Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: A systematic review and meta-analysis*

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LEARNING OBJECTIVES

After participating in this educational activity, the participant should be better able to:

1. Relate usefulness of various measures of antibiotic effectiveness for nosocomial pneumonia.
2. Assess effectiveness of linezolid and vancomycin for treatment of nosocomial pneumonia.
3. Evaluate measures of success in the treatment of nosocomial pneumonia.

Unless otherwise noted below, each faculty or staff's spouse/life partner (if any) has nothing to disclose.

The authors have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

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Introduction: **Compared with glycopeptides, linezolid achieves higher lung epithelial lining fluid concentrations, which may correlate with improved efficacy in the treatment of nosocomial pneumonia. However, clinical superiority has not been demonstrated.**

Objective: **To test the hypothesis that linezolid may be superior to glycopeptides.**

Methods: **Prospective randomized trials that tested linezolid vs. vancomycin or teicoplanin for treatment of nosocomial pneumonia were included. Heterogeneity was analyzed by I^2 and Q statistics. Meta-analysis relative risks were based on fixed and random-effects models. Outcomes evaluated consisted of clinical cure, microbiological eradication, and side effects.**

Results: **Nine linezolid trials (vancomycin [7]; teicoplanin [2]) were included (n = 2329). The linezolid vs. glycopeptide analysis shows clinical cure relative risk of 1.01 (95% confidence interval, 0.93–1.10; p = .83; I^2 = 0%) and microbiological eradication relative risk of 1.10 (95% confidence interval, 0.98 –1.22; p = .10; I^2 = 0%). Methicillin-resistant *Staphylococcus aureus* subgroup analysis yielded a microbiological eradication relative risk of 1.10 (95% confidence interval, 0.87–1.38; p = .44; I^2 = 16%). If linezolid is compared with vancomycin only, then clinical cure relative risk is 1.00 (95% confidence interval, 0.90–1.12), microbiological eradication and methicillin-resistant *Staphylococcus aureus* relative risks are 1.07 (95% confidence interval, 0.90–1.26; p = .45) and 1.05 (95% confidence interval, 0.82–1.33; p = .71). The risks of thrombocytopenia (relative risk, 1.93; 95% confidence interval, 1.30–2.87; p = .001) and gastrointestinal events (relative risk, 2.02; 95% confidence interval, 1.10–3.70; p = .02) are higher with linezolid, but no differences are seen for renal dysfunction (relative risk, 0.89; 95% confidence interval, 0.56–1.43; p = .64) or all-cause mortality (relative risk, 0.95; 95% confidence interval, 0.76–1.18; p = .63).**

Conclusions: **Our study does not demonstrate clinical superiority of linezolid vs. glycopeptides for the treatment of nosocomial pneumonia despite a statistical power of 95%. Linezolid shows a significant two-fold increase in the risk of thrombocytopenia and gastrointestinal events. Vancomycin and teicoplanin are not associated with more renal dysfunction than linezolid. (Crit Care Med 2010; 38:1802–1808)**

KEY WORDS: pneumonia; vancomycin; linezolid; teicoplanin

***See also p. 1910.**

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Dr. Kalil is responsible for the conception, design, literature search, statistical analysis, results interpretation, writing, and conclusions. Dr. Murthy is responsible for literature search, results interpretation, writing, and conclusions. Dr. Hermsen is responsible for results interpretation, writing, and conclusions. Dr. Neto is responsible for literature search, results interpretation, writing, and conclusions. Dr. Sun is responsible for statistical analysis, results interpretation, writing, and conclusions. Dr. Rupp is responsible for results interpretation, writing, and conclusions. Dr. Kalil had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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At the conclusion of this CME activity, participants should be able to select the most effective antibiotics for the treatment of nosocomial infection. Nosocomial pneumonia is currently among the most frequent type of infection acquired in intensive care unit settings (1) and is associated with substantial mortality, ranging from 24% to 57% (2).

Enhanced concentration of antibiotics at the site of infection (e.g., lungs) is thought to optimize efficacy. However, most antibiotics have variable distribution to different tissues, and antibiotic concentrations in a particular tissue often cannot be accurately predicted by the concentration in the serum. Thus, tissue penetration studies have become increasingly valued, particularly in the setting of pneumonia.

