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Clinical and Microbiologic Analysis of the Risk Factors for Mortality in Patients with Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus* Bacteremia

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The prevalence of the heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) phenotype among methicillin-resistant *S. aureus* (MRSA) blood isolates can reach 38%. hVISA bacteremia is known to be associated with vancomycin treatment failure, including persistent bacteremia. We conducted this study to evaluate risk factors for 12-week mortality in patients with hVISA bacteremia through a detailed clinical and microbiological analysis of a prospective cohort of patients with *S. aureus* bacteremia. All isolates were collected on the first day of bacteremia and subjected to population analysis profiling for hVISA detection, genotyping, and PCR analysis for 39 virulence factors. Of 382 patient with MRSA bacteremia, 121 (32%) had hVISA bacteremia. Deceased patients were more likely to have hematologic malignancy ($P = 0.033$), ultimately or rapidly fatal disease ($P = 0.007$), and a higher Pitt bacteremia score ($P = 0.010$) than surviving patients. The sequence type 239 (ST239) clonal type and definitive linezolid treatment were associated with a trend toward reduced mortality ($P = 0.061$ and 0.072, respectively), but a high vancomycin MIC (≥2 mg/liter) was not associated with increased mortality ($P = 0.368$). In a multivariate analysis, ultimately or rapidly fatal disease (adjusted odds ratio [aOR], 2.80; 95% confidence interval [CI], 1.14 to 6.85) and a high Pitt bacteremia score (aOR, 1.26; 95% CI, 1.07 to 1.48) were independent risk factors for mortality. Hematologic malignancy was associated with a trend toward increased mortality ($P = 0.094$), and ST239 was associated with a trend toward reduced mortality ($P = 0.095$). Our study suggests that ST239 hVISA is a possible predictor of survival in hVISA bacteremia.

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is one of the most serious bacterial infections and is associated with significant morbidity and mortality. In Europe and the United States, MRSA infections have been decreasing since the mid-2000s, probably owing to general efforts at infection control. However, the burden of MRSA infections is still high (from 28% to >70% of *S. aureus* infections) in Asia (1). Vancomycin has been the standard treatment for MRSA infections. However, MRSA strains with reduced susceptibility to vancomycin, such as vancomycin-intermediate *S. aureus* (VISA) and heterogeneous vancomycin-intermediate *S. aureus* (hVISA), have emerged and compromised the utility of vancomycin (2, 3). Most reported VISA and hVISA strains are from clonal complex 5 (sequence type 5 [ST5]) or 8 (mostly ST239), reflecting their adaptation as hospital MRSA clones (4, 5). VISA strains are rarely encountered in real clinical practice, and hVISA strains usually go undetected by the traditional MIC testing performed in clinical microbiology laboratories. Vancomycin heteroresistance refers to the presence of subpopulations (at a rate of 1 organism per 10^5 to 10^6) with lowered susceptibility within a larger population of fully vancomycin-susceptible *S. aureus* (VSSA). The gold standard for hVISA detection is modified population analysis profiling (PAP); however, this method is labor- and time-intensive and impractical in the clinical laboratory (6, 7).

In previous studies, the prevalence of the hVISA phenotype among MRSA blood isolates reached 38%. According to a recent meta-analysis of studies comparing hVISA and VSSA infections, the clinical consequences of hVISA infections were vancomycin treatment failure (defined as persistent bacteremia or infection and/or prolonged signs of infection) and high-inoculum infections, such as infective endocarditis (6, 8–10). Interestingly, despite these findings, mortality rates from hVISA and VSSA infections were found to be similar.

Although there are many studies that have identified clinical and microbiological risk factors for mortality in *S. aureus*/MRSA bacteremia, there are no studies that have evaluated the mortality risk factors in hVISA bacteremia. The objective of the present study was to evaluate risk factors for mortality in patients with hVISA bacteremia by means of a detailed clinical, microbiological, and molecular investigation of a MRSA bacteremia registry.

