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

COLISTIN: news from an old drug

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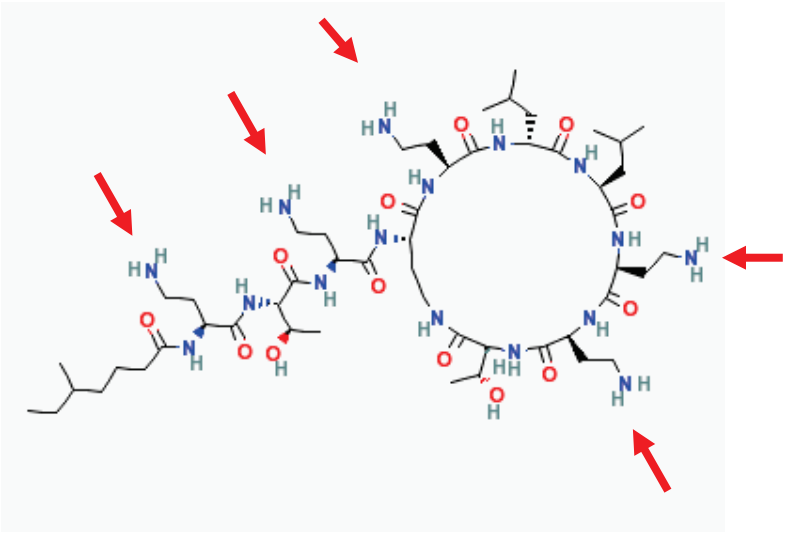
A reminder: what is colistin ?

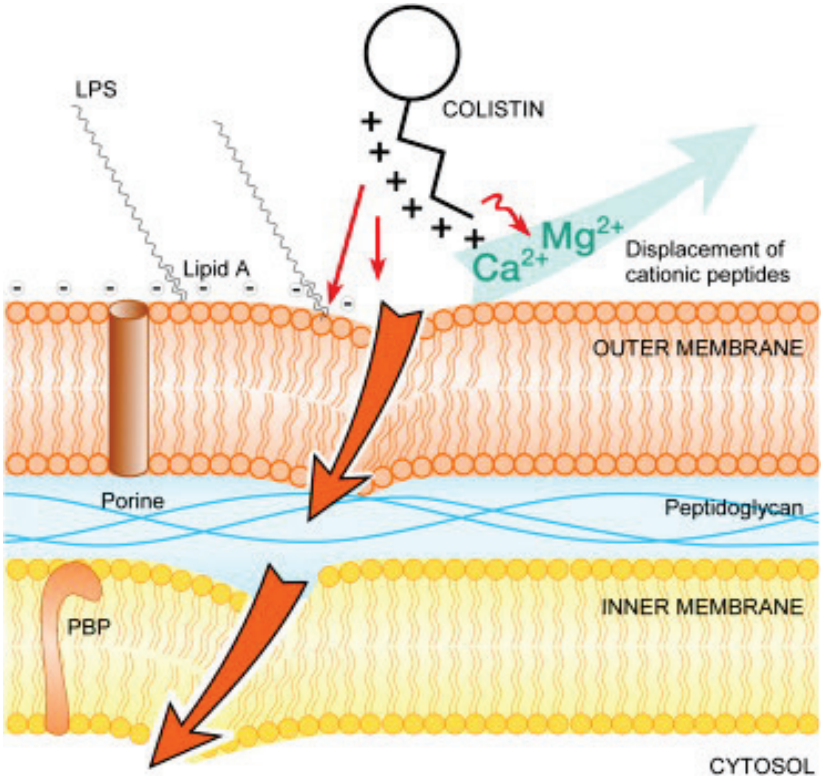


A cyclic **amphipathic** **polycationic peptide** with a short aliphatic side chain …

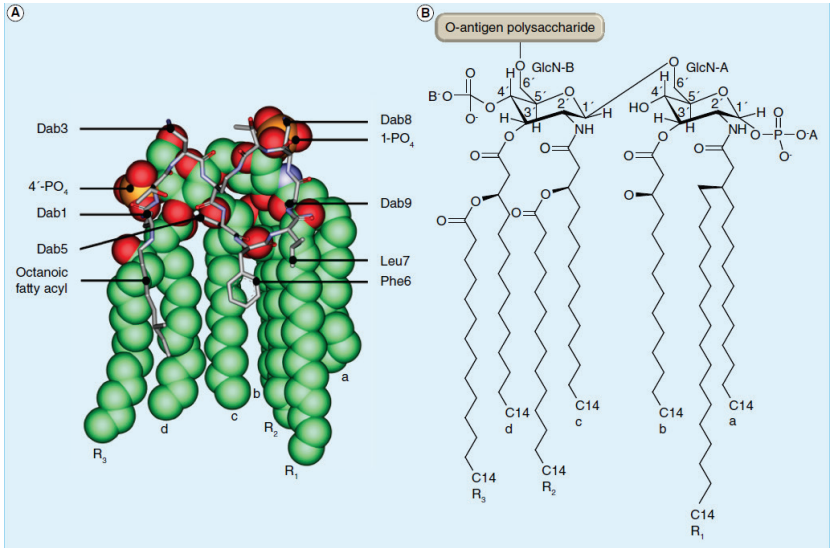
What does this structure tell you about the mode of action ?

How do polymyxins work ?

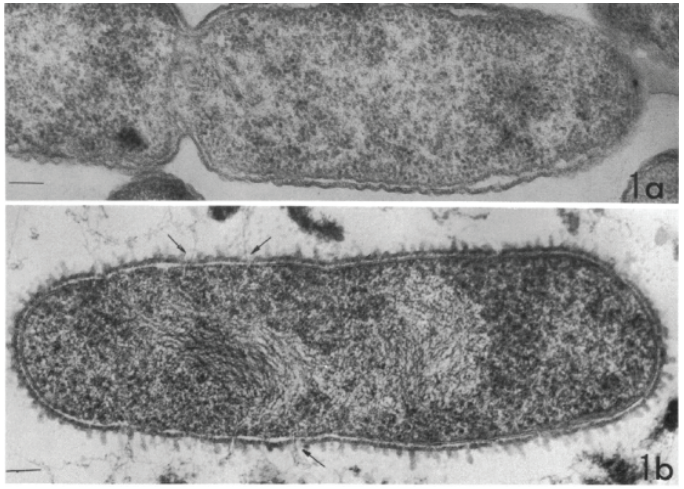
1. Interaction with LPS in the outer membrane



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



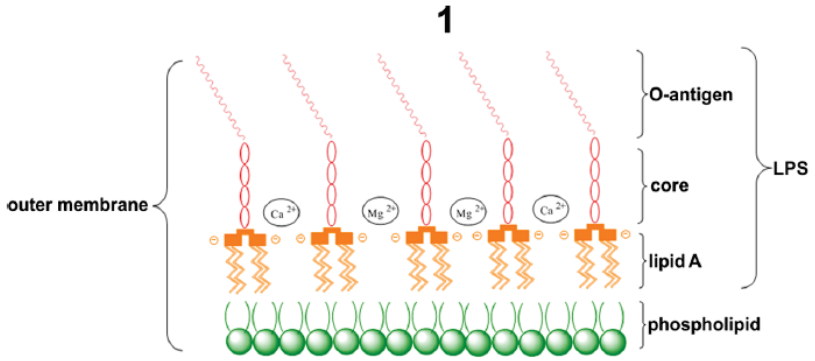
Velkov et al, Future Microbiol. 2013; 8:711–24

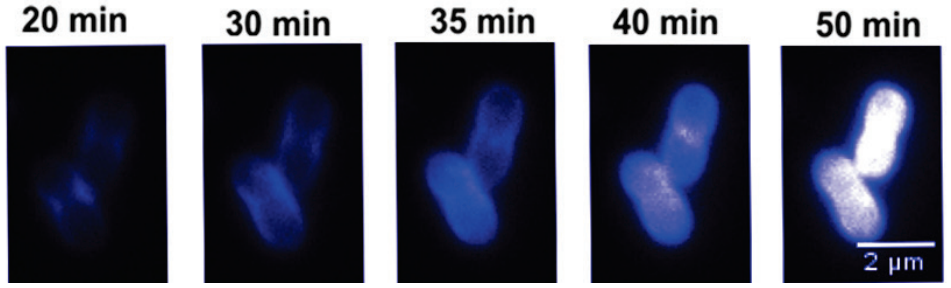


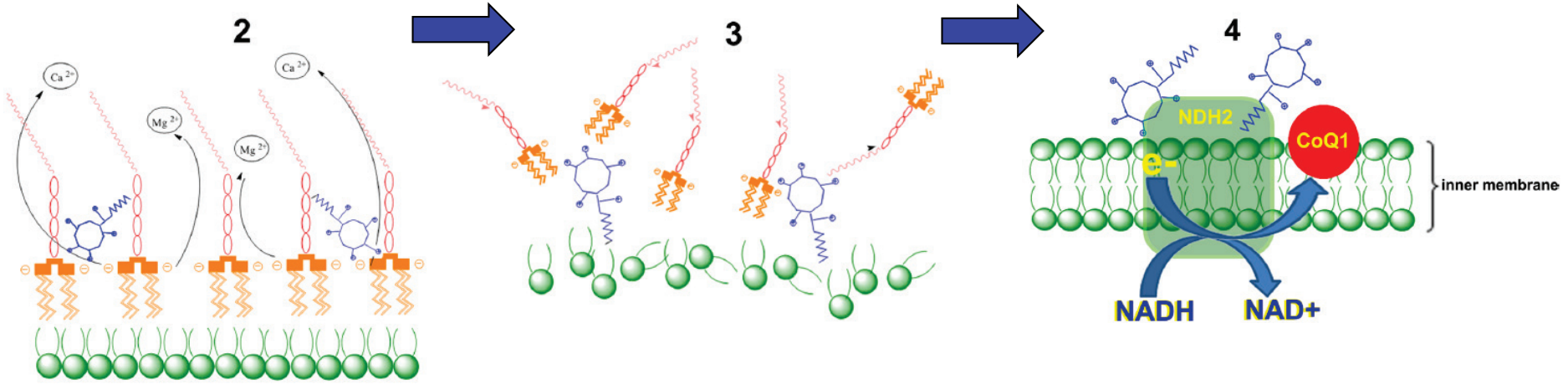
Koike et al, J. Bacteriol. 1969; 97:448-52

How do polymyxins work ?

2. Disruption of envelope integrity and access to bacterial cytosol







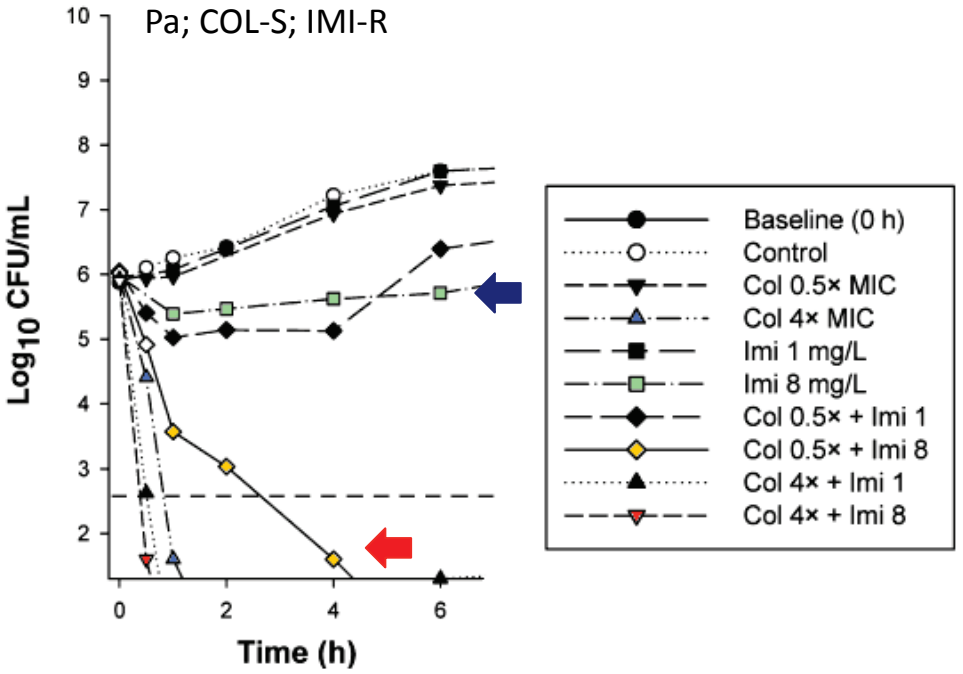
Deris et al, Bioconjugate Chem. 2014; 25:750−60; J Antibiot. 2014; 67:147–51

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 ?

