Colistin or Polymyxin B for Human Medicine?

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Overview

- Structure and characteristics
- Efficacy
- Nephrotoxicity
- Dosing
- Conclusion: is one polymyxin preferred?
- Future directions and needs

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Review

Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing

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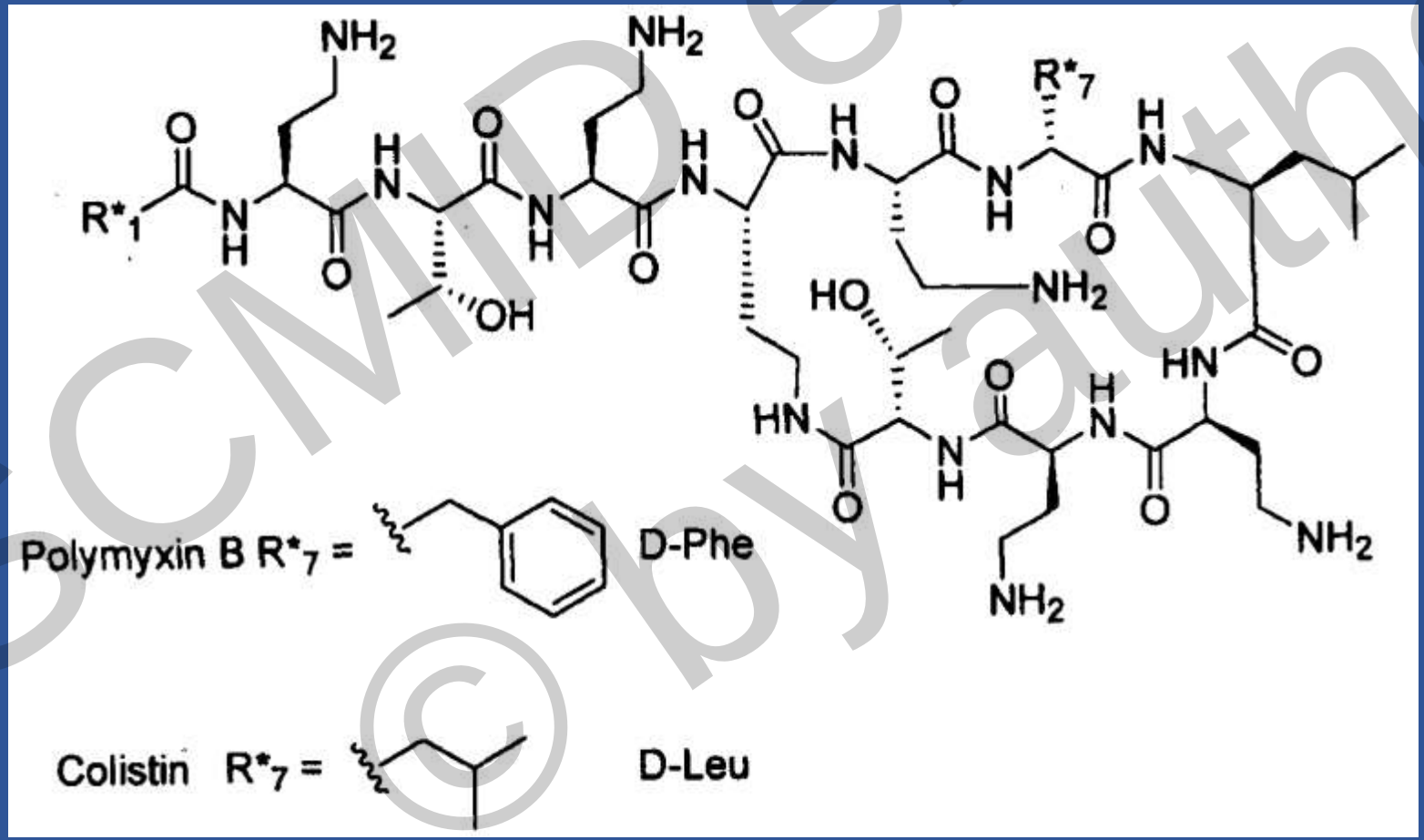
Structure

