

# Glicopeptídeos: Fatos e Mitos

Jaime Rocha X Alexandre Cunha

# Questão 1

A penetração tecidual de vancomicina, em especial no pulmão é ruim.



# FATOS

**Dr. Jaime Rocha – [www.travelclin.com.br](http://www.travelclin.com.br)**

**Especialista em medicina interna e infectologia.  
Especialista em medicina do viajante – CTH - ISTM.  
Prof. Infecto PUC-PR**

# Conflitos de Interesse

- **MSD**
- **Pfizer**
- **Novartis**
- **Sanofi Pasteur**
- **AztraZenca**
- **Bayer**
- **DASA**
- **Unimed Curitiba**

# Conflitos de Interesse

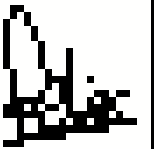
## ■ CONFLITO INTELECTUAL





# Lama do Mississippi

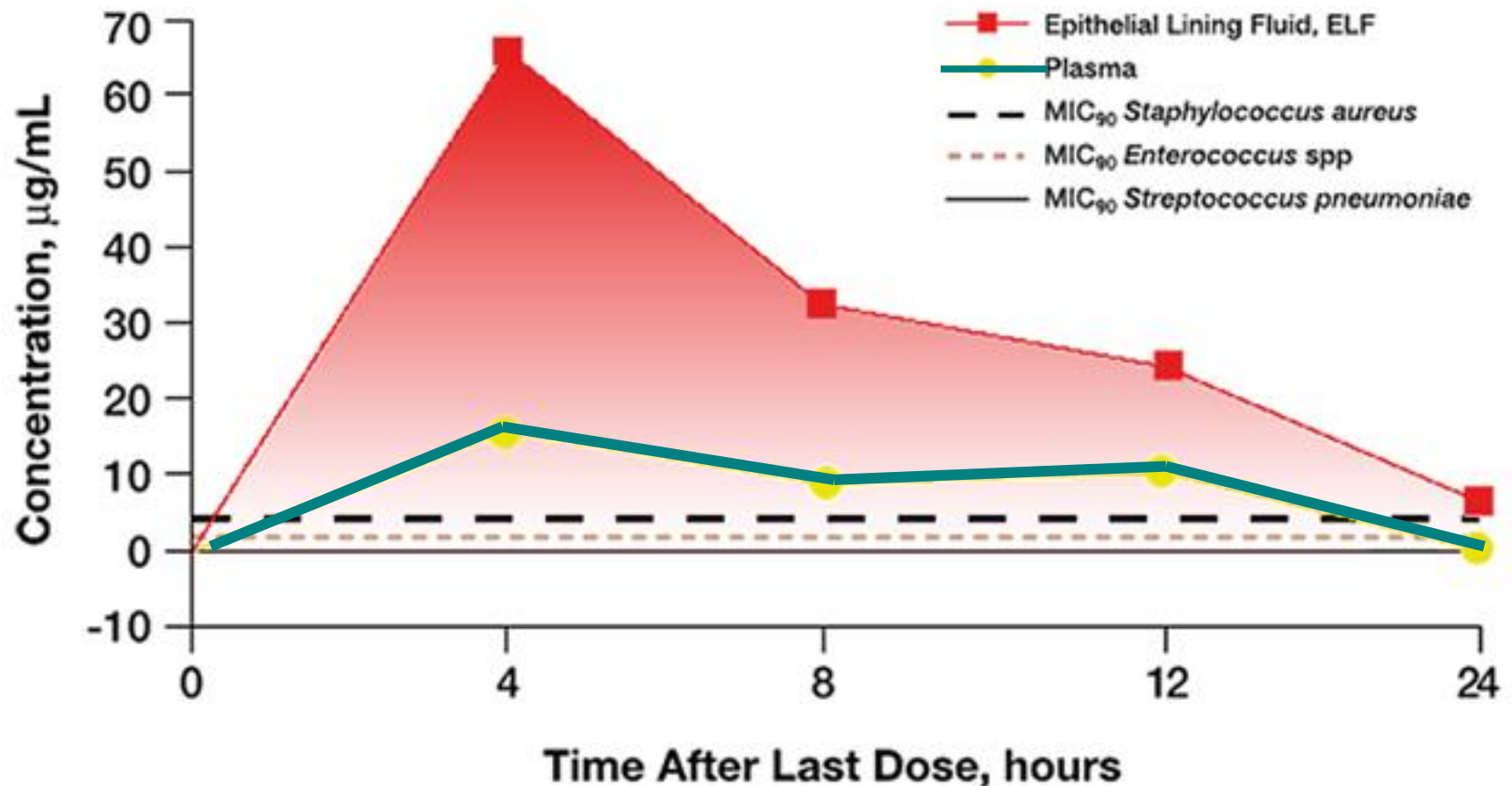




**FIGHT!**



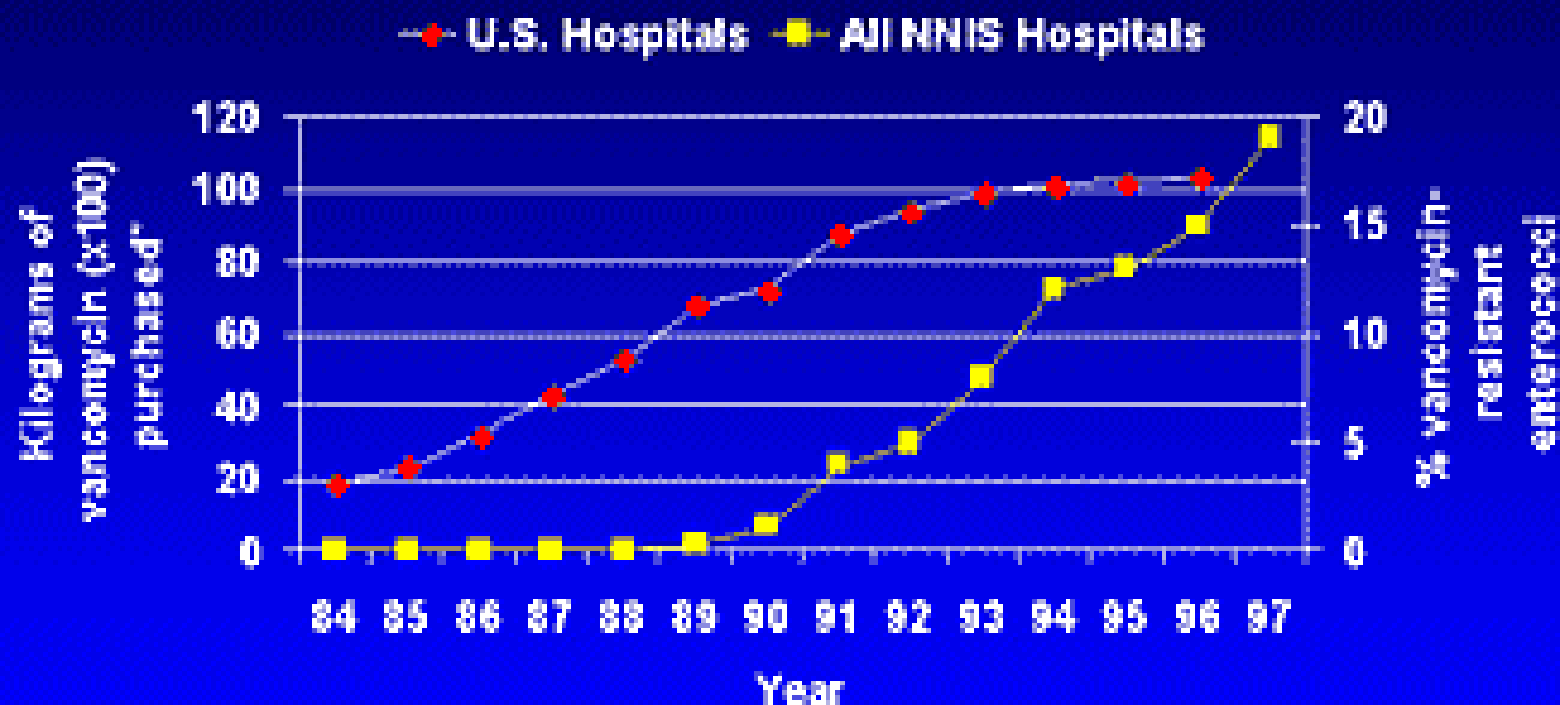
# Linezolid: Farmacocinética



## Concentrações teciduais de Linezolida comparada a Vancomicina (% concentração plasmática)

	LINEZOLIDA	VANCOMICINA
Saliva	120 %	Sem informação
Músculo	94 %	30%
Fluido inflamatório	104 %	Sem informação
Epithelial lining fluid (ELF)	450 % (sadios) 120% (PAV)*	19%
LCR	70 %	<10%

# Use of Vancomycin in U.S\*, and VRE at NNIS\*\* Hospitals



\* Kirst et al., Historical usage of vancomycin *Antimicrob Agents Chemo* 1998;1203-4

\*\* National Nosocomial Infections Surveillance System (CDC)



# MITOS

Alexandre Cunha

Especialista em Medicina Interna e Infectologia  
Químico pelo Instituto de Química da UNICAMP  
Professor do Curso de Pós Graduação Farmacologia Clínica na Unb

# Conflito de Interesses

*Conselho Federal de Medicina (CFM nº 1.595/00 de 18/05/2000)*

*Agência Nacional de Vigilância Sanitária (ANVISA nº 102/2000 de 30/11/2000)*

Advisory board:

Pfizer

Vínculo empregatício:

Laboratório Sabin ( Setor de microbiologia)

Honorários por palestras:

Biomerieux , MSD

Inscrição e/ou hospedagem e/ou passagens aéreas a congressos /simpósios:

- Merck-Sharp-Dome
- Sanofi-Aventis
- Abbott
- Novartis
- Wyeth
- Pfizer
- Jansen-Cilag

# Liga de Combate à Vanco



# Liga de Combate à Vanco





# Vancomicina





O maior defeito da vancomicina é  
a falta de penetração

Penetração Comercial!!!!

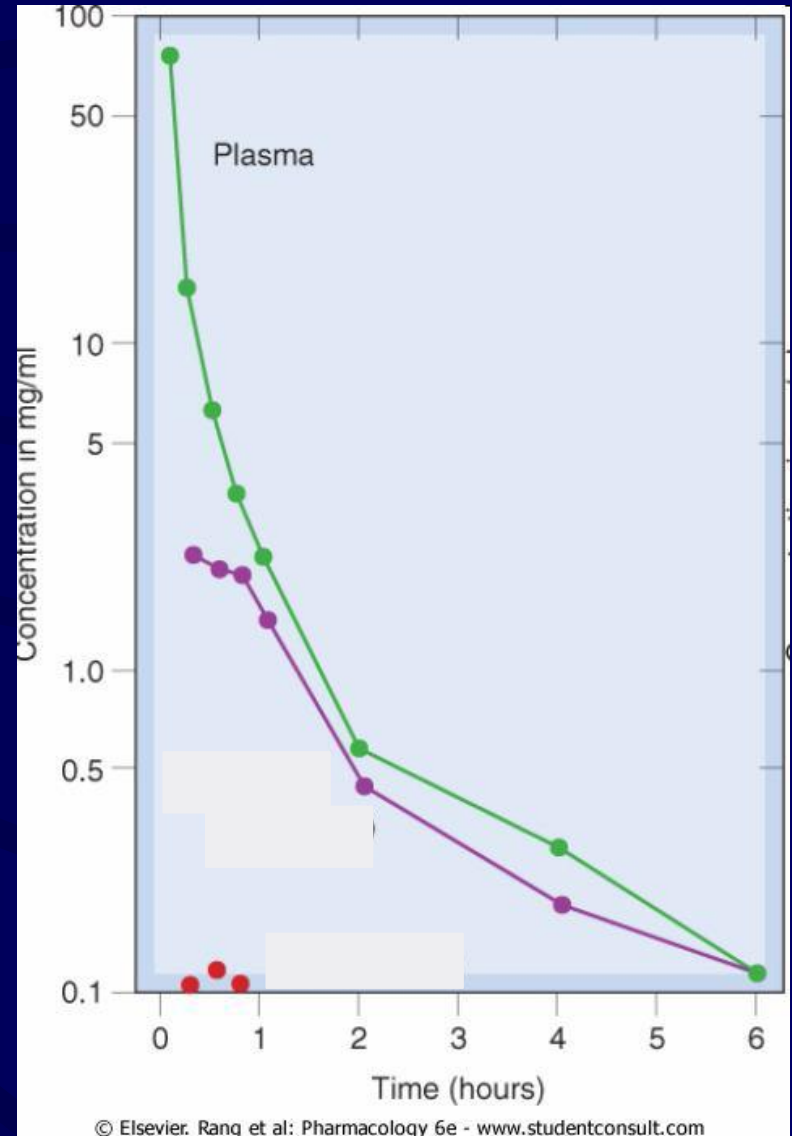
# O maior defeito da vancomicina é a falta de penetração comercial

- Droga "orfã"
  - Não dá canetas
  - Não tem "stand" com capuccino
  - Não tem representante amigo
  - Não paga jantares, viagens, congressos
  - Não financia / influencia / planeja / divulga trabalhos científicos a seu favor
  - Não tem quem a proteja...

# Níveis teciduais

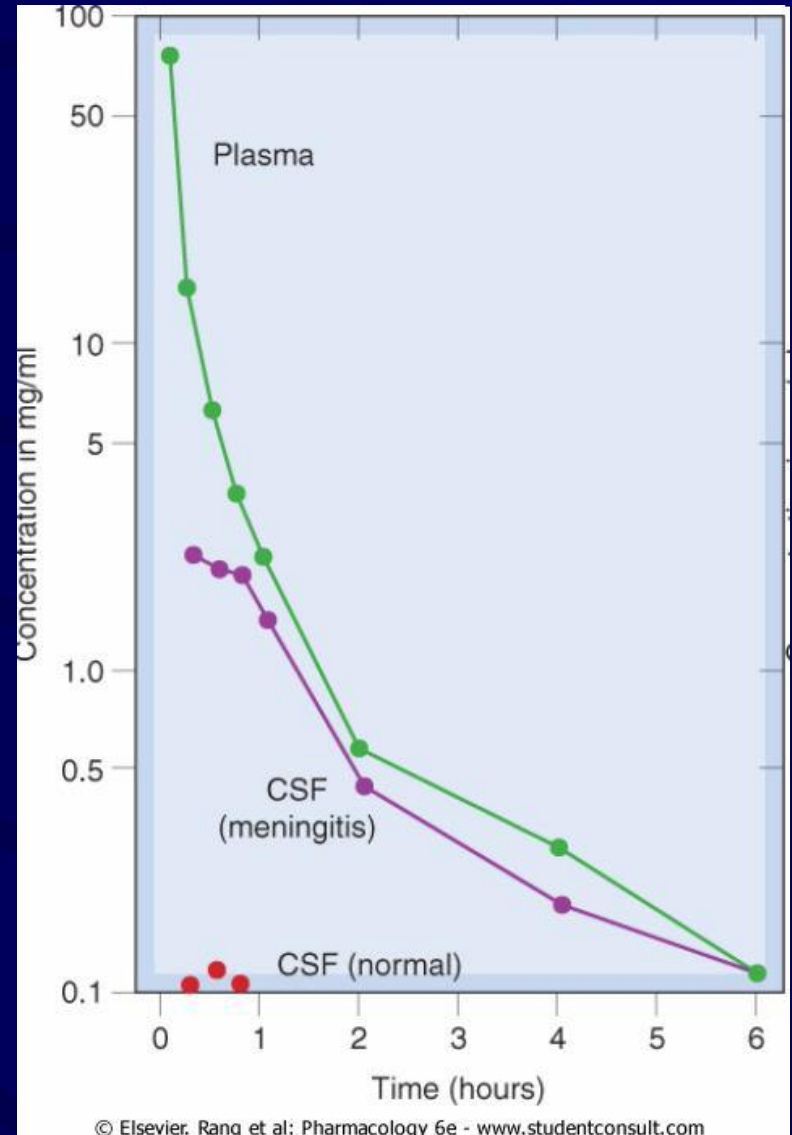
- Pouquíssima correlação entre níveis teciduais e eficácia terapêutica
  - Dificuldade de medição
  - Penetração alterada em estados patogênicos
  - Falta de correlação com desfecho clínico

# Níveis teciduais



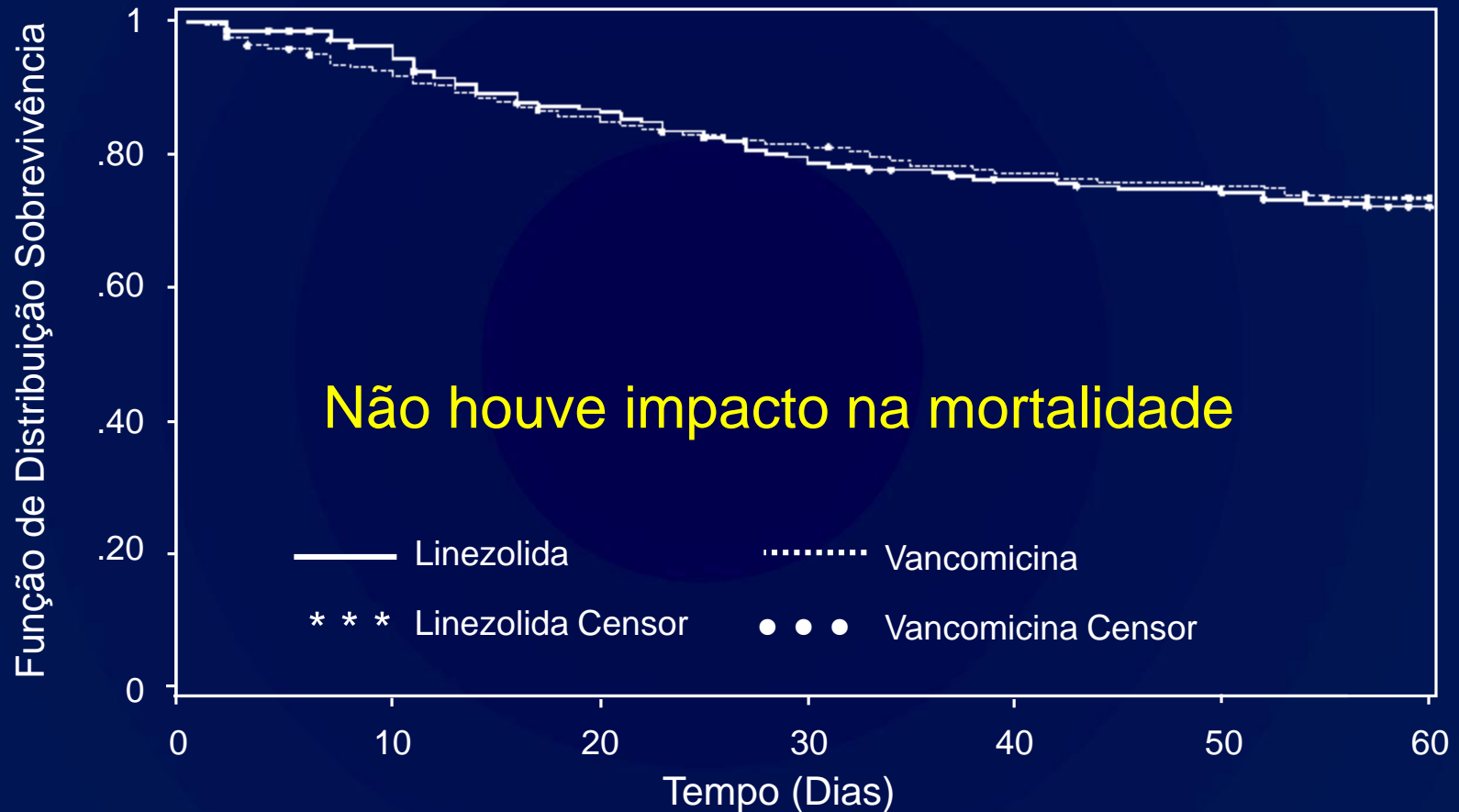
# Níveis teciduais

## Ceftriaxone!!!!



# Mortalidade: Kaplan-Meier – 60 Dias: grupo mITT

CID 2012:54 (1 March) d Wunderink et al



Óbito de 94 pacientes ( 15.7%) no braço Linezolid  
Óbito de 100 pacientes (17.0%) no braço Vancomicina