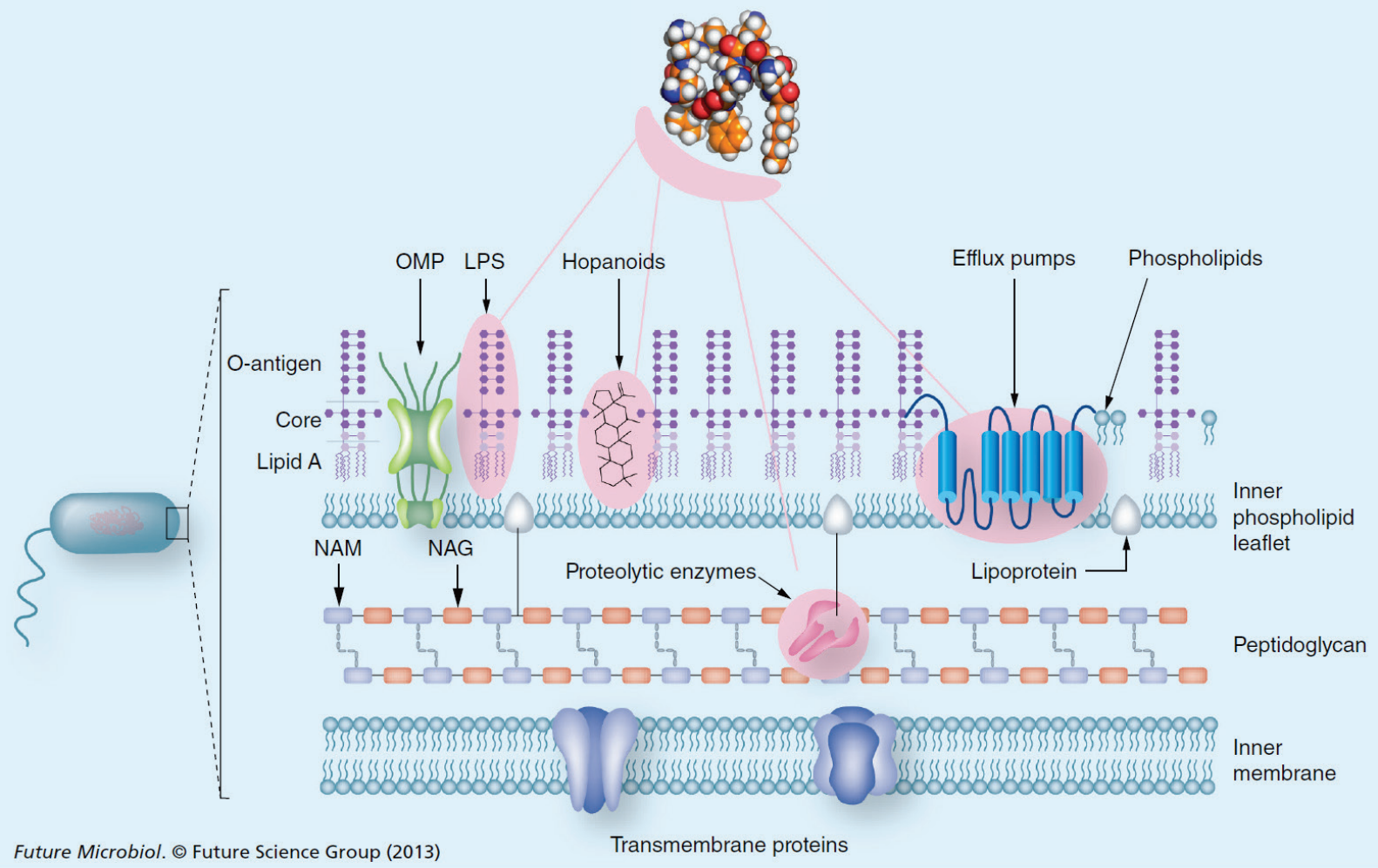


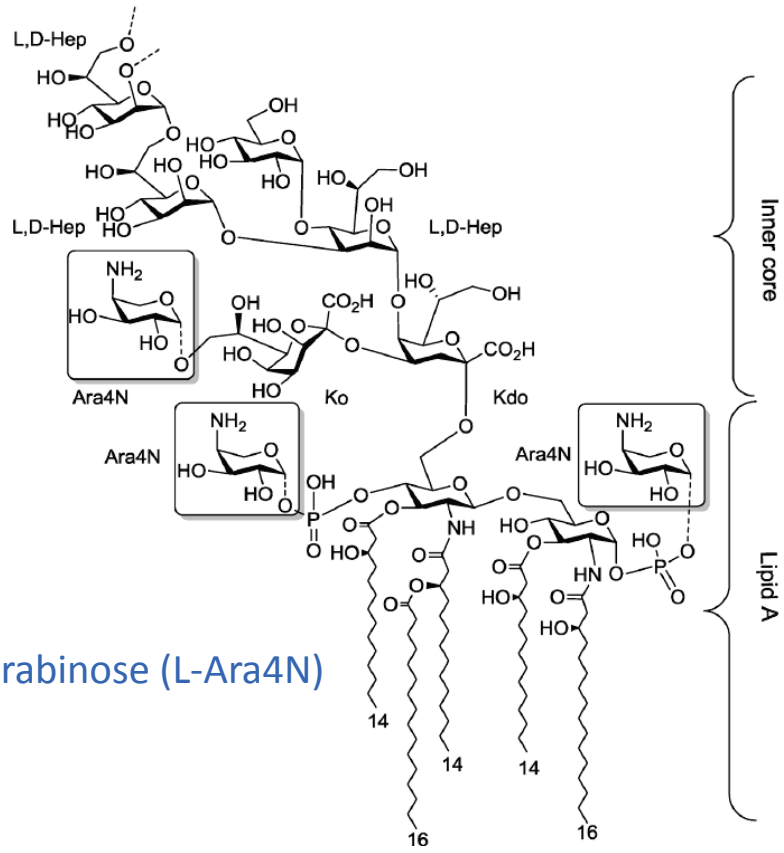
Figure 2. Key mechanisms of polymyxin resistance in Gram-negative bacteria. The pink shading indicates molecular determinants of polymyxin resistance.
LPS: Lipopolysaccharide; NAG: *N*-acetylglucosamine; NAM: *N*-acetylmuramic acid; OMP: Outer membrane protein.

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**



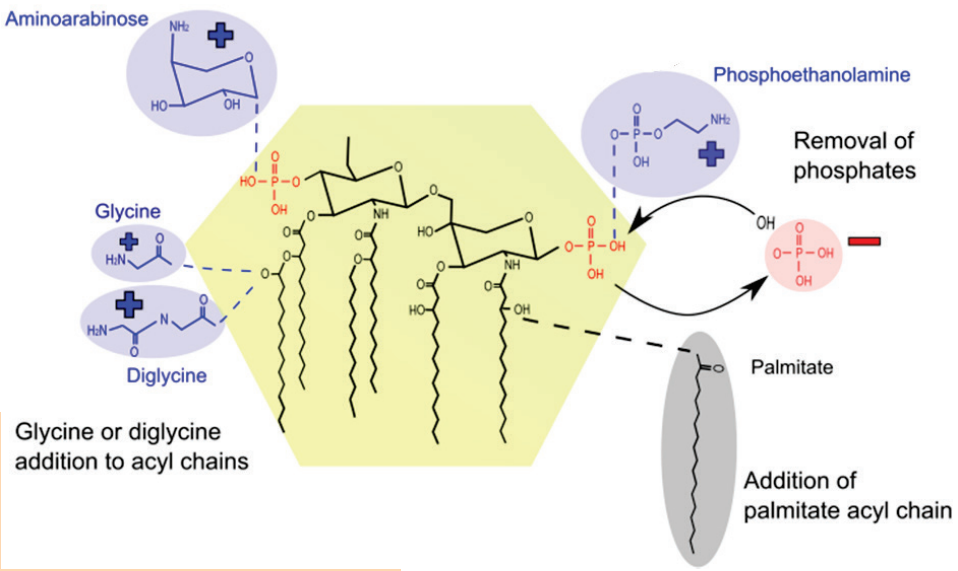
4-amino-4-deoxy-L-arabinose (L-Ara4N)

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

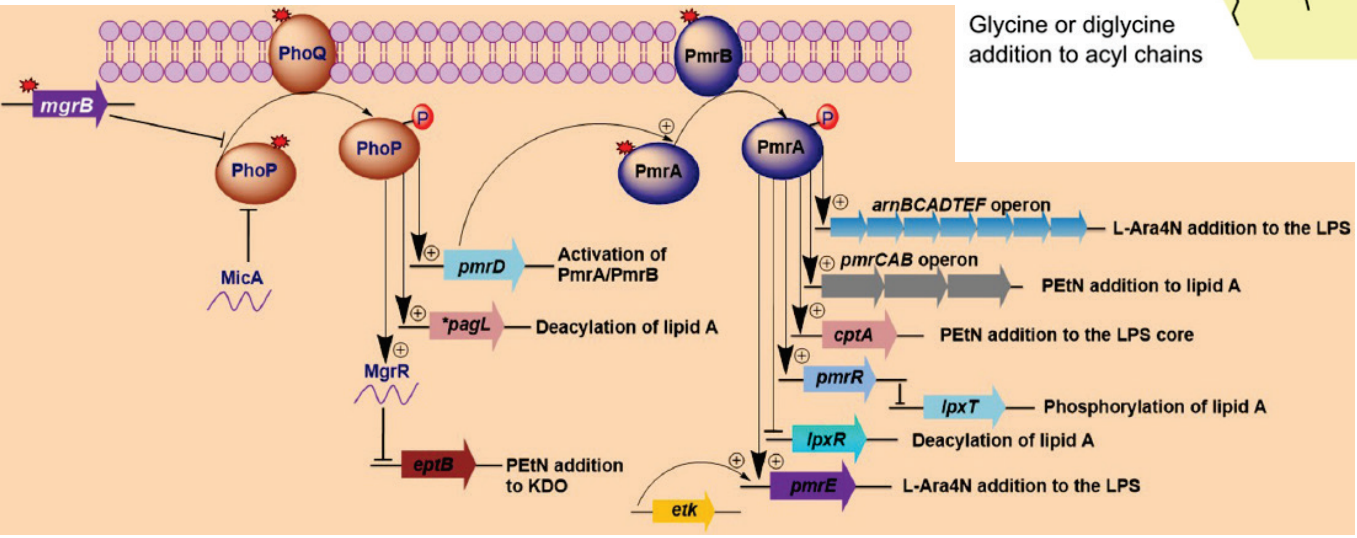
Underlying mechanisms and clinical implications

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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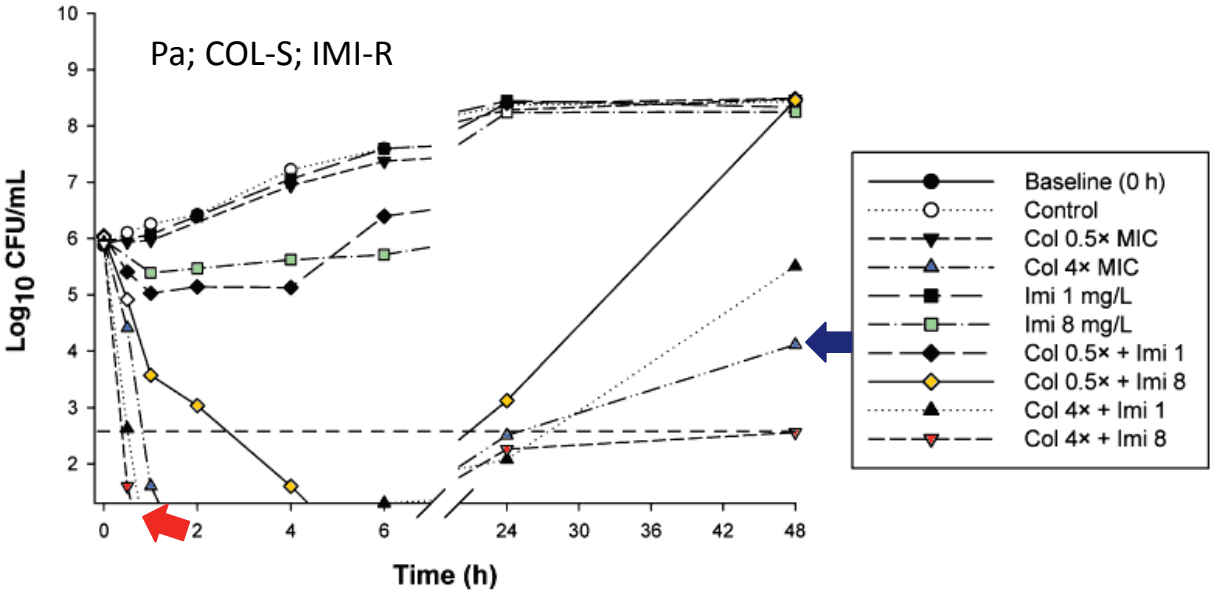
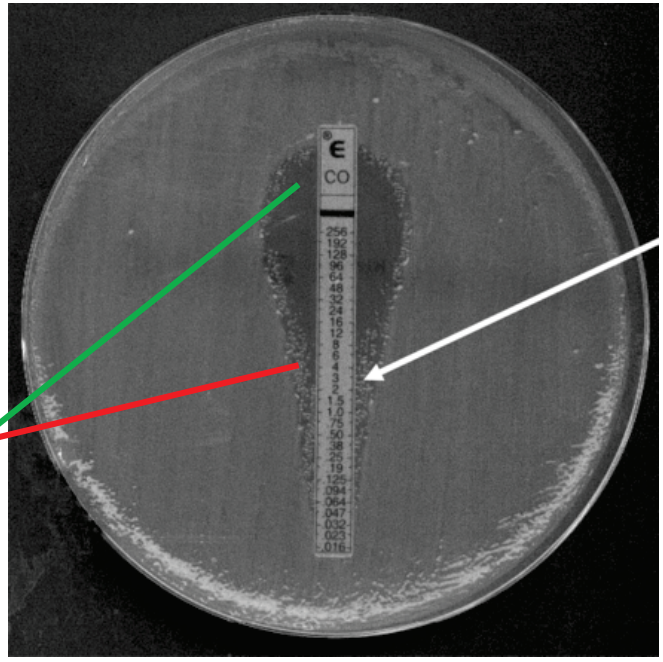


