Colistin versus Polymyxin B

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Medicine Co., Pfizer, Shionogi

Advisory Member: Clinical Laboratory Standards Institute (CLSI)

Colistin versus Polymyxin B

ONE

OR

BOTH

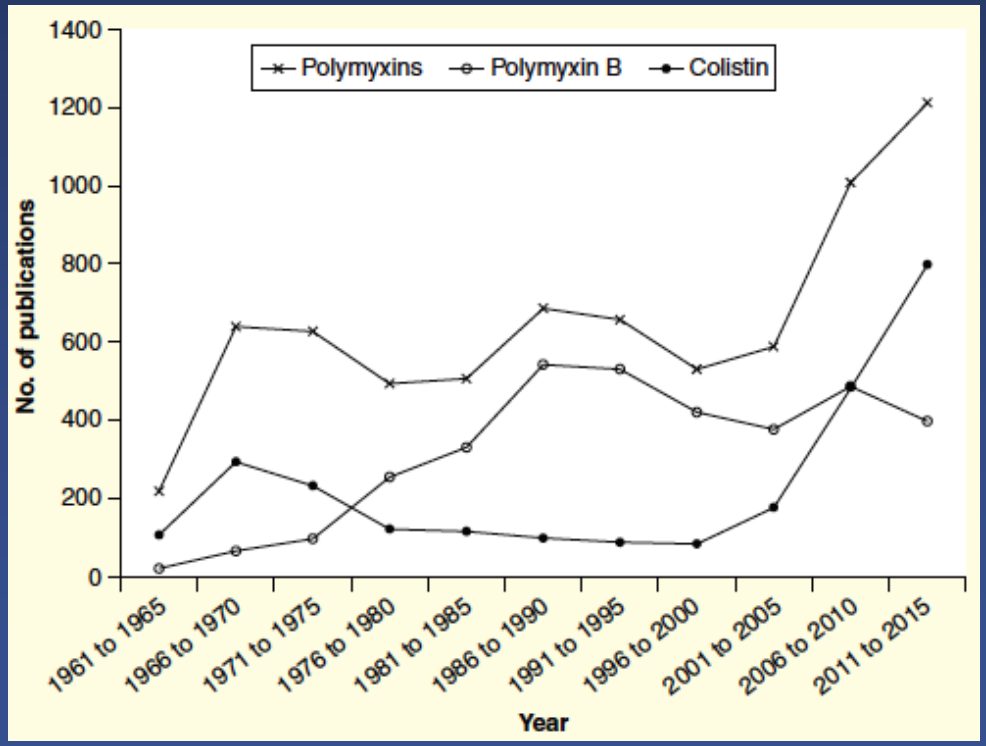
OR

NEITHER

Clinical Utilization of Polymyxins

- Polymixins were approved in the 1950s but fell out of favor when safer antimicrobial therapies became available
- Questions remain about place in therapy and dosing strategies

- Sharp increase in the number of publications since 2000, following a renewed interest in the class → MDR Gram-Negative Pathogens



Cai Y et al. Expert Rev Anti Infect Ther. 2015;13(12):1481-97

Colistin & Polymyxin B: Microbiologic Profile

Polymyxin B differs from colistin by a single amino acid change (D-phenylalanine replaces D-leucine)

Mechanism of action: Disrupts permeability of bacterial cell wall, resulting in leakage of intracellular components

***In vitro* activity against major Gram-Negatives inclusive of MDR Pathogens**

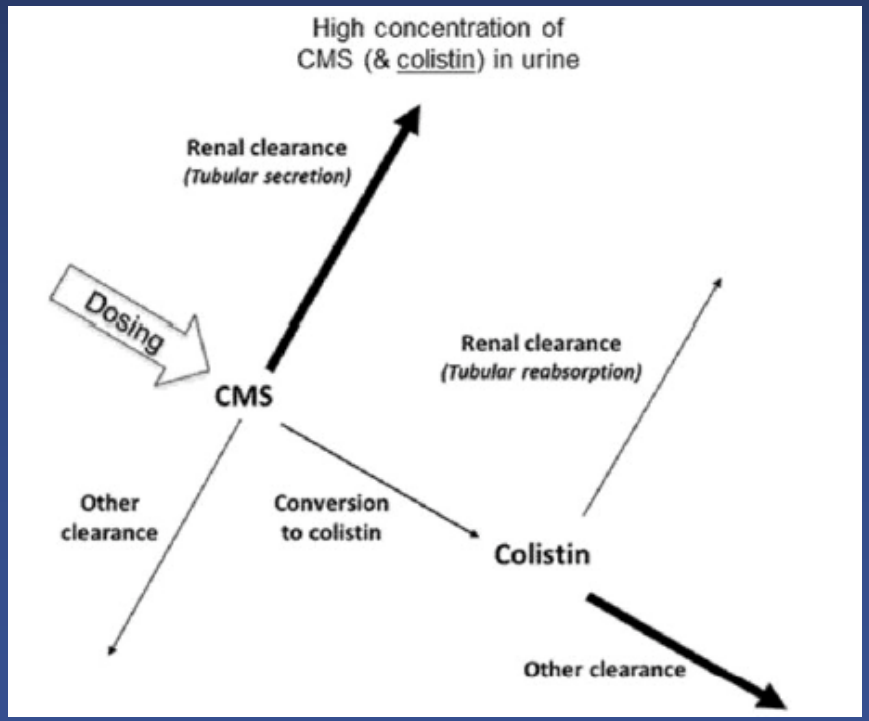
- ***Enterobacteriaceae*** *[E. coli, K. pneumoniae, Enterobacter spp.]*
- ***A. baumannii***
- ***P. aeruginosa***

