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The Natural History of Contemporary *Staphylococcus aureus* Nasal Colonization in Community Children

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Abstract

The natural history of contemporary *Staphylococcus aureus* nasal colonization was evaluated in community children during a one year period. MSSA nasal carriage was more persistent than MRSA nasal carriage, which was usually self-limited. Children with persistent staphylococcal colonization often carried identical strains. Identification of persistent MRSA carriers might inform strategies for decolonization and reduction of staphylococcal transmission.

Keywords

Staphylococcus aureus; colonization; methicillin resistance

The past decade has seen the emergence of community-associated (CA) strains of methicillin-resistant *S. aureus* (MRSA) that affect individuals without traditional risk factors for MRSA acquisition.1 The natural history and carriage states of nasal colonization with contemporary CA-*S. aureus* strains may differ from that of traditional *S. aureus* strains circulating in the past, dynamics that must be understood to develop strategies to prevent transmission of this pathogen. We investigated the natural history of contemporary *S. aureus* nasal colonization in community children, quantified colonization persistence using molecular typing, and identified current risk factors for prolonged *S. aureus* nasal colonization.

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PATIENTS AND METHODS

From October 2005 through June 2006, 1300 children ages birth to 18 years were recruited from community pediatric practices within a practice-based research network.2 Both anterior nares were cultured to determine *S. aureus* colonization status, and persistence was tracked for 1 year by repeat culturing. A questionnaire was administered to identify epidemiologic risk factors associated with *S. aureus* nasal colonization. All procedures were approved by the Washington University Human Research Protection Office. Written, informed parental consent was obtained, and written assent was provided by children of a developmentally appropriate age.

From the original 1300 study participants, 3 cohorts were developed according to baseline nasal colonization status (i.e., MRSA, methicillin-susceptible *S. aureus* [MSSA], or no *S. aureus*) with an equal distribution of participants based on age group, pediatric practice from which the child was enrolled, and date of enrollment. Investigators and participants were blinded to participants' colonization status throughout the study. A collaborator outside the study team performed frequency matching and selected cohort subjects.

Participants were telephoned 3, 6, and 12 months following study enrollment to ascertain the development of skin and soft tissue infection (SSTI) of any cause in participants or other household members. Information was also obtained regarding the use of interim antibiotics or decolonization measures (e.g., intranasal mupirocin, chlorhexidine, or bleach baths). At each time point, a collection packet was mailed to each participant, containing a culture swab (BD CultureSwab MaxV; Becton Dickinson, Sparks, MD), a biohazard-compliant diagnostic mailing box (Infecon Diagnostic Mailer; Com-Pac International, Inc., Carbondale, IL), and instructions for collecting and returning nasal specimens.

Specimens were plated to trypticase soy agar with 5% sheep blood (Becton Dickinson) and incubated at 35°C in 5% CO_2. *S. aureus* identification and antibiotic susceptibility testing were performed as previously described.2 All swabs yielded normal respiratory flora, indicating that specimens were in fact obtained from the anterior nares.

Methods for staphylococcal DNA extraction, repetitive sequence-based polymerase chain reaction (rep-PCR), and statistical analysis are provided as Supplemental Digital Content 1, (http://links.lww.com/INF/A629).

RESULTS

Of 105 participants in the longitudinal cohorts, 32 (30.5%) were colonized in the anterior nares with MRSA, 37 (35.2%) were colonized with MSSA, and 36 (34.3%) were not colonized with *S. aureus* at enrollment (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/A630) which summarizes the characteristics of these 3 groups). Thirty-nine (37.1%) participants were lost to follow-up and were excluded from analysis. Of the remaining 66 participants, at baseline, 25 (38%) were colonized with MRSA, 23 (35%) were colonized with MSSA, and 18 (27%) were not colonized.

