MAJOR ARTICLE

Antibiotic Choice May Not Explain Poorer Outcomes in Patients With *Staphylococcus aureus* Bacteremia and High Vancomycin Minimum Inhibitory Concentrations

Natasha E. Holmes,[1] John D. Turnidge,[2,3] Wendy J. Munckhof,[4,5] James O. Robinson,[6] Tony M. Korman,[7,8] Matthew V. N. O'Sullivan,[9] Tara L. Anderson,[10,11] Sally A. Roberts,[2] Wei Gao,[12] Keryn J. Christiansen,[13,14] Geoffrey W. Coombs,[13] Paul D. R. Johnson,[1,15,16,a] and Benjamin P. Howden[1,12,15,17,a]

[1]Department of Infectious Diseases, Austin Health, Heidelberg; [2]Division of Laboratory Medicine, Women's and Children's Hospital, North Adelaide; [3]Department of Pediatrics and Pathology, University of Adelaide; [4]Department of Infectious Diseases, Princess Alexandra Hospital, Woolloongabba; [5]Department of Medicine, University of Queensland, St Lucia; [6]Department of Infectious Diseases, Royal Perth Hospital, East Perth; [7]Department of Medicine, Monash University; [8]Department of Infectious Diseases, Southern Health, Clayton; [9]Department of Infectious Diseases, Westmead Hospital; [10]Department of Infectious Diseases, Royal Hobart Hospital; [11]Department of Medicine, University of Tasmania, Hobart; [12]Department of Microbiology, Austin Health, Heidelberg; [13]Department of Microbiology and Infectious Diseases, Royal Perth Hospital, East Perth; [14]School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Perth; [15]Department of Microbiology, Monash University; [16]Department of Medicine and [17]Department of Microbiology and Immunology, University of Melbourne, Parkville

(See the editorial commentary by Holland and Fowler Jr, on pages 329–31.)

Background. There are concerns about reduced efficacy of vancomycin in patients with *Staphylococcus aureus* bacteremia (SAB), especially when the minimum inhibitory concentration (MIC) nears the upper limit of the susceptible range.

Methods. We examined the relationship between antibiotic treatment, 30-day mortality, and microbiologic parameters in a large Australasian cohort of patients with SAB.

Results. We assessed 532 patients with SAB from 8 hospitals. All patients with methicillin-resistant *S. aureus* (MRSA) bacteremia were treated with vancomycin, and patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia received either flucloxacillin or vancomycin. Increasing vancomycin MIC was associated with increased mortality in vancomycin-treated patients. However, even in patients with MSSA bacteremia treated with flucloxacillin, mortality was also higher if the vancomycin Etest MIC of their isolate was >1.5 μg/mL, compared with those with lower MIC isolates (26.8% vs 12.2%; $P < .001$). After adjustment in a multivariate model, age, hospital-onset SAB and vancomycin MIC were independently associated with mortality, but methicillin resistance and antibiotic choice were not.

Conclusions. We have confirmed an association between higher vancomycin MIC and increased mortality in patients with SAB, but surprisingly this relationship was not related to the antibiotic treatment received, suggesting that the use of vancomycin per se is not responsible for the poorer outcome.

Staphylococcus aureus is a major cause of community and hospital infections. Mortality associated with *S. aureus* bacteremia (SAB) varies from 13% to 34% [1, 2], and risk factors associated with SAB mortality include age,

Received 17 December 2010; accepted 3 March 2011.

[a]P. D. R. J. and B. P. H. contributed equally to this work.

Potential conflict of interest: N. E. H., J. D. T., W. J. M., T. M. K., G. W. C., K. J. C., P. D. R. J., and B. P. H. have received financial support to attend the "Positive Perspectives" educational seminar sponsored by Novartis Australia. J. D. T. has received financial support from Pfizer Australia and Novartis Australia. W. J. M. has received financial support to attend the "Susceptibility and Resistance: Selecting Appropriate Therapy for Serious Gram Positive Infections" educational seminar sponsored by Novartis Australia. G. W. C. has received financial support to attend the Second Asia Pacific SMART (Study for Monitoring Antimicrobial Resistance Trends) Investigators Meeting 2010 from Merck Sharp & Dohme. B. P. H. was previously a daptomycin advisory board member for Novartis Australia. All other authors: no conflicts.

