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The Effects of Obesity on the Comparative Effectiveness of Linezolid and Vancomycin in Suspected Methicillin-Resistant *Staphylococcus aureus* Pneumonia

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Abstract

Background: Methicillin-Resistant Staphylococcus aureus (MRSA) has become a leading cause of pneumonia in the United States and there is limited data on treatment outcomes in obese patients.We evaluated the effectiveness of linezolid compared to vancomycin for the treatment of MRSA pneumonia in a national cohort of obese Veterans.

Methods: This retrospective cohort study included obese patients (body mass index ≥ 30) admitted to Veterans Affairs hospitals with MRSA-positive respiratory cultures and clinical signs of infection between 2002 and 2012. Patients initiating treatment with either vancomycin or linezolid, but not both, were selected for inclusion. Propensity matching and adjustment of Cox proportional hazards regression models quantified the effect of linezolid compared with vancomycin on time to hospital discharge, intensive care unit discharge, 30-day mortality, inpatient mortality, therapy discontinuation, therapy change, 30-day readmission, and 30-day MRSA reinfection. We performed sensitivity analyses by vancomycin Minimum Inhibitory Concentrations (MICs) and true trough levels.

Results: We identified 101 linezolid and 2,565 vancomycin patients. Balance in baseline characteristics between the treatment groups was achieved within propensity score quintiles and between propensity matched pairs (76 pairs). No significant differences were observed for the outcomes assessed. Among patients with vancomycin MICs of ≤ 1 μg/mL, the linezolid group had a significantly lower mortality rate, increased length of hospital stay, and longer therapy duration. There were no differences between the linezolid and vancomycin MICs of ≥ 1.5 μg/mL groups. Clinical outcomes among those with vancomycin trough concentrations of 15-20 mg/L were similar to patients treated with linezolid.

Conclusions: In our real-world comparative effectiveness study among obese patients with suspected MRSA pneumonia, linezolid was associated with a significantly lower mortality rate as compared to the vancomycin-treated patients with lower vancomycin MICs. Further studies are needed to determine whether this beneficial effect is observed in other study populations.

Keywords: Comparative effectiveness; Linezolid; Methicillin-resistant *Staphylococcus aureus* (MRSA) Pneumonia; Obesity; Vancomycin

Abbreviations: BAL: Bronchoalveolar Lavage; BMI: Body Mass Index; CI : Confidence Interval; HR: Hazard Ratio; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; ICU: Intensive Care Unit; MIC: Minimum Inhibitory Concentrations; MRSA: Methicillin-Resistant *Staphylococcus aureus*; US: United State

Introduction

Methicillin-Resistant *Staphylococcus aureus* (MRSA) is one of the most prevalent, pathogenic antimicrobial-resistant organisms, causing invasive infections worldwide [1]. MRSA has become a leading cause of pneumonia in both healthcare and community settings [2,3]. Furthermore, approximately 69% of adults in the United States (US) are either overweight or obese [4], which is concerning as obesity is an independent risk factor for developing pneumonia [5,6].

Limited treatment options exist for patients with MRSA pneumonia, and for many years, vancomycin, a glycopeptide antibiotic that inhibits Gram-positive bacterial cell wall synthesis by binding a D-alanyl-D-alanine cell wall precursor that is essential for peptidoglycan cross-linking, has served as the standard of care [7-9]. However, over time, clinical outcomes among vancomycin-treated patients with MRSA pneumonia have worsened [10]. In addition, the use of the vancomycin in MRSA pneumonia has been questioned due to poor penetration into alveolar fluid and the emergence of bacteria with decreased vancomycin susceptibility [2,7,10]. These limitations have prompted the need for additional therapeutic options. Linezolid, an oxazolidinone antibiotic that inhibits protein synthesis at the 50S ribosome, is recommended for the treatment of pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains) bacteria [11]. While linezolid has been shown to achieve high lung concentrations, there is limited evidence to support clinical superiority over vancomycin [10,12-15]. Moreover, the optimal treatment in obese patients is largely unknown.

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Obesity is associated with an increased risk of pneumonia [5,6]. Decreased immunity, a higher risk of aspiration, reduced lung volume, and an altered ventilation pattern, impact pneumonia risk in obese patients [5,6]. Furthermore, obesity itself is an independent predictor of antibiotic treatment failure [16]. To date, there is no published research comparing linezolid and vancomycin in obese patients with MRSA pneumonia in the real-world clinical setting. Due to the increasing complexity of treating MRSA pneumonia, controversial superiority data, and the scarcity of data in the obese, we sought to evaluate the effectiveness of linezolid therapy compared to vancomycin for the treatment of suspected MRSA pneumonia in a national cohort of obese Veterans.

Materials and Methods

Data sources

The Veterans Health Administration has utilized an electronic medical record system since 1999 [17]. Our study included national standardized databases capturing patient care including International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes, microbiology results, pharmacy records for prescriptions and barcode administration, laboratory results, vital status, and vital signs.

