

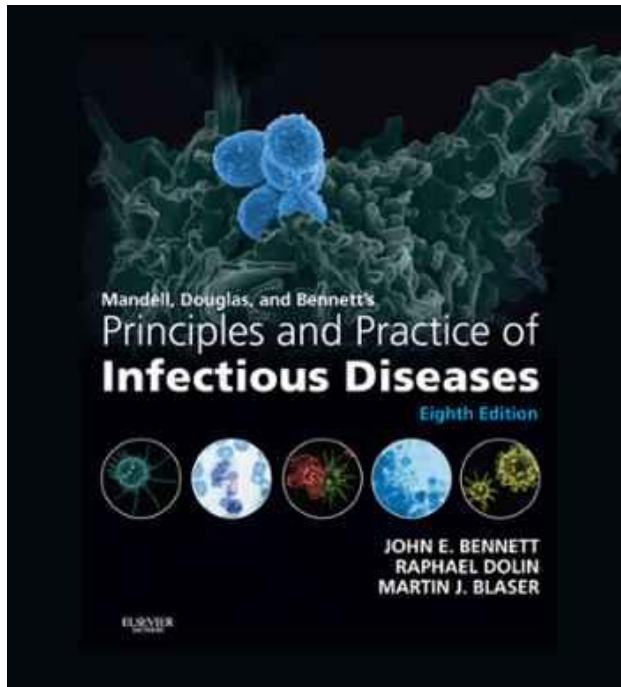
# **Polimixinas: *Desafios para estudos clínicos***

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**NENHUM CONFLITO DE  
INTERESSE**



*“Devido a altas taxas de toxicidade, a uma estratégia de dose ainda indefinida, e a questionáveis limiares de suscetibilidade, formulações parenterais de colistimetato e polimixina B devem ser reservados uso quando nenhuma outra droga menos tóxica ou potencialmente mais efetiva está disponível”*

(Kaye et al, 2015)

# NENHUM CONSOLO TAMBÉM

# Mais dúvidas que certezas...

Uso empírico?

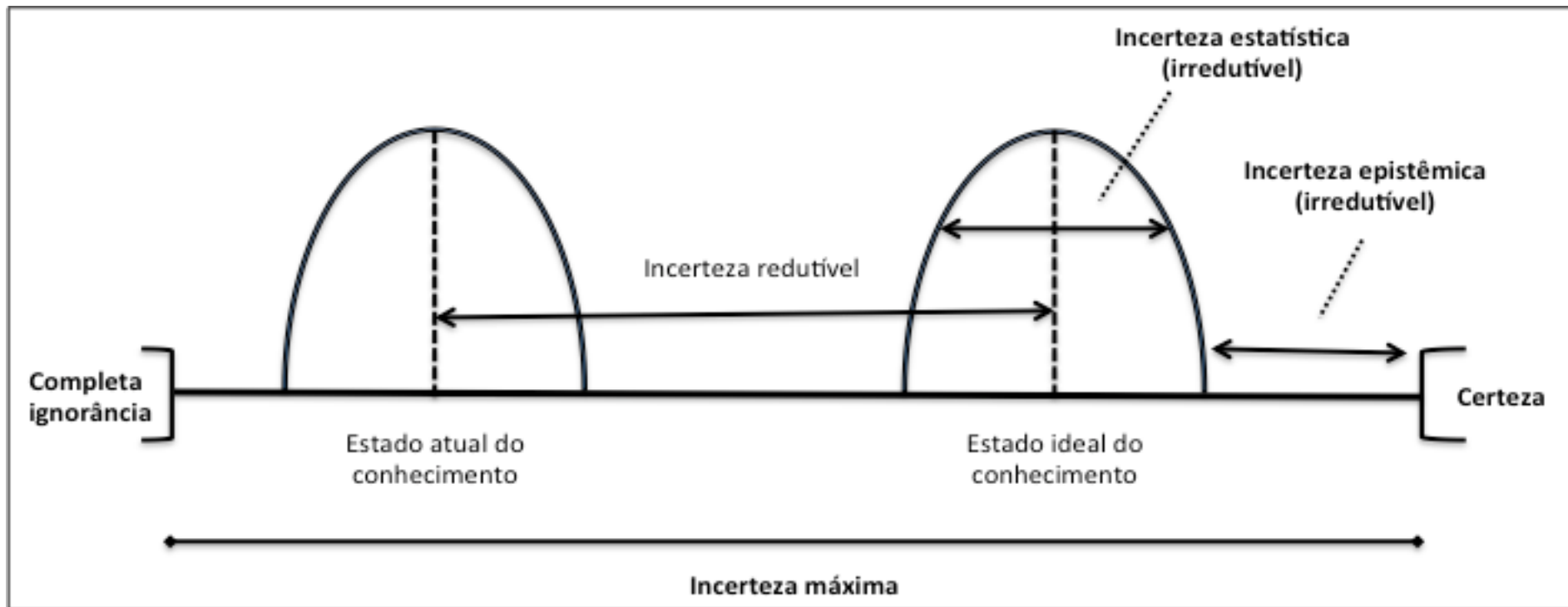
Monoterapia ou terapia combinada?

Posologia

Ajustes para obesidade e função renal

Eficácia / Efetividade

# Incerteza em medicina clínica



*Djulfbegovic et al. Uncertainty in clinical medicine. In: Gifford F (Ed) Philosophy of medicine. Oxford: Elsevier, 2012*

**ENORMES ESFORÇOS...**

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

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

Clinical Infectious Diseases 2013;57(4):524–31

**Table 2. Population Pharmacokinetic Parameter Estimates, Between-Subject Variability, and Precision of Estimates<sup>a</sup>**

Parameter (Unit)	Population Estimate	Between-Subject Variability (%CV)	Standard Error (%SE)
CL (L/h/kg) <sup>b</sup>	0.0276	32.4	7.49
V1 (L/kg)	0.0939	73.3	23.6
V2 (L/kg)	0.330	70.1	19.5
CLic (L/h/kg)	0.146	50.4	22.2
SD <sub>intercept</sub> (mg/L)	0.0392		
SD <sub>slope</sub>	9.59%		

Abbreviations: CL, total body clearance; CLic, intercompartmental clearance; CV, coefficient of variation; SD<sub>intercept</sub>, additive residual error; SD<sub>slope</sub>, proportional residual error; SE, standard error; V1, central volume of distribution; V2, peripheral volume of distribution.

