Polymyxin B and Colistin Debate: One of the Same Kind or Mutt and Jeff?

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- WDK
  - Nothing to disclose

Learning Objectives

- Compare and contrast dosing strategies, pharmacokinetics, and administration between colistin and polymyxin B
- Compare and contrast nephrotoxicity associated with colistin and polymyxin B
- Discuss the role of colistin and polymyxin B in the management of multi-drug resistant Gram-negative infections

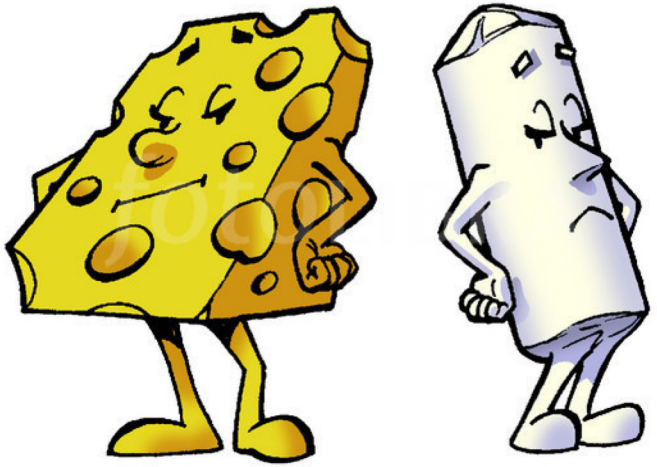
Debate Format

- What we can agree on
  - Pharmacology
  - Spectrum of activity
  - Mechanisms of resistance
- What we don't agree on
  - Dosing issues
  - Nephrotoxicity
  - Place in therapy

Colistin and Polymyxin B: Peas in a Pod, or Chalk and Cheese?

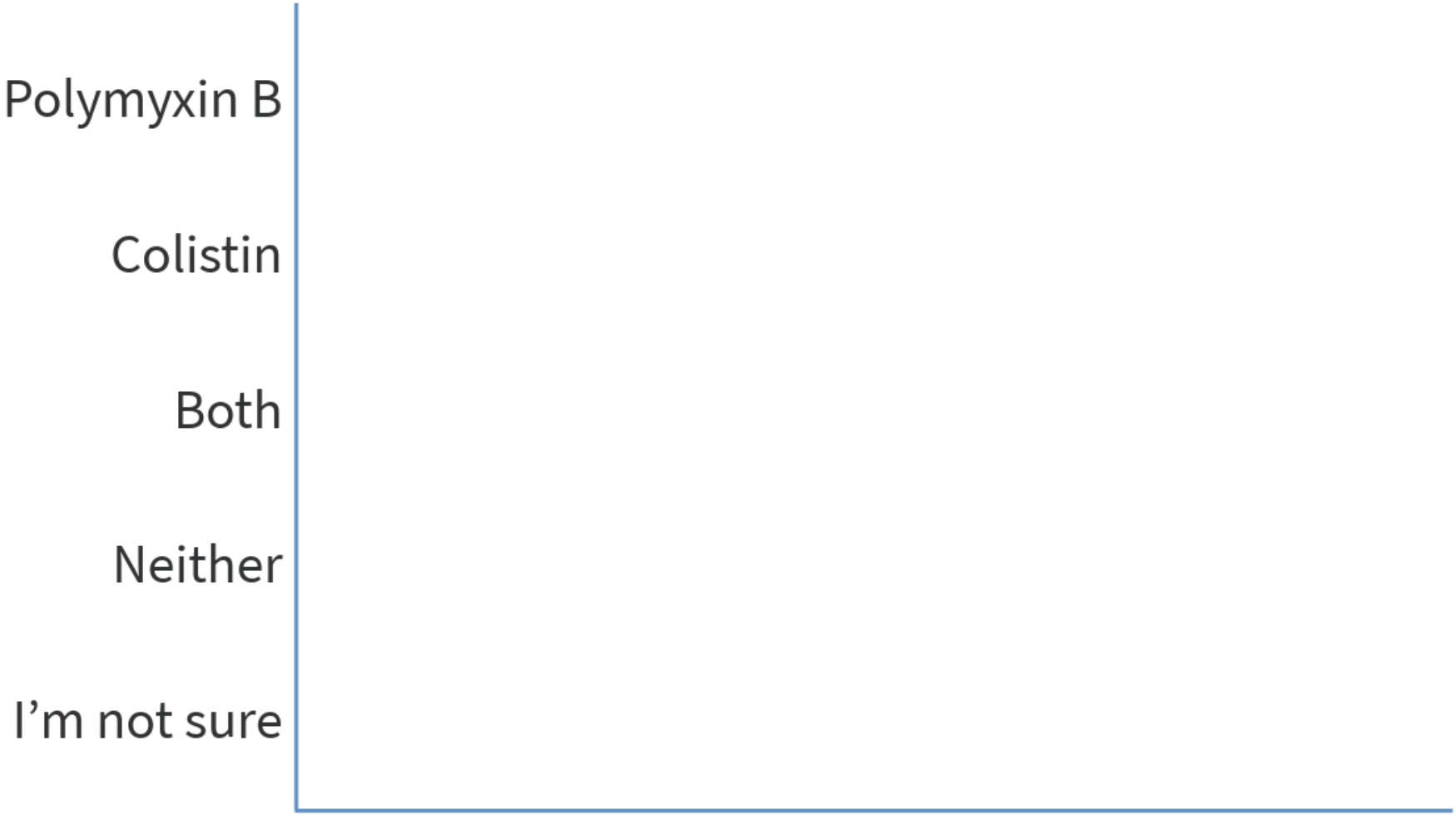
Roger L. Nation, Tony Velkov, and Jian Li

Drug Delivery, Disposition, and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia

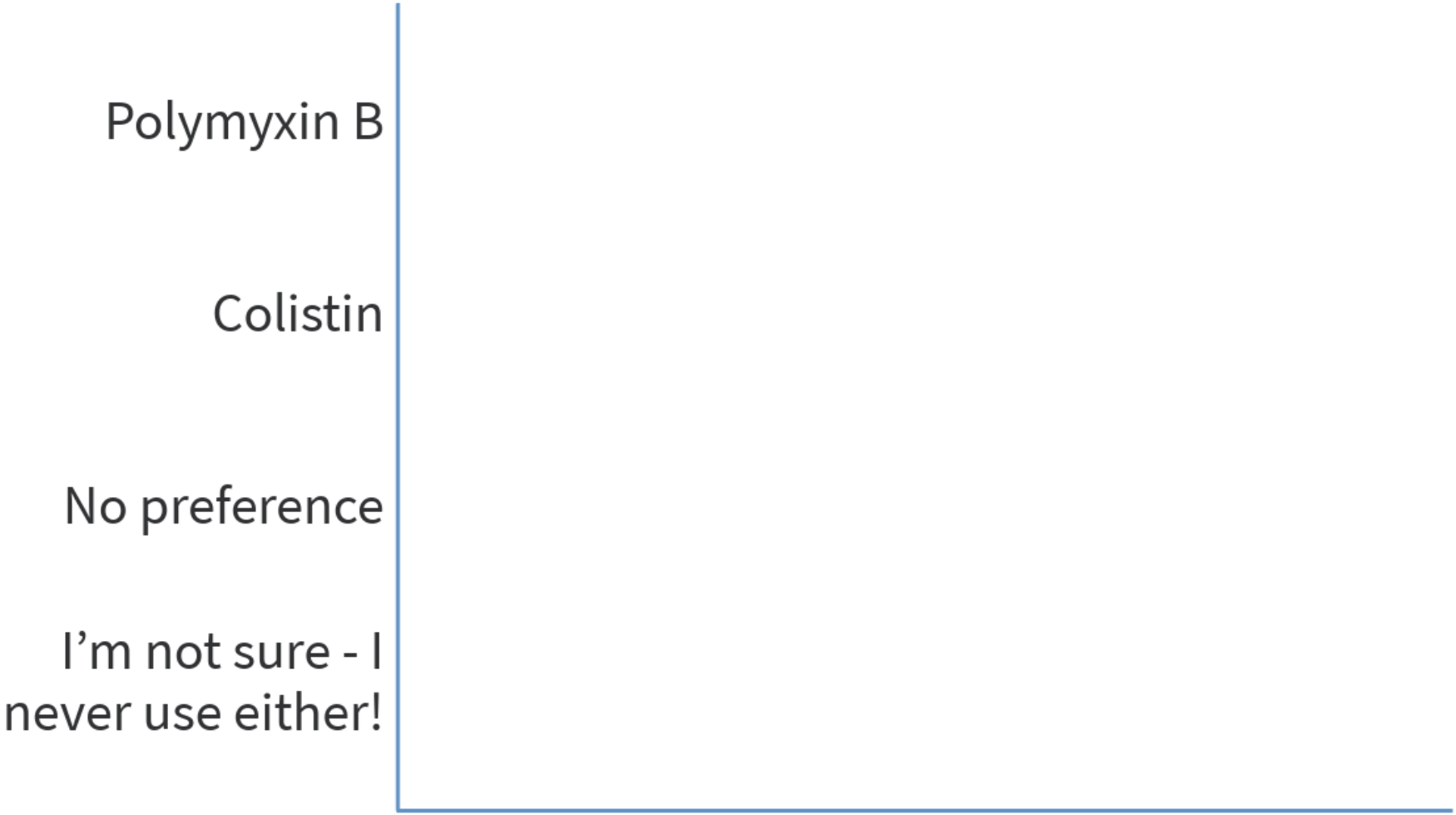


Nation RL, et al. *Clin Inf Dis*. 2014;59(1):88–94.
https://www.shopdisney.com/3-peas-in-a-pod-plush-toy-story-3-medium-19-1358380. Accessed 3/13/18.
https://www.123rf.com/photo_20220340_chalk-and-cheese-fighting-concept-opposites-or-dissimilar-types-not-getting-on-from-the-saying-like-.html. Accessed 3/13/18.