Received 11 November 2014 **Returned for modification** 21 January 2015
Accepted 31 March 2015

Accepted manuscript posted online 6 April 2015

Citation Chong YP, Park K-H, Kim ES, Kim M-N, Kim S-H, Lee S-O, Choi S-H, Jeong J-Y, Woo JH, Kim YS. 2015. Clinical and microbiologic analysis of the risk factors for mortality in patients with heterogeneous vancomycin-intermediate *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 59:3541–3547. doi:10.1128/AAC.04765-14.

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Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.04765-14.

doi:10.1128/AAC.04765-14

TABLE 1 Demographic and clinical characteristics of patients with hVISA bacteremia, according to treatment outcome[a]

Characteristic	Deceased patients ($n = 38$)	Surviving patients ($n = 83$)	All patients ($n = 121$)	*P* value
Age (yr), median (IQR)	64.5 (57–71)	66 (54–73)	65 (55–72)	0.888
Male	27 (71.1)	64 (77.1)	91 (75.2)	0.474
Site of acquisition				
Community acquired	2 (5.3)	3 (3.6)	5 (4.1)	0.649
Health care associated	4 (10.5)	15 (18.1)	19 (15.7)	0.218
Nosocomial	32 (84.2)	65 (78.3)	97 (80.2)	0.450
Underlying disease/condition				
Solid tumor	27 (32.5)	18 (47.4)	45 (37.2)	0.087
Hematologic malignancy	4 (10.5)	1 (1.2)	5 (4.1)	0.033
Diabetes mellitus	7 (18.4)	29 (34.9)	36 (29.8)	0.065
End-stage renal disease	4 (10.5)	10 (12.0)	14 (11.6)	>0.999
Liver cirrhosis	4 (10.5)	9 (10.8)	13 (10.7)	>0.999
Neutropenia	1 (2.6)	2 (2.4)	3 (2.5)	>0.999
Immunosuppressant use	14 (36.8)	17 (20.5)	31 (25.6)	0.056
Recent chemotherapy	3 (7.9)	4 (4.8)	7 (5.8)	0.677
McCabe and Jackson criteria				
Ultimately or rapidly fatal disease[b]	19 (50.0)	21 (25.3)	40 (33.1)	0.007
Charlson comorbidity index, median (IQR)	3 (2–5)	2 (1–4)	3 (2–4)	0.140
APACHE II score, median (IQR)	20 (16–28)	16 (11–21)	17 (11–23)	0.013
Pitt bacteremia score, median (IQR)	2 (0–6)	1 (0–2)	1 (0–3)	0.010
Septic shock	14 (36.8)	7 (8.4)	21 (17.4)	<0.001
Type of infection				
Persistent bacteremia (≥7 days)	10 (26.3)	27 (32.5)	37 (30.6)	0.491
Metastatic infection	7 (18.4)	19 (22.9)	26 (21.5)	0.578
Infective endocarditis	5 (13.2)	7 (8.4)	12 (9.9)	0.514
Catheter-related infection	18 (47.4)	41 (49.4)	59 (48.8)	0.836
Pneumonia	6 (15.8)	5 (6.0)	11 (9.1)	0.098
Skin and soft tissue infection	1 (2.6)	5 (6.0)	6 (5.0)	0.664
Bone and joint infection	1 (2.6)	5 (6.0)	6 (5.0)	0.664
Postoperative wound infection	2 (5.3)	7 (8.4)	9 (7.4)	0.718
Primary bacteremia	5 (13.2)	8 (9.6)	13 (10.7)	0.544

[a] Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified. IQR, interquartile range.
[b] Of 121 patients, only 1 person had rapidly fatal disease.

MATERIALS AND METHODS

Study population and design. The prospective observational cohort study was performed in patients with *S. aureus* bacteremia at the Asan Medical Center, a 2,700-bed tertiary referral center, between August 2008 and April 2011 (11). All adult patients with *S. aureus* bacteremia were prospectively enrolled and observed over a 12-week period. In our hospital, more than 90% of patients with *S. aureus* bacteremia receive infectious diseases consultation and are routinely recommended to undergo follow-up blood cultures at 2- to 4-day intervals until negative conversion, as well as echocardiography and monitoring of vancomycin trough concentrations. Patients were excluded if (i) they had polymicrobial bacteremia or (ii) they died or were discharged before positive blood culture results. Only the first episode of bacteremia was included in the analysis, and all MRSA isolates obtained on the first day of bacteremia were collected and stored for further testing. Of the patients with MRSA bacteremia, only those with hVISA bacteremia were included in the study. Attending physicians and infectious disease consultants were blinded to the presence of hVISA infection. This study was approved by the Asan Medical Center Institutional Review Board.