# **ALTERNATIVAS INESPERADAS**

# Clinical Experience of Colistin-Glycopeptide Combination in Critically Ill Patients Infected with Gram-Negative Bacteria

Nicola Petrosillo,<sup>a</sup> Maddalena Giannella,<sup>a</sup> Massimo Antonelli,<sup>b</sup> Marlo Antonini,<sup>c</sup> Bruno Barsic,<sup>d</sup> Laura Belancic,<sup>d</sup> Cagkan Inkaya A.,<sup>e</sup> Gennaro De Pascale,<sup>b</sup> Elisabetta Grilli,<sup>a</sup> Marlo Tumbarello,<sup>f</sup> Murat Akova<sup>e</sup>

February 2014 Volume 58 Number 2

Antimicrobial Agents and Chemotherapy p. 851–858

184 sujeitos

TABLE 7 Cox regression analysis of risk factors for 30-day mortality among patients with infection due to MDR *A. baumannii*<sup>a</sup>

Parameter	Univariate analysis		Multivariate analysis <sup>b</sup>	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (0.99–1.03)	0.16		
Male sex	1.55 (0.75–3.23)	0.24		
<b>Charlson index</b>	<b>1.27 (1.08–1.48)</b>	<b>0.003</b>	<b>1.18 (0.99–1.39)</b>	<b>0.06</b>
<b>APACHE II score</b>	<b>1.06 (1.01–1.11)</b>	<b>0.01</b>	<b>1.05 (0.99–1.11)</b>	<b>0.97</b>
VAP	0.92 (0.42–2.03)	0.84		
BSI	1.56 (0.65–3.93)	0.31		
Coinfection with a GPB	0.46 (0.17–1.21)	0.12		
Colistin alone	1.34 (0.61–2.95)	0.46		
Colistin plus a glycopeptide	0.90 (0.41–1.98)	0.79		
Colistin plus other anti-GNB drugs	0.67 (0.23–1.92)	0.45		
Colistin plus other anti-GNB drugs plus a glycopeptide	1.11 (0.47–2.60)	0.81		
Combination including a glycopeptide for ≥48 h	0.98 (0.47–2.05)	0.97		
Days of combination with a glycopeptide	0.94 (0.88–1.01)	0.09		
<b>Combination with a glycopeptide for ≥5 days</b>	<b>0.44 (0.19–0.99)</b>	<b>0.05</b>	<b>0.41 (0.17–0.98)</b>	<b>0.04</b>
Nephrotoxicity	0.61 (0.18–2.02)	0.42		

<sup>a</sup> Abbreviations: VAP, ventilator-associated pneumonia; BSI, bloodstream infection; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria. Data in bold are statistically significant.

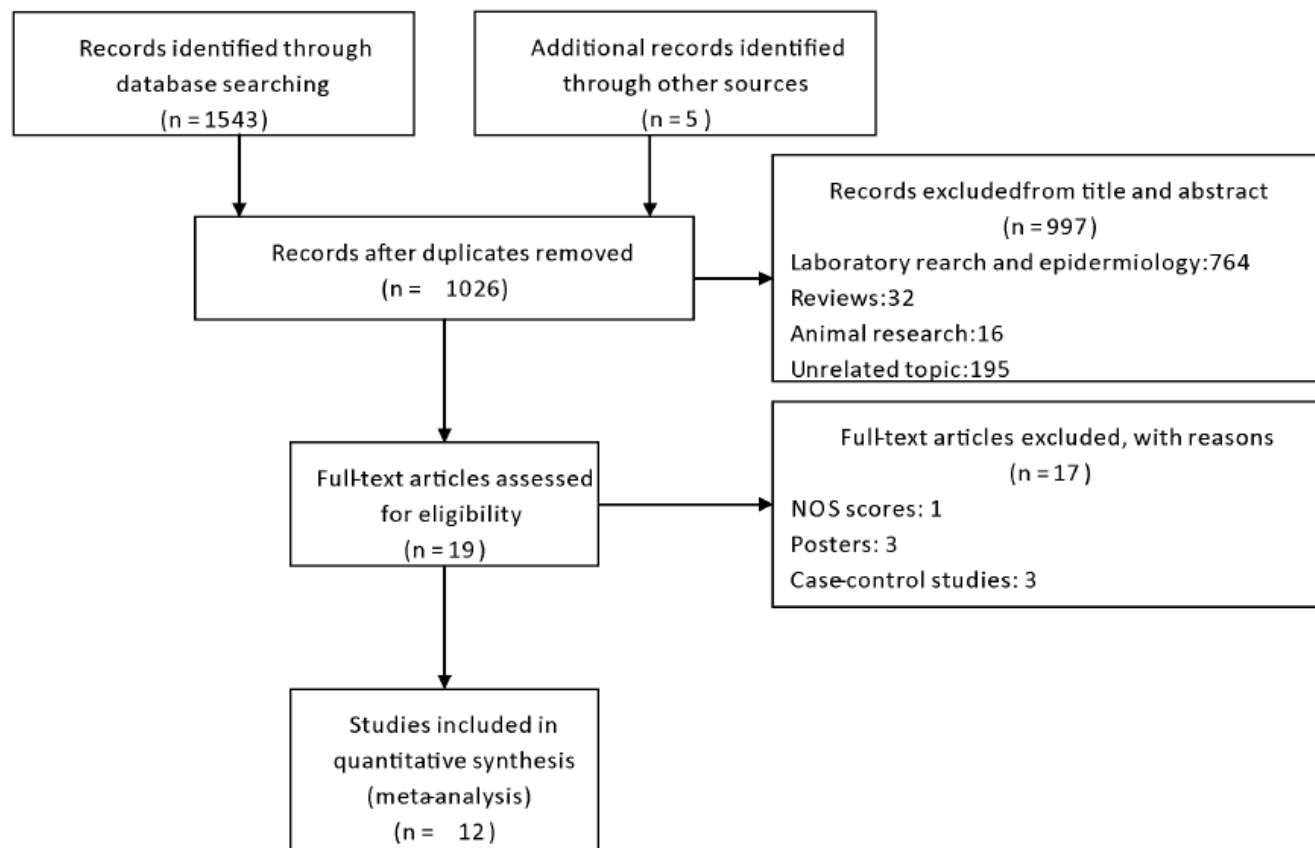
<sup>b</sup> The multivariate analysis was adjusted for age, sex, Charlson index, APACHE II score, coinfection with GPB, and combination with a glycopeptide for ≥5 days.