Correspondence: Natasha Holmes, MBBS, Department of Infectious Diseases, Austin Health, PO Box 5555, Heidelberg VIC 3084, Australia (natasha.holmes@austin.org.au).

The Journal of Infectious Diseases 2011;204:340–47

0022-1899 (print)/1537-6613 (online)/2011/2043-0005$14.00
DOI: 10.1093/infdis/jir270

comorbid conditions, methicillin resistance, and high bacterial burden infections [3, 4]. In a large prospective series published by the Australian and New Zealand Co-operative on Outcomes in Staphylococcal Sepsis (ANZCOSS) we observed a crude 30-day mortality for SAB of 20.6% [5].

The use of vancomycin, a key antimicrobial used to treat methicillin-resistant *S. aureus* (MRSA) bacteremia infections, has been associated with a higher mortality rate than β-lactam therapy for SAB in several observational studies [6–10], as observed in the ANZCOSS analysis [5]. Vancomycin use has been linked to treatment failure [11–13], persistent SAB [8, 12, 14], and increased length of stay [11] in several studies, and there is an established association between higher vancomycin minimum inhibitory concentration (MIC) within the susceptible range and poor vancomycin therapeutic outcomes in MRSA bacteremia [13, 15–20]. Although a range of methods for assessing vancomycin MIC have been used, vancomycin Etest MICs ≥1.5 μg/mL seemed to consistently predict poor outcome in multiple studies [13, 15–17]. These reports have led to increased clinician preference for alternative treatments, such as linezolid, daptomycin, and tigecycline, although none of these antibiotics have demonstrated superiority over vancomycin in head-to-head trials [21].

The ANZCOSS database now includes >7000 prospectively documented cases of SAB. To further investigate the relationship between vancomycin susceptibility and treatment outcome, we identified a subset of patients with either MRSA bacteremia treated with vancomycin or methicillin-susceptible *S. aureus* (MSSA) bacteremia who were treated with vancomycin or flucloxacillin. Using stored initial blood culture isolates and demographic, treatment, and outcome data, we investigated the relationship between isolate MIC, methicillin resistance, age, clinical history, and antibiotic treatment choice on 30-day mortality.

METHODS

Study Design and Population

Patients included in this study were recruited from a large multicenter observational cohort of patients with SAB across 27 sites in Australia and New Zealand (ANZCOSS); recruitment for this database has been described elsewhere [5]. Hospitals and laboratories already contributing data to ANZCOSS were invited to participate in this substudy that included patients who had an episode of MSSA or MRSA bacteremia between January 2007 and November 2008. All vancomycin-treated patients with either MRSA or MSSA bacteremia at each participating substudy site were included. Owing to large numbers of flucloxacillin-treated patients with MSSA, a ''next available'' sampling strategy was employed to create study groups with equal numbers of vancomycin and flucloxacillin-treated patients at each site. Each vancomycin-treated patient was matched with the next patient who received flucloxacillin in date order at each participating site. Patients transferred from nonparticipating hospitals with a diagnosis of SAB but without positive blood cultures at participating sites were excluded.

Ethics

Human ethics committee approval was obtained at each of the substudy participating centers.

Patient Data

Patient clinical data are routinely collected by ANZCOSS for each episode of SAB and submitted using an online web form. Clinical details collected were age, sex, ethnic origin, date of hospital admission, date of hospital discharge, place of onset of bacteremia (hospital vs community), methicillin susceptibility, principal clinical manifestation, presence of indwelling device, receipt of hemodialysis, antibiotic treatment, and mortality outcome at 30 days after first positive blood culture. Regular audits of data quality are undertaken in ANZCOSS, and any inconsistencies were corrected.

Definitions

Bacteremia was defined as ≥1 positive blood cultures with *S. aureus*. Community onset was defined as a blood culture collected within 48 hours of hospital admission or no hospital admission. The principal clinical manifestation was defined as the most prominent symptom or syndrome of the infection as assessed by the treating physician. If there was >1 manifestation, the treating physician assigned the most likely principal clinical manifestation. The presence of any indwelling device was recorded, and bacteremia was defined as device associated according to the treating physician. If >1 device was present, the treating physician determined the principal device associated with infection. Treatment was recorded as the antibiotic selected for definitive treatment once susceptibilities were available. If >1 antibiotic was used, the treating physician assigned the principal antibiotic used. The principal outcome measure was 30-day all-cause mortality from the date of the first positive *S. aureus* blood culture.

