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ORIGINAL ARTICLE

Comparison of vancomycin and linezolid in patients with peripheral vascular disease and/or diabetes in an observational European study of complicated skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus*

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Abstract

Suboptimal antibiotic penetration into soft tissues can occur in patients with poor circulation due to peripheral vascular disease (PVD) or diabetes. We conducted a real-world analysis of antibiotic treatment, hospital resource use and clinical outcomes in patients with PVD and/or diabetes receiving linezolid or vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections (MRSA cSSTIs) across Europe. This subgroup analysis evaluated data obtained from a retrospective, observational medical chart review study that captured patient data from 12 European countries. Data were obtained from the medical records of patients $\geq$ 18 years of age, hospitalized with an MRSA cSSTI between 1 July 2010 and 30 June 2011 and discharged alive by 31 July 2011. Hospital length of stay and length of treatment were compared between the treatment groups using inverse probability of treatment weights to adjust for clinical and demographic differences. A total of 485 patients had PVD or diabetes and received treatment with either vancomycin (n = 258) or linezolid (n = 227). After adjustment, patients treated with linezolid compared with vancomycin respectively had significantly shorter hospital stays (17.9 ± 13.6 vs. 22.6 ± 13.6 days; $p < 0.001$) and treatment durations (12.9 ± 7.9 vs. 16.4 ± 8.3 days; $p < 0.001$). The proportions of patients prescribed oral, MRSA-active antibiotics at discharge were 43.2% and 12.4% of patients in the linezolid and vancomycin groups, respectively ($p < 0.001$). The reduction in resource use may result in lower hospital costs for patients with PVD and/or diabetes and MRSA cSSTIs if treated with linezolid compared with vancomycin.

Keywords: Diabetes, length of stay, length of treatment, linezolid, peripheral vascular disease, vancomycin
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Introduction

Patients with peripheral vascular disease (PVD) or diabetes are at high risk of developing complicated skin and soft-tissue infections (cSSTIs), and when they occur, these infections may be more challenging to treat [1,2]. The ability of some antibiotics to penetrate into soft tissues, especially the lower extremities, can be compromised in these patients, resulting in lower

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antibiotic concentrations at the infection site than in the plasma [3]. Vancomycin, in particular, has been shown to distribute poorly into the soft tissues of diabetic patients, which has been hypothesized as a mechanism for treatment failures [2].

The clinical impact of suboptimal vancomycin penetration into infected tissue is not well documented. Patients with vascular disease given vancomycin for culture-proven methicillin-resistant *Staphylococcus aureus* (MRSA) cSSTIs had lower clinical success rates (p 0.02) than patients receiving linezolid in a subgroup analysis of pooled data from two clinical trials [1]. In contrast, patients with diabetes mellitus given linezolid or vancomycin for culture-proven MRSA cSSTIs had similar clinical success rates in a subgroup analysis of data from three clinical trials [2].

To our knowledge, the effects of an antibiotic regimen on outcomes in patients with MRSA cSSTIs and comorbid PVD or diabetes mellitus have not been evaluated in a real-world setting. Therefore, we conducted a real-world analysis of antibiotic treatment, hospital resource use, and clinical outcomes in patients with PVD and/or diabetes receiving linezolid or vancomycin for the treatment of MRSA cSSTIs across Europe.

Materials and methods

This subgroup analysis evaluated data obtained from a retrospective, observational medical chart review study that captured patient information via 342 physicians in 12 European countries (the UK, Ireland, France, Germany, Italy, Spain, Portugal, Austria, Greece, Poland, Slovakia and the Czech Republic) [4–6]. Data were obtained from hospital records of patients aged 18 years of age or older who were hospitalized with a documented MRSA cSSTI between 1 July 2010 and 30 June 2011 and discharged alive by 31 July 2011. Patients were excluded from the study if they had suspected or proven diabetic foot infection, osteomyelitis, infective endocarditis, meningitis, joint infection, necrotizing fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection, or significant concomitant infection at other sites (e.g. bacteraemia, pneumonia). To be included in this subgroup analysis, patients had to have received MRSA-targeted therapy with vancomycin or linezolid for the full duration of antibiotic therapy, either as monotherapy or in combination with other antibiotics.

