MAJOR ARTICLE

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

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**Linezolid, the first oxazolidinone, is active against gram-positive bacteria, including multidrug-resistant strains. This multinational, randomized, double-blind, controlled trial compared the efficacy, safety, and tolerability of linezolid with vancomycin in the treatment of nosocomial pneumonia. A total of 203 patients received intravenous linezolid, 600 mg twice daily, plus aztreonam, and 193 patients received vancomycin, 1 g intravenously twice daily, plus aztreonam for 7–21 days. Clinical and microbiological outcomes were evaluated at test of cure 12–28 days after treatment. Clinical cure rates (71 [66.4%] of 107 for linezolid vs. 62 [68.1%] of 91 for vancomycin) and microbiological success rates (36 [67.9%] of 53 vs. 28 [71.8%] of 39, respectively) for evaluable patients were equivalent between treatment groups. Eradication rates of methicillin-resistant *Staphylococcus aureus* and safety evaluations were similar between treatment groups. Resistance to either treatment was not detected. Linezolid is a well-tolerated, effective treatment for adults with gram-positive nosocomial pneumonia.**

Nosocomial pneumonia accounts for 15% of nosocomial infections in the United States and 46.9% of nosocomial infections in Europe [1–5] and is associated with significant morbidity and mortality and increased hospital costs [6–9]. Estimated mortality rates range from 20% to 50% and are as high as 70%–90% in patients with intensive care unit (ICU)–acquired pneumonia, ventilator-associated pneumonia, or adult respiratory distress syndrome [3, 5, 6, 10]. Nosocomial pneumonia is associated with a significant increase in hospital stay, with reported estimates of excess duration ranging from 4 to 13 days, resulting in increased medical resource use and health care costs [10–12].

Over the past 15 years, the incidence of nosocomial pneumonia due to gram-positive relative to gram-negative organisms has increased [13–15]. *Staphylococcus aureus*, methicillin-resistant *S. aureus*, and penicillin-resistant pneumococci are replacing gram-negative bacteria as predominant causes of nosocomial pneumonia [15]. The National Nosocomial Infections Surveillance System and others report that *S. aureus* is the most common cause of nosocomial infections and accounts for 20% of reported pathogens in adult patients with nosocomial pneumonia in ICUs [13, 16–20]. In addition, the number of nosocomial methicillin-resistant *S.*

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Informed consent was obtained from the patients or their guardians, and guidelines for human experimentation of the US Department of Health and Human Sciences and/or those of the authors' institutions were followed in the conduct of the clinical research.

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*aureus* isolates in the United States has increased from 2% in 1974 to 29% in 1991, with similar increases worldwide [21–26]. With continued empirical use of vancomycin in the treatment of suspected nosocomial pneumonia due to a gram-positive organism, the potential for reduced effectiveness of vancomycin and the development of vancomycin resistance increases [27–29]. Current practices indicate that prompt initiation of a potentially effective empirical parenteral antimicrobial regimen based on the most likely suspected organisms, including coverage against *S. aureus* [17, 30–34], is appropriate in many cases. Given the increasing incidence of gram-positive pathogens in nosocomial pneumonia, new therapies are needed.

Oxazolidinones, the newest class of antimicrobial agents to be developed in >30 years, act by inhibiting protein synthesis at a very early stage of bacterial replication [35–, 37]. Because of this unique mechanism of action, they lack cross-resistance with currently available antimicrobial agents that are used against gram-positive organisms [36, 38]. Linezolid, the first FDA-approved oxazolidinone, has demonstrated in vitro and in vivo activity against susceptible and resistant gram-positive bacteria, such as staphylococci, streptococci, and enterococci, including vancomycin-resistant strains [36, 39–44]. The safety and efficacy of linezolid in the treatment of pneumonia and skin and soft tissue infections due to gram-positive bacteria have been studied in phase III clinical trials [45–49]. The primary objectives of the present study were to assess the clinical and microbiological efficacy, safety, and tolerance of linezolid plus aztreonam compared with vancomycin plus aztreonam in the empirical treatment of adult patients with nosocomial pneumonia.

## PATIENTS AND METHODS

***Study design.*** This was a randomized, double-blind, comparator-controlled trial comparing iv linezolid plus aztreonam with iv vancomycin plus aztreonam for the empirical treatment of patients with nosocomial pneumonia. The trial included 90 investigator sites in North and South America, Europe, Israel, South Africa, and Australia and enrolled patients from 13 October 1998 through 16 July 1999.