Microbiologic Testing

All blood culture isolates were stored at −80°C at each contributing laboratory, and the first positive blood culture from each selected patient was retrieved and transported to a single laboratory for extended testing. All isolates were confirmed as *S. aureus* using tube coagulase and DNase, according to standard methods [22], and screened for methicillin susceptibility using a 30-μg cefoxitin disc, according to Clinical Laboratory and Standards Institute (CLSI) guidelines [23]. Oxacillin MIC testing was performed on MSSA isolates using Etest (bioMérieux), according to the manufacturer's instructions.

Vancomycin MIC measurements were performed on all isolates using Etest, according to the manufacturer's instructions, and broth microdilution, according to CLSI

guidelines [24]. In addition, Etest GRD (bioMérieux) was used to screen for heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and was performed and interpreted according to manufacturer's instructions. hVISA was defined as a strain with a positive Etest GRD and a vancomycin broth microdilution MIC ≤2 μg/mL. Vancomycin-intermediate *S. aureus* (VISA) was defined by vancomycin broth microdilution MIC of 4–8 μg/mL. Control strains used were *S. aureus* ATCC 29213 (positive control), *Enterococcus faecalis* ATCC 29212 (negative control), *S. aureus* ATCC 700698 (Mu3, hVISA control), and *S. aureus* ATCC 700699 (Mu70, VISA control). All MICs were read and confirmed by 2 operators (W. G., N. E. H), who were blinded with respect to the 30-day mortality of the patients from whom the isolates had been obtained. To investigate the clonality of SAB isolates included in the study, a random selection of isolates underwent pulsed-field gel electrophoresis with *Sma*I enzyme restriction using the CHEF DR III system (Bio-Rad), as described elsewhere [25].

Statistical Analysis

The χ^2 test or Fisher's exact test was used for categorical variables, and the Mann–Whitney test for continuous non–normally distributed data. Logistic regression for univariate and multivariate analysis was performed to identify predictors of outcome. Differences were considered statistically significant at $P < .05$. Analysis was performed using Stata software (version 11.0; StataCorp). Missing data per individual variable were excluded from statistical analysis. Goodness of fit of the final model was assessed using the Hosmer-Lemeshow statistic.

RESULTS

Demographics

A total of 568 patients from 8 sites in Australia and New Zealand were eligible for inclusion according to the study criteria (see Appendix); 284 patients were treated with vancomycin and matched with an equal number treated with flucloxacillin. Thirty-six patients were excluded because their isolates were not available ($n = 34$) or the received isolate was not *S. aureus* ($n = 2$). The remaining 532 patients were included, and their *S. aureus* blood culture isolates were tested. Patient characteristics are provided in Table 1. Where data were incomplete, only those patients with a complete response for the variable of interest were evaluated statistically. The majority of patients were adults; only 4.1% ($n = 22$) were <18 years of age. MSSA accounted for 62.0% ($n = 330$) of isolates despite 1:1 matching by principal antibiotic treatment because a subset of patients with MSSA

Table 1. Characteristics of Patients With *Staphylococcus aureus* Bacteremia According to Antibiotic Treatment Received ($n = 532$)

