ORIGINAL ARTICLE

Survival Time of Methicillin-Resistant *Staphylococcus aureus*–Free Status after Institutional Clearance

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OBJECTIVE. To determine the durability of methicillin-resistant *Staphylococcus aureus* (MRSA)–free status after patients are removed from contact precautions and the association of specific clearance policy variables with survival.

DESIGN. Retrospective cohort study from October 2007 to April 2013.

SETTING. Veteran Affairs Boston Healthcare System.

PARTICIPANTS. Patients with a prior history of MRSA who were removed from contact precautions after deemed cleared of their MRSA status by infection prevention.

METHODS. Active nasal screening results and clinical data from acute, long-term, and outpatient care facilities were evaluated to determine survival of MRSA-free status in a time-to-event analysis.

RESULTS. A total of 351 unique patients were followed for 107,112 patient-days. The median age was 68 years. Overall, 249 (71%) of patients remained MRSA-free, and 102 (29%) reverted to MRSA positive. The median MRSA-free survival was 880 days. Comorbidities, presence of indwelling devices, and the use of systemic antibiotics at the time of clearance screening were not associated with MRSA-free survival. More than 21,000 days of inpatient isolation days were avoided during the study period.

CONCLUSIONS. The majority of patients removed from contact precautions remained MRSA-free for more than 2 years. Antibiotic use at the time of clearance was not associated with reductions in MRSA-free survival. These findings can be used to simplify clearance criteria, promote clearance policies, and reduce patient isolation days.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of healthcare-associated infections in the United States. Since MRSA colonization is a major risk factor for infection,[1] the Healthcare Infection Control Practices Advisory Committee recommends contact precautions in order to decrease nosocomial transmission.[2] However, there is a lack of consensus as to when and how to remove patients from contact precautions, because the long-term success of different strategies used for clearance of MRSA status has never been evaluated or compared. In fact, a recent survey found 48 unique institutional policies among 2,580 surveyed institutions to allow the discontinuation of contact precautions in patients with a history of MRSA infection or colonization in the United States. Only 24% of institutions perform active surveillance for this purpose.[3]

Because it is common for patients with a history of MRSA colonization to continue on isolation indefinitely as long as they remain in the hospital, the group of patients requiring contact precautions is constantly expanding. This is particularly concerning not only because of the impact on hospital costs but also because of potential unintended consequences, such as infrequent assessments by healthcare providers and higher rates of patient dissatisfaction and anxiety.[5] In this study, we evaluated the success of the MRSA clearance after discontinuation of contact precautions by determining the MRSA-free survival time after removal of contact precautions; we also assessed factors associated with MRSA-free survival.

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METHODS

Study Population

We conducted a retrospective cohort study of patients admitted to any of the Veteran Affairs (VA) Boston Healthcare System facilities between October 2007 and April 2013. We captured data from 1 acute care hospital, 1 long-term care facility, and all associated VA outpatient community clinics. The VA has performed active surveillance for nasal MRSA since October 2007. Unique features of this program include multiple assessments of each patient during a single hospitalization (admission, unit transfer, and discharge) and high patient retention rate as the majority of veterans return to the VA integrated Healthcare System for care. Patients colonized or infected with MRSA are not routinely decolonized.

Patients are passively cleared of their MRSA status and removed from contact precautions if they meet the following criteria: (1) 2 negative nasal screens (polymerase chain reaction [PCR] or agar) at least 1 week apart if the last positive clinical culture or nasal screen was within the prior 12 months or (2) 1 negative nasal screen if the last positive result was more than 1 year prior. In addition, patients must be off all antibiotics for at least 1 week prior to nasal screening. Patients removed from contact precautions remain in the same room if not cohorted (but gowns and gloves are no longer required); otherwise, they are moved to a nonisolation room.

All patients admitted to the VA Boston Healthcare System during the study period that were cleared of their MRSA status and removed from contact precautions by infection prevention were eligible for the study, regardless of whether they met strict institutional criteria. Patients were included only once in the study and were excluded if there was no available follow-up data after removal from contact precautions.

