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Major Article

Risk factors for the development of active methicillin-resistant *Staphylococcus aureus* (MRSA) infection in patients colonized with MRSA at hospital admission

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Background: Patients who present to Veterans Affairs hospitals are screened for methicillin-resistant *Staphylococcus aureus* (MRSA) colonization. Those who test positive are isolated during their hospital stay. However, it is unknown which of these patients are most likely to subsequently develop active MRSA infections.
Methods: This retrospective case-control study characterized risk factors for active MRSA infection among patients colonized with MRSA at hospital admission. Potential demographic and clinical risk factors were identified using electronic queries and manual chart abstraction; data were compared by standard statistical tests, and variables with $P \leq .05$ in bivariable analysis were entered into a multivariable logistic regression model.
Results: There were 71 cases and 213 controls. Risk factors associated with MRSA infection included diabetes mellitus with or without end organ damage (26% vs 14%, $P = .02$), hemiplegia (9% vs 2%, $P = .01$), chronic kidney disease (33% vs 20%, $P = .03$), postcolonization inpatient admission within 90 days (44% vs 29%, $P = .03$), surgery (41% vs 9%, $P < .01$), and dialysis (10% vs 3%, $P = .02$). On multivariable analysis, surgery during follow-up, dialysis during follow-up, and hemiplegia remained significant.
Conclusions: Among patients with MRSA colonization, surgery or dialysis during follow-up and history of hemiplegia were associated with subsequent MRSA infection. Knowledge of these risk factors may allow for future targeted interventions to prevent MRSA infections among colonized patients.
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Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of health care–associated and community-acquired infections. MRSA causes invasive infections of multiple body sites, most commonly skin and soft tissues, but also lung, bone, joints, bloodstream, medical devices, and urinary tract.[1]

Close to 100,000 cases of invasive MRSA infections occur annually, and 20% of these patients will die from the infections.[2] Up to one-third of the U.S. population is colonized with *S aureus*, and nasal carriage of *S aureus* is associated with increased risk of developing active infections; therefore, it is very important to be able to define the risk factors for active infection in colonized patients.[3-6] MRSA colonization itself is the most important risk factor for invasive MRSA infection, even after adjusting for other comorbidities.[5] Several strategies have been developed to prevent MRSA infections, including active screening, isolation, hand hygiene and culture change to prevent infections, screening and decolonization before surgical procedures, use of chlorhexidine and mupirocin in all patients admitted to the intensive care unit (ICU), and even the use of universal isolation among ICU patients regardless of their colonization status.[7-10]

Many health care settings have therefore moved toward MRSA surveillance in order to implement barrier precautions and decrease MRSA transmission. At the veterans healthcare system, the implementation of an MRSA prevention bundle has led to a significant decrease in the rates of MRSA infections, by screening and isolating MRSA-positive patients, improving hand hygiene, and changing the institutional culture to make MRSA prevention everybody's business.[10] Given rigorous MRSA surveillance, there is a

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great need to define the patient population colonized by MRSA and assess their risk of developing active infection.

In this study, our aim was to elucidate risk factors associated with the development of invasive MRSA infection within a population of patients screened positive for MRSA colonization during their stay at an inpatient acute care facility. We followed these patients until development of MRSA infection or up to 18 months after discharge.

METHODS

Study design and population

In this retrospective case-control matched study, we analyzed risk factors associated with MRSA invasive infections among patients who screened positive for MRSA colonization during inpatient acute care admission. The study was conducted at the Audie L. Murphy Division of South Texas Veterans Health Care System, a tertiary care medical center. The study population was generated from the period of September 1, 2009-August 31, 2011. Patients were selected on the basis of positive MRSA carriage as determined by anterior nares surveillance specimens collected on admission, unit transfer (by polymerase chain reaction; Xpert MRSA; Cepheid, Sunnyvale, CA), and discharge (BBL CHROMagar; BD, Franklin Lakes, NJ). At the time of the study, mupirocin decolonization was only recommended among patients undergoing cardiothoracic surgery, but there was no active preoperative screening for MRSA.

