Title

High Nasal Burden of Methicillin-Resistant *Staphylococcus aureus* Increases Risk for Invasive Disease

Running Title

High Nasal Burden of MRSA Increases Infection Risk

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Abstract

In a retrospective cohort study of 1,140 patients harboring methicillin-resistant *Staphylococcus aureus*, nasal burden was few in 31%, 1+/2+ in 54%, and 3+/4+ in 15%. There was a significant trend in infection risk with increasing nasal burden (p=.007). In multivariate models, high nasal burden remained significantly associated with invasive infection.
Nasal colonization with *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), is an independent risk factor for infection (1-6). Approximately 10-20% of MRSA carriers develop infection during hospitalization, and risks persist after discharge (7-8). Such studies have driven practice guidelines for *S. aureus* screening and decolonization, including nasal mupirocin, in patients undergoing selected surgeries or dialysis (9-14). Additionally, many states now mandate nares screening for MRSA among high-risk inpatients (15).

While higher quantities of *S. aureus* nasal burden are associated with surgical site infection (16-17), it is unknown whether increased nasal carriage of MRSA predisposes to invasive infection in general. This is important because patients with high nasal burden may benefit from focused decolonization. We sought to assess whether patients with high nasal burden of MRSA as measured by standardized semi-quantitative methods incurred increased risks of invasive infection after adjusting for known risk factors for infection.

**Methods.** We conducted a retrospective cohort study of all adults with an MRSA-positive bilateral nares surveillance culture between March 2008 and June 2011 at a 400-bed tertiary care teaching hospital. Surveillance cultures reflected intensive care unit (ICU) screening and hospital-wide screening on admission. Patients decolonized with mupirocin were excluded, and patients receiving vancomycin, linezolid or tigecycline during hospitalization were identified. All nares specimens were routinely inoculated using standardized semi-quantitative methods (18) and reported as few, 1+, 2+, 3+, or 4+. Our analyses grouped them into few, 1+ to 2+, and 3+ to 4+, reflecting logarithmic increments. The University of California Regents Institutional Review Board approved this study.
The primary outcome was risk of invasive infection based on MRSA-positive blood or urine specimens from our institution within 6 months of the initial nares culture. Demographics were recorded, and diabetes mellitus, end-stage renal disease, and cause of admission were identified using ICD9 codes. Additional risk factors for infection were assessed, including length-of-stay, surgery, and ICU admission.

Across nasal burden strata, we assessed the proportion of patients who developed MRSA-positive blood or urine cultures. For patients developing infection, time from initial detection to infection was determined. For patients with multiple nares cultures, the concordance in burden across cultures was evaluated.

We used the Cochran-Armitage trend test to assess the trend in MRSA infection with increasing nasal burden. Using logistic regression (SAS, version 9.3), adjusted analyses were performed with the following risk factors a priori specified in a multivariate model: age, diabetes, end-stage renal disease, length-of-stay, surgery, and ICU admission.

Results. We identified 1,140 MRSA-positive patients during the study period. Mean age was 58 years (range, 18-100 years), and 59% were male. Nineteen percent had diabetes, and 11% had end-stage renal disease. MRSA carriage was detected upon hospital admission in 89% of patients. During hospitalization, 37% of patients had an ICU admission, and 28% underwent surgery. Mean length-of-stay was 9 days (median, 5 days). The top causes of admission were infection (23%) and cardiovascular (12%).

Overall, MRSA nasal burden was few in 31%, 1+/2+ in 54%, and 3+/4+ in 15% of patients. Within six months of detection, 58 (5.1%) patients developed MRSA-positive blood or urine cultures. The mean time from detection to infection was 21 days. Among patients...
developing infection, 32 (55%) had an MRSA-positive blood culture. Of those with MRSA-positive blood cultures, 6 (18%) also had an MRSA-positive urine culture.