Study population

We conducted a national retrospective cohort study quantifying the effectiveness of linezolid compared to vancomycin among obese patients with suspected MRSA pneumonia. We identified hospital in patients with positive MRSA cultures from a pulmonary site between January 1, 2002 and December 1, 2012. Patients exposed to at least 1 day of therapy with linezolid (intravenous or oral) or vancomycin (intravenous only) were selected for inclusion. Next we identified all obese patients with a body mass index (BMI) ≥ 30 [18]. BMI calculations were based on the most recent height and weight measurements within a year of treatment initiation. Additionally, we included patients initiating linezolid or vancomycin therapy within a window of 3 days prior to culture through 4 days after culture with an absence of linezolid or vancomycin therapy in the 7 days prior to treatment initiation.

Of the patients with culture-positive MRSA treated with either linezolid or vancomycin, an additional inclusion criterion included clinical signs of infection based on the presence of a chest x-ray, or a fever, or an elevated white blood cell count [3,19]. Each clinical sign was assessed between the admission date and treatment initiation date. Fever was defined as a temperature ≥ 100.4^{0}F. An elevated white blood cell count was defined as ≥10,000/mm^3. We excluded patients who died or were discharged within 2 days of treatment initiation and patients exposed to more than 2 consecutive days of other antibiotic therapy with activity against MRSA (clindamycin, daptomycin, doxycycline, linezolid, minocycline, tigecycline, trimethoprim/sulfamethoxazole, vancomycin) in the 3 days prior to or during treatment with linezolid or vancomycin. Only the first admission within the study period meeting all inclusion and exclusion criteria was included. The purpose of the exclusion criteria were three-fold, to identify patients: (1) with clinical signs of infection in addition to a positive culture, (2) who were still in the hospital the day after treatment initiation, and (3) treated with monotherapy.

Outcomes

The primary outcome of interest was time to hospital discharge. Therapy initiation was used to define the index date of treatment. Time calculations were made from the index date to the event date for each endpoint. The secondary endpoints of interest included time to Intensive Care Unit (ICU) discharge, 30-day mortality, inpatient mortality, therapy discontinuation, therapy change, 30-day readmission, and 30-day MRSA reinfection. For hospital discharge, patients who died during the admission were censored on their date of death. Transfer out of an ICU was assessed among patients initiating linezolid or vancomycin therapy in the ICU.

Antimicrobial drug exposures with activity against MRSA were assessed for each patient during the admission. These exposures were classified into dichotomous variables based on the class of the antimicrobial agent and by the duration of receipt of agents in each class. Therapy change was defined as discontinuation of linezolid or vancomycin and initiation of another agent with anti-MRSA activity. As such, therapy change could have included switching from linezolid to vancomycin, switching from vancomycin to linezolid, or switching from either linezolid or vancomycin to another anti-MRSA antibiotic (listed above). Switching an antibiotic (i.e. linezolid) from an intravenous to an oral route was not considered a therapy change. Clinical rationale for therapy change, such as de-escalation resulting from clinical improvement or change in therapy as a result of failure was not ascertained. For 30-day readmission to a VA medical unit and 30-day MRSA reinfection, patients who died after discharge were censored on their date of death. The end of the follow-up period was December 31, 2012.

Statistical analysis

To assess baseline differences between the two study groups, we utilized a Fisher's exact or χ^2 test for categorical data. For continuous variables of interest, we used a t-test for normally distributed data and the non-parametric Wilcoxon Rank Sum test was used otherwise. We employed propensity score methods, where the predicted probability of treatment with linezolid was derived from an unconditional logistic regression model using a manual backward, non–computer-generated, elimination approach [20-22]. Propensity score stratification and matching within propensity score calipers were implemented, related assumptions were assessed, and subsequent covariate balance was reviewed [20,21].

In the second stage of modeling, we used Cox proportional hazards regression models to quantify the effect of linezolid treatment in obese patients with MRSA pneumonia compared to vancomycin on the aforementioned outcomes. We further evaluated Cox proportional hazards model assumptions, including that of proportionality, with formal tests and graphical displays [23]. If the confidence interval of the hazard ratio included one, then the clinical outcome occurred at comparable rates in both the linezolid and vancomycin groups. A hazard ratio greater than one indicated an increased probability of the event occurring sooner in the linezolid group compared to the reference vancomycin group. In terms of the study outcomes, a hazard ratio greater than one would represent a higher mortality rate, decreased length of stay, or a higher readmission rate among patients treated with linezolid. Alternatively, a hazard ratio less than one would mean time to mortality was lower and length of stay was higher in the linezolid group as compared to vancomycin.

We conducted subgroup analyses among patients with morbid obesity (BMI ≥ 40) and with positive Bronchoalveolar Lavage (BAL) cultures. Additionally, we assessed the study outcomes among a restricted study population of those with a pneumonia-related diagnosis

code present during the hospital admission (ICD-9-CM codes 003.22, 020.3, 020.4, 020.5, 021.2, 022.1, 031.0, 039.1, 052.1, 055.1, 073.0, 083.0, 112.4, 114.0, 114.4, 114.5, 115.05, 115.15, 115.95, 130.4, 136.3, 480-486, 513.0, 517.1) [24].