Microbiologic activity of the compounds is indistinguishable

Colistin: Pharmacokinetic Profile

- **Colistin is formulated as a sulfomethylated prodrug, colistimethate sodium (CMS)**
  - **CMS undergoes *in-vitro* and *in-vivo* hydrolysis into active colistin**

- **CMS is predominantly cleared by renal excretion**
- **In renally competent subjects the renal clearance of CMS is more efficient than the conversion to active colistin, making it hard to reach therapeutic plasma levels**



Nation et al. Clin Infect Dis. 2014 Jul 1;59(1):88-94

Colistin: Ability to Rapidly Achieve Desired Plasma Concentrations

Antimicrob Agents Chemother. 2012 Aug; 56(8): 4241–4249. PMCID: PMC3421626
doi: 10.1128/AAC.06426-11

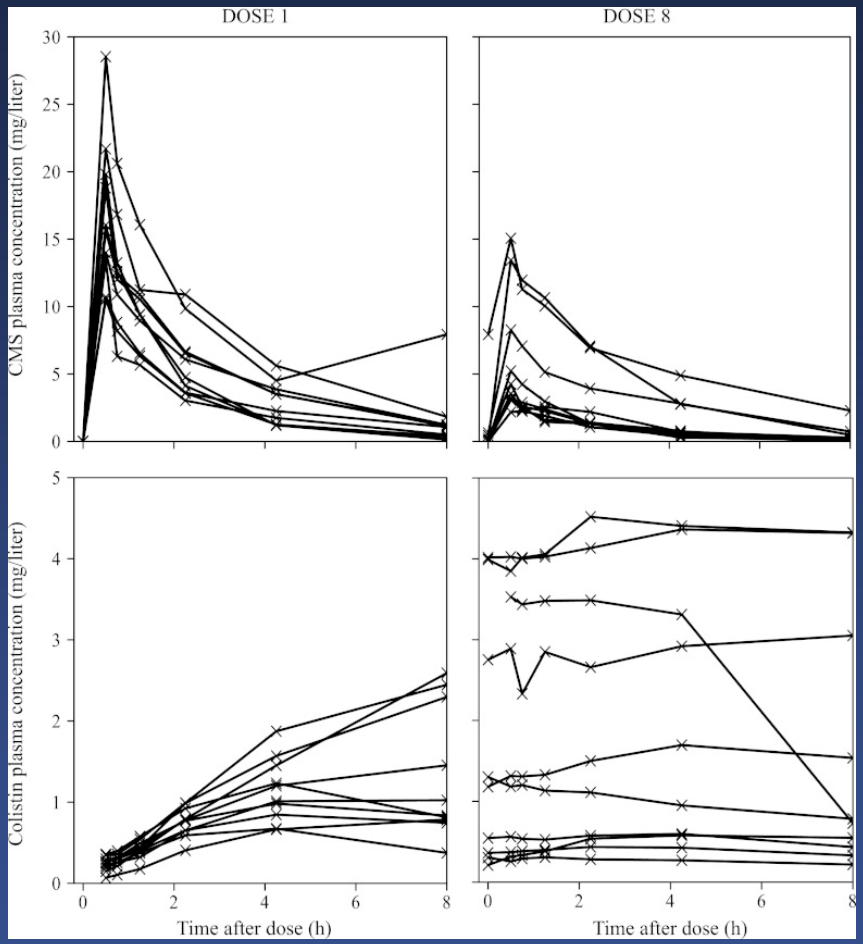
Application of a Loading Dose of Colistin Methanesulfonate in Critically Ill Patients: Population Pharmacokinetics, Protein Binding, and Prediction of Bacterial Kill

Ami F. Mohamed,[a,b] Ilias Karaiskos,[c] Diamantis Plachouras,[c] Matti Karvanen,[d] Konstantinos Pontikis,[e] Britt Jansson,[a] Evangelos Papadomichelakis,[e] Anastasia Antoniadou,[c] Helen Giamarellou,[c] Apostolos Armaganidis,[e] Otto Cars,[d] and Lena E. Friberg[a]

With a CMS loading dose of 480 mg (6 MU) it may take several hours to achieve effective plasma colistin concentrations

Results: Average colistin [C] were 1.34 mg/L (range, 0.374 to 2.59 mg/L) at 8h following the loading dose of 480 mg

Increase LD to 9 MU?



