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CLINICAL THERAPEUTICS

Impact of Vancomycin MIC on Treatment Outcomes in Invasive *Staphylococcus aureus* Infections

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ABSTRACT There are conflicting data on the association of vancomycin MIC (VAN-MIC) with treatment outcomes in *Staphylococcus aureus* infections. We investigated the relationship between high VAN-MIC and 30-day mortality and identified the risk factors for mortality in a large cohort of patients with invasive *S. aureus* (ISA) infections, defined as the isolation of *S. aureus* from a normally sterile site. Over a 2-year period, 1,027 adult patients with ISA infections were enrolled in 10 hospitals, including 673 (66%) patients with methicillin-resistant *S. aureus* (MRSA) infections. There were 200 (19.5%) isolates with high VAN-MIC (≥1.5 mg/liter) by Etest and 87 (8.5%) by broth microdilution (BMD). The all-cause 30-day mortality rate was 27.4%. High VAN-MIC by either method was not associated with all-cause 30-day mortality, and this finding was consistent across MIC methodologies and methicillin susceptibilities. We conclude that high VAN-MIC is not associated with increased risk of all-cause 30-day mortality in ISA infections. Our data support the view that VAN-MIC alone is not sufficient evidence to change current clinical practice.

KEYWORDS vancomycin, *Staphylococcus aureus*, methicillin resistant, methicillin susceptible, MIC, bacteremia

Infections caused by *Staphylococcus aureus* are a major health problem in both hospital-acquired and community-associated settings (1). Invasive *S. aureus* (ISA) infections, defined as the isolation of *S. aureus* from a normally sterile site (e.g., bacteremia), are associated with high morbidity and mortality (1). Methicillin-resistant *S. aureus* (MRSA) accounts for about 60% of nosocomial *S. aureus* infections, and community-associated MRSA disease has been increasing in Korea (1, 2). Although new antistaphylococcal antibiotics have been developed, vancomycin retains the first-line position as treatment for MRSA infections (3).

In the past decade, reduced susceptibility of *S. aureus* isolates to vancomycin has been a major medical concern. In a number of meta-analyses, infection by MRSA with high vancomycin MICs was associated with treatment failure (4–6). Even in methicillin-

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susceptible *S. aureus* (MSSA) bacteremia, an association between high vancomycin MIC (VAN-MIC) and poor outcomes has been reported, regardless of the choice of antibiotic (7, 8). However, others have found that high VAN-MIC alone was not significantly associated with treatment outcome (9–12). Therefore, we evaluated the relationship between VAN-MIC and 30-day mortality in a large cohort of patients with ISA infections.

RESULTS

Clinical characteristics. Over the 2-year period, a total of 1,600 cases of ISA infection were identified, including 995 (62%) cases of MRSA infection. *S. aureus* isolates were obtained in 1,200 (75%) cases (768 MRSA cases [64%]). Thirty-day mortality was recorded in 1,388 (87%) cases, and the all-cause 30-day mortality rate was 26% (366/1,388). Excluding cases where the data for 30-day mortality and/or the isolate causing the ISA infection was unavailable, 1,027 cases of ISA infection were enrolled in the final analysis.

The median age of the patients was 67 years (interquartile range [IQR], 54 to 74 years), and 649 (63%) were male. Most (87%) ISA infections were community-onset, health care-associated (HCA) infections: 577 (56%) were hospital onset and 314 (31%) were community onset; the remaining 136 (13%) were community-onset, community-associated (CA) infections. All-cause 30-day mortality and *S. aureus*-attributed mortality (SA-mortality) rates were 27% (281 cases) and 18% (185 cases), respectively. Excluding the cases with unknown primary site of infection, the most common primary diagnosis was catheter-associated infection (239 cases, 23%). Skin and soft tissue, bone and joint, and respiratory tract infections were also common.

The clinical spectra and characteristics of the ISA infections are listed in Table 1 according to their VAN-MIC. MRSA infections were more common in the high-VAN-MIC group in both tests. Cerebrovascular disease was the most common underlying disease in the high-VAN-MIC Etest group, and chronic pulmonary disease was the most common one in the high-VAN-MIC broth microdilution (BMD) group. Mediastinal infections were more common in the high-VAN-MIC infections in both tests. Inappropriate empirical antibiotics were more frequently used in the high-VAN-MIC Etest group. In the analysis of definitive antibiotics, beta-lactam antibiotics were used in 70% of MSSA infections, and the remaining 30% received glycopeptides (mostly vancomycin). For MRSA infections, vancomycin was used in 77% of the patients, teicoplanin was used in 15%, and the remaining 8% received linezolid, tigecycline, or other drugs. Daptomycin and anti-MRSA cephalosporins were not available in any of the 10 hospitals in this study.

Microbiological results. MRSA accounted for 66% (673/1,027) of all the infections, most of which (950, 93%) were bloodstream infections (BSIs). Eighteen (1.8%) patients gave positive results for peritoneal fluid, 14 for pleural fluid (1.4%), 12 for cerebrospinal fluid (1.2%), 8 for joint/synovial fluid (0.8%), 11 for deep-tissue samples (1.1%), and 14 for other sterile sites (1.4%).

