

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

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(See the Editorial Commentary by Torres, on pages 630–2.)

**Background.** Post hoc analyses of clinical trial data suggested that linezolid may be more effective than vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia. This study prospectively assessed efficacy and safety of linezolid, compared with a dose-optimized vancomycin regimen, for treatment of MRSA nosocomial pneumonia.

**Methods.** This was a prospective, double-blind, controlled, multicenter trial involving hospitalized adult patients with hospital-acquired or healthcare-associated MRSA pneumonia. Patients were randomized to receive intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7–14 days. Vancomycin dose was adjusted on the basis of trough levels. The primary end point was clinical outcome at end of study (EOS) in evaluable per-protocol (PP) patients. Prespecified secondary end points included response in the modified intent-to-treat (mITT) population at end of treatment (EOT) and EOS and microbiologic response in the PP and mITT populations at EOT and EOS. Survival and safety were also evaluated.

**Results.** Of 1184 patients treated, 448 (linezolid,  $n = 224$ ; vancomycin,  $n = 224$ ) were included in the mITT and 348 (linezolid,  $n = 172$ ; vancomycin,  $n = 176$ ) in the PP population. In the PP population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at EOS (95% confidence interval for difference, 0.5%–21.6%;  $P = .042$ ). All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).

**Conclusions.** For the treatment of MRSA nosocomial pneumonia, clinical response at EOS in the PP population was significantly higher with linezolid than with vancomycin, although 60-day mortality was similar.

Recent decades have seen steady increases in morbidity and mortality associated with nosocomial infections, attributable in part to increasing antibiotic resistance

[1, 2]. Pneumonia is the second most common hospital-associated infection in the United States [3], and its risk increases 6–21-fold in patients receiving mechanical ventilation [4]. Treatment of these life-threatening infections continues to be challenging as protracted mechanical ventilation becomes more common in the aging population [5].

Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), cause many of these infections. MRSA accounts for 10%–40% cases of healthcare-associated (HCAP), hospital-acquired (HAP), and ventilator-associated pneumonia (VAP) [5–9]. In some

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<sup>a</sup>At the time that the study was conducted.

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centers, MRSA pneumonia occurs with equal frequency in HCAP as in HAP and more commonly than in VAP [6]. A longitudinal study conducted in >1200 US intensive care units showed that the proportion of MRSA isolates increased from 36% in 1992 to 64% in 2003 [10]; however, rates may now be decreasing [11].

Two prospective, randomized, double-blind trials found that linezolid was statistically noninferior to fixed-dose vancomycin (1 g twice daily) for the treatment of nosocomial pneumonia [12, 13]. Post hoc analysis of both trials combined found that survival (80.0% vs 63.5%;  $P = .03$ ) and clinical cure (59.0% vs 35.5%;  $P < .01$ ) were significantly improved in the MRSA pneumonia subgroup when treated with linezolid, compared with vancomycin [14], including patients with MRSA VAP [15]. However, the lower efficacy and higher mortality seen with vancomycin may potentially have been attributable to lack of vancomycin dose-optimization in those trials; current guidelines recommend an initial vancomycin dose based on body weight and subsequently adjusted according to trough levels [16, 17].

This trial was conducted to prospectively assess the efficacy, safety, and tolerability of fixed-dose linezolid, compared with dose-optimized vancomycin for the treatment of proven MRSA nosocomial pneumonia in hospitalized adults. This approach was taken to validate the previous post hoc analyses in the context of appropriate vancomycin dosing.

## METHODS

### Design Overview

This phase IV, randomized, double-blind, multicenter, international, comparator-controlled study enrolled patients from 13 October 2004 through 31 January 2010. The study was approved by an institutional review board or ethics committee at each investigational site. Written informed consent was obtained from all patients or their legally authorized representative.

### Setting and Participants

Hospitalized patients aged  $\geq 18$  years with radiographically documented HAP or HCAP and relevant signs and symptoms were eligible (Appendix Figure 1). Patients were required to have a baseline respiratory or sputum specimen positive for MRSA. Microbiologic cultures were performed according to the standard of care at the study site, except for patients with chronic ventilation (>30 days) or tracheostomy, for whom invasive quantitative cultures were mandated. Patients had to have an expected survival of  $\geq 72$  hours.

Patients with treatment with linezolid, vancomycin, or teicoplanin for >48 hours within or before the 72-hour prestudy period (if treatment continued into that period) were excluded. All patients who were considered to have experienced clinical failure for any of these drugs were specifically excluded. Patients previously treated with any other MRSA-active antibiotic (for

>48 hours, but within the 72-hour prestudy period only) were also excluded, unless documented as having a treatment failure.