# **SISTEMATIZAÇÃO DA EVIDÊNCIA**

# Efficacy and Safety of Polymyxins for the Treatment of *Acinetobacter baumannii* Infection: A Systematic Review and Meta-Analysis

Qianqian Liu<sup>†1</sup>, Wenzhang Li<sup>†2</sup>, Yulin Feng<sup>3\*</sup>, Chuanmin Tao<sup>1\*</sup>

**1** Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China, **2** Department of Cardiology, First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan Province, China, **3** Department of Respiratory Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

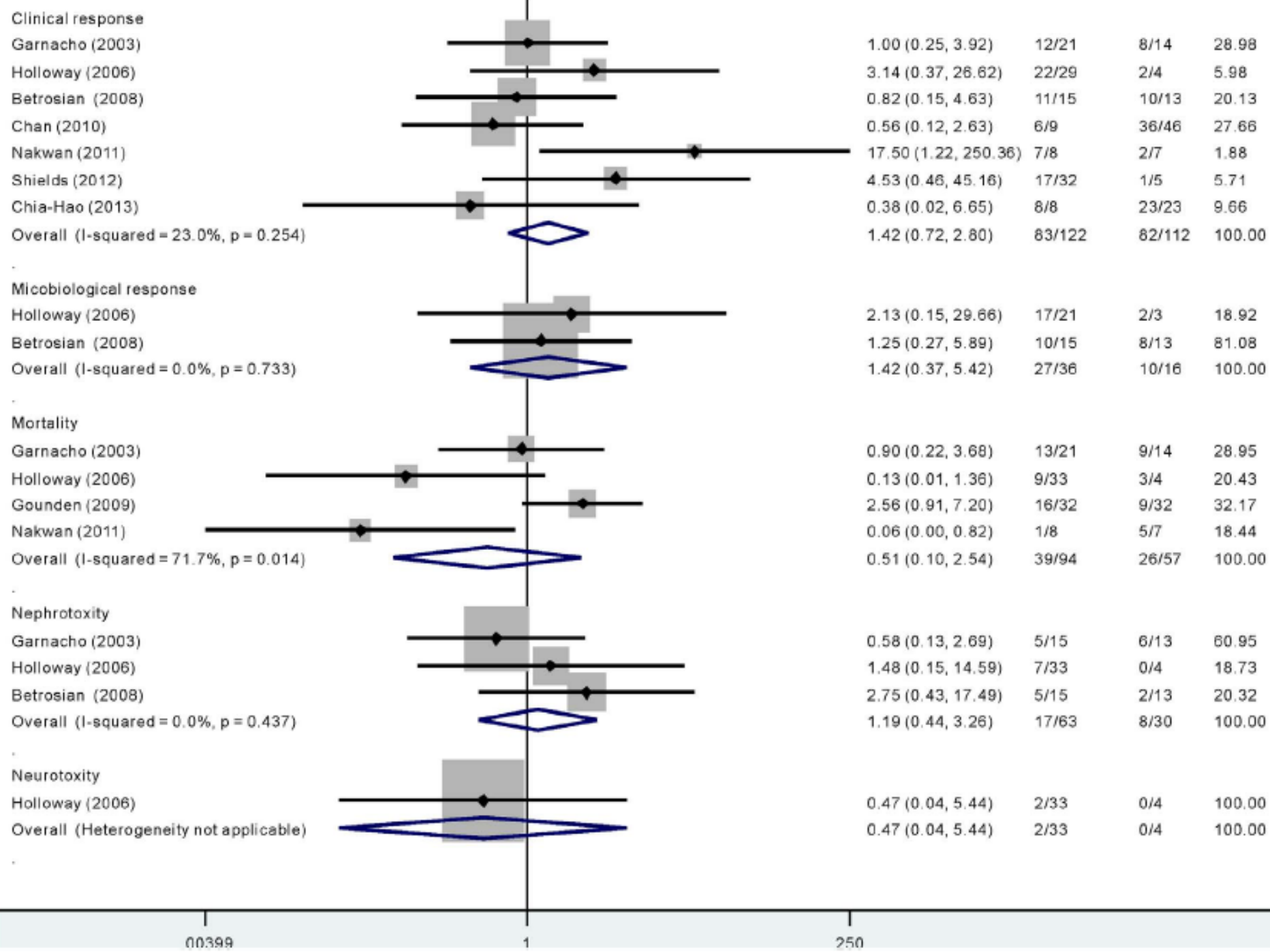


Author (Year)	Country	Type of study	Experimental group	Route of Polymyxins	(Experimental group/Control group)	Type of infection	Organisms isolated	Age (Experimental group vs Control group)	Sex (male/female)
Betrosian (2008) [20]	Greece	Prospective cohort	Colistin	intravenous	15/13	VAP	MDRAB	67±9 vs 72±5 (years)	14/14
Chan (2010) [23]	USA	Retrospective cohort	Polymyxin B or colistin	nebulized; intravenous; nebulized+ intravenous	9/46	VAP	CRAB	40 (15–87) (years)	40/15
Garnacho (2003) [19]	Spain	Prospective cohort	Colistin	intravenous	21/14	VAP	AB	56.9±13.1 vs 64.5±11 (years)	26/9
Nakwan (2011) [24]	Thailand	Retrospective cohort	Colistin	nebulized	8/7	VAP	EDRAB	38 (28–41) vs 29 (28–34) (weeks)	10/5