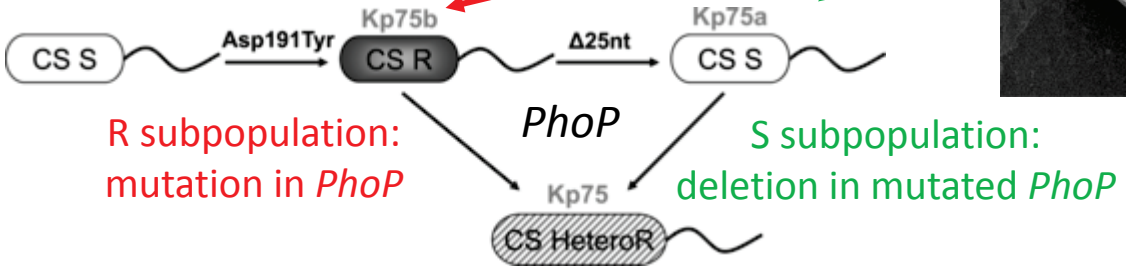
Bergen et al, Pharmacotherapy 2015; 35:34–42

Underlying mechanisms and clinical implications

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

→ **visible on E-tests only**





R subpopulation:
mutation in *PhoP*

S subpopulation:
deletion in mutated *PhoP*

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

Breaking news: plasmidic resistance to colistin

THE LANCET Infectious Diseases

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Articles

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, BS[†], Yang Wang, PhD[†], Prof Timothy R Walsh, DSc, Ling-Xian Yi, BS, Rong Zhang, PhD, James Spencer, PhD, Yohei Doi, MD, Guobao Tian, PhD, Baolei Dong, BS, Xianhui Huang, PhD, Lin-Feng Yu, BS, Danxia Gu, PhD, Hongwei Ren, BS, Xiaojie Chen, MS, Luchao Lv, MS, Dandan He, MS, Hongwei Zhou, PhD, Prof Zisen Liang, MS, Prof Jian-Hua Liu, PhD, Prof Jianzhong Shen, PhD

Published Online: 18 November 2015
DOI: http://dx.doi.org/10.1016/S1473-3099(15)00424-7

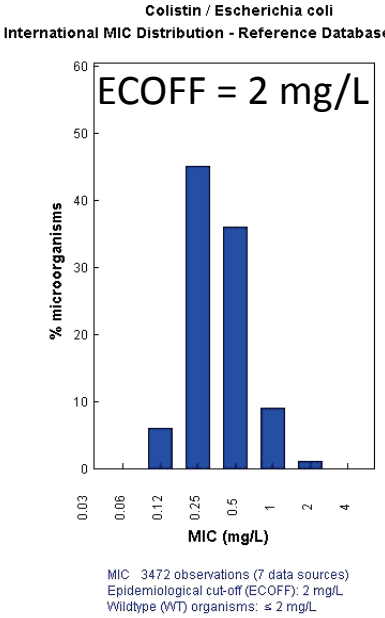
Liu and colleagues[4] present data from China showing that *E coli* from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in *E coli* and *K pneumoniae* isolates from Chinese patients in hospital.

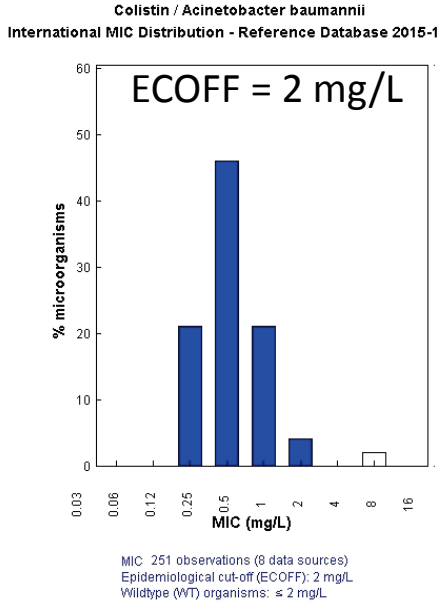
the plasmid bearing the colistin resistance mechanism was readily passed between *Escherichia coli* strains, including strains with known epidemic potential

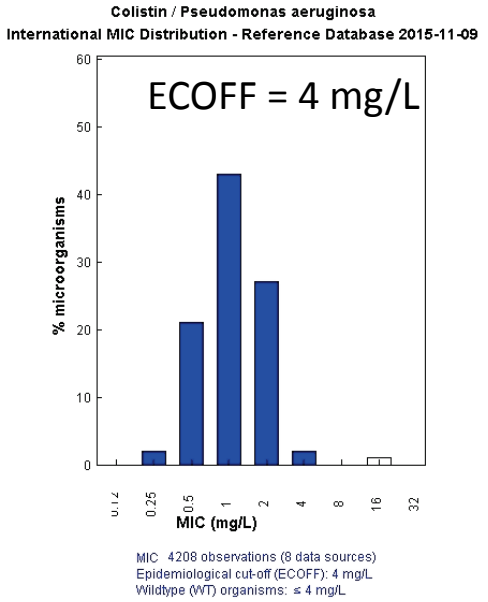
Paterson & Harris, Lancet ID 2015 - dx.doi.org/10.1016/S1473-3099

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





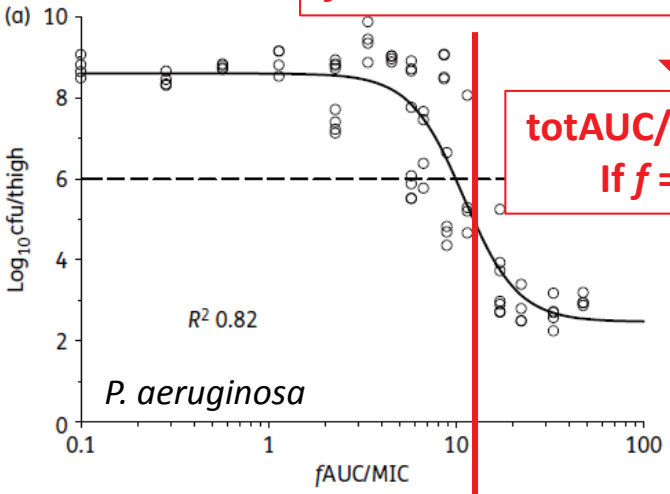


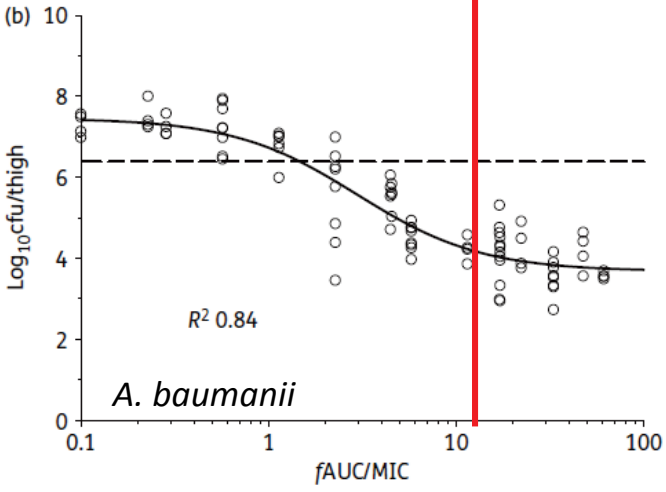
PK/PD : lessons from animal models

Thigh infection

*f*AUC/MIC = 12 → 2 log kill

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

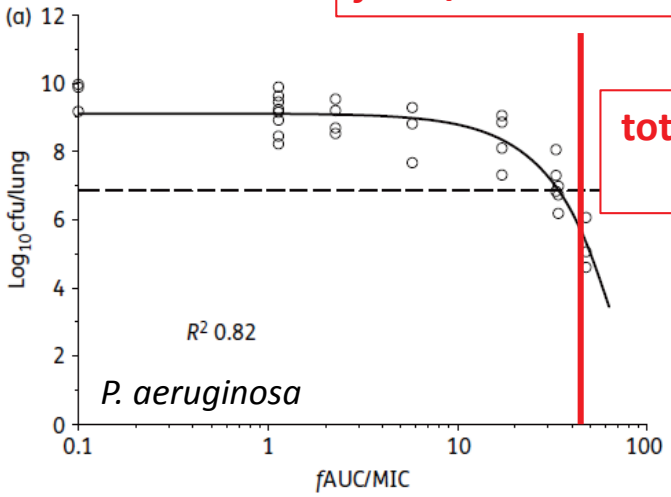




Lung infection

*f*AUC/MIC = 48 → 1 log kill

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



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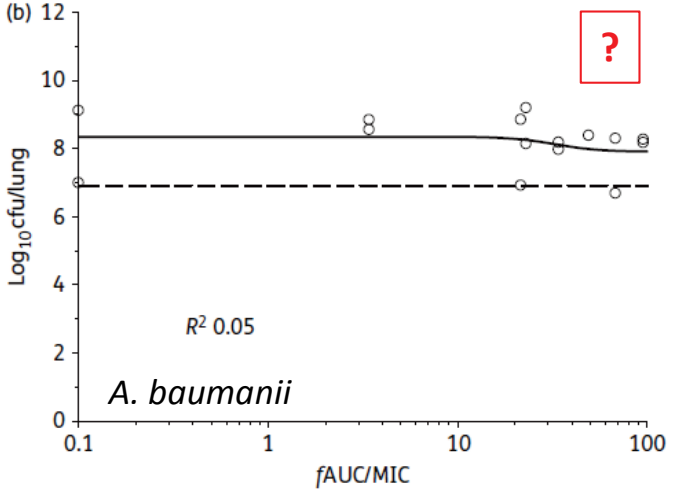
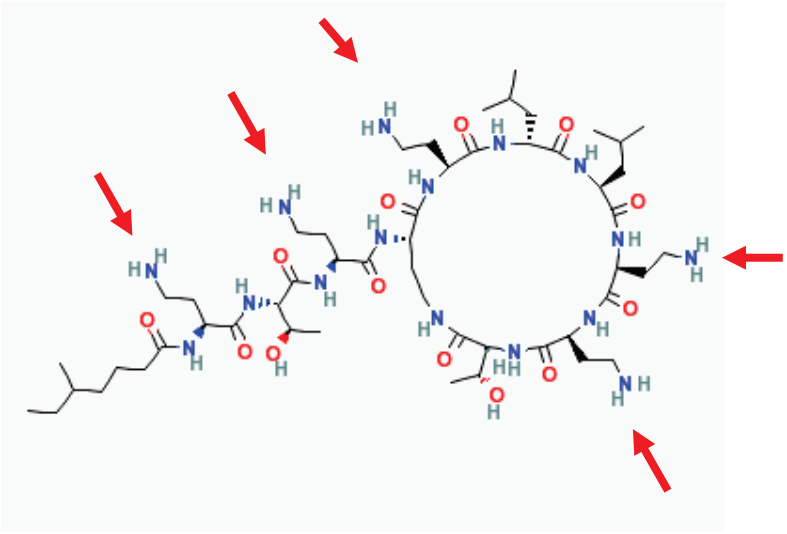


Cheah et al, JAC 2015; 70: 3291-3297

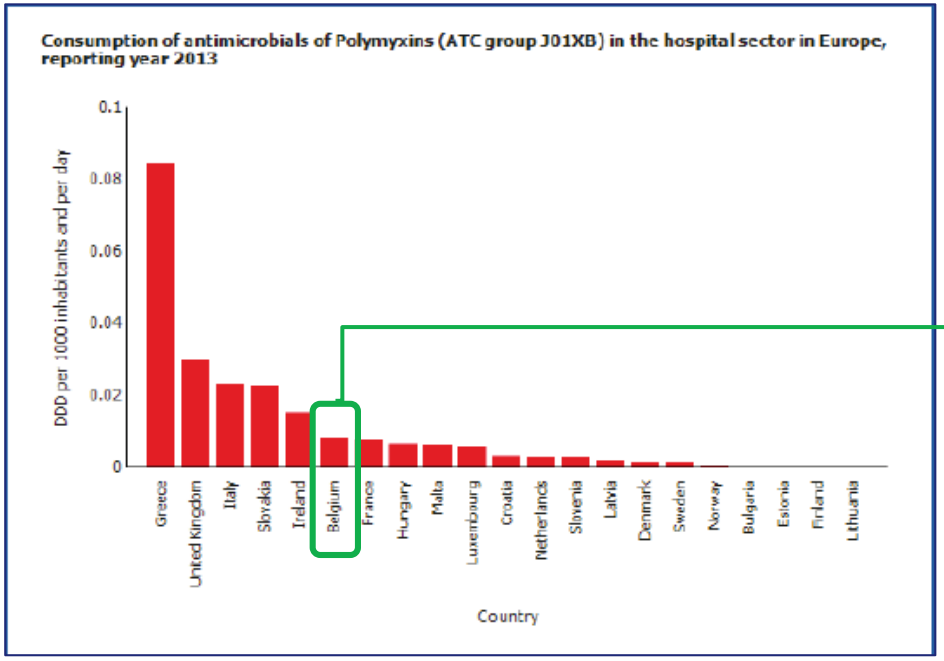
A reminder: what is colistin ?