### Randomization and Interventions

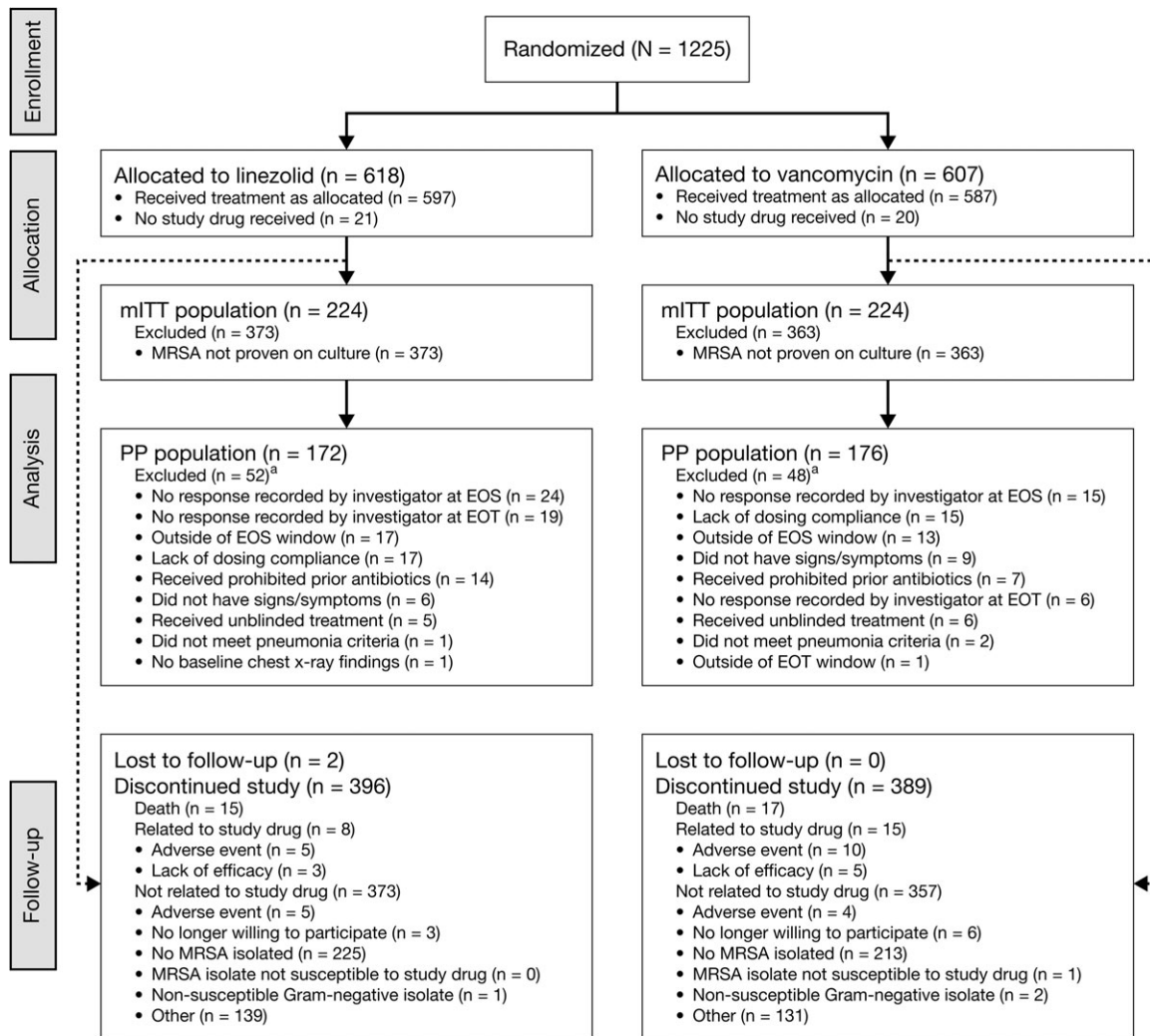
Treatment was randomized centrally without regard to institution with use of an interactive phone system. Patients were assigned to receive either intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7–14 consecutive days (21 days if bacteremia was documented). A local, unblinded pharmacist prepared study medication; investigators and study staff remained blinded to study medication. Blinding was maintained until a patient was excluded from the study (eg, because of lack of response). The pharmacist monitored and adjusted vancomycin doses according to local protocols based on trough levels and renal impairment, while maintaining investigator blinding. All patients received a Gram-negative antibiotic without MRSA activity, which was discontinued if no Gram-negative pathogens were identified. In mixed infection, patients were discontinued from the study if the investigator felt that the Gram-negative bacterium was the predominant pathogen. Patients coinfecting with Gram-negative bacteria resistant to the empirical antibiotic were also discontinued. Therefore, all patients with mixed infections had adequate Gram-negative antibiotic coverage.