Only patients who tested positive for MRSA carriage at an inpatient acute care setting were included. Consequently, patients residing at the rehabilitation or long-term care facilities when first found to be MRSA positive were excluded. Cases were defined as MRSA-colonized patients who subsequently developed MRSA invasive infections during follow-up. The follow-up period terminated once a patient developed invasive infection or otherwise up to 18 months after discharge. Invasive MRSA infection was defined as infection in accordance with the Centers for Disease Control and Prevention (CDC) definition, except for pneumonia, which was defined as the presence of supporting clinical features (ie, cough, fever, sputum production, pleuritic chest pain) and supported by infiltrates on chest radiographs, with an MRSA-positive sputum culture of a good-quality specimen, tracheal aspirate, or bronchoalveolar lavage.[11,12] If the initial testing for MRSA carriage was positive, but simultaneously the patient had invasive MRSA infection, then that patient was excluded. Controls were defined as MRSA-colonized patients who did not develop active MRSA infections during the 18-month follow-up period. For each case, 3 controls were randomly selected through the random number generator function in Microsoft Excel (Microsoft Corp, Redmond, WA). Data collection for patient's demographic and clinical characteristics was through chart review of electronic medical records. Patients' comorbidities were used to generate the Charlson Comorbidity Index. Among patients that received anti-MRSA antibiotics, we exclude those that received them <48 hours after the positive cultures and those where there was clinical evidence of the end point MRSA infection when the antibiotics were prescribed.

Statistical analysis was performed using JMP 8 software (SAS Institute, Cary, NC). Statistical significance was defined as a 2-sided P value ≤.05. The comparison of demographic and clinical characteristics between cases and controls was generated by χ^2, Fisher exact, and Wilcoxon rank-sum tests.

RESULTS

Seventy-one cases and 213 controls were identified. No significant differences were found between the groups with respect to mean age, sex, alcohol or intravenous drug use, and homelessness (Table 1). The body sites most often affected by MRSA invasive infections were skin and soft tissues, lungs, and urinary tract (Table 2). Bivariable analysis between cases and controls demonstrated that a medical history of hemiplegia ($P = .01$), diabetes mellitus with organ damage ($P = .02$), and chronic kidney disease ($P = .03$) were significantly associated with the development of invasive MRSA infections (Table 1).

Prior inpatient admission in 12 months ($P = .01$) and readmission 90 days postdischarge ($P = .03$) were all significantly associated with MRSA invasive infections (Table 3). Independent risk factors for MRSA infections postcolonization included the following: hemiplegia (odds ratio [OR], 8.68; 95% confidence interval [CI], 1.86-48.11), surgery (OR, 9.77; 95% CI, 4.55-21.77), and dialysis during follow-up (OR, 4.53; 95% CI, 1.14-18.18) (Table 3).

DISCUSSION

Despite advances in the prevention of health care–associated infections, MRSA continues to be a significant cause of morbidity and mortality in the United States.[1] Currently, there is no universal agreement regarding the optimal preventive strategy to decrease invasive MRSA infections. Some authors propose a horizontal approach to prevention, focusing on strategies that would prevent this and other health care–associated infections, such as hand hygiene and central line insertion bundles. Others prefer a vertical strategy, which focuses on screening and decolonizing for MRSA. Finally, some others prefer to combine both of these strategies.[6] It is challenging for the clinician to know how to manage the colonized patients discovered during hospital screening and who is at greatest risk for invasive MRSA infection.

Our study assesses the long-term risk of invasive MRSA infection in patients identified by active surveillance to be MRSA colonized during hospitalization. We found that MRSA-colonized patients with diabetes mellitus with end organ damage, hemiplegia, admission to the hospital within the previous 12 months, readmission within 3 months, surgery postcolonization, and undergoing dialysis postcolonization were at increased risk of developing an MRSA infection. On multivariable analysis, hemiplegia, surgery postcolonization, and dialysis after MRSA colonization remained significant risk factors.