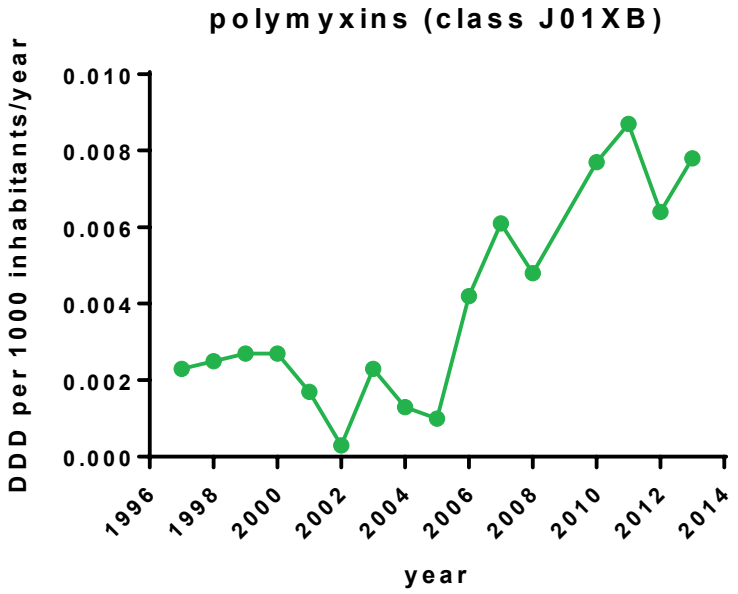


A last-resort antibiotic ….

Do we need this drug ?

Polymyxin consumption in Europe and in Belgium



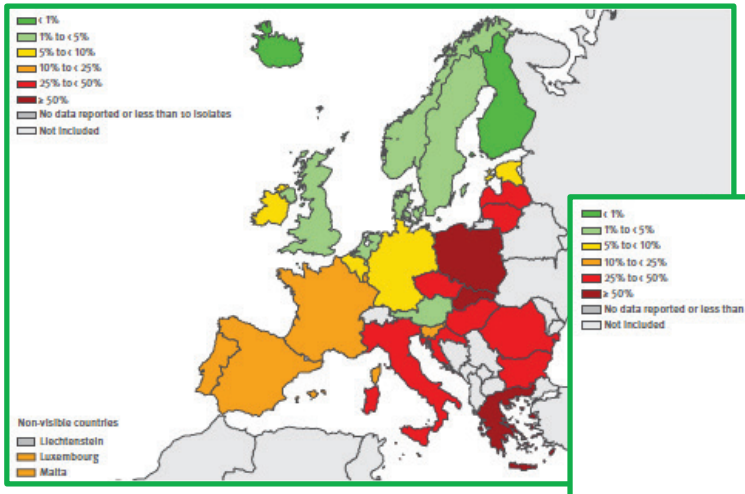


Do we need this drug ?

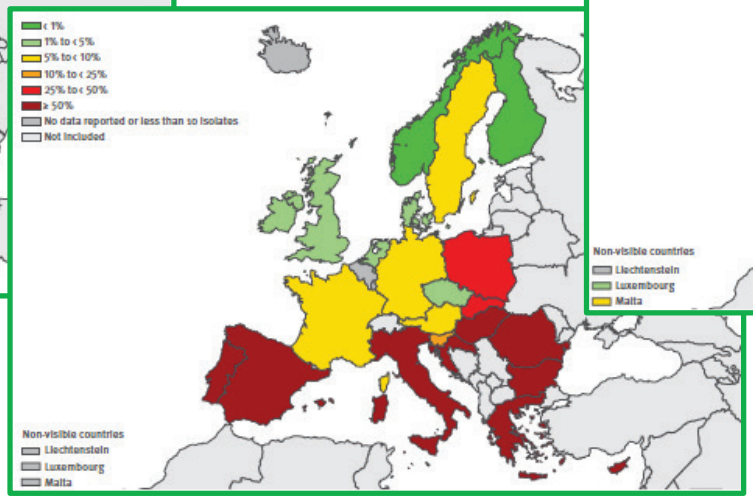
Well, it seems so !

Carbapenem resistance in ESKAPE pathogens in Europe

P. aeruginosa



A. baumanii



K. pneumoniae

Do we need this drug ?

Well, it seems so !

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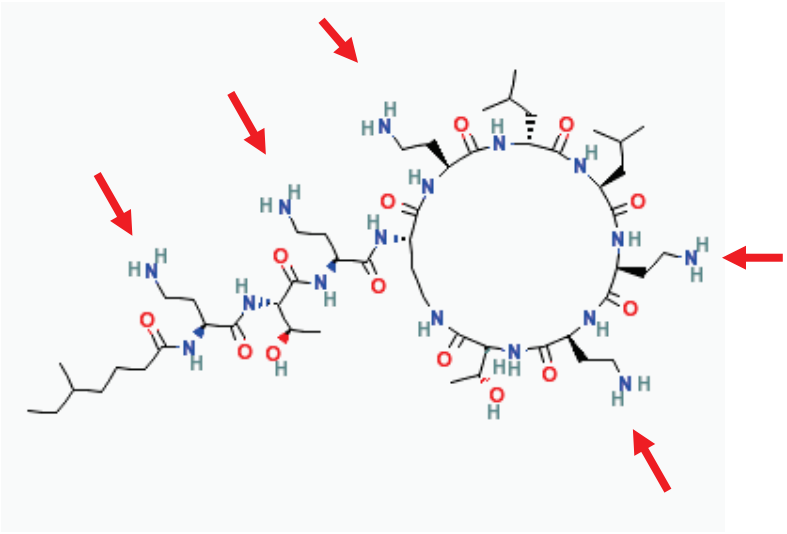
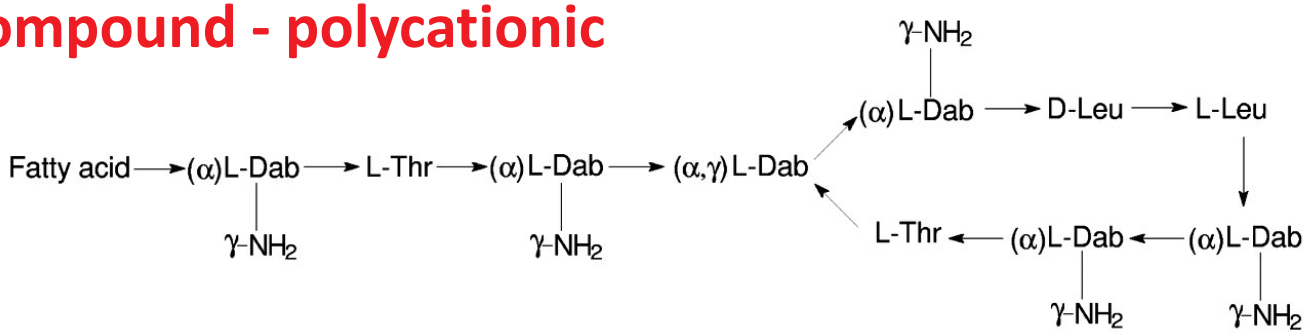


A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain administered as a prodrug …

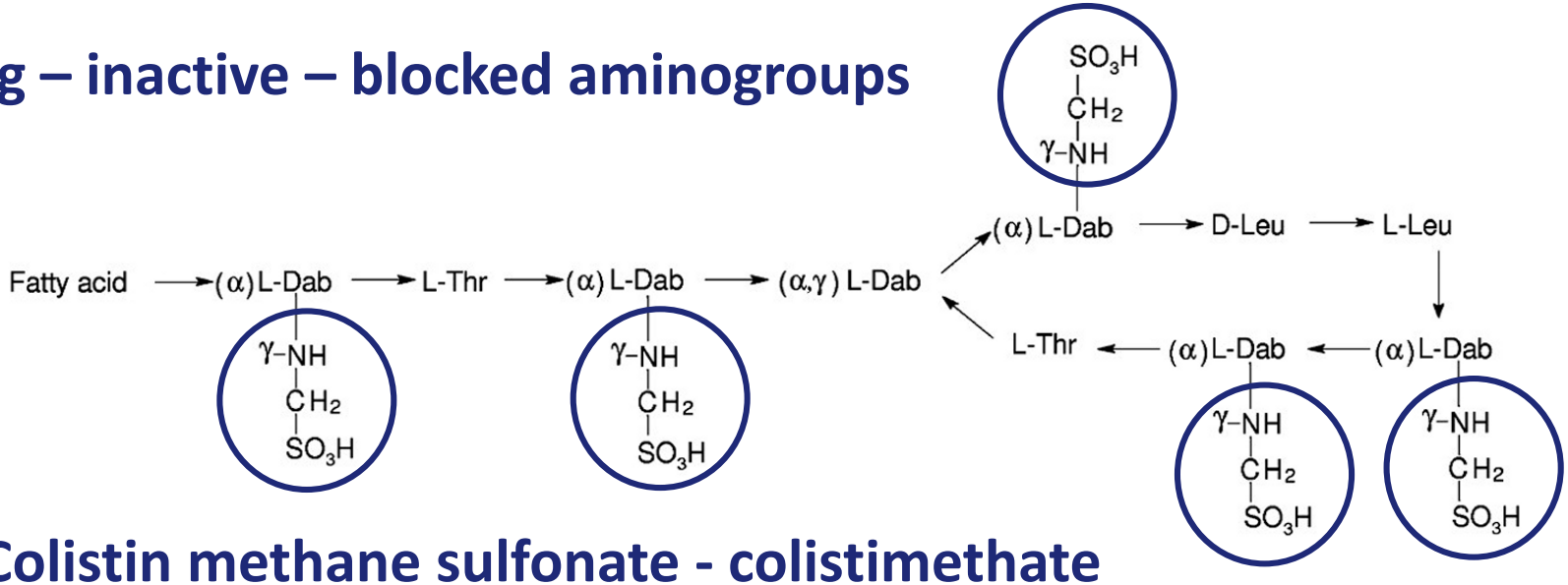
From the molecule to the drug …

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

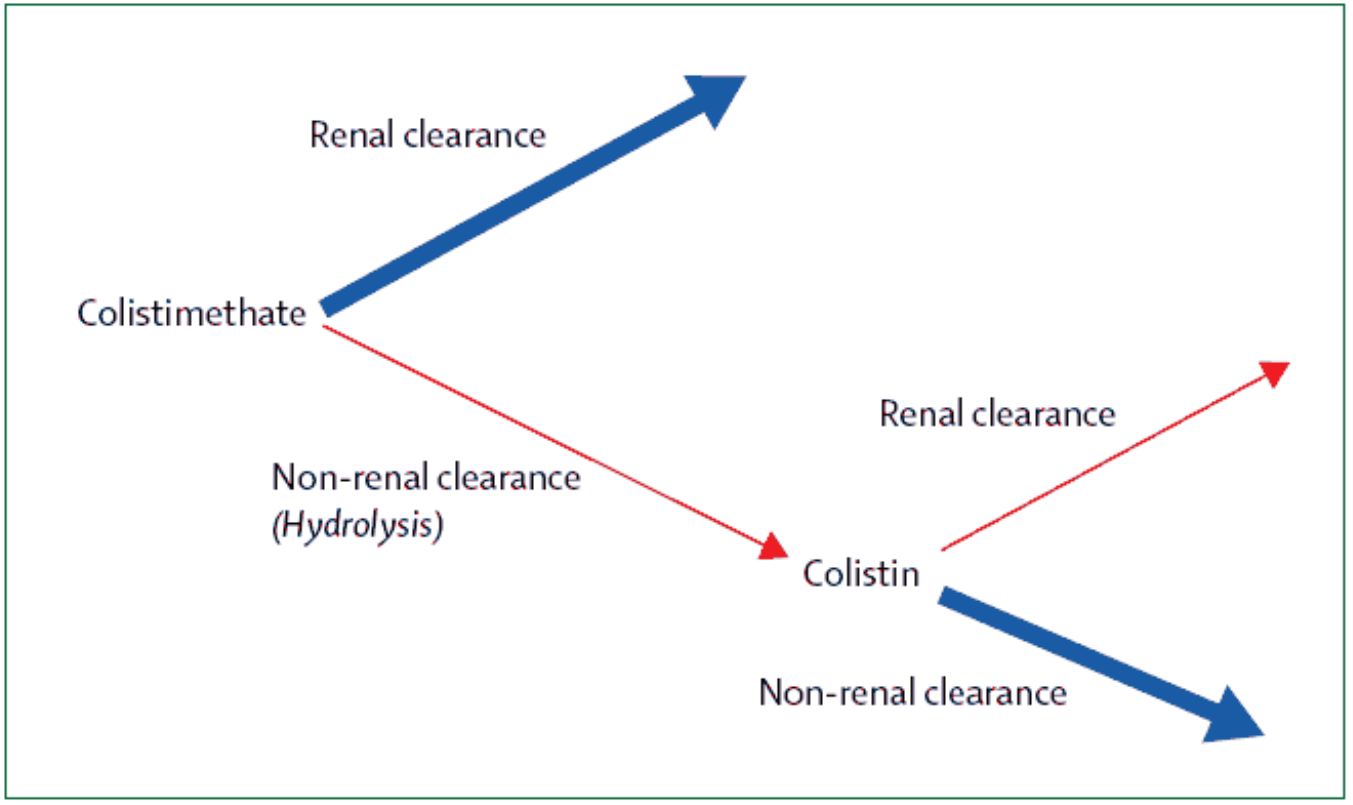


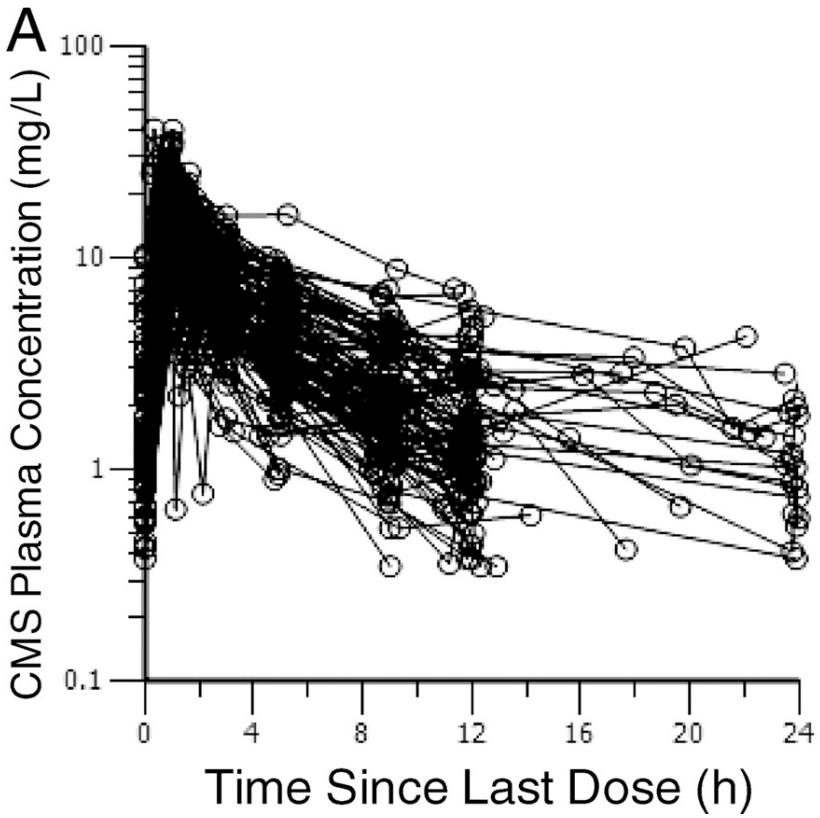
Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