Study Design

We used the electronic medical record to capture comorbidities and antibiotic and healthcare exposures. The primary end point was reversion to MRSA positive, defined as any nasal screening (PCR or agar) or clinical culture positive for MRSA subsequent to the date of removal from contact isolation. MRSA nasal screen was defined as any PCR or nasal culture performed at admission to the facility upon unit transfer or at discharge. Clinical culture was defined as a culture obtained from any body site (other than nares or screening surveillance swab) that was positive for MRSA. The clearance screen was defined as the most recent nasal screen result that determined the eligibility for removal of contact precautions.

For survival analysis, the time to reversion to MRSA positive was recorded in days and denoted as MRSA-free survival time. Patients that did not reach the outcome were censored at the time of the last available nasal screen. In order to find determinants of MRSA-free survival, we recorded patient characteristics, healthcare exposure after clearance, and the specific components of the clearance policy. In addition, we assessed whether meeting a different set of clearance criteria previously used by Shenoy et al[4] predicted MRSA-free survival (positive clinical culture or nasal screen performed no more than 90 days prior and 1 negative nasal screen in the absence of any antimicrobials the week prior to screening).

Statistical Analysis

Baseline characteristics are presented as medians with interquartile ranges (IQRs) for continuous variables and as frequencies with percentages for categorical variables. The primary end point MRSA-free survival was described with the use of Kaplan-Meier estimates. Patients were censored at the last available negative MRSA screening test. A Cox proportional hazards model was used to identify factors associated with reversion to MRSA positive. Variables with $P \leq .2$ in the univariate analyses were included in the multivariate model. Statistical significance was assessed at the 0.05 level. Data were analyzed using the JMP software (ver. 11.0.0; SAS Institute).

RESULTS

A total of 418 unique patients were removed from contact precautions during the study period. We excluded 67 patients (16%) from further analysis because they had no follow-up screens or culture data available, leaving 351 patients in the final analysis (Figure 1). Patients were mostly white males (93%) with a median age of 68 years (range, 22–93; standard deviation, 12) and a wide range of comorbidities (Table 1).

MRSA-Free Survival

Overall, 71% of patients remained MRSA-free (249), and 29% (102) reverted to MRSA positive over a total of 107,112 patient-days, with a median of 147 days (IQR, 40–527) of

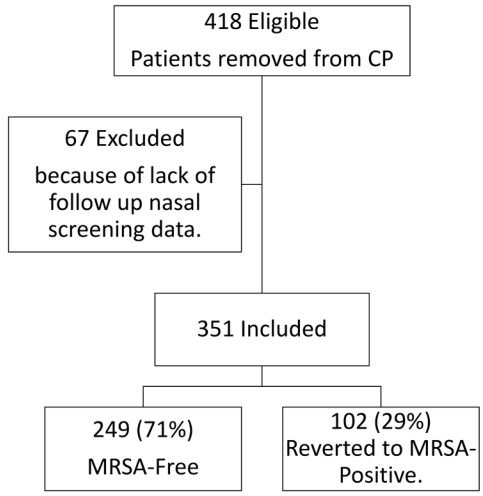

FIGURE 1. Flow chart of the study. CP, contact precautions; MRSA, methicillin-resistant *Staphylococcus aureus*.

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TABLE 1. Unadjusted Hazard Ratios (HRs) for the Association between Patient Factors and Time to Reversion to Methicillin-Resistant *Staphylococcus aureus* (MRSA) Positive