Study investigators randomly selected hospital records for review for patients meeting the enrolment criteria. Data collected included demographic and clinical characteristics, MRSA-targeted intravenous (IV) and oral antibiotic use, hospital resource use and clinical outcomes. Additionally, records of patients with MRSA cSSTIs and PVD treated with linezolid were oversampled so as to have a sufficient sample size for comparisons.

Study investigators identified patients with PVD and/or diabetes following review of the patient's medical chart. The full analysis set for this sub-study included patients with PVD, diabetes, or both. The PVD analysis set included only patients with PVD, regardless of whether or not they had diabetes. The lower extremity cSSTI analysis set included all of the patients in the PVD analysis set who had a lower extremity cSSTI (foot, toes, leg or groin).

The primary outcome was hospital length of stay (LOS; total and by type of hospital unit). Secondary outcomes included MRSA-targeted antibiotic length of treatment (LOT; total and IV) and number of cSSTI-associated surgical procedures required during hospitalization. Clinical response at discharge was evaluated and defined as cure (resolution of all signs and symptoms/improvement to such an extent that further antimicrobial therapy was not necessary), improvement (improvement in signs and symptoms), failure (persistence, incomplete clinical resolution, or worsening in signs and symptoms), or indeterminate (inability to determine an outcome).

The primary study comparison was between vancomycin- and linezolid-treated patients. Inverse probability of treatment weights based on propensity scores were used to adjust for demographic and clinical differences between patients receiving these antibiotics. Variables used to construct the inverse probability of treatment weights included patient demographics (age, gender, race, body mass index, smoking history, intravenous drug abuse, alcohol use), clinical characteristics (diagnoses (PVD, diabetes, or both), comorbid conditions, cSSTI type, cSSTI source, cSSTI location, co-infection, MRSA infection within the past 12 months, previous MRSA infection, time to MRSA-targeted therapy), and hospital characteristics (type of hospital, location, early discharge protocol, discharge physician type). Weighted groups were compared using Pearson's chi-square test for categorical or ordinal characteristics and a *t* test for continuous characteristics. All inferences were made assuming a two-sided test with an α 0.05.

Results

The parent study cohort included a total of 1542 patients with a documented MRSA cSSTI (Fig. 1). This subgroup analysis included data from 485 patients with a documented MRSA cSSTI and PVD and/or diabetes treated with linezolid or vancomycin for the full duration of therapy.

Patients with PVD and/or diabetes

A total of 258 patients received vancomycin and 227 patients received linezolid. Although differences in demographic and

