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MAJOR ARTICLE

Staphylococcal Enterotoxin P Predicts Bacteremia in Hospitalized Patients Colonized With Methicillin-Resistant *Staphylococcus aureus*

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(See the editorial commentary by Stevenson and Wang on pages 488–90.)

Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization predicts later infection, with both host and pathogen determinants of invasive disease.

Methods. This nested case-control study evaluates predictors of MRSA bacteremia in an 8–intensive care unit (ICU) prospective adult cohort from 1 September 2003 through 30 April 2005 with active MRSA surveillance and collection of ICU, post-ICU, and readmission MRSA isolates. We selected MRSA carriers who did (cases) and those who did not (controls) develop MRSA bacteremia. Generating assembled genome sequences, we evaluated 30 MRSA genes potentially associated with virulence and invasion. Using multivariable Cox proportional hazards regression, we assessed the association of these genes with MRSA bacteremia, controlling for host risk factors.

Results. We collected 1578 MRSA isolates from 520 patients. We analyzed host and pathogen factors for 33 cases and 121 controls. Predictors of MRSA bacteremia included a diagnosis of cancer, presence of a central venous catheter, hyperglycemia (glucose level, >200 mg/dL), and infection with a MRSA strain carrying the gene for staphylococcal enterotoxin P (*sep*). Receipt of an anti-MRSA medication had a significant protective effect.

Conclusions. In an analysis controlling for host factors, colonization with MRSA carrying *sep* increased the risk of MRSA bacteremia. Identification of risk-adjusted genetic determinants of virulence may help to improve prediction of invasive disease and suggest new targets for therapeutic intervention.

Keywords. Bacteremia; methicillin-resistant *Staphylococcus aureus*; epidemiology; hospital infections; microbial genetics.

Staphylococcus aureus is a major cause of healthcare-associated infections [1], and patients are often colonized with this bacterium before developing invasive disease [2, 3]. Increasing carriage of methicillin-resistant *S. aureus* (MRSA), an antibiotic-resistant strain, has resulted in a doubling of MRSA-related hospitalizations, including up to 56 000 US hospitalizations per year for MRSA bacteremia [4–6]. Overall, nearly 19 000 patients die annually in US hospitals from MRSA infections [7].

MRSA carriage in the United States is at least 7% in general hospital populations [8] and as high as 24% in intensive care units (ICUs) [9]. The risk of MRSA infection in the year following colonization is as high as 33%, with 18% being primary bloodstream infections [10]. Nasal carriers of MRSA versus methicillin-susceptible *S. aureus* (MSSA) have a 4 times higher incidence of bacteremia, with >80% of cases involving an identical strain in the nares and the blood [3, 11, 12]. In addition, the mortality for bacteremia is 2 times higher with MRSA as compared to MSSA [13].

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Both host and pathogen factors play a role in the development of MRSA infections. Host factors include prolonged hospitalization [14–17], advanced age [10, 14], intravenous catheterization [15, 17–19], mechanical ventilation [18, 20, 21], antibiotic exposure [17, 21], soft-tissue wounds [15, 19], and chronic diseases, such as diabetes, renal insufficiency, cancer, and malnutrition [10, 18, 22].

Pathogen factors predicting MRSA bacteremia are the subject of ongoing debate [23]. Studies accounting for epidemiologic factors of the host in addition to genetic variation in different MRSA strains are lacking. We therefore sought to look at combined host and pathogen factors in a prospective cohort.

METHODS

Study Population and Study Design

Our hospital began active surveillance for MRSA in July 2003. This included screening for MRSA colonization in the nares of patients upon ICU admission and weekly thereafter. For patients admitted to 8 adult ICUs between 1 September 2003 and 30 April 2005, we prospectively collected ICU, post-ICU, and all readmission MRSA isolates (ICU and non-ICU). We excluded isolates collected within 7 days from the same body site.

We then performed a nested case-control study. Cases were patients with culture-confirmed MRSA colonization followed by hospital-associated MRSA primary bacteremia occurring >2 days after admission. Controls were patients with culture-confirmed MRSA colonization without subsequent MRSA bacteremia or other evidence of invasive disease. Inclusion in the study required that MRSA colonization be documented during the study period. Sites of colonization included nares, respiratory specimens without evidence of pneumonia, and wound specimens without evidence of wound infection. We selected 4 times as many controls as cases. These controls were selected randomly without matching to cases.

