Partly based on data presented at POLYMYXINS 2015 September 22 - 24, San Diego, USA

COLISTIN:
what is new for an old antibiotic ?

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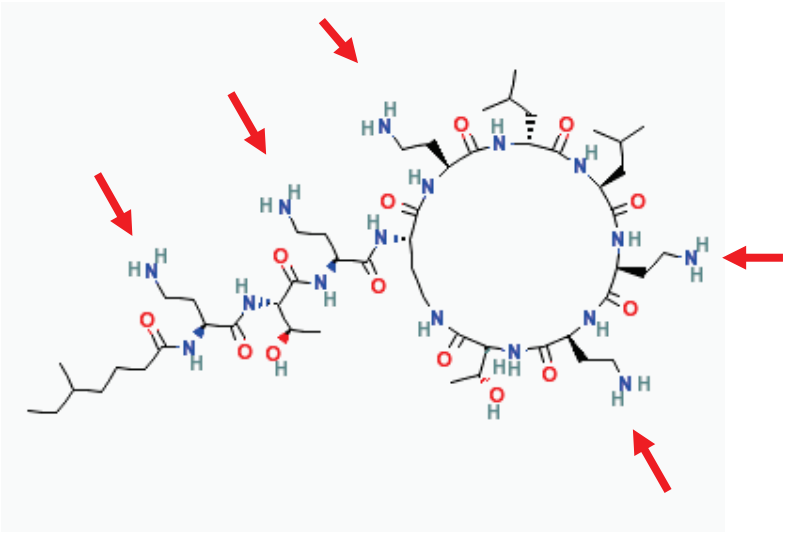
A reminder: what is colistin ?

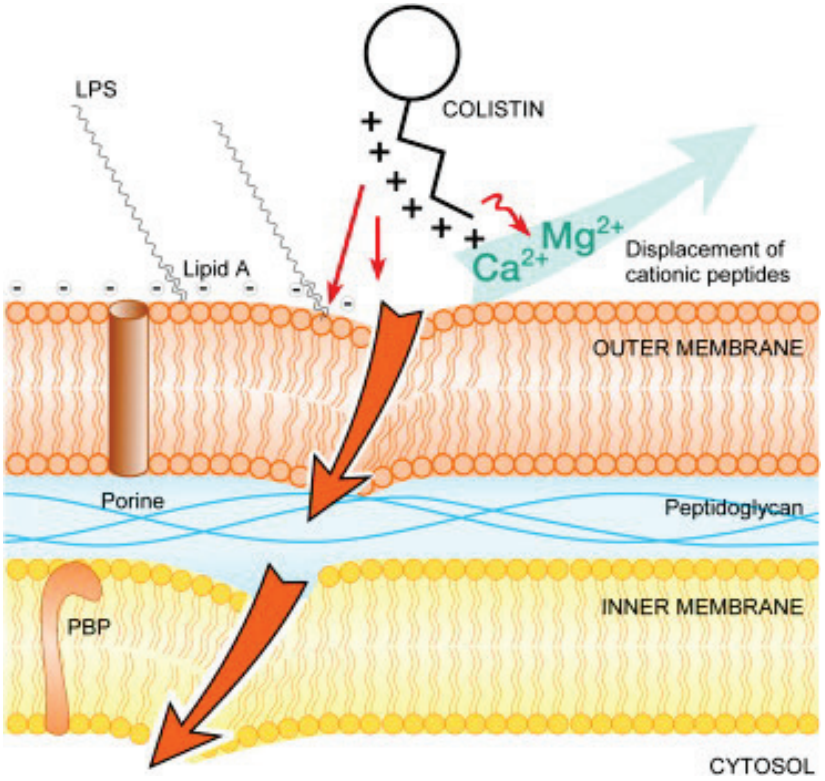


A cyclic **amphipathic** **polycationic peptide** with a short aliphatic side chain …

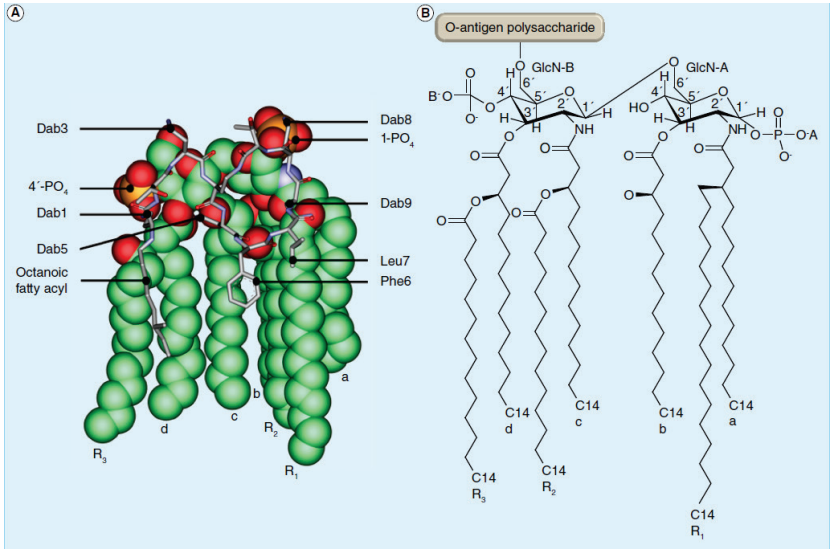
What does this structure tell you about the mode of action ?

How do polymyxins work ?

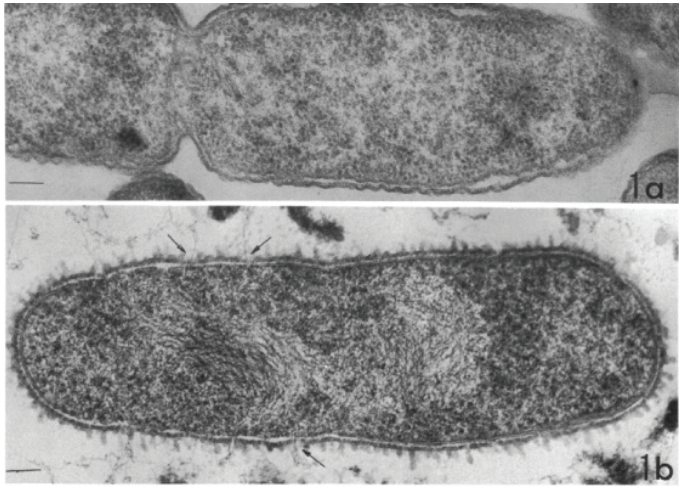
1. Interaction with LPS in the outer membrane



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



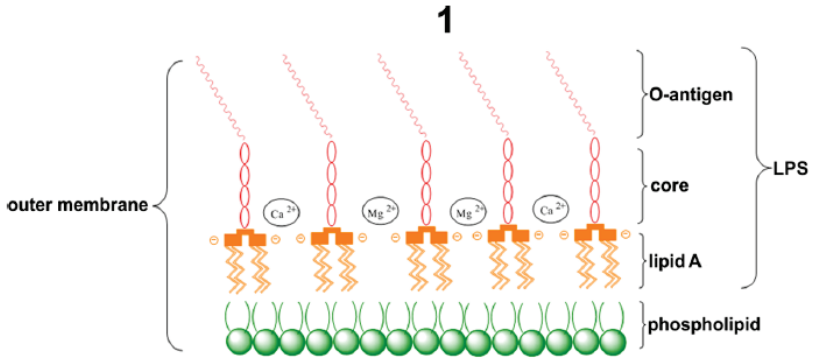
Velkov et al, Future Microbiol. 2013; 8:711–24

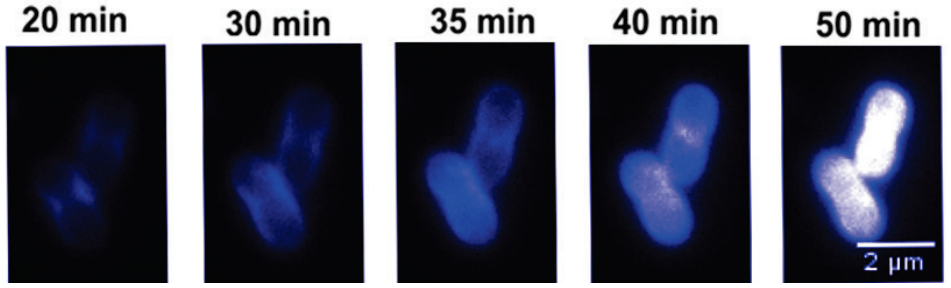


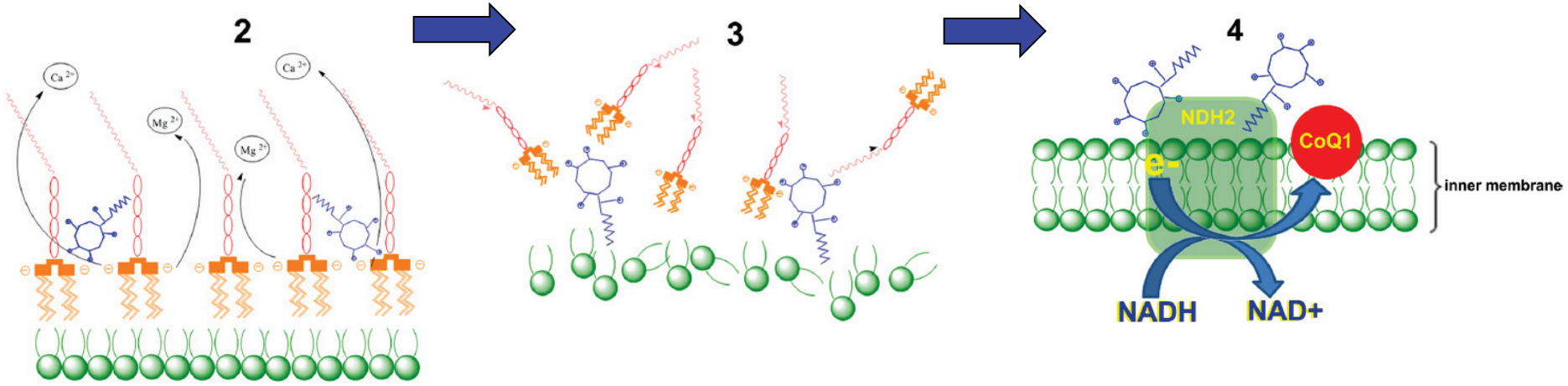
Koike et al, J. Bacteriol. 1969; 97:448-52

How do polymyxins work ?