The distributions of VAN-MIC results according to the methodology employed and methicillin susceptibility are shown in Fig. 1 and in Table S1 in the supplemental material. The numbers of isolates with high VAN-MIC ($\geq$1.5 mg/liter) were 200 (19.5%) by Etest and 87 (8.5%) by BMD. The median proportions of isolates with high VAN-MIC by Etest and BMD in the 10 hospitals were 17.7% (IQR, 12.7 to 21.4%; range, 3.8 to 39.5%) and 8.1% (IQR, 5.6 to 9.9%; range, 1.9 to 16.0%), respectively.

We carried out both tests in triplicate for the 173 isolates showing major discrepancies between the two methods (30 isolates with BMD MIC of 2 mg/liter but Etest MIC of $\leq$1 mg/liter, 143 isolates with Etest MIC of $\geq$1.5 mg/liter but BMD MIC of $\leq$1 mg/liter). The interassay precision of BMD was acceptable (mean of the means, 0.98-fold; standard deviation [SD] of means, 0.094; coefficients of variability [CV], 9.7%). The interassay precision of the Etest was also generally acceptable (mean of the means, 1.04-fold; SD of means, 0.143; CV, 13.7%). The proportion of Etest results that were identical to or differed from the BMD MIC results according to the $\log_2$ dilutions are shown in Fig. S1 in the supplemental material. All MICs by BMD measured by the 2

TABLE 1 Clinical characteristics of 1,027 patients with invasive *Staphylococcus aureus* infections according to vancomycin MIC[d]