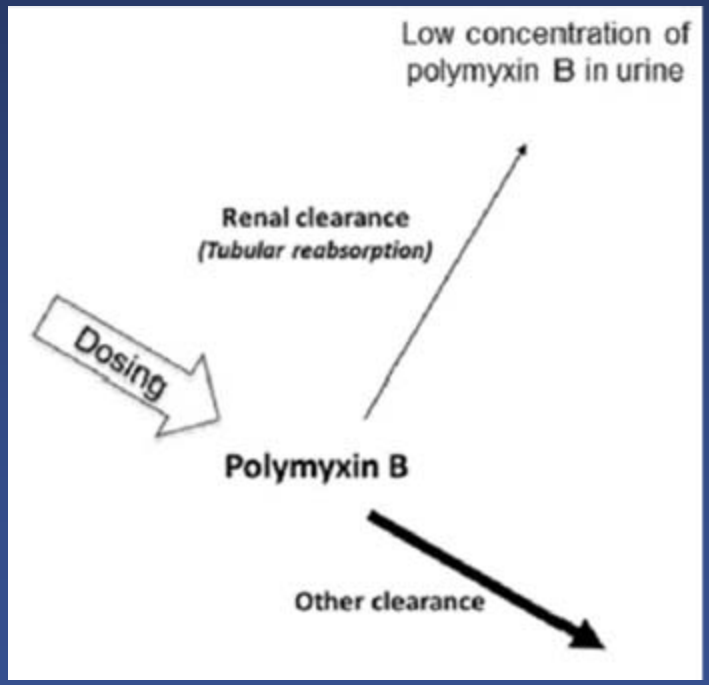
Observed individual plasma [C] of CMS (top) and colistin (bottom) after administration of the first and eighth doses of CMS

Mohamed et al. Antimicrob Agents Chemother 2012; 56:4241–9.

Polymyxin B: Pharmacokinetic Profile

- **Polymyxin B is formulated as an active drug**
  - » **NO Loading dose required**
- **Simplified dosing regimen: 1.25-2.5 mg/kg/d given Q12**

- **Polymyxin B is eliminated mainly by non-renal clearance mechanisms, and urinary concentrations are relatively low**



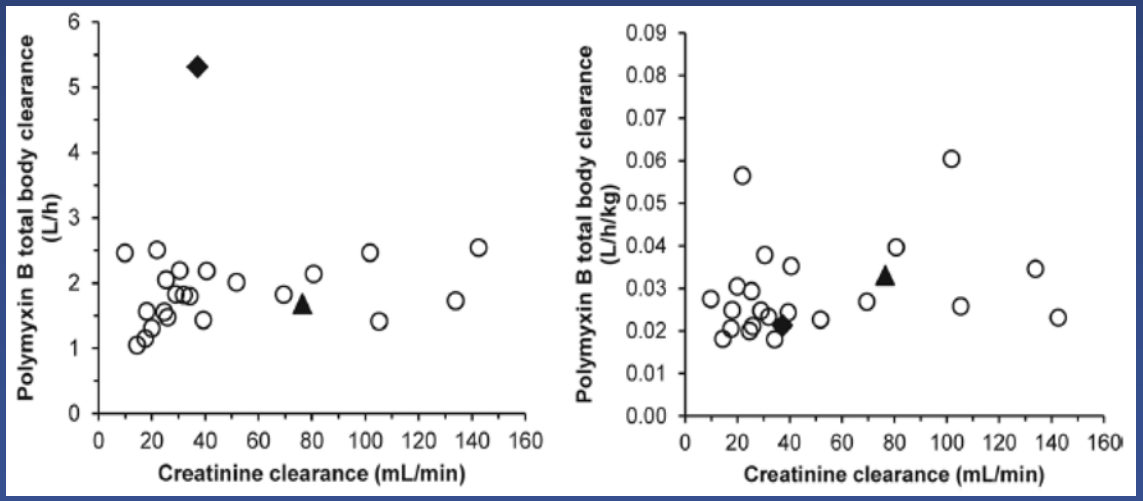
Nation et al. Clin Infect Dis. 2014 Jul 1;59(1):88-94

