MAJOR ARTICLE

Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Among 122 Hospitals

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Background. Previous studies indicate that vancomycin is inferior to beta-lactams for treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections. However, it is unclear if this association is true for empiric and definitive therapy. Here, we compared beta-lactams with vancomycin for empiric and definitive therapy of MSSA bloodstream infections among patients admitted to 122 hospitals.

Methods. This retrospective cohort study included all patients admitted to Veterans Affairs hospitals from 2003 to 2010 who had positive blood cultures for MSSA. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression. Empiric therapy was defined as starting treatment 2 days before and up to 4 days after the first MSSA blood culture was collected. Definitive therapy was defined as starting treatment between 4 and 14 days after the first positive blood culture was collected.

Results. Patients who received empiric therapy with a beta-lactam had similar mortality compared with those who received vancomycin (HR, 1.03; 95% CI, .89–1.20) after adjusting for other factors. However, patients who received definitive therapy with a beta-lactam had 35% lower mortality compared with patients who received vancomycin (HR, 0.65; 95% CI, .52–.80) after controlling for other factors. The hazard of mortality decreased further for patients who received cefazolin or antistaphylococcal penicillins compared with vancomycin (HR, 0.57; 95% CI, .46–.71).

Conclusions. For patients with MSSA bloodstream infections, beta-lactams are superior to vancomycin for definitive therapy but not for empiric treatment. Patients should receive beta-lactams for definitive therapy, specifically antistaphylococcal penicillins or cefazolin.

Keywords. beta-lactams; vancomycin; MSSA; bloodstream infection.

Staphylococcus aureus bloodstream infections can cause poor patient outcomes such as increased length of stay in the hospital, septic shock, recurrent infections, and death [1–3]. Vancomycin is often prescribed empirically for patients suspected of having *S. aureus* bloodstream infections since it has activity against both methicillin-resistant and methicillin-susceptible strains. However, for a patient infected with methicillin-susceptible *S. aureus* (MSSA), organizations such as the Infectious Diseases Society of America (IDSA) recommend switching therapy to a beta-lactam such as cefazolin or an antistaphylococcal penicillin (nafcillin or oxacillin) once the isolate is known to be MSSA [4].

Previous small studies have shown that patients with MSSA bloodstream infections who are treated with vancomycin are more likely to have poor outcomes such as

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recurrence, treatment failure, and death compared with MSSA-infected patients who are treated with a beta-lactam [1, 5–7]. Additionally, empiric therapy with an agent that has reduced activity against the infecting organism may negatively affect patient outcomes [8–11]. Therefore, patients with MSSA bloodstream infections may also have improved outcomes if they receive empiric therapy (eg, initial treatment before culture results are known) with a beta-lactam instead of vancomycin. In the current study, we compared empiric therapy with beta-lactams vs vancomycin and definitive therapy with beta-lactams vs vancomycin among patients with MSSA bloodstream infections admitted to Veterans Affairs (VA) medical centers.

METHODS

Study Design and Patient Population

This retrospective cohort study included patients with medical or surgical admissions to the 122 acute care VA medical centers from 2003 to 2010. Patients were included if they had 1 or more blood cultures positive for *S. aureus* in which the isolates were susceptible to either methicillin or oxacillin by antimicrobial susceptibility testing and if they received a beta-lactam agent active against *S. aureus* or vancomycin for treatment of their bloodstream infections. The beta-lactams examined in this study were antistaphylococcal penicillins, cefazolin, cefotetan, cefoxitin, cefotaxime, ceftriaxone, cefepime, ceftaroline, carbapenems, and beta-lactamase inhibitors (piperacillin-tazobactam, ampicillin-sulbactram, and ticarcillin-clavulanate). Patients having multiple admissions with a MSSA-positive blood culture were included only once. Patients who had missing or inaccurate data or who were admitted to a VA facility that had fewer than 25 cases of *S. aureus* bloodstream infections throughout the study period or who did not receive either a beta-lactam or vancomycin for treatment of their bloodstream infections were excluded.