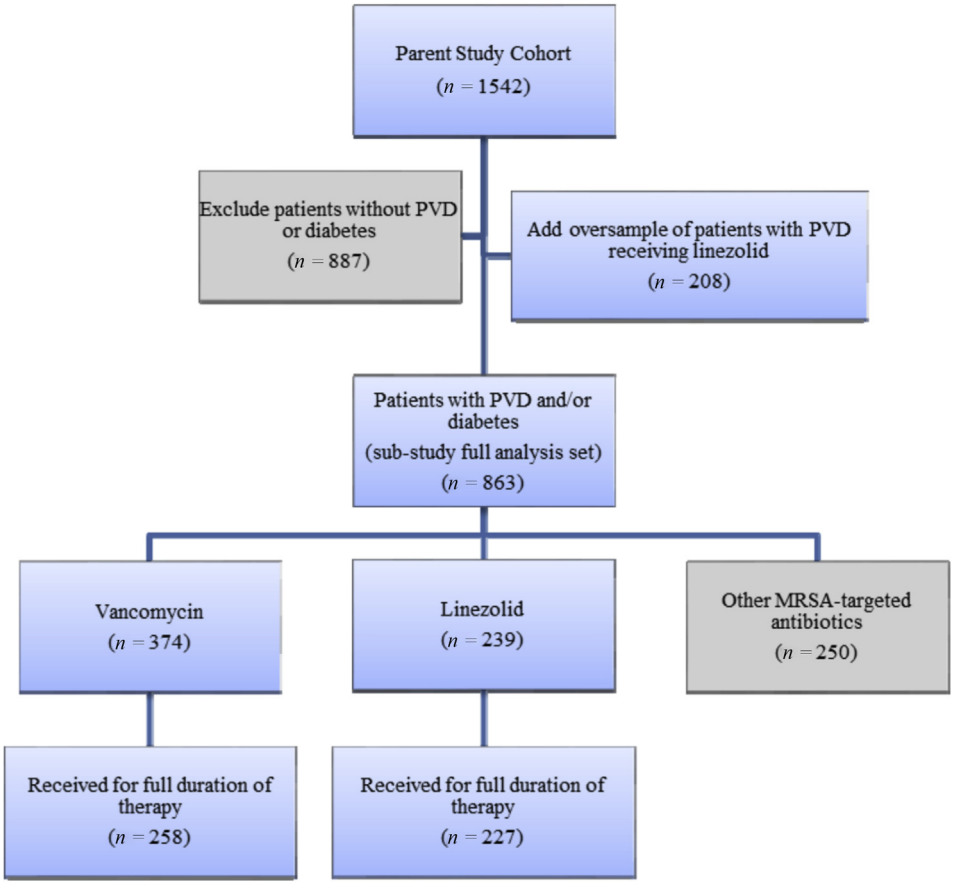

FIG. 1. Cohort selection for patient subgroup with methicillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft-tissue infections and peripheral vascular disease (PVD) and/or diabetes.

clinical characteristics between these two treatment groups were identified (Table 1), they were not statistically significant after propensity-score-based weights were applied.

Overall hospital LOS was more than 4 days shorter in linezolid-treated patients (17.9 ± 13.6 days) compared with vancomycin-treated patients (22.6 ± 13.6 days) with MRSA cSSTIs and PVD and/or diabetes ($p < 0.001$; Fig. 2). The difference in hospital LOS was driven primarily by a significant reduction in general ward LOS in linezolid-treated patients (13.9 days) compared with vancomycin-treated patients (18.2 days) ($p < 0.001$). Additionally, both total ($p < 0.001$) and IV ($p < 0.001$) LOT, respectively, were >3 days shorter in linezolid-treated patients (12.9 ± 7.9 days and 12.7 ± 7.8 days) compared with vancomycin-treated patients (16.4 ± 8.3 days and 16.4 ± 8.4 days) (Fig. 3).

Although significantly more patients receiving linezolid (46.2%) than vancomycin (34.6%) underwent any surgical procedure (p 0.009), the number of procedures per patient was not significantly different between groups (p 0.069). Clinical success rates at discharge (defined as cure or improvement) were >99% in both groups.

Patients with PVD, with or without diabetes

Of the 485 patients with PVD and/or diabetes, 300 patients had PVD and received either vancomycin (n = 134) or linezolid (n = 166) therapy for the full duration of treatment. Significant between-group differences existed for age, prevalence of comorbid diabetes, Charlson Comorbidity Index, cSSTI source, prevalence of co-infection, previous MRSA infections, hospital type and location, discharge physician type, and prevalence of severe sepsis before propensity-score weighting. Only the prevalence of comorbid diabetes (vancomycin 43.1%, linezolid 31.6%; p 0.039) and prevalence of severe sepsis (vancomycin 15.6%, linezolid 6.3%; p 0.010) remained unbalanced between treatment groups following propensity-score weighting.

Hospital LOS was >4 days shorter in linezolid-treated patients (17.5 ± 12.3 days) compared with vancomycin-treated patients (22.1 ± 14.0 days) with PVD (p 0.002; Fig. 4). Similarly, linezolid-treated patients compared with vancomycin-treated patients respectively had shorter antibiotic LOT (13.6 ± 8.2 vs. 16.1 ± 7.6 days; p 0.006) and IV LOT (13.3 ± 8.2 vs. 16.1 ± 7.7 days; p 0.003). Total LOT and IV LOT were similar in both groups, with a few patients switching from IV to

TABLE 1. Demographic and clinical characteristics of patients with peripheral vascular disease and/or diabetes by methicillin-resistant *Staphylococcus aureus*-targeted antibiotic received (unweighted)