We also performed several sensitivity analyses. First, we assessed linezolid effectiveness as compared to patients with vancomycin minimum inhibitory concentrations (MICs) of ≤ 1 μg/mL and those with vancomycin MICs of ≥ 1.5 μg/mL. Second, we assessed linezolid effectiveness as compared to patients with true vancomycin trough concentrations of 15-20 mg/L and no evidence of acute kidney injury (defined as an increase in serum creatinine of 0.3 mg/dL or 50% prior to starting vancomycin) [25]. True vancomycin troughs were defined as levels obtained at steady state, with at least 3 vancomycin doses before the level, that were taken less than 2 hours before the next vancomycin dose or within 2 hours of the average interval between the two prior vancomycin doses [25]. Only the first trough level after the third vancomycin dose which met our steady state definition was assessed. We did not assess change in vancomycin dosing based on trough results. All analyses were performed using SAS (SAS Institute Inc., Cary, NC,Version 9.3).

Results

We identified 2,666 obese patients with suspected MRSA pneumonia who met our inclusion and exclusion criteria (Figure 1). There were 2,565 (96.2%) patients in the vancomycin group and 101 (3.8%) in the linezolid group. Among those treated with linezolid, approximately 91% (n=92) were dosed twice daily. The mean patient age at the time of culture collection was 66 years for linezolid and 68 years for vancomycin (Table 1). Several statistically significant differences in the frequency of current comorbidities, present during the suspected MRSA pneumonia admission, were observed, including chronic ulcer, dialysis, rheumatoid arthritis, and cerebrovascular disease. Medical histories in the year prior to the suspected MRSA pneumonia hospitalization, including pneumonia, osteomyelitis, and allergy to vancomycin, differed significantly between the treatment groups. Patients in the linezolid group had higher utilization of linezolid in the 90 days prior to the suspected MRSA pneumonia hospitalization (Table 2). Furthermore, surgical procedures in the previous 90 days and MRSA bronchial culture sites were more common in the linezolid group compared to the vancomycin group.

Though differences in baseline variables were observed between the treatment groups, balance was achieved within propensity score quintiles and between propensity matched pairs (linezolid=76, vancomycin=76). In propensity score quintile adjustment, quintile I served as the reference. Propensity score matching was achieved within 0.001 caliper. The propensity score model can be found in the footnote of Table 3. This model demonstrated excellent discrimination between the treatment groups (C-statistic 0.84) [22].

The median time to discharge was 15 days (interquartile range [IQR] 7-30) among linezolid-treated patients versus 12 days (IQR 7-23) in vancomycin-treated patients. Time to discharge was significantly longer in the linezolid group compared to the vancomycin group in the unadjusted analysis (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.60-0.96) and non-significantly longer in propensity adjusted (HR 0.85, 95% CI 0.66-1.08) and propensity matched analyses (HR 0.96, 95% CI 0.56-1.65; Table 3). The inpatient mortality (28%) and 30-day mortality (28%) rates were high but similar between treatment groups among this obese cohort with positive MRSA pulmonary cultures. No significant differences were observed in unadjusted, adjusted, or matched Cox proportional hazards models for time to ICU discharge, 30-day mortality, inpatient mortality, therapy discontinuation, therapy change, 30-day MRSA pneumonia reinfection, or 30-day readmission.

Results similar to the overall cohort were observed in subgroup analyses among morbidly obese patients (BMI ≥ 40; linezolid n=29, vancomycin n=562) and those with positive BAL cultures (linezolid n=13, vancomycin n=165). Time to hospital discharge in the morbidly obese was significantly longer in the linezolid group in the unadjusted (HR 0.50, 95% CI 0.32-0.79) and propensity adjusted (HR 0.51, 95% CI 0.32-0.81) analyses and non-significant in propensity matched analyses (HR 0.50, 95% CI 0.15-1.66). No significant differences were observed for the other outcomes or by BAL subgroup. Regarding the subgroup analysis among patients with a pneumonia diagnosis code (linezolid n=67, vancomycin n=1,612), patients treated with linezolid demonstrated a significantly lower rate of therapy discontinuation (propensity matched HR 0.42, 95% CI 0.20-0.87) compared to patients treated with vancomycin, indicating length of therapy was longer in the vancomycin group.