Polymyxin B: No Dosage Adjustments in Patients with Renal Impairment

MAJOR ARTICLE

Population Pharmacokinetics of Intravenous Polymyxin B in Critically Ill Patients: Implications for Selection of Dosage Regimens

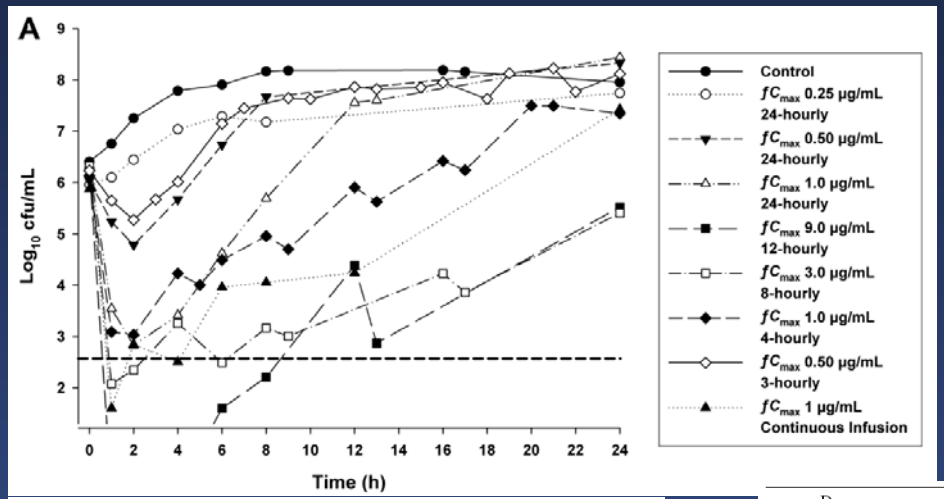
Ana M. Sandri,[1,a] Cornelia B. Landersdorfer,[2,3,a] Jovan Jacob,[4] Márcio M. Boniatti,[5] Micheline G. Dalarosa,[6] Diego R. Falci,[6] Tainá F. Behle,[7] Rosaura C. Bordinhão,[6] Jiping Wang,[4] Alan Forrest,[3] Roger L. Nation,[4] Jian Li,[4,b] and Alexandre P. Zavascki[7,b]

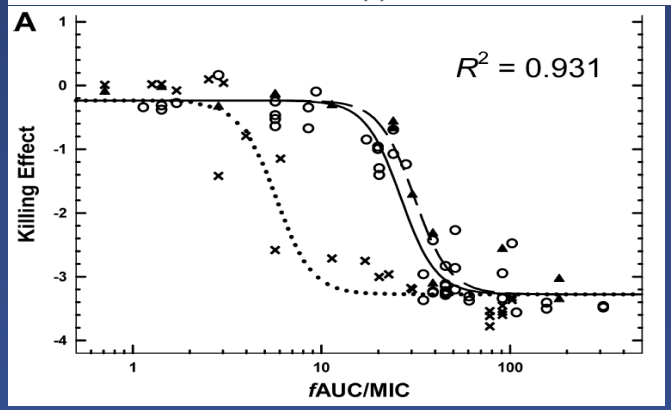


- Polymyxin B was predominantly non-renally cleared with median urinary recovery of 4.04%
- Polymyxin B total body clearance did not show any relationship with creatinine clearance (r^2 = 0.008)

Sandri AM et al. Clin Infect Dis. 2013 Aug;57(4):524-31

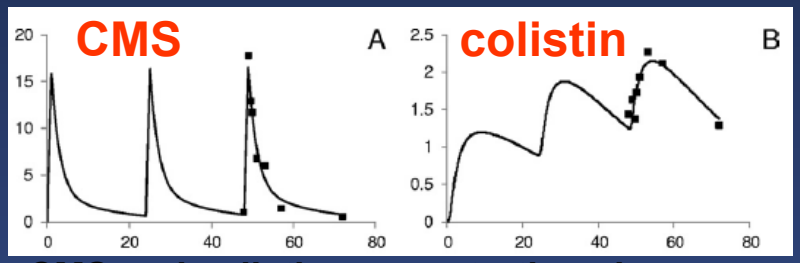
Colistin: Pharmacodynamics against *P. aeruginosa*: Impact on Dose Optimization





fAUC/MIC of 25 and 35 resulted in 1- and 2- log reductions in area under the CFU/ml curve relative to growth control

60mg colistin base activity = 160mg colistin methanesulfonate (CMS) = 2 million units of CMS



CMS and colistin concentrations in a

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.
	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

Can't achieve required *f*AUC/MIC exposures for CrCL >70 ml/min or MIC > 0.5 mcg/mL → ComboTx Required!

