Linezolid vs Glycopeptide Antibiotics for the Treatment of Suspected Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia

A Meta-analysis of Randomized Controlled Trials

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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of nosocomial pneumonia. Societal guidelines suggest linezolid may be the preferred treatment of MRSA nosocomial pneumonia. We investigated the efficacy of linezolid compared with glycopeptide antibiotics (vancomycin or teicoplanin) for nosocomial pneumonia.

Methods: This was a systematic review and meta-analysis of English language, randomized, controlled trials comparing linezolid to glycopeptide antibiotics for suspected MRSA pneumonia in subjects > 12 years of age. A highly sensitive search of PubMed MEDLINE and Cochrane Central Register of Controlled Trials databases identified relevant studies.

Results: Eight trials encompassing 1,641 subjects met entry criteria. Linezolid was not superior to glycopeptide antibiotics for end points of clinical success (relative risk [RR] linezolid vs glycopeptide, 1.04; 95% CI, 0.97-1.11; $P = .28$), microbiologic success (RR, 1.13; 95% CI, 0.97-1.31; $P = .12$), or mortality (RR, 0.91; 95% CI, 0.69-1.18; $P = .47$). In addition, clinical success in the subgroup of subjects with MRSA-positive respiratory tract culture (RR, 1.23; 95% CI, 0.97-1.57; $P = .09$) was not significantly different from those without MRSA (RR, 0.95; 95% CI, 0.83-1.09; $P = .48$), P for interaction, 0.07. The risk for adverse events was not different between the two antibiotic classes (RR, 0.96; 95% CI, 0.86-1.07; $P = .48$).

Conclusion: Randomized controlled trials do not support superiority of linezolid over glycopeptide antibiotics for the treatment of nosocomial pneumonia. We recommend that decisions between linezolid or glycopeptide antibiotics for empirical or MRSA-directed therapy of nosocomial pneumonia depend on local availability, antibiotic resistance patterns, preferred routes of delivery, and cost, rather than presumed differences in efficacy. *CHEST* 2011; 139(5):1148-1155

Abbreviations: EOT = end of treatment; ITT = intention to treat; MIC = minimal inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PVL = Panton-Valentine leukocidin; RR = relative risk; TOC = test of cure

Methicillin-resistant *Staphylococcus aureus* (MRSA) represents the most common pathogen associated with nosocomial pneumonia^{1,2} and is an increasing cause of severe community-acquired pneumonia.^{3,4} MRSA pneumonia is associated with increased morbidity and use of health-care resources compared with methicillin-sensitive *S aureus* (MSSA) strains.⁵ Although glycopeptide antibiotics (eg, vancomycin and teicoplanin) have long been the standard treatment of MRSA pneumonia, recent American Thoracic Society/Infectious Disease Society of America guidelines have suggested that the oxazolidinone

antibiotic linezolid (Zyvox) may be preferred over glycopeptides for MRSA pneumonia.⁶ This recommendation is based on a post hoc analysis of data from a randomized controlled trial that demonstrated a survival advantage in the subgroup of subjects with documented MRSA nosocomial pneumonia treated with linezolid compared with those treated with vancomycin.⁷ This retrospective analysis has been criticized on methodologic and statistical grounds.⁸⁻¹¹

In light of this controversy, further investigation of the comparative efficacy of linezolid is important,

especially given the approximately tenfold increase in cost per dose¹² and increased risk of thrombocytopenia¹³ for linezolid compared with vancomycin. Two recent meta-analyses have demonstrated superior efficacy for linezolid in the treatment of skin and soft tissue infections.^{13,14} However, neither of these reviews focused specifically on pneumonia, resulting in the omission of relevant studies as well as important pneumonia-specific mortality, adverse events, and MRSA subgroup analyses. The purpose of this systematic review and meta-analysis was to investigate the efficacy and adverse event profile of linezolid compared with glycopeptide antibiotics in nosocomial pneumonia.

