ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2008, p. 192–197 Vol. 52, No. 1
0066-4804/08/$08.00+0 doi:10.1128/AAC.00700-07

Outcome of Vancomycin Treatment in Patients with Methicillin-Susceptible *Staphylococcus aureus* Bacteremia▽

Sung-Han Kim,[1,3] Kye-Hyung Kim,[1] Hong-Bin Kim,[1] Nam-Joong Kim,[1] Eui-Chong Kim,[2,3] Myoung-don Oh,[1,3]* and Kang-Won Choe[1,3]

Departments of Internal Medicine[1] and Laboratory Medicine,[2] Seoul National University College of Medicine, and Clinical Research Institute, Seoul National University Hospital,[3] Seoul, Republic of Korea

Received 30 May 2007/Returned for modification 10 August 2007/Accepted 26 October 2007

Limited data on the clinical outcome of vancomycin treatment compared with that of beta-lactam treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia (MSSA-B) are available. We used different and complementary approaches: (i) a retrospective cohort study using a propensity score to adjust for confounding by treatment assignment and (ii) a matched case-control study. Of all patients with *S. aureus* bacteremia (SAB) in two university-affiliated hospitals over a 7-year period, 294 patients with MSSA-B were enrolled in the cohort study. The cases for the case-control study were defined as patients who received vancomycin treatment for MSSA-B; the controls, who were patients that received beta-lactam treatment for MSSA-B, were selected at a 1:2 (case:control) ratio according to the objective matching scoring system and the propensity score system. In the cohort study, SAB-related mortality in patients with vancomycin treatment (37%, 10/27) was significantly higher than that in those with beta-lactam treatment (18%, 47/267) ($P = 0.02$). In addition, multivariate analysis revealed that vancomycin treatment was associated with SAB-related mortality when independent predictors for SAB-related mortality and propensity score were considered (adjusted odds ratio of 3.3, 95% confidence interval of 1.2 to 9.5). In the case-control study using the objective matching scoring system and the propensity score system, SAB-related mortality in case patients was 37% (10/27) and in control patients 11% (6/54) ($P < 0.01$). Our data suggest that vancomycin is inferior to beta-lactam in the treatment of MSSA-B.

Vancomycin is used widely for empirical treatment of patients with suspected gram-positive bacteremia, as the prevalence of methicillin-resistant *Staphylococcus aureus* infections has increased (20). Occasionally, some physicians continue to administer vancomycin as the principal antibacterial treatment for confirmed methicillin-susceptible *S. aureus* bacteremia (MSSA-B) (20). Previous in vitro studies demonstrated that vancomycin may be less efficient than β-lactam antibiotics (1, 15, 18). However, limited clinical studies on the outcome of vancomycin treatment compared with that of beta-lactam treatment in patients with MSSA-B are available (1, 4, 6, 7, 8, 10, 18, 20, 21). Use of a careful study design would answer this important clinical question, as prospective clinical trials on this issue are neither feasible nor ethical. We thus performed this study to evaluate the effect of vancomycin treatment compared with that of beta-lactam treatment on the outcome of patients with MSSA-B, using different and complementary approaches: a retrospective cohort study using propensity score to adjust for confounding by treatment assignment and a matched case-control study.

MATERIALS AND METHODS

Study population. This study was conducted at Seoul National University Hospital, Seoul, South Korea, and Seoul National University Bundang Hospital, Gyunggi province, South Korea. These two hospitals are university-affiliated hospitals with 1,500 beds and 900 beds, respectively. The hospitals provide specialized medical and surgical care, including bone marrow and solid-organ transplantation for adult (>15 years of age) patients.

All patients with blood cultures positive for *S. aureus* were identified from a retrospective review of the computerized records of the clinical microbiology laboratories between 1 January 1998 and 31 December 2006. Methicillin susceptibility was determined by the oxacillin test using criteria of the CLSI (formerly NCCLS) (17). Only the first clinically significant episode of *S. aureus* bacteremia (SAB) for each patient was included in the analysis. Patients who had SAB as part of a polymicrobial bloodstream infection were excluded.

Study design. The first part of the study was a retrospective cohort study including 294 MSSA-B cases out of total SAB cases. The outcomes for 27 patients with vancomycin treatment were compared with the outcomes for 267 patients with beta-lactam treatment. The second part of the study was two matched (1:2) case-control studies. For the purpose of this study, the patients with MSSA-B treated with vancomycin are designated "cases" and those with MSSA-B treated with beta-lactam "controls".

