# Molecular Epidemiology of Recurrent Cutaneous Methicillin-Resistant *Staphylococcus aureus* Infections in Children

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We assessed the relatedness by repetitive-sequence polymerase chain reaction of isolates obtained from children with recurrent methicillin-resistant *Staphylococcus aureus* cutaneous infections over 6 years. Ninety percent of the cases could be attributed to recurrence of the same strain type, suggesting that optimized decolonization methods in children might effectively prevent recurrent infection.

**Key words.** decolonization; repetitive-sequence polymerase chain reaction; skin and soft-tissue infection; *Staphylococcus aureus*.

Methicillin-resistant *Staphylococcus aureus* (MRSA) skin- and soft-tissue infection (SSTI) poses a significant public health burden. Recurrent MRSA SSTIs are especially problematic. In a recent study, greater than 50% of patients experienced recurrent SSTIs over 1 year despite undergoing decolonization measures [1]. Information regarding the relatedness of isolates causing repeated MRSA infections is limited, and studies to date have largely focused on recurrent bacteremia in hospitalized adults [2, 3]. The Infectious Diseases Society of America (IDSA) recommends decolonization for select populations in an attempt to prevent recurrent infection [4]. An understanding of the epidemiology of MRSA infection, specifically recurrent infection, is important to inform disease-prevention strategies. If recurrent infections are due to serial acquisition of disparate strain types, decolonization might be less effective in preventing these recurrences. The objectives of this study were to elucidate whether recurrent MRSA SSTIs in healthy children are attributable to re-infection with the strain causing the patient's previous infection, or acquisition of a distinct strain, and whether strain similarity correlated with patient- and infection episode–specific characteristics.

## METHODS

### Cohort Assembly

We performed a retrospective analysis of patients whose MRSA isolates were routinely banked in the Saint Louis Children's Hospital (SLCH) microbiology laboratory or for prior studies [1, 5]. For this investigation, we included otherwise healthy children ages birth to 18 years presenting to SLCH with recurrent MRSA SSTI from January 2005 to January 2011. Medical records were reviewed by a Pediatric Infectious Diseases specialist who determined that recurrent episodes were discrete, defined as occurring more than 10 days apart with documentation of resolution of the prior infection episode. Patients with underlying disease (ie, immunodeficiency, malignancy, cystic fibrosis, neurologic and genetic disorders, congenital heart disease, diabetes, and severe hemophilia), those whose infections were not discrete, and those whose isolates were recovered from sites of colonization (rather than infection) were excluded. Each two consecutive episodes in any patient comprised a "pair" of infecting isolates. Data collection included patient demographics, characterization of illness and hospitalization, antibiotics prescribed, and time between episodes.

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Study procedures were approved by the Washington University Human Research Protection Office.

### Antimicrobial Susceptibility, Molecular Characterization, and Relatedness of Isolates

Routine antibiotic susceptibility data were retrieved from the medical record. Mupirocin resistance was detected using a 200-μg mupirocin disk (ThermoFisher Scientific) [6].

The relatedness of MRSA isolates was determined by strain typing with repetitive-sequence polymerase chain reaction (repPCR) and analyzed with Diversilab Bacterial Barcodes (bioMerieux, Durham, NC) as previously described [7]. Strains with a similarity index of ≥95% were considered identical.

### Statistical Analysis

Variables were compared by Fisher's exact or $\chi^2$ tests (categorical) and Mann-Whitney test (continuous) using SPSS 19.0 for Windows (IBM SPSS, Chicago, IL). *P* values ≤.05 were considered significant.

## RESULTS

Of patients with banked isolates, 264 had more than 1 discrete MRSA SSTI episode. Our analysis included 105 patients, including all patients with 3 or more discrete episodes of MRSA SSTI (n = 28), as well as a random sample of patients with 2 infections (n = 77). Given the low level of background genetic diversity, molecular typing of additional isolates was not performed.

The median age of our population was 1.8 years (range, 0.3–18.5). Over half of the study patients were female (61%), and the majority were African-American (73%). Seventy-seven (73%) patients had 2 SSTI episodes, 21 (20%) had 3, 6 (6%) had 4, and 1 (1%) had 7 SSTI episodes, totaling 248 discrete infections.