MATERIALS AND METHODS

Data Sources

A “highly sensitive search method”^{15,16} was used to search MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL). The highly sensitive search strategy is a previously validated search method, with a reported sensitivity of 98% for method identifying relevant articles against a gold standard database.¹⁶ The search was conducted November 11, 2009, with the following terms designed to identify published randomized controlled trials investigating linezolid: (“Randomized Controlled Trial” [Publication Type] OR “Controlled Clinical Trial” [Publication Type] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) AND “linezolid” [Substance Name]. In addition, we searched published abstracts from major international conferences (CHEST 2003-2009, American Thoracic Society 2008-2009, and Infectious Diseases Society of North America 2001, 2003-2006) and the ClinicalTrials.gov registry to identify unpublished trials.

Study Selection

Two investigators (A. J. W. and M. R. O.) independently reviewed results of the search to identify randomized controlled trials comparing linezolid to a glycopeptide antibiotic in subjects diagnosed with pneumonia. Potentially eligible trials were excluded if they were not written in English and study details were not available

from the abstract, did not assess clinical success as an end point, studied strictly immunocompromised subjects, or enrolled only subjects < 12 years of age.

Validity Assessment

All studies meeting entry criteria were included in this meta-analysis. Jadad scores,¹⁷ a simple instrument with high interrater reliability used to assess randomized controlled trial quality, were calculated for each study.

Data Abstraction

Data were abstracted independently in duplicate (A. J. W. and M. R. O.). All corresponding authors of the included studies were contacted via e-mail and asked to provide unpublished summary data pertinent to the outcomes of interest. Specifically, we requested unpublished summary data regarding outcomes (eg, test-of-cure [TOC] and end-of-treatment [EOT] outcomes, adverse events) and prespecified subject subgroups (eg, MRSA and non-MRSA pneumonia) related to subjects with pneumonia.

The primary outcome assessed in this analysis was clinical success at the TOC study follow-up evaluation in clinically evaluable subjects. This end point was chosen for its clinical relevance. Two studies (Wilcox et al¹⁸ and Wunderink et al¹⁹) did not record TOC results; results from the EOT outcome assessment were analyzed for these studies. TOC visits ranged from 5 to 28 days after antibiotic course completion in the studies included in this analysis. Clinical success in these studies was defined as resolution of clinical signs and symptoms of pneumonia compared with baseline. The intention-to-treat (ITT) population was defined as subjects who were randomized and received at least one dose of the study medication; clinical success in the ITT population was analyzed as a secondary outcome. Other secondary outcomes included clinical success at EOT in the clinically evaluable subjects, microbiologic success (sputum pathogen eradication), all-cause mortality during the study period in the ITT sample, and drug-related adverse events (total adverse events, as well as thrombocytopenia and acute renal failure) in the ITT sample.

A prespecified subgroup analysis was performed investigating the primary outcome in subjects with culture-proven MRSA as compared with non-MRSA pneumonia. Data regarding subjects with non-MRSA pneumonia were unavailable from four studies (Wilcox et al,¹⁸ Wunderink et al,¹⁹ Kohno et al,²⁰ and Lin et al²¹) but could be inferred from information given regarding total subjects and subjects with MRSA pneumonia in three studies (Rubinstein et al,²² Wunderink et al,²³ and Stevens et al²⁴) and were supplied directly upon request in one study (Cepeda et al²⁵).

Additional data were collected regarding study design, methods of blinding and randomization, study population, criteria for diagnosis of pneumonia, criteria for assessment of treatment success, and antibiotic dosing, duration, and monitoring procedures. Sensitivity analyses were also performed based on differences in blinding (unblinded vs blinded) and type of glycopeptide comparator (vancomycin vs teicoplanin).

Statistical Analysis

In order to reach 90% power to demonstrate a relative 15% difference between linezolid and vancomycin clinical success rates (75% vs 65%), 450 subjects were necessary in each of the primary analysis intervention groups. Pooled relative risks (RRs) and 95% CIs of outcome comparisons between glycopeptide antibiotics and linezolid were calculated using the Mantel-Haenszel random effects method. Random effects models were chosen for primary statistical analysis due to their more conservative CIs and underlying

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assumptions that allow for greater generalizability of the study findings.²⁶ As a sensitivity analysis, all models were also run using fixed-effects methods, without any significant change in effect estimates or statistical significance. All results reported herein are from random-effects models. Heterogeneity was assessed with χ^2 testing and I^2 statistics. Interaction between subgroups (eg, MRSA and MSSA pneumonia) was calculated using the method of Bland and Altman.²⁷ Visual inspection of funnel plots was used to assess the potential for publication bias. Review Manager, Version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen, Denmark) was used for all statistical analyses. An α level of 0.05 was selected for all analyses.

