

Vancomicina Versus Outras Drogas: Pulmão

Alexandre Cunha

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



Vancomicina





Joseph Goebbles – Ministro de Propaganda de Hitler

“Uma mentira repetida mil vezes torna-se verdade”

A vancomicina tem vários defeitos

- Droga antiga
- Molécula “pesada”, com baixa penetração tecidual
- Falta de medicamento de referência
- Reações Alérgicas
- Necessidade de ajuste de dose na IR
- MIC
- Nefrotoxicidade

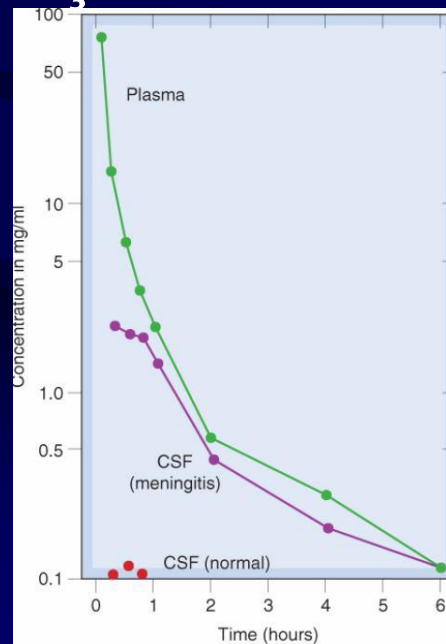
O maior defeito da vancomicina

- Ser uma 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...

Os “defeitos”

Níveis teciduais

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



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!

Eventos Adversos

Nem tão raros...

- Linezolida – Sd. Serotoninérgica, plaquetopenia

Necessidade de ajuste na IR

- Vancomicina é droga ajustável, com possibilidade de mensuração RÁPIDA e BARATA de níveis séricos
- 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)

Nephrol Dial Transplant 2006, 21

MIC creep

- A 1ª grande falácia!!!
- MIC creep não foi demonstrado no Brasil
- >90% das cepas com MIC ≤ 1mcg/dL
- 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)

- 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)

Nefrotoxicidade

- A 2ª 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

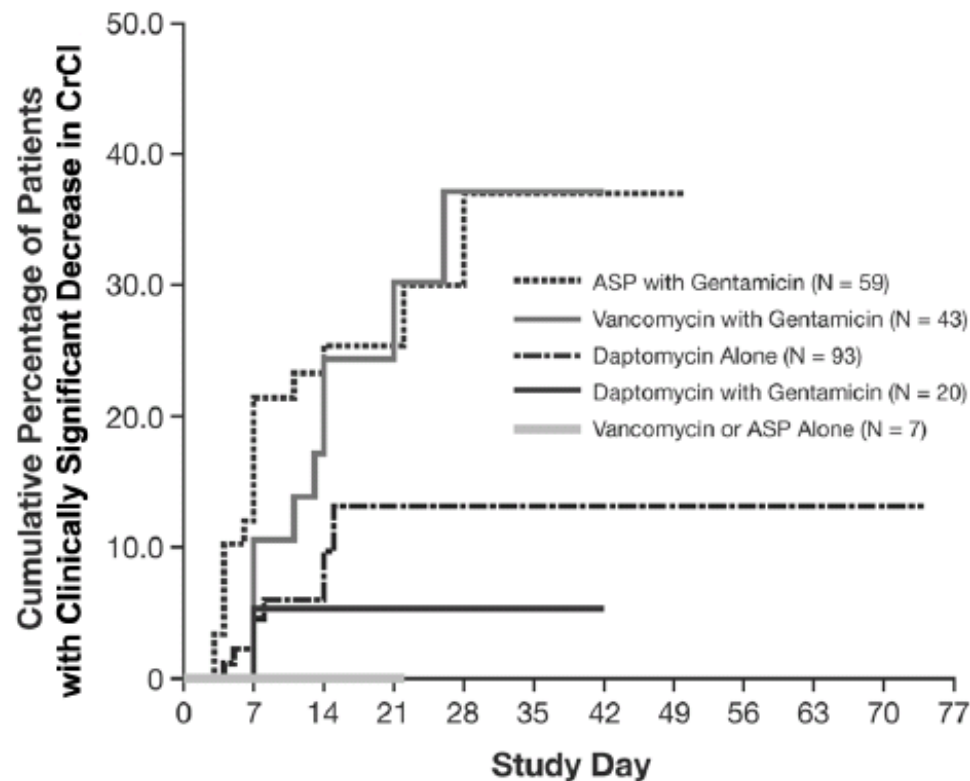



Figure 2. Time to a clinically significant decrease in creatinine clearance (CrCl). ASP, antistaphylococcal penicillin.

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 ^α	1.8±0.1	1.7±0.09	0.29
Max Creatinine During Treatment ^β	1.1 (0.8,1.9)	1.2 (0.8,2.0)	0.9
Final Creatinine After Treatment ^α	1.4±0.07	1.2±0.07	0.24
Final Creatinine After Treatment ^β	0.9 (0.7,1.4)	0.9 (0.7,1.4)	0.92
Change in Creatinine (Max-Initial) ^α	0.4±0.04	0.3±0.04	0.16
Change in Creatinine (Max-Initial) ^β	0.1 (0.0,0.3)	0.1 (0.0,0.3)	0.55
Change in Creatinine (Final-Initial) ^α	-0.1±0.05	-0.2±0.05	0.44
Change in Creatinine (Final-Initial) ^β	-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) ^α	28.3±1.4	26.2±1.7	0.35
Length of Stay After Treatment (Days) ^β	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 used in high dosage, i.e., twice the usual dose.

Extensive use over time has demonstrated vancomycin is not nephrotoxic even when



As outras drogas

Tygeciclina

- Não precisaria nem falar...
- Não tem nível sérico adequado
- Bacteriostático
- Enormes interações medicamentosas
- Náuseas e vômitos
- Todos os trials em pacientes críticos interrompidos por excesso de mortalidade
- Praticamente abandonada para Gram +
(Talvez útil para peritonite por VRE...)

Tygacil[®] indications¹

**Tygacil[®] is indicated in adults
for the treatment of:¹**

- Complicated intra-abdominal infections (cIAIs).
- Complicated skin and soft tissue infections (cSSTIs), excluding diabetic foot infections.

**Tygacil[®] should be used only in situations where it is known or suspected
that other alternatives are not suitable.¹**

Teicoplanina

- Droga excelente. Para infecções crônicas...
- Para pacientes críticos, grave problema farmacocinético:
- Meia vida da Teicoplanina: 160 horas
 - Após 33,3 dias ainda há 3 % teicoplanina circulante
 - Demora de 4-5 dias para atingir steady-state

Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose

Journal of Antimicrobial Chemotherapy (2003) **51**, 971–975

- 202 pacientes
- Porcentagem de pacientes que alcançaram $C_{min} > 10 \text{ mg/L}$:
 - D2= 3,2% !!!
 - D4= 35% !!!
 - D7= 70% !!!
 - D11=90%
 - D15=95%