Patient characteristic	Total (*n* = 1,027)	Etest			BMD		
		Low MIC (*n* = 827)	High MIC (*n* = 200)	*P* value	Low MIC (*n* = 940)	High MIC (*n* = 87)	*P* value
Age, ≥65 yrs	560 (54.5)	441 (53.3)	119 (59.5)	0.116	516 (54.9)	44 (50.6)	0.439
Male sex	649 (63.2)	520 (62.9)	129 (64.5)	0.669	588 (62.6)	61 (70.1)	0.162
MRSA infection	673 (65.5)	503 (60.8)	170 (85.0)	0.000	603 (64.1)	70 (80.5)	0.002
Blood isolate	950 (92.5)	766 (92.6)	184 (92.0)	0.764	870 (92.6)	80 (92.0)	0.839
Health care-associated infection	891 (86.8)	711 (86.0)	180 (90.0)	0.132	811 (86.3)	80 (92.0)	0.135
Receipt of immunosuppressant	183 (17.8)	142 (17.2)	41 (20.5)	0.270	166 (17.7)	17 (19.5)	0.661
Steroid use within 1 mo	153 (14.9)	117 (14.1)	36 (18.0)	0.170	140 (14.9)	13 (14.9)	0.990
Underlying illness							
Charlson's WIC ≥3	431 (42.0)	348 (42.1)	83 (41.5)	0.881	393 (41.8)	38 (43.7)	0.735
Cardiovascular disease	53 (5.2)	40 (4.8)	13 (6.5)	0.340	49 (5.2)	4 (4.6)	1.000
Diabetes mellitus	340 (33.1)	269 (32.5)	71 (35.5)	0.423	309 (32.9)	31 (35.6)	0.601
Cerebrovascular disease	175 (17.0)	130 (15.7)	45 (22.5)	0.022	161 (17.1)	14 (16.1)	0.806
Chronic pulmonary disease	67 (6.5)	55 (6.7)	12 (6.0)	0.738	57 (6.1)	10 (11.5)	0.050
Connective tissue disease	36 (3.5)	27 (3.3)	9 (4.5)	0.394	33 (3.5)	3 (3.4)	1.000
Ulcer disease	106 (10.3)	82 (9.9)	24 (12.0)	0.385	95 (10.1)	11 (12.6)	0.457
Chronic kidney disease	187 (18.2)	145 (17.5)	42 (21.0)	0.254	174 (18.5)	13 (14.9)	0.409
Hematologic malignancy	43 (4.2)	36 (4.4)	7 (3.5)	0.589	39 (4.1)	4 (4.6)	0.779
Advanced liver disease	84 (8.2)	71 (8.6)	13 (6.5)	0.334	81 (8.6)	3 (3.4)	0.092
Metastatic solid tumor	95 (9.3)	82 (9.9)	13 (6.5)	0.135	88 (9.4)	7 (8.0)	0.685
Primary diagnosis, infection site							
Catheter associated	239 (23.3)	188 (22.7)	51 (25.5)	0.406	218 (23.3)	21 (24.1)	0.842
Respiratory tract	112 (10.9)	88 (10.6)	24 (12.0)	0.580	101 (10.7)	11 (12.6)	0.587
Skin and soft tissue	145 (14.1)	123 (14.9)	22 (11.0)	0.158	135 (14.4)	10 (11.5)	0.462
Bone and joint	129 (12.6)	100 (12.1)	29 (14.5)	0.356	119 (12.7)	10 (11.5)	0.754
Endovascular	40 (3.9)	36 (4.4)	4 (2.0)	0.123	39 (4.1)	1 (1.1)	0.167
Intra-abdominal	71 (6.9)	56 (6.8)	15 (7.5)	0.716	65 (6.9)	6 (6.9)	0.995
Urinary tract	25 (2.4)	23 (2.8)	2 (1.0)	0.200	24 (2.6)	1 (1.1)	0.716
Central nervous system	16 (1.6)	13 (1.6)	3 (1.5)	1.000	16 (1.7)	0	0.387
Mediastinum	11 (1.1)	6 (0.7)	5 (2.5)	0.045	7 (0.7)	4 (4.6)	0.010
Others	4 (0.4)	4 (0.5)	0	1.000	4 (0.4)	0	1.000
Unknown	235 (22.9)	190 (23.0)	45 (22.5)	0.886	212 (22.6)	23 (26.4)	0.409
Severe sepsis or septic shock	201 (19.6)	155 (18.7)	46 (23.0)	0.173	177 (18.8)	24 (27.6)	0.049
Presence of metastatic infection	142 (13.8)	118 (14.3)	24 (12.0)	0.404	133 (14.1)	9 (10.3)	0.325
Heart	18 (1.8)	15 (1.8)	3 (1.5)	1.000	18 (1.9)	0	0.391
Eye	16 (1.6)	14 (1.7)	2 (1.0)	0.751	15 (1.6)	1 (1.1)	1.000
Bone	21 (2.0)	17 (2.1)	4 (2.0)	1.000	21 (2.2)	0	0.247
Lung	76 (7.4)	65 (7.9)	11 (5.5)	0.253	72 (7.7)	4 (4.6)	0.297
Skin	19 (1.9)	13 (1.6)	6 (3.0)	0.236	16 (1.7)	3 (3.4)	0.213
Inappropriate empirical antibiotics	446 (43.4)	346 (41.8)	100 (50.0)	0.037	405 (43.1)	41 (47.1)	0.467
Receipt of empirical vancomycin	232 (22.6)	183 (22.1)	49 (24.5)	0.472	207 (22.0)	25 (28.7)	0.152
Definitive antibiotics[a]	828						
MSSA	308	281 (91.2)	27 (8.8)		295 (95.8)	13 (4.2)	
Beta-lactams	214 (69.5)	193 (68.7)	21 (77.8)	0.327	204 (69.2)	10 (76.9)	0.761
Cephalosporin	136 (44.2)	123 (43.8)	13 (48.1)	0.662	129 (43.7)	7 (53.8)	0.472
Nafcillin	78 (25.3)	70 (24.9)	8 (29.6)	0.590	75 (25.4)	3 (23.1)	1.000
Glycopeptides	94 (30.5)	88 (31.3)	6 (22.2)	0.327	91 (30.8)	3 (23.1)	0.761
MRSA	520	381 (73.3)	139 (26.7)		466 (89.6)	54 (10.4)	
Glycopeptides	477 (91.7)	350 (91.9)	127 (91.4)	0.856	428 (91.8)	49 (90.7)	0.793
Vancomycin	401 (77.1)	301 (79.0)	100 (71.9)	0.090	360 (77.3)	41 (75.9)	0.826
Teicoplanin	76 (14.6)	49 (12.9)	27 (19.4)	0.061	68 (14.6)	8 (14.8)	0.965
Others	43 (8.3)	31 (8.1)	12 (8.6)	0.856	38 (8.2)	5 (9.3)	0.793
Receipt of vancomycin treatment	530 (51.6)	417 (50.4)	113 (56.5)	0.123	482 (51.3)	48 (55.2)	0.487
Inappropriate definitive antibiotics[b]	77/905 (8.5)	62/724 (8.6)	15/181 (8.3)	0.905	72/833 (8.6)	5/72 (6.9)	0.620
Persistent bacteremia[c]	132/950 (13.9)	104/766 (13.6)	28/184 (19.4)	0.564	125/870 (13.3)	7/80 (8.8)	0.164
S. aureus-attributed 30-day mortality	185 (18.0)	133 (16.1)	52 (26.0)	0.001	162 (17.2)	23 (26.4)	0.033
All-cause 30-day mortality	281 (27.4)	221 (26.7)	60 (30.0)	0.351	251 (26.7)	30 (34.5)	0.119

[a]Patients who died before the culture results were available or received inappropriate definitive antibiotics were excluded from the analysis.
[b]A total of 122 patients who died before the culture results were available were excluded from the analysis.
[c]Positive blood cultures ≥7 days after antimicrobial treatment in bacteremic infection.
[d]Values in MIC columns are no. (%) of patients. High vancomycin MIC was defined as ≥1.5 mg/liter. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; Charlson's WIC, Charlson's weighted index of comorbidity; BMD, broth microdilution.