Patients can carry MRSA in their nares for >1 year, with one study estimating the half-life of MRSA colonization to be 40 months[13]; therefore, long-term follow-up for MRSA infection in the outpatient setting, as seen in our study, is important. Several prior studies have found that MRSA-colonized patients are at increased risk for invasive MRSA infection compared with noncolonized patients.[5,14-17] One such study by Epstein et al was a case-control design using data from the CDC Active Bacterial Case Surveillance Program to identify cases of invasive MRSA infection after discharge from 15 hospitals in 6 states.[14] Factors associated with postdischarge MRSA infection included MRSA colonization, discharge to a nursing home, presence of a chronic wound during the postdischarge period, and discharge with a central venous catheter or a different invasive device in place. MRSA colonization was the most significant risk factor for development of MRSA infection, with 78% of cases being bloodstream infections.[14] This multicenter study did not include active surveillance for MRSA colonization in every facility and did not detail the particular risk factors for MRSA infection postcolonization.

We previously performed a case-control study on MRSA-colonized patients who developed skin and soft tissue infections after hospital discharge.[15] We found that prior hospital admission within 12 months, prior MRSA infection, and previous myocardial infarction were independent predictors for MRSA skin and soft tissue infections posthospital discharge.

Another study performed at the Veterans Affair (VA) Pittsburgh Healthcare System,[16] evaluated the risk factors for MRSA

Table 1
Patient baseline characteristics

Characteristic	MRSA-colonized patients who developed invasive infections (n = 71)	MRSA-colonized patients who did not develop invasive infections (n = 213)	*P* value (2-sided)
Demographics			
Age, y, mean ± SD	64 ± 13	66 ± 13	.53
Male sex	67 (94.4)	201 (94.4)	>.99
Social factors			
Smoking	22 (31.0)	58 (27.2)	.54
Alcohol abuse	10 (14.3)	36 (16.9)	.61
IV substance abuse	2 (2.8)	9 (4.2)	.74
Homeless	2 (2.8)	4 (1.9)	.64
Comorbidities			
Charlson Comorbidity Index, mean ± SD	6.3 ± 3.2	5.5 ± 3.1	.09*
Myocardial infarction	9 (12.9)	18 (8.7)	.33
Congestive heart failure	13 (18.6)	35 (17.0)	.76
Dyslipidemia	45 (64.3)	119 (57.8)	.33
Hypertension	59 (8.3)	160 (77.8)	.23
Peripheral vascular disease	15 (21.4)	34 (16.5)	.36
Cerebrovascular accident	13 (18.6)	46 (22.3)	.50
Dementia	6 (8.6)	7 (3.4)	.10*
COPD	21 (30.0)	70 (34.0)	.54
Rheumatologic disorders	2 (2.9)	4 (1.9)	.66
Peptic ulcer disease	3 (4.3)	9 (4.4)	.98
Cirrhosis	7 (10.0)	29 (14.1)	.37
Liver disease, mild	4 (5.7)	17 (18.3)	.48
Diabetes mellitus, no organ damage	43 (61.4)	99 (48.1)	.05*
Diabetes mellitus, organ damage	18 (25.7)	28 (13.6)	.02*
Chronic kidney disease	23 (32.9)	41 (19.9)	.03*
Hemiplegia	6 (8.6)	3 (1.5)	.01*
Active cancer	19 (27.1)	47 (22.8)	.47
Metastasis	3 (4.3)	5 (2.4)	.44
Active leukemia (acute or chronic)	3 (4.3)	3 (1.5)	.19
AIDS	0 (0.0)	3 (1.5)	.57
Immunocompromised at admission	8 (11.3)	19 (8.9)	.57
Pressure ulcers during admission	6 (8.6)	15 (7.1)	.68
Chronic skin conditions	15 (21.1)	49 (23.1)	.73
New acquisition MRSA colonization	17 (23.9)	52 (24.4)	.94
Other history (last 12 mo)			
MRSA infection	13 (18.3)	21 (9.9)	.07*
Admission to hospital	44 (62.0)	94 (44.1)	.01*
Admission to long-term care facility	22 (31.0)	57 (26.8)	.49
Admission to ICU	8 (11.3)	23 (10.8)	.91
Surgery	16 (22.5)	37 (17.4)	.34
Heath care utilization and medical intervention postcolonization (up to 18 mo)			
Central line	16 (22.5)	30 (14.1)	.10*
Gastrostomy tube	11 (15.7)	17 (8.1)	.08*
Surgery	29 (40.8)	19 (8.9)	<.01*
Dialysis	7 (9.9)	6 (2.8)	.02*
Steroid therapy	8 (11.3)	17 (8.0)	.41
Antibiotic therapy	41 (57.7)	125 (58.7)	.09*
Fluoroquinolone therapy	67 (31.5)	22 (31.0)	.94
Cephalosporin therapy	27 (38.0)	67 (31.5)	.31
Anti-MRSA therapy	27 (38.0)	83 (39.0)	.89
Admission to hospital in 90 d	31 (43.7)	62 (29.1)	.03*
Admission to hospital	44 (62.0)	108 (50.7)	.10*
Admission to long-term care facility	27 (38.0)	69 (32.3)	.39