RESULTS

The flow diagram for selection of the relevant trials of ITT subjects included in this analysis is shown in Figure 1. One study (Cepeda et al²⁵) supplied requested data regarding unpublished pneumonia outcomes. No additional data from unpublished abstracts were identified.

Of 762 articles retrieved with the search strategy, eight¹⁸⁻²⁵ trials enrolling a total of 1,641 subjects met entry criteria and were selected for this meta-analysis. Table 1 summarizes the trial characteristics. All trials were multicenter, and four of eight were double-blind, with an average Jadad score of 3 ± 0.93 . Studies that received a Jadad score of 2 did so because they were not double-blind and did not describe the method of randomization.

All subjects were hospitalized; two studies included only critically ill or mechanically ventilated patients. Two studies investigated teicoplanin as the comparator medication; the remaining studied vancomycin. In no study were vancomycin or teicoplanin drug levels assessed as part of a study protocol. All studies used linezolid doses of 600 mg IV every 12 h and

allowed use of concomitant antibiotics with gram-negative, but not MRSA, activity. The mean duration of therapy in the four studies reporting these data were 10.5 ± 1.18 days for linezolid and 9.96 ± 1.13 days for glycopeptide ($P = .56$). The proportion of the ITT subjects who had outcome assessments was not different between the two treatments; 493/841 (58.6%) subjects who received linezolid and 476/800 (59.5%, $P = .72$) subjects who received a glycopeptide antibiotic were evaluable for the primary outcome of clinical success at TOC follow-up.

Our primary outcome of clinical success at TOC was not different between the two antibiotic classes (pooled RR of treatment success for linezolid compared with glycopeptide, 1.04; 95% CI, 0.97-1.11; $P = .28$) (Fig 2A). This effect estimate was not different for meta-analyses of the EOT end point (1.04; 95% CI, 0.98-1.11) or the TOC end point in entire ITT population (1.02; 95% CI, 0.93-1.12) (Fig 2B). Sensitivity analyses of primary outcome stratifying by allocation concealment type (double-blinded RR, 1.04; 95% CI, 0.93-1.16; open-label RR, 1.04; 95% CI, 0.95-1.13) or type of glycopeptide comparator (vancomycin RR, 1.05; 95% CI, 0.94-1.17; teicoplanin RR, 1.03; 95% CI, 0.95-1.13) also did not result in outcome differences.

Clinical success for subjects with culture-confirmed MRSA pneumonia was not different from those without MRSA. The RR of clinical success for linezolid compared with glycopeptide in those with MRSA (1.23; 95% CI, 0.97-1.57) (Fig 3A) was not different from those without MRSA (0.95; 95% CI, 0.83-1.09; P for interaction 0.07) (Fig 3B). Microbiologic eradication (Fig 4A), mortality (Fig 4B), and total adverse events (Fig 4C) were also similar in linezolid and glycopeptide groups.

Risk for thrombocytopenia was a nonstatistically significant 2.97 times higher for linezolid (95% CI, 0.81-10.94; $P = .10$) in three studies reporting these data. The risk of renal impairment was not significantly different comparing linezolid and glycopeptides (RR, 1.09; 95% CI, 0.35-3.38; $P = .89$).

A funnel plot of effect size vs SE in the primary analysis of clinical success was used to evaluate for publication bias (Fig 5). This plot shows a slight imbalance of effects toward linezolid.

DISCUSSION

This meta-analysis of randomized controlled trials comparing linezolid to glycopeptide antibiotics for suspected MRSA nosocomial pneumonia does not support the assertion that linezolid is a more efficacious antibiotic. Specifically, clinical and microbiologic outcomes in subjects randomized to linezolid

FIGURE 1. Flowchart of process of study identification. HSS = highly sensitive search strategy; RCT = randomized controlled trial.

