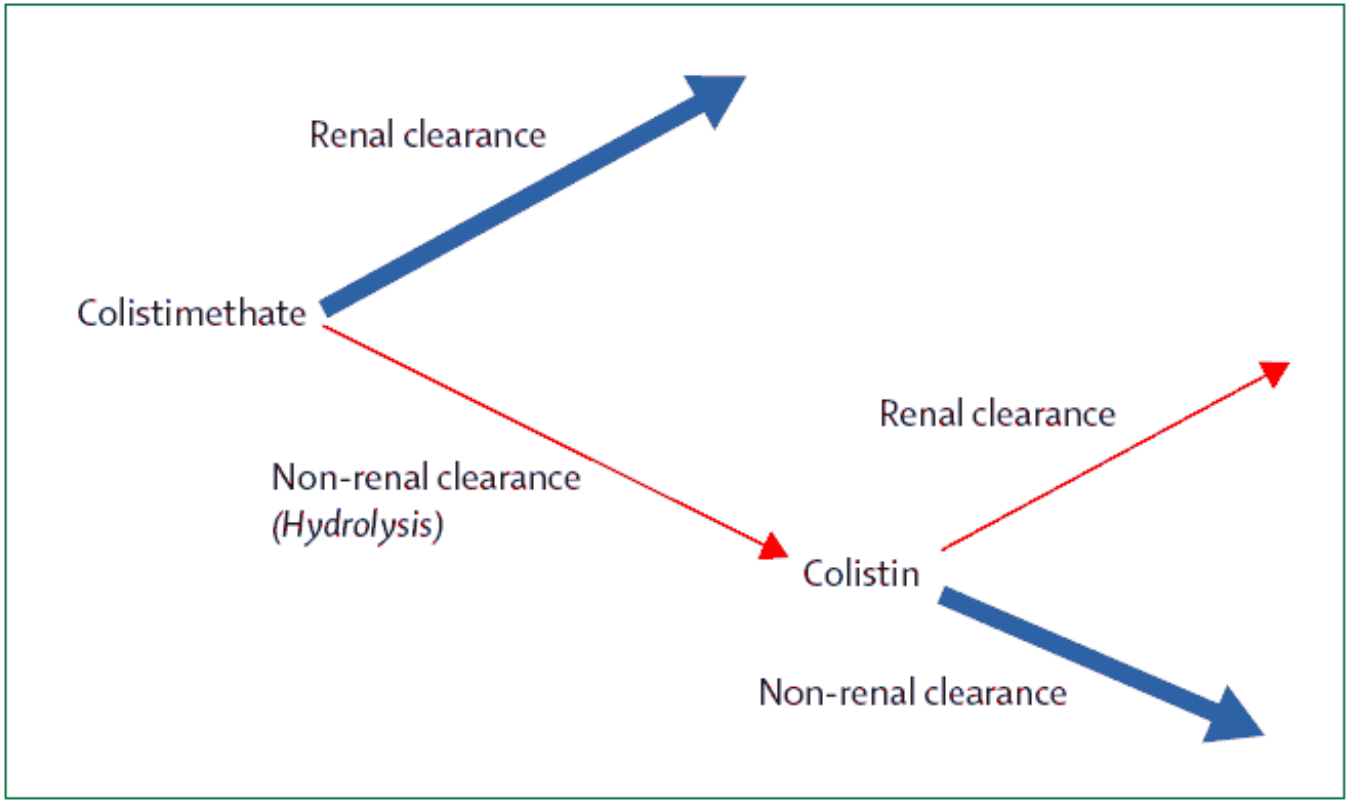


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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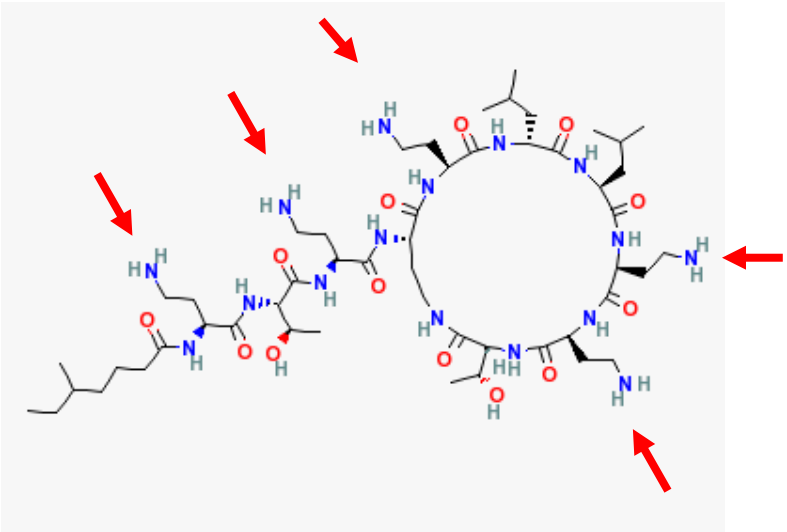
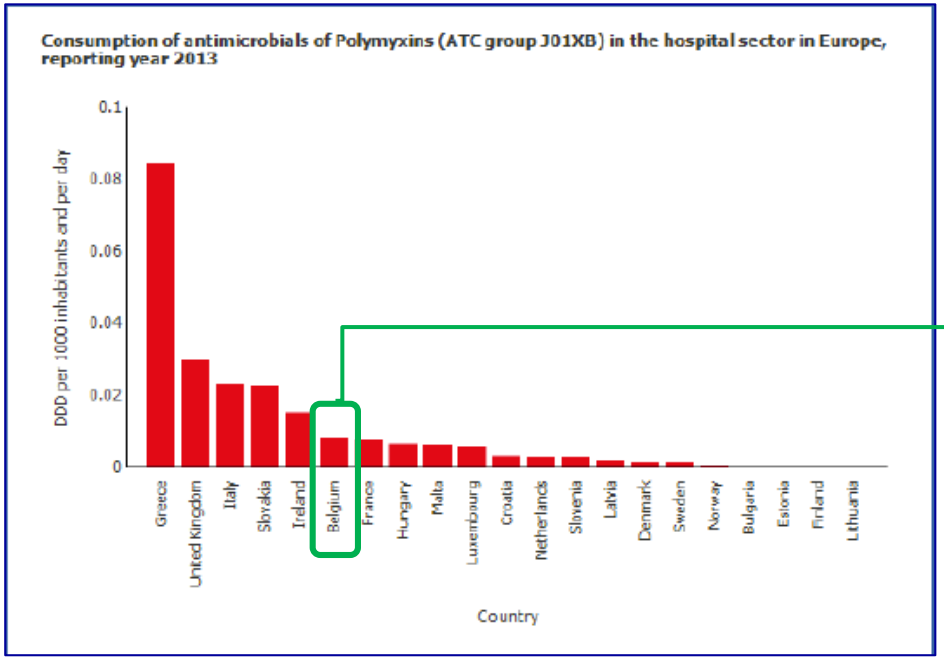
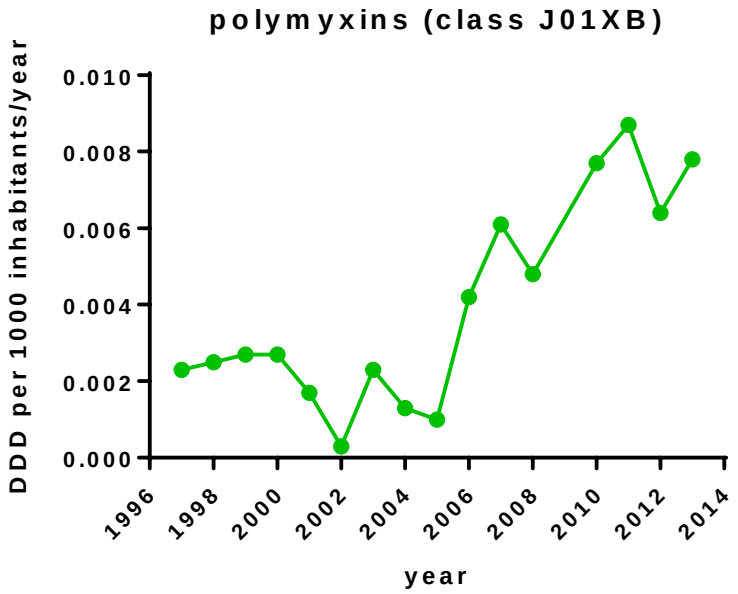


A last-resort antibiotic ….

Do we need this drug ?

Polymyxin consumption in Europe and in Belgium





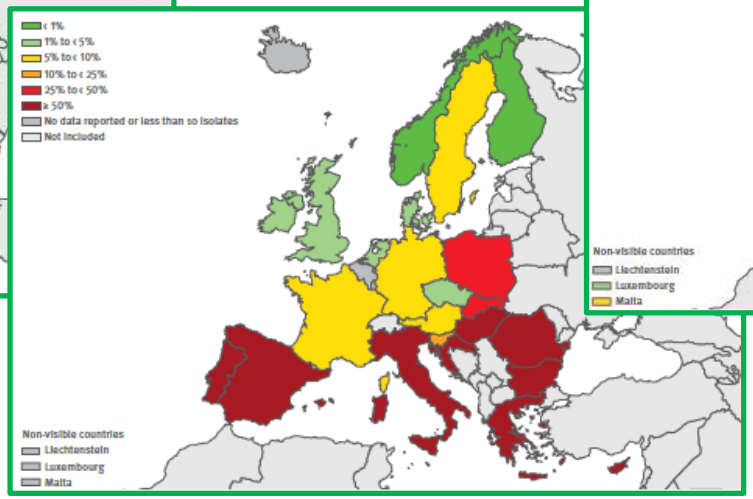
Do we need this drug ?

Well, it seems so !

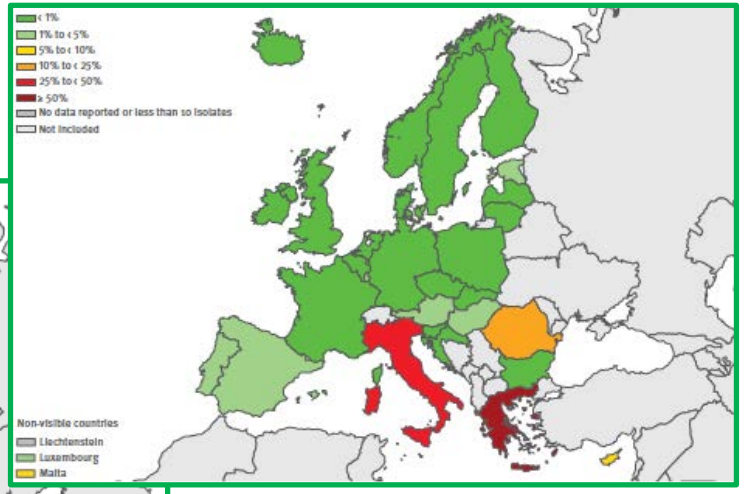
Carbapenem resistance in ESKAPE pathogens in Europe

P. aeruginosa

A. baumanii



K. pneumoniae



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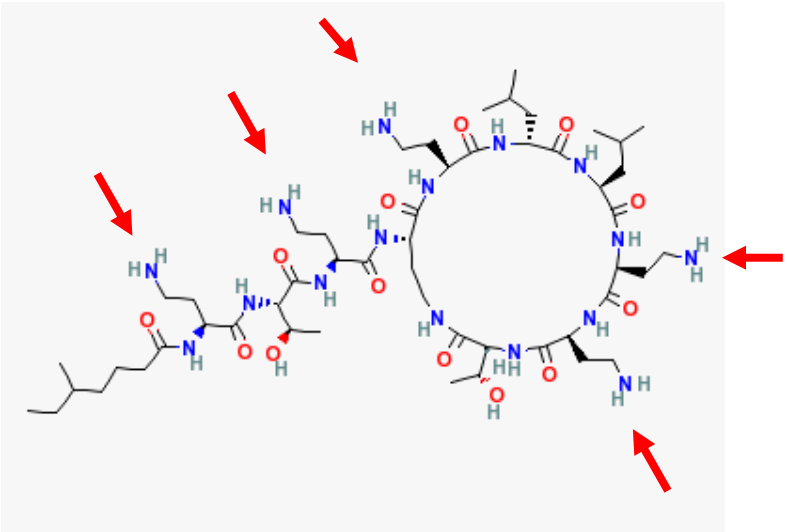
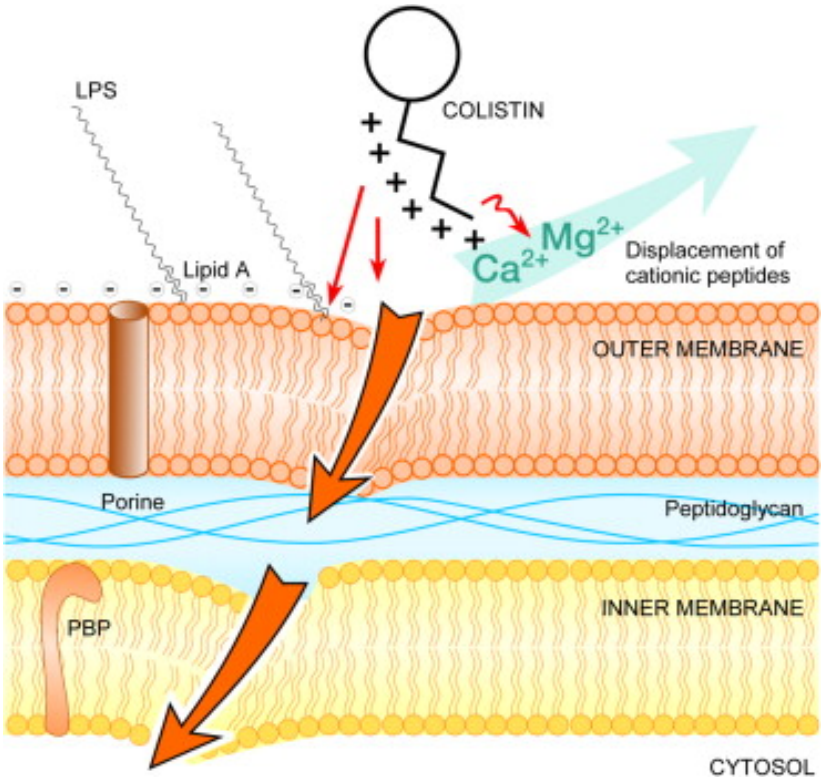


A cyclic **amphipathic** **polycationic peptide** with a short aliphatic side chain …

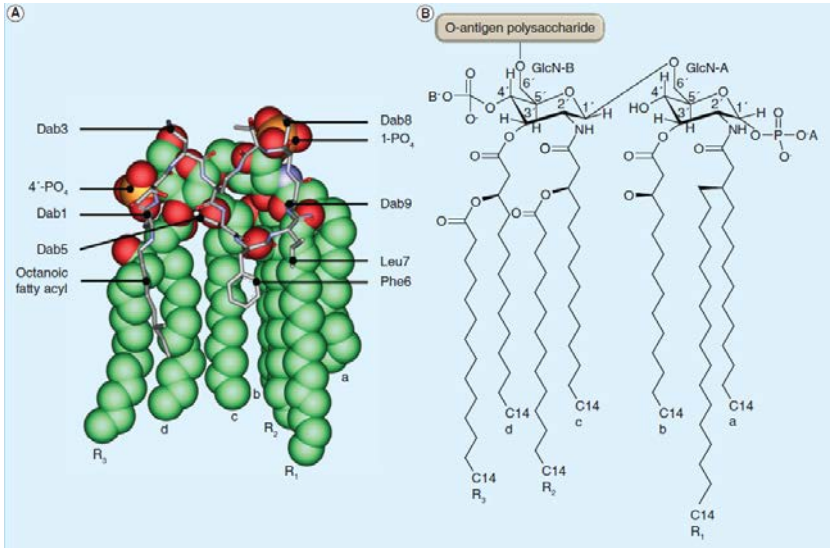
What does this structure tell you about the mode of action ?

