Comparison of Length of Hospital Stay for Patients with Known or Suspected Methicillin-Resistant *Staphylococcus* Species Infections Treated with Linezolid or Vancomycin: A Randomized, Multicenter Trial

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Study Objective. To compare hospital length of stay (LOS), weekly discharges, and days of antibiotic treatment with linezolid (intravenous with oral follow-up) and vancomycin (intravenous only).

Design. Multinational, randomized, phase III trial.

Settings. Hospitals in North America, Latin America, and Europe.

Patients. Four hundred sixty hospitalized patients with infections of known or suspected methicillin-resistant *Staphylococcus* species.

Intervention. Administration of linezolid or vancomycin.

Measurements and Main Results. For linezolid recipients, median LOS was 5 and 8 days shorter (p=0.05 and 0.003) in the complicated skin and soft tissue infection intent-to-treat (230 patients) and clinically evaluable (144) samples, and slightly but not significantly shorter in the overall intent-to-treat (460) and clinically evaluable (254) samples. In all samples, linezolid recipients had more discharges in the first week of treatment and fewer days of intravenous therapy than vancomycin recipients.

Conclusion. Our results support linezolid's ability to reduce medical resource use.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen; numerous reports describe outbreaks in various countries. In 1994 the frequency of MRSA in European countries ranged from less than 1% in Scandinavia to more than 30% in Spain, France, and Italy.[1] In Japan, up to 60% of *S. aureus* strains were methicillin resistant.[2, 3] The prevalence of MRSA appears to be increasing. In the United States, data from hospitals that participated in the National Nosocomial Infections Surveillance showed an increase from 2.4% in 1975 to 29% in 1991[4] and 35% in 1996.[5] The later figures appear to be typical of recent findings. The frequency in intensive care units is even higher,[5–8] and MRSA increasingly has spread from hospital settings to noninstitutional environments.[9–15]

Methicillin resistance not only limits the options for treating infections caused by *S. aureus*, because strains that are resistant to methicillin are also resistant to most other antibiotics, but also increases the length of hospital stay (LOS) and costs of treatment compared with sensitive strains.[16–19] Antibiotics with activity against MRS species are limited, and until recently, vancomycin (and teicoplanin in some countries) was considered the drug of choice. Lack of an oral antibiotic with anti-MRSA activity comparable with vancomycin may

have been a major contributor to the added costs of treatment in cited studies, as the drug must be administered either in the hospital or with the assistance (and costs) of a health professional at home or in a physician's office.

Linezolid is the first of a new class of oxazolidinone antibiotics that have in vitro and in vivo activity against gram-positive organisms, including those resistant to penicillin and other antibiotics.[20] Its in vitro and in vivo antibacterial activity is similar to that of vancomycin against staphylococci, including methicillin-resistant strains, and streptococci, including penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. In vitro and in vivo efficacy studies also showed that linezolid is efficacious against enterococci, including vancomycin-resistant strains. In clinical trials linezolid had good efficacy in treating community- or hospital-acquired pneumonia, complicated or uncomplicated skin and soft tissue infections, and infections caused by MRSA and vancomycin-resistant enterococci.[21–27]

Clinical results indicated that linezolid and vancomycin had similar clinical efficacy. For the intent-to-treat sample, overall cure rates were 56.8% in the linezolid group and 55.0% in the vancomycin group (p=0.74); for the clinically evaluable sample, cure rates were 77.0% and 74.4%, respectively (p=0.63). Mortality rates were also similar (18.3% and 15.0%, respectively, p=0.34), and no deaths were judged to be related to the study drugs. Finally, the percentage of patients with at least one study drug-related adverse event was higher (p=0.0014) with linezolid (18.3%) than with vancomycin (8.2%). Frequencies of these events were comparable between groups with the exception of adverse events in the digestive system (9.2% vs 1.4%, predominantly nausea and diarrhea) and sensory system (2.5% vs 0%, predominantly taste perversion), which were higher with linezolid. These differences were most likely related to the oral formulation, which was available only to patients receiving linezolid. Most drug-related adverse events in both groups were classified as mild or moderate, and resulted in discontinuation of the study agents in five patients (2.1%) receiving linezolid and three (1.4%) receiving vancomycin (p=0.56).[28]

A major advantage of linezolid over vancomycin is that it has a 100% bioavailable oral formulation. Although the drugs have similar efficacy,[24] the oral formulation may allow patients to be discharged earlier while continuing antibiotic treatment.

Methods

This resource use study compared LOS, discharge rates, and duration of intravenous antibiotic therapy in patients with infections of known or suspected methicillin-resistant streptococcal (MRS) species who received linezolid (intravenous with oral follow-up) and those who received vancomycin (intravenous only) as part of a randomized, controlled trial designed for new-drug registration purposes.

Design

Data were collected as part of an open-label, comparator-controlled, multinational, multicenter, randomized phase III clinical trial, whose primary goal was to assess the efficacy, safety, and tolerability of linezolid compared with vancomycin. The trial was conducted in accordance with recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), and in compliance with principles of good clinical practice.

