10 de Agosto de 2018

III ENCONTRO INTERNACIONAL BRCAST E EUCAST

Polimixinas: da bancada à beira do leito

Uso Clínico das Polimixinas

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Polimixinas

- *Breakpoint* Clínico – PK/PD
- *Breakpoints – Joint Working Group*
- Uso clínico, *Breakpoints*, Limitações

3rd International Conference on Polymyxins

Polymyxins: Facing Forward

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

University at Buffalo
The State University of New York

SaludMadrid Hospital Universitario 12 de Octubre

medicine.umich.edu/dept/intmed/education-training/cme/3rd-international-conference-polymyxins

Coming Soon from

Pharmacotherapy

Polymyxin Therapeutic Guidelines: A Summary of Consensus Recommendations. To be endorsed pending approval from the American College of Clinical Pharmacy, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, International Society of Anti-Infective Pharmacology, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists.

Pharmacotherapy, an official journal of the American College of Clinical Pharmacy, is providing free access to the recommendations for usage and dosing of Polymyxin E (colistin) and Polymyxin B.

Authors:

Brian T. Tsuji, Jason M. Pogue, Alexandre P. Zavascki, Mical Paul, George L. Daikos, Alan Forrest, Daniele R. Giacobbe, Claudio Viscoli, Helen Giamarellou, Ilias Karaiskos, Donald Kaye, Johan W. Mouton, Vincent H. Tam, Visanu Thamlikitkul, Richard G. Wunderink, Jian Li, Roger L. Nation, and Keith S. Kaye

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WILEY

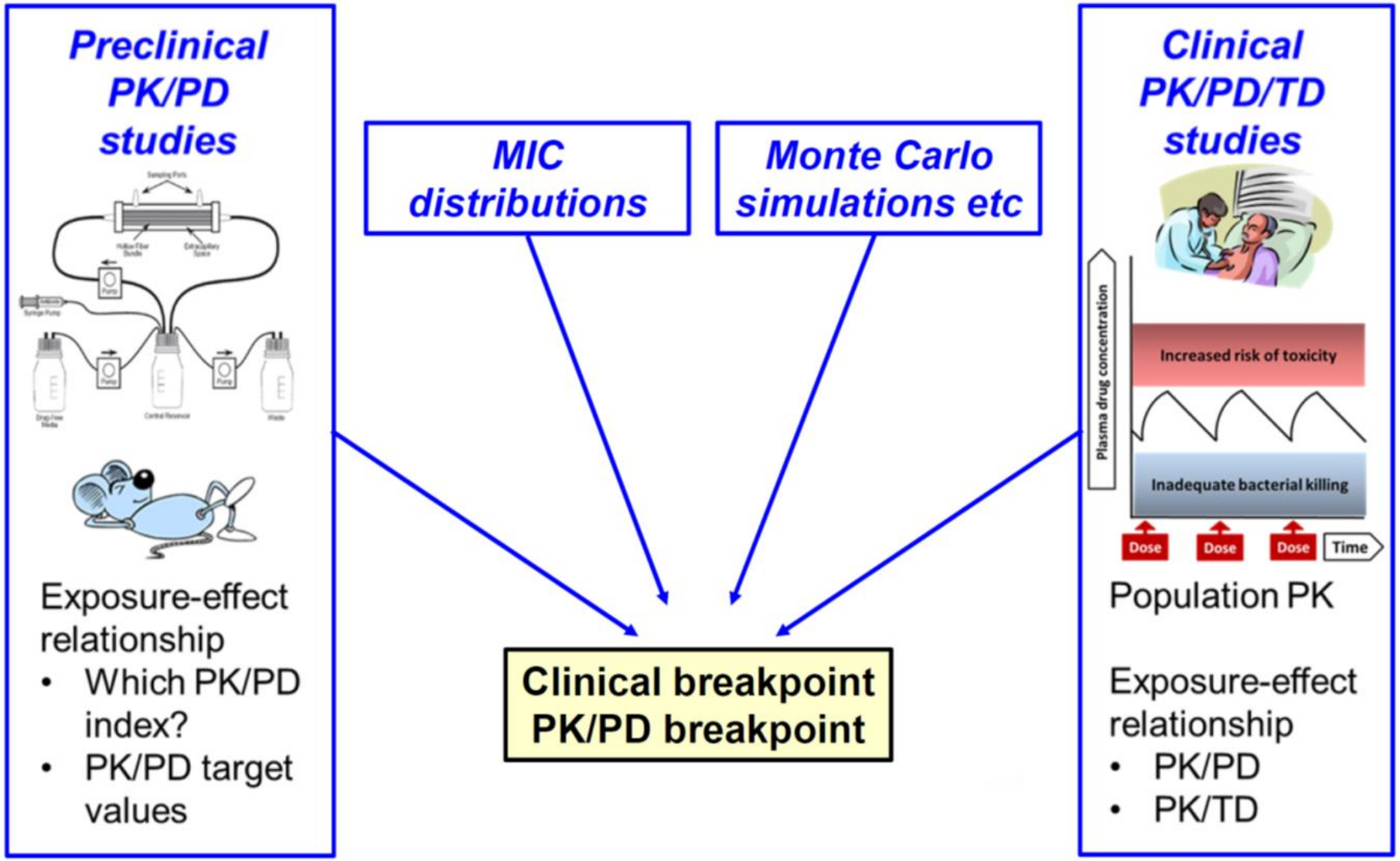
- EUCAST e CLSI estabeleceram um *Joint Working Group* para avaliar os testes e os *breakpoints* para colistina
- Polimixina B não foi avaliada → BrCAST
- *Joint Working Group* → *breakpoints* clínicos → *Acinetobacter* spp. and *P. aeruginosa*.
- *Enterobacterales* → dados insuficientes e *breakpoint* clínico não foi definido → *Cutoff* epidemiológico foi proposto como *breakpoint*