Definitions. (i) Terms. SAB was classified as community acquired if *S. aureus* was isolated from blood cultures drawn within 72 h of admission and if the patient had any suggestive symptoms or signs of infection on admission (14). Previous admission history was defined as hospitalization within 30 days before the onset of SAB. Previous antibiotic use was defined as a case in which a patient had been treated with any antimicrobial agent for more than 7 days during the month prior to the SAB. Previous surgery was defined as a case in which a patient had had an operation within the last month before the SAB (19). Neutropenia was defined as an absolute neutrophil count of $\leq 500/mm^3$ when bacteremia occurred.

(ii) Foci of bloodstream infection. The primary foci of infection were determined using the following definitions. Catheter-related infection was considered the source of bacteremia (11) if (a) the culture of a specimen of purulent drainage from the insertion site grew *S. aureus* which had the same resistance pattern as the culture isolate from the peripheral blood or the clinical signs improved within 2 to 3 days after the catheter had been removed and (b) no other source for bacteremia existed. Pneumonia was considered the source of SAB if (a) the patient had clinical symptoms and signs of a lower respiratory tract infection and (b) there was radiological evidence of pulmonary infiltrates not attributable to other causes (9). Soft tissue infection was considered the source

* Corresponding author. Mailing address: Department of Internal Medicine, Seoul National University College of Medicine, 28 Yongundong, Chongrogu, Seoul 110-744, Republic of Korea. Phone: 82-2-2072-2945. Fax: 82-2-762-9662. E-mail: mdohmd@snu.ac.kr.

▽ Published ahead of print on 5 November 2007.

of SAB in cases where patients (a) had a culture of *S. aureus* from a tissue or a drainage specimen from the affected site and (b) had signs of infection (9). Surgical wound infection was defined according to the definitions of the Centers for Disease Control and Prevention (5). If a primary focus of infection could not be determined, it was considered to be unknown. Eradicated foci of infection were classified as described in a previous report (14).

(iii) Antibiotic treatment and outcome. The vancomycin treatment group was defined as the patients for whom vancomycin or teicoplanin was used for the majority of their treatment course (more than 75% of the total duration of antibiotic treatment) (20). The beta-lactam treatment group was defined as the patients for whom beta-lactam was used for the majority of their treatment course (more than 75% of the total duration of antibiotic treatment) (20). The treatment outcomes of SAB were assessed at 12 weeks after the onset of SAB, according to the following criteria: cure (resolution of clinical signs of infection during therapy and no evidence of recurrent SAB within 12 weeks of follow-up), recurrence (clinical resolution of signs and symptoms of infection during therapy but recurrent SAB within 12 weeks of follow-up), non-SAB-related mortality (death due to underlying diseases or another process, with no evidence of *S. aureus* infection at the time of death), and SAB-related mortality (death occurring before the resolution of symptoms or signs or within 7 days from the onset of SAB and if there was no other explanation) (13, 14).

Propensity score and matching process. Logistic regression was used to model the probability of treatment with vancomycin, based on observed baseline characteristics (Table 1). The predicted probability of the model was used as the propensity score for each patient. The multivariate regression model of propensity for using vancomycin had an area under the receiver operating characteristic curve of 0.80, indicating good discrimination between patients treated with vancomycin and those treated with beta-lactam.

We conducted two matched case-control studies. One used an objective matching scoring system. Each patient with vancomycin treatment (case patient) was matched with a patient (1:2 ratio) with β-lactam treatment (control patient) who was selected according to age, sex, McCabe and Jackson classification of severity of underlying illness (classified as rapidly fatal when death was expected within a period of days or weeks, ultimately fatal when death was expected within a period of months or years, and nonfatal when death was not expected), main underlying disease, and length of hospital stay before SAB (stratified in four categories: <72 h, 3 to 7 days, 8 to 28 days, and >28 days) (9, 13). To select the best control for each case patient, we used a 14-point scoring system, based on the above-listed matching variables, similar to that described elsewhere (9, 13): matching for age (three points if age difference was ≤5 years, two points if age difference was 6 to 10 years, no points if age difference was >10 years); matching for sex (two points in case of concordance, no points in case of discordance); matching for the same McCabe and Jackson classification of severity of illness as rapidly fatal, ultimately fatal, or nonfatal (three points for concordance, no points for discordance); matching for the same main underlying disease as hematologic malignancy, solid tumor, liver cirrhosis, end stage renal disease, cardiovascular disease, other diseases, or no disease (three points for concordance, no points for discordance); and matching for the same length of hospital stay before SAB (three points if in the same category as mentioned above, no points if not). The best control patient was selected on a subject-to-subject basis using the above-described scoring system. If several control patients had the same point score, two of them were selected at random. Control patients were chosen without knowledge of the patients' survival status.