Characteristic	Flucloxacillin (Flu) treatment ($n = 266$)(MSSA)	Vancomycin (Van) treatment ($n = 266$)		P [a]		
		MSSA ($n = 64$)	MRSA ($n = 202$)	Flu-MSSA vs Van-MSSA	Flu-MSSA vs Van-MRSA	Van-MSSA vs Van-MRSA
Age, median (IQR), y [b]	59.2 (42.7–72.8)	63.5 (44.4–78.2)	62.9 (49.0–74.3)	.108	.057	.680
Male sex	184 (69.2)	39 (60.9)	142 (70.3)	.235	.839	.169
White ethnicity	215 (80.8)	55 (85.9)	167 (82.7)	.470	.632	.700
Hospital onset	92 (34.6)	28 (43.8)	118 (58.4)	.393	<.001	.044
Device associated [c]	100/255 (39.2)	20/59 (33.9)	112/191 (58.6)	.552	<.001	.001
Hemodialysis	24/233 (10.3)	10/61 (16.4)	30/142 (21.1)	.184	.006	.564
Principal clinical manifestation [d]						
Device infection without a secondary focus	49 (18.4)	13 (20.3)	54 (26.7)	.723	.033	.327
Skin and skin structure	47 (17.7)	11 (17.2)	31 (15.4)	1.000	.533	.698
Sepsis syndrome	27 (10.2)	4 (6.3)	36 (17.8)	.475	.020	.026
Osteoarticular	32 (12.0)	5 (7.8)	12 (5.9)	.507	.026	.566
Infective endocarditis	33 (12.4)	0 (0)	10 (5.0)	.001	.006	.124
Pneumonia/empyema	13 (4.9)	3 (4.7)	17 (8.4)	1.000	.131	.422
30-d mortality	35/261 (13.4)	11/63 (17.5)	44/199 (22.1)	.423	.018	.482

NOTE. Data represent numbers (%) of patients, unless otherwise indicated. For variables for which data were incomplete, the total number of evaluable patients is indicated. IQR, interquartile range; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a] *P* values were determined by 2-tailed Fisher's exact test for categorical data and by Wilcoxon rank sum test for categorical data. Flu-MSSA vs Van-MSSA, comparison different antibiotic treatments for MSSA bacteremia; Flu-MSSA vs Van-MRSA, comparison of reference standard treatments according to susceptibility; Van-MSSA vs Van-MRSA, comparison vancomycin treatment according to susceptibility.

[b] Data were skewed.

[c] Denominator excludes patients in whom device association was unknown or not recorded.

[d] Owing to small numbers, not all collected subcategories are shown.

Table 2. Distribution of Vancomycin Minimum Inhibitory Concentration (MIC) by Etest and Broth Microdilution Among All Patients ($n = 532$)

	Vancomycin MIC broth microdilution, μg/mL				
Vancomycin MIC Etest, μg/mL	.25	.5	1	2	Total no. (%)
.38	1	0	0	0	1 (.2)
.5	0	2	1	0	3 (.6)
.75	0	8	3	0	11 (2.1)
1	0	26	31	1	58 (10.9)
1.5	0	31	241	5	277 (52.0)
2	0	3	144	12	159 (29.9)
3	0	0	16	7	23 (4.3)
Total no. (%)	1 (.2)	70 (13.1)	436 (82.0)	25 (4.7)	532 (100)

NOTE. Data are expressed as numbers of patients.

bacteremia were predominantly treated with vancomycin. MRSA accounted for 76.0% of isolates in vancomycin-treated patients.

Clinical characteristics of patients were similar between patient groups: MSSA bacteremia treated with flucloxacillin, MSSA bacteremia treated with vancomycin, or MRSA bacteremia treated with vancomycin. The notable exception was endocarditis in MSSA bacteremia; no patients in this category received vancomycin. Overall, vancomycin-treated patients (regardless of the methicillin susceptibility of their isolate) were more likely to be older, have hospital-onset or device-associated SAB, and be recipients of hemodialysis. We were able to establish 30-day mortality in 523 evaluable patients (98.3%). In 9 patients 30-day mortality outcomes were unknown; 6 of these patients had been transferred to institutions not affiliated with ANZCOSS, and medical records were not available for the remaining 3. The 30-day mortality for the whole group was 17.2% (90/523), but was significantly higher for vancomycin-treated patients (55/262; 21.0%) compared with flucloxacillin-treated patients (35/261; 13.4%) ($P = .027$).

Antimicrobial Susceptibility

The distribution of vancomycin MICs by Etest and broth microdilution are shown in Table 2. Vancomycin MICs were higher by Etest than by broth microdilution; however, all isolates were considered vancomycin susceptible according to CLSI broth microdilution methods. Only 2 isolates (0.4%) were categorized as hVISA according to Etest GRD, and VISA was not detected. Approximately one-quarter of MSSA isolates (86/330; 26.1%) had a vancomycin Etest MIC >1.5 μg/mL. The oxacillin MIC in MSSA isolates were all within the susceptible range (≤2 μg/mL); the modal oxacillin MIC was 0.38 μg/mL, and the oxacillin MIC_{90} was 1 μg/mL. Vancomycin MIC was not positively correlated with oxacillin MIC in MSSA isolates (Spearman coefficient $\rho = -.16$; $P = .003$).