Breakpoints do JWG CLSI/EUCAST para Colistina

Organismo	MIC (mg/L)	
	Sensível	Resistente
Acinetobacter spp.	≤2	>2
P. aeruginosa	≤2	>2
Enterobacteriaceae*	≤2	>2

* Distribuição de MICs de *Klebsiella aerogenes*, *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae* e *Raoultella ornithinolytica*.

O que é necessário para estabelecer o breakpoint clínico - PK/PD?



Adaptado de slide de Prof. Roger Nation apresentado em *III International Conference on Polymyxins*

J Antimicrob Chemother 2015; **70**: 3291–3297
doi:10.1093/jac/dkv267 Advance Access publication 27 August 2015

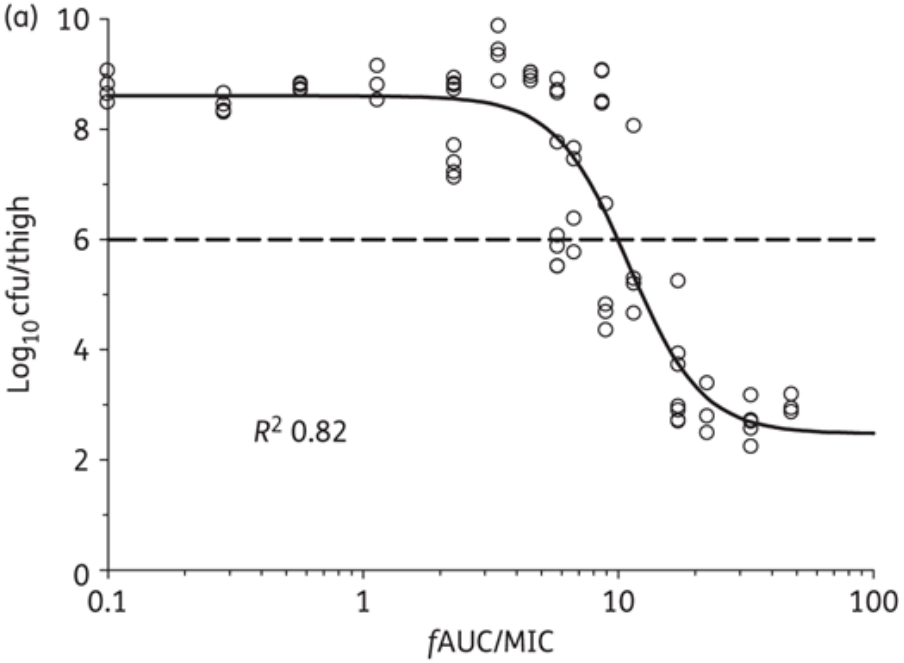
Journal of Antimicrobial Chemotherapy

New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection

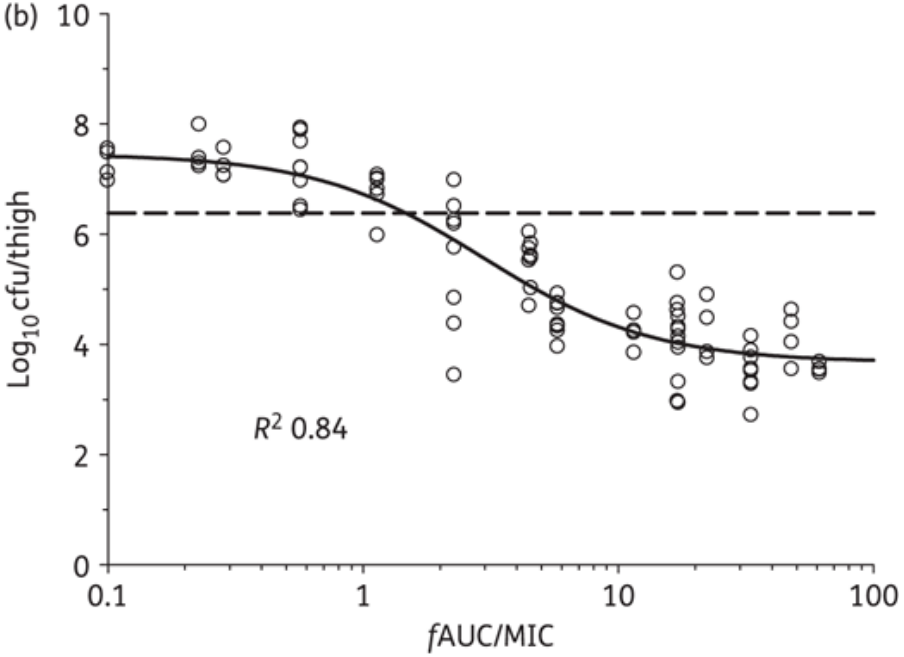
Soon-Ee Cheah[1], Jiping Wang[1], Van Thi Thu Nguyen[1], John D. Turnidge[2], Jian Li[1]† and Roger L. Nation[1]*†

[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Victoria 3052, Australia; [2]Departments of Pathology and Paediatrics and School of Molecular and Biomedical Sciences, University of Adelaide, Adelaide, South Australia 5005, Australia