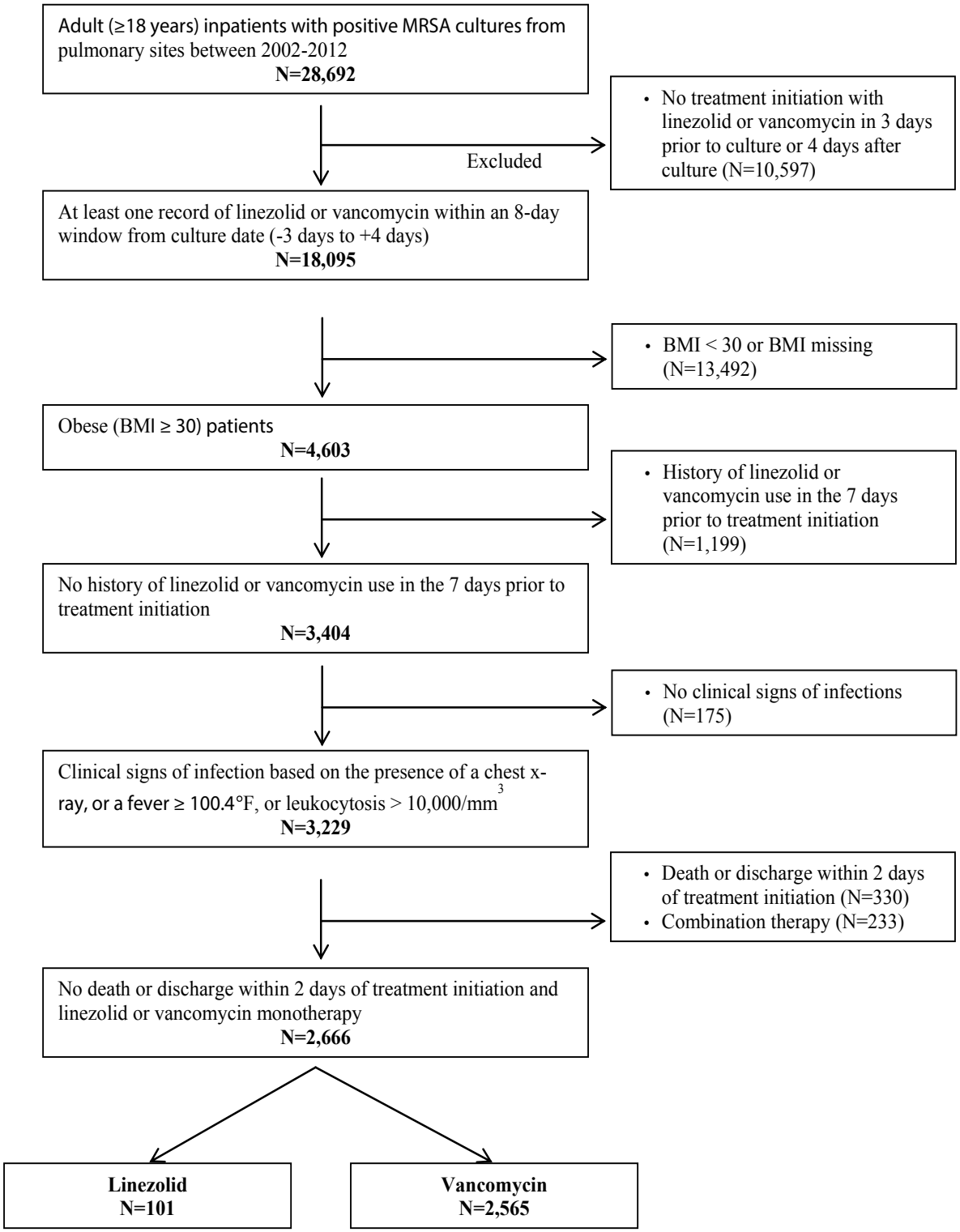
Among the vancomycin group, we identified 984 eligible patients (38%) for the sensitivity analyses evaluating effectiveness by vancomycin MICs. Of them, 85% (n=833) had vancomycin MICs ≤ 1 μg/mL, 1% (n=10) had a MIC=1.5 μg/mL, 14% (n=141) had a MIC=2 μg/mL, and no patients had MICs > 2 μg/mL. Patients on linezolid showed significantly lower rates of 30-day mortality (Table 4; propensity matched HR 0.35, 95% CI 0.14-0.90) and therapy discontinuation (propensity matched HR 0.49, 95% CI 0.27-0.87) than those with vancomycin MICs of ≤ 1 μg/mL, meaning linezolid patients had longer survival in the 30 days after discharge and a longer duration of therapy than vancomycin patients with MICs of ≤ 1 μg/mL. Time to hospital discharge was significantly longer in the linezolid group compared to the vancomycin group with MICs of ≤ 1 μg/mL (unadjusted HR 0.69, 95% CI 0.54-0.89; propensity adjusted HR 0.72, 95% CI 0.55-0.93; and propensity matched HR 0.52, 95% CI 0.29-0.93).

Only 12% (n=301) of vancomycin patients had accurately obtained through concentrations without evidence of acute kidney injury. In sensitivity analyses among these patients with vancomycin trough levels obtained at steady state, 19% (n=58) had therapeutic trough concentrations less than 10 mg/L, 29% (n=86) had 10-15 mg/L, 22% (n=66) had 15-20 mg/L, and 30% (n=91) had greater than or equal to 20 mg/L. All clinical outcomes were similar among linezolid patients as compared to vancomycin patients with vancomycin trough concentrations between 15-20 mg/L.

Discussion

To our knowledge, this is the first real-world comparative effectiveness study assessing linezolid and vancomycin for the treatment of suspected MRSA pneumonia in obese patients. Rates of hospital discharge, ICU discharge, 30-day mortality, inpatient mortality, therapy discontinuation, therapy change, 30-day MRSA pneumonia reinfection, and 30-day readmission did not differ significantly between linezolid and vancomycin in our study.