Overall, repeat infections in 94 (90%) patients were due to identical strain types, while 11 (10%) patients were infected with ≥2 distinct strain types (Table 1). The median number of infection episodes for patients with identical strains was 2 (range, 2–7) and for those with distinct strains was 3 (range, 2–4; *P* = .04).

A total of 143 pairs (ie, 2 consecutive infection episodes) were analyzed for strain relatedness. While we identified 9 distinct strain types, 89% of the 248 MRSA isolates were represented by 1 of 2 strain types. Among the 143 infection pairs, 132 (92%) comprised identical strain types, and 11 (8%) comprised distinct strain types (Table 1). Identical-strain infection pairs tended to occur at a related body site more often than distinct-strain infection pairs (43% versus 18%; *P* = .12). The median interval between episodes in infection pairs trended lower for identical strains (124 days) than for distinct strains (212 days; *P* = .09).

Of 236 infections for which antibiotic data were available, antibiotics were prescribed in 197 (83%), most commonly clindamycin or trimethoprim–sulfamethoxazole (96% of such cases). The class of antibiotic prescribed, and susceptibility of the first isolate in a pair to the prescribed antibiotic, did not affect strain relatedness between isolates in the pair. Overall, 94% of isolates were resistant to erythromycin, 13% to clindamycin, 0% to trimethoprim–sulfamethoxazole and vancomycin, and 4.8% to mupirocin. Of 132 infection pairs that were identified as identical strain types by repPCR, 24 (18%) had differing antibiotic susceptibility patterns for erythromycin, clindamycin, or mupirocin, compared with 3 of 11 (27%) pairs identified as distinct by repPCR.

One patient in our study suffered 7 MRSA SSTIs over 3 years (2008–2011), resulting in 3 hospitalizations (totaling 10 days). The interval between episodes ranged from 21 to 315 days, and all 7 were caused by an identical strain. Four infections occurred on the lower extremity, 2 on the buttock, and 1 on the neck; the patient received antibiotics for 6 episodes. Information regarding performance of decolonization measures by this patient was not available.

From our cohort, 6 patients with 3 or more episodes had at least 1 episode caused by a distinct strain type. For 3 patients, the first 2 episodes were caused by identical strain types, while the third episode was caused by a distinct strain type. In each of the remaining 3 patients, all episodes after the first were caused by a single strain type distinct from the first strain.

## DISCUSSION

This study revealed that 90% of our otherwise healthy pediatric study population experienced recurrent MRSA SSTI caused by a strain type identical to their prior infection. Patients infected with distinct strain types had a higher number of recurrences and tended to have a longer time interval between infections compared to patients infected with identical strain types. Prescription of systemic antibiotics had no effect on strain relatedness.

To our knowledge, this study is the first to evaluate the molecular epidemiology of recurrent contemporary MRSA SSTI in children in the United States. Our observations are consistent with other studies, largely in adults and using various typing methods, indicating that recurrent MRSA infection is typically caused by relapse of a previously infecting strain type [2, 3, 8]. Huang and colleagues [2] reported that 89% of 37 adults with

**Table 1.** Characteristics of Patients and Infection Pairs With Identical and Distinct Methicillin-Resistant *Staphylococcus aureus* Strains