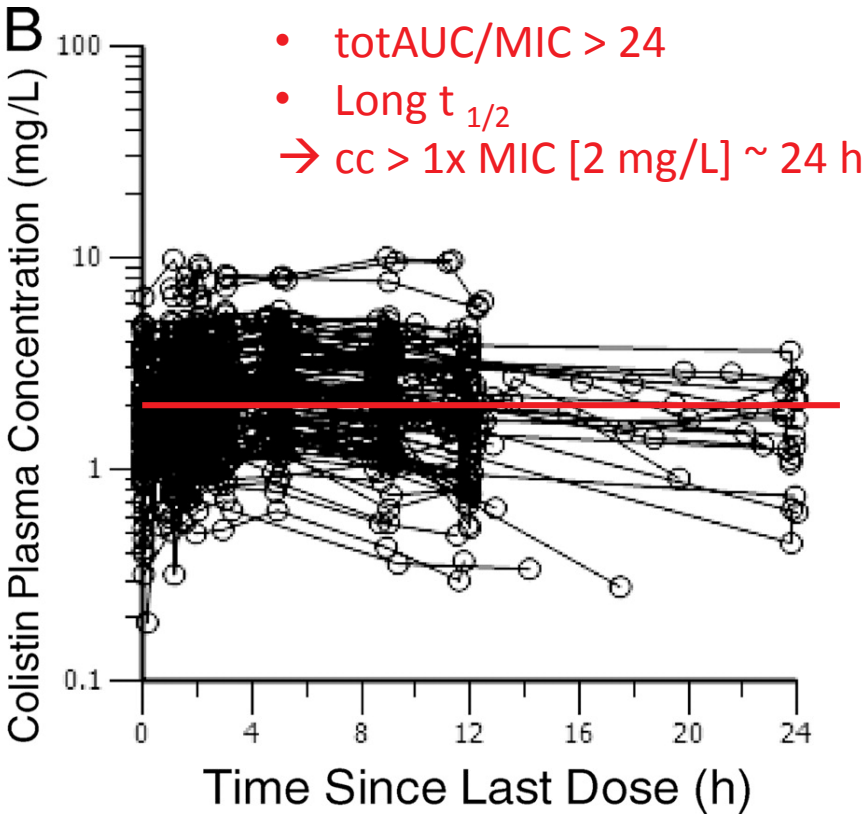
Li et al, Lancet Infect. Dis. 2006; 6:589-601

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 $t_{1/2}$

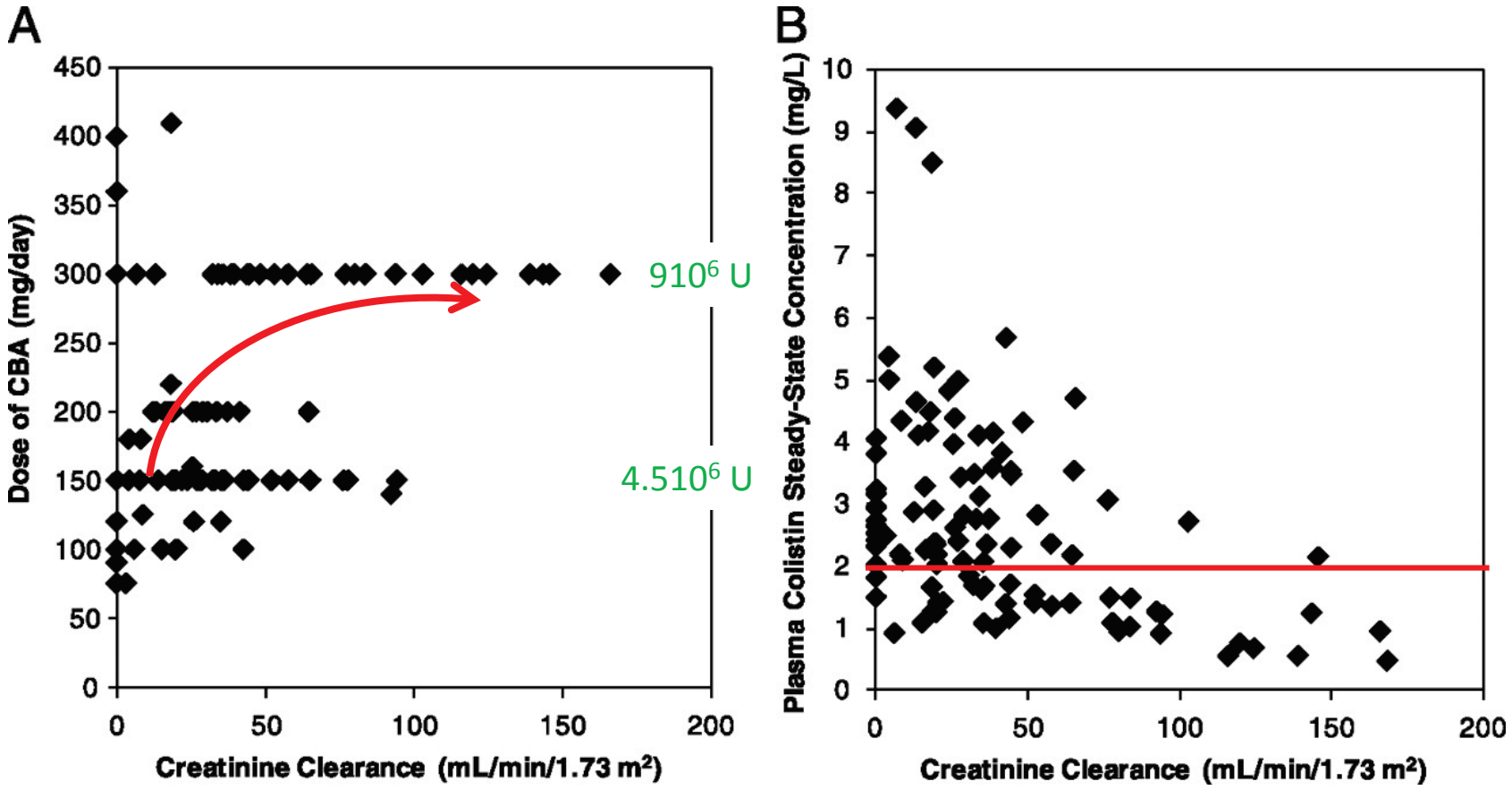
→ cc > 1x MIC [2 mg/L] ~ 24 h

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.

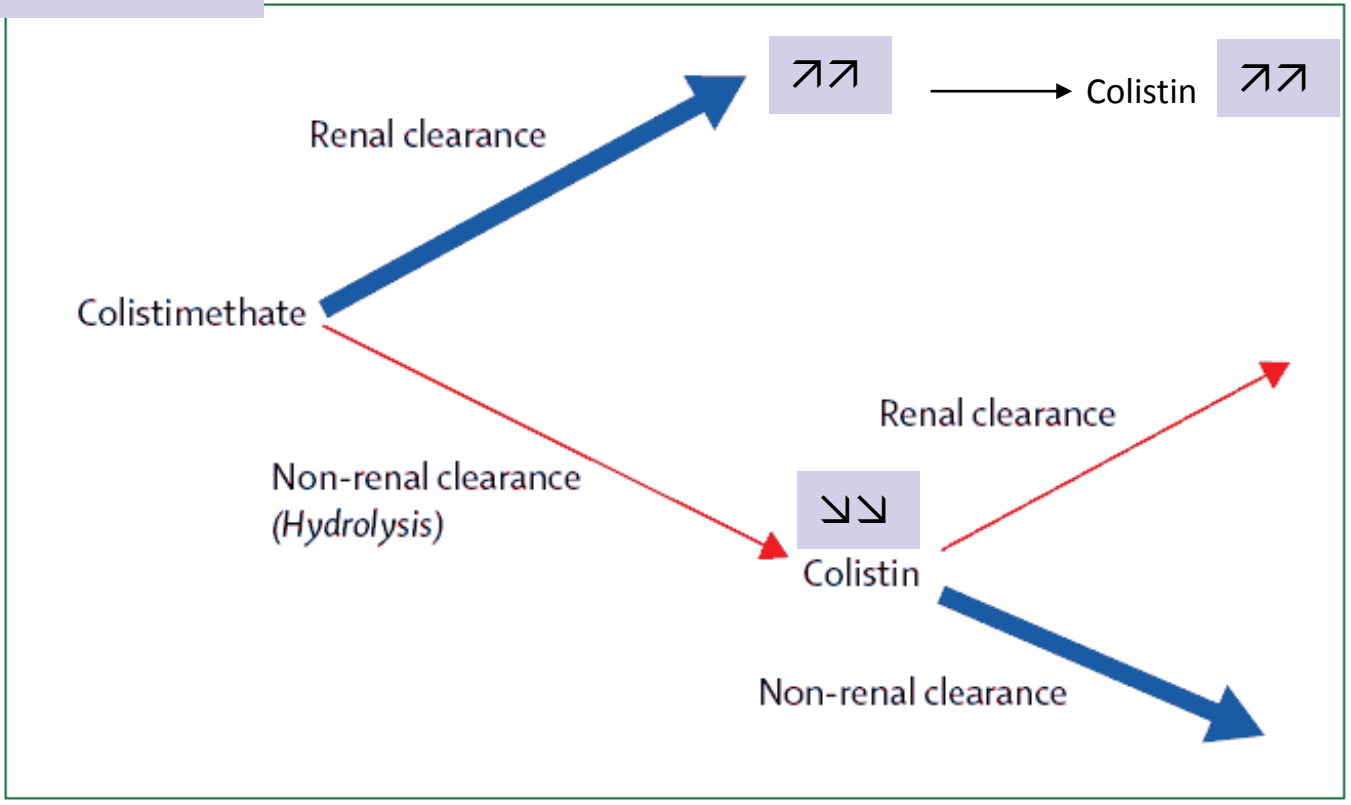
Relationship of physician-selected daily dose of colistin base activity (CBA) (A) and the resultant average steady-state plasma colistin concentration (B) with creatinine clearance in 105 critically ill patients.