30-Day Mortality

Factors potentially associated with 30-day mortality using univariate logistic regression were age, hospital-onset bacteremia, MRSA, treatment with vancomycin, and vancomycin MIC (Table 3).

High Vancomycin MIC and Mortality

Mortality increased as vancomycin MIC by Etest or broth microdilution increased. This was particularly evident when the Etest MIC was >1.5 μg/mL (Figure 1A). We confirmed that an Etest MIC cutoff of 1.5 μg/mL was appropriate by comparing mortality rates according to vancomycin Etest MIC results (1 vs 1.5 μg/mL, $P = 1.000$; 1.5 vs 2 μg/mL, $P = .001$; 2 vs 3 μg/mL, $P = .801$). When patients were stratified into low and high vancomycin MIC groups according to Etest result (≤1.5 and >1.5 μg/mL respectively), mortality rates were 12.2% and 26.8%, respectively, and the difference was highly significant (odds ratio [OR], 2.64; 95% confidence interval [CI], 1.66–4.17; $P < .001$) (Figure 1B).

Surprisingly, the increase in mortality in the high vancomycin MIC group occurred regardless of treatment with vancomycin or flucloxacillin (Figure 1C) with an OR for vancomycin of 2.25 (95% CI, 1.24–4.11; $P = .009$) and an OR for flucloxacillin of 2.82 (95% CI, 1.37–5.82; $P = .007$). Similar mortality results were seen when comparing methicillin susceptibility (MSSA vs MRSA) against the stratified vancomycin MIC groups (Figure 1D), with ORs of 2.52 for MSSA (95% CI, 1.33–4.78; $P = .006$) and 2.36 for MRSA (95% CI, 1.19–4.68; $P = .017$). In patients with MSSA bacteremia, treatment with vancomycin was not associated with increased mortality ($P = .410$) but high vancomycin MIC was ($P = .005$). (This lack of effect for vancomycin treatment was probably due to small sample size, because in the entire ANZCOSS data set, univariate analysis showed a statistically significant association with vancomycin treatment [5]) This means that patients with MSSA infections appropriately treated with flucloxacillin also had higher 30-day mortality rates if the vancomycin Etest MIC of their isolate was >1.5 μg/mL.

Factors associated with high vancomycin MIC on univariate analysis ($P < .05$) were methicillin resistance, hospital onset,

Table 3. Factors Associated With 30-Day All-Cause Mortality Using Logistic Regression With Univariate and Multivariate Models

	All patients (n = 523)			Patients with MSSA bacteremia (n = 324)		
		Multivariate analysis [a]			Multivariate analysis [a]	
Variable	Univariate analysis, P	OR(95% CI)	P	Univariate analysis, P	OR(95% CI)	P
Age	<.001	1.06 (1.04–1.08)	<.001	<.001	1.06 (1.04–1.08)	<.001
High vancomycin Etest MIC [b]	<.001	2.08 (1.24–3.47)	.005	.005	2.44 (1.21–4.92)	.012
Hospital onset	.008	1.75 (1.05–2.92)	.033	.041	1.68 (.85–3.31)	.136
MRSA	.021	1.24 (.55–2.80)	.606	…	…	…
Vancomycin treatment	.023	1.03 (.46–2.31)	.949	.410	…	…
Principal clinical manifestation	.163	1.05 (.97–1.14)	.198	.204	…	…
Device associated [c]	.529	…	…	.242	…	…
Male sex	.551	…	…	.517	…	…
White ethnicity	.761	…	…	.609	…	…

NOTE. Logistic regression was performed using age as a continuous variable and principal clinical manifestation as a categorical variable; the remaining variables were all binary. Analyses excluded patients whose 30-day mortality outcome was recorded as unknown. CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio.

[a] multivariate analysis included variables with P values < .2 at univariate analysis.

[b] Low vancomycin MIC was defined as an Etest result ≤1.5 μg/mL; high vancomycin MIC, as Etest result >1.5 μg/mL.