2. Disruption of envelope integrity and access to bacterial cytosol







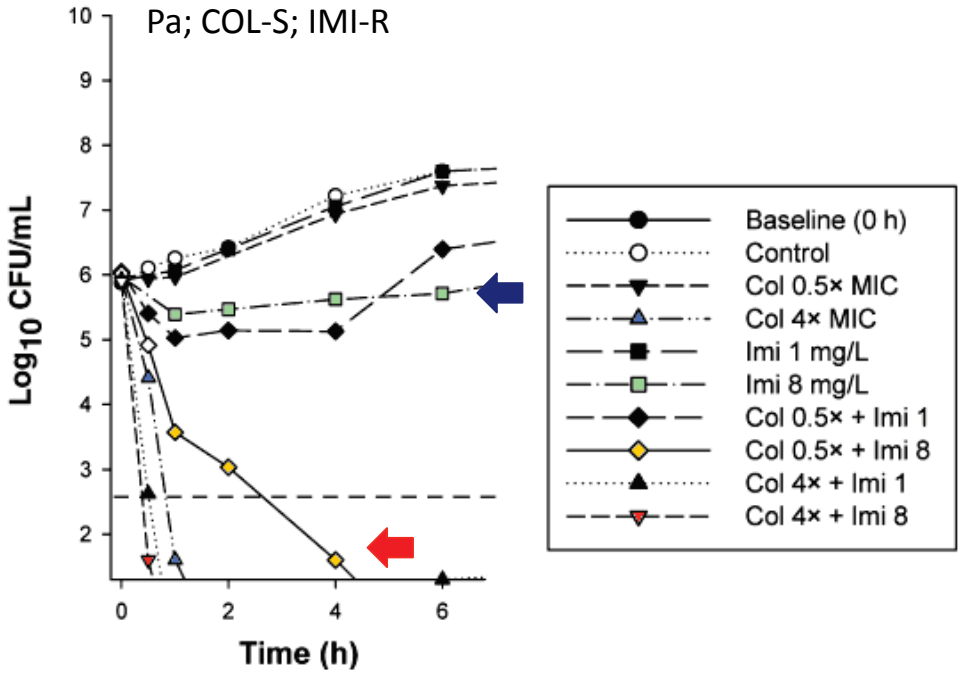
Deris et al, Bioconjugate Chem. 2014; 25:750−60; J Antibiot. 2014; 67:147–51

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 ?

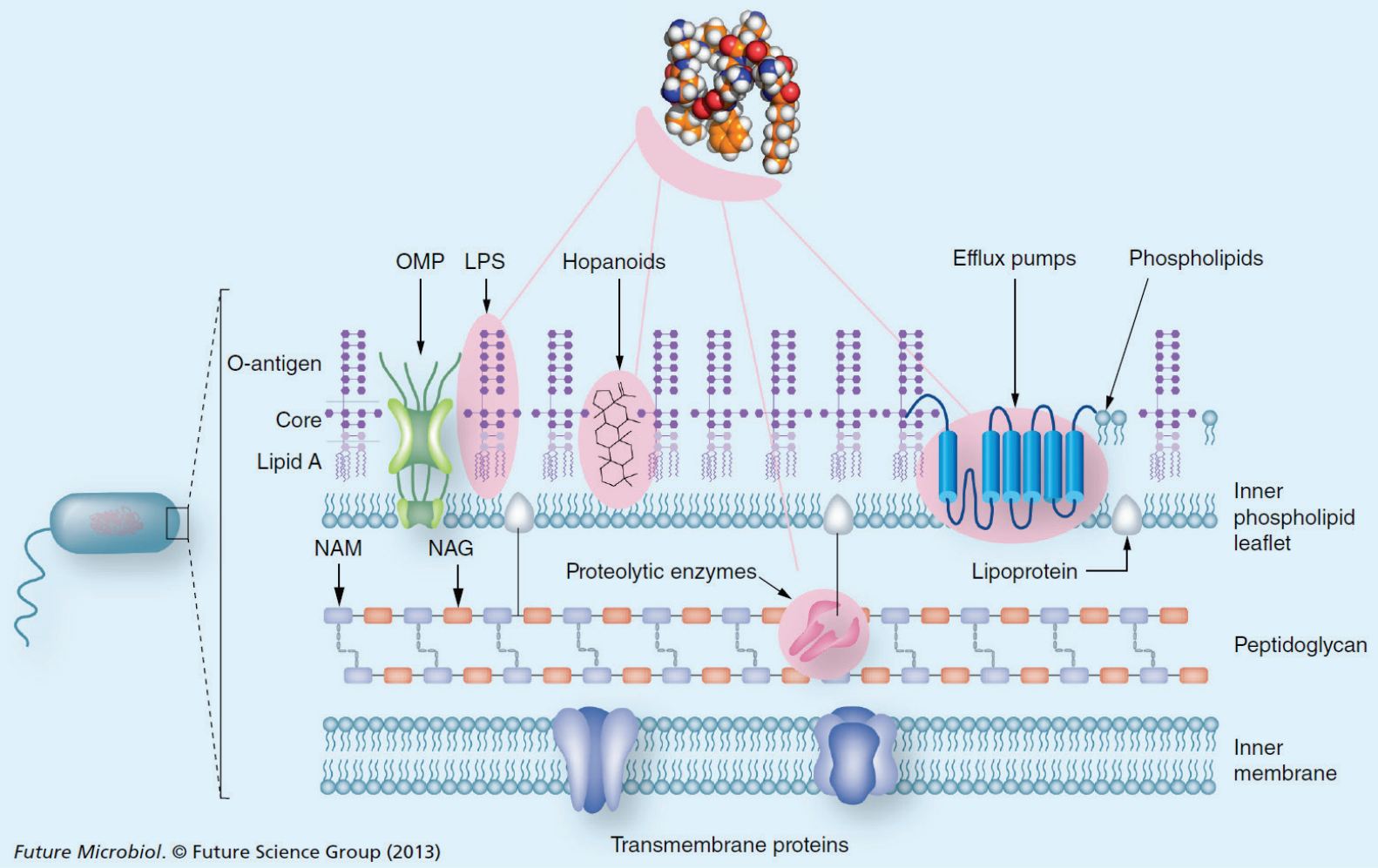


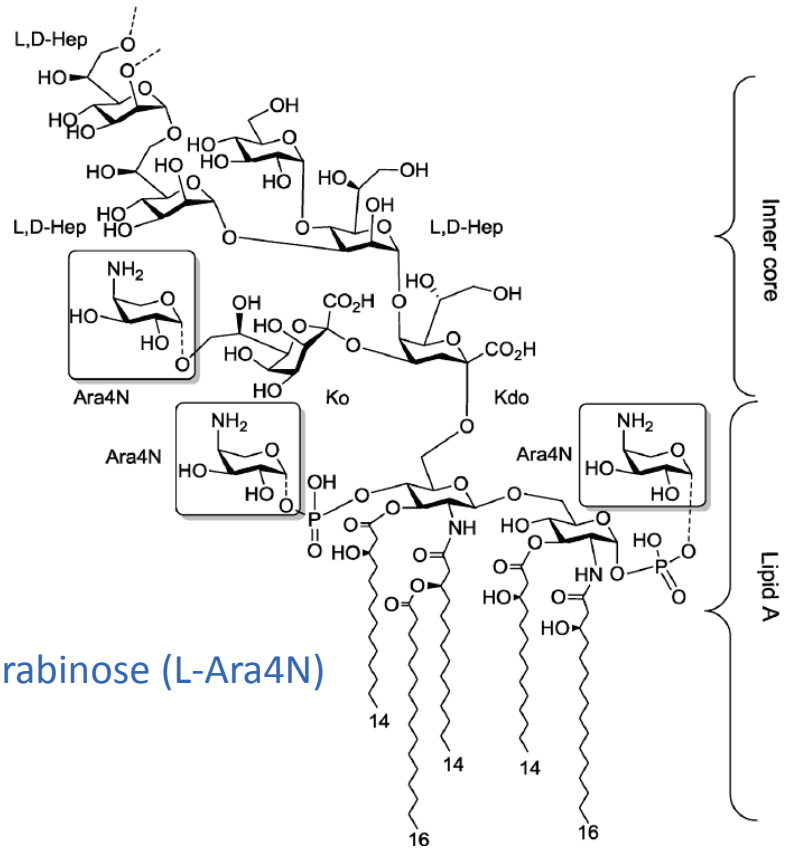
Figure 2. Key mechanisms of polymyxin resistance in Gram-negative bacteria. The pink shading indicates molecular determinants of polymyxin resistance.
LPS: Lipopolysaccharide; NAG: *N*-acetylglucosamine; NAM: *N*-acetylmuramic acid; OMP: Outer membrane protein.

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**



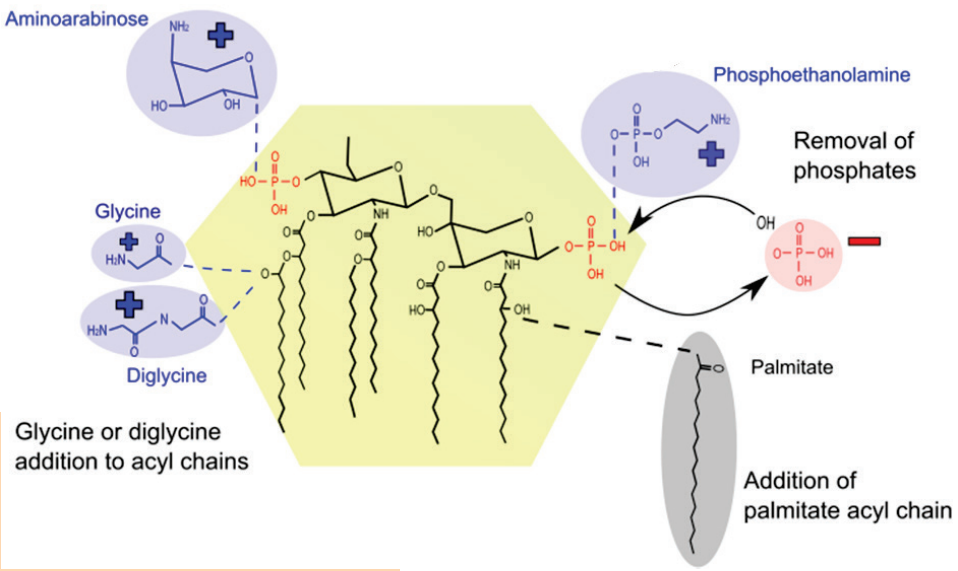
4-amino-4-deoxy-L-arabinose (L-Ara4N)