This study used medical, pharmaceutical, microbiological, and demographic data extracted from the VA electronic health record for the VA's Corporate Data Warehouse and Patient Care Services database and accessed through the VA Informatics and Computing Infrastructure. These data were last updated in February 2014 and validated by the VA Healthcare System through the VA Information Resource Center [12]. The institutional review board of the University of Iowa and the Research and Development Committee of the Iowa City VA Medical Center approved this study.

Variable Definitions

The primary outcome was 30-day all-cause mortality, defined as death occurring within 30 days after the collection of the first blood culture positive for MSSA. Deaths that occurred outside of the hospital or on a subsequent admission were included. The VA uses multiple sources (VA data, Social Security Administration Death Master File, Medicare Vital Status, and Beneficiary Identification Records Locator Subsystem Death File) to collect information on death. The VA-National Death Index (NDI) Mortality Data Merge Project found a 98% agreement between these combined sources and the NDI [13].

Antimicrobials started during the 2 days before the first blood culture positive for MSSA and the following 14 days after the blood culture was collected were analyzed. Empiric therapy was defined as receipt of an antimicrobial started between 2 days before the first MSSA positive blood culture was collected and 4 days after the blood culture was collected. Definitive therapy was defined as receipt of an antimicrobial between 4 and 14 days after the first positive blood culture was collected. The cut point of 4 days was selected because the largest proportion of patients switched treatment at that time and based on the assumption that susceptibility results are usually available at 4 days. Patients were excluded from the empiric therapy analysis if they received empiric therapy with both beta-lactam agents and vancomycin and from the definitive therapy analysis if they received definitive therapy with both beta-lactam agents and vancomycin. Patients were included in both the empiric and definitive analyses if they remained on the same antibiotic during both the empiric and definitive time periods.

The Charlson comorbidity index, which is based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes, was used to assess comorbid conditions [14]. The modified acute physiology and chronic health evaluation (APACHE) III score was used to measure patients' severity of illness on hospital admission [15, 16]. ICD-9-CM codes were used to identify chronic health conditions and also to identify patients who had additional infections including pneumonia, endocarditis, and osteomyelitis. Age and APACHE III score were dichotomized on their medians.

Dialysis was defined as receipt of outpatient dialysis, receipt of dialysis during the index hospital admission, or having end stage renal disease (ESRD). Inpatient dialysis was defined as the presence of an ICD-9-CM code for dialysis (39.95 and 54.98) on the index hospital admission. ESRD was defined as an ICD-9-CM for ESRD (585.6) either during the index admission or during an outpatient visit at a VA clinic within 90 days before the index hospital admission. Outpatient dialysis was defined as the presence of a Current Procedural Terminology code for dialysis in the outpatient setting within 90 days before the index hospital admission. Outpatient dialysis included patients who received dialysis at a VA clinic or at an institution outside of VA medical centers if the VA medical centers paid for that procedure. The fee/purchased care file was used to obtain information regarding medical care paid by VA medical centers that was provided at an entity outside of the VA medical centers.

Facility types are based on complexity scores, which are created by the VA Healthcare Analysis and Information Group.

Table 1. Characteristics of Patients With Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Who Received Empiric Therapy With a Beta-Lactam Alone or Vancomycin Alone (N = 5784)

