The Impact of Linezolid Versus Vancomycin on Surgical Interventions for Complicated Skin and Skin Structure Infections Caused by Methicillin-Resistant *Staphylococcus aureus*

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BACKGROUND

- Surgical intervention (SI), such as debridement of devitalized tissues and drainage of abscesses or fluid collections, is an integral component in the management of complicated skin and skin structure infections (cSSSI) in addition to antimicrobial therapy.[1,2]
- The need for additional SIs following initial source control may be postulated to contribute to a higher risk of morbidity as well as resource utilization.
- A paucity of data exists regarding the extent to which antimicrobial therapy may impact the need for additional SIs in the management of cSSSI following initial source control.
- The primary objective of this study was to explore the difference in frequency and type of SI implemented in patients treated with linezolid versus vancomycin for the management of methicillin-resistant *Staphylococcus aureus* (MRSA) cSSSI.
- The secondary objectives were to identify independent predictors of multiple SIs and to assess clinical outcomes in patients who underwent an SI.

METHODS

Study Design

- We analyzed data generated from a phase 4, randomized, open-label, controlled clinical trial comparing linezolid with vancomycin for the management of documented MRSA cSSSI.[3]
- Eligible adults (≥18 years) were randomized (1:1) to receive either linezolid 600 mg intravenously or orally q12h or vancomycin 15 mg/kg intravenously q12h (adjusted by an unblinded pharmacist based on renal function and trough concentration) for 7 to 14 days to treat a documented MRSA cSSSI.

Inclusion Criteria

- At least 2 symptoms associated with a cSSSI that involved deep tissue (purulent drainage, erythema, swelling or induration, tenderness or pain, and local warmth) and at least 1 sign of systemic infection (fever, hypotension, or elevated white blood count ≥10,000 mm^3 or >15% immature neutrophils regardless of the total white blood count).
- Patients with diabetic foot infections were considered eligible by evidence of a deep infection of the foot, ankle, or lower leg that required a surgical procedure or with an identifiable wound with evidence of purulence or erythema in more than 50% of the surface area of the foot, ankle, lower leg, or medial arch streaking.

Exclusion Criteria

- Cellulitis, necrotizing fasciitis, septic arthritis, osteomyelitis, and those with receipt of a MRSA-active antibiotic for more than 24 hours within 72 hours of enrollment.
- Aztreonam (or other antibiotic known to be inactive against Gram-positive organisms) and metronidazole were permitted for treatment of Gram-negative and anaerobic pathogens, respectively.

Clinical and Microbiologic Assessments

- Clinical and microbiologic responses were evaluated at the end of treatment (EOT) as cure, improvement, failure, or unknown. Clinical response was categorized at the end of study (EOS) visit at 6 to 28 days after the EOT as cure, failure, or unknown.
  - Classification of clinical cure required receipt of 4 or more full days of study medication, and classification of failure required 2 or more full days of study medication.
  - Clinical success was defined as the resolution of clinical signs and symptoms of infection that were identified at baseline.
  - Microbiologic success was defined as a negative MRSA culture from the original site of infection, or presumed eradication when no culture data were available, and clinical outcome was a success.
- The current analysis included the surgical intervention population (SI population) or those who received at least 1 dose of study medication, had a positive culture at screening (modified intent-to-treat [mITT] population), and underwent at least 1 SI after study start.

Surgical Intervention Assessments

- Three independent reviewers coded the surgical procedure data (BC, LAP, MJ) collected from the clinical trial to assess and categorize SI as incision/drainage, excision/debridement, surgical closure, or amputation among mITT patients.
- Data were entered and reviewed for inter-rater reliability. Any discrepancies were resolved through an independent fourth reviewer (TMD) and final categorization was unanimous among all reviewers.
- SI type and frequency were collected per patient during specific time periods as follows:
  - **SI on DO, D1, D2, and D3:** initial SI within first 72 hours of antimicrobial therapy initiation
  - **SI D0 to D3:** SI during estimate of time to reach steady-state drug concentrations
  - **SI D4 to D14:** SI during drug treatment period
  - **SI D15 to D28:** SI after the end of drug treatment to the EOS
  - **SI frequency assessment:** the incidence of at least 2 SIs was assessed to reflect additional SIs following initial source control.

Statistical Analyses

- Descriptive analyses were performed to assess equal distribution of covariates among treatment regimens. Statistical comparisons between groups were performed using the chi-square test for categorical variables and 2-sample *t* test for continuous variables with significance at $P \leq 0.05$.
- Frequencies of SIs also were tabulated for the 2 treatment groups by time and type of intervention.
- Multivariate logistic regression was used to identify factors associated with the occurrence of at least 2 SIs during D4 to D14. Several factors were considered for inclusion into the model and a final model was selected via a backward elimination process.