### Outcomes and Follow-Up

Patients were clinically assessed at baseline, on day 3, and every 3 days during treatment. Repeat respiratory cultures were performed 48–72 hours after treatment initiation, at end of treatment (EOT), and at end of study (EOS; defined as 7–30 days after EOT). All patients with baseline bacteremia were required to have blood cultures repeated after 48–72 hours to confirm clearance of bacteremia. Final MRSA identification and minimum inhibitory concentration (MIC) testing were performed at a central laboratory with use of broth microdilution methods according to Clinical and Laboratory Standards Institute guidelines current at the time of study initiation [18].

Clinical outcome was primarily assessed by the investigator within 5 days of EOT and at EOS, with occasional override by the sponsor based on the criteria of Appendix 1. All revisions were made before unblinding. Microbiologic responses were determined at EOT and EOS, based on culture results from the original infection site. Definitions of clinical and microbiologic outcomes are provided in Appendix Table 1. Overall survival was assessed at 60 days after therapy.

Laboratory safety data were collected regularly during treatment, at EOT, and at EOS. Data for determining Acute Physiology and Chronic Health Evaluation (APACHE) II scores [19] were collected at baseline and, for Clinical Pulmonary Infection Scores (CPIS; modified from a previously published method [20] to capture minute ventilation) (Appendix Table 2), at baseline and on day 3 in patients receiving mechanical ventilation only. Directly observed and spontaneously reported adverse events



**Figure 1.** Patient flow chart. Abbreviations: EOS, end of study; EOT, end of therapy; mITT, modified intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; PP, per-protocol. <sup>a</sup>Patients may have been excluded for >1 reason.

(AEs) were monitored until 28 days after the last dose of study treatment. A post hoc analysis of nephrotoxicity, defined as a 0.5-mg/mL increase in serum creatinine level if normal at baseline or 50% increase if abnormal at baseline, was performed. Treatment safety was assessed in the intent-to-treat (ITT) population (ie, all randomized patients who received  $\geq 1$  dose of study drug).

The modified ITT (mITT) population included all ITT patients with a diagnosis of nosocomial pneumonia caused by MRSA. The per-protocol (PP) population was defined on a by-visit basis and included those mITT patients who met all key inclusion/exclusion criteria, received adequate study medication (ie,  $\geq 5$  days of treatment, or  $\geq 2$  days for patients whose clinical outcome was considered to be a failure), and had an observed outcome for that visit (unless already declared as a treatment failure). The primary efficacy end point was clinical outcome at

EOS in PP patients. Clinical cure was defined as resolution of clinical signs and symptoms of pneumonia, compared with baseline; improvement or lack of progression in chest imaging; and no requirement for additional antibacterial treatment (Appendix Table 1). Secondary efficacy end points included microbiologic outcome at EOS and EOT, clinical outcome at EOT in the mITT and PP populations, and clinical outcome at EOS in the mITT population. Other secondary end points were patient survival and incidence of AEs.

### Statistical Analysis

This was a noninferiority trial with a nested superiority hypothesis. Noninferiority of linezolid, compared with vancomycin, was concluded if the lower boundary of the 95% confidence interval (CI) for the difference between treatments was  $> -10\%$ . Superiority was declared if the entire CI was  $> 0$ . See Appendix 1

**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 <sup>a</sup>	26 (15.1)	30 (17.1)
Nosocomial	146 (84.9)	146 (83.0)
Ventilator-associated <sup>b</sup>	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) <sup>c</sup>		
Mean (SD)	9.7 (2.1)	9.4 (2.3)
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)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CPIS, Clinical Pulmonary Infection Score; SD, standard deviation.

<sup>a</sup> Defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home, rehabilitation center) or in a patient who was admitted with pneumonia following a recent hospitalization (discharged within 90 days of the current admission and previously hospitalized for at least 48 hours) or pneumonia in a patient who had received chronic dialysis care within 30 days prior to study enrollment.

<sup>b</sup> Defined as onset of pneumonia after >48 hours of mechanical ventilation. Subgroup of nosocomial pneumonia.