***Patient selection.*** Male and female patients ⩾18 years old with clinical signs and symptoms consistent with pneumonia acquired after 48 h in an inpatient health care or chronic-care facility were eligible for enrollment. At the time of inclusion, patients were to have at least 2 of the following signs and symptoms: cough; purulent sputum; auscultatory findings of pneumonia; dyspnea, tachypnea, or hypoxemia; or identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples. Patients also had to have at least 2 of the following: fever or hypothermia, respiratory rate >30 breaths/min, systolic blood pressure <90 mm Hg, pulse rate ⩾120 beats/min, altered mental status, need for mechanical ventilation, elevated total peripheral WBC count >10,000 cells/mm$^3$, >15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count <4500 cells/mm$^3$. Also required were a chest radiograph that revealed findings consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion), adequate respiratory and sputum specimens for Gram's stain and culture, venous access for iv dosing, and a life expectancy of at least 7 days.

Patients were excluded from the study if they had any of the following: an infection due to organisms known to be resistant to either of the study medication regimens before study entry; known or suspected pulmonary disease that precluded evaluation of therapeutic response (e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs); recent clinically significant coagulopathy; cystic fibrosis, active tuberculosis, pheochromocytoma, untreated hyperthyroidism, untreated or uncontrolled hypertension, carcinoid syndrome, meningitis, endocarditis, or osteomyelitis; a $CD4^+$ cell count of <200 cells/mm$^3$ secondary to HIV infection; unstable psychiatric conditions or seizure disorders requiring chronic medications; previous antibiotic treatment for >24 h (unless documented to be a treatment failure or if the isolated pathogen for the current pneumonia was resistant in vitro to previous nonstudy antibiotic); hypersensitivity to any of the study medications (and excipients); known liver disease and total bilirubin level >5 times the upper limit of normal; or neutropenia (<500 cells/mm$^3$). Patients were also excluded if they were pregnant, lactating, or unable to take adequate contraceptive measures.

***Treatment regimens.*** Patients were allowed to receive up to 24 h of nonstudy antimicrobial treatment before study entry. Patients were randomized in a 1:1 fashion to receive 1 of the following regimens for at least 7 consecutive days, up to a maximum of 21 consecutive days: linezolid, 600 mg iv every 12 h, plus aztreonam, 1–2 g iv every 8 h; or vancomycin, 1 g iv every 12 h, plus aztreonam, 1–2 g iv every 8 h. The vancomycin regimen was monitored and adjusted on the basis of renal function by unblinded personnel who were not involved in assessment of patient outcome or care. Linezolid does not require dose adjustment based on renal function. Aztreonam therapy may have been discontinued if gram-negative pathogens were not identified at baseline. Patients in whom only gram negative pathogens were identified at baseline were to be removed from the study. Therapy with potentially effective nonstudy medications during treatment or before the follow-up visit was not permitted unless study medication failed.

***Clinical assessments.*** Clinical assessments at baseline included a history and physical examination, with vital signs and clinical observations (i.e., assessment of cough, chills, dyspnea, chest pain, breath sounds, and sputum production), electrocardiogram, acute physiology and chronic health evaluation

(APACHE) II score, and chest radiograph. Clinical observations and vital signs were assessed every 3 days while the subject was receiving study medication and were repeated at end of therapy and at follow-up with the physical examination and chest radiograph. The test of cure (TOC) was conducted at the follow-up visit 12–28 days after the end of therapy, with the clinical evaluation of pneumonia based on the improvement and resolution of clinical signs and symptoms of infection, including fever, leukocytosis, purulent sputum production, and radiographic lung infiltrates. Laboratory assessments, including hematology and clinical chemistry analyses, were completed at baseline, on days 3, 9, and 15, at the end of therapy, and at follow-up.

***Microbiological assessments.*** Expectorated sputum or endotracheal suction specimens were collected at baseline and follow-up by the investigator for Gram's stain and culture. In addition, at baseline only, specimens were obtained for culture by other methods, including protected specimen brush, bronchoalveolar lavage (BAL), transthoracic or transtracheal aspirate, or thoracentesis. All isolated pathogens were submitted to a central laboratory for identification to ensure consistency of results. Susceptibility testing was done in accordance with National Committee for Clinical Laboratory Standards guidelines. Sponsor-defined breakpoints were used for linezolid susceptibility testing ($\leq$4 mg/mL, sensitive; $>$4 mg/mL, resistant).

***Populations for analysis.*** Three patient populations were determined at the outset of the study. Intent-to-treat (ITT) included all randomized patients who received $\geq$1 dose of study medication; this population was evaluated for efficacy and safety. Clinically evaluable patients included those who had a chest radiograph at baseline consistent with the diagnosis of pneumonia, had not received a potentially effective nonstudy antibiotic during the study, had received study medication for at least 7 days (14 doses) unless the patient discontinued treatment because of lack of efficacy, had received at least 80% of the prescribed study medications without missing $\geq$2 consecutive doses through the first 7 days of treatment, and had a postbaseline assessment during the 12- to 28-day follow-up window except for patients who had failure of therapy. Microbiologically evaluable patients included those who were clinically evaluable and had a confirmed pathogen from respiratory specimens or blood cultures at baseline that was not resistant to either study medication.

