Long-Term Risk for Readmission, Methicillin-resistant Staphylococcus aureus (MRSA) Infection, and Death among MRSA-Colonized Veterans

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ABSTRACT

Background: While numerous studies assessed outcomes of MRSA colonization over the short term, little is known about longer-term outcomes after discharge. An assessment of long-term outcomes could inform the utility of various MRSA prevention approaches.

Methods: A matched cohort study was performed among Veterans Affairs (VA) patients screened for MRSA colonization between the years 2007 and 2009 and followed to evaluate outcomes until 2010. Cox proportional hazard models were used to evaluate the association between MRSA colonization and long-term outcomes such as infection-related readmission, and crude mortality.

Results: 404 veterans were included, 206 of whom were MRSA carriers and 198 who were non-carriers. There were no culture-proven MRSA infections on readmission among the non-carriers, but 13% of MRSA-carriers were readmitted with culture proven MRSA infections on readmission (P<0.01). MRSA carriers were significantly more likely to be readmitted, be readmitted more than once due to proven or probable MRSA infections, and be readmitted within 90 days of discharge compared to non-carriers (p<0.05). Infection-related readmission (adjusted hazard ratio [AHR] =4.07; 95% confidence interval [CI]: 2.16, 7.67) and mortality (AHR=2.71; 95% CI: 1.87, 3.91) were significantly higher among MRSA carriers compared to non-carriers, after statistically adjusting for potential confounders.

Conclusions: Among a cohort of VA patients, MRSA carriers are at high risk of infection-related readmission, MRSA infection and mortality compared to non-carriers. Non-carriers are at very low risk of subsequent MRSA infection. Future studies should address whether interventions such as nasal or skin decolonization could result in improved outcomes for MRSA carriers.
INTRODUCTION

*Staphylococcus aureus* frequently causes serious infections involving the bloodstream, lower respiratory tract, and skin and soft tissue.[1] Methicillin-resistant *S. aureus* (MRSA) emerged in the 1960s and has since become a major cause of illness and death in the healthcare setting.[2] In the 2008 National Healthcare Safety Network, MRSA represented over half of all *S. aureus* healthcare-associated infections in the United States.[3]

Approximately 10 to 40 percent of people carry *S. aureus* in their anterior nares.[4-6] Nasal carriage of MRSA can be found among 1-2% of the general population but in as many as 10-15% of patients admitted to acute care hospitals and intensive care units (ICUs).[7,8] Several studies have found that MRSA-colonized patients are at higher risk for invasive MRSA infection compared with non-colonized patients.[6,9-12] In a systematic review of ten observational studies, nasal colonization by MRSA was associated with a fourfold-increase in the risk of infection.[12]

While numerous studies have focused on the impact of MRSA colonization over the short term, such as among inpatient populations during their acute care stay, little is known about longer term outcomes after discharge. Only two prior studies have assessed long-term outcomes among MRSA colonized or infected patients. However, neither study compared these patients to an uninfected, uncolonized control group.[13,14]

The purpose of our study was to examine the long-term (> 1 year) risk for MRSA infection among patients found to be MRSA colonized during an acute-care admission, using an MRSA-uninfected and non-colonized control group and adjusting for pertinent comorbidities. Additionally, we aimed to compare rates of infection and death among colonized versus non-colonized patients. With an increasing number of facilities such as all VA facilities collecting...
MRSA surveillance swabs on admission, outcomes data concerning patients colonized with MRSA on admission could potentially impact clinical practice and target prevention efforts. [15]

MATERIALS AND METHODS

We performed a matched cohort study of patients admitted to the Iowa City VAHCS between January 2007 and November 2009. This study is nested within a previously described cohort study in which patients were screened for MRSA on admission, subsequently during hospitalization, and at the time of discharge. [8] Patients identified as MRSA carriers who had an MRSA positive nares surveillance swab as measured via polymerase chain reaction (PCR) at any time during the index admission were frequency matched by month of admission to patients identified as non-carriers. Non-carriers were defined as patients whose nares surveillance screen and any clinical cultures were all negative for MRSA during the index hospitalization.

Detailed chart review was performed for the MRSA carriers and non-carriers, by an infectious disease physician fellow (NMQJ) to identify MRSA infection-related outcomes. MRSA infections were categorized into culture proven infections and probable infections. Culture proven MRSA infections represent all positive clinical cultures for MRSA associated with signs and symptoms of infection. Probable MRSA infections were defined as signs and symptoms of infection, and response to therapy focused on MRSA with either negative cultures or no cultures obtained.