How do polymyxins work ?

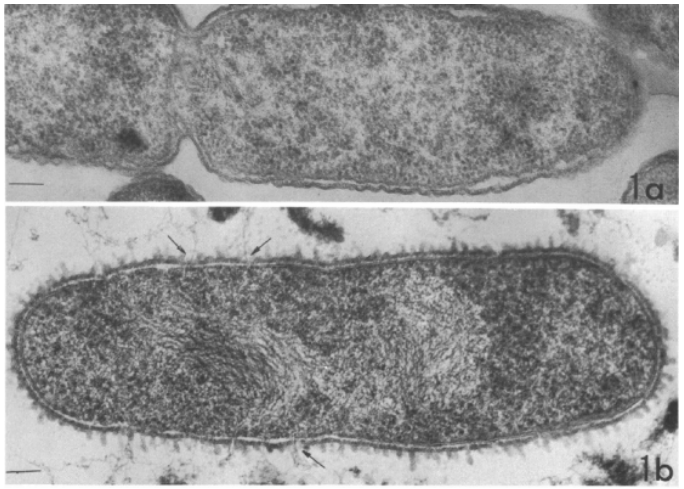
1. Interaction with LPS in the outer membrane



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



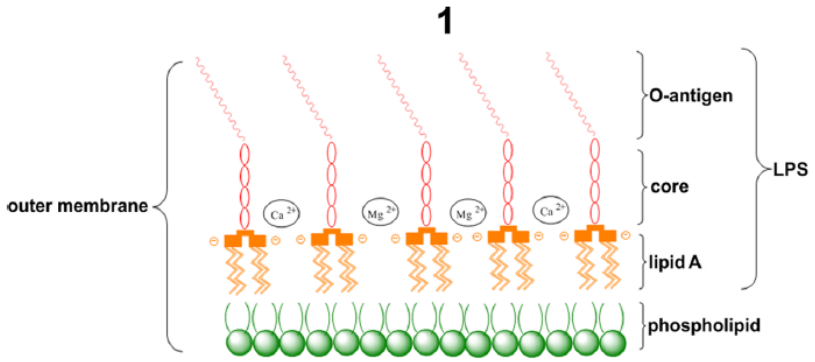
Velkov et al, Future Microbiol. 2013; 8:711–24

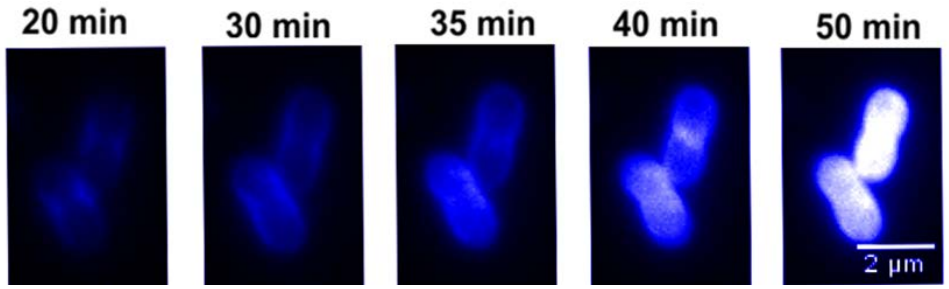


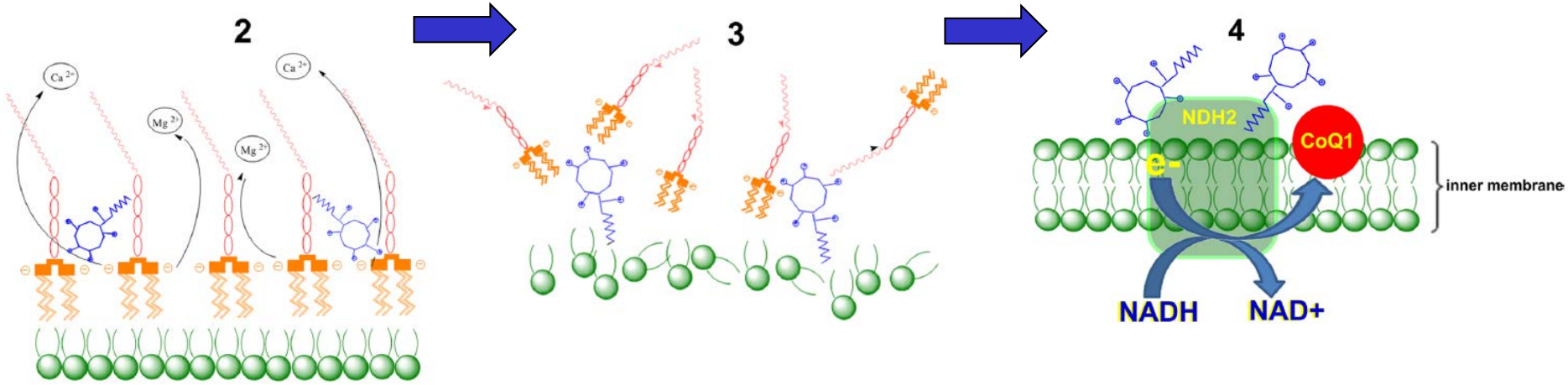
Koike et al, J. Bacteriol. 1969; 97:448-52

How do polymyxins work ?

2. Disruption of envelope integrity and access to bacterial cytosol







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

When can you use colistin ?

when you have MDR organisms only…

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

Clinical implications ?

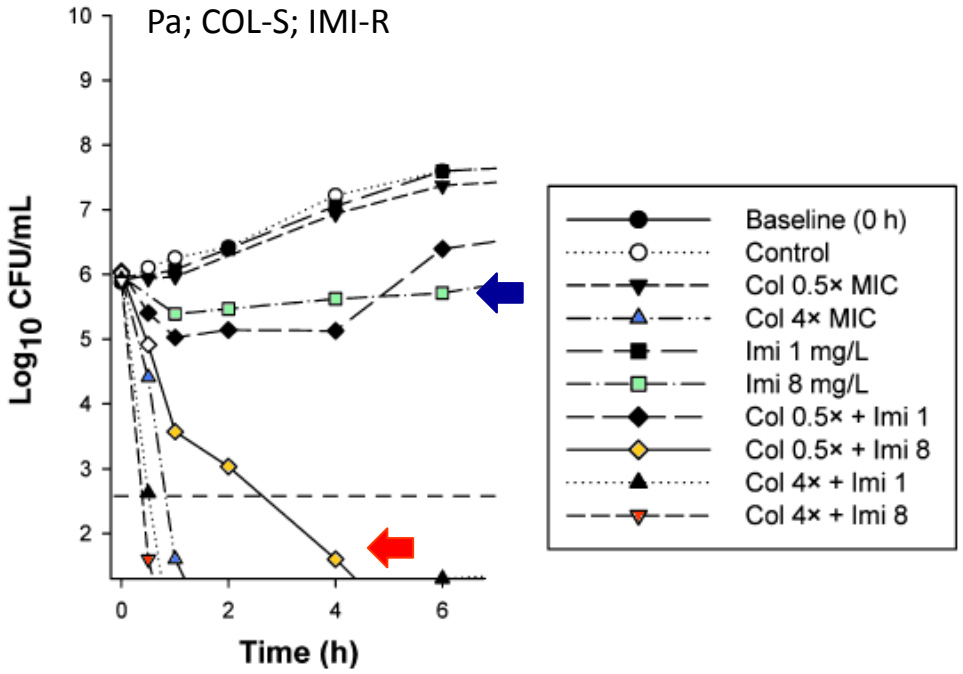
1. Preferential interaction with LPS → spectrum restricted to Gram-negative bacteria

2. Alteration of bacterial integrity → bactericidal activity

3. Facilitated penetration of other drugs inside bacteria

→ synergy in combination

- **Carbapenems, sulbactam**
- **Rifampicin**
- **Tigecycline, minocycline**
- **Fosfomycin**
- **Aminoglycosides**
- **Fusidic acid**
- **Glycopeptides**
- **Daptomycin**



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

How do bacteria resist to polymyxins ?

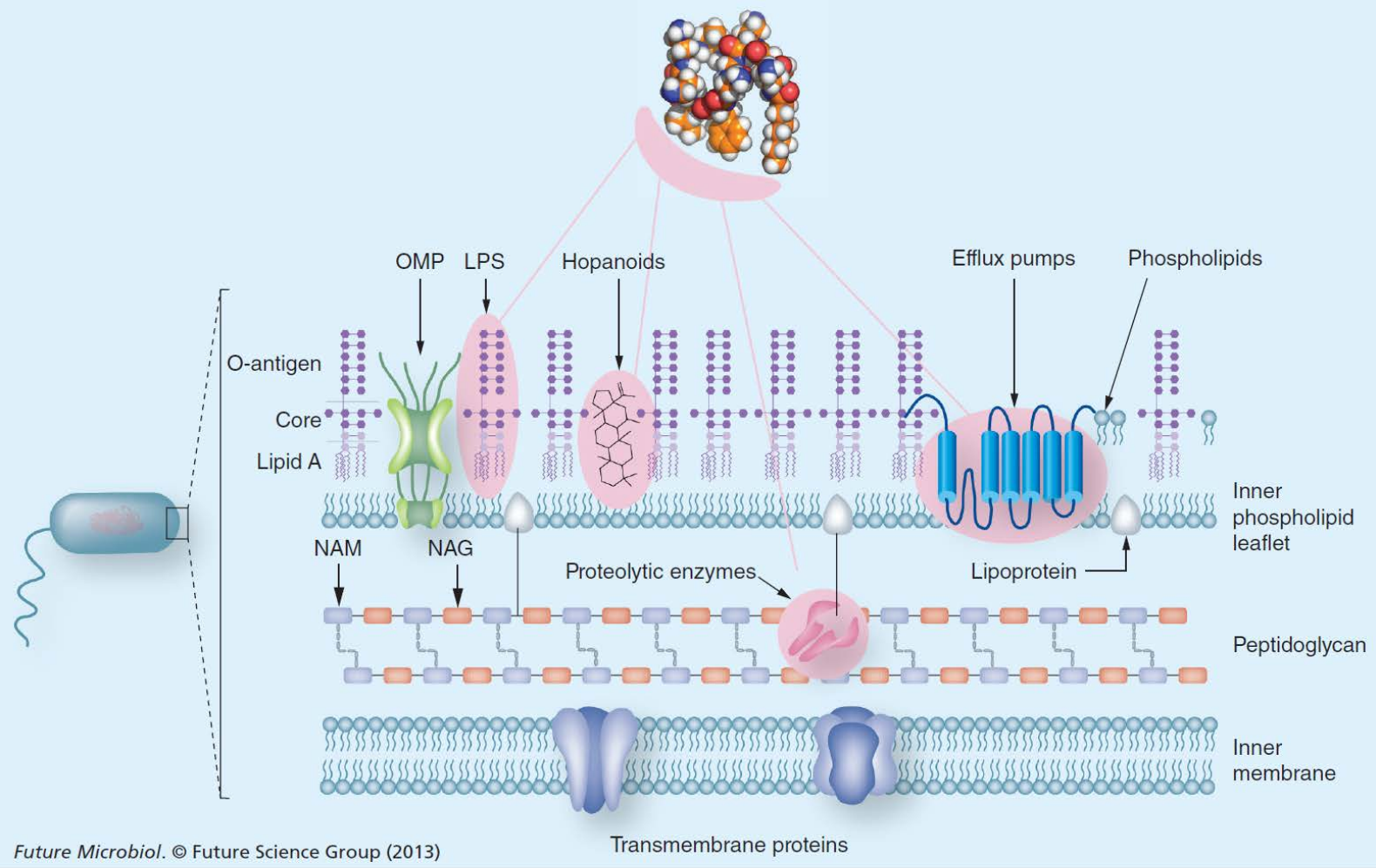


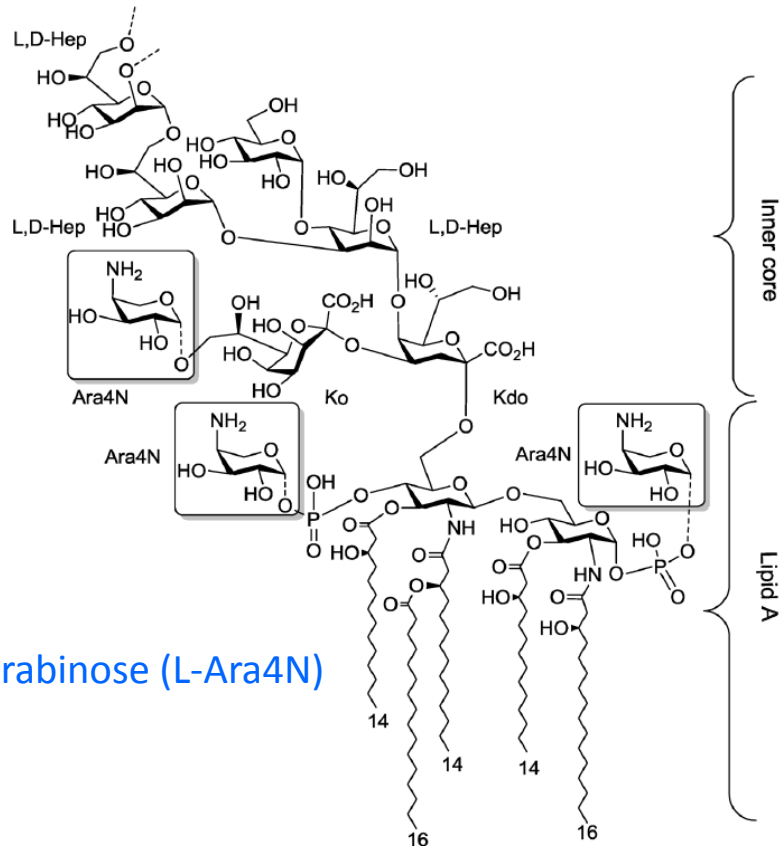
Figure 2. Key mechanisms of polymyxin resistance in Gram-negative bacteria. The pink shading indicates molecular determinants of polymyxin resistance.
LPS: Lipopolysaccharide; NAG: *N*-acetylglucosamine; NAM: *N*-acetylmuramic acid; OMP: Outer membrane protein.