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

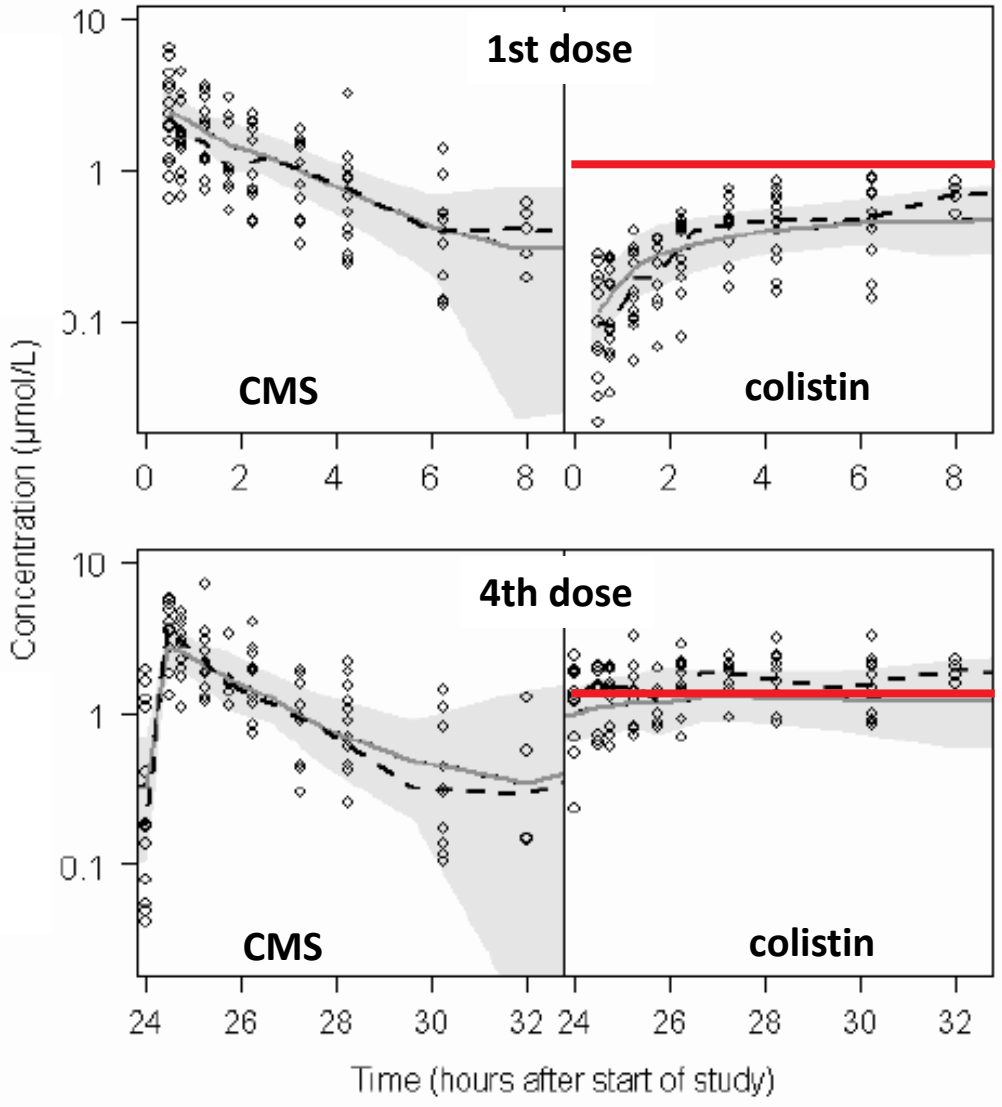
PK in critically-ill patients

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

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

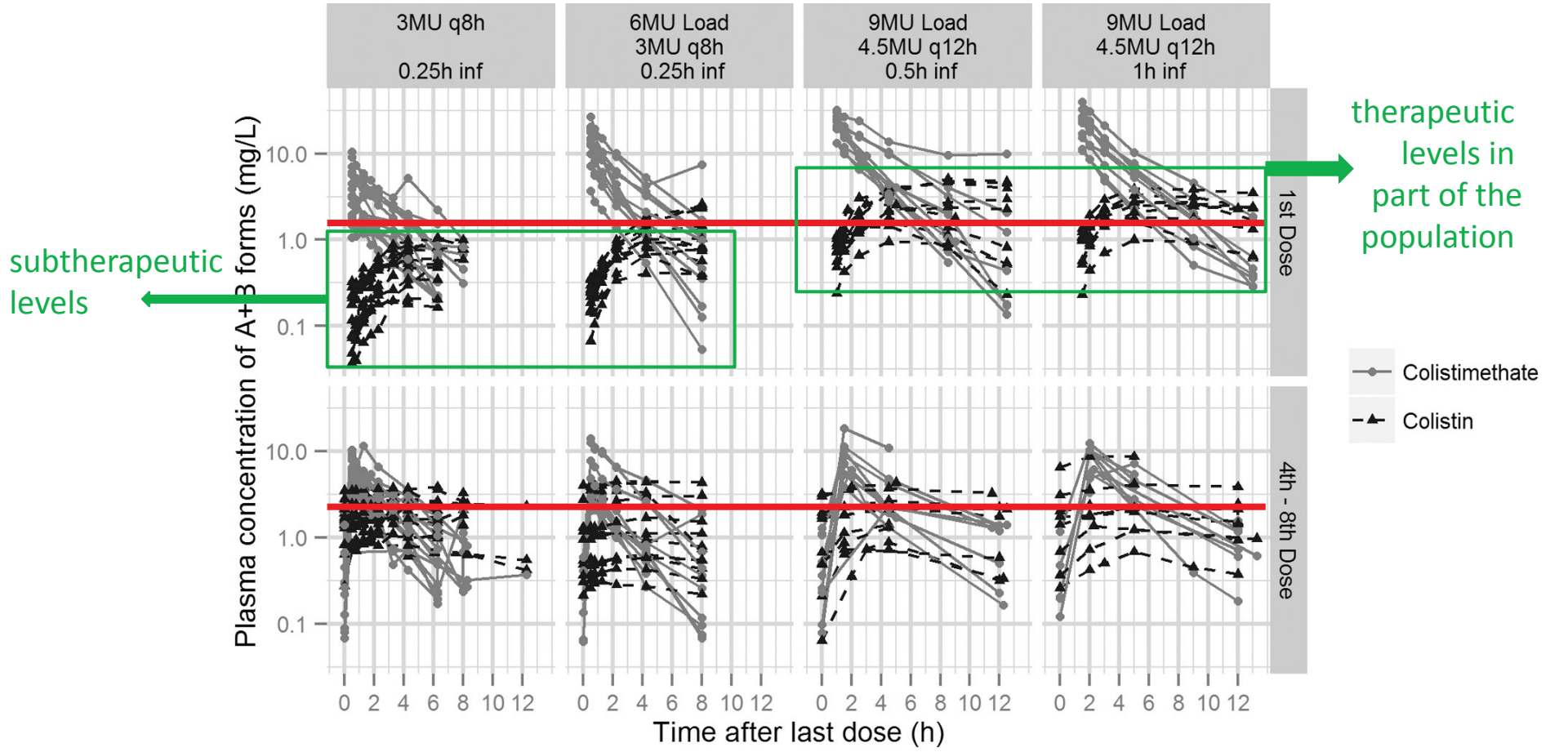
Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.

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]

Colistin penetration in CSF

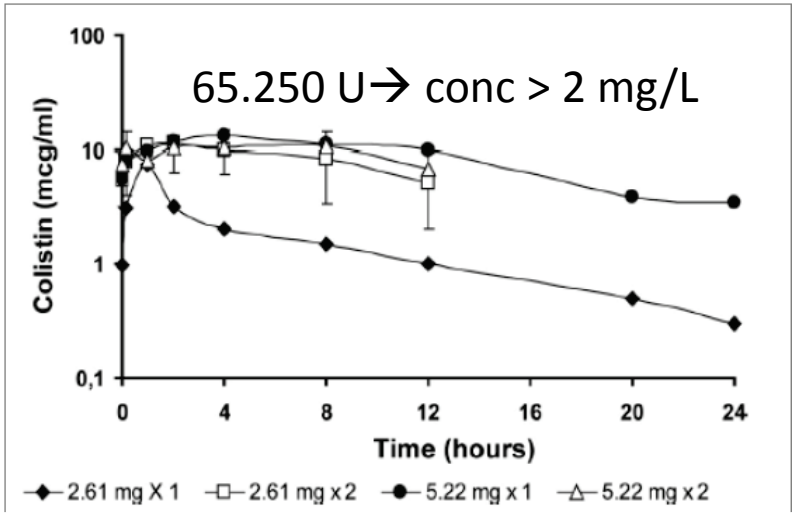
By IV route: subtherapeutic levels[1-2] !

- 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

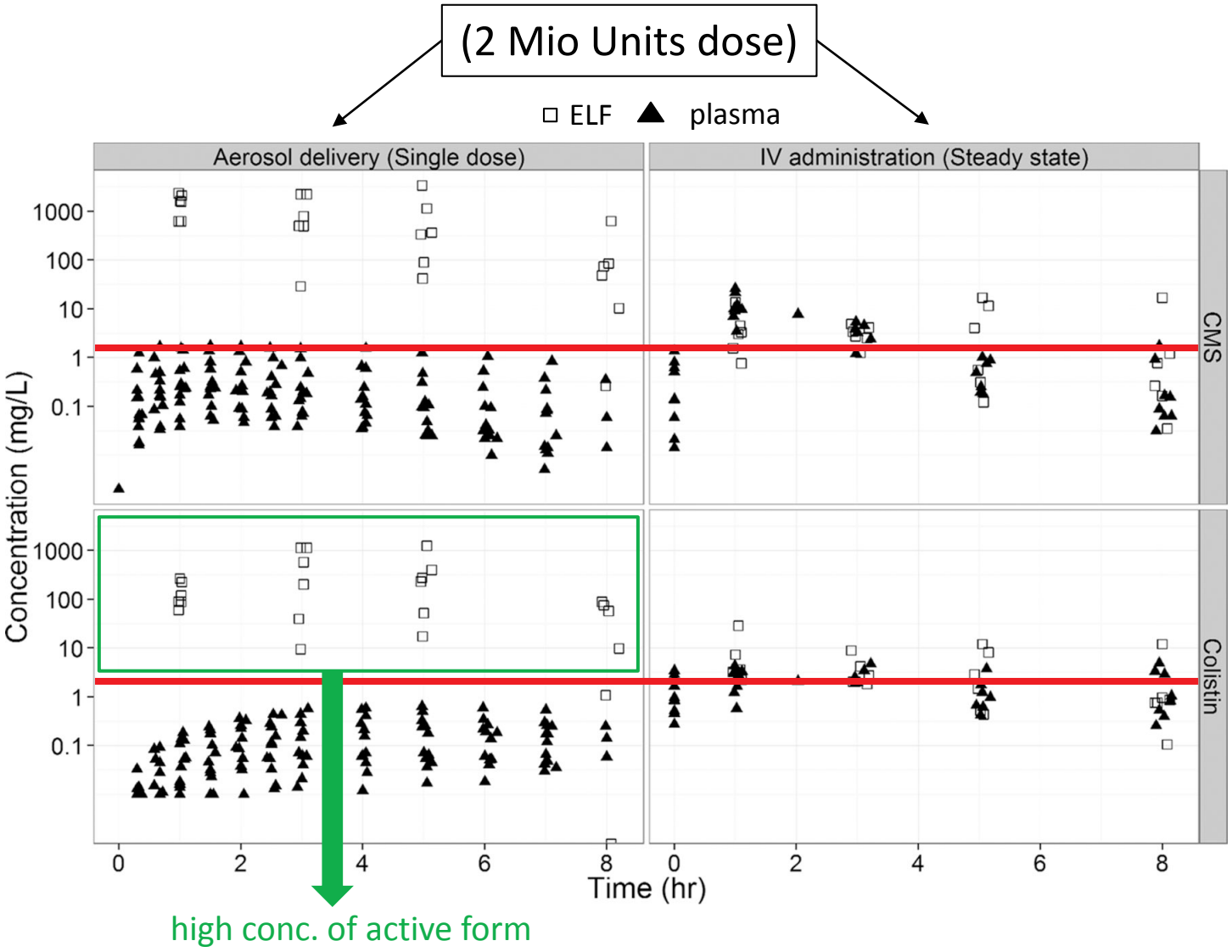
  0.05 mg/L if meningitis (34-67% serum conc.)

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*

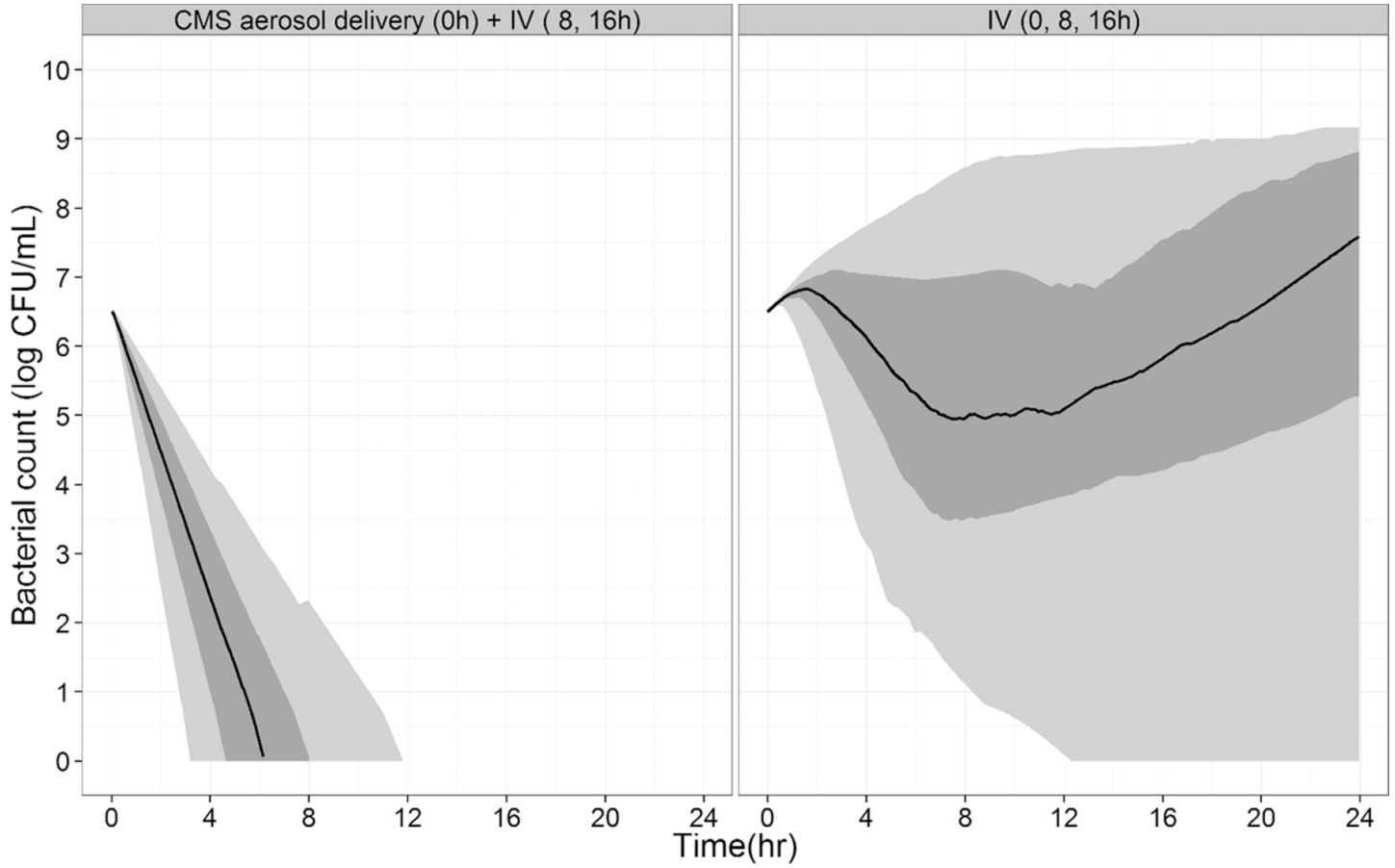
Pulmonary delivery: PK/PD rationale



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).



