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Analysis of Two Double-Blind Studies of Patients With Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia

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Objective: **To assess the effect of baseline variables, including treatment, on outcome in patients with nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA).**
Design: **Retrospective analysis of data from two prospective, randomized, double-blind studies.**
Setting: **Multinational study with 134 sites.**
Patients: **A total of 1,019 patients with suspected Gram-positive nosocomial pneumonia, including 339 patients with documented *S aureus* pneumonia (*S aureus* subset) and 160 patients with documented MRSA pneumonia (MRSA subset).**
Interventions: **Linezolid, 600 mg, or vancomycin, 1 g, q12h for 7 to 21 days, each with aztreonam.**
Measurements and results: **Outcome was measured by survival and clinical cure rates (assessed 12 to 28 days after the end of therapy). Logistic regression analysis was used to determine the effect of treatment and other baseline variables on outcome. Kaplan-Meier survival rates for linezolid vs vancomycin were 80.0% (60 of 75 patients) vs 63.5% (54 of 85 patients) for the MRSA subset ($p = 0.03$). Logistic regression analysis confirmed that the survival difference favoring linezolid remained significant after adjusting for baseline variables (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.0 to 4.8; $p = 0.05$). Other baseline variables associated with significantly higher survival rates in MRSA pneumonia were serum creatinine levels less than or equal to two times the upper limit of normal and absence of cardiac comorbidities. Clinical cure rates for linezolid vs vancomycin (excluding indeterminate or missing outcomes) were 59.0% (36 of 61 patients) vs 35.5% (22 of 62 patients) for the MRSA subset ($p < 0.01$). Logistic regression analysis confirmed that the difference favoring linezolid remained significant after adjusting for baseline variables (OR, 3.3; 95% CI, 1.3 to 8.3; $p = 0.01$). Other baseline variables associated with significantly higher clinical cure rates in MRSA pneumonia were single-lobe pneumonia, absence of ventilator-associated pneumonia, and absence of oncologic and renal comorbidities.**
Conclusions: **In this retrospective analysis, initial therapy with linezolid was associated with significantly better survival and clinical cure rates than was vancomycin in patients with nosocomial pneumonia due to MRSA.** ***(CHEST 2003; 124:1789–1797)***

Key words: linezolid; methicillin resistance; nosocomial pneumonia; regression analysis; *Staphylococcus aureus*; vancomycin

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; ELF = epithelial lining fluid; EOT = end of treatment; EPIC = European Prevalence of Infection in Intensive Care; ITT = intent to treat; MIC = minimal inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; OR = odds ratio; VAP = ventilator-associated pneumonia

Pneumonia was the most common nosocomial infection among patients in combined medical-surgical ICUs in the National Nosocomial Infections Surveillance[1]; nosocomial pneumonia occurred in 31% of patients. Similarly, pneumonia was the leading cause of ICU-acquired infection in the European Prevalence of Infection in Intensive Care (EPIC) Study[2]; the crude mortality rate for ICU-acquired pneumonia was 31%, and the associated odds ratio (OR) for death was 1.9.

In the past, Gram-negative aerobes were the most frequently reported pathogens, but Gram-positive pathogens are being reported with increasing frequency. *Staphylococcus aureus* was the most frequently reported isolate, and accounted for 17% of the pathogens in patients with nosocomial pneumonia in the National Nosocomial Infections Surveillance[1] and for 30% of pathogens in patients in the EPIC Study,[2] which included pneumonia and other

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types of ICU-acquired infections. Methicillin-resistant *S aureus* (MRSA) is an increasingly common cause of infections and accounted for 60% of *S aureus* isolates in the EPIC Study.[2]

Vancomycin has been the standard and, until recently, only option for the treatment of patients with MRSA infections; however, only limited data on the treatment of patients with MRSA nosocomial pneumonia are available from large comparator-controlled studies. Two double-blind, registration studies[3,4] of patients with Gram-positive nosocomial pneumonia have recently been completed in which patients were randomly assigned to receive initial empiric treatment with linezolid or vancomycin, each with aztreonam. Each registration study was powered for equivalence, and there were no outcome differences between treatment groups. We were intrigued by subset analyses that revealed a survival difference favoring linezolid when patients were stratified by APACHE (acute physiology and chronic health evaluation) II scores.[5,6] The identical design of these studies and their combined sample size offer an opportunity to evaluate a large database of patients with nosocomial pneumonia, including patients with *S aureus* and MRSA pneumonia. To assess the effect of baseline variables, including treatment, on survival and clinical cure in patients with nosocomial pneumonia due to MRSA, we conducted a retrospective logistic regression analysis of data that were collected prospectively in these studies.[3,4]

Materials and Methods

Data from two prospective, randomized, double-blind, registration studies[3,4] comparing linezolid with vancomycin, each with aztreonam, in patients with suspected nosocomial pneumonia were combined and retrospectively analyzed to identify variables that affected outcome as measured by survival and clinical cure rates in patients with documented *S aureus* and MRSA pneumonia.