Data collection and study definitions. Demographic characteristics, underlying diseases or conditions, severity of the underlying disease, severity of bacteremia, site of infection, antibiogram results, patient management, and clinical outcome were recorded. Charlson's comorbidity index was used to score the severity of the underlying disease (12). Prognosis of the underlying disease was classified, according to the system of McCabe and Jackson, as rapidly fatal (when death was expected within several months), ultimately fatal (when death was expected within 4 years), and nonfatal (when life expectancy was >4 years) (13). The severity of bacteremia was based on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Pitt bacteremia score (14). Bacteremia was classified as hospital acquired if a positive blood culture was obtained from patients who had been hospitalized for 48 h or longer. Community-onset bacteremia was classified as health care associated or community acquired as defined by Friedman et al. (15).

The site of infection causing hVISA bacteremia was defined according to the Centers for Disease Control and Prevention criteria (16). Infective endocarditis was defined according to the modified Duke criteria (17). Catheter-related infection was considered to be the source of bacteremia in patients with an intravascular device according to the Infectious Diseases Society of America guidelines (18). A definitive antibiotic was defined as an antibiotic that was administered for more than two-thirds of the course of treatment. Treatment outcome of bacteremia was evaluated based on 12-week all-cause mortality.

TABLE 2 Microbiological characteristics and clinical management of patients with hVISA bacteremia, according to treatment outcome[a]

Characteristic of patients or isolates	Deceased patients ($n = 38$)	Surviving patients ($n = 83$)	All patients ($n = 121$)	*P* value
No. patients with eradicable focus	23 (60.5)	59 (71.1)	82 (67.8)	0.286
No. showing removal of eradicable focus/total no. with eradicable focus (%)	22/23 (95.7)	52/59 (88.1)	74/82 (90.2)	0.431
No. who received delayed antibiotic treatment[b]	5 (13.2)	16 (19.3)	21 (17.4)	0.409
No. who received initial treatment with vancomycin	32 (84.2)	76 (91.6)	108 (89)	0.342
No. with vancomycin trough level[c] < 15 mg/liter/ total no. with vancomycin trough level monitoring	8/29 (27.6)	25/65 (38.5)	33/94 (35.1)	0.308
Definitive antibiotic treatment				
Vancomycin	29 (76.3)	53 (63.9)	82 (67.8)	0.173
Teicoplanin	3 (7.9)	4 (4.8)	7 (5.8)	0.677
Linezolid	6 (15.8)	26 (31.3)	32 (26.4)	0.072
hVISA isolate characteristics				
Vancomycin MIC (Etest)				0.645
≤1.0 mg/liter	7 (18.4)	16 (19.3)	23 (19.0)	
1.5 mg/liter	14 (36.8)	37 (44.6)	51 (42.1)	
≥2.0 mg/liter	17 (44.7)	30 (36.1)	47 (38.8)	
PAP-AUC ratio,[d] median (IQR)	1.01 (0.97–1.04)	1.02 (0.97–1.08)	1.02 (0.97–1.07)	0.182
SCC*mec* type[e]				
I		1 (1.2)	1 (0.8)	>0.999
II	31 (81.6)	57 (68.7)	88 (72.7)	0.139
III	1 (2.6)	13 (15.7)	14 (11.6)	0.062
IV	5 (13.2)	11 (13.3)	16 (13.2)	0.999
Multilocus sequence type				
ST5	31 (81.6)	58 (69.9)	89 (73.6)	0.176
ST72	4 (10.5)	12 (14.5)	16 (13.2)	0.553
ST239	1 (2.6)	12 (14.5)	13 (10.7)	0.061
Other[f]	2 (5.3)	1 (1.2)	3 (2.5)	0.232
agr genotype[g]				0.288
I	6 (15.8)	23 (27.7)	29 (24.0)	
II	31 (81.6)	58 (69.9)	89 (73.6)	
agr dysfunction	32 (84.2)	64 (77.1)	96 (79.3)	0.370

[a] Data are presented as the number of patients (with the corresponding percentage shown in parentheses), unless otherwise specified. IQR, interquartile range.
[b] Administration of adequate antibiotic 2 days after bacteremia onset.
[c] Mean trough level during the first 7 days of vancomycin therapy.
[d] Ratio of the AUC for the test isolate and the AUC for Mu3.
[e] For one isolate, SCC*mec* was not detected by PCR.
[f] Two isolates were ST254 and one was ST1.
[g] Three isolates were nontypeable.