- Nearly identical
  - Structure – only one amino acid difference in peptide ring
  - In vitro efficacy/potency



Formulation and Pharmacokinetics: Colistin

- Colistin is administered as a prodrug, colistimethate sodium (CMS)
  - Must be hydrolyzed in vivo to colistin
    - Leads to delays in attainment of optimal (ie therapeutic) colistin serum levels
    - Delays estimated to be as long as 7 hours
  - Prodrug CMS rapidly eliminated renally
    - Challenging to safely achieve consistent, predictable therapeutic levels ~ 2.0 mg/L in patients
      - Concerns regarding efficacy vs pathogens with MIC≥2.0
      - Particularly challenging to achieve and maintain therapeutic levels in patients with normal renal function
    - Renal dosing adjustments necessary

Formulation and Pharmacokinetics: Polymyxin B

- Polymyxin B administered as an active moiety, sulfate salt
- Peak concentrations more rapidly attained
- Levels of 3.0 mg/L or higher reliably attained with package insert doses (upper end)
- Polymyxin B not renally excreted
  - No need for dosing adjustments based on renal function

Structure and Characteristics: Summary

- Polymyxin B and colistin are likely very similar with regards to activity and exposure-response relationships
- Major differences in commercially available formulations
  - Impacts differences in pharmacokinetics between these agents, which clearly favor polymyxin B
- Due the differences in available formulations lead to differences in efficacy and/or toxicity?

Comparative Efficacy

- Polymyxin studies notoriously difficult to conduct
  - Delays in time to effective therapy, complex patients, variety of dosing regimens/antimicrobial combinations
  - Often don't adequately assess many important variables including type of infection/colonization, pathogen, MIC, severity of infection, polymyxin dose
- Comparative studies of polymyxin B and colistin are few and methodologically limited
  - Oliveria et al* 41 CMS vs 41 poly B patients – no differences in success, mortality
  - Phe et al: 121 CMS and 104 poly B patients – overall increased mortality in poly B; in matched subgroup/exclusion of CF patients, no difference
  - Tuon et al: 36 CMS vs 96 poly B no difference in mortality
  - Rigatto et al: 81 CMS and 410 poly B patients – higher bivariate mortality in poly B group; no difference in multivariate analyses