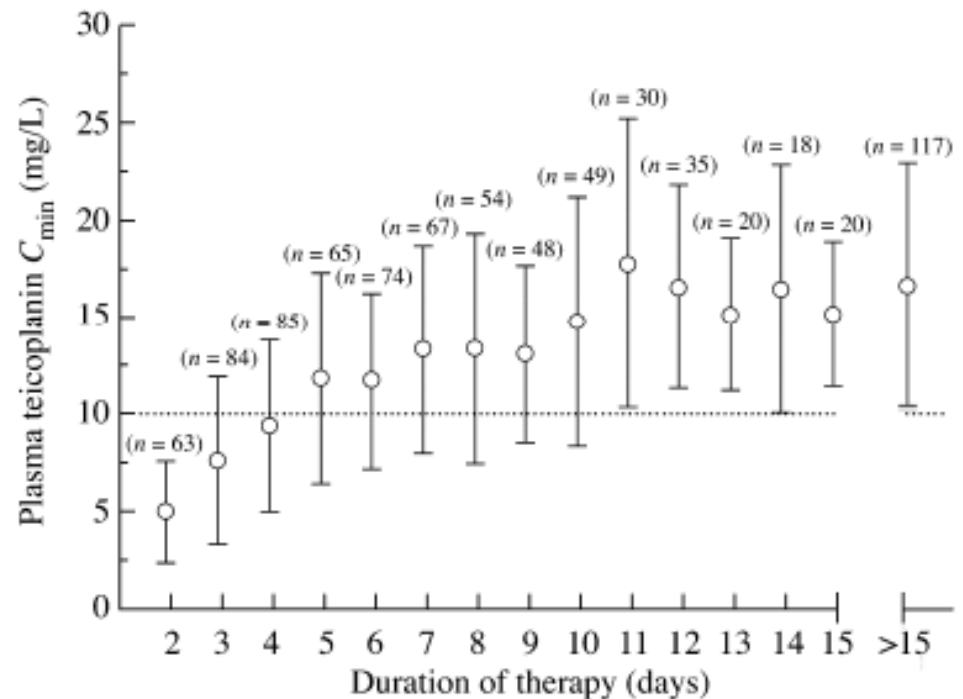


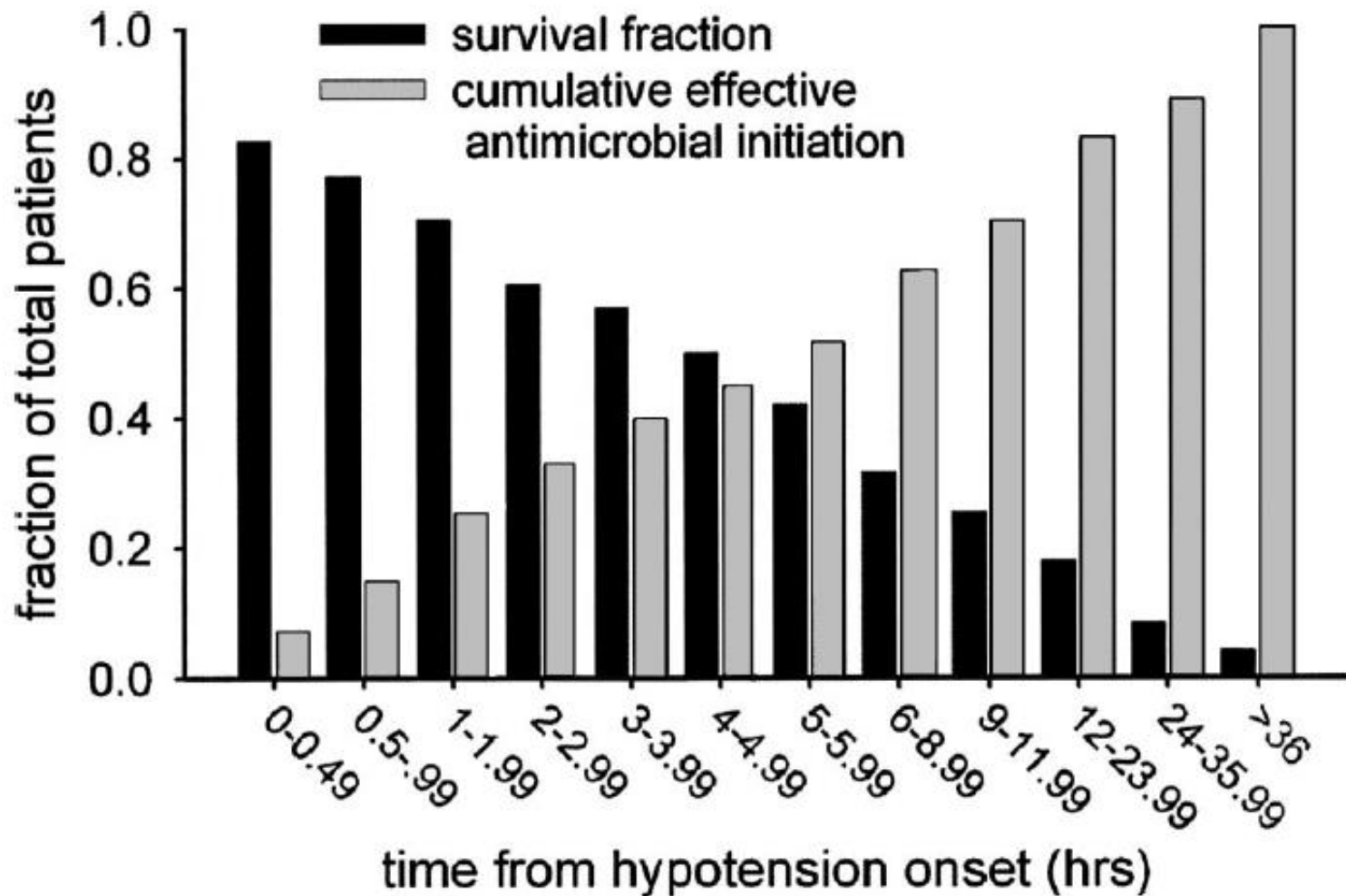
Figure 1. Mean (\pm S.D.) trough plasma levels of teicoplanin in critically ill patients. The dotted line is the minimum concentration recommended in serious infection (10 mg/L).

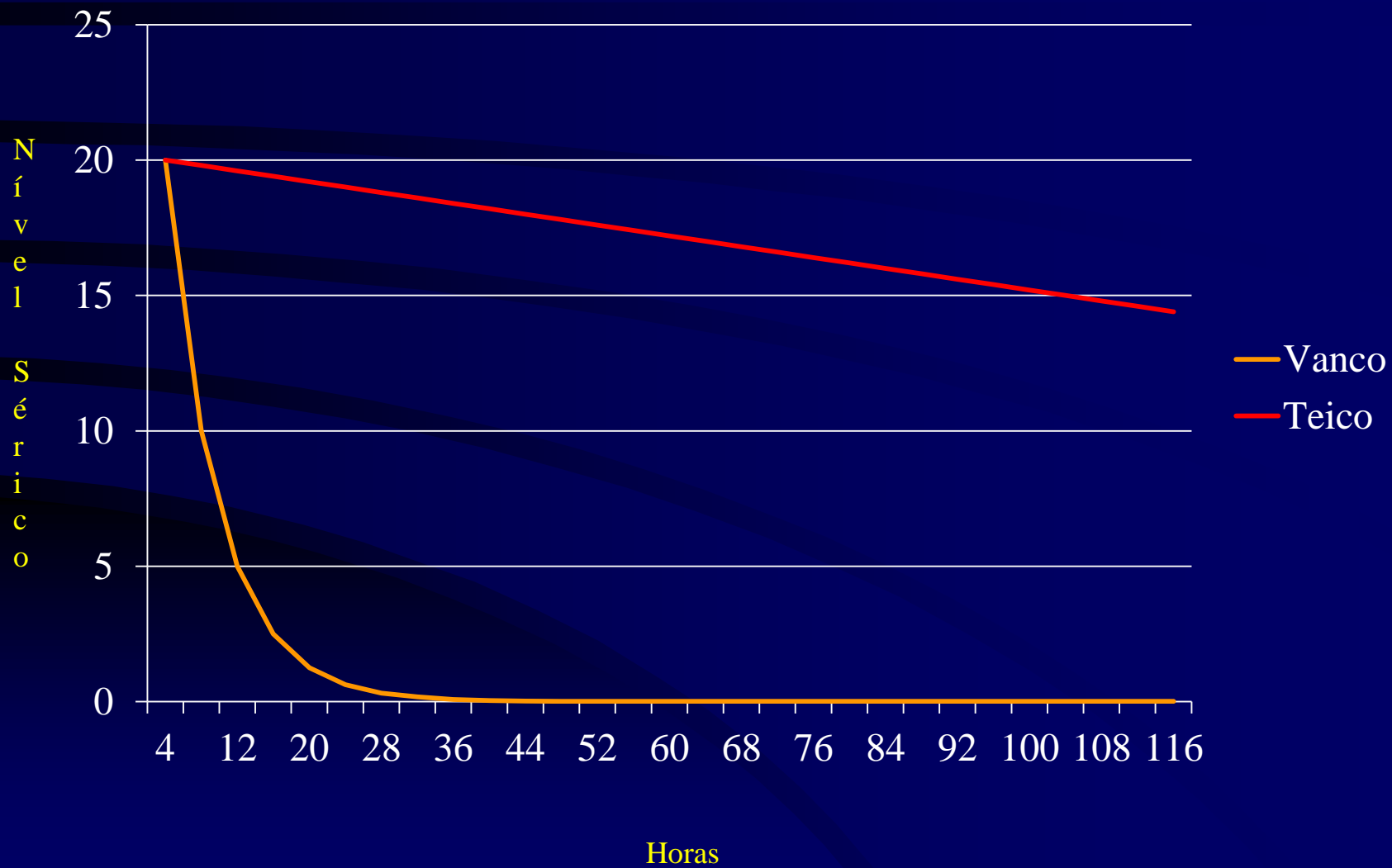
➔ Mesmo com dose de ataque correta: C_{min} média no D2=6,47mg/L !!!