Our results agree with a recently published analysis of two linezolid clinical trials in which clinical success and microbiologic success were similar across all quartiles of weight in patients with nosocomial MRSA pneumonia [26]. This appears to be the only other study evaluating clinical outcomes among obese MRSA pneumonia patients treated with linezolid or vancomycin. Additionally, our findings are consistent with previous research comparing linezolid and vancomycin in non-obese



MRSA: Methicillin-Resistant *Staphylococcus*; BMI: Body Mass Index

Figure 1: Study Cohort Identification

Demographic characteristics	Linezolid N=101	Vancomycin N=2,565	P-value
Age (years)	66.2 ± 12.3	67.6 ± 11.2	0.22
Male	98 (97.0)	2,489 (97.0)	0.99
Body mass index			0.15
30-35	63 (62.4)	1,652 (64.4)	
35-40	9 (8.9)	351 (13.7)	
40+	29 (28.7)	562 (21.9)	
Current comorbid conditions[1)]			
Charlson score	3.7 ± 2.7	3.6 ± 2.5	0.84
Elixhauser score	4.7 ± 2.5	4.3 ± 2.0	0.18
Chronic renal disease	34 (33.7)	718 (28.0)	0.21
Peripheral vascular disease	9 (8.9)	236 (9.2)	0.92
Cancer	17 (16.8)	487 (19.0)	0.59
Cerebrovascular disease	6 (5.9)	363 (14.2)	0.02*
Congestive heart failure	43 (42.6)	1,031 (40.2)	0.63
Diabetes	53 (52.5)	1,196 (46.6)	0.25
Rheumatoid arthritis	5 (5.0)	27 (1.1)	< 0.001*
Hypertension	53 (52.5)	1,532 (59.7)	0.15
Hypothyroidism	10 (9.9)	148 (5.8)	0.08
Coagulopathy	6 (5.9)	233 (9.1)	0.28
Fluid and electolyte disorder	45 (44.6)	986 (38.4)	0.22
Depression	25 (24.8)	365 (14.2)	0.003*
Other neurological disorders	22 (21.8)	440 (17.2)	0.23
Bactremia	11 (10.9)	419 (16.3)	0.14
Skin/subcutaneous infection	32 (31.7)	638 (24.9)	0.12
Chronic ulcer	26 (25.7)	424 (16.5)	0.02*
Dialysis	18 (17.8)	285 (11.1)	0.04*
Pneumonia	67 (66.3)	1,612 (62.9)	0.48
Culture-confirmed infections with			
Enterococcus	31 (30.7)	463 (18.1)	0.001*
VRE	20 (19.8)	218 (8.5)	< 0.001*
Psudomonas aeruginosa	31 (30.7)	508 (19.8)	0.008*
Concomitant[2)] MRSA infection site			
Blood	12 (11.9)	359 (14.0)	0.55
Bone	5 (5.0)	25 (1.0)	0.002*
Nares	< 5 (<5.0)	112 (4.4)	1.00
Skin	20 (19.8)	404 (15.8)	0.27
Urine	9 (8.9)	183 (7.1)	0.50
Medical history[3)]			
Previous Elixhauser score	5.4 ± 3.1	5.0 ± 3.0	0.24
Previous chronic renal disease	31 (30.7)	593 (23.1)	0.08
Previous diabetes	63 (62.4)	1,350 (52.6)	0.05*
Previous rheumatoid arthritis	5 (5.0)	56 (2.2)	0.07
Previous congestive heart failure	44 (43.6)	903 (35.2)	0.09
Previous hypothyroidism	16 (15.8)	248 (9.7)	0.04
Previous bactremia	7 (6.9)	115 (4.5)	0.25
Previous osteomyelitis	8 (7.9)	74 (2.9)	0.004*
Previous surgery/medical care complication	13 (12.9)	234 (9.1)	0.20
Previous allergy to vancomycin	9 (8.9)	14 (0.6)	< 0.001*
Previous pneumonia	32 (31.7)	598 (23.3)	0.05*
Previous culture-confirmed infections with			
Enterococcus	12 (11.9)	163 (6.4)	0.03*
VRE	6 (5.9)	48 (1.9)	0.004*

Data are mean ± standard deviation or number (%) of patients. MRSA: Methicillin-Resistant Staphylococcus aureus; VRE: Vancomycin-Resistant Enterococcus

1. Present during the MRSA pneumonia hospitalization.

2 Present between the MRSA pneumonia admission and the end of treatment

3. Present in the 1 year prior to the admission with a positive MRSA pulmonary culture.

* p<0.05

Table 1: Demographics and Comorbid Conditions by Treatment Group

Healthcare and antibiotic exposures	Linezolid N=101	Vancomycin N=2,565	P-value
Hospital unit at treatment initiation			
Intensive care	39 (38.6)	895 (34.9)	0.44
General medicine / Other	62 (61.4)	1,669 (65.1)	
Surgery during the current admission	46 (45.5)	1,039 (40.5)	0.31
MRSA culture site			
Bronchial	13 (12.9)	165 (6.4)	0.01*
Non-bronchial (i.e. lung)	88 (87.1)	2,400 (93.6)	
Year			
2002	5 (5.0)	112 (4.4)	
2003	5 (5.0)	238 (9.3)	
2004	10 (9.9)	271 (10.6)	
2005	8 (7.9)	258 (10.1)	
2006	5 (5.0)	247 (9.6)	0.15
2007	11 (10.9)	253 (9.9)	
2008	16 (15.8)	253 (9.9)	
2009	7 (6.9)	235 (9.2)	
2010	16 (15.8)	234 (9.1)	
2011	8 (7.9)	263 (10.2)	
2012	10 (9.9)	201 (7.8)	
Region of facility			
Northeast	14 (13.9)	434 (16.9)	
South	53 (52.5)	1,198 (46.7)	0.23
Midwest	24 (23.8)	515 (20.1)	
West	10 (9.9)	418 (16.3)	
Length of therapy (days)	8.3 ± 5.3	7.3 ± 5.9	0.08
Previous hospitalization, 90 days	38 (37.6)	991 (38.6)	0.84
Previous surgery, any, 90 days	22 (21.8)	324 (12.6)	0.01*
Previous nursing home stay, 90 days	7 (6.9)	166 (6.5)	0.85
Previous anti-MRSA antibiotic[1)]			
Number of antibiotics	1.6 ± 0.6	1.3 ± 0.5	< 0.001*
Number of days with antibiotic use	13.3 ± 11.6	8.2 ± 9.4	0.01*
Linezolid	10 (9.9)	22 (0.9)	<0.001*
Vancomycin	18 (17.8)	300 (11.7)	0.06
Other antibiotics	9 (8.9)	120 (4.7)	0.05*