Characteristics	Vancomycin (n = 258)	Linezolid (n = 227)	p
Male, %	58.5	60.8	0.612
Age at hospital admission, years, mean ± SD	65.7 ± 12.7	64.2 ± 13.9	0.202
Body mass index, %			0.039
<18.5 kg/m^2 (underweight)	2.3	0.4	
18.5–24.9 kg/m^2 (normal)	22.5	22.9	
25–30 kg/m^2 (overweight)	36.4	30.8	
>30 kg/m^2 (obese)	15.5	12.0	
Undocumented	23.3	33.9	
Intravenous drug abuse, %	3.9	4.4	0.770
Diagnosis, %			<0.001
Diabetes	48.1	26.9	
Peripheral vascular disease	26.4	52.0	
Both	25.6	21.1	
Charlson comorbidity index, %			0.286
1	21.3	27.3	
2	24.8	24.2	
≥3	53.9	48.5	
cSSTI, type %			0.041
Infected wound or ulcer	31.8	35.2	
Deep/extensive cellulitis	22.1	22.9	
Major abscess	19.0	12.8	
Surgical site infection	13.2	8.4	
Posttraumatic wound infection	11.6	14.1	
Infected burn	2.3	6.6	
cSSTI, site %			0.015
Lower extremity	67.1	56.4	
Torso/abdomen	23.6	25.5	
Upper extremity	7.0	12.3	
Head/skull/neck	2.3	5.7	
Severe sepsis, %	22.5	10.6	<0.001

Abbreviation: cSSTI, complicated skin and soft-tissue infection; SD, standard deviation.

oral therapy during hospitalization (one patient in the vancomycin group and seven patients in the linezolid group). However, of the 227 patients who received IV linezolid while hospitalized, 98 (43.2%) received an oral, MRSA-active discharge antibiotic, of which 80 (81.6%) were linezolid. In contrast, of the 258 patients receiving vancomycin while hospitalized, only 32 (12.4%) received a discharge prescription for an oral, MRSA-active antibiotic (p < 0.001).

A similar proportion of patients receiving linezolid (36.6%) and vancomycin (36.6%) underwent a surgical procedure (p 0.736); the number of procedures per patient did not differ between the linezolid (1.1 procedures) and vancomycin (1.1 procedures) treatment groups (p 0.346). Clinical success rates also did not differ between groups (p 0.773).

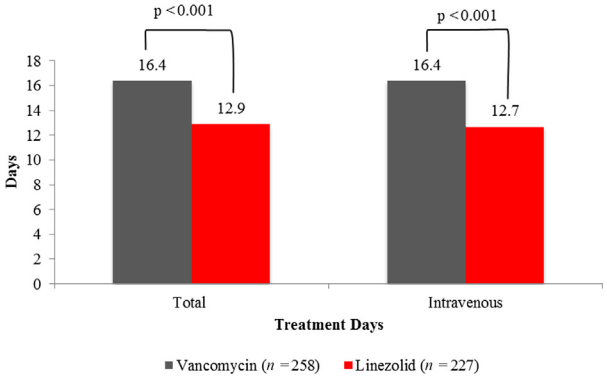

FIG. 3. Total and intravenous length of treatment in patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections and peripheral vascular disease and/or diabetes receiving vancomycin or linezolid (propensity-score weighted).

Patients with PVD and a lower extremity MRSA cSSTI, with or without diabetes

Of the 300 patients with PVD, 198 (66%) had a lower extremity cSSTI and received either vancomycin (n = 94) or linezolid (n = 104) for the full duration of therapy. Before weighting,

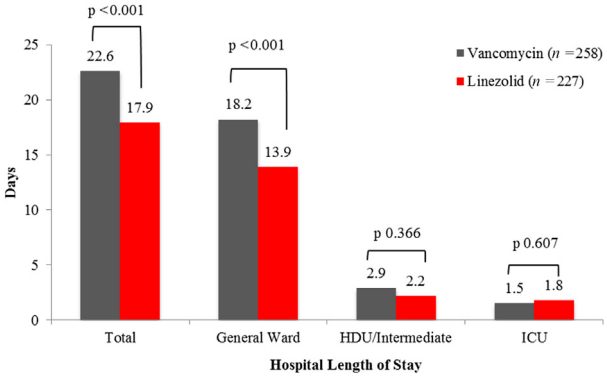

FIG. 2. Hospital length of stay in patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections and peripheral vascular disease and/or diabetes receiving vancomycin or linezolid (propensity-score weighted). HDU, high-dependency unit; ICU, intensive care unit.