Characteristic	Patients Who Received Beta-Lactams[a] (N = 2659)	Patients Who Received Vancomycin[a] (N = 3125)	*P* Value
Gender, male	2604 (98)	3046 (97)	.247
Age, >64 y	1421 (53)	1573 (50)	.019
Acute physiology and chronic health evaluation III score, >33	1259 (47)	1509 (48)	.476
Charlson comorbidity index, median (range[b]) score	2 (1–3)	2 (1–3)	<.001
Diabetes	916 (34)	1100 (35)	.550
Moderate or severe liver disease	97 (4)	96 (3)	.224
Additional infections			
Pneumonia	573 (22)	378 (12)	<.001
Osteomyelitis	172 (6)	194 (6)	.685
Endocarditis	46 (2)	89 (4)	.005
Dialysis/end stage renal disease[c]	139 (5)	417 (13)	<.001
Community-onset infection[d]	2168 (82)	2298 (74)	<.001
Prior hospitalization	1341 (50)	1802 (58)	<.001
Beta-lactam allergy	280 (11)	1109 (35)	<.001
Prior methicillin-resistant *Staphylococcus aureus* nasal colonization	73 (3)	176 (6)	<.001
Year of admission			
2003	533 (20)	395 (13)	<.001
2004	466 (18)	387 (12)	
2005	384 (14)	389 (12)	
2006	353 (13)	434 (14)	
2007	274 (10)	423 (14)	
2008	226 (9)	425 (14)	
2009	220 (8)	360 (12)	
2010	203 (8)	312 (10)	
Facility type[e]			<.001
1a (most complex)	973 (37)	1588 (51)	
1b	451 (17)	668 (21)	
1c	505 (19)	418 (13)	
2	418 (16)	272 (9)	
3 (least complex)	178 (7)	50 (2)	
Other empiric antimicrobials			
Clindamycin	133 (5)	220 (7)	.001
Aminoglycosides	128 (5)	313 (10)	<.001
Quinolones	555 (21)	1265 (40)	<.001
Macrolides	436 (16)	128 (4)	<.001
Trimethoprim/Sulfamethozazole	80 (3)	126 (4)	.036
Linezolid	59 (2)	36 (1)	.002
Post-infection length of stay, median (range[b]) days[f]	7 (4–12)	8 (4–14)	<.001
30-day mortality[g]	361 (14)	437 (14)	.654

Empiric therapy is defined as starting an antimicrobial from 2 days before the date of the first blood culture positive for methicillin-susceptible *Staphylococcus aureus* (MSSA) was collected through the fourth day after the first positive blood culture was collected.

[a] The numbers in parentheses are percentages unless otherwise specified.

[b] Interquartile range.

[c] Dialysis was defined as receipt of outpatient dialysis, receipt of dialysis during the index hospital admission, or having end stage renal disease (ESRD). Inpatient dialysis was defined as the presence of an *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code for dialysis (39.95 and 54.98) on the index hospital admission. ESRD was defined as an ICD-9-CM for ESRD (585.6) either during the index admission or during an outpatient visit at a Veterans Affairs (VA) clinic within 90 days before the index hospital admission. Outpatient dialysis was defined as the presence of a Current Procedural Terminology code for dialysis in the outpatient setting within 90 days before the index hospital admission. Outpatient dialysis included patients who received dialysis at a VA clinic or at an institution outside of VA medical centers if the VA medical centers paid for that procedure.

[d] Positive MSSA culture was collected ≤48 hours after admission.

[e] Facility types are based on complexity scores, which are created by the VA's Healthcare Analysis and Information Group. Hospitals are scored according to patient population, clinical services (intensive care unit and surgery services), and education and research.

[f] Defined as the day the first blood culture positive for MSSA was collected until the patient was either discharged from the hospital or died.

[g] Defined as death occurring within the 30 days immediately after the day when the first blood culture positive for MSSA was obtained.

Table 2. Characteristics of Patients With Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Who Received Definitive Therapy With a Beta-Lactam Alone or Vancomycin Alone (N = 5633)