Of the 25 participants with baseline MRSA nasal colonization, 41% remained colonized with MRSA at 3 months, 30% at 6 months, and 18% at 12 months (Figure 1). In contrast, of the 23 participants with baseline MSSA nasal colonization, subsequent rates of MSSA colonization were 74%, 63%, and 56% at 3, 6, and 12 months respectively. Among participants with baseline MRSA colonization, 6 (24%) carried MSSA at least once during the follow-up period, while only 1 (4%) of those with baseline MSSA colonization carried MRSA at a subsequent sampling. Of the 18 participants not initially colonized with *S.*

aureus, 6 (33%) carried MSSA at least once during follow-up and 1 (6%) carried MRSA at a subsequent sampling.

Of 66 participants with follow-up data, 38 provided ≥3 consecutive samples. Among these, *S. aureus* (MRSA or MSSA) was present at 3 consecutive samplings in 13 (34%). Nineteen (50%) of these 38 participants had intermittent colonization (colonized with *S. aureus* at ≥1 sampling and not colonized at ≥1 intervening sampling), while 6 (16%) did not carry *S. aureus* at any point.

Heterogeneity of strains (determined by rep-PCR) was observed among individual participants enrolled from within each pediatric practice, although several clones appeared to predominate (see Figure, Supplemental Digital Content 3, http://links.lww.com/INF/A631) for a dendrogram of *S. aureus* isolates recovered from participants recruited from a single practice).

Thirteen (20%) of the 66 participants had a positive nares culture for MRSA at least once during follow-up (7 colonized once, 5 twice, and 1 three times). Univariate analyses of risk factors for MRSA and MSSA nasal colonization, and for *S. aureus* colonization at ≥2 longitudinal samplings, are shown in the Table (Supplemental Digital Content 4, http://links.lww.com/INF/A632). Factors independently associated with longitudinal MRSA colonization in the multivariable model included prior MRSA colonization (adjusted OR [aOR] 12.5, 95% CI 2.1 – 75.7, p=0.007), Medicaid or no health insurance (aOR 10.2, 95% CI 1.7 – 61.3, p=0.01), healthcare worker in the household (aOR 5.9, 95% CI 1.3 – 27.6, p=0.02), and interval SSTI in a household member (aOR 6.5, 95% CI 1.0 – 42.8, p=0.05).

Twenty-nine participants (44%) had a positive nares culture for MSSA at least once during follow-up (13 once, 9 twice, 7 three times). In the multivariable model, prior MSSA colonization (aOR 16.2, 95% CI 5.9 – 44.4, p<0.001), school attendance (aOR 3.8, 95% CI 1.4 – 10.8, p=0.01), and fingernail biting (aOR 3.1, 95% CI 1.0 – 9.5, p=0.05) remained significant risk factors for longitudinal MSSA colonization.

Thirty-seven of the 66 children with follow-up information (56%) were colonized with *S. aureus* (MRSA or MSSA) at ≥2 samplings. Independent risk factors for *S. aureus* colonization at ≥2 samplings by multivariable analysis were MSSA nasal colonization at baseline (aOR 5.9, 95% CI 1.5 – 23.4, p=0.01), asthma (aOR 6.0, 95% CI 1.4 – 25.1, p=0.02), and school attendance (aOR 4.0, 95% CI 1.2 – 13.7, p=0.03). Of the 37 participants with colonization at ≥2 samplings, 22 (60%) carried an identical strain (by rep-PCR) throughout the study: 47% of those with baseline MRSA and 67% of those with baseline MSSA.

DISCUSSION

In the current epidemic of *S. aureus* infections in community children, an understanding of the natural history, dynamics, and determinants of CA-*S. aureus* carriage is essential to devise targeted approaches to interrupt CA-*S. aureus* transmission. The interplay of host and bacterial factors likely influences the staphylococcal carrier state, and optimal interaction of these factors may result in persistent carriage.