This study was approved by the Brigham and Women's Hospital institutional review board with a waiver of informed consent.

Clinical Data Elements

An infectious diseases physician reviewed medical records for the cases and controls, categorizing all MRSA infections on the basis of definitions from the Centers for Disease Control and Prevention [24]. Abstracted data on potential risk factors included sex, age, dates of hospitalizations, whether the patient was admitted from a skilled-nursing facility or rehabilitation hospital, and underlying comorbidities, including cancer, diabetes, end-stage renal disease, and immunocompromised status. We also identified the following potential risk factors in the 7 days before through 2 weeks after the culture that detected colonization: active wound or skin abnormality, intubation, central venous catheter presence and duration, antibiotic administration and duration for each of 12 antibiotic classes, and laboratory abnormalities, including a creatinine level of >2.0 mg/dL, an albumin level of <2.0 g/dL, and a glucose level of >200 mg/dL. For cases, we only recorded risk factors through the day before bacteremia.

Whole-Genome Sequencing of MRSA Isolates

We performed whole-genome sequencing of clinical isolates of MRSA from cases and controls. We sequenced the bacteremia strain for cases and the colonizing strain for controls.

Illumina 101–base paired end reads were sequenced from 2 libraries, one of 180-bp fragments and one of 3-kb jumps. De novo assemblies were constructed using ALLPATHS-LG [25]. Protein-coding genes were predicted with Prodigal [26] and filtered to remove genes with at least 70% overlap of transfer RNAs or ribosomal RNAs, as detected by tRNAscan-SE [27] and RNAmmer [28], respectively. Annotated genome sequences were deposited in Genbank (accession numbers AIVQ01000000-AIWV01000000, AIXB01000000-AIZP01000000, AJBO01000000-AJDF01000000, ANZK01000000-AOBJ01000000, and AQFY 01000000-AQGF01000000).

All strains were confirmed as MRSA, first by standard microbiologic techniques and subsequently by detection of the *mecA* gene.

Selection of MRSA Virulence Genes

We constructed a list of genes, a priori, thought to encode virulence factors that mediate host invasion and immune evasion. Inclusion was based on the prior association with MRSA bacteremia and likelihood that the presence of the gene correlates with expression. The list included Panton-Valentine leukocidin (*lukS* and *lukF*) [29, 30], other leukocidins (*lukD* and *lukE*) [31], staphylococcal enterotoxins a-u (*sea*, *seb*, *sec*, *sed*, *see*, *seg*, *seh*, *sei*, *sej*, *sek*, *sel*, *sem*, *sen*, *seo*, *sep*, *seq*, *ser*, and *ψent1/2*) [30, 32–36], chemotaxis inhibitor protein of *S. aureus* (CHIPS) [37, 38], staphylococcal complement inhibitor (SCIN) [38, 39], staphylokinase (*sak*) [38], toxic shock syndrome toxin (*tst*) [35, 36], staphylococcal cassette chromosome mec (SCC*mec*) type [40, 41], and accessory gene regulator (*agr*) locus group [41]. For each isolate, we assessed the presence or absence of these genes. For 2 others, α-hemolysin (*hla*) and phenol soluble modulin (*psm-alpha*) [30, 31, 42], we evaluated single-nucleotide polymorphisms.

Statistical Analysis

All analyses were performed in SAS, version 9.3 (SAS Institute, Cary, NC). Cox proportional hazards regression was used to evaluate the outcome of time to MRSA bacteremia following identification of MRSA colonization. A univariable hazard ratio (HR) with a 95% confidence interval (CI) and *P* value was calculated for each selected host and pathogen factor. Covariates with a *P* value of $\leq .2$ were entered into a multivariable model.

Based on the clinical importance of antistaphyloccocal therapy, we forced receipt of an anti-MRSA medication into the multivariable model. Anti-MRSA medications included vancomycin, linezolid, quinopristin/dalfopristin, daptomycin, and tigecycline.

For each gene entered into the multivariable model, we tested for 2-way interactions with each of the included host factors, taking a P value of $< .05$ to be statistically significant. Any significant interaction terms were included in the multivariable model. We then used time-dependent covariates to test the proportional hazards assumption of each covariate in the final model. There is an assumption in Cox proportional hazards regression that the HR between any 2 individuals is constant over time. For each predictor, we accepted the proportional hazards assumption as valid if the time-dependent covariate had a P value of $\geq .05$ [43].