For the other matched case-control study, patients who received vancomycin treatment were matched to patients who received beta-lactam treatment and had the closest propensity scores. In the case of three or more potential controls, two control patients were selected randomly. Control patients were also chosen without knowledge of the patients' survival status.

Statistical analysis. The results were analyzed using the SPSS version 12.0 for Windows software package (SPSS Inc., Chicago, IL). The categorical variables were compared by Fisher's exact tests or Pearson χ^2 tests, as appropriate, and the continuous variables were compared by the Mann-Whitney U test or the Student *t* test. McNemar's test with continuity correction was performed to test the comparison of SAB-related mortality for the case and control patients. All tests of significance were two-tailed, and a *P* value of ≤0.05 was considered significant. The effect of vancomycin treatment on SAB-related mortality was analyzed by performing a forward stepwise logistic regression analysis, with and without calculating the propensity score into the model.

TABLE 1. Clinical characteristics and outcomes of 294 patients with MSSA-B who were enrolled in the cohort study

Characteristic	Vancomycin treatment (n = 27)[a]	Beta-lactam treatment (n = 267)[a]	*P* value
Age (yr, mean ± SD)	52.1 ± 18.4	56.0 ± 17.4	0.26
Male gender	16 (59)	164 (61)	0.83
Community-acquired infection	12 (44)	147 (55)	0.29
Length of hospital stay before SAB			
<72 h	12 (44)	147 (55)	0.29
3–7 days	3 (11)	32 (12)	0.89
8–28 days	8 (30)	65 (24)	0.47
>28 days	4 (15)	23 (9)	0.29
McCabe classification			
Nonfatal	6 (22)	97 (36)	0.14
Ultimately fatal	13 (48)	120 (45)	0.75
Rapidly fatal	8 (30)	50 (19)	0.18
Underlying diseases			
Solid tumor	5 (19)	55 (21)	0.80
Hematologic malignancy	7 (26)	51 (19)	0.40
Liver cirrhosis	5 (19)	49 (18)	0.98
End stage renal disease	3 (11)	32 (12)	0.89
Cardiovascular disease	7 (26)	17 (6)	0.003
Primary sites of infection			
Unknown	10 (37)	84 (32)	0.55
Catheter-related infection[b]	3 (11)	62 (23)	0.15
Pneumonia	3 (11)	25 (9)	0.77
Soft tissue infection	2 (7)	42 (16)	0.40
Surgical wound infection	2 (7)	10 (4)	0.30
Eradicated foci of infection	8 (30)	94 (35)	0.56
Neutropenia	8 (30)	40 (15)	0.06
Infection acquired in intensive care unit	5 (19)	17 (6)	0.04
Previous admission history	10 (37)	86 (32)	0.61
Previous antibiotic use	15 (56)	71 (27)	0.002
Previous surgery	3 (11)	23 (9)	0.72
Defervescence (days, mean ± SD)	5.0 ± 6.2	3.5 ± 2.8	0.08
Duration of treatment[c] (days, mean ± SD)	20.2 ± 12.4	21.9 ± 13.9	0.63
Combination treatment	0 (0)	11 (4)	0.61
Metastatic infection	8 (30)	50 (18)	0.18
Infective endocarditis	4 (15)	9 (3)	0.02
Overall deaths	11 (41)	65 (24)	0.06
30-day deaths	9 (33)	49 (18)	0.06
14-day deaths	9 (33)	40 (15)	0.03
SAB-related deaths	10 (37)	47 (18)	0.02
Deaths not related to SAB	1 (4)	20 (8)	0.71
Recurrence	0 (0)	7 (3)	0.39
Cure	16 (59)	200 (75)	0.08

[a] Data are presented as the number (%) of patients unless indicated otherwise.
[b] Catheter was removed in 60 (92%) of 65 patients with catheter-related infection.
[c] A total of 218 patients, excluding 76 patients who died, were included in this analysis.