| Patient Characteristics | Total N = 105 (%) | Distinct N = 11 (%) | Identical N = 94 (%) | *P* |
|---|---|---|---|---|
| Female | 64/105 (61) | 6/11 (55) | 58/94 (62) | .75 |
| Age, years, median (range) | 1.8 (0.3–18.5) | 1.2 (0.6–17.2) | 1.9 (0.3–18.5) | .23 |
| Medicaid | 79/101 (78) | 9/10 (90) | 70/91 (77) | .69 |
| African-American race | 76/104 (73) | 10/11 (91) | 66/93 (71) | .28 |
| Weight for age >97%[a] | 18/101 (18) | 3/11 (27) | 15/90 (17) | .41 |
| Day care attendance[b] | 28/76 (37) | 4/9 (44) | 24/67 (36) | .72 |
| Eczema | 24/104 (23) | 3/11 (27) | 21/93 (23) | .71 |
| Number of SSTI episodes, median (range) | 2 (2–7) | 3 (2–4) | 2 (2–7) | .04 |
| *S. aureus* Isolate Pair Characteristics | Total N = 143 (%) | Distinct N = 11 (%) | Identical N = 132 (%) | *P* |
| Related body site of 2 infections in pair | 59/143 (41) | 2/11 (18) | 57/132 (43) | .12 |
| Interval between infections, days, median (range) | 127 (11–1645) | 212 (23–1121) | 124 (11–1645) | .09 |
| Antibiotic was prescribed for 1st infection in pair | 115/136 (85) | 7/10 (70) | 108/126 (86) | .19 |
| Antimicrobial therapy for 1st infection in pair | | | | .96[c] |
| Clindamycin | 61/115 (54) | 4/7 (57) | 57/108 (53) | |
| Trimethoprim–sulfamethoxazole | 50/115 (44) | 3/7 (43) | 47/108 (44) | |
| Other[d] | 3/115 (3) | 0/7 (0) | 3/108 (3) | |
| Unspecified | 1/115 (1) | 0/7 (0) | 1/108 (1) | |
| Prescribed antibiotic to which isolate was susceptible for 1st infection in pair | 101/136 (74) | 6/10 (60) | 95/126 (75) | .28 |

Abbreviation: SSTI, skin and soft-tissue infection.
[a]Weight for age was determined using the Centers for Disease Control and Prevention Growth Charts for the United States.
[b]Children ≤5 years included, N = 76.
[c]$\chi^2$ test; all others analyzed by Mann–Whitney (continuous variables) or Fisher's exact test (categorical variables).
[d]Other antimicrobial therapy prescribed: ciprofloxacin (1), amoxicillin–clavulanate (2).

hospital-acquired, recurrent MRSA bacteremia had subsequent infections caused by an identical strain type over 1–2 years. Among 32 Taiwanese adults with recurrent MRSA bacteremia, 91% of the infections were caused by identical strain types over 5 years [3]. Another 3-year study in Taiwan focusing on children with recurrent invasive (59%) and superficial (41%) MRSA infections found that 90% of reinfections were with identical strain types [8]. In these studies of largely hospitalized patients with invasive infection, longer durations between MRSA infections were not predictive of differing strain types [2, 8], in contrast to the finding in our cohort.

Thomsen et al. [9] analyzed MRSA isolates recovered from children in Nashville and found that 82% of randomly selected infecting isolates were of the same genetic lineage (pulsed field gel electrophoresis group USA300), suggesting low overall diversity in currently circulating MRSA strains. This is consistent with our study and those by other investigators, in which limited genetic diversity in clinical MRSA isolates was evident within a defined region over a short time period [8, 10, 11].

Interval placement of adults at rehabilitation facilities between MRSA infection episodes has been associated with a recurrent infection caused by a distinct strain type compared to patients residing at home or remaining in the hospital [2], likely due to exposure to other patients and healthcare workers from various settings with diverse strain types. In our cohort of healthy children, we evaluated daycare attendance as an analogous possible risk factor for infection with a distinct strain type [12], but daycare attendance did not have an effect on strain relatedness. This study is limited by the retrospective study design, such that data regarding decolonization, household contacts with SSTI, and adherence to antibiotic therapy were not available.

In their Clinical Practice Guidelines for the Management of MRSA Infections, the IDSA recommends decolonization for patients with recurrent SSTI after optimizing wound care and hygiene measures [4]. In the present study, the majority of patients with recurrent MRSA SSTI were infected with identical strain types, which might suggest that decolonization alone ought to be effective. Measures aimed at eradication should theoretically eliminate the endogenous colonizing strain that is likely causing recurrent infection. However, in a study conducted by our group, 63% of children employing a commonly prescribed 5-day decolonization regimen (intranasal mupirocin application and chlorhexidine body washes) developed subsequent SSTI over 1 year [1], suggesting that single brief courses of decolonization may not be sufficient for sustained eradication in individual patients. Thus, further studies are required to opti-mize decolonization methodology, including the agents and doses prescribed, sites of application,

and consideration of repetitive application of these measures. In addition, our group is currently investigating household transmission dynamics and household-wide approaches to prevent recurrent MRSA infection. Finally, a small proportion of patients in our population experienced recurrent MRSA SSTI caused by distinct strain types, suggesting exogenous sources of acquisition that may or may not be amenable to such elimination efforts.

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All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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