Finally, we used a Wilcoxon rank sum test to compare length of time in the study between cases and controls. Data for all cases were censored at the time of bacteremia. Controls were considered to be at risk for all days between colonization and the date of discharge of the last hospitalization during the study period.

RESULTS

Study Population

There were 8203 patients with 11 528 ICU admissions between 1 September 2003 and 30 April 2005. We banked 1578 MRSA isolates from 492 patients with a positive MRSA culture. Overall, 6% of patients had at least 1 positive MRSA culture during the study period, with 63% of these patients having >1 positive MRSA culture. The banked isolates included 122 (8%) from blood specimens, 715 (45%) from nares specimens, 502 (32%) from respiratory specimens, 78 (5%) from wound specimens, and the remaining 161 (10%) from specimens from alternate sites (eg, abscess fluid, drains, and tissue).

We identified 52 patients with hospital-associated MRSA bacteremia occurring after or concurrent with culture-confirmed MRSA colonization. After excluding 12 patients with bacteremia secondary to MRSA pneumonia and 7 patients with bacteremia secondary to MRSA surgical site infection, we included 33 cases with a primary bacteremia in our study.

Full-genome sequencing was completed on isolates from all cases and 127 of 132 controls. Isolates from the 5 controls without sequence data included 1 mixed culture, 1 *Staphylococcus epidermidis* isolate, 1 *Staphylococcus carnosus* isolate, and 2 isolates for which there was difficulty with DNA extraction. Isolates from all cases and 121 of 127 controls had the *mecA* gene. Isolates from the 6 controls without the *mecA* gene included 3 that were phenotypically MRSA and 3 that were phenotypically MSSA. The isolates that were phenotypically MSSA were erroneously collected and labeled as MRSA. A total of 33 cases and 121 controls were included in our study.

Clinical Data Elements

Table 1 shows clinical predictors of MRSA bacteremia. Three host factors were selected for inclusion in the multivariable model: diagnosis of cancer, presence of a central venous catheter, and a glucose level of >200 mg/dL.

None of the antibiotic exposure classes were statistically significant in terms of increasing or decreasing MRSA bacteremia following colonization. This was true both for receipt of the antibiotic and after accounting for duration of antibiotic therapy. As discussed previously, receipt of an anti-MRSA medication was forced into the multivariable model.

MRSA Virulence Genes

Twenty nine (88%) of the MRSA bacteremias and 108 (89%) of the MRSA colonizations involved clonal complex 5 (USA 100 genotype). This is consistent with hospital-associated MRSA bacteremia during this period. Four (12%) of the MRSA bacteremias and 8 (7%) of the MRSA colonizations involved clonal complex 8 (USA 300/500 genotypes). The remaining 5 MRSA colonization isolates were from other clonal complexes.

Table 2 shows genes from our a priori list. Only the gene for staphylococcal enterotoxin P (*sep*) had a P value of $\leq .2$ and was included in the multivariable model. This gene was found in isolates from 5 cases (15%) and 6 controls (5%). These 11 isolates with *sep* all contained the following: innate immune evasion cluster (CHIP, SCIN, and *sak*), enterotoxin gene cluster (*seg*, *sei*, *sem*, *sen*, *seo*, and *ψent1/2*), and the same single-nucleotide polymorphism of *psm-alpha*. In addition, all of these isolates were SCC*mec* type II and *agr* group II, consistent with clonal complex 5 (USA 100 genotype). These 11 isolates were not identical, however, with differences in the presence of *sed* and 3 different single-nucleotide polymorphisms of *hla*.

Multivariable Model

Table 3 shows the multivariable model. We discovered an interaction between *sep* and receipt of an anti-MRSA medication (P=.03). Patients with a MRSA strain carrying *sep* had an increased risk of bacteremia if they were not receiving an anti-MRSA medication (HR, 26.74; 95% CI, 4.74–150.79). This risk was reduced, however, in patients receiving an anti-MRSA medication while harboring a MRSA strain carrying *sep* (HR, 1.46; 95% CI, .39–5.39). This protective effect from receipt of an anti-MRSA medication was also seen in patients with MRSA strains not carrying *sep*, although the CI overlapped the null value of equal risk (HR, 0.53; 95% CI, .24–1.15). Patients receiving an anti-MRSA medication may be less likely to progress from MRSA colonization to bacteremia, because of the protective effect of receiving an antibiotic that treats invasive disease.