Antibiotic concentrations in alveolar macrophages and epithelial lining fluid (ELF) are thought to reflect antibiotic activity for pneumonia; although lung tissue levels may be the most reliable predictor of efficacy, they are difficult to obtain. Antibiotic concentrations in alveolar macrophages are studied to predict efficacy against obligatory intracellular pathogens, such as the atypical organisms *Legionella* species and *Chlamydia* species. ELF concentrations reflect extracellular concentrations in the lung, which may be useful for upper respiratory tract infections and common extracellular pathogens. Although antibiotics that achieve high concentrations at these sites, such as the macrolides and fluoroquinolones, are advocated for treatment of pneumonia over those that do not reach high concentrations at these sites, such as beta-lactams or aminoglycosides, differences in clinical or microbiological outcomes have not been correlated with such pharmacologic properties in clinical trials.

Linezolid has been shown to have ELF concentrations several-fold higher than serum concentrations, and this has been perceived as a significant advantage over vancomycin, which has demonstrated ELF concentrations of approximately 5% to 25% of serum concentrations (3–9). The low concentration of vancomycin in ELF has contributed to the recommendation for alternative dosing of vancomycin in patients with pneumonia to achieve higher serum trough levels (15–20 mg/L). However, measurement of antibiotic concentrations in ELF is typically performed via bronchoalveolar lavage, and several confounding factors (e.g., amount of lavage fluid, cell contamination, protein binding, incomplete lysis) are associated with this technique (10). In addition, most clinical trials have not measured ELF concentrations of these drugs. Therefore, the use of ELF concentrations for clinical decision-making remains questionable because of the substantial number of confounding factors associated with such measurement and the lack of a correlation with clinical outcomes.

Although linezolid achieves high ELF concentrations and has been perceived to be superior to glycopeptides in the treatment of nosocomial pneumonia, clinical superiority has not been demonstrated except for one subgroup retrospective analysis (11), which was controversial because of its methodologic flaws (12, 13). A potential explanation for this lack of correlation between ELF concentrations and patient outcomes may be related to the noninferiority design of the linezolid trials. Based on the fact that several randomized trials have already been performed, we plan to perform a systematic review and meta-analysis with the objective to test the hypothesis that linezolid is superior to glycopeptides, i.e., vancomycin and teicoplanin, for the treatment of nosocomial pneumonia.

MATERIALS AND METHODS

Literature Search

A systematic literature search was independently performed from database inception to February 2010 in MEDLINE/PubMed, EMBASE, and Cochrane Library by two authors (M.M. and F.N.). Any disagreement was resolved by consensus. We also searched abstracts published in the same time period from the following meetings: Infectious Diseases Society of America, the Interscience Conference on Antimicrobial Agents and Chemotherapy, Chest, and American Thoracic Society. Relevant internet sites such as the Food and Drug Administration reports and trial results repositories (www.clinicalstudyresults.org and www.clinicaltrialresults.org) were also searched. The key words used were: linezolid; oxazolidinone; vancomycin; teicoplanin; glycopeptides; *Staphylococcus*; Gram-positive; infections; randomized; prospective; lungs; respiratory; and pneumonia. No language restrictions were used. This study was exempted from Institutional Review Board approval.

Study Selection

All randomized prospective trials comparing linezolid to vancomycin or teicoplanin for the treatment of nosocomial pneumonias were included in our analysis. Trials that did not use vancomycin or teicoplanin as the comparator were excluded. Also excluded were articles not containing original research (e.g., reviews, editorials, case reports).

Data Extraction

Among included articles, the following variables were abstracted and collected in a standardized form: authors; publication year; study design; gender; mean age; sample size; site of infection; microorganism species and susceptibility; clinical outcome; microbiological eradication; survival; adverse events; and serious adverse events. For studies that included multiple sites of infection, we extracted data only from the patient population with nosocomial pneumonia. Two reviewers (A.C.K. and M.M.) independently rejected or accepted each article based on the inclusion and exclusion criteria. Any disagreement was resolved by further review of the study and consensus among the two reviewers.

Safety and Efficacy Definitions

Clinical cure was defined as clinical cure at the test of cure evaluation for the clinically evaluable population. If test of cure data were not available, then clinical cure at last study follow-up was used. Similarly, microbiological eradication was defined as microbiological eradication at test of cure for the microbiologically evaluable population. If test of cure data were not available, then microbiological eradication at last study follow-up was used. Mortality was defined as all-cause deaths. Gastrointestinal events included nausea, vomiting, and diarrhea. Renal failure and thrombocytopenia were defined as reported by the authors of each article.