Bergen PJ, et al. *Antimicrob Agents Chemother* 2010;54:3783-9,
Garonzik SM et al. *Antimicrob Agents Chemother* 2011;55:3284-94

Colistin: PK/PD against *P. aeruginosa* and *Acinetobacter baumannii*

TABLE 3. Target values of colistin *f*AUC/MIC for stasis and 1-, 2-, and 3-$\log_{10}$ kill against all three *P. aeruginosa* strains in the thigh and lung infection models

Model and kill effect	Target value of colistin *f*AUC/MIC for strain:		
	ATCC 27853	PAO1	19056
Thigh infection			
Static effect	17.3	14.4	8.34
1-$\log_{10}$ kill	22.7	22.8	15.6
2-$\log_{10}$ kill	31.2	36.1	27.6
3-$\log_{10}$ kill	55.1	66.7	53.3
Lung infection			
Static effect	6.43	5.42	4.07
1-$\log_{10}$ kill	15.6	16.7	12.2
2-$\log_{10}$ kill	37.9	45.9	36.9
3-$\log_{10}$ kill	105	135	141

Table 2. Target values of colistin *f*AUC/MIC for stasis, and for 1 and 2 $\log_{10}$ kill against all three *A. baumannii* strains in thigh and lung infection models

	*f*AUC/MIC		
Kill effect	ATCC 19606	248-01-C.248[a]	N-16870.213
Thigh infection model			
Static effect	1.89	6.75	7.41
1 $\log_{10}$ kill	6.98	13.6	11.9
2 $\log_{10}$ kill	43.0	24.7	17.5
Lung infection model			
Static effect	1.57	6.08	6.52
1 $\log_{10}$ kill	8.18	12.9	42.1
2 $\log_{10}$ kill	95.0	22.5	[b]

[a]Multidrug-resistant clinical strain.
[b]2 $\log_{10}$ kill was not achieved for this strain in the lung infection model

_f_AUC/MIC needed for 2 log kill is approximately 30 in the thigh

Poor penetration → Higher Exposures required for pulmonary infection

Dudhani RV, et al. *Antimicrob Agents Chemother* 2010;54:1117-24
Dudhani RV, et al. *J Antimicrob Chemother* 2010;65:1984-90.

Recently Updated European Medicines Agency & US FDA – Approved Daily Maintenance Doses for Colistimethate in Patients With Various Degrees of Renal Function

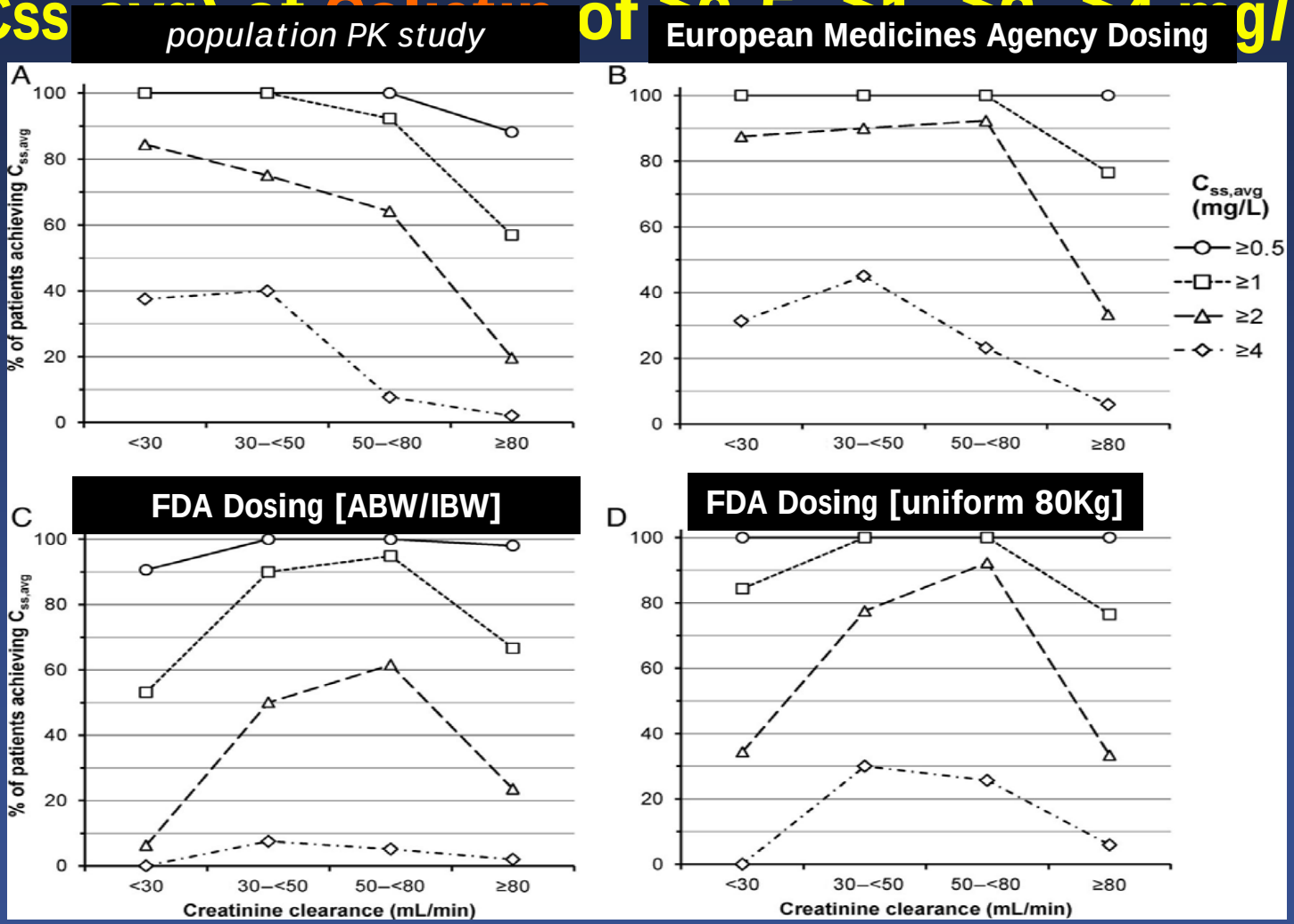
Creatinine Clearance (mL/min)	European Medicines Agency Daily Dose[a]	US FDA Daily Dose[b]
≥80	9 MIU[c] (~ 300 mg CBA)	2.5–5 mg CBA/kg
50 to <80	9 MIU[c] (~ 300 mg CBA)	2.5–3.8 mg CBA/kg
30 to <50	5.5–7.5 MIU (~183–250 mg CBA)	2.5 mg CBA/kg
10 to <30	4.5–5.5 MIU (~150–183 mg CBA)	1 mg CBA/kg[d]
<10	3.5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

