

# **Resistência à polimixina, é possível prevenir? SIM**

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- **Conflito de Interesse**

# Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco<sup>1,2</sup>, T Giani<sup>2,3</sup>, M Raffone<sup>1,4</sup>, F Arena<sup>3</sup>, A Garcia-Fernandez<sup>1</sup>, S Pollini<sup>3</sup>, Network EuSCAPE-Italy<sup>5</sup>, H Grundmann<sup>6</sup>, A Pantosti (annalisa.pantosti@iss.it)<sup>1</sup>, G M Rossolini<sup>3,7,8</sup>

Euro Surveill. 2014

“Antimicrobial susceptibility data for the 178 KPC-KP isolates revealed that 76 (43%) were resistant to colistin...”



# MIC of *Klebsiella* spp. to polymyxin B in carbapenem sensitive and carbapenem non-sensitive strains collected in 2013.

## BLOODSTREAM

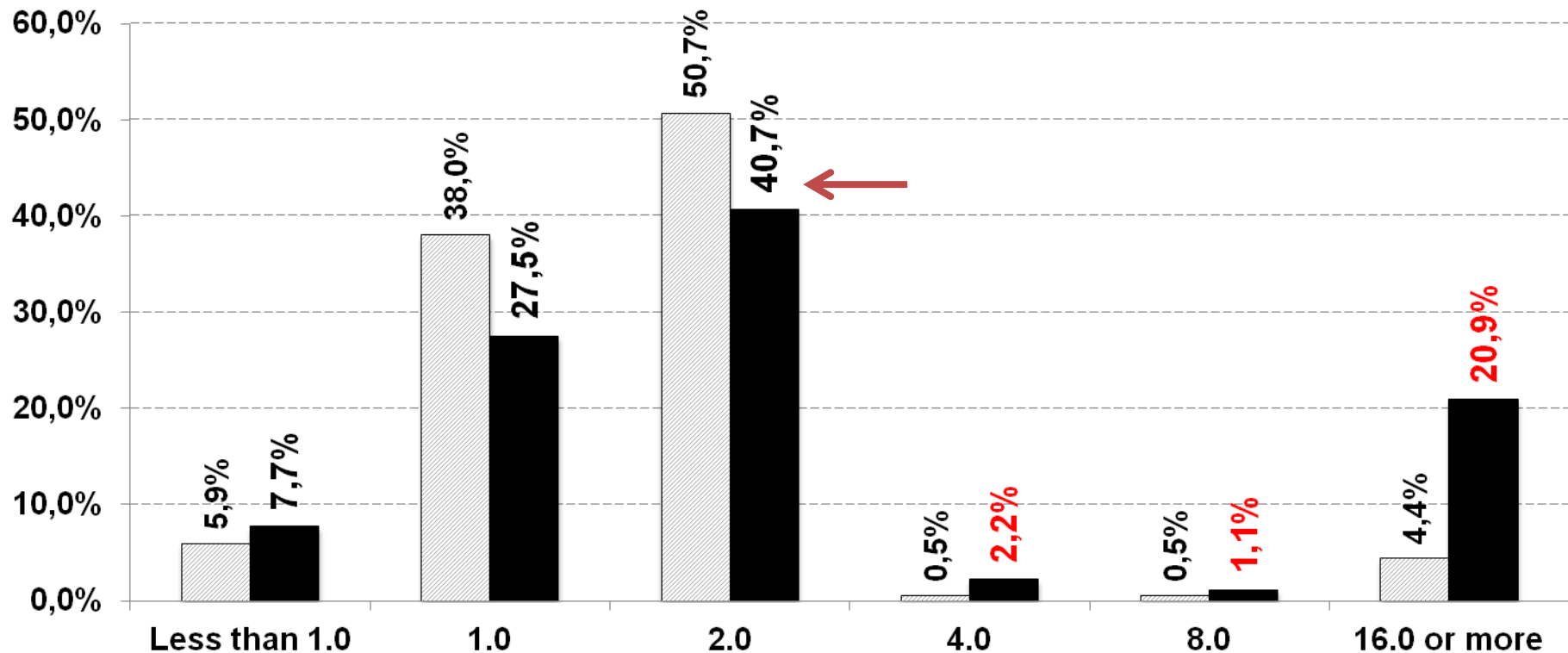
P<0.001

▨ Carbapenem sensitive

N=205

■ Non-sensitive

N=91



**MIC of *Klebsiella* spp. to polymyxin B in carbapenem sensitive and carbapenem non-sensitive strains collected in 2013.**

**RESPIRATORY TRACT**

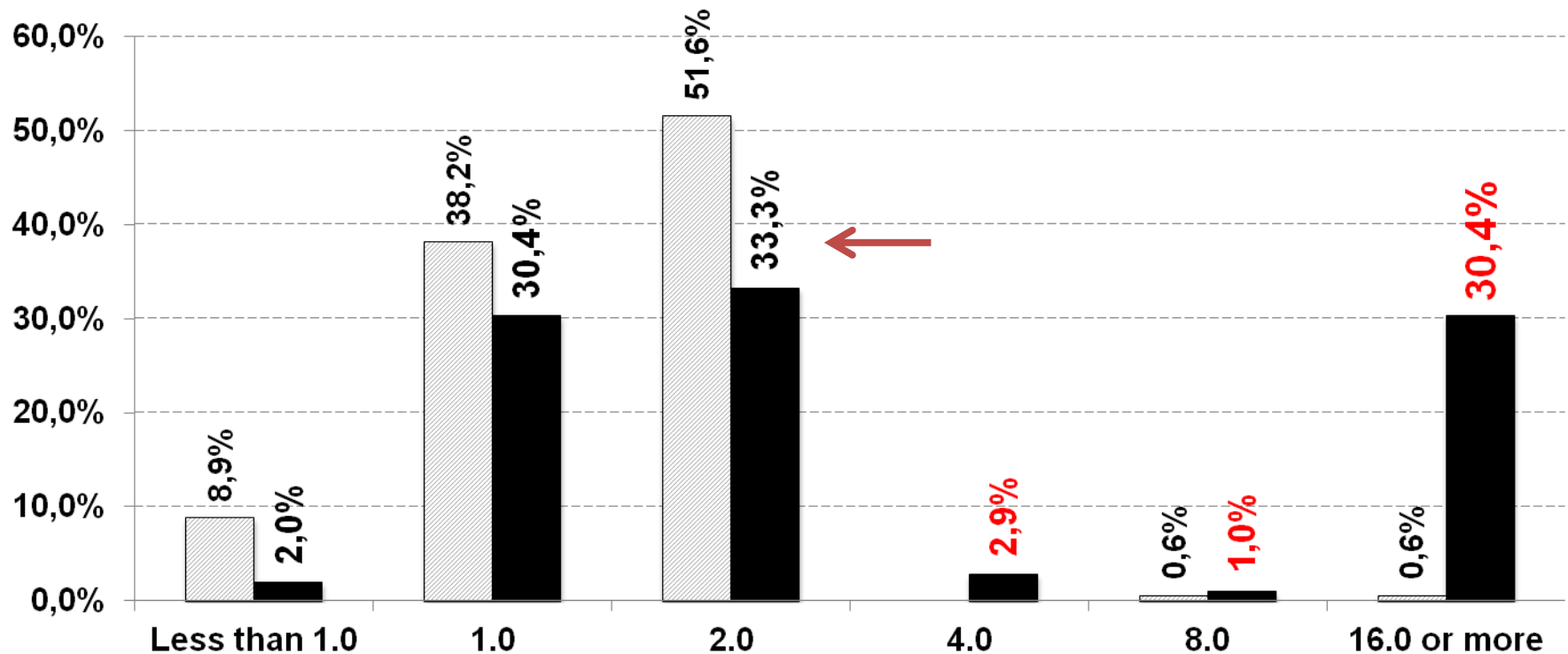
P<0.001

▨ Carbapenem sensitive

N=157

■ Non-sensitive

N=102



# March to December 2011 – 3 Hosp. POA 84 CRAB

**4 (4.8%) = CRAB resistant to POB**

Clone	Hospital	PMB	IMP	MER	CAZ	CEF	SAM	CIP	AMK	TIG
B	HCPA	≥ 64	16	16	≥ 256	≥ 512	32	≥ 64	64	2
B	HPS	≥ 64	64	16	128	32	64	64	2	1
B	HSL	8	64	32	64	32	32	32	16	2
E	HSL	≥ 64	64	64	≥ 256	≥ 512	32	≥ 64	512	0.5