## Questão 2

Vancomicina é muito nefrotóxica, principalmente em pacientes já com insuficiência renal , nos quais não se deve usar vancomicina

# MITOS



# Nefrotoxicidade

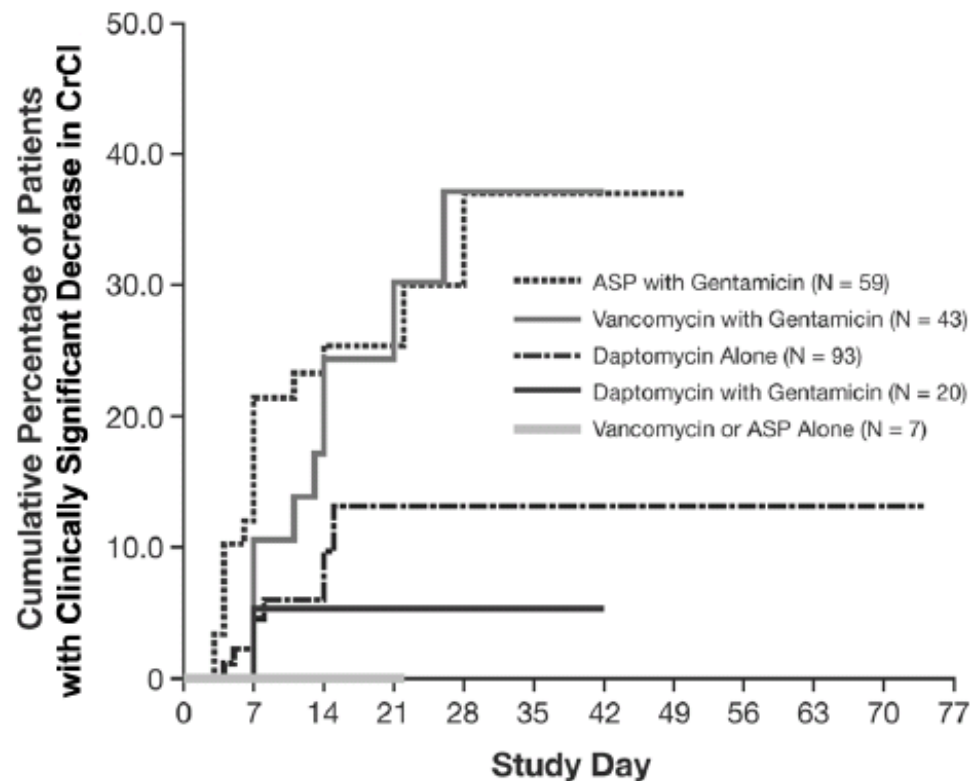
- A 1ª grande falácia!
- Estudos são incapazes, mesmo com análise estatística apurada, estabelecer que o uso de vancomicina é a causa da nefrotoxicidade.

# Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

Table 2. Numbers of patients receiving study drugs and gentamicin.


Patients	No. of patients			
	Daptomycin (n = 120)	Vancomycin (n = 53)	ASP (n = 63)	Total (n = 236)

Clinical Infectious Diseases 2009;48:713-21



**Figure 2.** Time to a clinically significant decrease in creatinine clearance (CrCl). ASP, antistaphylococcal penicillin.

600 pacientes em uso de Vancomicina, PT ou combinação



Regimen	Incidence of Acute Kidney Injury
Vancomycin alone	4.9%
Piperacillin-tazobactam alone (either infusion)	11.1%; P=0.0241 vs vancomycin alone
Combination therapy	18.6%; P<0.001 vs vancomycin alone

SCCM 2012, Abstract 301

67 pacientes em uso de Vancomicina

73 pacientes em uso da combinação Vanco-PT

Mais pacientes da monoterapia com vancomicina receberam outros antibióticos nefrotóxicos (p=0,02)

**IRA: Vancomicina 8,9% x Combinação 49,3%**  
**(p<0,001)**

SCCM 2012, Abstract 714

# Vancomycin and Nephrotoxicity; Just Another Myth?

*J Trauma Acute Care Surg.* 2013 November ; 75(5): 830–835.

A causal association linking vancomycin with nephrotoxicity is inconsistently documented

Demographics/Comorbidities	Vancomycin (298)	Linezolid (247)	P-Value
Gender (Male)	63.8% (n=190)	64% (n=158)	0.960
Age (Years)	52.8±1.0	53.8±1.0	0.510
Race (White)	84.2% (n=251)	85.8% (n=212)	0.630
Race (Black)	12.4% (n=37)	10.5% (n=26)	0.500
Race (Hispanic)	2.3% (n=7)	2.4% (n=6)	1.000
Diabetes Mellitus	18.5% (n=55)	23.9% (n=59)	0.120
Hypertension	30.5% (n=91)	38.1% (n=94)	0.065
Hyperlipidemia	4.0% (n=12)	7.7% (n=19)	0.066
Cardiovascular Disease	4.0% (n=12)	3.6% (n=9)	0.820
Peripheral Vascular Disease	4.4% (n=13)	5.7% (n=14)	0.480
Coronary Arterial Disease	17.1% (n=51)	21.5% (n=53)	0.200
Renal Insufficiency	5.7% (n=17)	3.6% (n=9)	0.260
Hemodialysis	10.4% (n=31)	8.9% (n=22)	0.560
APACHE II Score	18.8±0.5	18.5±0.5	0.680
Acute Physiological Score	13.4±0.4	12.9±0.5	0.450
Initial Creatinine (<1.2)	66.8% (n=199)	63.6% (n=157)	0.470
Initial Creatinine (1.2 to 1.5)	8.4% (n=25)	10.9% (n=27)	0.380
Initial Creatinine (1.5 to 2.0)	7.7% (n=23)	8.5% (n=21)	0.750
Initial Creatinine (>2.0)	17.1% (n=51)	17.0% (n=42)	1.000

Outcomes	Vancomycin (298)	Linezolid (247)	P-Value
Max Creatinine During Treatment <sup>α</sup>	1.8±0.1	1.7±0.09	0.29
Max Creatinine During Treatment <sup>β</sup>	1.1 (0.8,1.9)	1.2 (0.8,2.0)	0.9
Final Creatinine After Treatment <sup>α</sup>	1.4±0.07	1.2±0.07	0.24
Final Creatinine After Treatment <sup>β</sup>	0.9 (0.7,1.4)	0.9 (0.7,1.4)	0.92
Change in Creatinine (Max-Initial) <sup>α</sup>	0.4±0.04	0.3±0.04	0.16
Change in Creatinine (Max-Initial) <sup>β</sup>	0.1 (0.0,0.3)	0.1 (0.0,0.3)	0.55
Change in Creatinine (Final-Initial) <sup>α</sup>	-0.1±0.05	-0.2±0.05	0.44
Change in Creatinine (Final-Initial) <sup>β</sup>	-0.1 (-0.3,0.1)	-0.1 (-0.3,0.1)	0.62
New Onset Hemodialysis	9.4% (n=28)	9.7% (n=24)	0.9
Risk (RIFLE Criteria)	7.0% (n=21)	6.1% (n=15)	0.73
Injury (RIFLE Criteria)	3.0% (n=9)	0.8% (n=2)	0.122
Failure (RIFLE Criteria)	10.4% (n=31)	7.7% (n=19)	0.3
Loss (RIFLE Criteria)	1.0% (n=3)	1.6% (n=4)	0.707
ESRD (RIFLE Criteria)	0.7% (n=2)	0.4% (n=1)	1
Length of Stay After Treatment (Days) <sup>α</sup>	28.3±1.4	26.2±1.7	0.35
Length of Stay After Treatment (Days) <sup>β</sup>	20 (11,38)	19 (11,32)	0.15
Death	17.8% (n=53)	16.6% (n=41)	0.72

Crit Care Clin. 2008 Apr;24(2):393-420, x-xi.

## **Vancomycin revisited: a reappraisal of clinical use.**

Cunha BA.

Infectious Disease Division, Winthrop-University Hospital, Mineola, NY 11501, USA.

Vancomycin has been used for decades to treat serious systemic gram positive infections. Extensive use over time has demonstrated vancomycin is not nephrotoxic even when used in high dosage, i.e., twice the usual dose.



Crit Care Clin. 2008 Apr;24(2):393-420, x-xi.

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# Ajuste na IR

- Vancomicina é droga ajustável, com possibilidade de mensuração RÁPIDA e BARATA de níveis séricos
- Daptomicina: Ajuste empírico, dias alternados
- Linezolida:
  - Concentrações aumentadas 4-5 vezes na IRC , aumento dos efeitos adversos
  - Em diálise, estudos conflitantes, com até 1/3 da droga removida por diálise.

J Infect Chemother, 2008 Apr;14(2)



# Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

CID 2012:54 (1 March)

No grupo de menos clearance não  
houve diferença!

Glomerular filtration rate			
<50 mL/min	12/28 (42.9)	15/35 (42.9)	-24.6 to 24.6
≥50 mL/min	82/134 (61.2)	64/133 (48.1)	1.2 to 24.9

FATO



# **VANCOMYCIN-ASSOCIATED NEPHROTOXICITY : CRITICAL APPRAISAL OF RISK WITH HIGH-DOSE THERAPY**

Annie Wong-Beringerab , Julianne Jooc, Edmund Tsed, Paul Beringera

2011 Feb;37(2):95-101.

**Incidência**

**20 a 30%**



# Orientações para coleta das amostras

- Níveis séricos, após o *steady - state* , após 4 meias-vidas (24h)
- Concentração sérica no pico são coletadas 1 hora após administração IV
- Concentrações de vale a coleta é feita 1 hora antes da próxima dose
- Ajuste: Vancocinemia:
  - 5-10 mg/dL (basal)
  - 30-40mg/dL(terapêutico)
  - > 90mg/dL (tóxico)

Função renal normal	Cl cr>50-90mL/min	Cl cr>10-50mL/min	Cl cr<10mL/min	Diálise
1g 12x12h	1g 12x12h	1g 24x96h	1g 4-7 dias	Hemo/CAPD= Cl cr<10

# Protocolo para Controle de Vancocinemia

## Nível terapêutico (10 - 20 mcg/dL)

Concentração Sérica - Vale	Ajuste de dose recomendada	Monitorização
< 10 mcg/dL	Diminuir o intervalo de dose, conforme o último aprazamento realizado: Se dose a cada 48h = cada 24h Se dose a cada 24h = cada 12h Se dose a cada 12h = cada 8h Se dose a cada 8h = cada 6h ou Aumentar a dose de 250 a 500mg manter a frequência	Colher vale conforme rotina estabelecida
10-20 mcg/dL	Sem alterações na posologia	Colher vale conforme rotina estabelecida
20-30 mcg/dL	Diminuir a dose em 500mg (ou metade da dose quando 500mg), mantendo o aprazamento	Colher vale conforme rotina estabelecida
> 30 mcg/dL	Suspende aprazamento até realização da próxima vancocinemia	Colher vale conforme rotina estabelecida

# Glicopeptídeos

- tempo acima da MIC é um factor crítico para a melhorar a atividade bactericida
  - vancomicina e teicoplanina
  - MRSA
    - MIC (0,25-2mg/L)
    - acima de 10-15mg/L
    - $AUC/MIC > 400$



## Questão 3

Se você não sabe o MIC do *S aureus*, ou se não faz E-test, ou se é  $>1$ , não se deve usar vancomicina.

FATO

# Glicopeptídeos

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  - vancomicina e teicoplanina
  - MRSA
    - MIC (0,25-2mg/L)
    - acima de 10-15mg/L
    - $AUC/MIC > 400$

# Vancomycin: We Can't Get There From Here

Nimish Patel,<sup>1</sup> Manjunath P. Pai,<sup>1</sup> Keith A. Rodvold,<sup>5</sup> Ben Lomaestro,<sup>3,4</sup> George L. Drusano,<sup>2</sup> and Thomas P. Lodise<sup>1,2</sup>

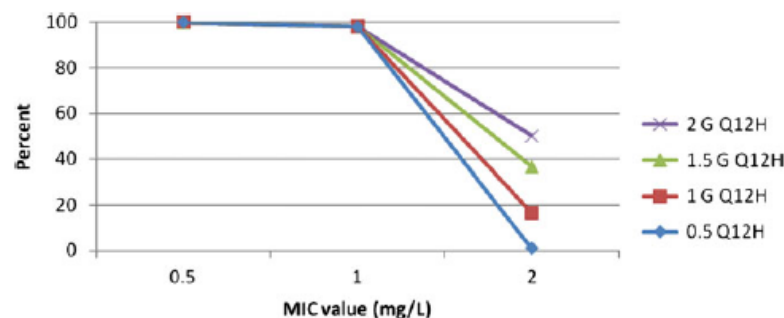
<sup>1</sup>Albany College of Pharmacy and Health Sciences, <sup>2</sup>Ordway Research Institute, <sup>3</sup>Albany Medical Center Hospital; <sup>4</sup>Albany Medical College, Albany, New York; and <sup>5</sup>University of Illinois at Chicago, Chicago, Illinois

***Patel et al. CID 2011; 52:969-74***

Values were improved relative to those seen at an MIC of 2 mg/L. Despite this improvement in PTA, the PTA was highly variable across CL<sub>CR</sub> strata when daily doses of  $\leq 2$  g were used. Vancomycin regimens consisting of at least 3 g daily were necessary

**Table 4. Overall Probability of Achieving an AUC/MIC Ratio of 400, by MIC Value, Versus the Probability of a Nephrotoxic Event**

MIC value	AUC/MIC ratio $\geq 400$			Nephrotoxic event	
	0.5mg/L (%)	1.0mg/L (%)	2.0mg/L (%)	Non-ICU (%)	ICU (%)
500 mg IV Q12H	57	15	0.7	3	10
1000 mg IV Q12H	90	57	15	6	16
1500 mg IV Q12H	97	79	38	9	25
2000 mg IV Q12H	98	90	57	14	34



**Figure 1.** Probability of achieving AUC/MIC ratio  $\geq 400$  for vancomycin regimens of varying intensity when C<sub>min</sub> values were between 15 and 20 mg/L. Among the 9999 subjects simulated, the total number of subjects with C<sub>min</sub> values 15–20 mg/L were (A) 406 subjects (0.5G Q12h), (B) 1100 subjects (1G Q12h), (C) 1190 subjects (1.5G Q12h), and (D) 1096 subjects (2G Q12h).

# Sensibilidade de MRSA à vancomicina 2008 (CLSI e FDA)



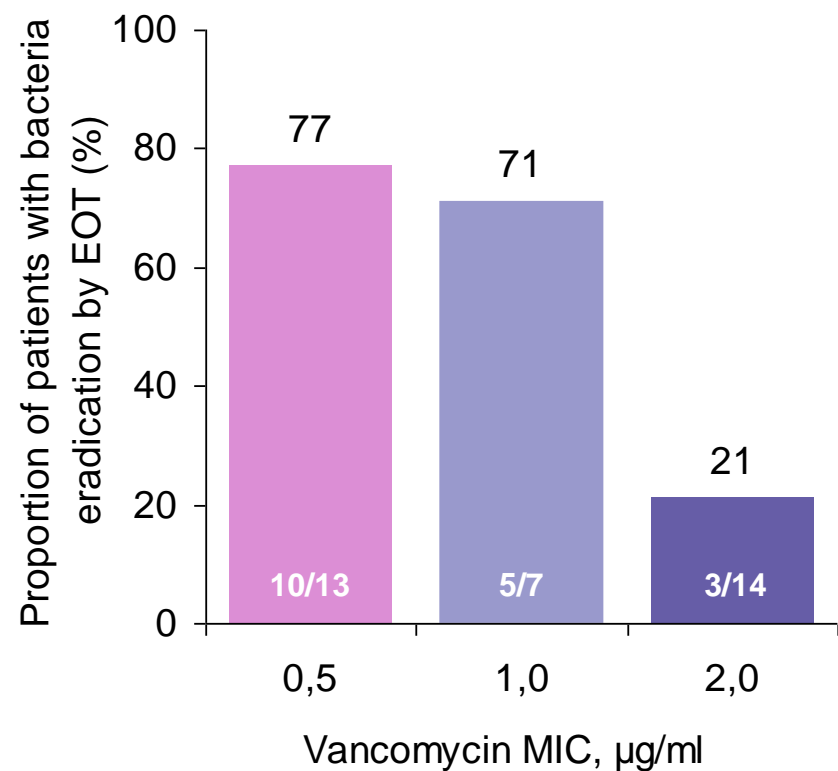
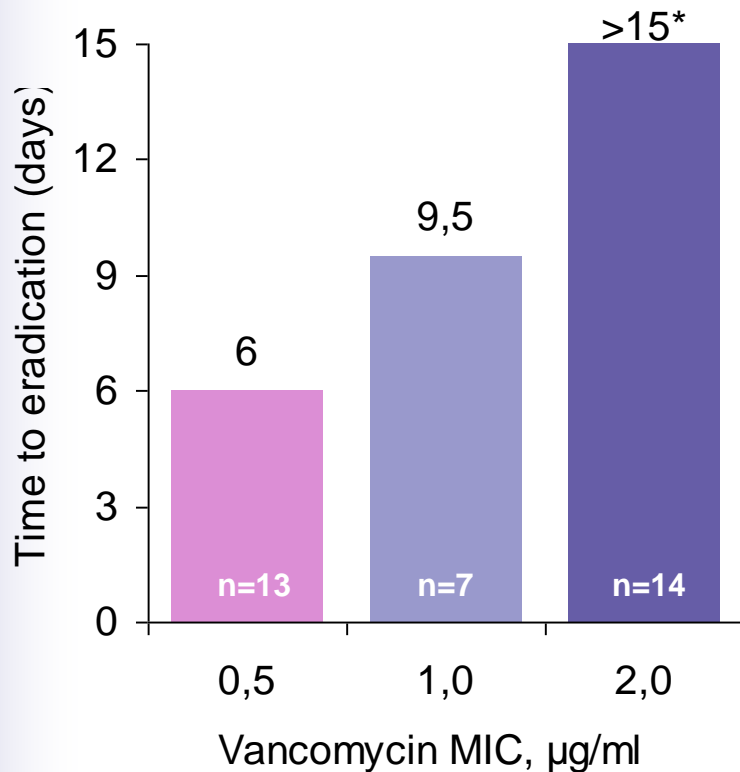
Resistente  $\geq 16 \mu\text{g/ml}$  (VRSA)