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The design of the two studies was identical and is summarized briefly in this article. Both studies were randomized, double blind, multicenter, multinational, and comparator controlled. Both were designed as registration studies according to guidelines for industry specified by the US Food and Drug Administration for the assessment of patients with nosocomial pneumonia.[7] The studies included 134 investigator sites in North America, Europe, Israel, South Africa, Australia, and Latin America, and enrolled patients from October 13, 1998, to April 28, 2000; 70 sites (52.2%) participated in both studies. Studies were approved by the Institutional Review Board for each investigator site, and informed consent was obtained from all patients or their legally authorized representative.

Patients in the Prospective Studies

Adult men and women with pneumonia acquired after 48 h in an inpatient facility were eligible for enrollment. Patients had to have at least two of the following: cough; purulent sputum; auscultatory findings of pneumonia; dyspnea, tachypnea, or hypoxemia; or isolation of a respiratory pathogen from respiratory or blood cultures. Patients also had to have at least two of the following: fever or hypothermia, respiratory rate > 30 breaths/min, systolic BP < 90 mm Hg, pulse rate ≥ 120 beats/min, altered mental status, need for mechanical ventilation, total peripheral WBC count $> 10{,}000/\mu L$ or $< 4{,}500/\mu L$, or $> 15\%$ immature neutrophils. Patients had to have radiographic findings of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion), adequate respiratory and sputum specimens for Gram stain and culture, and life expectancy ≥ 7 days. Exclusion criteria were infecting Gram-positive organism resistant to either study medication; known or suspected meningitis, endocarditis, osteomyelitis, or pulmonary disease that could preclude evaluation of therapeutic response (*eg*, granulomatous diseases, lung cancer, or another malignancy metastatic to the lung); history or evidence of coagulopathy; cystic fibrosis or suspected active tuberculosis; pheochromocytoma, untreated hyperthyroidism, untreated or uncontrolled hypertension, or carcinoid syndrome; CD4 cell count $< 200/\mu L$ secondary to HIV infection; unstable psychiatric condition or seizure disorder requiring long-term medications; previous antibiotic treatment for > 24 h, unless documented treatment failure or pathogen resistant to previous nonstudy antibiotic therapy; hypersensitivity to any study medication; liver disease and total bilirubin more than five times the upper limit of normal; and severe neutropenia ($< 500/\mu L$). Patients were also excluded if they were pregnant, lactating, or unable to take adequate contraceptive measures.

Interventions and Assessments in the Prospective Studies

Patients were randomly assigned to receive either linezolid, 600 mg, or vancomycin, 1 g, which were administered by IV infusion q12h for 7 to 21 consecutive days. Vancomycin dosage adjustments were required for patients with renal impairment and were permitted for other patients according to the local standard of care. To maintain blinding, a research pharmacist or equivalent nonstudy personnel monitored vancomycin dosages. All patients received concurrent aztreonam, 1 to 2 g q8h, for possible mixed infection; aztreonam therapy could be discontinued if no Gram-negative pathogens were identified. If no Gram-positive pathogens were identified, then the patient was dropped from the study.

Baseline microbiologic specimens were obtained for diagnosis through the day after enrollment. Acceptable culture methods included expectorated sputum, endotracheal suction specimen, and blood cultures as well as "invasive methods" such as pro-

tected specimen brush, BAL, transtracheal aspirate, transthoracic aspirate, and thoracentesis. Final pathogen identification and susceptibility testing were determined at a central laboratory by microdilution techniques according to National Committee for Clinical Laboratory Standards guidelines.

Survival analyses were conducted for all treated patients with nosocomial pneumonia, and for the subsets with *S aureus* and MRSA pneumonia. For analysis of cure rates, patients were required to have had at least 5 days of therapy to be assessed as cured and at least 2 days of therapy to be assessed as failed.

Clinical cure or failure was assessed at the end of treatment (EOT) and was repeated at the follow-up visit 12 to 28 days after EOT. Results at the follow-up visit were used for all clinical analyses. Clinical cure was defined as the resolution of baseline signs and symptoms of pneumonia, with improvement or lack of progression of radiographic findings. Clinical failure was defined as persistence or progression of pneumonia, or the administration of a nonstudy antibiotic for pneumonia.