Among the other covariates, a diagnosis of cancer (HR, 3.06; 95% CI, 1.48–6.35) and presence of a central venous catheter (HR, 2.94; 95% CI, 1.22–7.10) also elevated the risk of bacteremia. The 95% CI for hyperglycemia (glucose level, >200 mg/dL) included the null value of equal risk, but the estimate suggested an elevated risk (HR, 1.90; 95% CI, .90–4.00). For each of the covariates included in our final model, we found no significant time-covariate interactions when testing the proportional hazards

Table 1. Clinical Predictors of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia

Variable	MRSA Bacteremia (n = 33)	MRSA Colonization (n = 121)	Univariable HR (95% CI)	*P*
Age at colonization, y, mean ± SD	63.7 ± 18.3	66.5 ± 15.0	1.00 (.97–1.02)	.65
Female sex	19 (58)	57 (47)	1.29 (.65–2.58)	.47
Comorbidity				
Diabetes	8 (24)	39 (32)	0.63 (.29–1.40)	.26
End-stage renal disease	3 (9)	7 (6)	1.19 (.36–3.90)	.78
Immunocompromised	3 (9)	5 (4)	1.62 (.49–5.32)	.43
Cancer	16 (48)	28 (23)	2.63 (1.32–5.22)	.01
Admitted from skilled-nursing facility or rehabilitation hospital	0 (0)	6 (5)	. . .	
Presence of active wound or skin abnormality[a]	23 (70)	94 (78)	0.64 (.30–1.35)	.24
Intubated[a]	19 (58)	60 (50)	1.45 (.73–2.89)	.29
Use of central venous catheter[a]	26 (79)	76 (63)	2.34 (1.01–5.43)	.05
Laboratory abnormality[a]				
Creatinine level >2.0 mg/dL	7 (21)	22 (18)	0.91 (.39–2.10)	.82
Albumin level <2.0 g/dL	6 (18)	16 (13)	1.44 (.59–3.51)	.42
Glucose level >200 mg/dL	20 (61)	57 (47)	1.97 (.97–3.98)	.06
Antibiotic exposure[a,b]				
Anti-MRSA agent[c]	18 (55)	79 (65)	0.68 (.34–1.35)	.27
Other MRSA agent[d]	0 (0)	3 (2)	. . .	
First-generation penicillin	0 (0)	6 (5)	. . .	
First-generation cephalosporin	4 (12)	18 (15)	0.80 (.28–2.27)	.67
Second-generation cephalosporin	1 (3)	0 (0)	2.48 (.33–18.34)	.38
Third/fourth-generation cephalosporin	5 (15)	28 (23)	0.56 (.22–1.46)	.24
Carbapenem	1 (3)	0 (0)	2.48 (.33–18.34)	.38
Aminoglycoside	0 (0)	4 (3)	. . .	
Fluoroquinolone	19 (58)	77 (64)	0.84 (.42–1.67)	.61
Macrolide	1 (3)	13 (11)	0.30 (.04–2.17)	.23
Metronidazole	13 (39)	49 (41)	1.05 (.52–2.11)	.89
Clindamycin	0 (0)	4 (3)	. . .	

Data are no. (%) of individuals, unless otherwise indicated. Cancer, use of central venous catheter, and glucose level >200 mg/dL were the only variables with a *P* value of ≤ .2 on univariable testing.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Evaluated from 7 days before through 2 weeks after colonization. For cases, we only recorded risk factors through the day before bacteremia.

[b] No patients received a second-generation penicillin or a β-lactam/β-lactamase inhibitor.

[c] Vancomycin, linezolid, quinopristin/dalfopristin, daptomycin, and tigecycline.

[d] Trimethoprim/sulfamethoxazole, doxycycline, and rifampin.

assumption. In addition, the presence of *sep* was not differentially associated with the other covariates included in the model.

Finally, it is important to note that controls were followed for significantly more time (*P*=.02) than cases (median duration, 23 days [interquartile range, 7–104 days] vs 16 days [interquartile range, 2–43 days]). Therefore, a shorter follow-up period for the controls is unlikely to explain the difference.