# **Resistência à polimixina B**

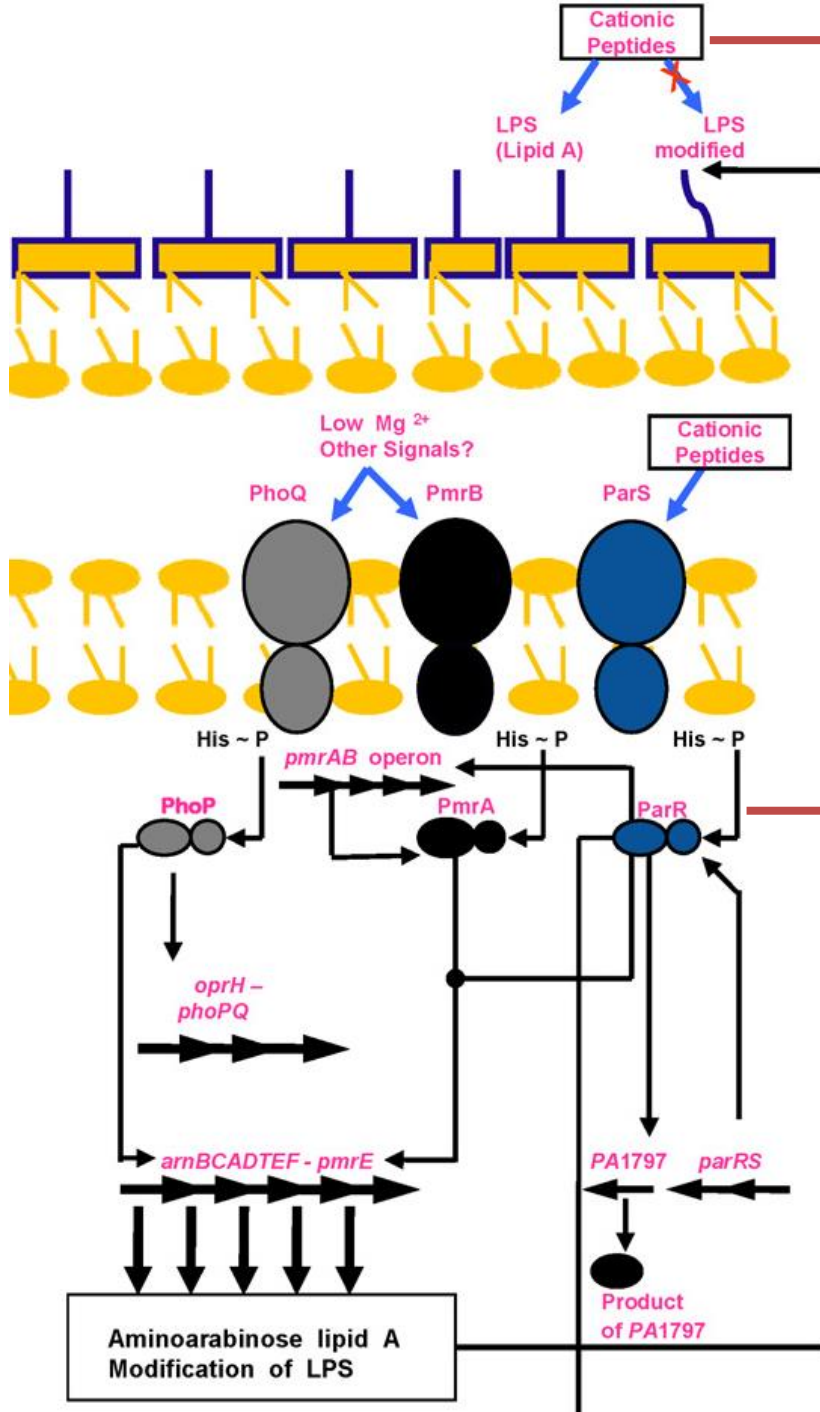
- **Mutacional (De Novo)→ heterorresistência (?)**
- **Adaptativa**
- **Adquirida de elementos genéticos externos→ até o momento, não**
- **Disseminação horizontal de cepas mutantes resistentes**

# Resistência à polimixina B

- *P. aeruginosa*
- *A. baumannii*
- Enterobacteriaceae:  
*K. pneumoniae*

Modificação do lipídio A → adição de 4-amino-4-deoxi-L-arabinose ou fosfoetanolamina → *redução da carga negativa*

Sistemas de 2 componentes → *Proteína sensora ligada à membrana* → *estímulos ambientais como  $\downarrow$  pH,  $\downarrow$   $Mg^{2+}$ , peptídeos catiônicos + proteína efetora citoplasmática* → *regula a transcrição dos genes em resposta à proteína sensora*



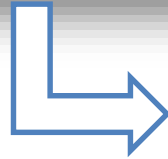
**Concentração Subinibitórias →**  
*resistência adaptativa →*  
*depende da presença da*  
*polimixina*

**Mutações → ativação**  
*constitutiva do sistema →*  
*modificação permanente do*  
*lípidio A →*  
*resistência estável às*  
*polimixinas*

