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Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin

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Abstract *Objective:* To assess the effect of baseline variables, including treatment, on clinical cure and survival rates in patients with Gram-positive, ventilator-associated pneumonia (VAP). *Design:* Retrospective analysis of two randomized, double-blind studies. *Setting:* Multinational study with 134 sites. *Patients:* 544 patients with suspected Gram-positive VAP, including 264 with documented Gram-positive VAP and 91 with methicillin-resistant *S. aureus* (MRSA) VAP. *Interventions:* Linezolid 600 mg or vancomycin 1 g every 12 h for 7–21 days, each with aztreonam. *Measurements and results:* Clinical cure rates assessed 12–28 days after the end of therapy and excluding indeterminate or missing outcomes significantly favored linezolid in the Gram-positive and MRSA subsets. Logistic regression showed that linezolid was an independent predictor of clinical cure with odds ratios of 1.8 for all patients, 2.4 for Gram-positive VAP, and 20.0 for MRSA VAP. Kaplan-Meier survival rates favored linezolid in the MRSA subset. Logistic regression showed that linezolid was an independent predictor of survival with odds ratios of 1.6 for all patients, 2.6 for Gram-positive VAP, and 4.6 for MRSA VAP. *Conclusions:* Initial linezolid therapy was associated with significantly better clinical cure and survival rates than was initial vancomycin therapy in patients with MRSA VAP.

Keywords Linezolid · Vancomycin · Gram-positive pneumonia · Methicillin-resistant *Staphylococcus aureus* · Mechanical ventilation · Regression analysis

Introduction

Appropriate initial antimicrobial treatment is associated with lower mortality in patients with ventilator-associated pneumonia (VAP) [1, 2]. Until recently vancomycin and teicoplanin were the only options for treating patients with MRSA infections, but large comparator-controlled studies of patients with VAP, including methicillin-

resistant *Staphylococcus aureus* (MRSA) VAP are limited. Two double-blind registration studies with identical design [3, 4] have recently been completed in which patients with Gram-positive nosocomial pneumonia were randomly assigned to receive empirical treatment with linezolid or vancomycin, each with aztreonam. An analysis of the two studies demonstrated a survival benefit favoring linezolid in patients with MRSA nosocomial pneumonia [5]. However, the attributable mortality of MRSA VAP has been questioned [6], and VAP represented a subset of the entire study population in the previous report [5]. Therefore we conducted a retrospective logistic regression analysis of data from these studies [3, 4] to investigate the effect of baseline variables, including treatment, on survival and clinical cure specifically in patients with VAP.

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 Gram-positive VAP. All patients who received at least one dose of study drug and were mechanically ventilated at diagnosis of nosocomial pneumonia were included in this intention-to-treat (ITT) analysis. The design of the two randomized, double-blind, comparator-controlled studies is briefly summarized [3, 4].

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; and 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 higher than 30 breaths/min, systolic blood pressure less than 90 mmHg, pulse rate 120 beats/min or higher, altered mental status, need for mechanical ventilation, total peripheral white blood cell count greater than 10,000/mm^3 or less than 4,500/mm^3, and more than 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's stain and culture, and life expectancy of at least 7 days. Exclusion criteria included infecting Gram-positive organism resistant to either study medication [5].

Interventions and assessments

Patients were randomly assigned to receive either 600 mg linezolid or 1 g vancomycin administered by intravenous infusion every 12 h for 7–21 consecutive days (Fig. 1). Vancomycin dosage adjustments were required for patients with renal impairment and were permitted for other patients according to the local standard of care. If drug monitoring for vancomycin was performed, trough serum values were to be obtained not more than 1 h before the next dose, and peak serum levels were to be obtained 1–2 h after completion of the intravenous dose. A trough target of 5–10 μg/ml was recommended, and a peak target of 25–40 μg/ml was recommended. To maintain blinding each site designated a research pharmacist or equivalent nonstudy individual to monitor vancomycin levels and to make dosing adjustments. The local research pharmacist secured all vancomycin dosing and drug level records to maintain blinding. The physicians and investigators caring for patients and making clinical assessments were completely blinded to vancomycin serum levels and dosing changes. All patients received concurrent aztreonam 1–2 g every 8 h for possible Gram-negative infection; aztreonam therapy could be discontinued if no Gram-negative pathogens were identified. If only Gram-negative pathogens were identified, the patient was dropped from the study.