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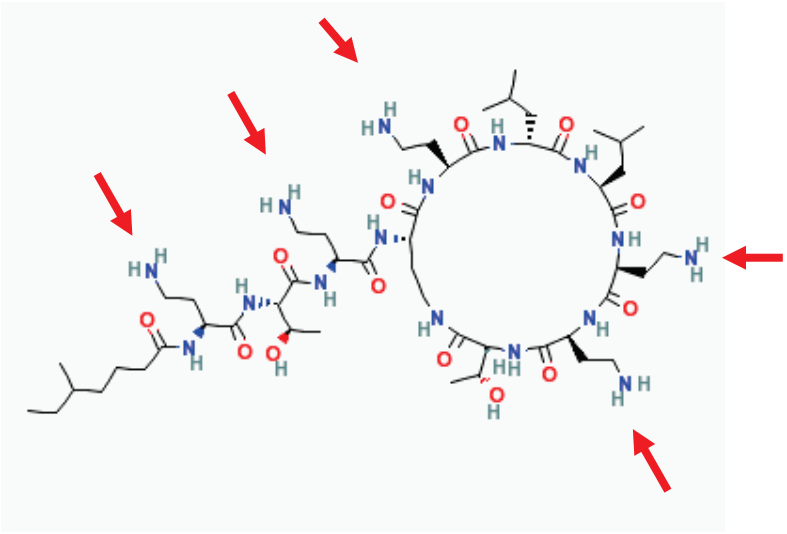


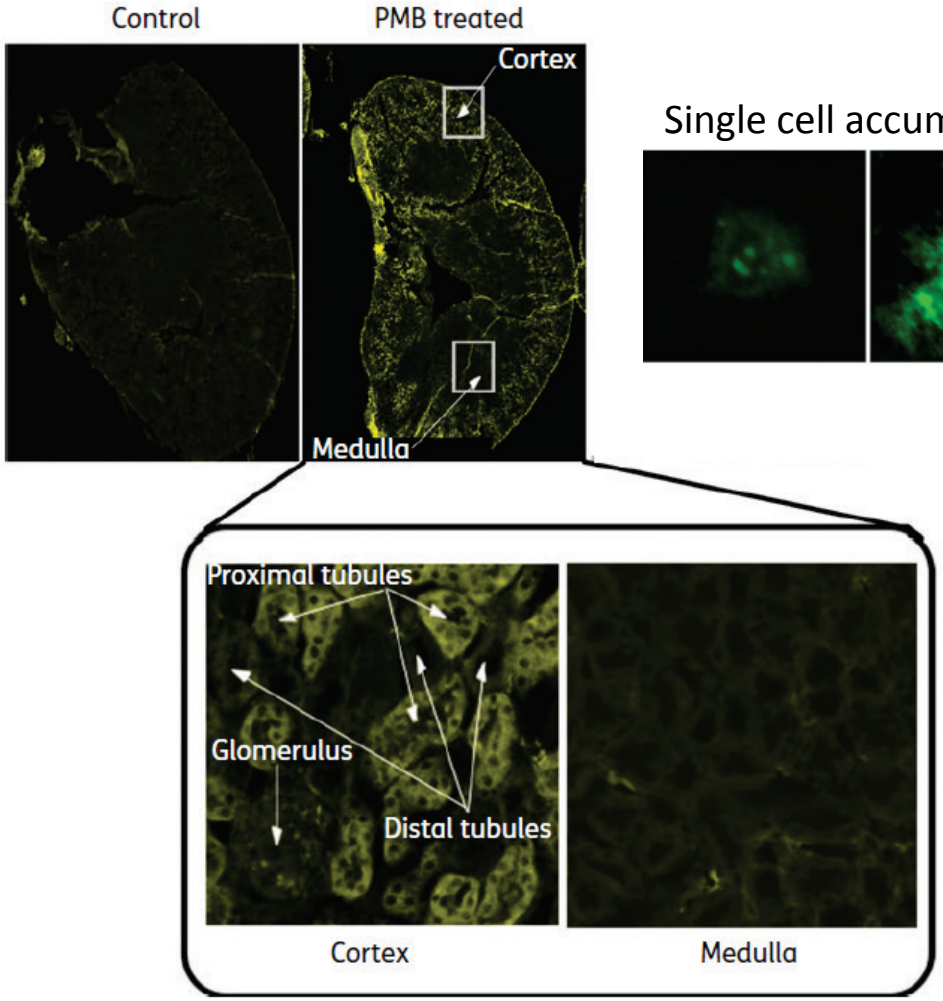
A cyclic **amphipathic polycationic peptide** with a short aliphatic side chain

→ Interaction with eukaryotic cells ?

Toxicity:
the other flip of the coin

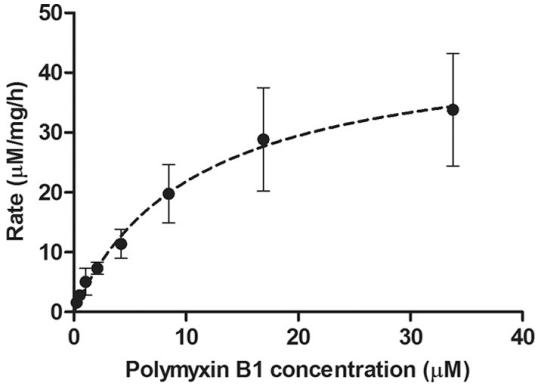
What about renal toxicity ?

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

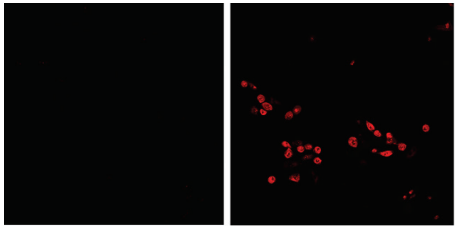


Single cell accumulation

Saturable process (megalin)

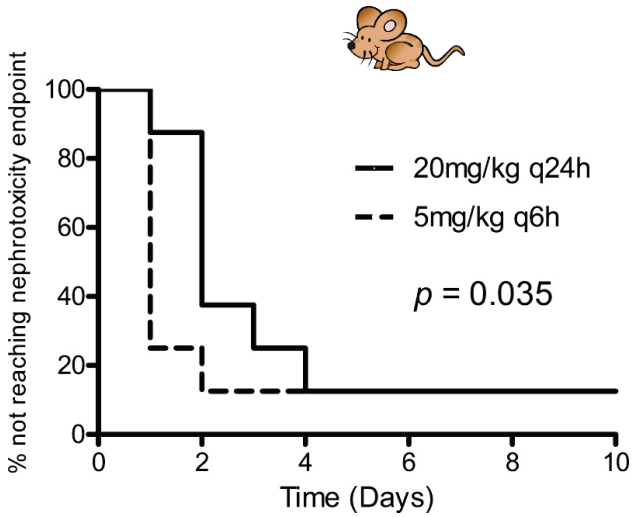


ROS production



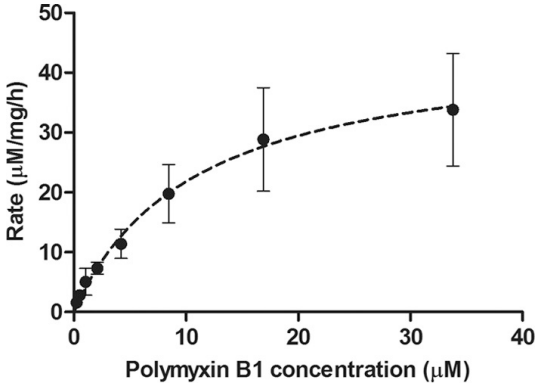
What about renal toxicity ?

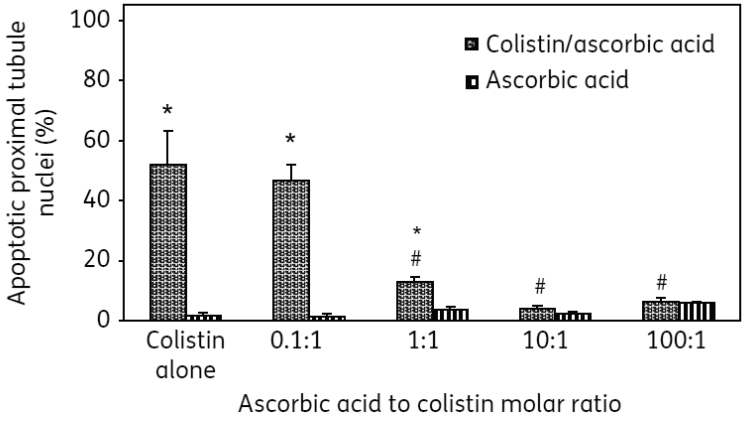
2. Strategies to reduce toxicity



non fractionated doses

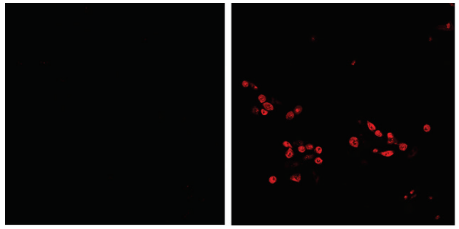
Saturable process (megalin)





combination with ascorbic acid

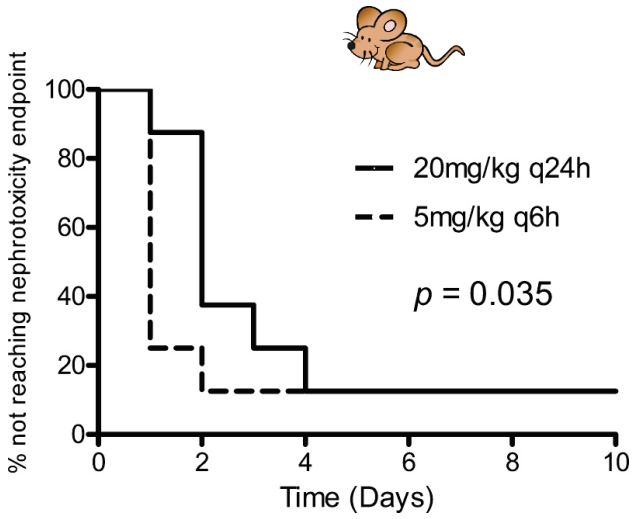
ROS production



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

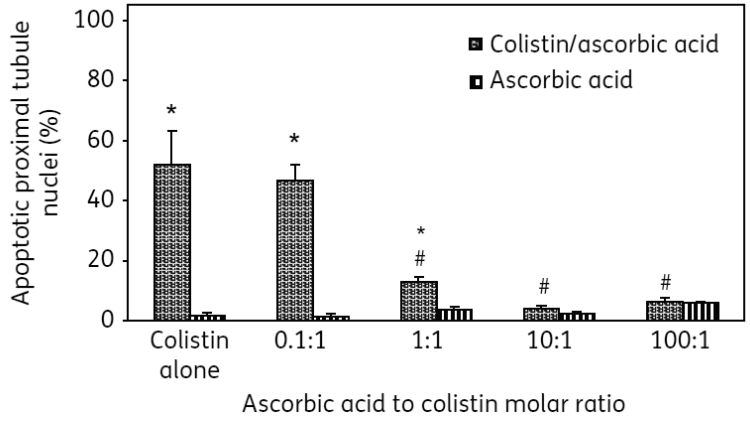
What about renal toxicity ?