Characteristic	Patients (n = 351)	Unadjusted HR (95% CI)[a]	P
Age, years, mean ± SD	68.1 ± 12.1	1.0 (0.98–1.0)	.48
Race, white	327 (93.7)	1.07 (0.5–2.7)	.87
Sex, male	343 (97.7)	2.0 (0.6–12.1)	.27
Comorbidities			
Hypertension	215 (61.2)	0.7 (0.6–1.3)	.45
Diabetes mellitus	130 (37)	1.1 (0.7–1.5)	.72
Human immunodeficiency virus	7 (1.9)	1.7 (0.4–4.5)	.41
Malignancy	51 (14.5)	1.3 (0.7–2.1)	.30
Skin disease	36 (10.2)	1.2 (0.6–2.1)	.56
Decubitus ulcer	25 (7.1)	1.5 (0.7–2.7)	.24
Renal replacement therapy	8 (2.28)	0.7 (0.1–2.3)	.63
Spinal cord injury	45 (12.8)	1.0 (0.6–1.7)	.85
End-stage liver disease	10 (2.8)	1.1 (0.3–2.8)	.88
Any indwelling device[b]	94 (27.5)	1.3 (0.8–1.9)	.26
Foley catheter	56 (16.4)	1.4 (0.8–2.3)	.15
Central line	28 (8.2)	1.2 (0.5–2.3)	.59
Percutaneous gastrostomy tube	4 (1.1)	1.2 (0.07–5.7)	.82
Tracheostomy	9 (2.6)	1.9 (0.5–5.3)	.29
Other device	23 (6.7)	0.6 (0.2–1.5)	.33
Outpatient procedures[c]	26 (7.6)	0.9 (0.6–1.6)	.98

NOTE. Data are no. (%), unless otherwise indicated. CI, confidence interval; SD, standard deviation.

[a] For HRs, values less than 1.0 indicate a negative association with reversion to MRSA positive, while values greater than 1.0 indicate a positive association.

[b] Present at the time of removal of contact precautions.

[c] After removal of contact precautions.

follow-up. The median MRSA-free survival was 880 days (29 months), with a mean of 962 days (32 months) and an estimated survival rate of 95% at 7 days, 91% at 30 days, 84% at 90 days, 76% at 6 months, and 70% at 1 year (Figure 2).

Most of the patients that reverted to MRSA positive were detected by nasal screening (81/102, 79.4%); 20 patients (19.6%) were detected by clinical culture, and 1 patient (0.98%) had both tests positive the same day. Eleven of the 21 patients (53%) with positive clinical cultures had a nasal screen performed within the following 7 days; 6 of those 11 patients (54.3%) had a positive PCR. The total days in contact isolation that were averted in the study cohort totaled 21,789 days in any inpatient facility, including 7,891 days in acute care and 13,898 days in long-term care (nursing home or psychiatric).

Patient-Related Factors Associated with MRSA-Free Survival

MRSA-free survival did not differ significantly with age, gender, race, or comorbidities. The presence of any indwelling device at the time of clearance of MRSA did not impact MRSA-free survival either (Table 1). However, having a Foley catheter in place at the time of clearance was associated with an increased risk of reversion to MRSA positive (hazard ratio [HR], 1.4 [95% confidence interval (CI), 0.9–2.3]; $P = .15$); although not statistically significant, it met criteria for inclusion in the multivariable model.

Clearance Policy and MRSA-Free Survival

We also examined whether factors related to MRSA clearance criteria were determinants of MRSA-free survival after clearance (Table 2). The median time elapsed between the last documented MRSA positivity by culture or nasal screen and removal of contact precautions was 23.8 months (IQR, 11.4–41.8). Patients for whom 2 or more years elapsed since that time were less likely to revert to MRSA positive (HR, 0.7 [95% CI, 0.4–1.0]; $P = .058$) after contact precautions were removed. The number of negative nasal screens performed between the last positive MRSA result and removal from contact precautions ranged from 1 to 57, with a median of 5 (IQR, 3–9). The number of negative screens in this interval prior to clearance was not associated with MRSA-free survival (HR, 1.0 [95% CI, 0.7–1.0]; $P = .36$).