Subjects were hospitalized patients with infections of known or suspected MRS species randomly assigned to receive one of the following regimens: linezolid 600 mg intravenously every 12 hours and either continued for the entire treatment or, at the discretion of investigators, switched to 600 mg orally every 12 hours; or vancomycin 1 g intravenously every 12 hours for

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the entire treatment. Oral antibiotics were not an option for patients randomized to receive vancomycin because no such agents other than linezolid have comparable activity against MRSA. For targeted infections (complicated skin and soft tissue infections, pneumonia, urinary tract infections, bacteremia), the maximum length of treatment was 28 days. The protocol explicitly allowed a patient to be discharged from the hospital while still receiving intravenous or oral therapy, as long as an outpatient intravenous delivery system (physician's office, intravenous care at home) was available to patients discharged on intravenous therapy.

The trial consisted of a baseline (screening) visit, hospitalization during at least the first intravenous dose of study drug, outpatient or inpatient treatment evaluations every 6 days while receiving treatment after day 3, an end-of-treatment visit within 72 hours of the last dose of study drug, and follow-up visits based on the type of infection. Clinical and microbiological assessments were performed throughout the study; test-of-cure assessments were completed at the short-term follow-up visit between 14 and 28 days after end of treatment. Safety was evaluated throughout the study by physical examination, vital sign and laboratory assessments, and adverse events.

Patients

The study enrolled hospitalized patients, including those in long-term care facilities, who were at least 13 years of age and weighed at least 40 kg. Patients were required to have a known or suspected staphylococcal infection, as determined by laboratory findings consistent with such an infection (Gram's stain, culture). They also were required to have signs and symptoms of an active infection: pneumonia, complicated skin and soft tissue infection, urinary tract infection, or bacteremia (Appendix 1). Patients were excluded from participation if they had any of the following: infected devices that could not be removed; pheochromocytoma, carcinoid syndrome, untreated hyperthyroidism, or uncontrolled hypertension; baseline absolute neutrophil count less than 500 cells/mm^3; known liver disease with total bilirubin level greater than 5 times the upper limit of normal; or hypersensitivity to either of the study drugs. Women were excluded if they were pregnant, breastfeeding, and unable or unwilling to practice contraception. Patients also were excluded if they had received a potentially effective antibiotic agent for more than 24 hours within 48 hours of study entry. Eight patients who met inclusion and exclusion criteria and were enrolled did not take a study drug and were excluded from analysis.

Our primary analysis was based on the overall intent-to-treat sample, which consisted of 460 patients (240 receiving linezolid, 220 vancomycin). A subsample of 254 patients was defined as clinically evaluable. They satisfied entry criteria, did not have previous or concomitant antibiotic therapy, continued taking study drug for at least 7 days, and took more than 80% of allocated study agent. Among 254 clinically evaluable patients, 124 received linezolid and 130 received vancomycin.

Use of overall sample results for decision making is most appropriate when results are homogeneous for different sites of infection. Such pooling of results may be less appropriate for economic analysis, in which various indications are associated with various treatment intensities and comorbid conditions. The already greater variance in resource use over clinical variables, as noted by others,[29] is increased further by various infectious diagnoses that are included in the pooled sample, and this may frustrate statistical inference. To explore this issue (but recognizing the limitations of power in such subanalyses), we performed analyses in two subsamples: patients with complicated skin and soft tissue infections and patients with all other infections. We chose this breakdown because patients with skin and soft tissue infections made up the largest subgroup in our data (intent-to-treat sample: 230 patients with and 230 without complicated skin and soft tissue infections; clinically evaluable sample: 144 and 110, respectively). However, we did not prospectively identify these subsamples in the protocol. Among patients with complicated skin and soft tissue infections in the intent-to-treat sample, 122 received linezolid and 108 received vancomycin; in those with other infections, respective numbers were 118 and 112. In the clinically evaluable sample, 70 patients with complicated skin and soft tissue infections received linezolid and 74 received vancomycin; in patients with other infections, respective figures were 54 and 56.

Patient Characteristics and Outcome Measures

For this resource use study, maximum study

period was 56 days after receipt of the first dose of study drug (up to 28 days of treatment plus up to 28 days of follow-up). Length of stay and days of antibiotic therapy were identified prospectively as secondary end points.

We evaluated LOS and duration of antibiotic treatment by treatment group. To illustrate the rate of hospital discharge over time, we also examined Kaplan-Meier curves and the proportion of patients discharged from the hospital by days 7, 14, 21, 28, and 56.

Patient Characteristics

Age, race, gender, geographic region, and primary site of infection were recorded when patients were randomized. Specimens were taken at the same time for culture and susceptibility testing to determine pathogens. Historical and current medical conditions in 10 anatomic systems were recorded; the number of anatomic systems with conditions was counted to derive the number of historical and current medical conditions.

Length of Stay

For 87% of patients in the intent-to-treat sample, LOS was measured as the difference between discharge date and date of starting antibiotic treatment. For 4%, the discharge date was missing because study participation ended before patients were discharged, patients were lost to follow-up, or for other reasons. For these patients, LOS was calculated as the difference between the last day on which their location in the hospital was known to study investigators and date of start of therapy with the study drug. For 9% of patients who were known to be in the hospital on day 56 after starting therapy with the study agent, LOS was coded as 55 days. For statistical analysis, the LOS for these last two groups was treated as censored.

Proportion of Patients Discharged

The proportion of patients discharged by the end of weeks 1, 2, 3, 4, and 8 was determined by dividing the number of patients discharged by the end of the given week by the total number of patients in the group.

Duration of Antibiotic Treatment

Duration of antibiotic treatment was defined as the number of days that the patient received linezolid or vancomycin.