Patients whose follow-up outcomes were missing or indeterminate were excluded from analyses of cure rates (but not from survival analyses). A follow-up outcome of missing or indeterminate was possible in the following scenarios. Patients who received < 2 days of treatment were assigned a follow-up outcome of missing. Patients assessed by the investigator as cured or improved at EOT, and whose assessment at follow-up was indeterminate (or not reported) were assigned an outcome of indeterminate. Patients with an investigator's assessment of clinical failure at EOT, followed by indeterminate (or not reported) at follow-up were assigned an outcome of failure. Patients assessed by the investigator as indeterminate at both EOT and follow-up were also assigned an outcome of failure.

Statistics in the Retrospective Analysis

All results were locked into the database before the retrospective analysis was conducted. Statistics were calculated using Statistical Analysis System Version 6.12 (SAS Institute; Cary, NC). The Kaplan-Meier method was used to assess survival rate. χ^2 test was used to assess the association between treatment and categorical variables. Stepwise analysis was performed using logistic regression to identify the most parsimonious model for clinical cure and survival. Baseline variables used as potential predictors in the stepwise analysis were similar to those used in another logistic regression analysis[8] and included treatment with linezolid or vancomycin; age $<$ or $\geq$ 65 years; APACHE II score ≤ 20 or > 20; single- or multiple-lobe pneumonia; presence or absence of pleural effusion, bacteremia, and ventilator-associated pneumonia (VAP); bilirubin $\leq$ or $>$ 41.0 μmol/L (2.4 mg/dL); creatinine $\leq$ or $>$ 229.8 μmol/L (2.6 mg/dL) for men and $\leq$ or $>$ 212.2 μmol/L (2.4 mg/dL) for women; and presence or absence of cardiac, diabetic, hepatic, oncologic, renal, respiratory, or vascular comorbidities. Stepwise analyses used significance levels of 0.25 for entry in the model and 0.10 for staying in the model; statistical significance was assessed by the likelihood ratio test. ORs, 95% confidence intervals (CIs), and p values for baseline variables associated with clinical cure and survival were calculated for the most parsimonious logistic regression model; $p \leq 0.05$ was considered statistically significant.

Results

Patients

A total of 1,019 patients with suspected nosocomial pneumonia were enrolled in the two studies,[3,4] received at least one dose of either linezolid or vancomycin, and composed the ITT group (Fig 1). A total of 339 patients had documented *S aureus* pneumonia (*S aureus* subset), including 223 patients (66%) in whom it was diagnosed by invasive procedure (*ie*, as protected specimen brush, BAL, transtracheal or transthoracic aspiration, or thoracentesis) or blood culture. All but one of the *S aureus* isolates had vancomycin minimal inhibitory concentrations (MICs) of ≤ 2 μg/mL, and 90% had MICs of ≤ 1 μg/mL. A total of 160 had documented MRSA pneumonia (MRSA subset), including 95 patients (59.4%) in whom it was diagnosed by invasive procedures or blood culture.

Patient characteristics were similar between the two studies, and data were combined. Patient characteristics for the *S aureus* and MRSA subsets are shown in Table 1. Characteristics for patients included in the analyses of clinical cure (excluding those with indeterminate or missing outcomes) were comparable to those for the corresponding ITT populations (data not shown).

Survival Analysis

All patients were included in the ITT analysis of survival. Overall Kaplan-Meier survival rates for all patients with nosocomial pneumonia (ITT group) were 80.9% (424 of 524 patients) for linezolid and 77.8% (385 of 495 patients) for vancomycin ($p = 0.21$). As shown in Figure 2, Kaplan-Meier survival rates for linezolid vs vancomycin therapy were 78.0% (131 of 168 patients) vs 70.8% (121 of 171 patients) for the *S aureus* subset ($p = 0.13$), and 80.0% (60 of 75 patients) vs 63.5% (54 of 85 patients) for the MRSA subset ($p = 0.03$). Similar trends were seen in the 223 patients in whom the presence of S *aureus* was confirmed at baseline by invasive diagnostic procedure or blood culture; 79% (86 of 109 patients) receiving linezolid and 72% (82 of 114 patients) receiving vancomycin survived ($p = 0.23$). In the subset with MRSA confirmed by invasive procedure or blood culture, 85% (34 of 40 patients) receiving linezolid and 67% (37 of 55 patients) receiving vancomycin survived ($p = 0.05$).

Bacteremia was confirmed in 13% (44 of 339 patients) from whom *S aureus* was isolated, including 6% (22 of 339 patients) with MRSA bacteremia. Of the patients with *S aureus* bacteremia, 18 of 22 linezolid-treated patients and 16 of 22 vancomycin-treated patients survived ($p = 0.47$). Of the patients with MRSA bacteremia, 7 of 8 linezolid-treated patients and 9 of 14 vancomycin-treated patients survived ($p = 0.24$).