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock *

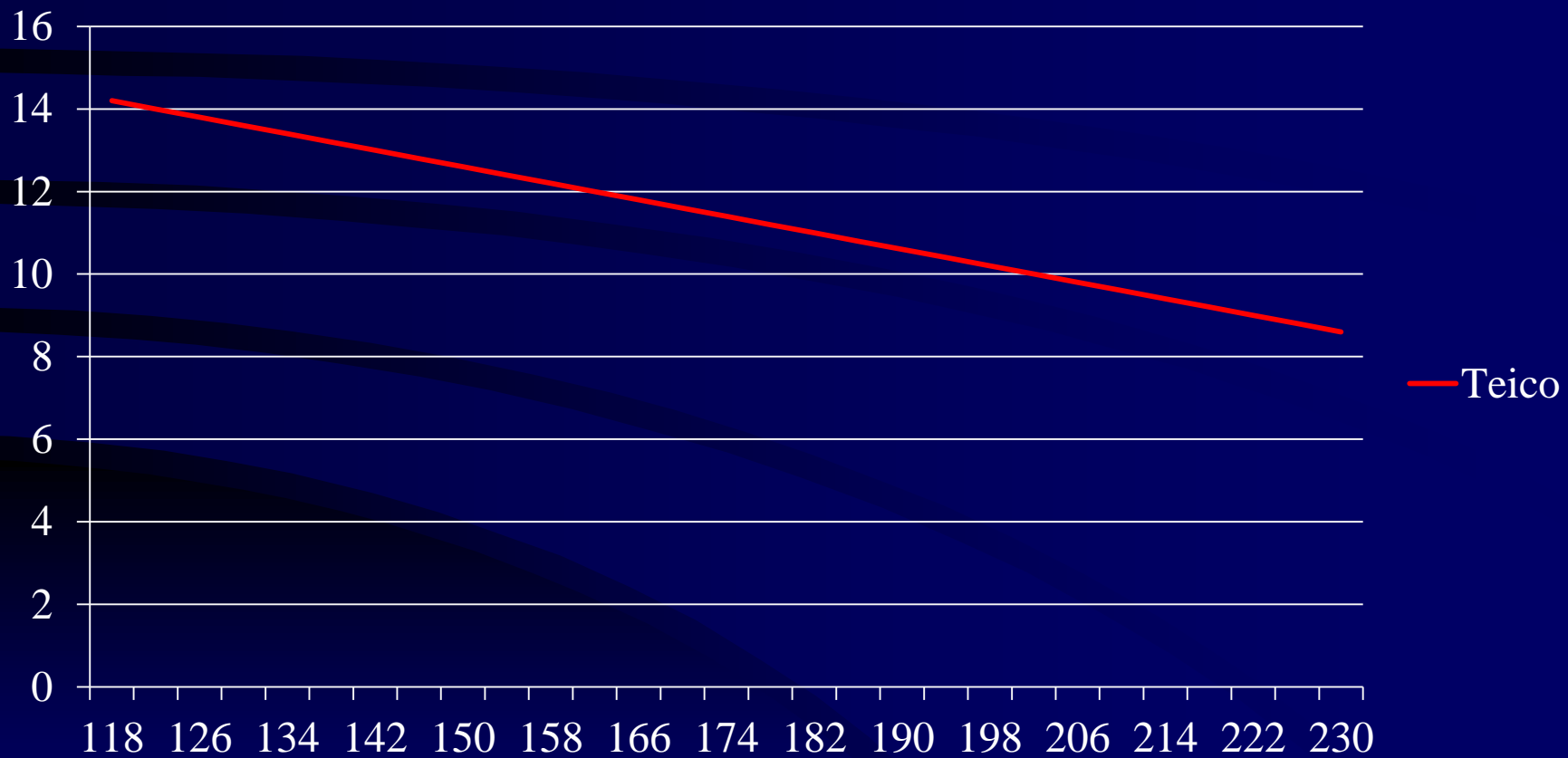
Kumar, Anand MD; Roberts, Daniel MD; Wood, Kenneth E. DO; Light, Bruce MD; Parrillo, Joseph E. MD; Sharma, Satendra MD; Suppes, Robert BSc; Feinstein, Daniel MD; Zanotti, Sergio MD; Taiberg, Leo MD; Gurka, David MD; Kumar, Aseem PhD; Cheang, Mary MSc

[Crit Care Med.](#) 2006 Jun;34(6):1589-96.

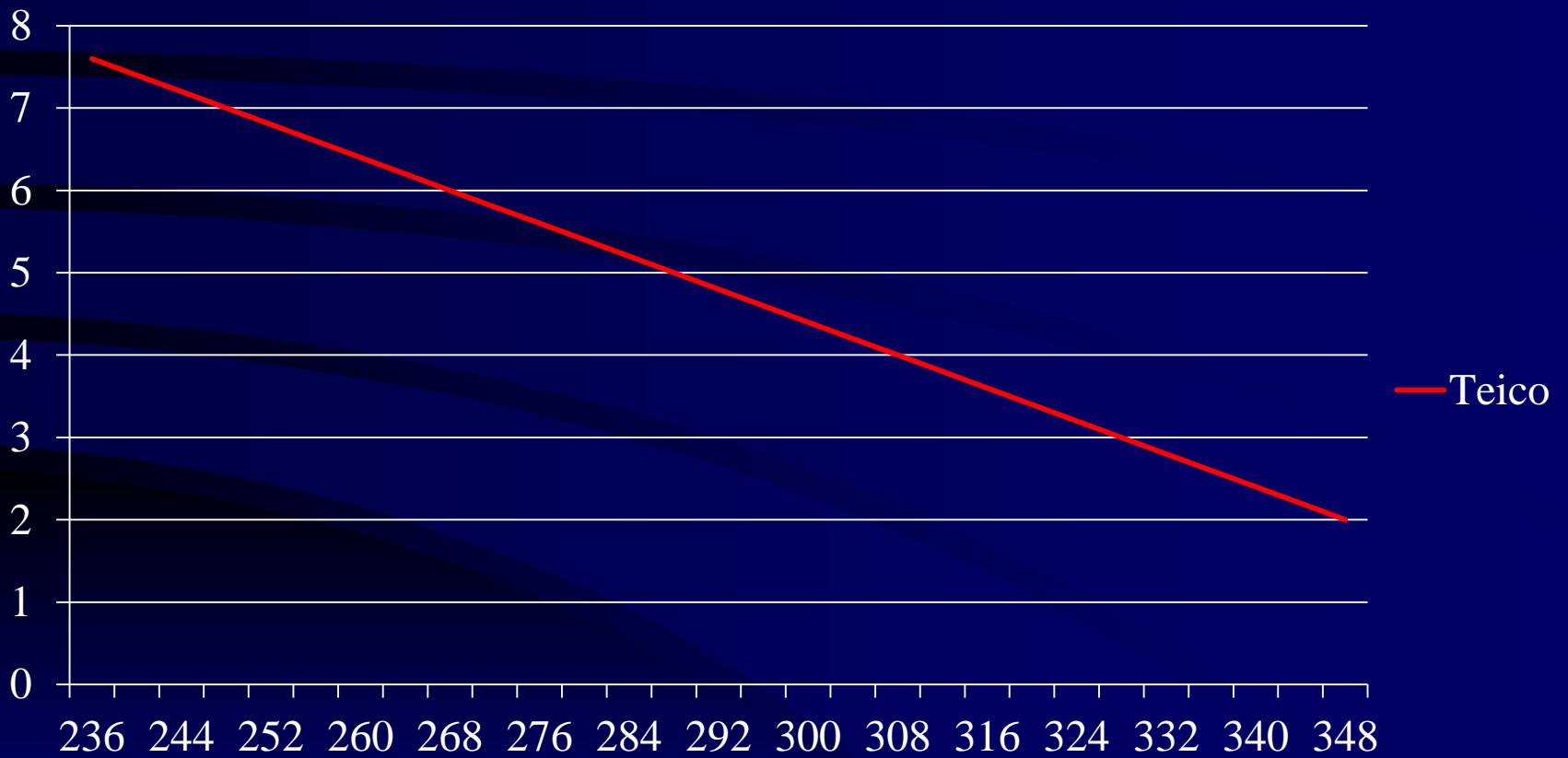




Teico



Teico



Teicoplanin versus vancomycin for proven or suspected infection (Review)