***Efficacy variables.*** The primary efficacy variables included patient clinical outcome in the clinically evaluable population and patient microbiological outcome in the microbiologically evaluable population determined at the TOC follow-up visit. Criteria for assessing clinical outcome were as follows: cure, resolution of the baseline clinical signs and symptoms of pneumonia with improvement or lack of progression of radiographic findings; failure, persistence or progression of the signs and symptoms of pneumonia after at least 2 days of therapy, administration of a potentially effective nonstudy antibiotic during treatment because of lack of efficacy, or absence of clinical assessments at end of therapy and follow-up; indeterminate, clinically improved or cured at end of therapy and no assessment at the TOC; and missing, receiving $<$2 days of therapy or $<$4 doses. Criteria for assessing microbiological outcome were as follows: success, documented eradication or presumed eradication or colonization; failure, documented persistence or presumed persistence, superinfection (pathogen isolated during the end-of-therapy visit that was not present at baseline), or reinfection (pathogen isolated at the TOC visit that was different from the original pathogen[s]); indeterminate, no microbiological data at the TOC; and missing, absence of clinical determination and no microbiological data at the TOC. Patients were to receive at least 5 days and 10 doses of study medication for a cure; at least 2 days and 4 doses were required for failure. Other efficacy assessments included clinical signs and symptoms of pneumonia, chest radiograph, and pathogen eradication rate.

***Safety evaluation.*** All patients who received at least 1 dose of study medication were included in the safety analyses. Safety evaluations included clinical laboratory assays, including hematology and clinical chemistry analyses, as well as an assessment of adverse events.

***Statistical analysis.*** Analyses to determine the comparative efficacy and safety of linezolid versus vancomycin were done. All statistical tests were 2-sided, and $P \leq .05$ was considered statistically significant. All analyses were done by use of SAS version 6.0 (SAS Institute). Analyses of efficacy variables were done for the ITT, clinically evaluable, and microbiologically evaluable patient populations. As determined by means of a 2-sided test level of 5% and a desired statistical power of 80% under the assumption that each treatment group would yield a 70% success rate, the 30 evaluable patients were required per treatment group for a determination of equivalence between the 2 treatment groups to within 20%. Assuming an evaluability rate of 35%, this translated to a requirement of 238 enrolled patients per treatment group. For TOC evaluations, 95% CIs were calculated for the differences between linezolid and vancomycin groups for clinical cure, microbiological success, and pathogen eradication rates. These CIs were considered consistent with equivalence if the following conditions were met: there were at least 83 patients per treatment group, the CI included zero, and the lower limit of the CI exceeded $-20\%$. $\chi^2$ tests for evaluating homogeneity of the distributions of clinical and microbiological responses between treatment groups were done. Because of the expected small number of evaluable patients at each center, terms for investigator effect and treatment group–by-investigator interactions were not included in the statistical analyses models. Comparability of treatment groups with respect to baseline variables was assessed by use of one-way analysis of variance fixed-effects model for continuous variables and $\chi^2$ tests for categorical variables. $\chi^2$ tests

were used to compare the proportions of patients with adverse events in the treatment groups. Quantitative clinical laboratory assays were evaluated by use of the *t* test for mean change from baseline within treatment groups and a one-way analysis of variance fixed-effects model with a factor for treatment group for mean change from baseline between treatment groups.

## RESULTS

***Study population.*** The patient populations are shown in table 1. Of the 402 patients enrolled, 396 were included in the ITT analyses; 203 patients received linezolid plus aztreonam, 193 received vancomycin plus aztreonam, and 6 patients did not receive study medication. The primary reasons for clinical nonevaluability in the ITT population for either treatment arm were the absence of follow-up in the TOC window (47 linezolid recipients [23.2%], 57 vancomycin recipients [29.5%]), insufficient therapy (46 linezolid recipients [22.7%], 48 vancomycin recipients [24.9%]), or treatment noncompliance (43 linezolid recipients [21.2%], 49 vancomycin recipients [25.4%]). The primary reasons for microbiological nonevaluability in the ITT population for both treatment arms were either absence of baseline pathogen (111 linezolid recipients [54.7%], 114 vancomycin recipients [59.1%]) or absence of clinical evaluability (95 linezolid recipients [46.8%], 97 vancomycin recipients [50.3%]) for reasons noted above.

Characteristics of the ITT population are summarized in table 2. There were no significant differences between treatment groups with respect to age and sex distributions, and >52% of patients were aged ⩾65 years. More than 50% of the patients enrolled were receiving mechanical ventilation before study entry (table 2). The mean APACHE II scores at the time of study entry were similar in both treatment groups and reflected the severity of illness in this patient population. About one-third of patients had a pleural effusion, and multiple lobe involvement was seen in slightly more than half of the patients. The mean ages and APACHE II scores, as well as the distributions of patients by sex, race, prior days undergoing mechanical ventilation, and appearance of chest radiograph in the clinically evaluable and microbiologically evaluable populations were similar to those of the ITT population, with no significant differences between treatment groups.