Table 1—Characteristics of Included Studies

Study/Year	Design	Population	Comparator	ITT, No.	% ITT Subjects Evaluable for Outcome	Jadad Study Quality Score
Rubinstein et al ²² /2001	Multicenter Double-blind	Age > 18 y Nosocomial pneumonia	V 1 g/12 h	L 203 V 193	L 53 V 47	3
Stevens et al ²⁴ /2002	Multicenter Open label	Age > 13 y Hospitalized, presumed MRSA pneumonia, cSSTI, UTI, bacteremia	V 1 g/12 h	L 50 V 49	L 78 V 65	2
Wunderink et al ²³ /2003	Multicenter Double-blind	Age > 18 y Nosocomial pneumonia	V 1 g/12 h	L 321 V 302	L 53 V 58	3
Wilcox et al ¹⁸ /2004	Multicenter Open label	Age > 13 y Hospitalized, suspected gram+ pneumonia, bacteremia, cSSTI	T Dosed per local prescribing guidelines	L 57 T 59	L 93 T 95	3
Cepeda et al ²⁵ /2004	Two centers Double-blind	Age > 16 y Critically ill, suspected gram+ pneumonia or bacteremia	T 400 mg/12 h for three doses then 400 mg/24 h IV	L 47 T 57	L 86 T 100	5
Kohno et al ²⁰ /2007	Multicenter Open label	Age > 20 y MRSA only, nosocomial pneumonia and cSSTI	V 1 g/12 h	L 51 V 26	L 69 V 73	2
Lin et al ²¹ /2008	Multicenter Double-blind	Age 18-75 y Nosocomial pneumonia and cSSTI	V 1 g/12 h	L 38 V 42	L 71 V 81	3
Wunderink et al ¹⁹ /2008	Multicenter Open label	Age > 18 y MRSA only, ventilator- associated pneumonia; BAL at 0, 72 h	V 1 g/12 h	L 75 V 74	L 36 V 26	3

+ = positive; cSSTI = complicated skin and soft tissue infection; ITT = intention to treat; L = linezolid; MRSA = methicillin-resistant *Staphylococcus aureus*; T = teicoplanin; UTI = urinary tract infection; V = vancomycin.

were not superior to subjects randomized to glycopeptides, regardless of the confirmed presence of MRSA. In addition, adverse events were not significantly different between the two antibiotics.

These results are consistent with other meta-analyses that have compared linezolid against glycopeptides for the treatment of multiple sources of infection.^{13,14} Although complicated skin and soft tissue infections have shown to have improved outcomes with linezolid,^{13,14} none of the prior meta-analyses observed significant differences between linezolid and comparators for pneumonia outcomes. Similar to our results for pneumonia, the prior meta-analyses that pooled infectious source showed no difference in total adverse events between treatments. However, Beibei et al¹⁴ found an increased odds of nephrotoxicity for vancomycin, and Falagas et al¹³ demonstrated increased thrombocytopenia with linezolid. Neither of these adverse events was reported with high incidence in the in the patients with pneumonia included in our meta-analysis. This may be because of the shorter courses of antibiotics typically prescribed for pneumonia compared with other infections, such as MRSA bacteremia.

Reports suggesting linezolid as superior for MRSA pneumonia⁷ hypothesize superior drug concentra-

tions in the lung as a potential mechanism of benefit. This is supported by a study of lung epithelial lining fluid levels after one dose of vancomycin in subjects without pneumonia that showed levels below *S aureus* minimal inhibitory concentration (MIC) after 3 h in many subjects.²⁸ In contrast, evidence from studies of humans²⁹ and animals³⁰ with pneumonia did not show subtherapeutic lung concentrations of glycopeptides. Additionally, Lamer et al²⁹ demonstrated higher epithelial lining fluid concentrations of vancomycin with increasing degrees of lung inflammation, which may weaken the validity of drug penetration studies in subjects without pneumonia. Last, when comparing two studies of subjects with nosocomial pneumonia, the proportion of subjects demonstrating trough drug concentrations above the MRSA MIC cited in each study was greater with vancomycin (79% > MIC 2.0 µg/mL)²⁹ than linezolid (31% > MIC 4 µg/mL).³¹ Because no single study in humans has compared pulmonary concentrations of these drugs in patients with pneumonia, it is currently not known if subtherapeutic pulmonary drug levels are more common in patients with pneumonia with glycopeptides compared with linezolid.