Significant predictors of survival in all patients with nosocomial pneumonia were linezolid therapy

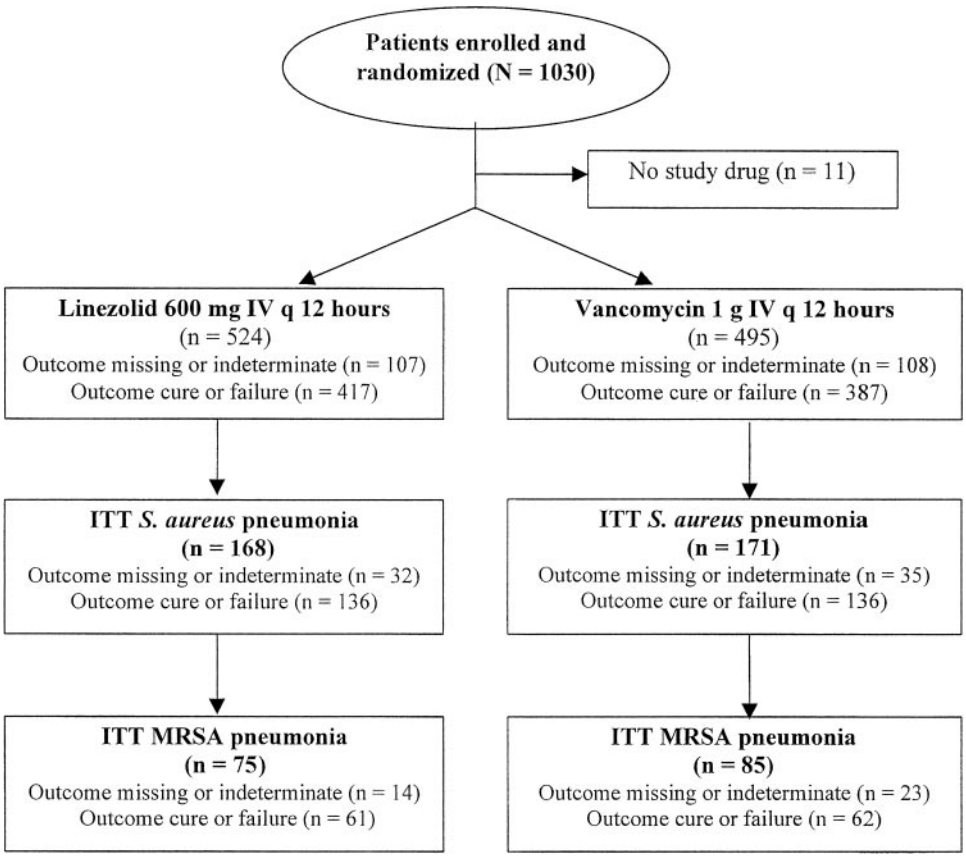

FIGURE 1. Flow diagram for patients with nosocomial pneumonia.

(OR, 1.4; 95% CI, 1.0 to 2.0; $p = 0.03$), APACHE II score ≤ 20 (OR, 2.5; 95% CI, 1.7 to 3.7; $p < 0.01$), single-lobe pneumonia (OR,1.9; 95% CI, 1.3 to 2.6; $p < 0.01$), age < 65 years (OR, 2.3; 95% CI, 1.6 to 3.3; $p < 0.01$), and serum creatinine less than or equal to two times the upper limit of normal (OR, 2.6; 95% CI, 1.4 to 4.9; $p < 0.01$). As shown in Table 2, significant predictors of survival in the *S aureus* subset were APACHE II score ≤ 20, and absence of cardiac and renal comorbidities. Logistic regression analysis confirmed that the survival difference favoring linezolid therapy in the MRSA subset remained significant after adjusting for baseline variables. Additional significant predictors of survival in the MRSA subset were serum creatinine less than or equal to two times the upper limit of normal and absence of cardiac comorbidities.

Clinical Cure Analysis

In the clinical cure regression analysis, 804 of 1,019 treated patients were included and 215 were excluded because their clinical outcome at follow-up was either missing (n = 79) or indeterminate (n = 136). Clinical outcome was missing at follow-up in 37 linezolid recipients and 42 vancomycin recipients for the following reasons: death (n = 9 and n = 12), loss to follow-up and other administrative reasons (n = 11 and n = 16), isolation of Gram-negative pathogens only (n = 12 and n = 10), and adverse events (n = 5 and n = 4), respectively. Clinical outcome was indeterminate at follow-up in 70 linezolid and 66 vancomycin recipients; these patients were assessed as cured or improved at their EOT visit.