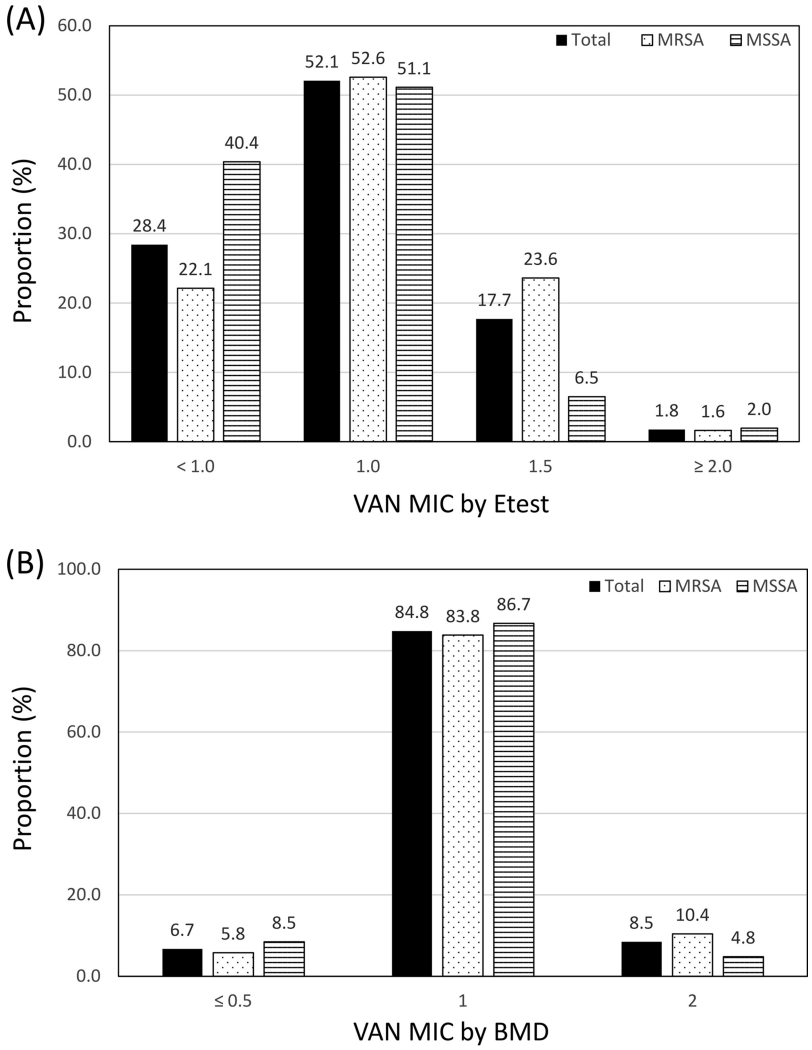

FIG 1 Distribution of vancomycin MICs (VAN-MIC) by Etest (A) and broth microdilution (B), according to methicillin susceptibility. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

observers were identical. Mean MICs by Etest measured by the 2 observers were comparable ($P > 0.05$), but major discrepancies were observed for 37 MSSA and 18 MRSA isolates. The interobserver agreement for categorical VAN-MIC by Etest stratification (low versus high MIC) was substantial ($\kappa = 0.80$).

Vancomycin MIC and treatment outcomes. The all-cause 30-day mortality rates of the high-VAN-MIC groups did not differ from those of the low-VAN-MIC groups (high versus low VAN-MIC: 30.0% versus 26.7% [Etest] and 34.5% versus 26.7% [BMD]) (Table 2). This finding was unchanged when the data were limited to BSIs, irrespective of methicillin susceptibility. *S. aureus*-attributed 30-day mortality rates were significantly higher in the high-VAN-MIC group than the low-VAN-MIC group in both tests (high versus low VAN-MIC: 26.0% versus 16.1% [Etest] and 26.4% versus 17.2% [BMD]) (Table 1). Figure S2 in the supplemental material displays the Kaplan-Meier survival curves according to the Etest and BMD MICs for the all-cause 30-day mortality for all patients. Log rank tests did not reveal significant differences of all-cause mortality between the high- versus low-MIC groups in the two tests. There were no significant differences in the use of definitive antibiotics according to high versus low MIC by Etest or BMD. When we grouped the cases receiving appropriate definitive antibiotics into (i) beta-lactams in MSSA infections, (ii) glycopeptides in MSSA infections, and (iii) glycopeptides

TABLE 2 All-cause 30-day mortality rates of patients with invasive *Staphylococcus aureus* infections according to vancomycin MIC and patient subgroup[a]

MIC methodology subgroup	Mortality rate (no. of 30-day mortality cases/total no. of patients)	Etest			Broth microdilution		
		Low MIC	High MIC	*P* value	Low MIC	High MIC	*P* value
Total	27.4 (281/1,027)	26.7 (221/827)	30.0 (60/200)	0.351	26.7 (251/940)	34.5 (30/87)	0.119
MRSA infection	29.4 (198/673)	28.4 (143/503)	32.4 (55/170)	0.332	28.7 (173/603)	35.7 (25/70)	0.222
MSSA infection	23.4 (83/354)	24.1 (78/324)	16.7 (5/30)	0.360	23.1 (78/337)	29.4 (5/17)	0.561
Bloodstream infection	28.6 (272/950)	28.2 (216/766)	30.4 (56/184)	0.547	28.0 (244/870)	35.0 (28/80)	0.188
MRSA infection	30.7 (189/616)	30.1 (138/459)	32.5 (51/157)	0.571	30.1 (166/551)	35.4 (23/65)	0.385
MSSA infection	24.9 (83/334)	25.4 (78/307)	18.5 (5/27)	0.427	24.5 (78/319)	33.3 (5/15)	0.540