Risk of subsequent infection increased significantly with increasing MRSA nasal burden (p=.007) (Table). This trend persisted when evaluating MRSA-positive blood cultures (p=0.05) and urine cultures (p=0.01) alone. Nasal burden remained associated with infection after excluding patients developing infection within 7 days of detection (p=0.01).

Across all patients, 158 (14%) had multiple MRSA-positive surveillance swabs. Most (72%) had one subsequent swab. The mean interval between adjacent swabs was 35 days. Overall, a minority had subsequent swabs with discordant growth when compared to the initial swab (as defined by a ≥2-category shift in semi-quantitative grouping). When burden groups were reclassified according to maximum growth across swabs, there was no impact on trend in infection risk with increasing burden.

In multivariate testing, high nasal burden was predictive of infection (few: 1.0, reference; 1+/2+: OR=2.0 (95% CI:1.0, 4.2); 3+/4+: OR=3.7 (95% CI:1.6, 8.6)). This effect persisted even after excluding patients receiving vancomycin, linezolid or tigecycline.

Discussion. These data highlight potential focused decolonization strategies for MRSA-positive patients. Prior interventions have targeted all MRSA carriers, despite the fact that subsequent infection risks may vary. Our study shows that carriers with high nasal burden incur increased risks of MRSA infection. While heavy *S. aureus* nasal carriage is associated with surgical site infection (16-17), we show that high MRSA nasal burden is further associated with bacteremia and urinary tract infection [which often indicates concomitant bloodstream infection (19-22)]. As MRSA screening becomes increasingly common, nasal burden measurement may
enable focused efforts to educate patients and decolonize. This may be particularly important as mupirocin resistance threatens to limit the utility of decolonization (23), and targeted usage may be warranted. Further studies are needed to evaluate whether high nasal burden predisposes to mupirocin resistance in patients undergoing decolonization.

Our study may underestimate infection risks. Nearly 20% of severe infections are missed when restricting infection surveillance to the same institution where detection occurred (8). Additionally, other infections types were not assessed.

This study has limitations. First, we did not determine whether MRSA isolates from nares and clinical isolates were genetically identical, but this was shown previously (9). Second, we did not evaluate extranasal carriage, and whether infection was related to extranasal burden. Nevertheless, high nasal burden predisposes to multi-site colonization (24). Third, while high nasal burden distinguishes persistent from intermittent carriage (25), systematic serial cultures were not performed to exclude intermittent carriage. However, time from detection to infection was short. Fourth, the cause of discordant growth in subsequent swabs was not evaluated, but this affected a minority of patients. Fifth, subsequent antibiotic exposures were not assessed.

In summary, we found that patients with high MRSA nasal burden incurred increased risks of invasive disease, even after accounting for host factors for infection. These patients may benefit from targeted decolonization to reduce MRSA-attributable infection.
Acknowledgements

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References


Table. Frequency of subsequent methicillin-resistant *Staphylococcus aureus* (MRSA) blood or urine infection in the 6 months after detection with MRSA.

<table>
<thead>
<tr>
<th>Nasal Burden</th>
<th>No. of Patients</th>
<th>Blood Culture</th>
<th>Urine Culture</th>
<th>Blood or Urine Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Few</td>
<td>350</td>
<td>7 (2.0%)</td>
<td>4 (1.1%)</td>
<td>10 (2.9%)*</td>
</tr>
<tr>
<td>1+ or 2+</td>
<td>621</td>
<td>16 (2.6%)</td>
<td>20 (3.2%)</td>
<td>34 (5.5%)*</td>
</tr>
<tr>
<td>3+ or 4+</td>
<td>169</td>
<td>9 (5.3%)</td>
<td>8 (4.7%)</td>
<td>14 (8.3%)*</td>
</tr>
<tr>
<td>Total</td>
<td>1140</td>
<td>32 (2.8%)</td>
<td>32 (2.8%)</td>
<td>58 (5.1%)</td>
</tr>
</tbody>
</table>

* P=0.007 by Cochran-Armitage trend test.