Alexandre B Cavalcanti¹, Anderson R Goncalves², Claudia S Almeida³, Diogo DG Bugano³, Eliezer Sibra⁴

¹Education and Research Institute, Hospital do Coração, São Paulo, Brazil. ²Departamento de Medicina, Unirville - Universidade da Região de Joinville, Joinville, Brazil. ³Medical School, Universidade de São Paulo, São Paulo, Brazil. ⁴Intensive Care Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil

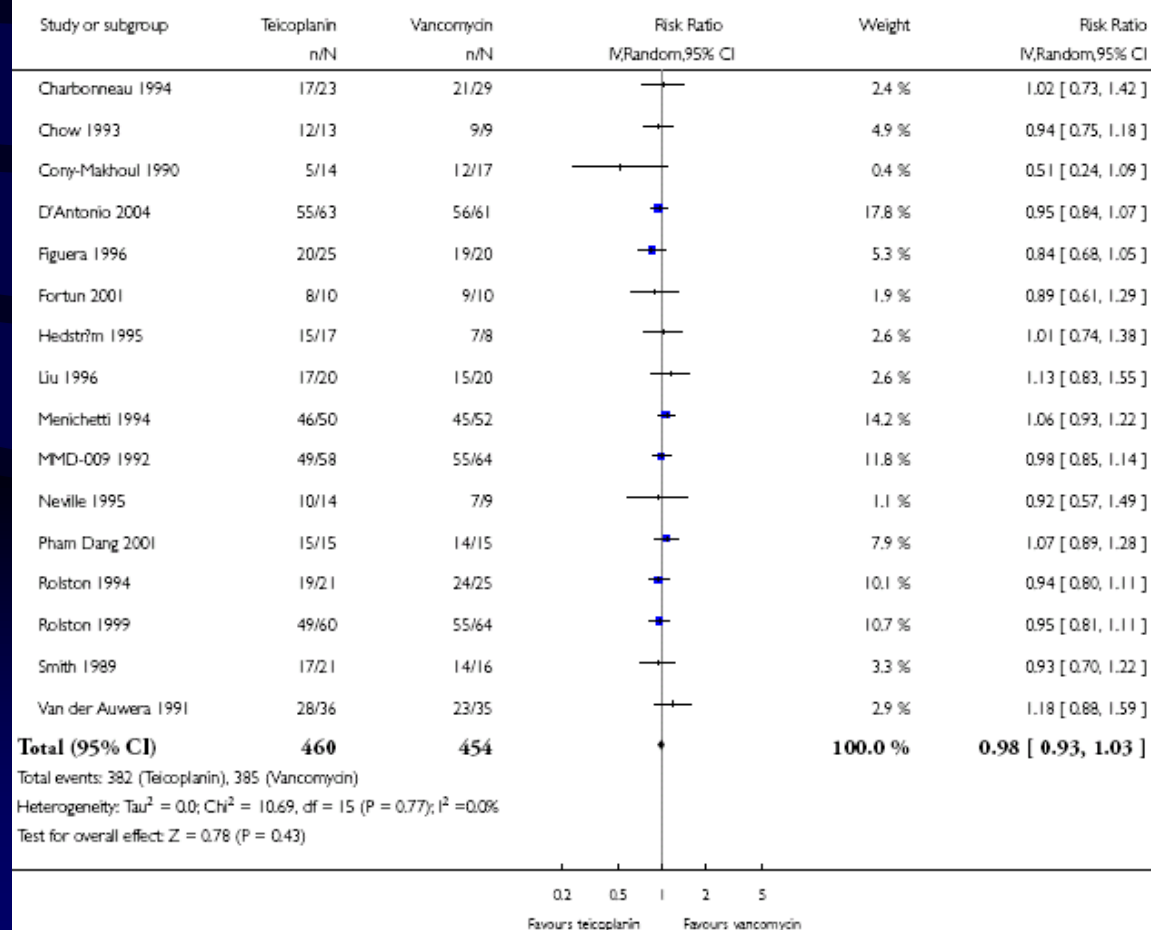
THE COCHRANE
COLLABORATION®

Analysis 1.3. Comparison 1 Teicoplanin versus vancomycin, Outcome 3 Microbiological cure.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 3 Microbiological cure



Teicoplanin versus vancomycin for proven or suspected infection (Review)

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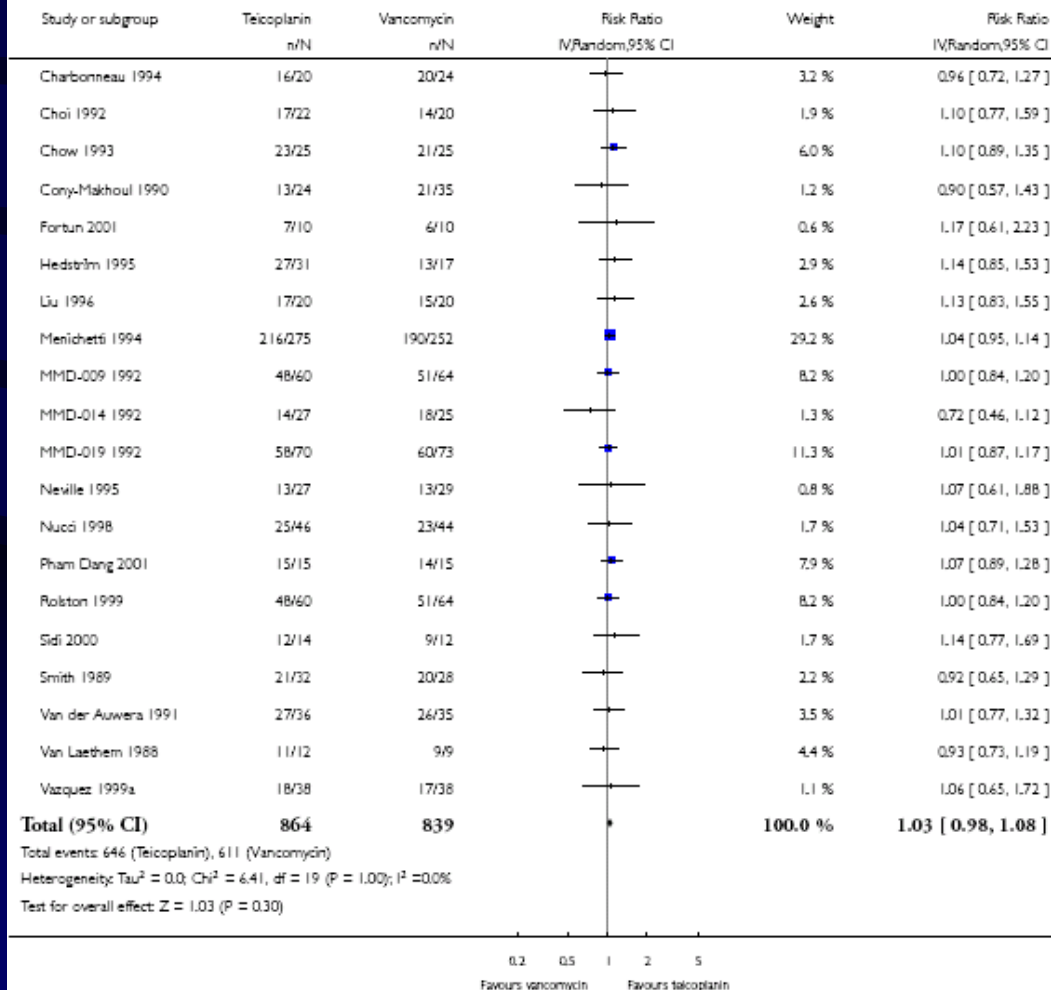
THE COCHRANE
COLLABORATION®