<sup>c</sup> Calculated for ventilated patients only (see Appendix Table 2 for details of scoring system).

for sample size calculations. A formal interim analysis was conducted by an independent data monitoring committee halfway during study enrollment. The overall type I error was controlled using an O'Brien-Fleming [21] spending function, with a final significance level of 0.048 for the primary end point.

Two multiple imputation (MI) analyses [22] were conducted, in which missing outcomes at EOS were imputed separately for each treatment arm based on EOT outcome and observed relapse rate among patients with complete data (MI1) and a highly

predictive variable of outcome (baseline pressor use; yes/no) in addition to MI1 information (MI2). Outcomes for patients who experienced failure at EOT and for those who died between EOT and EOS were carried forward as failures. Patients who received nonstudy antibiotics with activity against their specific MRSA isolates were also deemed to have experienced failure, regardless of investigator-assigned outcome.

The distribution of time to death from first day of study drug was estimated using the Kaplan-Meier procedure [23]. All analyses were conducted using SAS, versions 8.2 and 9.2 (SAS Institute).

## RESULTS

### Patient Disposition and Characteristics

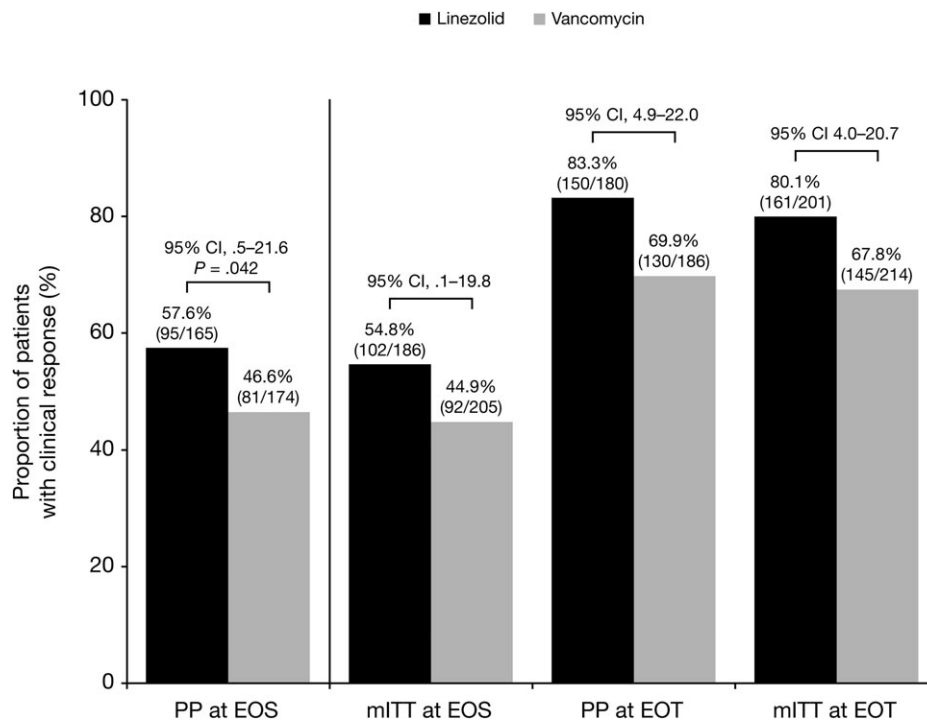
The ITT population included 1184 patients (Figure 1). MRSA pneumonia was confirmed in 448 patients who comprised the mITT population (linezolid, n = 224; vancomycin, n = 224). Of these, 348 (linezolid, n = 172; vancomycin, n = 176) comprised the PP population (Figure 1); the most common reasons for exclusion were EOT/EOS responses not recorded on the case report form and lack of dosing compliance (Appendix Table 3). In PP patients, infection was diagnosed by tracheal aspirate (43.4%), (mini-) bronchoalveolar lavage (31.3%), sputum specimen (16.7%), blood culture (6.6%), or other methods (2.0%).

Patient characteristics were generally balanced between PP treatment groups (Table 1). Slightly more vancomycin-treated than linezolid-treated patients received mechanical ventilation at baseline (73.9% vs 66.9%) and had MRSA bacteremia (10.8% vs 5.2%); mITT populations were similar. Most patients had received antibiotics within 7 days before study entry; they were evenly distributed between treatment arms. The most common prior antibiotics were (>1 possible): vancomycin (64.3%), cefepime (46.4%), ciprofloxacin-levofloxacin (42.2%), piperacillin-tazobactam (39.5%), ceftriaxone (20.1%), linezolid (11.4%), and amikacin (11.0%). Mean duration of prestudy treatment was ~3 days, with the exception of vancomycin (1.5 days). Median duration of study treatment was 10.0 days (range, 2–22 days) in both arms.