[a]High vancomycin MIC was defined as ≥1.5 mg/liter. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*. Values in MIC columns are mortality rates (no. of 30-day mortality cases/total no. of patients).

in MRSA infections, there were no significant differences in all-cause 30-day mortality according to high versus low VAN-MIC, irrespective of MIC methodology (see Fig. S3 in the supplemental material).

Risk factors for all-cause 30-day mortality and *S. aureus*-attributed mortality. The results of univariate analysis for the relationship between risk factors and all-cause 30-day mortality are listed in Table S2 in the supplemental material. Table 3 gives the significant risk factors associated with all-cause 30-day mortality identified by univariate analysis, and the results of multivariate analysis of the risk factors according to patient subgroup. In multivariate analysis, old age, MRSA infection, bacteremia, recent receipt

TABLE 3 Multivariate analysis of risk factors for all-cause 30-day mortality in patients with invasive *Staphylococcus aureus* infections according to patient subgroup[a]

Risk factor	OR (95% CI) for total patients		
	All isolates (*n* = 1,027)	MRSA (*n* = 673)	MSSA (*n* = 354)
Age, ≥65 yrs	1.83 (1.32–2.53)	NS	4.29 (2.22–8.28)
MRSA infection	1.55 (1.04–2.32)	—	—
Blood isolate	2.42 (1.10–5.49)	NS	—
Health care-associated infection	—	—	—
Receipt of immunosuppressant	1.55 (1.03–2.34)	1.65 (1.00–2.73)	—
Underlying illness			
Charlson's WIC ≥3	2.28 (1.65–3.16)	2.60 (1.70–3.80)	NS
Chronic pulmonary disease	NS	NS	—
Connective tissue disease	3.23 (1.46–7.12)	3.32 (1.25–8.80)	—
Ulcer disease	NS	NS	—
Chronic kidney disease	—	—	NS
Hematologic malignancy	—	NS	—
Advanced liver disease	3.05 (1.77–5.26)	3.34 (1.70–6.59)	—
Metastatic solid tumor	2.99 (1.78–5.03)	3.39 (1.71–6.72)	2.87 (1.22–6.76)
Primary diagnosis, infection site			
Respiratory tract	1.93 (1.17–3.20)	1.96 (1.11–3.47)	2.88 (1.07–7.78)
Skin and soft tissue	NS	—	NS
Bone and joint	0.37 (0.19–0.73)	0.30 (0.12–0.74)	NS
Unknown	NS	NS	2.99 (1.29–6.91)
Severe sepsis or septic shock	5.25 (3.55–7.76)	4.29 (2.69–6.84)	5.86 (2.73–12.59)
Presence of metastatic infection	1.81 (1.17–2.80)	1.81 (1.07–3.07)	—
Lung	2.06 (1.18–3.60)	2.05 (1.05–4.01)	NS
Inappropriate empirical antibiotics	—	—	2.97 (1.14–7.78)
Receipt of empirical vancomycin	—	—	NS
Receipt of vancomycin treatment	NS	NS	NS

[a]MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; Charlson's WIC, Charlson's weighted index of comorbidity; NS, not significant (the variable was included in the multivariate model but did not yield a statistically significant result); —, the variable was not included in the multivariate model because it was not significant enough in univariate analysis ($P > 0.10$).

of immunosuppressant, severe underlying disease (Charlson's weighted index of comorbidity [WIC] of ≥3), respiratory tract infection, presentation with severe sepsis or septic shock, and presence of metastatic infection (especially of the lung) were significantly associated with all-cause 30-day mortality. On the other hand, bone and joint infection was associated with decreased risk of 30-day mortality. However, high VAN-MIC was not associated with all-cause 30-day mortality, and this finding was unchanged when the data were limited to MRSA, MSSA, and bloodstream infections (Table 3; Table S3). Even when we forced high VAN-MIC by both tests into the multivariate models, it was not associated with all-cause 30-day mortality.

The significant risk factors for *S. aureus*-attributed 30-day mortality (SA-mortality) in univariate analysis are listed in Table S4 in the supplemental material. High VAN-MIC by Etest was associated with increased risk of SA-mortality in multivariate analysis (odds ratio [OR], 1.59; 95% confidence interval [CI_{95}], 1.03 to 2.46; $P = 0.036$), but this association was secondary to MRSA infection (OR, 1.72; CI_{95}, 1.08 to 2.72; $P = 0.021$) because high VAN-MIC by Etest was not associated with SA-mortality in patients with MSSA infection. When the data were limited to bacteremic patients, high VAN-MIC by Etest remained a significant risk factor for SA-mortality in patients with MRSA infections only (see Table S5 in the supplemental material).