TABLE 2. Variables associated with *S. aureus*-related mortality in 294 patients with MSSA-B (cohort study)

Characteristic	Univariate analysis		Multivariate analysis[a]		Multivariate analysis[b]	
	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Old age (≥65 yr)	1.4 (0.8–2.5)	0.29				
Male gender	1.0 (0.6–1.8)	0.98				
Community-acquired infection	1.2 (0.7–2.2)	0.52				
McCabe classification (ultimately fatal or rapidly fatal)	7.3 (2.8–19.0)	<0.001	2.7 (0.9–7.7)	0.06	2.7 (0.9–7.7)	0.06
Underlying diseases						
Solid tumor	6.8 (3.6–13.1)	<0.001	4.7 (2.2–9.9)	<0.001	4.8 (2.2–10.3)	<0.001
Hematologic malignancy	0.4 (0.2–1.0)	0.06				
Liver cirrhosis	4.5 (2.4–8.6)	<0.001	3.4 (1.6–7.3)	0.002	3.4 (1.6–7.4)	0.002
End stage renal disease	0.4 (0.1–1.2)	0.09				
Cardiovascular disease	0.8 (0.3–2.5)	0.75				
Primary sites of infection						
Unknown	3.0 (1.7–5.4)	0.001				
Catheter-related infection	0.1 (0.0–0.4)	0.002				
Pneumonia	2.6 (1.1–6.0)	0.03	2.7 (0.9–7.3)	0.046	2.7 (0.9–7.3)	0.06
Soft tissue infection	0.6 (0.2–1.5)	0.30				
Surgical wound infection	0.8 (0.2–3.9)	0.81				
Eradicated foci of infection	0.2 (0.1–0.4)	<0.001	0.3 (0.1–0.7)	0.006	0.3 (0.1–0.7)	0.006
Infection acquired in intensive care unit	1.6 (0.6–4.4)	0.34				
Inappropriate empirical treatment	1.0 (0.4–2.3)	0.98				
Vancomycin treatment	2.8 (1.2–6.4)	0.02	3.4 (1.2–9.3)	0.02	3.3 (1.2–9.5)	0.02

[a] Adjusted for the variables associated with *S. aureus*-related mortality.
[b] Adjusted for the variables associated with *S. aureus*-related mortality and the propensity score of each patient's likelihood of being treated with vancomycin.

RESULTS

Cohort study. During the study period, 298 patients with MSSA-B were identified. Of these, one patient who received teicoplanin and three patients who received quinolone were excluded in the final analysis. Of 294 MSSA-B patients, 216 (73%) were cured and 7 (2%) recurred. The overall death rate, non-SAB-related death rate, and SAB-related death rate at 12 weeks after the onset of SAB were 26% (76/294), 7% (21/294), and 19% (57/294), respectively. Of 57 patients with SAB-related deaths, 48 (84%) died within 14 days of collection of a blood sample for culture and 54 (95%) within 30 days. The mean time (±standard deviation [SD]) from the onset of bacteremia to SAB-related death was 9.3 ± 8.9 days (range of 1 to 38 days). Twenty-seven (9%) of 294 patients with MSSA-B were classified as the vancomycin treatment group. Serum vancomycin levels were monitored in 14 (52%) of the total 27 patients with vancomycin treatment. The mean trough vancomycin level (±SD) was 14.8 (±6.3) μg/ml. The remaining 267 MSSA-B patients were classified as the beta-lactam treatment group.

The clinical characteristics of MSSA-B patients receiving vancomycin and those receiving beta-lactam are shown in Table 1. MSSA-B patients treated with vancomycin were more associated with factors such as previous antibiotic use, neutropenia, underlying cardiovascular disease, and infection acquired in an intensive care unit than those treated with beta-lactam. By use of these characteristics, a multivariate logistic regression model to calculate the propensity score was developed, and this model included the following variables: old age (>65 years), previous antibiotic use, and underlying cardiovascular disease.

SAB-related mortality (37% versus 18%, $P = 0.02$) and 14-day mortality (33% versus 15%, $P = 0.03$) were significantly higher in the vancomycin group than in the beta-lactam group, while overall mortality (41% versus 24%, $P = 0.06$) and 30-day mortality (33% versus 18%, $P = 0.06$) did not show statistical significant differences between the vancomycin treatment group and the beta-lactam treatment group. Table 2 shows results of univariate analysis and multivariate analysis of the association of possible risk factors with SAB-related mortality.