In patients who had a clinical outcome assessment of cure or failure, overall clinical cure rates for all patients with nosocomial pneumonia were 53.0% (221 of 417 patients) for linezolid and 52.2% (202 of 387 patients) for vancomycin ($p = 0.82$). As shown in Figure 3, clinical cure rates for linezolid vs vancomycin therapy were 51.5% (70 of 136 patients) vs 43.4% (59 of 136 patients) for the *S aureus* subset ($p = 0.18$), and 59.0% (36 of 61 patients) vs 35.5% (22 of 62 patients) for the MRSA subset ($p < 0.01$). Similar trends were seen in patients in whom the presence of *S aureus* was confirmed by invasive diagnostic procedure or blood culture; 51% (47 of 92 patients) receiving linezolid and 43% (39 of 90

Table 1—*Patient Characteristics, Including Those Used in Logistic Regression Analysis

Characteristics	ITT *S aureus* (n = 339)		ITT MRSA (n = 160)	
	Linezolid (n = 168)	Vancomycin (n = 171)	Linezolid (n = 75)	Vancomycin (n = 85)
Age ≥ 65 yr	97 (57.7)	93 (54.4)	50 (66.7)	62 (72.9)
Sex†				
Male	109 (64.9)	100 (58.5)	44 (58.7)	48 (56.5)
Female	59 (35.1)	71 (41.5)	31 (41.3)	37 (43.5)
Race†				
White	150 (89.3)	153 (89.5)	70 (93.3)	74 (87.1)
Black	12 (7.1)	5 (2.9)	4 (5.3)	3 (3.5)
Other	6 (3.6)	13 (7.6)	1 (1.3)	8 (9.4)
Treatment duration†				
Mean ± SD, d	10.9 ± 4.6	10.6 ± 4.9	11.3 ± 4.3	10.7 ± 5.3
Range, d	1–27	1–27	1–22	2–27
Death†	37 (22.0)	50 (30.2)	15 (20.0)	31 (36.5)
Bacteremia	22 (13.1)	22 (12.9)	8 (10.7)	14 (16.5)
VAP	118 (70.2)	114 (66.7)	49 (65.3)	47 (55.3)
APACHE II score > 20	39 (23.2)	33 (19.3)	18 (24.0)	21 (24.7)
Chest radiographic variables				
Multilobe pneumonia	99 (58.9)	91 (53.2)	43 (57.3)	49 (57.7)
Pleural effusion	50 (29.8)	50 (29.2)	23 (30.7)	28 (32.9)
Bilirubin > 41.0 mol/L (2.4 mg/dL)	4 (2.4)	8 (4.7)	2 (2.7)	2 (2.4)
Serum creatinine > 229.8 mol/L‡	7 (4.2)	7 (4.1)	3 (4.0)	4 (4.7)
Comorbidities				
Cardiac	39 (23.2)	50 (29.2)	18 (24.0)	34 (40.0)
Diabetic	30 (17.9)	46 (26.9)	13 (17.3)	33 (38.8)
Hepatic	8 (4.8)	4 (2.3)	5 (6.7)	1 (1.2)
Oncologic	18 (10.7)	11 (6.4)	9 (12.0)	7 (8.2)
Renal	19 (11.3)	21 (12.3)	10 (13.3)	18 (21.2)
Respiratory	62 (36.9)	62 (36.3)	28 (37.3)	34 (40.0)
Vascular	8 (4.8)	7 (4.1)	4 (5.3)	4 (4.7)

*Data are presented as No. of patients (%) unless otherwise indicated.
†Characteristic not included in logistic regression analysis.
‡Less than 229.8 μmol/L (2.6 mg/dL) for men and 212.2 μmol/L (2.4 mg/dL) for women.

patients) receiving vancomycin had a clinical cure ($p = 0.30$). In the subset with MRSA confirmed by invasive procedure or blood culture, 58% (19 of 33 patients) receiving linezolid and 33% (13 of 39 patients) receiving vancomycin had a clinical cure ($p = 0.04$).

Of the patients with *S aureus* bacteremia, 10 of 18 linezolid-treated patients and 7 of 16 vancomycin-treated patients had a clinical cure ($p = 0.49$). Of the patients with MRSA bacteremia, four of six linezolid-treated patients and three of eight vancomycin-treated patients had a clinical cure ($p = 0.28$).

Significant predictors of clinical cure in all patients with nosocomial pneumonia were APACHE II score ≤ 20 (OR, 2.9; 95% CI, 1.9 to 4.7; $p < 0.01$), single-lobe pneumonia (OR, 1.7; 95% CI, 1.3 to 2.4; $p < 0.01$), absence of VAP (OR, 2.1; 95% CI, 1.5 to 2.9; $p < 0.01$), and absence of oncologic (OR, 2.3; 95% CI, 1.3 to 4.0; $p < 0.01$) and renal comorbidities (OR, 2.3; 95% CI, 1.4 to 3.8; $p < 0.01$). As shown in Table 3, significant predictors of clinical cure in both the *S aureus* and MRSA subsets were single-lobe pneumonia, absence of VAP, and absence of oncologic and renal comorbidities. Additional significant predictors of cure in the *S aureus* subset were APACHE II score ≤ 20 and absence of cardiac comorbidities. Logistic regression analysis confirmed that the difference in clinical cure rate favoring linezolid therapy in the MRSA subset remained significant after adjusting for baseline variables.