Data are mean ± standard deviation or number (%) of patients. MRSA: Methicillin-Resistant *Staphylococcus aureus*.
1. Present in the 90 days prior to the admission with a positive MRSA pulmonary culture.
* p<0.05

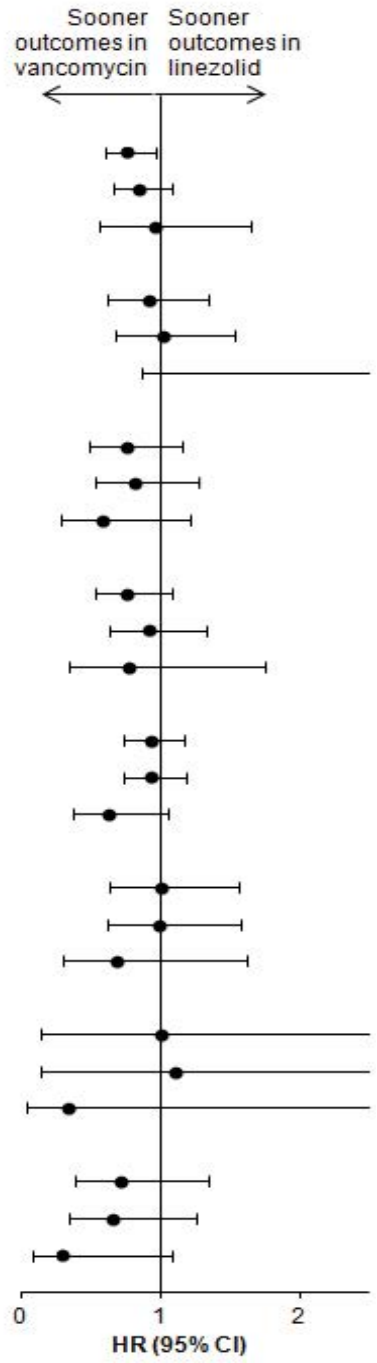
Table 2: Healthcare and Antibiotic Exposures and Hospitalization-Related Characteristics by Treatment Group

patients [15,27-30]. Two meta-analyses which compared vancomycin and linezolid for nosocomial pneumonia, found no differences in clinical and microbiologic outcomes or mortality [29,30]. While many trials have demonstrated equivalent efficacy between linezolid and vancomycin [12,14], a recent prospective, randomized, double-blind trial of MRSA pneumonia demonstrated higher clinical and microbiologic success rates with linezolid over vancomycin, however mortality was similar between the two groups [15]. Although several studies have shown benefits for linezolid treatment compared with vancomycin [10,15,31], their methodological and statistical limitations have been frequently debated in the literature [32-34].

There is conflicting evidence surrounding treatment outcomes with vancomycin at higher MICs. Some studies suggest patients with MRSA infections are more likely to experience clinical success with vancomycin if the vancomycin MIC is < 1 μg/mL as compared to patients with higher MICs [35,36]. In an observational study of 158 patients with hospital-acquired, ventilator-associated or healthcare-associated MRSA pneumonia, mortality increased as a function of the vancomycin MIC [37]. The overall all-cause 28-day mortality rate in these patients was 32.3%, with the majority of isolates having a vancomycin MIC ≥ 1.5 μg/mL (115/158, 72.8%) [37]. However, a recent meta-analysis examining the association between vancomycin MIC and mortality rates in patients with *Staphylococcus aureus* bacteremia demonstrated no significant differences in mortality between patients with lower-vancomycin MICs (< 1.5 μg/mL) and those with higher-MICs (≥ 1.5 μg/mL) [38].

In our sensitivity analyses, we observed significant differences between treatment groups when restricting the vancomycin group to patients with lower MICs (≤ 1 μg/mL). Linezolid was associated with a significantly lower discharge rate, representing an increased length of stay, a significantly decreased rate of therapy discontinuation, indicating longer therapy duration, and a significantly lower rate of 30-day mortality, representing greater survival, as compared to the vancomycin group with MICs of ≤ 1 μg/Ml. We believe this is the first study to demonstrate improved outcomes with linezolid in obese patients, as compared to those receiving vancomycin and infected with