Overall, 82 of 351 patients (23.3%) received a systemic or topical antibiotic within the 7 days prior to the clearance screen. There was no significant difference in MRSA-free survival between patients who received systemic antibiotics proximal to clearance and those who did not (HR, 0.9 [95% CI,

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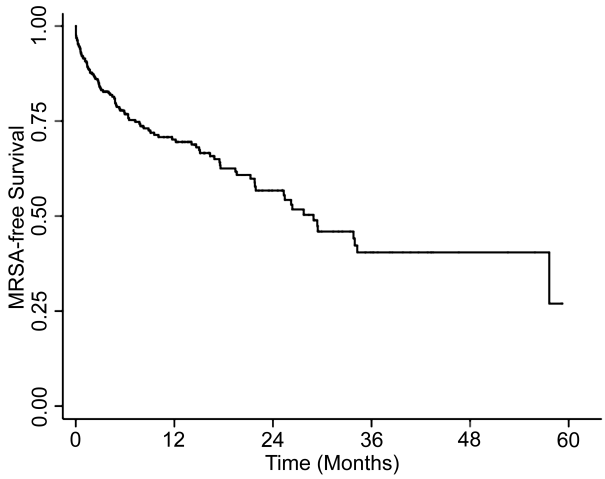

FIGURE 2. Methicillin-resistant *Staphylococcus aureus* (MRSA)–free survival in patients cleared of MRSA status.

0.5–1.6]; $P = .87$). Individual classes of systemic antibiotics, including any β-lactam, any fluoroquinolone, or any MRSA-active antibiotic (including vancomycin, daptomycin, trimethoprim-sulfamethoxazole, clindamycin, linezolid, doxycycline, and aminoglycosides) were also not significantly associated with MRSA-free survival. Twenty-nine of 351 patients (8.2%) received topical antibiotics within 7 days prior to nasal screening; the majority of these patients (19) received chlorhexidine (69%), 8 (27.5%) received bacitracin, and 2 (6.8%) received mupirocin. The use of chlorhexidine within the week prior to the nasal clearance screen was associated with a trend for reversal to MRSA positive (HR, 2.0 [95% CI, 0.98–3.7]; $P = .053$; Table 2). Most of those patients (15/19, 78%) were prescribed chlorhexidine baths for preoperative decolonization.

Overall, 260 of 351 patients (74%) met the strict institutional criteria for clearance of MRSA status. Fulfilling such criteria was not associated with a higher rate of remaining MRSA-free compared with those who did not meet clearance criteria (HR, 0.8 [95% CI, 0.5–1.3]; $P = .4$). We also evaluated the proportion of patients that met the alternative set of criteria published by Shenoy et al.[4] Meeting these criteria was also not associated with MRSA-free survival (HR, 0.8 [95% CI, 0.5–1.4]; $P = .46$).

Postclearance Healthcare Exposure and MRSA-Free Survival

We examined postclearance variables as predictors of MRSA-free survival time. There was no association between the number of outpatient procedures performed after removal of contact precautions and the outcome (HR, 0.8 [95% CI, 0.3–1.6]; $P = .61$). The number of nasal swabs done after the removal of contact precautions was associated with a reduced risk of reversion to MRSA positive (HR, 0.9 [95% CI, 0.8–0.9]; $P < .001$); thus, a higher number of nasal screens were performed in patients who remained MRSA-free. Similarly, the number of inpatient admissions after removal from contact precautions was associated with a reduced risk of reversion to MRSA positive (HR, 0.8 [95% CI, 0.7–0.9]; $P < .0001$); this was driven by admissions to acute care facilities (HR, 0.70 [95% CI, 0.70–0.9]; $P < .0001$) but not long-term care facilities (HR, 0.9 [95% CI, 0.7–1.0]; $P = .24$). The total number of inpatient days at an acute facility was not associated with MRSA-free survival (HR, 0.9 [95% CI, 0.99–1.0]; $P = .17$).