Which of the following polymyxin antibiotics do you currently have on formulary or available at your institution?



Which of the following polymyxin antibiotics do you prefer based on your current viewpoint?



Polymyxins: What we can agree on

Evolution of Resistance to Gram-negatives

Highly resistant MCR-1 'superbug' found in US for first time

Filed Under: **Antimicrobial Stewardship; MCR-1**

Jim Wappes | Editorial Director | CIDRAP News | May 26, 2016 Share Tweet LinkedIn Email Print & PDF

- *E. coli*
  - TEM
  - SHV

- *E. coli*, *Klebsiella* spp., *P. aeruginosa*
  - *bla*TEM
  - *bla*SHV
  - AmpC

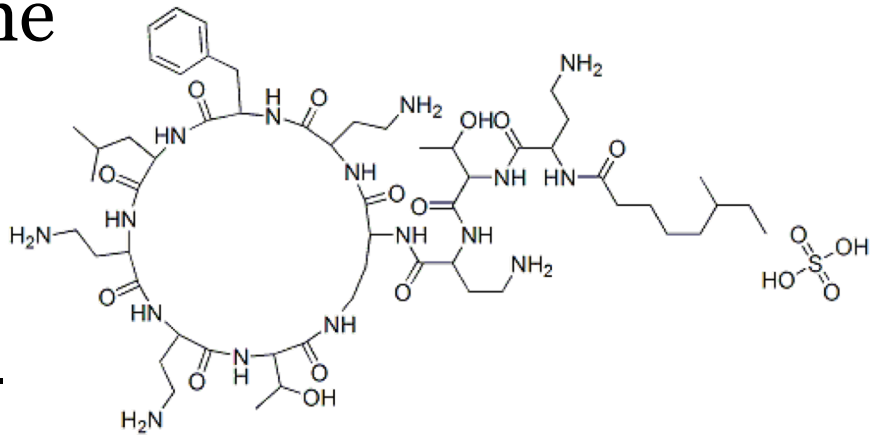
- *E. coli*, *Klebsiella* spp., *P. aeruginosa*, *Enterobacter* spp.
  - CTX-M
  - KPC
  - Metallo-β-Lactamase

- *E. coli*, *Klebsiella* spp., *P. aeruginosa*, *Enterobacter* spp.
  - *mcr-1*

Hawkey PM. *J Antimicrob Chemother*. 2008 62, Suppl. 1, i1–i9

History of the Polymyxins

- Entered into clinical use in the 1950s
  - Limited clinical data



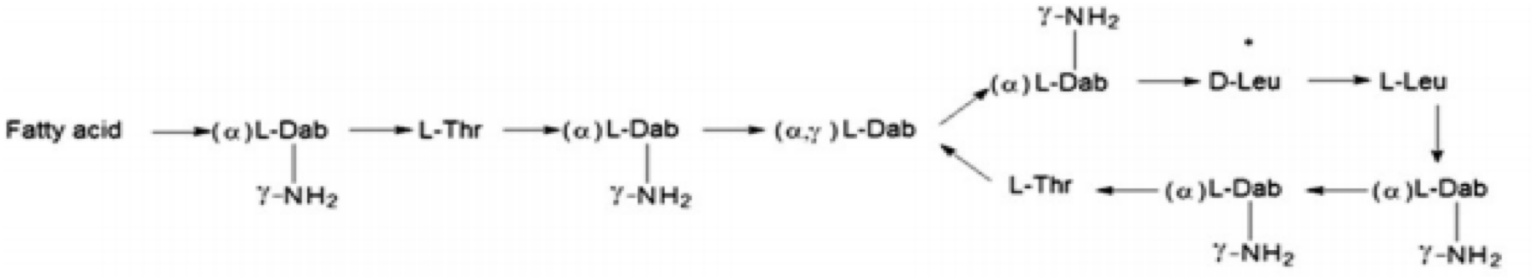
- Due to increasing multidrug-resistant gram-negatives, have seen a resurgence over the years

- Often regarded as equivalent and used interchangeably

Nation RL, et al. *Clin Inf Dis*. 2014;59(1):88–94.

What are the polymyxins?

- Many polymyxins exist yet 2 are used clinically
- Polymyxin B
- Colistin
  - Polymyxin E
  - Colistin methanesulfonate (prodrug)

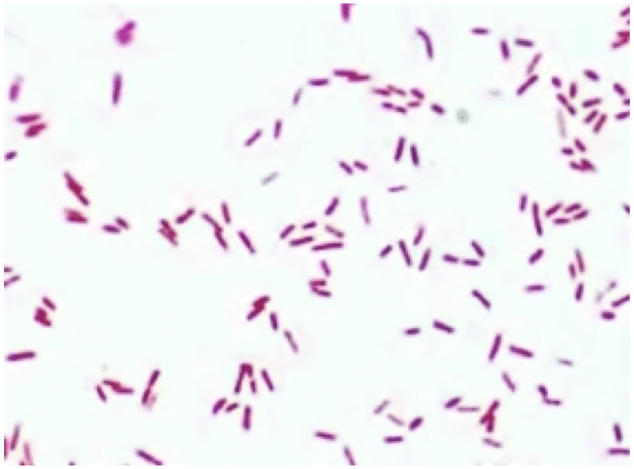


Nation RL et al. *Clin Inf Dis*. 2014;59(1):88–94.

Spectrum of Activity

- Myth! Polymyxins cover every Gram-negative organism

- Gram-negative bacilli (generally)
  - *Acinetobacter baumannii*
  - *Pseudomonas aeruginosa*
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
  - *Klebsiella aerogenes*
- Intrinsic resistance
  - *Providencia spp.*
  - *Proteus spp.*
  - *Serratia spp.*
  - *Morganella spp.*
  - *Burkholderia spp.*



1. Lim LM, Ly N, Anderson D, et al. Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. Pharmacotherapy. 2010;30(12):1279-91.
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050108s026lbl.pdf. Accessed 3/13/18

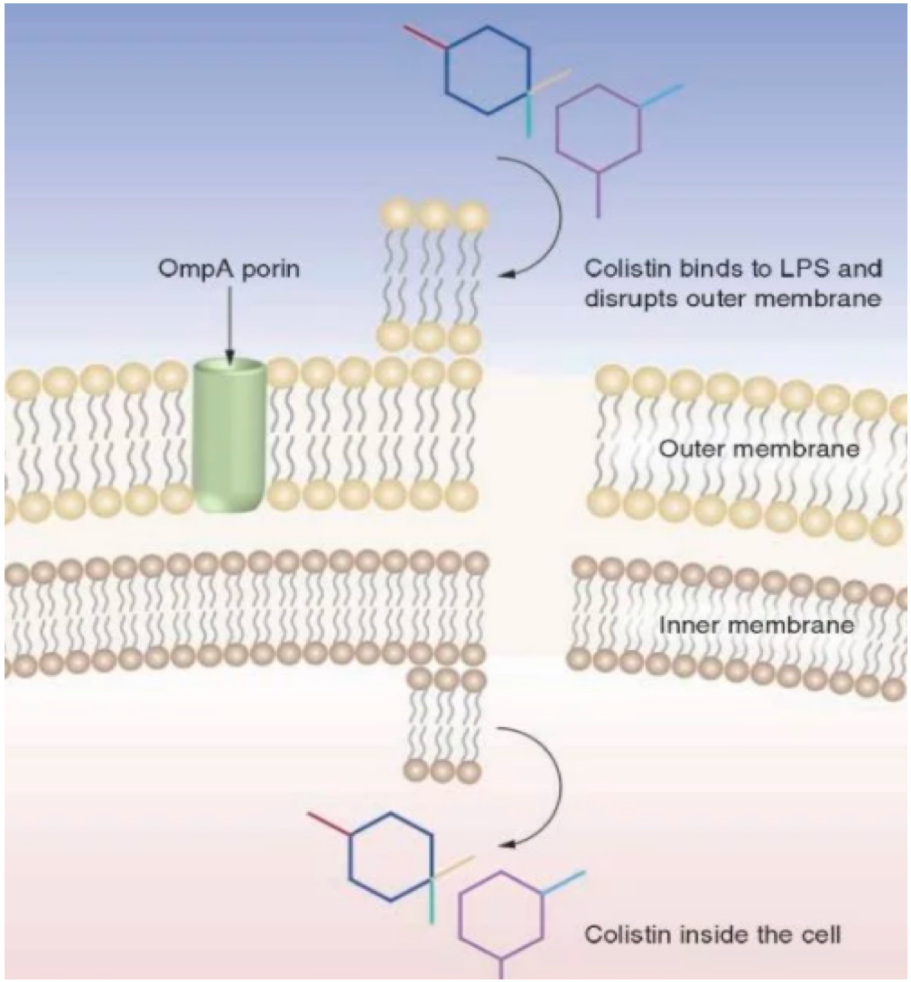
Pharmacology/MOA

- Rapidly bactericidal and positively charged
- Binds to LPS of outer cell membrane