DISCUSSION

In the present study, we found that high VAN-MIC was not associated with all-cause 30-day mortality in a single large uniform cohort with invasive *S. aureus* infections (ISAs). This was also true when only bacteremic patients were considered, irrespective of their methicillin susceptibility and the method of measuring MICs. Our data support a recent meta-analysis showing that there was no statistically significant difference in all-cause mortality between high and low VAN-MIC (13). The independent risk factors for 30-day mortality derived from our data were the classical factors of old age, severe underlying disease, and presentation with severe sepsis or septic shock, etc. This is consistent with a previous study by Walraven et al. (14), which revealed the importance of underlying disease state and severity of disease rather than VAN-MIC in predicting treatment outcomes of MRSA bacteremia. In our study, respiratory tract infection and the presence of metastatic infection (especially in the lungs) were independent risk factors for mortality. As van Hal et al. (15) pointed out, the outcomes of patients with *S. aureus* infections are related to various clinical factors such as source control (whether the focus is eradicable and/or eradicated or not), and these factors may be more important than VAN-MIC in determining mortality.

Despite subgroup analyses, we could not find significant association between high VAN-MIC and all-cause mortality in MRSA infections. A meta-analysis and systematic review has shown that complicated MRSA BSIs with high VAN-MIC (>1 mg/liter) are associated with a higher mortality than low VAN-MIC (6). Prolonged use and suboptimal dosing of vancomycin may possibly have led to the emergence of MRSA strains with reduced susceptibility, including heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-intermediate *S. aureus* (VISA) strains (16). It has been reported that patients with high-inoculum infections, such as infective endocarditis, appear to have a higher proportion of hVISA than other sites of infection (17). Heterogeneous vancomycin susceptibility has previously been associated with treatment failure (18). In light of the above-mentioned literature, high VAN-MIC may be associated with increased risk of mortality in high-inoculum MRSA infections. However, although vancomycin MIC may influence the outcome in specific high-risk MRSA infections, the vancomycin area under the time-concentration curve over MIC ratio may be more accurate than just the MIC, since it takes into account the pharmacokinetic (PK) characteristics of vancomycin when treating MRSA infections (10, 12).

In invasive MSSA infections and bacteremia, high VAN-MIC was also not associated with all-cause mortality and SA-mortality, irrespective of MIC methodology. Although two recent studies involving bacteremia and another study involving left-sided infective endocarditis concluded that high VAN-MIC was associated with poor prognosis (7,

8, 19), there are other studies showing no relationship between high VAN-MIC and mortality in MSSA bacteremia (6, 20). As Kaasch et al. (21) have pointed out, the lack of biological plausibility and the high risk of bias in retrospective analyses do not allow firm conclusions to be drawn about the relationship between high VAN-MIC and mortality in MSSA infection. Unfortunately, we had only 24 patients with MSSA bacteremic endocarditis. Thus, we could not derive any conclusions on this topic from our data. Further prospective studies are needed.

In addition to all-cause 30-day mortality, we also evaluated *S. aureus*-attributed mortality to assess the association between high VAN-MIC and mortality. High VAN-MIC by Etest was associated with increased risk of SA-mortality in a multivariate analysis of MRSA infections. Thus, we cannot definitely exclude a relationship between high VAN-MIC and infection-related mortality, especially in MRSA infections. However, since efforts to designate outcomes as "attributable" to infection are often subjective and inconsistent, prospective studies to clarify the relationship are warranted.

In our study, the Etest was 0.5 to 1 dilution higher than the BMD at low MICs (BMD MIC, 0.5 mg/liter) (Fig. S1). MICs by Etest were 56.9% concordant with isolates with MICs by BMD of 1.0 mg/liter. However, 16.1% of the BMD of 1.0 mg/liter isolates gave Etest MICs at 0.5 to 1 dilution higher. Because we used a cutoff of 1.5 mg/liter as the uniform breakpoint of high versus low MIC, irrespective of the MIC methodology, the isolates with BMD of 1.0 and Etest of 1.5 were classified into different categories (low VAN-MIC by BMD versus high VAN-MIC by Etest). This effect meant that the observed proportion of high VAN-MICs by the Etest (19.5%) was 2-fold higher than by the BMD (8.5%). In contrast, the Etest results were −0.5 to −1.0 dilution lower than the BMDs at high MIC (BMD MIC, 2.0 mg/liter). The reason for this difference in outcomes in the two tests (especially in high-MIC isolates) could not be assessed in the present study and remains unclear. However, a similar result has been described in studies by Keel et al. (22) and van Hal et al. (23). If treatment is to be based on MIC values, then MIC testing with the Etest would be the methodology of choice, as van Hal states (23). Our results suggest that the Etest would consistently underreport in high-MIC isolates and overestimate in low-MIC isolates. If MIC values by the Etest predicted treatment outcomes, we might accept this discrepancy, even though the BMD is the gold standard for determining MIC values. However, high MIC by the Etest was correlated with outcome in a specific subgroup only (attributable mortality in invasive MRSA infections) in this study, and the relationship between Etest MIC and treatment outcome is controversial. Therefore, we conclude that this dependence of MIC on the particular methodology used does not justify changing clinical practice in invasive *S. aureus* infections.

