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

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In a retrospective cohort study of 1,140 patients harboring methicillin-resistant *Staphylococcus aureus*, the nasal burden was low in 31%, category 1+ to 2+ in 54%, and category 3+ to 4+ in 15%. There was a significant trend in infection risk with increasing nasal burden ($P = 0.007$). 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% to 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 administration, in patients undergoing selected surgeries or dialysis (9–14). Additionally, many states now mandate nasal 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 a high nasal burden of MRSA as measured by standardized semiquantitative methods incurred increased risks of invasive infection after adjustment for known risk factors for infection.

We conducted a retrospective cohort study of all adults with an MRSA-positive bilateral naris 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 naris specimens were routinely inoculated using standardized semiquantitative methods (18), and the levels of nasal burden were reported as low, 1+, 2+, 3+, or 4+. Our analyses grouped them into low, 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 naris culture. Demographics were recorded, and diabetes mellitus, end-stage renal disease, and cause of admission were identified using International Classification of Diseases (ninth revision) (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, the time from initial detection to

infection was determined. For patients with multiple naris 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.

We identified 1,140 MRSA-positive patients during the study period. The mean age was 58 years (range, 18 to 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. The mean length of stay was 9 days (median, 5 days). The top causes of admission were infection (23%) and cardiovascular symptoms (12%).

Overall, the MRSA nasal burden was low in 31% of patients, 1+ to 2+ in 54%, and 3+ to 4+ in 15%. Within 6 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.

The risk of subsequent infection increased significantly with increasing MRSA nasal burden ($P = 0.007$) (Table 1). This trend persisted in evaluations of 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

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TABLE 1 Frequency of subsequent methicillin-resistant *Staphylococcus aureus* (MRSA) blood or urine infection in the 6 months after detection with MRSA

Nasal burden	No. of patients	No. (%) of patients developing MRSA infection		
		Blood culture	Urine culture	Blood or urine culture ^a
Low	350	7 (2.0)	4 (1.1)	10 (2.9)*
1+ or 2+	621	16 (2.6)	20 (3.2)	34 (5.5)*
3+ or 4+	169	9 (5.3)	8 (4.7)	14 (8.3)*
Total	1,140	32 (2.8)	32 (2.8)	58 (5.1)

^a *, $P = 0.007$ by Cochran-Armitage trend test.

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

In multivariate testing, high nasal burden was predictive of infection (low, 1.0 [reference]; 1+ to 2+, odds ratio [OR] = 2.0 [95% confidence interval {CI}, 1.0 to 4.2]; 3+ to 4+, OR = 3.7 [95% CI, 1.6 to 8.6]). This effect persisted even after excluding patients receiving vancomycin, linezolid, or tigecycline.

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 report 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 and decolonize patients. 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 report 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 types of infections were not assessed.

This study had 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 multisite colonization (24). Third, while high nasal burden distinguishes persistent from intermittent carriage (25), systematic serial cultures were not performed to exclude intermittent carriage. However, the 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.

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