### Clinical and Microbiologic Response

In the PP population, 95 (57.6%) of 165 linezolid-treated patients were clinically cured at EOS, compared with 81 (46.6%) of 174 vancomycin-treated patients (95% CI for the difference between success rates, 0.5%–21.6%; *P* = .042). Linezolid also showed clinical efficacy superior to vancomycin at EOT and in mITT patients at both times (Figure 2). MI analyses to account for missing primary end point data confirmed the results seen in the primary population (MI1: *P* = .035; MI2: *P* = .029).

Response differences of 10%–15% remained present in most subgroups (Table 2), including patients with mixed infections and those receiving either mechanical ventilation



**Figure 2.** Clinical response rates in per-protocol (PP) and modified intent-to-treat (mITT) patients at end-of-study (EOS) and end of therapy (EOT). P values and 95% confidence intervals (CI) are included for the differences between treatment groups in the primary end point.

or concomitant systemic steroids. Vancomycin-treated patients had similar treatment outcomes regardless of their day 3 vancomycin trough levels (analyzed by quartile).

In the PP population at EOS, 58.1% of linezolid-treated patients had microbiologic success (eradication or presumed eradication), compared with 47.1% of vancomycin-treated patients (Figure 3). At EOT, 81.9% of linezolid-treated and 60.6% of vancomycin-treated PP patients had microbiologic success. Similar microbiologic outcomes were observed in the mITT population. At EOT in the PP group, among patients who had material for microbiologic culture, documented persistence of MRSA (ie, positive culture result) was recorded for 16 (17.4%) of 92 in the linezolid arm, compared with 50 (45.9%) of 109 in the vancomycin arm (Figure 3). All patients with bacteremia experienced microbiologic cure, with no positive repeat blood culture results. At EOS, documented persistence or recurrence occurred in 22 (38.5%) of 57 and 26 (50.0%) of 52 linezolid- and vancomycin-treated patients, respectively. Although the number of isolates with a vancomycin MIC of 2 µg/mL was small, no differences in response to vancomycin were seen, compared with isolates with lower MICs.

### Safety

In the IIT population, 427 patients experienced 657 serious AEs (SAEs). SAEs were similar in incidence and type between both arms: 209 linezolid-treated patients (315 events) and 210 vancomycin-

treated patients (334 events). Twenty-six SAEs (in 20 patients) were judged related to study drug by investigator, sponsor, or both: 7 linezolid-treated patients (with 8 SAEs; 2 cases of *Clostridium difficile* infection and 1 each of shock, death, chronic renal failure, acute renal failure, thrombocytopenia, and rash) and 13 vancomycin-treated patients (with 18 SAEs; 8 cases of renal failure/azotemia and 1 each of hyperkalemia, septic shock, sepsis, neutropenia, anemia, lung infiltrate, deterioration of *S. aureus* infection, general health deterioration, atrial fibrillation, and hypersensitivity). Four linezolid-treated patients discontinued treatment because of SAEs (endocarditis, ischemic hepatitis, rash, and abdominal pain/diverticular perforation), as did 7 vancomycin-treated patients (2 acute renal failure and 1 each of staphylococcal infection/respiratory failure, sepsis, worsening renal failure, intracranial hemorrhage, and hypersensitivity).

Clinically important AEs (all-causality) are shown in Table 3. Investigator-reported renal failure was twice as common in the vancomycin arm than in the linezolid arm. Investigator-reported rates of anemia, neutropenia, and thrombocytopenia were similar in both groups.

Laboratory results were generally comparable between study arms. Laboratory evidence of nephrotoxicity (defined as 0.5-mg/mL increase in serum creatinine level if normal at baseline or 50% increase if abnormal at baseline) occurred in 8.4% of linezolid-treated patients, compared with 18.2% of