Characteristic	Patients Who Received Beta-Lactams[a] (N = 4698)	Patients Who Received Vancomycin[a] (N = 935)	*P* Value
Gender, male	4598 (98)	909 (97)	.218
Age, >64 y	2261 (48)	470 (50)	.232
Acute physiology and chronic health evaluation III score, >33	2475 (53)	437 (47)	.001
Charlson comorbidity index, median (range[b]) score	2 (1–3)	2 (1–3)	.199
Diabetes	1671 (36)	331 (35)	.922
Moderate or severe liver disease	199 (4)	28 (3)	.078
Additional infections			
Pneumonia	926 (20)	112 (12)	<.001
Osteomyelitis	498 (11)	40 (4)	<.001
Endocarditis	189 (4)	21 (2)	.009
Dialysis/end stage renal disease[c]	473 (10)	128 (14)	.001
Community-onset infection[d]	3582 (76)	671 (72)	.004
Prior hospitalization	2632 (56)	572 (61)	.004
Beta-lactam allergy	595 (13)	440 (47)	<.001
Prior methicillin-resistant *Staphylococcus aureus* nasal colonization	204 (4)	57 (6)	.020
Year of admission			.133
2003	674 (14)	126 (13)	
2004	644 (14)	117 (13)	
2005	602 (13)	133 (14)	
2006	563 (12)	125 (13)	
2007	542 (12)	111 (12)	
2008	587 (12)	118 (13)	
2009	525 (11)	120 (13)	
2010	561 (12)	85 (9)	
Facility type[e]			.001
1a (most complex)	2186 (47)	439 (47)	
1b	933 (20)	236 (25)	
1c	739 (16)	118 (13)	
2	514 (11)	90 (10)	
3 (least complex)	125 (3)	19 (2)	
Length of stay in the hospital, median (range[b]) days[f]	12 (8–21)	8 (6–13)	<.001
30-day mortality[g]	679 (14)	112 (12)	.047

Definitive therapy is defined as starting or remaining on an antimicrobial from ≥4 days after the first blood culture positive for methicillin-susceptible *Staphylococcus aureus* (MSSA) was collected through the 14th day after the day the first blood culture positive for MSSA was collected.

[a] The numbers in parentheses are percentages unless otherwise specified.

[b] Interquartile range.

[c] Dialysis was defined as receipt of outpatient dialysis, receipt of dialysis during the index hospital admission, or having end stage renal disease (ESRD). Inpatient dialysis was defined as the presence of an *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code for dialysis (39.95 and 54.98) on the index hospital admission. ESRD was defined as an ICD-9-CM for ESRD (585.6) either during the index admission or during an outpatient visit at a Veterans Affairs (VA) clinic within 90 days before the index hospital admission. Outpatient dialysis was defined as the presence of a Current Procedural Terminology code for dialysis in the outpatient setting within 90 days before the index hospital admission. Outpatient dialysis included patients who received dialysis at a VA clinic or at an institution outside of VA medical centers if the VA medical centers paid for that procedure.

[d] Positive MSSA culture was collected ≤48 hours after admission.

[e] Facility types are based on complexity scores, which are created by the VA's Healthcare Analysis and Information Group. Hospitals are scored according to patient population, clinical services (intensive care unit and surgery services), and education and research.

[f] Defined as the day the first blood culture positive for MSSA was collected until the patient was either discharged from the hospital or died.

[g] Defined as death occurring within the 30 days immediately after the day when the first blood culture positive for MSSA was obtained.

Hospitals are scored according to patient population, clinical services (intensive care unit [ICU] and surgery services), and education and research. A score of 1a is most complex while a score of 3 is least complex. Patients were defined as having community-onset bloodstream infections if their first blood cultures that grew MSSA were collected less than 48 hours after

hospital admission. Length of stay was defined as the number of days from the day the first positive MSSA culture was collected until the day of hospital discharge or in-hospital death.

Statistical Analyses

For the bivariable analyses assessing relationships between patient characteristics and therapy or mortality, the χ^2 test or Fisher exact test was used for categorical variables, and the Student *t* test or the Wilcoxon rank sum test was used for continuous variables.

Multivariable models were created using Cox proportional hazard regression to examine the association between therapy with either a beta-lactam or with vancomycin and mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on the models. Patients were censored if death occurred more than 30 days after the first positive blood culture was collected. The variables provided in Tables 1 and 2 were examined for inclusion in the multivariable models.

