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Major article

MRSA nasal colonization burden and risk of MRSA infection

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Background: *Staphylococcus aureus* nasal colonization burden has been identified as a risk factor for infection. This study evaluates methicillin-resistant *S aureus* (MRSA) nasal burden, as defined by the cycle threshold (C_t) and risk of subsequent infection.

Methods: In a retrospective cohort study, United States veterans were classified into 3 MRSA nasal colonization groups: noncarriers, low burden ($C_t > 24$ cycles), and high burden ($C_t \leq 24$ cycles). MRSA infections were identified prospectively, and clinical information was obtained by chart review. Multivariate logistic regression assessed the association of MRSA nasal burden and risk of MRSA infection.

Results: During 4-years of follow-up, 4.3% of noncarriers, 18.5% of low burden, and 17.2% of high burden developed a MRSA infection. In multivariate analysis, MRSA nasal colonization was a risk factor for MRSA infection ($P = .008$) with low burden (risk ratio [RR], 3.62; 95% confidence interval [CI]: 1.47−8.93) and high burden (RR, 2.71; 95% CI: 0.95−7.72) associated with subsequent MRSA infection when compared with noncarriers. When compared with low burden, high burden nasal carriers were not at increased risk of infection (RR, 0.75; 95% CI 0.36−1.55).

Conclusion: MRSA nasal colonization was a risk factor for MRSA infection. High nasal burden of MRSA did not increase the risk of infection.

The association of *Staphylococcus aureus* nasal colonization and staphylococcal infection was first described in the 1930s.[1] Since 1930, the epidemiology of *S aureus* has changed dramatically, and methicillin-resistant *S aureus* (MRSA) has reached epidemic levels in both hospitals and community settings.[2-6] With the changing epidemiology of MRSA, multiple studies have confirmed nasal colonization as a risk factor for subsequent infection,[7-10] with most infections caused by the colonizing strain.[11,12]

Longitudinal studies clearly identify 3 patterns of *S aureus* carriage: persistent carriage, intermittent carriage, and noncarriage.[13-16] Persistent nasal carriage, defined as ≥80% of weekly nasal swabs positive, is associated with a higher colonization burden when compared with intermittent carriage.[17-19] In high-risk patients (postsurgical or peritoneal dialysis), increased nasal colonization burden and/or the persistently colonized state are associated with an increased infection risk when compared with intermittent or noncarriers.[20-22] The clinical implications of *S aureus* nasal burden have yet to be defined, and comparative effectiveness research is needed utilizing quantitative colonization data.

In response to the United States MRSA epidemic, the Veterans Health Administration (VHA) implemented active surveillance of MRSA colonization for all patients admitted to acute care facilities. To reduce the time needed to identify MRSA from surveillance cultures, molecular tests have now become standard in identification of patients with MRSA colonization. Molecular methods utilize polymerase chain reaction (PCR) technology to detect and amplify regions of MRSA-specific DNA. These tests can detect the presence of MRSA DNA within 2 hours and dramatically reduce the time to result in surveillance testing. In addition to time saved, PCR-based tests can be used for quantification of bacteria. The number of cycles the test completes before target DNA is detected (cycle threshold [C_t]) is inversely proportional to the amount of DNA in the sample. The C_t from Cepheid's Xpert MRSA Assay (Cepheid, Sunnyvale, CA) has recently been shown to be an excellent quantitative measure of MRSA on nasal swabs.[23]

Standard quantitative culture techniques are burdensome and labor intensive, whereas the C_t from MRSA nasal surveillance swabs is readily accessible and routinely collected in active surveillance

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programs. Using data from the VHA MRSA surveillance program and the C_t to define MRSA nasal burden, we performed a retrospective cohort study to assess the affect of nasal MRSA colonization burden on the risk of subsequent MRSA infection among veterans in Atlanta.

METHODS

The study population consisted of US veterans at the Atlanta VA Medical Center (AVAMC). The AVAMC is a large, integrated health care system with approximately 200 inpatient beds, 8 community-based outpatient clinics, and 1 nursing home care unit. Approximately 82,000 veterans receive care through the AVAMC and account for over 30,000 annual bed-days of care at the acute care facility. All AVAMC medical facilities utilize the VA's computerized patient records system to access medical information. The AVAMC uses 1 central microbiology laboratory that receives specimens from the surrounding VA outpatient clinics, nursing home, and acute care facility. Most veterans at the AVAMC do not have private insurance coverage and rely solely on the VA for their medical needs. The Emory University Institutional Review Board and the VA Research and Development Committee approved this study.