**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
Age			
<65 years	51/87 (58.6)	42/80 (52.5)	-8.9 to 21.2
≥65 years	44/78 (56.4)	39/94 (41.5)	.1 to 29.8
≥75 years	18/40 (45.0)	21/45 (46.7)	-22.9 to 19.6
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
APACHE II score			
<20	69/112 (61.6)	59/121 (48.8)	.2 to 25.5
≥20	25/50 (50.0)	20/49 (40.8)	-10.4 to 28.7
Type of pneumonia <sup>c</sup>			
Healthcare-associated	15/24 (62.5)	13/30 (43.3)	-7.1 to 45.4
Nosocomial/hospital-acquired	80/141 (56.7)	68/144 (47.2)	-2.0 to 21.1
Ventilator-associated	55/101 (54.5)	53/116 (45.7)	-4.5 to 22.1
Causative pathogen			
MRSA only	60/102 (58.8)	53/109 (48.6)	-3.2 to 23.6
Mixed MRSA/other pathogen	35/63 (55.6)	28/65 (43.1)	-4.7 to 29.7
Vancomycin trough levels (day 3)			
0-7.9 µg/mL	...	17/35 (48.6)	
8-12.3 µg/mL	...	17/37 (46.0)	
12.4-17.4 µg/mL	...	15/33 (45.5)	
>17.4 µg/mL	...	15/33 (45.5)	
Vancomycin MIC			
<1 µg/mL	10/16 (62.5)	7/14 (50.0)	-22.8 to 47.8
1 µg/mL	77/122 (61.5)	64/134 (47.8)	1.6 to 25.8
≥2 µg/mL	3/8 (37.5)	7/13 (53.8)	-59.5 to 26.8
Systemic steroids			
Yes	21/39 (53.9)	16/36 (44.4)	-13.1 to 32.0
No	74/126 (58.7)	65/138 (47.1)	-.3 to 23.6
Prior vancomycin (7 days)			
Yes	52/86 (60.5)	43/89 (48.3)	-2.5 to 26.8
No	43/79 (54.4)	38/85 (44.7)	-5.5 to 25.0

*Table 2 continued.*

Subgroup	Linezolid Arm, No. (%)	Vancomycin Arm, No. (%)	95% CI for Difference <sup>a</sup>
Vasopressors			
Yes	13/36 (36.1)	16/40 (40.0)	-25.7 to 17.9
No	82/129 (63.6)	65/134 (48.5)	3.2 to 26.9
Diagnosis by quantitative culture			
Yes	30/58 (51.7)	31/72 (43.1)	-8.5 to 25.9
No	65/107 (60.8)	50/102 (49.0)	-1.7 to 25.1
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

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup> CI for difference between clinical success rates for linezolid minus those for vancomycin.

<sup>b</sup> Patients with end of study outcome of "indeterminate" were excluded from efficacy analysis. For other table parameters, only those evaluable for that criterion were included.

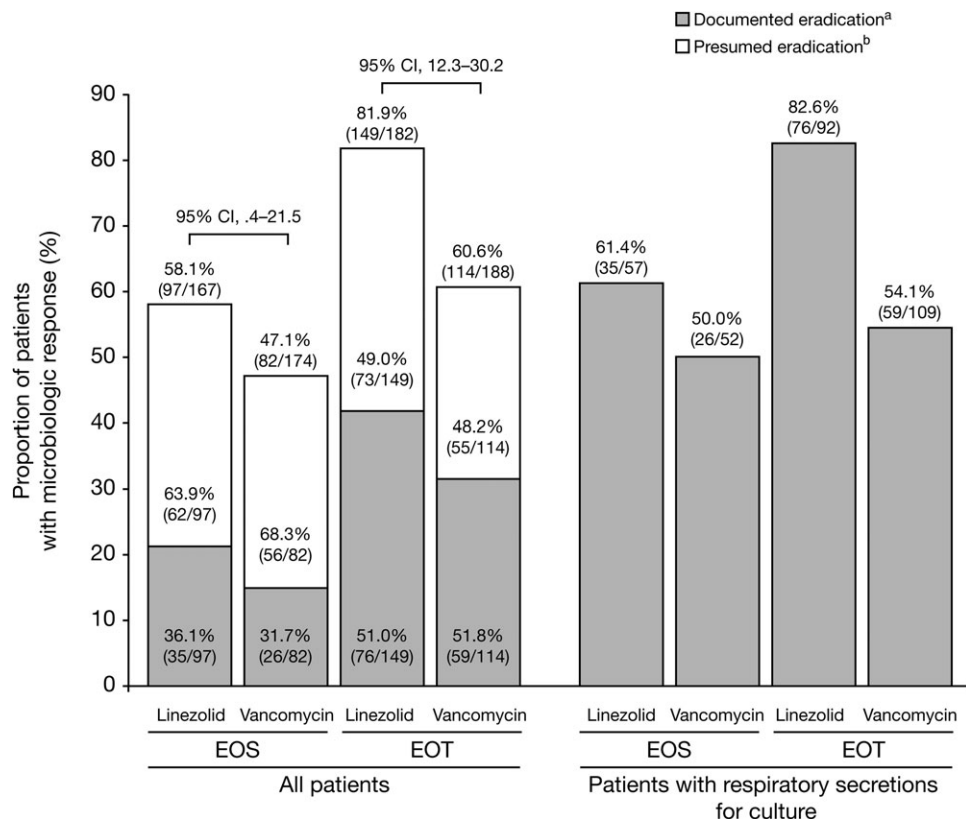
<sup>c</sup> Defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home, rehabilitation center) or in a patient who was admitted with pneumonia following a recent hospitalization (discharged within 90 days of the current admission and previously hospitalized for at least 48 hours) or pneumonia in a patient who had received chronic dialysis care within 30 days prior to study enrollment. Note: denominators were different for each patient subgroup; some values were recorded as "missing."