Matched case-control study. There were 54 pairs of case and control patients who were matched for age, sex, McCabe and Jackson classification of severity of underlying illness, main underlying disease, and length of hospital stay. Overall, on the 14-point matching scale, the 54 controls had an average score of 12.2 points (SD of 1.7, range of 8 to 14). Baseline clinical characteristics and outcomes are shown in Table 3. SAB-related mortality in case patients was 37% (10/27) and in control patients 11% (6/54) ($P < 0.001$, McNemar's test). Thirty-six matched pairs had a concordant outcome (31 pairs lived and five died). Eighteen pairs had a discordant outcome; in 17 of these, the case patient died and the control patient lived, and in one the case patient lived and the control patient died. Furthermore, time-specific mortality, such as 14-day or 30-day

TABLE 3. Comparison of clinical characteristics and outcomes of patients with MSSA-B receiving vancomycin treatment versus beta-lactam antibiotic treatment in the matched case-control study

Characteristic	Objective matching scoring system			Propensity score system		
	Vancomycin treatment ($n = 27$)[a]	Beta-lactam treatment ($n = 54$)[a]	*P* value	Vancomycin treatment ($n = 27$)[a]	Beta-lactam treatment ($n = 54$)[a]	*P* value
Propensity score for vancomycin treatment (mean ± SD)	0.17 ± 0.10	0.13 ± 0.14	0.16	0.17 ± 0.10	0.18 ± 0.14	0.77
Age (yr, mean ± SD)	52.1 ± 18.4	52.9 ± 17.6	0.85	52.1 ± 18.4	51.6 ± 17.6	0.92
Male gender	16 (59)	36 (67)	0.51	16 (59)	40 (74)	0.17
Community-acquired infection	12 (44)	27 (50)	0.64	12 (44)	21 (39)	0.63
Length of hospital stay before SAB						
<72 h	12 (44)	27 (50)	0.64	12 (44)	21 (39)	0.63
3–7 days	3 (11)	4 (7)	0.68	3 (11)	4 (7)	0.68
8–28 days	9 (30)	17 (35)	0.87	9 (30)	23 (43)	0.42
>28 days	4 (15)	6 (11)	0.72	4 (15)	6 (11)	0.72
McCabe classification						
Nonfatal	6 (22)	13 (24)	0.85	6 (22)	16 (30)	0.48
Ultimately fatal	13 (48)	30 (56)	0.53	13 (48)	31 (57)	0.43
Rapidly fatal	8 (30)	11 (20)	0.35	8 (30)	7 (13)	0.13
Main underlying diseases						
Solid tumor	5 (19)	11 (20)	0.84	5 (19)	4 (7)	>0.99
Hematologic malignancy	7 (26)	15 (28)	0.86	7 (26)	21 (39)	0.25
Liver cirrhosis	5 (19)	10 (19)	>0.99	5 (19)	6 (11)	0.85
End stage renal disease	3 (11)	7 (13)	0.81	3 (11)	7 (13)	0.81
Cardiovascular disease	7 (26)	8 (15)	0.23	7 (26)	10 (19)	0.44
Primary sites of infection						
Unknown	10 (37)	22 (41)	0.75	10 (37)	15 (28)	0.40
Catheter-related infection	3 (11)[b]	8 (15)[b]	0.74	3 (11)[c]	16 (30)[c]	0.06
Pneumonia	3 (11)	7 (13)	0.81	3 (11)	4 (7)	0.68
Soft tissue infection	2 (7)	5 (9)	0.78	2 (7)	10 (19)	0.32
Surgical wound infection	2 (7)	4 (7)	>0.99	2 (7)	5 (9)	0.78
Eradicated foci of infection	8 (30)	13 (24)	0.59	8 (30)	22 (41)	0.33
Neutropenia	8 (30)	15 (28)	0.78	8 (30)	16 (30)	0.92
Infection acquired in intensive care unit	5 (19)	7 (13)	0.52	5 (19)	5 (9)	0.29
Previous admission history	10 (37)	21 (39)	0.87	10 (37)	30 (56)	0.12
Previous antibiotic use	15 (56)	22 (41)	0.21	15 (56)	40 (74)	0.09
Previous surgery	3 (11)	7 (13)	0.81	3 (11)	8 (15)	0.65
Defervescence (days, mean ± SD)	5.0 ± 6.2	4.0 ± 3.1	0.41	5.1 ± 6.3	3.4 ± 2.1	0.14
Duration of treatment (days, mean ± SD)	20.2 ± 12.4[d]	23.0 ± 14.4[d]	0.49	20.2 ± 12.4[e]	20.8 ± 12.1[e]	0.86
Combination treatment	0 (0)	0 (0)	>0.99	0 (0)	0 (0)	>0.99
Metastatic infection	8 (30)	12 (22)	0.47	8 (30)	15 (28)	0.86
Infective endocarditis	4 (15)	3 (6)	0.21	4 (15)	1 (2)	0.04
Overall deaths	11 (41)	8 (15)	0.009	11 (41)	10 (19)	0.03
30-day deaths	9 (33)	7 (13)	0.03	9 (33)	6 (11)	0.02
14-day deaths	9 (33)	7 (13)	0.03	9 (33)	4 (7)	0.008
SAB-related deaths	10 (37)	6 (11)	0.006	10 (37)	6 (11)	0.006
Deaths not related to SAB	1 (4)	2 (4)	>0.99	1 (4)	5 (9)	0.66
Recurrence	0 (0)	3 (6)	0.55	0 (0)	2 (4)	0.56
Cure	16 (59)	44 (82)	0.03	16 (59)	43 (80)	0.05