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

Underlying mechanisms and clinical implications

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

→ **Limitation of the activity spectrum**



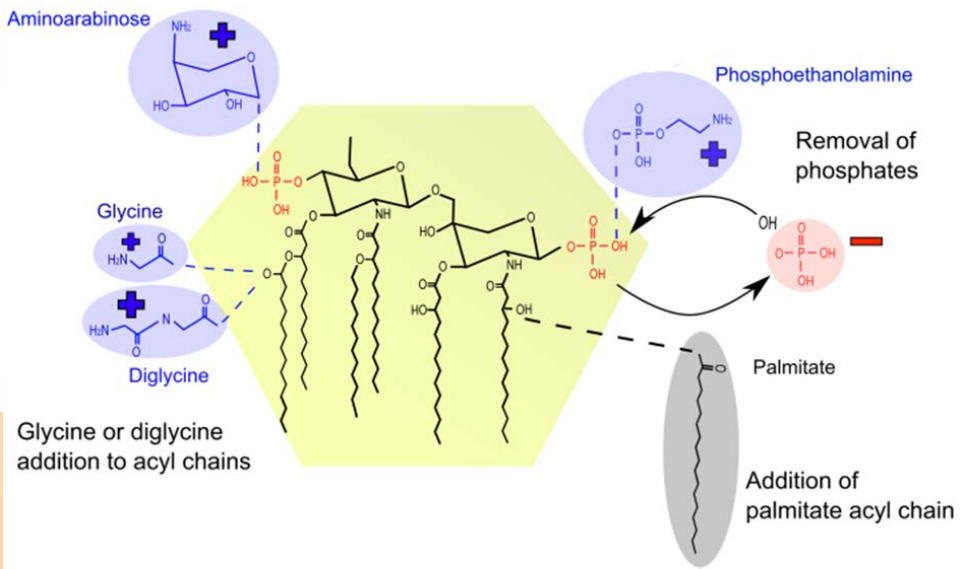
4-amino-4-deoxy-L-arabinose (L-Ara4N)

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

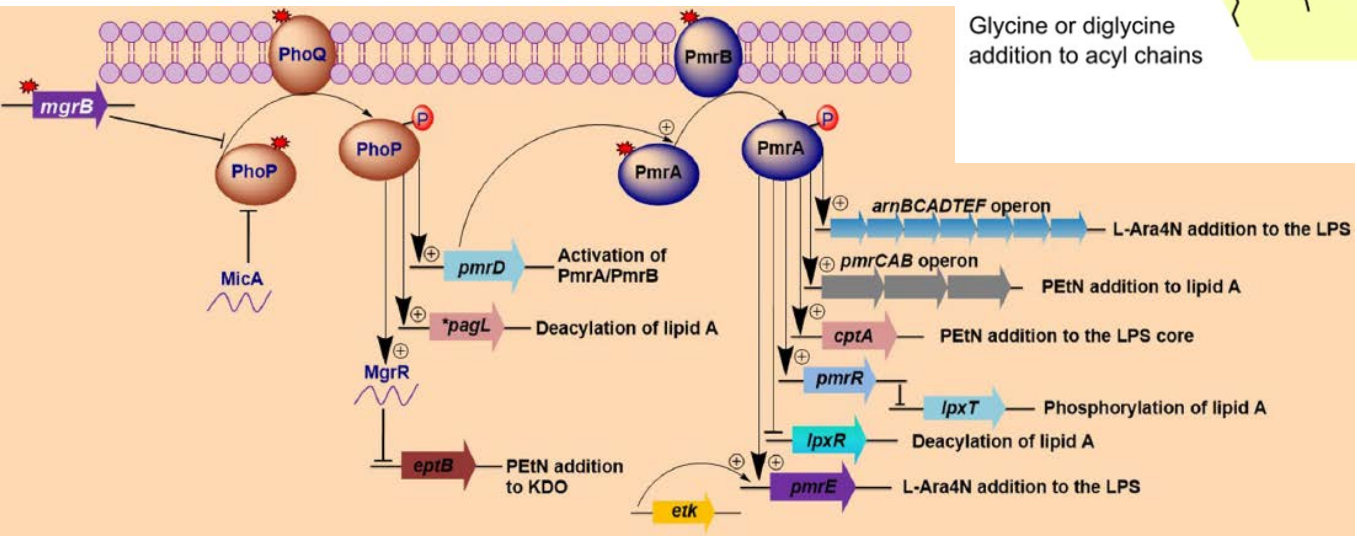
Underlying mechanisms and clinical implications

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

→ Rational use
→ Dose optimization
→ Combinations



Up-regulation of 2-component regulatory systems



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

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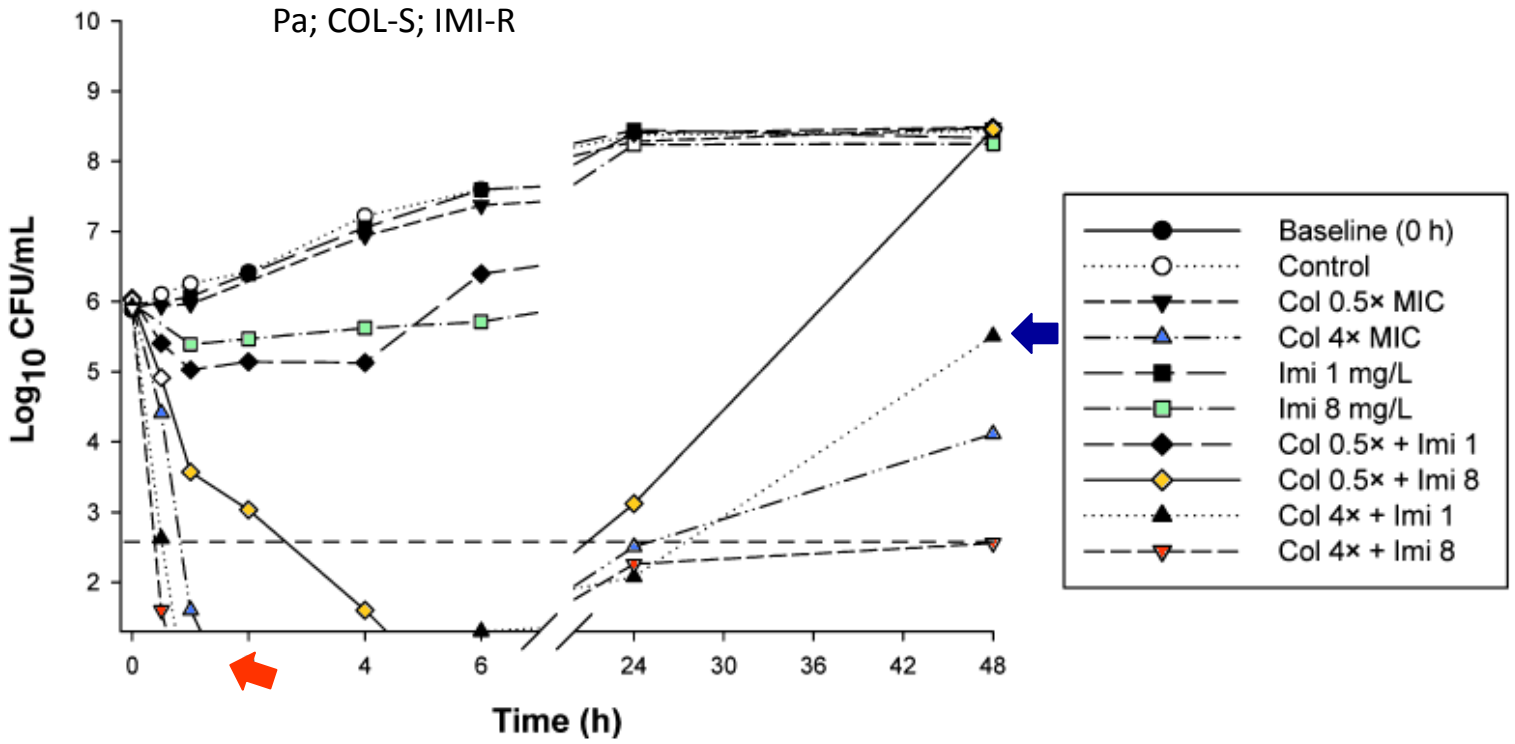
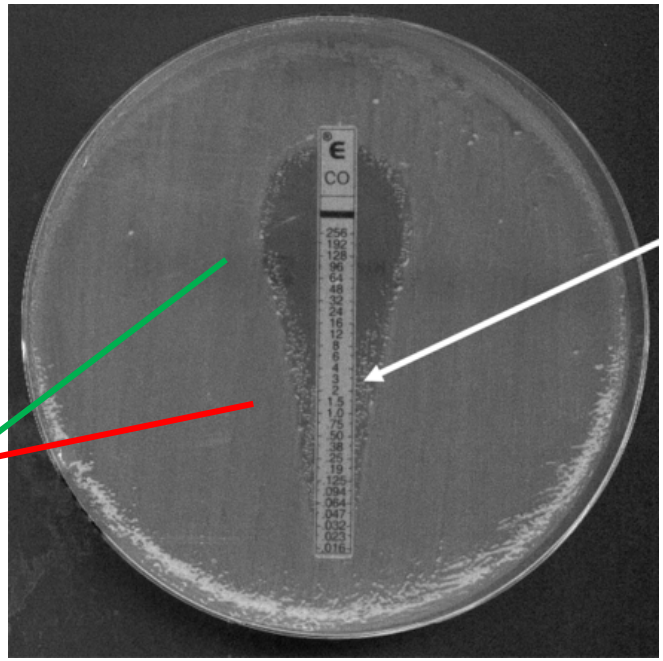


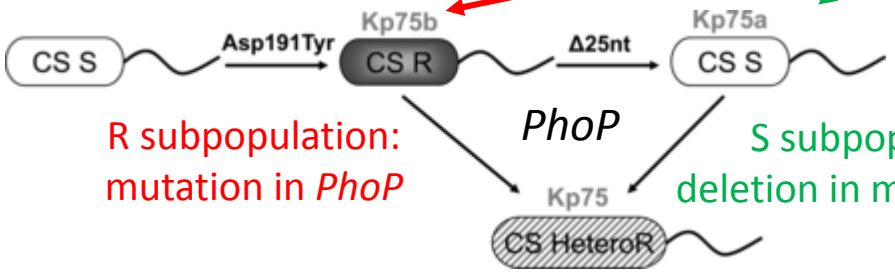
Bergen et al, Pharmacotherapy 2015; 35:34–42

Underlying mechanisms and clinical implications

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

→ **visible on E-tests only**





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

Underlying mechanisms and clinical implications

4. Rversibility

- variable between strains
- slow process
- will not help patients

Lee et al. (2015)
Antimicrob. Agents Chemother.
doi:10.1128/AAC.01574-15
Unedited manuscript

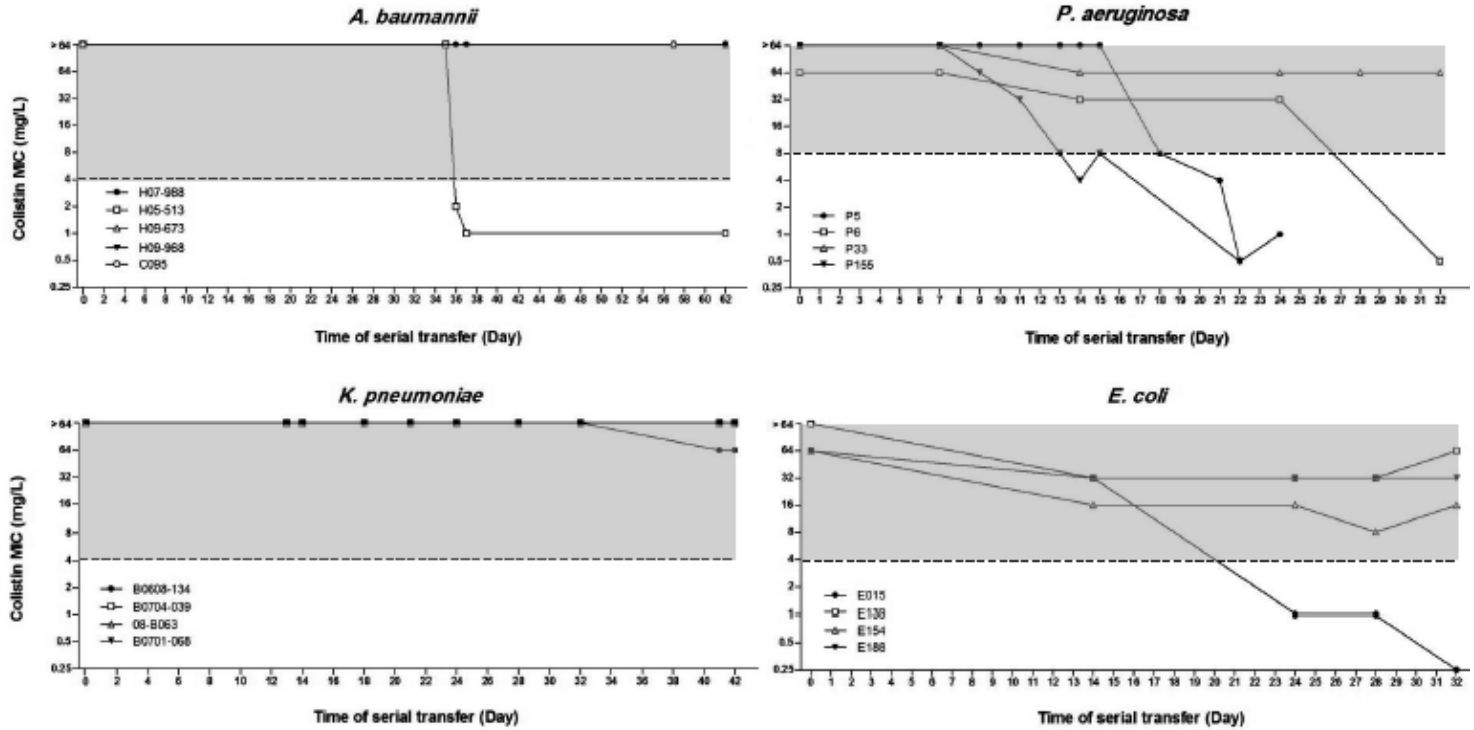
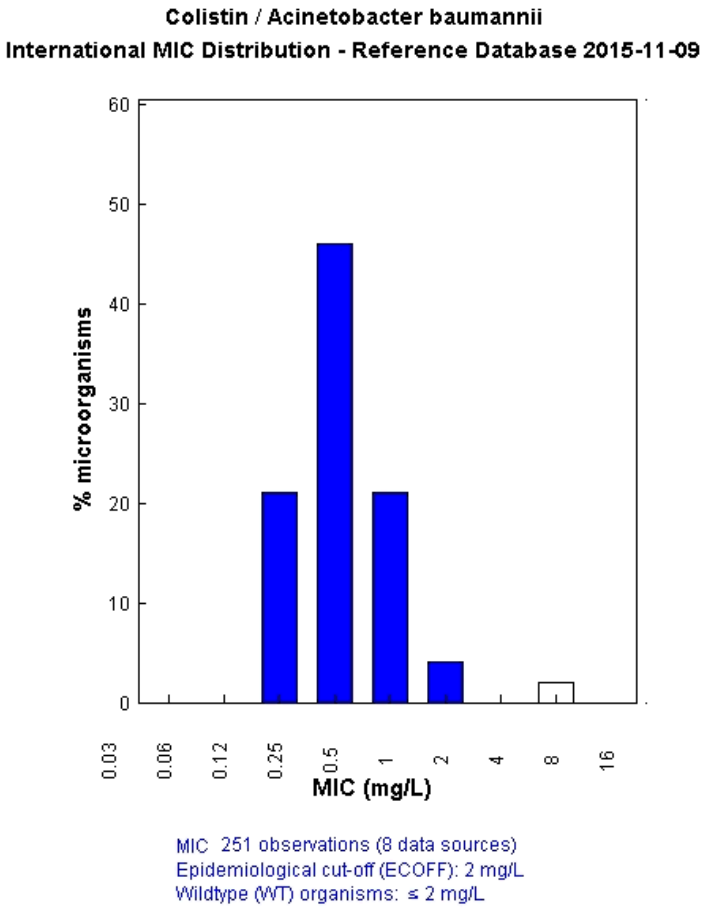
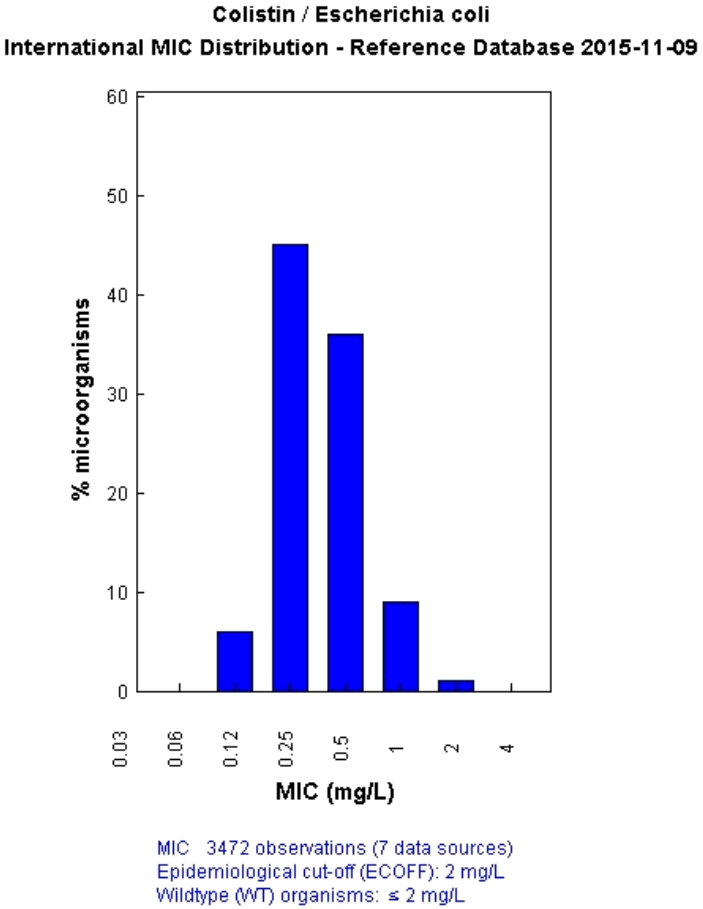


Figure 1. Change in colistin MIC of resistant mutants obtained by serial passage in colistin-free medium. (a) *A. baumannii*, (b) *P. aeruginosa*, (c) *K. pneumoniae*, and (d) *E. coli* colistin-resistant mutant strains. The Y-axis represents colistin MIC in the log2 scale. Colistin-susceptible revertants were obtained from three *P. aeruginosa* and one each of *A. baumannii* and *E. coli* resistant mutant strains. Dashed lines indicate the breakpoint of colistin resistance.

