

The Prevalence of Methicillin-Resistant *Staphylococcus aureus* Colonization in Patients with Complicated Skin and Skin Structure Infections after Treatment with Linezolid or Vancomycin

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Abstract

Background: Complicated skin and skin structure infections (cSSSIs) due to *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), are associated with significant morbidity. Reducing MRSA carriage has been a focus of infection control interventions. The prevalence of MRSA colonization after successful treatment of a MRSA cSSSI is unknown. **Methods:** Secondary analysis of a randomized controlled trial comparing linezolid and vancomycin for the treatment of MRSA cSSSI. Adult patients that had a colonization culture, confirmed MRSA cSSSI, received at least one dose of study treatment, and had an outcome recorded at end of study. Patient, clinical characteristics and prevalence of colonization were compared by treatment regimens. A multivariate regression model identified predictors of MRSA colonization at EOS. **Results:** There were 456 patients evaluated. The prevalence of MRSA colonization was higher for vancomycin treated patients compared to linezolid treated patients at end of treatment (EOT) (28% vs. 5%, $p < 0.001$) and EOS (34% vs. 22%, $p < 0.01$). Independent predictors of colonization at EOS after treatment for a MRSA cSSSI included diagnosis, primarily driven by abscess, black race, treatment with vancomycin, MRSA mixed infection and male gender. **Conclusion:** Patients treated with linezolid for a cSSSI had less MRSA colonization at EOT and EOS compared to those treated with vancomycin. Multiple independent predictors of MRSA colonization were identified. Additional studies evaluating the relationship of MRSA colonization after treatment of cSSSI are needed.

Keywords

Staphylococcus aureus, Complicated Skin and Skin Structure Infection, Colonization, Linezolid,

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Vancomycin

1. Introduction

Staphylococcus aureus, including methicillin-resistant *S. aureus* (MRSA), is a prominent nosocomial and community pathogen causing complicated skin and skin structure infections (cSSSI) [1] [2]. Approximately 30% of the human population is colonized with *S. aureus* in their nasal passages [3] [4]. Multiple studies have shown an association between *S. aureus* or MRSA colonization and subsequent infection [4]-[8].

MRSA colonization is a reservoir for horizontal transmission both within the hospital setting and in the community [4] [9] [10]. When host immune defenses are impaired, colonization may result in infection [4] [5]. As a result, infection control interventions have focused on reducing MRSA carriage as a way to control the transmission of MRSA [11] [12]. However, the efficacy and cost effectiveness of these strategies vary by study. There is a lack of consensus regarding optimal screening and decolonization strategies to prevent infections in persons colonized with MRSA [4] [10] [13]-[18].

The prevalence of MRSA colonization after successful treatment of a MRSA cSSSI is unknown. In addition, it is unknown whether colonization with MRSA affects the outcomes of treatment of a MRSA cSSSI or the extent that treatment with an anti-MRSA agent affects colonization status. If certain treatment regimens diminish colonization, even if it is transient, this could impact the resolution of the infection while also reducing horizontal transmission and recurrence.

The aims of this study were: 1) To determine the prevalence of MRSA colonization among patients treated with linezolid or vancomycin for MRSA cSSSI; and 2) To identify predictors of MRSA colonization.

2. Methods

2.1. Study Design

This analysis used data from a prospective, open-labeled, comparator-controlled, multicenter, Phase 4 trial (NCT00087490) that occurred from 2004-2007, evaluating the efficacy of linezolid and vancomycin in the treatment of MRSA cSSSI. Patients received either linezolid 600 mg intravenously (IV) or orally every 12 h or IV vancomycin 15 mg/kg every 12 h (dose adjusted for creatinine clearance) for 7 - 14 days [19]. Patients with documented MRSA bacteremia could receive up to 21 days of therapy at the discretion of the investigator with prior approval from the medical monitor. Based on the protocol, nares and groin cultures were obtained at EOT and EOS [19].

2.2. Patient Population and Assessment

Adult patients meeting the primary study's modified intent to treat population (mITT), which was defined as patients receiving at least 1 dose of study medication and culture confirmed MRSA, who also had a colonization culture (nares and/or groin) at end of treatment (EOT) and end of study (EOS), defined as 6 - 28 days after EOT were considered the study population for this analysis [19].