Shields (2012) [25]	USA	Retrospective cohort	Colistin	intravenous	32/5	VAP,VAT, Primary bacteremia	EDRAB	56 (21–80) (years)	26/15
Chia-Hao (2013) [26]	Taiwan	Retrospective cohort	Colistin	nebulized	8/23	VAP	AB	29.60±3.93 vs 29.17±2.92 (years)	13/18
Gounden (2009) [27]	South Africa	Retrospective cohort	Colistin	intravenous	32/32	BSI,RTI,SSII, meningitis, CRI,UTI	MDRAB	43.5±15.6 vs 45.6±18.2 (years)	N5
Holloway (2006) [28]	USA	Retrospective cohort	Polymyxin B	intravenous	33/4	VAP,BSI,UTI,SSI	MDRAB	41 (15–77) (years)	8/29
Aydemi (2013) [29]	Turkey	RCT	Colistin	intravenous	22/21	VAP	CRAB	61±20 (years)	30/13
Durante-Mangoni (2013) [30]	Italy	RCT	Colistin	intravenous	105/104	HAP, VAP,BSI,CIAI	EDRAB	61±15.7 vs 62±15.1 (years)	137/72
Kalin (2013) [31]	Turkey	Retrospective cohort	Colistin	intravenous	47/35	VAP	MDRAB	52 (19–96) vs 63 (20–89) (years)	54/25
Jang (2009) [32]	Korea	Retrospective cohort	Colistin	intravenous	22/19	VAP	MDRAB	62.5±17.5 vs 57.0±16.5 (years)	25/19

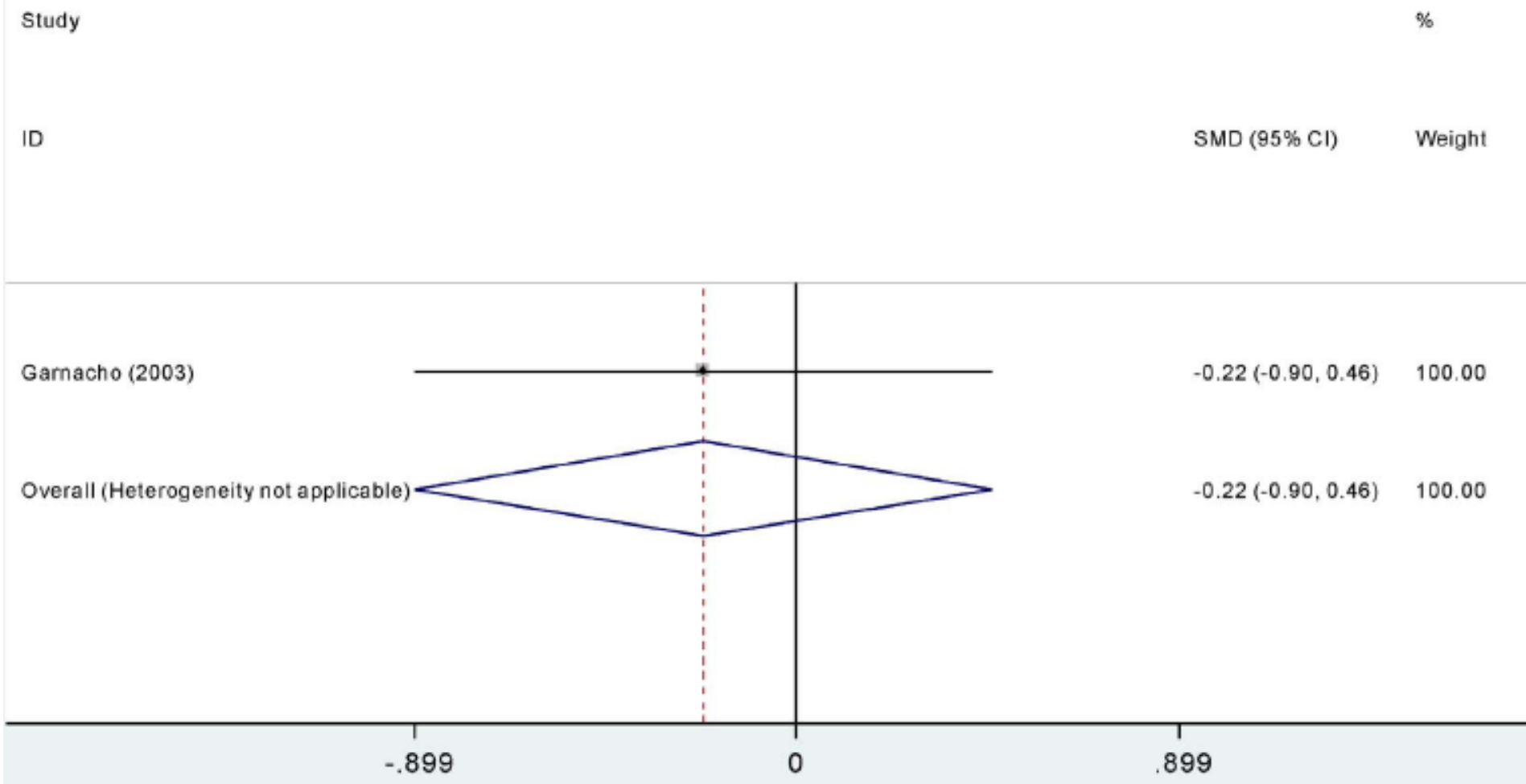
Desenho	N de Estudos	Experimental / Controle
Ensaio Clínico	2	22/21 e 105/104
Coorte prospectiva	2	15/13 e 21/14
Coorte retrospectiva	8	Entre 8/7 e 47/35



Aydemi (2013) [29]	Turkey	RCT	VAP	CRAB
Durante- Mangoni (2013) [30]	Italy	RCT	HAP, VAP,BSI,CIAI	EDRAB