Abbreviations: CBA, colistin base activity; MIU, million international units.

[a]The European Medicines Agency (EMA) expressed doses in terms of MIU. The EMA doses have been converted to approximately equivalent doses expressed as milligrams of CBA, and these are shown in parentheses. [b]The US Food and Drug Administration (FDA)–approved product label indicates that in obese individuals, the dosage should be based on ideal body weight. [c]The EMA-approved product label indicates that daily doses up to 12 MIU (approximately 400 mg CBA) may be required in patients with good renal function in some cases. [d]The FDA-approved product label states 1.5 mg CBA/kg every 36 hours, which has been converted in the table to the corresponding daily rate.

Nation RL et al. Clin Infect Dis. 2016;62:552-558

Percentage of Patients in each Creatinine Clearance Cluster Achieving Steady-State Plasma [C] (Css,avg) of Colistin of ≥0.5, ≥1, ≥2, ≥4 mg/L



Nation RL et al. Clin Infect Dis. 2016;62:552-558

Polymyxin B: Pharmacodynamic Profile

J Antimicrob Chemother. 2017 Nov 14. doi:10.1093/jac/dkx409. [Epub ahead of print]
Landersdorfer CB, et al.

Pharmacokinetics/pharmacodynamics of systemically administered polymyxin B against Klebsiella pneumoniae in mouse thigh and lung infection models
-Plasma binding constant
-*f*AUC/MIC pharmacodynamic driver
-Thigh model: achieved status and 1 log kill, no 2 log efficacy despite high dose
-Pneumonia model: **Insufficient efficacy**

- **Insufficient pharmacodynamic data [*in vitro* pharmacodynamic models, *in vivo* murine studies or in man] to fully understand the implications of current Polymyxin B dosing regimens and probability of clinical outcomes**

Summary of Polymyxin Breakpoints

Lab Organ-ization	Version (year)	Drug	Susceptibility breakpoints (mg/L)											
			Enterobacteriaceae			*Pseudomonas* spp.[a]			*Acinetobacter* spp.			Other non-Enterobacteriaceae		
			S	I	R	S	I	R	S	I	R	S	I	R
EUCAST[b]	Ver. 5.0 (2015)	Colistin	≤2	–	>2	≤4 ≤2	– –	>4 ≥4	≤2 ≤2	– –	>2 ≥4	–	–	–
CLSI[c]	M100-S24 (2014)	Colistin & ~~Polymyxin B~~	– –	– –	– –	≤2 ≤2	4 –	≥8 ≥4	≤2 ≤2	– –	≥4 ≥4	≤2 –	4 –	≥8 –
FDA		Polymyxin B only	–	–	–	≤2	4	≥8	–	–	–	–	–	–
BSAC[d]	Ver. 14 (2015)	Colistin	≤2	–	>2	≤4	–	>4	≤2	–	>2	–	–	–