Demographics and patient characteristics were compared separately for two cohorts: 1) *Colonization comparison*, comparing those that were MRSA colonized versus those who were not MRSA colonized at EOT and EOS, and 2) *Treatment comparison*, comparing linezolid versus vancomycin treated patients by MRSA colonization or no MRSA colonization at EOT and EOS.

2.3. Study Definitions

Inclusion criteria: Patients were included in the primary trial if they had signs or symptoms of a cSSSI involving deep tissues and at least two of the following: purulent drainage, erythema, swelling or induration, tenderness or pain, and local warmth. In addition, patients had at least one sign of systemic infection, such as fever, hypotension, increased white blood cell count ($\geq 10,000 \text{ mm}^3$), or more than 15% immature neutrophils regardless of the total peripheral white blood cell count. Specific enrollment criteria were applied for patients with diabetic foot infections, which included evidence of a deep infection extending below the subcutaneous tissue of the foot, an

kle, or lower leg that required a surgical procedure or an identifiable wound [19].

Exclusion criteria: Patients were excluded from the primary clinical trial if there was known or suspected necrotizing fasciitis, gangrene, septic arthritis, osteomyelitis, or who were previously treated with a MRSA-active antibiotic (systemic or topical) for more than 24 hours and within 72 hours of receiving first dose of study drug [19].

Colonization Cultures: A sterile swab from culturette moistened with transport media was used to obtain MRSA cultures from the nares and groin.

2.4. Statistical Analysis

Statistical comparisons between groups were performed using the Chi-square test or Fisher's Exact test for categorical variables and ANOVA or t-test for continuous variables. We constructed risk differences with 2-sided 95% confidence intervals (CI) of MRSA colonization after treatment with linezolid compared to vancomycin; $p \leq 0.05$ was considered statistically significant.

Backwards multivariate logistic regression was used to identify factors that were significantly related to MRSA colonization at EOS. The regression was built using criteria of $p \leq 0.10$ and $p \leq 0.05$ to remain in different iterations of possible models. Covariate reduction techniques were applied prior to model building including near zero variance (NZV), missingness, and covariate correlations, associations, and clusters. In addition, 1000 bootstrap samples were generated to check the model results for all models, including the final model chosen. The validity of the final model was checked with the Hosmer-Lemeshow goodness-of-fit test.

3. Results

There were 640 subjects in the primary study mITT population. Of these, 456 patients had a colonization culture at EOS (linezolid treated = 239 and vancomycin treated = 217) and comprised the study population. There were 414 patients (linezolid = 220 and vancomycin = 194) that had a colonization culture at EOT. **Table 1** describes the patient and clinical characteristics by colonization status at end of study for patients treated for a MRSA cSSSI. There were no differences in baseline characteristics between those treated with linezolid or vancomycin. There were significant differences in the frequency of primary diagnosis between those patients colonized and not colonized at EOS. Specifically, the majority of patients colonized at EOS had an abscess 76 (60.8%) compared to those not colonized 152 (45.9%). Patients with ulcers and surgical wounds had similar frequency of colonization. Patients who were not colonized ($n = 44$, 13.3%) had more "other" diagnosis which included blister, erysipelas, bursitis, haematoma, insect bite and burn infections compared to those colonized ($n = 3$, 2.4%).

The prevalence of MRSA colonization at EOT and EOS was 15.5% and 27.4%, respectively. Patients receiving linezolid were significantly less likely to be colonized at EOT, compared to those treated with vancomycin (4.5% vs. 27.8%, $p < 0.01$). This trend remained significant at EOS with 21.8% of linezolid patients being colonized versus 33.6% of patients receiving vancomycin ($p < 0.01$).

Patients were more frequently colonized in the nares compared to the groin at both EOT and EOS (75% vs. 45%, $p < 0.05$; and 73% vs. 63%, $p < 0.05$, respectively). Patients were colonized at both sites 20% of the time at EOT and 36% at EOS. There were 16 (25%) and 34 (27%) patients colonized in the groin, but not in the nares at EOT and EOS, respectively.