For the regression analyses, a manual stepwise method was used in which variables were entered into the model one at a time if $P < .25$ in the bivariable analysis. Variables remained in the model if $P < .05$. The proportional hazard assumption was evaluated on the final model by assessing the interaction of therapy with the log of survival time. Variables were considered confounders if the regression coefficients for therapy type were altered by more than 20%. The final model included the confounders. Statistically significant interaction terms were considered to be effect modifiers ($P < .05$). Models were created based on the stratified effect modifier. The APACHE III score and Charlson comorbidity index were retained in all models regardless of statistical significance since these variables are strong predictors of mortality and may influence therapy type.

Three regression analyses were performed. First, empiric therapy with vancomycin was compared with empiric therapy with all beta-lactam antibiotics. Second, definitive therapy with vancomycin was compared with definitive therapy with all beta-lactam antibiotics. Last, definitive therapy with vancomycin was compared with definitive therapy with guideline-concordant beta-lactams (antistaphylococcal penicillins or cefazolin) [4]. All data analyses were completed using SAS Enterprise Guide, version 5.1 (SAS Institute, Cary, North Carolina).

RESULTS

Patients With MSSA Bloodstream Infections

We identified 16 973 patients who had at least 1 MSSA-positive blood culture and who were admitted to a VA medical center. Most patients were male (98%), and the median age was 64 years (interquartile range [IQR], 57–76). Sixteen percent of the patients died within 30 days after collection of the first blood culture positive for MSSA. The median post-infection length of stay in the hospital was 8 days (IQR, 4–15). Fourteen percent (2356/16 973) of the patients did not receive a beta-lactam or vancomycin during the treatment period.

Patients Receiving Empiric Therapy With a Beta-Lactam or Vancomycin

Of the 16 973 patients, 5784 received either a beta-lactam alone or vancomycin alone for empiric therapy of their bloodstream infections; 46% received a beta-lactam alone and 54% received vancomycin alone (Table 1). Compared with patients who received vancomycin, patients who received empiric therapy with a beta-lactam were more likely to be older (>64 years; 53% vs 50%; $P = .019$), have a community-onset infection (82% vs 74%; $P < .001$), and have pneumonia (22% vs 12%; $P < .001$) but were less likely to have endocarditis (2% vs 4%; $P = .005$). Piperacillin/tazobactam (32%) and ceftriaxone (29%) were the most common beta-lactams that patients received for empiric therapy. The mortality rate was similar between the patients who received empiric therapy with beta-lactams compared with those who received vancomycin (14% vs 14%; $P = .654$). In the multivariable analysis, patients who received empiric therapy with a beta-lactam had a similar hazard of mortality compared with patients who received vancomycin after adjusting for severity of illness, aggregate comorbidities, age, osteomyelitis, pneumonia, facility type, community-onset infection, dialysis/ESRD, and additional empiric therapy with a quinolone, linezolid, or trimethoprim/sulfamethozazole (HR, 1.03; 95% CI, .89–1.20).

Patients Receiving Definitive Therapy With a Beta-Lactam or Vancomycin

Of the 16 973 patients, 5633 patients received definitive therapy for their bloodstream infections; 17% were treated with vancomycin and 83% were treated with a beta-lactam (Table 2). Compared with patients who received vancomycin, patients who received definitive therapy with a beta-lactam were more likely to have a higher APACHE III score (>33 points; 53% vs 47%; $P = .001$), have a community-onset infection (76% vs 72%; $P = .004$), and have pneumonia (20% vs 12%; $P < .001$) or osteomyelitis (11% vs 4%; $P < .001$) but were less likely to have endocarditis (2% vs 4%; $P = .009$). Among patients who received definitive beta-lactam therapy, the top 5 beta-lactams that patients received were nafcillin (35%), cefazolin (30%), piperacillin/tazobactam (15%), ceftriaxone (14%), and oxacillin (9%). The proportion of patients who died within 30 days slightly differed among the patients who received a beta-lactam compared with those who received vancomycin (14% vs 12%; $P = .047$). Yet, in the multivariable analysis, patients who were prescribed a beta-lactam for therapy of MSSA bloodstream infections had a 35% lower hazard of dying within 30 days compared with patients who received vancomycin after adjusting for severity of illness, aggregate comorbidities, osteomyelitis, beta-lactam

allergy, facility type, age, and dialysis/ESRD (HR, 0.65; 95% CI, .52–.80).