Determinants of MRSA-Free Survival

In the multivariate analysis including all variables with an α of 0.2 or less, no factors were independently associated with MRSA-free survival. Having a remote history of MRSA more than 2 years ago at the time of removal of contact precautions was associated with a statistical trend for a reduced risk of reverting to MRSA positive (HR, 0.7 [95% CI, 0.45–1.06]; $P = .07$). The numbers of nasal screens and inpatient admissions after removal of contact precautions were collinear with the outcome and thus were not included in the final multivariate model. However, if the number of nasal screens after removal of contact precautions was included in the

TABLE 2. Unadjusted Hazard Ratios (HRs) for the Association between Clearance Policy Criteria and Time to Reversion to Methicillin-Resistant *Staphylococcus aureus* (MRSA) Positive

Characteristic	Patients ($n = 351$)	Unadjusted HR (95% CI)[a]	P
Last positive MRSA (≥2 years)	174 (50)	0.7 (0.4–1.0)	.058
Any systemic antibiotic[b]	60 (17)	0.9 (0.5–1.6)	.87
β-lactams	39 (11)	1.1 (0.6–2.0)	.61
Fluoroquinolones	14 (4)	1.2 (0.4–3.0)	.70
MRSA active[c]	30 (9)	1.2 (0.6–2.3)	.52
Topical antibiotics[b]	29 (8)	1.6 (0.8–2.7)	.13
Chlorhexidine	19 (5)	2.0 (0.98–3.7)	.053
Met VA criteria[d]	260 (74)	0.8 (0.5–1.3)	.40
Met Shenoy criteria[e]	300 (85)	0.8 (0.5–1.4)	.46

NOTE. Data are no. (%), unless otherwise indicated. CI, confidence interval; VA, Veterans Affairs.

[a] For HRs, values less than 1.0 indicate a negative association with reversion to MRSA positive, while values greater than 1.0 indicate a positive association.

[b] Use within the 7 days prior to the most recent nasal screen.

[c] Vancomycin, daptomycin, trimethoprim-sulfamethoxazole, clindamycin, linezolid, doxycycline, and aminoglycosides.

[d] VA criteria: (1) 2 negative nasal screens (polymerase chain reaction or agar) at least 1 week apart if the last clinical culture or nasal screen was positive within the prior 12 months or (2) 1 negative nasal screen if the last positive clinical culture or nasal screen was more than 1 year prior. In addition, patients must be off all antibiotics for a minimum of 1 week prior to nasal screens.

[e] Modified Shenoy's criteria: positive clinical culture or nasal screen performed no more than 90 days prior and 1 negative nasal polymerase chain reaction screen in the absence of any antimicrobials the week prior to screening.

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model, the HRs of the other variables remained unchanged (data not shown).

DISCUSSION

This is the first large cohort study within an integrated healthcare system to evaluate the MRSA-free survival of patients removed from contact precautions once deemed cleared of their MRSA status by infection prevention. With the current MRSA clearance policy at our institution, the number of inpatient isolation days avoided for this cohort totaled more than 21,000 days for any inpatient setting, with 7,891 isolation days avoided in acute care and 13,898 in long-term care settings. Approximately 71% of the original cohort remained MRSA-free, and the median MRSA-free survival was almost 2.5 years. The only other study that evaluated patients after clearance of contact precautions analyzed 21 patients previously colonized with MRSA but with negative MRSA screens in multiple body sites at study entry. Follow-up data was available in 14 who were readmitted to the same institution over a 9-month period; 5 (35.7%) patients were eventually positive for MRSA.[6] Differences in study design preclude direct comparison between studies, but both suggest that clearance of MRSA status can be successful in a large proportion of patients. The large sample size, availability of 5 years of data from a national integrated healthcare system that performs routine screening, and ability to capture additional clinical and policy-related factors from the electronic health record add to the strength of our study findings.

Our study also is the first to evaluate the robustness of specific MRSA clearance criteria as predictors of MRSA-free survival time in patients with history of infection or colonization. In the multivariate analysis, we observed a lower rate of reversion to MRSA-positive status in patients with a remote history of MRSA colonization or infection (2 years or more). Two recent studies have reported that a longer time since last documented MRSA positivity increased the likelihood of meeting clearance criteria.[4,6] We expand upon this concept by demonstrating that among patients who do become cleared of MRSA precautions, the time from last documented MRSA positivity and clearance may be associated with the duration of successful clearance time. We found no association between the number of negative nasal screens done prior to removal of contact precautions and reversion to MRSA positive. Thus, increasing the number of screens in patients once they are negative does not appear to be helpful in predicting a longer clearance time.