Statistical Analysis

Patient Characteristics

Differences in proportions of patients with regard to age, race, gender, geographic region, primary site of infection, pathogen isolated, number of historical medical conditions (grouped), and number of current medical conditions (grouped) were tested by χ^2 tests. Differences in mean age, number of historical medical conditions, and number of current medical conditions were tested by one-way analysis of variance.

Length of Stay

Estimates of the median and mean LOS for the two treatment groups were obtained by estimating the order (for median) and area (for mean) under the Kaplan-Meier survival curve. This method, widely used for analyzing time to event (survival) data,[30] was adopted to account for censoring observed among 13% of patients. Because censoring can greatly affect estimates of the mean, the median is the preferred measure of central tendency for censored survival data. Consequently, we focused our discussion on median LOS and included means in the table for reference only. We used the Wilcoxon statistic to test for statistical differences in LOS.

Proportion of Patients Discharged

Differences in the proportion of patients discharged at 1, 2, 3, 4, and 8 weeks were tested by χ^2 tests. No adjustment was made for multiple comparisons.

Duration of Antibiotic Treatment

Differences in mean and median duration of treatment were tested by Student's *t* and Wilcoxon tests, respectively. A nominal p value of 0.05 denoted statistical significance.

Sensitivity Analysis

In the preceding analyses, we treated patients who died as having complete follow-up information (LOS, probability of discharge, and days of antibiotic therapy were known), and we treated patients whose discharge dates were missing as censored. To investigate whether these two assumptions had an undue influence on our results, we reanalyzed the data by making alternative censoring definitions. In one analysis, we excluded patients who died. In a second

Table 1. Demographic and Clinical Characteristics at Baseline of the Total Intent-to-Treat Sample

	Linezolid Group (n=240)		Vancomycin Group (n=220)		
Variable	Number	%[b]	Number	%[b]	p Value[a]
Age (yrs)					0.001
15–44	32	13.3	59	26.8	
45–64	78	32.5	52	23.6	
≥ 65	130	54.2	109	49.5	
Mean ± SD	63.9 ± 16.1		59.8 ± 20.2		0.02
Race					0.16
White	195	81.3	168	76.4	
Black	18	7.5	30	13.6	
Asian or Pacific Islander	4	1.7	5	2.3	
Other	23	9.6	17	7.7	
Gender					0.99
Men	143	59.6	131	59.5	
Women	97	40.4	89	40.5	
Geographic region					0.92
North America	113	47.1	98	44.5	
Latin America	55	22.9	51	23.2	
Europe	68	28.3	66	30.0	
Other	4	1.7	5	2.3	
Primary infection					
Complicated skin and soft tissue	122	50.8	108	49.1	0.71
Pneumonia	50	20.8	49	22.3	0.71
Urinary tract	12	5.0	15	6.8	0.41
Other[c]	30	12.5	24	10.9	0.60
Bacteremia of unknown origin	26	10.8	24	10.9	0.98
Bacteremia confirmed by blood culture	45	18.8	40	18.2	0.88
Hospital location when treatment started					0.02
Medical-surgical unit	175	72.9	175	79.5	
Step-down unit	15	6.3	3	1.4	
Intensive care unit	50	20.8	42	19.1	
Pathogen isolated at baseline					1.00
MRSA	117	48.8	107	48.6	
Other staphylococci[d]	40	16.7	37	16.8	
Unknown	83	34.5	76	34.6	
Number of historical medical conditions					0.05
0–2	78	32.5	67	30.5	
3–6	82	34.2	98	44.6	
≥ 7	80	33.3	55	25.0	
Mean ± SD	4.8 ± 3.4		4.4 ± 3.1		0.17
Number of current medical conditions				0.21	
0–2	68	28.3	63	28.6	
3–6	93	38.8	100	45.5	
≥ 7	79	32.9	57	25.9	
Mean ± SD	4.9 ± 3.1		4.6 ± 2.9		0.35

[a]Probability is based on a one-way analysis of variance for age and weight and on χ^2 test for race, gender, and region.
[b]Percentages are based on the number of patients reporting and may not total 100% because of rounding.
[c]Clinical syndromes represented in by "other" were catheter-associated infections (25 patients), intraabdominal or pelvic infection (12), laryngotracheal bronchitis (4), mediastinitis (3), infected device (2), and (1 patient each) bacteremia secondary to parotitis, empyema, peripheral collection from a lumbar fistula, peritonitis, sinusitis, subgaleal empyema, and right-sided endocarditis. These clinical syndromes were similar in both treatment groups.
[d]Including methicillin-sensitive *S. aureus* and *S. auricularis, S. epidermidis, S. hemolyticus, S. hominis,* and *S. xylosus.*

analysis, we considered the LOS for patients who died as censored on the day they died. Both analyses eliminated the "reward" that a therapy received (in terms of shortened stay) when a patient died.