Discussion

As seen in other analyses,[9–14] our retrospective analysis identified the presence of some baseline variables, such as APACHE II score ≤ 20 or absence of comorbidities, as independent predictors of survival. However, the only baseline variable amenable to intervention in this setting is the choice of initial antimicrobial therapy. The importance of appropriate initial empiric therapy is well known. Crude mortality rates in critically ill patients are 8.5 to 39.9% lower if initial empiric antimicrobial therapy is appropriate than if modification is required.[15–17] Whereas appropriate therapy is necessary, ours is the

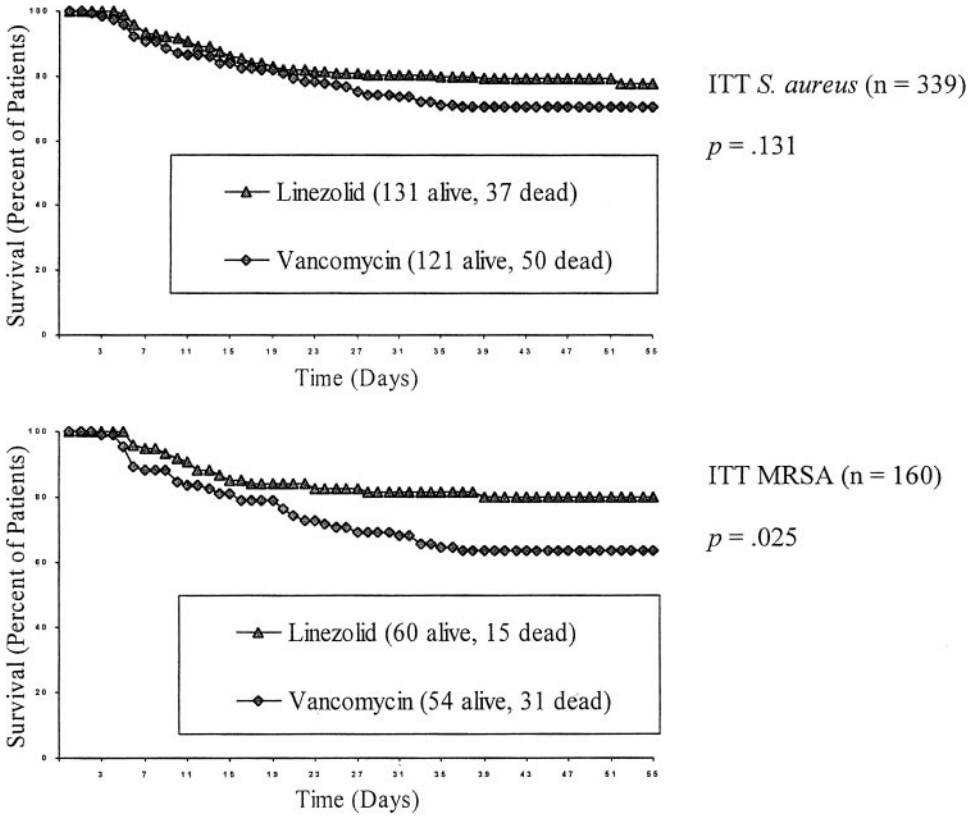

FIGURE 2. Kaplan-Meier survival curves for uncensored data.

first analysis, based on randomized, double-blind clinical study data,[3,4] to demonstrate a survival advantage for one appropriate antimicrobial agent over another appropriate agent in patients treated for MRSA pneumonia.

Patients in the MRSA subset had better survival (80.0% vs 63.5%, p = 0.03) and clinical cure rates (59.0% vs 35.5%, p < 0.01) if they were treated with linezolid than with vancomycin. Patients were enrolled based on their clinical diagnoses, before culture results were known; a potential exists for imbalances to occur between treatment groups in risk factors that might have affected outcomes. However, logistic regression analysis confirmed that the advantages favoring linezolid therapy remained significant after adjusting for differences in baseline variables in the subset with MRSA pneumonia.