NOTE. Values are n (%) or as otherwise indicated.
COPD, chronic obstructive pulmonary disease; *ICU*, intensive care unit; *IV*, intravenous; *MRSA*, methicillin-resistant *Staphylococcus aureus*.
*$P \leq .01$.

infection while hospitalized or within 30 days of discharge and determined that prior history of MRSA colonization or infection in 1 year, transfer from a nursing home, respiratory failure, and receipt of a transfusion were significant risk factors for infection. A limitation to this study was that MRSA surveillance was introduced on a single unit during the study period and then expanded to other units during the study. The only significant risk factor for infection in non-ICU patients was transfer from a nursing home, and this finding was likely biased by a significant proportion of patients being transferred from a single VA long-term care facility where the average MRSA prevalence rate was 44%. The short duration of the follow-up and the exclusion of MRSA hospital-acquired colonization were additional limitations and may be important because MRSA

Table 2
Patients with ≥1 body site affected by invasive MRSA infection (n = 71)

Site of infection	No.	%
Blood	3	4.2
Blood and lungs	1	1.4
Bone	1	1.4
Joint	1	1.4
Lungs	21	29.6
Skin-soft tissue	31	43.7
Skin-soft tissue and blood	1	1.4
Surgical site	4	5.6
Urinary tract	8	11.3

MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 3
Independent risk factors for developing MRSA invasive infection among MRSA-colonized patients

Characteristic	OR	95% CI
Charlson Comorbidity Index	0.93	0.71-1.21
Dementia	3.31	0.83-12.74
Diabetes mellitus with end organ damage	1.53	0.61-3.74
Chronic kidney disease	0.99	0.40-2.44
Hemiplegia	8.68*	1.86-48.11*
Prior history of MRSA infection	1.69	0.65-4.21
Prior history of admission to hospital	1.63	0.83-3.25
Central line during follow-up	0.92	0.36-2.19
Gastrostomy tube during follow-up	1.57	0.55-4.35
Surgery during follow-up	9.77*	4.55-21.77*
Dialysis during follow-up	4.53*	1.14-18.18*
Antibiotic therapy during follow-up	0.58	0.29-1.13
Admission to hospital within 90 d during follow-up	1.59	0.81-3.09

Vancomycin, linezolid, doxycycline, Trimethoprim-sulfamethosazole, or clindamycin; *CI*, confidence interval; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *OR*, odds ratio.
*CI > 1.0.