Analysis 1.2. Comparison 1 Teicoplanin versus vancomycin, Outcome 2 Clinical cure or improvement.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 2 Clinical cure or improvement



Teicoplanin versus vancomycin for proven or suspected infection (Review)

Alexandre B Cavalcanti¹, Anderson R. Gonçalves², Claudia S Almeida³, Diogo DG Bugano³, Eliezer Silva⁴

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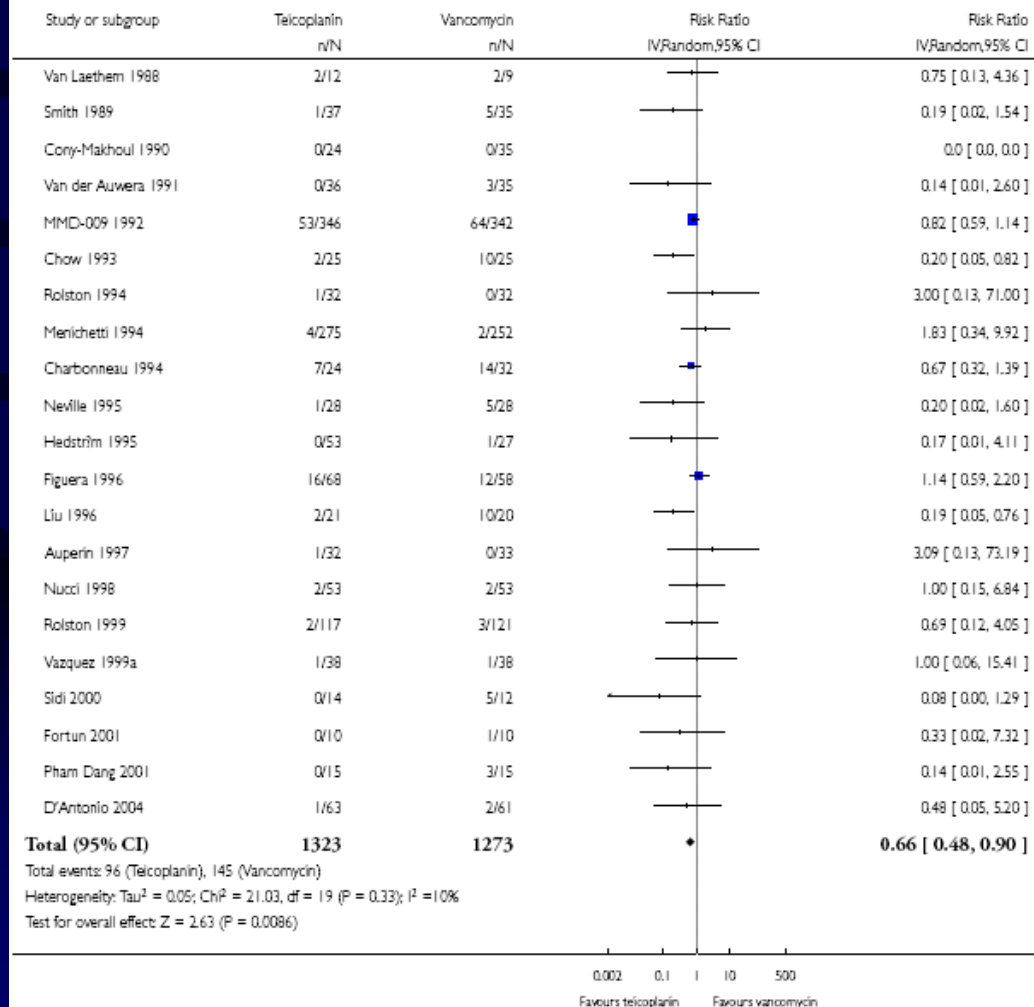
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Analysis 1.1. Comparison 1 Teicoplanin versus vancomycin, Outcome 1 Nephrotoxicity.

Review: Teicoplanin versus vancomycin for proven or suspected infection

Comparison: 1 Teicoplanin versus vancomycin

Outcome: 1 Nephrotoxicity



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

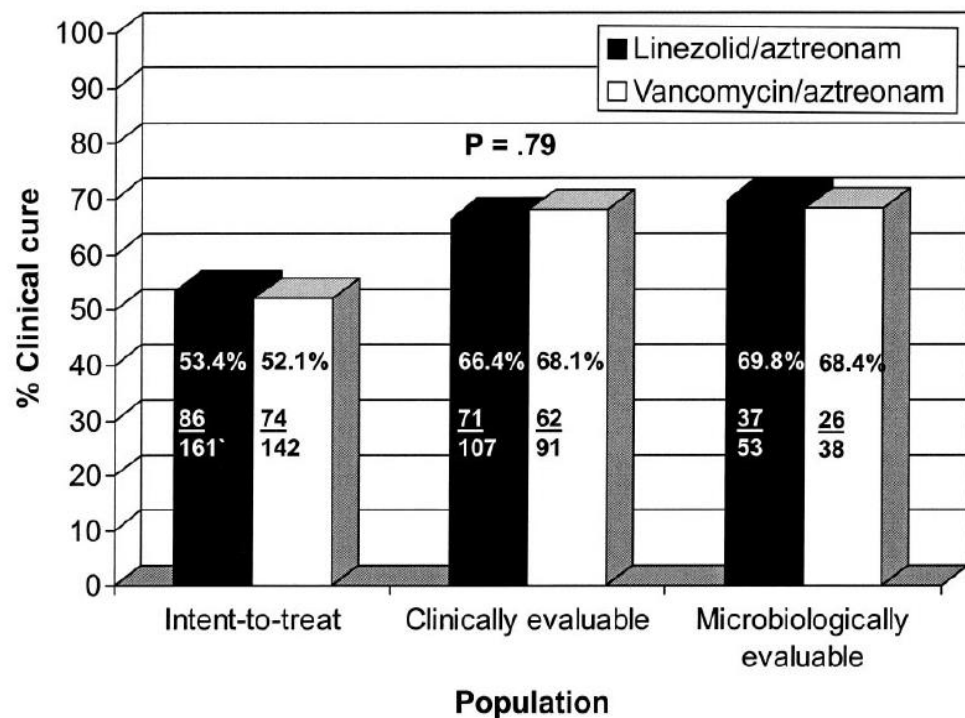
Ethan Rubinstein,¹ Sue K. Cammarata,² Thomas H. Oliphant,² Richard G. Wunderink,³
and the Linezolid Nosocomial Pneumonia Study Group^a

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[®]

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 μ 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)
Sex, No. (%)		
Male	116 (67.4)	112 (63.6)
Female	56 (32.6)	64 (36.4)
Race, No. (%)		
White	119 (69.2)	112 (63.6)
Black	18 (10.5)	28 (15.9)
Asian	27 (15.7)	28 (15.9)
Preexisting condition, No. (%)		
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 ^a	26 (15.1)	30 (17.1)
Nosocomial	146 (84.9)	146 (83.0)
Ventilator-associated ^b	104 (60.5)	117 (66.5)
Bacteremia, No. (%)	9 (5.2)	20 (10.8)

APACHE II score

Mean (SD)	17.2 (6.4)	17.4 (6.0)
Modified CPIS (maximal score 17)^c		
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 ^a
Evaluable for efficacy analyses ^b	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^{*2}

Treatment Day	n	Mean Concentration (mcg/mL)	Median Concentration (mcg/mL)	Concentration Range (mcg/mL)
mITT				
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)
PP				
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:

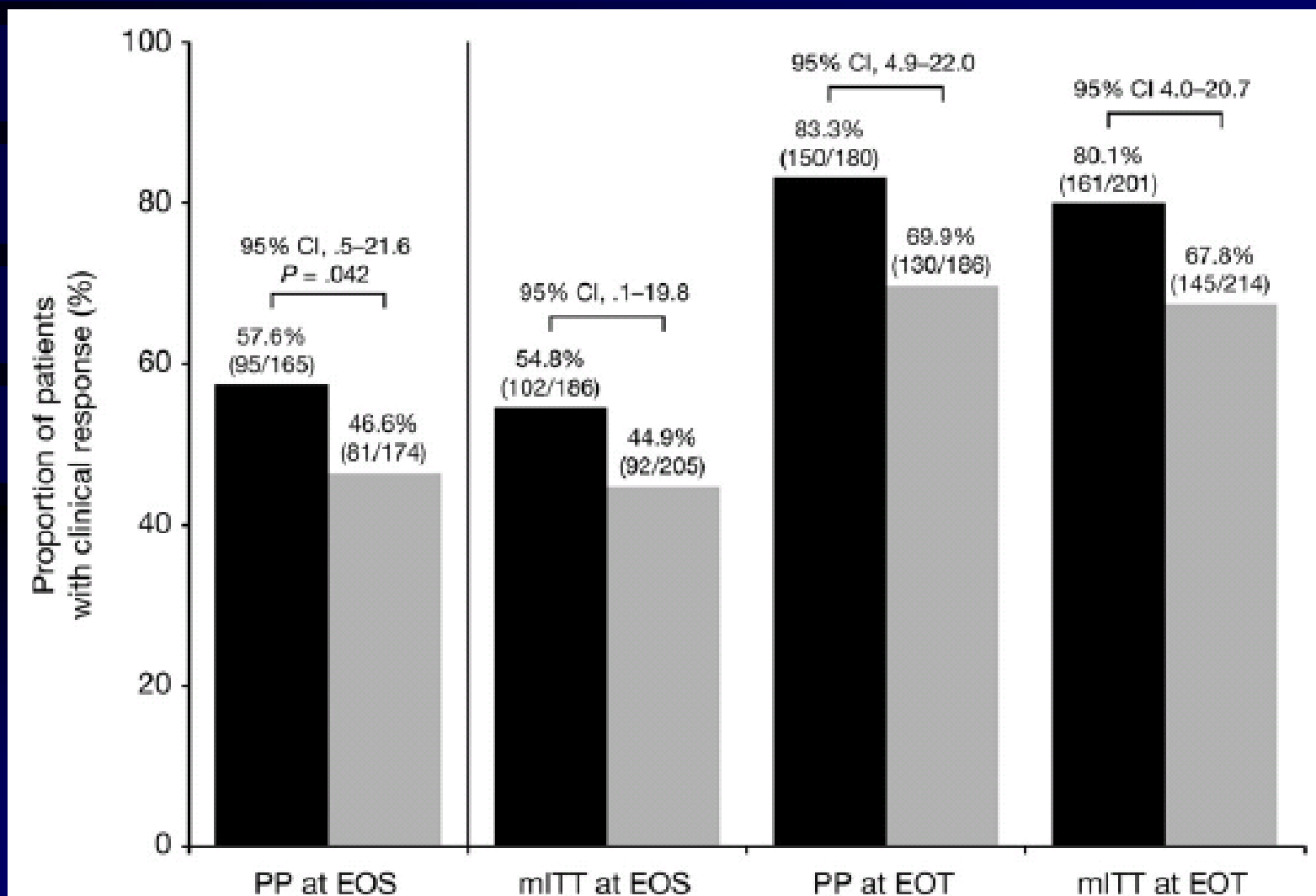
The pharmacist monitored and adjusted vancomycin doses according to local protocols based on trough levels and renal impairment, while maintaining investigator blinding.

- *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)
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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 ^a
Evaluable for efficacy analyses ^b	165	174	

^b 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,¹ Jean-Louis Vincent,¹
Olivier Denis,² and Frédérique Jacobs³

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

Timothy Lahey
Dartmouth Medical School, Lebanon, New Hampshire

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

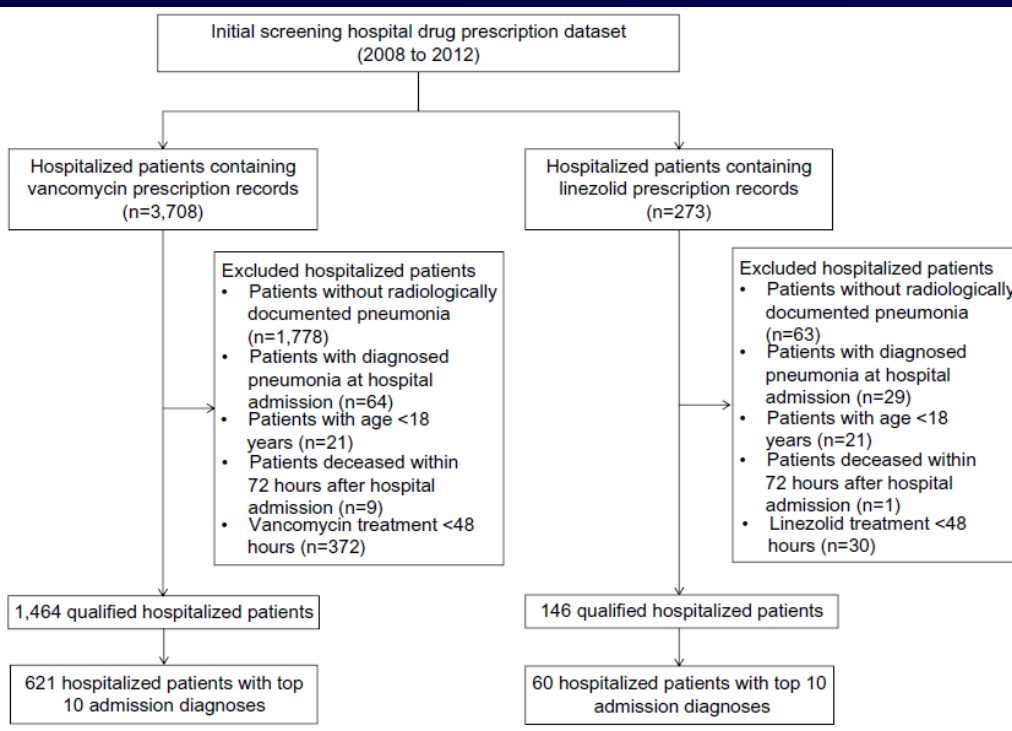


Table 2 Head-to-head comparisons on clinical outcomes between empirical use of vancomycin and linezolid for difficult hospital-acquired pneumonia in propensity score matched patients

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.