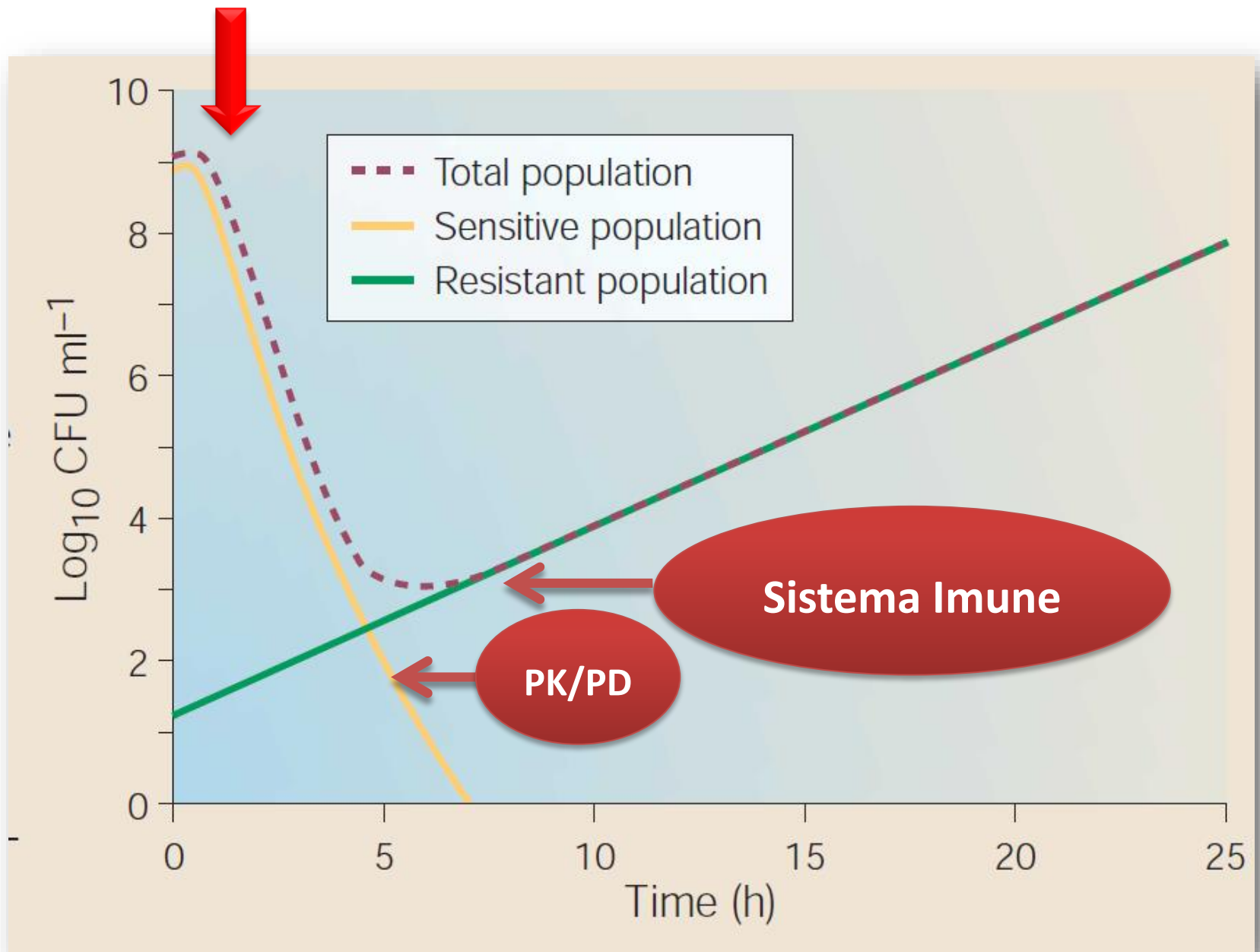
## Description

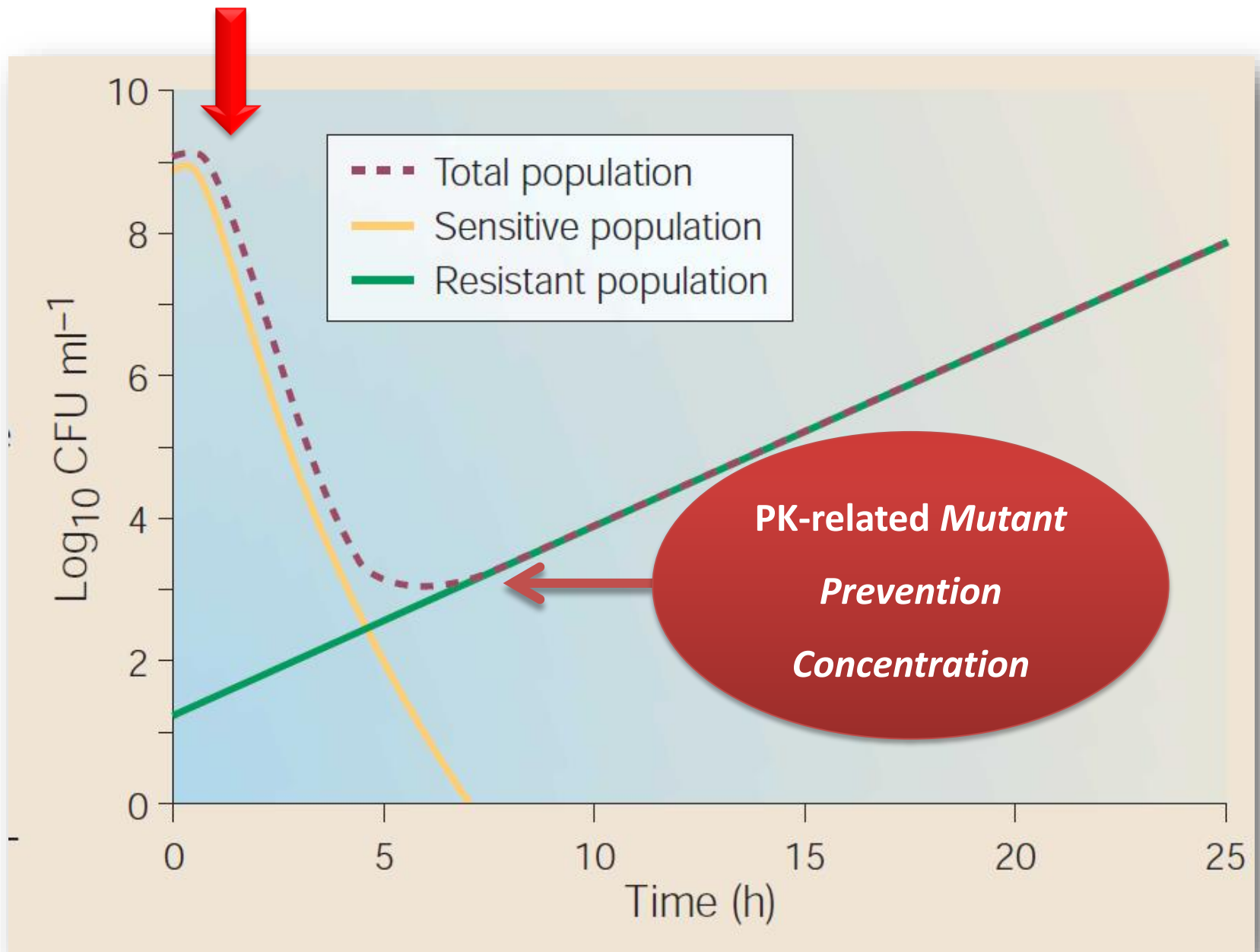
## gene

PhoP/PhoQ regulator protein MgrB	<i>mgrB</i>
polymyxin resistance protein PmrD	<i>pmrD</i>
lipid A phosphoethanolamine transferase PmrC	<i>pmrC</i>
response regulator receiver domain protein PmrA	<i>pmrA</i>
histidine kinase domain protein PmrB	<i>pmrB</i>
response regulator receiver domain protein PhoP	<i>phoP</i>
virulence sensor histidine kinase PhoQ	<i>phoQ</i>
UDP-4-amino-4-deoxy-L-arabinose--oxoglutarate aminotransferase	<i>pmrH</i>
glycosyltransferase, group 2 family protein	<i>pmrF</i>
bifunctional UDP-glucuronic acid decarboxylase	<i>pmrI</i>
polysaccharide deacetylase family protein	<i>pmrJ</i>
undecaprenyl phosphate- $\alpha$ -4-amino-4-deoxy-L-arabinose arabinosyl transferase	<i>pmrK</i>
4-amino-4-deoxy-L-arabinose-phosphoundecaprenol flippase subunit ArnE	<i>pmrL</i>
4-amino-4-deoxy-L-arabinose-phosphoundecaprenol flippase subunit ArnF	<i>pmrM</i>
outer membrane lipoprotein, membrane integrity	<i>slyB</i>
magnesium-importing ATPase, mgtA	<i>mgtA</i>
undecaprenyl-pyrophosphatase	<i>ybjG</i>
transfers a palmitate chain from a phospholipid to lipid A	<i>pagP</i>
lipid A hydroxylase	<i>lpxO</i>
glycosyltransferase, TupA-like ATPgrasp protein	
histidine kinase domain protein	<i>crrB</i>
response regulator receiver domain protein	<i>crrA</i>
conserved hypothetical membrane protein	
divalent cation transporter	
cation diffusion facilitator family transporter	
high-affinity nickel-transport protein, NicO-like	
ABC type transporter	
alkyl guanine transferase I, transcriptional regulator	<i>ada</i>
thiamine biosynthesis lipoprotein, FAD binding	<i>apbE</i>
efflux transporter, RND family, MFP subunit	
conserved hypothetical protein	
P-type ATPase, Mg <sup>2+</sup> transport	
chloride transporter, CIC family	
MacB-like periplasmic core domain protein	<i>macB</i>
macrolide-specific efflux protein MacA	<i>macA</i>
nucleotide sugar dehydrogenase	<i>ugd</i>
transcriptional regulatory protein RstA	<i>rstA</i>
histidine kinase protein RstB	<i>rstB</i>
UDP-GlcNAc:Und-P GlcNAc-1-P transferase	<i>wecA</i>



1. **Inoculo  $\rightarrow 10^6$  a  $10^9$  UFC/ml**
2. **Mutantes em um dos genes dos sistemas de dois componentes em uma frequência de  $10^{-x}$  capazes de determinar ativação constitutiva do mesmo  $\rightarrow$  Heterorresistência**
3.  **$>$  inóculo  $\rightarrow >$  frequência de mutantes**





Colistin heteroresistance in carbapenemase-producing *Klebsiella pneumoniae*

Georgios Meletis<sup>1\*</sup>, Egki Tzampaz<sup>1</sup>, Effrosyni Sianou<sup>1</sup>, Ioannis Tzavaras<sup>2</sup> and Danai Sofianou<sup>1</sup>

*J Antimicrob Chemother* 2011

Strain	Colistin treatment	Carbapenemase type	Broth MIC (mg/L)	Highest concentration of growth in BAPs (mg/L)	Proportion of resistant subpopulation	Resistant colonies MIC before daily passages onto colistin-free medium (mg/L)	Resistant colonies MIC after 2 week daily passages onto colistin-free medium (mg/L)	Susceptibility	PFGE group
1	yes	VIM-1	2	8	$1.7 \times 10^{-5}$	32	16	heteroresistant	A
2	yes	VIM-1	2	8	$1.5 \times 10^{-5}$	32	16	heteroresistant	
9	no	VIM-1	1	8	$1.2 \times 10^{-6}$	32	64	heteroresistant	B
3	yes	KPC	2	8	$2 \times 10^{-6}$	32	16	heteroresistant	
6	yes	KPC	1	8	$3.6 \times 10^{-7}$	32	16	heteroresistant	C
12	no	KPC	1	8	$3.5 \times 10^{-5}$	32	NA	resistant	
17	no	KPC	1	8	$3.5 \times 10^{-5}$	32	NA	resistant	D
18	no	KPC	1	8	$3.5 \times 10^{-5}$	32	32	heteroresistant	
19	no	KPC	1	8	$3.5 \times 10^{-5}$	32	16	heteroresistant	E
8	yes	KPC	1	8	$3.5 \times 10^{-5}$	32	NA	resistant	
5	yes	KPC	4	8	$3.5 \times 10^{-5}$	32	NA	resistant	ND
7	yes	KPC	4	8	$3.5 \times 10^{-5}$	32	NA	resistant	
13	no	VIM-1	4	8	$3.5 \times 10^{-5}$	32	32	heteroresistant	ND
10	no	VIM-1	2	8	$3.5 \times 10^{-5}$	32	16	heteroresistant	
20	no	VIM-1	2	8	$3.5 \times 10^{-5}$	32	16	heteroresistant	ND
4	yes	KPC	4	8	$3.5 \times 10^{-5}$	32	NA	resistant	
11	no	KPC	0.5	0.5	NA	NA	NA	susceptible	ND
14	no	KPC	0.5	0.5	NA	NA	NA	susceptible	
15	no	KPC	0.5	0.5	NA	NA	NA	susceptible	ND
16	no	VIM-1	0.5	0.5	NA	NA	NA	susceptible	

Bacteria	PFGE	Original PMB MIC (mg/L)	Highest concentration where growth occurred in PAP (mg/L)	Frequency (%) of appearance of subpopulations	MIC PMB 4 days daily passages in drug -free medium (mg/L)	MIC PMB 2 months storage (mg/L)	MIC PMB 6 months storage (mg/L)
<i>E. cloacae</i>	E1	0.125	1	NA	≤ 0.125	NP	NP
<i>E. cloacae</i>	E2a	0.125	1	NA	≤ 0.125	NP	NP
<i>E. cloacae</i>	E2b	0.125	1	NA	≤ 0.125	NP	NP
<i>K. pneumoniae</i>	K1	0.125	3	0.000087 (10 <sup>-7</sup> )	4	4	2
<i>K. pneumoniae</i>	K2	0.0625	2	0.00025 (10 <sup>-6</sup> )	16	16	16
<i>K. pneumoniae</i>	K3	0.125	8	0.00015 (10 <sup>-6</sup> )	16	16	16
<i>K. pneumoniae</i>	K4	0.25	3	0.00036 (10 <sup>-6</sup> )	2	2	2
<i>E. coli</i>	C1	≤ 0.03	0,5	NA	≤ 0.125	NP	NP

Bacteria	PFGE	Original PMB MIC (mg/L)	Highest concentration where growth occurred in PAP (mg/L)	Frequency (%) of appearance of subpopulations	MIC PMB 4 days daily passages in drug -free medium (mg/L)	MIC PMB 2 months storage (mg/L)	MIC PMB 6 months storage (mg/L)
<i>E. cloacae</i>	E1	0.125	1	NA	≤ 0.125	NP	NP
<i>E. cloacae</i>	E2a	0.125	1	NA	≤ 0.125	NP	NP
<i>E. cloacae</i>	E2b	0.125	1	NA	≤ 0.125	NP	NP
<i>K. pneumoniae</i>	K1	0.125	3	0.000087 (10 <sup>-7</sup> )	4	4	2
<i>K. pneumoniae</i>	K2	0.0625	2	0.00025 (10 <sup>-6</sup> )	16	16	16
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<i>K. pneumoniae</i>	K4	0.25	3	0.00036 (10 <sup>-6</sup> )	2	2	2
<i>E. coli</i>	C1	≤ 0.03	0,5	NA	≤ 0.125	NP	NP