Statistical Analysis

The Q statistic method was used to assess statistical heterogeneity, and the I-squared method was used to assess the magnitude of variation secondary to heterogeneity (14). All results were reported with the fixed-effects model, except when significant heterogeneity ($p < .1$ or $I^2 > 30\%$) was detected. The data were pooled by using the Mantel-Haenszel fixed-effects model (15) and the DerSimonian and Laird random-effects model (16). For studies with no event of interest in a treatment group, 1.0 was added to all cells for continuity correction. The quality of every trial was evaluated by the Jadad criteria, and the QUOROM guidelines (17) for reporting meta-analysis were followed. All analyses were

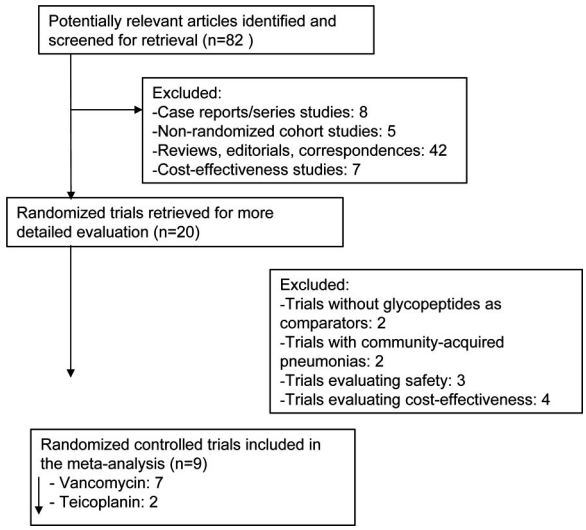


Figure 1. QUOROM flow of randomized control trials.

adjusted for the type of comparator drug, vancomycin or teicoplanin. The software used was Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ). The Egger regression and the Begg and Mazumdar methods (18) were used to evaluate publication bias. Statistical power calculations were performed based on the comparison of two independent proportions using the software StatMate version 2.0 (GraphPad, San Diego, CA).

RESULTS

Efficacy Analyses: Clinical Cure

Nine trials (Fig. 1) met our study inclusion/exclusion criteria (19–27) with a total of 2329 patients (Table 1). The relative risk (RR) for clinical cure (n = 903, clinical evaluable population) is 1.01 (95% confidence interval [CI], 0.93–1.10; $p = .83$; $I^2 = 0\%$) when linezolid is compared with both vancomycin and teicoplanin (Fig. 2*A*). If linezolid is compared with vancomycin only (n = 747), then the RR for clinical cure is 1.00 (95% CI, 0.90–1.12; $p = .94$; $I^2 = 0\%$), and if it is compared with teicoplanin only (n = 109), then the RR is 1.03 (95% CI, 0.93; 1.13; $p = .57$; $I^2 = 0\%$) (Fig. 2*A*).

Microbiological Eradication

The microbiologically evaluable population of all randomized trials (n = 667, microbiological evaluable population) demonstrated the following results for microbiological eradication: RR = 1.10 (95% CI, 0.98–1.22; $p = .10$; $I^2 = 0\%$) when linezolid is compared with both vancomycin and teicoplanin (Fig. 2*B*). If linezolid is compared with vancomycin only (n = 371), then the RR for microbiological eradication is 1.07 (95% CI, 0.90–1.26; $p = .45$; $I^2 = 0\%$), and if it is compared with teicoplanin only (n = 296), then the RR is 1.12 (95% CI, 0.98–1.29; $p = .10$; $I^2 = 0\%$) (Fig. 2*B*).

Methicillin-Resistant *Staphylococcus Aureus* Eradication

The microbiological eradication for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) only (n = 261) shows RR of 1.10 (95% CI, 0.87–1.38; $p = .44$; $I^2 = 16\%$) (Fig. 3). If linezolid is compared with vancomycin only (n = 198), then the RR for MRSA eradication is 1.05 (95% CI, 0.82–1.33; $p = .71$; $I^2 = 0\%$), and if it is compared with teicoplanin only (n = 63), then the RR is 2.56 (95% CI, 0.93–7.08; $p = .07$; $I^2 = 100\%$) (Fig. 3).

Safety Analyses: Gastrointestinal Events

There is a significant increase in gastrointestinal events with linezolid compared with glycopeptides (n = 2264; RR, 2.02; 95% CI, 1.10–3.70; $p = .02$; $I^2 = 62\%$) (Fig. 4). When linezolid is compared with vancomycin only (n = 1630), the RR of gastrointestinal events is 1.86 (95% CI, 0.97–3.59; $p = .06$; $I^2 = 56\%$), and when compared with teicoplanin only (n = 634), RR is 3.24 (95% CI, 0.68–15.52; $p = .14$; $I^2 = 76\%$).