Intermediário 4-8  $\mu\text{g/ml}$  (VISA)

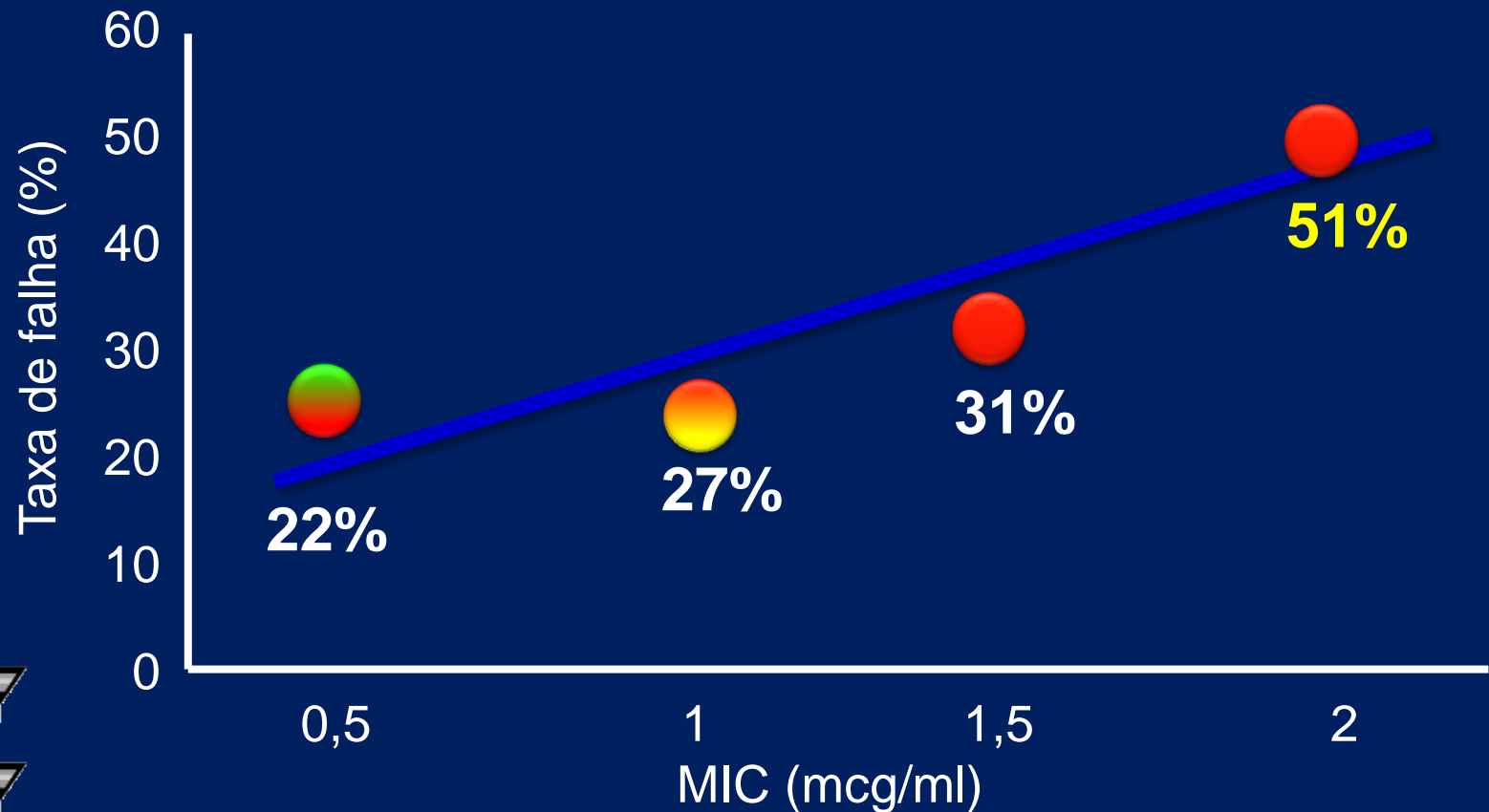
Sensível  $\leq 2 \mu\text{g/ml}$

# Time to MRSA eradication with vancomycin treatment, stratified by MIC

Vancomycin dose-adjusted to attain target trough of 8–12 µg/ml, n=34



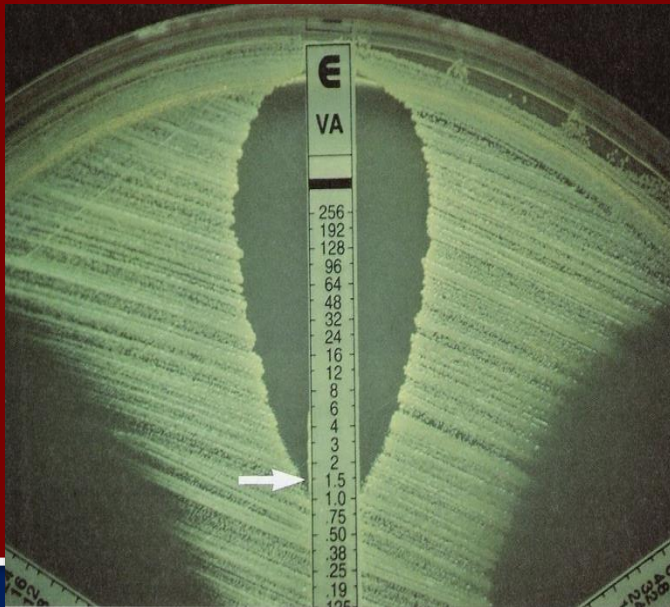
# Relação: MIC para vancomicina e falha terapêutica no tratamento de MRSA



# Como saber se *MRSA* é sensível à vancomicina ?

Quantitativas: MIC ou CIM

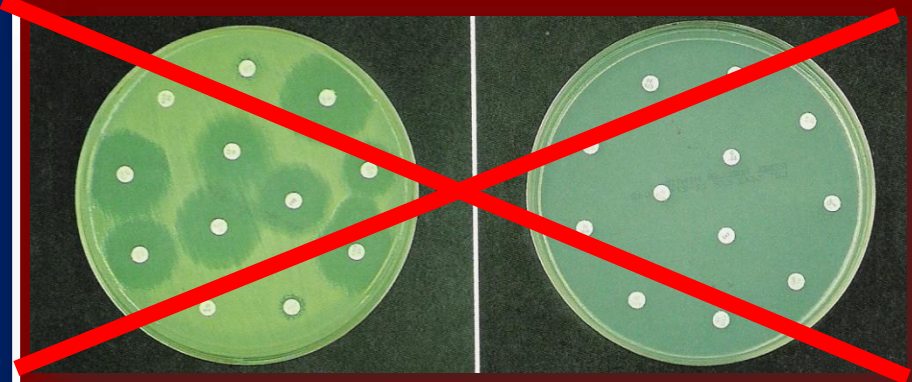
- ◆ Macro ou microdiluição em caldo
- ◆ Gradiente de difusão (fitas de E-test)



Qualitativas

- ◆ Disco de difusão

**2009: Não mais aceito para vancomicina**





# Evaluation of the accuracy of automated systems and Etest

- 210 amostras de MRSA de 9 hospitais (9 regiões; 20-25 amostras/hospital)
- Avaliação da sensibilidade a vancomicina por:
  - Microdiluição em caldo (referência; Wayne State/JMI Labs)
  - Vitek2 (St John's Hospital)
  - MicroScan (Detroit Med Center)
  - BD Phoenix (University of Texas)
  - Etest (Wayne State/JMI Labs)

# Evaluation of the accuracy of automated systems and Etest

Susceptibility testing system	Lob <sub>2</sub> dilution variation when compared to reference BMD				
	-2	-1	0	+1	+2
MicroScan	-	-	72 (34.3)	131 (62.4)	7 (3.3)
Phoenix	-	59 (28.1)	139 (66.2)	12 (5.7)	-
Vitek-2	2 (1.0)	70 (33.3)	114 (54.3)	24 (11.4)	-
Etest			77 (36.7)	126 (60.0)	7 (3.3)
System provided lower MIC (chance of <u>false-susceptible</u> )			Agreement	System provided higher MIC (chance of <u>false-resistance</u> )	

MITO

# MIC creep

- A 2ª grande falácia!!!
- MIC creep não foi demonstrado no Brasil
- Número total de amostras de *S. aureus* = 893
  - Comunitárias: 710 amostras (79,5%)
  - Hospitalares: 183 amostras (20,5%)

MIC  $\leq$  0,5 ug/mL

453 amostras(50,7%), 88 hospitalares

MIC = 1 ug/mL

406 amostras(45,4%), 93 hospitalares

MIC = 2 ug/mL

34 amostras(3,8%), 2 hospitalares

# MIC creep

- Nas cepas com MIC para Vanco >1mcg/dL
  - Não se demonstrou aumento de mortalidade

Kalil AC et al JAMA, 2014, 312(15)

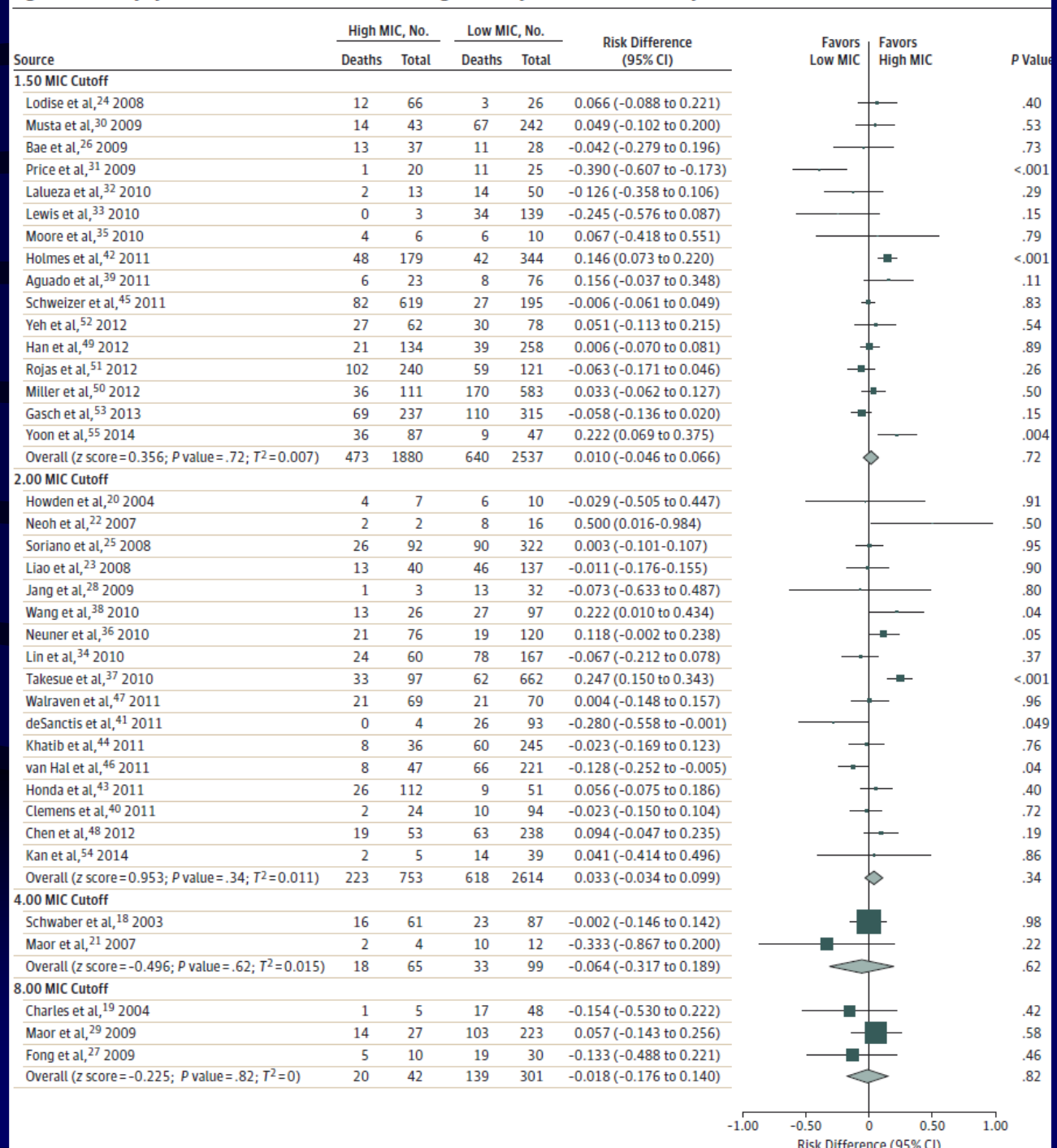
Park SY et al Antimicrob Agents Chemother. 2013 Nov;57(11)

Gasch O et al Clin Microbiol Infect. 2013 Nov;19(11)

## Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections A Systematic Review and Meta-analysis

Andre C. Kalil, MD, MPH; Trevor C. Van Schooneveld, MD; Paul D. Fey, PhD; Mark E. Rupp, MD

Figure 4. Mortality by Different MIC Cutoffs and Overall for High-Vancomycin MIC vs Low-Vancomycin MIC



# MIC creep

- Demonstrou-se aumento de mortalidade mesmo para MSSA tratados com oxacilina!

Caston JJ et al Scand J Infect Dis. 2014 Nov;46(11)

Cervera C et al Clin Infect Dis. 2014 Jun;58(12)

- Demonstrou-se aumento de mortalidade para MSSA, mas não para MRSA!

Han JH Antimicrob Agents Chemother. 2012 Oct;56(10)

# Questão 4

Ninguém sabe a qualidade da vancomicina genérica



MITO

# Falta do medicamento referência

- Patente da vancomicina expirou em 1980.
- Desde de 2004 a Ely Lilly parou de produzir a Vancomicina
- Portanto, todos os trials nos últimos 10 anos foram realizados contra Vancomicina de outros fabricantes!

# In vitro potency evaluations of various piperacillin/tazobactam generic products compared with the contemporary branded (Zosyn<sup>®</sup>, Wyeth) formulation

Ronald N. Jones<sup>a,b,\*</sup>, Thomas R. Fritsche<sup>a</sup>, Gary J. Moet<sup>a</sup>

<sup>a</sup>JMI Laboratories, North Liberty, IA 52317, USA

<sup>b</sup>Tufts University School of Medicine, Boston, MA 02111, USA

Diagnostic Microbiology and Infectious Disease 61 (2008) 76–79

Listing of 13 screened piperacillin/tazobactam intravenous generic formulations

Manufacturer	Product name	Vial strength (g)	Lot no.	Dates <sup>a</sup>		Country of origin
				Expiration	DOT	
Wyeth	Zosyn <sup>®</sup>	3.375	B75011	06/2008	5 dates	United States
Astral Pharmaceuticals Industries	PIPTAZ	2.25	AUPM-601	10/2008	06/07/07	Philippines <sup>b</sup>
Astral Pharmaceuticals Industries	PIPTAZ	4.5	AUPI-601	10/2008	06/07/07	Philippines <sup>b</sup>
Astral Pharmaceuticals Industries	PIPTAZ	4.5	AUPI-701	03/2009	08/22/07	Philippines <sup>b</sup>
Aurobindo	Zobactin	4.5	ZBNPB7048	07/2008	10/05/07	India
China Chem	Pisutam	2.25	58P713	08/2008	11/29/07	Taiwan
Demo	Tazorex	4.5	0701172	08/2008	06/07/07	Greece <sup>c</sup>
FARMA-APS	—	4.5	A005	05/2009	08/23/07	Portugal
Hainan Sanyang	Pip/Tazo	4.5	70703	06/2009	11/29/07	China
Hikma	Prizmai	4.5	A001	07/2009	11/29/07	Jordan
Hong Kong United	Pip/Tazo	4.5	7080401	07/2009	11/29/07	China
Meditrina Pharmaceuticals	Tazidron	4.5	07076	02/2009	08/22/07	Greece
Meditrina Pharmaceuticals	Tazidron	4.5	07077	02/2009	08/22/07	Greece
Orchid/Aeiss	Zopercin	4.5	151018	04/2009	10/05/07	India
Orchid Healthcare	Piptamate	4.5	1517004	01/2009	08/23/07	India
STADA	—	4.5	A001	02/2009	06/07/07	Spain <sup>d</sup>
STADA	—	4.5	A013	06/2009	10/05/07	Spain
YSS Laboratories	Vigocid	4.5	8002C	10/2008	08/23/07	Philippines <sup>e</sup>
YSS Laboratories	Vigocid	4.5	8003C	01/2009	08/23/07	Philippines <sup>e</sup>
YSS Laboratories	Vigocid	2.25	8004C	02/2009	08/23/07	Philippines <sup>e</sup>
YSS Laboratories	Vigocid	2.25	8501C	10/2008	06/07/07	Philippines <sup>e</sup>
Yung Shin	Tapimycin	2.25	TY12T039	05/2010	11/29/07	Taiwan
Zuventus	Tazotum	4.5	7003	02/2009	10/05/07	India
Zuventus	Tazotum	4.5	7001	01/2009	10/05/07	India

Disk diffusion results for zones of inhibition (100/12.5- $\mu$ g disks prepared from vial content) were compared with a commercial disk (BBL) that contained 100/10  $\mu$ g of piperacillin/tazobactam (internationally used diagnostic product content). Zone diameter results showed no significant variation in the measured potencies of the generic lots when compared with the branded lot or the commercially prepared diagnostic disk. The differences were generally no more than 1 mm among all 4 assay strains (data not shown). Moreover,

Lowest reproducible replicate MIC derived from the generic product vial (23 product lots, 15 manufacturers) compared with a randomly selected contemporary lot of Wyeth-produced piperacillin/tazobactam (Zosyn® [B75011])

