Treatment Outcomes Among Patients With Nosocomial Pneumonia Caused by MRSA Only Versus MRSA Mixed Infections

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BACKGROUND

- *Staphylococcus aureus* causes nosocomial pneumonia and is a significant cause of morbidity and mortality.
- The prevalence of methicillin-resistant *S. aureus* (MRSA) associated with nosocomial infections has been increasing in frequency, particularly in intensive care units, and can account for more than 50% to 70% of *S. aureus* isolates.[1,2]
- Outcomes by treatment for patients with nosocomial pneumonia due to MRSA versus those with MRSA-mixed infection are unknown.
- The objective of this study was to determine the clinical outcomes and safety among patients with nosocomial pneumonia caused by MRSA-only versus MRSA-mixed infections.

METHODS

Study Population

- We used data from a prospective phase 4 clinical trial conducted from 2006 to 2010 that compared the safety and efficacy of linezolid (600 mg twice a day) with that of vancomycin (15 mg/kg twice a day; with dose adjustment as necessary based on trough levels and creatinine clearance) for the treatment of culture-proven MRSA nosocomial pneumonia.
- We included patients with a respiratory specimen taken by either an invasive technique (bronchoscopic or nonbronchoscopic) or an endotracheal aspirate. Alternatively, a suitable sputum sample, defined as having <10 squamous epithelial cells and >25 leukocytes per low power field, was submitted for Gram stain and culture.
- Patients also received Gram-negative coverage at randomization until culture results were available and no Gram-negative pathogens were recovered.
- Clinical and microbiologic outcomes and safety were assessed among the modified intent-to-treat population (patients who received ≥1 dose of study drug and had culture-proven MRSA) at the end of treatment (EOT; defined as 7–14 days or up to 21 days in presence of bacteremia) and end of study (EOS; defined as 7–30 days after EOT).
- Clinical success was evaluated at the EOT visit as cure or improvement and at the EOS visit as cure.
  - Cure was defined as resolution of the clinical signs and symptoms of pneumonia when compared with baseline; improvement or lack of progression of all abnormalities on the chest X-ray; and no additional MRSA antibacterial treatment required.
  - Improvement (EOT only) was defined as improvement in 2 or more, but not all, of the clinical signs and symptoms of pneumonia when compared with baseline (eg, body temperature, white blood cell count, respiratory rate, auscultatory findings, cough, sputum production); improvement or lack of progression of all abnormalities on chest X-ray; and no additional MRSA antibacterial treatment.
- Microbiologic success was evaluated by the sponsor for patients with a pathogen isolated at baseline at EOT and EOS.
  - Success was defined as documented microbiologic eradication where MRSA was absent from the culture at the original site of infection or presumed microbiologic eradication where the patient was clinically cured and no appropriate material was available for culture from the original site of infection.

Statistical Analysis

- Patient characteristics, outcomes, and safety were compared between patients with MRSA-only and MRSA-mixed infections utilizing the Fisher exact test or chi-square test, as appropriate, for categorical variables and one-way analysis of variance for continuous variables.
- Statistical significance for all tests was defined at $P \leq 0.05$.

RESULTS

- There were 448 patients included in the analysis, 247 (55%; 119 linezolid, 128 vancomycin) MRSA-only and 201 (45%; 105 linezolid, 96 vancomycin) MRSA-mixed infections (**Table 1**).
- Compared with patients with MRSA-mixed infections, patients with MRSA-only infections were more likely to have diabetes (47% vs 34%), cardiac disease (64% vs 54%), hepatic comorbidities (18% vs 10%), have received corticosteroids at baseline (25% vs 16%) and concomitantly (26% vs 16%), and have a higher mean weight (79.6 kg vs 75.4 kg) (**Table 1**).
- The majority of mixed infections were MRSA and Gram-negative organisms (n=116 [58%]), followed by MRSA and Gram-positive organisms (n=40 [20%]), Gram-positive and Gram-negative organisms (n=26 [13%]), fungal infections (n=17 [8%]), and mixed-MRSA and anaerobe organisms (n=2 [1%]) (**Table 2**).
- Clinical success rates were similar for MRSA-only versus MRSA-mixed infections at both EOT (74% vs 73%; P=1.00) and EOS (53% vs 46%; P=0.19) (**Figure 1**).
  - For MRSA-only infections, clinical success rates were 80% and 69% (P=0.07) at EOT and 59% and 47% (P=0.08) at EOS for linezolid and vancomycin, respectively.
  - For MRSA-mixed infections, clinical success rates were 80% and 66% (P=0.04) at EOT and 49% and 42% (P=0.36) at EOS for linezolid and vancomycin, respectively.
- Among patients with MRSA-only infections, the rate of mortality at day 28 was 18% for linezolid-treated and 19% for vancomycin-treated patients. For patients with MRSA-mixed infections, these rates were 19% and 17%, respectively.