[c] Denominator excludes patients in whom device association was unknown or not recorded.

vancomycin treatment, device-associated infection, and death. Bivariate comparisons of patient characteristics were performed comparing the low and high vancomycin MIC groups with antibiotic treatment received. In those treated with flucloxacillin, patients in the high vancomycin MIC group were more likely to have skin and skin structure infections (P = .017) and to die (P = .007) compared with the low vancomycin MIC group. In vancomycin-treated patients, those in the high vancomycin MIC group were more likely to have hospital-onset SAB (P = .004), MRSA (P = .004), sepsis syndrome (P = .055) and more likely to die (P = .009).

Molecular Typing of Strains

The subgroup of isolates that underwent pulsed-field gel electrophoresis (n = 60; 11.3%) had characteristics similar to those of the whole cohort; MSSA accounted for 32 (53.3%) of isolates and 30-day mortality was 23.3% (14/60). There was considerable strain diversity in this subgroup, with >20 different pulsotypes, and heterogeneity of pulsotypes was also present among low and high vancomycin MIC isolates (Supplementary Data, Figure 1).

Antibiotic Treatment

Although patients were included in a treatment group based on the predominant therapy received, some patients may have received an alternate antibiotic before their definitive therapy. In particular, patients treated with β-lactams may have been initially treated with vancomycin, which could have caused an increase in vancomycin MIC. To explore this possibility, a large subset of patients (n = 330) had complete antibiotic treatment details available, allowing us to identify 72 patients who received exclusive β-lactam treatment. In these patients treated exclusively with β-lactams, the mortality rates in low and high vancomycin MIC groups were 9.4% and 36.8%, respectively (P = .011).

Multivariate Analysis of Factors Associated With Mortality

Logistic regression was performed with clinical and microbiologic covariates to determine independent factors associated with mortality. Covariates with a P value of <.2 on univariate analysis were included in a multivariate logistic regression model. Patient age, hospital onset of bacteremia, and high vancomycin MIC by Etest >1.5 μg/mL remained statistically significant variables, but methicillin resistance and vancomycin treatment were no longer significant after adjustment in the model (Table 3). Looking specifically at the MSSA subset, patient age and high vancomycin MIC by Etest remained significant variables associated with mortality in the multivariate model, but vancomycin treatment was not (Table 3). Goodness of fit of the final logistic regression models appeared to be satisfactory (Hosmer–Lemeshow statistic, 9.63 [P = .292] for whole cohort and 8.36 [P = .399] for MSSA cohort).

DISCUSSION

SAB and its associated metastatic complications remain a major cause of morbidity, mortality, and cost in community and hospital patients. Vancomycin has been the mainstay of treatment for MRSA infections but there are growing concerns about its efficacy in the treatment of serious staphylococcal infections. Although antistaphylococcal β-lactams are superior to vancomycin for the management of MSSA [7, 9–11], there are situations when vancomycin is preferred, most notably when the patient has a known β-lactam hypersensitivity or a history of β-lactam–related hepatitis and for ease of administration in patients receiving hemodialysis. A number of studies have demonstrated inferior outcomes with vancomycin when the MIC is at the higher end of the susceptible range, although