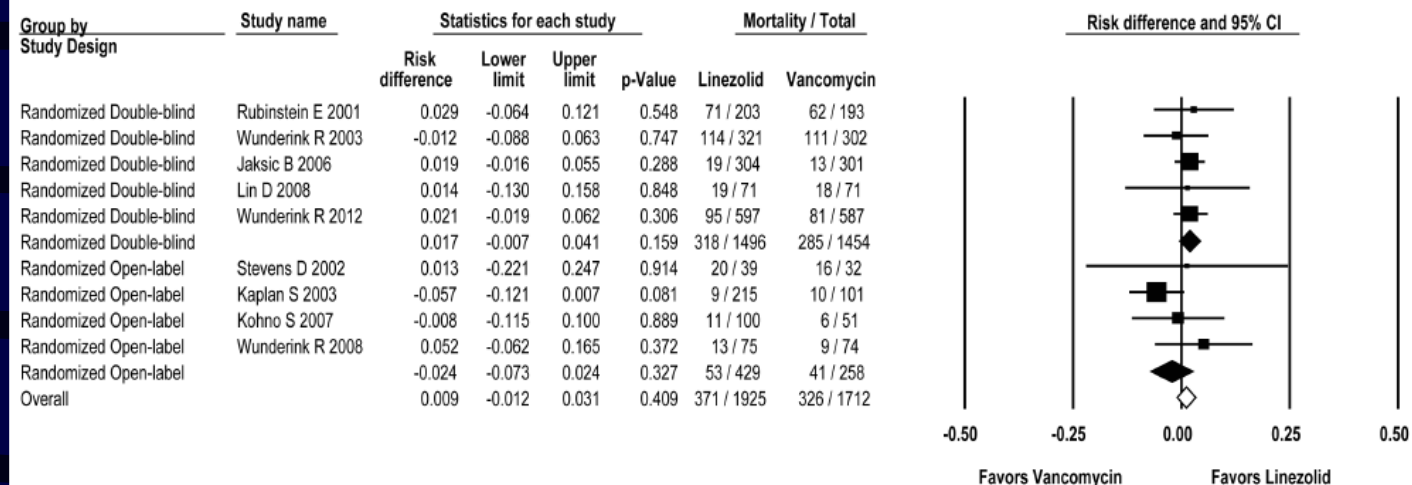
Conclusion

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

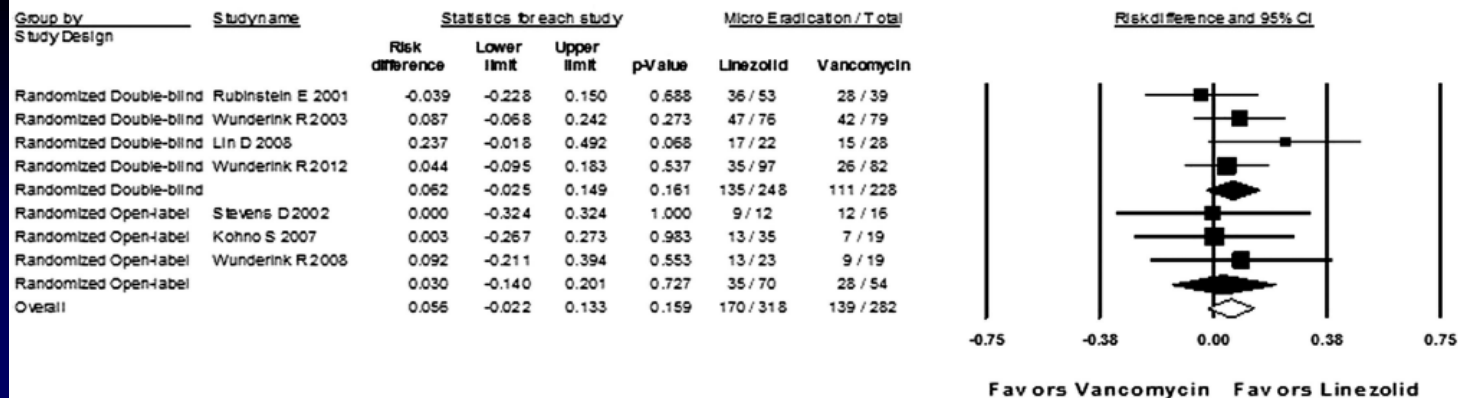
Kalil AC, Klompas M, Haynatzki G, *et al. BMJ Open* 2013;3:e003912.

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



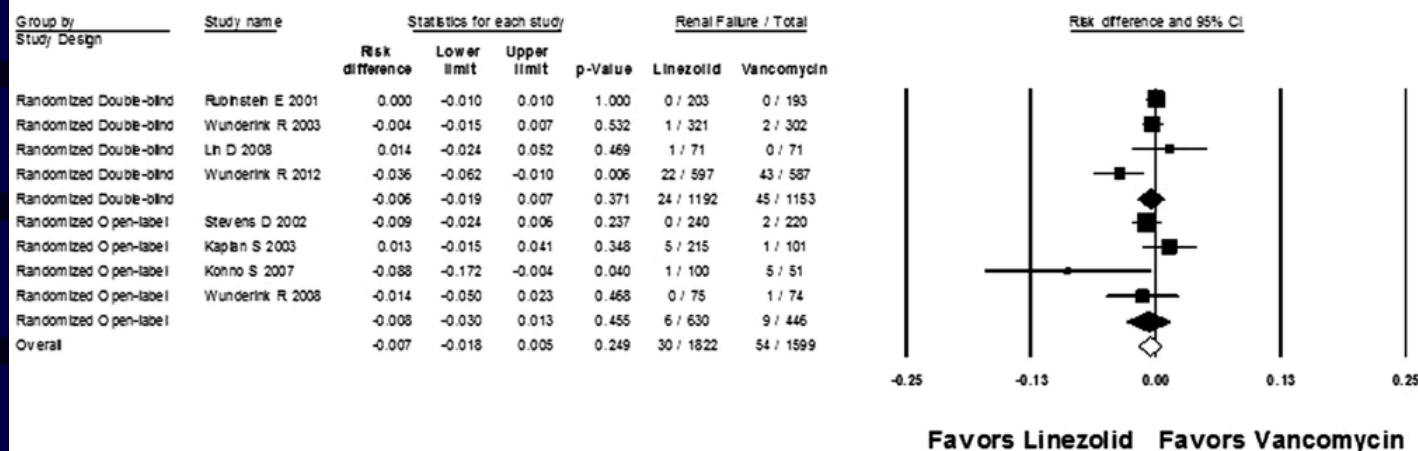
*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I²=0%

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



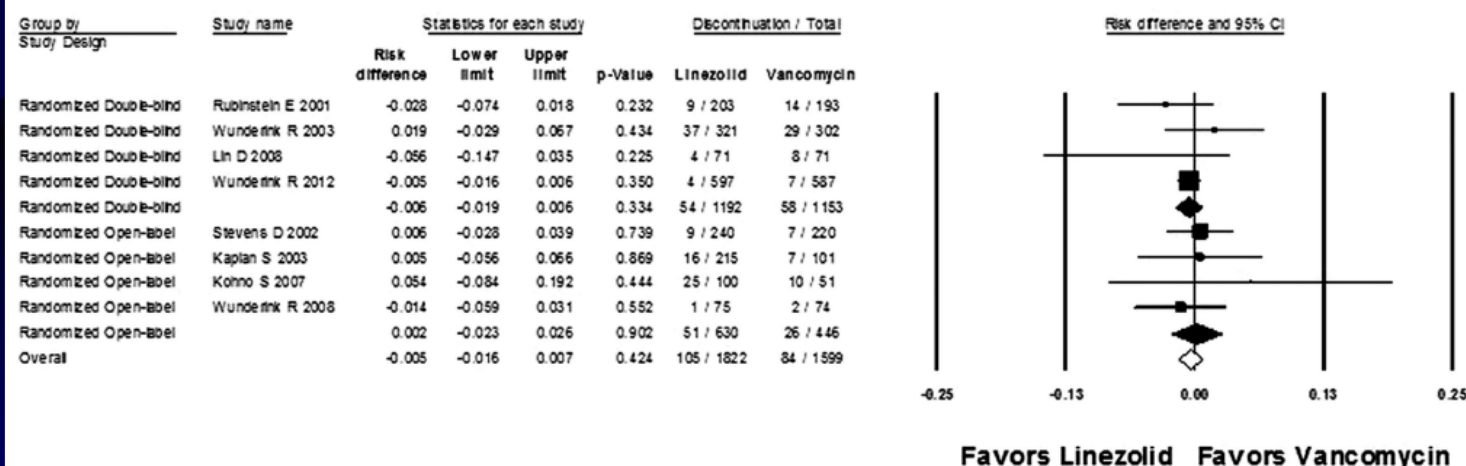
*Microbiological Evaluable/Per-Protocol Population. Z=1.408; P=0.159; Heterogeneity: Q=3.404; P=0.757; I²=0%

