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# Dissemination of Methicillin-resistant *Staphylococcus aureus* among Healthy Children in Northern Taiwan

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**Background:** We previously reported the incidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections among children in Taiwan was increasing. This study examined the extent of MRSA colonization in the healthy pediatric population existed in parallel with this trend. **Method:** In this prospective observational study, nasal swabs were obtained from healthy children presenting for child healthcare visits or attending one of seven kindergartens during a 2-year period. A case-control study and molecular typing studies were performed. **Results:** Of 1195 children, 89 (7.4%) had nares cultures positive for MRSA. Risk factors for MRSA colonization included household contact with a high-risk individual (odds ratio [OR], 8.971; 95% confidence interval [CI], 2.968-27.117) and recent antibiotic use (OR, 5.997; 95% CI, 3.605-9.976). Staphylococcal cassette chromosome *mec* (SCC*mec*) typing showed most community MRSA strains were SCC*mec* types IV and type $V_T$. Pulsed-field gel electrophoresis revealed MRSA clones distinct from nosocomial MRSA isolates have disseminated in healthy children, and Panton-Valentine leukocidin genes were present in 15 of 89 MRSA isolates (16.9%). **Conclusions:** As colonization typically precedes infection, the characteristics of children with MRSA nasal carriage may be useful for distinguishing those who may be at risk of MRSA infection.

Key words: nasal colonization, methicillin-resistant *Staphylococcus aureus*, Taiwan

## INTRODUCTION

The traditional notion of methicillin-resistant *Staphylococcus aureus* (MRSA) as a pathogen that is seemingly confined to the nosocomial arena has been recently challenged with the recognition of community-associated MRSA (CA-MRSA) in children and adults lacking traditional risk factors[1-4]. Additionally, reports of pediatric deaths resulting from CA-MRSA infection further alerted medical professionals to face the seriousness of this emergence[5]. Due to the geographic diversity of the prevalence and genetic backgrounds of the colonizing MRSA strains, as well as probable transmission from any asymptomatically colonized individual, an understanding of the epidemiology of MRSA nasal carriage in the community would be helpful to estimate the potential for spread of CA-MRSA. Further, it would be crucial for primary care physicians to appropriately manage children with suspected CA-MRSA infections.

The purpose of our study was to determine the prevalence of and risk factors for MRSA colonization among healthy community children. In addition, we also characterized these colonizing MRSA strains through molecular analyses.

## METHODS

### Study Design, Population and Location

This prospective observational survey was conducted during a 2-year study period at Tri-Service General Hospital, a tertiary medical center in northern Taiwan. The study proposal was reviewed and approved by the National Defense Medical Center Institutional Review Board. All children 14 years of age or younger with no acute medical problem, who either presented for a child healthcare visit or attended one of seven kindergartens in different districts in Taipei, were considered eligible to participate. Participants and their guardians were approached by the same investigative team throughout the study period. After written consent was obtained, study personnel verbally administered a questionnaire to the guardian regarding the participant's age, gender, medical history, and risk factors for MRSA colonization including hospitalization or antibiotic use in the previous 12

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months, underlying chronic disorder (e.g., atopic dermatitis), household contact with an individual with an identified risk factor (e.g., long-term care facility residence, intravenous drug abuse, recurrent skin infections, history of MRSA infection or colonization) or a worker in a health care environment in the 12 months preceding the culture.[1]