Outcomes	No.of events/No.of patients		HR (95% CI)
	Linezolid	Vancomycin	
Discharge			
Unadjusted	70/101	1,852/2,565	0.76 (0.60 - 0.96)
Propensity Adjusted[1)]	70/101	1,852/2,565	0.85 (0.66 - 1.08)
Propensity Matched[2)]	56/76	53/76	0.96 (0.56 - 1.65)
ICU discharge			
Unadjusted	27/39	643/895	0.92 (0.62 - 1.35)
Propensity Adjusted[1)]	27/39	643/895	1.02 (0.68 - 1.53)
Propensity Matched[2)]	18/26	21/30	7.00 (0.86 - 56.9)
30-day mortality			
Unadjusted	22/101	731/2,565	0.75 (0.49 - 1.15)
Propensity Adjusted[1)]	22/101	731/2,565	0.82 (0.53 - 1.27)
Propensity Matched[2)]	14/76	20/76	0.58 (0.28 - 1.22)
Inpatient mortality			
Unadjusted	31/101	713/2,565	0.76 (0.53 - 1.08)
Propensity Adjusted[1)]	31/101	713/2,565	0.91 (0.63 - 1.33)
Propensity Matched[2)]	20/76	23/76	0.77 (0.34 - 1.75)
Therapy discontinuation			
Unadjusted	74/101	1,903/2,565	0.93 (0.73 - 1.17)
Propensity Adjusted[1)]	74/101	1,903/2,565	0.93 (0.73 - 1.19)
Propensity Matched[2)]	56/76	56/76	0.62 (0.37 - 1.05)
Therapy change			
Unadjusted	20/101	470/2,565	1.00 (0.64 - 1.56)
Propensity Adjusted[1)]	20/101	470/2,565	0.99 (0.62 - 1.58)
Propensity Matched[2)]	16/76	15/76	0.69 (0.30 - 1.62)
30-day MRSA pneumonia reinfection			
Unadjusted	<5/70	26/1,852	1.01 (0.14 - 7.45)
Propensity Adjusted[1)]	<5/70	26/1,852	1.11 (0.14 - 8.81)
Propensity Matched[2)]	<5/56	<5/53	0.33 (0.04 - 3.21)
30-day readmission			
Unadjusted	10/70	367/1,852	0.71 (0.38 - 1.34)
Propensity Adjusted[1)]	10/70	367/1,852	0.66 (0.35 - 1.26)
Propensity Matched[2)]	6/56	14/53	0.30 (0.08 - 1.09)



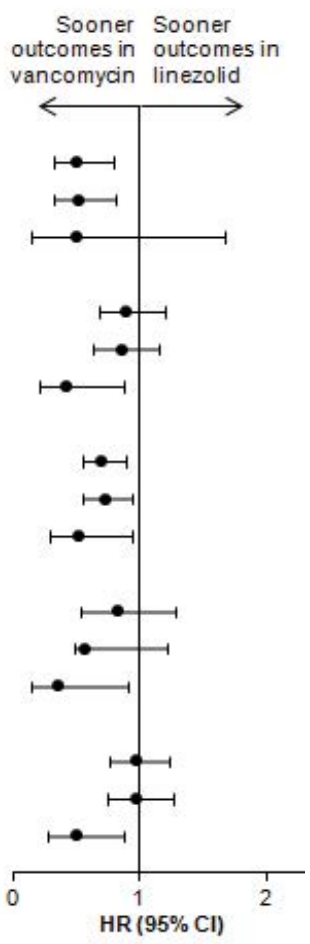
HR: Hazard Ratio; CI: Confidence Interval; ICU: Intensive Care Unit; MRSA: Methicillin-Resistant *Staphylococcus aureus*.

1. Adjusted by propensity score quintiles (reference quintile I).
2. Propensity score matched within 0.001 caliper.

The propensity score was derived from an unconditional logistic regression model controlling for age, body mass index, Elixhauser score, time to therapy initiation from culture date, year, region of facility, hospital unit at treatment initiation, culture site, history of MRSA infection, elevated white blood cell count, current diabetes complications, current myocardial infarction, current cerebrovascular disease, current rheumatoid arthritis, current hypertension, current other neurological disorders, current coagulopathy, current fluid and electolyte disorder, current depression, current skin infection, current chronic ulcer, current bacteremia, current immune disorder, current dialysis, current VRE infection, current *Psudomonas aeroginosa* infection, concomitant MRSA infection in bone, history of chronic renal disease, history of diabetes, history of cancer, history of congestive heart failure, history of hypothyroidism, history of burn, history of pneumonia, history of bacteremia, history of osteomyelitis, history of neutropenia, history of VRE infection, history of allergy to vancomycin, nursing home stay in previous 30 days, surgery in previous 90 days, linezolid in previous 90 days, trimethoprim/sulfamethoxazole in previous 90 days, daptomycin in previous 90 days, number of antibiotic used in previous 90 days (C-statistic 0.84).