[a] Data are presented as the number (%) of patients unless indicated otherwise.
[b] Catheter was removed in 10 (91%) of 11 patients with catheter-related infection.
[c] Catheter was removed in 16 (84%) of 19 patients with catheter-related infection.
[d] A total of 62 patients, excluding 19 patients who died, were included in this analysis.
[e] A total of 60 patients, excluding 21 patients who died, were included in this analysis.

mortality, and overall mortality in case patients were significantly higher than those in control patients in this case-control study using the objective matching scoring system.

In addition, we performed a propensity score-matched case-control study. There were 54 pairs of case and control patients who were matched on the basis of randomly selected closest propensity scores (Table 3). SAB-related mortality in case patients was 37% (10/27) and in control patients 11% (6/54) (P = 0.006, McNemar's test). Thirty-two matched pairs had a concordant outcome (30 pairs lived and two died). Twenty-two pairs had a discordant outcome; in 18 of these, the case patient died and the control patient lived, and in four the case patient lived and the control patient died. Furthermore, time-specific mortality, such as 14-day or 30-day mortality, and overall mortality in case patients were significantly higher than those in control patients in this propensity score-matched case-control study.

DISCUSSION

Glycopeptides are intrinsically less active against staphylococci than are antistaphylococcal beta-lactams (2, 3). However, this is based on in vitro and in vivo experimental data (1, 15, 18). There are limited clinical studies which have addressed the outcome of vancomycin treatment compared with that of beta-lactam treatment in patients with MSSA-B. Previous small studies suggested that vancomycin treatment was associated with higher mortality and relapse rate or longer duration of bacteremia than beta-lactam treatment (6, 7, 8, 10, 18). However, these studies included patients with methicillin-resistant *S. aureus* infections treated with vancomycin (6, 7, 8, 10, 18). Two previous studies addressed this issue extensively (4, 21). However, the conclusion was weakened by the inadequate adjustment of confounding variables (4, 21). A recent study analyzed 123 hemodialysis-dependent patients with MSSA-B, including 77 patients receiving vancomycin and 46 receiving beta-lactam (20). The authors showed that vancomycin treatment in these patients with MSSA-B was associated with treatment failure (composite end point defined as death or recurrent infection). However, they found no significant difference in mortality between patients undergoing vancomycin treatment and patients undergoing beta-lactam treatment. In the current study, we demonstrated that patients with MSSA-B treated with vancomycin were at a higher risk of SAB-related deaths than were those receiving beta-lactam.

Vancomycin treatment was more closely correlated with previous antibiotic use, underlying cardiovascular disease, neutropenia, infection acquired in an intensive care unit, severe underlying disease, or long hospitalization than beta-lactam treatment. Therefore, uneven baseline clinical characteristics may distort the comparison of outcomes between vancomycin and beta-lactam treatment groups. Thus, an association of vancomycin treatment with mortality may have underestimated the efficacy of the vancomycin treatment due to inadequate adjustment for underlying disease or severity of clinical condition. Therefore, we applied different and complementary approaches for reducing the effects caused by these potential confounders. First, univariate and multivariate analyses in our cohort study revealed a significant association of vancomycin treatment with SAB-related mortality in patients with MSSA-B (odds ratio [OR] of 2.8, 95% confidence interval [95% CI] of 1.2 to 6.4; adjusted OR of 3.4, 95% CI of 1.2 to 9.3). In addition, when patients with vancomycin treatment were carefully matched with those with beta-lactam treatment by the objective score system, the impact of vancomycin treatment on outcome also remained significant (attributable SAB-related mortality of 26.0%, 95% CI of 6.4 to 45.6).