- Competitively displaces Mg^{++} and Ca^{++} from PO4

- Leakage of intracellular content

- Cell death



Cai Y, et al. Expert Rev Anti Infect Ther. 2015;13(12):1481-97.
Lim LM, et al. Pharmacotherapy. 2010;30(12):1279-91.
Biswas et al. Expert Rev Anti Infect Ther. 2012 Aug;10(8):917-34.

Susceptibility Testing

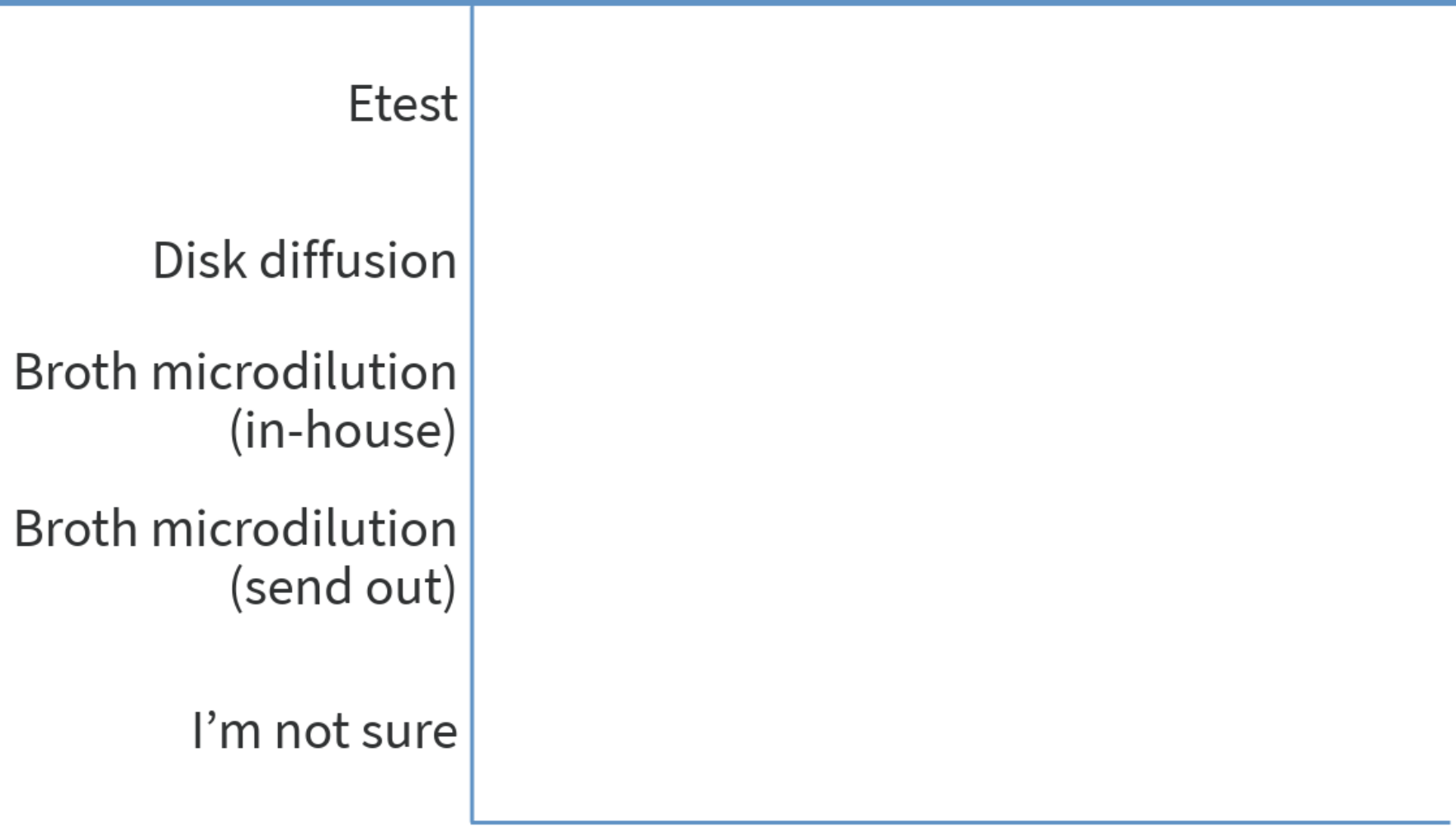
- Polymyxins are large molecules
  - Etest and disk diffusion methods may be unreliable

- Broth microdilution (BMD) is gold standard for susceptibility testing (EUCAST and CLSI)

Bacteria per CLSI	S	I	R
Pseudomonas aeruginosa	≤2	4	≥8
Acinetobacter spp.	≤2		≥8

Vasoo. J Clin Microbiol. 2017 Sep;55(9):2573-2582.

Which of the following susceptibility testing methods do you currently use at your institution?

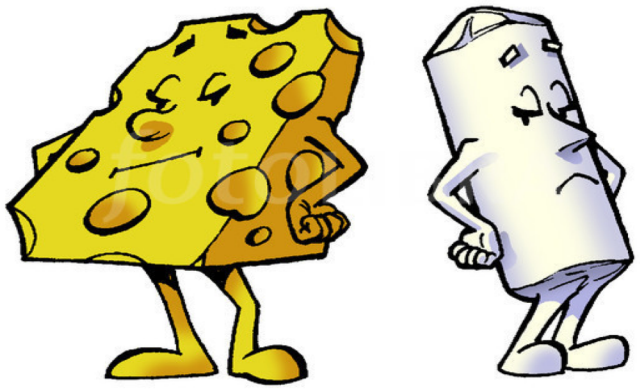


Current issues with use

- *In vitro* susceptibility testing issues
- Adverse Effects
  - Nephrotoxicity
  - Neurotoxicity
    - Dose-dependent (7%-27% occurrence)
    - Paresthesias, ataxia, nystagmus, diplopia, seizures
- Provider unfamiliarity
  - Dosing and place in therapy
  - Institutional formularies