Per protocol all baseline microbiological specimens, including lower airway cultures obtained bronchoscopically, were obtained for diagnosis through the day of enrollment in both study groups. Cultures were obtained by a variety of methods and in some cases by more than one. Acceptable culture methods included endotracheal suction specimen, and blood cultures as well as "invasive methods" such as protected specimen brush, bronchoalveolar lavage, and thoracentesis. Blood cultures and thoracentesis with an identified Gram-positive pathogen (e.g., MRSA) and bronchoalveolar lavage or protected specimen brush cultures yielding a quantitative culture of 10^3 and 10^4 cfu/ml, respectively, were employed to establish the presence of infection. Final pathogen identification and susceptibility testing were determined at a central laboratory by microdilution techniques according to National Committee for Clinical Laboratory Standards guidelines.

Hospital survival analyses were conducted for all treated patients with VAP, and for the subsets with documented Gram-positive, *S. aureus* , and MRSA VAP. Hospital survival was analyzed by Acute Physiology and Chronic Health Evaluation (APACHE) II score, using the cutoffs from a previous study [4]. Clinical cure or failure was assessed at the end of treatment (EOT) and was repeated at the follow-up visit 12–28 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 less than 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.

The total number of patients in the two studies was 1,019. Patient characteristics were generally similar between the two studies, and data were combined. Patient characteristics in the ITT VAP group and MRSA subset are presented in Table 1. Patient characteristics in the Gram-positive and *S. aureus* subsets (data not shown) were generally intermediate between those of the ITT VAP group and MRSA subset. Characteristics of 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).

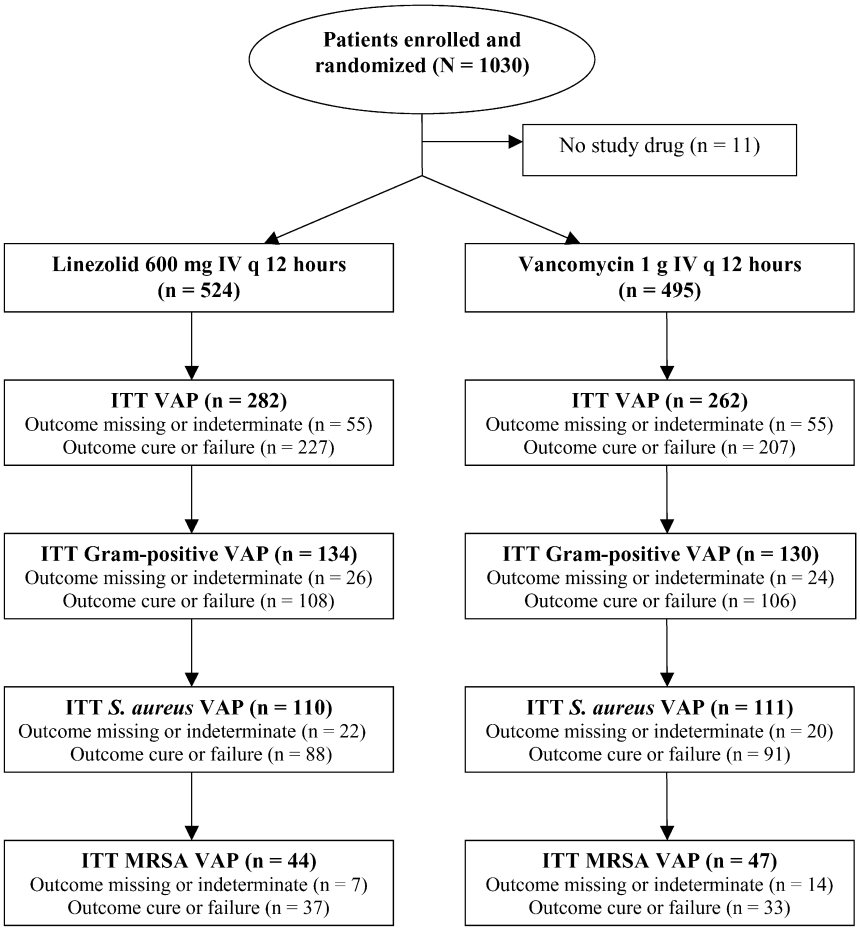


Fig. 1 Flow diagram for patients with nosocomial pneumonia. *Cure* Clinical cure; *IV* intravenous; *ITT* intention to treat; *q* every; *VAP* ventilator-associated pneumonia; *MRSA* methicillin-resistant *S. aureus*

Cure, clinical cure; IV, intravenous; ITT, intent to treat; q, every; VAP, ventilator-associated pneumonia; MRSA, methicillin-resistant *S. aureus*.