vancomycin-treated patients in the mITT population. Renal toxicity was roughly equivalent in patients with baseline glomerular filtration rate <50 mL/min (16.2% vancomycin vs 13.8% linezolid) but was higher in vancomycin-treated patients with glomerular filtration rate >50 mL/min at baseline (18.8% vs 5.6% for linezolid). Renal toxicity for the vancomycin groups was greater if the day 3 trough level was ≥20 µg/mL (37%), compared with 15-20 µg/mL (22%) or <15 µg/mL (18%). Anemia (hemoglobin level, ≤10 g/dL, or 0.2-g/dL decrease during study period) was reported in 18.1% of linezolid-treated patients and 19.3% of vancomycin-treated patients. Thrombocytopenia (platelet count, <150 000 platelets/mm<sup>3</sup> if normal at baseline or 50% decrease if low at baseline) occurred in 16.3% of linezolid-treated patients and 13.2% of vancomycin-treated patients.

All-cause 60-day mortality in the ITT population was 15.7% in the linezolid arm and 17.0% in the vancomycin arm (Appendix Figure 2). Sixty-day mortality in the mITT population was 28.1% and 26.3%, respectively.

## DISCUSSION

This large, randomized, double-blind, controlled trial demonstrated greater clinical efficacy (primary trial end point) of linezolid, compared with adjusted-dose vancomycin, for the



**Figure 3.** Microbiologic response rates in the per-protocol (PP) population at end-of-study (EOS) and end-of-treatment (EOT). Data include 95% confidence intervals (CI) for the differences between treatment groups. Results are shown for both the overall PP population (left) and only for patients who had microbiologic culture data available at these time points, which therefore excludes all patients with presumed eradication. For the overall PP population, the numbers and percentages within the bars represent the proportions of patients within each group who had presumed eradication (white) versus documented eradication (gray). <sup>a</sup>Microbiologic data available, confirmed microbiologic eradication. <sup>b</sup>No microbiologic data, but confirmed clinical cure.

treatment of MRSA nosocomial pneumonia. These results confirm the pattern of clinical efficacy seen in prior subgroup analyses of studies comparing linezolid with vancomycin in this

**Table 3. Clinically Important Investigator-Reported All-Cause Adverse Events in the Intent-to-Treat Population**

Adverse Event	Linezolid Arm, No. (%) (n = 597)	Vancomycin Arm, No. (%) (n = 587)
Anemia	30 (5.2)	42 (7.2)
Renal failure/impairment/azotemia <sup>a</sup>	22 (3.7)	43 (7.3)
Cardiac arrest	11 (1.8)	13 (2.2)
Thrombocytopenia	8 (1.3)	13 (2.2)
Pancreatitis	5 (0.8)	1 (0.2)
Polyneuropathy	...	1 (0.2)
Pancytopenia/neutropenia	4 (0.6)	2 (0.4)
Paresthesia	...	1 (0.2)

<sup>a</sup> Patient was reported to have at least 1 (>1) of the following: renal failure, renal impairment, and/or azotemia.

context [14, 15]. The response pattern observed for the primary end point (ie, clinical response at EOS in the PP population) was maintained in important patient subgroups. Sensitivity analyses for indeterminate or missing responses in the primary end point, using MI methodology, supported these results. These differences were achieved despite optimization of vancomycin dosing, a limitation of prior clinical trials conducted to the previous standard of care. The trough vancomycin levels attained and the relatively low vancomycin MICs suggest that the study outcome reflects true differences in efficacy, rather than potentially inadequate vancomycin dosing.