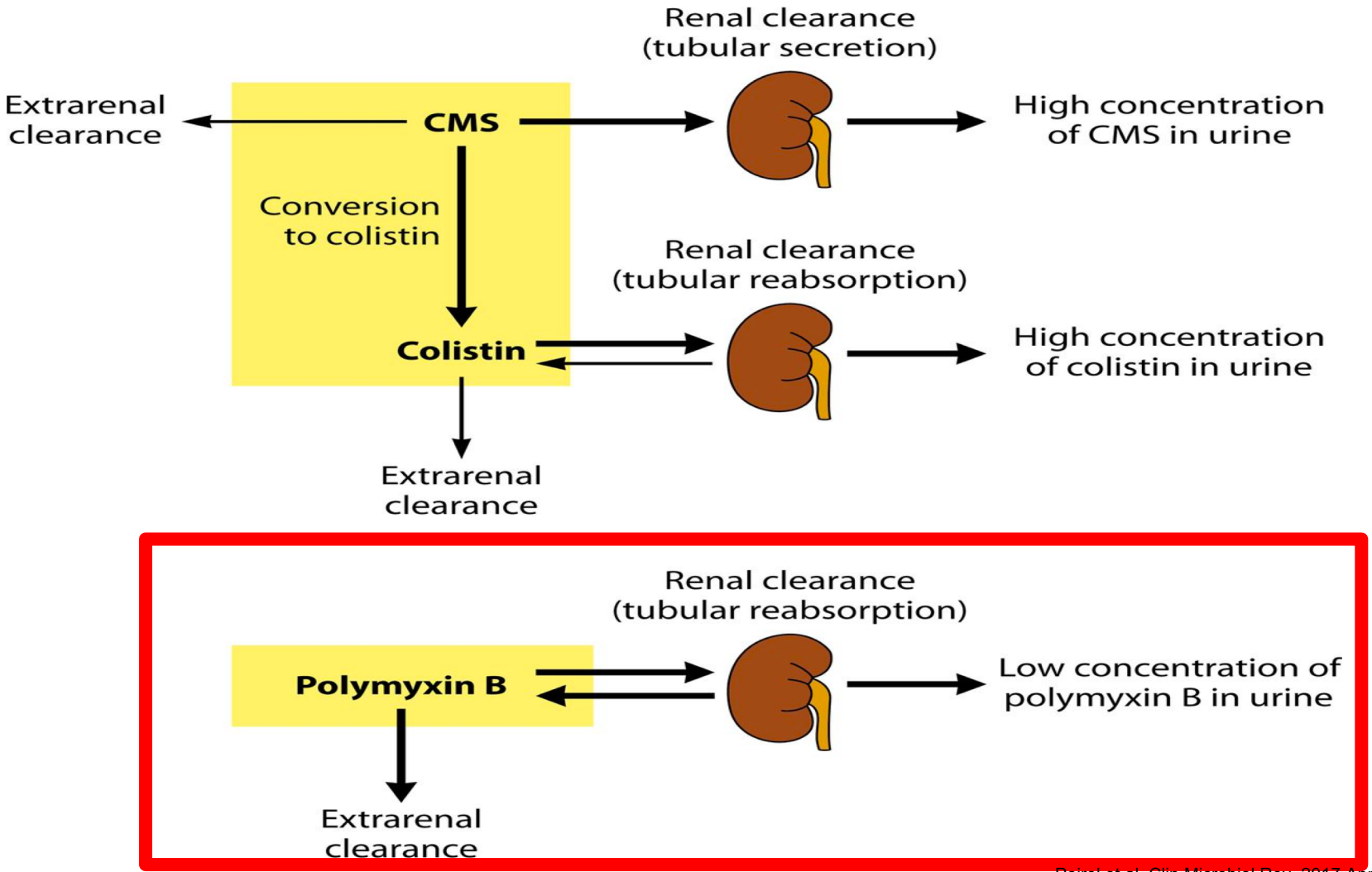
Grill et al. Br J Clin Pharmacol. 2011 Sep;72(3):381-93.

Debate #1:
Dosing and Administration



FOR: Polymyxin B

- Pharmacokinetic challenges with colistin



Poirel et al. Clin Microbiol Rev. 2017 Apr; 30(2): 557–596.

FOR: Polymyxin B

- Administered as ACTIVE drug
- Peak concentrations are higher and achieved faster
  - CMS to colistin conversion via hydrolysis is slow and often incomplete (≥7 hours for max concentrations)
- More reliable systemic concentrations (>3mg/L)
- Eliminated via non-renal mechanisms

Morrill et al. Open Forum Infect Dis. 2015 May 5;2(2):ofv050.

FOR: Polymyxin B

- Less of an “alphabet soup” for dosing units

- Colistin
  - mg colistin methanesulfonate
  - mg colistin base activity
  - International units (IU) CMS

- Polymyxin B
  - mg polymyxin B
  - IU polymyxin B

Colistin	Polymyxin B
1 mg CBA=30,000 IU CMS	1 mg=10,000 IU
1 mg CMS~12,500 IU CMS	
2.67 mg CMS~1 mg CBA	

FOR: Polymyxin B

- Polymyxin B Dosing
  - 1.25-2.5 mg/kg/day divided q12h over 60 min (upper end will likely achieve target Css ≥3 mg/L)

    Recommended loading dose: 2.5 mg/kg

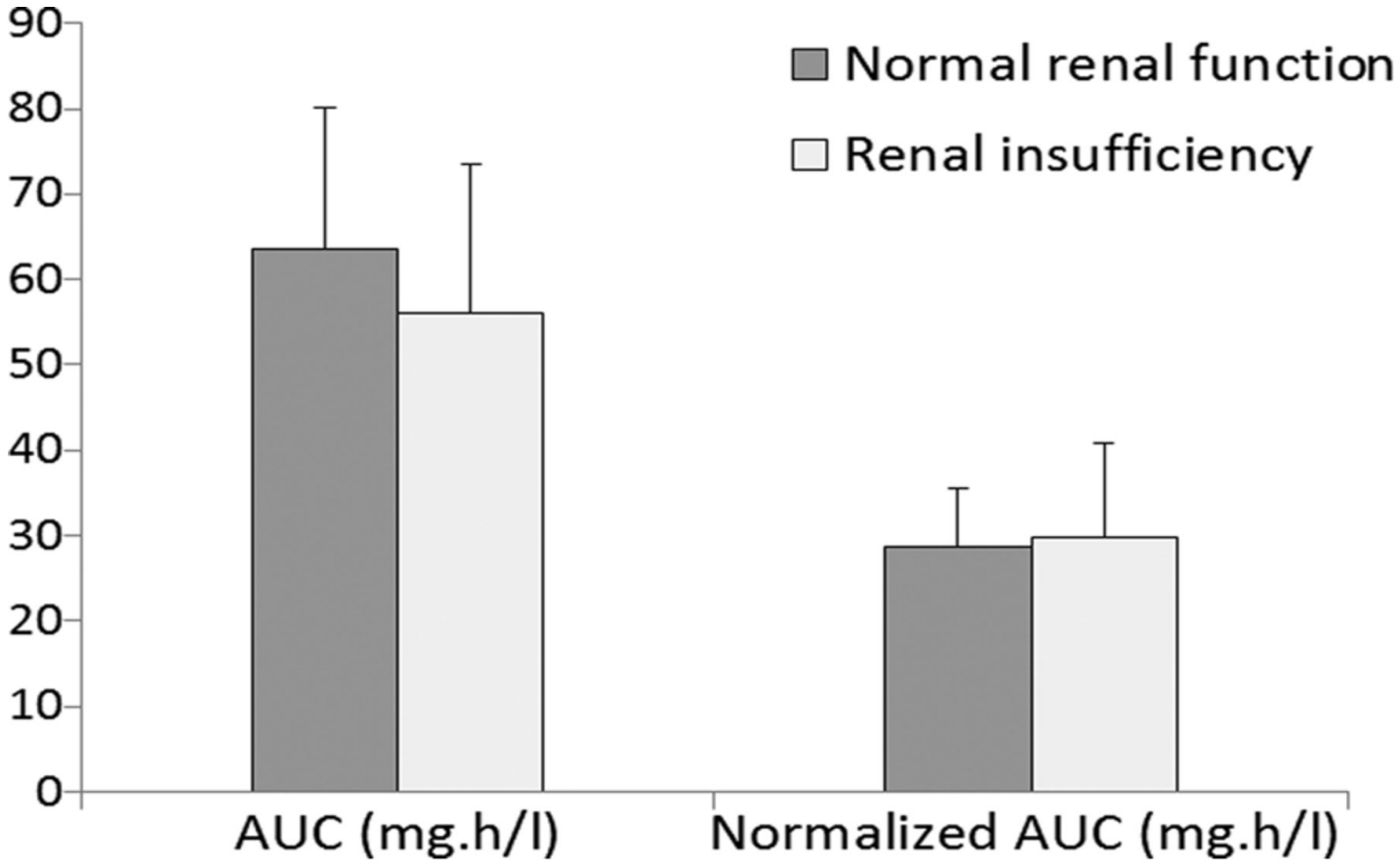
    <1.3 mg/kg/day associated with increased mortality

Study	Objective/Population	Conclusions
Zavascki et al., 2008	Determine PolyB dosing in critically ill; 8 critically ill patients with impaired renal function	Total body clearance is insensitive to impaired renal function; no dose adjustment
Sandri et al., 2013	Determine PolyB dosing in CVVH; 2 patients on CVVH (8 blood samples)	No dose adjustment for patients on CVVH
Sandri et al., 2013	Determine PolyB dosing in critically ill;247 critically ill patients with impaired renal function	No dose adjustments for renal impairment; dose should be based on TBW
Elias et al., 2010	Determine impact of PolyB dosing on in-hospital mortality; 276 patients	Lower risk for in-hospital mortality associated with dose >200 mg/day (aOR 0.43; 95% CI 0.23–0.79); higher incidence of nephrotoxicity

Sandri et al. Clin Infect Dis. 2013 Aug;57(4):524-31.
Elias et al. J Antimicrob Chemother. 2010 Oct;65(10):2231-7.
Sandri et al. J Antimicrob Chemother. 2013 Mar;68(3):674-7.
Zavascki et al. Clin Infect Dis. 2008 Nov 15;47(10):1298-304.

FOR: Polymyxin B

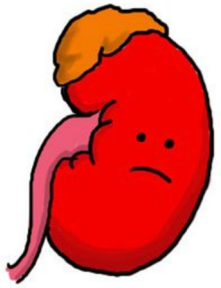
- Comparison of drug exposure by renal function



Thamlikitkul et al. Antimicrob Agents Chemother. 2016 Dec 27;61(1).