In an attempt to reduce nosocomial MRSA transmission, the VHA issued a directive in 2007 mandating the use of a MRSA bundle in all acute care settings. The MRSA bundle utilized, in addition to other measures, active surveillance for MRSA nasal colonization in all patients admitted to the hospital, transferred between units, and upon discharge from the hospital. At the AVAMC, MRSA admission screening is performed using a Liquid Stuart double swab (Copan, Murrieta, CA) inserted 1 cm into each nasal vestibule and rotated 4 revolutions while maintaining even contact with the nasal mucosa. Nursing staff collects all nasal surveillance specimens within 12 to 24 hours of admission. All nursing staff has undergone training on appropriate collection techniques, but no system is in place to ensure adequate collection techniques are utilized. Colonization results were obtained from the electronic medical record via a Web-based hospital surveillance system (TheraDoc; Hospira, Lake Forest, IL).

Admission nasal swabs are sent directly to the microbiology laboratory for testing using the Xpert MRSA assay. The Xpert MRSA assay is performed according to the manufacturer's instructions with a C_t of 15 to 36 cycles considered positive for MRSA. All C_t data are archived and easily extracted from the Xpert system. Patients with a $C_t > 24$ cycles were considered to have low nasal MRSA burden, and those $\leq$24 cycles were considered to have high MRSA nasal burden. The decision to dichotomize the C_t was based on previous work from our laboratory that demonstrated the logarithmic association of quantitative cultures and C_t.[23] Extranasal sites are not routinely screened for MRSA, and decolonization strategies are not routinely recommended for colonized patients.

At the AVAMC, surveillance of MRSA-positive clinical cultures from all body sites began October 1, 2005. All positive cultures were identified prospectively on a monthly basis by utilizing the microbiology option for specific organisms in the electronic medical record (Veterans Health Information Systems and Technology [VISTA]). All clinical MRSA cultures and corresponding clinical data (anatomic site of culture, radiographic studies, laboratory results, and physician notes) were reviewed by the same experienced infectious disease physician on a monthly basis to identify true infections and exclude cultures representing colonization.

Infections were classified according to the Centers for Disease Control and Prevention criteria.[24] Cultures not associated with a true infection were excluded. The infections were categorized according to primary site of infection into the following categories: skin and soft tissue, bone and joint, bloodstream, genitourinary, lower respiratory tract, surgical site, and other.

Patient selection

All patients admitted to the AVAMC acute care medical facility from October 1, 2007, through February 1, 2008 (4 months), were eligible to be included in the study population. This allowed for at least 4 years of follow-up. All patients with positive admission nasal MRSA surveillance results were included in the study. A random sample of patients from the same time period with negative admission nasal MRSA surveillance results was also included. Patients sent to the AVAMC for a surgical procedure with no prior or subsequent follow-up within the AVAMC system were excluded. The inpatient psychiatric department does not perform MRSA nasal surveillance routinely and thus were excluded from the study population.

The electronic medical record for each study participant was reviewed. Admission history and physical, discharge summaries, operative notes, last primary care note, progress notes within 30 days of admission, and pertinent laboratory values were reviewed. Problem lists were not used as a source of clinical information. External devices were considered anything foreign that entered the body and had an externalized segment (ie, urinary catheter, central vascular access, suprapubic urinary catheter, tracheostomy, feeding tube). End stage renal disease (ESRD) included only those patients on renal replacement therapy. Patients not known to be HIV positive were assumed to be negative. Wounds were considered anything that caused the integrity of the skin to be compromised and included severe psoriasis, decubitus ulcers, chronic diabetic wounds, surgical wounds not yet healed, and burns. Chronic liver disease was defined as cirrhosis or chronic liver failure and did not include hepatitis A, hepatitis B, or hepatitis C without liver failure of acute liver failure. Malignancies were considered active if the patient was actively being treated with chemotherapy, was under hospice care secondary to malignancy, had metastatic disease, or had active disease in which treatment was recommended. Localized prostate cancer was not considered an active malignancy. All other comorbidities were obtained from the medical record.

Statistical analysis

Sample size was determined by the known distribution of the admission C_t of Atlanta veterans[23] and an estimated risk of subsequent infection of 2.5% for noncolonized, 10% with low burden ($C_t > 24$ cycles), and 30% with high burden ($C_t \leq 24$ cycles).

Descriptive statistics were used to compare the study population stratified by colonization status (negative, low burden, high burden) to identify potential factors that are associated with colonization status. Differences in categorical variables were tested using χ^2. If expected cell counts were less than 5, Fisher exact test was utilized. Continuous variables were analyzed with a 1-way analysis of variance to compare means or 2-sample *t* test. A *P* value of $\leq$.05 was considered significant unless otherwise stated.

Unadjusted risk ratios were obtained for all covariates and the outcome (infection). Because of the limited published clinical data on nasal colonization burden, an exploratory analysis for potential interaction terms was performed. In this analysis, the study population was stratified on individual covariate levels and risk ratios for each level of the exposure variable (colonization status) were compared with the Breslow-Day test. A *P* value $\leq$.10 was considered significant in addition to biologically plausible interaction terms.

A multivariate logistic regression model was used to analyze the relationship between MRSA nasal colonization burden and subsequent infection. All covariates significant in bivariate analysis