EUCAST MICs distributions…



ECOFF = 2 mg/L



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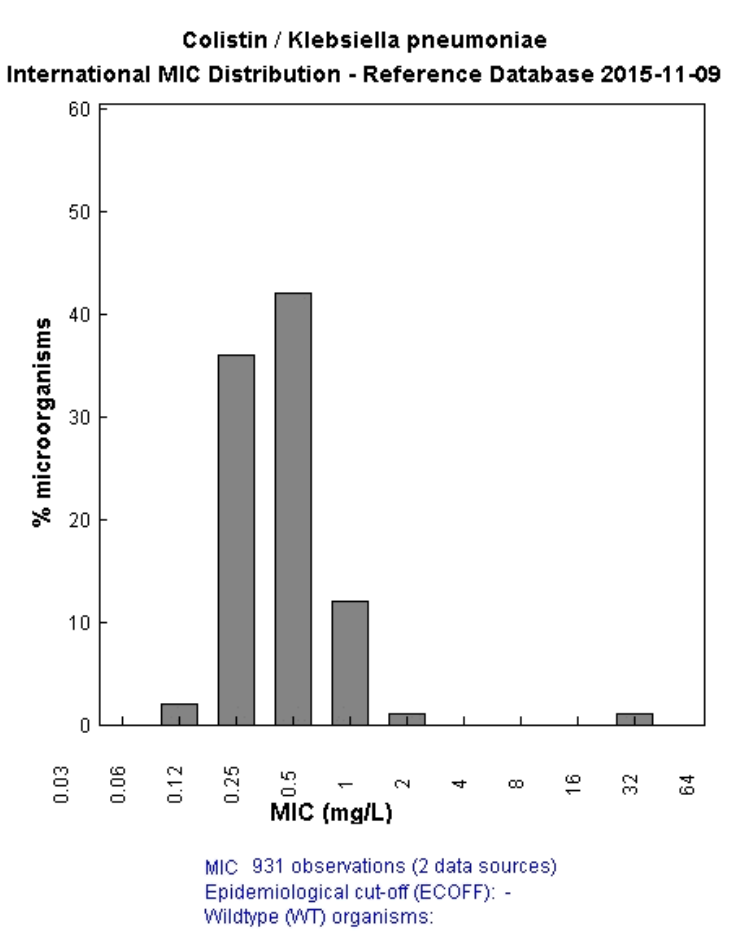
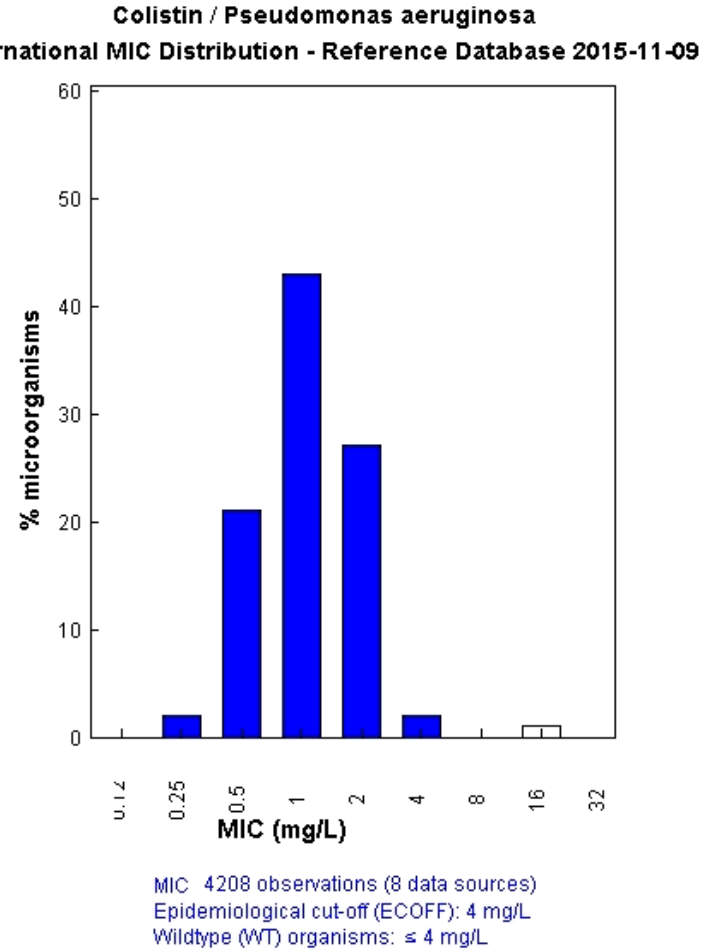


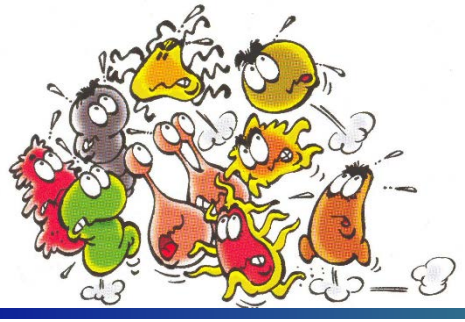
ECOFF undetermined



ECOFF 4 mg/L

Current susceptibility breakpoints

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

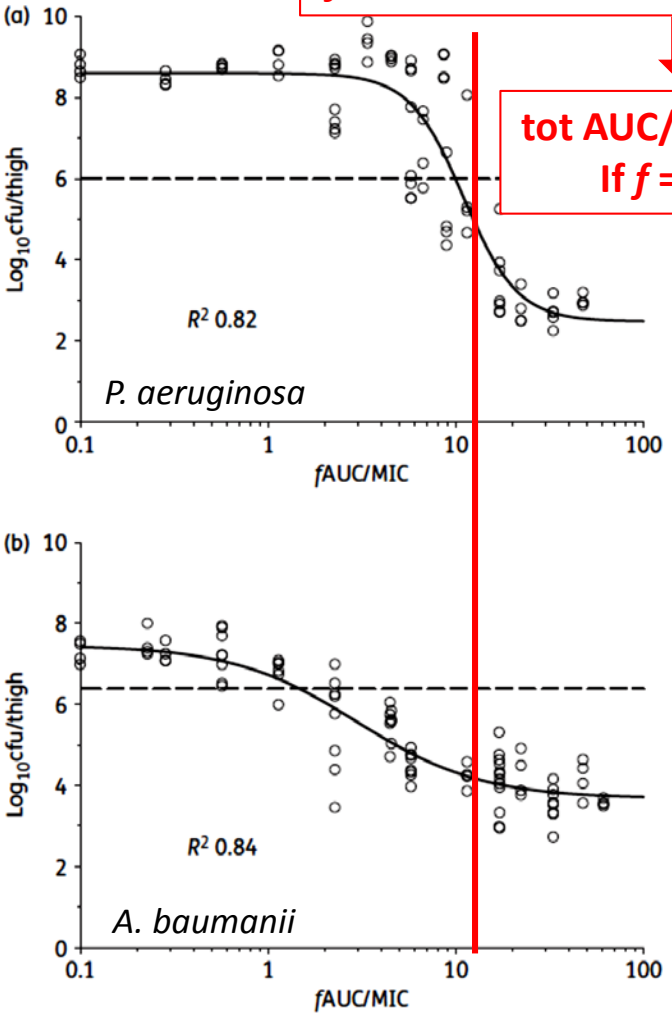


PK/PD : lessons from animal models

Thigh infection

*f*AUC/MIC = 12 → 2 log kill

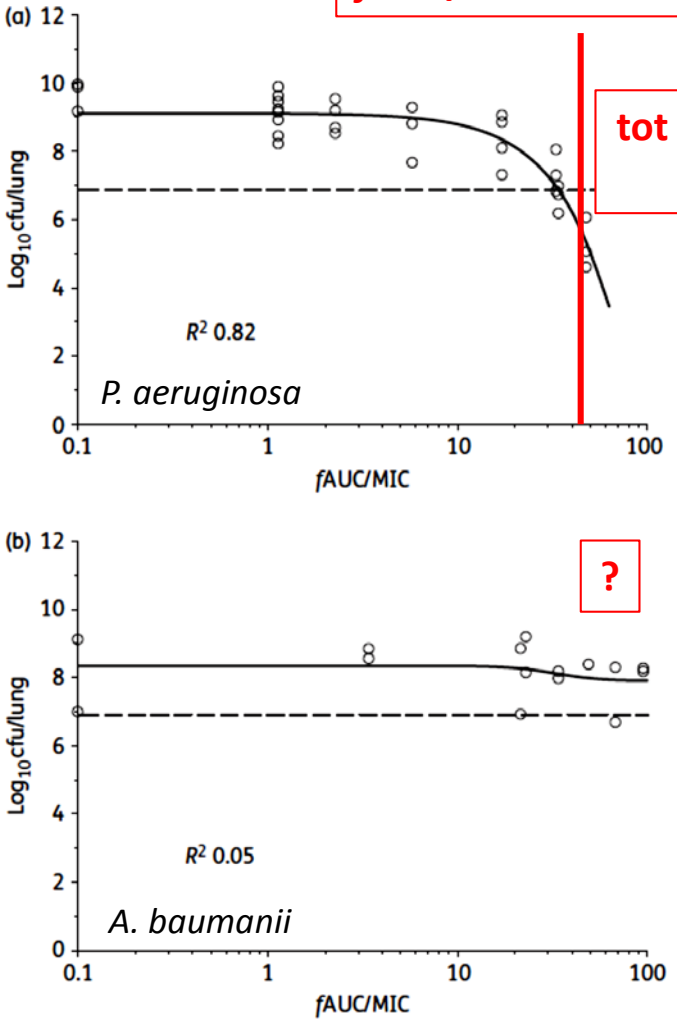
tot AUC/MIC = 24
If *f* =50%



Lung infection

*f*AUC/MIC = 48 → 1 log kill

tot AUC/MIC = 96
If *f* =50%



Cheah et al, JAC 2015; doi:10.1093/jac/dkv267

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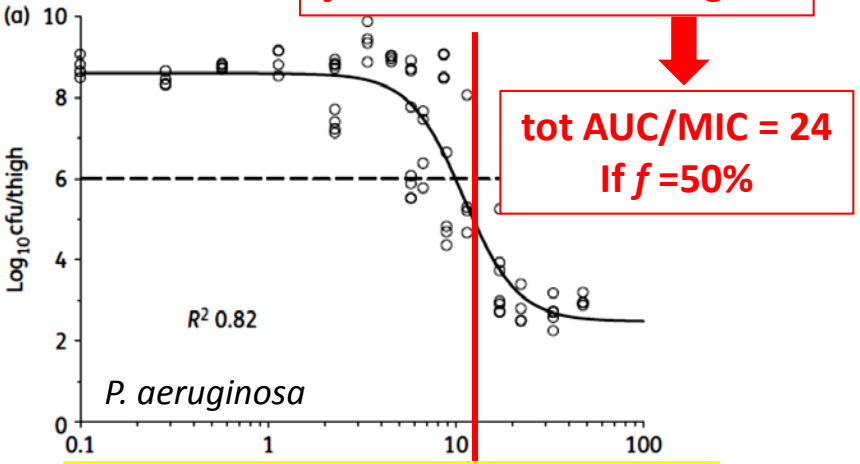
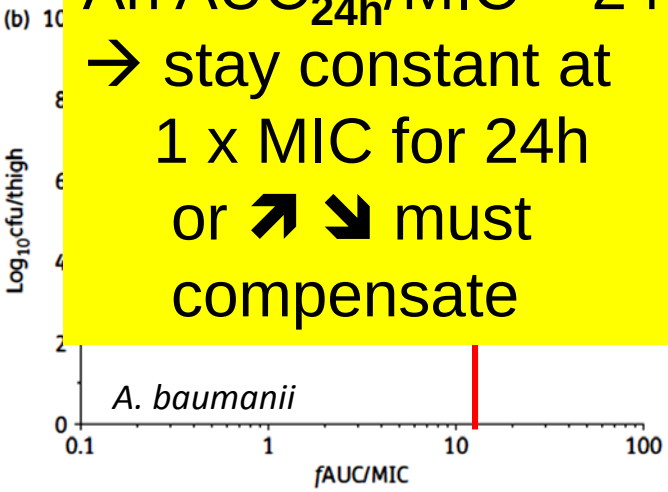


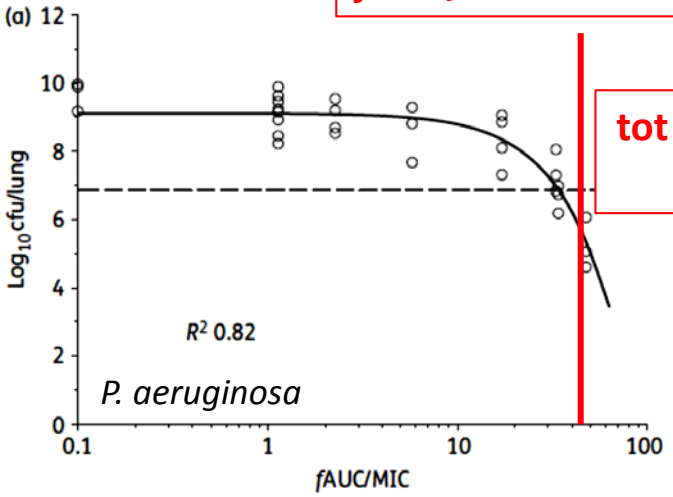


An AUC_{24h}/MIC = 24
→ stay constant at
1 x MIC for 24h
or ↗ ↘ must
compensate

Lung infection

*f*AUC/MIC = 48 → 1 log kill

tot AUC/MIC = 96
If *f* =50%



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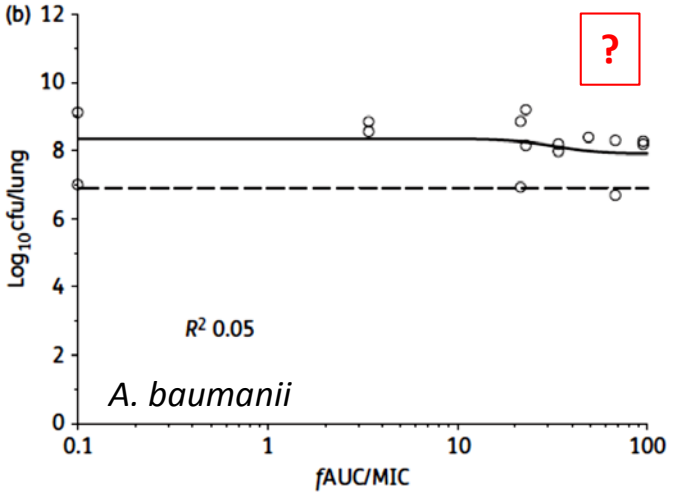