Because a relatively large number (573) of ISA cases without stored isolates and/or 30-day mortality data were not included, the missing cases could bias the results in either direction. Fortunately, because we collected data on nearly all significant clinical characteristics of these patients, we were able to perform additional analyses. First, when we compared the 212 cases without mortality data to the 1,027 enrolled cases, there were no significant differences in age, MRSA infection, bloodstream infection, severity of underlying diseases, and invasive *S. aureus* infection (see Table S6 in the supplemental material). Unknown primary site of infection and inappropriate definitive antibiotics were more frequent, and vancomycin was less used, in the 212 cases without mortality data. However, considering that these cases were lost to follow-up early in the ISA infection, the primary site of infection would have been more often identified and appropriate definitive antibiotics (including appropriate vancomycin) would have been more often used if follow-up had been performed sufficiently often. Thus, we may conclude that these two groups had similar clinical characteristics. As a second step, we attempted to verify our main result that high VAN-MIC is not related to all-cause 30-day mortality in the 1,388 cases with mortality data by analyzing the effects of two extreme assumptions. We assumed that all 361 cases without stored isolates had high VAN-MIC in one case or low VAN-MIC in the other. Despite making these extreme assumptions, the main result was not changed (see Table S7 in the supplemental material). Hence, we conclude that our main result is reliable.

Our study has several limitations. First, as it was retrospective in design and observational, there is a risk of unmeasured confounding effects. Second, serum vancomycin concentrations could have affected the outcomes of *S. aureus* infections and acted as a confounding factor, but these values were not included in the analysis because serum vancomycin levels were not measured in all the patients. However, vancomycin exposure (and glycopeptide exposure) did not affect the outcomes or the association of high VAN-MIC with mortality. Also, most previous studies of the relationship between mortality and VAN-MIC also provided only limited information pertaining to vancomycin concentration profiles. Moreover, a recent meta-analysis of observational studies reported that higher vancomycin trough concentration was not associated with reduced treatment failure and mortality (24). Thus, missing vancomycin concentrations minimally affected the conclusion of our study. Third, other virulence or genetic factors implicated in invasiveness and disease severity, such as *agr* polymorphisms or dysfunction and clonality, were not considered; including these markers might have affected mortality (25, 26). Additional molecular studies are needed to determine whether the presence or absence of some specific markers influences the relationship between VAN-MIC and mortality. Fourth, the use of stored *S. aureus* isolates for measuring MIC may have affected MIC values, as reported by Ludwig et al. (27). Also, as Falcon et al. (28) indicate, intra- and interinstitutional differences of MIC measurements should be considered. However, because the MIC measurements were performed by two trained researchers in the head center, erroneous categorization of high versus low MIC should have been minimal. Finally, this was not a prospective cohort study with a predefined sample size providing adequate statistical power, especially in the subgroup analyses. Because of the relatively large number of cases, the statistical powers of the main result were relatively high (90.0% for Etest and 70.8% for BMD). However, the subgroup analyses did not have adequate statistical power. Because of statistical multiplicity, we cannot rule out the possibility that risk factors identified as significant in the subgroup analyses were actually the result of chance. Thus, further research on these subgroups is needed. In addition, the relatively low proportion of high-VAN-MIC isolates in this study could also be an obstacle to subgroup analysis because of the small number of cases.

In conclusion, high VAN-MIC (≥1.5 mg/liter) is not associated with increased risk of all-cause 30-day mortality in ISA infections, including BSIs. This finding is consistent across MIC methodologies and methicillin susceptibilities. Our data support the view that VAN-MIC alone does not provide sufficient evidence to change current clinical practice.

MATERIALS AND METHODS

Patient population. All adult patients (aged ≥15 years) with *S. aureus* isolated from normally sterile sites were identified prospectively both from clinical microbiology laboratories and by active surveillance on the part of infectious disease specialists in 10 hospitals over a 2-year period from 1 July 2009 to 30 June 2011; nine of the patients had participated in a previous cohort study (1). The patients' demographic characteristics, underlying diseases, infection sites, vital signs, and laboratory findings were examined. This clinical information was collected by trained research nurses or infectious disease specialists using standardized case record forms. All available *S. aureus* isolates from normally sterile sites were sent to the main center (Seoul National University Bundang Hospital) for confirmation of their microbiologic profiles. This study was approved by the Hospital's institutional review board.