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

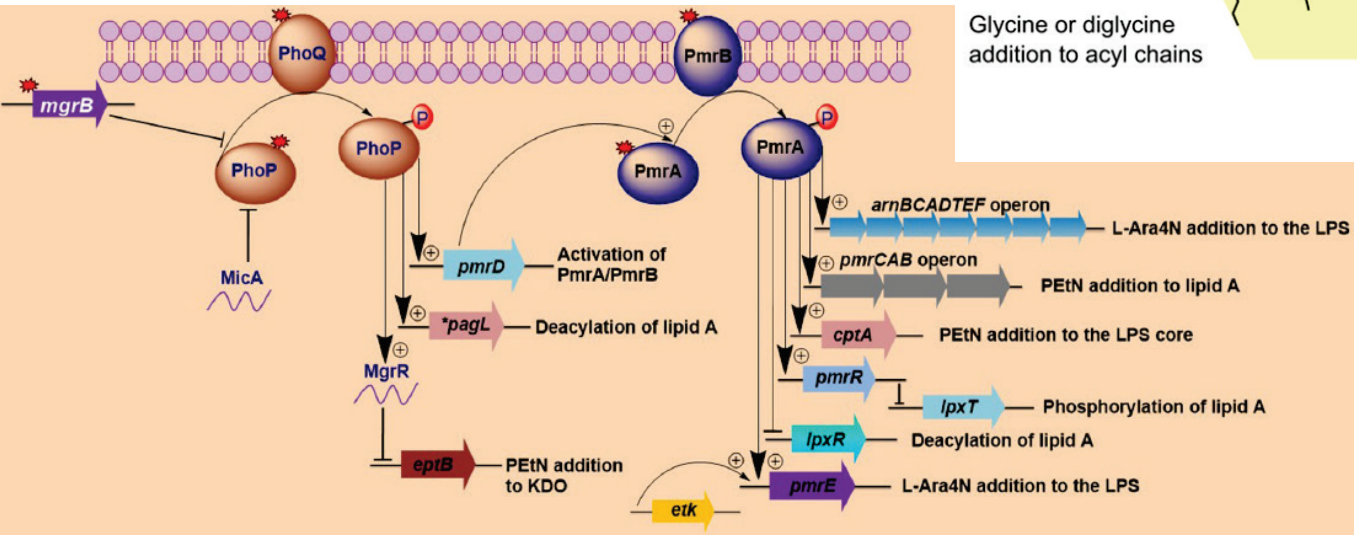
Underlying mechanisms and clinical implications

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

Underlying mechanisms and clinical implications

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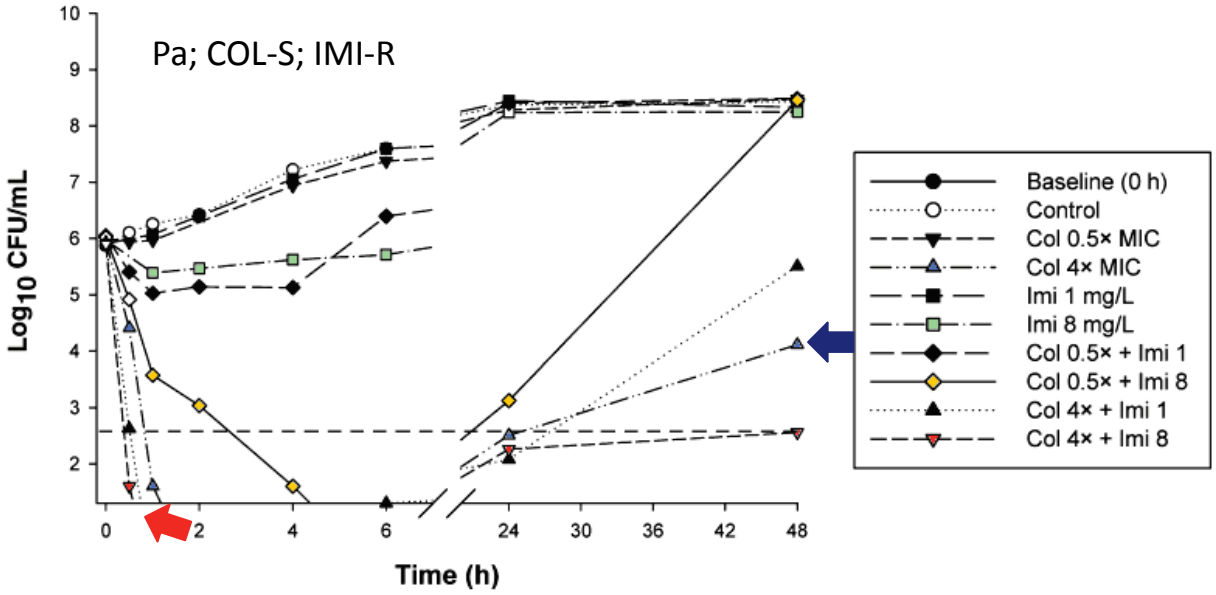
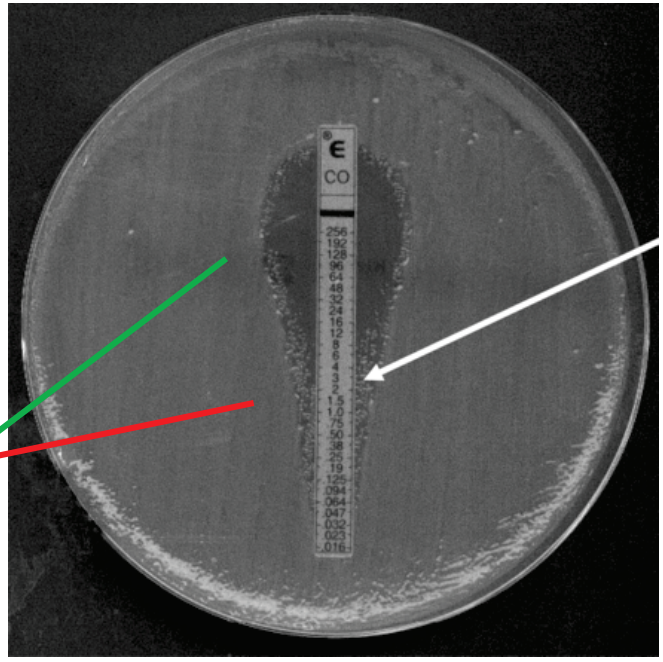


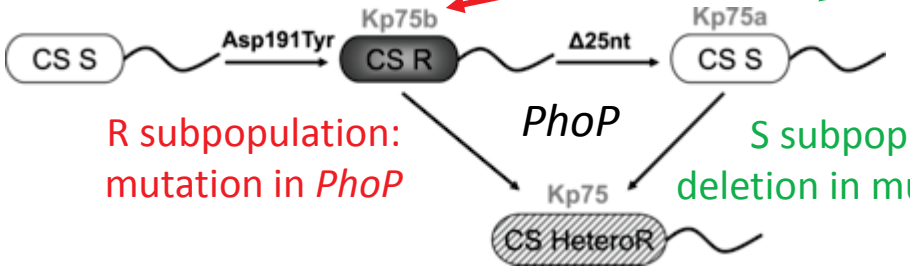
Bergen et al, Pharmacotherapy 2015; 35:34–42