P. aeruginosa ATCC 27853



A. baumannii ATCC 19606



Cheah et al. J Antimicrob Chemother 2015.

Model/species/strain	Target value of colistin *f*AUC/MIC[a]		
	stasis	1 $\log_{10}$ kill	2 $\log_{10}$ kill
Thigh infection			
P. aeruginosa			
ATCC 27853	8.7 (7.9–9.4)	10.9 (10.0–11.8)	13.7 (12.5–15.3)
PAO1	6.0 (5.9–6.1)	6.6 (6.4–6.7)	7.4 (7.1–7.8)
19056	7.5 (6.6–8.5)	10.0 (8.8–11.5)	13.5 (11.5–16.4)
A. baumannii			
ATCC 19606	1.4 (1.1–1.8)	3.5 (2.8–4.2)	9.0 (6.6–14.2)
248-01-C.248	3.9 (3.1–4.6)	6.0 (5.6–6.5)	7.4 (7.0–7.9)
N-16870.213	9.3 (8.4–10.2)	13.9 (13.1–14.6)	17.6 (16.7–18.4)

***f*AUC/MIC → 12mg/L.h**

Cheah et al. J Antimicrob Chemother 2015.

Model/species/strain	Target value of colistin *f*AUC/MIC[a]		
	stasis	1 $\log_{10}$ kill	2 $\log_{10}$ kill
Lung infection			
P. aeruginosa			
ATCC 27853	34.1	43.3	51.8
PAO1	15.2	44.8	x
19056	38.6	57.9	105
A. baumannii			
ATCC 19606	x	x	x
248-01-C.248	11.6	20.8	36.8
N-16870.213	x	x	x

Cheah et al. J Antimicrob Chemother 2015.