Table 1. Patient and Clinical Characteristics of MRSA-Only Versus MRSA-Mixed Infections in the Modified Intent-to-Treat Population

	MRSA Only (N=247)		MRSA Mixed (N=201)	
Characteristic	**Linezolid (n=119)**	**Vancomycin (n=128)**	**Linezolid (n=105)**	**Vancomycin (n=96)**
Mean age ± SD, y	61.7 ± 17.3	61.9 ± 18.0	61.7 ± 18.8	62.0 ± 18.3
Gender: male, n (%)	80 (67.2)	78 (60.9)	71 (67.6)	65 (67.7)
Race, n (%)				
White	82 (68.9)	85 (66.4)	74 (70.5)	67 (69.8)
Black	13 (10.9)	19 (14.8)	12 (11.4)	12 (12.5)
Asian	19 (16.0)	23 (18.0)	13 (12.4)	10 (10.4)
Other	5 (4.2)	1 (0.8)	6 (5.7)	7 (7.3)
Mean weight ± SD, kg[a]	80.2 ± 25.3	79.1 ± 23.8	75.5 ± 18.9	75.3 ± 17.1
Comorbidities, n (%)				
≥1 in present admission	118 (99.2)	128 (100)	103 (98.1)	96 (100)
Diabetes[a]	53 (44.5)	62 (48.4)	34 (32.4)	34 (35.4)
Cardiac[a]	74 (62.2)	85 (66.4)	57 (54.3)	52 (54.2)
Oncologic	11 (9.2)	13 (10.2)	10 (9.5)	13 (13.5)
Hepatic[a]	24 (20.2)	20 (15.6)	10 (9.5)	11 (11.5)
Renal/urinary	52 (43.7)	55 (43.0)	31 (29.5)	39 (40.6)
Pulmonary disorders	83 (69.7)	86 (67.2)	69 (65.7)	68 (70.8)
Vascular disorders	46 (38.7)	47 (36.7)	30 (28.6)	31 (32.3)
Mean treatment duration ± SD, d	9.9 ± 3.8	9.8 ± 4.4	10.1 ± 4.1	9.4 ± 4.6
Mean vancomycin trough concentration ± SD, µg/mL				
Day 3		N=103; 14.6 ± 8.7		N=63; 14.2 ± 8.9
Day 6		N=59; 16.5 ± 8.9		N=47; 18.0 ± 8.5
Readmission rate, n (%)	8 (6.7)	11 (8.6)	9 (8.6)	7 (7.3)
Related to infection, n (%)	0	1 (0.8)	2 (1.9)	1 (1.0)
Mean discharge to readmission ± SD, d	10.9 ± 9.8	10.8 ± 7.8	12.4 ± 6.2	20.0 ± 15.4
Bacteremia at baseline, n (%)[a]				
Yes	8 (6.7)	15 (11.7)	7 (6.7)	9 (9.4)
No	109 (91.6)	113 (88.3)	85 (81.0)	82 (85.4)
Unknown	2 (1.7)	0	13 (12.4)	5 (5.2)
Baseline Gram-negative coverage, n (%)	117 (98.3)	124 (96.9)	103 (98.1)	95 (99.0)
Baseline anerobe coverage, n (%)	64 (53.8)	72 (56.3)	54 (51.4)	54 (56.3)
Baseline corticosteroid receipt, n (%)[a]	34 (28.6)	28 (21.9)	14 (13.3)	18 (18.8)
Concomitant Gram-negative coverage, n (%)	100 (84.0)	109 (85.2)	93 (88.6)	86 (89.6)
Concomitant anerobe coverage, n (%)	69 (58.0)	56 (43.8)	62 (59.0)	53 (55.2)
Concomitant corticosteroid receipt, n (%)[a]	34 (28.6)	30 (23.4)	15 (14.3)	18 (18.8)
Ventilated at baseline, n (%)	81 (68.1)	93 (72.7)	72 (68.6)	70 (72.9)

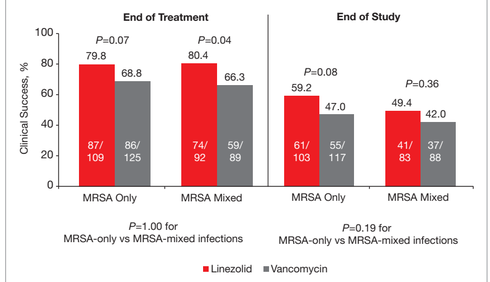
MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.
[a] Denotes significance at $P<0.05$ for MRSA-only compared with MRSA-mixed infections.