Underlying mechanisms and clinical implications

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

→ **visible on E-tests only**

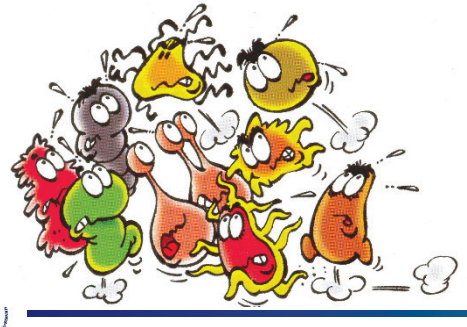




Javol et al, AAC 2015; 59:2780-4

Current susceptibility breakpoints

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

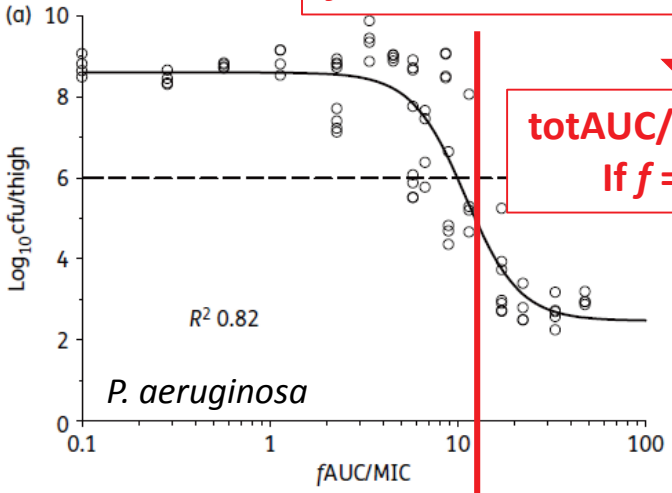


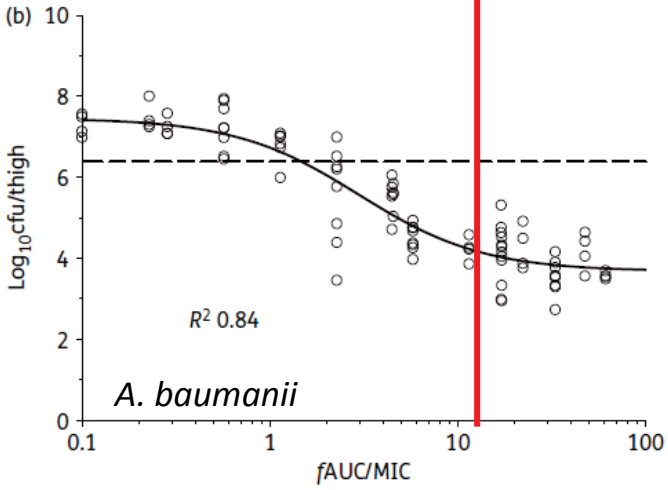
PK/PD : lessons from animal models

Tigh infection

*f*AUC/MIC = 12 → 2 log kill

totAUC/MIC = 24
If *f* =50%

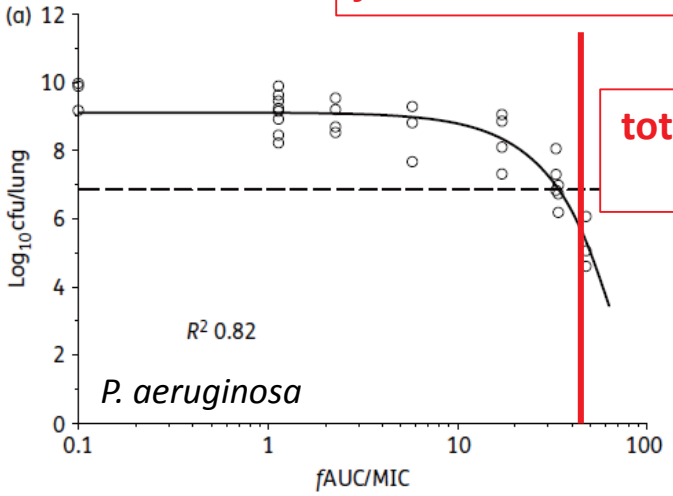




Lung infection

*f*AUC/MIC = 48 → 1 log kill

totAUC/MIC = 96
If *f* =50%



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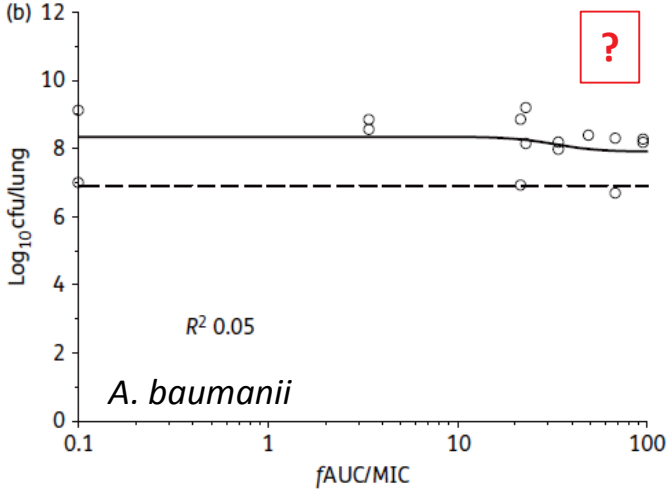
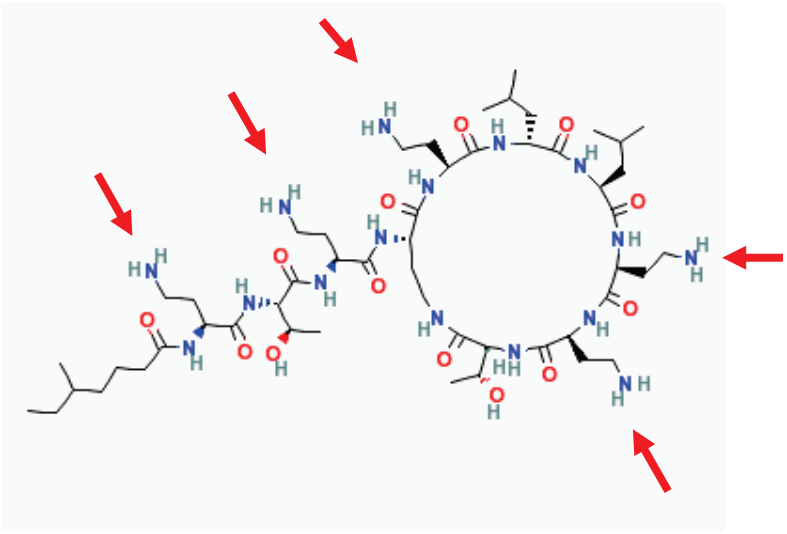


Cheah et al, JAC 2015; doi:10.1093/jac/dkv267

A reminder: what is colistin ?

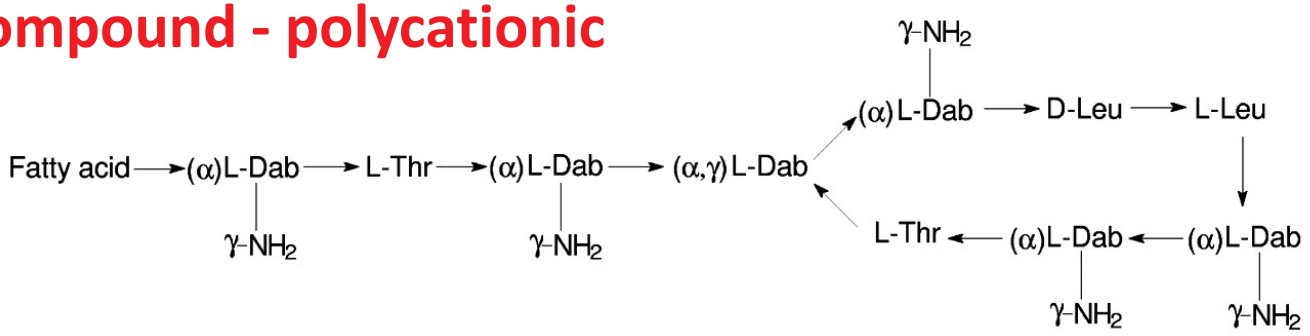


A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain administered as a prodrug …

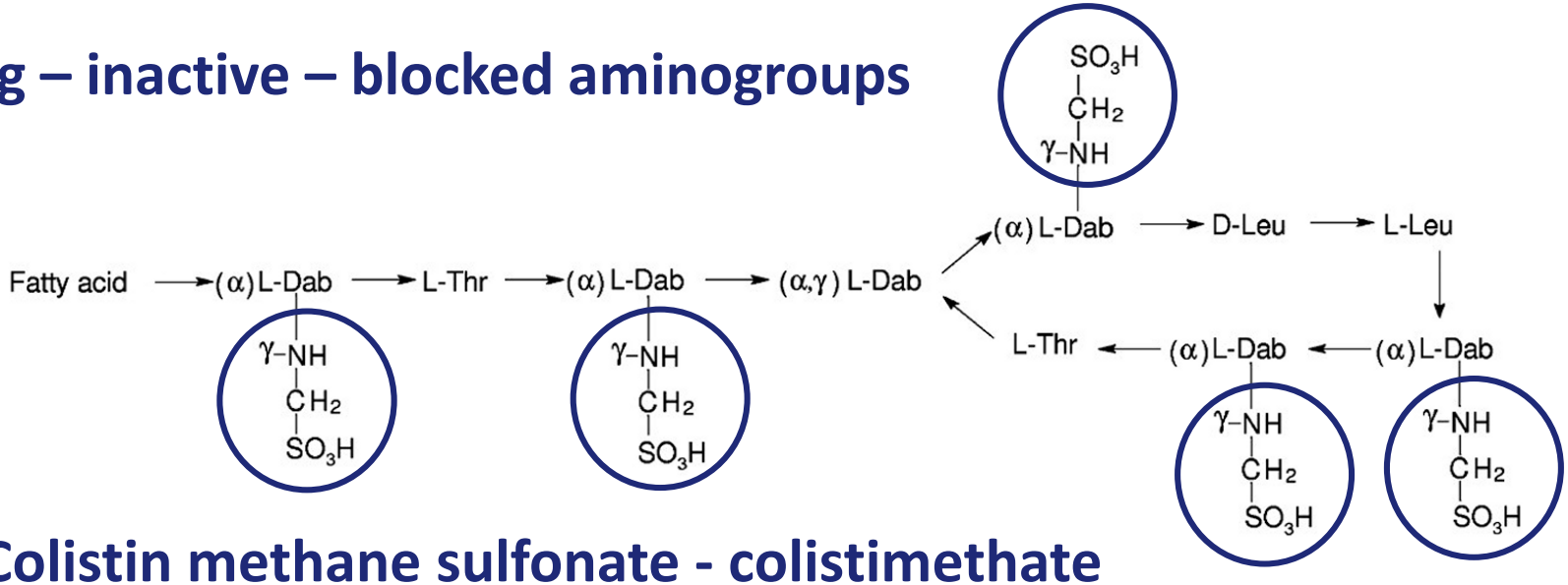
From the molecule to the drug …

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

Clinical form of colistin

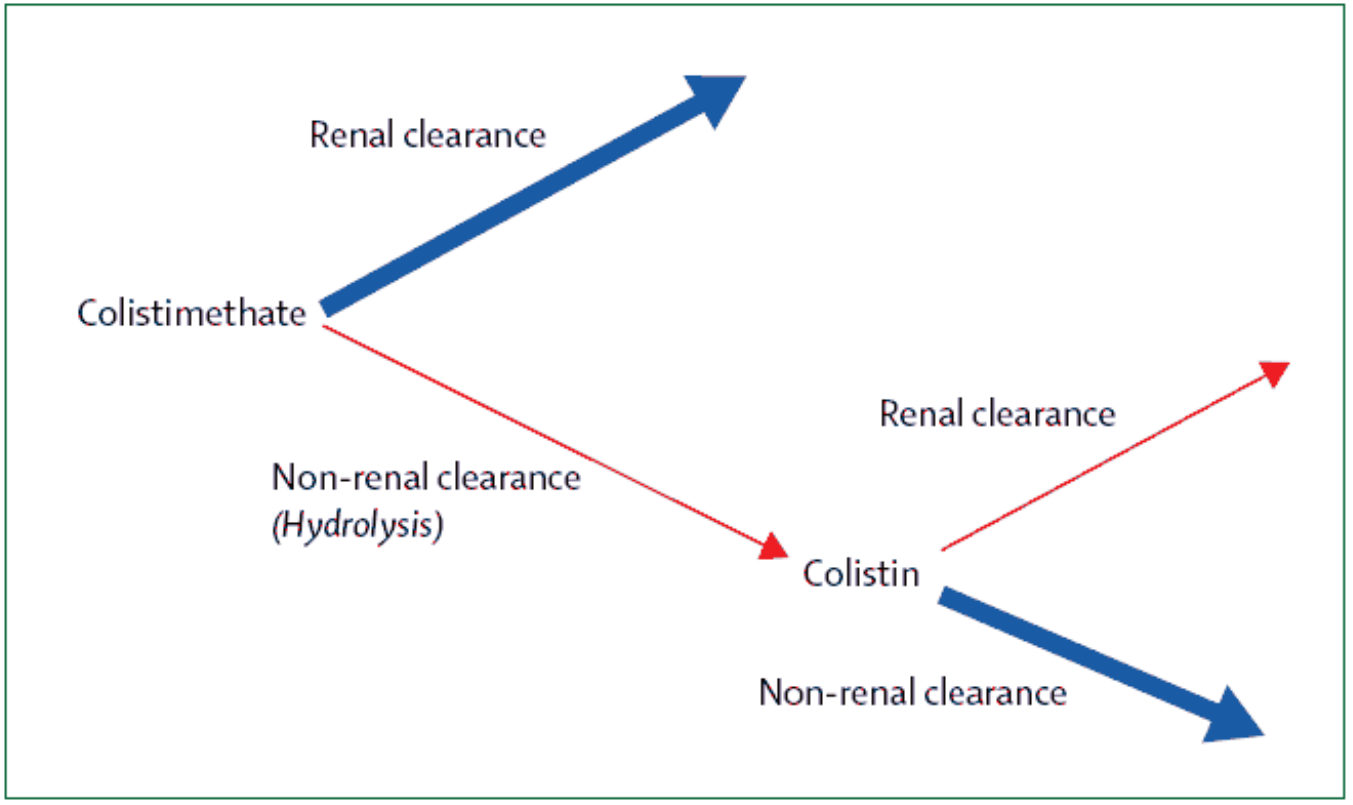


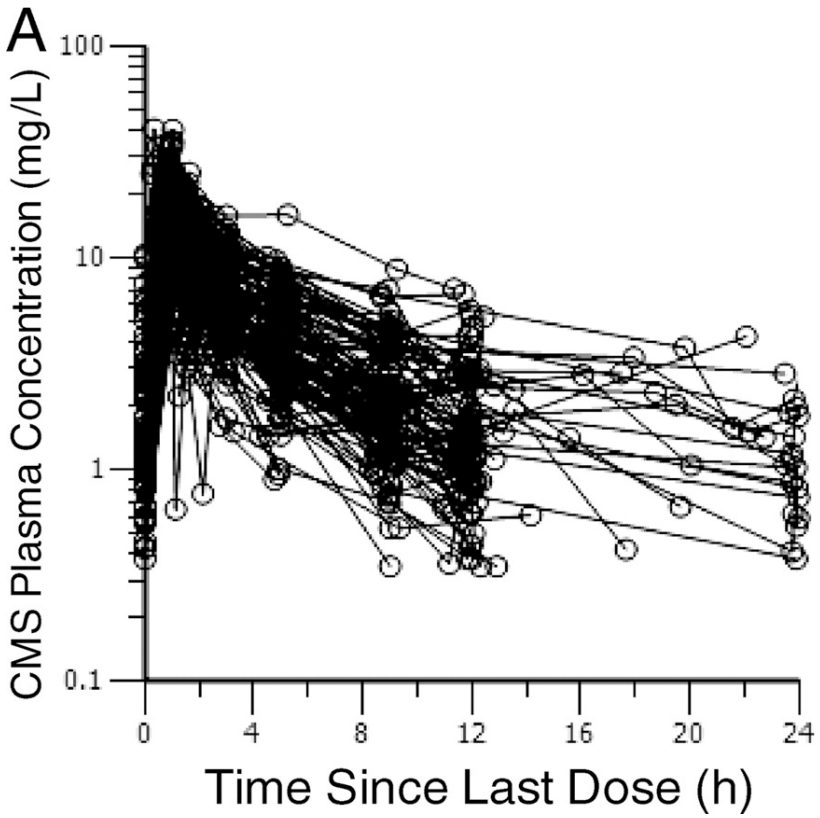
Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