# Mutant prevention concentrations of colistin for *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* clinical isolates

Myung-Jin Choi and Kwan Soo Ko\*

*J Antimicrob Chemother* 2014

Species/isolate	Colistin MIC (mg/L)	Colistin MPC (mg/L)	Amino acid alterations				
			PmrB	PhoP	PhoQ	ParR	ParS
<i>A. baumannii</i>							
C072	0.5	>128	P233S	NA	NA	NA	NA
<i>P. aeruginosa</i>							
P1	2	64				N24S	
P10	2	>128					Q232E
P29	1	64					G361R
P70	2	>128	V281I		K123E		
P83	1	>128				L18I, S24N	
P88	2	64		N188H			G361R
P112	2	64				Syn	
P147	2	128			Syn		
P155	1	>128			R214H		
P179	2	128			V184G		
P185	2	128	V281I		Q133E		
P199	2	128			A207R		
P206	2	128	Syn		N104I		
P213	2	128	F237L				
<i>K. pneumoniae</i>							
513 BTB	0.5	>128	Δ3 nt position 14			NA	NA
507 BTB	0.5	>128	T157P			NA	NA
08-u-899		>128	S208N, Δ3 nt position 209			NA	NA
K08-Bact-08-039	4	>128			S174N	NA	NA
YDJ	0.5	>128	T157P			NA	NA

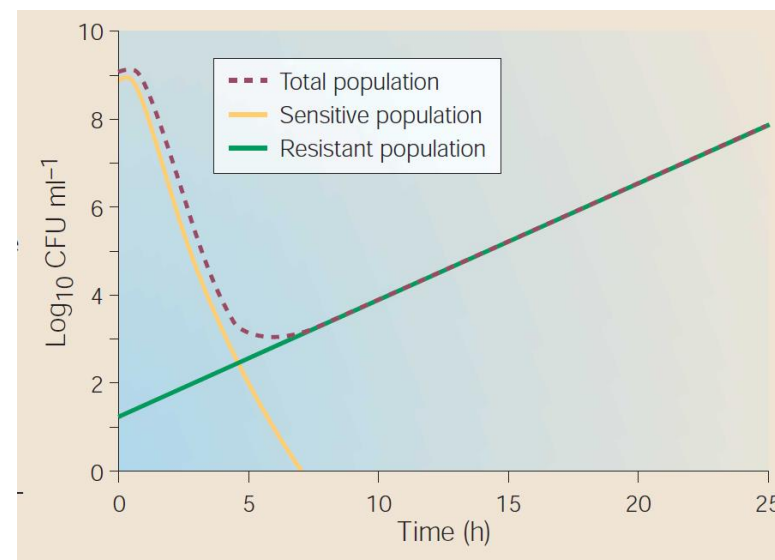
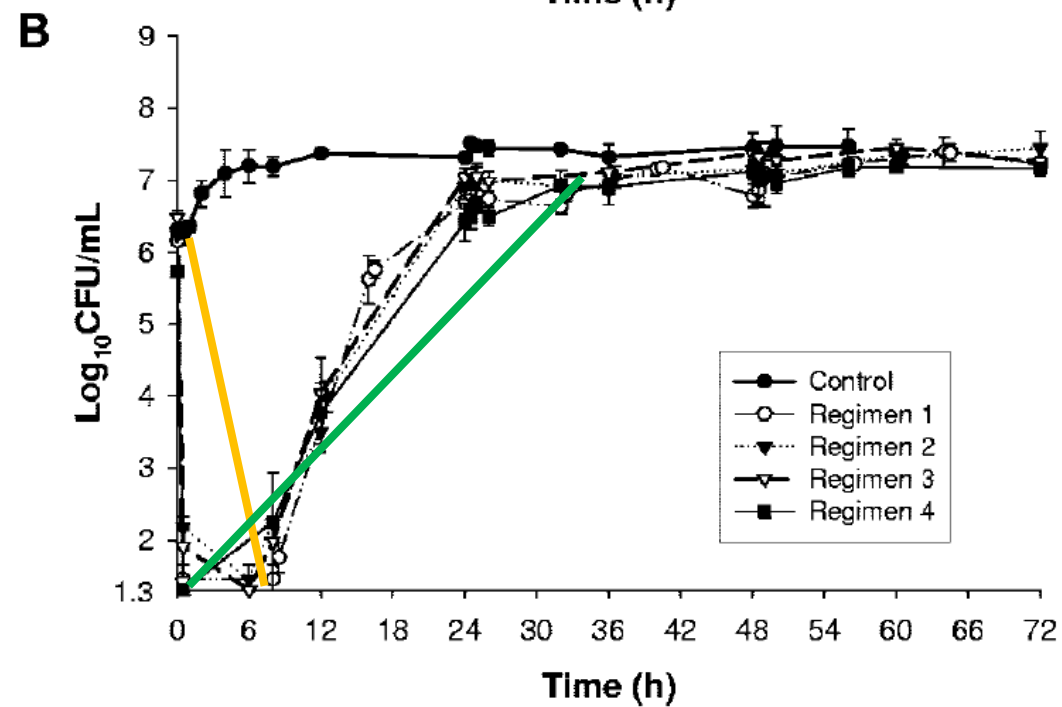
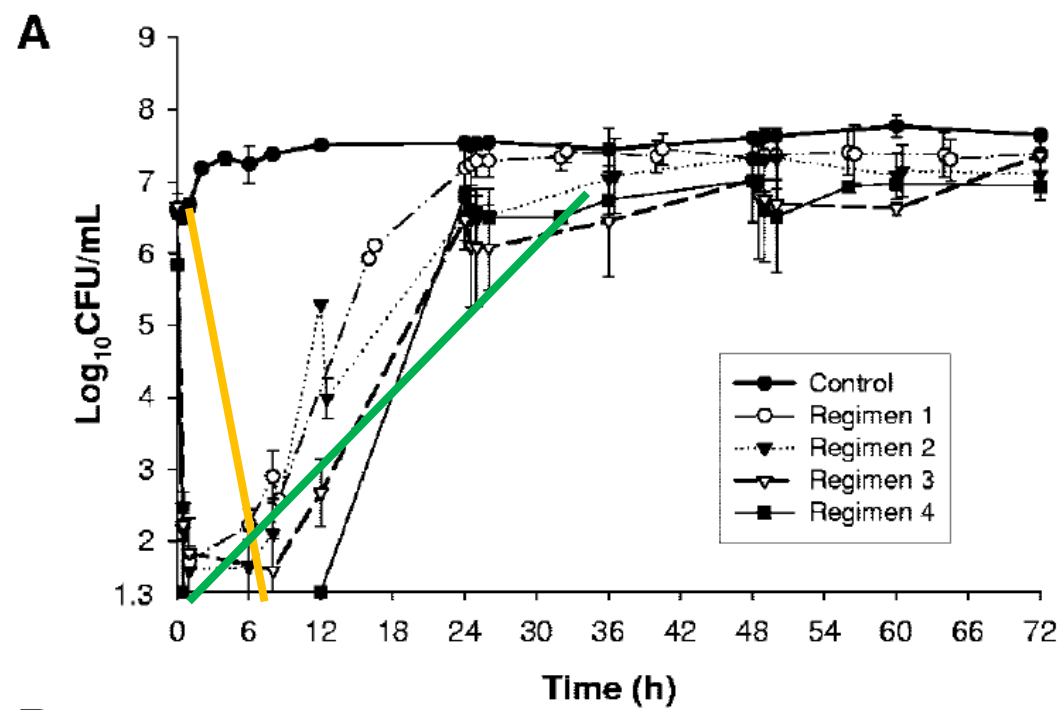
# Activity of Colistin against Heteroresistant *Acinetobacter baumannii* and Emergence of Resistance in an In Vitro Pharmacokinetic/Pharmacodynamic Model<sup>∇</sup>

Chun-Hong Tan, Jian Li, and Roger L. Nation\*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2007

- **Concentrações livres ≈5mg/kg/dia**
- **A) *A. baumannii* – clínico**
- **B) *A. baumannii* - ATCC**
- **MIC colistina = 1mg/L**

	8/8h	12/12h	24/24h	IC
Parameter	Result for:			
	Regimen 1	Regimen 2	Regimen 3	Regimen 4
Loading dose (mg)	0.30	0.45	0.90	NA <sup>b</sup>
Maintenance dose (mg)	0.23	0.39	0.89	NA <sup>b</sup>
Dosage interval (h)	8	12	24	NA <sup>b</sup>
Target $C_{\max}$ (μg/ml)	3.0	4.5	9.0	NA <sup>b</sup>
Target $C_{\min}$ (μg/ml)	0.75	0.56	0.14	NA <sup>b</sup>
Target $C_{ss}$ (μg/ml)	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	4.5