FOR: Polymyxin B

- Issues with colistin dosing
  - MIC (i.e. ≥ 1)
  - Css achievement (2-2.5 mg/L)
  - Renal function



- Different colistin dosing recommendations for various clearance clearance ranges
  - Balance between severity of infection and toxicity

Garonzik et al. *Antimicrob Agents Chemother*. 2011 Jul;55(7):3284-94.

FOR: Colistin

- Dosing and Administration
  - Administered as inactive pro-drug that must be converted in the body to colistin
  - Must administer 4-5 x the amount of CMS to achieve plasma concentration needed
  - 1mg colistin base activity (CBA) = 30,000 units CMS = ~2.4mg CMS
  - Recommended dose - 5 mg CBA/kg/day in 2 to 4 divided doses

Pogue et al. Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing. *Clin Microbiol Infect*. 2017; 23:229-233.

FOR: Colistin

Colistin Calculator

Parenteral colistimethate sodium (CMS) pharmacokinetic tool

ClinCalc.com » Infectious Disease » Colistin Calculator

Renal Function

Not on renal replacement

Creatinine _____ mg/dL

Stable | Unstable creatinine

Therapeutic Goal

$C_{ss,avg}$ target (?) 2.5 mg/L

Patient Parameters

Age _____ years

Height _____ in | cm

Weight _____ kg | lbs

Gender Male | Female

Reset | Calculate

http://clincalc.com/colistin/

FOR: Colistin

Dosing and Administration

- 70 year old male
- 5'9", 85kg
- SCr 1.1 mg/dL
- Therapeutic goal = 2mg/L

Loading dose	Maintenance dose
280 mg CBA IV	70 mg CBA IV Q8hr *or* 110 mg CBA IV Q12hr

▸ Initiate maintenance regimen 24 hours following the start of loading dose administration

http://clincalc.com/colistin/

FOR: Colistin

Preferred Therapy

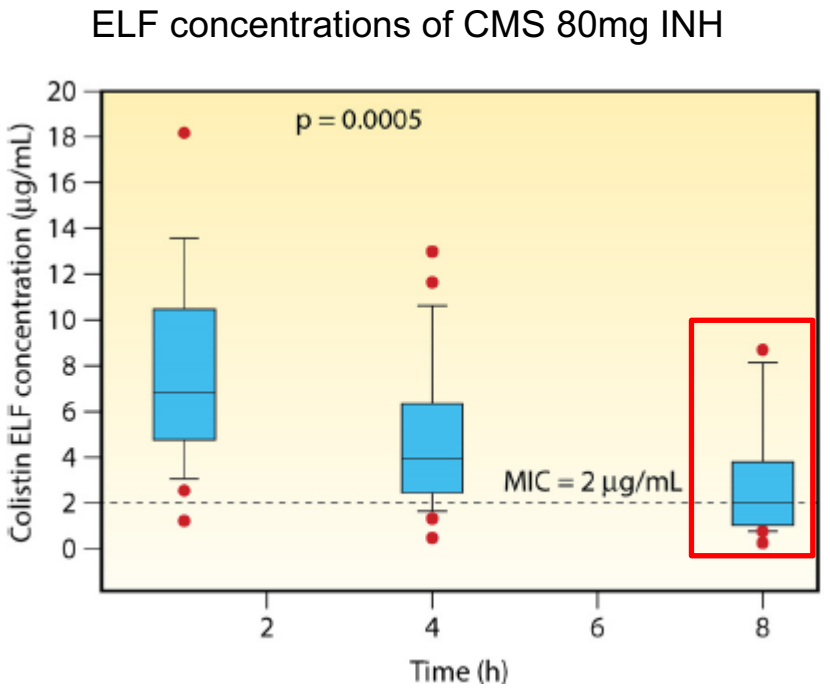
- Urinary tract infections
  - ~65% of CMS is excreted into the urine where it continues to convert to colistin
  - Polymyxin B does not attain high enough concentrations in the urine
- Intrathecal/Intraventricular
  - Preferred by some due to experience and known dosing

Pogue et al. Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing. *Clin Microbiol Infect*. 2017; 23:229-233.

FOR: Colistin

Preferred Therapy

- Inhalation
  - Requires in vivo conversion
  - In a human study, 16/20 patients achieved clinical cure
  - Most patients grew *A. baumannii*
  - No significant changes in renal function



Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. 2016. Inhaled antibiotics for Gram-negative respiratory infections. *Clin Microbiol Rev*. 29:581– 632.

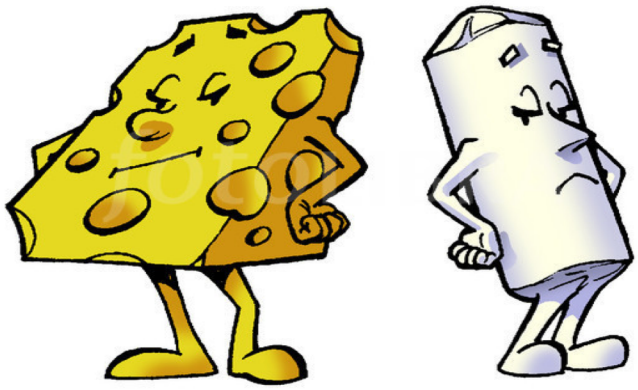
FOR: Colistin

Preferred Therapy

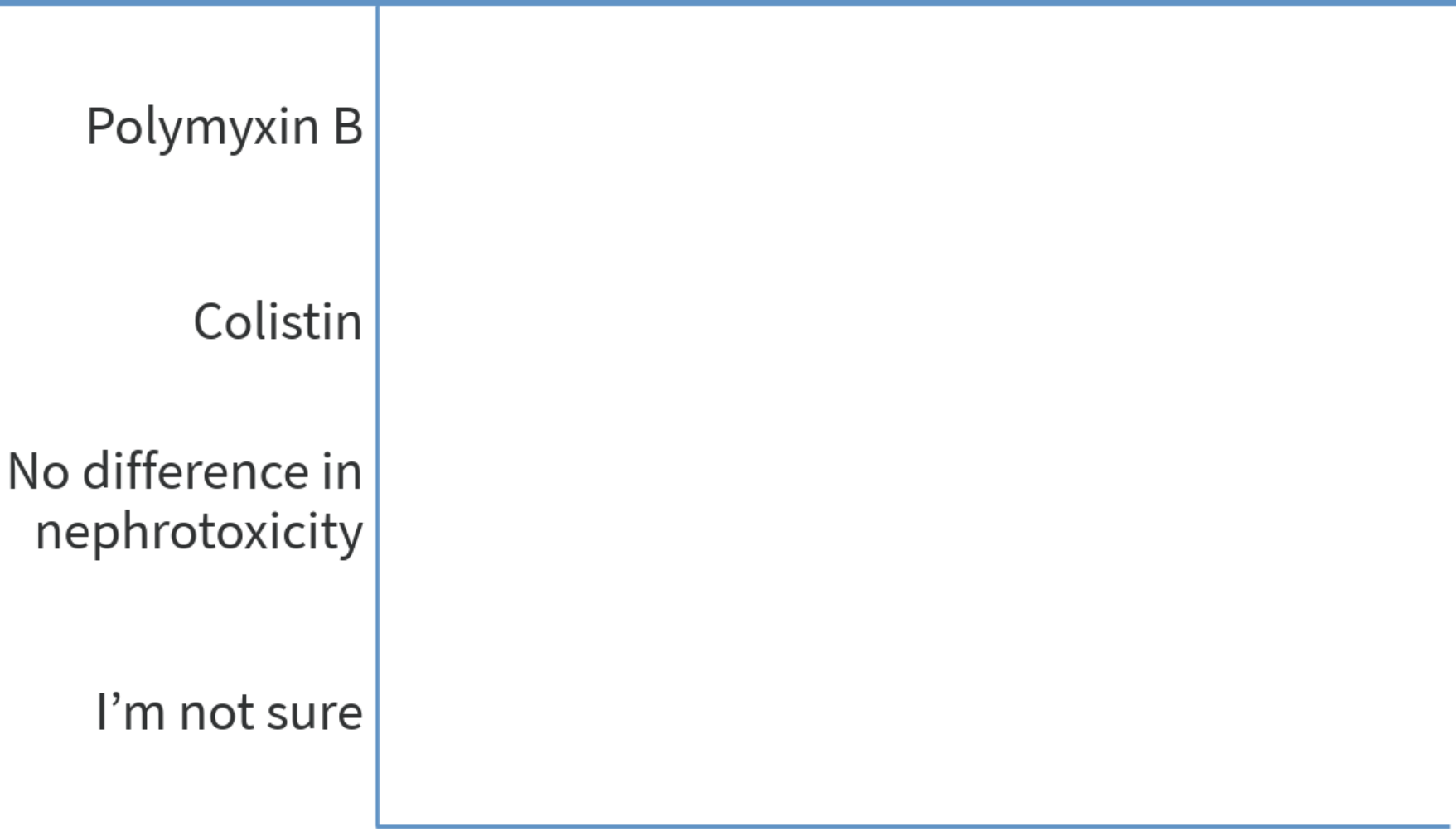
- Inhalation
  - Colistin is preferred over polymyxin B due to limited experience & potential PK advantages
  - Studies (12) show >50% clinical efficacy despite a high level baseline severity of illness
  - Only one study addresses polymyxin B for the same indication
    - No difference in outcomes in IV vs. Inhaled
    - Hard to draw conclusions due to lack of standardization

1. Kalil AC et al. Management of adults with hospital-acquired and ventilatorassociated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of American and the American Thoracic Society. *Clin Inf Dis*. 2016;63(5):e61-111.
2. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. 2016. Inhaled antibiotics for Gram-negative respiratory infections. *Clin Microbiol Rev*. 29:581– 632.