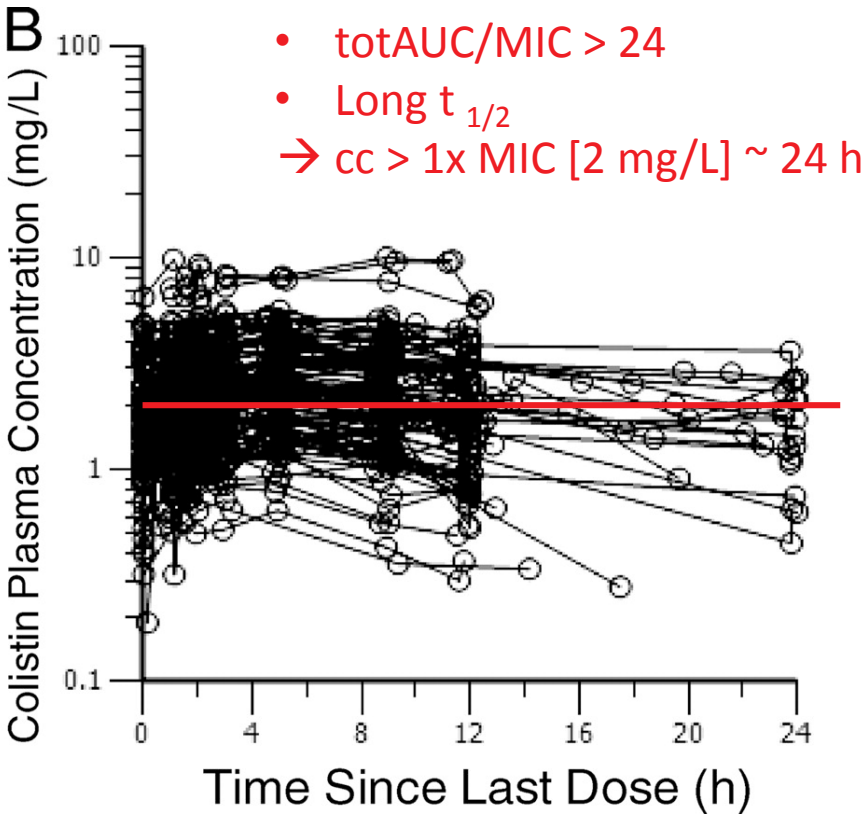
Li et al, Lancet Infect. Dis. 2006; 6:589-601

PK/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).





- totAUC/MIC > 24
- Long $t_{1/2}$

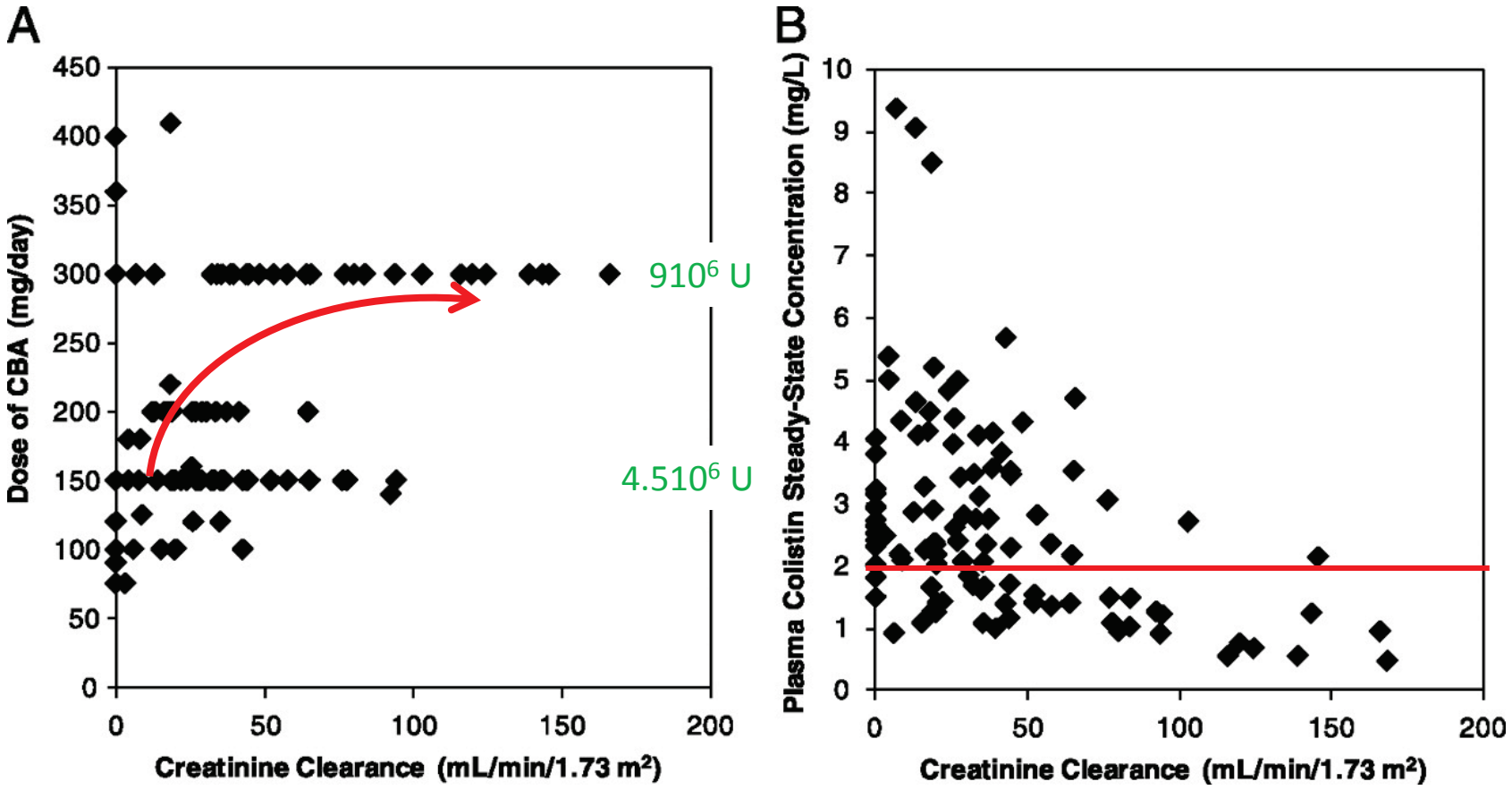
→ cc > 1x MIC [2 mg/L] ~ 24 h

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.

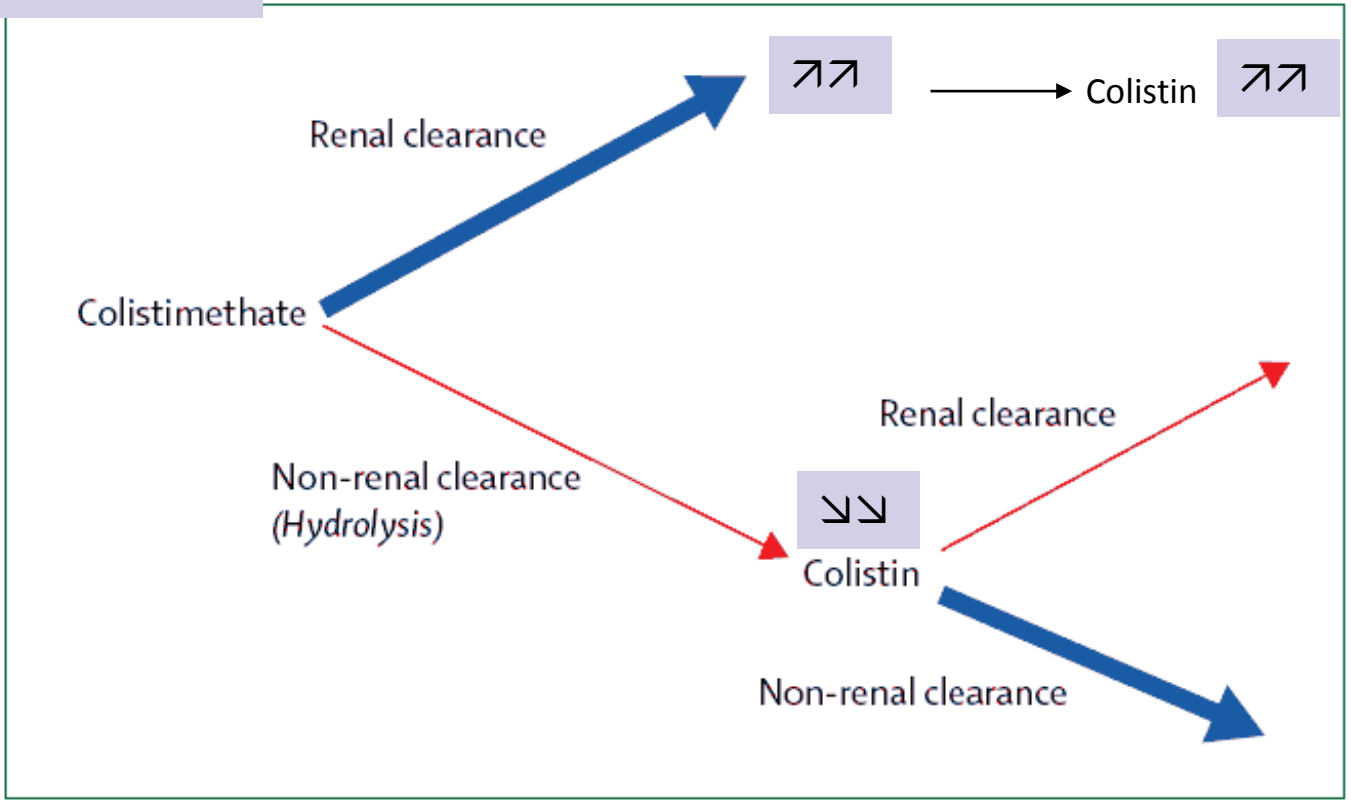
Relationship of physician-selected daily dose of colistin base activity (CBA) (A) and the resultant average steady-state plasma colistin concentration (B) with creatinine clearance in 105 critically ill patients.