Microbiologic responses paralleled clinical outcomes, and MRSA clearance at EOT was 30% greater with linezolid than with vancomycin. A difference of at least 20% persisted until EOS, suggesting that linezolid treatment may result in more complete bacterial eradication. Insufficient patient numbers prevented a separate analysis of infection due to isolates with vancomycin MICs higher than 1 µg/mL, although other studies suggest vancomycin efficacy deteriorates as MICs increase [24]. Prior vancomycin therapy was not associated with significantly

worse outcomes, even when patients were randomized to receive vancomycin. Patients suspected to have experienced vancomycin treatment failure were specifically excluded from the study, minimizing any bias against vancomycin.

Linezolid also appeared to be better tolerated than was vancomycin. Although overall SAEs and AEs were equivalent, nephrotoxicity was nearly twice as common in vancomycin-treated patients. More frequent hematologic abnormalities (including anemia and thrombocytopenia) reported with linezolid in some previous analyses [25] were not observed, possibly because of the short duration of therapy. SAEs requiring study drug discontinuation were more common with vancomycin.

The higher rate of nephrotoxicity with vancomycin may partially reflect the use of adjusted vancomycin doses in this trial, as recommended by current clinical guidelines [16, 17]. A higher incidence of renal injury was seen in patients with vancomycin trough levels  $>20$   $\mu\text{g/mL}$  on day 3, as previously reported [26, 27]. Although this may result from acute kidney injury rather than being the direct cause, the finding of an equivalent rate of nephrotoxicity with vancomycin in patients with normal baseline renal function to those with an abnormal baseline glomerular filtration rate raises concern. In contrast, the majority of nephrotoxicity associated with linezolid treatment occurred in patients with abnormal baseline renal function. Of note, vancomycin trough levels  $>15$   $\mu\text{g/mL}$  on day 3 were not associated with any improved clinical response in this study.

Despite better clinical and microbiologic responses, mortality was not lower in linezolid-treated patients, which contrasts with previously published findings [14, 15]. Mortality among linezolid-treated patients was similar to that in the previous post hoc analyses, whereas mortality among vancomycin-treated patients was lower (ie, 17% in the current trial versus  $>35\%$  observed previously) [14, 15]. This decreased mortality in the vancomycin group may reflect the optimized vancomycin dosing used in the current study, overall improved quality of care in patients with nosocomial pneumonia, or the availability of linezolid for salvage therapy of patients experiencing vancomycin failure; treatment that was not available during the phase III trials. Attributable mortality in MRSA VAP is substantial if vancomycin is not dosed effectively, but is  $<15\%$  with appropriately dosed vancomycin [28, 29]. Furthermore,  $\leq 48$  hours of prior therapy was allowed before randomization, compared with 24 hours in previous registration trials [14, 15]. This period may have excluded patients experiencing early vancomycin treatment failure. It seems unlikely that investigators would have enrolled patients experiencing failure with vancomycin treatment during that period into a trial in which they might be randomized to continued vancomycin treatment. Exclusion of these patients, along with those excluded because of overt clinical failure of prior therapy, may have limited enrollment of a subgroup associated with increased mortality in prior studies.

We specifically included HCAP cases because this is an important and relatively common type of MRSA pneumonia [6, 16]. Patients with HCAP are excluded from registration trials of new agents; therefore, clinical experience with antibiotic response is limited. In the  $\sim 15\%$  of the PP population characterized as having HCAP, the relative clinical success rates of linezolid and vancomycin were similar to those in the more conventional populations.

Weaknesses of our study include the number of mITT patients excluded from the PP population and the higher proportion of cases of MRSA bacteremia and mechanical ventilation in the vancomycin arm. Because of the recognized inaccuracies of using expectorated sputum and endotracheal aspirate specimens for pneumonia diagnosis, some patients may not truly have had MRSA pneumonia. However, clinical success rates were nearly identical in quantitative culture-diagnosed and nonquantitatively diagnosed cases. Treatment of colonization only would probably diminish any treatment-related differences in clinical response and was equally likely in both arms.

In this direct, prospective comparison, clinical response at EOS in the PP population was significantly better with linezolid than with vancomycin for the treatment of nosocomial pneumonia due to MRSA; no statistically significant differences in mortality were demonstrated. Tolerability profiles of both agents appeared to be equivalent, although nephrotoxicity was more common with vancomycin.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online ([http://www.oxfordjournals.org/our\\_journals/cid/](http://www.oxfordjournals.org/our_journals/cid/)). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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