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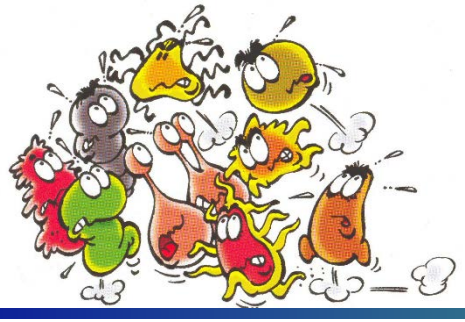
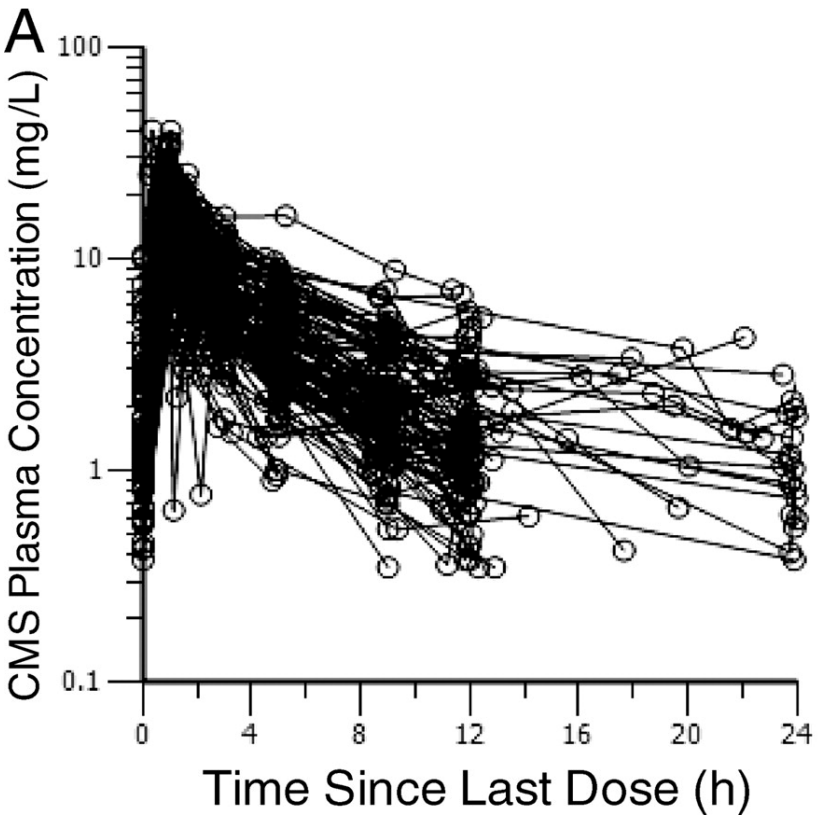
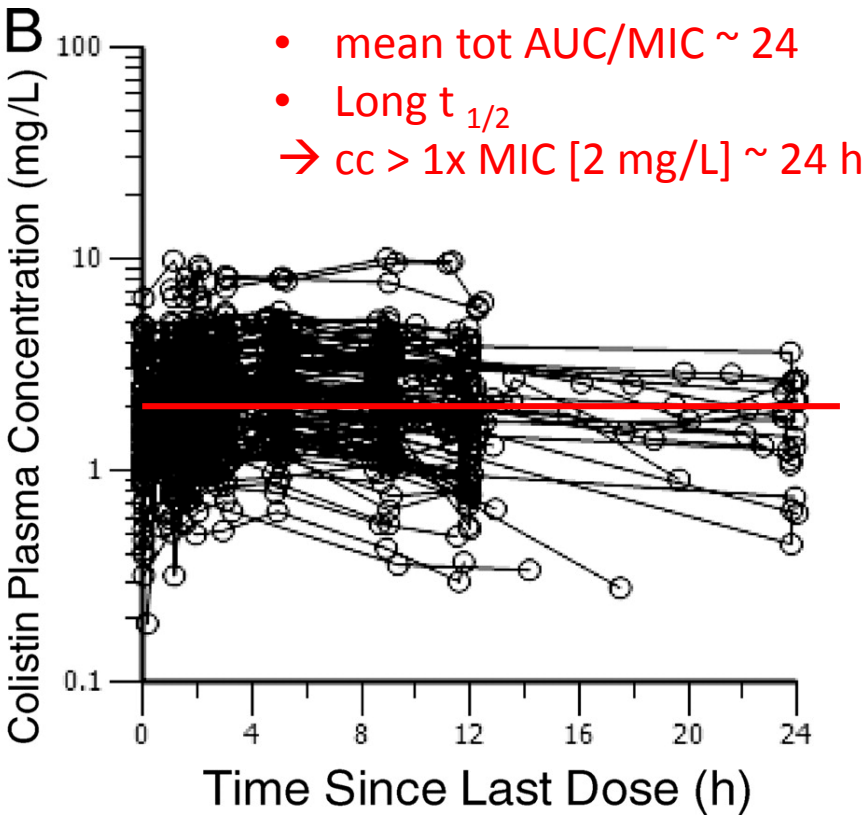


PK/PD : from animals to men

1. Prolonged half-life → optimize daily dose

Steady-state plasma concentration-time profiles of the prodrug CMS (A) or formed colistin (B) in 105 critically ill patients (89 not on renal replacement, 12 on intermittent HD, and 4 on CRRT).





- mean tot AUC/MIC ~ 24
- Long $t_{1/2}$

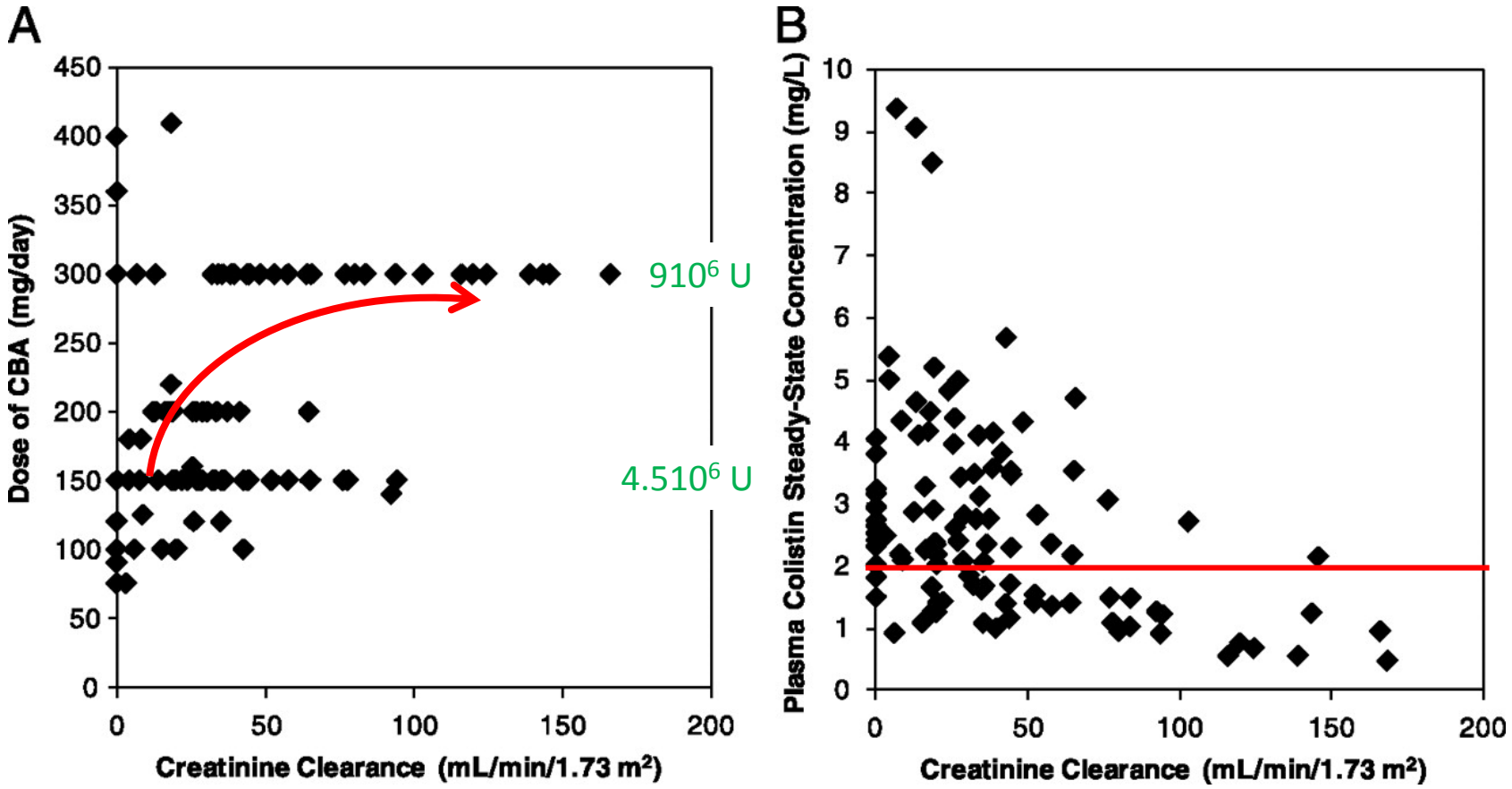
→ cc > 1x MIC [2 mg/L] ~ 24 h

Garonzik et al, AAC 2011; 55:3284-94; Landesdorfer et al, Semin Respir Crit Care Med 2015; 36:126–35

PK/PD and renal function

2. Elimination rate depending on renal function → select dose based on creat. clear.

Relationship of physician-selected daily dose of colistin base activity (CBA) (A) and the resultant average steady-state plasma colistin concentration (B) with creatinine clearance in 105 critically ill patients.