Pathogens identified at baseline were categorized as either target pathogens (gram-positive organisms), mixed pathogens (target pathogens plus other gram-negative pathogens), or gram-negative pathogens only. Predominant organisms identified at baseline were either target or mixed pathogens in the ITT and clinically evaluable populations. Among ITT patients, 94 (46.3%) of 203 in the linezolid group and 83 (43.0%) of 193 in the vancomycin group had target or mixed pathogens detected on culture. For ITT patients, gram-negative bacilli were detected as the only pathogen on baseline culture in 30 linezolid-treated patients (14.8%) and 21 vancomycin-treated patients (10.9%). Because patients with only gram-negative pathogens identified at baseline were to be discontinued from the study, the percentages of clinically evaluable patients with gram-negative pathogens only were lower than those seen in the ITT population (11 [10.2%] of 108 linezolid recipients, 8 [8.3%] of 96 vancomycin recipients).

**Table 1. Disposition of patients in study of linezolid vs. vancomycin to treat nosocomial pneumonia.**

| Population | Linezolid recipients | Vancomycin recipients |
|---|---|---|
| ITT population | 203 (100) | 193 (100) |
| Clinically evaluable population | 108 (53.2) | 96 (49.7) |
| Clinically nonevaluable | | |
| Absence of follow-up in TOC window | 47 (23.2) | 57 (29.5) |
| Insufficient therapy | 46 (22.7) | 48 (24.9) |
| Treatment noncompliance | 43 (21.2) | 49 (25.4) |
| Concomitant antibiotics | 21 (10.3) | 13 (6.7) |
| Prior antibiotic use | 3 (1.5) | 5 (2.6) |
| Negative chest radiograph | 0 (0) | 3 (1.6) |
| Microbiologically evaluable population | 54 (26.2) | 40 (20.7) |
| Microbiologically nonevaluable | | |
| Absence of baseline pathogen | 111 (54.7) | 114 (59.1) |
| Clinically nonevaluable | 95 (46.8) | 97 (50.3) |
| Baseline pathogens resistant to study medication | 2 (1.0) | 0 (0) |

**NOTE.** Data are no. (%) of patients. Patients may have had multiple reasons for nonevaluability; thus, evaluable and nonevaluable percentages may total >100%. ITT, intent-to-treat; TOC, test-of-cure.

***Discontinuations.*** The percentages of patients who discontinued therapy during the treatment period were similar between treatment groups in the ITT population. The most common reasons for discontinuation of treatment for both treatment groups was lack of efficacy (10 [4.9%] of 203 linezolid recipients, 11 [5.7%] of 193 vancomycin recipients), death (14 linezolid recipients [6.9%], 17 vancomycin recipients [8.8%]), or presence of gram-negative pathogen only (21 linezolid recipients [10.3%], 16 vancomycin recipients [8.3%]). The percentage of patients who discontinued treatment because of an adverse event was slightly higher, but not statistically different, in the vancomycin group (14 [7.3%] of 193) than in the linezolid group (9 [4.4%] of 203].

***Treatment.*** In ITT patients, the overall mean duration of treatment ( ± SD) was 9.6 ± 4.4 days in the linezolid group and 8.9 ± 4.4 days in the vancomycin group. This differs from those patients who remained in the study and were clinically evaluable; mean duration of treatment for clinically evaluable pa-

**Table 2. Baseline characteristics in intent-to-treat population in study of linezolid vs. vancomycin to treat nosocomial pneumonia.**

| Parameter | Linezolid recipients ($n$ = 203) | Vancomycin recipients ($n$ = 193) |
|---|---|---|
| Sex | | |
| Male | 142 (70.0) | 131 (67.8) |
| Female | 61 (30.0) | 62 (32.1) |
| Mean age, y ± SD | 62.8 ± 18.0 | 61.3 ± 18.7 |
| Race | | |
| White | 181 (89.2) | 170 (88.1) |
| Black | 11 (5.4) | 10 (5.2) |
| Other | 11 (5.4) | 13 (6.7) |
| Mean APACHE II score ± SD | 15.7 ± 6.5 | 15.4 ± 6.9 |
| No. undergoing intubation at baseline | 116 (57.1) | 111 (57.5) |
| Days on ventilator before enrollment | | |
| 0 | 83 (40.9) | 84 (43.5) |
| 1–7 | 85 (41.9) | 78 (40.4) |
| 8–14 | 18 (8.9) | 18 (9.3) |
| >14 | 17 (8.4) | 13 (6.7) |
| Chest radiograph variables | | |
| Presence of infiltrate | 203 (100) | 190 (99.5) |
| Presence of pleural infusion | 60 (29.6) | 56 (29.3) |
| Single lobe involvement | 98 (48.3) | 91 (47.9) |
| Multiple lobe involvement | 105 (51.7) | 99 (52.1) |
| Neutrophil count of 500–1000 cells/mm$^3$ | 1 (0.49) | 2 (1.0) |
| Baseline pathogen | | |
| Target pathogens only[a] | 73 (36.0) | 67 (34.7) |
| Mixed pathogens[a] | 21 (10.3) | 16 (8.3) |
| Gram-negative pathogens only | 30 (14.8) | 21 (10.9) |
| No baseline pathogen | 79 (38.9) | 89 (46.1) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. Percentages are based on no. of patients reporting and may not total 100 because of rounding. APACHE, acute physiology and chronic health evaluation.