As per our institutional policy, patients were eligible for removal of contact precautions if they met specific criteria. Only 74% of patients removed from contact precautions met these criteria fully, since 23% of the cohort had received antimicrobial therapy within the week prior to nasal screening but were still cleared of their MRSA status. This provided an opportunity to evaluate the practice of not removing contact precautions in patients receiving concomitant or recent antibiotics out of concern that antimicrobials could transiently decrease the bacterial load in the nares and result in a false-negative screen. In our study, the use of any systemic antibiotic—with or without MRSA activity—within 7 days prior to screening was not associated with a reduction in the MRSA-free survival time. This is in concordance with a recent study that observed that patients colonized with MRSA in the nares treated with systemic MRSA active antimicrobials was not associated with a decrease in the bacterial load.[7] In fact, those treated with non-MRSA active antimicrobials had an increase in the MRSA load in the anterior nares. Similar results have been reported for vancomycin-resistant enterococci (VRE), where antimicrobial exposure has been associated with increased loads of VRE in the stool and an increased yield of rectal screens.[8] On the contrary, we observed a higher rate of reversion to MRSA positivity among patients that received chlorhexidine concomitantly or recently in relationship to the clearance screening, but this result was not statistically significant when adjusted for other factors and warrants further study. Overall, our findings suggest that the concomitant or recent use of systemic antimicrobials may not be relevant as criteria for removal of contact precautions, but the use of topical antimicrobials may be an important factor. We had very little mupirocin use in our population and thus could not assess it independently as a risk factor for shorter MRSA-free survival time.

Other factors—such as admissions to an acute care hospital and number of nasal screens after removal of contact precautions—were significantly associated with prolonged MRSA-free survival. These findings initially appear to be contrary to what might be expected—longer MRSA-free survival with more healthcare exposure. However, the number of inpatient admissions closely correlates with the number of nasal screens (on the basis of the screening policy), and screening is the main measure for the outcome (reverting to MRSA positive). Thus, these variables are highly colinear and cannot be assessed as predictors of the outcome. Importantly, the total number of acute care inpatient days was not different between groups.

Our study has several limitations. The MRSA-free survival rates may not be generalizable to other patient populations. The estimates of MRSA-free survival in our study are based on clinical culture and screening of the anterior nares but not on active screening of nonnasal sites. Rates of exclusive extranasal colonization in the veteran population are estimated at 2%, whereas studies in other patient populations report much higher prevalence rates.[9,10] Institutions that target certain groups for screening—intensive care units and residents of long-term care facilities—are likely to observe shorter MRSA-free survival times compared with institutions that perform universal screening because at baseline such individuals are at a higher risk of colonization with MRSA compared with the total hospital population. Because of the retrospective nature of our study, the screening data was obtained at different time intervals and only during encounters

with the healthcare system. Furthermore, not all patients removed from contact precautions met a homogenous set of criteria. A prospective study would be best suited to assess the impact of healthcare exposure on MRSA-free survival.

Despite these limitations, our data can be used by institutions to simplify clearance criteria by removing concurrent use of systemic antibiotics as an exclusion factor. Furthermore, it supports the reduction of nasal screening in patients at the time of readmission once they have been removed from contact precautions. The interval for repeated screening would have to be individualized depending on the threshold for missing recolonized patients. According to our data, there was about a 10% drop in MRSA-free survivors between 3 and 6 months and then an additional 6% drop by 1 year. Thus, an interval of 3–6 months could be considered. Unfortunately, we did not identify specific predictors of remaining MRSA free after clearance, although a longer interval between last MRSA positivity and removal of contact precautions appears to be protective.

In conclusion, this large cohort study spanning 5 years and more than 100,000 patient-days suggests that clearance from MRSA contact precautions can be successful over a long period of time and is not adversely affected by concurrent use of antimicrobials at the time of clearance. These findings can be used to support and optimize institutional clearance policies by simplifying clearance criteria, reducing postclearance screening, and substantially reducing the number of days inpatients spend in isolation.

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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