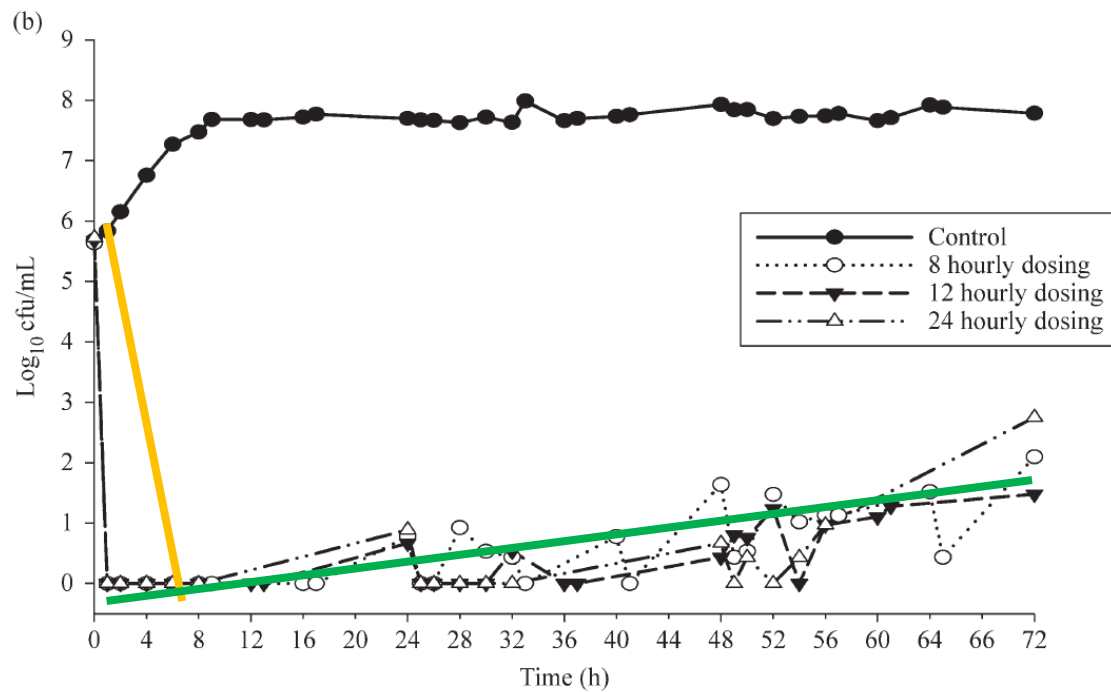
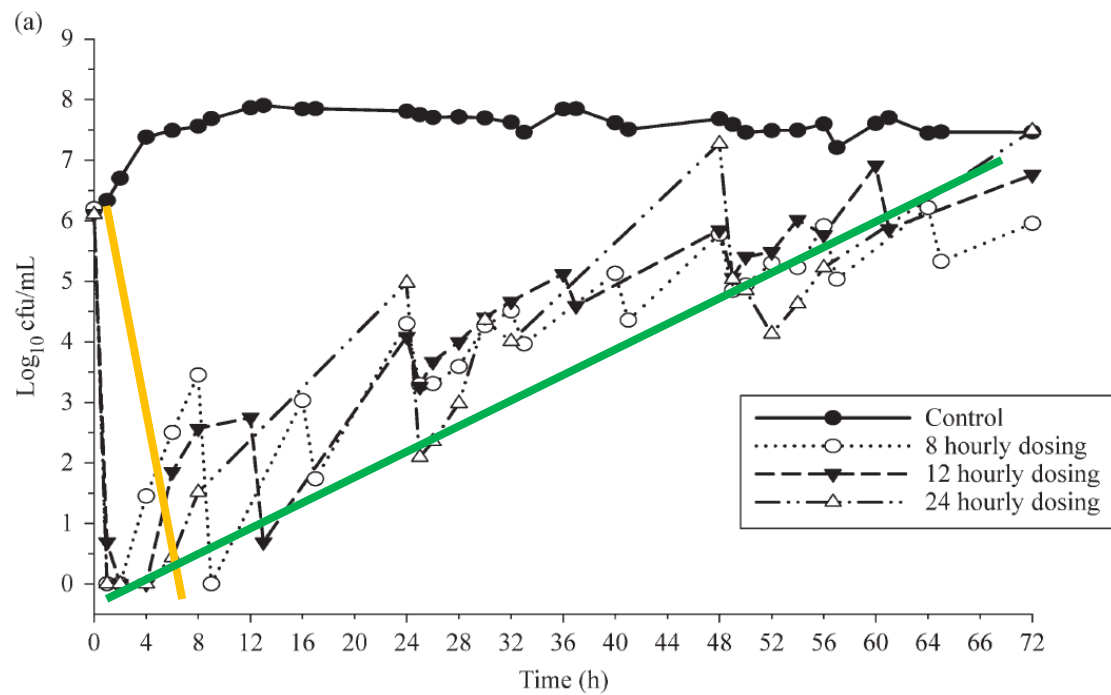
# Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: studies with *Pseudomonas aeruginosa* in an *in vitro* pharmacodynamic model

Phillip J. Bergen<sup>1</sup>, Jian Li<sup>1</sup>, Roger L. Nation<sup>1\*</sup>, John D. Turnidge<sup>2</sup>, Kingsley Coulthard<sup>3,4</sup>  
and Robert W. Milne<sup>4</sup>

*Journal of Antimicrobial Chemotherapy* (2008)

- **Concentrações livres ≈5mg/kg/dia**
- **A) *P. aeruginosa* – ATCC (MIC colistina = 1mg/L)**
- **B) *P. aeruginosa* – clínico (MIC colistina = 1mg/L)**

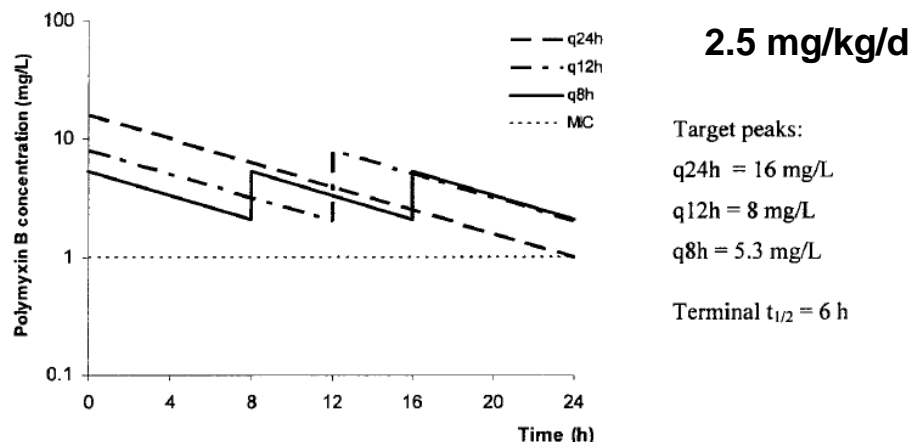
	8 hourly dosing	12 hourly dosing	24 hourly dosing
Loading dose (mg)	0.30	0.45	0.90
Maintenance dose (mg)	0.23	0.39	0.89
Target $C_{\max}/C_{\min}$ (mg/L)	3.0/0.75	4.5/0.56	9.0/0.14
ATCC 27853/clinical isolate 19056			
AUC/MIC <sup>a</sup>	39.0/77.9	45.4/91.0	51.1/102.3
$C_{\max}/MIC^a$	3.0/6.0	4.5/9.0	9.0/18.0
$t > MIC^a$	79.3/100	72.3/100	52.8/69.5



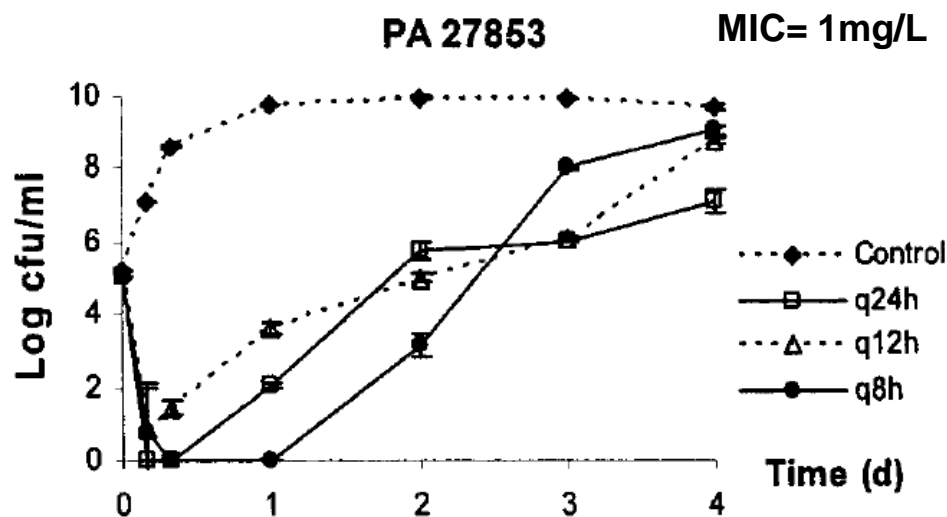
# Pharmacodynamics of Polymyxin B against *Pseudomonas aeruginosa*

Vincent H. Tam,<sup>1\*</sup> Amy N. Schilling,<sup>1</sup> Giao Vo,<sup>1</sup> Samer Kabbara,<sup>1</sup> Andrea L. Kwa,<sup>2</sup>  
Nathan P. Wiederhold,<sup>1†</sup> and Russell E. Lewis<sup>1</sup>

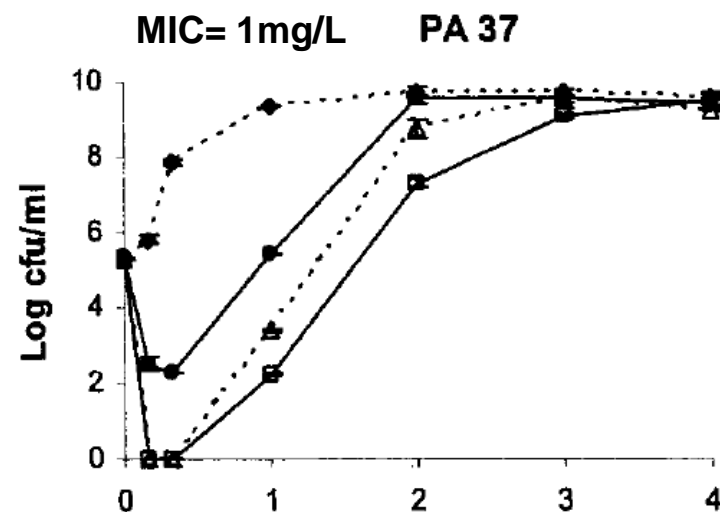
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2005