Garonzik et al, AAC 2011; 55:3284-94

Impact of renal function on elimination

If renal function ↗↗

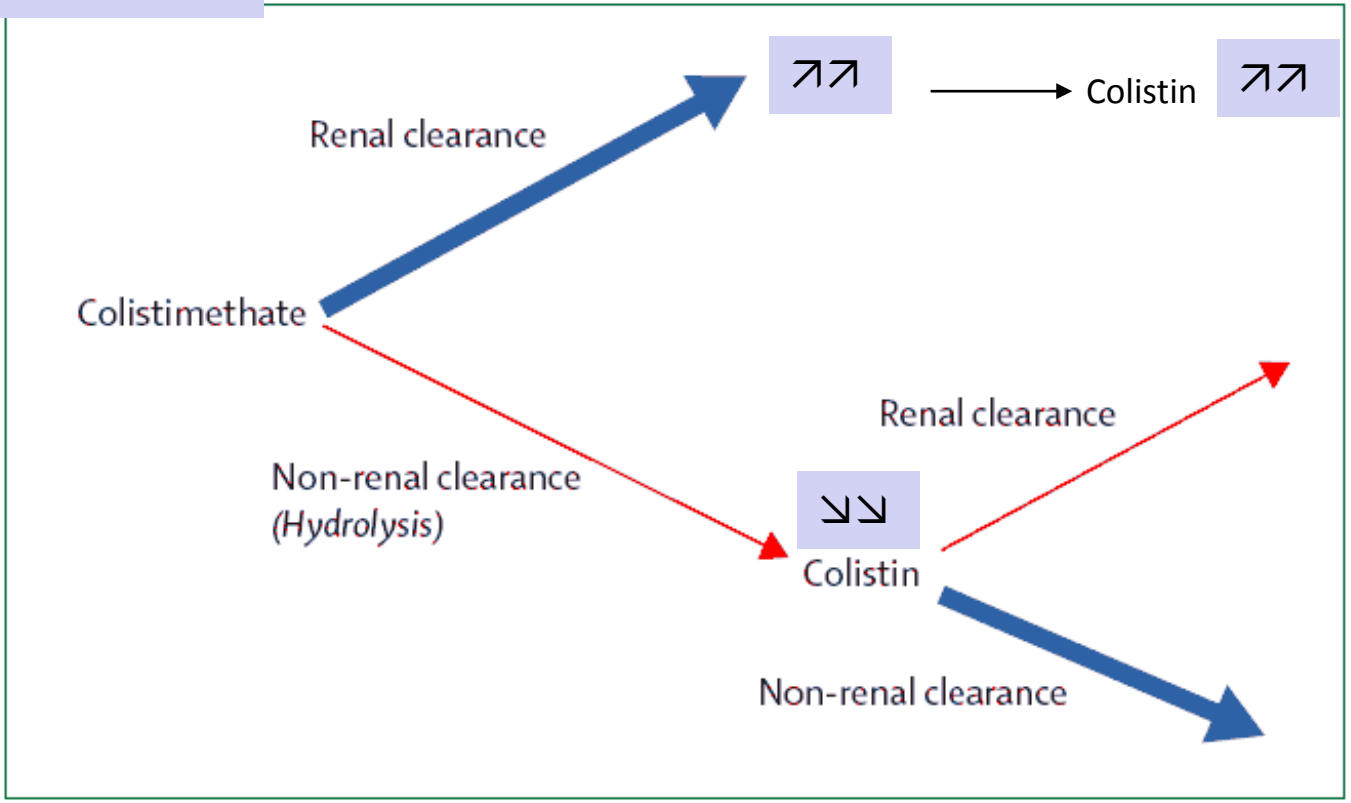


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

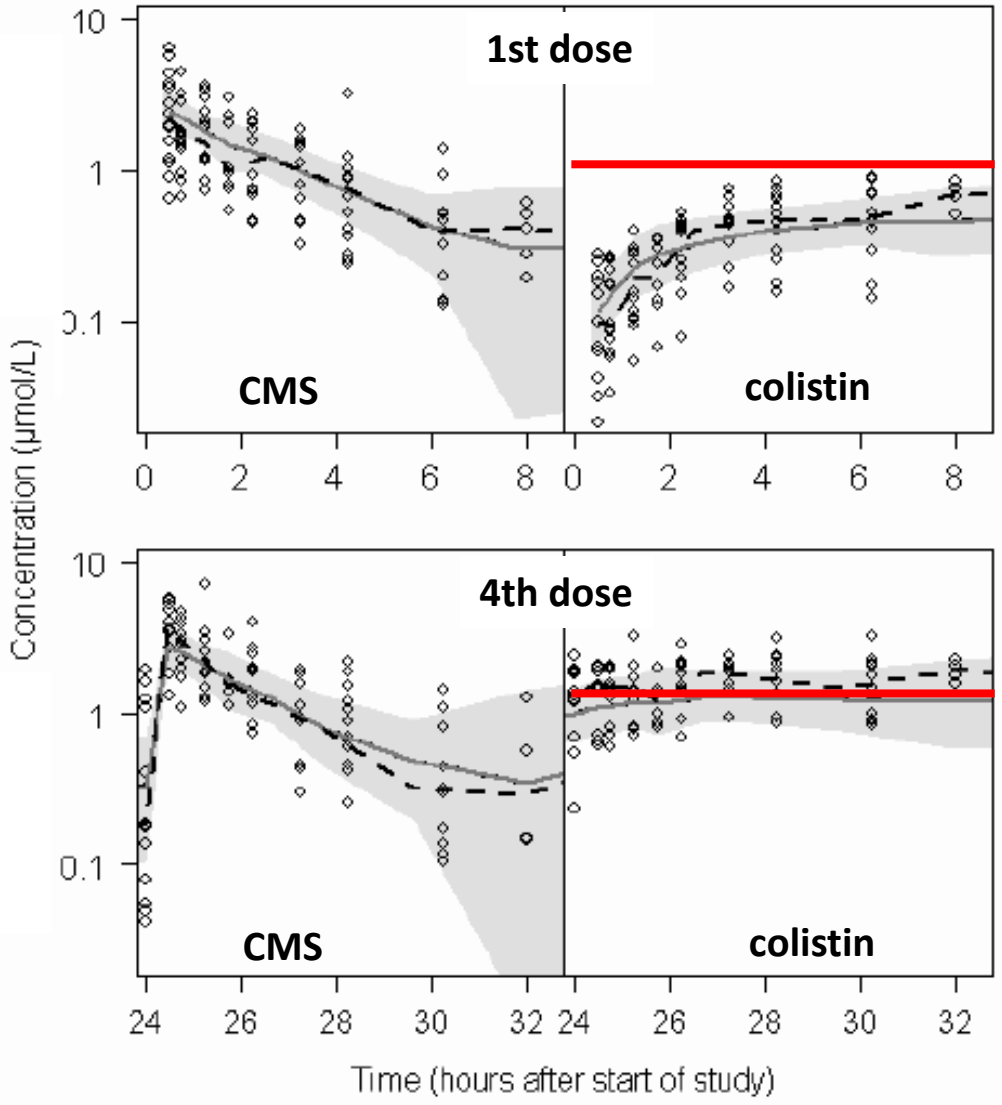
PK in critically-ill patients

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

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

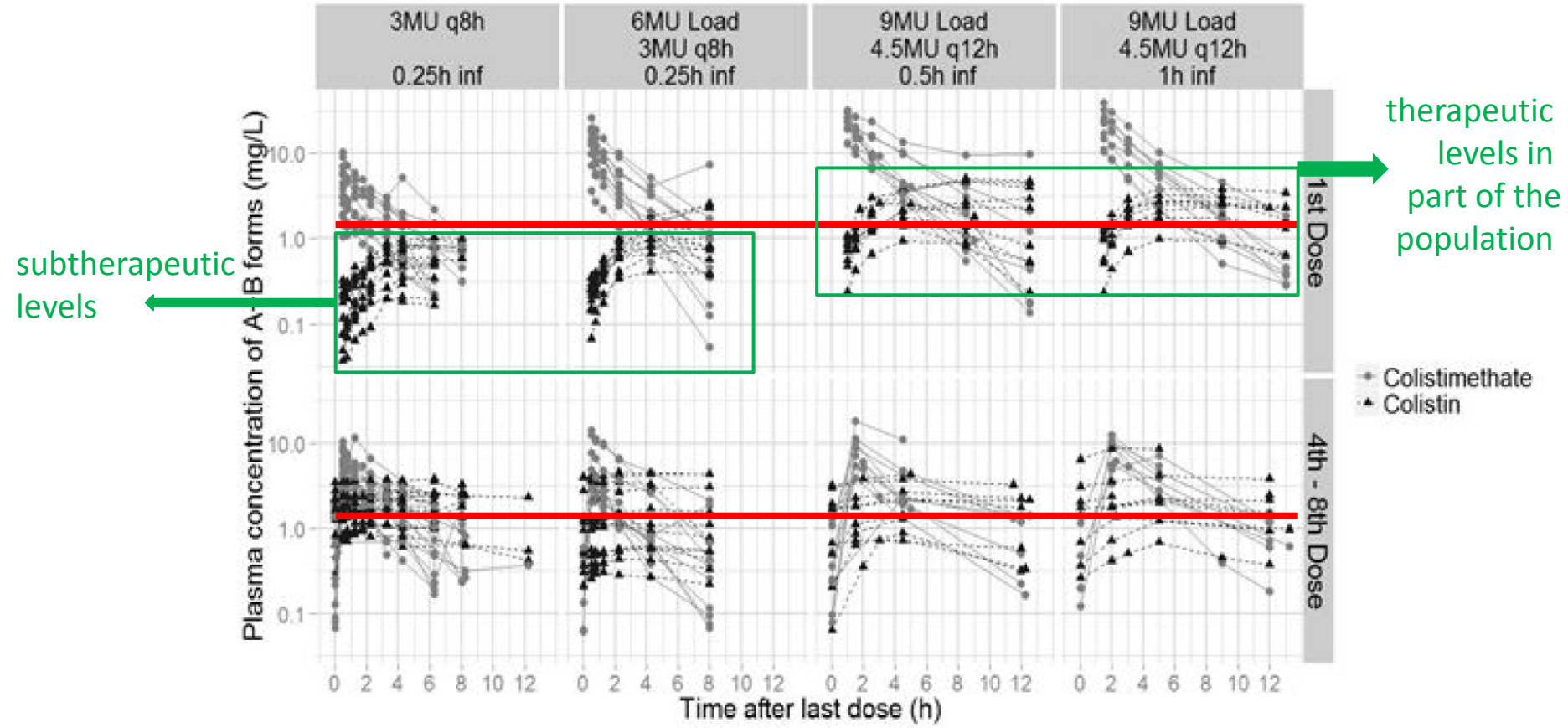
Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

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



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

Usefulness of a loading dose in critically-ill patients



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

Colistin penetration in CSF

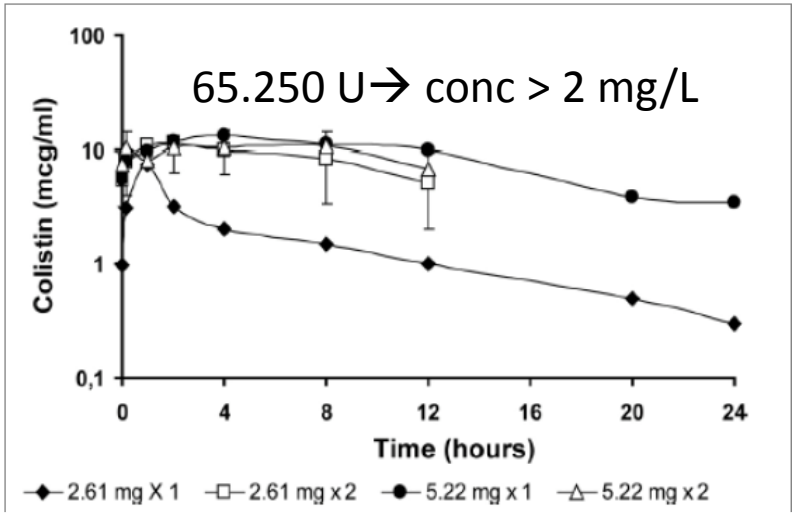
By IV route: subtherapeutic levels[1-2] !

- 5 adults: 2-3 MU x 3/day: ratio CSF/ serum: 0.05
- 5 children: 60.000-225.000 UI/kg/day:

  colistin in CSF 0.02 mg/L

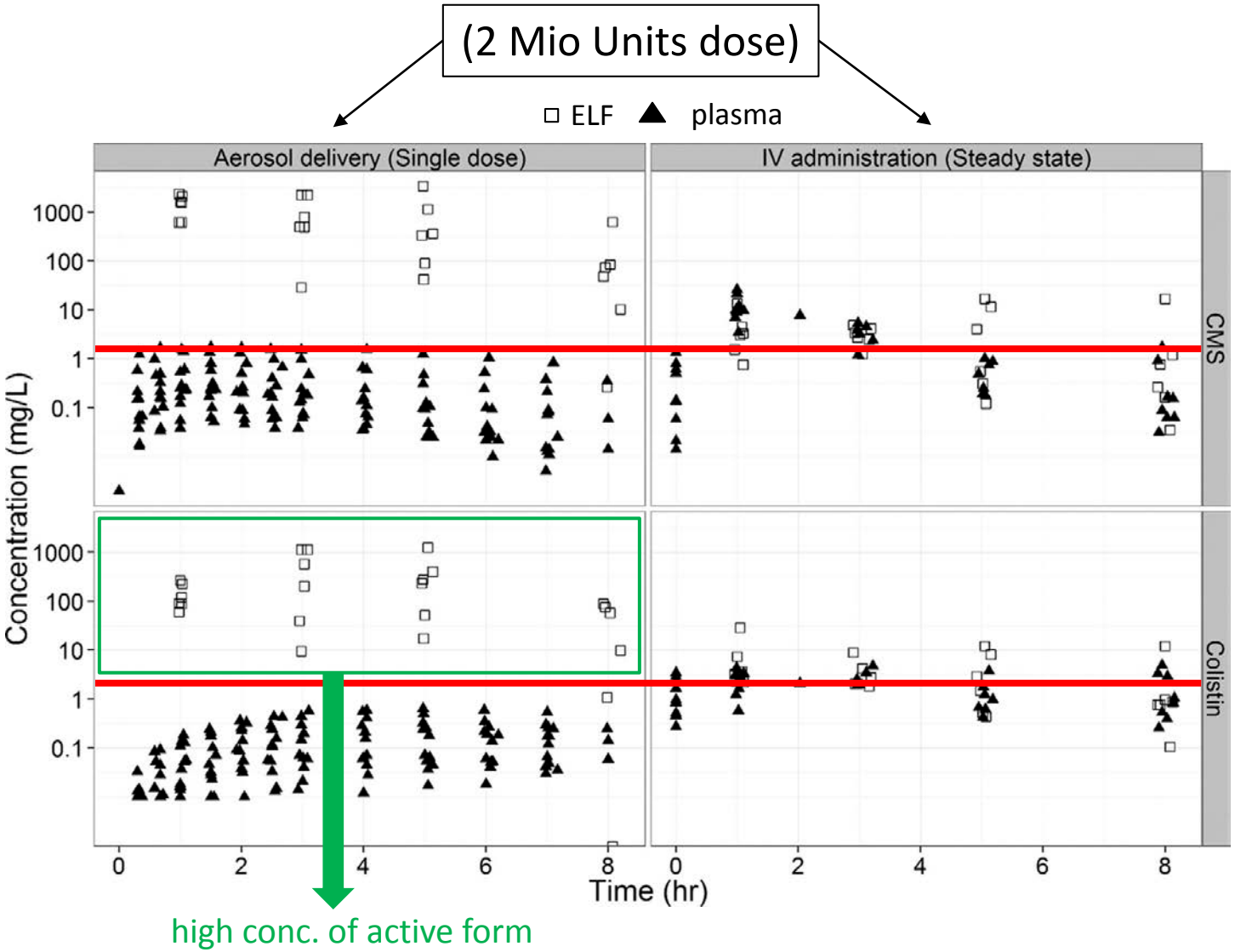
  0.05 mg/L if meningitis (34-67% serum conc.)

By intraventricular route[3]



[1]Markantonis et al, AAC 2009;53:4907-10; [2]Antachopoulos et al, AAC 2010; 54:3985-87
[3]Imberti et al, AAC 2012; 56:4416-21

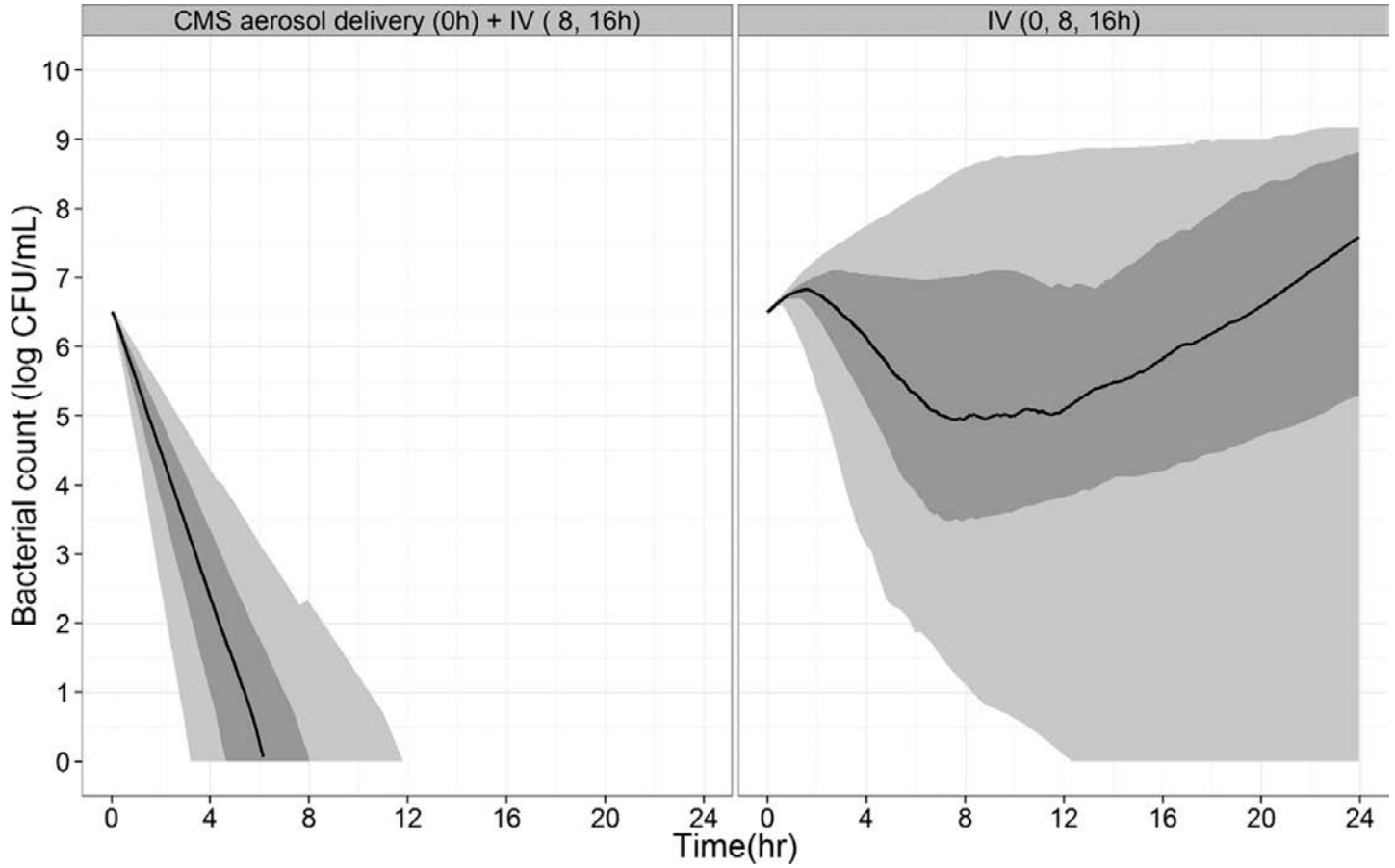
Pulmonary delivery: PK/PD rationale



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

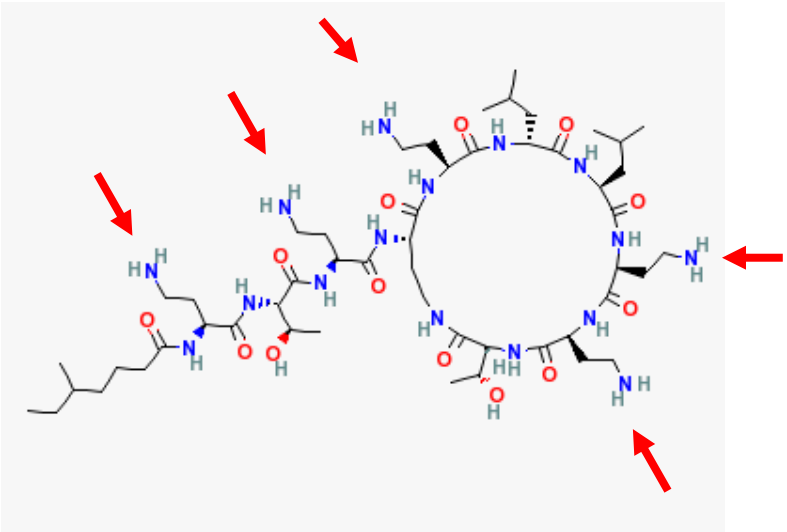
Pulmonary delivery: PK/PD rationale

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



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

A reminder: what is colistin ?