All data analysis was done with SAS, version 6.12 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Table 1 summarizes demographic and clinical characteristics of patients in the total intent-to-treat sample. Treatment groups were similar with regard to race, gender, and geographic region, as

well as baseline physical examinations, vital signs, and other clinical signs and symptoms. However, patients who received linezolid were significantly older than those who received vancomycin (63.9 vs 59.8 yrs p=0.0157). Approximately 50% of patients had complicated skin and soft tissue infections, 22% had pneumonia, 6% had urinary tract infections, and 11% had bacteremia of unknown source. In addition, 18% of patients had confirmed bacteremia. Methicillin-resistant *S. aureus* was isolated from 49% of patients, other staphylococci were isolated from 17%, and no pathogen could be isolated from the remaining 34%. No statistically significant differences between groups were seen in distribution of primary site of infection, pathogen, or proportion of patients with MRSA infection. However, the number of patients in different hospital locations (medical-surgical units, step-down units, intensive care units) when antibiotic treatment was started differed: the linezolid group had more patients enrolled from intensive care (20.8%) and step-down units (6.3%), but fewer from medical-surgical units (72.9%) than the vancomycin group (19.1%, 1.4%, and 79.5%, respectively, p=0.02). The number of comorbid conditions also differed: 33.3% of patients receiving linezolid had seven or more historical medical conditions versus 25.0% receiving vancomycin (p=0.05); respective values for current medical conditions were 32.9% and 25.9% (p=0.10).

We examined between-treatment differences of demographic and clinical characteristics in subsamples of complicated skin and soft tissue infections and other infections. In general, these differences were similar to differences in the total sample with several exceptions. For intent-to-treat patients with complicated skin and soft tissue infections, the between-treatment difference in the number of patients starting antibiotic treatment in different hospital locations was no longer significant (p=0.37), nor was the difference in number of historical comorbid conditions (p=0.41). However, the number of current comorbid conditions became significantly different (p=0.02), with patients in the linezolid group more likely to have seven or more current comorbid conditions than those in the vancomycin group (27.9% vs 13.0%). For patients with other infections, the age difference was no longer significant (p=0.2), whereas the difference in race became significant (p=0.02), with the linezolid group having a higher proportion of whites than the vancomycin group (84.5% vs 77.7%). Whereas no formal severity of illness measure (such as Acute Physiology and Chronic Health Evaluation [APACHE] score) was collected, evidence on available pretreatment characteristics suggests that linezolid recipients were not less severely ill, and possibly were more severely ill, than vancomycin recipients.

Outcomes for All Patients and Sensitivity Analysis

Table 2 reports results of analyses of LOS, proportion discharged (by week), and duration of antibiotic treatment for patients in the intent-to-treat and clinically evaluable samples.

Length of Stay

In the intent-to-treat sample, median LOS was 14 days (95% confidence interval [CI] 9–17 days) for patients who received linezolid compared with 15 days (95% CI 13–17 days) for those who received vancomycin (p=0.19). In the clinically evaluable sample, the difference in

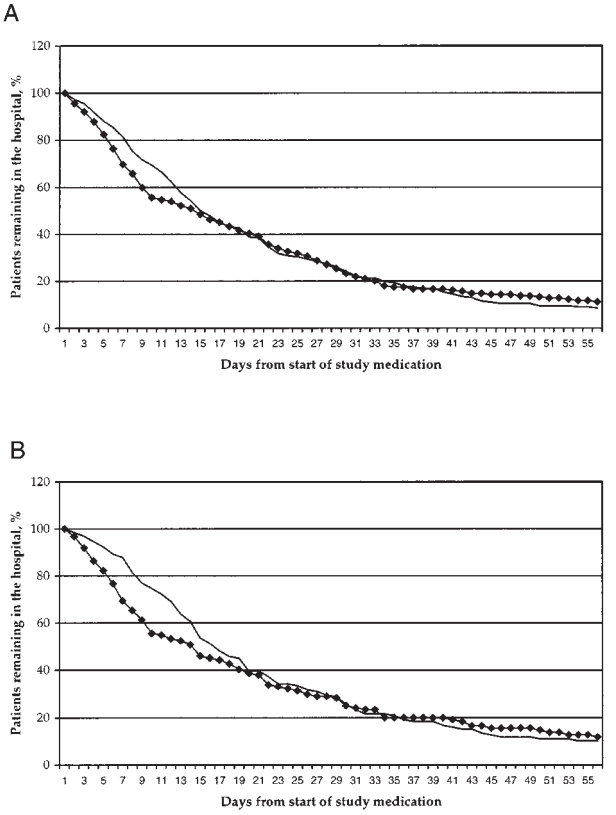

Figure 1. Kaplan-Meier curves for discharge from hospital in the (A) total intent-to-treat sample and (B) clinically evaluable sample. —◆— = linezolid; — = vancomycin.

Table 2. Length of Stay, Discharges by Week, and Duration of Antibiotic Treatment in Overall Pooled Sample

	Intent-to-Treat Sample			Clinically Evaluable Sample		
Variable	Linezolid Group	Vancomycin Group	p Value	Linezolid Group	Vancomycin Group	p Value
Including patients who died, number in sample	240	220		124	130	
Length of stay (days)[a]						
Median (95% CI)	14 (9–17)	15 (13–17)	0.19	14 (9–18)	16 (14–19)	0.08
Mean	19.6	20.2		20.0	21.3	
Patients discharged by week (%)						
Week 1	30	19	0.005	31	12	0.001
Week 2	48	45	0.47	49	39	0.11
Week 3	60	60	0.92	62	60	0.73
Week 4	72	71	0.86	71	70	0.87
Week 8	86	89	0.44	87	88	0.74
Duration of antibiotic treatment (days)						
Intravenous only						
Mean	6.7	11.3	0.0001	6.8	13.8	0.0001
Median	5	10	0.0001	6	13	0.0001
Intravenous and oral						
Mean	12.6	11.3	0.05	15.4	13.8	0.02
Median	13	10	0.03	15	13	0.003
Excluding patients who died (sensitivity analysis)						
Number (%) of deaths	44 (18)	33 (15)	0.34	10 (8)	9 (7)	0.73
Number in sample, excluding deaths	196	187		114	121	
Length of stay (days)[a]						
Median (95% CI)	14 (9–19)	15 (13–19)	0.14	13.5 (9–18)	16 (14–19)	0.09
Mean	20.5	21.1		20.0	21.0	
Patients discharged by week (%)						
Week 1	29	16	0.001	32	12	0.001
Week 2	48	43	0.31	50	40	0.11
Week 3	58	60	0.66	61	62	0.93
Week 4	69	69	0.98	71	71	1.00
Week 8	84	87	0.42	87	88	0.86
Duration of antibiotic treatment (days)						
Intravenous only						
Mean	6.4	11.8	0.0001	6.6	13.8	0.0001
Median	5	11	0.0001	5	13	0.0001
Intravenous and oral						
Mean	13.1	11.8	0.06	15.5	13.8	0.02
Median	14	11	0.03	15	13	0.002