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

Impact of renal function on elimination

If renal function ↗↗



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

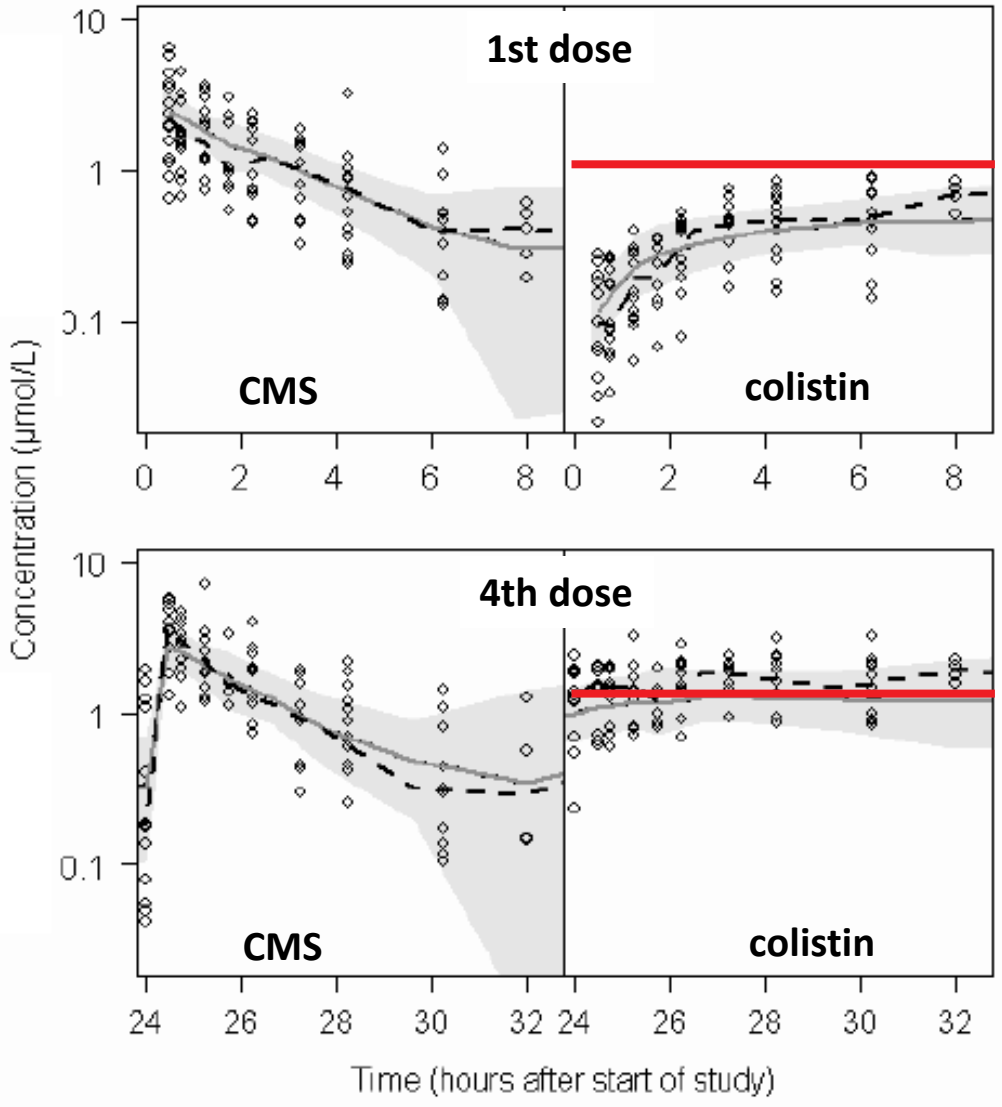
PK in critically-ill patients

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

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

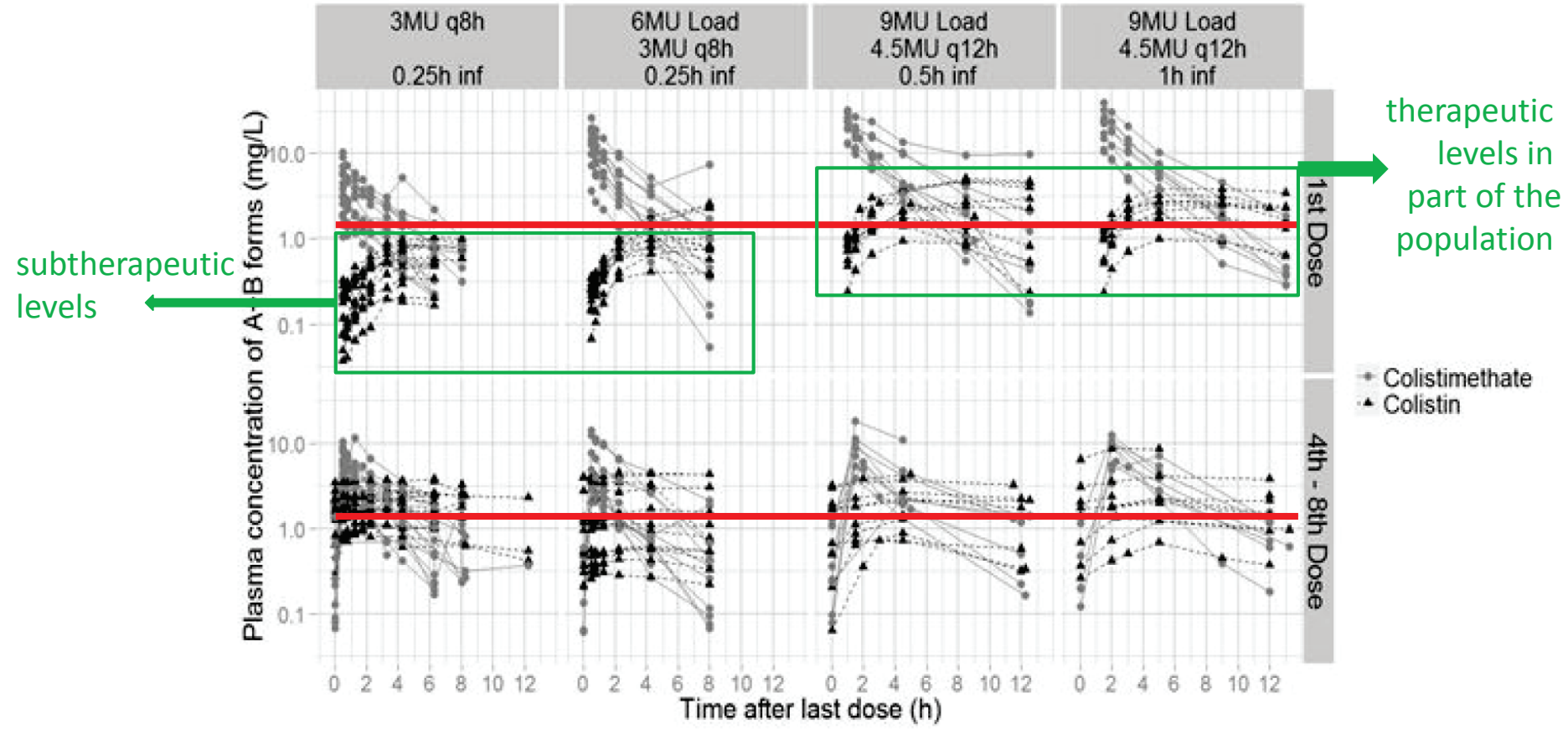
Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