Microbiological data and genotypic assays. All *S. aureus* isolates were identified by standard methods. Antimicrobial susceptibilities were determined using the MicroScan system (Dade Behring, West Sacramento, CA, USA) and the standard criteria of the Clinical and Laboratory Standards Institute. Methicillin resistance was confirmed by detection of the *mecA* gene by PCR. hVISA was detected by population analysis profiling of all MRSA isolates, as previously described (7). All MRSA isolates were cultured in tryptone soy broth for overnight growth, and then cultures were diluted in saline to 10^{-3} and 10^{-6}. Aliquots of each dilution (15 μl) were spiral plated (Don Whitley spiral platers, West Yorkshire, United Kingdom) onto brain heart infusion agar plates containing 0, 0.5, 1, 1.5, 2, 3, 4, and 8 mg/liter vancomycin. Colonies were counted after a 48-hour incubation at 35°C, and the viable count was plotted against the vancomycin concentration by using SigmaPlot 9.0 (Systat Software, Inc., Richmond, CA). An isolate was identified as hVISA if the ratio of the area under the viable count-vancomycin curve (AUC) of the test isolate versus the AUC of the reference strain (Mu3; ATCC 700698) was ≥0.9. VISA was defined as the same ratio at a level of ≥1.3. Vancomycin MICs of the hVISA isolates were determined with the vancomycin Etest (AB Biodisk, Piscataway, NJ, USA) on Mueller-Hinton agar, according to the manufacturer's instructions.

The staphylococcal cassette chromosome *mec* (SCC*mec*) type and *agr* genotype of each hVISA isolate were identified using previously described methods (19, 20). The *agr* functionality was determined based on delta-hemolysin activity, as described elsewhere (21), because *agr* dysfunction results in a defect in delta-hemolysin production. Multilocus sequence typing (MLST) was performed for all strains as described elsewhere (22). MLST allele names and STs were derived from the MLST database (http://www.mlst.net). The presence of 39 virulence genes, including adhesions and toxins, was determined as previously described (23–25).

Statistical analysis. We compared surviving and deceased patients who had hVISA bacteremia. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate, and continuous variables were compared using the Mann-Whitney U test. To identify independent risk factors for mortality in patients with hVISA bacteremia, all significant variables in the univariate analysis, and other variables of clinical importance, were included in a multiple logistic regression model. The final

model was constructed using the backward stepwise selection procedure. A two-tailed *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics. A total of 382 Asan Medical Center patients with MRSA bacteremia were prospectively enrolled during the study period, and their first MRSA isolates were collected and tested. Of these 382 MRSA isolates, 121 (32%) had the hVISA phenotype. No VISA isolates were found. MRSA strains were isolated from 27 different Medical Center departments, and hVISA strains were isolated from 24 different departments. The demographic and clinical characteristics of the 121 patients with hVISA bacteremia are shown in Table 1. Most patients (75%) were male, and nosocomial and health care-associated infections were common (96%). Most patients (89%) were initially treated with vancomycin. As the definitive antibiotic, 68% of patients received vancomycin and 26% received linezolid. Eighty-three patients (69%) survived and 38 (31%) died within 12 weeks.

Comparisons of the clinical characteristics of the deceased and surviving patients are shown in Tables 1 and 2. The deceased patients were more likely than the surviving patients to have hematologic malignancy ($P = 0.033$), ultimately or rapidly fatal disease ($P = 0.007$), higher APACHE II ($P = 0.013$) and Pitt bacteremia ($P = 0.010$) scores, and septic shock ($P < 0.001$). There were tendencies for solid tumor, immunosuppressant use, pneumonia, and definitive treatment with other than linezolid to be associated with mortality. Complications of bacteremia and sites of infection other than the lung were not associated with mortality. Because most patients with eradicable foci underwent source control, removal of eradicable foci was not associated with mortality.