Demographic variables on the index admission were collected such as sex, age, presence of a central venous catheter or peripherally inserted central catheter (PICC), intensive care unit (ICU) admission, and healthcare facility exposure including admission from home, an outside hospital, or a long term care facility, and discharge to a long-term care facility or home. The Charlson comorbidity index was calculated using discharge International Classification of
Diseases, Ninth Revision (ICD-9) codes and included comorbidities such as heart disease, hypertension, diabetes mellitus, renal disease, liver disease, malignancy and AIDS. Severity of illness on admission to the index hospitalization (e.g. study entry) was measured using the McCabe Jackson score.

All MRSA carriers and non-carriers were followed from time of enrollment (admission) until death or until November 2010. The primary outcome was hospital readmissions due to culture-proven or probable MRSA infection. The secondary outcomes included crude mortality, time to readmission, and infectious diagnosis at readmission (e.g., osteomyelitis, skin and soft tissue infection, sepsis). Data were also collected on the source of a positive MRSA culture (e.g., pleural fluid, sputum, blood).

Bivariate analyses were performed using the chi-square test or Fisher’s exact test (for categorical variables) and the t-test (for continuous variables) as required. Cox proportional hazards modeling was performed to statistically adjust for underlying illness between the groups. All variables that were significant in the bivariable analysis (alpha<0.1) were selected for inclusion in the initial (full) multivariable Cox proportional hazards model. Variables that were not significantly associated with the outcome (alpha<0.05) were removed from the full multivariable model in succession. Each removed variable was then reinserted into the model to assess whether the variable altered the regression coefficient of the primary exposure variable by greater than 20 percent. If so, that variable was included in the model. A priori we chose the following variables as biologically important: Charlson comorbidity index and McCabe Jackson severity of illness score. These variables were included in each model irrespective of their statistical significance. The proportional hazards assumption that the effect of a variable is constant over time was tested for each variable in the final model by assessing the interaction of the variable with a function of time. Crude mortality among MRSA carriers and non-carriers was compared using a Kaplan-Meier survival model. The log-rank test was used to compare survival...
curves. All analyses were performed using SAS software (SAS Institute, Cary, NC) version 9.3.

This study was approved by both the University of Iowa Institutional Review Board and the Iowa City VA Health Care System Research and Development Committee.

RESULTS

A cohort of 404 veterans, 206 of whom were MRSA carriers and 198 of whom were non-carriers was examined. All 206 MRSA carriers had a positive MRSA nasal surveillance swab during their index admission. In addition, 22 of the 206 MRSA carriers (11%) also had an MRSA infection on the index admission. As expected in an elderly veteran population, over 95% of the patients were male in both groups. Patient age and prevalence of individual comorbidities (heart disease, renal disease, liver disease, diabetes mellitus, malignancies and AIDS) were similar in both groups (Table 1). However, the Charlson comorbidity index and the McCabe Jackson Score were significantly higher among the MRSA carriers than among the non-carriers (Table 1).

There were 31 (15%) patients admitted from an outside hospital and 20 (10%) patients admitted from a long-term care facility among the MRSA carriers and only 10 (5%) and 1 (0.5%) admitted from outside hospitals and a long-term care facility, respectively, among the non-carriers (p<0.01). Forty-seven (23%) patients were discharged to a long-term care facility among the MRSA carriers and only 13 (7%) among the non-carriers. Eleven (5%) MRSA carriers and 1 (0.5%) non-carrier died during the index admission. (Table 1)

The mean duration of follow-up was 23 months for the MRSA carriers and 34 months in the non-carriers. The shorter mean duration of follow-up was related in large part to the higher crude mortality among carriers (49% versus 23% among the non-carriers). The excess mortality was most prominent during the first year post discharge (Figure).
There were no culture-proven MRSA infections on readmission among the non-carriers, while 28 (13.6%) MRSA carriers had a total of 35 culture proven MRSA infections on readmission (p<0.01). Eleven of these MRSA positive cultures were from wound cultures, seven from blood cultures, six from sputum cultures, two from bone cultures, and one each from a pleural fluid culture, a cerebral spinal fluid culture, and a joint fluid culture.