Thrombocytopenia

The rate of thrombocytopenia (n = 2329) is significantly increased with linezolid compared with glycopeptides (RR, 1.93; 95% CI, 1.30–2.87; $p = .001$; $I^2 = 38\%$) (Fig. 5). If linezolid is compared with vancomycin only (n = 1695), then the RR of thrombocytopenia is 2.66 (95% CI, 1.56–4.56; $p < .0001$; $I^2 = 36\%$), and if compared with teicoplanin only (n = 634), then RR is 1.15 (95% CI, 0.63–2.08; $p = .66$; $I^2 = 0\%$).

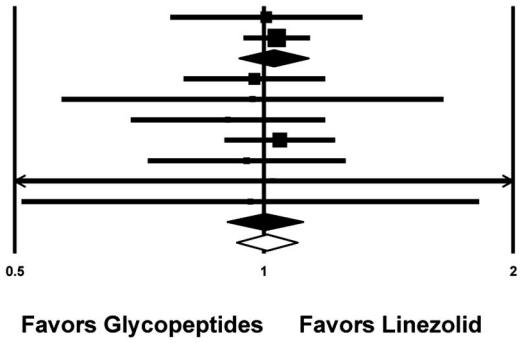
Table 1. Study characteristics

Study, Year	Total Sample Size	Mean Age (Treatment/ Control)	Type of Infection	Treatment Arm	Control Arm	Primary Outcome	Jadad Score
Rubinstein E, 2001 (21)	402	63/61	Pneumonias	Linezolid	Vancomycin	CC and ME at TOC	4
Stevens DL, 2002 (22)	460	64/60	MRSA infections, including pneumonias	Linezolid	Vancomycin	CC and ME at TOC	3
Kaplan SL, 2003 (23)	316	2.2/2.9	Gram-positive infections, including pneumonias	Linezolid	Vancomycin	CC and ME at TOC	3
Wunderink R, 2003 (24)	623	63/62	Pneumonias	Linezolid	Vancomycin	CC and ME at TOC	3
Cepeda JA, 2004 (19)	204	59/57	Gram-positive infections, including pneumonias	Linezolid	Teicoplanin	CC and ME at TOC	4
Wilcox M, 2004 (20)	430	53/55	Gram-positive infections, including pneumonias	Linezolid	Teicoplanin	CC and ME at TOC	3
Jaksic B, 2006 (25)	421	48/47	Neutropenic fever, including pneumonias	Linezolid	Vancomycin	CC and ME at TOC	4
Kohno S, 2007 (26)	151	68/67	MRSA infections, including pneumonias	Linezolid	Vancomycin	CC and ME at TOC	3
Wunderink R, 2008 (27)	50	56/55	MRSA pneumonias	Linezolid	Vancomycin	CC and ME at TOC	3

MRSA, methicillin-resistant *Staphylococcus aureus*; CC, clinical cure; ME, microbiological eradication; TOC, test of cure visit.

A

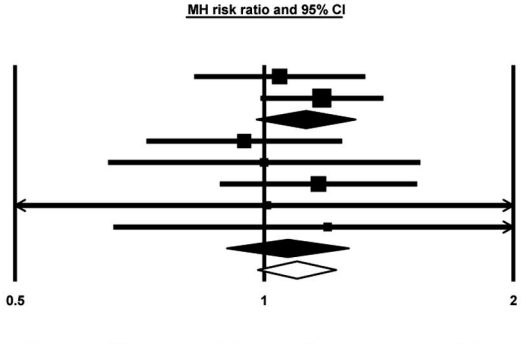
Group by Comparator Drug	Study name	MH risk ratio	Lower limit	Upper limit	p-Value	Linezolid	Glycopeptides
Teicoplanin	Cepeda J 2004	1.01	0.77	1.31	0.96	15 / 18	24 / 29
Teicoplanin	Wilcox M 2004	1.04	0.95	1.13	0.44	51 / 53	52 / 56
Teicoplanin		1.03	0.93	1.13	0.57	66 / 71	76 / 85
Vancomycin	Rubinstein E 2001	0.97	0.80	1.18	0.79	71 / 107	62 / 91
Vancomycin	Stevens D 2002	0.97	0.57	1.64	0.91	12 / 23	14 / 26
Vancomycin	Kaplan S 2003	0.90	0.69	1.18	0.46	9 / 10	10 / 10
Vancomycin	Wunderink R 2003	1.05	0.90	1.22	0.57	114 / 168	111 / 171
Vancomycin	Jaksic B 2006	0.95	0.73	1.25	0.73	19 / 23	13 / 15
Vancomycin	Kohno S 2007	1.02	0.45	2.33	0.95	11 / 34	6 / 19
Vancomycin	Wunderink R 2008	0.96	0.51	1.82	0.91	13 / 30	9 / 20
Vancomycin		1.00	0.90	1.12	0.94	249 / 395	225 / 352
Overall		1.01	0.93	1.10	0.83	315 / 466	301 / 437