Debate #2: Nephrotoxicity

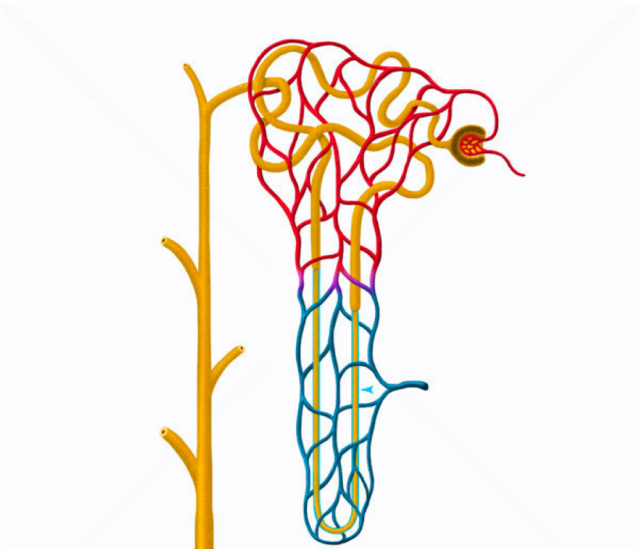


Which of the following antibiotics is associated with higher rates of nephrotoxicity?



Nephrotoxicity with Polymyxins

- Acute kidney injury can occur in 50-60% of patients
  - Dose-dependent
- Both polymyxins undergo extensive tubular reabsorption
- Toxicity to renal tubular cells
  - Oxidative stress
  - Apoptosis
  - Cell cycle arrest



Zavascki et al. Antimicrob Agents Chemother. 2017 Feb 23;61(3).

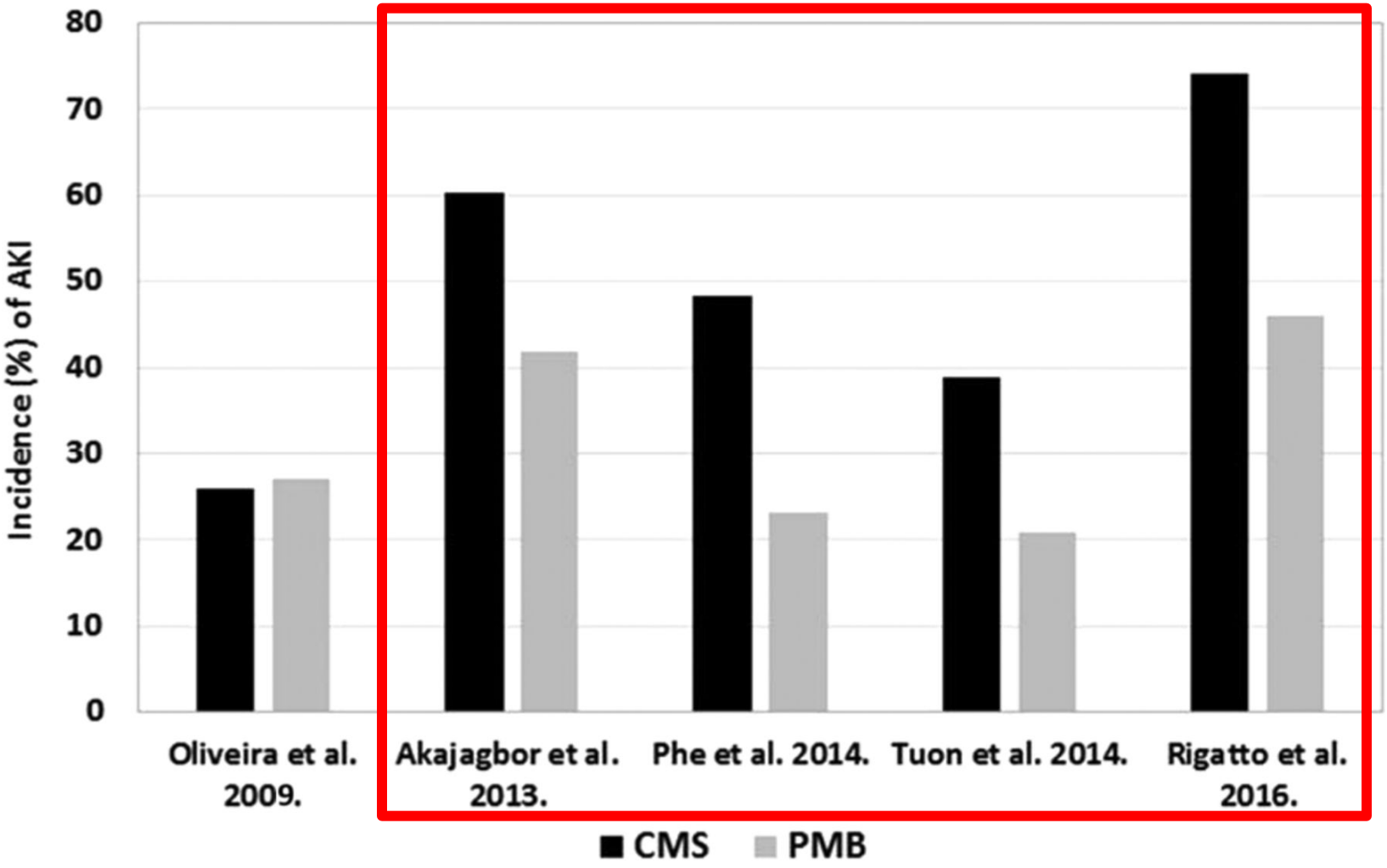
FOR: Polymyxin B

Study	Nephrotoxicity Criteria	Population	Results/Conclusions
Akajagbor et al., 2013	RIFLE	Retrospective study; n=173 (106 CMS vs 67 polyB)	60% CMS vs 42% polyB (p=0.02) Multivariate analysis: CMS HR=2.27 (p=0.002)
Tuon et al., 2014	AKIN	Retrospective study; n=132 (36 CMS vs 96 polyB)	39% CMS vs 21% polyB (p=0.06) Multivariate analysis: CMS HR 1.74, p=0.15; p=0.04 when adjusted for concurrent vancomycin and higher doses
Phe et al., 2014	RIFLE (patients excluded if baseline Scr >1.5)	Retrospective study of CMS vs polyB in serious infections; n=225 (121 CMS vs 104 polyB)	34% CMS vs 23% PolyB (p=0.08) Matched subgroup 55.3% CMS vs 21.1% polyB (p=0.003)
Rigatto et al., 2016*	**RIFLE**	**Multicenter, prospective cohort study; n=491 (81 CMS vs 410 polyB)**	**38% CMS vs 13% polyB (p<0.001)** **Multivariate analysis: CMS HR 3.35 (p<0.001)**