S **= susceptible,** I = **intermediate, R = resistant, – no breakpoint determined**

[a]CLSI M100-S24 contains separate sections for *P. aeruginosa* and *Pseudomonas* spp. with identical breakpoints; either breakpoint maybe altered in future versions of CLSI M100; FDA = US Food & Drug Administration; [b]The European Committee on Antimicrobial Susceptibility Testing; [c]Clinical and Laboratory Standards Institute; [d]The British Society for Antimicrobial Chemotherapy

Bergen PJ, et al. Infect Dis Ther. 2015;4(4): 391–415, **CLSI / EUCAST revised Jan 2016** .

Polymyxins: Ability to Achieve Adequate Urinary Concentrations

Colistin

- In animals and humans with good renal function, ~70% of administered CMS is excreted into urine
- CMS is then converted into colistin in the urine

Polymyxin B

- Polymixin B undergoes extensive tubular reabsorption (90-95%) following glomerular filtration i.e., only a small percentage of polymyxin B is excreted unchanged in the urine

Zavascki et al. *Antimicrobial Agents and Chemotherapy* 2017;61(3):e02319-16; Sandri AM et al. Clin Infect Dis. 2013 Aug;57(4):524-31; Cai Y et al. Expert Rev Anti Infect Ther. 2015;13(12):1481-97.

Steady-State Pharmacokinetics and BAL Concentration of Colistin in Critically Ill Patients After IV Colistin Methanesulfonate Administration

Imberti R, Cusato M, Villani P, Carnevale L, Iotti GA, Langer M, Regazzi M.

In critically-ill patients with VAP, colistin was **undetectable** in BAL following IV adminstrition of CMS 2 MU / 8h

Polymyxin B poor pulmonary penetration

Chest 2010; 138: 1333-39

Colistin Dosing in CRRT

Colistin is substantially removed from the circulation in critically ill patients undergoing CVVHDF [Markou N, et al. J Antimicrob Chemother 2012; 67: 2459–62]

Challenge for higher colistin dosage in critically ill patients receiving CVVHDF → **LD of 12 MU CMS appears more appropriate, whilst a CMS maintenance dosage of at least 6.5-7.5 MU q12h** [Karaiskos I et al. Int J Antimicrob Agents 2016;48(3):337-41]

Polymyxin B unknown pharmacokinetic profile

Polymyxins: Incidence of Nephrotoxicity

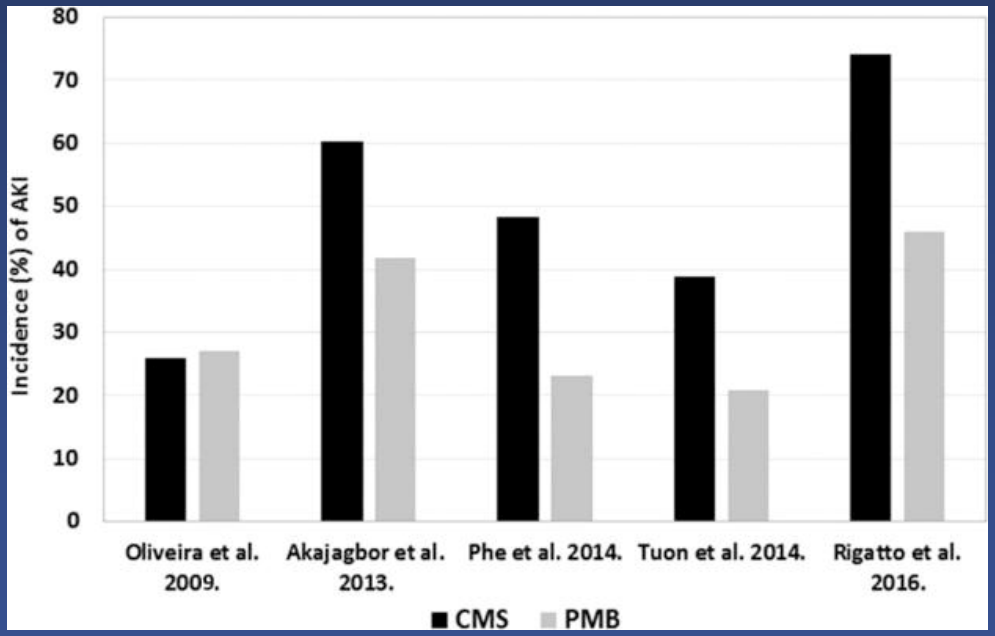
Antimicrob Agents Chemother. 2017 Mar; 61(3): e02319-16.
Published online 2017 Feb 23. Prepublished online 2016 Dec 19.
doi: 10.1128/AAC.02319-16
PMCID: PMC5328560

Nephrotoxicity of Polymyxins: Is There Any Difference between Colistimethate and Polymyxin B?