Statistics

All data were locked into the database before the retrospective analysis was conducted. Statistics were calculated using Statistical Analysis System (SAS) version 6.12 (SAS Institute, Cary, N.C., USA). The Kaplan-Meier method was used to assess survival rate. The 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 [7] and included treatment with linezolid or vancomycin; age younger than vs. 65 years or older; APACHE II score 20 or less vs. higher; single- vs. multiple-lobe pneumonia; presence or absence of pleural effusion and of bacteremia; ventilation for maximum 7 days vs. longer; bilirubin maximum 41.0 µmol/l (2.4 mg/dl) vs. higher; creatinine maximum 229.8 µmol/l (2.6 mg/dl) in men and 212.2 µmol/l (2.4 mg/dl) in women vs. higher; and presence or absence of cardiac, diabetic, hepatic, oncological, 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. The odds ratios, 95% confidence interval (95% CI), and *p* value for baseline variables associated with clinical cure and survival were calculated for the most parsimonious logistic regression model. A *p* value of 0.05 or less was considered statistically significant.

Results

Culture findings

A total of 544 patients had VAP, including 264 with Gram-positive VAP (Gram-positive subset). *S. aureus* was the most commonly identified pathogen, recovered in 221 patients (*S. aureus* subset) including 91 with MRSA VAP (MRSA subset). Other Gram-positive pathogens identified included *Streptococcus pneumoniae* (*n*=32, including 9 with penicillin-resistant *S. pneumoniae*), *Enterococcus faecalis* (*n*=18), *Streptococcus agalactiae* (*n*=10), *Staphylococcus hemolyticus* (*n*=8), *Enterococcus faecium* (*n*=5), and *Streptococcus pyogenes* (*n*=3); some patients had more than one pathogen. The minimum

Table 1 Patient characteristics (*parentheses* percentages, *VAP* ventilator-associated pneumonia, *ITT* intention to treat, *MRSA* methicillin-resistant *S. aureus*, *APACHE* Acute Physiology and Chronic Health Evaluation)

	ITT VAP (*n*=544)		ITT MRSA VAP (*n*=91)	
	Linezolid (*n*=282)	Vancomycin (*n*=262)	Linezolid (*n*=44)	Vancomycin (*n*=47)
Age ≥65 years	144 (51.1)	117 (44.7)	28 (63.6)	30 (63.8)
Sex				
Male	187 (66.3)	171 (65.3)	27 (61.4)	28 (59.6)
Female	95 (33.7)	91 (34.7)	17 (38.6)	19 (40.4)
Race				
White	245 (86.9)	228 (87.0)	41 (93.2)	41 (87.2)
Black	20 (7.1)	19 (7.3)	3 (6.8)	3 (6.4)
Other	17 (6.0)	15 (5.7)	0	3 (6.4)
Treatment duration (days)				
Mean ±SD	9.3±4.1	9.4±4.5	11.2±3.4	11.4±4.9
Range	1–22	1–27	5–22	3–22
Death	59 (20.9)	69 (26.3)	7 (15.9)	18 (38.3)
Bacteremia	16 (5.7)	18 (6.9)	3 (6.8)	7 (14.9)
Mechanical ventilation >7 days	79 (28.0)	82 (31.3)	15 (34.1)	23 (48.9)
APACHE II score >20	64 (22.7)	56 (21.4)	11 (25)	11 (23.4)
Chest radiographic variables				
Multilobe pneumonia	176 (62.4)	149 (56.9)	25 (56.8)	29 (61.7)
Pleural effusion	90 (31.9)	85 (32.4)	11 (25.0)	17 (36.2)
Bilirubin >41.0 μmol/l	14 (5.0)	13 (5.0)	2 (4.6)	2 (4.3)
Serum creatinine >229.8 μmol/l[a]	18 (6.4)	14 (5.3)	1 (2.3)	2 (4.3)
Comorbidities[b]				
Cardiac	74 (26.2)	76 (29.0)	9 (20.5)	20 (42.6)
Diabetic	62 (22.0)	61 (23.3)	8 (18.2)	21 (44.7)
Hepatic	19 (6.7)	13 (5.0)	5 (11.4)	0
Oncological	30 (10.6)	21 (8.0)	4 (9.1)	4 (8.5)
Renal	47 (16.7)	38 (14.5)	6 (13.6)	10 (21.3)
Respiratory	104 (36.9)	90 (34.4)	19 (43.2)	19 (40.4)
Vascular	12 (4.3)	5 (2.0)	3 (6.8)	1 (2.1)