Table 2—*Results of Logistic Regression Analysis for Survival in Patients With Nosocomial Pneumonia*

Predictors	OR (95% CI)	p Value
ITT *S aureus* (n = 339)		
Linezolid therapy	1.7 (1.0–2.9)	0.068
Age < 65 yr	1.7 (0.9–3.0)	0.081
APACHE II score ≤ 20	3.7 (2.0–6.9)	< 0.001†
Single-lobe pneumonia	1.7 (1.0–2.9)	0.072
Presence of pleural effusion	1.6 (0.9–3.0)	0.127
Absence of cardiac comorbidities	2.3 (1.3–4.1)	0.005†
Absence of renal comorbidities	2.2 (1.0–4.8)	0.042†
ITT MRSA (n = 160)		
Linezolid therapy	2.2 (1.0–4.8)	0.050†
APACHE II score ≤ 20	2.1 (0.8–5.1)	0.116
Presence of pleural effusion	1.9 (0.8–4.6)	0.145
Creatinine ≤ 229.8 μmol/L*	11.9 (1.1–125.0)	0.038†
Absence of cardiac comorbidities	3.0 (1.4–6.6)	0.005†

*Less than or equal to 229.8 μmol/L (2.6 mg/dL) for men and ≤ 212.2 μmol/L (2.4 mg/dL) for women.
†Significant at 0.05 level.

Only two other randomized studies[8,18] of patients with Gram-positive nosocomial pneumonia in which vancomycin was the control agent are available. Quinupristin/dalfopristin and vancomycin had equivalent clinical cure rates in all patients (43.3% vs 45.3%; 95% CI, − 13.2 to 9.3; n = 298) and statistically equivalent clinical cure rates in the subset with MRSA pneumonia (19.4% vs 40.0%; 95% CI, − 46.2 to 4.9; n = 51).[8] Linezolid and vancomycin had equivalent clinical cure rates in all patients with pneumonia (51.3% vs 50.0%, n = 71) and in the subset with MRSA pneumonia (52.2% vs 53.8%, n = 49)[18]; this study was not included in the current analysis because the protocol was different and allowed enrollment of patients who had other types

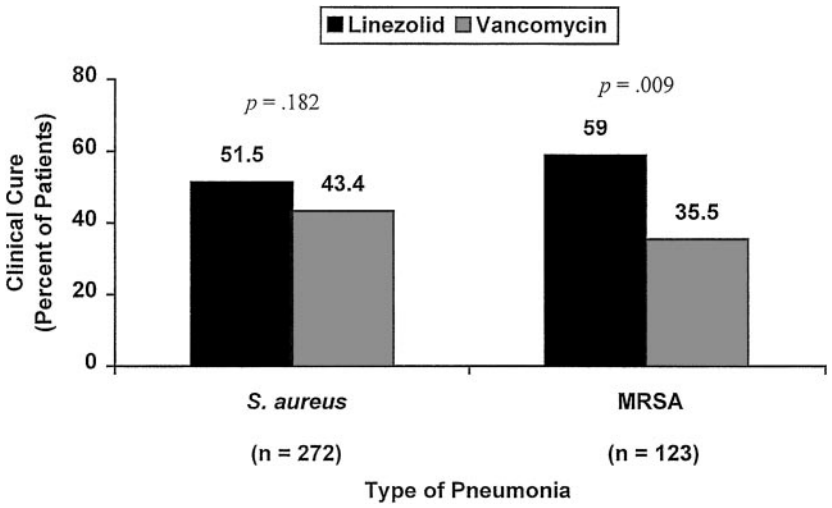

FIGURE 3. Clinical cure rates for linezolid and vancomycin therapy in patients with Gram-positive, nosocomial pneumonia. Data from patients with indeterminate or missing clinical outcomes were excluded.

of infections, such as skin and soft-tissue infections. Survival rates were not reported in either study.[8,18] An important difference between those two studies and ours was the enrollment of more than three times as many patients with nosocomial Gram-positive pneumonia and MRSA pneumonia in the combined linezolid studies[3,4] than in the next largest study.[8]

One possible reason for the association between linezolid and improved survival is the poor penetration of vancomycin into the lungs seen in pharmacokinetic studies. Mean concentrations of vancomycin in lung tissue were lower than those in serum at 1 h (9.6 mg/kg vs 40.6 mg/L) and at 12 h (2.8 mg/kg vs 6.7 mg/L) in 30 patients.[19] In contrast, mean concentrations of linezolid were higher in epithelial lining fluid (ELF) than in plasma at 4 h (64.3 μg/mL vs 7.3 μg/mL) and at 12 h (24.3 μg/mL vs 7.6 μg/mL) in 25 volunteers,[20] and in ELF than in blood at 2 to 4 h (29.5 μg/mL vs 15.9 μg/mL) and at 6 to 10 h (26.6 μg/mL vs 10.9 μg/mL) in 10 patients.[21] The distribution of antimicrobial agents may be different into ELF and lung tissue; however, the ratio of vancomycin concentration in the lung sample to that in serum or plasma was higher in the study involving lung tissue[19] than in an earlier study of vancomycin concentrations in ELF.[22] The collective results of these studies indicate that linezolid, but not vancomycin, concentrations exceeded the MIC breakpoint for susceptible *S aureus* throughout the 12-h dosing interval; the break point is 4 μg/mL for both antimicrobial agents.