Alexandre P. Zavascki[a,b] and Roger L. Nation[c]

Summary: Current clinical data suggest that CMS may be more nephrotoxic than Polymixin B in patients

Hypothesis: Renal handling of colistin results in extensive accumulation in kidney proximal tubular cells.



Zavascki et al. *Antimicrobial Agents and Chemotherapy* 2017;61(3):e02319-16
Vardakas et al. Int J Antimicrob Agents. 2017 Feb;49(2):233-238.

Colistin – Clinical Utility as Monotherapy?

TABLE 2 Outcome of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen

Antimicrobial regimen	No. of patients			Mortality, %
	Total	Survived	Died	
Combination therapy	103	75	28	27.2
Carbapenem-containing regimen	31	25	6	19.3
Carbapenem + tigecycline + aminoglycoside or colistin		11	0	
Carbapenem + tigecycline		2	2	
Carbapenem + aminoglycoside		8	1	
Carbapenem + colistin		4	3	
Carbapenem-sparing regimen	72	50	22	30.6
Tigecycline + aminoglycoside + colistin		8	3	
Tigecycline + aminoglycoside		11	9	
Tigecycline + colistin		16	5	
Aminoglycoside + colistin		12	5	
Other		3	0	
Monotherapy	72	40	32	44.4
Tigecycline		16	11	
Colistin		10	12	
Aminoglycoside		7	2	
Carbapenem		5	7	
Other		2	0	
No active agent	12[a]	8	4	33.3

205 Patients with KPC bacteremia

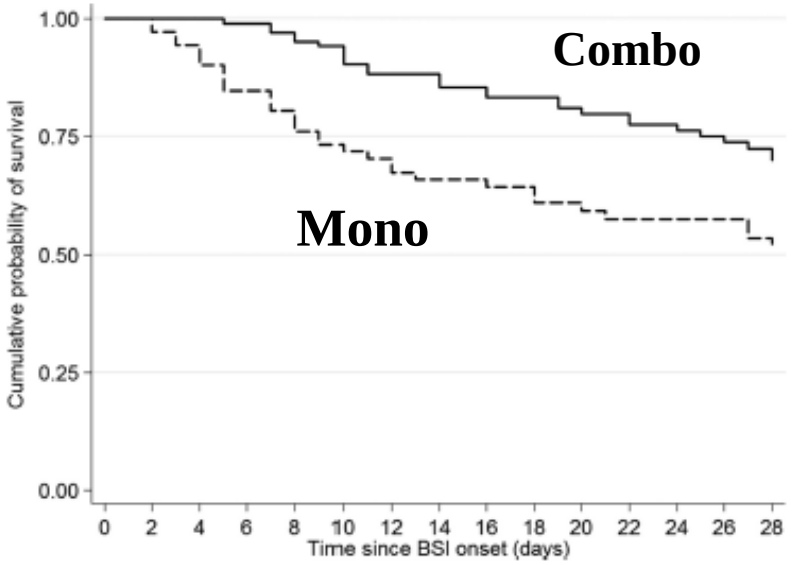


FIG 1 Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). $P = 0.003$ (log rank test).

Daikos GL et al. Antimicrob Agents Chemother 2014;58: 2322

How to Manage CRE
(Historical Perspective)

- **Role of colistin, meropenem, tigecycline**
  - **» Colistin 9MU load, 4.5MU q12-8**

PLUS

- **» Meropenem 2g q8 Prolonged Inf (3hr)**

Importance of phenotypic profile, MIC≤16mg/L

[Tumbarello M, et al. CID 2012;55(7):943–50]

PLUS

- **» Tigecycline 200mg load, 100mg q12**

Colistin versus Polymyxin B:

- The polymyxins were terrible drugs (Efficacy/Toxicity) and they still are.. Nothing has changed in 6 decades
- Relatively poor potency, variable PK, ↓ lung penetration, optimal dosing in critical care population (i.e., CRRT)?
- Dosing regimens do not appear to produce high probability of achieving optimal exposures; Can't increase dose due to toxicity → LOW PD exposures
- Polymyxin B appears to be the safer of the compounds
- Colistin will continued to utilized for aerosol & renal [C]
- With the introduction of new medicines with more reliable pharmacokinetic, pharmacodynamic and safety profiles what is the future role of the polymyxins?