Z=0.217; P=0.828. Heterogeneity: Q=1.52; P=0.99; I2=0%

B

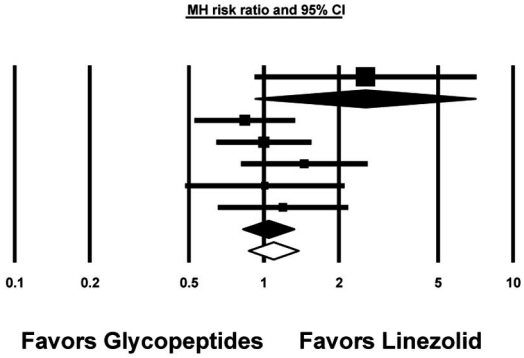
Group by Drug Comparator	Study name	MH risk ratio	Lower limit	Upper limit	p-Value	Linezolid	Glycopeptides
Teicoplanin	Cepeda J 2004	1.04	0.82	1.32	0.72	44 / 61	38 / 55
Teicoplanin	Wilcox M 2004	1.17	0.99	1.39	0.06	77 / 94	60 / 86
Teicoplanin		1.12	0.98	1.29	0.10	121 / 155	98 / 141
Vancomycin	Rubinstein E 2001	0.95	0.72	1.24	0.69	36 / 53	28 / 39
Vancomycin	Stevens D 2002	1.00	0.65	1.54	1.00	9 / 12	12 / 16
Vancomycin	Wunderink R 2003	1.16	0.89	1.53	0.28	47 / 76	42 / 79
Vancomycin	Kohno S 2007	1.01	0.49	2.09	0.98	13 / 35	7 / 19
Vancomycin	Wunderink R 2008	1.19	0.66	2.16	0.56	13 / 23	9 / 19
Vancomycin		1.07	0.90	1.26	0.45	118 / 199	98 / 172
Overall		1.10	0.98	1.22	0.10	239 / 354	196 / 313



Z=1.646; P=0.100. Heterogeneity: Q=2.43; P=0.88; I2=0%

Figure 2. Linezolid vs. glycopeptides clinical cure (*A*) and microbiological eradication (*B*). *CI*, confidence interval.

Group by Drug Comparator	Study name	MH risk ratio	Lower limit	Upper limit	p-Value	Linezolid	Glycopeptides
Teicoplanin	Cepeda J 2004	2.56	0.93	7.08	0.07	12 / 34	4 / 29
Teicoplanin		2.56	0.93	7.08	0.07	12 / 34	4 / 29
Vancomycin	Rubinstein E 2001	0.84	0.53	1.33	0.45	15 / 23	7 / 9
Vancomycin	Stevens D 2002	1.00	0.65	1.54	1.00	9 / 12	12 / 16
Vancomycin	Wunderink R 2003	1.45	0.81	2.59	0.21	12 / 19	10 / 23
Vancomycin	Kohno S 2007	1.01	0.49	2.09	0.98	13 / 35	7 / 19
Vancomycin	Wunderink R 2008	1.19	0.66	2.16	0.56	13 / 23	9 / 19
Vancomycin		1.05	0.82	1.33	0.71	62 / 112	45 / 86
Overall		1.10	0.87	1.38	0.44	74 / 146	49 / 115