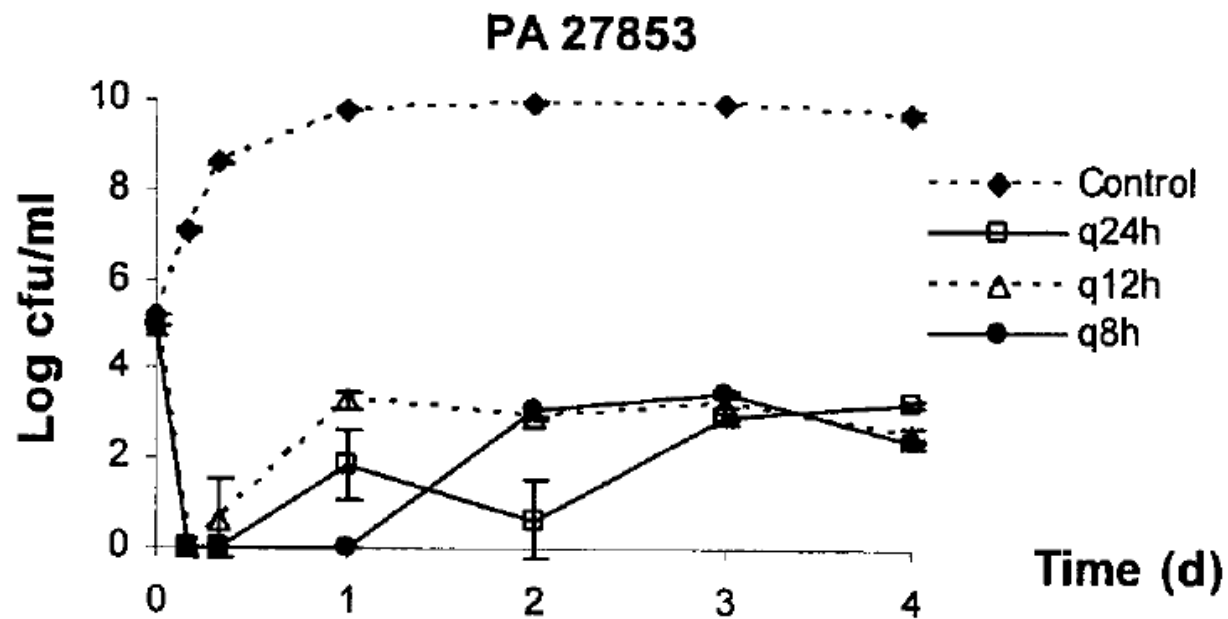
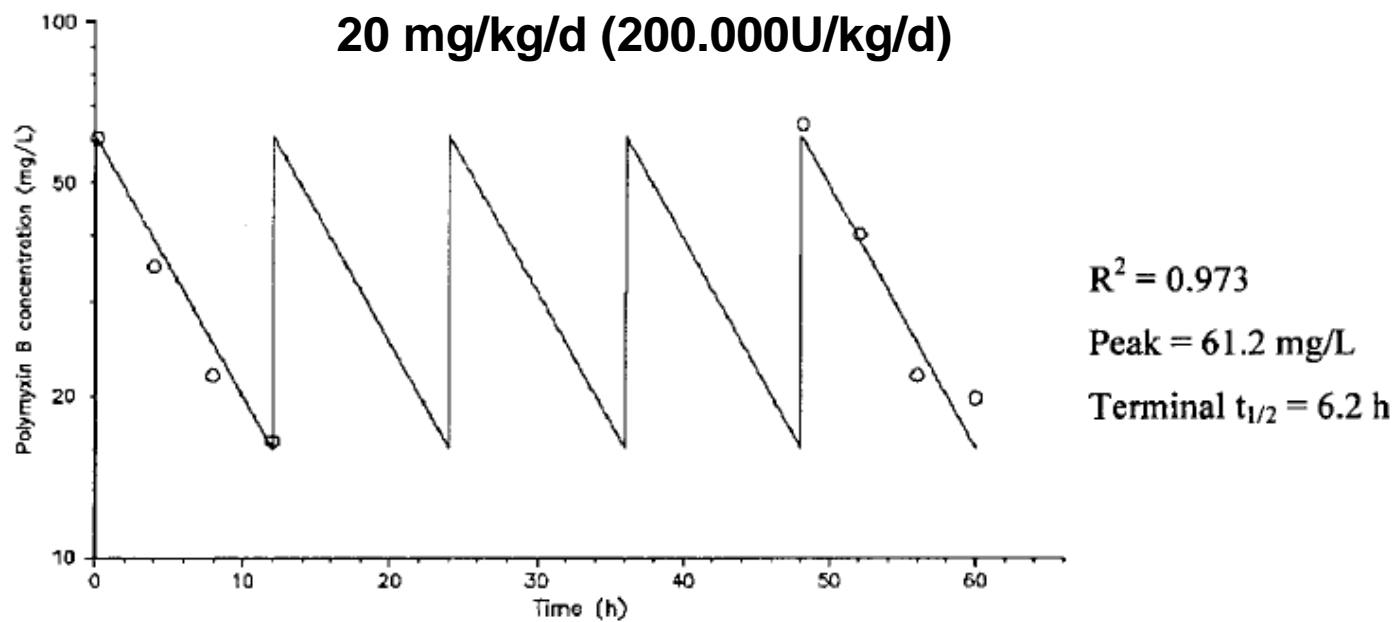


A



B





# **Otimizando a terapia para minimizar resistência**

- **É possível, ao mesmo tempo, otimizar dosagem de forma a melhorar atividade, reduzir o potencial de seleção e minimizar toxicidade?**

Day	C <sub>max</sub> (mg/L)	
	P <sub>10</sub>	P <sub>50</sub>
Day 1	2.59	5.17
Day 4	4.34	7.09
Day 1	3.06	5.71
Day 4	4.35	7.06
Day 1	3.11	6.21
Day 4	5.20	8.51
Day 1	3.95	7.39
Day 4	5.40	8.76

Day	C <sub>max</sub> (mg/L) <sup>b</sup>		
	P <sub>10</sub>	P <sub>50</sub>	P <sub>90</sub>
Day 1 ←	2.59	5.17	9.38
Day 4	4.34	7.09	11.3
2 mg/kg loading as 2			
Day 1 ←	3.06	5.71	10.5
Day 4	4.35	7.06	11.3
Day 1 ←	3.11	6.21	11.25
Day 4	5.20	8.51	13.56
2.5 mg/kg loading as			
Day 1 ←	3.95	7.39	13.5
Day 4	5.40	8.76	14.0

24 hours (mg·h/L)	
P <sub>50</sub>	P <sub>90</sub>
46.4	81.1
72.0	114
61.7	108
72.7	115
55.7	97.3
86.4	137.3
78.9	137.9
90.4	142.7

**O que fazer?**

**O que não fazer...**

✓ **Descontaminação**  
**Seletiva do Trato**  
**Gastrointestinal com**  
**polimixinas**



Short Communication

Rapid emergence of secondary resistance to gentamicin and colistin following selective digestive decontamination in patients with KPC-2-producing *Klebsiella pneumoniae*: a single-centre experience

Christoph Lübbert<sup>a,\*</sup>, Sarah Fauchoux<sup>b</sup>, Diana Becker-Rux<sup>c</sup>, Sven Laudi<sup>c</sup>, Axel Dürrbeck<sup>d</sup>, Thilo Busch<sup>c</sup>, Petra Gastmeier<sup>e</sup>, Tim Eckmanns<sup>f</sup>, Arne C. Rodloff<sup>g</sup>, Udo X. Kaisers<sup>c</sup>

<sup>a</sup> Division of Infectious Diseases and Tropical Medicine, Department of Gastroenterology and Rheumatology, Leipzig University Hospital, Liebigstr. 20,



Emergence of Colistin Resistance in *Enterobacteriaceae* after the Introduction of Selective Digestive Tract Decontamination in an Intensive Care Unit

Teyssir Halaby,<sup>a</sup> Nashwan al Naiemi,<sup>a,b</sup> Jan Kluytmans,<sup>b,c</sup> Job van der Palen,<sup>d</sup> Christina M. J. E. Vandenbroucke-Grauls<sup>b</sup>



CASE REPORT

Emergence of OXA-48 and OXA-181 Carbapenemases among *Enterobacteriaceae* in South Africa and Evidence of *In Vivo* Selection of Colistin Resistance as a Consequence of Selective Decontamination of the Gastrointestinal Tract

Adrian J. Brink,<sup>a</sup> Jennifer Coetzee,<sup>b</sup> Craig Corcoran,<sup>b</sup> Cornelis G. Clay,<sup>b</sup> Danusha Hari-Makkan,<sup>b</sup> Rachael K. Jacobson,<sup>c</sup> Guy A. Richards,<sup>d</sup> Charles Feldman,<sup>e</sup> Louise Nutt,<sup>f</sup> Johan van Greune,<sup>g</sup> J. D. Deetlefs,<sup>g</sup> Karin Swart,<sup>h</sup> Lesley Devenish,<sup>h</sup> Laurent Poirer,<sup>i</sup> Patrice Nordmann<sup>i</sup>

# Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus



Roger L Nation, Jian Li, Otto Cars, William Couet, Michael N Dudley, Keith S Kaye, Johan W Mouton, David L Paterson, Vincent H Tam, Ursula Theuretzbacher, Brian T Tsuji, John D Turnidge

*Lancet Infect Dis* 2014

## Inappropriate use of polymyxins

An area of concern with polymyxins is their clinical use in some parts of the world for selective decontamination of the digestive tract (SDD) of patients.<sup>48,49</sup> This exposes gut flora to polymyxin and has been reported to lead to rapid emergence of resistance to these last-line antibiotics.<sup>48</sup> If SDD is undertaken, alternatives to polymyxins should be used.