[a] Constitutes microbiologically evaluable population.

tients was similar between treatment groups, with 11.6 ± 3.4 days in the linezolid arm and 10.6 ± 3.1 days in the vancomycin arm.

***Clinical outcome.*** The clinical cure rates for the ITT, clinically evaluable, and microbiologically evaluable patients treated with linezolid were equivalent to those for patients treated with vancomycin (figure 1). Cure rates for clinically evaluable patients at the TOC visit were 71 [66.4%] of 107 linezolid-treated patients, compared with 62 [68.1%] of 91 vancomycin-treated patients (95% CI, −14.9% to 11.3%; table 3). In patients with cultures verified by protected specimen brush, BAL, transtracheal or transthoracic aspiration, or thoracentesis, clinical cure was similar between treatment groups, 24 (70.6%) of 34 in the linezolid group and 21 (67.7%) of 31 in the vancomycin group.

***Microbiological outcome.*** In microbiologically evaluable patients, there was no statistically significant difference in patient microbiological success rate between treatment groups: 36 (67.9%) of 53 linezolid recipients and 28 (71.8%) of 39 vancomycin recipients (95% CI, −22.8% to 15.0%). Success rates among patients with cultures verified by protected specimen brush, BAL, transtracheal or transthoracic aspiration, or thoracentesis were not significantly different between the groups: 23 (67.6%) of 34 in the linezolid group and 23 (71.9%) of 32 in the vancomycin group. Further, the development of resistance among patients with sensitive organisms at baseline was not detected during treatment or follow-up.

***Pathogen eradication.*** Pathogen eradication rates included documented and presumed eradication. Documented pathogen eradication was defined as the absence of the original pathogen(s) from culture at TOC; eradication was presumed in the absence of specimens suitable for culture when patients were clinically cured. In all presumed cases, second culture was

attempted. If patients were unable to produce sputum and were clinically cured, the pathogen was presumed eradicated. Linezolid and vancomycin had similar rates of pathogen eradication (table 4). Microbiological eradication rates for microbiologically evaluable patients were 25 (61.0%) of 41 versus 15 (65.2%) of 23 for all *S. aureus,* 15 (65.2%) of 23 versus 7 (77.8%) of 9 for methicillin-resistant *S. aureus* isolates, and 9 (100%) of 9 versus 9 (100%) of 9 for *Streptococcus pneumoniae* in the linezolid versus vancomycin groups.

***Other efficacy variables.*** There were no clinically relevant differences between treatment groups with respect to secondary end points of clinical signs and symptoms, chest radiograph, temperature, respiratory rate, and WBC counts. There was a comparable improvement in both treatment groups, with fewer patients reporting clinical signs and symptoms of pneumonia throughout the course of the study, consistent with the resolution of infection. At TOC in the clinically evaluable population, the most common remaining symptom was sputum production in both treatment groups (32 [32.3%] of 99 in the linezolid group and 36 [40.4%] of 90 in the vancomycin group). In the clinically evaluable population, 54 (61.4%) of 88 linezolid-treated patients and 56 (68.3%) of 82 vancomycin-treated patients had a chest radiograph assessed as resolved at the follow-up visit. There were no statistically significant differences in clinical and microbiological outcomes between treatment groups when analyzed by sex, age (<65 years; ⩾65 years), race, geographical region, intubation status at baseline, or baseline APACHE II scores.

***Analysis of therapeutic failure.*** In the ITT population, a total of 143 patients (36.1%) were considered to have clinical failure (75 patients in the linezolid group and 68 patients in the vancomycin group). Among clinically evaluable patients treated with linezolid, 36 (33.6%) of 107 had failure of therapy, compared with 29 (31.9%) of 91 treated with vancomycin at the TOC. In microbiologically evaluable patients, 17 (32.1%) of 53 linezolid-treated patients and 11 (28.2%) of 39 vancomycin-treated patients were considered to have microbiological failure. No patient who had microbiological failure developed a resistant organism to either linezolid or vancomycin. No treatment differences were noted between linezolid and vancomycin groups or across the 3 populations regarding therapeutic failure.