Product (lot no.)	Assay organism MIC ( $\mu$ g/mL):				Variation (%) <sup>a</sup>
	<i>E. coli</i>		<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	
	ATCC 25922	ATCC 35218	ATCC 27853	ATCC 29213	
Zosyn® control	1.75–2.0 <sup>b</sup>	3.5 <sup>c</sup>	2.0 <sup>d</sup>	1.0–1.25 <sup>e</sup>	NA
PIPTAZ (AUPM-601)	2.0–2.5	4.0–5.0	2.5	1.25	–22 <sup>f</sup>
PIPTAZ (AUPI-601)	1.75–2.0	4.0	2.5	1.25	–13 <sup>f</sup>
PIPTAZ (AUPI-701)	2.0	4.0	2.5	1.25	–20
Vigocid (8002C)	2.0–2.5	3.5–5.0	2.0–2.5	1.25	–13 <sup>f</sup>
Vigocid (8003C)	2.0	3.5	2.5	1.25	–10
Vigocid (8004C)	1.75	3.5	2.5	1.25	–6
Vigocid (8501C)	2.5	5.0	3.0	1.5	–35
Tazidron (07076)	1.75	3.5	2.5	1.25	–13
Tazidron (07077)	2.0	5.0	2.5	1.25	–27
STADA (A0001)	2.5	5.0	2.5	1.25	–23
STADA (A013)	2.5	5.0	3.5	1.5	–15
Tazotum (7003)	2.5	5.0	3.0	1.25	–11
Tazotum (7001)	2.5	5.0	3.0	1.5	–16
Pip/Tazo (7080401)	2.5	5.0	2.5	1.25	–13
Pip/Tazo (70703)	2.0	4.0	3.0	1.25	–5
Tazorex(0701172)	2.5	5.0	2.5	1.25	–23
FARMA-APS (A005)	2.0	3.5	2.5	1.25	–10
Zobactin (ZBNPB7048)	2.5	5.0	3.0	1.25	–11
Zopercin (151018)	2.5	5.0	3.5	1.5	–21
Tapimycin (TY12T039)	2.5	5.0	3.0	1.25	–18
Pisutam (58P713)	2.5	4.0	3.0	1.5	–16
Prizma (A001)	2.5	6.0	3.0	1.25	–24
Piptamate (1517004)	1.75	3.5	2.0	1.25	EQ

# Expanded studies of piperacillin/tazobactam formulations: variations among branded product lots and assessment of 46 generic lots

Gary J. Moet<sup>a</sup>, Amy A. Watters<sup>a</sup>, Helio S. Sader<sup>a,b</sup>, Ronald N. Jones<sup>a,c,\*</sup>

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<sup>b</sup>Universidade Federal de São Paulo, São Paulo, SP 04023-900, Brazil

<sup>c</sup>Tufts University School of Medicine, Boston, MA 02111, USA

*Diagnostic Microbiology and Infectious Disease 65 (2009) 319–322*

Listing of 23 additional (14 manufacturers) lots of generic intravenous piperacillin/tazobactam formulations screened by a multiorganism in vitro MIC assay

Manufacturer (lot no.)	Product name	Vial strength	Dates		Country of origin	Assay variation (%)
			Expiration	DOT <sup>c</sup>		
Cellofarm (7100789)	Tazpen	4.5 g	01/2009	01/2008	Brazil	−27
Cellofarm (7100794)	Tazpen	4.5 g	01/2009	03/2008	Brazil	−5
Eurofarma (121609C)	Piperacillin/tazobactam	4.5 g	09/2009	01/2008	Brazil	−4 <sup>d</sup>
Eurofarma (117968B)	Piperacillin/tazobactam	2.25 g	08/2009	01/2008	Brazil	−11
Eurofarma (126133A)	Piperacillin/tazobactam	2.25 g	12/2009	03/2008	Brazil	−26
Eurofarma (124032E)	Piperacillin/tazobactam	4.5 g	12/2009	03/2008	Brazil	4 <sup>e</sup>
Novafarma (0760088)	Piperacillin/tazobactam	4.5 g	12/2009	03/2008	Brazil	−18
Novafarma (0760076)	Piperacillin/tazobactam	4.5 g	12/2009	01/2008	Brazil	−27
Farmalogica (11704-1)	Piperacillin/tazobactam	4.5 g	06/2009	09/2008	Colombia	−16
Vitrofarma (B050822)	Vitalis <sup>®</sup>	4.5 g	05/2010	09/2008	Colombia	−13
SUMI Med (08050434)	Piperacillin/tazobactam	4.5 g	01/2010	09/2009	Colombia	−10
Kendrik (6JB030)	Tasovak <sup>®</sup>	4.5 g	08/2008	01/2008	Mexico	−3
Kendrik (7LB016)	Tasovak <sup>®</sup>	4.5 g	08/2009	09/2008	Mexico	−13
Teva (A002)	Piperacillin/tazobactam (Teva <sup>®</sup> )	4.5 g	12/2009	03/2008	Switzerland	−11
Ratiopharm (H22498)	Piperacillin/tazobactam	4.5 g	02/2010	09/2008	Germany	−18
Hospira (B058004)	DBL <sup>®</sup>	4.5 g	02/2010	03/2009	Australia (India)	−42
Hospira (B088001)	DBL <sup>®</sup>	4.5 g	10/2010	04/2009	Australia (India)	−14
Orchid (B058005)	Zopercin <sup>®</sup>	4.5 g	02/2010	03/2009	India	−26
Ibigen (8F06TR)	Ibigen <sup>®</sup>	4.5 g	05/2010	03/2009	Czech Republic (Italy)	−21
Ibigen (8L12TR)	Ibigen <sup>®</sup>	4.5 g	07/2010	03/2009	Czech Republic (Italy)	−26
Sandos (155534)	Piperacillin/tazobactam	3.375 g	03/2010	03/2009	Canada	10
Stragen (1PT08030)	Piperacillin/tazobactam	2.25 g	10/2010	03/2009	Norway	−15
Stragen (1PT08010)	Piperacillin/tazobactam	4.5 g	10/2010	03/2009	Norway	−16

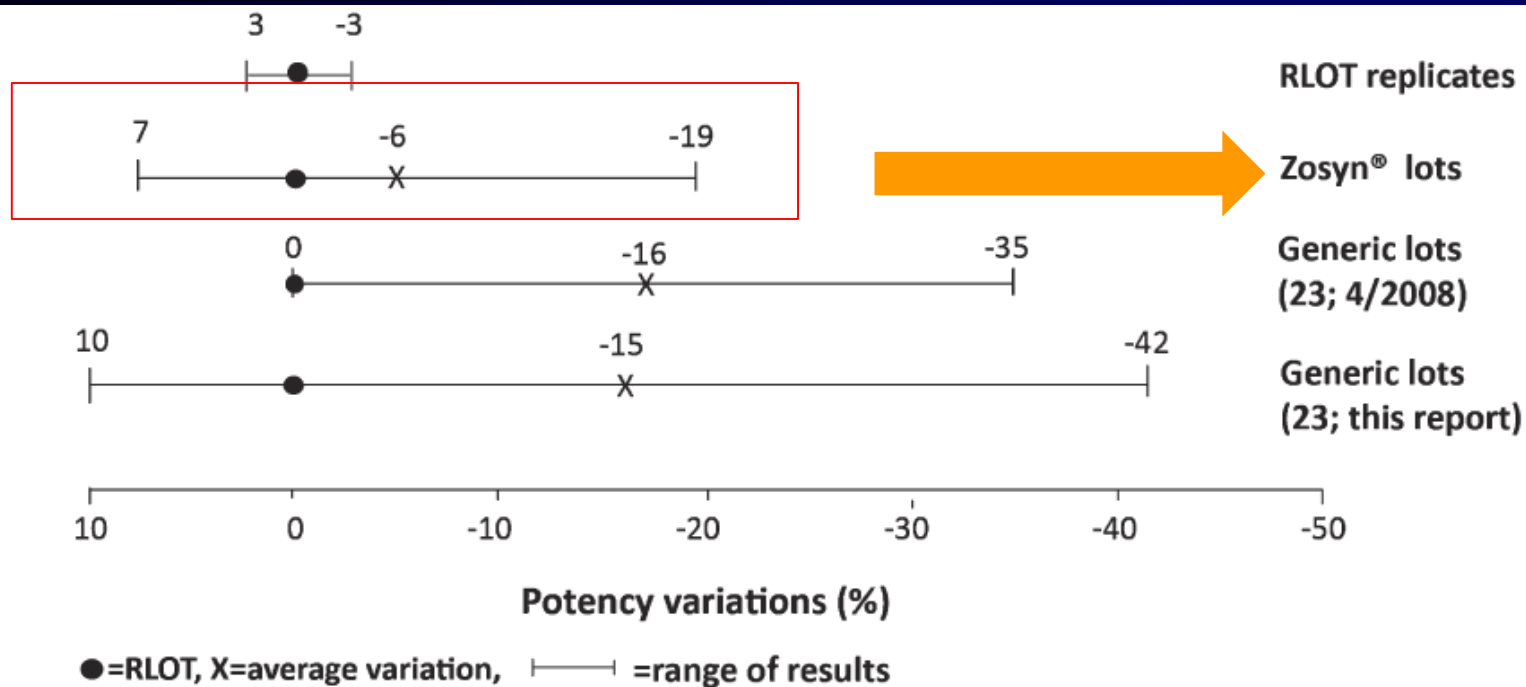


Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

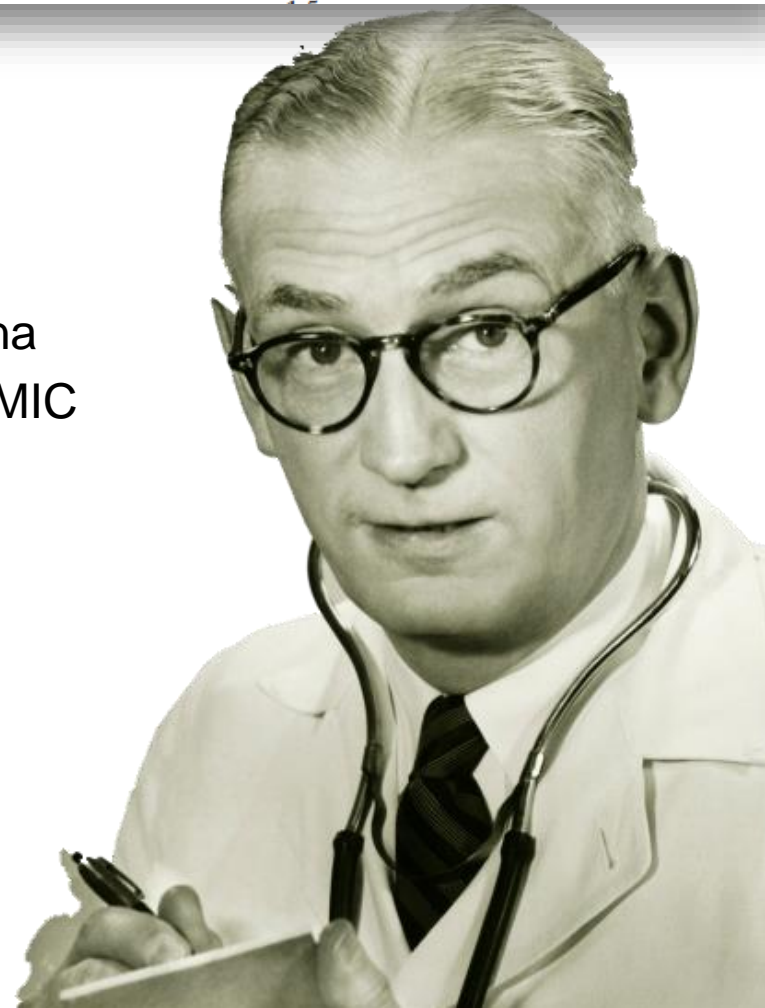
FATO



## Generic Vancomycin Products Fail *In Vivo* despite Being Pharmaceutical Equivalents of the Innovator<sup>▽</sup>

Omar Vesga,<sup>1,2\*</sup> Maria Agudelo,<sup>1,3</sup> Beatriz E. Salazar,<sup>1,4</sup>

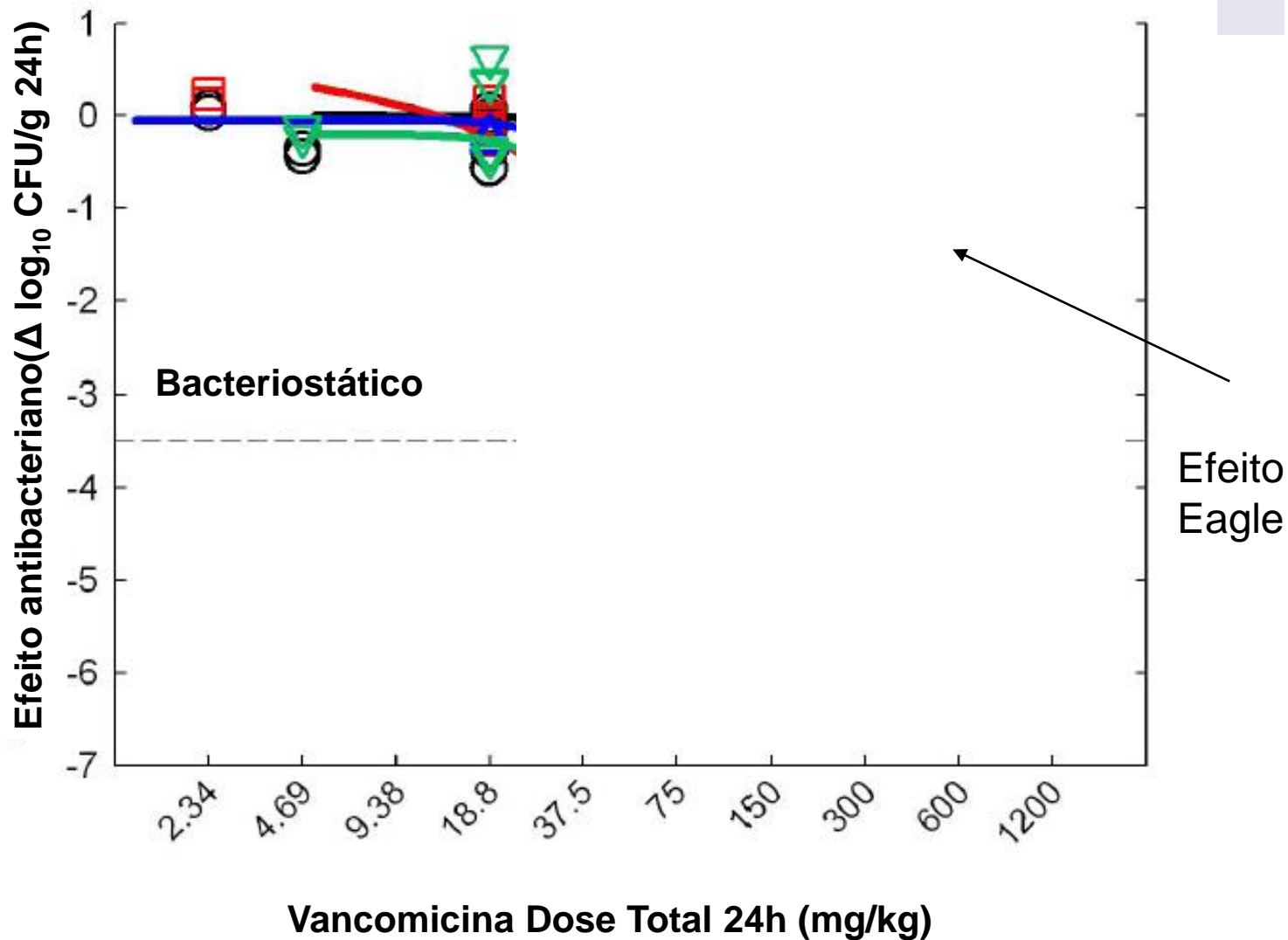
- Concentração do produto ativo
  - VAN-Abbott
    - 125% a concentração do excipiente
    - 123% a concentração da vancomicina
- Demais não tinham diferença em relação ao MIC e MBC
- Todos genéricos falharam in vivo !





# Vancomicina

— Lily  
— Proclin- Argentina  
— Baxter  
— Abbot



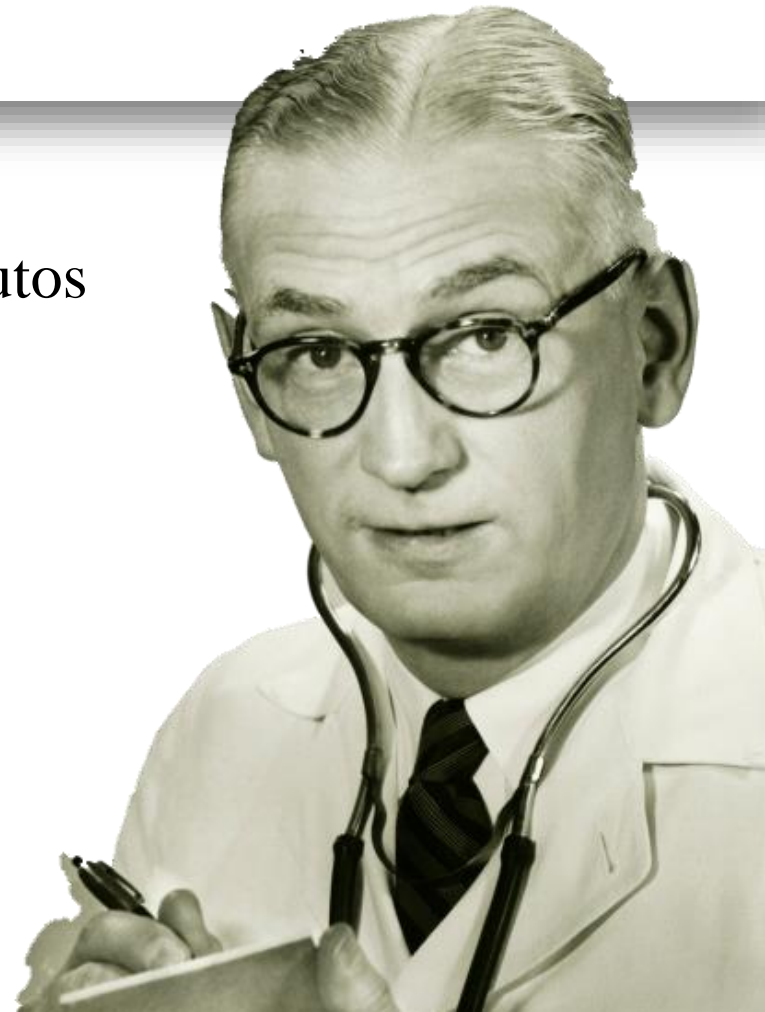
**Antibacterial effects of brand-name teicoplanin and generic products against clinical isolates of methicillin-resistant *Staphylococcus aureus***

Shigeru Fujimura · Katsuhiko Fuse · Hidenari Takane ·  
Yoshihisa Nakano · Kazunori Gomi · Toshiaki Kikuchi ·  
Akira Watanabe

“Dentre os genéricos, podem existir produtos nos quais o efeito antimicrobiano

**não é igual**

ao da Teicoplanina original.”