[a]Estimated by Kaplan-Meier survival function.

median LOS was greater: linezolid group, 14 days (95% CI 9–18 days), vancomycin group, 16 days (95% CI 14–19 days, p=0.08).

Proportion of Patients Discharged

Kaplan-Meier curves showed the proportion of patients who remained in the hospital from day 1–day 56 for intent-to-treat and clinically evaluable samples (Figure 1). For both samples, the proportion of patients discharged in the first week differed substantially (intent-to-treat sample, 30% in the linezolid group, 19% in the vancomycin group, p=0.005; clinically evaluable sample, 31% and 12%, respectively, p=0.005). The proportion of discharged patients remained higher among patients who received linezolid until the fourth week after the first dose of study drug, but none of these other differences were significant.

Duration of Antibiotic Treatment

As expected, in both samples, mean and median durations of intravenous antibiotic treatment were significantly shorter for linezolid than for vancomycin (p<0.001). The mean difference between drugs was 5.6 days for the intent-to-treat sample and 7.0 days for the clinically evaluable sample. In the linezolid

Table 3. Length of Stay, Discharges by Week, and Duration of Antibiotic Treatment in Subsamples of Patients with Complicated Skin and Soft Tissue and Other Infections

	Intent-to-Treat Sample			Clinically Evaluable Sample		
Variable	Linezolid Group	Vancomycin Group	p Value	Linezolid Group	Vancomycin Group	p Value
Patients with complicated skin and soft tissue infections						
Number of patients	122	108		70	74	
Length of stay (days)[a]						
Median (95% CI)	9 (8–16)	14 (12–18)	0.052	8 (6–13)	16 (13–19)	0.0025
Mean	17.2	19.4		15.4	20.3	
Patients discharged by week (%)						
Week 1	36	17	0.001	44	12	0.001
Week 2	54	46	0.24	61	39	0.008
Week 3	62	65	0.69	69	64	0.52
Week 4	75	76	0.93	80	74	0.42
Week 8	88	90	0.61	93	88	0.31
Duration of antibiotic treatment (days)						
Intravenous only						
Mean	5.8	12.6	0.0001	5.4	14.8	0.0001
Median	4	11	0.0001	4	14	0.0001
Intravenous and oral						
Mean	14.2	12.6	0.09	16.6	14.8	0.07
Median	14	11	0.056	15	14	0.027
Patients with other infections						
Number of patients	118	112		54	56	
Length of stay (days)[a]						
Median (95% CI)	16 (12–21)	15 (12–21)	0.99	18 (14–29)	15 (13–25)	0.46
Mean	21.6	20.7		25.7	22.0	
Patients discharged by week (%)						
Week 1	24	21	0.56	13	13	0.94
Week 2	42	44	0.83	33	39	0.52
Week 3	58	56	0.83	54	55	0.86
Week 4	68	66	0.78	59	64	0.59
Week 8	85	88	0.55	80	89	0.16
Duration of antibiotic treatment (days)						
Intravenous only						
Mean	7.6	10.1	0.0005	8.7	12.5	0.0001
Median	7	10	0.0005	7	12	0.0001
Intravenous and oral						
Mean	10.9	10.1	0.33	13.8	12.5	0.13
Median	10.5	10	0.28	14	12	0.054

[a]Estimated by Kaplan-Meier survival function.

group, 60.8% of patients in the intent-to-treat sample and 81.4% in the clinically evaluable sample also received oral linezolid. When oral therapy was taken into account, however, the mean duration of antibiotic treatment was 1–2 days shorter in the vancomycin group.

Sensitivity Analysis

When patients who died during the study were excluded from the pooled sample, outcomes were similar to results obtained when deaths were included in the analysis as having complete LOS information. They were also similar when patients who died were treated as censored.

Outcomes for Patients with Complicated Skin and Soft Tissue Infections and Other Infections

When the sample was subdivided into patients with and without complicated skin and soft tissue infections, one begins to see that the results of the analysis depended on primary site of infection (Table 3).

Length of Stay

Among patients with complicated skin and soft tissue infections, the median LOS was significantly shorter for patients who received linezolid than for those who received vancomycin, 5 days

shorter (p=0.05) in the intent-to-treat sample and 8 days shorter (p=0.003) in the clinically evaluable sample. No statistically significant differences were observed among patients with other infections (p=0.99 and 0.46, intent-to-treat and clinically evaluable samples, respectively).