Other studies¹⁹ suggest that inhibition of protein synthesis and bacterial toxin production, particularly

FIGURE 2. Forest plots for clinical success outcomes. A, Clinical success at test-of-cure (TOC) follow-up in clinically evaluable subjects. B, Clinical success at TOC follow-up in the intention-to-treat population.

the Panton-Valentine Leukocidin (PVL) toxin associated with necrotizing pneumonias,^{32,33} is the mechanism of putative superiority for linezolid. Importantly, the studies included in our meta-analysis focused on nosocomial MRSA pathogens, which are less likely to produce the PVL toxin, as compared with emerging community-acquired MRSA.³⁴ Thus, our results showing no significant difference in efficacy between linezolid and glycopeptides in nosocomial pneumonia

should not be generalized to community-acquired MRSA pneumonias or MRSA pneumonia with characteristics of a PVL toxin-producing strain (eg, necrosis, parapneumonic effusion).³⁵

Multiple studies have investigated the cost-effectiveness of linezolid for MRSA pneumonia,³⁶⁻³⁹ using pooled data from Rubinstein et al²² and Wunderink et al.²³ These studies conclude that, despite linezolid costs approximately 10 times that

FIGURE 3. A, Forest plot for clinical success in subjects with culture-positive MRSA pneumonia. B, Forest plot for clinical success in subjects without culture-positive MRSA pneumonia. *Also includes the data from Rubinstein et al 2001. MRSA = methicillin-resistant *Staphylococcus aureus*.

FIGURE 4. A, Forest plot for mortality. B, Forest plot for microbiologic success. C, Forest plot for adverse events.

of vancomycin, linezolid is cost-effective given the assumption of improved outcomes. These analyses should be reassessed given our findings of no significant difference in clinical success or mortality between these antibiotics.

Our findings argue against widespread routine use of linezolid for suspected MRSA nosocomial pneu-

monia based on the presumption of superior efficacy. Targeted use of linezolid may be of greater importance given the recent outbreak of linezolid-resistant *S aureus*, directly correlating with linezolid use in a Spanish ICU.⁴⁰ This outbreak highlights the importance of thoughtful antibiotic stewardship, especially given the paucity of effective treatments for MRSA pneumonia.⁴¹

Our study has limitations. The proportion of ITT subjects who were evaluated for clinical outcomes was low across all studies. Whether certain characteristics of the study medications differentially affected loss to follow-up is unknown; however, the proportion of subjects lost to follow-up was not different between interventions. Although this study was adequately powered to detect differences in clinical success between the two antibiotics, it was not powered for subgroup analysis or for detecting interaction between MRSA and non-MRSA groups. Ongoing randomized controlled trials (NCT00084266) comparing these antibiotics for MRSA ventilator-associated pneumonia may provide further information regarding the comparative efficacy of these antibiotics. The funnel plot used to investigate publication bias suggests the possibility of publication bias in favor of linezolid. This weak suggestion is not supported by our

FIGURE 5. Funnel plot for analysis of clinical success at test-of-cure for all included studies. The x axis demonstrates the effect estimate (RR) and the y axis demonstrates the log of the SE. The vertical line demonstrates the pooled effect size and the open squares represent effect estimates for each study plotted against the study SE. RR = relative risk.

review of unpublished abstract or clinical trial registry data. In addition, subgroup comparisons of MRSA vs non-MRSA-related outcomes were not performed in the studies in this meta-analysis; thus, it would be difficult to argue for publication bias against null findings in this subgroup. Importantly, this meta-analysis does not investigate the efficacy of linezolid as a treatment of community-acquired MRSA; in vitro data, animal studies, and case reports suggest that linezolid may be of benefit for these toxin-producing strains.^{32-34,42,43}

In conclusion, this meta-analysis does not show superiority of linezolid as compared with glycopeptide antibiotics for the treatment of nosocomial pneumonia. We recommend that decisions between linezolid or glycopeptide antibiotics for empirical or MRSA-directed therapy of nosocomial pneumonia depend on local availability, antibiotic resistance patterns, preferred routes of delivery, and cost, rather than presumed difference in efficacy.

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Dr Walkey: contributed to conception, design, data analysis and interpretation, manuscript draft, and critical revision.

Dr O'Donnell: contributed to conception, design, data interpretation, and manuscript revision for critical intellectual content.

Dr Wiener contributed to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study.

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