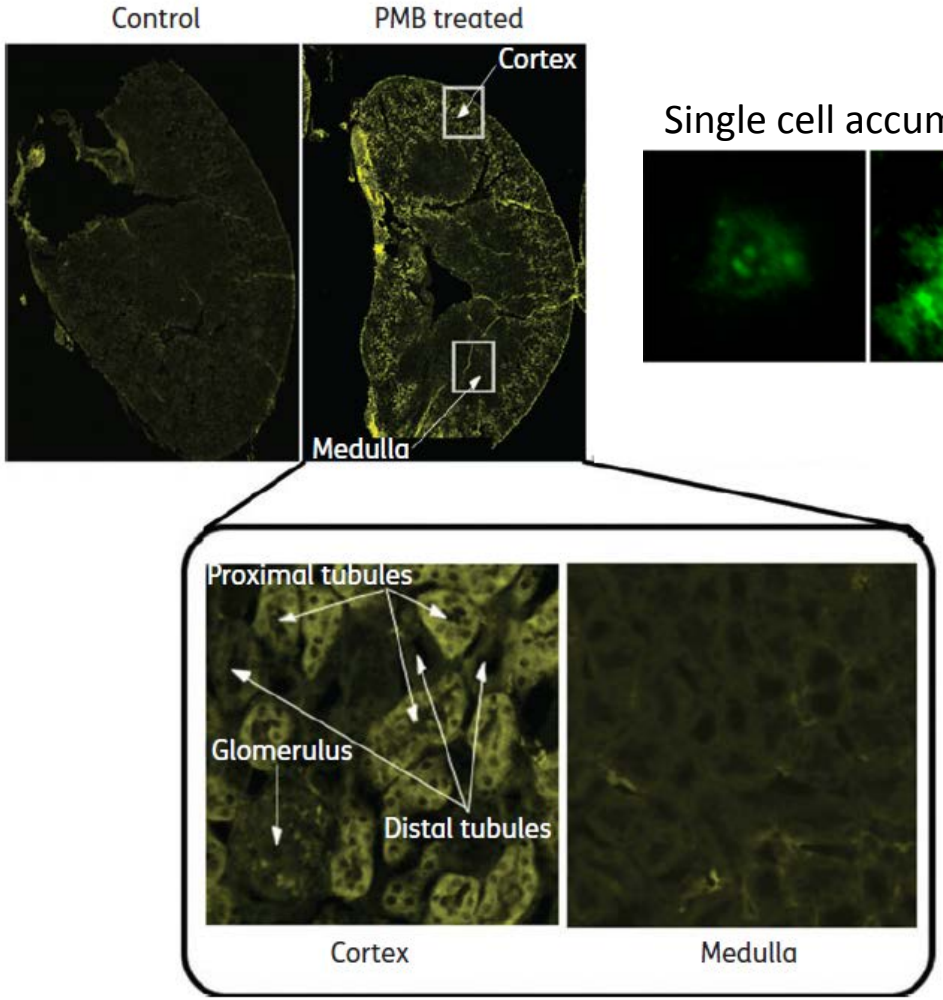
A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain

→ Interaction with eukaryotic cells ?

Toxicity:
the other flip of the coin

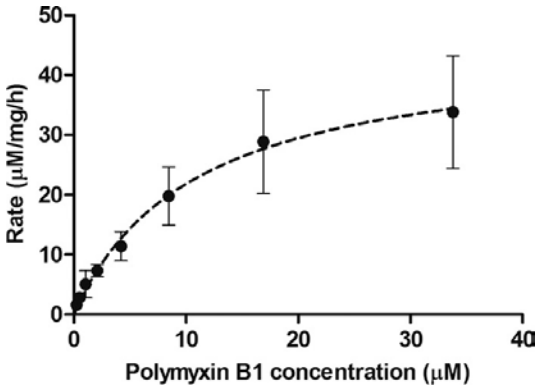
What about renal toxicity ?

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

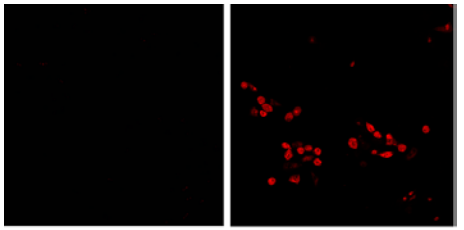


Single cell accumulation

Saturable process (megalin)



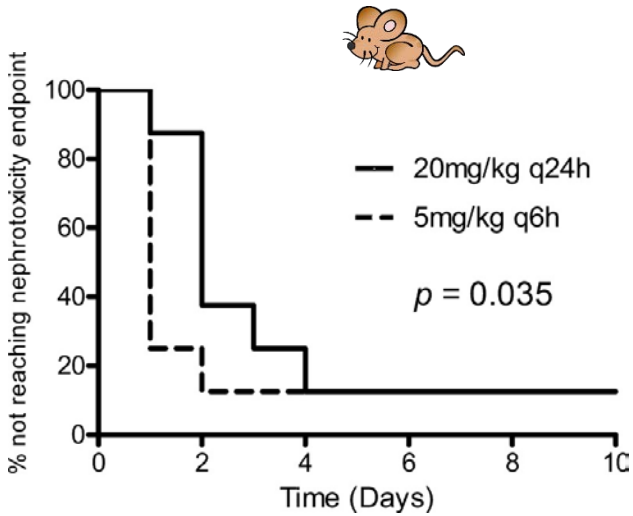
ROS production



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

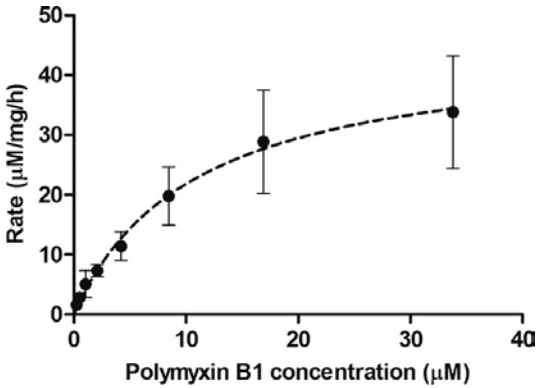
What about renal toxicity ?

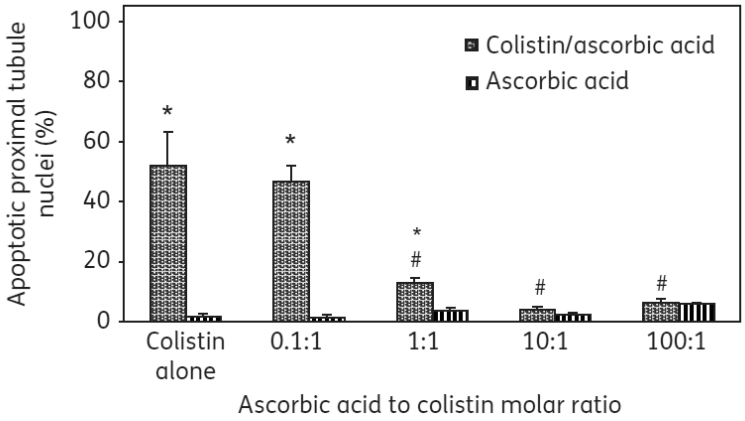
2. Strategies to reduce toxicity



non fractionated doses

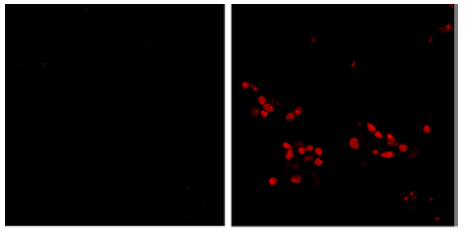
Saturable process (megalin)





combination with ascorbic acid

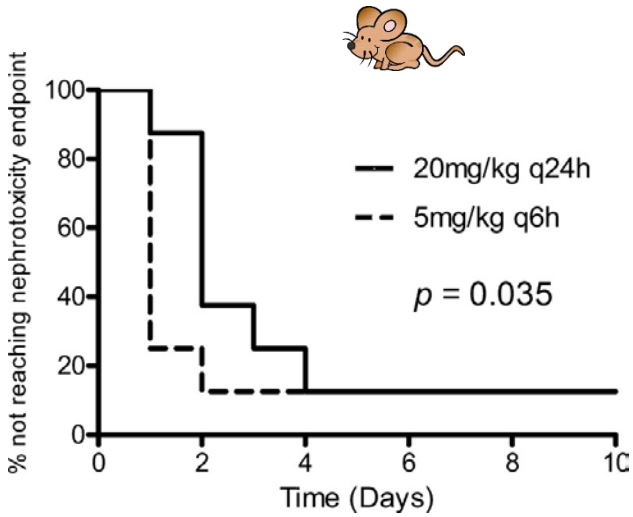
ROS production



Abdelraouf et al, AAC 2012; 56:4625-9; Yousef et al, JAC 2012; 67:452-9

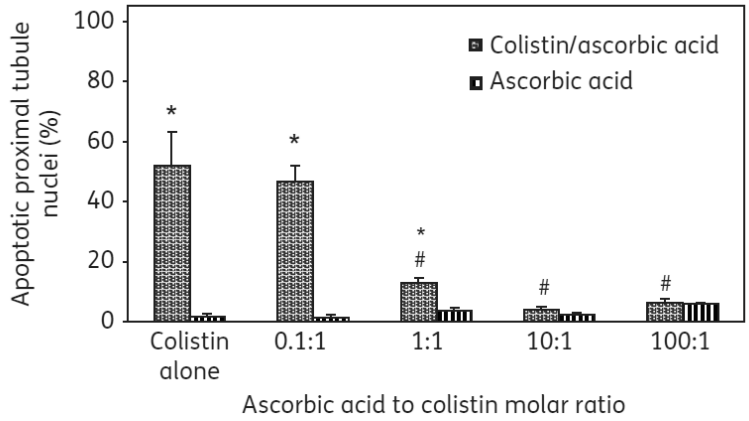
What about renal toxicity ?

2. Strategies to reduce toxicity: do they work in the clinics ?



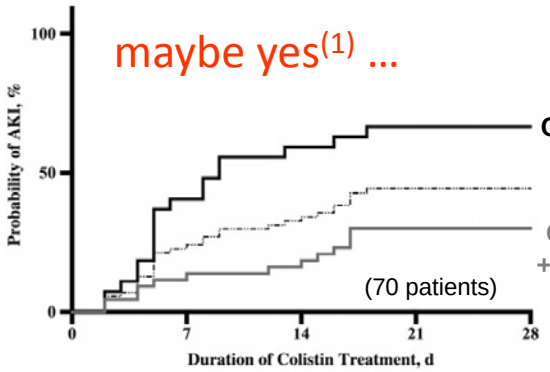
non fractionated doses

Serum half-life too long in humans …



combination with ascorbic acid

maybe yes[1] …



maybe no[2] …

Creatinine data and classification of AKI according to the RIFLE criteria for the patients in each treatment group

Outcome	Value for treatment group: Colistin-ascorbic acid (n = 13)	Colistin (n = 15)	P value
AKI (RIFLE criteria) [n (%)]			
Risk	0 (0)	2 (13.3)	0.484
Injury	2 (15.4)	6 (40.0)	0.221
Failure	5 (38.5)	1 (6.7)	0.069
All	7 (53.8)	9 (60.0)	0.956

[1] Dalfino et al, CID 2015; doi 10.1093/cid/civ717; [2] Sirijatuphat et al, AAC 2015; 59:3224-32

Renal toxicity in clinical practice

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

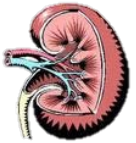
- Limited number of patients included
- Severity of underlying renal disease variable
- Dose of colistin variable
- Definition of nephrotoxicity variable:

The impact of definition on an individual cohort

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

Pogue JM et al ECCMID 2014

Risk factors for nephrotoxicity (1/2)



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

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

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

Risk factors for nephrotoxicity (2/2)

Multivariate analysis for independent risk factors for colistin-associated nephrotoxicity

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

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

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

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

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

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

Relationship between C_{min} and toxicity

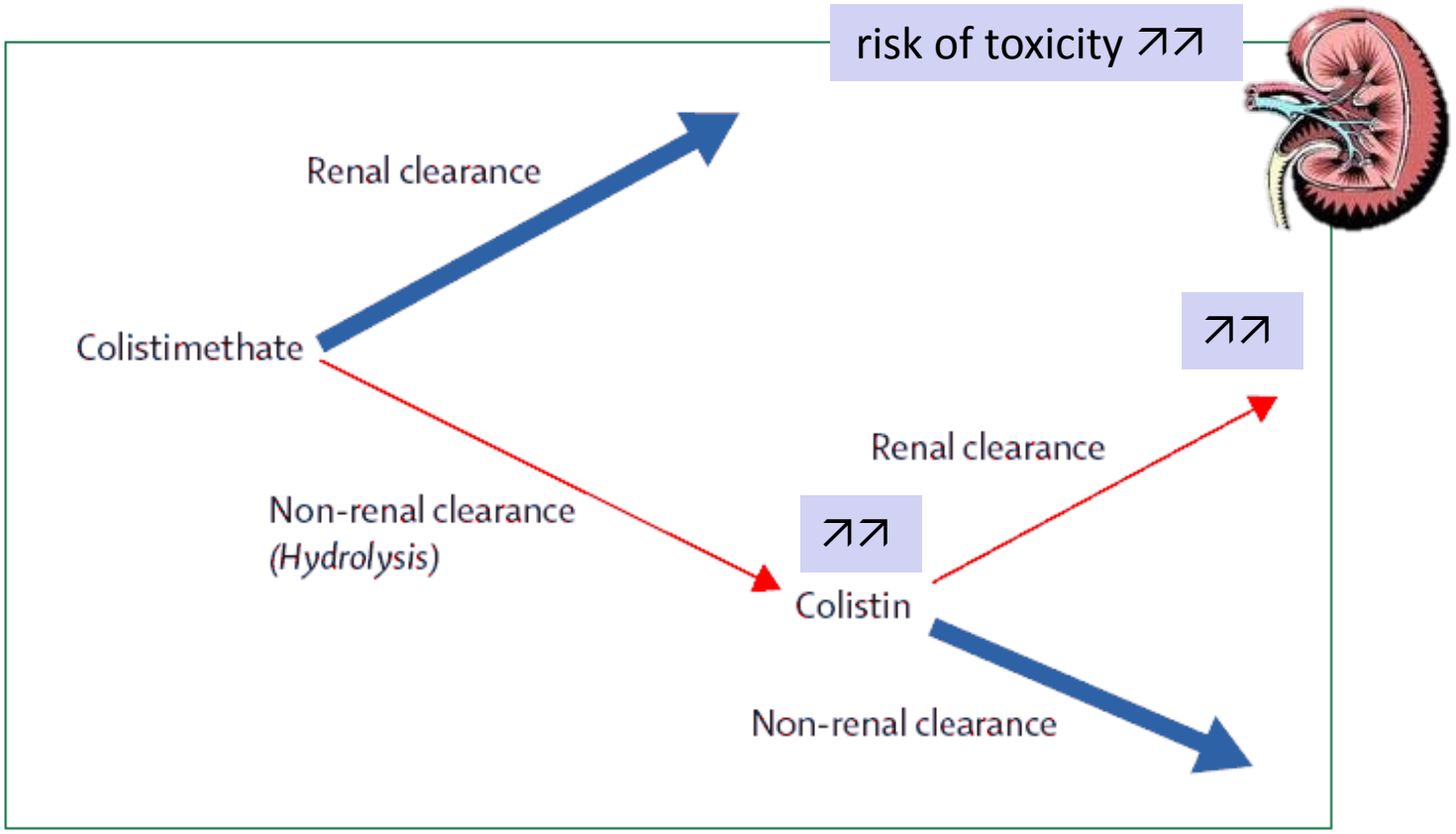


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

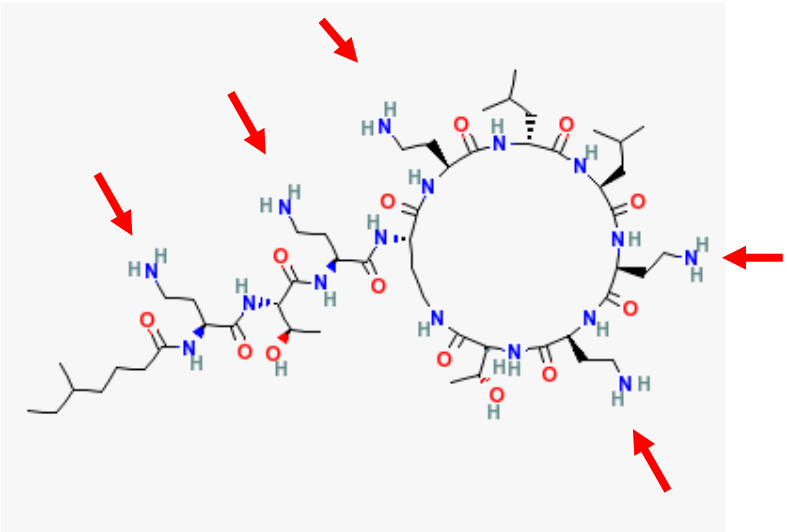
Toxicity by intratechal/intraventricular route