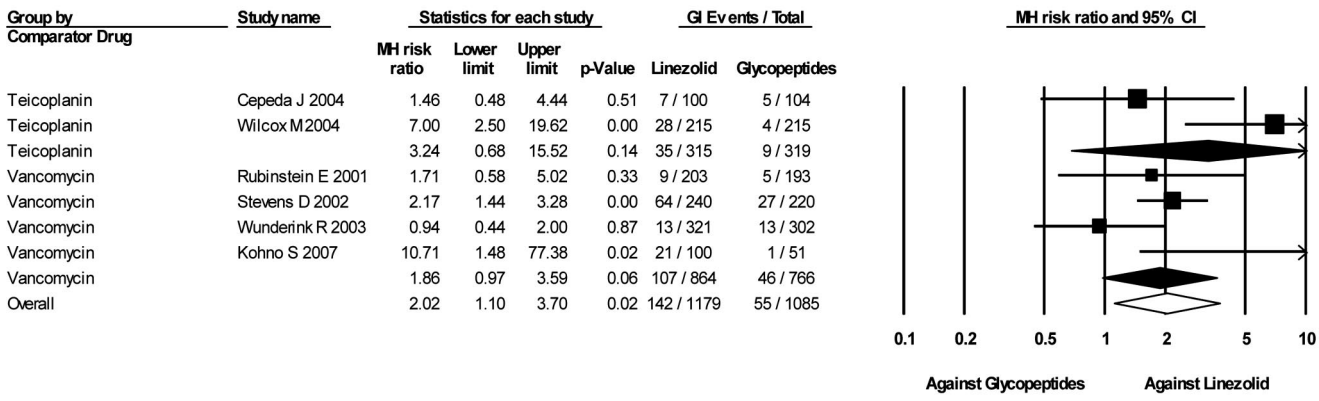


***Methicillin Resistant Staphylococcus Aureus. Z=0.771; P=0.441. Heterogeneity: Q=5.93; P=0.06; I2=16%**

Figure 3. Linezolid vs. glycopeptides: Methicillin-resistant *Staphylococcus aureus*. *MH*, Mantel-Haenszel; *CI*, confidence interval.

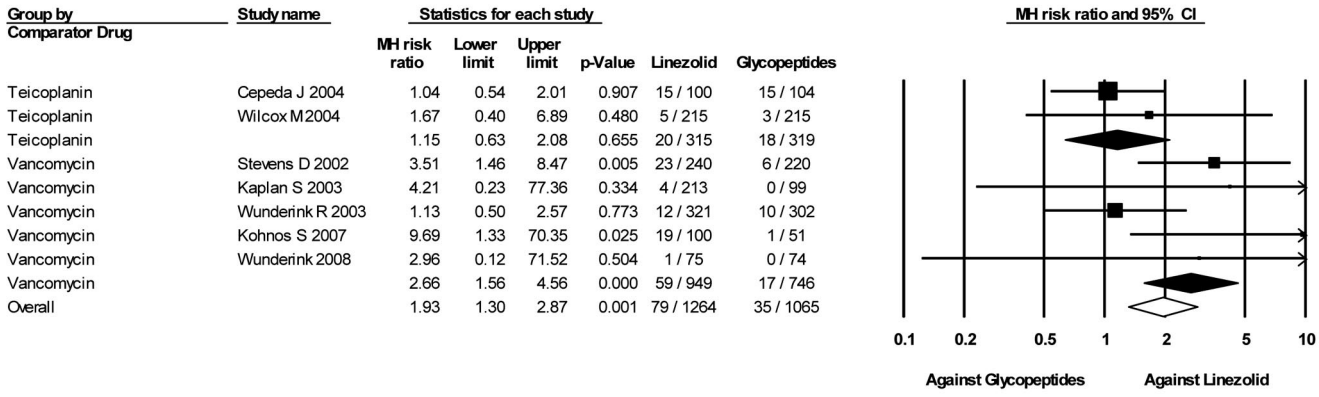
Renal Failure

Treatment with glycopeptides is not associated with a significant increase in the risk of renal failure compared with linezolid (n = 1894; RR, 0.89; 95% CI, 0.56–1.43; $p = .64$; $I^2 = 29\%$) (Fig. 6). If linezolid is compared with vancomycin only (n = 1690), the RR of renal failure is 0.40 (95% CI, 0.12–1.29; $p = .13$; $I^2 = 11\%$), and if compared with teicoplanin only (n = 204), then RR is 1.04 (95% CI, 0.63–1.73; $p = .88$; $I^2 = 100\%$).