DISCUSSION

Controlling for host factors [10, 14–22], we found that colonization with a MRSA strain carrying the gene for staphylococcal enterotoxin P was a significant risk factor for developing MRSA bacteremia. This gene is part of an innate immune evasion cluster encoding proteins that help *S. aureus* evade the host immune response through inhibition of neutrophil chemotaxis, binding, and phagocytosis [38, 44, 45]. Additionally, enterotoxin P disrupts immune response by inducing T-cell anergy via polyclonal stimulation of T cells [44, 46], and the presence of enterotoxin P was previously linked to higher mortality in *S. aureus* bacteremia [47]. Therefore, staphylococcal enterotoxin P is a possible target for immunotherapeutics or vaccine development [48].

Different strains of *S. aureus* carry different immune evasion cluster genes. One study found bacteriophages carrying immune evasion cluster genes in approximately 90% of clinical *S. aureus*

Table 2. Gene Loci Evaluated for Association with Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia

Variable	MRSA Bacteremia (n = 33)	MRSA Colonization (n = 121)	Univariable HR (95% CI)	*P*
Panton-Valentine leukocidin				
lukS	0 (0)	1 (1)	. . .	
lukF	0 (0)	1 (1)	. . .	
Other leukocidin				
lukD	33 (100)	117 (97)	. . .	
lukE	33 (100)	117 (97)	. . .	
Staphylococcal enterotoxin[a]				
Enterotoxin A	3 (9)	8 (7)	1.77 (.54–5.83)	.35
Enterotoxin B	4 (12)	7 (6)	1.93 (.68–5.50)	.22
Enterotoxin C	0 (0)	1 (1)	. . .	
Enterotoxins D, J, and R[b]	12 (36)	62 (51)	0.68 (.33–1.38)	.28
Enterotoxins G, I, M, N, O, and U[c]	29 (88)	112 (93)	0.67 (.24–1.92)	.46
Enterotoxins K and Q[d]	4 (12)	8 (7)	1.83 (.64–5.22)	.26
Enterotoxin L	0 (0)	1 (1)	. . .	
Enterotoxin P	5 (15)	6 (5)	2.97 (1.14–7.73)	.03
Chemotaxis inhibitor protein	27 (82)	108 (89)	0.68 (.28–1.64)	.38
Staphylococcal complement inhibitor protein family	30 (91)	114 (94)	0.94 (.29–3.10)	.92
Staphylokinase	30 (91)	115 (95)	0.88 (.27–2.91)	.84
Toxic shock syndrome toxin	0 (0)	4 (3)	. . .	
SCC*mec* type				
Type II	29 (88)	110 (91)	Reference	
Type IV	4 (12)	10 (8)	1.52 (.53–4.32)	.43
Unknown	0 (0)	1 (1)	. . .	
Accessory gene regulator locus group				
Group I	4 (12)	10 (8)	1.31 (.46–3.74)	.61
Group II	29 (88)	108 (89)	Reference	
Group III	0 (0)	3 (2)	. . .	

Data are no. (%) of individuals. The gene encoding enterotoxin P was the only variable with a *P* value of ≤ .2 on univariable testing.

Abbreviations: CI, confidence interval; HR, hazard ratio; SCC*mec*, staphylococcal cassette chromosome *mec*.

[a] No isolates had the genes encoding enterotoxin E or enterotoxin H.

[b] Genes encoding enterotoxins D, J, and R are transferred together via pIB485-like plasmids.

[c] Components of the enterotoxin gene cluster.

[d] Genes encoding enterotoxins K and Q are found on the same mobile element.

Table 3. Multivariable Model of Factors Associated With Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia in Colonized Patients

Variable	Multivariable HR (95% CI)	*P*
Staphylococcal enterotoxin P gene	26.74 (4.74–150.79)	<.01
Anti-MRSA antibiotic[a]	0.53 (.24–1.15)	.11
Staphylococcal enterotoxin P gene with anti-MRSA antibiotic[a]	1.46 (.39–5.39)	.57
Cancer	3.06 (1.48–6.35)	<.01
Use of central venous catheter[a]	2.94 (1.22–7.10)	.02
Glucose level >200 mg/dL[a]	1.90 (.90–4.00)	.09

There was a significant interaction between the presence of the gene for staphylococcal enterotoxin P and receipt of an anti-MRSA antibiotic in the model predicting the time to MRSA bacteremia following identification of MRSA colonization. The multivariable model therefore includes an interaction term for these 2 variables.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Evaluated from 7 days before through 2 weeks after colonization. For cases, we only recorded risk factors through the day before bacteremia.

strains [38]. These bacteriophages carry genes for staphylokinase, CHIPS, SCIN, enterotoxin A, and enterotoxin P. Prior work reported the prevalence of *sep* as 7.7%, similar to the prevalence of 7.1% in our study [38]. The gene for enterotoxin P is present in both MSSA and MRSA. Therefore, enterotoxin P may have a similar role in MSSA bacteremia.