Microbiological data and genotypic characteristics. Most hVISA isolates (81%) had vancomycin MICs of ≥1.5 mg/liter. Common genotypes were ST5-SCC*mec* type II-*agr* group II, ST72-SCC*mec* type IV-*agr* group I, and ST239-SCC*mec* type III-*agr* group I. As shown in Table 2, there was no significant difference in vancomycin MICs between the deceased and surviving groups. *agr* genotype and *agr* functionality were not associated with mortality. However, SCC*mec* type III and the ST239 clone were associated with trends toward lower mortality ($P = 0.062$ and $P = 0.061$, respectively). A comparison of virulence factors in the deceased and surviving group is shown in Table 3. The *map/eap* gene was significantly associated with survival ($P = 0.020$), and *sec*, *seg*, and *sei* were marginally associated with mortality.

Table 4 shows the clinical, microbiological, and molecular characteristics of major hVISA strains. Clinical characteristics were similar among MLSTs. However, molecular characteristics (in particular exotoxins) were significantly different between ST239 hVISA and ST5/ST72 hVISA.

Risk factors for mortality. Significant univariate variables in Tables 1 and 2 and other variables of clinical importance were included in a logistic regression model to identify independent risk factors. Because the Pitt bacteremia score was highly correlated with the APACHE II score and septic shock, and each of these reflect the severity of bacteremia, we retained the Pitt bacteremia score. Similarly, as ST239 was highly correlated with *map/eap* and with none of the *sec*, *seg*, or *sei* genes (Table 4), we retained ST239. Thus, we used hematologic malignancy, ultimately or rapidly fatal disease, Pitt bacteremia score, definitive treatment with linezolid, and presence of the ST239 clone in the logistic regression modeling. Multivariate analysis indicated that ultimately or rapidly fatal disease (adjusted odds ratio [aOR], 2.80; 95% confidence interval [CI], 1.14 to 6.85) and a high Pitt bacteremia score (aOR, 1.26; 95% CI, 1.07 to 1.48) were independent risk factors for mortality (Table 5). Hematologic malignancy was associated with a trend toward increased mortality ($P = 0.094$), and ST239 was associated with a trend toward reduced mortality ($P = 0.095$). When these variables plus age and other marginally significant clinical variables were used in the logistic regression modeling, the same results were obtained.

TABLE 3 Associations between putative virulence genes of hVISA isolates and treatment outcomes for patients

Gene product category and gene name	No. (%) in whom gene was detected			*P* value
	Deceased patients ($n = 38$)	Surviving patients ($n = 83$)	All patients ($n = 121$)	
Adhesins				
fnbA	38 (100)	83 (100)	121 (100)	NA[a]
fnbB	38 (100)	83 (100)	121 (100)	NA
bbp	37 (97.4)	79 (95.2)	116 (95.9)	0.599
ebpS	36 (94.7)	80 (96.4)	116 (95.9)	0.679
map/eap	1 (2.6)	13 (15.7)	14 (11.6)	0.020
sdrC	35 (92.1)	72 (86.7)	107 (88.4)	0.545
sdrD	36 (94.7)	77 (92.8)	113 (93.4)	>0.999
sdrE	35 (92.1)	80 (96.4)	115 (95.0)	0.377
clfA	38 (100)	83 (100)	121 (100)	NA
clfB	38 (100)	83 (100)	121 (100)	NA
cna				NA
Toxins				
sea	3 (7.9)	12 (14.5)	15 (12.4)	0.385
seb				NA
sec	30 (78.9)	52 (62.7)	82 (67.8)	0.075
sed				NA
see				NA
seg	37 (97.4)	70 (84.3)	107 (88.4)	0.062
seh				NA
sei	36 (94.7)	68 (81.9)	104 (86.0)	0.060
sej				NA
sek	3 (7.9)	11 (13.3)	14 (11.6)	0.545
sel	32 (84.2)	62 (74.7)	94 (77.7)	0.243
sem	34 (89.5)	71 (85.5)	105 (86.8)	0.553
sen	36 (94.7)	71 (85.5)	107 (88.4)	0.221
seo	36 (94.7)	71 (85.5)	107 (88.4)	0.221
sep		2 (2.4)	2 (1.7)	>0.999
seq	1 (2.6)	10 (12.0)	11 (9.1)	0.170
eta				NA
etb				NA
lukE-lukD	38 (100)	81 (97.6)	119 (98.3)	>0.999
tst	29 (76.3)	57 (68.7)	86 (71.1)	0.390
hla	37 (97.4)	79 (95.2)	116 (95.9)	>0.999
hlb	28 (73.7)	49 (59.0)	77 (63.6)	>0.999
hld	36 (94.7)	77 (92.8)	113 (93.4)	>0.999
hlg				NA
hlg-2	38 (100)	78 (94.0)	116 (95.9)	0.324
pvl				NA
Other putative virulence genes				
icaA	38 (100)	83 (100)	121 (100)	NA
edin				NA