Proportion of Patients Discharged

As with the pooled sample, the proportion of patients with complicated skin and soft tissue infections who were discharged in the first week of hospitalization was significantly higher in the linezolid group than in the vancomycin group (36% and 17% intent-to-treat sample; 44% and 12% clinically evaluable sample, p=0.001 both samples). Unlike the total sample result, in the clinically evaluable sample the proportion of patients with complicated skin and soft tissue infections who were discharged in the first 2 weeks was still significantly higher (p=0.008). However, among patients with other infections, the proportion discharged did not significantly differ between treatment groups for any week of follow-up.

Duration of Antibiotic Treatment

The duration of intravenous antibiotic treatment was significantly shorter for patients who received linezolid regardless of whether or not they had complicated skin and soft tissue infections or whether or not intent-to-treat or clinically evaluable samples were evaluated (p=0.0001 for all but the intent-to-treat sample of patients with infections other than complicated skin and soft tissue infections, p=0.0005). When oral therapy was taken into account, patients receiving linezolid tended to have a longer duration of treatment.

Discussion

In our primary analysis, based on the intent-to-treat sample, we found no significant difference in mean or median LOS between patients who received linezolid or vancomycin, but we did observe a significant increase in the proportion of patients discharged in the first week of therapy and a significant decrease in the duration of intravenous antibiotic therapy for patients who received linezolid. Among patients in the clinically evaluable sample, the tendency was toward a significant reduction in LOS associated with linezolid, and we continued to observe significant differences in the proportion of patients discharged in the first week of therapy and in the duration of intravenous antibiotic therapy.

In our evaluation of the homogeneity of these results, among patients with complicated skin and soft tissue infections (who made up 50% of the entire study group) linezolid led to statistically significant reductions in LOS, significant increases in the proportion of patients discharged after the first (all patients) and second (clinically evaluable patients) weeks of therapy, and significant decreases in the duration of intravenous therapy. Among patients with other sites of infection, the only significant differences between the drugs were related to reduction in duration of intravenous therapy.

The 100% bioavailable oral formulation of linezolid led directly to significant reduction in duration of intravenous antibiotic therapy. In addition, we hypothesize that it also led to reductions in LOS and the increased number of patients discharged in the first and second weeks of therapy. For patients who are switched to oral therapy and are discharged early, the cost of hospitalization may be reduced and the cost of home intravenous treatment may be avoided. Economic advantages of oral formulations of other antibiotics are well documented.[31–33]

After the first week, the proportion of patients discharged converged between treatment groups. This should be expected given similar efficacy of the two agents and the eventual controlling influence that factors (comorbid conditions) other than the availability of an oral formulation or antibiotic treatment in general had on LOS. This pattern of discharge rates is consistent with an opportunity for earlier discharge with linezolid in patients whose clinical condition allows them to be sent home or transferred to a less intensive treatment setting. Earlier discharge stems from the ease of oral continuation of antibiotic therapy.

Failure to observe a significant difference in LOS when patients of all types were evaluated and the ability to detect a difference when a more homogeneous subset was evaluated (5-day reduction in median LOS for patients with complicated skin and soft tissue infections) were not unexpected. The presence of patients who had various types of infections, with varied treatment intensities, comorbid conditions, and consequently varied potential for early discharge, dilutes the potential economic advantages of linezolid and adds substantial variation to LOS measures. In addition, 9% of patients had LOS

that exceeded 56 days. These patients probably had very severe underlying comorbidities or infections; in both cases they would be less likely to be discharged early and thus could not be influenced by the availability of an oral antibiotic. In combination, these effects reduce the LOS difference and decrease the likelihood that an observed difference would be statistically significant.

The issue surrounding different formulations warrants discussion. Specifically, patients treated with linezolid were allowed to switch from intravenous to oral therapy, but no such option was available for those treated with vancomycin. Although unavailability of an oral agent for patients receiving vancomycin was a major contributing factor to differences in LOS, proportion of patients discharged, and duration of intravenous antibiotic treatment, this also reflected current clinical practice for MRSA infections for two reasons. First, whereas some oral antibiotics such as trimethoprim-sulfamethoxazole and minocycline have activities against certain MRS strains, their coverage is far narrower than vancomycin's. Therefore, few physicians would consider these drugs as options to continue antibiotic treatment begun with vancomycin, especially for patients with serious MRSA infections, such as those enrolled in this trial. Second, the trial explicitly allowed patients receiving vancomycin to be discharged and continue therapy outside if an outpatient intravenous service was available. This is also current practice, at least in the U.S.

This study had limitations. Possibly the most important was the fact that analysis of subgroups who did and did not have complicated skin and soft tissue infections was not prespecified. Although there are logical reasons for examining these subgroups, such retrospective analysis makes clear statistical conclusions difficult and suggests the need for confirmation of the results. In addition, as is well known, randomized trials for registration purposes are somewhat artificial and perhaps overcontrolled. They may not represent effects that would be seen in a real-world setting. Differences between trial and real-world settings may either favor or work against the experimental treatment. Patients may be more likely to continue to receive a complete regimen of the study drug, and perhaps to stay in the hospital longer, during the trial than in a real-world setting. They may be more closely monitored during a trial, limiting the negative effects of adverse events. Patients selected for the trial may not be typical of those who would be treated clinically; this applies to participating hospitals as well. These factors limit the ability to generalize our results to actual-use situations.