**Microbiological Analysis**

Nasal samples were obtained with a sterile cotton swab, placed in a transport medium (Venturi Transystem, Copan Diagnostics, Corona, CA, USA), and then transported to and processed in our microbiology laboratory within 4 hours. *S. aureus* isolates were identified according to the methods previously described[6,7] and further screened for methicillin resistance following the Clinical Laboratory Standards Institute (CLSI; formerly known as the NCCLS) guidelines[8]. All MRSA isolates were frozen at -70°C for additional testing of organism characteristics. These tests included antimicrobial susceptibility testing using the disk-diffusion method[9], double-disk diffusion assay (D test) for detecting *in vitro* macrolide-lincosamide-streptogramin (MLS) inducible phenotype[10], singleplex polymerase chain reaction (PCR) for detection of genes encoding Panton-Valentine leukocidin (PVL) toxin[11] and MLS resistance[12,13], staphylococcal cassette chromosome *mec* (SCC*mec*) typing by PCR[14,15], and strain typing by pulsed-field gel electrophoresis (PFGE) using *Sma*I enzyme (New England Biolabs, Beverly, Mass, USA)[16]. To identify PFGE polymorphisms, band patterns were analyzed using Molecular Analyst Fingerprinting, Fingerprinting Plus, and Fingerprinting DST software (Bio-Rad Laboratories, Richmond, CA, USA). The grouping method was performed to deduce a dendrogram from the matrix by the unweighted pair group method with the arithmetic averages clustering technique after calculating the similarities using the Pearson correlation coefficient between each pair of organisms; the PFGE patterns were distinguished at the 70% similarity level.[17]

**Case-control Study**

A case-control study was performed to identify the risk factors for colonization with MRSA. Cases were defined as children with results of nasal cultures revealing colonization with MRSA. Controls were defined as children who were not colonized with MRSA (i.e., they were either colonized with methicillin-susceptible *S. aureus* or had negative culture results).

**Statistical Analysis**

Data were entered into Microsoft Access XP software and exported to the SPSS statistical software, version 10.0 (SPSS), which was used for data analyses. Identification of potential risk factors for MRSA colonization was initially determined by univariate analyses. Variables statistically significantly associated with MRSA colonization in the univariate analysis were entered into a multivariate unconditional logistic regression model controlling for age and sex. All analyses were 2-tailed, and a *P* value of < .05 was considered statistically significant.

## RESULTS

**Population Characteristics and Prevalence of MRSA Nasal Colonization**

A total of 1195 children with ages ranging from 1 month to 12 years participated in the study: 552 were from child healthcare visits and 643 were from seven kindergartens. The median age of the children was 3.6 years, and 600 (50.2%) were male. Of the 1195 nares cultures, 89 (7.4%) were positive for MRSA, 211 (17.7%) were positive for MSSA, and 895 (74.9%) were culture negative. The percentage of MRSA isolates among all *S. aureus* isolates was 29.7%. In addition, MRSA colonization rates among children attending the seven different kindergartens were similar and the children were not linked on review of epidemiologic data derived from the medical records.

**Risk Factors for MRSA Nasal Colonization**

In the univariate analyses, there were no differences in MRSA colonization based on age, gender, presence of atopic dermatitis, or hospitalization during the previous year (Table 1). Risk factors for colonization with MRSA in the univariate analysis are also shown in Table 1.

In multivariate analysis, factors independently associated with an increased risk of MRSA colonization included household contact with an individual with an identified risk factor within the past 12 months (odds ratio [OR], 8.971; 95% confidence interval [CI], 2.968-27.117), and antibiotic use within the 12 months preceding sampling (OR, 5.997; 95% CI, 3.605-9.976). Children with a family member who worked in a hospital were at significant risk of MRSA colonization, according to the univariate analysis (P = 0.003); however, this factor did not remain significant on multivariate analysis.

**Antibiotic Susceptibility Profiles of MRSA Colonization Isolates**

Table 1 Characteristics of enrolled children and results of univariable analysis of risk factors for nasal colonization with MRSA