[a] NA, not applicable.

TABLE 4 Clinical, microbiological, and molecular characteristics of hVISA bacteremia patients, according to MLST result

Characteristic of patients or isolates	No. (%) of hVISA bacteremia patients with ST[a]		
	ST5 (n = 89)	ST72 (n = 16)	ST239 (n = 13)
Age (yr), median (IQR)	67 (59–73)	60 (54–73)	55 (48–64)
Male	68 (77.5)	8 (50.0)	11 (84.6)
Nosocomial infection	79 (88.8)	7 (43.8)	9 (69.2)
Underlying disease/condition			
Solid tumor	36 (40.4)	7 (43.8)	1 (7.7)
Hematologic malignancy	3 (3.4)	1 (6.3)	1 (7.7)
Diabetes mellitus	26 (29.2)	6 (37.5)	3 (23.1)
End-stage renal disease	11 (12.4)	2 (12.5)	1 (7.7)
Liver cirrhosis	7 (7.9)	3 (18.8)	1 (7.7)
Immunosuppressant use	22 (24.7)	3 (18.8)	5 (38.5)
McCabe and Jackson criteria			
Ultimately or rapidly fatal disease[b]	29 (32.6)	7 (43.8)	4 (30.8)
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2.5–5.5)	2 (0–4)
APACHE II score, median (IQR)	18 (13–25)	13 (10–19.5)	15 (10–19.5)
Pitt bacteremia score, median (IQR)	1 (0–4)	1 (0–1.5)	1 (0–2)
Septic shock	19 (21.3)	2 (12.5)	1 (7.7)
Type of infection			
Persistent bacteremia (≥7 days)	29 (32.6)	4 (25.0)	4 (30.8)
Metastatic infection	16 (18.0)	8 (50.0)	2 (15.4)
Infective endocarditis	8 (9.0)	2 (12.5)	1 (7.7)
Catheter-related infection	46 (51.7)	4 (25.0)	8 (61.5)
Pneumonia	10 (11.2)		1 (7.7)
Skin and soft tissue infection	2 (2.2)	1 (6.3)	2 (15.4)
Bone and joint infection	4 (4.5)	2 (12.5)	
Postoperative wound infection	8 (9.0)		1 (7.7)
Primary bacteremia	9 (10.1)	4 (25.0)	
All-cause mortality	31 (34.8)	4 (25.0)	1 (7.7)
Vancomycin MIC (Etest)			
≤1.0 mg/liter	18 (20.2)	2 (12.5)	3 (23.1)
1.5 mg/liter	37 (41.6)	5 (31.3)	7 (53.8)
≥2.0 mg/liter	34 (38.2)	9 (56.3)	3 (23.1)
PAP-AUC ratio,[c] median (IQR)	1.01 (0.97–1.07)	0.98 (0.95–1.08)	1.04 (1.00–1.10)
SCC*mec* type[d]	II	IV	III
agr genotype[e]	II	I	I
agr dysfunction	86 (96.6)	1 (6.3)	9 (69.2)
Virulence gene[f]			
map/eap	1 (1.1)	1 (6.3)	11 (84.6)
sdrC	86 (96.6)	6 (37.5)	13 (100)
sea	1 (1.1)	1 (6.3)	12 (92.3)
sec	80 (89.9)		1 (7.7)
seg	87 (97.8)	15 (93.8)	2 (15.4)
sei	88 (98.9)	14 (87.5)	
sek	1 (7.9)	1 (6.3)	11 (84.6)
sel	87 (97.8)	4 (25.0)	2 (15.4)
sem	87 (97.8)	15 (93.8)	1 (7.7)
sen	88 (98.9)	15 (93.8)	2 (15.4)
seo	88 (98.9)	15 (93.8)	2 (15.4)
sep	2 (2.2)		
seq			11 (84.6)
tst	84 (94.4)	1 (6.3)	