Thirteen (6.3%) MRSA carriers had a probable MRSA infection on readmission. Of these, four had osteomyelitis, six had a skin and soft tissue infection, two had pneumonia and one had osteomyelitis and pneumonia. Fifteen (7.5%) non-carriers were readmitted secondary to a probable MRSA infection, including four who were admitted more than once. Of these, nine had skin and soft tissue infections, three had osteomyelitis, one had meningitis, one had pneumonia and one had osteomyelitis and pneumonia.

Among the 392 patients who were alive at discharge from the index hospitalization, 45% of MRSA carriers and 23% of non-carriers died during the long-term follow-up. The mortality rate for MRSA carriers was 89 per 389 person-years (228 per 1,000 person-years) and the mortality rate for non-carriers was 45 per 557 person-years (81 per 1,000 person-years). In the unadjusted analysis, MRSA carriers had twice the risk of mortality compared to non-carriers (unadjusted relative risk (RR) =2.01; 95% confidence interval [CI]: 1.49, 2.71). This significant association remained after statistically adjusting for McCabe Jackson score, Charlson comorbidity index, age and ICU admission on index hospitalization (adjusted hazard ratio (HR) =2.71; 95% CI: 1.87, 3.91).

MRSA carriers were significantly more likely to be readmitted, be readmitted more than once due to proven or probable MRSA infections, and be readmitted within 90 days of index discharge compared to non-carriers. (Table 2) Among the 392 patients who were alive at discharge from the index hospitalization, MRSA carriers had over four times the risk of infection-
related readmission compared to non-carriers, after statistically adjusting for Charlson
comorbidity index, McCabe Jackson score, intensive care unit admission on the index
admission and MRSA infection on the index admission (adjusted HR=4.07; 95% CI: 2.16, 7.67).

DISCUSSION

Our study is the first, to our knowledge, to assess the long-term risk of subsequent
MRSA infection and mortality, and to compare these outcomes with a control group of non-
carriers. We confirmed that the risks of subsequent infection-related readmission and MRSA
infection were elevated among MRSA carriers, with the increased risk concentrated in the first
year of follow up. In addition, the risk of mortality was more than twice as high among MRSA
carriers than non-carriers, even after controlling for patient comorbidities.

Several prior studies have found that MRSA-colonized patients are at higher risk for
invasive MRSA infection compared with non-colonized patients.[6,11,12] Our findings add to
this literature by extending the period of follow up to over 2 years. Two prior studies assessed
long-term outcomes among MRSA carriers but did not include an uninfected control group. One
such study, by Huang et al., followed 209 patients who newly acquired MRSA during an acute
care hospitalization, and found that 29% developed MRSA infection in the 18 months after
discharge, with almost half of the infections becoming apparent after the patients had been
discharged from the hospital.[13] More recently, another study by Huang et al reported long-
term results from a cohort of 591 newly-detected MRSA carriers. However, most of those
patients (77%) were infected on detection, whereas our population consisted primarily of
colonized, uninfected patients at study entry. In that study, almost one-quarter developed post-
discharge MRSA infections in the year following detection, most of them more than 90 days post
discharge. Additionally, that study had a large proportion of MRSA carriers who died (46%),
which was similar to the proportion of MRSA carriers who died in our study.[14]

It is interesting to note that none of the non-carrier patients in our cohort had a
subsequent culture proven MRSA infection during the follow-up period. Thus negative MRSA
PCR screening, along with other clinical symptoms, could potentially aid in guiding empiric
antibiotic therapy during readmissions. However, further prospective data are needed to confirm
these findings.

Our study had several limitations. First, this study is limited by its retrospective
observational design. It is also possible that bias may exist due to unmeasured confounding
since we did not include variables such as prior hospitalization or prior antibiotic use in our
dataset. However, such variables are highly correlated with severity of illness and comorbidities,
both of which are included in our statistical analysis. Furthermore, since the MRSA surveillance
assay is not 100% sensitive, MRSA carriers may have been misclassified as non-carriers.
Readmission due to MRSA infection, our primary outcome, is also subject to misclassification
because providers may have been more likely to test MRSA carriers for MRSA infections, and
because our chart review was not blinded, thus we may have inadvertently searched harder for
documentation of MRSA infections among MRSA carriers. In addition, all MRSA infections
might not be captured using the VA medical records, although most serious infectious should
have been captured. Lastly, a predominantly elderly male population limits our ability to
extrapolate these findings to the general population.