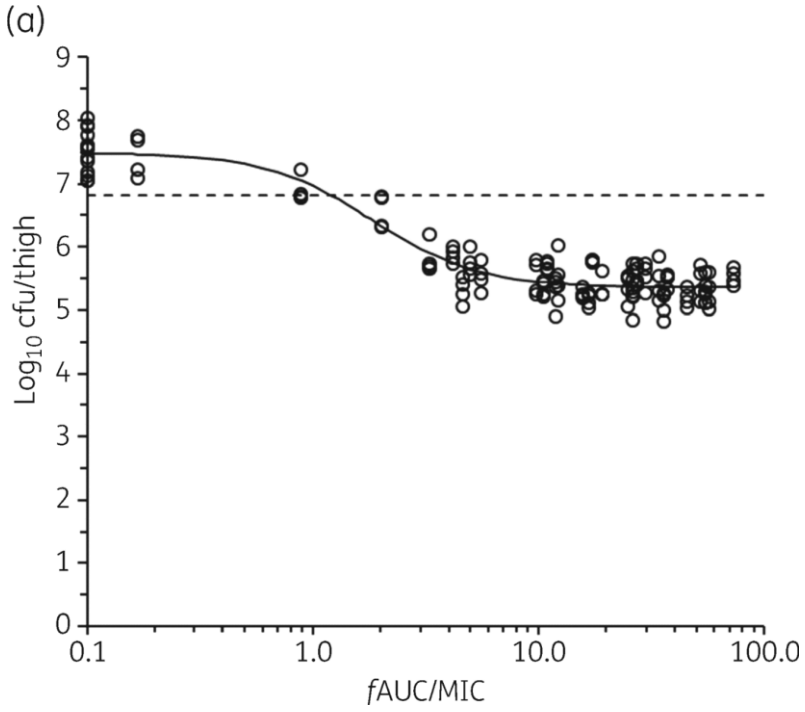
J Antimicrob Chemother 2018; **73**: 462–468
doi:10.1093/jac/dkx409 Advance Access publication 14 November 2017

Journal of Antimicrobial Chemotherapy

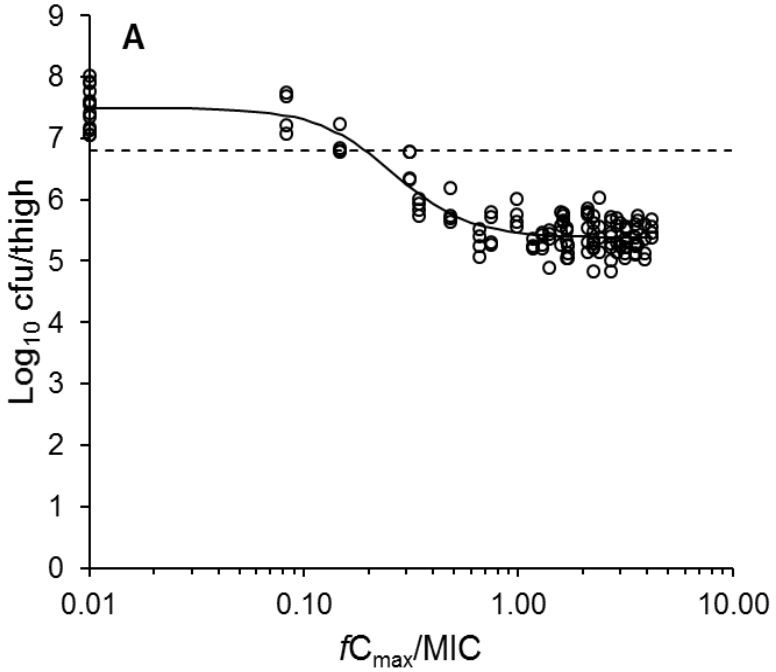
Pharmacokinetics/pharmacodynamics of systemically administered polymyxin B against *Klebsiella pneumoniae* in mouse thigh and lung infection models

Cornelia B. Landersdorfer[1–3]†, Jiping Wang[1]†, Veronika Wirth[1], Ke Chen[1], Keith S. Kaye[4], Brian T. Tsuji[3,5], Jian Li[1,6] and Roger L. Nation[1]*