**Table 3. Assessment of efficacy in clinically evaluable and microbiologically evaluable populations.**

| Assessment at TOC | Linezolid recipients | Vancomycin recipients | *P* | 95% CI |
|---|---|---|---|---|
| Clinical outcome[a] | 107 | 91 | .79 | −14.9 to 11.3 |
| Cure | 71 (66.4) | 62 (68.1) | | |
| Failure | 36 (33.6) | 29 (31.9) | | |
| Indeterminate | 1 | 5 | | |
| Microbiological outcome[b] | 53 | 39 | .69 | −22.8 to 15.0 |
| Success | 36 (67.9) | 28 (71.8) | | |
| Failure | 17 (32.1) | 11 (28.2) | | |
| Indeterminate | 1 | 1 | | |

**NOTE.** Data are no. (%) of patients assessed, unless otherwise indicated. Percentages are based on no. of assessed patients, excluding missing and indeterminate patients. Percentages may not total 100 because of rounding. TOC, test-of-cure.

[a] Among clinically evaluable patients.
[b] Among microbiologically evaluable patients.

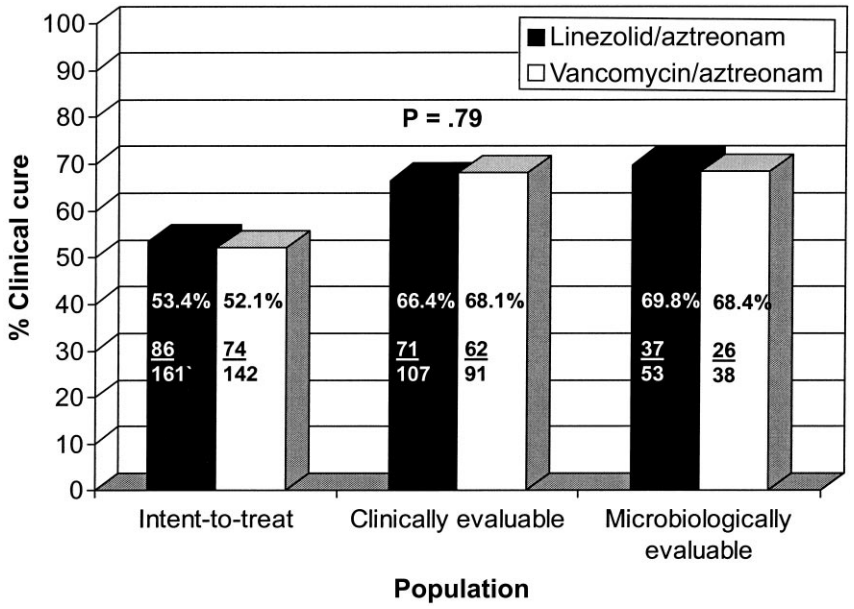


**Figure 1.** Rates of clinical cure for intent-to-treat, clinically evaluable, and microbiologically evaluable populations. Clinical cure was defined as resolution or improvement in baseline symptoms and radiograph, with no further requirement for antimicrobial therapy. Data exclude missing or indeterminate values.

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

| Pathogen | Linezolid recipients | Vancomycin recipients |
|---|---|---|
| *Staphylococcus aureus* | 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 *S. aureus* | 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) |
| *Streptococcus pneumoniae* | 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 (%).

Reasons for clinical failure among ITT patients treated with linezolid are summarized in table 5. Of the 4 linezolid-treated patients with gram-positive pathogens documented at baseline, 2 had life support withdrawn at the request of the family, 1 (66 years old) with an *S. aureus* infection at baseline who was not undergoing mechanical ventilation received ampicillin for enterococcal septicemia between the end of therapy and follow-up, and 1 (85 years old) undergoing mechanical ventilation had persistent *S. aureus* culture in sputum and BAL fluid and an APACHE II score of 15.

***Adverse events.*** Safety assessments were done for the ITT population. Overall, 143 (70.4%) of 203 linezolid-treated patients experienced at least 1 adverse event, compared with 143 (74.1%) of 193 vancomycin-treated patients. The most common adverse event irrespective of relationship to study medication was diarrhea in both treatment groups (19 [9.4%] of 203 linezolid, 15 [7.8%] of 193 vancomycin recipients). The most common drug-related adverse events occurring in >1% of patients in either treatment group are shown in table 6. Reports of serious adverse events, irrespective of relationship to study medication, were comparable (63 [31.0%] of 203 for linezolid, 65 [33.7%] of 193 for vancomycin) and attributed to the underlying infection. In addition, 2 cases of diarrhea/colitis due to *Clostridium difficile* were reported in the vancomycin group and none reported for linezolid. Intravenous linezolid was well tolerated, with only 1 reported case of drug-related catheter site complication (0.5%). Overall, adverse events were generally of mild-to-moderate intensity as judged by the investigator, were of limited duration, and did not routinely require discontinuation of study medication. Adverse events resulting in discontinuation of study medication occurred in 13 (6.4%) of 203 linezolid-treated patients and in 20 (10.4%) of 193 vancomycin-treated patients.