*Only study where mortality was primary endpoint

Comparative Efficacy: Summary

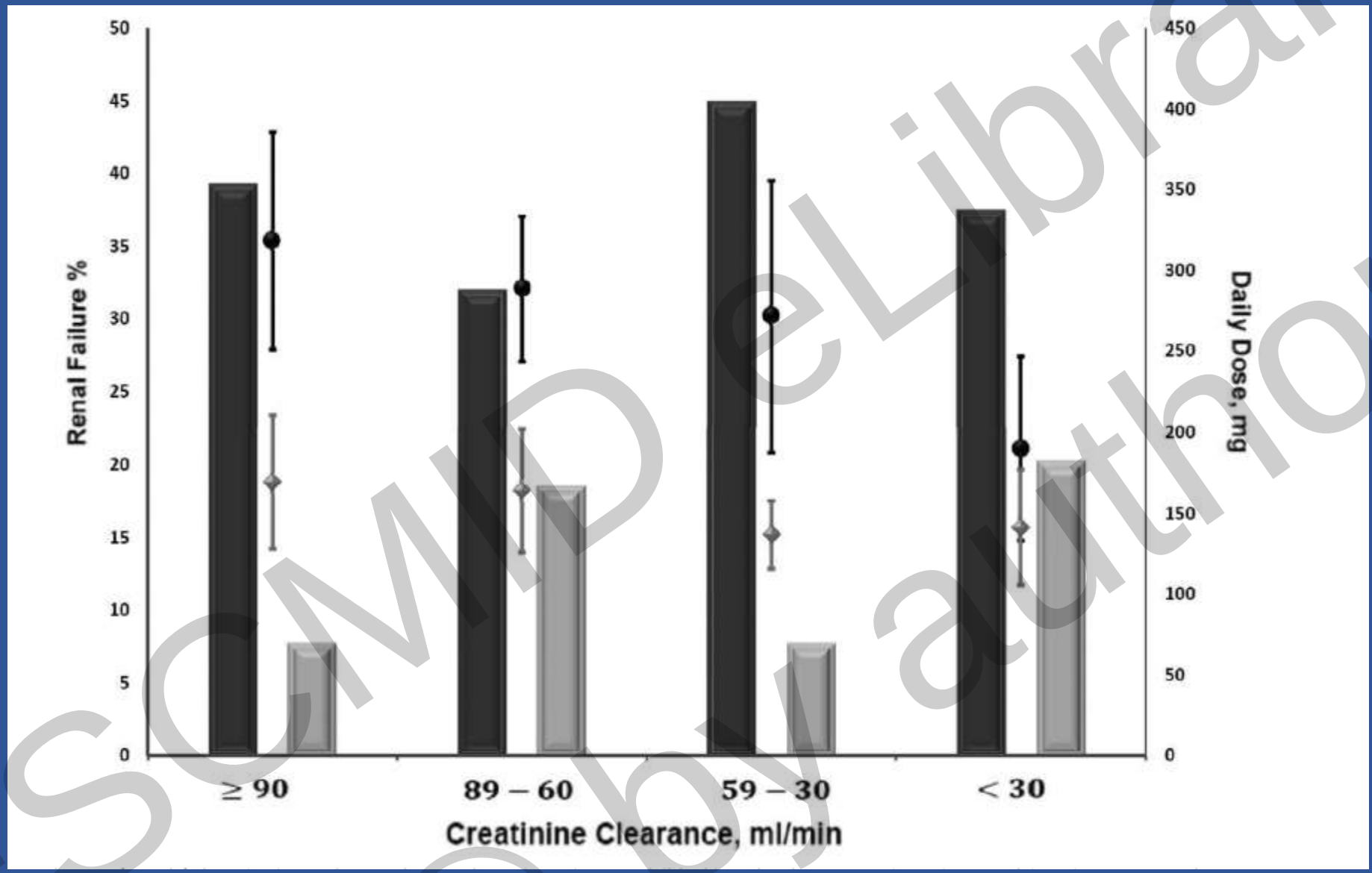
- Studies are methodologically limited and subjects complex
- No randomized controlled trials
- No clear advantage of one agent over the other

Nephrotoxicity (NTX)

Author	NTX Criteria	Size	Findings: NTX
Oliveria et al, 2009, Diag Micro Infect Dis*	2-fold increase in Cr or 1 mg/dl increase	41 CMS vs 41 poly B	26% vs 27% (p=0.92)
Akajagbor, 2013, Clin Infect Dis*	RIFLE	106 CMS vs 67 poly B	60% vs 42% (p=0.02); In MVA CMS HR=2.27, p<0.05
Tuon, 2014, Int J Antimicrob Agents*	AKIN	36 CMS vs 96 poly B	39% vs 21% (p=0.06) In MVA CMS HR 1.74, p>0.05
Phe, 2014, AAC	RIFLE (pts with baseline Cr >1.5 excluded)	121 CMS vs 104 poly B	34% vs 23% (p=0.08) Matched subgroup 55% vs 21%, p=0.003
Rigatto, 2016, AAC**	RIFLE	81 CMS vs 410 poly B	38% vs 13%, p<0.001 In MVA CMS HR 3.35, p<0.001
Crass, 2017, AAC	RIFLE	340 CMS vs 74 poly B Included CF and non-CF	50% vs 43% non-CF, (p=0.46) 30% vs 35% in CF (p=0.77)

*Polymyxin B renally dose-adjusted – major limitation

**Prospective cohort, optimized dosing regimens



CMS treated– black; polymyxin B treated – gray

Vertical lines represent daily dose

Rigatto, AAC, 2016

Comparative Nephrotoxicity: Summary

- Available literature limited
- Potential safety advantage for polymyxin B
  - Polymyxin B with more distinct peaks and troughs – potentially less renal uptake
  - CMS delivers high colistin load to kidneys with limited exposure systemically
- RCT needed to definitively determine if polymyxin B is less nephrotoxic