[a] Data are presented as the number of patients with hVISA bacteremia and the indicated ST (with the corresponding percentage shown in parentheses), unless otherwise specified. IQR, interquartile range.

[b] Of 118 patients, only 1 (in the ST72 group) had rapidly fatal disease.

[c] From the population analysis profile, the AUC for the test isolate versus that for Mu3.

[d] The SCC*mec* type associated with the ST.

[e] The *agr* genotype associated with the ST.

[f] All isolates had *fnbA*, *fnbB*, *clfA*, *clfB*, and *icaA*. More than 90% of ST5, ST72, and ST239 isolates had *bbp*, *ebpS*, *sdrD*, *sdrE*, *lukE-lukD*, *hla*, *hld*, and *hlg-2*. No isolates had *cna*, *seb*, *sed*, *see*, *seh*, *sej*, *eta*, *etb*, *hlg*, *pvl*, or *edin*.

TABLE 5 Results of analyses of risk factors for mortality in 121 patients with hVISA bacteremia

Risk factor	Univariate analysis result [OR (95% CI)]	Multivariate analysis result[a]	
		aOR (95% CI)	*P* value
Hematologic malignancy	9.65 (1.04–89.49)	10.24 (0.67–156.25)	0.094
Ultimately or rapidly fatal disease[b]	2.95 (1.32–6.61)	2.80 (1.14–6.85)	0.024
Pitt bacteremia score	1.27 (1.09–1.48)	1.26 (1.07–1.48)	0.005
Linezolid as definitive antibiotic	0.41 (0.15–1.10)		
ST239 clone	0.16 (0.02–1.28)	0.13 (0.01–1.43)	0.095

[a] This model fit the data well in terms of discrimination (C-statistic = 0.76) and calibration (Hosmer-Lemeshow goodness-of-fit statistic = 7.03; $P = 0.32$).
[b] Of all patients, only one in the deceased group had rapidly fatal disease.

DISCUSSION

Many studies have evaluated the risk factors for mortality in patients with *S. aureus* bacteremia (26). Host factors, pathogen-host interactions, pathogen-specific factors, and clinical management can influence mortality. In most studies, important predictors for mortality are (i) age and comorbidities as host factors and (ii) severity of bacteremia (APACHE II score, septic shock) and primary site of infection as pathogen-host interactions. Microbiological factors, such as methicillin resistance, high vancomycin MIC, and bacterial toxins and factors related to clinical management, were inconsistently associated with increased mortality (26). In studies comparing hVISA and MRSA bacteremia, hVISA was associated with persistent bacteremia rather than higher mortality (8, 10, 26, 27). In the present study, we evaluated risk factors for mortality in patients with hVISA bacteremia and found that ultimately or rapidly fatal disease, which reflects the severity of comorbidities, and Pitt bacteremia score, which reflects the severity of bacteremia, were independent risk factors. These findings are consistent with those of previous studies that examined all patients with *S. aureus* bacteremia or MRSA bacteremia (26). A high vancomycin MIC by Etest (≥2 mg/liter) was not associated with increased mortality in hVISA bacteremia patients in the present study ($P = 0.368$). On the other hand, a recent meta-analysis of 22 studies reported that a high vancomycin MIC by Etest was significantly associated with a higher mortality rate in MRSA bacteremia (28). There are several possible explanations for this difference. The first explanation is that, because regardless of the actual vancomycin MIC hVISA infections themselves contain a vancomycin-intermediate subpopulation, the impact of a high vancomycin MIC may not be evident. Second, the proportion of isolates with a high vancomycin MIC was about 40% in the present study, whereas it was 20% in the meta-analysis. This high proportion of high vancomycin MICs may have diminished their impact. Third, the high vancomycin MIC was generally not significantly associated with increased mortality in each of the studies included in the meta-analysis. Therefore, its impact on outcome in hVISA bacteremia may be apparent only in a larger study. In another recent meta-analysis that included 38 studies of *S. aureus* bacteremia, a vancomycin MIC of ≥1.5 mg/liter was not significantly associated with increased mortality (29).