| Variable | No. (%) of children: With MRSA nasal carriage (n = 89) | No. (%) of children: Without MRSA nasal carriage (n = 1106) | OR (95% CI) | *P* value* |
|---|---|---|---|---|
| Age, yr | | | | |
| <1 | 21 (24) | 262 (24) | 1.0 | |
| 1-5 | 27 (30) | 459 (41) | 0.734 (0.407-1.324) | .303 |
| >5 | 41 (46) | 385 (35) | 1.329 (0.767-2.300) | .309 |
| Sex | | | | |
| Female | 47 (53) | 548 (49.5) | 1.0 | |
| Male | 42 (47) | 558 (50.5) | 0.878 (0.569-1.353) | .554 |
| Antibiotic use in past 12 months | | | | |
| Yes | 32 (36) | 81 (7) | 7.104 (4.359-11.579) | <.001 |
| No | 57 (64) | 1025 (93) | | |
| Diagnosis of atopic dermatitis | | | | |
| Yes | 1 (1) | 29 (3) | 0.422 (0.057-3.135) | .385 |
| No | 88 (99) | 1077 (97) | | |
| Hospitalization in past 12 months | | | | |
| Yes | 18 (20) | 203 (18) | 1.128 (0.658-1.934) | .662 |
| No | 71 (80) | 903 (82) | | |
| Household contact with hospital staff** | | | | |
| Yes | 6 (7) | 21 (2) | 3.735 (1.467-9.507) | .003 |
| No | 83 (93) | 1085 (98) | | |
| Household contact with an individual with an identified risk factor*** | | | | |
| Yes | 8 (9) | 8 (1) | 13.556 (4.959-37.056) | <.001 |
| No | 81 (91) | 1098 (99) | | |

**P* value by Mantel-Haenszel test.

**Lived with a health care worker within 1 year.

***Lived with a person with chronic disease (diabetes mellitus, asthma, chronic obstructive pulmonary disease, dialysis, vascular disease, organ transplant) or a person who was admitted to a hospital within 1 year.

Antimicrobial susceptibility testing of the 89 colonizing MRSA isolates showed uniform susceptibility to vancomycin, teicoplanin, and fusidic acid. Erythromycin resistance was present among 81 (91%) of 89 isolates and the results of PCR for macrolide resistance gene detection demonstrated all 81 isolates had an *erm* determinant. Overall, *ermB* was found in 93.8% (76/81) of these isolates and *ermA* in 6.2% (5/81). None had *ermC*, *msrA*, or more than one *erm* determinant. In addition, clindamycin resistance was present among 77 of 89 isolates (87% total, 85% constitutive and 2% inducible). Inducible clindamycin resistance (positive D test) was detected in two (50%) of the four clindamycin-susceptible but erythromycin-resistant isolates.

**Molecular Characterization of MRSA Community Colonizing Isolates**

All 89 community colonizing MRSA isolates had the *mecA* gene. SCC*mec* type IV (77/89; 86.5%) was the most common type among the community colonizing isolates; one isolate each had SCC*mec* type II, type III, or type IIIA. The remaining nine (10.1%) isolates carried SCC*mec* type $V_T$. Additionally, PCR amplification of the PVL toxin genes was detected in only 15 (16.9%) of the 89 colonizing MRSA isolates. Most of the PVL-positive MRSA colonizing isolates carried SCC*mec* $V_T$ (9/15; 60%), whereas a high prevalence of SCC*mec* IV was found among PVL-negative MRSA colonizing isolates (71/74; 95.9%). With regard to the antibiotic susceptibility profiles, both PVL-positive and PVL-negative MRSA colonizing isolates had consistent antibiograms.

All MRSA isolates including four predominant nosocomial MRSA strains from our institution matched by area and study period were further analyzed for epidemiologic relatedness using PFGE. A wide diversity of pulsotypes was found among the 93 MRSA isolates subjected to PFGE typing, as shown in Fig. 1. Four clusters that included 61 (65.6%) isolates were distinguished at the 70% similarity level, and their banding patterns demonstrated they differed from one another by fewer than 4 bands. Except for one isolate from a kindergarten child (corresponding to isolate C82) in MRSA cluster IV, all the remaining 88 (98.9%) colonizing MRSA isolates tested differed from those of the four predominant nosocomial MRSA isolates from our institution.