Colistin Dosing – Maintenance Dose

- 1 million international units (MIUs) of CMS = 30 (33.3) mg of colistin base activity (CBA)

- Three different approaches to dosing
  - US package insert (weight-based)
  - Europeans Medicines Agency (EMA)
  - Pharmacokinetic equation per Nation, Garonzik and colleagues
    - Recently published manuscript – analysis of complete cohort from Garonzik 2011 study

Dose (in mg CBA/day for a 70 kg patient)	US Package Insert	EMA package insert	Nation et al*
Clcr ≥ 80 mL/min	350	270	340-360
Clcr 50-79 mL/min	266	270	245-300
Clcr 30-49 mL/min	175	165 – 225	195-220
Clcr 10-29 mL/min	70	135 – 165	160-175
Clcr <10 mL/min	70	105	130-145

Daily dose of CBA (mg) = Css,avg target (mg/L) × 10(0.0048 × CrCl + 1.825)

*Nation et al, CID, 2017, p 565-571

Table 3. Average Steady-State Plasma Colistin Concentration ($C_{ss,avg}$) With European Medicines Agency– and US Food and Drug Administration–Approved Daily Dose Suggestions for Each Renal Function Group

		Median (Range) Plasma Colistin $C_{ss,avg}$ (mg/L)			
				US Food and Drug Administration–Approved Dose	
Group[a]	Creatinine Clearance (mL/min)	Physician-Selected Dose	European Medicines Agency–Approved Dose	Patient Body Weight Approach[b]	Uniform Weight of 80 kg Approach[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 to <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 to <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 to <30 mL/min and <10 mL/min, respectively. See Table 2 for details of the number of patients in each creatinine clearance cluster.

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

Nation et al, CID, 2016, 552-558

Polymyxin B: Maintenance Dose

- Package insert dosing reasonable
  - Recommended label dose – 1.5-2.5 mg/kg/d divided into twice daily dosing
- Upper end of dosing recs will reliably achieve levels ~ 3.0 mg/l or higher
  - 1.25 mg/kg IV q 12 hours
- Package insert recommends decreasing dose as renal function declines
  - Unnecessary and potentially harmful – no renal adjustment needed