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



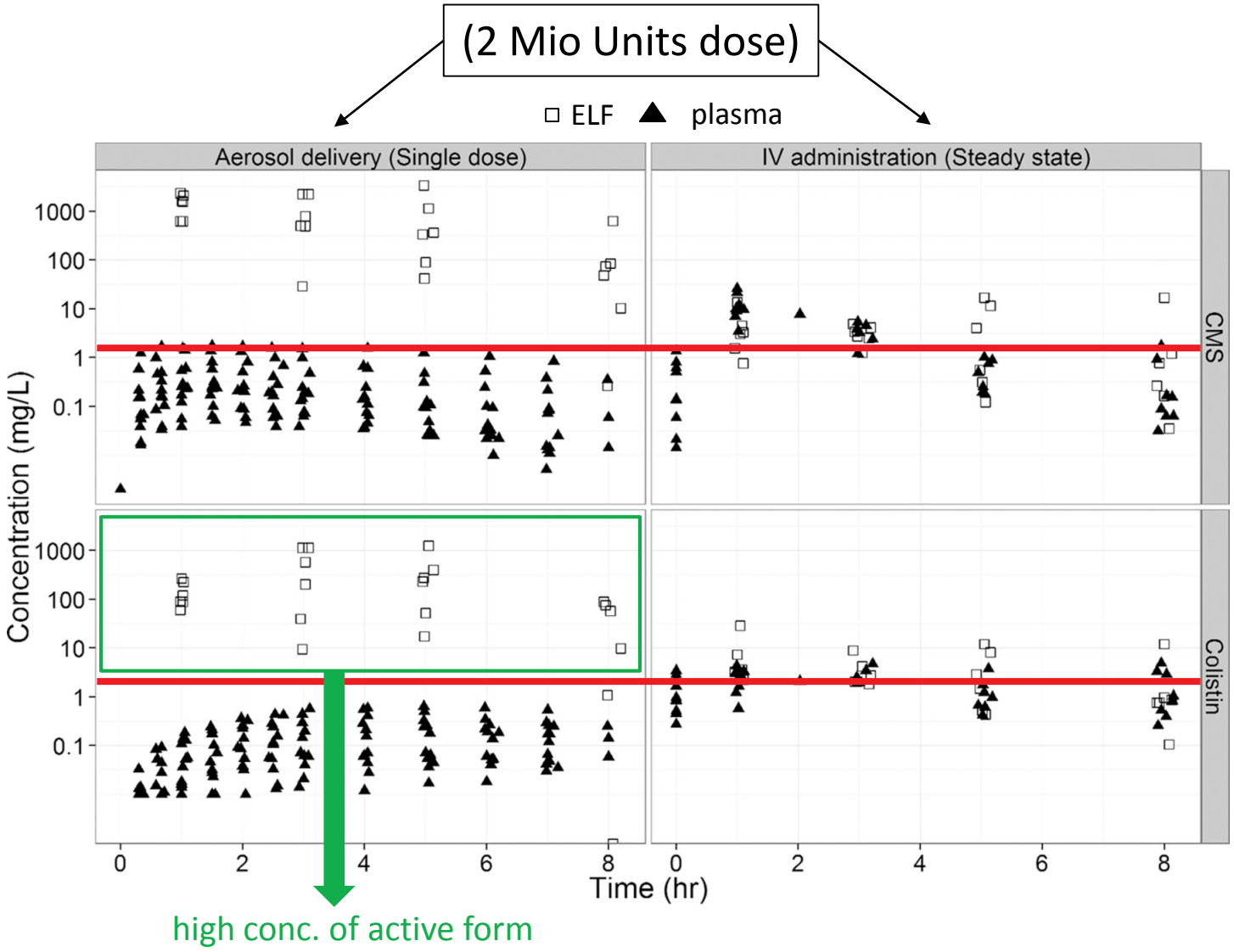
Plachouras et al, AAC 2009; 53:3430-6

Usefulness of a loading dose in critically-ill patients



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

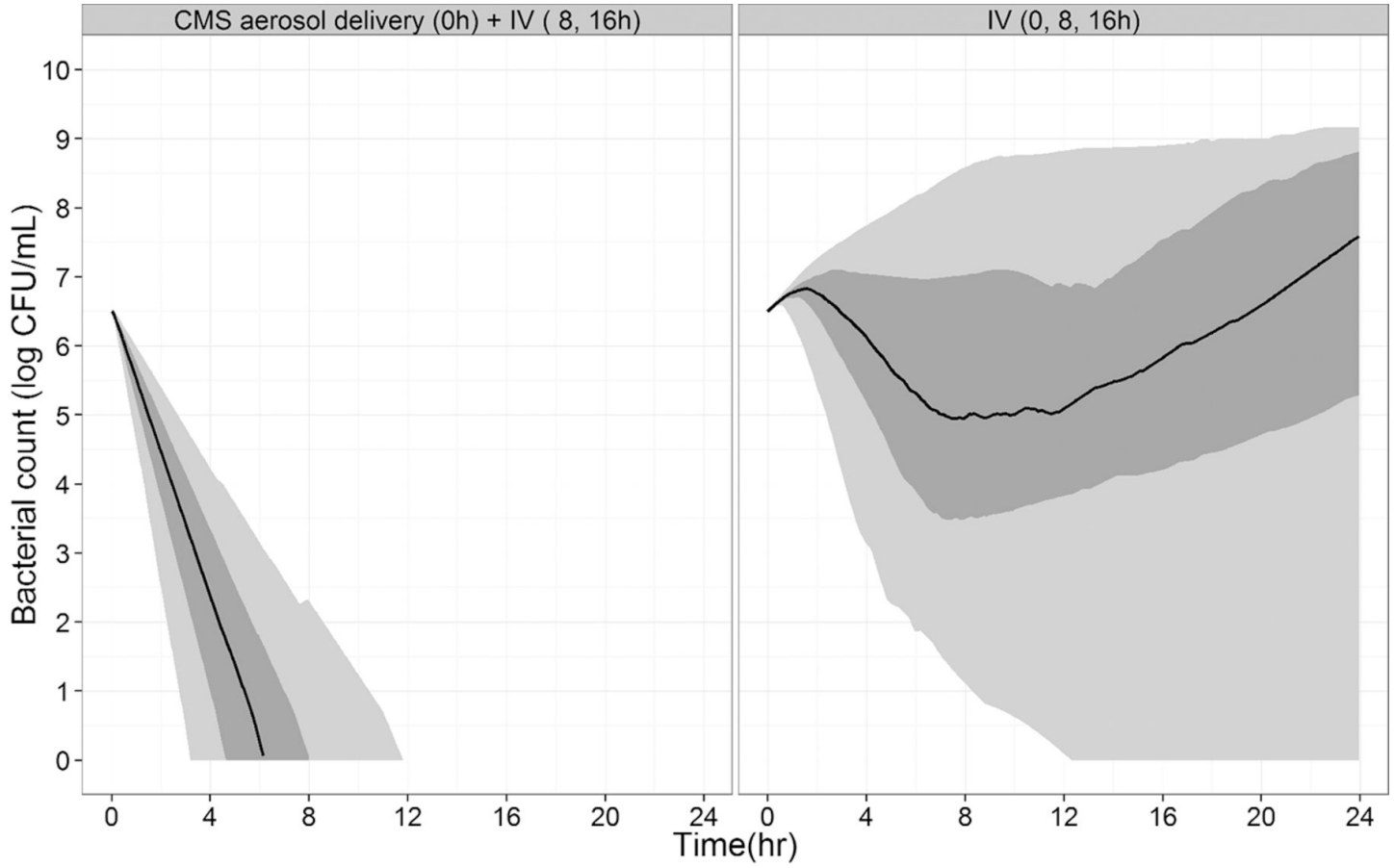
Pulmonary delivery: PK/PD rationale



Matthieu 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).



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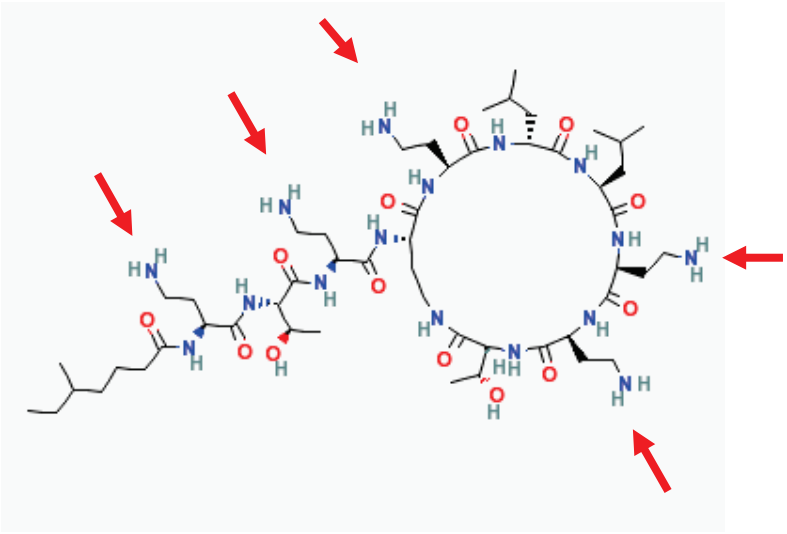


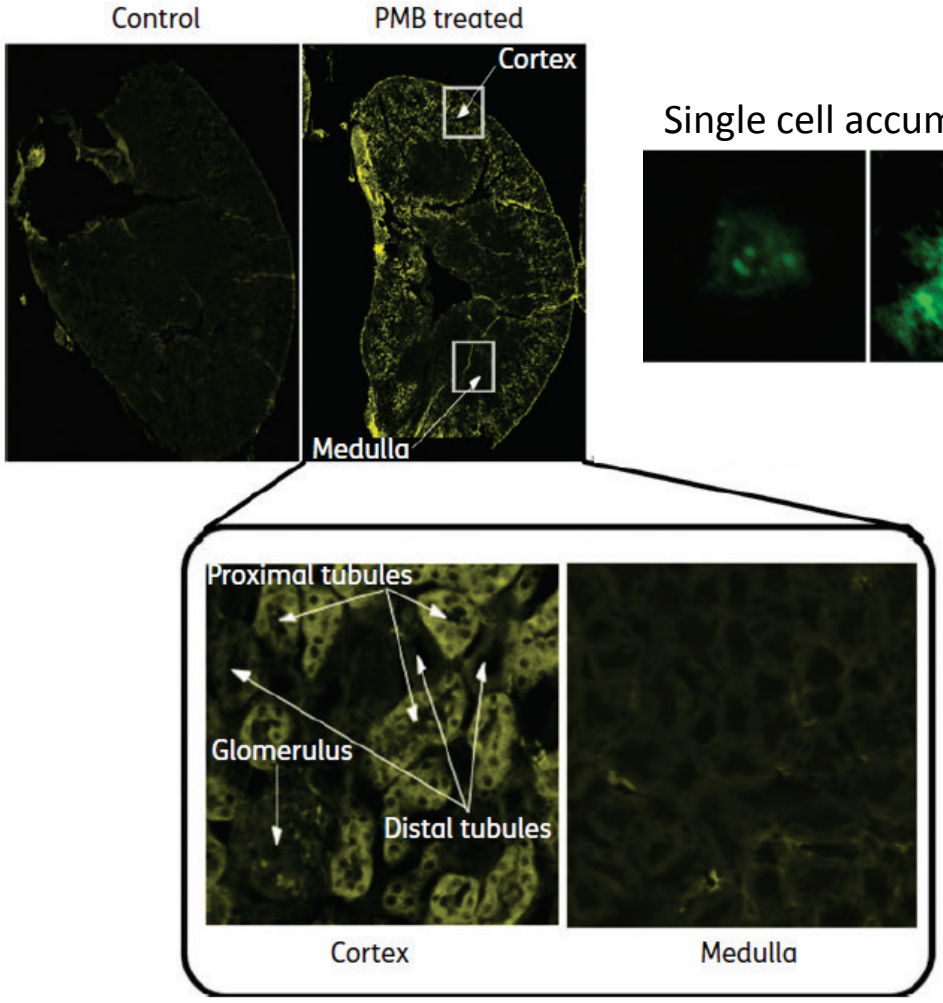
A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain

→ Interaction with eukaryotic cells ?

Toxicity:
the other flip of the coin

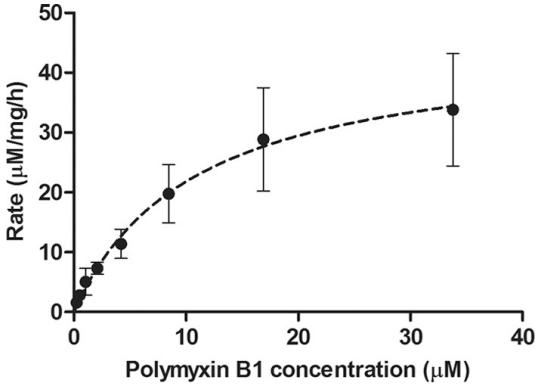
What about renal toxicity ?

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

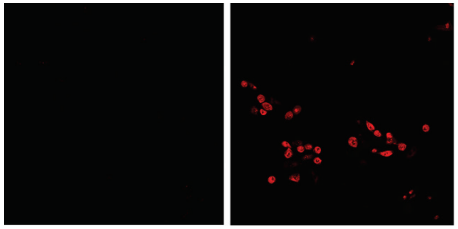


Single cell accumulation

Saturable process (megalin)



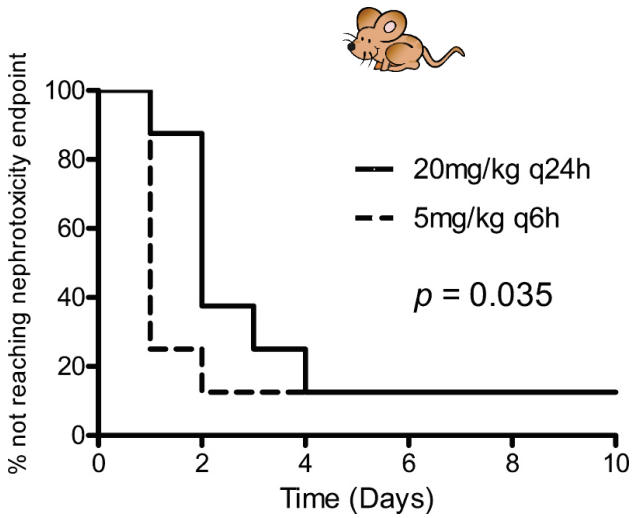
ROS production



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

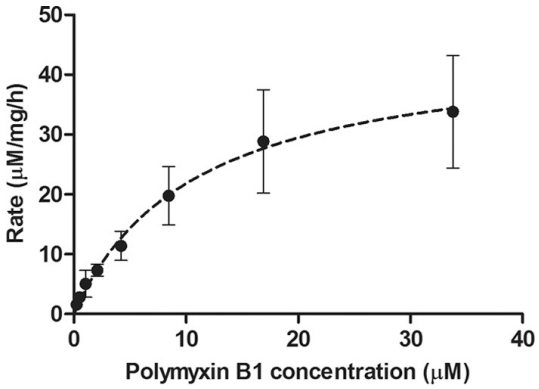
What about renal toxicity ?