Definitions. ISA infection was defined as the isolation of *S. aureus* from a normally sterile site. Normally sterile sites consisted of blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body sites (lymph node, brain, heart, liver, spleen, vitreous fluid, kidney, pancreas, or ovary), and other normally sterile sites. Only the first episode was analyzed if a patient had recurrent episodes of ISA infection during the study period. Community-onset, community-associated (CA), community-onset, health care-associated (HCA), and hospital-onset infections were classified as described in reference 29. High VAN-MIC was defined as greater than or equal to 1.5 mg/liter in both the BMD (MIC values of ≤1.0 mg/liter for the low-vancomycin group; MIC values of ≥2.0 mg/liter for the high-vancomycin group) and Etest (MIC values of <1.5 mg/liter for the low-vancomycin group; MIC values of ≥1.5 mg/liter for the high-vancomycin group).

All-cause 30-day mortality was defined as death within 30 days after the first positive culture was obtained, irrespective of the cause of death. Mortality associated with *S. aureus* was classified as (i) definitely associated or (ii) possibly associated. The former was defined as (i) positive *S. aureus* culture from sterile specimens at the time of death or (ii) death within 14 days of the documentation of positive

S. aureus culture from sterile specimens without any other explanation. The latter was defined as death within 30 days of the documentation of positive *S. aureus* culture from sterile specimens without any other explanation (30). Definitely and possibly associated mortality was considered *S. aureus*-attributed mortality (SA-mortality).

Persistent bacteremia was defined as positive blood cultures ≥7 days after antimicrobial treatment in bacteremic infection (10). Charlson's weighted index of comorbidity (WIC) was used to evaluate the presence and severity of underlying disease (31). Use of immunosuppressant was defined as use of an immunosuppressive agent within 30 days of onset of illness, including anticancer chemotherapy, more than prednisolone (20-mg/day equivalent steroid) over 1 week, or other immunosuppressive agent.

Empirical antimicrobial therapy was defined as the initial antibiotic choice before the results of culture and antimicrobial susceptibility tests were available, and definitive antimicrobial therapy was defined as the antibiotic choice after report of the microbiologic tests. Patients who died before the culture results were available were excluded from the assessment of definitive antimicrobial therapy. Antibiotic therapy was considered appropriate if the treatment regimen included antibiotics active *in vitro* and the dosage and route of administration were in conformity with current medical standards. A primary diagnosis was made on the basis of the clinical, radiological, and microbiological information.

Microbiological methods. Clinical isolates were confirmed as *S. aureus* and were tested for antimicrobial susceptibility by standard techniques. We used the first isolate for microbiologic tests, irrespective of the site of culture. When *S. aureus* was isolated from multiple sterile sites at the same time, we used the isolate from blood for the MIC tests. All cryopreserved (−70°C) *S. aureus* isolates were evaluated. Primary subcultures were made on 2 blood agar plates. The Etest was performed using a 0.5 McFarland standard inoculum streaked on Mueller-Hinton agar plates, followed by application of vancomycin Etest strips (AB Biodisk, Solna, Sweden). The MIC measurements were made using the same lots of media and Etest strips. The plates were read visually after 24 h of incubation at 35°C in ambient air. All isolates also underwent vancomycin susceptibility testing by broth microdilution (BMD) according to the Clinical and Laboratory Standards Institute (CLSI) methodology (32). In brief, isolate suspensions prepared in Mueller-Hinton broth at a starting concentration of 1×10^6 CFU/ml were incubated with increasing concentrations of vancomycin (0.0625 to 16 mg/liter). Following 24 h of incubation at 35°C in ambient air, the MIC was recorded as the concentration of drug in the first well with complete inhibition of growth by the naked eye. An American Type Culture Collection (ATCC) methicillin-susceptible *S. aureus* (29213), a vancomycin-intermediate *S. aureus* (VISA) strain (Mu50), and a negative control (without bacteria) were run in parallel as controls in both tests. Results were read independently by two independent researchers, blinded to the outcomes of infection. Discordant results between researchers were resolved by a third researcher in consensus. The reproducibility and interobserver variance of Etest and BMD were also assessed. Isolates with major discrepancies, which were defined as instances in which MIC values were not within the same susceptibility category (low versus high), were used for evaluating reproducibility. Both tests were performed in triplicate for these isolates.

Data management and analysis. Differences in proportions were compared by Fisher's exact test or the chi-square test, and means were compared by Student's *t* test. To identify independent risk factors for 30-day mortality, a stepwise multiple logistic regression model was used. Risk factors with *P* values of <0.10 in the univariate analysis were included in the multivariate analysis. Charlson's WIC and all underlying diseases were analyzed in a separate multivariate model to avoid collinearity. *P* values of <0.05 were considered statistically significant in the multivariate analyses. In the multivariate analyses of independent risk factors for all-cause mortality and SA-mortality, bivariate and multinomial logistic regression analyses using a generalized linear mixed model were used to take account of random effects of the individual hospitals. IBM PASW for Windows (version 20 software package; SPSS Inc., Chicago, IL, USA) was used for all analyses except the multivariate logistic regression analyses. Logistic regression analyses using a generalized linear mixed model were performed using Stata version 13 (Stata Corp LP, USA).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01845-16.

TEXT S1, PDF file, 0.80 MB.

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We declare that we have no potential conflicts of interest.

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