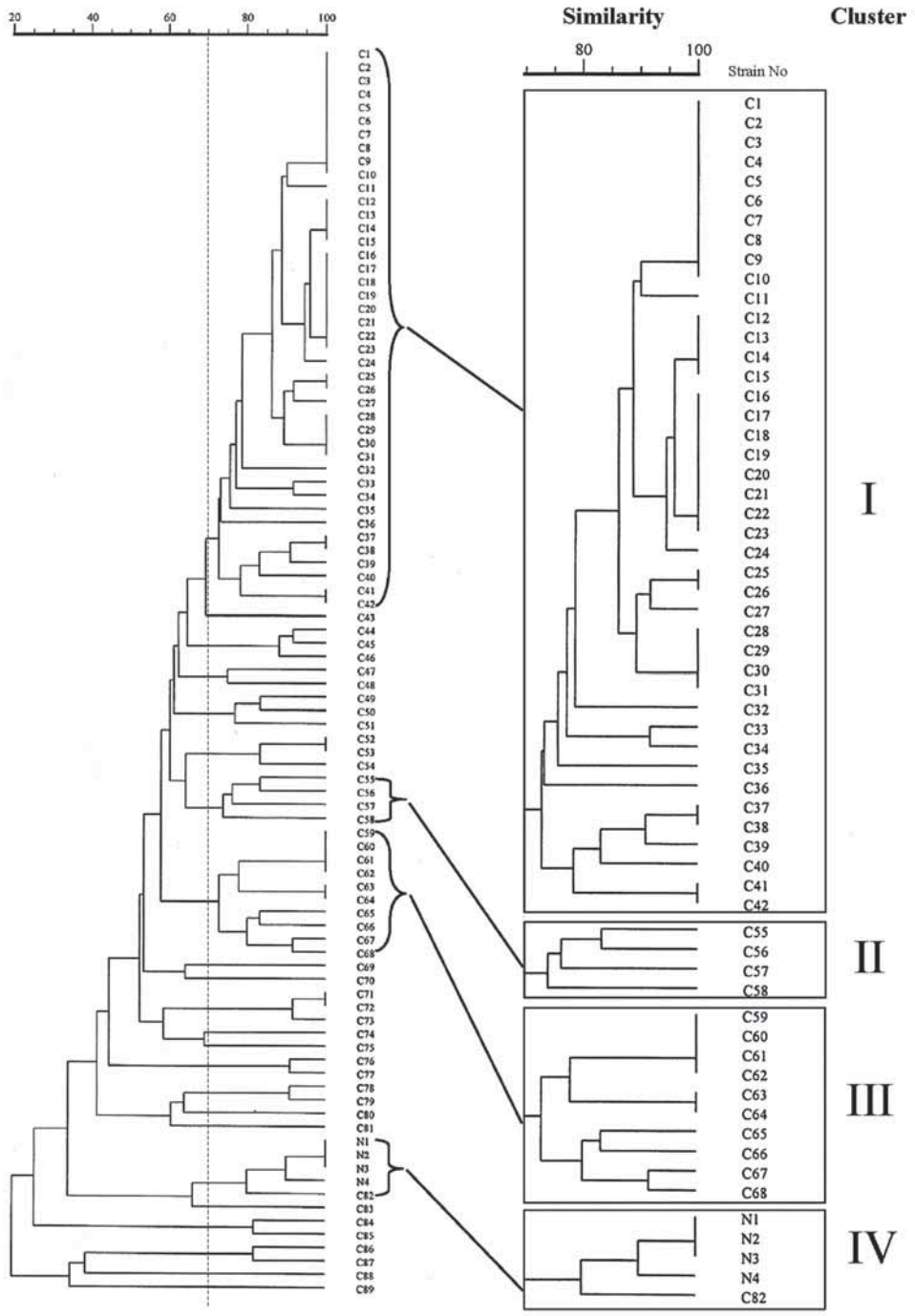


Fig. 1 Dendrogram of pulsed-field gel electrophoresis banding patterns of 93 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates including 89 community colonizing MRSA isolates and four predominant nosocomial MRSA isolates from our institution. Banding patterns were digitalized and analyzed using Molecular Analyst Fingerprinting, Fingerprinting Plus, and Fingerprinting DST software (Bio-Rad Laboratories, Richmond, Calif). The grouping method was performed to deduce a dendrogram from the matrix by the unweighted pair group method with arithmetic averages clustering technique after calculation of similarities using the Pearson correlation coefficient between each pair of organisms. The scale indicates the level of pattern similarity. Similarities greater than 70% represent the clonal spread of strains. The first letter of each isolate designation indicates the type of the isolate. Abbreviations: C, colonizing MRSA isolate; N, nosocomial MRSA isolate.

## DISCUSSION

The MRSA prevalence in our community pediatric population in northern Taiwan was 7.4%, a relatively high rate compared to those (0.2 to 9.2%) reported in previous surveys of healthy children and outpatients[1,7,18-20]. However, without additional data points, it is impossible to determine whether this finding represents the trend in the prevalence of colonization or simply short-term modulation due to sampling variability or fluctuations in unmeasured variables, such as temperature or humidity. Further, PFGE revealed three clusters of MRSA isolates were mainly from colonized children in the community and no predominant nosocomial MRSA strain from our institution was in these clusters, indicating the occurrence of transmission of MRSA was mainly outside the health care setting. Therefore, our study clearly showed MRSA isolates are now endemic in the community, and a reservoir of asymptomatic nasal colonization exists among healthy children in northern Taiwan.

In the present study, we found 87% of MRSA nasal isolates expressed either constitutive or inducible resistance to clindamycin; moreover, half of the clindamycin-susceptible but erythromycin-resistant colonizing MRSA isolates actually possessed inducible resistance. From the management standpoint, clindamycin is currently unsuitable for treating children with putative CA-MRSA infections in Taiwan. Further, *ermB* was more widespread than *ermA* among our colonizing MRSA isolates, a finding that differs from the reports of Almer et al.[12] and other investigators[21,22] who concluded *ermA* is the dominant *erm* gene among their MRSA isolates, and the prevalence of *ermB* in staphylococci was less than 2%.