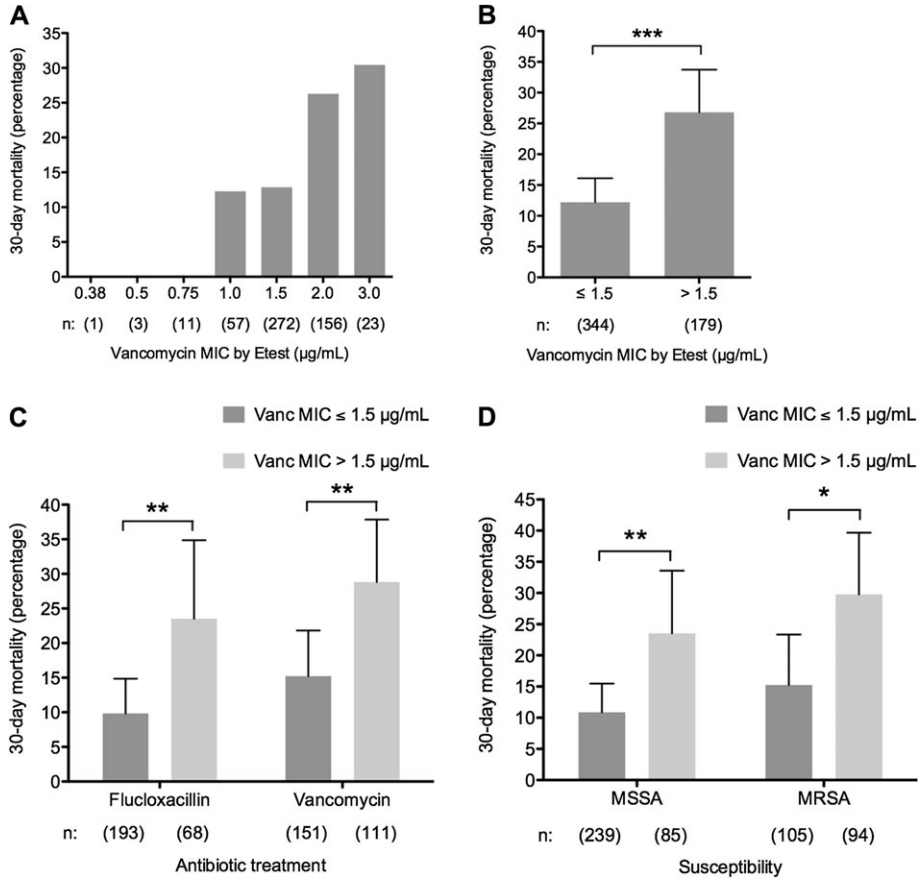

Figure 1. Thirty-day mortality rates according to vancomycin minimum inhibitory concentration (MIC) by Etest (*A*) and stratified by low vs high vancomycin MIC by Etest (*B*), vancomycin (Vanc) MIC group and antibiotic treatment (no patients with methicillin-resistant *Staphylococcus aureus* [MRSA] bacteremia were treated with flucloxacillin) (*C*), or vancomycin MIC group and methicillin susceptibility (*D*). MSSA, methicillin-susceptible *S. aureus*. Error bars represent upper limits of 95% confidence intervals; *P* values, significance of differences between low and high vancomycin MIC groups; numbers below x-axis, total numbers of evaluable patients in each group. Patients with unknown 30-day outcome data were excluded. $***P < .001$, $**P < .01$, $*P < .05$.

most were single-center studies limited to MRSA bacteremia [13, 15–20, 26]. It is therefore understandable that clinicians are increasingly likely to choose alternative agents for high vancomycin MIC infections, despite the lack of evidence that outcomes will be superior.

In this large, multicenter, prospective study of patients with SAB in Australia and New Zealand, there was a 15% difference in mortality between low and high vancomycin MIC groups, similar to rates reported from other MRSA bacteremia studies [13, 15, 16, 18]. However, we have demonstrated for the first time that *S. aureus* vancomycin MIC is associated with 30-day mortality after SAB *irrespective* of whether the antibiotic used for treatment was vancomycin or flucloxacillin. This surprising result suggests that factors other than poor vancomycin efficacy per se are responsible for the inferior outcome in these patients. The implication of this finding is that the increasing use of alternative antimicrobials for the treatment of SAB when the vancomycin MIC of the isolate is >1.5 μg/mL may not lead to the hoped-for improvement in outcome. To explain our surprising results we hypothesize that vancomycin MIC is a still-unidentified marker of host or organism factors that significantly affect treatment outcome. Although counterintuitive, a striking observation from our study is that patients treated with flucloxacillin for MSSA bacteremia also did poorly if their isolate's vancomycin MIC was high despite even if they did not receive vancomycin during their bacteremia episode.

Our decision to use a vancomycin Etest MIC of >1.5 mg/mL as a cutoff between low and high vancomycin MIC is supported by published reports from other authors [13, 15–17]. In a large prospective single-center MRSA bacteremia study by Soriano et al [17], vancomycin Etest MIC ≥2 μg/mL was associated with higher mortality but shock was paradoxically less common. In contrast to Soriano et al, we found a higher rate of sepsis syndrome in patients with a higher vancomycin MIC. Inferior outcomes have also been reported with other methods for MIC determination, such as agar dilution [19] and broth microdilution [20, 26]. Although we also found that increased mortality was associated with increased broth microdilution MIC (data not shown), the trend was not as prominent. MIC by Etest appeared superior to broth microdilution when evaluating

possible predictors of mortality, perhaps because of the increased range of concentrations tested.