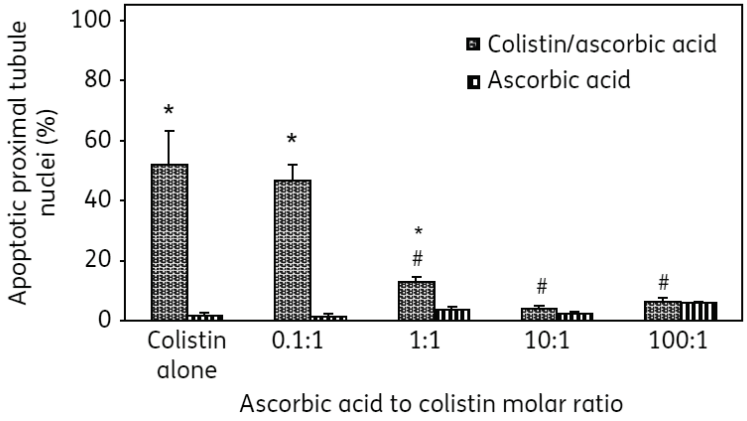
2. Strategies to reduce toxicity



non fractionated doses

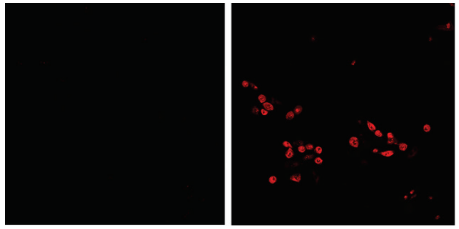
Saturable process (megalin)





combination with ascorbic acid

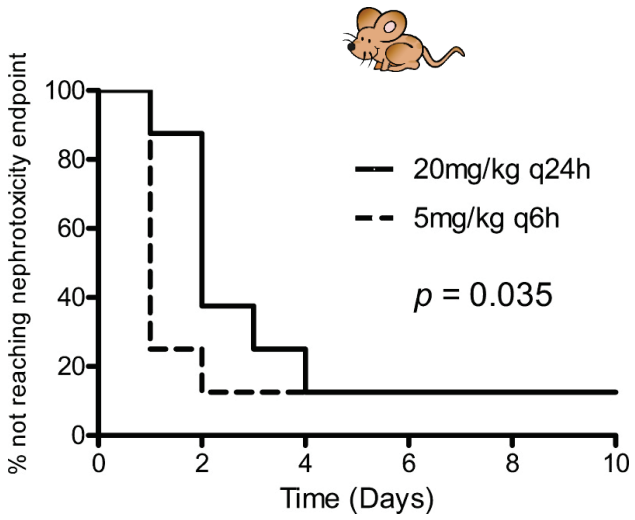
ROS production



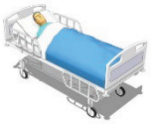
Abdelraouf et al, AAC 2012; 56:4625-9; Yousef et al, JAC 2012; 67:452-9

What about renal toxicity ?

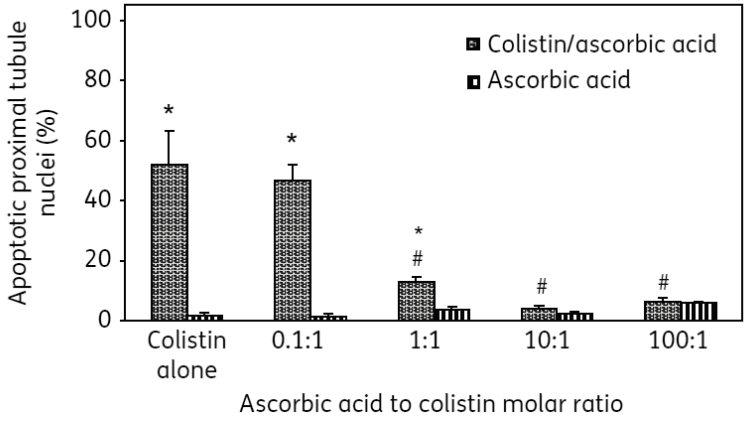
2. Strategies to reduce toxicity: do they work in the clinics ?



non fractionated doses



Serum half-life too long in humans …



combination with ascorbic acid

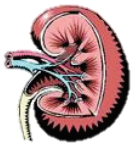
Creatinine data and classification of AKI according to the RIFLE criteria for the patients in each treatment group

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

no difference in toxicity…

Sirijatuphat et al, AAC 2015; 59:3224-32

Risk factors for nephrotoxicity



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

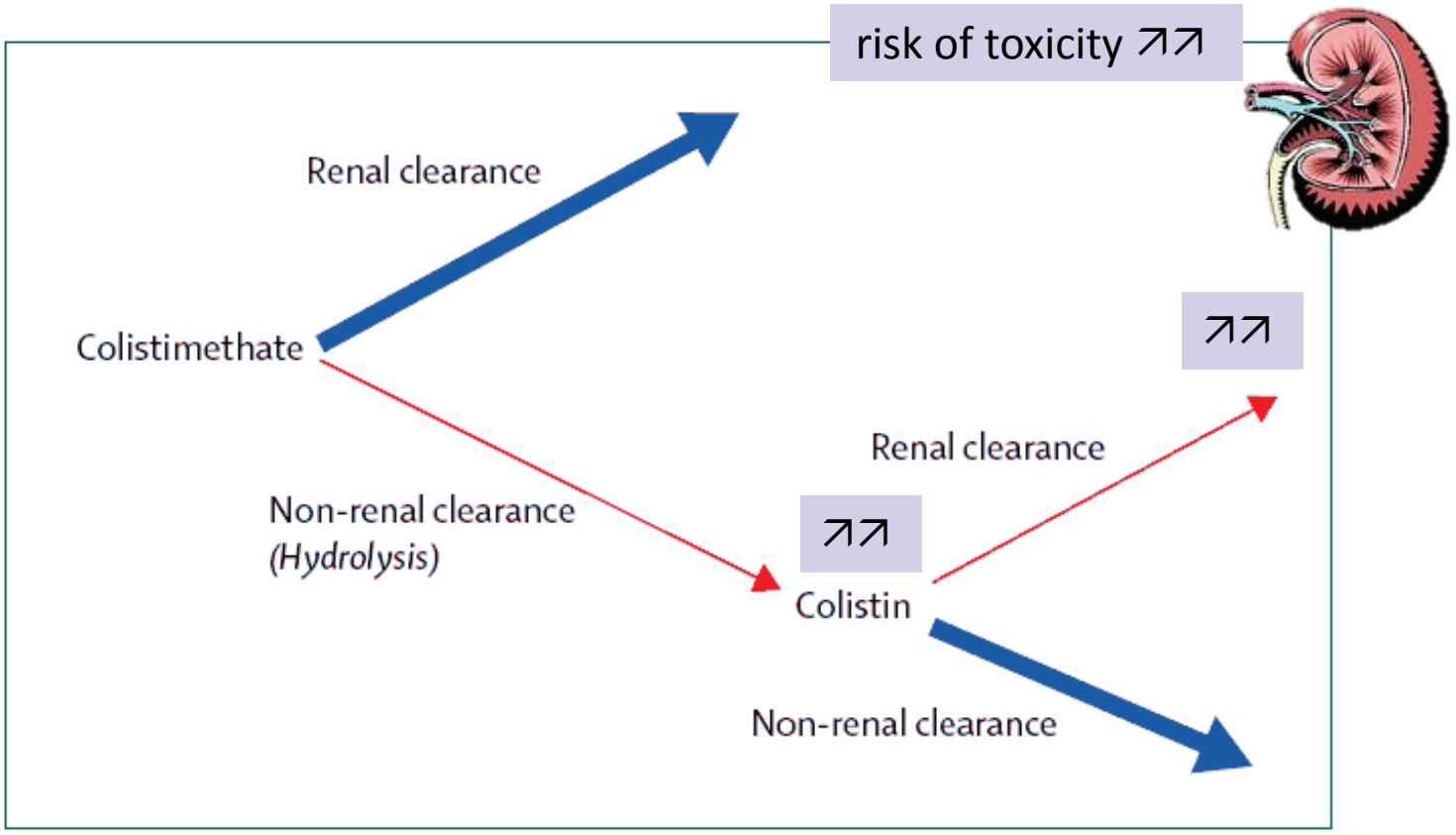
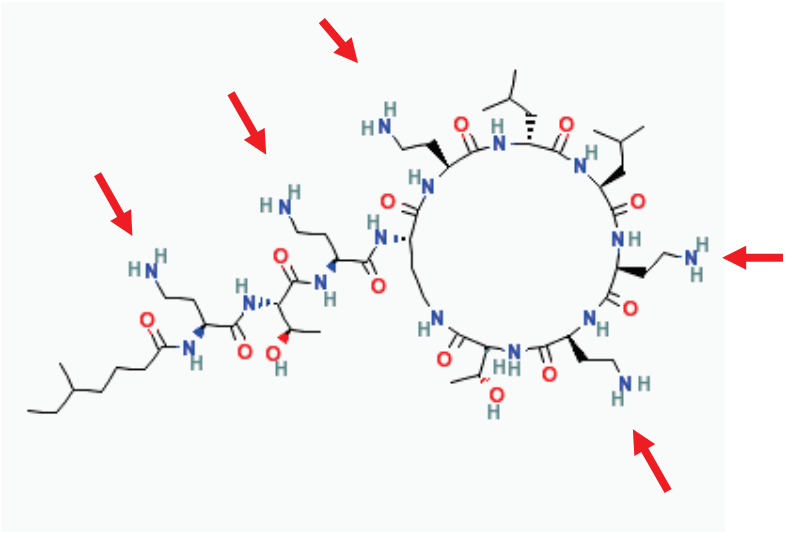


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

A reminder: what is colistin ?



from bench to bedside…

Current dosing recommendations

Target Css ≥ 2 mg/L
< 2.5 mg/L

→ If MIC > 1 mg/L: consider combinations

→ minimize risk of nephrotoxicity

- very narrow therapeutic window
- way to optimal dosing difficult

EMA approved dose:

Creatinine clearance (mL/min)	Daily dose (Mio units)
≥ 80	9
50-80	9
30-50	5.5-7.5
10-30	4.5-5.5

→ conc. remain low … think combination

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

Partly based on data presented at POLYMYXINS 2015
September 22 - 24, San Diego, USA