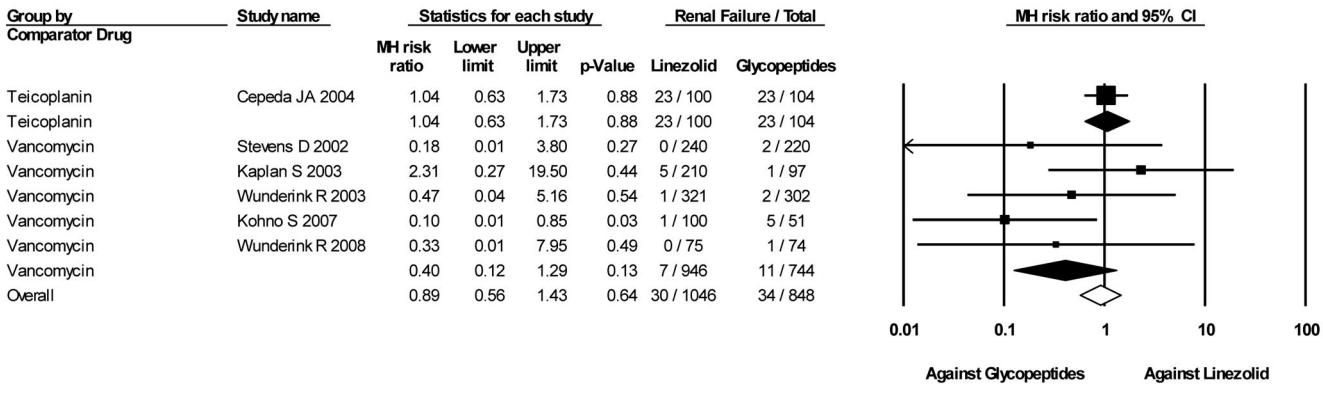
Z=2.283; P=0.022; Heterogeneity: Q=13.30; P=0.02; I2=62%

Figure 4. Linezolid vs. glycopeptides: Gastrointestinal (*GI*) events. *MH*, Mantel-Haenszel; *CI*, confidence interval.



Z=3.274; P=0.001; Heterogeneity: Q=9.71; P=0.14; I2=38%

Figure 5. Linezolid vs. glycopeptides: Thrombocytopenia. *MH*, Mantel-Haenszel; *CI*, confidence interval.



Z=0.471; P=0.637; Heterogeneity: Q=7.00; P=0.22; I2=29%

Figure 6. Linezolid vs. glycopeptides: Renal failure. *MH*, Mantel-Haenszel; *CI*, confidence interval.

All-Cause Mortality

The mortality risk between linezolid and glycopeptides (n = 1864) is not different (RR, 0.95; CI, 0.76–1.18; $p = .63$; $I^2 = 0\%$).

Sensitivity Analyses

The analyses based on the quality of studies, Jadad scores, and the analyses based on the exclusion of studies that included pediatric patients were not significantly different from the overall results (data not shown). The results were also evaluated by presence or not of double-

blinding design for clinical cure (blinded studies only: RR, 1.01; CI, 0.91–1.12; p = .82; I^2 = 0%; unblinded studies only: RR, 1.00; CI, 0.87–1.15; p = .97; I^2 = 0%) and for microbiological eradication (blinded studies only: RR, 1.06; CI, 0.91–1.23; p = .45; I^2 = 0%; unblinded studies only: RR, 1.14; CI, 0.98–1.33; p = .10; I^2 = 0%). The blinding design produced no significant differences for gastrointestinal effects and thrombocytopenia, but it suggested an ascertainment bias for the renal failure analysis; unblinded studies favored linezolid (RR, 0.37; CI, 0.08–1.75; p = .21; I^2 = 33%), whereas blinded studies did not (RR, 1.01; CI, 0.61–1.65; p = .98; I^2 = 0%).

Power Calculations

Based on the clinical cure rate of 69% found in the control arm of our main analysis (Fig. 2*A*) and an expected clinical cure rate 10% higher with linezolid, a sample size of 450 in each group has a 95% power to detect an increase of 0.10, with a significance level (alpha) of 0.05 (two-tailed). Based on the microbiological eradication rate of 63% found in the control arm of our main analysis (Fig. 2*B*) and an expected microbiological cure rate 10% higher with linezolid, a sample size of 333 in each group has a 80% power to detect an increase of 0.10, with a significance level (alpha) of 0.05 (two-tailed).

Publication Bias Analyses

No publication bias was detected by Egger regression (intercept = 0.28; standard error = 0.29; p = .364) or by Begg and Mazumdar rank correlation (Kendall's tau = 0.104; p = .916).

DISCUSSION

Our hypothesis that linezolid is superior to vancomycin/teicoplanin was not proven to be correct despite the large study sample size, which provided 95% power to detect differences between comparator groups. The overall estimate for the RR for clinical cure was remarkably similar for linezolid and glycopeptides (RR = 1.01). In addition, side effects were significantly more frequent with linezolid.