RESULTS

- Baseline characteristics of the mITT and SI patient populations were similar between treatment groups (**Table 1**).
- More males underwent at least 1 SI in the vancomycin group compared with the linezolid group (**Table 1**).
- The majority of patients (linezolid, 81% vs vancomycin, 83%; P=0.88) in both treatment groups underwent an initial SI within the first 72 hours of study initiation and drug commencement (**Table 1**).

Table 1. Patient Demographics of the mITT and SI Populations

	mITT Population			SI Population		
Characteristic	LZD (N=322)	VAN (N=318)	*P* Value (LZD vs VAN)	LZD (N=167)	VAN (N=156)	*P* Value (LZD vs VAN)
Male gender, n (%)[a]	183 (57)	199 (63)	0.15	96 (58)	107 (69)	0.05[b]
Mean age ± SD, y	50 ± 18	49 ± 18	0.37	48 ± 18	48 ± 17	0.86
Mean weight ± SD, kg	85 ± 27	83 ± 26	0.39	86 ± 29	87 ± 27	0.75
Race, n (%)[a]			0.71			0.75
White	238 (74)	223 (70)		121 (73)	113 (72)	
Black	47 (15)	50 (16)		28 (17)	25 (16)	
Asian	3 (1)	3 (1)		3 (2)	1 (1)	
Other[c]	34 (11)	42 (13)		15 (9)	17 (11)	
Region, n (%)[a]			0.79			0.50
United States	213 (66)	198 (62)		132 (79)	114 (73)	
Latin America	40 (12)	44 (14)		9 (5)	13 (8)	
Europe	67 (21)	74 (23)		24 (14)	28 (18)	
Asia	2 (1)	2 (1)		2 (1)	1 (1)	
Initial SI within D0 and D3, n (%)				136 (81)	129 (83)	0.88

mITT, modified intent-to-treat; LZD, linezolid; VAN, vancomycin; SI, surgical intervention; SD, standard deviation.
[a] Percentages were rounded and may not add up to 100.
[b] P=0.050.
[c] Other category was not qualified on the case report form.

- Baseline clinical characteristics of the SI population were also similar between treatment groups (**Table 2**).
- The most common comorbidity among the SI population in both treatment groups was vascular disease, with the most common infection type being abscess followed by surgical wound infection (**Table 2**).
- Average vancomycin trough concentrations of ~10 ug/mL and 12 ug/mL were reached on D3 and D7, respectively. Therefore, it appears that steady-state drug concentrations were achieved after 3 days of treatment in most patients (**Table 2**).

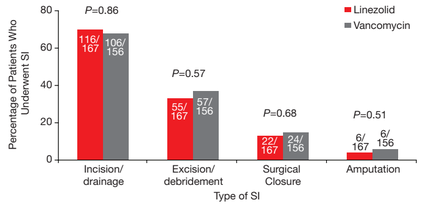
Table 2. SI Population Baseline Clinical Characteristics

Characteristic	Linezolid (N=167)	Vancomycin (N=156)	*P* Value
Comorbidities, n (%)			
Vascular disease	80 (48)	73 (47)	0.91
Diabetes	60 (36)	57 (37)	1.00
Cardiac disease	45 (27)	44 (28)	0.81
Renal insufficiency	21 (13)	20 (13)	1.00
Skin infection diagnosis, n (%)			0.86
Abscess	98 (59)	94 (60)	
Surgical wound infection	20 (12)	25 (16)	
Diabetic ulcer	21 (13)	16 (10)	
Other type of infected ulcer	10 (6)	9 (6)	
Decubitus ulcer	5 (3)	4 (3)	
Trauma wound	3 (2)	3 (2)	
Infected burn wound	4 (2)	3 (2)	
Other type of infection[a]	6 (4)	2 (1)	
Lower-extremity infection site, n (%)	84 (50)	79 (51)	0.52
MRSA only, n (%)	125 (75)	114 (73)	0.54
Polymicrobial infection, n (%)	42 (25)	42 (27)	0.54
Mean Wilson Severity Score[b] ± SD	29 ± 23	33 ± 25	0.12
Bacteremia, n (%)	4 (2)	1 (1)	0.26
Mean wound measures ± SD			
Wound depth, cm	1.7 ± 2 (n=136)	1.7 ± 2 (n=130)	0.82
Induration length, cm	8.8 ± 9 (n=163)	8.6 ± 9 (n=153)	0.82
Induration width, cm	7.8 ± 10 (n=163)	6.4 ± 6 (n=153)	0.15
Mean vancomycin trough ± SD at D3, µg/mL (n=94)		9.8 ± 7	NA
Mean vancomycin trough ± SD at D7, µg/mL (n=36)		11.8 ± 7	NA

SI, surgical intervention; SD, standard deviation; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.
[a] Other for modified intent-to-treat population included blister, bursitis, cellulitis, diabetic foot infection, erysipelas, hematoma, infected insect bite, soft tissue infection, and wound infection.
[b] Wilson severity score[4] is a validated scoring system in which baseline variables predict outcome. Points are assigned based on age, physical exam, laboratory tests, size and degree of wound involvement, presence of surgical wound infection, bacteremia, and comorbid conditions.