Table 3—*Results of Logistic Regression Analysis for Clinical Cure in Patients With Nosocomial Pneumonia

Predictors	OR (95% CI)	p Value
S aureus pneumonia (n = 272)		
Linezolid therapy	1.6 (0.9–2.7)	0.090
APACHE II score ≤ 20	2.2 (1.0–4.6)	0.046†
Single-lobe pneumonia	2.0 (1.2–3.5)	0.014†
Absence of VAP	2.5 (1.4–4.6)	0.003†
Absence of cardiac comorbidities	2.1 (1.1–4.1)	0.034†
Absence of oncologic comorbidities	4.4 (1.4–13.5)	0.011†
Absence of renal comorbidities	13.5 (3.0–62.5)	< 0.001†
MRSA pneumonia (n = 123)		
Linezolid therapy	3.3 (1.3–8.3)	0.011†
Single-lobe pneumonia	3.7 (1.5–9.5)	0.006†
Absence of VAP	2.9 (1.1–7.5)	0.028†
Absence of oncologic comorbidities	21.7 (3.7–125.0)	< 0.001†
Absence of renal comorbidities	16.4 (3.2–83.3)	< 0.001†
Absence of hepatic comorbidities	4.2 (0.6–31.3)	0.154

*Data from patients with clinical outcomes assessed as indeterminate or missing were excluded.
†Significant at 0.05 level.

Our study design had some limitations. Our study was a retrospective subgroup analysis. However, the data were from prospective, randomized, double-blind studies, and the database was locked before the retrospective analysis was conducted. The predetermined primary end point of both studies was clinical cure, which was assessed at follow-up and defined conservatively; clinical outcome was assessed as failure if the assessment was either failure or indeterminate at EOT followed by indeterminate at follow-up. Although not a prospectively defined end point, mortality is an objective, clinically relevant parameter. In addition, our analysis included microbiologically documented cases of *S aureus* nosocomial pneumonia from the entire ITT population. Sec-

ondly, results of two studies were combined; however, the protocols were identical, approximately half of the investigators were identical, and we found no differences between the two study populations. Combining studies allowed us to examine the largest cohort of patients with MRSA pneumonia enrolled in randomized, double-blind studies identified by a computerized search of the published literature, which in turn reduced the risk of β error and allowed us to confirm findings noted in the original cohorts.[5,6] In contrast, the lack of significant difference in clinical cure rates between vancomycin and quinupristin/dalfopristin in the MRSA subset of the study by Fagon and colleagues[8] (40% vs 19.4%) may have been attributable to the small sample size.

The optimal method for dosing vancomycin has been debated.[23–26] The dose of vancomycin chosen for the registration studies, 1 g q12h, is the approved dose, approximates the 15 mg/kg dose in a standard guide,[27] and is identical to that used in other randomized studies[8,18] of vancomycin. Pharmacokinetic monitoring is often advocated to avoid toxicity or even to improve efficacy, especially when combined with pharmacodynamic modeling[28,29]; and our protocol did allow dosage adjustments and pharmacokinetic monitoring according to the local standard of care.

Finally, the use of quantitative cultures was not required for diagnosis of nosocomial pneumonia, either at study entry or on continuation. More than 50% of the patients in both the *S aureus* and MRSA subgroups had diagnoses made by invasive methods or blood culture. The use of sputum or tracheal suctioning for culture reflects common medical practice in the United States, where most critically ill patients continue to be treated according to the results of nonquantitative, noninvasive diagnostic studies. Interestingly, the response pattern, both for survival and clinical cure, in patients diagnosed by invasive methods or blood culture mirrored the results in the entire cohort. Therefore, the results of our study are likely to represent the responses to antimicrobial therapy in patients with MRSA pneumonia by usual nonquantitative diagnostic methods.

In conclusion, linezolid therapy was associated with significantly higher survival rates and clinical cure rates than was vancomycin therapy in patients with nosocomial pneumonia due to MRSA. This benefit remained significant after using logistic regression analysis to adjust for baseline variables. Future studies may document the benefit of this approach, but fully powered, comparator-controlled, prospective studies in patients with MRSA nosocomial pneumonia would be difficult to complete. Because of the documented importance of initial treatment in critically ill patients with nosocomial pneumonia including VAP,[15–17] appropriate empiric treatment must be initiated promptly. The results of this retrospective analysis suggest that initial empiric therapy with linezolid should be considered in patients with suspected nosocomial pneumonia who are at risk for infection due to MRSA. Candidates for this approach may include patients who are admitted to facilities where MRSA is present, whose stain is positive for Gram-positive cocci, and who have risk factors for MRSA as shown epidemiologic studies.[30,31]

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Linezolid vs Vancomycin*

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