Patients treated with linezolid had significantly less colonization at the nares, groin and both sites compared to vancomycin treated patients, $p < 0.01$ for all observations at EOT. At EOS, linezolid treated patients had significantly less colonization overall, primarily driven by differential colonization rates in the nares, $p < 0.05$.

Figure 1 illustrates microbiologic outcomes at EOT and EOS by colonization status and treatment. Patients treated with linezolid had a significantly greater microbiological success rate than patients treated with vancomycin at EOT among those colonized as well as those not colonized.

There were no differences in clinical success rates at EOT by treatment or by colonization status. However, there was a significant difference in clinical success rates for linezolid treated patients compared to vancomycin treated patients among those not colonized (RD: 8.7, 95% CI: 0.2, 17.1) at EOS.

Table 2 describes results from the multivariate model. Independent predictors of colonization at EOS after treatment for a MRSA cSSSI included diagnosis, primarily abscess, black race, treatment with vancomycin, MRSA mixed infection and male gender. The best fit model was adjusted for diabetes and vascular status.

Table 1. Patient and clinical characteristics by colonization status at end of study for patients treated for a cSSSI.

Characteristic	Colonized (n = 125)			Not Colonized (n = 331)			Colonized vs. Not Colonized
	Linezolid (n = 52)	Vancomycin (n = 73)	P Value	Linezolid (n = 187)	Vancomycin (n = 144)	P Value	P Value
Age, Mean (SD), y	45.9 (19.4)	49.7 (16.3)	0.24	49.8 (17.4)	49.3 (19.1)	0.80	0.44
Gender, Male, n (%)	31 (59.6)	49 (67.1)	0.45	100 (53.5)	78 (54.2)	0.91	0.06
Race, n (%)							
White	35 (67.3)	50 (68.5)	0.77	135 (72.2)	95 (66.0)	0.19	0.06
Black	10 (19.2)	16 (21.9)		26 (13.9)	16 (11.1)		
Asian	0	0		2 (1.1)	2 (1.4)		
Other	7 (13.5)	7 (9.6)		24 (12.8)	31 (21.5)		
Weight, kg (SD)	89.8 (36.9)	83.8 (23.6)	0.27	85.8 (24.8)	82.1 (29.1)	0.21	0.47
Prior Hospitalization, n (%)	23 (44.2)	28 (38.4)	0.58	77 (41.2)	63 (43.8)	0.66	0.83
Route of Initial Treatment, n (%)							
IV	27 (51.9)	73 (100)	<0.01	103 (55.1)	144 (100)	<0.01	0.27
Oral	25 (48.1)	0		84 (44.9)	0		
Concomitant Gram-Negative Coverage, n (%)	29 (55.8)	35 (47.9)	0.47	80 (42.8)	68 (47.2)	0.44	0.25
Corticosteroid Receipt, n (%)	5 (9.6)	5 (6.8)	0.74	10 (5.3)	11 (7.6)	0.50	0.54
Immunosuppressant Receipt, n (%)	0	0		1 (0.5)	1 (0.7)	1.0	1.0
Primary Diagnosis, n (%)							
Abscess	30 (57.7)	46 (63.0)	0.77	88 (47.1)	64 (44.4)	0.70	<0.01
Ulcer	7 (13.5)	11 (15.1)		33 (17.6)	23 (16.0)		
Surgical Wound	12 (23.1)	14 (19.2)		39 (20.9)	38 (26.4)		
Other	3 (5.8)	2 (2.7)		27 (14.4)	19 (13.2)		
Comorbidities							
Diabetes	16 (30.8)	27 (37.0)	0.57	56 (29.9)	41 (28.5)	0.80	0.30
Cardiac	11 (21.2)	14 (19.2)	0.82	45 (24.1)	35 (24.3)	1.0	0.38
Immune System Disorders	11 (21.2)	11 (15.1)	0.48	40 (21.4)	26 (18.1)	0.49	0.69
Psychiatric Disorders	20 (38.5)	26 (35.6)	0.85	72 (38.5)	41 (28.5)	0.06	0.66
Respiratory Disorders	10 (19.2)	12 (16.4)	0.81	45 (24.1)	32 (22.2)	0.79	0.20
Vascular Disorders	21 (40.4)	32 (43.8)	0.72	101 (54.0)	63 (43.8)	0.08	0.48
Isolated Pathogens, n (%)							
MRSA Only	36 (69.2)	53 (72.6)	0.69	142 (75.9)	105 (72.9)	0.61	0.48
MRSA Mixed Infection	16 (30.8)	20 (27.4)		45 (24.1)	39 (27.1)		