Polymyxin B Exposures and Renal Function

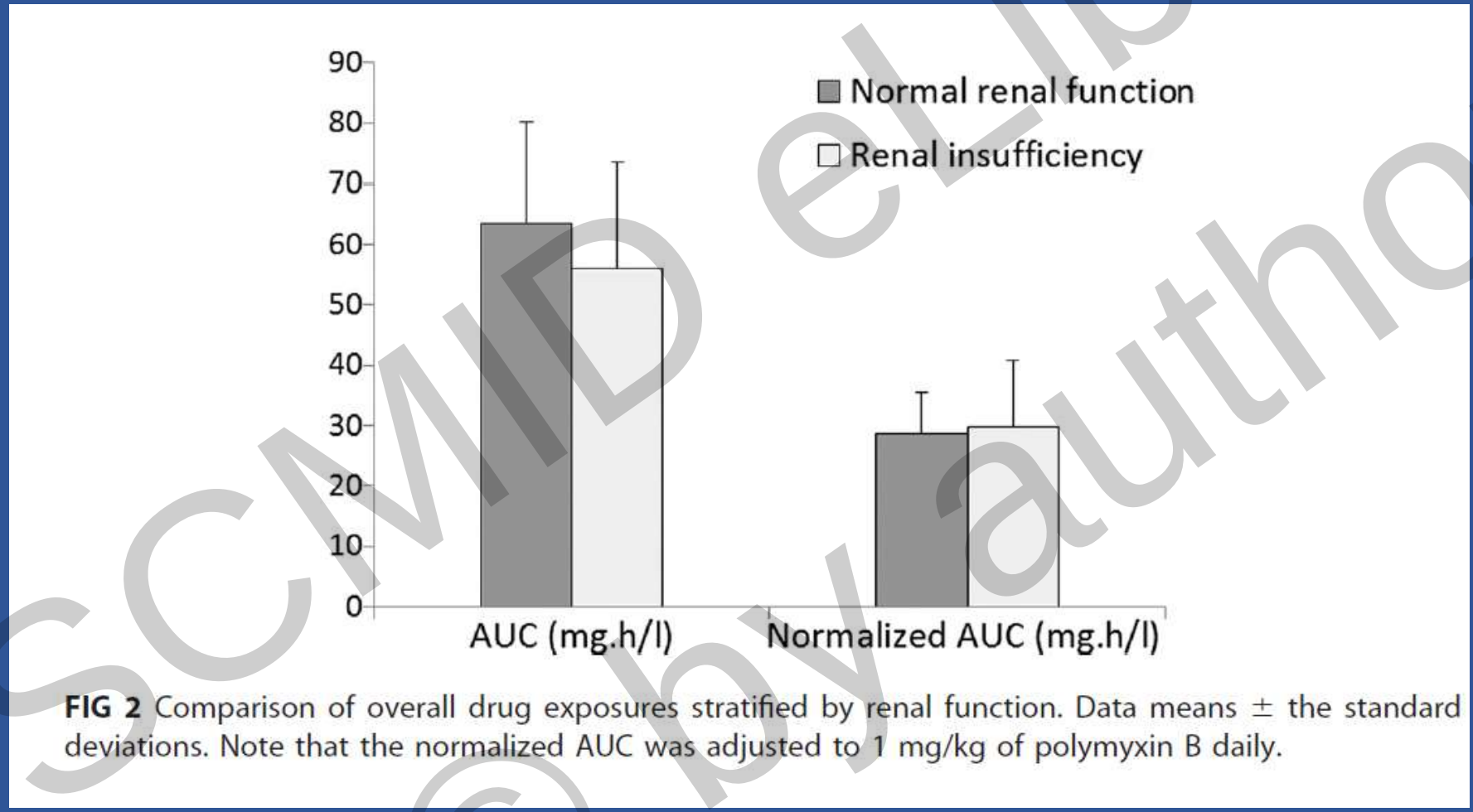


FIG 2 Comparison of overall drug exposures stratified by renal function. Data means ± the standard deviations. Note that the normalized AUC was adjusted to 1 mg/kg of polymyxin B daily.