# Monoterapia X Combinação

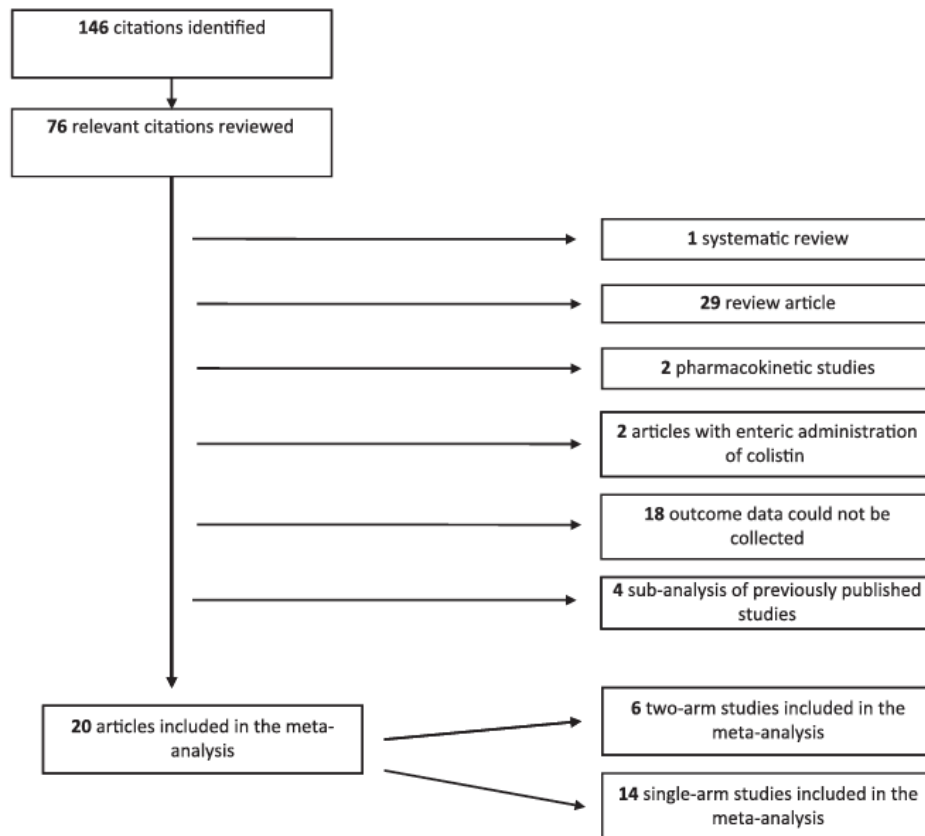


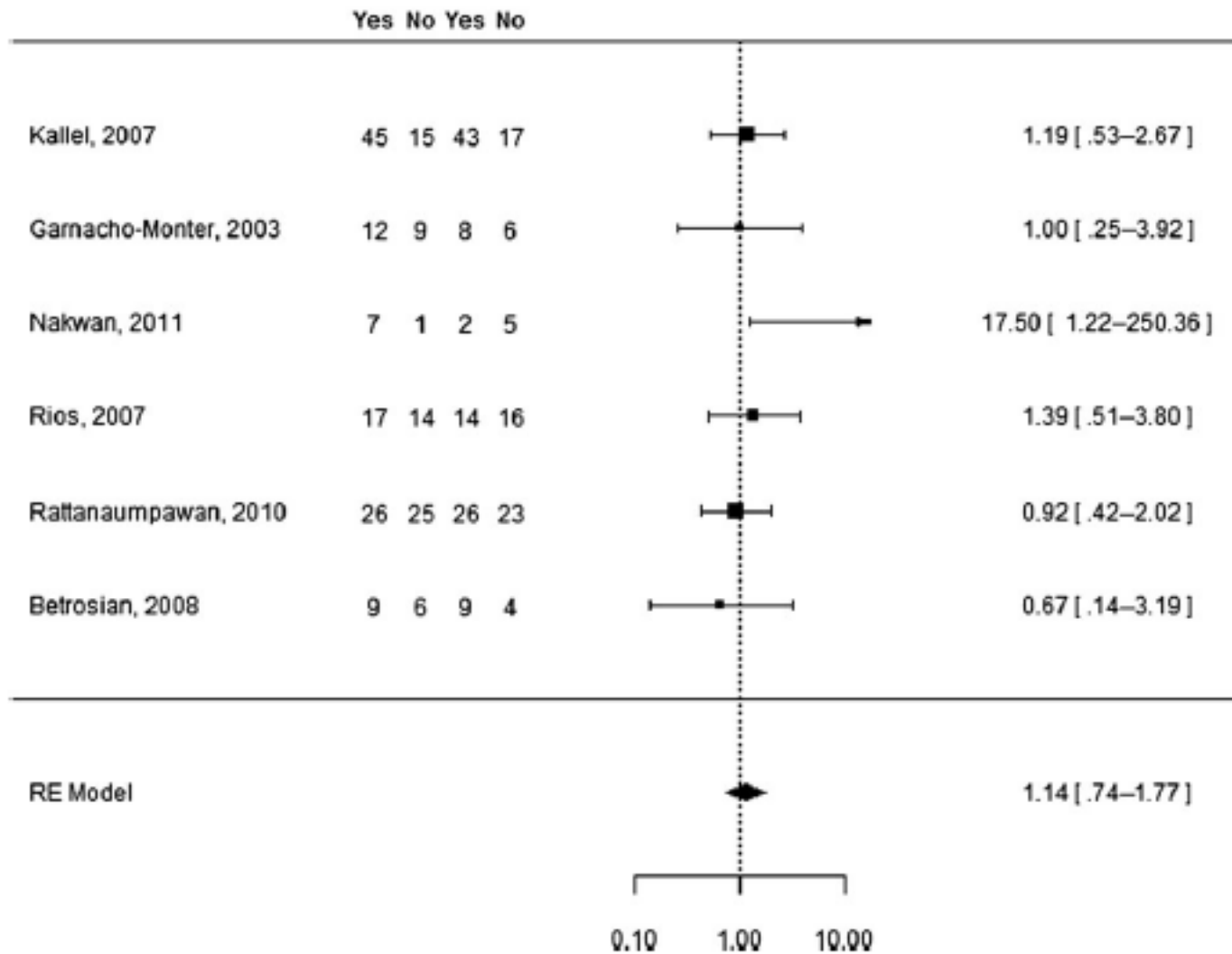
# What Is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression

Diana F. Florescu,<sup>1</sup> Fang Qiu,<sup>2</sup> Megan A. McCartan,<sup>3</sup> Cezarina Mindru,<sup>1</sup> Paul D. Fey,<sup>4</sup> and A. C. Kalil<sup>1</sup>

<sup>1</sup>Infectious Diseases Division, <sup>2</sup>Biostatistics Department, <sup>3</sup>Department of Pharmaceutical and Nutrition Care, and <sup>4</sup>Pathology Microbiology Department, Nebraska Medical Center, Omaha

**Clinical Infectious Diseases** 2012;54(5):670–80





**Table 2. Subgroup Analysis of Clinical Response With Colistin Versus Control Antibiotics for Treatment of Ventilator-Associated Pneumonia in Controlled Studies**

Variables	Studies, No. (Patients, No.)	Efficacy of Colistin Compared With Control OR (95% CI); <i>P</i>	Heterogeneity of Studies Included
Adult patients only	5 (344)	1.06 (.68–1.65); <i>P</i> = .81	$I^2 = 0\%$ ; $Q = 0.82$ ; <i>P</i> = .96
By route of administration			
Intravenous	4 (244)	1.13 (.66–1.93); <i>P</i> = .66	$I^2 = 0\%$ ; $Q = 0.64$ ; <i>P</i> = .89
Aerosolized	2 (115)	3.02 (.18–51.19); <i>P</i> = .44	$I^2 = 76.9\%$ ; $Q = 4.33$ ; <i>P</i> = .04
By study design			
Prospective	3 (163)	0.89 (.48–1.66); <i>P</i> = .71	$I^2 = 0\%$
Retrospective	3 (196)	1.45 (.79–2.68); <i>P</i> = .23	$I^2 = 0\%$
Randomized	2 (128)	0.86 (.43–1.74); <i>P</i> = .68	$I^2 = 0\%$
By geographic region			
Europe	3 (183)	1.04 (.55–1.96); <i>P</i> = .91	$I^2 = 0\%$ ; $Q = 0.41$ ; <i>P</i> = .81
Asia	2 (115)	3.02 (.18–51.19); <i>P</i> = .44	$I^2 = 76.9\%$ ; $Q = 4.33$ ; <i>P</i> = .04

Abbreviations: CI, confidence interval; OR, odds ratio.

# **POLIXIMINAS PARECEM INFERIORES ÀS DROGAS ALTERNATIVAS**

# Colistina: múltiplos agentes e sítios

- Estudo de Coorte
- 200 pacientes tratados com Colistina
  - Em geral mais graves
- 295 tratados com outros antimicrobianos.
- Mortalidade: 39% x 28% (OR=1,52 [1,08-2,31])
  - OR ajustado 1,44 (0,91-2,66)
  - Para bacterêmicos: 1,99 (1,06-3,77).

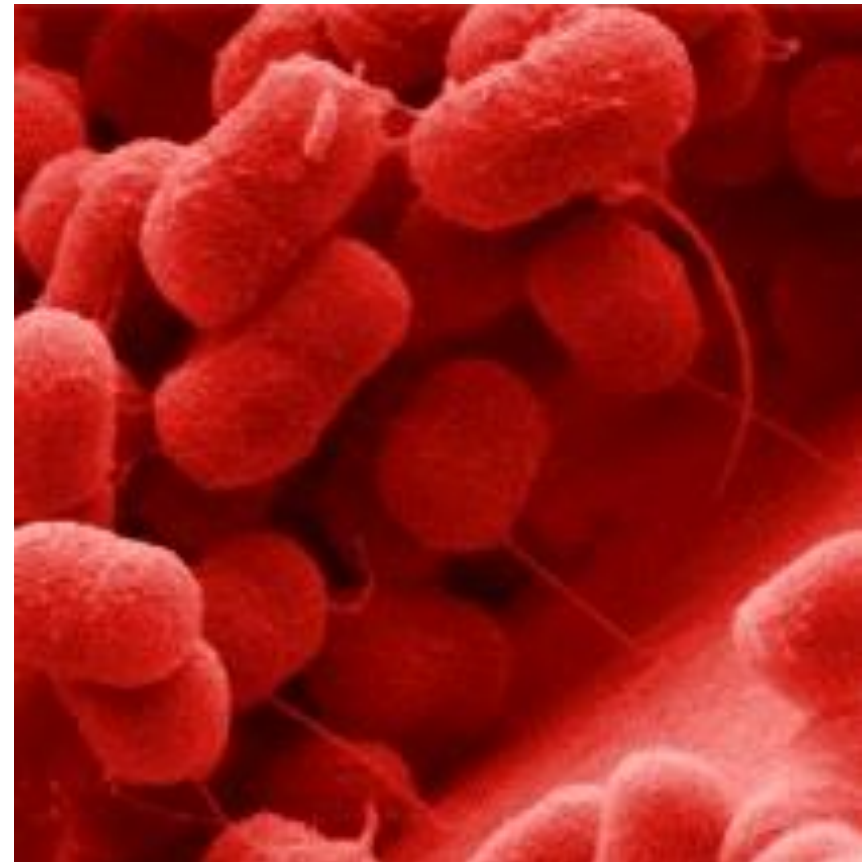
# Polymyxin B versus other antimicrobials for the treatment of *Pseudomonas aeruginosa* bacteraemia

Carlos H. Kvitko<sup>1</sup>, Maria H. Rigatto<sup>2</sup>, Ana L. Moro<sup>2</sup> and Alexandre P. Zavascki<sup>2,3\*</sup>

- Estudo observacional: coorte retrospectiva.
- 45 tratados com Polimixina B
- 88 tratados com outros antimicrobianos.
- Mortalidade: 66,7% x 28,4% ( $p < 0,001$ )
- “Hazard Ratio” ajustado: 1,91 (1,05-2,45).
- Nefrotoxicidade: 24,4% x 4,5% ( $p = 0,002$ ).