Propensity scoring is a powerful tool to compensate for the bias created by unequal chances of receiving different antibiotic treatments (12). We have thus performed an additional analysis by using a propensity score to adjust for potential differences between vancomycin treatment and beta-lactam treatment. This additional analysis showed that vancomycin treatment was associated with SAB-related mortality when independent predictors for SAB-related mortality and propensity score were considered (adjusted OR of 3.3, 95% CI of 1.2 to 9.5). Furthermore, the propensity score-matched case-control study revealed that vancomycin treatment was significantly associated with increased mortality. We think that consistency in these different analytic approaches strengthens our finding on this important clinical question. Thus, our data support that vancomycin should be avoided as an alternative treatment to beta-lactam in patients with MSSA-B.

The limitation of this study was that we did not attempt to determine the factors influencing vancomycin treatment in the attending physicians' use of antibiotic treatment in patients with MSSA-B. Hence, we cannot rule out the possibility that any unmeasured confounding factor affects our results. One may be concerned that the comparative analysis between the vancomycin treatment group and the beta-lactam treatment group is not reasonable because the number of case patients was about 10-fold smaller than the number of control patients. However, we conducted a matched case-control study with a 1:2 ratio to overcome this uneven distribution of patients.

Some might also criticize that overall mortality or time-specific mortality is more objective as an outcome measure than infection-specific (or -related) mortality. However, we think that infection-related mortality, if it could be measured objectively, is more suitable for the object of our study since time-specific mortality might be affected by several factors other than infection itself. Indeed, according to a recent paper on a systemic review of the methods used to access the association between antibiotics and mortality, six (75%) of eight studies of SAB used infection-related mortality as the definition of mortality (16). In our study, SAB-related mortality was relatively high (19%, 57 of 294 patients). This is because many of our patients had other serious underlying conditions, including old age, liver cirrhosis, and cancer. This may limit the generalizability of our findings.

In conclusion, our data suggest that vancomycin treatment adversely affects outcome in patients with MSSA-B. Therefore, our study supports the view that vancomycin treatment should be avoided in patients with MSSA-B when the use of beta-lactam antibiotics is possible.

REFERENCES

1. **Apellaniz, G., M. Valdes, R. Perez, F. Martin, F. Soria, A. Garcia, J. Gomez, and T. Vicente.** 1991. Comparison of the effectiveness of various antibiotics in the treatment of methicillin-susceptible *Staphylococcus aureus* experimental infective endocarditis. J. Chemother. **3:**91–97.
2. **Chambers, H. F.** 1997. Parenteral antibiotics for the treatment of bacteremia and other serious staphylococcal infections, p. 583–601. *In* K. B. Crossley and