Finally, patients were not observed beyond day 56; as a result of this and the fact that discharge dates before day 56 were missing for a small number of patients, complete LOS information was not available for approximately 13% of patients. This may introduce unknown bias into the analysis. However, because of the balance of missing observations between treatment groups and use of Kaplan-Meier techniques to address censoring, the potential for such bias appears relatively small. It is worth noting that the mean LOS for the vancomycin group in the intent-to-treat sample (20.2 days) was similar to the mean of 19.7 days in a prospective study of 100 patients treated with vancomycin in a U.S. community hospital.[34] Characteristics and settings for U.S. patients in our trial were not unlike those in that study.

Summary

Compared with vancomycin, treatment with linezolid allowed hospitalized patients with known or suspected MRS species infections to have shortened duration of intravenous antibiotic treatment and increased the chance of being discharged in the first week of hospitalization. There was also a trend toward a reduction in LOS for patients who received linezolid, but the difference between groups was not statistically significant. Between-treatment differences in all three outcomes were statistically significant in favor of linezolid for a large and more homogeneous (retrospectively identified) subgroup of patients with complicated skin and soft tissue infections. More research is necessary to confirm these inferences and to explore their full medical and economic implications.

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References

1. Voss A, Milatovic D, Wallrauch-Schwarz C, Rosdahl VT, Braveny I. Methicillin-resistant *Staphylococcus aureus* in Europe. Eur J Clin Microbiol Infect Dis 1994;13:50–5.
2. Kimura A, Igarashi H, Ushioda H, Okuzumi K, Kobayashi H, Otsuka T. Epidemiological study of *Staphylococcus aureus*

Appendix 1. Infection-Specific Inclusion Criteria

Pneumonia

Clinical features compatible with pneumonia (condition was hospital acquired or patient was hospitalized during community-acquired infection) with at least two of the following signs and symptoms:

Cough; production of purulent sputum or a change (worsening) in character of sputum; auscultatory findings on pulmonary examination of rales and/or pulmonary consolidation; dyspnea, tachypnea, or hypoxemia, particularly if any or all were progressive.

At least two of the following:

Fever; respiratory rate greater than 30 breaths/minute; systolic hypotension; pulse rate greater than or equal to 120 beats/minute; altered mental status; mechanical ventilation required; elevated total peripheral leukocyte count greater than 10,000 cells/mm^3; greater than 15% immature neutrophils (bands) regardless of total peripheral leukocyte count; leukopenia with total leukocyte count less than 4500 cells/mm^3.

Chest radiograph (periapical and lateral), obtained at baseline or screening or within 48 hours of starting treatment, consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, pleural effusion).

No known or suspected pulmonary conditions that were likely to preclude evaluation of therapeutic response (granulomatous diseases, lung cancer, another malignant condition metastatic to the lungs).

No known cystic fibrosis or known or suspected active tuberculosis.

If patient was infected with the human immunodeficiency virus, $CD4^+$ cell count greater than 200 cells/mm^3.

Complicated skin and soft tissue infection

Accessible infection site for Gram stain and culture.

Abscess that required more than surgical draining at the time of enrollment.

At least 2 of the following:

Drainage or discharge, erythema, fluctuance, heat or localized warmth, pain or tenderness to palpation, swelling or induration.

No infection with a high surgical incision cure rate (isolated furunculosis, folliculitis).

No medical conditions in which inflammation may be prominent for an extended period even after successful bacterial eradication (superinfected eczema, atopic dermatitis).

No infection requiring concomitant systemic corticosteroid therapy.

No diabetic foot, decubitus, and ischemic ulcers; necrotizing fasciitis; gas gangrene; or burns greater than 20% of body surface.

Urinary tract infection

At least one of the following (except for patients unable to provide a history):

Dysuria; frequency; urgency; suprapubic pain; positive, pretreatment, clean-catch, midstream urine culture (or urine sample collected from a catheter) within 48 hours of study enrollment; positive culture defined as greater than 10^5 colony-forming units/ml; urinalysis documenting greater than or equal to 10 leukocytes/mm^3.

Bacteremia

At least one of the following:

Fever; chills; leukocytosis with prominent left shift; changes in vital signs.

isolated from the Japanese National University and Medical College hospitals with coagulase typing, and production of enterotoxins and toxic shock syndrome toxin-1 [in Japanese]. Kansenshogaku Zasshi 1992;66:1543–9.

3. Centers for Disease Control and Prevention. Reduced susceptibility of *Staphylococcus aureus* to vancomycin—Japan, 1996. MMWR 1997;46:624–6.
4. Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975–1991. Infect Control Hosp Epidemiol 1992;13:582–6.
5. Polk RE, Rotschafer JC, Hoang AD, et al. Emerging resistance with gram-positive aerobic infections. Fact or fiction? Binghamton, NY: Pharmaceutical Products Press, 1997.
6. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999;29:239–44.
7. Fridkin SK, Steward CD, Edwards JR, et al. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2. Project intensive care antimicrobial resistance epidemiology hospitals. Clin Infect Dis 1999;29:245–52.
8. Gerding DN, Fridkin SK, Jorgensen JH, et al. Highly resistant gram-positive infections: epidemiology of VRE and VISA. Presentations in focus. Data presented at a symposium at the 37th annual meeting of the Infectious Diseases Society of America, Philadelphia, Pennsylvania. New York: Medical Education Network, 1999.
9. Moreno F, Crisp C, Jorgensen JH, Patterson JE. Methicillin-resistant *Staphylococcus aureus* as a community organism. Clin Infect Dis 1995;21:1308–12.
10. Layton MC, Hierholzer WJ Jr, Patterson JE. The evolving epidemiology of methicillin-resistant *Staphylococcus aureus* at a university hospital. Infect Control Hosp Epidemiol 1995;16:12–17.
11. Steinberg JP, Clark CC, Hackman BO. Nosocomial and community-acquired *Staphylococcus aureus* bacteremias from 1980 to 1993: impact of intravascular devices and methicillin resistance. Clin Infect Dis 1996;23:255–9.
12. Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. JAMA 1998;279:593–8.
13. Frank AL, Marcinak JF, Mangat PD, Schreckenberger PC. Increase in community-acquired methicillin-resistant *Staphylococcus aureus* in children. Clin Infect Dis 1999;29:935–6.
14. Gorak EJ, Yamada SM, Brown JD. Community-acquired methicillin-resistant *Staphylococcus aureus* in hospitalized adults and children without known risk factors. Clin Infect Dis 1999;29:797–800.
15. Centers for Disease Control and Prevention. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997–1999. MMWR 1999;48:707–10.
16. Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. JAMA 1999;282:1745–51.