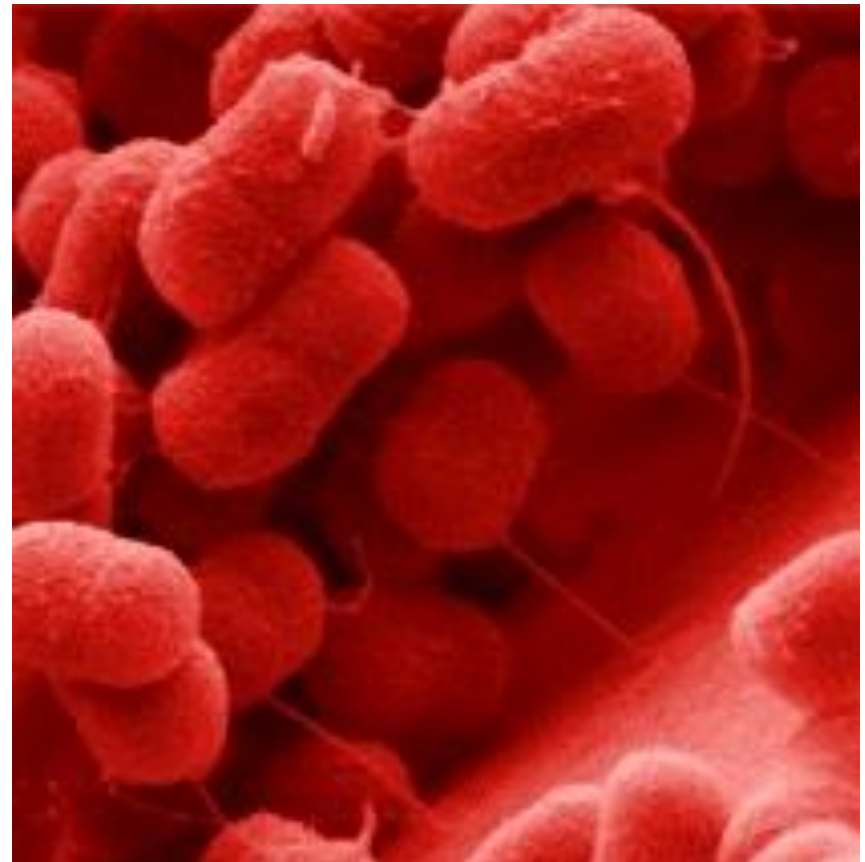
# *Acinetobacter baumannii*

- Colistina X Tigeciclina
- Estudo retrospectivo
- 82 pacientes:
  - 71 Colistina
  - 16 Tigeciclina
  - 19 Ambos
- Resultados:
  - Pacientes que receberam Colistina tinham maior risco de morte ( $p=0,002$ ).
  - No entanto, esses pacientes tinham retardo significativo na introdução de terapia apropriada ( $p<0,001$ ).



# *Acinetobacter baumannii*

- Polimixinas X AmpSulb
- Estudo retrospectivo
- Pacientes
  - 82 Polimixinas
  - 85 AmpSulb
- Resultados:
  - Pacientes do grupo das polimixinas eram mais graves.
  - Porém, após ajuste da gravidade, o uso da Polimixina foi preditor independente de óbito.



**MAS SERÃO OS  
COMPARADORES VÁLIDOS?**

# Colistin in Ventilator-Associated Pneumonia

M. E. Falagas<sup>1,2,3</sup> and Petros I. Rafailidis<sup>1,2</sup>

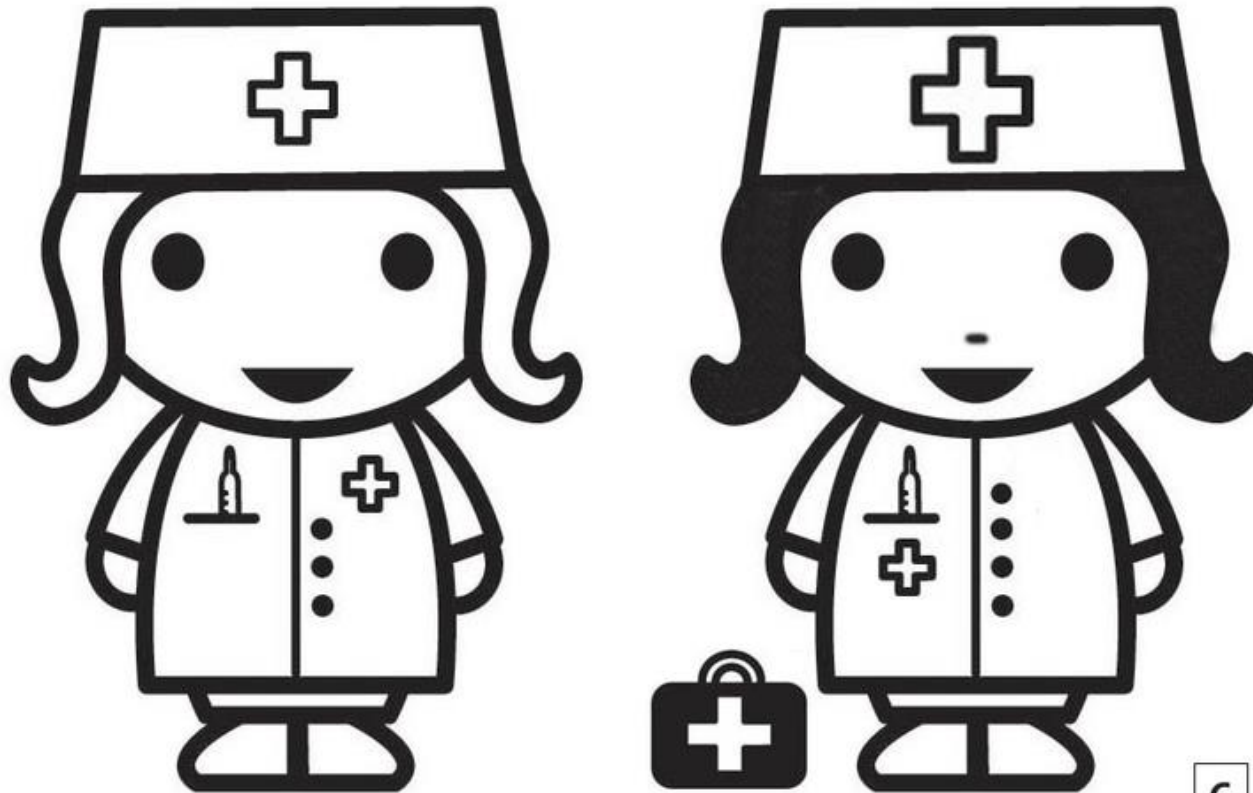
<sup>1</sup>Alfa Institute of Biomedical Sciences (AIBS), <sup>2</sup>Department of Medicine, Henry Dunant Hospital, Athens, Greece; and <sup>3</sup>Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