In conclusion, we demonstrated that among Veterans Affairs patients, MRSA carriers
are at high risk of infection-related readmission, MRSA infection and mortality compared to non-
carriers. These associations remained even after statistically adjusting for potential confounders
such as patient comorbidities. In contrast, patients who are not MRSA carriers are at very low
risk of subsequent MRSA infection. Future studies should address whether nasal or skin decolonization or other targeted interventions will result in improved outcomes for MRSA carriers.

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Authors’ Contribution: NMQJ participated in the study design, performed medical chart review, and wrote the manuscript. DJD conceived the study idea, and participated in its design and coordination and helped to draft the manuscript. ENP participated in the study design and helped to draft the manuscript. GB created and maintained the databases and helped to draft the manuscript. PLW conceived of the study, and participated in its design and coordination and helped to draft the manuscript. MLS participated in the study design and coordination, performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.
REFERENCES


Table 1. Comparison of Demographics, Comorbidities, Severity of Illness and Healthcare Facility Exposure Between Carriers and Non-Carriers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MRSA carriers (n=206)</th>
<th>Non-carriers (n=198)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>200 (97%)</td>
<td>195 (98%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>65 years</td>
<td>64 years</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Comorbidities</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>96 (47%)</td>
<td>86 (44%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>94 (46%)</td>
<td>75 (38%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Renal disease</td>
<td>26 (13%)</td>
<td>26 (13%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Liver disease</td>
<td>20 (10%)</td>
<td>16 (8%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Malignancy</td>
<td>49 (24%)</td>
<td>39 (20%)</td>
<td>0.33</td>
</tr>
<tr>
<td>AIDS</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Median Charlson Score (IQR)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (1,3)</td>
<td>1 (0,2)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>McCabe Jackson</strong> Score at Admission to Index Hospitalization&lt;sup&gt;a&lt;/sup&gt;:</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non fatal</td>
<td>36 (18%)</td>
<td>51 (26%)</td>
<td></td>
</tr>
<tr>
<td>Ultimately fatal</td>
<td>120 (58%)</td>
<td>139 (70%)</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>49 (24%)</td>
<td>8 (4%)</td>
<td></td>
</tr>
<tr>
<td>Admitted from:</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Home</td>
<td>154 (75%)</td>
<td>187 (94%)</td>
<td></td>
</tr>
<tr>
<td>OSH</td>
<td>31 (15%)</td>
<td>10 (5%)</td>
<td></td>
</tr>
<tr>
<td>LTCF</td>
<td>20 (10%)</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Discharge to:</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Home</td>
<td>148 (75%)</td>
<td>184 (93%)</td>
<td></td>
</tr>
<tr>
<td>LTCF</td>
<td>47 (23%)</td>
<td>13 (7%)</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>11 (5%)</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>39 (19%)</td>
<td>20 (10%)</td>
<td>0.01</td>
</tr>
<tr>
<td>CVC/PICC line</td>
<td>31 (14%)</td>
<td>7 (4%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Comorbidity data and McCabe Jackson score were missing for 1 patient. Note: All values are n, % unless otherwise specified. OSH, outside hospital; LTCF, long-term care facility; ICU, intensive care unit; CVC, central venous catheter; PICC, peripherally inserted central catheter.
Table 2. Infection-related Readmission and Infection Outcomes by MRSA Carriage Status

<table>
<thead>
<tr>
<th></th>
<th>MRSA carriers (n=206)</th>
<th>Non-carriers (n=198)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of infection-related readmissions</strong>&lt;br&gt; (n, % of total):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (13.6%)</td>
<td>11 (5.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;1</td>
<td>13 (6.3%)</td>
<td>4 (2.0%)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Time to readmission</strong>&lt;br&gt; (n. % of readmitted):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90 days</td>
<td>17 (41.5%)</td>
<td>2 (13.3%)</td>
<td>0.05</td>
</tr>
<tr>
<td>90 days-1 year</td>
<td>13 (31.7%)</td>
<td>7 (46.7%)</td>
<td>0.30</td>
</tr>
<tr>
<td>1-2 years</td>
<td>5 (12.2%)</td>
<td>4 (26.7%)</td>
<td>0.19</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>6 (14.6%)</td>
<td>2 (13.3%)</td>
<td>0.90</td>
</tr>
</tbody>
</table>
Figure 1: Kaplan Meier survival plot for MRSA Carriers and Non-carriers

Log-rank p<0.01