*Optimized dosing regimens and study design

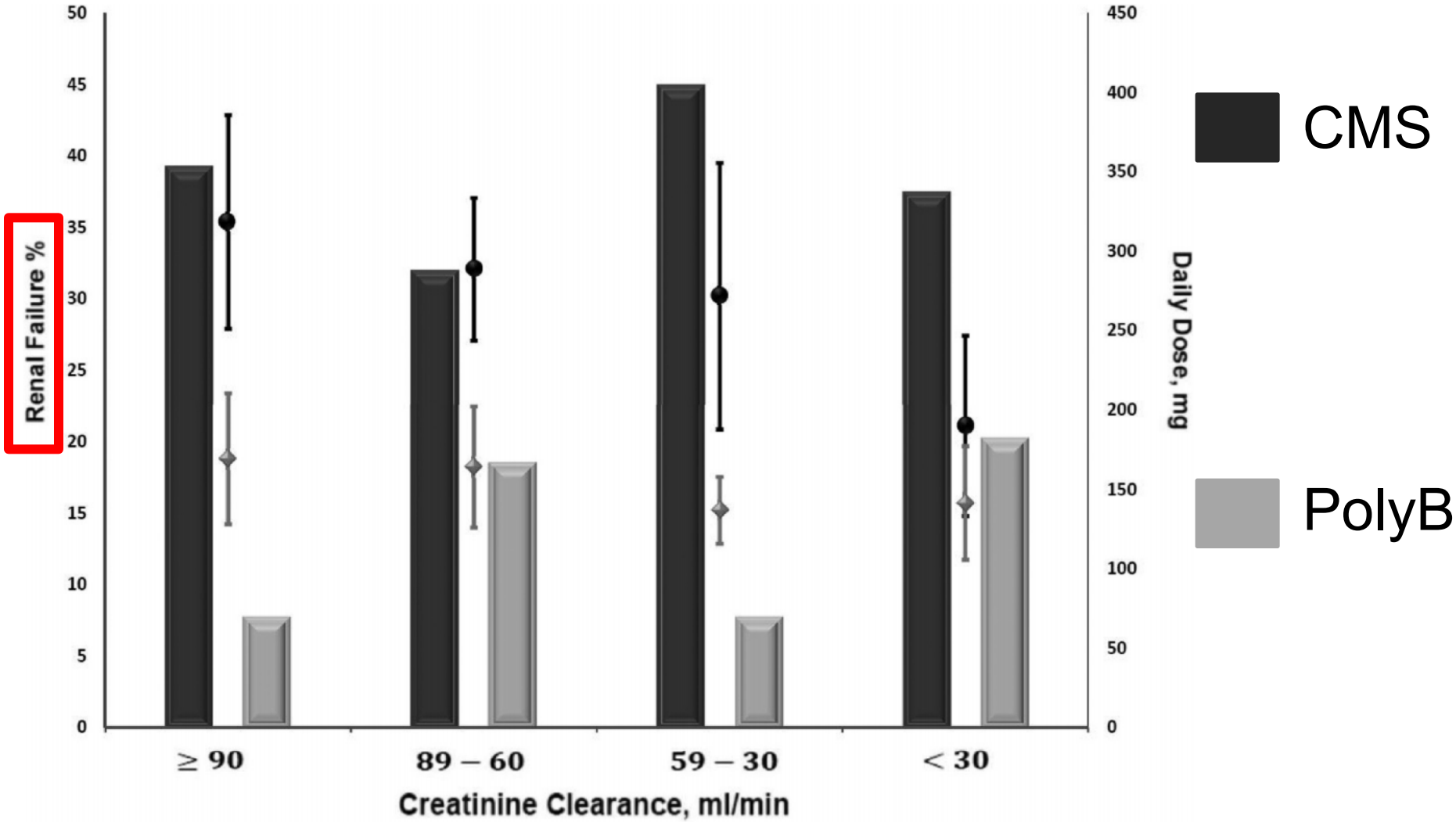
Akajagbor et al. Clin Infect Dis. 2013 57:1300–1303.
Tuon et al. Int J Antimicrob Agents. 2014 Apr;43(4):349-52.
Phe et al. Antimicrob Agents Chemother. 2014 May;58(5):2740-6.
Rigatto et al. Antimicrob Agents Chemother. 2016 Mar 25;60(4):2443-9.

FOR: Polymyxin B



Zavascki et al. Antimicrob Agents Chemother. 2017 Feb 23;61(3).

FOR: Polymyxin B



Rigatto et al. Antimicrob Agents Chemother. 2016 Mar 25;60(4):2443-9.

FOR: Polymyxin B

- Greatest differences in rates of 'Failure' in RIFLE/AKIN
  - Akajagbor et al. 17.9% CMS vs 9.0% polyB
  - Tuon et al. 21.4% CMS vs 5.0% polyB
  - Rigatto et al. 38.3% CMS vs 12.7% polyB

- Pooled CMS AKI RR 2.16 (95% CI, 1.43-3.27)

- AKI episodes shown to occur EARLIER with CMS

- Colistin has flat concentration vs time profiles compared to polyB with larger peak-trough fluctuations
  - Influences extent of accumulation in renal tubular cells

Zavascki et al. Antimicrob Agents Chemother. 2017 Feb 23;61(3).
Vardakas et al. Int J Antimicrob Agents. 2017 Feb;49(2):233-238.

FOR: Colistin

- Five studies have assessed comparative nephrotoxicity of colistin & polymyxin B
  - Oliveira et al. – No significant difference
  - Akajagbor et al.
  - Tuon et al. – No significant difference
  - Phe et al. – No significant difference
  - Rigatto et al.
- A recent review found “potential safety advantage for polymyxin B over CMS”

Pogue et al. Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing. *Clin Microbiol Infect*. 2017; 23:229-233.

Study	Nephrotoxicity Criteria	Population	Results/Conclusions
Oliveira et al., 2009	2x ↑ in SCr compared with baseline or 1 for Scr >1.4	Retrospective study; n=82 (41 Colistin & 41 Polymyxin B)	26% (Colistin) vs 27% (Polymyxin B) rates of nephrotoxicity
Akajagbor et al., 2013	RIFLE	Retrospective study; n=173 (106 CMS vs 67 polyB)	60% CMS vs 42% polyB (p=0.02) Multivariate analysis: CMS HR=2.27 (p=0.002)
Tuon et al., 2014	AKIN	Retrospective study; n=132 (36 CMS vs 96 polyB)	39% CMS vs 21% polyB (p=0.06) Multivariate analysis: CMS HR 1.74, p=0.15; p=0.04 when adjusted for concurrent vancomycin and higher doses
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Oliveira et al. *Diagn Microbiol Infect Dis*. 2009; 65:431-434.
Akajagbor et al. *Clin Infect Dis*. 2013 57:1300–1303.
Tuon et al. *Int J Antimicrob Agents*. 2014 Apr;43(4):349-52.
Phe et al. *Antimicrob Agents Chemother*. 2014 May;58(5):2740-6.
Rigatto et al. *Antimicrob Agents Chemother*. 2016 Mar 25;60(4):2443-9.

FOR: Colistin

- Nephrotoxicity conclusion: They are both bad

https://endtimesprophecyreport.com/2015/01/09/false-choices-the-corporate-media-provides-two-choices-to-complex-questions/

Place in Therapy

Where should we be using the polymyxins?

Comparative Efficacy of Polymyxins

- Studies are methodologically difficult to conduct
  - Complex patients
  - Dosing regimens
  - Delays in time to effective therapy
  - Severity of infection
  - Pathogen and MIC
  - Infection vs colonization

- No randomized controlled trials available

Pogue et al. Clin Microbiol Infect. 2017 Apr;23(4):229-233.

Comparative Efficacy of Polymyxins

- No clear advantage in clinical efficacy between polymyxin B and colistin

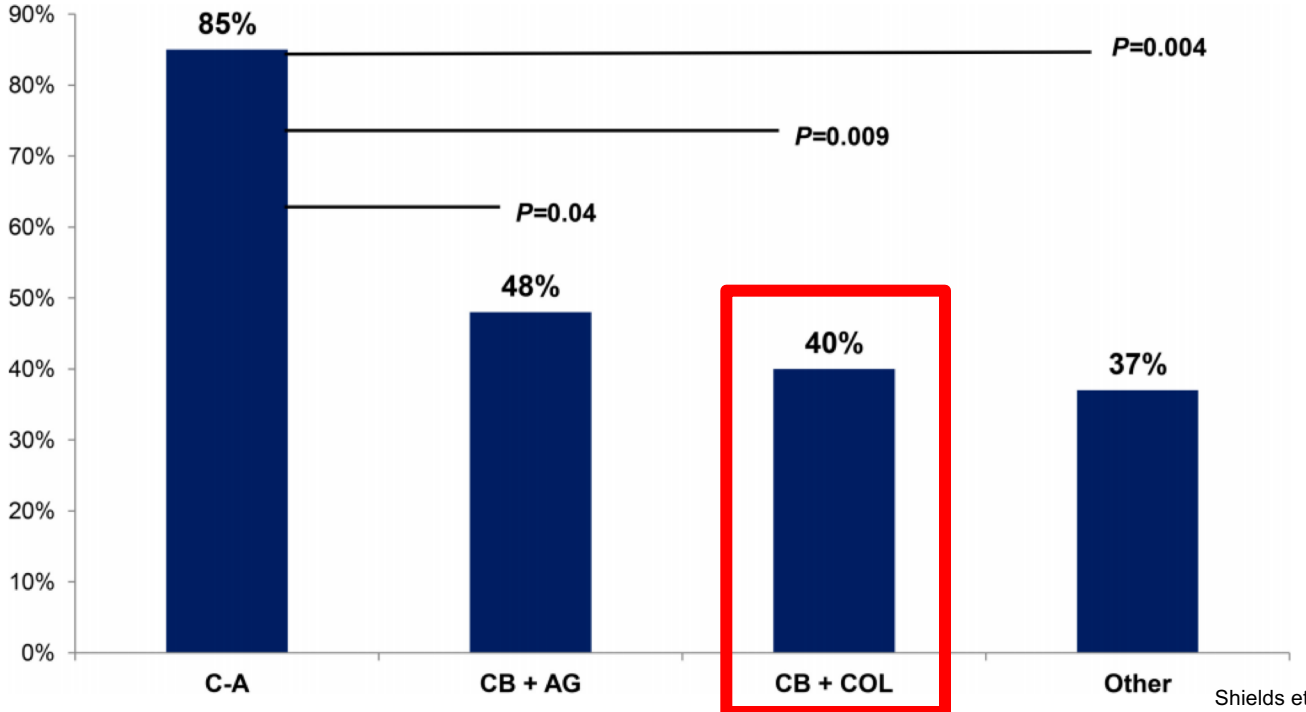
Study	Population	Results
Oliveria et al., 2009	Retrospective study of CMS vs. polyB in serious infections caused by CR *Acinetobacter spp.*; n=82 (41 vs. 41)	-Treatment: Success 39% vs 39%; Failure 41% CMS vs 32% polyB (p=0.48) -**30-day mortality**: 56% CMS vs 61% polyB (p=0.66)
Tuon et al., 2014	Retrospective study of CMS vs. polyB in serious infections; n=132 (36 CMS vs 96 polyB)	-In-hospital mortality: 45.8% CMS vs 50% polyB (p=0.48)
Phe et al., 2014	Retrospective study of CMS vs polyB in serious infections; n=225 (121 CMS vs 104 polyB)	-In-hospital mortality: 30.8% polyB vs 8.3% CMS (p<0.001) -No difference in mortality (21.4% vs. 21.4%) in matched subgroup and exclusion of CF patients
Rigatto et al., 2016	Multicenter, prospective cohort study with 30-day mortality as secondary outcome; n=491 (81 CMS vs 410 polyB)	-30-day mortality: 43.4% polyB vs 30.9% CMS (p=0.083) -Multivariate model (adjust for age, ICU, Charleston comorbidity index); HR 0.89 (95% CI 0.56-1.38)