Patients Receiving Definitive Therapy With Guideline-Concordant Beta-Lactams or Vancomycin

Patients who received definitive therapy with either cefazolin or an antistaphylococcal penicillin had a 43% reduced hazard of mortality compared with patients who received vancomycin after adjusting for severity of illness, aggregate comorbidities, osteomyelitis, age, beta-lactam allergy, and dialysis/ESRD (HR, 0.57; 95% CI, .46–.71).

Among the patients who received definitive therapy with vancomycin, 47% (440/935) had a beta-lactam allergy, 14% (128/935) were on dialysis and/or had ESRD, and/or 5% (42/935) died within 7 days of their first positive MSSA blood culture.

DISCUSSION

The IDSA guidelines indicate that patients with MSSA bloodstream infections should be treated with beta-lactam agents such as first-generation cephalosporins or antistaphylococcal penicillins after the antimicrobial susceptibility results are available [4]. In this study, beta-lactam agents were associated with better outcomes compared with vancomycin when used for definitive therapy of MSSA bloodstream infections. Furthermore, the protective effect was enhanced when patients received guideline-concordant definitive therapy with cefazolin or antistaphylococcal penicillins compared with vancomycin.

The results from this study are similar to those from previous studies that identified better outcomes among patients who received a beta-lactam compared with vancomycin for treatment of MSSA bloodstream infections [1, 5–7]. Kim et al determined that patients with MSSA bloodstream infections who were treated with vancomycin were 3-fold more likely to die than those treated with beta-lactam agents [6]. Similarly, Stryjewski et al found an association between therapy failure and receipt of vancomycin for MSSA bacteremia compared with cefazolin among patients on hemodialysis [7]. Others have demonstrated that patients treated with nafcillin or cefazolin were less likely to have poor outcomes compared with patients who received vancomycin for therapy of MSSA bloodstream infections [1, 5].

Some of the patients in our cohort who received vancomycin for definitive therapy had a flagged beta-lactam allergy and thus did not receive definitive treatment with cefazolin or antistaphylococcal penicillins. However, beta-lactam allergy is likely overreported, and many patients could ultimately receive a beta-lactam antibiotic if properly screened and allergy tested [17]. Prior studies have found that when patients with a history of nonanaphylactic penicillin allergy were skin tested, 86% had negative skin tests for penicillin allergy and were able to tolerate beta-lactam antibiotics [17, 18]. Therefore, facilities should consider offering beta-lactam allergy testing services to improve patient care.

This study has several potential limitations. The results may not be generalizable to all patient populations since the patients in this study were predominantly male and admitted to a VA medical center. Also, the cause of mortality was not collected for the deceased patients. Therefore, some patients may have died from an illness or comorbidity other than MSSA bloodstream infections within the 30-day period. Third, information on treatment received after hospital discharge, dose of antibiotics, antibiotic administration (oral vs intravenous), admission to the ICU prior to infection, having an infectious disease consult, the source of infection, and source control of the MSSA bloodstream infection was not available. Finally, a manual chart review was not completed to determine the accuracy of the data. However, the data were validated by the VA Healthcare System through the VA Information Resource Center [12].

In general, there is always a trade-off between internal validity and external validity. Studies that include a small number of sites and patients can collect fine details about each patient, such as the primary source of infection and source control (eg, removal of a catheter), through manual chart review. This leads to high internal validity. However, the results may only be able to be generalized to the specific hospital or region where the study took place and thus have low external validity. Large multicenter studies, including the study described here, have high external validity and can be generalized to large groups of people. However, these studies include thousands of patients, and it is impractical to perform manual chart review for each patient. Instead, large multicenter studies rely on validated databases [12] that may not include the fine details that chart review provides, which leads to limited internal validity. Many small studies with high internal validity have evaluated the association between vancomycin use and poor outcomes among patients with MSSA bloodstream infections [1, 5–7]. Our goal in this study was to evaluate that association among patients in 122 hospitals, including thousands of patients with MSSA bloodstream infections, in order to assess the external validity of the association between vancomycin use and poor outcomes.