In 9/82 patients (11 %)

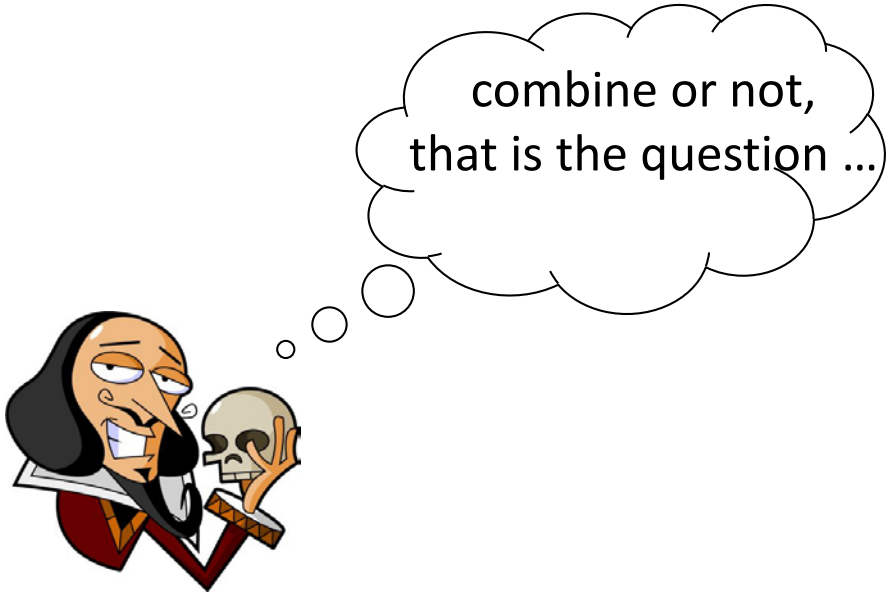
- chemical meningitis (3)
- chemical ventriculitis (2)
- seizures (3)
- *cauda equina* syndrome (1)

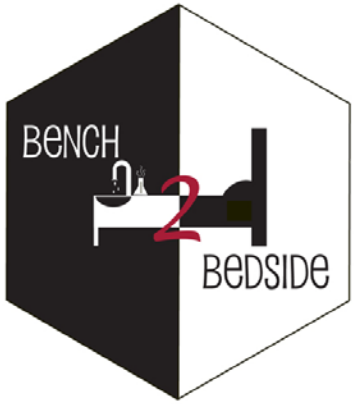
Karaiskos et al, IJAA 2013; 41:499-508

A reminder: what is colistin ?



Clinical experience:





from bench to bedside…

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

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

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

K. pneumoniae infections (2/3 bloodstream)

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

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

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

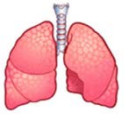
Tumbarello et al; JAC 2015;70:2133-43

CNS infections : intratechal-intraventricular route

Pathogen	N episodes	Median dose of CST IT/IVentr	Success rate
Acinetobacter spp.	83	125.000 UI	89%
Pseudomonas spp.	12	125.000 UI	83%
Klebsiella spp.	15	62.500- 250.000 UI	79%

Karaiskos et al, IJAA 2013; 41:499-508; Bargiacchi et al, Infection 2014;42:801-9; Remes et al, J Neurosurg 2014;119:1596-602; Karagoz et al, IJAA 2014; 43:93-94; Ziaka et al, AAC 2013;57:1938-40; Nevrekar et al, Ann Pharm. 2014; 48:274-8

Pulmonary infections : inhalation route



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

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

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

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

Current dosing recommendations

Target Css ≥ 2 mg/L
< 2.5 mg/L

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

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

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

Current dosing recommendations: EMA vs FDA

Table 1. Recently Updated EMA- and FDA-approved Daily Maintenance Dose Suggestions for Colistimethate in Patients with Various Degrees of Renal Function

Creatinine Clearance (mL/min)	EMA-approved Daily Dose[a]	FDA-approved Daily Dose[c]
≥80	9 MIU[b] (~300 mg CBA)	2.5-5 mg CBA per kg
50 - <80	9 MIU[b] (~300 mg CBA)	2.5-3.8 mg CBA per kg
30 - <50	5.5-7.5 MIU (~183-250 mg CBA)	2.5 mg CBA per kg
10 - <30	4.5-5.5 MIU (~150-183 mg CBA)	1 mg CBA per kg[d]
<10	3.5 MIU (~117 mg CBA)	Not stated

[a] EMA expressed doses in terms of millions of International Units (MIU). The EMA doses have been converted to approximately equivalent doses expressed as milligrams of colistin base activity (CBA) and these are shown in parentheses.

[b] The EMA-approved product label indicates that daily doses up to 12 MIU (~400 mg CBA) may be required in patients with good renal function in some cases.

[c] The FDA-approved product label indicates that in obese individuals the dosage should be based on ideal body weight.

[d] The FDA-approved product label states 1.5 mg CBA per kg every 36 h, which has been converted in the table to the corresponding daily rate.

Nation *et al.* Updated United States and European dose recommendations for intravenous colistin: How do they perform? Clin. Infect. Dis., in press

EMA vs FDA

Table 2. EMA- and FDA-approved Daily Maintenance Dose Suggestions Evaluated

Group (Number of patients)	Creatinine Clearance (mL/min)	EMA Daily Dose Evaluated[a]	FDA Daily Doses Evaluated[c]	
			PBW	BW80kg
1 (51)	≥80	360mg CBA[b]	5mg/kg CBA	360mg CBA
2 (39)	50 - <80	300mg CBA	3.8mg/kg CBA	304mg CBA
3 (40)	30 - <50	250mg CBA	2.5mg/kg CBA	200mg CBA
4a (30)[e]	10 - <30	183mg CBA	1mg/kg CBA	80mg CBA
4b (2)[e]	<10	117mg CBA	1mg/kg CBA[d]	80mg CBA[d]

[a] EMA daily doses are expressed in terms of milligrams of CBA in accordance with Table 1. Where a range of doses for a given renal function category was suggested (Table 1), the highest dose in that range was evaluated.

[b] A daily dose of 360 mg CBA was used since the EMA guidelines state up to 400mg (12 MIU) may be used for patients with good kidney function.

[c] For FDA-approved dose suggestions, two approaches were evaluated. The first (PBW approach) involved use of the body weight of each of the 162 critically-ill patients; for obese patients, the ideal body weight was used. For the second approach (BW80kg), a body weight of 80 kg was used. With both approaches, the mg/kg daily dose of CBA in Table 1 was used; where a range of mg/kg daily doses for a given renal function category was suggested, the highest dose in that range was evaluated. With both approaches, the maximum absolute daily dose was 360 mg CBA.

[d] For the two patients with a creatinine clearance of 5.4 and 9.2 mL/min, calculations were conducted using a daily dose of CBA of 1 mg/kg as suggested in the FDA-approved product label for patients having creatinine clearance of 10 - <30 mL/min (Table 1).

[e] For the evaluation (results of which are presented in Table 3 and Figure 1), groups 4a and 4b were merged into one group comprising 32 patients.

Nation *et al.* Updated United States and European dose recommendations for intravenous colistin: How do they perform? Clin. Infect. Dis., in press

EMA vs FDA

Table 3. Average Steady-state Plasma Colistin Concentration ($C_{ss,avg}$) with EMA- and FDA-approved Daily Dose Suggestions for Each of the Renal Function Groups

Group[a]	Creatinine Clearance (mL/min)	Median (Range) Plasma Colistin $C_{ss,avg}$ (mg/L)			
		Physician-selected Dose	EMA-approved Dose	FDA-approved Dose	
				PBW[b]	BW80kg[b]
1	≥80	1.09 (0.24 – 5.20)	1.46 (0.65 - 6.24)	1.29 (0.45 – 5.28)	1.46 (0.65 – 6.24)
2	50 - <80	2.20 (0.78 – 7.39)	3.17 (1.12 - 7.68)	2.20 (0.77 – 6.37)	3.22 (1.14 – 7.78)
3	30 - <50	3.08 (1.12 – 7.79)	3.82 (1.73 - 7.55)	1.96 (0.78 – 4.36)	3.05 (1.38 – 6.04)
4	<30	3.04 (1.20 – 9.81)	3.43 (1.18 - 7.33)	1.08 (0.36 – 2.91)	1.53 (0.51 – 3.20)

[a] Group 4 comprised 30 and 2 patients with creatinine clearance in the ranges 10 - <30 mL/min and <10 mL/min, respectively. See Table 2 for details of number of patients in each creatinine clearance cluster.

[b] PBW: the actual body weight of each of the 162 critically-ill patients (ideal body weight for obese patients) was used. BW80kg: a uniform body weight of 80 kg was used.

Nation *et al.* Updated United States and European dose recommendations for intravenous colistin: How do they perform? Clin. Infect. Dis., in press

EMA vs FDA

Table 3. Average Steady-state Plasma Colistin Concentration ($C_{ss,avg}$) with EMA- and

Conclusions. The study highlights important differences between the FDA- and EMA-approved dose recommendations and informs the setting of clinical breakpoints.

				PBW[b]	BW80kg[b]
1	≥80	1.09 (0.24 – 5.20)	1.46 (0.65 - 6.24)	1.29 (0.45 – 5.28)	1.46 (0.65 – 6.24)
2	50 - <80	2.20 (0.78 – 7.39)	3.17 (1.12 - 7.68)	2.20 (0.77 – 6.37)	3.22 (1.14 – 7.78)
3	30 - <50	3.08 (1.12 – 7.79)	3.82 (1.73 - 7.55)	1.96 (0.78 – 4.36)	3.05 (1.38 – 6.04)
4	<30	3.04 (1.20 – 9.81)	3.43 (1.18 - 7.33)	1.08 (0.36 – 2.91)	1.53 (0.51 – 3.20)

[a] Group 4 comprised 30 and 2 patients with creatinine clearance in the ranges 10 - <30 mL/min and <10 mL/min, respectively. See Table 2 for details of number of patients in each creatinine clearance cluster.

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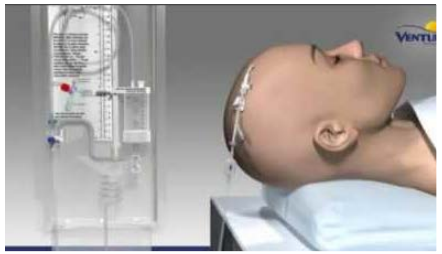
Nation *et al.* Updated United States and European dose recommendations for intravenous colistin: How do they perform? Clin. Infect. Dis., in press

Current dosing recommendations: EMA 2014

Intraventricular/thecal routes

- 125.000 U/day
  - Dilution in 3-4 ml NaCl
  - Drainage or evacuation of 3-4 ml CSF
  - Injection of 3-4 ml colistin solution
  - Purge tubules with 2 ml NaCl
  - Clamp deviation during 1 h
  - Change external deviation

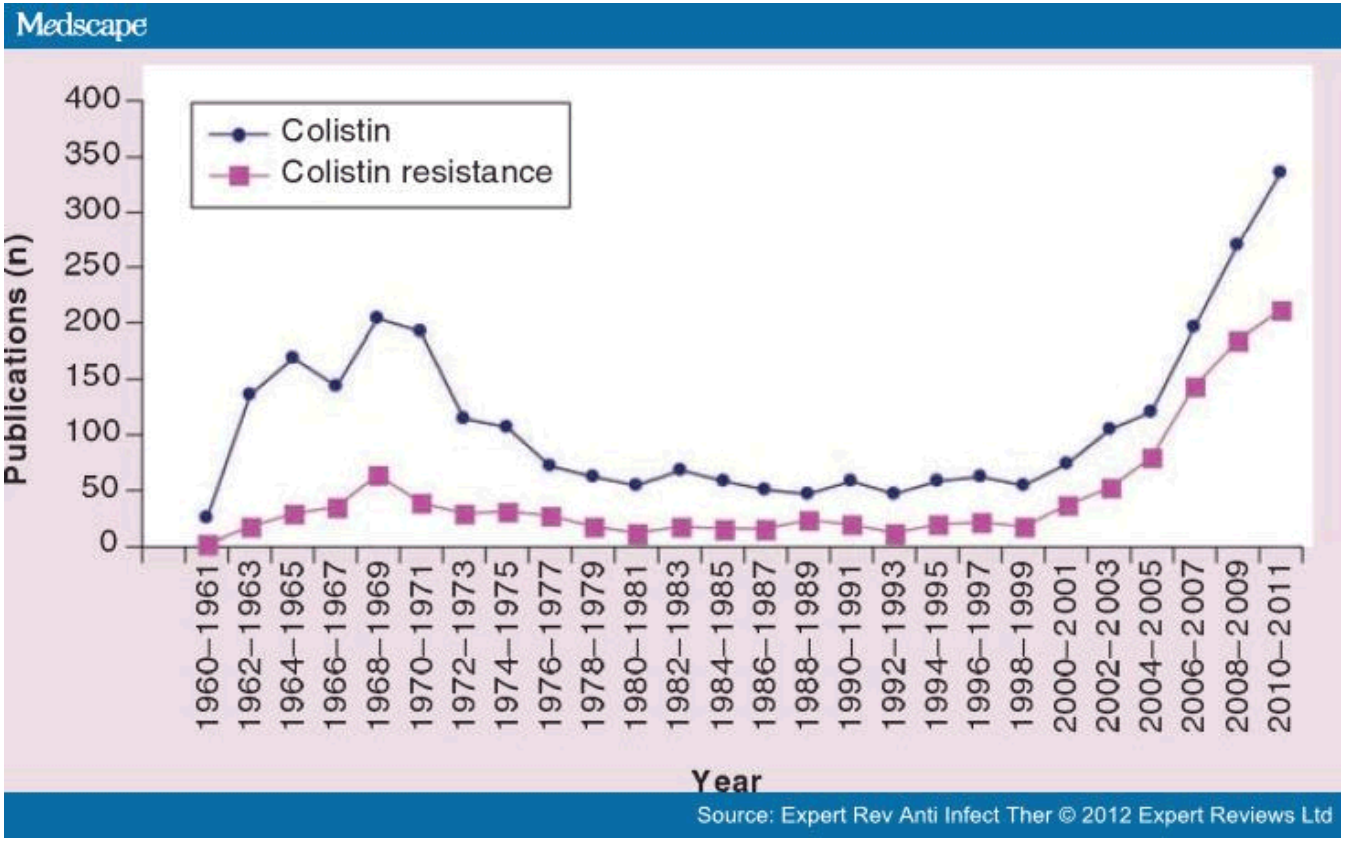


Nebulization

- 1-2 Mio U 3 X/day
  - Adults, adolescents and children ≥ 2 years
- 0.5-1 Mio U 2 X/day
  - Children < 2 years

Still a lot f work ahead of us….

But beware …



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