## ■ Falsificação

- **Too much, too little, or none at all: dealing with substandard and fake drugs**

The Lancet 2001(357);9272:1904

- **WHO fights fake pharmaceuticals**

The Lancet Infectious Diseases 2006; 6( April 2006):195

## Questão 5

Existem bons trials clínicos e várias metanálises mostrando superioridade de outras drogas em relação à vancomicina.

FATO

## Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

**Richard G. Wunderink,<sup>1</sup> Michael S. Niederman,<sup>2</sup> Marin H. Kollef,<sup>3</sup> Andrew F. Shorr,<sup>4</sup> Mark J. Kunkel,<sup>5</sup> Alice Baruch,<sup>5,a</sup> William T. McGee,<sup>6</sup> Arlene Reisman,<sup>5</sup> and Jean Chastre<sup>7</sup>**

<sup>1</sup>Department of Pulmonary and Critical Care, Northwestern University Feinberg School of Medicine, Chicago, Illinois; <sup>2</sup>Department of Medicine, Winthrop-University Hospital, Mineola, New York; <sup>3</sup>Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri; <sup>4</sup>Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, D.C.; <sup>5</sup>Specialty Care, Pfizer, New York, New York; <sup>6</sup>Baystate Medical Center, Springfield, Massachusetts; and <sup>7</sup>Service de Réanimation Médicale, Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

# ***Endpoint Primário de Eficácia: Grupo Per Protocol (PP) ao Final do Estudo (EOS)***

	<b>Linezolid n (%)</b>	<b>Vancomicina n (%)</b>	<b>Valor de P</b>	<b>95% IC</b>
<b>Pacientes</b>	<b>165 (100)</b>	<b>174 (100)</b>		
<b>Sucesso/Cura</b>	<b>95 (57.6)</b>	<b>81 (46.6)</b>	<b>0.042</b>	<b>0.5%, 21.6%</b>
<b>Falha</b>	<b>70 (42.4)</b>	<b>93 (53.4)</b>		
<b>Desconhecido*</b>	<b>7</b>	<b>2</b>		

\*Excluídos da análise.

# ***Endpoint Secundário de Eficácia: Grupo PP ao Final do Tratamento (EOT)***

	<b>Linezolida n=180 n (%)</b>	<b>Vancomicina n=186 n (%)</b>	<b>Valor de P</b>	<b>95% IC</b>
<b>Sucesso (Cura + Melhora)</b>	<b>150 (83.3)</b>	<b>130 (69.9)</b>	<b>0.002</b>	<b>4.9%. 22.0%</b>
<b>Falha</b>	<b>30 (16.7)</b>	<b>56 (30.1)</b>		
<b>Desconhecido*</b>	<b>3</b>	<b>2</b>		


\*Excluídos da análise.



**Linezolid versus vancomycin for meticillin-resistant *Staphylococcus aureus* infection: a meta-analysis of randomised controlled trials.**

An MM et al. 2013 Int J Antimicrob Agents May;41(5):426-33

- “This meta-analysis provides evidence that linezolid possesses significant advantages compared with vancomycin and may be a superior alternative for MRSA-related infection.”



# Daptomycin Versus Vancomycin for Bloodstream Infections Due to Methicillin-Resistant *Staphylococcus aureus* With a High Vancomycin Minimum Inhibitory Concentration: A Case-Control Study

Carol L. Moore,<sup>1,2</sup> Paola Osaki-Kiyan,<sup>1</sup> Nadia Z. Haque,<sup>1,2</sup> Mary Beth Perri,<sup>1</sup> Susan Donabedian,<sup>1</sup> and Marcus J. Zervos<sup>1,3</sup>

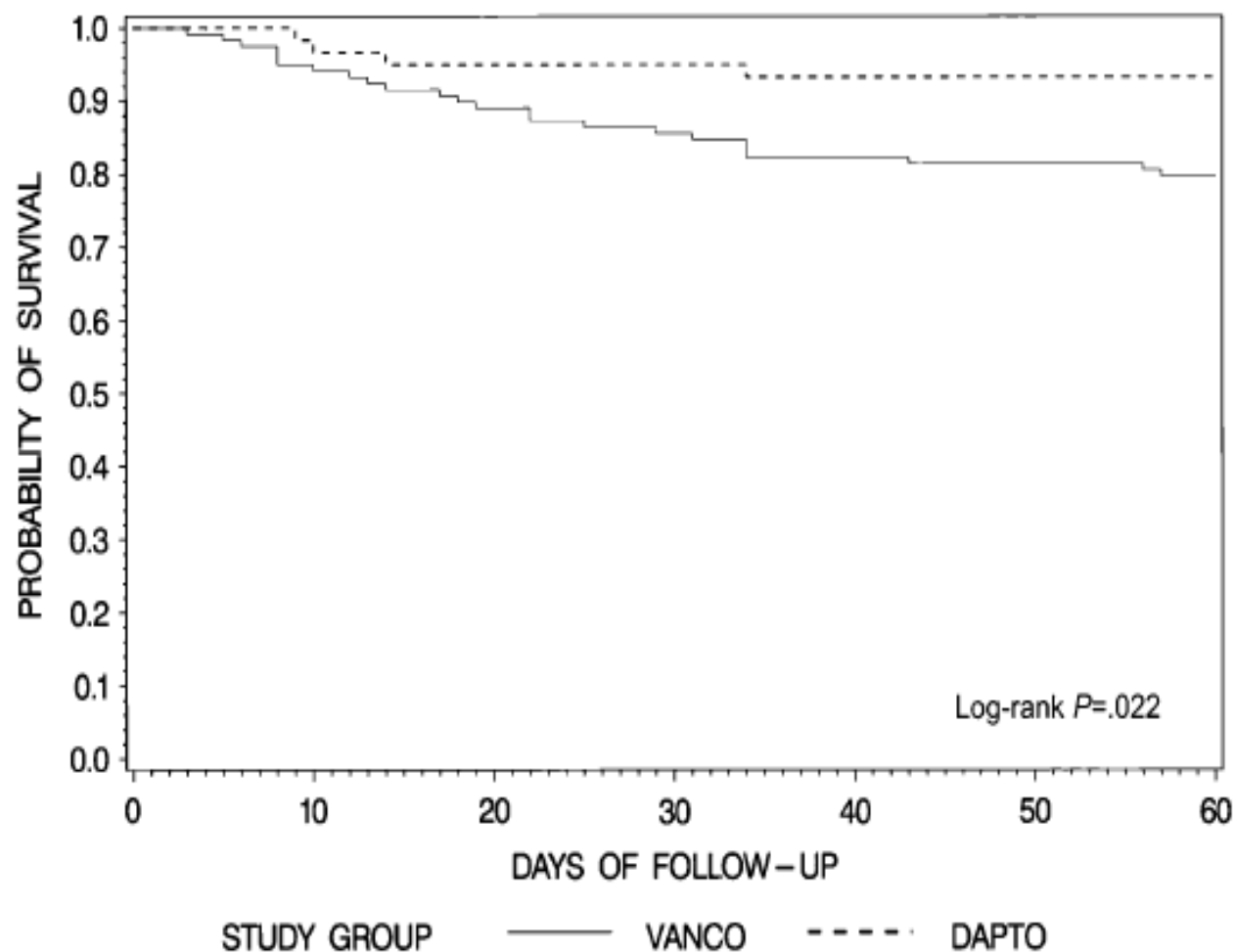
<sup>1</sup>Department of Internal Medicine, Division of Infectious Diseases and <sup>2</sup>Department of Pharmacy Services, Henry Ford Hospital, and <sup>3</sup>Wayne State University School of Medicine, Detroit, Michigan

**Clinical Infectious Diseases 2012;54(1):51–8**

- Estudo Caso-controle: 118 pacientes Vancomicina e 59 no grupo Daptomicina (2:1) – 2005 -2009
- MIC > 1 mcg/mL
- Infecção da corrente sanguínea
- Falência clínica: mortalidade e recorrência da infecção

**Table 2. Comparative Outcomes of Vancomycin- and Daptomycin-Treated Subjects With Susceptible Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection With a Vancomycin Minimum Inhibitory Concentration >1 µg/mL**

Factor	Vancomycin, (n = 118)	Daptomycin, (n = 59)	P
Clinical failure <sup>a</sup>	37 (31)	10 (17)	.084
60-d mortality <sup>b</sup>	24 (20)	5 (8)	.046
Microbiologic failure <sup>c</sup>	11 (9)	6 (10)	.855
Recurrence of MRSA BSI <sup>d</sup>	6 (5)	2 (3)	.620
Clinical failure, by MIC <sup>e</sup>			
1.5 µg/mL	31 (30)	6 (24)	.530
2 µg/mL	6 (38)	4 (12)	.065
Clinical failure, by risk level of infection source <sup>f</sup>			
Low risk	7 (27)	2 (15)	.459
Intermediate risk	11 (29)	2 (11)	.166
High risk	19 (35)	6 (22)	.189



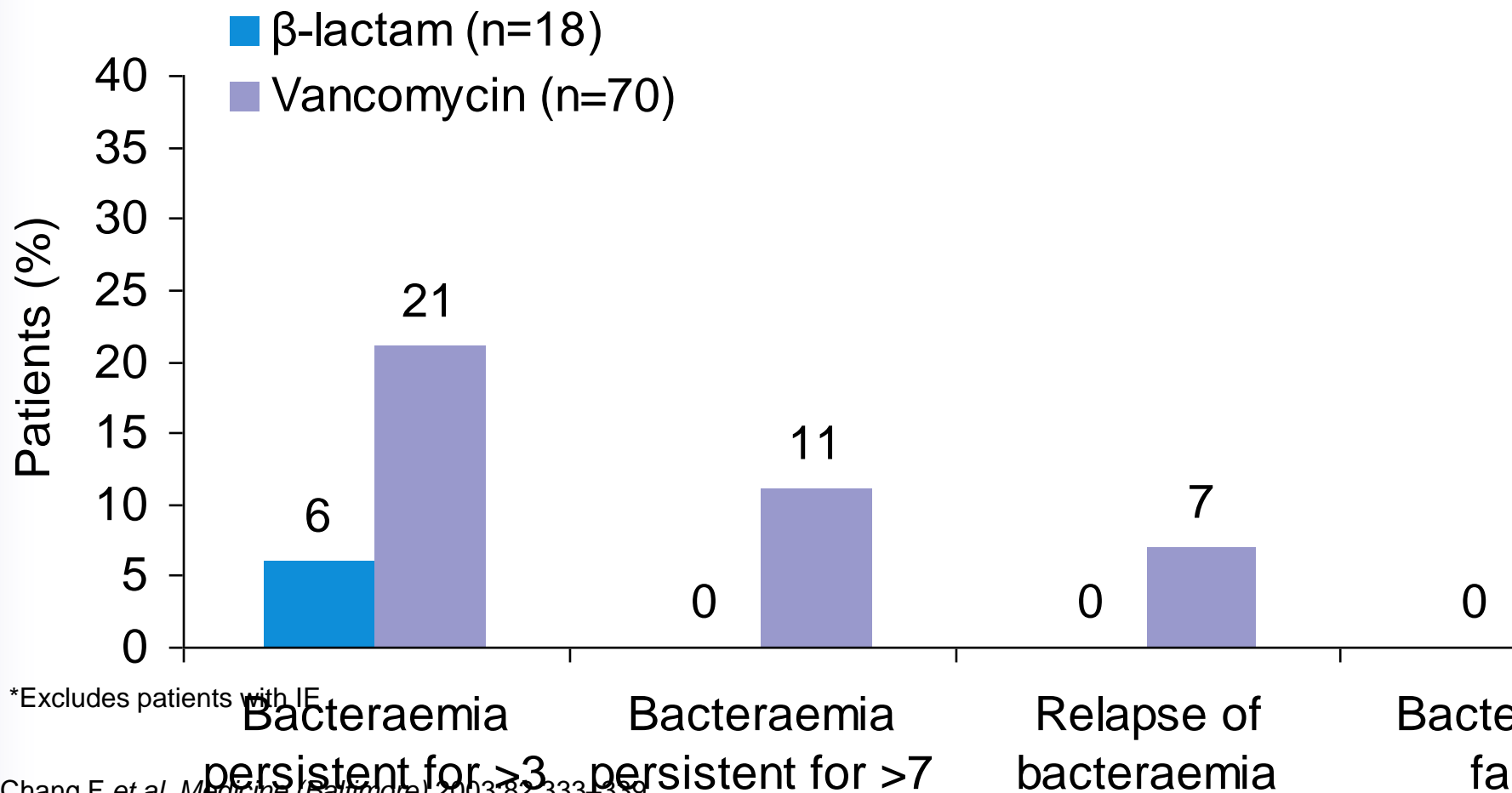
**Figure 1.** Kaplan-Meier estimates of the probability of 60-d mortality, shown here as the probability of survival at 60 d between vancomycin-treated subjects (vanco) and daptomycin-treated subjects (dapto) with methicillin-resistant *Staphylococcus aureus* bloodstream infection with a higher vancomycin minimum inhibitory concentration.

**Table 3. Independent Predictors of Failure in Susceptible Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection With a Vancomycin Minimum Inhibitory Concentration >1 µg/mL**

Factor	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
Right-sided endocarditis	0.18 (0.04–0.87)	.033	0.08 (0.01–0.83)	.035
Acute renal failure	2.11 (0.91–4.91)	.082	3.91 (1.05–14.56)	.042
Vancomycin treatment group	1.85 (0.92–3.72)	.084	3.13 (1.00–9.76)	.049

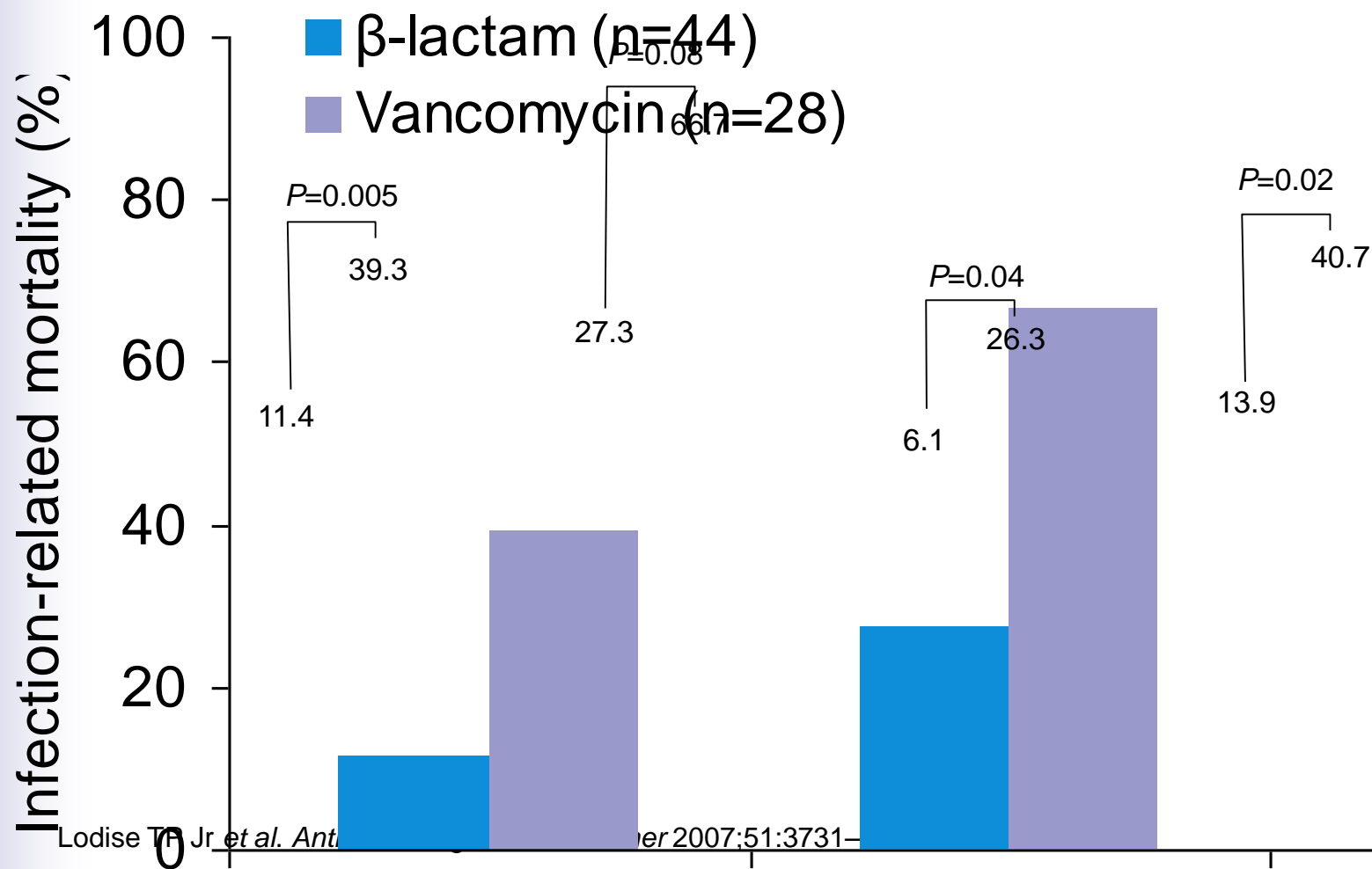
Abbreviations: CI, confidence interval; OR, odds ratio.