In a comparative effectiveness analysis, one must consider confounding by indication [19, 20]. Our analysis adjusted for confounding by indication by including variables such as APACHE III score and Charlson comorbidity index in the multivariable model; however, this may not have eliminated its effect completely. Patients who received vancomycin therapy may still have had more unmeasured underlying illnesses compared with those who received beta-lactam therapy. However, among the covariates measured, patients who received vancomycin were generally healthier than patients who received beta-lactam therapy.

This study used a cutoff day to define empiric and definitive therapy instead of examining each patient's record to identify

the day a physician changed the treatment. Therefore, biases may have been introduced when analyzing empiric and definitive therapy. Additionally, this study did not stratify on the drug used for empiric therapy in the definitive therapy analysis. It is possible that patients who received vancomycin for both empiric and definitive therapy may have a survival disadvantage compared with patients who were switched from empiric therapy with vancomycin to definitive therapy with beta-lactams.

This large, multicenter study found that definitive therapy with a beta-lactam, especially cefazolin or an antistaphylococcal penicillin, was associated with lower mortality compared with vancomycin. As new technologies are adopted, physicians will receive organism identification sooner, which will result in a greater opportunity to prescribe early and appropriate definitive therapy. Thus, clinicians are encouraged to consider the IDSA guidelines when prescribing definitive antimicrobial therapy for MSSA bloodstream infections.

Notes

Disclaimer. The opinions expressed are those of the authors and not necessarily those of the Department of Veterans Affairs (VA) or the US Government. The VA Office of Research and Development had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript.

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References

1. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore) **2003**; 82: 333–9.
2. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis **2003**; 36:53–9.
3. Lam SW, Bauer SR, Neuner EA. Predictors of septic shock in patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Int J Infect Dis **2012**; 16:e453–6.
4. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis **2011**; 52:e18–55.
5. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. BMC Infect Dis **2011**; 11:279.
6. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2008**; 52:192–7.
7. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Clin Infect Dis **2007**; 44:190–6.
8. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. Antimicrob Agents Chemother **2008**; 52:3188–94.
9. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. Clin Infect Dis **2003**; 36:1418–23.
10. Gomez J, Garcia-Vazquez E, Banos R, et al. Predictors of mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: the role of empiric antibiotic therapy. Eur J Clin Microbiol Infect Dis **2007**; 26:239–45.
11. Kaasch AJ, Rieg S, Kuetscher J, et al. Delay in the administration of appropriate antimicrobial therapy in *Staphylococcus aureus* bloodstream infection: a prospective multicenter hospital-based cohort study. Infection **2013**; 41:979–85.
12. Jones M, DuVall SL, Spuhl J, Samore MH, Nielson C, Rubin M. Identification of methicillin-resistant *Staphylococcus aureus* within the nation's Veterans Affairs medical centers using natural language processing. BMC Med Inform Decis Mak **2012**; 12:34.
13. Arnold N, Sohn MW, Maynard C, Hynes DM. VIReC Technical Report 2: VA-NDI Mortality Data Merge Project. VA Information Resource Center, **2006**. Edward Hines, Jr. VA Hospital, Hines, IL.
14. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol **1992**; 45:613–9.
15. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest **1991**; 100:1619–36.
16. Sunenshine RH, Wright MO, Maraqakis LL, et al. Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. Emerg Infect Dis **2007**; 13:97–103.
17. Harris AD, Sauberman L, Kabbash L, Greineder DK, Samore MH. Penicillin skin testing: a way to optimize antibiotic utilization. Am J Med **1999**; 107:166–8.
18. Perencevich EN, Weller PF, Samore MH, Harris AD. Benefits of negative penicillin skin test results persist during subsequent hospital admissions. Clin Infect Dis **2001**; 32:317–9.
19. Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. JAMA **2010**; 304:897–8.
20. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol **1999**; 149:981–3.