- There were no differences between treatment groups in the number of patients who underwent specific types of SIs (**Figure 1**).

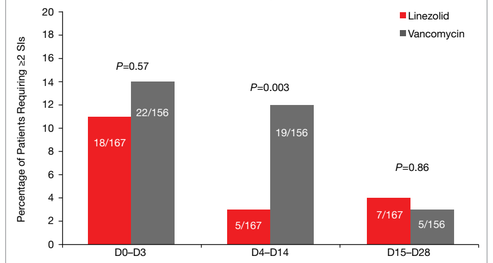
Figure 1. Surgical Interventions.



SI, surgical intervention.

- More vancomycin-treated than linezolid-treated patients required 2 or more SIs during the drug treatment period (D4–D14) (**Figure 2**).

Figure 2. Percentage of SI Population Requiring ≥2 SIs Over Study Time Period.



SI, surgical intervention.

- Treatment with vancomycin was predictive of at least 2 SIs during the treatment period (D4–D14) (**Table 3**).
- Other predictive factors of multiple SIs during the treatment period were management in the United States, extent of wound induration, lower-extremity infection, and polymicrobial infection (**Table 3**).

Table 3. Independent Predictors of ≥2 SIs During D4 to D14 (Drug Treatment Period)

Parameter	Odds Ratio	95% Confidence Interval
Vancomycin treatment	4.90	1.71 to 14.09
Polymicrobial infection	3.21	1.29 to 7.94
US region	2.87	0.99 to 8.37
Lower-extremity cSSSI	2.24	0.92 to 5.47
Degree of wound induration width	1.05	1.02 to 1.09

SI, surgical intervention; cSSSI, complicated skin and skin structure infection.

- While the clinical success rates were similar between treatment groups at the EOT (linezolid, 88% vs vancomycin, 80%; P=0.14), a greater proportion of patients achieved clinical success at the EOS when treated with linezolid versus vancomycin (linezolid, 80% vs vancomycin, 68%; P=0.04) (**Table 4**)
- A greater proportion of patients with an SI achieved microbiologic success at the EOT (linezolid, 83% vs vancomycin, 68%; P=0.004) and the EOS (linezolid, 71% vs vancomycin, 60%; P=0.05) when treated with linezolid versus vancomycin (**Table 4**).

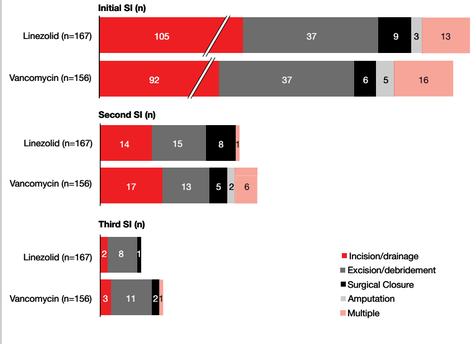
Table 4. Clinical and Microbiologic Outcomes in SI Population[a]

Parameter	Linezolid, n/N (%)	Vancomycin, n/N (%)	*P* Value
Clinical success (EOT)	126/144 (88)	111/138 (80)	0.14
Clinical success (EOS)	109/137 (80)	79/116 (68)	0.04
Microbiologic success (EOT)	120/145 (83)	94/139 (68)	0.004
Microbiologic success (EOS)	101/142 (71)	74/124 (60)	0.05[b]

EOT, end of treatment; EOS, end of study.
[a] Patients with missing responses are excluded.
[b] P=0.053.

- Frequencies of specific SIs as first, second, or third intervention are shown below (**Figure 3**).
- The most common type of initial or source control intervention in both groups was incision/drainage and/or excision/debridement (**Figure 3**).

Figure 3. SI Category and Frequency.



	P Values		
	Initial SI	Second SI	Third SI
Incision/drainage	0.495	0.457	0.675
Excision/debridement	0.792	0.846	0.480
Surgical closure	0.602	0.576	0.611
Amputation	0.490	0.232	NA
Multiple	0.560	0.059	0.483

SI, surgical intervention; NA, not applicable.

CONCLUSIONS

- An initial SI was implemented within the first 3 study days in the majority of patients, with the types of SIs being similar between treatment groups.
- Patients who received linezolid for the management of cSSSI had a lower probability of undergoing at least 2 SIs during the treatment period of 4 to 14 days (the time period during which steady-state drug concentrations are assumed to be reached) versus vancomycin-treated patients.
- In our study, the type of antibiotic received was the only modifiable predictor of increased SI rates during the drug treatment period.
- In this population of patients with MRSA cSSSI, the majority of whom underwent an initial SI within 72 hours of antibiotic initiation, linezolid was associated with a higher clinical success at the EOS as well as a higher microbiologic success rate at the EOT and EOS.

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