Thamlikitkul et al, AAC January 2016 Volume 61

Lower Polymyxin B Dosing Associated With Mortality

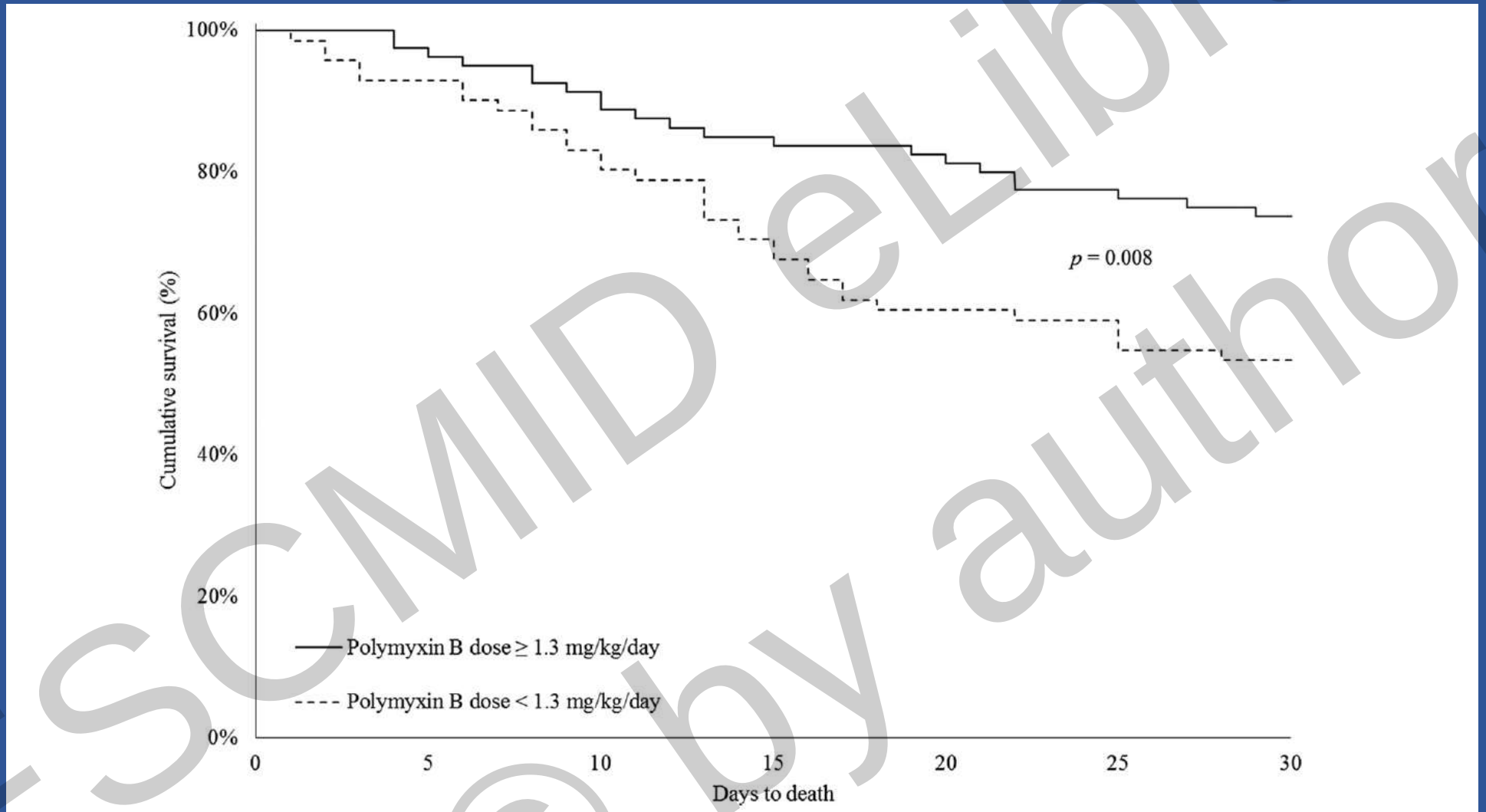


FIG 1 Kaplan-Meier 30-day survival curve comparing patients who received <1.3 mg/kg of polymyxin B to those who received ≥1.3 mg/kg.

Nelson et al, AAC, 2015, 7000-7006

Loading Dose for CMS

- Delays in attaining “optimal” colistin levels due to need for prodrug hydrolysis
- Loading dose reduces this delay
- Recommended loading dose of CBA (mg) = Css,avg target (mg/L) × 2.0 × ideal body weight (kg)
  - Maximum dose = 300 mg