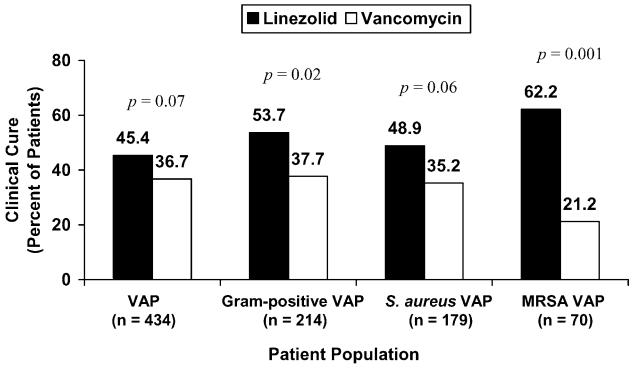
[a] >229.8 μmol/l (2.6 mg/dl) in men and 212.2 μmol/l (2.4 mg/dl) in women
[b] Defined as organ-specific medical conditions present prior to study enrollment and requiring medical treatment or follow-up

inhibitory concentration for *S. aureus* to vancomycin among patients treated with vancomycin was 0.25 μg/ml or less in one patient (0.9%), 0.5 μg/ml in 11 (9.9%), 1 μg/ml in 87 (78.4%), and 2 μg/ml in 12 (10.8%). No isolate of *S. aureus* had a minimum inhibitory concentration greater than 2 μg/ml for vancomycin. In those patients in whom Gram-positive pathogens were identified, positive cultures were obtained by endotracheal suction in 206 patients (78.0%), bronchoalveolar lavage in 100 (37.9%), and protected specimen brush in 39 (14.8%); blood cultures were positive in 34 (12.9%) patients.

Clinical outcome analysis

The clinical cure regression analysis included 434 of the 544 treated patients with VAP and excluded 110 because clinical outcome at follow-up was either missing (n =87) or indeterminate (n =23). Clinical outcome was missing at follow-up in 41 linezolid and 46 vancomycin recipients for the following reasons: death (n =14 and n =24), loss to follow-up and other administrative reasons (n= 18 and n= 11), isolation of Gram-negative pathogens only (n =6 and n =4), and adverse events (n =3 and n =7). Clinical outcome was indeterminate at follow-up in 11 linezolid and 12 vancomycin recipients; these patients were assessed as cured or improved at their EOT visit.

In the 434 patients with VAP who had a clinical outcome assessment of cure or failure clinical cure rates for linezolid vs. vancomycin therapy are shown in Fig. 2. Similar trends were seen in the subsets of patients in whom the diagnosis of *S. aureus* VAP was confirmed by invasive diagnostic procedure or blood culture; 49% (26/53) of linezolid-treated patients and 34% (20/59) of vancomycin-treated patients had a clinical cure (p =0.10). Logistic regression analysis identified two significant independent predictors of clinical cure common to each of the four populations analyzed; patients treated with linezolid and patients whose baseline APACHE II scores were 20 or lower had significantly better odds in favor of cure (Table 2). Bacterial eradication rates for the study subsets are shown in Table 3.



VAP, ventilator-associated pneumonia; MRSA, methicillin-resistant *S. aureus*.

[a]Data from patients with indeterminate or missing clinical outcomes were excluded.