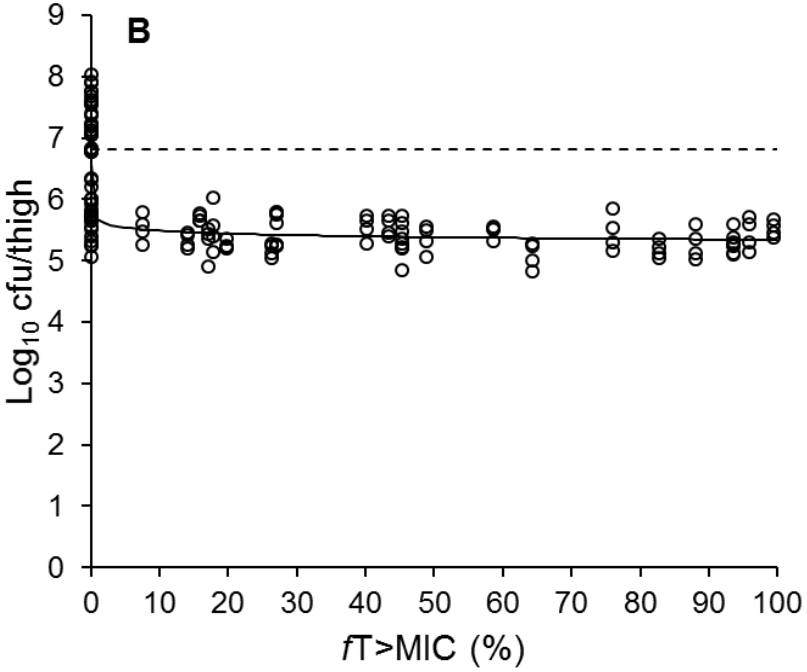
[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; [2]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia; [3]School of Pharmacy and Pharmaceutical Sciences, University at Buffalo State University of New York, Buffalo, NY, USA; [4]Department of Medicine, University of Michigan Medical School, Ann Arbor, MI, USA; [5]Laboratory for Antimicrobial Pharmacodynamics, NYS Centre of Excellence in Bioinformatics & Life Sciences, Buffalo, NY, USA; [6]Monash Biomedicine Discovery Institute, Department of Microbiology, Monash University, Clayton, Victoria, Australia



$R^2 = 0.89$



$R^2 = 0.88$



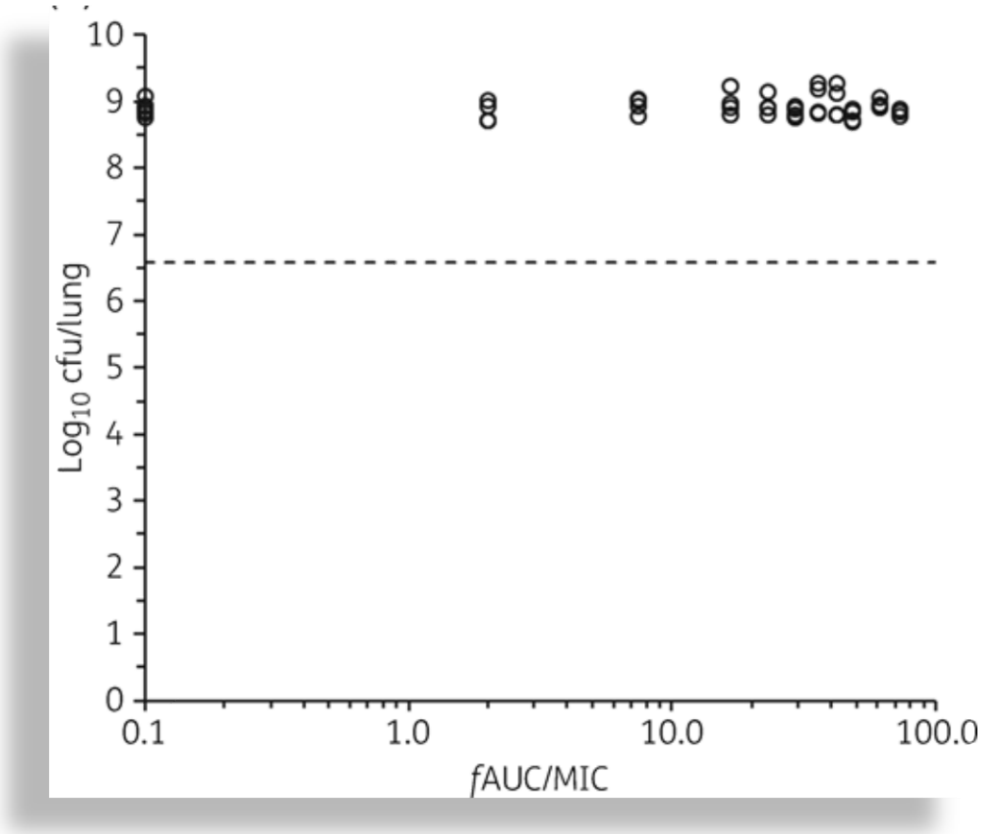
$R^2 = 0.50$

Landersdorfer et al. J Antimicrob Chemother 2018.