There were 36 deaths (17.7%) in the linezolid group and 49 (25.4%) in the vancomycin group during the course of the study ($P = .06$). The majority of these deaths occurred during the follow-up period (26 of 36 in the linezolid group, 38 of 49 in the vancomycin group). The mortality rate due to concomitant underlying diseases was 30 (83.3%) of 36 in the linezolid group compared with 36 (73.4%) of 49 in the vancomycin group (table 7). The majority of these deaths were attributed to the progression or complication of severe underlying comorbidities. There were no deaths due to therapeutic failure (lack of clinical response) in the linezolid group and 4 (8.2%) in the vancomycin group. None of the deaths in either study group were attributed to study medications.

Preclinical animal data indicated that linezolid exerts a mild, reversible inhibition of monoamine oxidase [50, 51]. This potential interaction is not as severe as those reported for the significant and irreversible monoamine oxidase inhibitors, such as phenelzine or tranylcypromine, and there were no significant food restrictions during this study. A total of 118 linezolid-treated patients received medications with the potential for a monoamine oxidase interaction, including analgesics, $\beta$-agonists, selective serotonin-reuptake inhibitors, and vasopressors. There was no clinical evidence of a monoamine oxidase inhibitor interaction with linezolid.

***Laboratory evaluations.*** There were no clinically relevant statistically significant differences between treatments for any hematology assay. Mean hemoglobin levels were 11.0 g/dL for both treatment groups at baseline and increased at follow-up by 0.56 g/dL and 0.74 g/dL in the linezolid and vancomycin treatment groups, respectively. There were corresponding increases in hematocrit levels. Consistent with resolution of infection, mean WBC and neutrophil counts decreased to normal ranges, with an increase in mean lymphocyte count during the study. As an acute-phase reactant, mean platelet count increased

**Table 5. Causes for clinical failure among patients in linezolid group in intent-to-treat population.**

| Cause | Linezolid group ($n$ = 75) |
|---|---|
| Gram-negative pathogen only identified at baseline | 21 (28.0) |
| No baseline or follow-up pathogens identified | 18 (24.0) |
| Gram-positive pathogens identified at baseline, with subsequent development of gram-negative pathogens during treatment | 9 (12.0) |
| No pathogens identified at baseline, with subsequent development of gram-negative pathogens during treatment | 8 (10.7) |
| Gram-positive pathogens identified at baseline among those who were elderly or had significant underlying disease | 8 (10.7) |
| Mixed pathogens identified at baseline | 7 (9.3) |
| Gram-positive pathogens only identified at baseline | 4 (5.3) |

**NOTE.** Data are no. (%) of patients.

**Table 6. Drug-related adverse events occurring in >1% of patients in intent-to-treat population.**

| Adverse event | Linezolid recipients ($n$ = 203) | Vancomycin recipients ($n$ = 193) |
|---|---|---|
| Diarrhea | 9 (4.4) | 5 (2.6) |
| Abnormal liver function tests | 2 (1.0) | 3 (1.6) |
| Rash | 0 (0) | 3 (1.6) |

**NOTE.** Data are no. (%) of patients.

in both treatment groups through day 12 and then remained above baseline until the end of the study.

There were no clinically relevant changes from baseline or differences between treatments for any chemistry assay. Mean γ-glutamyl transpeptidase levels generally remained elevated in both treatment groups throughout the study. Mean alanine aminotransferase and lipase levels remained normal during the study.

## DISCUSSION

This study evaluated the efficacy and safety of linezolid plus aztreonam compared with vancomycin plus aztreonam in the treatment of suspected nosocomial pneumonia due to a gram-positive organism in adult patients. Of the 396 patients enrolled in the trial, ~204 (52%) were clinically evaluable and 94 (24%) were microbiologically evaluable. These numbers may appear modest; however, these percentages are consistent with other clinical trials of nosocomial pneumonia [52–57], and to our knowledge, this study represents the largest evaluation of suspected nosocomial pneumonia due to a gram-positive organism to date.

Overall, baseline characteristics of the 2 treatment groups were similar, with patients having a similar severity of illness. Linezolid plus aztreonam demonstrated clinical cure rates equivalent to those reported with vancomycin plus aztreonam in the ITT, clinically evaluable, and microbiologically evaluable populations. About 50% of patients with suspected nosocomial pneumonia had a pathogen identified at baseline, which is consistent with reports in similar pneumonia patient populations that identified baseline pathogens in ≤50% of patients [52, 53, 56]. Although some patients may not have had a pathogen identified at baseline, clinical outcomes were comparable across treatment groups within the ITT, clinically evaluable, and microbiologically evaluable populations, suggesting that the overall response in the 2 groups of patients was similar. Clinical cure rates in both treatment groups are among the highest reported to date in a clinical trial including patients with suspected nosocomial pneumonia due to a gram-positive organism and are consistent with cure rates reported in other studies of patients with nosocomial pneumonia due to gram-positive organisms [52–55, 57]. Similarly, cure rates were equivalent between the 2 groups when baseline demographic variables, intubation status at baseline, and severity of disease were evaluated. As expected, patients in both treatment groups at risk for a concomitant or subsequent gram-negative infection, including those who underwent intubation at baseline (~57% of patients per treatment group) and/or who had high APACHE II scores (mean score, ~15 or 16), demonstrated lower cure rates. Among microbiologically evaluable patients, pathogen eradication rates for linezolid and vancomycin were equivalent irrespective of specific pathogen, including *S. aureus,* methicillin-resistant *S. aureus,* and *S. pneumoniae.* Both linezolid and vancomycin demonstrated greater activity against *S. pneumoniae* than against *S. aureus.*