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(See the Major Article by Florescu et al, on pages 670–80.)

It is almost predictable that colistin is administered in patients in whom there is no other therapeutic choice. In contrast, in the comparator group, there are always more classes of antibiotics that could be used. This difference may be an important confounding factor when comparing outcomes. Also, the attributable mortality associated with MDR bacteria, including *Acinetobacter baumannii*, cannot be questioned nowadays, because inappropriate empirical antibiotic treatment is associated with increased mortality [5]. Hence, phy-

# Violação da hipótese contrafactual



6

# Desafios para ensaios clínicos

Representatividade de sujeitos

Homogeneidade

Desfechos

Posologia empregada

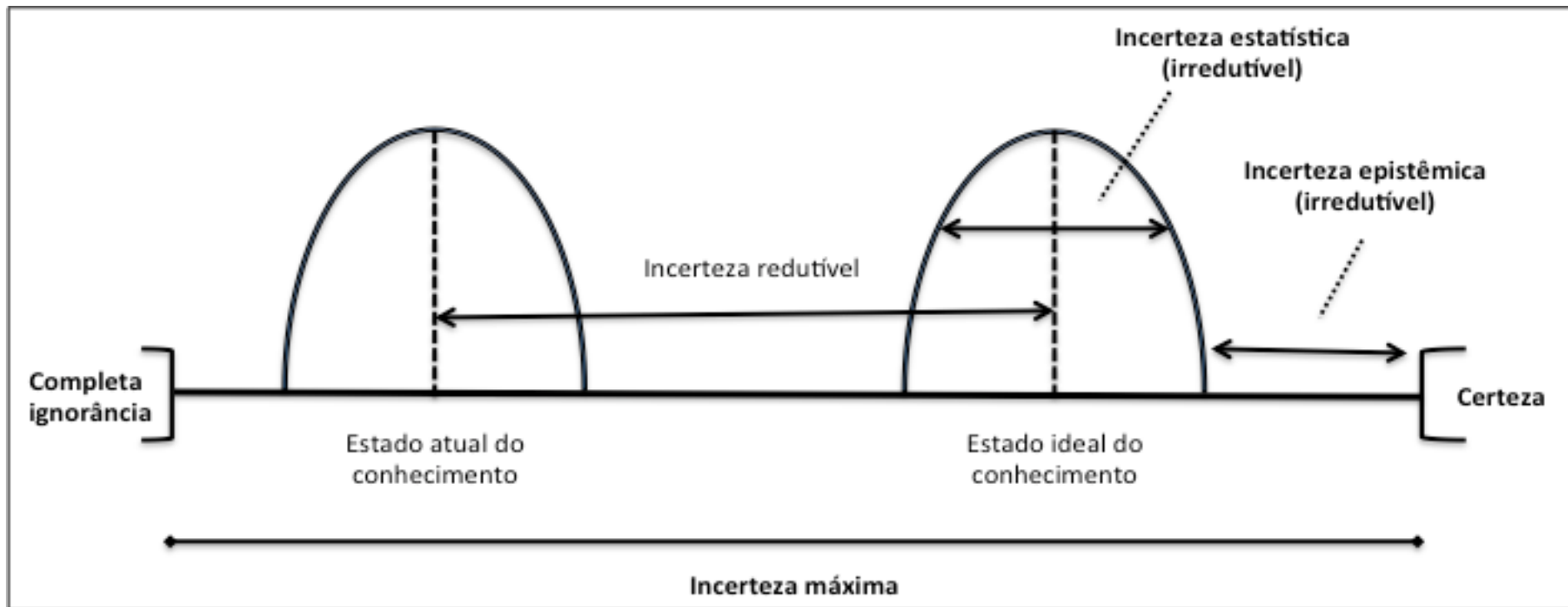
Antimicrobianos “adjuvantes” ou  
“complementares”

**COORTES AINDA SÃO  
PEQUENAS**

**E ENTÃO?**



# Incerteza em medicina clínica



*Djulfegovic et al. Uncertainty in clinical medicine. In: Gifford F (Ed) Philosophy of medicine. Oxford: Elsevier, 2012*

# Uma alternativa falibilista

## VERDADE



*Grau de Incerteza Epistêmica*

Revisões sistemáticas de ECR

Ensaio Clínicos Randomizados (ECR)

*Quasi-experimentais* e Coortes

Caso-Controle

Séries de Casos

Opinião de Experts

Hierarquia da MBE



*Crítica  
racional  
permanente*

Grande “N” e controle de confundimento.  
Sub-ótimos em relação aos critérios acima

Séries de Casos  
Opinião de Experts

Alternativa Falibilista



# Encontrando um caminho...

Estudo observacional multicêntrico de uso de Polimixinas



# Encontrando um caminho...

Estudo observacional multicêntrico de uso de Polimixinas

Grande número de hospitais

Comparadores diversificados

Poder estatístico

Resposta clínica e toxicidade





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**OBRIGADO**