Although predictors of high vancomycin MIC have been described for MRSA [27, 28] and include prior vancomycin exposure and intensive care unit onset of bacteremia, this has not been assessed for MSSA. In this study, patients with high vancomycin MIC MSSA were more likely to be older and have skin or skin structure infections. We did not observe a positive correlation between oxacillin MIC and vancomycin MIC; this suggests that rising oxacillin MIC in MSSA is not a confounder for poor outcome in patients treated with flucloxacillin.

There was significant heterogeneity in genetic lineage of *S. aureus* strains, which has been reported by Robinson et al [29] in an Australian study of MRSA bacteremia. Different pulsotypes were present in both MSSA and MRSA, and low and high vancomycin MIC isolates. We interpret this to mean that our results are not explained by the expansion of certain clones that may be associated with elevated vancomycin MIC. We did not find a large subpopulation of hVISA, so vancomycin heteroresistance was unlikely to be the explanation for increased mortality in patients with high vancomycin MIC.

Our study has a number of limitations. First, we did not assess infection-related mortality but instead relied on 30-day all-cause mortality. Although attributable mortality is important, especially considering the proportion of older patients in our study, all-cause mortality is frequently used in SAB studies [12, 15–17, 30]. The ANZCOSS data set does not include information on prior antibiotic exposure, in particular to vancomycin, and data regarding intensive care unit admission was not collected as a routine variable during the study time frame. Specific information about polymicrobial bacteremia was also not collected. This made an analysis of factors leading to higher vancomycin MICs in the *S. aureus* isolates incomplete, but nonetheless we demonstrated a highly significant difference in mortality between vancomycin MIC groups. Other outcomes, such as persistence or recurrence of SAB, were also not evaluated; however, these would be interesting end points to assess the potential impact of high vancomycin MIC on these parameters. Potentially important confounding factors, such as patient comorbidity and pharmacologic data regarding vancomycin dosing and therapeutic drug monitoring, were not recorded within the ANZCOSS framework. We were surprised that we did not find more hVISA in the isolates with vancomycin Etest MICs of 3 μg/mL, but we did not perform the reference standard test (population analysis profile) for detection of hVISA. Nonetheless, after 48 hours of incubation, the Etest GRD has 82%–95% specificity [31]. Finally, molecular typing was performed only in a subset of isolates, but our results suggest that high vancomycin MIC was unlikely to be explained by expansion of a single clone of *S. aureus*.

In summary, this study has demonstrated for the first time that *S. aureus* vancomycin MIC is associated with outcome from SAB irrespective of methicillin susceptibility and choice of antimicrobial treatment. This raises questions regarding the trend in using alternate antimicrobials for the treatment of SAB when the vancomycin MIC of the isolate is >1.5 μg/mL, because the antibiotic choice itself may not be the problem. Although more detailed analysis of factors associated with a high vancomycin MIC in the ANZCOSS cohort may shed light on other factors associated with a poor outcome in SAB, ultimately prospective multicenter studies will be required to investigate further the relationship between vancomycin MIC and outcome in SAB.

Supplementary Data

Supplementary data are available at *The Journal of Infections Diseases* online.

Funding

Funding for microbiologic testing of the isolates was provided by the Australian Society for Antimicrobials.

Acknowledgments

The authors would like to thank Despina Kotsanas for assistance with the ANZCOSS database and Allen Cheng for his thoughtful review of the manuscript. N. E. H. would like to thank Julie Pearson and Hui-Leen Tan from the Gram Positive Bacteria Typing and Research Unit at Royal Perth Hospital for assistance with epidemiologic characterization of strains.

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Appendix

The proportions of isolates contributed according to each site were as follows (in decreasing frequency): Monash Medical Centre, 30.8%; Princess Alexandra Hospital, 23.3%; Westmead Hospital, 16.0%; Austin Health, 12.0%; Royal Perth Hospital, 11.3%; Royal Hobart Hospital, 3.0%; Auckland District Health, 2.8%; and Ipswich Hospital, 0.8%.