The findings of our study raise questions with respect to the clinical relevance of the lung penetration methods used currently. If linezolid ELF drug concentrations were related to clinical cure for patients with pneumonia, then we would expect to observe a numeric and statistical advantage for linezolid in our study. Neither numeric nor statistical clinical cure benefits were demonstrated by our results. Importantly, the lack of superiority was not influenced by the type of glycopeptide drug. Similarly, another recent published meta-analysis on linezolid (28) for all types of infection did not demonstrate differences in efficacy for linezolid against any beta-lactam antibiotic in patients with pneumonia (odds ratio, 1.02; CI, 0.75–1.42).

Similar findings were found with respect to microbiological eradication. The only instance in which a nonsignificant trend for better efficacy with linezolid was observed was with the very small (n = 63) subgroup of MRSA patients treated with teicoplanin.

Our meta-analysis raises the question of how can we reconcile the high linezolid ELF concentration with the absence of clinical (and micro) cure superiority. The study by Kiem and Schentag (10) describes a number of confounding factors and pitfalls associated with the measurement of ELF drug concentrations. The following factors can alter drug measurements and potentially provide misleading results: protein binding; cellular components of the ELF, which may account for increased ELF concentrations; decreased alveolar macrophage concentrations through cell lysis; volume and dwell time of fluid during the bronchoalveolar lavage; and antibiotic diffusibility. None of these important factors have been considered when interpreting the concentrations of antibiotics, such as linezolid and vancomycin in ELF (10). Unless we refine our ELF methodology through the standardization of these factors or develop a more reliable technique, we subscribe that drug concentrations of oxazolidinones, such as linezolid, measured by current ELF technology should not be assumed to correlate with clinical or microbiological outcomes.

Based on the fact that MRSA is among the common etiologies of nosocomial pneumonia, and linezolid, vancomycin, and teicoplanin have predominantly anti-Gram-positive activity, we performed MRSA subset analyses. We could not combine the clinical cure rate for the MRSA subpopulation because of the lack of reporting in most trials. However, we were able to determine the microbiological eradication for this specific population because all trials reported these results. The overall MRSA eradication was similar for linezolid when compared with vancomycin (RR, 1.05). We believe that this is an important finding because patients with MRSA pneumonia could theoretically be more responsive to linezolid therapy based on the possibility of vancomycin "MIC creep." None of the nine trials reported vancomycin MICs; however, this issue would only favor linezolid. However, if MIC creep was not present during these trials execution period (2001–2008) but it becomes evident now, then additional trials systematically monitoring drug levels and MICs should be conducted to evaluate the use of vancomycin compared with linezolid.

We also evaluated the principal drug side effects reported in these pneumonia trials. The risk of gastrointestinal effects and thrombocytopenia was approximately doubled with linezolid compared with glycopepides, but no differences were observed with respect to renal failure. The event rates for renal failure were lower than those for thrombocytopenia and gastrointestinal effects; this could have made more difficult to detect nephrotoxicity with either drug. Although rare renal toxicity with either linezolid or vancomycin is not excluded, the sample size of 1690 for this analysis is substantial and indicates that, under the conditions of the original studies, vancomycin is not more nephrotoxic than linezolid. Of note, most studies were unblinded, which could have favored linezolid outcomes because clinicians are naturally more aware of the potential for renal toxicity with vancomycin (i.e., ascertainment bias). In agreement with this ascertainment bias hypothesis, our sensitivity analysis demonstrated that unblinded studies showed a nonsignificant increase in renal failure with vancomycin, whereas the blinded studies analysis showed no differences. The gastrointestinal events analysis showed substantial heterogeneity; this could be secondary to the subjectivity of these symptoms' manifestations as well as to differences in reporting among trials. Another limitation of our study is related to the fact that the original trials used last observation carried forward to impute outcomes in patients lost to follow-up before test of cure; although this is common practice in clinical trials, it may lead to less conservative results.

CONCLUSION

In conclusion, despite an excellent statistical power, our meta-analysis did not detect superiority of linezolid vs. glycopeptides for the treatment of nosocomial pneumonia in terms of clinical cure or microbiological eradication, including MRSA eradication. Linezolid showed a significant increase in the risk of thrombocytopenia and gastrointestinal events. Compared with linezolid, vancomycin was not associated with more renal dysfunction. Available data do not support the claim that linezolid is superior to vancomycin for the treatment of nosocomial pneumonia. However, we recognize the need for vancomycin alternatives for the treatment of MRSA infections. Thus, linezolid should be recognized as an alternate (not replacement) for vancomycin for nosocomial pneumonia. At the conclusion of this CME activity, participants should be able to select the most effective antibiotics for the treatment of nosocomial infection.

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