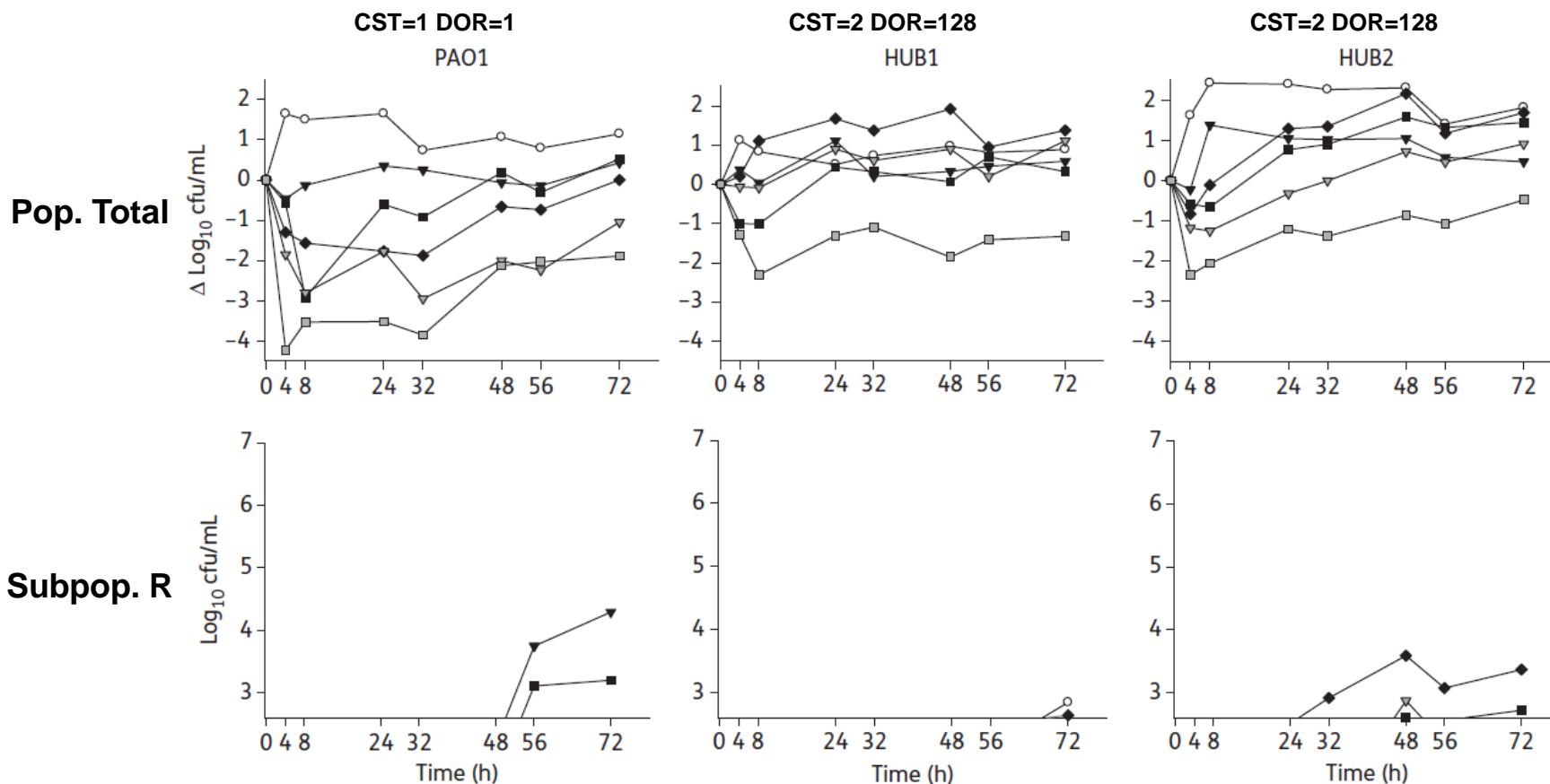
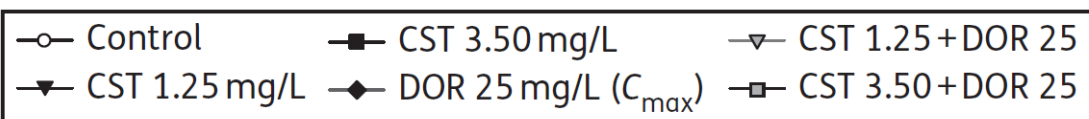
# O que fazer?

1. Evitar Transmissão Horizontal
2. Prescrever dose mais alta possível.
3. Dose de ataque!
4. **SEMPRE** combinar com um segundo antimicrobiano quando houver sensibilidade *in vitro* (MICs próximos do *breakpoint*), preferencialmente  $\beta$ -lactâmicos.
5. **SEMPRE (?)** usar terapia combinada, principalmente imunossuprimidos → particularmente neutropênicos!

# Activity of colistin combined with doripenem at clinically relevant concentrations against multidrug-resistant *Pseudomonas aeruginosa* in an *in vitro* dynamic biofilm model

Jaime Lora-Tamayo<sup>1,2</sup>, Oscar Murillo<sup>2</sup>, Phillip J. Bergen<sup>3</sup>, Roger L. Nation<sup>1</sup>, Anima Poudyal<sup>1</sup>, Xianling Luo<sup>1</sup>, Heidi Y. Yu<sup>1</sup>, Javier Ariza<sup>2</sup> and Jian Li<sup>1\*</sup>

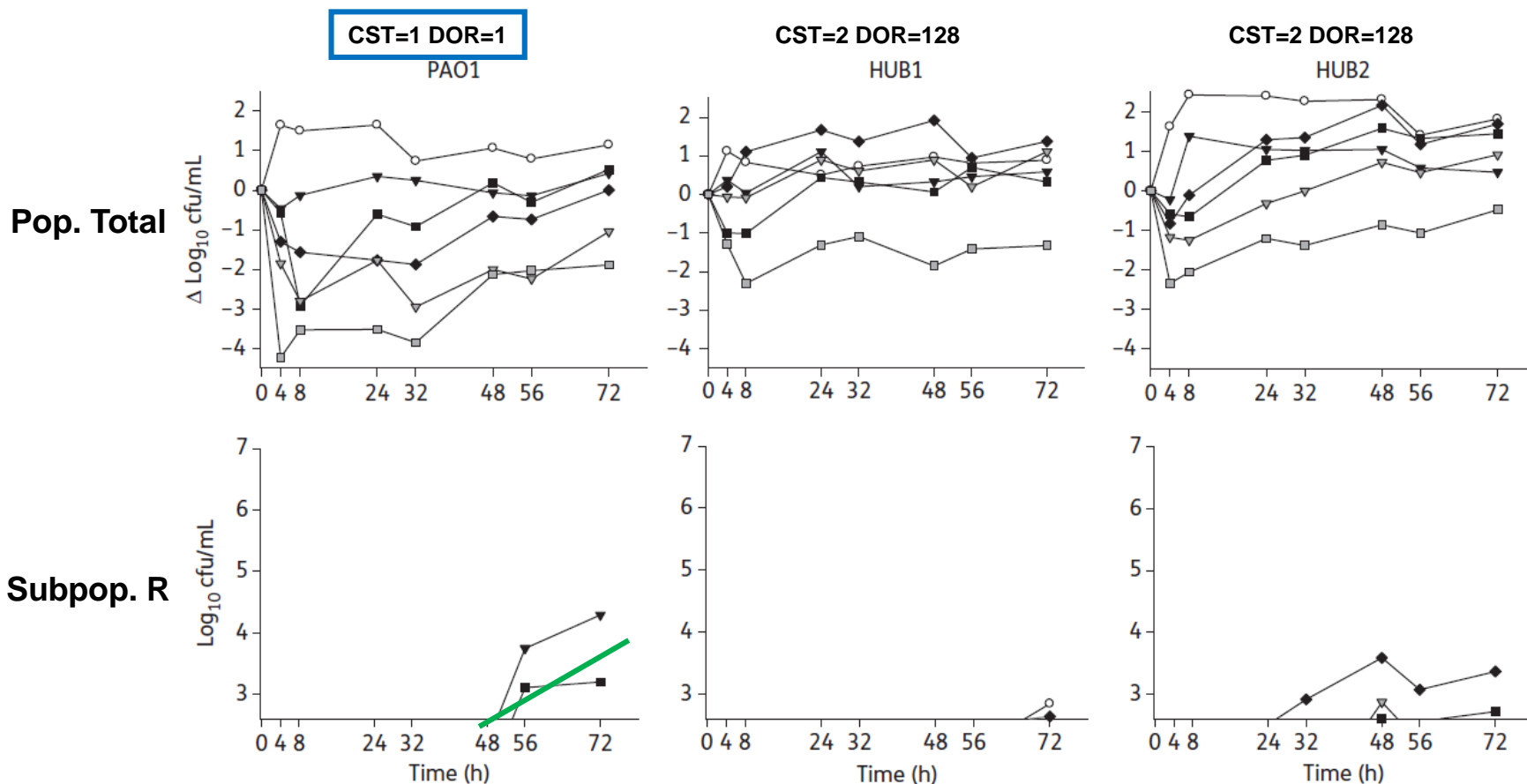
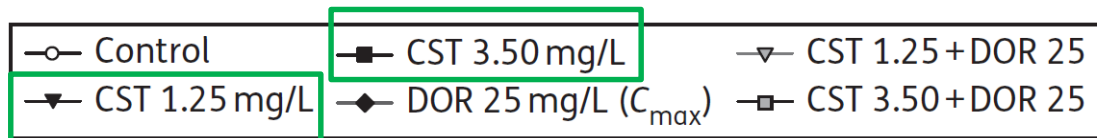
*J Antimicrob Chemother* 2014