G. L. Archer (ed.), The staphylococci in human disease. Churchill Livingstone, Inc., New York, NY.
3. **Chang, F. Y.** 2000. *Staphylococcus aureus* bacteremia and endocarditis. J. Microbiol. Immunol. Infect. **33:**63–68.
4. **Chang, F. Y., J. E. Peacock, Jr., D. M. Musher, P. Triplett, B. B. MacDonald, J. M. Mylotte, A. O'Donnell, M. M. Wagener, and V. L. Yu.** 2003. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine **82:**333–339.
5. **Culver, D. H., T. C. Horan, R. P. Gaynes, W. J. Martone, W. R. Jarvis, T. G. Emori, S. N. Banerjee, J. R. Edwards, J. S. Tolson, and T. S. Henderson.** 1991. Surgical wound infection rates by wound class, operative procedure, and patient risk index: National Nosocomial Infections Surveillance System. Am. J. Med. **91**(Suppl. 3B)**:**152S–157S.
6. **Fowler, V. G., Jr., L. K. Kong, G. R. Corey, G. S. Gottlieb, R. S. McClelland, D. J. Sexton, D. Gesty-Palmer, and L. J. Harrell.** 1999. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. J. Infect. Dis. **179:**1157–1161.
7. **Gentry, C. A., K. A. Rodvold, R. M. Novak, R. C. Hershow, and O. J. Naderer.** 1997. Retrospective evaluation of therapies for *Staphylococcus aureus* endocarditis. Pharmacotherapy **17:**990–997.
8. **Gonzalez, C., M. Rubio, J. Romero-Vivas, M. Gonzalez, and J. J. Picazo.** 1999. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin. Infect. Dis. **29:**1171–1177.
9. **Harbarth, S., O. Rutschmann, P. Sudre, and D. Pittet.** 1998. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus*. Arch. Intern. Med. **158:**182–189.
10. **Khatib, R., L. B. Johnson, M. G. Fakih, K. Riederer, A. Khosrovaneh, M. Shamse Tabriz, M. Sharma, and S. Saeed.** 2006. Persistence in *Staphylococcus aureus* bacteremia: incidence, characteristics of patients and outcome. Scand. J. Infect. Dis. **38:**7–14.
11. **Kim, S. H., C. I. Kang, H. B. Kim, S. S. Youn, M. D. Oh, E. C. Kim, S. Y. Park, B. K. Kim, and K. W. Choe.** 2003. *Staphylococcus aureus* bacteremia and outcomes of Hickman catheter salvage in febrile neutropenic cancer patients. Infect. Control Hosp. Epidemiol. **24:**897–904.
12. **Kim, S. H., W. B. Park, C. S. Lee, C. I. Kang, J. W. Bang, H. B. Kim, N. J. Kim, M. D. Oh, E. C. Kim, and K. W. Choe.** 2006. Outcome of inappropriate empirical antibiotic therapy in patients with *Staphylococcus aureus* bacteremia: analytical strategy using propensity scores. Clin. Microbiol. Infect. **12:** 13–21.
13. **Kim, S. H., W. B. Park, K. D. Lee, C. I. Kang, J. W. Bang, H. B. Kim, M. D. Oh, E. C. Kim, and K. W. Choe.** 2004. Outcome of inappropriate initial antimicrobial treatment in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. J. Antimicrob. Chemother. **54:**489–497.
14. **Kim, S. H., W. B. Park, K. D. Lee, C. I. Kang, H. B. Kim, M. D. Oh, E. C. Kim, and K. W. Choe.** 2003. Outcome of *Staphylococcus aureus* bacteremia in patients with eradicable foci versus noneradicable foci. Clin. Infect. Dis. **37:**794–799.
15. **LaPlante, K. L., and M. J. Rybak.** 2004. Impact of high-inoculum *Staphylococcus aureus* on the activities of nafcillin, vancomycin, linezolid, and daptomycin, alone and in combination with gentamicin, in an in vitro pharmacodynamic model. Antimicrob. Agents Chemother. **48:**4665–4672.
16. **McGregor, J. C., S. E. Rich, A. D. Harris, E. N. Perencevich, R. Osih, T. P. Lodise, Jr., R. R. Miller, and J. P. Furuno.** 2007. A systemic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin. Infect. Dis. **45:**329–337.
17. **National Committee for Clinical Laboratory Standards.** 2003. Performance standards for antimicrobial disk susceptibility tests, 8th ed. Approved standard M100-S13(M2). NCCLS, Wayne, PA.
18. **Small, P. M., and H. F. Chambers.** 1990. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug abusers. Antimicrob. Agents Chemother. **34:**1227–1231.
19. **Soriano, A., J. A. Martínez, J. Mensa, F. Marco, M. Almela, A. Moreno-Martínez, F. Sánchez, I. Muñoz, M. T. Jiménez de Anta, and E. Soriano.** 2000. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. Clin. Infect. Dis. **30:**368–373.
20. **Stryjewski, M. E., L. A. Szczech, D. K. Benjamin, Jr., J. K. Inrig, Z. A. Kanafani, J. J. Engemann, V. H. Chu, M. J. Joyce, L. B. Reller, G. R. Corey, and V. G. Fowler, Jr.** 2007. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Clin. Infect. Dis. **44:**190–196.
21. **Tam, V. H., N. L. Jumbe, L. L. Briceland, and M. H. Miller.** 2001. Treatment of staphylococcal bacteremia in hemodialysis patients: a report of 30 cases. J. Infect. Dis. Pharmacother. **5:**11–20.