Nation et al, CID, 2016, 552-558

CMS and Loading Dose

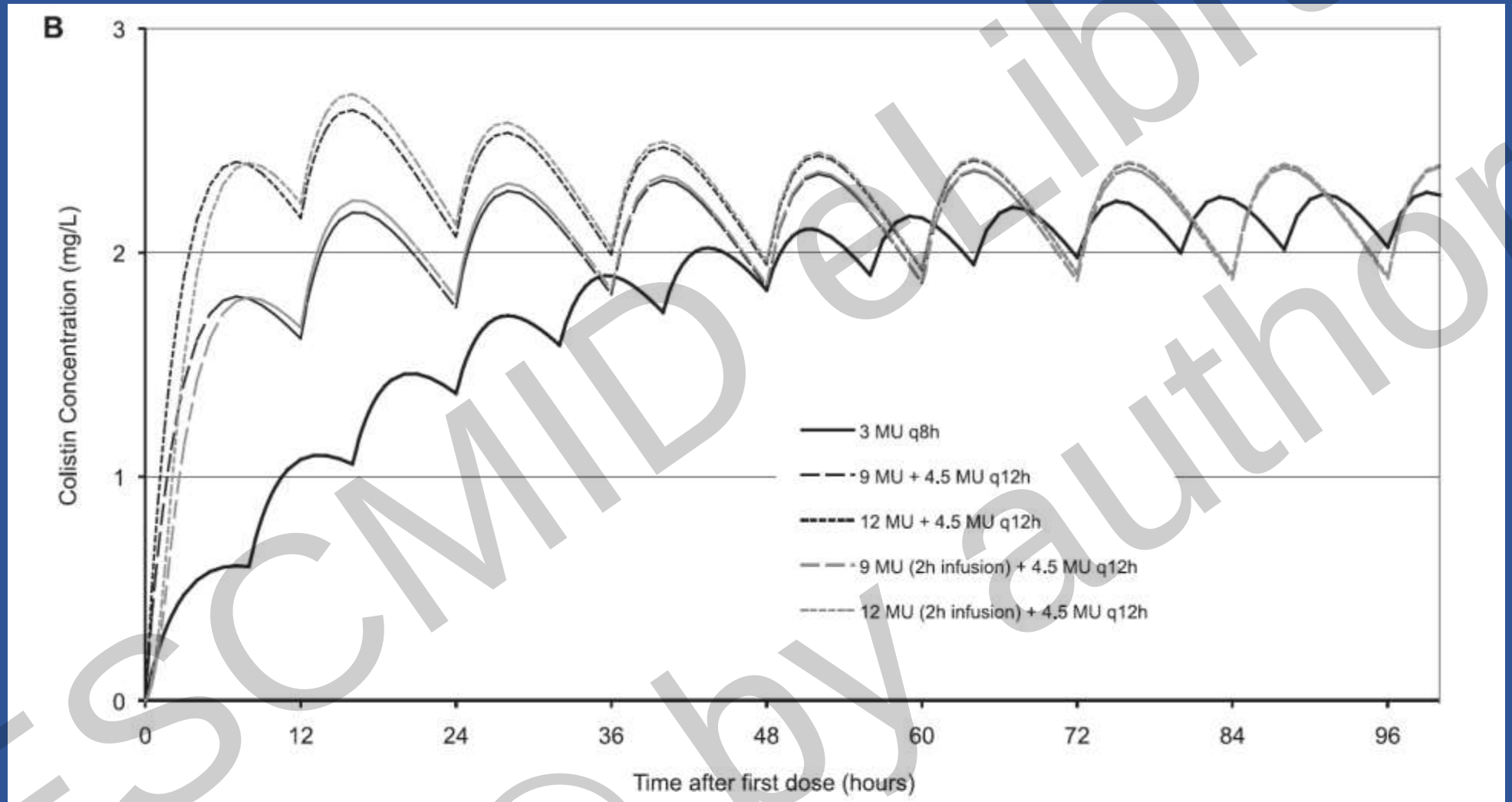


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min or 2 h and a maintenance dose of 4.5 MU CMS every 12 h (q12h).

Plachorous et al, AAC, Aug. 2009, p. 3430–3436

Polymyxin B Loading Dose

Table 3. Polymyxin B Exposure for 6 Different Dosage Regimens on the First and Fourth Day of Treatment Based on Monte Carlo Simulations[a]