# Activity of colistin combined with doripenem at clinically relevant concentrations against multidrug-resistant *Pseudomonas aeruginosa* in an *in vitro* dynamic biofilm model

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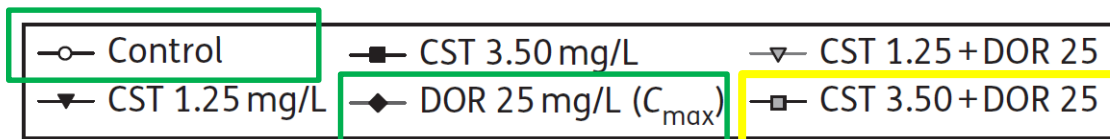
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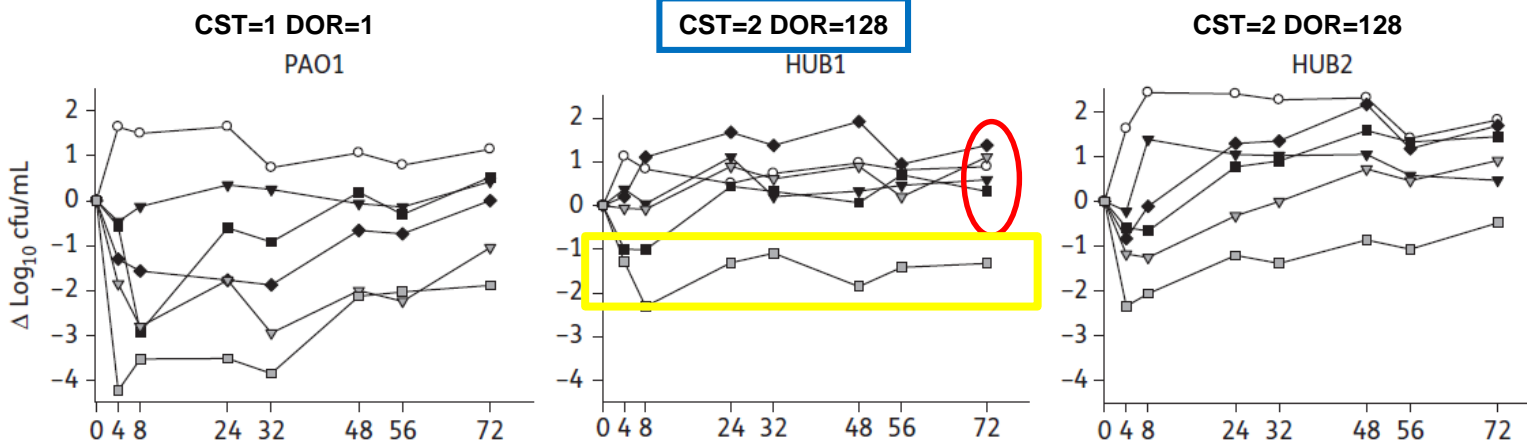
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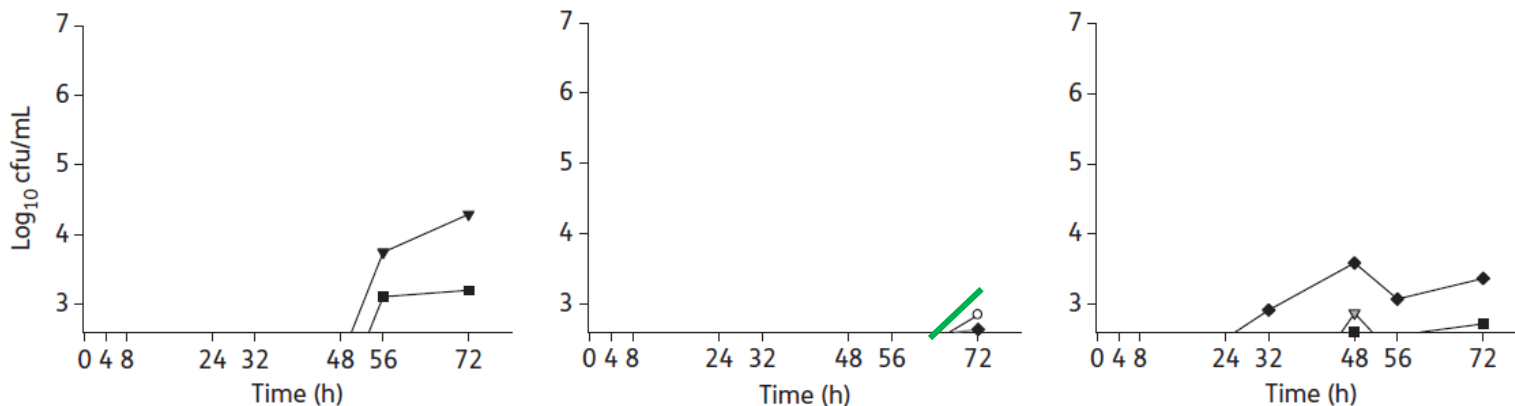
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Pop. Total



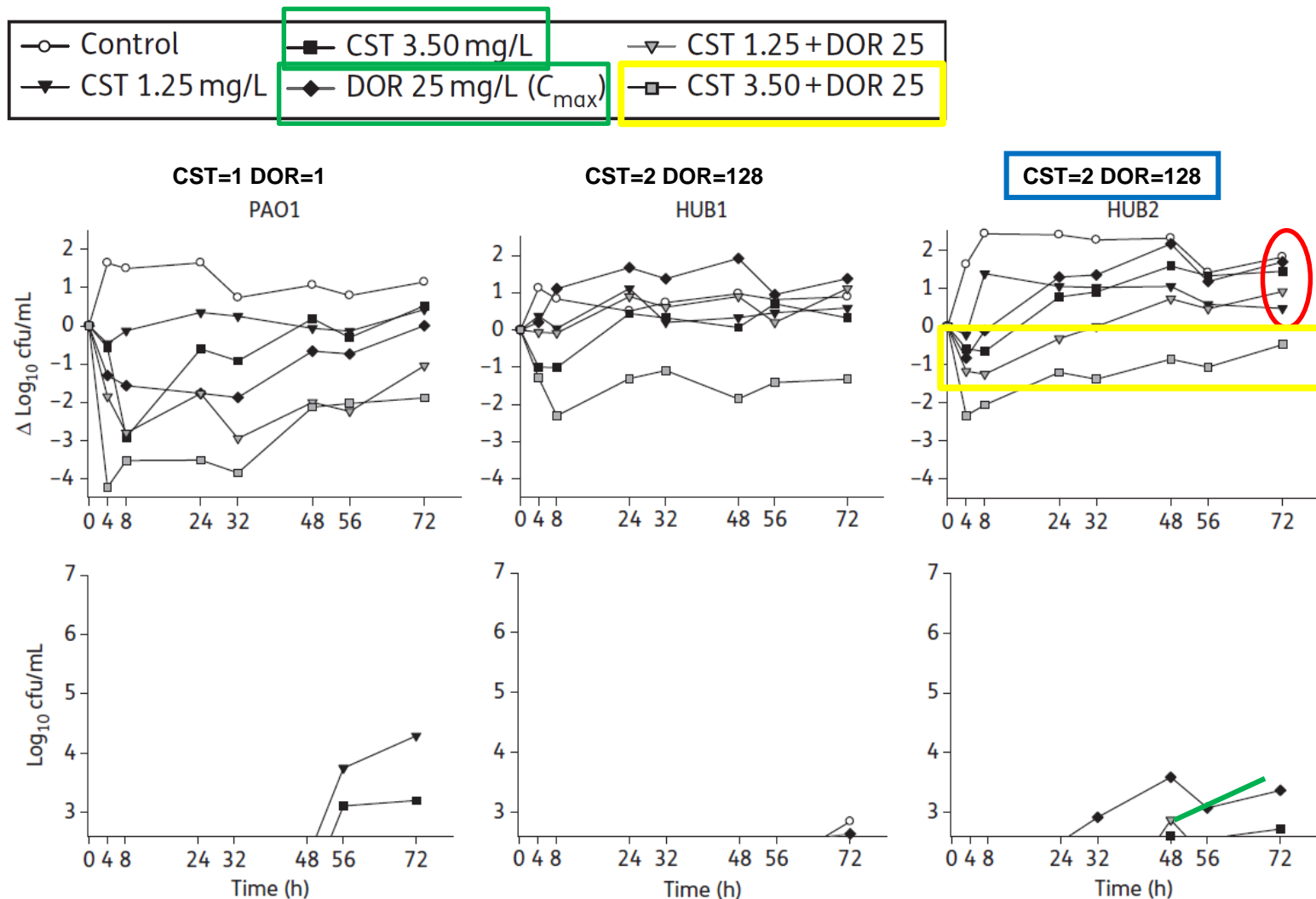
Subpop. R



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# O que fazer?

1. Evitar Transmissão Horizontal
2. Prescrever dose mais alta possível.
3. Dose de ataque!
4. SEMPRE combinar com um segundo antimicrobiano quando houver sensibilidade *in vitro* (MICs próximos do *breakpoint*), preferencialmente  $\beta$ -lactâmicos.
5. SEMPRE usar terapia combinada, principalmente imunossuprimidos → particularmente neutropênicos!



# Resistência à polimixina, é possível prevenir?

## SIM

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