Fig. 2 Clinical cure rates for linezolid and vancomycin therapy in patients with Gram-positive, ventilator-associated pneumonia. *VAP* Ventilator-associated pneumonia; *MRSA* methicillin-resistant *S. aureus*; data from patients with indeterminate or missing clinical outcomes are excluded

Table 2 Results of logistic regression analysis for clinical cure in patients (*n*=434) with ventilator-associated pneumonia (*VAP*); data from patients with clinical cure outcomes assessed as indeterminate or missing are excluded (*OR* odds ratio, *CI* confidence interval, *APACHE* Acute Physiology and Chronic Health Evaluation, *MRSA* methicillin-resistant *S. aureus*

Predictor	OR	95% CI	*p*
VAP *n*=434			
Linezolid therapy	1.8	1.2–2.7	0.008
APACHE II score ≤20	2.8	1.6–5.1	<0.001
Age <65 years	2.0	1.3–3.0	0.001
Single-lobe pneumonia	1.6	1.0–2.4	0.038
Mechanical ventilation ≤7 days	1.6	1.0–2.5	0.048
Creatinine ≤229.8 μmol/l[a]	5.6	1.3–25.0	0.024
ITT Gram-positive VAP *n*=214			
Linezolid therapy	2.4	1.3–4.3	0.005
APACHE II score ≤20	2.8	1.2–6.4	0.014
Absence of renal comorbidities	4.1	1.3–13.7	0.020
Absence of oncological comorbidities	3.5	1.1–11.8	0.039
S. aureus VAP *n*=179			
Linezolid therapy	2.1	1.1–4.0	0.031
APACHE II score ≤20	3.5	1.3–9.3	0.011
Mechanical ventilation ≤7 days	2.2	1.0–4.5	0.039
Absence of renal comorbidities	11.8	1.5–100.0	0.021
MRSA VAP *n*=70			
Linezolid therapy	20.0	4.3–92.0	<0.001
APACHE II score ≤20	18.2	2.8–125.0	0.003
Single-lobe pneumonia	4.0	1.1–15.4	0.041
Absence of hepatic comorbidities	31.3	2.1–500.0	0.013
Absence of vascular comorbidities	23.8	1.3–500.0	0.032

[a] ≤229.8 μmol/l (2.6 mg/dl) in men and 212.2 μmol/l (2.4 mg/dl) in women

Table 3 Bacterial eradication rates (*ITT* intention to treat, *MRSA* methicillin-resistant *S. aureus*, *VAP* ventilator-associated pneumonia)

	Linezolid		Vancomycin		*p*
	n	%	*n*	%	
ITT Gram-positive VAP	63/128	49.2	44/112	37.6	0.067
ITT *S. aureus*	41/90	45.6	31/93	33.3	0.091
ITT MRSA VAP	23/38	60.5	8/35	22.9	0.001

Table 4 Results of logistic regression analysis for hospital survival in patients with ventilator-associated pneumonia (*OR* odds ratio, *CI* confidence interval, *ITT* intent to treat, *VAP* ventilator-associated pneumonia, *APACHE* Acute Physiology and Chronic Health Evaluation, *MRSA* methicillin-resistant *S. aureus*)

Predictor	OR	95% CI	*p*
ITT VAP (*n*=544)			
Linezolid therapy	1.6	1.0–2.4	0.040
APACHE II score ≤0	2.0	1.2–3.2	0.006
Age <65 years	2.2	1.4–3.5	<0.001
Single-lobe pneumonia	1.8	1.1–2.8	0.014
Creatinine ≤229.8 μmol/l[a]	3.8	1.7–8.4	<0.001
Absence of cardiac comorbidities	1.6	1.2–2.5	0.047
ITT Gram-positive VAP (*n*=264)			
Linezolid therapy	2.6	1.3–5.1	0.006
APACHE II score ≤20	3.3	1.5–7.0	0.002
Age <65 years	2.7	1.4–5.3	0.004
Presence of pleural effusion	2.3	1.1–5.0	0.030
Absence of cardiac morbidities	2.2	1.1–4.4	0.034
ITT *S. aureus* VAP (*n*=221)			
APACHE II score ≤20	2.9	1.4–5.9	0.005
Creatinine ≤229.8 μmol/l[a]	10.8	1.1–100.0	0.039
Absence of cardiac comorbidities	2.7	1.4–5.4	0.004
ITT MRSA VAP (*n*=91)			
Linezolid therapy	4.6	1.5–14.8	0.010
APACHE II score ≤20	7.2	2.0–26.3	0.003
Presence of pleural effusion	4.9	1.3–18.7	0.022
Absence of bacteremia	5.3	1.1–24.4	0.034