PK/PD model-fitted parameter estimates for the fAUC/MIC target values of polymyxin B against *K. pneumoniae* in the thigh infection model

	Target value of polymyxin B *f*AUC/MIC for various magnitudes of effect		
Strain	**stasis**	**1 $\log_{10}$kill**	**2 $\log_{10}$kill**
ATCC BAA-2146	**13.5**	**17.4**	x
FADDI-KP032	**1.22**	**3.72**	x
FADDI-KP042	**5.47**	**28.0**	x

Landersdorfer et al. J Antimicrob Chemother 2018.



K. pneumoniae FADDI-KP032 between $\log_{10}$ cfu per lung at 24 h and fAUC/MIC

- Lung → "Bacteriostasis" → not achieved for any of the 3 *K. pneumoniae* strains, even at the highest dose tolerated by the mice → the antibacterial activity was substantially lower than observed in the thigh infection model (Similar to findings with colistin)

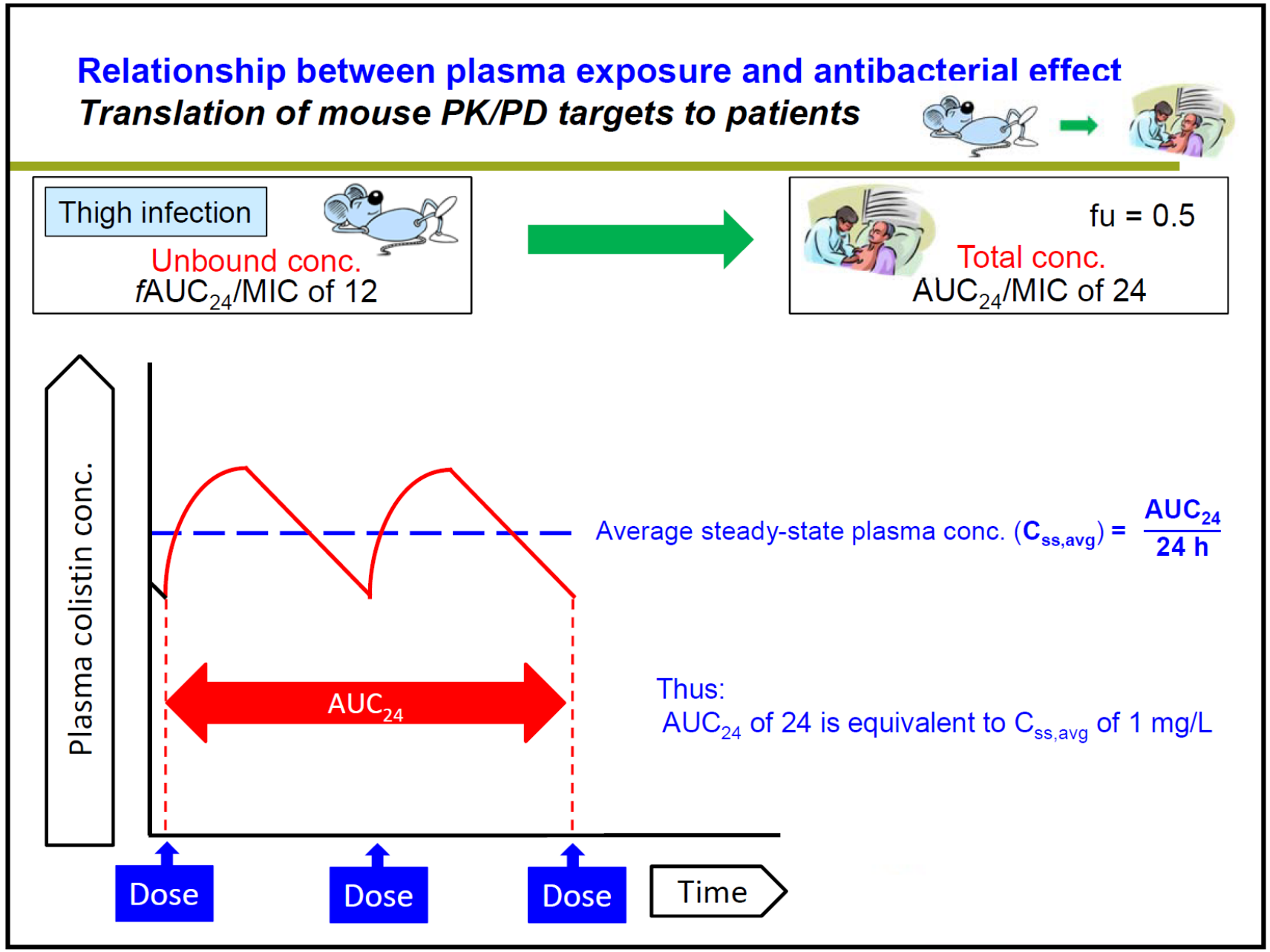
Landersdorfer et al. J Antimicrob Chemother 2018.