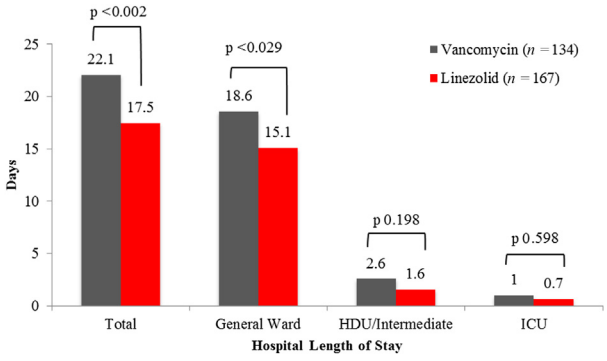

FIG. 4. Hospital length of stay in patients with methicillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections and peripheral vascular disease receiving vancomycin or linezolid (propensity-score weighted). HDU, high dependency unit; ICU, intensive care unit.

there were significant between-group differences in the prevalence of comorbid diabetes, Charlson Comorbidity Index, cSSTI source, prevalence of co-infection, previous MRSA infections, hospital type and location, discharge physician type and prevalence of severe sepsis. Only the prevalence of severe sepsis (vancomycin 14.5%, linezolid 4.1%; p 0.012) remained unbalanced between treatment groups after weighting.

Hospital LOS was numerically shorter in linezolid-treated patients (17.8 ± 14.0 days) compared with vancomycin-treated patients (20.3 ± 11.6 days) with PVD and a lower extremity MRSA cSSTI (p 0.171); LOS by type of hospital unit did not differ significantly between groups. Both total (p 0.215) and IV LOT (p 0.179), respectively, were not significantly different between patients receiving linezolid (13.7 ± 9.6 and 13.5 ± 9.8 days) and those receiving vancomycin (15.1 ± 6.3 and 15.0 ± 6.4 days).

There was no difference in the proportion of patients requiring surgery (p 0.736) or the number of surgeries per patient (p 0.985) between linezolid-treated and vancomycin-treated patients with PVD and a lower extremity MRSA cSSTI (data not shown).

Discussion

Among patients hospitalized with an MRSA cSSTI and PVD or diabetes, hospital LOS and LOT were over 4 days and 3 days shorter, respectively, in patients who received linezolid compared with vancomycin. Patients who received linezolid were over three times more likely to be discharged with an oral MRSA-active antibiotic, which suggests that patients in the linezolid group were discharged earlier to complete oral therapy at home, whereas patients receiving vancomycin remained in the hospital until the course of therapy was completed.

Evidence from clinical trials enrolling patients with MRSA cSSTIs suggests poorer outcomes in patients with PVD and/or diabetes mellitus compared with patients without these conditions [1,2]. Among patients with these comorbidities, the effects of antibiotic selection on outcomes in patients with MRSA cSSTIs had not been evaluated in a real-world study. We found that patients with PVD and/or diabetes treated with linezolid compared with vancomycin for an MRSA cSSTI had a 3-day shorter LOT and 4-day shorter hospital LOS, but similar rates of clinical cure or improvement, after adjusting for patient demographic and clinical characteristics using propensity-score weights. The clinical cure rates at discharge in both groups were 100% and 99.4%, much higher than those from clinical trials with cSSTIs due to MRSA [2]. These very high rates of clinical cure may have been influenced by the fact that many patients in this retrospective review have been treated in hospital until they clinically improved or they were cured. This is reflected by the long overall LOS. Moreover, patients who died in the hospital were excluded. The number of surgical procedures required was similar for vancomycin-treated and linezolid-treated patients. Similar results were seen when the analysis was limited to patients with PVD but not when we limited the population to those with PVD and lower extremity infection. The non-significant decrease in LOT and LOS in patients with PVD and lower extremity infection between the linezolid and vancomycin treatment groups could be explained by a loss of power when comparing differences within this smaller subgroup.

One component essential to the successful treatment of MRSA cSSTIs is attainment of pharmacologically active antibiotic concentrations at the site of infection [7]. Suboptimal antibiotic tissue concentrations in infected tissue are hypothesized to be an important cause of treatment failure. Impairment of drug penetration into infected tissue was observed for many types of infections including SSTIs [8]. Analysis of tissue penetration studies is complicated by differences in methods used to measure tissue penetration. For example, studies using skin blister fluid sampling and tissue biopsy specimens provide information on total drug concentrations whereas *in vivo* microdialysis studies provide information on only unbound drug. As only unbound and not bound drug is pharmacologically active, only study results using unbound drug concentrations are summarized below.