Table 3: Outcomes in Overall Cohort: Linezolid Compared with Vancomycin

Subgroups	Outcomes	No.of events/No.of patients		HR (95% CI)
		Linezolid	Vancomycin	
Morbidly obese (BMI ≥ 40)	Discharge			
	Unadjusted	20/29	421/562	0.50 (0.32 - 0.79)
	Propensity Adjusted[1)]	20/29	421/562	0.51 (0.32 - 0.81)
	Propensity Matched[2)]	12/17	12/17	0.50 (0.15 - 1.66)
ICD-9-CM pneumonia diagnosis	Therapy discontinuation			
	Unadjusted	47/67	1,188/1,612	0.89 (0.67 - 1.19)
	Propensity Adjusted[1)]	47/67	1,188/1,612	0.85 (0.63 - 1.15)
	Propensity Matched[2)]	32/48	34/48	0.42 (0.20 - 0.87)
MIC ≤1.0 µg/mL	Discharge			
	Unadjusted	70/101	623/833	0.69 (0.54 - 0.89)
	Propensity Adjusted[1)]	70/101	623/833	0.72 (0.55 - 0.93)
	Propensity Matched[2)]	47/62	43/62	0.52 (0.29 - 0.93)
	30-day mortality			
	Unadjusted	22/101	221/833	0.82 (0.53 - 1.27)
	Propensity Adjusted[1)]	22/101	221/833	0.56 (0.48 - 1.21)
	Propensity Matched[2)]	9/62	18/62	0.35 (0.14 - 0.90)
	Therapy discontinuation			
	Unadjusted	74/101	589/833	0.97 (0.76 - 1.23)
	Propensity Adjusted[1)]	74/101	589/833	0.97 (0.74 - 1.26)
	Propensity Matched[2)]	46/62	49/62	0.49 (0.27 - 0.87)



HR: Hazard Ratio; CI: Confidence Interval; BMI: Body Mass Index; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; MIC: Minimum Inhibitory Concentration.
1. Adjusted by propensity score quintiles (reference quintile I).
2. Propensity score matched within 0.001 caliper.

Table 4: Subgroup and Sensitivity Analyses: Linezolid Compared with Vancomycin

low MIC strains. On the contrary, there were no significant differences in clinical outcomes between treatment groups when restricting the vancomycin group to those with vancomycin MICs of ≥ 1.5 µg/mL. Since this was a national study, MIC testing systems varied by facility and MIC testing methodology was not specified in the data.

Appropriate dosing of antibiotics in obese patients is extremely difficult and may result in underdosing [9,39]. Furthermore, 28% of our cohort had a diagnosis of chronic renal disease during the admission, which further complicates appropriate dosing in the obese population. Obese patients treated with vancomycin may be less likely to achieve optimal dosing, which puts patients at risk for poor outcomes [40], even if they had a favorable vancomycin susceptibility.

Vancomycin trough concentrations of 15-20 mg/L are recommended for severe infections, including MRSA pneumonia, in order to improve penetration, increase the probability of optimal serum vancomycin concentrations, and improve clinical outcomes [25]. However the optimal trough in obese patients is largely unknown. Among patients with true vancomycin trough concentrations, only 22% (n=66) were in therapeutic range. All clinical outcomes were similar in patients with vancomycin trough levels of 15-20 mg/L compared to patients receiving linezolid. Although we found no significant differences between linezolid and vancomycin, the relatively small number of patients with true trough levels of 15-20 mg/L may have affected our ability to detect differences between the treatment groups.

There is always the potential for observational studies to be impacted by bias and residual confounding. To address these potential limitations, we took steps in the design and analytic phases to minimize bias. To capture potential confounders, we assessed a variety of patient data, including pharmacy data, microbiology data, and records of inpatient and outpatient care. To address the impact of confounding by indication, we utilized propensity score methods in the analytic phase [20,21,41]. Although balance was achieved within propensity score quintiles and between propensity matched pairs, there is the potential for residual confounding by unobserved covariates. Additionally, due to the relatively small sample size after matching propensity scores, we may have been unable to detect small differences in clinical outcomes between the two treatment groups.

Though we sought to develop accurate definitions for exposures, outcomes, and known potential confounders, misclassification bias may have impacted our study results. Our definition of suspected MRSA pneumonia may not have captured all MRSA pneumonia infections. Previous research has shown that as many as 30% of patients

never have cultures taken [27]. In addition, we included patients with positive MRSA respiratory cultures from both sputum and BAL. The sensitivity of culture-positive isolates from non-bronchoscopic lung lavage for confirming ventilator-associated pneumonia is reported to be 72% with a Positive Predictive Value (PPV) of 14%, while the sensitivity of BAL for confirming pneumonia is 89% with a PPV of 33% [42]. Since our cohort definition for suspected MRSA pneumonia was based on culture confirmation and the presence of clinical signs of infection, we performed a subgroup analysis restricting the cohort to patients with a pneumonia diagnosis code in addition to a positive culture from a respiratory culture site and clinical signs of infection. This subgroup analysis demonstrated consistent results with those of the overall cohort.

Lastly, our study findings were further impacted by the limited generalizability of the VA population to the general US population. However, the Veterans Health Administration is the largest integrated healthcare system in the US. Due to the implementation of electronic medical records in 1999, large standardized databases, unique in size and content, include a wealth of information not available from other national data sources, including barcode medication administration, microbiology, and lab chemistry data [43].

Conclusions

We evaluated the effectiveness of linezolid therapy compared to vancomycin in obese patients with culture-confirmed MRSA from a pulmonary site and found no significant differences in clinical outcomes between the two treatment groups. In sensitivity analyses, however, we found that linezolid was associated with a significantly higher survival rate compared to vancomycin patients with lower MICs (≤ 1 μg/mL). Based on our review of the literature, this is the first study to demonstrate improved survival with linezolid as compared to vancomycin among obese patients with suspected MRSA pneumonia infected with low vancomycin MICs. As such, further studies are needed to determine whether this beneficial effect is observed in other study populations and to determine the clinical implications of this finding.

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