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



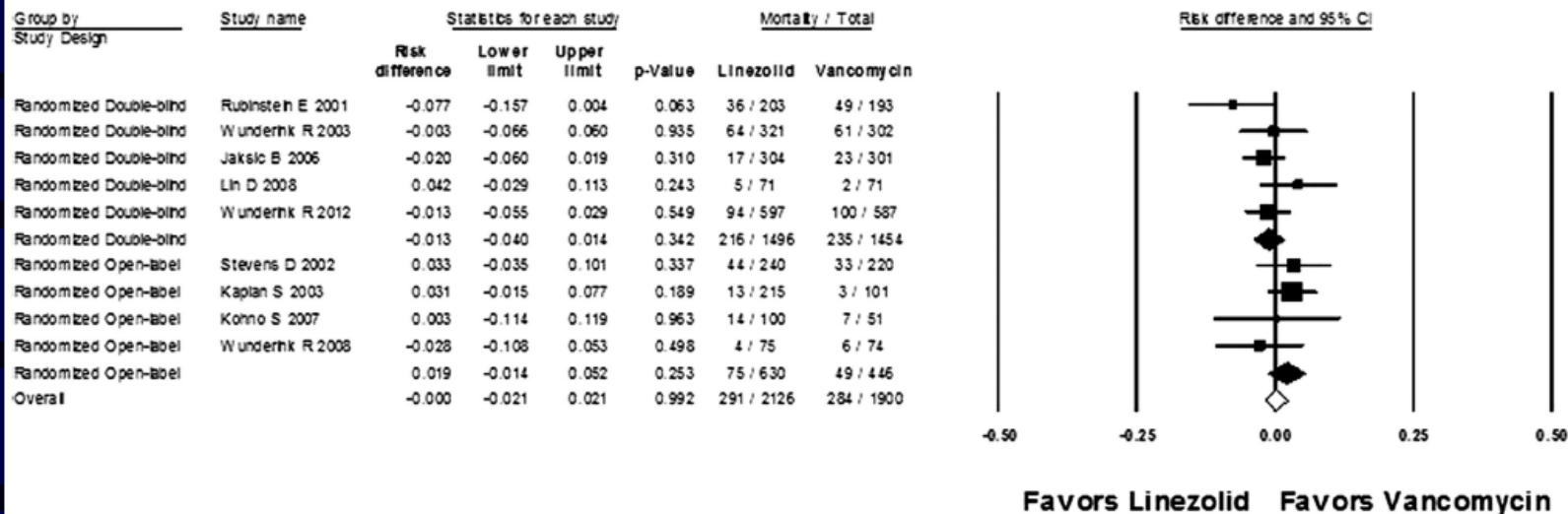
*Intention-to-Treat Population. Z=-1.152; P=0.249; Heterogeneity: Q=13.525; P=0.06; I²=48%

(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; I²=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; I²=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 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^a

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 ^b	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 ^b	No	December 2011		Urine	E	ST838		G2576T	2	<0.25	0.5	8	1	8	0.5	4	0.25	0.5

^a 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.

^b 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.

OBRIGADO!

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Higher clinical success in patients with ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus* treated with linezolid compared with vancomycin: results from the IMPACT-HAP study

Primary study outcome: clinical success

Unadjusted

The unadjusted clinical success rates for each study arm were as follows: linezolid, 86/101 (85%); vancomycin, 60/87 (69%; $P = 0.009$).

Peyrani et al. *Critical Care* 2014, **18**:R118

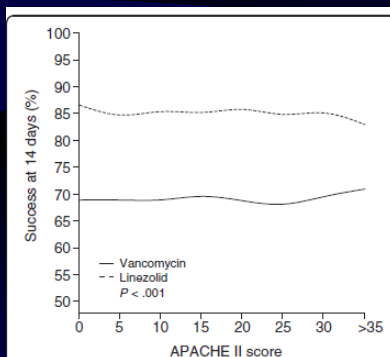
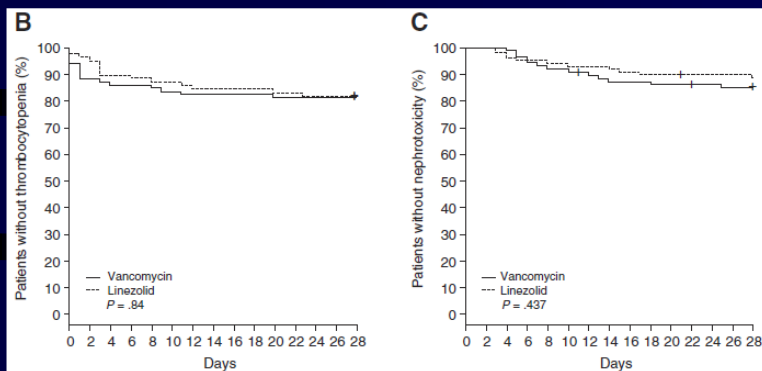


Figure 1 Propensity-adjusted logistic regression model for clinical success at day 14 across a range of Acute Physiology and Chronic Health Evaluation (APACHE) II scores.

Table 2 Unadjusted secondary outcomes

Outcome	Linezolid (n = 101)	Vancomycin (n = 87)	P value
Mortality, n (%)	10 (9.9)	8 (9.2)	1.00
Thrombocytopenia, n (%)	18 (17.8)	16 (18.4)	1.00
Anemia, n (%)	43 (42.6)	41 (47.1)	0.559
Nephrotoxicity, n (%)	11 (10.9)	13 (14.9)	0.541
Days on mechanical ventilation, median (IQR)	11 (14)	13 (11.5)	0.276
Length of stay in the ICU, median (IQR)	11 (14)	13 (11.5)	0.823
Length of stay in the hospital, median (IQR)	18 (19)	16 (14.5)	0.773

ICU, intensive care unit; IQR, interquartile range.

Table 1 Baseline characteristics of adult intensive care unit patients with ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus* treated with linezolid or vancomycin

Characteristic	Linezolid (n = 101)	Vancomycin (n = 87)	P value
Male, n (%)	63 (62.4)	49 (56.3)	0.457
Hospitalization ≥ 5 days before therapy for VAP, n (%)	74 (73.3)	50 (57.5)	0.030
Tracheostomy, n (%)	8 (7.9)	1 (1.1)	0.020
Colonization with MDRO, n (%)	34 (33.7)	32 (36.8)	0.759
Hospitalization ≥ 2 days in previous 90 days, n (%)	20 (19.8)	17 (19.5)	1.000
Nursing home resident, n (%)	6 (5.9)	5 (5.7)	1.000
Home infusion therapy, n (%)	2 (2.0)	0	0.500
Home wound care, n (%)	5 (5.0)	3 (3.4)	0.727
Active malignancy, n (%)	8 (7.9)	5 (5.7)	0.774
End-stage liver disease, n (%)	9 (8.9)	1 (1.1)	0.072
COPD, n (%)	15 (14.9)	8 (9.2)	0.271
Steroid use, n (%)	4 (4.0)	7 (8.0)	0.351
Risk factors for MDROs, n (%)	88 (87.1)	70 (80.5)	0.236
Cardiac disease, n (%)	29 (28.7)	25 (28.7)	1.000
Renal disease, n (%)	8 (7.9)	6 (6.9)	1.000
Vascular disease, n (%)	20 (19.8)	27 (31.0)	0.092
End-stage renal disease and/or dialysis, n (%)	4 (4.0)	3 (3.4)	1.000
Diabetes, n (%)	29 (28.7)	17 (19.5)	0.174
Respiratory disease, n (%)	24 (23.8)	18 (20.7)	0.726
Multilobar infiltrates, n (%)	39 (38.6)	25 (28.7)	0.168
Severe sepsis, n (%)	78 (77.2)	55 (63.2)	0.038
Appropriate empiric antimicrobial therapy, n (%)	100 (99.0)	85 (97.7)	0.597
Age, median (IQR)	59 (20)	56 (26)	0.246
Body mass index, median (IQR)	28.7 (11.9)	27.7 (9.9)	0.359
CPS at diagnosis, median (IQR)	6 (3)	6 (2)	0.177
CPS at day 3, median (IQR)	7 (3)	7 (3)	0.051
APACHE II score, median (IQR)	21 (11)	19 (9)	0.041
Platelet count at diagnosis, median (IQR)	219 (143)	204 (115.5)	0.397
Hemoglobin at diagnosis, median (IQR)	9.5 (1.9)	10 (2.1)	0.026
Creatinine clearance at diagnosis, median (IQR)	78.5 (59.3)	95.9 (69.3)	0.054
Vancomycin MIC ($\mu\text{g/mL}$, E-test), n (%)			0.087
0.75	1 (2.4)	0	
1	5 (11.9)	0	
1.5	22 (52.4)	26 (72.2)	
2	14 (33.3)	10 (27.8)	
Vancomycin serum trough level ($\mu\text{g/mL}$), mean \pm SD			
Day 3	...	13 \pm 8	
Overall	...	21 \pm 11	

APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CPS, Clinical Pulmonary Infection Score; IQR, interquartile range; MDRO, multidrug-resistant organism; MIC, minimum inhibitory concentration; VAP, ventilator-associated pneumonia.