infection risk among colonized patients may be present for many months after colonization is detected, and new MRSA acquisition may be a risk factor for MRSA infection.[16]

Finally, a study at the VA Health Care System in Iowa City, Iowa, assessed the long-term outcomes of MRSA colonization, evaluating the association between MRSA colonization and infection-related readmission and crude mortality.[17] The study demonstrated that there were no culture-proven MRSA infections on readmission among the noncarriers, but 13% of MRSA carriers were readmitted with culture-proven MRSA infection, and mortality was significantly higher among MRSA carriers than noncarriers. In contrast with our study, they did not otherwise detail the particular risk factors for MRSA infection in MRSA-colonized patients.

Our study confirms that MRSA colonization is associated with surgical site infection. In fact, there have been several studies that have shown that *S aureus* decolonization before surgery is associated with a decreased rate of *S aureus* surgical site infections.[7,18] Surgical site infections caused by MRSA are predictors of increased 90-day readmissions, mortality, and hospital length of stay. Some authors have estimated that an MRSA surgical site infection can increase cost of care by >$61,000.[19]

Several studies have shown that dementia and hemiplegia are risk factors for MRSA colonization, but to our knowledge, we are the first to show that hemiplegia is a risk factor for invasive MRSA infection. Patients with stroke that are colonized by MRSA tend to have worse neurologic recovery and prolonged length of rehabilitation stay, but they tend to have a worse functional status on admission.[20] Frail long-term care facility residents with stroke and MRSA colonization have been shown to have increased mortality.[21] A study performed at a low MRSA prevalence setting found that cognitive impairment, stroke, and diabetes mellitus were associated with *S aureus* carriage, but no MRSA infections were reported.[22]

In our study, we were unable to show a significant association between antibiotic use and MRSA infection among colonized patients. A previous study performed in Scotland found that restriction of cephalosporins, amoxicillin–clavulanic acid, clindamycin, fluoroquinolones, and macrolides led to a decreased prevalence of MRSA infection, and the authors suggested that decreasing antibiotic pressure could be linked to fewer invasive MRSA infections.[23] Furthermore, the CDC has estimated that use of an integrated approach of transmission interruption and antibiotic stewardship could have a significant impact on the rates of multidrug-resistant organisms, including MRSA.[24]

Patients undergoing hemodialysis that are colonized by *S aureus* are at increased risk of subsequent MRSA infection. This increased risk is because of multiple factors, such as the presence of vascular access devices, immunosuppression because of uremia, frequent contact with health care setting, among others. Interestingly enough, although decolonization attempts have limited success, patients who remain colonized with *S aureus* have a higher risk of bacteremia.[25] Two recent systematic reviews with meta-analyses evaluated the effectiveness of decolonization to prevent *S aureus* infection among colonized dialysis patients. In the first review, Grothe et al evaluated the effectiveness of decolonization among dialysis patients colonized with *S aureus*. They found that mupirocin decolonization was associated with an 82% decrease in bloodstream infection, but other methods of decolonization were not as effective.[26] In the second review, Gebreselassie et al[27] evaluated the effectiveness of a regimen of decolonization, including mupirocin, to eliminate MRSA carriage. They found it was effective in approximately 88% of the cases, but there are very limited data regarding recolonization and long-term effectiveness. There was a very low rate of infection among MRSA-colonized patients (4%), but this included only 94 patients, without a control group. In our study, dialysis during the follow-up period after colonization was detected was associated with an OR of 4.5 of subsequent infection.

Our article has limitations inherent to its retrospective design, including the possibility of selection bias and the presence of unmeasured variables that can lead to confounding. However, it has important strengths, such as the use of data from an integrated inpatient and outpatient health care system, follow-up as long as 18 months, a relatively large sample size, and the inclusion of important variables and risk factors associated with MRSA infection.

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