# Vancomycin shows inferior outcomes to $\beta$ -lactams in MSSA bacteraemia\*

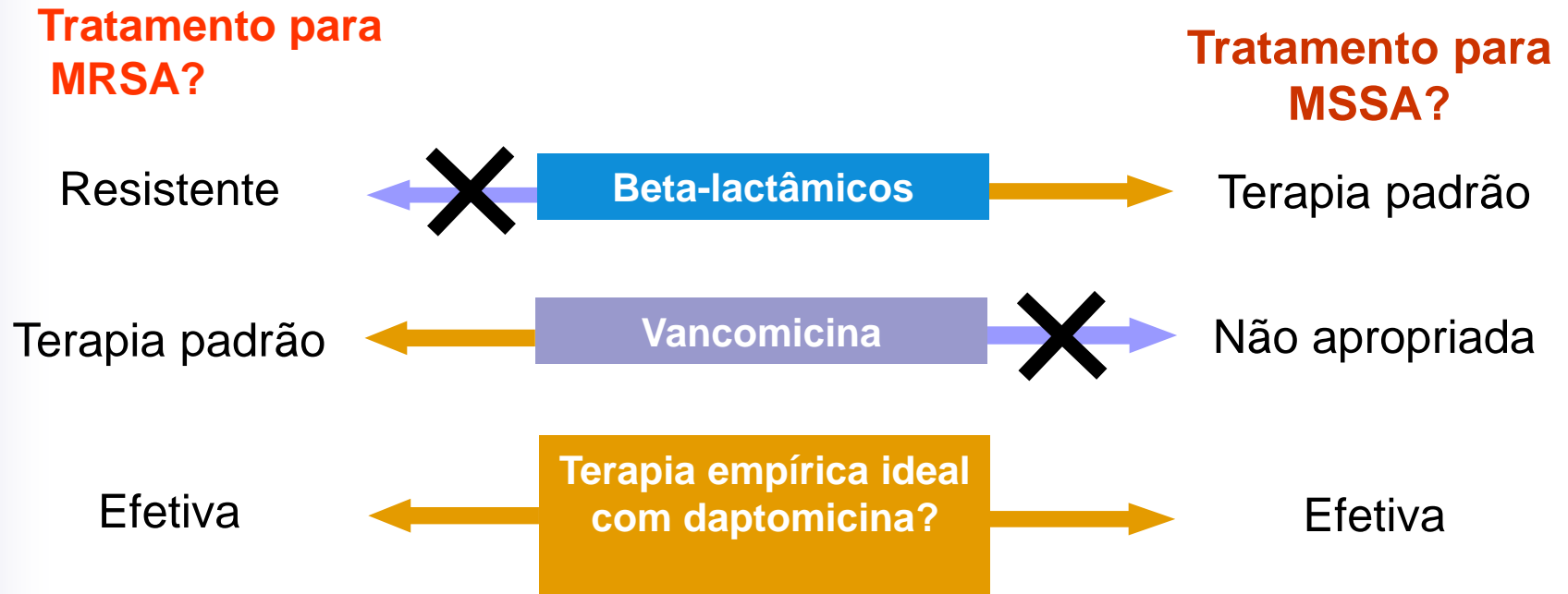


\*Excludes patients with IE

# Higher infection-related mortality in IVDU with MSSA IE for vancomycin vs $\beta$ -lactams



# O dilema da terapia empírica de bacteriemia por *Staphylococcus aureus*



1. Khatib R *et al.* *Eur J Clin Microbiol Infect Dis* 2006;25:181–185

2. Lodise T *et al.* *Clin Infect Dis* 2003;36:1418–1423



MITO

# Daptomicina

- Droga excelente. Com uma única finalidade...
- Volume de distribuição pequeno (6L)
- Trabalho contém viés importante:
  - Uso de gentamicina no braço da Vanco
  - Mesmo assim, sem superioridade...

Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

CID 2009;48 (15 March)

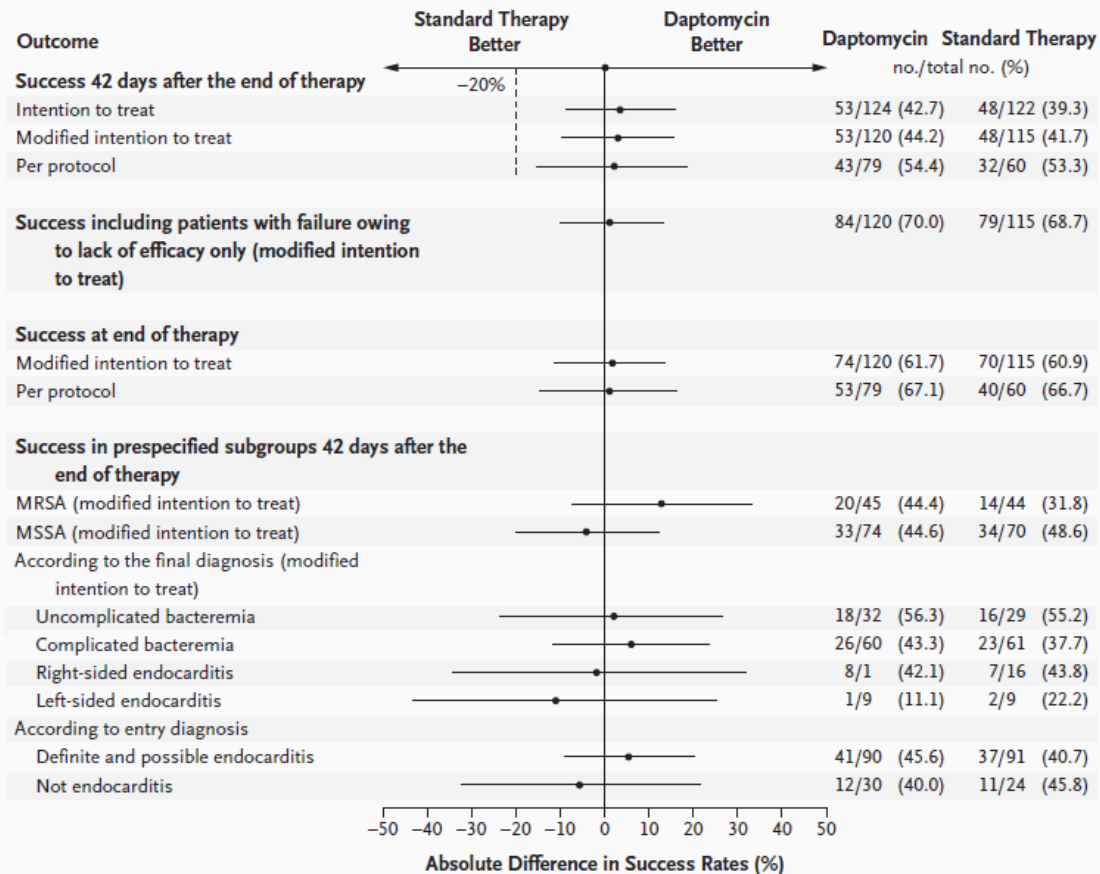
# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 17, 2006

VOL. 355 NO. 7

## Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*



**Figure 1.** Comparison of the Rates of Success of Daptomycin and Standard Therapy for *Staphylococcus aureus* Bacteremia and Endocarditis.

Horizontal bars represent 95 percent confidence intervals.

# Linezolida

- Boa droga...Para VRE e GISA !!!!!
- Mecanismo de ação único
- Sem resistência cruzada
- Concentração pulmonar 3,5x maior que a sérica
- E mesmo assim, após uma dezena de trials e meta-analises, não conseguiu mostrar superioridade à velha Vancomicina!!!!!!!!!!!!!!

# Linezolida

- Efeitos adversos:
  - Plaquetopenia (pior na insuficiência renal!!!)
  - Neuropatia periférica irreversível
  - Síndrome serotoninérgica (Black box warning!)
- Interações medicamentosas:
  - IMAO, Triptanos, TCA, ISRS, agentes adrenérgicos

# Linezolid (PNU-100766) versus Vancomycin in the Treatment of Hospitalized Patients with Nosocomial Pneumonia: A Randomized, Double-Blind, Multicenter Study

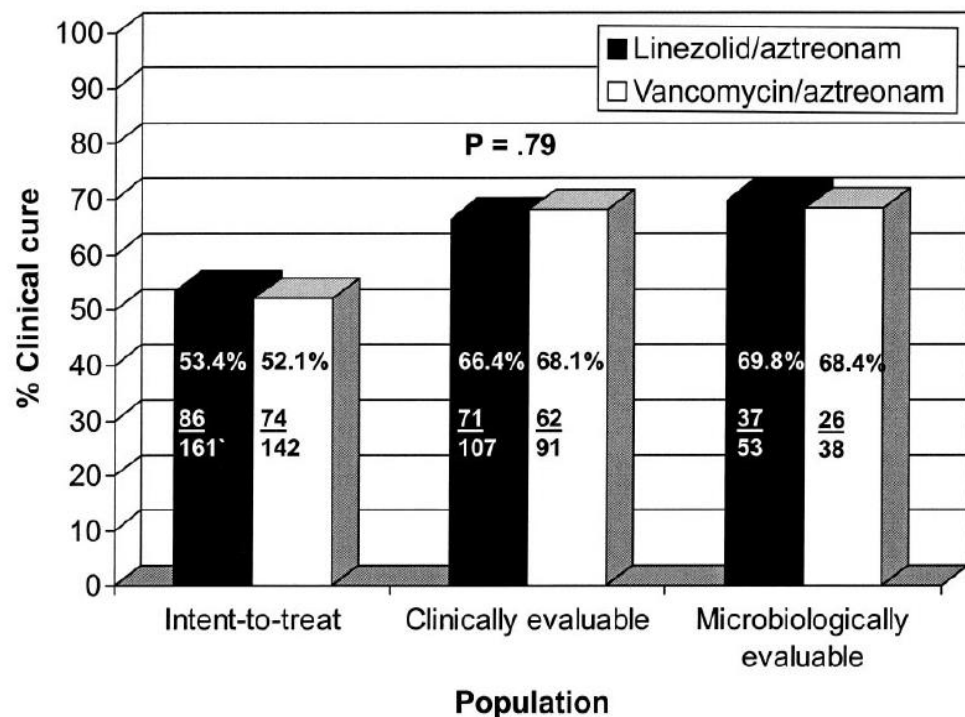
Ethan Rubinstein,<sup>1</sup> Sue K. Cammarata,<sup>2</sup> Thomas H. Oliphant,<sup>2</sup> Richard G. Wunderink,<sup>3</sup>  
and the Linezolid Nosocomial Pneumonia Study Group<sup>a</sup>

CID 2001:32 (1 February)

**Table 4. Eradication rates at follow-up by pathogen among microbiologically evaluable patients.**

Pathogen	Linezolid recipients	Vancomycin recipients
<i>Staphylococcus aureus</i>	25/41 (61.0)	15/23 (65.2)
Documented	3/41 (7.3)	5/23 (21.7)
Presumed	22/41 (53.7)	10/23 (43.5)
Methicillin-resistant <i>S. aureus</i>	15/23 (65.2)	7/9 (77.8)
Documented	1/23 (4.3)	2/9 (22.2)
Presumed	14/23 (60.9)	5/9 (55.6)
<i>Streptococcus pneumoniae</i>	9/9 (100)	9/9 (100)
Documented	3/9 (33.3)	6/9 (66.7)
Presumed	6/9 (66.7)	3/9 (33.3)

**NOTE.** Data are no. of patients with eradication/total (%).



# CHEST<sup>®</sup>

Official publication of the American College of Chest Physicians

## Linezolid vs Vancomycin: Analysis of Two Double-Blind Studies of Patients With Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia

Richard G. Wunderink, Jordi Rello, Sue K. Cammarata, Rodney V. Croos-Dabrera and Marin H. Kollef

*Chest* 2003;124:1789-1797

**Table 2—Results of Logistic Regression Analysis for Survival in Patients With Nosocomial Pneumonia**

Predictors	OR (95% CI)	p Value
ITT <i>S aureus</i> (n = 339)		
Linezolid therapy	1.7 (1.0–2.9)	0.068
Age < 65 yr	1.7 (0.9–3.0)	0.081
APACHE II score $\leq$ 20	3.7 (2.0–6.9)	< 0.001†
Single-lobe pneumonia	1.7 (1.0–2.9)	0.072
Presence of pleural effusion	1.6 (0.9–3.0)	0.127
Absence of cardiac comorbidities	2.3 (1.3–4.1)	0.005†
Absence of renal comorbidities	2.2 (1.0–4.8)	0.042†
ITT MRSA (n = 160)		
Linezolid therapy	2.2 (1.0–4.8)	0.050†
APACHE II score $\leq$ 20	2.1 (0.8–5.1)	0.116
Presence of pleural effusion	1.9 (0.8–4.6)	0.145
Creatinine $\leq$ 229.8 $\mu$ mol/L*	11.9 (1.1–125.0)	0.038†
Absence of cardiac comorbidities	3.0 (1.4–6.6)	0.005†

### Survival Analysis

All patients were included in the ITT analysis of survival. Overall Kaplan-Meier survival rates for all patients with nosocomial pneumonia (ITT group) were 80.9% (424 of 524 patients) for linezolid and 77.8% (385 of 495 patients) for vancomycin ( $p = 0.21$ ). As shown in Figure 2, Kaplan-Meier

**Table 1—Patient Characteristics, Including Those Used in Logistic Regression Analysis\***

Characteristics	ITT <i>S aureus</i> (n = 339)		ITT MRSA (n = 160)	
	Linezolid (n = 168)	Vancomycin (n = 171)	Linezolid (n = 75)	Vancomycin (n = 85)
Age ≥ 65 yr	97 (57.7)	93 (54.4)	50 (66.7)	62 (72.9)
Sex†				
Male	109 (64.9)	100 (58.5)	44 (58.7)	48 (56.5)
Female	59 (35.1)	71 (41.5)	31 (41.3)	37 (43.5)
Race†				
White	150 (89.3)	153 (89.5)	70 (93.3)	74 (87.1)
Black	12 (7.1)	5 (2.9)	4 (5.3)	3 (3.5)
Other	6 (3.6)	13 (7.6)	1 (1.3)	8 (9.4)
Treatment duration†				
Mean ± SD, d	10.9 ± 4.6	10.6 ± 4.9	11.3 ± 4.3	10.7 ± 5.3
Range, d	1–27	1–27	1–22	2–27
Death†	37 (22.0)	50 (30.2)	15 (20.0)	31 (36.5)
Bacteremia	22 (13.1)	22 (12.9)	8 (10.7)	14 (16.5)
VAP	118 (70.2)	114 (66.7)	49 (65.3)	47 (55.3)
APACHE II score > 20	39 (23.2)	33 (19.3)	18 (24.0)	21 (24.7)
Chest radiographic variables				
Multilobe pneumonia	99 (58.9)	91 (53.2)	43 (57.3)	49 (57.7)
Pleural effusion	50 (29.8)	50 (29.2)	23 (30.7)	28 (32.9)
Bilirubin > 41.0 mol/L (2.4 mg/dL)	4 (2.4)	8 (4.7)	2 (2.7)	2 (2.4)
Serum creatinine > 229.8 mol/L‡	7 (4.2)	7 (4.1)	3 (4.0)	4 (4.7)
Comorbidities				
Cardiac	39 (23.2)	50 (29.2)	18 (24.0)	34 (40.0)
Diabetic	30 (17.9)	46 (26.9)	13 (17.3)	33 (38.8)
Hepatic	8 (4.8)	4 (2.3)	5 (6.7)	1 (1.2)
Oncologic	18 (10.7)	11 (6.4)	9 (12.0)	7 (8.2)
Renal	19 (11.3)	21 (12.3)	10 (13.3)	18 (21.2)
Respiratory	62 (36.9)	62 (36.3)	28 (37.3)	34 (40.0)
Vascular	8 (4.8)	7 (4.1)	4 (5.3)	4 (4.7)



# Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

CID 2012;54 (1 March)

# Desbalanço de Comorbidades

**Table 1. Baseline Demographics and Clinical Characteristics of the Per-Protocol Population**

Characteristic	Linezolid (n = 172)	Vancomycin (n = 176)
<b>Sex, No. (%)</b>		
Male	116 (67.4)	112 (63.6)
Female	56 (32.6)	64 (36.4)
<b>Race, No. (%)</b>		
White	119 (69.2)	112 (63.6)
Black	18 (10.5)	28 (15.9)
Asian	27 (15.7)	28 (15.9)
<b>Preexisting condition, No. (%)</b>		
Diabetes mellitus	62 (36.1)	74 (42.5)
Pulmonary	117 (68.0)	118 (67.1)
Kidney	48 (27.9)	65 (36.9)
Cardiac	97 (56.4)	106 (60.2)
Age, years, mean (SD)	60.7 (18.0)	61.6 (17.7)
Weight, kg, mean (SD)	78.1 (23.3)	76.5 (21.8)
Mechanical ventilation, No. (%)	115 (66.9)	130 (73.9)

## Type of pneumonia, No. (%)

Healthcare-associated <sup>a</sup>	26 (15.1)	30 (17.1)
Nosocomial	146 (84.9)	146 (83.0)
<b>Ventilator-associated<sup>b</sup></b>		
Bacteremia, No. (%)	9 (5.2)	20 (10.8)
<b>APACHE II score</b>		
Mean (SD)	17.2 (6.4)	17.4 (6.0)
<b>Modified CPIS (maximal score 17)<sup>c</sup></b>		
Mean (SD)	9.7 (2.1)	9.4 (2.3)

# Pior resposta no subgrupo com comorbidades

**Table 2. Clinical Success Rates in the Per-Protocol Population at End of Study, by Patient Subgroup**

Subgroup	Linezolid Arm, No. (%)	Vancomycin Arm, No. (%)	95% CI for Difference <sup>a</sup>
Evaluable for efficacy analyses <sup>b</sup>	165	174	
Overall	95/165 (57.6)	81/174 (46.6)	.5 to 21.6
Mechanical ventilation			
Yes	61/110 (55.5)	57/129 (44.2)	-1.4 to 23.9
No	34/55 (61.8)	24/45 (53.3)	-10.9 to 27.0
Bacteremia			
Yes	4/9 (44.4)	6/19 (31.6)	-25.7 to 51.5
No	91/156 (58.3)	75/155 (48.4)	-1.1 to 21.0
Glomerular filtration rate			
<50 mL/min	12/28 (42.9)	15/35 (42.9)	-24.6 to 24.6
≥50 mL/min	82/134 (61.2)	64/133 (48.1)	1.2 to 24.9

No grupo de menos clearance não  
houve diferença!

Glomerular filtration rate			
<50 mL/min	12/28 (42.9)	15/35 (42.9)	−24.6 to 24.6
≥50 mL/min	82/134 (61.2)	64/133 (48.1)	1.2 to 24.9

# Sub-Dose de Vancomicina

Vancomycin serum trough levels,  
median (interquartile range) µg/mL

Day 3 (n = 140)	...	12.3 (9.45)
Day 6 (n = 90)	...	14.7 (10.40)
Day 9 (n = 33)	...	16.1 (11.30)

Table 5. Summary of Vancomycin Trough Levels – mITT and PP Populations per Treatment Day<sup>\*2</sup>

Treatment Day	n	Mean Concentration (mcg/mL)	Median Concentration (mcg/mL)	Concentration Range (mcg/mL)
<b>mITT</b>				
3	166	14.4	12.7	(2.8 – 50.8)
6	107	17.1	14.8	(2.7 – 45.0)
9	38	17.1	16.0	(2.0 – 46.9)
<b>PP</b>				
3	140	14.1	12.3	(2.8 – 50.8)
6	90	16.9	14.7	(2.7 – 45.0)
9	33	17.4	16.1	(2.0 – 46.9)

\* As a double-blind study, only the research pharmacist and unblinded monitor were aware of the vancomycin levels.

- Não foi realizada dose de ataque de Vancomicina!
- Não foi feito o ajuste da dose de vancomicina de acordo com a Vancocinemia!

Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 2011; 52:975–81.

CID 2012;54 (1 March)

# Informação inverídica no abstract

- Abstract:

Vancomycin dose was adjusted on the basis of trough levels.