Vancomycin concentrations were lower in tissue than in plasma in a study conducted in patients following cardiac surgery [3]. Tissue concentrations were even lower in patients with compared with those without diabetes. In this study, vancomycin tissue concentrations were determined using *in vivo* microdialysis in six patients with and six patients without diabetes following cardiac surgery. Patients received vancomycin at a dose of 80–120 mg/h; tissue concentrations were measured on day 8 ± 4 of treatment. Vancomycin tissue concentrations in both patients with and without diabetes were lower than plasma concentrations. Vancomycin tissue concentrations were lower in patients with diabetes than those without. The authors speculated that insufficient tissue concentrations could contribute to treatment failure and antimicrobial resistance in patients with diabetes. Other proposed mechanisms for impaired tissue penetration in patients with diabetes include changes in vancomycin plasma protein binding [3] and local and systemic inflammation [9].

In contrast, there appears to be little difference between linezolid tissue and plasma concentrations in patients with diabetes [10,11]. Linezolid steady-state tissue concentrations determined using *in vivo* microdialysis in three patients with

diabetes and severe bacterial lower limb infections were similar to plasma and bone concentrations within 1 h of initiating a linezolid infusion, indicating rapid and complete linezolid penetration into the interstitial space [10]. Inflammation did not influence the linezolid interstitial concentration in soft tissue. Linezolid steady-state tissue concentrations determined using *in vivo* microdialysis in nine patients with diabetes and chronic lower limb infections were similar in infected and healthy subcutaneous tissue [11]. Penetration ratios (area under the curve $(AUC)_{tissue}$/free AUC_{plasma}) were similar for healthy thigh tissue (1.42) and wound tissue (1.27; p 0.648). One additional study using microdialysis reported lower linezolid tissue concentrations compared with plasma concentrations [12]. However, this study was not conducted at steady state.

Results from the vancomycin [3] but not the linezolid [10,11] microdialysis studies suggest the possibility of suboptimal drug concentrations at the site of infection in patients with MRSA cSSTIs and diabetes. Because of the retrospective nature of this study, we were not able to evaluate the effect of vancomycin MIC on outcome. Lower vancomycin tissue concentrations could have more of an effect in patients with MRSA isolates that have a MIC greater than 1–2 mg/L. Study results suggest that even small increases in vancomycin MICs can affect clinical efficacy [13]. Future studies should evaluate the effect of vancomycin MICs on clinical outcomes in patients with MRSA cSSTIs and PVD and/or diabetes.

In addition to those described above, limitations of this study include the inclusion of only hospitalized patients and the exclusion of patients who died in the hospital. These selection criteria were essential for the parent study, which aimed to identify opportunities for early switch from IV to oral antibiotics (so necessitating the inclusion of only hospitalized patients) and early hospital discharge (so requiring the inclusion of only patients discharged alive) among patients with MRSA cSSTIs. As a result of the oversampling of patients with PVD receiving linezolid, the results of the study do not reflect practice patterns related to drug selection in the countries studied. Finally, information about adjunctive therapies such as wound dressings and use of hyperbaric oxygen was not collected, and could have influenced outcomes if these therapies were used more frequently in one of the groups. In addition, we did not evaluate the timing of surgical procedures in relation to the initiation of antibiotic therapy, and we are therefore unable to determine whether the greater proportion of patients undergoing surgical procedures in the vancomycin group can be attributed to failure of antibiotic therapy.

In conclusion, patients with MRSA cSSTIs and PVD and/or diabetes receiving linezolid compared with vancomycin experience a shorter LOT and hospital LOS, which may ultimately lead to a reduction in hospital costs.

Transparency declaration

C. Eckmann has received lecture fees, travel support for attending meetings and fees for advisory boards from Bayer, AstraZeneca, Cubist, Durata and Pfizer. D. Nathwani has received lecture fees, travel support for attending meetings and fees for advisory boards from Astellas, Astra-Zeneca, Bayer, Cubist, Durata, Medicines Company, Biomerieux & Pfizer Inc. He has received no fees in relation to this manuscript. W. Lawson has received travel support for attending meetings and fees for advisory boards from Astellas and Pfizer. S. Corman, C. Solem, and J. Stephens are employees if Pharmerit International, who were paid consultants to Pfizer in connection with this study. C. Macahilig is an employee of Medical Data Analytics, a subcontractor to Pharmerit International for this project. J. Li, C. Charbonneau, N. Baillon-Plot, and S. Haider are employees of Pfizer.

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