	C_{max} (mg/L)[b]			C_{min} (mg/L)[b]			$AUC_{0-24\ hours}$ (mg·h/L)		
Day	P_{10}	P_{50}	P_{90}	P_{10}	P_{50}	P_{90}	P_{10}	P_{50}	P_{90}
1.25 mg/kg q12h as 1-h infusion									
Day 1	2.59	5.17	9.38	0.79	0.903	1.48	25.0	46.4	81.1
Day 4	4.34	7.09	11.3	1.06	1.87	3.08	44.3	72.0	114
2 mg/kg loading as 2-h infusion, followed by 1.25 mg/kg q12h as 1-h infusion[c]									
Day 1	3.06	5.71	10.5	0.86	1.48	2.43	34.0	61.7	108
Day 4	4.35	7.06	11.3	1.07	1.90	3.11	44.7	72.7	115
1.5 mg/kg q12h as 1-h infusion									
Day 1	3.11	6.21	11.25	0.620	1.08	1.77	29.9	55.7	97.3
Day 4	5.20	8.51	13.56	1.27	2.25	3.69	53.1	86.4	137.3
2.5 mg/kg loading as 2-h infusion followed by 1.5 mg/kg q12h as 1-h infusion[c]									
Day 1	3.95	7.39	13.5	1.11	1.92	3.15	43.4	78.9	137.9
Day 4	5.40	8.76	14.0	1.33	2.36	3.87	55.5	90.4	142.7
2.5 mg/kg/d as continuous infusion									
Day 1	. . .	. . .	. . .	. . .	. . .	. . .	20.4	36.9	63.4
Day 4	. . .	. . .	. . .	. . .	. . .	. . .	47.0	72.3	110
2 mg/kg loading as 2-h infusion, then 2.5 mg/kg/d as continuous infusion[d]									
Day 1	. . .	. . .	. . .	. . .	. . .	. . .	42.4	75.8	128
Day 4	. . .	. . .	. . .	. . .	. . .	. . .	48.0	73.9	111

Abbreviations: $AUC_{0-24\ hours}$, area under the plasma concentration-time curve over 24 hours; C_{max}, maximum polymyxin B concentration; C_{min}, minimum polymyxin B concentration; P_{10}, 10th percentile; P_{50}, 50th percentile; P_{90}, 90th percentile; q12h, every 12 hours.

Recommended loading dose: 2.5 mg/kg, maximum = 300 mg

Sandri et al, Clin Infect Dis, 2013, 524-31

CMS vs Polymyxin B: Other Considerations

- Availability and clinical experience
  - CMS more available throughout the world (no poly B in Europe)
  - In many countries only one agent is available
  - Overall much more clinical experience, familiarity with CMS

- Neurotoxicity
  - Can occur with either agent
  - Comparative rates unknown

- Hyperpigmentation
  - Appears to be unique to polymyxin B; pathophysiology poorly understood

- Penetration into the urine, clearance of bacteruria
  - CMS excreted in high concentrations in the urine where it is converted to colistin
  - Polymyxin B inferior to other agents (ie aminoglycosides) – poor urinary penetration

CMS vs Polymyxin B: Head to Head Comparison

More + signs indicate more favorable characteristics

	CMS	Polymyxin B
PK*	+	+++
Clinical efficacy	+	+
Nephrotoxicity	+	++
Clinical experience, understanding of drug	+++	+

*Major differentiating characteristic

Knowledge Gaps/Research Needs

- Clinical experience with polymyxin B
  - NIH R01AI119446 - ongoing
- RCT comparing CMS and polymyxin B
  - Efficacy, nephrotoxicity
- Combination vs monotherapy
  - Particularly for non-fermenters
  - Which agents to use in combination
  - Ongoing studies
    - EU AIDA study – patient enrollment completed
    - NIH 10-065 – enrollment ongoing

Knowledge Gaps/Research Needs (Continued)

- Therapeutic drug monitoring (TDM) algorithms
- Role of inhaled polymyxins
- Novel approaches to minimizing nephrotoxicity

Future of the Polymyxins

- With newer agents becoming available active against extremely-drug resistant Gram-negative bacilli (XDR-GNB), there will be more (? better) therapeutic options that are less toxic

- Potential for using polymyxins in lower doses
  - Take advantage of in vitro activity as well as synergy with other agents
  - Lower doses will cause less toxicity

- Use of inhaled polymyxins in combination with other systemic agents

- Newer generation polymyxins with greater potency, less toxicity

Acknowledgements and Thanks

- Jason Pogue
- Jian Li
- Roger Nation

Questions?

CMS Dosing: Alternative US (Weight-based) Algorithm

CrCl>50: 5mg/kg/d

CrCl 30-49: 3.5 mg/kg/d

CrCl 10-29: 2.5 mg/kg/d

CrCl<10 or HD: 1.5 mg/kg/d

This algorithm leads to doses similar to those obtained using Nation, EMA dosing algorithms