- Methods:

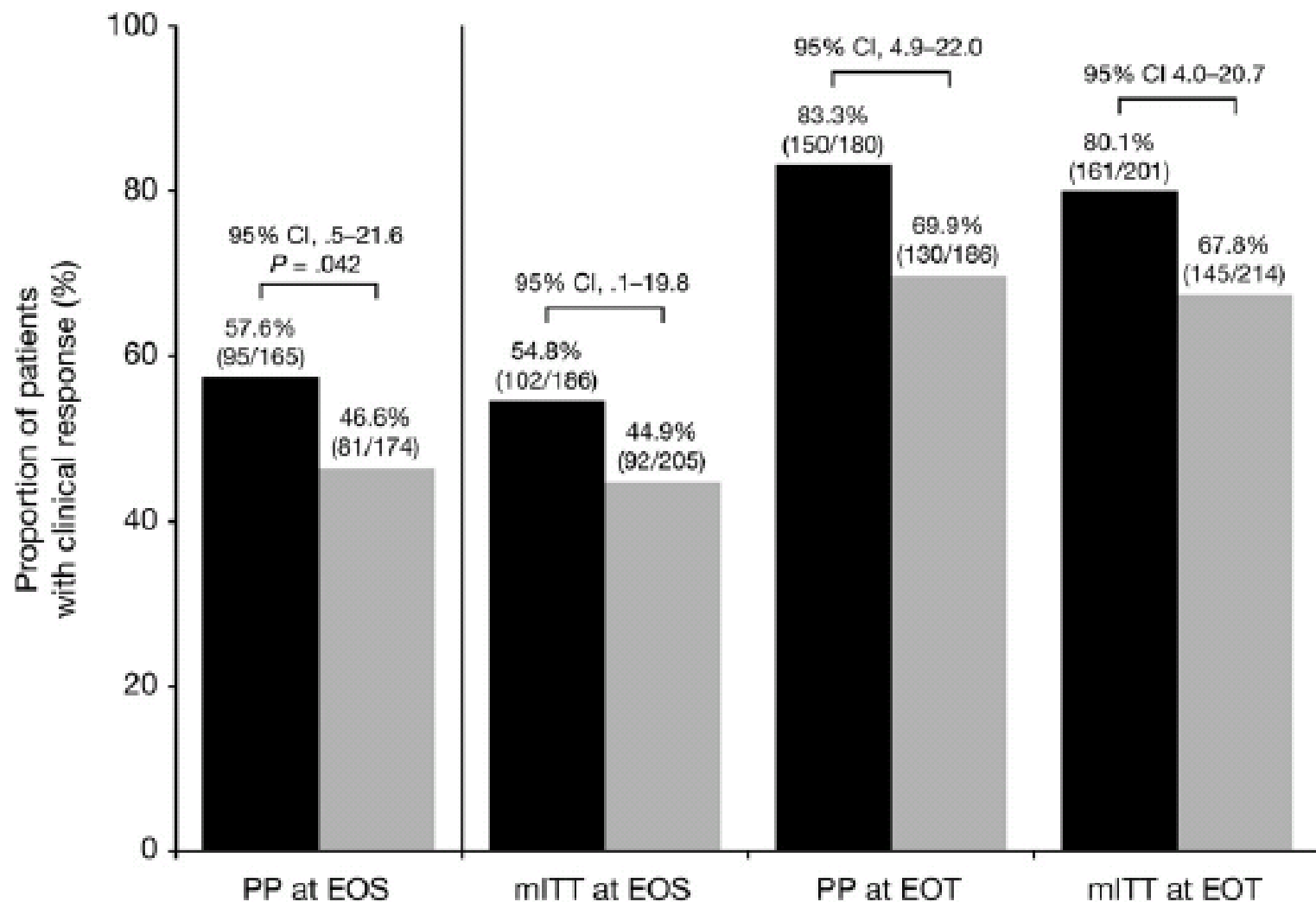
The pharmacist monitored and adjusted vancomycin doses according to local protocols based on trough levels and renal impairment, while maintaining investigator blinding.

- *No protocolo:*

### 7.3. Central Laboratory

*Laboratory assessments for study medication trough levels will be performed by the central laboratory on days 3 and 6.*

# Ausência de significância nas análises ITT



# Algo de podre no reino da dinamarca...

**Table 1. Baseline Demographics and Clinical Characteristics of the Per-Protocol Population**

Characteristic	Linezolid (n = 172)	Vancomycin (n = 176)
----------------	------------------------	-------------------------

**Table 2. Clinical Success Rates in the Per-Protocol Population at End of Study, by Patient Subgroup**

Subgroup	Linezolid Arm, No. (%)	Vancomycin Arm, No. (%)	95% CI for Difference <sup>a</sup>
Evaluable for efficacy analyses <sup>b</sup>	165	174	

<sup>b</sup> Patients with end of study outcome of "indeterminate" were excluded from efficacy analysis.



**Should We Abandon  
Vancomycin for Treatment  
of Methicillin-Resistant  
*Staphylococcus aureus*  
Pneumonia? Still Questions  
to Answer**

Fabio Silvio Taccone,<sup>1</sup> Jean-Louis Vincent,<sup>1</sup>  
Olivier Denis,<sup>2</sup> and Frédérique Jacobs<sup>3</sup>

**Questionable Superiority of  
Linezolid for Methicillin-  
Resistant *Staphylococcus*  
*aureus* Nosocomial  
Pneumonia: Watch Where  
You Step**

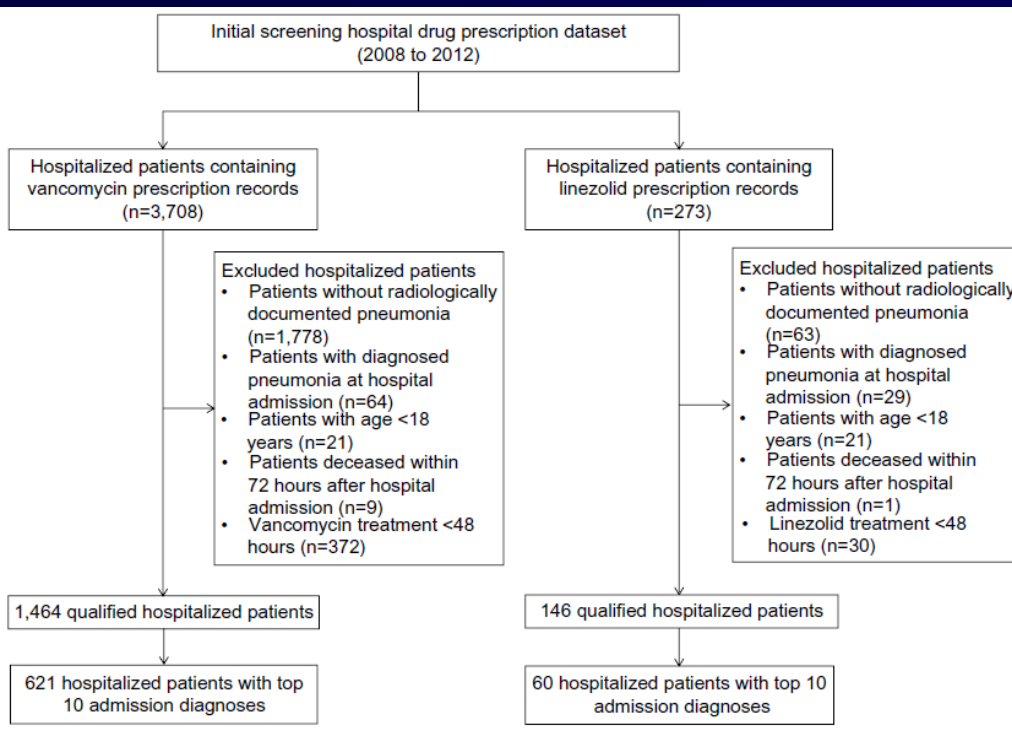
Timothy Lahey  
Dartmouth Medical School, Lebanon, New Hampshire

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CID 2012:55 (1 July)

# Clinical response and hospital costs associated with the empirical use of vancomycin and linezolid for hospital-acquired pneumonia in a Chinese tertiary care hospital: a retrospective cohort study

ClinicoEconomics and Outcomes Research 2014;6 451–461



**Table 2** Head-to-head comparisons on clinical outcomes between empirical use of vancomycin and linezolid for difficult hospital-acquired pneumonia in propensity score matched patients

Treatment	Vancomycin		Linezolid		P-value
Sample size	60		60		
Clinical outcomes	n	%	n	%	
At the end of treatment					
Clinical cure	18	30.0	19	31.7	0.847
Clinical improvement	4	6.7	6	10.0	0.480
Treatment failure	33	55.0	27	45.0	0.289
Pneumonia-related complications					
Respiratory failure	1	1.7	3	5.0	0.317
Infection shock	0	0.0	1	1.7	1.000
Pneumonia-related mortality	0	0.0	1	1.7	1.000
All-cause death	0	0.0	1	1.7	1.000
At hospital discharge					
Pneumonia-related mortality	1	1.7	6	10.0	0.059
All-cause mortality	2	3.3	11	18.3	0.013

**Note:** The P-value in bold is significant.

Linezolid versus vancomycin for the treatment of suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a systematic review employing meta-analysis

## Results

Nine trials involving 2618 pneumonia patients were reviewed.

Linezolid was not found to be superior to vancomycin for clinical cure when categories of pathogen were not considered and in a subgroup of NP patients with MRSA infection [relative risk (RR) = 1.16, 95 % confidence interval (CI) = 0.95–1.43,  $P = 0.15$ ]. Compared with vancomycin, linezolid has no difference in the overall microbiological eradication rate (RR = 1.12, 95 % CI = 0.96–1.30,  $P = 0.15$ ) and specific MRSA eradication rate (RR = 1.16, 95 % CI = 0.93–1.45,  $P = 0.19$ ) in NP patients.

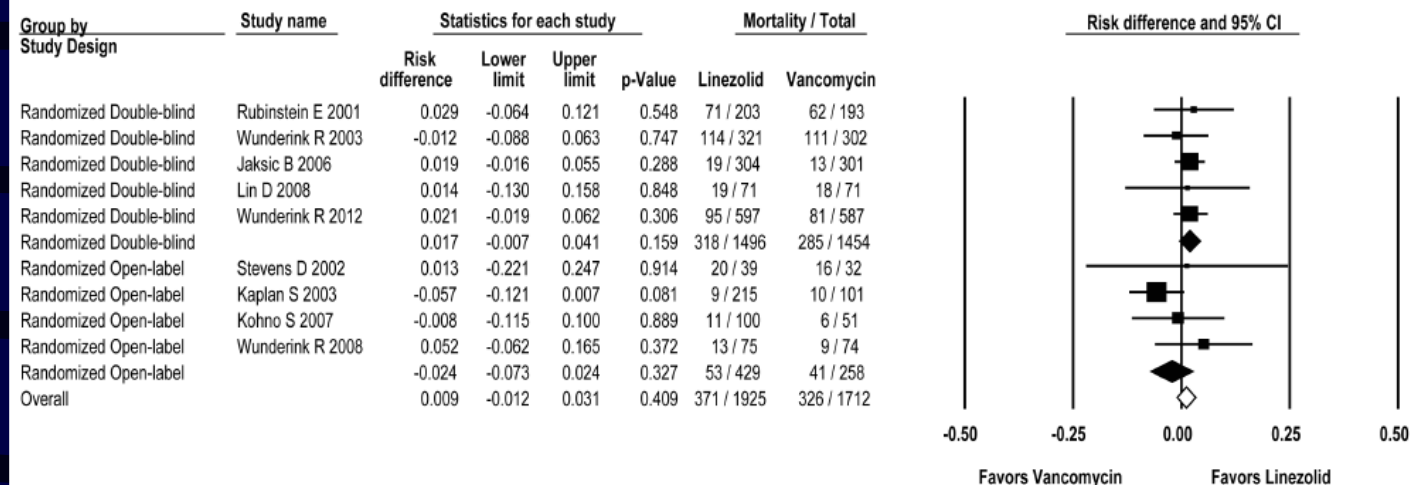
## Conclusion

These results suggest that linezolid is not superior to vancomycin with respect to both clinical and microbiological cure rates in patients with MRSA NP.

# Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis

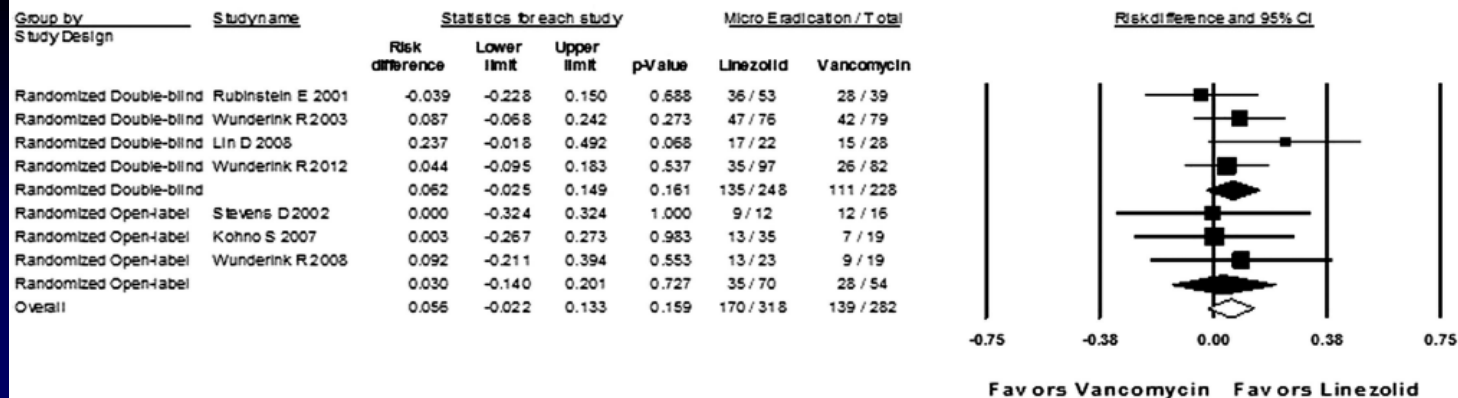
Kalil AC, Klompas M, Haynatzki G, *et al. BMJ Open* 2013;3:e003912.

## (a) Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Clinical Response\*



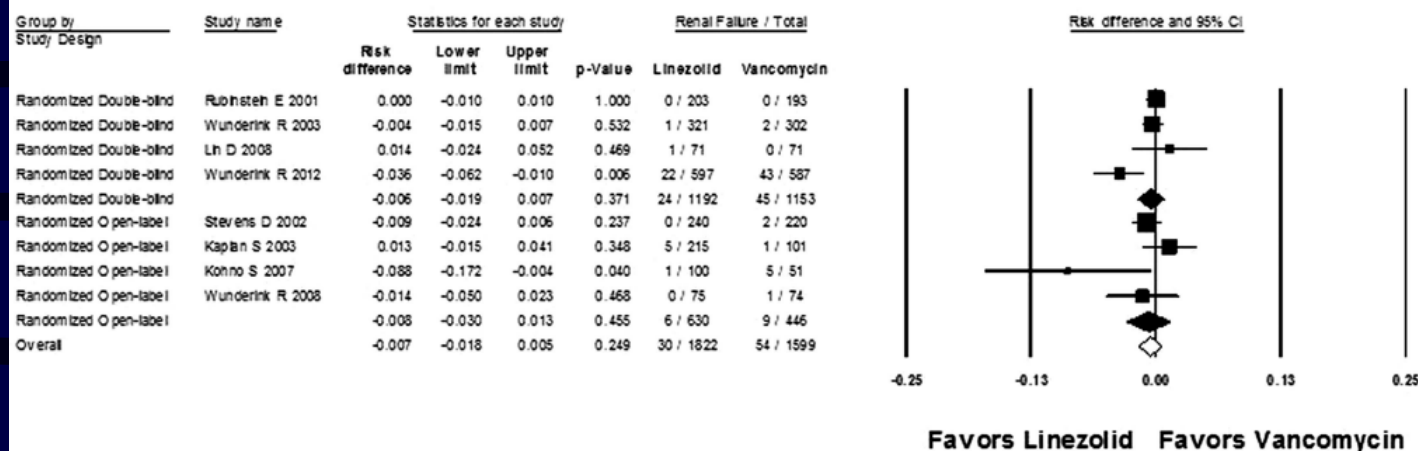
\*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I<sup>2</sup>=0%

## (a) Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Microbiological Eradication\*



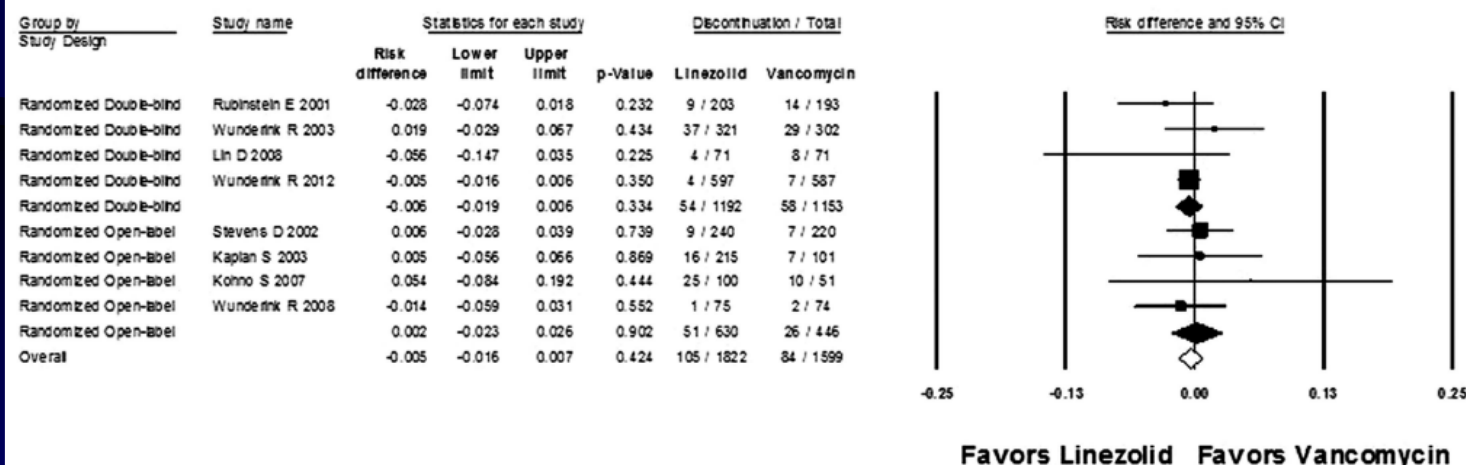
\*Microbiological Evaluable/Per-Protocol Population. Z=1.408; P=0.159; Heterogeneity: Q=3.404; P=0.757; I<sup>2</sup>=0%