Oliveria et al. Diagn Microbiol Infect Dis. 2009 Dec;65(4):431-4.
Tuon et al. Int J Antimicrob Agents. 2014 Apr;43(4):349-52.
Phe et al. Antimicrob Agents Chemother. 2014 May;58(5):2740-6.
Rigatto et al. Antimicrob Agents Chemother. 2016 Mar 25;60(4):2443-9.

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

Ryan K. Shields,[a,c] M. Hong Nguyen,[a,c] Liang Chen,[d] Ellen G. Press,[a] Brian A. Potoski,[a,c,e] Rachel V. Marini,[c] Yohei Doi,[a,c] Barry N. Kreiswirth,[d] Cornelius J. Clancy[a,b,f]

- Retrospective, single-center, cohort study
- Rates of 30-day clinical success



Shields et al. Antimicrob Agents Chemother. 2017 Jul 25;61(8).

Clinical Infectious Diseases
MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

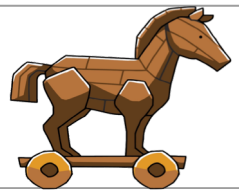
David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

- Prospective, multi-center, observational study of initial treatment of KPC-producing CRE
  - CAZ-AVI (n=38) and CMS (n=99)
- All-cause mortality 30 days after starting treatment
  - 9% CAZ-AVI vs 32% CMS (p = .001)
  - Improved clinical outcomes
  - Decreased all-cause hospital mortality
  - Improved benefit-risks outcomes

van Duin et al. Clin Infect Dis. 2018 Jan 6;66(2):163-171.

Out with the old and in with the new?

+ = favorable activity

	ESBL	AmpC	KPC	Oxa48	Metallo BL	Pseudomonas	Acinetobacter
Ceftolozane-tazobactam	++	-	-	-	-	++	-
Ceftazidime-avibactam	++	++	++	+	-	+/++	-
Meropenem-vaborbactam	++	++	++	-	-	+/++	-
Imipenem-relebactam (Phase III)	++	++	++	-	-	+/++	-
Aztreonam-avibactam (Phase III)	++	++	++	+	++	+	-
Cefiderocol (S49266) (Phase III) 	++	++	++	++	++	++	+/++

Wrap-up Comparison

Characteristic	Polymyxin B	Colistin
Clinical efficacy	+	+
Nephrotoxicity	++	+
Neurotoxicity	+	+
Dosing, administration, PK	**++**	**+**
Urinary Concentrations	-	++
Clinical experience	+	++
Inhalation data/experience	+	++
Cost	++	++

+ = favorable characteristic

Final Comments – Polymyxin B

- **Colistin displays unpredictable and erratic pharmacokinetics** compared to polymyxin B
- **Polymyxin B dosing is convenient** and simple, particularly in renal impairment
- Multiple studies have demonstrated **LESS nephrotoxicity with polymyxin B**
- No difference in clinical efficacy at this point
- Polymyxin B  Colistin 

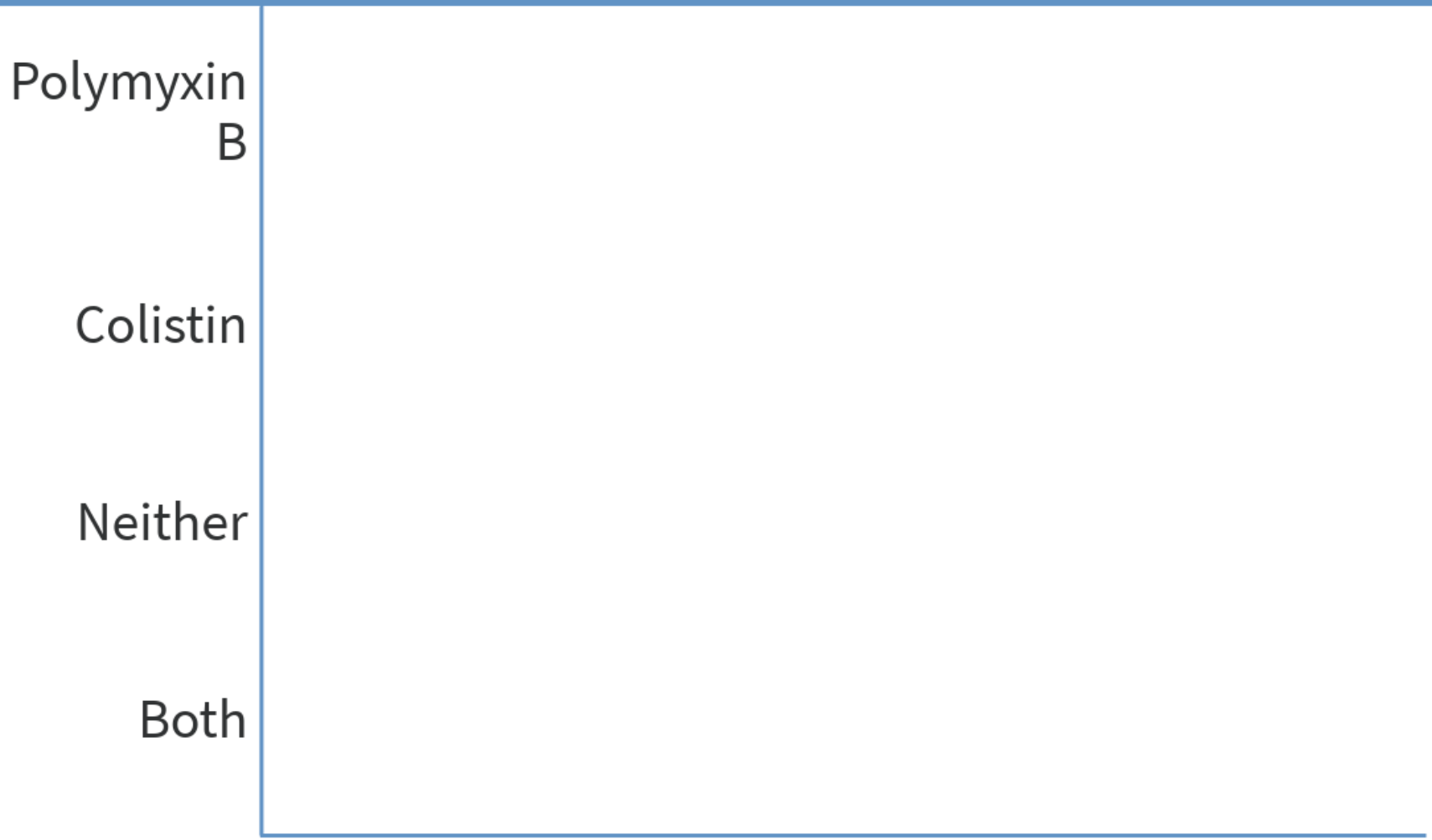
Final Comments - Colistin

- While nephrotoxicity is a risk and dosing seems more complicated, there is more literature available to help us dose colistin

- Polymyxin B has some theoretical advantages, however, from the five comparative efficacy studies we know that there is no difference in mortality

- While no difference in clinical efficacy exists, colistin is probably the preferred agent for:
  - UTI
  - Intrathecal/Intraventricular
  - Inhalation

After this debate, which of the following polymyxin antibiotics would you prefer to have on your formulary?



Questions???

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