In the present study, 34% of participants carried *S. aureus* in the anterior nares at 3 consecutive samplings over one year (i.e., were persistent carriers), while 50% were intermittently colonized and 16% were persistent noncarriers. In concordance with a study in which Nouwen and colleagues inoculated staphylococcal carriers and noncarriers with multiple strains of *S. aureus*,3 the majority (60%) of carriers in our study subsequently harbored an identical strain, arguing that an optimized host-microbe pair results in persistent

carriage. We found that initial MRSA and MSSA colonization were associated with subsequent colonization with these organisms, respectively, and individuals colonized at ≥2 time points were more likely to be prolonged carriers. However, our observation that nasal carriage of MRSA was less persistent than MSSA, coupled with the lower prevalence of MRSA colonization in the community compared with MSSA,2 may reflect that a minority of individuals in the community offer a host environment that favors persistent carriage of contemporary MRSA. In support of this concept, host genetic polymorphisms associated with nasal *S. aureus* carriage were recently identified in a modest Amazonian cohort.4

Alternatively, factors intrinsic to each *S. aureus* clone may underlie differences in carriage patterns. For example, while novel gene content in contemporary MRSA strains might enhance cutaneous virulence,5 traditional MSSA strains might be better equipped to compete for the colonization niche. In support of this hypothesis, we observed a trend toward more frequent strain substitution in children initially colonized with MRSA. One fourth of these patients carried MSSA subsequently, while acquisition of MRSA by those initially colonized with MSSA was infrequent; baseline noncarriers also acquired MSSA more frequently than MRSA.

While our study is an important gateway to understanding the natural history of contemporary *S. aureus* colonization in community children, it is limited by cohort size and sampling of only the nares; we and others have recently demonstrated that the groin and axilla are also important sites of CA-MRSA colonization.6, 7 While rep-PCR does not assign specific sequence types, the conclusions of this study are applicable to the contemporary clinician managing patients with CA-*S. aureus* colonization and infection.

Because individuals with CA-MRSA colonization are at risk for subsequent SSTI,8, 9 and CA-MRSA SSTI are often recurrent, many practitioners prescribe decolonization measures in an effort to prevent recurrent CA-MRSA SSTI.10 We found that contemporary MRSA colonization frequently resolves spontaneously, and that multiple positive cultures identify those individuals likely to remain colonized. Such information may help to target decolonization measures to those patients at highest risk for developing recurrent SSTI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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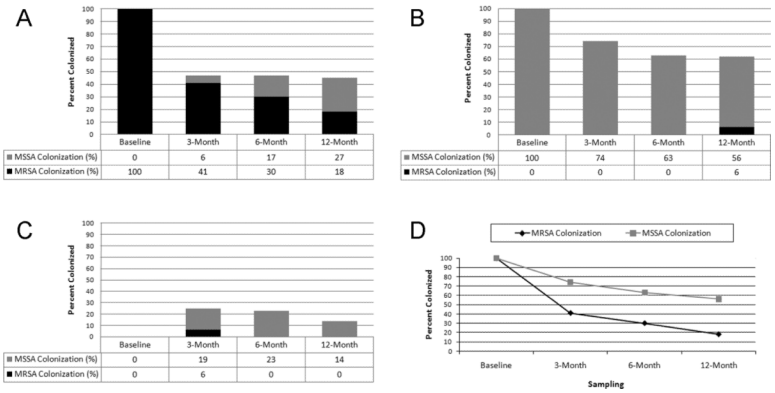

Figure 1.

Rates of MRSA and MSSA nasal colonization over the one-year longitudinal study. A) Rates of MRSA (black bars) and MSSA colonization (grey bars) in participants with baseline MRSA colonization. B) Rates of MRSA and MSSA colonization in participants with baseline MSSA colonization. C) Rates of MRSA and MSSA colonization in participants not colonized with *S. aureus* at baseline. D) Comparison of longitudinal MRSA colonization in participants with baseline MRSA colonization (black line) and longitudinal MSSA colonization in participants with baseline MSSA colonization (grey line).