In the present study, several virulence factors were candidate risk factors for mortality. However, the magnitude of their impact was small and they were associated with specific clonal types, as shown in Table 4. The *seg* and *sei* genes were highly associated with ST5 and ST72: *sec* with ST5 and *seq* and *map/eap* with ST239. In turn, ST239 was associated with a trend toward reduced mortality. Whether some specific virulence factor or clonal type makes a major contribution to clinical outcome needs to be further investigated. An Australian study by van Hal et al. also found that ST239 hVISA was an independent predictor of reduced mortality in MRSA bacteremia (aOR, 0.27; 95% CI, 0.09 to 0.83; $P = 0.022$) (30). In that study, most VSSA isolates (75%) and all hVISA isolates were ST239. The reduced mortality of hVISA was not observed in studies conducted in other countries with different predominant STs (8, 9, 27, 31). Therefore, the reduced mortality of ST239 hVISA may be due to ST239-hVISA-specific characteristics rather than vancomycin heteroresistance itself. The ST239 hVISA clone in the present study was probably less virulent than ST5 hVISA. This should be checked in further work.

Vancomycin has been the standard treatment for MRSA bacteremia. Although vancomycin treatment failure is higher in hVISA infections (10), in actual clinical practice, most patients with hVISA bacteremia are treated with vancomycin, because testing for hVISA is not routinely performed. There is no clinical study that has compared the efficacy of vancomycin and another antibiotic in hVISA bacteremia. In the present study, linezolid treatment was associated with a trend toward reduced mortality in the univariate analysis, although characteristics (site of infection) of hVISA bacteremia were similar between patients who received definitive linezolid treatment and those who received definitive glycopeptide treatment, as shown in Table S1 in the supplemental material. We could not evaluate the efficacy of daptomycin, because it was not available in our country. Linezolid has been successfully used in several cases of hVISA or VISA bacteremia (6). A possible explanation for this was provided by a recent study by Watanabe et al. (32). They showed that there was a significant inverse relationship in terms of vancomycin and linezolid susceptibilities between VSSA and VISA. hVISA isolates are more likely to have thicker cell walls with more binding sites that sequester vancomycin than are isolates fully susceptible to vancomycin (6), and this physiologic change may enhance linezolid activity. The usefulness of linezolid in treating hVISA bacteremia requires further study.

Our study has two main limitations. First, we did not use infection-attributable mortality due to the low event rate (11%). Also, in many previous studies that evaluated risk factors for mortality due to *S. aureus* bacteremia, the main outcome of interest was all-cause mortality (26, 29). When we used attributable mortality, the risk factors for outcome in the univariate analysis were similar to those for all-cause mortality. Second, the number of ST239 isolates and linezolid-treated patients was small, and so significant associations could not be demonstrated. A large study involving a variety of clonal types and/or a randomized study is needed to confirm our findings.

In conclusion, ultimately or rapidly fatal disease, reflecting the severity of comorbidities, and the Pitt bacteremia score, which indicates the severity of bacteremia, were independent risk factors for mortality in patients with hVISA bacteremia. ST239 hVISA was a possible predictor of survival. A high vancomycin MIC was not associated with increased mortality. Further studies are required to validate these findings.

ACKNOWLEDGMENTS

We sincerely thank Jang Mi Go, Kyung-Mi Bang, Su-Jin Park, Hee Sueng Kim, So Young Kim, and Mi Young Kim for support with data collection.

This work was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health and Welfare, Republic of Korea (grant number A120964).

We declare we have no competing interests.

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