Lower antibody levels to *S. aureus* enterotoxins have been linked to bacteremia [30], and a genetically modified staphylococcal enterotoxin A showed success as a vaccine candidate, offering protection against *S. aureus* bacteremia in mice [49]. There is 77% amino acid similarity between staphylococcal enterotoxin A and enterotoxin P [50], with these enterotoxins both known to bind to human T-cell receptors [46]. Interestingly, the presence of *sea* was not a significant risk factor for developing MRSA bacteremia in our study. This is likely because the majority of patients in our study were colonized or infected with clonal complex 5 strains (USA 100 genotype). None of the clonal complex 5 strains carried the gene for enterotoxin A; however, *sea* was found in 9 of 12 patients colonized or infected with clonal complex 8 strains (USA 300/500 genotype). None of these clonal complex 8 strains carried the gene for enterotoxin P.

Our study has the strength of analyzing combined host and pathogen factors in a prospective cohort. Because of the significant effort involved in the collection of isolates, this study will be difficult to replicate. We do note, however, several limitations to this work. First, we assumed that the genetic sequences of the colonizing strain and subsequent bacteremic strain were identical. To the extent that this is not true, genetic associations may not hold, although prior studies have found that nearly all bacteremic strains are identical or nearly identical to prior colonizing strains [3, 12]. Second, we limited our evaluation to putative genes selected a priori. Other genes could be associated with progression to MRSA bacteremia. Evaluation of these genes will require testing in a novel cohort, to avoid problems

with multiple testing. Third, we only looked for the presence or absence of the a priori selected genes. While we selected genes where the presence of the gene correlates with expression, we did not perform formal expression studies.

Fourth, our study relied on a limited number of isolates, possibly limiting our power to identify important host or pathogen factors. We were unable to account for clustering of effect at the level of individual ICUs, because of insufficient data on patient location at the time of specimen collection and the small sample size. Fifth, the median follow-up time for patients who did not develop MRSA bacteremia following colonization was <30 days. Prior work has shown that 50% of patients with a primary MRSA bloodstream infection in the year following colonization develop this infection after discharge (ie, median 72 days after colonization) [10]. Therefore, it is possible that the risk factors described are more associated with short-term risk.

Sixth, for standardized collection in both cases and controls, we evaluated clinical risk factors occurring in a window around documented MRSA colonization. It is possible that clinical risk factors outside this window were not accounted for in our analysis, but we selected a high-risk window for clinical interventions. Finally, findings were derived from a single hospital where a specific genetic background served as the predominant strain. It is possible that other virulence factors that are important either in the general population or in other hospitals with a different predominant MRSA genotype (eg, USA 300) may not have been captured in this analysis.

Our relatively small number of observed MRSA bacteremia cases prevented us from performing a formal model validation via split-half or a related technique. Nevertheless, the risk of an overfitted model is mitigated by the inclusion of all covariates with a univariable P value of $\leq .2$. There was no variable selection at the multivariable stage, greatly diminishing the possibility that the model was tailored to the data. We also assessed the need for each of 4 interaction terms between the one included gene and the included host factors. This assessment was based on a priori concerns about effect modification, not excessive reliance on iterative model fitting.

The successful identification of risk-adjusted genetic determinants of virulence may help to improve prediction of invasive disease and suggest new targets for therapeutic intervention. Our results suggest the need to further evaluate staphylococcal enterotoxin P and the innate immune evasion complex genes as pathogen-specific determinants of invasive MRSA infection. While the prevalence of *sep* was only 7.1% in our study population, the presence of this gene was quite significantly associated with the development of primary MRSA bacteremia following documented colonization. Larger studies in novel cohorts are needed to confirm these findings and to further investigate the joint role of host and pathogen factors in determining the invasive potential of colonizing MRSA strains.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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