Equimolar SC dose levels (associated with near maximal bacterial killing) against two strains of *K. pneumoniae*

		Strain			
		FADDI-KP032		ATCC BAA-2146	
Log_{10} cfu/thigh at 0 h		6.80 ± 0.08		6.78 ± 0.13	
	Dose level	Polymyxin B	Colistin	Polymyxin B	Colistin
Log_{10} cfu/thigh at 24 h	1	5.30 ± 0.27	5.42 ± 0.22	7.62 ± 0.81	7.03 ± 1.34
	2	5.41 ± 0.17	5.57 ± 0.07	5.29 ± 0.25*	5.68 ± 0.14
	3	5.31 ± 0.20	5.55 ± 0.07	5.67 ± 0.98	5.28 ± 0.16
	4	5.52 ± 0.13	5.43 ± 0.11	Not tested	Not tested

* Different from the corresponding value for colistin for this strain ($p = 0.044$)

Landersdorfer et al. J Antimicrob Chemother 2018.



Adaptado de slide de Prof. Roger Nation apresentado em *III International Conference on Polymyxins*

$fAUC_{24h}/MIC = 12$

MIC	$fAUC_{24h}$	AUC_{24h}	$C_{ss, avg}$	Dose PMB	Dose CBA (CMS)
0,5	6	12	0,5		
1	12	24	1		
2	24	48	2	2.5-3.0mg/kg	300-360 mg (9-10,9 MIU)
4	48	96	4	Toxicidade	Toxicidade

2.5-3.0 mg/kg/dia (equivalente a 25,000-30,000 IU/kg/day), 90% dos pacientes terão uma $AUC_{24h, SS}$ de PMB de pelo menos 44.3 e 53.1 mg/L.h → $C_{ss,avg}$ = 1.8 e 2.2 mg/L.

Sandri et al. CID 2013.

Breakpoints de polimixinas e uso clínico

- Alvo PK/PD → corresponde a uma resposta de queda de UFCs de 1-2log em 24h em modelo de infecção musculo
- Em modelo de infecção pulmonar → Alvo PK/PD → insuficiente para garantir morte bacteriana
- Alvo definido para infecções por *A. baumannii e P. aeruginosa* → *K. pneumoniae* aparentemente necessita um alvo PK/PD maior

Qual o papel das polimixinas com os novos antimicrobianos?

Estudos Observacionais	**colistina**	**Ceftazidima-avibactam**
CRACKLE ***mortalidade em 30 dias***	**32%**	**9%**
Pittsburgh ***mortalidade em 30 dias***	**31%**	**8%**

Van Duin, Clin Infect Dis 2017; Shields, Antimicrob Agents Chemother 2017

ECR	**Colistina**	**Comparador**
Plazomicina ***mortalidade em 28 dias***	**40%**	**7%**
Imipenem-relebactam ***mortalidade geral***	**30%**	**9.5%**

Achaogen, ECCMID 2017; Kaye, ECCMID 2018

Qual o papel das polimixinas com os novos antimicrobianos?

- Antimicrobianos de 2ª. linha no tratamento de infecções por CRE
  - Terapia de resgate
  - Associação
  - Alergia a beta-lactâmicos
- Ainda terão papel relevante para *A. baumannii* e *P. aeruginosa* produtora de MBL

10 de Agosto de 2018

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