Linezolid was well tolerated and safe in the treatment of nosocomial pneumonia. Mean duration of treatment was shorter in the ITT population than in the clinically evaluable population. However, alternative nonpneumonia diagnoses were not a primary reason for patients in the ITT group to have their treatment discontinued. Overall, patients in the ITT group who improved quickly, had received insufficient therapy, had received concomitant antibiotics during the study, had received antibiotics for >24 h before enrollment, or had a negative result of chest radiography were more likely to receive shorter courses of study drug than were patients in the clinically evaluable group.

Most adverse events in both treatment groups were of mild-to-moderate intensity, were of limited duration, and did not require the discontinuation of study medication. No adverse drug-drug or drug-food interactions were reported. The proportions of patients who experienced adverse events were similar between treatment groups; however, the percentage of patients who discontinued treatment because of an adverse event was slightly higher, but not statistically different, in the vancomycin group (10.4%) than in the linezolid group (6.4%). Linezolid was well tolerated when administered by the iv route; only 1 catheter-related adverse event was attributed to linezolid treatment. Although a greater percentage of patients died in the vancomycin group (49 [25.4%] of 193) than in the linezolid group (36 [17.7%] of 203), these deaths were considered by the investigators to be unrelated to the study medications. The analyses of adverse events, clinical laboratory assays, and other safety data suggest that linezolid was well tolerated compared with vancomycin.

Delay of appropriate antimicrobial therapy is reported to significantly increase morbidity and to increase mortality 4-fold in critically ill patients with nosocomial pneumonia, irrespective of diagnostic technique [17, 33, 34]. This elevated risk is often due to the presence of antibiotic-resistant bacteria, including methicillin-resistant *S. aureus* [33]. Prompt initiation of treatment with an appropriate antimicrobial agent with activity against gram-positive organisms is prudent for patients in ICUs, where nosocomial pneumonia is common and often caused by *S. aureus* [33, 58]. Currently, for patients with late-onset ventilator-asso-

**Table 7. Summary of mortality in study of linezolid vs. vancomycin to treat nosocomial pneumonia.**

| Cause | Linezolid recipients ($n$ = 36) | Vancomycin recipients ($n$ = 49) |
|---|---|---|
| Complications of underlying disease[a] | 30 (83.3) | 36 (73.4) |
| Gram-negative sepsis | 5 (13.9) | 5 (10.2) |
| Shock | 1 (2.8) | 4 (8.2) |
| Therapeutic failure or lack of clinical response | 0 (0) | 4 (8.2) |

**NOTE.** Data are no. (%) of patients.

[a] Includes progression of primary disease, cardiac complications, stroke, multisystem organ failure, pulmonary embolism, and withdrawal of life support.



ciated pneumonia or nosocomial pneumonia with other risk factors for methicillin-resistant *S. aureus*, treatment recommendations include administration of vancomycin until methicillin-resistant *S. aureus* can be excluded [31]. Despite the continued usefulness of vancomycin, the number of alternative agents, such as linezolid, that offer efficacy equal to that of vancomycin are limited; thus, preservation of the antimicrobial activity of vancomycin and the development of novel and effective alternative agents are important.

The availability of linezolid may substantially affect treatment of gram-positive infections in susceptible and resistant gram-positive species. Linezolid has significant activity against gram-positive species and a unique mechanism of action, and it lacks cross-resistance with other antimicrobial classes. Parenteral antimicrobial drug therapy remains the standard of care for most cases of nosocomial pneumonia. However, linezolid is highly bioavailable (~100%), and although only iv formulations were compared in this trial, the availability of oral linezolid offers health care practitioners and patients a convenient dosing option that may reduce medical resource use and length of stay in the hospital or ICU. Linezolid may be an attractive alternative for the initial treatment of serious gram-positive infections.

In summary, this multicenter, randomized, blinded, comparator-controlled trial demonstrated that linezolid and vancomycin were equally effective in treating nosocomial pneumonia with respect to clinical and microbiological outcomes. Linezolid, 600 mg iv twice daily, is an effective and safe alternative to vancomycin in the treatment of adults with nosocomial pneumonia due to susceptible gram-positive bacteria.

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