In the multivariate analysis, children living with an individual who had an identified risk factor and those who were treated with antimicrobial agents in the prior year were more likely to have MRSA recovered. The finding that recent household contact with a high-risk individual was one of the major factors associated with childhood MRSA colonization in the community concurs with the results of the meta-analysis conducted by Salgado et al.[23] but is contrary to other reports[1,24] not showing any predictable risk factor associated with MRSA carriage. In addition, the association between recent antibiotic use and MRSA nasal colonization may be explained, in part, by the previously reported excessive use of antibiotics in Taiwan[25,26], pointing to the presence of strong selective pressure from antimicrobial use in the community.

Highly virulent CA-MRSA strains carrying PVL genes exist and PVL genes seem to be a stable genetic marker for CA-MRSA[27], which explain the frequency of primary skin infections and, occasionally, necrotizing pneumonia associated with these strains[11]. Nonetheless, until recently, few studies documented the prevalence of the PVL locus among MRSA colonizing asymptomatic individuals in non-outbreak settings. The results of our study show only 16.9% of nasal carriage MRSA isolates in the healthy pediatric population carried PVL genes, which is within the range (0%-58%) from colonization isolates previously reported elsewhere[7,19,28-32].

In conclusion, we found MRSA colonization is already prevalent among healthy children in northern Taiwan. The emergence of the multiply resistant MRSA as a common cause of community-associated staphylococcal infections[33,34] and nares colonization has important implications for the practical treatment of MRSA infections, as well as for the judicious use of antimicrobial agents to reduce antibiotic selective pressure. Comprehensive large-scale prospective surveillance is warranted to further clarify the molecular epidemiology of community MRSA colonization, to improve understanding of the pathogenesis of CA-MRSA infection, and finally, to guide the development of more effective prevention strategies.

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