[a] ≤229.8 μmol/l (2.6 mg/dl) in men and 212.2 μmol/l (2.4 mg/dl) in women

Survival analysis

All patients with VAP were included in the ITT analysis of survival. Kaplan-Meier survival rates for linezolid vs. vancomycin therapy were 79.1% (223/282) vs. 73.7% (193/262) in all patients with VAP (ITT group; p =0.15), 80.6% (108/134) vs. 70.8% (92/130) in the Gram-positive subset (p =0.07), 78.2% (86/110) vs. 70.3% (78/111) in the *S. aureus* subset (p =0.19), and 84.1% (37/44) vs. 61.7% (29/47) in the MRSA subset (p =0.02). Similar trends were seen in the 139 patients in whom the presence of *S. aureus* was confirmed at baseline by invasive diagnostic procedure or blood culture; 77% (49/64) of linezolid-treated patients and 68% (51/75) of vancomycin-treated patients survived (p =0.26). Table 4 provides

the independent predictors of survival identified by logistic regression analysis in all patient subsets.

Discussion

Our analysis confirms that the survival advantage previously reported with linezolid in patients with nosocomial MRSA pneumonia [5] also characterizes the subset with MRSA VAP. The absolute mortality differences between treatment groups in patients in the previous study [5] who had nosocomial MRSA pneumonia (16.5%) and in our patients with MRSA VAP (22.4%) were statistically significant in both studies. If the observed mortality differences represent attributable mortality, the number needed to treat with linezolid to save one life is 6 in patients with nosocomial MRSA pneumonia and 5 in patients with MRSA VAP.

A potential explanation for our results is that the dose of vancomycin employed was insufficient for achieving adequate lung levels in patients with MRSA pneumonia. In pharmacokinetic studies the mean vancomycin concentrations in lung tissue were two-fifths or less [8] and in epithelial lining fluid were one-fifth or less of those in plasma [9, 10]. Specifically, Lamer and colleagues [10] reported that 36% of critically ill ventilated patients had epithelial lining fluid concentrations of lower than 4 μg/ml. In contrast, mean linezolid concentrations in lung tissue and epithelial lining fluid were higher than those in blood or plasma [11, 12]. The unstable hemodynamic and renal conditions and greater volume of distribution in critically ill patients may exacerbate the problem of lung penetration and explain the worse outcome with vancomycin in the ventilated population. The difficulties of achieving adequate local levels of vancomycin have led to the use of higher doses and pharmacokinetic monitoring to avoid toxicity and improve efficacy [13, 14]. Continuous infusion of vancomycin has also been studied [15]. However, none of these strategies has been demonstrated to improve clinical outcome, much less survival, compared with standard-dose vancomycin in a prospective study of patients with MRSA VAP.

The limitations of this analysis are identical to those in the previous paper [5]. Whereas ours was a retrospective analysis, the data were from prospective, randomized, double-blind studies and the database was locked before this analysis was conducted. An important limitation was not requiring quantitative cultures for the diagnosis of VAP. However, more than 50% of the patients in the MRSA subset were diagnosed by invasive methods or blood culture, and the response pattern for both survival and clinical cure in this MRSA subset mirrored that for the entire cohort. Another limitation of this study is that we did not demonstrate a statistically significant difference in mortality in the subgroup of VAP patients having rigorous microbiological confirmation of VAP (e.g., positive blood or pleural fluid cultures or quantitative lower respiratory tract cultures) or in the subset with *S. aureus* VAP. This was likely due to the small sample size of such patients; however, a true lack of effect cannot be excluded. Finally, we cannot exclude the possibility that some isolated pathogens (e.g., enterococci) were simply colonizing the airway and not true pathogens.

Combining data from the two studies is appropriate because the protocols were identical, approximately one-half of the investigators were the same, and no baseline differences between the two study populations were found. Combining studies allowed analysis of the largest cohort of patients with VAP, including MRSA VAP, enrolled in a randomized, double-blind study identified by a computerized search of the published literature. The larger number of patients reduced the risk of β error and allowed us to confirm findings noted in the original cohorts [3, 4]. In contrast, the small sample size in the MRSA subset of another study [7] may have contributed to the lack of statistical significance despite obvious differences in clinical cure rates between vancomycin and quinupristin/dalfopristin (40% vs. 19%).

In conclusion, initial linezolid therapy was associated with a higher clinical cure rate and hospital survival than was standard-dose vancomycin therapy in patients with MRSA VAP.

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