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



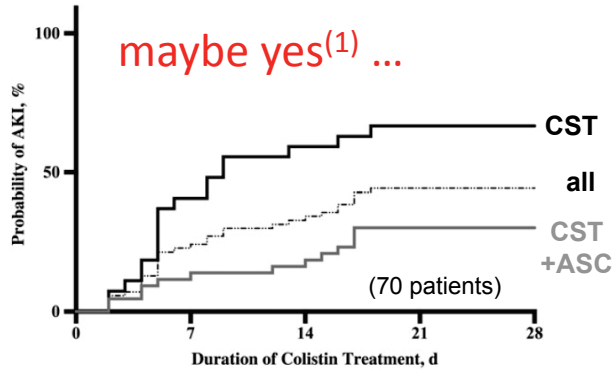
non fractionated doses

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%)

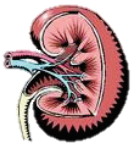
- Limited number of patients included
- Severity of underlying renal disease variable
- Dose of colistin variable
- Definition of nephrotoxicity variable:

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)

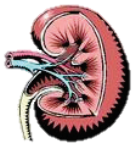


Cox Proportional Hazard Regression Model for Acute Kidney Injury Risk Based on Cumulative Colistin Dose

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

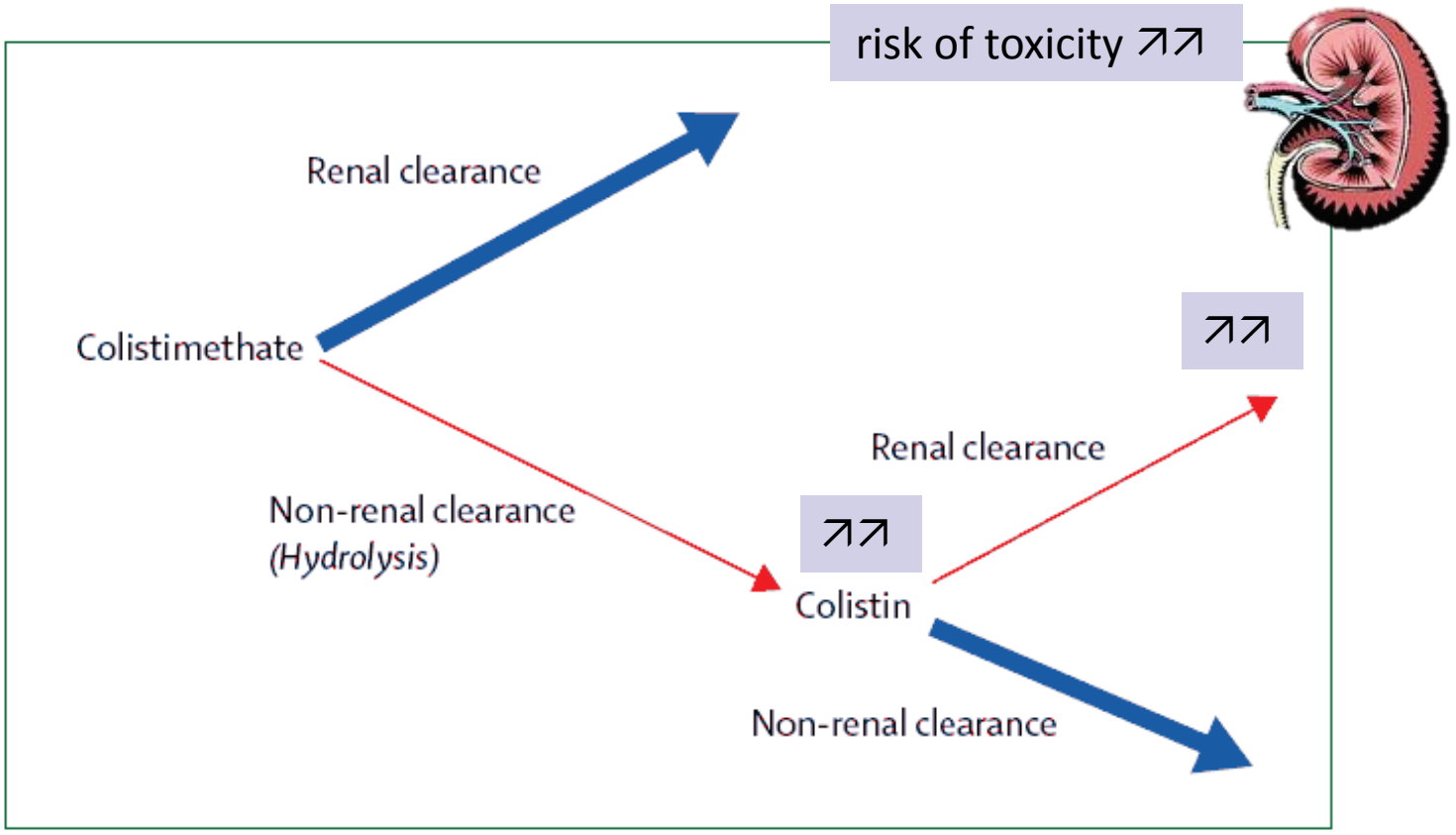


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

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

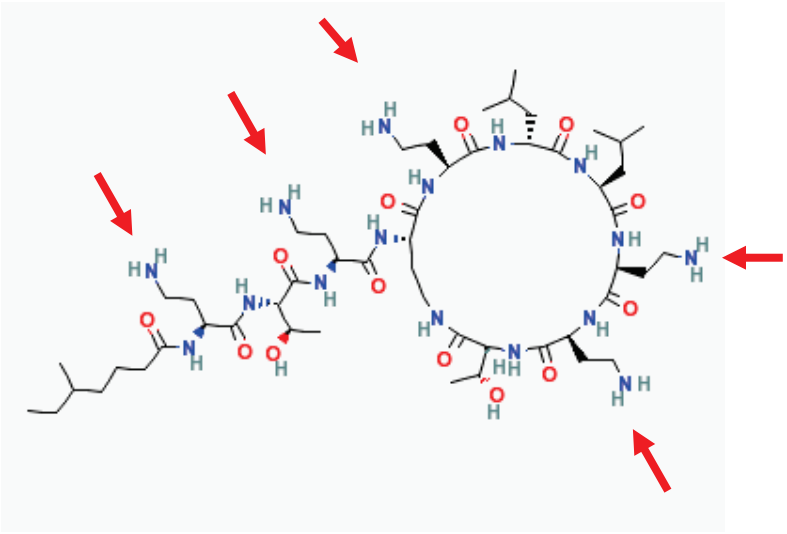
Toxicity by intratechal/intraventricular route

In 9/82 patients (11 %)

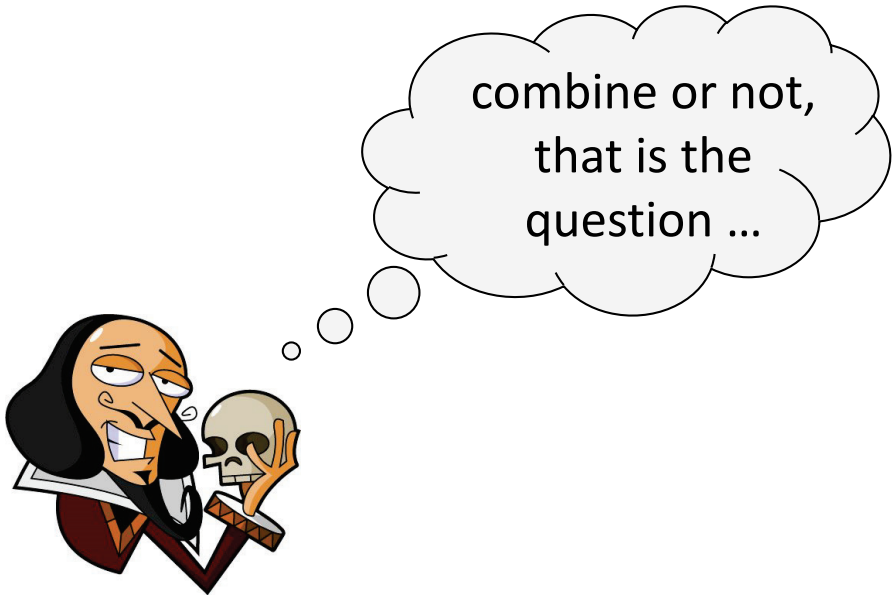
- chemical meningitis (3)
- chemical ventriculitis (2)
- seizures (3)
- *cauda equina* syndrome (1)

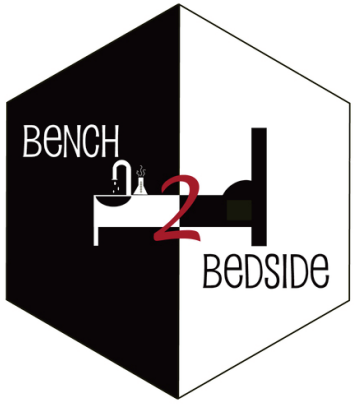
Karaiskos et al, IJAA 2013; 41:499-508

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)

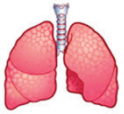
Tumbarello et al; JAC 2015;70:2133-43

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 2014

Depending on renal function :

Creatinine clearance (mL/min)	Daily dose (Mio units)
≥ 80	9-12
50-80	9
30-50	5.5-7.5
10-30	4.5-5.5
<10	3.5

Limited experience; safety ???

Children ≤ 40kg
25.000-50.000 U/kg 3 X/day

In dialyzed patients:

Dialysis procedure	Daily dose (Mio units)
Intermittent hemodialysis	2.25 on non-dialysis days 3 after dialysis on dialysis days
CVVHF/CVVHDF	3 x /day as in patients with normal renal function

Current dosing recommendations: EMA 2014

Depending on renal function :

Creatinine clearance (mL/min)	Daily dose (Mio units)
≥ 80	9-12
50-80	9
30-50	5.5-7.5
10-30	4.5-5.5
<10	3.5

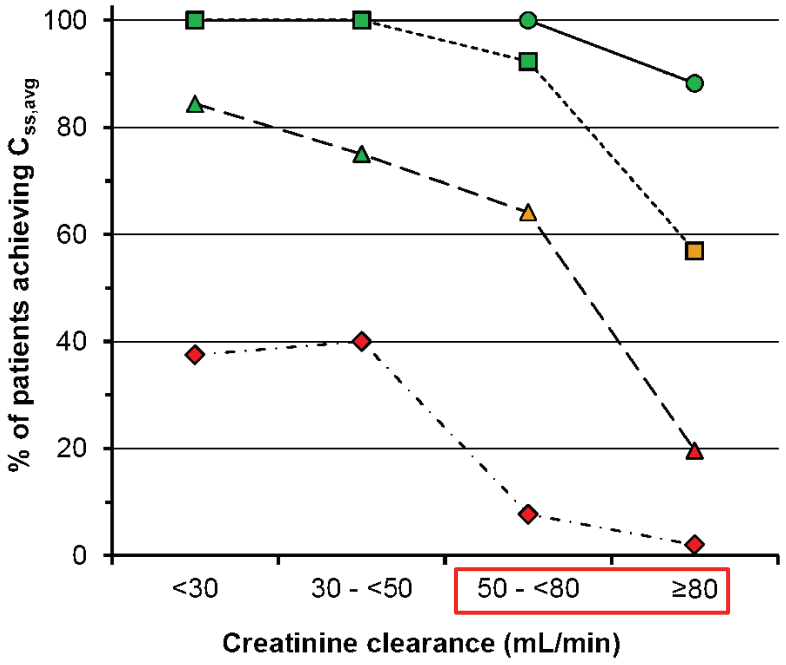
Limited experience; safety ???

Belgian SmPc

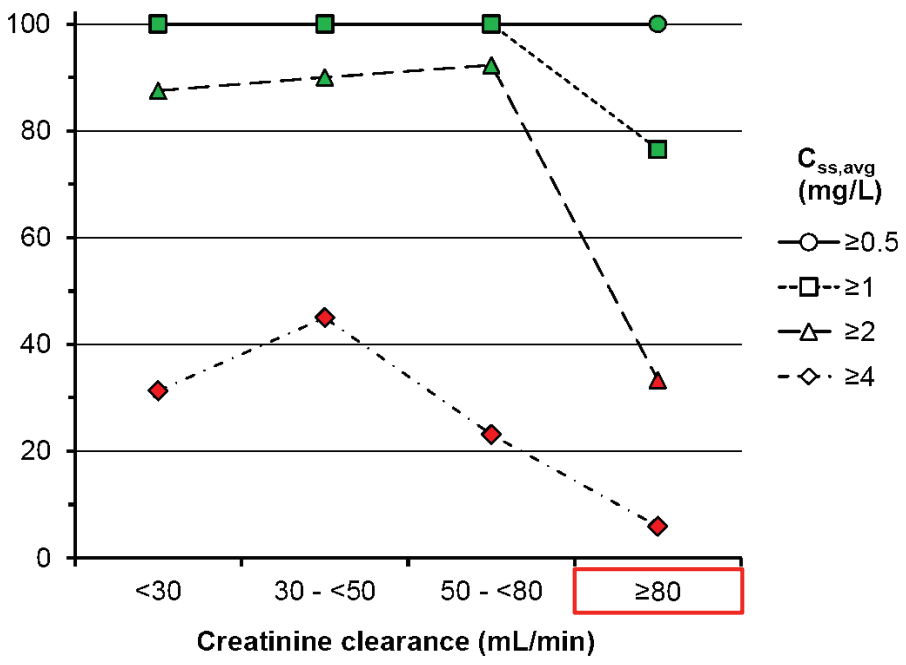
Creatinine clearance (mL/min)	Daily dose (Mio units)
≥ 20	6 (2 Mio q8h)
10-20	1.5-2 (1 Mio q12-18h)
<10	1.3 (1 Mio q18-24h)

Current dosing recommendations: target attainment

Clinician selected dose:



EMA recommended dose:

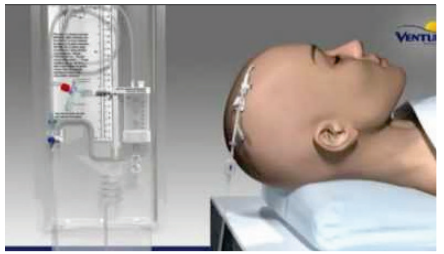


Nation et al, CID 2015; in the press

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

Comments on these guidelines

Issues in reviving old antibiotics

- No data on rational dosing at the time of registration
- "Generic" → no more investment from pharmaceutical companies

⇨ Re-developed thanks to academic efforts with the support of public authorities

Issues in establishing dosing recommendations

- Divergence between susceptibility breakpoints [FDA/EUCAST]
- Divergence in dosing recommendations [FDA/EMA]
- Narrow therapeutic window

⇨ Therapeutic drug monitoring → free concentrations vs MIC

Van Bambeke & Tulkens, CID 2015; in the press

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