17. Welch KE, Goff DA, Fish DN, Sierawski SJ, Paladino JA. A multicenter economic analysis of bacteremia caused by methicillin-resistant *Staphylococcus aureus* [abstr]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 26–29, 1999. Washington, DC: American Society for Microbiology, 1999:742.
18. Abramson MA, Sexton DJ. Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* primary bacteremia: at what costs? Infect Control Hosp Epidemiol 1999;20:408–11.
19. Harbarth S, Rutschmann O, Sudre P, Pittet D. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus*. Arch Intern Med 1998;158:182–9.
20. Ford CW, Hamel JC, Stapert D, et al. Oxazolidinones: new antibacterial agents. Trends Microbiol 1997;5:196–200.
21. Cammarata SK, Echevarria J, Fabian G, et al. Linezolid in the treatment of community-acquired pneumonia: the results of phase II and phase III studies [abstr]. In: Abstracts of the 9th International Congress on Infectious Diseases, Buenos Aires, Argentina, April 10–13, 2000. Boston, MA: International Society for Infectious Diseases, 2000:182.
22. Cammarata SK, Bermudez M, Golin V, et al. Comparison of linezolid versus ceftriaxone/cefpodoxime in the treatment of hospitalized community-acquired pneumonia [abstr]. In: Abstracts of the 9th International Congress on Infectious Diseases, Buenos Aires, Argentina, April 10–13, 2000. Boston, MA: International Society for Infectious Diseases, 2000:182.
23. Leach TS, Cammarata SK, Hempsall, KA, et al. Linezolid for the treatment of community or hospital-acquired pneumonia caused by *Staphylococcus aureus:* results of four randomized, phase III trials [abstr]. In: Abstracts of the 9th International Congress on Infectious Diseases, Buenos Aires, Argentina, April 10–13, 2000. Boston, MA: International Society for Infectious Diseases, 2000:224.
24. Leach TS, Kaja RW, Eckert SE, Schaser R, Todd WM, Hafkin B. Linezolid versus vancomycin for the treatment of MRSA infections: results of a randomized phase III trial [abstr]. In: Abstracts of the 9th International Congress on Infectious Diseases, Buenos Aires, Argentina, April 10–13, 2000. Boston, MA: International Society for Infectious Diseases, 2000:224.
25. Stevens DL, Smith LG, Bruss JB, et al. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2000;44:3408–12.
26. Duvall SE, Bruss JB, McConnel-Martin MA, Todd WM, Hafkin B. Comparison of oral linezolid to oral clarithromycin in the treatment of uncomplicated skin infections: results from a multinational phase III trial [abstr]. In: Abstracts of the 9th International Congress on Infectious Diseases, Buenos Aires, Argentina, April 10–13, 2000. Boston, MA: International Society for Infectious Diseases, 2000:181.
27. Pharmacia & Upjohn. Linezolid for the treatment of vancomycin-resistant enterococcal infections: a double-blinded trial comparing 600 mg linezolid every 12 hours with 200 mg linezolid every 12 hours: final report of the trial M/1260/0054A. Pharmacia & Upjohn study report a0052356, 1999.
28. Pharmacia & Upjohn. Linezolid for the treatment of methicillin-resistant *Staphylococcus* species (MRSS) infections: a randomized, open-label trial comparing linezolid IV/PO and vancomycin IV: final report of the trial M/1260/0031. Pharmacia & Upjohn study report a0052076, 1999.
29. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. Med Care 1994;32:150–63.
30. Hosmer DW Jr, Lemeshow S. Applied survival analysis: regression modeling of time to event data. New York: Wiley, 1999.
31. Fliegelman RM, Mattingly PM, Dempsey CL, Sokalski SJ. Economic impact of oral ciprofloxacin following standard intravenous therapy. Diagn Microbiol Infect Dis 1990;13:187–9.
32. Paladino JA, Sperry HE, Backes JM, et al. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. Am J Med 1991;91:462–70.
33. Przybylski KG, Rybak MJ, Martin PR, et al. A pharmacist-initiated program of intravenous to oral antibiotic conversion. Pharmacotherapy 1997;17:271–6.
34. Garrelts JC, Horst WD, Silkey B, Gagnon S. A pharmacoeconomic model to evaluate antibiotic costs. Pharmacotherapy 1994;14:438–45.