4. Discussion

In this study, patients treated with linezolid compared to vancomycin for a cSSSI had less MRSA colonization at EOT and EOS. These findings may be explained by the level of tissue penetration of linezolid [20] [21]. Pharmacokinetic studies demonstrate that linezolid reaches peak concentrations rapidly with an absolute bioavailability that exceeds 100% and penetrates well into perfused body spaces including skin blister fluid [21]. Vancomycin possesses a complex pharmacokinetic profile and its skin penetration is variable and may be affected by inflammation and patient comorbidities [22].

Although linezolid compared to vancomycin treated patients had less MRSA carriage, complete eradication of colonization immediately following treatment was not observed. These results may be due to the fact that benefits from treatment may be transient on carriage, which is similar to what is seen with the use of mupirocin [4] [12] or related to the fact that for about 20% of the general population, *S. aureus* carriage is persistent and represents a balanced microbiota for that person [5] [7] [23].

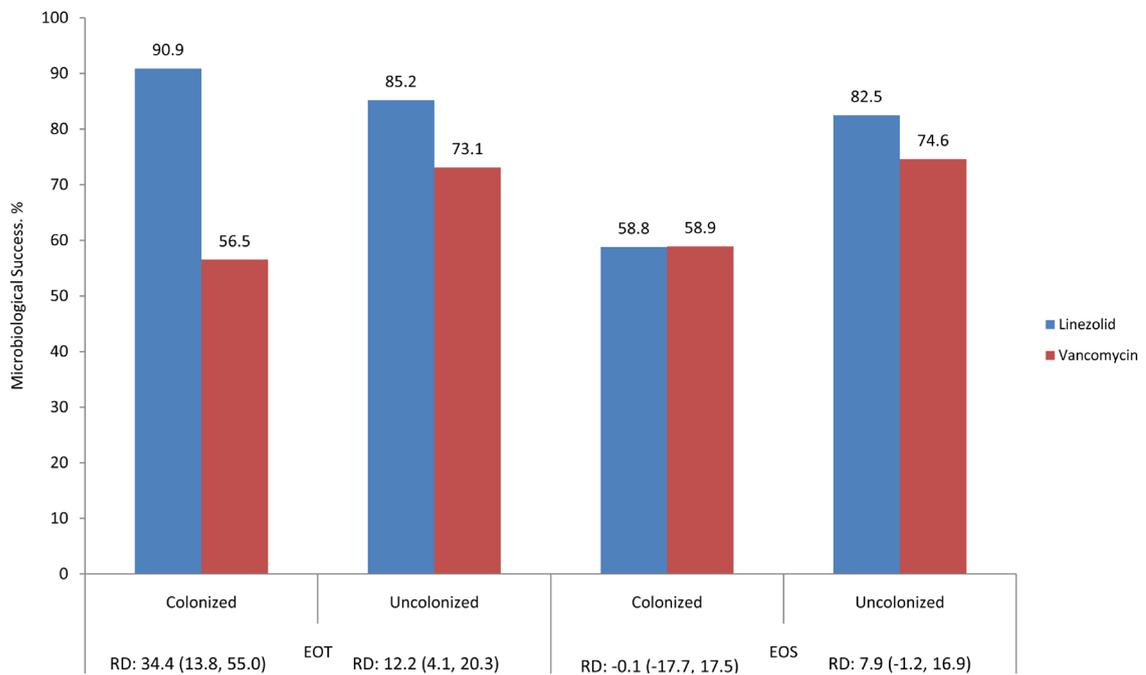


Figure 1. Microbiological success at EOT and EOS by colonization status and treatment. RD, risk difference; EOT, end of treatment; EOS, end of study.

Table 2. Predictors of MRSA colonization at end of study.