Table 2. Type and Distribution of MRSA-Mixed Infection (N=201)

Type of MRSA-Mixed Infection	n (%)
MRSA + Gram-positive	40 (19.9)
MRSA + Gram-negative	116 (57.7)
MRSA + Gram-positive + Gram-negative	26 (12.9)
MRSA + anaerobe	2 (1.0)
MRSA + fungal	17 (8.5)

MRSA, methicillin-resistant *Staphylococcus aureus*.

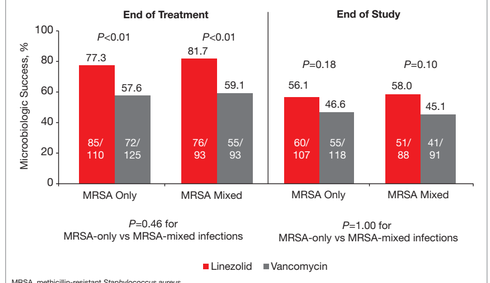
Figure 1. Clinical Success at End of Treatment and End of Study by Treatment and Type of Infection (Modifed Intent-to-Treat).



MRSA, methicillin-resistant *Staphylococcus aureus*.

- Microbiologic success rates were similar for MRSA-only versus MRSA-mixed infections at both EOT (67% vs 70%; P=0.46) and EOS (51% vs 51%; P=1.00) (**Figure 2**).
  - For MRSA-only infections, microbiologic success rates were 77% and 58% (P<0.01) at EOT and 56% and 47% (P=0.18) at EOS for linezolid and vancomycin, respectively.
  - For MRSA-mixed infections, microbiologic success rates were 82% and 59% (P<0.01) at EOT and 58% and 45% (P=0.10) at EOS for linezolid and vancomycin, respectively.

Figure 2. Microbiologic Success at End of Treatment and End of Study by Treatment and Type of Infection (Modified Intent-to-Treat).



MRSA, methicillin-resistant *Staphylococcus aureus*.

- Rates of adverse events were similar for linezolid and vancomycin within both the MRSA-only and MRSA-mixed infections, except for the MRSA-only infections cohort in regard to renal toxicity by treatment (4% linezolid vs 20% vancomycin) (**Table 3**).

Table 3. AEs of MRSA-Only and MRSA-Mixed Infections by Treatment (Modified Intent-to-Treat)

	MRSA-Only Infection		MRSA-Mixed Infection	
	Linezolid (N=119)	**Vancomycin (N=128)**	**Linezolid (N=105)**	**Vancomycin (N=96)**
Number of AEs	571	534	430	490
Patients with AEs, n (%)	110 (92.4)	108 (84.4)	95 (90.5)	88 (91.7)
Patients with serious AEs, n (%)	49 (41.2)	47 (36.7)	40 (38.1)	34 (35.4)
Patients discontinued due to AE, n (%)	7 (5.9)	7 (5.5)	5 (4.8)	10 (10.4)
Anemia, n/N (%)[a]	19/113 (16.8)	25/123 (20.3)	20/102 (19.6)	16/90 (17.8)
Thrombocytopenia, n/N (%)[a]	19/113 (16.8)	14/122 (11.5)	16/102 (15.7)	14/91 (15.4)
Renal toxicity, n/N (%)[a]	4/114 (3.5)	25/124 (20.2)	14/100 (14.0)	14/90 (15.6)

MRSA, methicillin-resistant *Staphylococcus aureus*; AE, adverse event.
[a] Anemia, thrombocytopenia, and renal toxicity are defined by laboratory measures and percentages are calculated excluding missing data:
Anemia: any drop from baseline hemoglobin ≥2, or if normal at baseline, a hemoglobin value <10.
Thrombocytopenia: platelet count of <150,000/µL, if platelet count was normal at baseline, or a 50% drop if platelet count was not normal at baseline.
Renal toxicity: if serum creatinine is normal at baseline and there is a rise of 0.5 during study, or if not normal at baseline (only with regard to upper limit) and there is a rise of 50%.

CONCLUSIONS

- There were significant differences in baseline demographics between patients with MRSA-only infections and MRSA-mixed infections, including diabetes, cardiac disease, hepatic comorbidities, higher weight, and receipt of corticosteroids (at baseline and concomitantly).
- Clinical and microbiologic success rates were similar for nosocomial pneumonia caused by MRSA-only versus MRSA-mixed infections.
- Rates of microbiologic success were significantly higher among those treated with linezolid compared with vancomycin for both MRSA-only and MRSA-mixed infections at EOT but not at EOS. Rates of clinical success were significantly higher among those treated with linezolid compared with vancomycin, among patients with MRSA-mixed infections at EOT.
- Frequency of adverse events were similar between patients with MRSA and MRSA-mixed profiles and was consistent with the known safety profile of each drug.

REFERENCES

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