# (a) Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Renal Failure\*



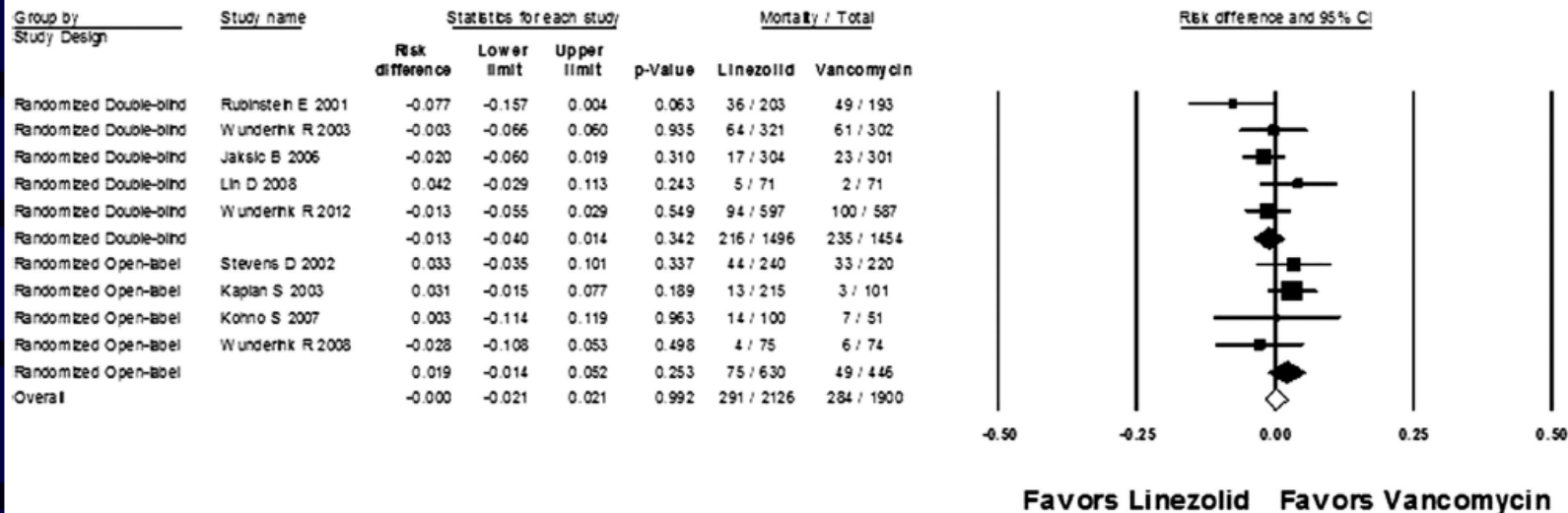
\*Intention-to-Treat Population. Z=-1.152; P=0.249; Heterogeneity: Q=13.525; P=0.06; I<sup>2</sup>=48%

# (b) Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Discontinuation due to Adverse Events\*



\*Intention-to-Treat Population. Z=-0.800; P=0.424; Heterogeneity: Q=4.499; P=0.721; I<sup>2</sup>=0%

## Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Mortality\*



\*Intention-to-Treat Population. Z=0.010; P=0.992; Heterogeneity: Q=9.251; P=0.322; I<sup>2</sup>=13.5%

### ARTICLE SUMMARY

#### Strengths and limitations of this study

- Linezolid and vancomycin have similar efficacy and safety profiles.
- The near-zero efficacy difference between both antibiotics demonstrates that no drug is superior for the treatment of hospital-acquired pneumonia.
- Our results remained consistent across different patient populations and study designs for both clinical response and mortality outcomes.
- Randomised controlled trials set selective inclusion criteria that can limit their generalisability to unselected populations.



# Which antibiotic for hospital acquired pneumonia caused by MRSA?

Vancomycin is as safe and effective as newer alternatives

BMJ 2014;348:g1469 doi: 10.1136/bmj.g1469 (Published 13 February 2014)

**EDITORIALS**

Given the findings of this well conducted meta-analysis, and because additional trial evidence comparing linezolid with vancomycin is unlikely to become available, clinicians can conclude with confidence that these agents have similar clinical efficacy for adults with hospital acquired pneumonia caused by MRSA.

In conclusion, newer is not necessarily better, and clinicians can continue to prescribe vancomycin for MRSA hospital acquired pneumonia with the confidence that it is as equally efficacious and safe as any of the newer alternatives.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None.

## **Linezolid versus vancomycin for meticillin-resistant *Staphylococcus aureus* infection: a meta-analysis of randomised controlled trials.**

An MM et al. 2013 Int J Antimicrob Agents May;41(5):426-33

“This meta-analysis provides evidence that linezolid possesses significant advantages compared with vancomycin and may be a superior alternative for MRSA-related infection.”

## **Comments on new linezolid's meta-analysis.**

Cunha A,

Rocha JL., Int J Antimicrob Agents 2013 Oct;42(4):377-8.

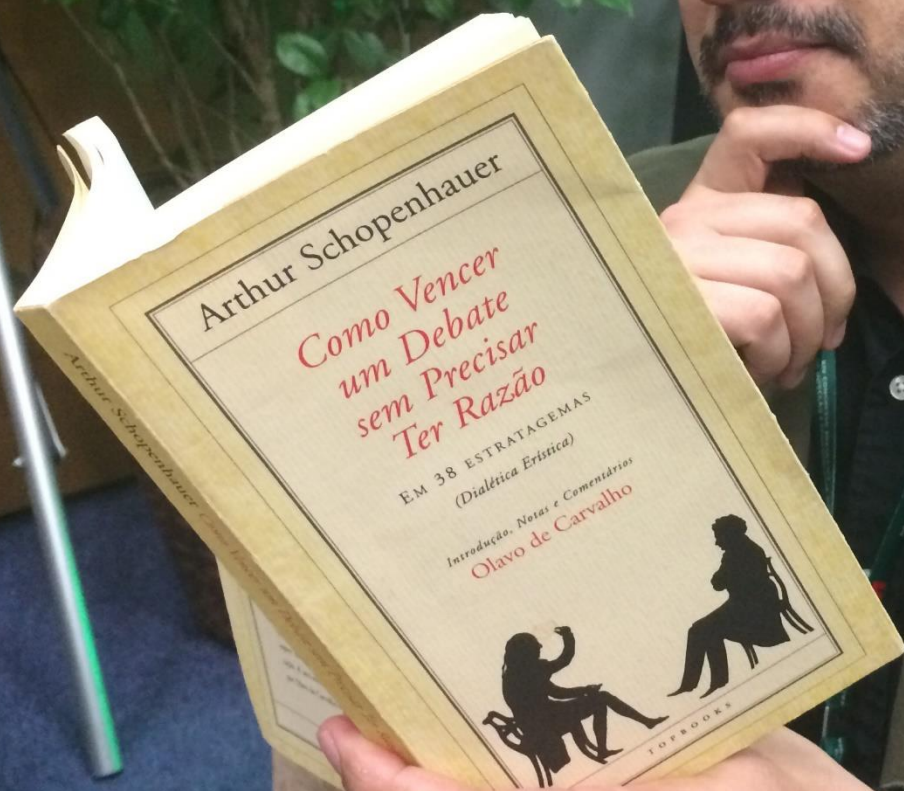
“There was no difference in mortality, and whilst a small difference in clinical cure at the test-of-cure (TOC) visit was found, this analysis was based largely on trials in which patients with SSTIs accounted for the totality or a large number of patients. Regarding the analysis of clinical cure at TOC visit, 2800 (54.9%) of 5100 patients enrolled had SSTIs. Since linezolid is clearly superior to vancomycin for this subgroup, a bias in the meta-analysis has been created.”



# Considerações Finais

Alexandre Cunha

Dr. Jaime flagrado poucos  
minutos antes da apresentação:



Arthur Schopenhauer

*Como Vencer  
um Debate  
sem Precisar  
Ter Razão*

EM 38 ESTRATAGEMAS  
(Dialética Eristica)

Introdução, Notas e Comentários  
Olavo de Carvalho



TOPBOOKS

Arthur Schopenhauer

*Como Vencer  
um Debate  
sem Precisar  
Ter Razão*

EM 38 ESTRATAGEMAS

*(Dialética Prática)*

*Introdução, Notas e Comentários*

Olavo de Carvalho



TOPBOOKS





Joseph Goebbles – Ministro de Propaganda de Hitler

“Uma mentira repetida mil vezes torna-se verdade”

# High rate of decreasing daptomycin susceptibility during the treatment of persistent *Staphylococcus aureus* bacteremia

Eur J Clin Microbiol Infect Dis (2008) 27:433–437

- 18 SAB = 10 persistentes

**Table 2** Minimal inhibitory concentration (MIC) of serial blood *S. aureus* isolates pre- and post-daptomycin (DAP) therapy

Case	(SCCmec)	DAP (day)	DAP dose mg/kg <sup>a</sup>	Pre-therapy MIC (μg/ml)	Post-therapy MIC (μg/ml) day					
					2–4	5–8	9–12	13–14	15–20	≥21
1	II	10	4; 6	ND <sup>b</sup>		0.125				
2	II	27	4	0.5	0.5	2	4	4	4	4
3	NA <sup>c</sup> (MSSA)	4	6	0.125		0.125				
4	II	18	5	0.25	0.25					
5	II	15	4; 6	ND		2		2	2	2
6	II	UD <sup>d</sup>	6	0.25						0.25
7	II	27	5	0.25						2
8	NT <sup>e</sup>	28	5	ND	0.5		2			2
9	IVa	26	4; 6	0.25	0.5		2	2		
10	II	13	5	0.5	0.5	1	2	2	2	

<sup>a</sup>Cases 1, 2, 4, 6, and 7 were hemodialysis patients on daptomycin every 48 h

<sup>b</sup>Not done

<sup>c</sup>Not applicable

<sup>d</sup>Undefined duration (transferred to another facility on daptomycin)

<sup>e</sup>Non-typeable

Daptomycin versus Standard Therapy for Bacteremia  
and Endocarditis Caused by *Staphylococcus aureus*

treated with daptomycin; six of these patients had microbiologic failure. Five of these six patients had isolates that were MRSA. In six patients with microbiologic failure, the baseline MIC was 0.25  $\mu\text{g}$  of daptomycin per milliliter in five isolates and 0.5  $\mu\text{g}$  per milliliter in one isolate and rose to 2  $\mu\text{g}$  per milliliter in five isolates and 4  $\mu\text{g}$  per milliliter in one isolate. In the central microbiology laboratory, the isolates from one of the nine patients treated with vancomycin who had microbiologic failure had an increase in the MIC of a diagnosis of complicated bacteremia. The MIC of daptomycin of the *S. aureus* isolates increased from baseline values in seven patients who were

Development of decreased susceptibility to  
daptomycin and vancomycin in a *Staphylococcus aureus* strain during prolonged therapy

Paul G. Mariani<sup>1</sup>†, Helio S. Sader<sup>2\*</sup> and Ronald N. Jones<sup>2,3</sup>

Meritcare Hospital, Fargo, ND, USA; <sup>2</sup>JMI Laboratories, North Liberty, IA 52317, USA; <sup>3</sup>Tufts University School of Medicine, Boston, MA, USA

*Journal of Antimicrobial Chemotherapy*  
doi:10.1093/jac/dkl232

Advance Access publication 3 June 2006

J Antimicrob Chemother. 2007 Aug;60(2):334-40. Epub 2007 May 31.

**Evaluation of daptomycin treatment of *Staphylococcus aureus* bacterial endocarditis: an in vitro and in vivo simulation using historical and current dosing strategies.**

Rose WE, Rybak MJ, Kaatz GW.

Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, and Detroit Receiving Hospital, MI 48201, USA.

**OBJECTIVES:** A failure to daptomycin therapy and subsequent emergence of a daptomycin non-susceptible isolate occurred during the 1990 clinical investigation of daptomycin for the treatment of *Staphylococcus aureus* bacteraemia and endocarditis. We attempted to determine if this occurrence was reproducible in vitro and if it could be prevented by various daptomycin dosing strategies. **METHODS:** The daptomycin susceptible parent strain (SA-675) and the subsequent non-susceptible derivative (SA-684) were evaluated. In the rabbit endocarditis model, daptomycin 3 mg/kg every 8 h for 4 days was administered to simulate the study patient's pharmacokinetic exposure. Daptomycin doses of 1.5 and 3 mg/kg every 12 h and 6 and 10 mg/kg every 24 and 48 h were simulated in the in vitro model with simulated endocardial vegetations (SEVs). **RESULTS:** Daptomycin significantly reduced bacterial counts of SA-675 in rabbits, but one in 10(5)-10(6) organisms from vegetations of one animal had an 8-fold increase in MIC. Daptomycin 1.5 mg/kg every 12 h in the in vitro model demonstrated no activity against either strain; reduced susceptibility emerged in SA-675 (4-fold increase in MIC). Bactericidal activity was noted with 6 and 10 mg/kg dosing against SA-675 with no resistance detected. The activity of the 6 mg/kg regimen was reduced against SA-684 but significantly improved activity was noted with 10 mg/kg daily. **CONCLUSIONS:** The emergence of resistance was successfully recreated at suboptimal dosing regimens while the current recommended regimen of 6 mg/kg/day prevented the emergence of non-susceptible mutants. Daptomycin 10 mg/kg/day demonstrated even more enhanced killing. Further investigation with daptomycin 10 mg/kg is warranted.

PMID: 17540670 [PubMed - indexed for MEDLINE]



# Linezolid Resistance in Vancomycin-Resistant *Enterococcus faecalis* and *Enterococcus faecium* Isolates in a Brazilian Hospital

May 2014 Volume 58 Number 5

Antimicrobial Agents and Chemotherapy p. 2993–2994

TABLE 1 Demographic data and antimicrobial susceptibility profiles of linezolid and vancomycin-resistant *E. faecalis* and *E. faecium* clinical strains<sup>a</sup>

Patient	Strain	ICU	Culture date	Total no. of treatment days	Clinical specimen	PFGE type	MLST result	Glycopeptide resistance gene	23S rRNA mutation	Resistance profile MIC (μg/ml)									
										LZD	VAN	TEC	PEN	AMP	ERY	TET	CHL	CIP	LEV
1	<i>E. faecalis</i> 18/755	Yes	August 2009	10	Blood	A	ST525	<i>vanA</i>	G2576T	8	>256	96	16	4	2	64	16	>32	>32
2	<i>E. faecalis</i> 28/279	Yes	April 2010	NA	Urine	A	ST525	<i>vanA</i>	G2576T	16	>256	96	16	4	2	64	16	>32	>32
3	<i>E. faecalis</i> 37/245	No	November 2010	27	Blood	A	ST525	<i>vanA</i>	G2576T	32	>256	96	16	4	2	64	16	>32	>32
3	<i>E. faecalis</i> 38/443	Yes	January 2011	27	Blood	A	ST525	<i>vanA</i>	G2576T	8	>256	96	16	4	2	64	16	>32	>32
4	<i>E. faecalis</i> 40/1258	Yes	April 2011	30	Urine	B	ST526	<i>vanA</i>	G2576T	16	>256	>256	16	2	>256	0.25	256	>32	>32
5	<i>E. faecalis</i> 50/515 <sup>b</sup>	No	December 2011		Urine	C	ST62			2	1	0.5	4	1	2	64	4	1	1
6	<i>E. faecium</i> 42/448	Yes	November 2011	32	Urine	D	ST412	<i>vanA</i>	G2576T	64	>256	96	>32	512	>256	1	>256	>32	>32
7	<i>E. faecium</i> 51/426 <sup>b</sup>	No	December 2011		Urine	E	ST838		G2576T	2	<0.25	0.5	8	1	8	0.5	4	0.25	0.5

<sup>a</sup> ICU, intensive care unit; LZD, linezolid; VAN, vancomycin; TEC, teicoplanin; PEN, penicillin; AMP, ampicillin; ERY, erythromycin; TET, tetracycline; CHL, chloramphenicol; CIP, ciprofloxacin; LEV, levofloxacin. NA, data not available. Gray shading represents resistance values; boldface type represents intermediate values.

<sup>b</sup> Strains 50/515 and 51/426 corresponding to the linezolid-susceptible *E. faecalis* and *E. faecium* control strains were recovered from clinical specimens obtained from other patients who were hospitalized at the same institution.

resistance to linezolid in VRE strains, and it strengthens the idea that combination therapies with ampicillin plus an aminoglycoside can still be good therapeutic options for serious enterococcal infections.



JAIME ROCHA

# The New-England Journal

OF

## MEDICINE AND SURGERY.

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Vol. VIII.

OCTOBER, 1819.

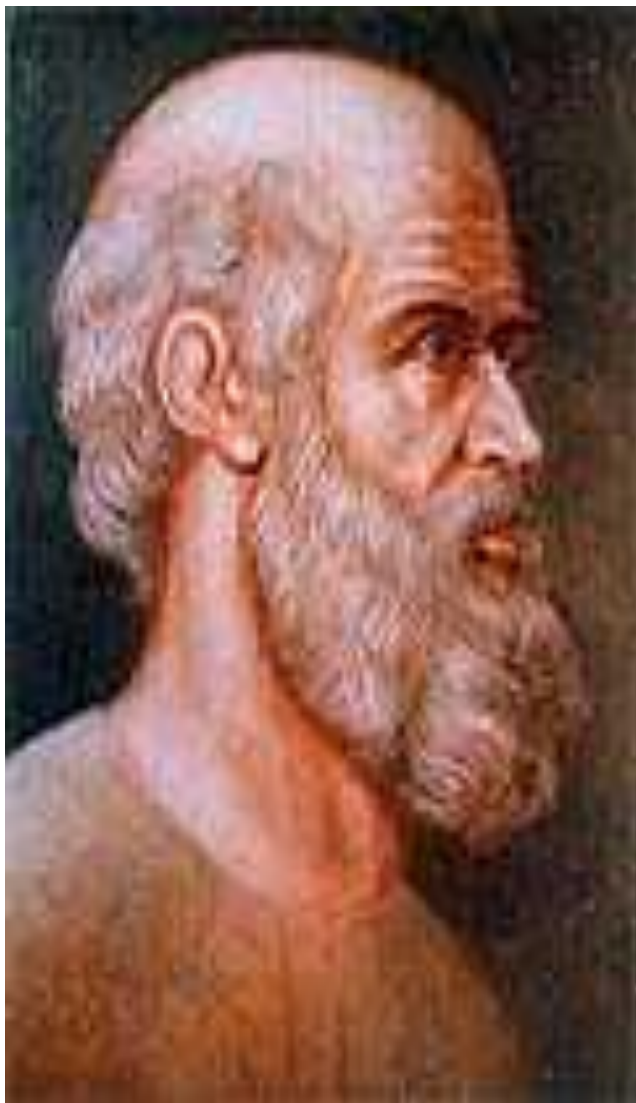
No. IV.

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*On the efficacy of Mercury in the treatment of Fever.* By  
DR. ABNER HOWE.

[Communicated for the New-England Journal of Medicine and Surgery.]

**A**S fever, in its various forms, destroys more of the human race, than any other disease, it demands the first and unwearied attention of every physician, that its nature may be better understood and its termination less frequently fatal. Sydenham affirms, that the various forms of fever constitute two thirds of the diseases of mankind, and that as large a proportion as eight of nine of all who die, are cut off by febrile diseases.



**HIPÓCRATES**

- **Primum non nocere**
- **Bonum facere**
- **Moralidade centrada no agente de saúde**