Variable	Comparisons	Odds Ratio (95% CI)
Diabetes Comorbidity	Yes vs. No	1.6 (0.9, 2.8)
Diagnosis	Abscess vs. Surgical Wound	1.4 (0.8, 2.4)
	Abscess vs. Ulcer	1.5 (0.8, 3.0)
	Abscess vs. Other	7.6 (2.2, 25.8)
Race	Black vs. Non-Black	1.9 (1.0, 3.3)
Treatment	Vancomycin vs. Linezolid	1.7 (1.1, 2.7)
Vascular	No vs. Yes	1.5 (0.9, 2.5)
Pathogen Type	MRSA Mixed vs. MRSA Only	1.6 (0.9, 2.7)
Gender	Male vs. Female	1.5 (1.0, 2.3)

In our study, there were multiple predictors of MRSA colonization at end of study including type of infection, black race, MRSA mixed infection and male gender. Previous studies have shown a higher prevalence of MRSA colonization among African Americans and those with chronic conditions which is consistent with our findings [5] [23]-[28]. Treatment with vancomycin was also identified as a predictor of MRSA colonization at end of study.

Consistent with findings of other studies, we found that, patients were colonized more frequently in the nares than the groin [4] [15]-[17]. Endogenous nasal colonization is believed to be the source for most staphylococcal diseases. However, there are a growing number of studies evaluating the frequency of non-nasal colonization [4] [15] [17]. In this study there were 16 patients that had negative MRSA cultures of the nares, but had positive MRSA cultures of the groin at EOT and 34 patients at EOS. This finding highlights the potential for non-nasal colonization as a reservoir for transmission and suggests that screening and decolonization prophylaxis should be considered for the nares and groin and other potential sites for colonization (e.g. pharynx, axilla and other re-

gions), particularly in high risk patients. There is growing evidence regarding the underestimation of MRSA colonization with a nares-only screening program and the high prevalence of non-nares MRSA colonization [4] [9] [13] [15]-[18]. A recent meta-analysis shows that approximately one third of *S. aureus* colonized patients would be missed with nasal screening alone [18].

This study has important limitations. First, this was a secondary analysis of an open label randomized clinical trial designed to assess efficacy and safety of treatment of MRSA cSSSI and not to evaluate the impact of colonization. By using existing data, some variables of interest were absent from the analysis. It would have been beneficial to have data regarding surgical interventions for the patients. Second, although the data was from a randomized control trial, we did not have the benefit of prospective randomization specific to our study hypotheses. However, we did find that the observed baseline characteristics were similar between linezolid and vancomycin treated patients for both those colonized and not colonized at EOS. Third, due to the original study design, we could only evaluate two time points for MRSA colonization status, EOT and EOS. It would have been beneficial to ascertain the patient's colonization status at time of infection to better understand the frequency of colonization conversion or lack of conversion between baseline and EOT and EOS. Fourth, we did not evaluate vancomycin trough levels and the relationship with colonization within the study cohorts. However, the original study reported the lack of correlation between vancomycin weight-based dosing and trough levels on microbiologic outcomes at EOT and EOS [19]. Finally, we did not have microbiological typing data available to determine the concordance of the colonizing strain and the infecting strain. This data would be beneficial in assessing the interplay between the infecting and carriage strain [26]-[29].

There are many decolonization strategies, including the use of topical and oral therapies for MRSA [4] [5] [11] [12]. However, these strategies can impact selection pressure in the microbiota and resistance tends to develop quickly [4] [29]. If there is an additional benefit to a therapeutic agent in both treating the infection and reducing colonization, it could be beneficial in interrupting horizontal transmission and recurrence of infection.

5. Conclusion

In this study, treatment with linezolid compared to vancomycin was associated with decreased colonization at the end of the study. By reducing carriage in patients that are infected, even if it is transient, it may reduce horizontal transmission and recurrence for that patient. Non-nasal MRSA carriage rates are important in assessing the true burden of MRSA colonization and should be considered in developing screening or decolonization strategies. Additional prospective studies evaluating the impact of MRSA colonization status on treatment and treatment impact on MRSA colonization as the primary aim are warranted.

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Disclosure Statement

KDF is an employee and shareholder of Pfizer Inc. LAP and DBH were Pfizer Inc. employees and shareholders at the time the manuscript was developed.

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