

The association between *Staphylococcus aureus* nasal colonization and symptomatic infection in children in Korea where ST72 is the major genotype

A prospective observational study

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Abstract

This study was performed to investigate the concordance in terms of molecular characteristics and antimicrobial susceptibility between colonizing and clinical *Staphylococcus aureus* isolates obtained from children in Korea, where ST72 is the major genotype.

This was a prospective observational descriptive study of culture-confirmed *S aureus* infections obtained from children ≤ 18 years old admitted to Asan Medical Center Children's Hospital in Seoul, Korea, from March 2014 to April 2015. Molecular studies including multilocus sequence typing (MLST), SCCmec typing, polymerase chain reaction amplification of the Pantone-Valentine leukocidin (PVL) genes, and antibiotic susceptibility tests were performed on *S aureus* isolates obtained from nares and clinical specimens.

During the study period, 126 clinically significant *S aureus* infections were identified. Nasal swab cultures were made from 113 of the 126 children, and 46.0% (52/113) showed *S aureus* colonization. The overall concordance between colonizing and clinical isolates by methicillin susceptibility was 94.2% (49/52); all 3 discordant cases were HA-MSSA cases with nasal MRSA. Among the 37 pairs of colonizing and clinical *S aureus* isolates included in the genotyping analysis, ST72-SCCmec type IV was the most prevalent clone and the PVL genes were positive in 2 patients. Among the 31 pairs of healthcare-associated cases, concordance rates by methicillin susceptibility and sequence type (ST) were 90.3% (28/31) and 84% (26/31), respectively. For the 6 pairs of community-associated (CA) *S aureus* including 3 CA-MRSA cases, 100% concordance was observed by methicillin susceptibility and ST.

The concordance between isolates obtained from children who required medical services was relatively high in Korean children where ST72-SCCmec type IV is the predominant clone as the colonizer and the pathogen. It is suggested that decolonization and continuous care to prevent transmission could be effective in managing and preventing both HA- and CA-SA infections in our setting.

Abbreviations: CA = community-associated, HA = healthcare-associated, MLST = multilocus sequence typing, MR = methicillin-resistant, MS = methicillin-susceptible, PVL = Pantone-Valentine leukocidin, SA = *S aureus*, SCCmec = staphylococcal cassette chromosome *mec*, SSTIs = skin and soft tissue infections, ST = sequence type.

Keywords: children, colonization, concordance, Korea, MRSA, *S aureus*, ST72

1. Introduction

Staphylococcus aureus is a leading cause of skin and soft tissue infections (SSTIs) throughout the world and can lead to serious invasive infections, such as bone and joint infection, pneumonia,

bacteremia, and infective endocarditis, which are associated with significant morbidity and mortality.^[1,2] *S aureus* normally colonizes the anterior nares^[3]; 38.1% of healthy Korean preschool children attending a day care center were found to be colonized by *S aureus* strains, a quarter of which were methicillin-resistant (MRSA).^[4] Recently, an increasing rate of MRSA colonization has been noted throughout the world, including the United States.^[5]

It is well known that endogenous *S aureus* colonization is closely related to nosocomial infection^[6] and is associated with healthcare-associated bacteremia, increased risk of wound infection after surgery, and mortality among long-term healthcare facility patients.^[6,7] However, it is relatively unclear whether any community-associated *S aureus* infections are of endogenous origin. Only 59% of *S aureus* clinical and colonizing isolates obtained from children were identical according to methicillin susceptibility tests and pulsed field gel electrophoresis (PFGE).^[1] Even in colonized individuals, more than one-third of community-associated *S aureus* (CA-SA) infections were caused by strains different from the colonizing form.^[8] These findings suggest that CA-SA infections in children are not always of endogenous origin. However, most previous studies measuring the concordance between colonizing and clinical isolates were based on SSTIs caused by the USA300 (sequence type [ST]8) strain, which

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is the major genotype in community settings in the United States,^[1,9] and there have been few studies of isolates from other geographic regions such as Asia, where the prevalent *S aureus* genotype is different—for examples, ST59 in China and Taiwan; ST8 and 30 in Japan^[10]; and ST72 in Korea.^[10–12] The relationship between colonizing and clinical isolates obtained from children in regions where ST72 is the major genotype has not been much studied. In addition, few studies have focused on not only SSTIs but also diverse clinical entities such as bacteremia and pneumonia in children.

The purpose of this study was to examine the concordance between the genotypes of colonizing and clinical *S aureus* isolates in children in Korea, where ST72 is the predominant clone in healthcare as well as community settings. In addition, we aimed to evaluate the nasal colonization rate in clinically significant *S aureus* infections in children.

2. Methods

2.1. Study populations

This was a prospective observational descriptive study. We prospectively enrolled children ≤ 18 years of age with culture-confirmed *S aureus* infections who were hospitalized or visited the pediatric emergency department or outpatient clinic at Asan Medical Center Children's Hospital, Seoul, Korea, over 13 consecutive months from March 2014 to April 2015. We used the electronic databases of the bacterial surveillance system at our institute to collect *S aureus* isolates obtained from children with clinical infections and exclude those obtained for surveillance from specimens such as urine, eye discharges, and skin swabs, which were considered to be without clinical significance. The isolates with clinical significance were kept at -70°C .

Nasal swab cultures for screening both methicillin-susceptible (MS) and MR *S aureus* colonization were performed as soon as possible during each clinical episode in cases of CA-SA infections including SSTIs, suppurative lymphadenitis, abscesses, and bone and joint infections that were mainly caused by *S aureus*. Surveillance cultures of nasal swabs for detecting MRSA carriage were made at the outset of periods of stay in pediatric units or neonatal intensive care units (ICU), and contact precautions were applied to the patients colonized by MRSA as a standard of care in our institute; in cases of healthcare-associated *S aureus* infections such as ventilator-associated pneumonia, hospital-acquired pneumonia, and catheter-related infections, nasal swab cultures were made to detect only MRSA colonizers.

The colonizing *S aureus* isolates were also kept at -70°C . Only the first *S aureus* isolates detected during a single clinical episode were included in the analysis, and duplicates from the same patient were excluded. Demographic data and clinical information including primary site of infection, hospitalization, and underlying medical condition were abstracted from the electronic medical records. This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2014-0175).

2.2. Definitions

Healthcare-associated *S aureus* (HA-SA) infection was defined as an *S aureus* infection with risk factors for healthcare-associated infection (e.g., hospitalized within the previous year, recent surgery, residence in a long-term care facility, dialysis patient, indwelling catheter at time of admission).^[13,14] A CA-SA infection was defined as a case in which the isolate was obtained

from a patient with no risk factors for healthcare-associated infections including prior hospitalization in the 12 months preceding culture.

2.3. Strain identification and antimicrobial susceptibility testing

S aureus isolates were identified and their antimicrobial susceptibilities established using a MicroScan WalkAway96 with a MicroScan-Pos BP Combo Panel Type 28 (Siemens, West Sacramento, CA). Eight antibiotics were tested: gentamycin, ciprofloxacin, trimethoprim/sulfamethoxazole, rifampin, tetracyclin, clindamycin, linezolid, and vancomycin. Intermediate resistance and full resistance were both considered resistance. The in vitro macrolide-lincosamide-streptogramin B (MLS_B)-inducible phenotype was detected by the D-zone test (double-disk diffusion test).

Nasal swab specimens were obtained from both anterior nares with Amies agar gel double plastic swabs (Copan Diagnostics, Brescia, Italy) after soaking the rayon bulbs of the swabs in sterile normal saline, and inoculated onto MRSASelect (BioRad, Redmond, WA) agar the same day. After incubation at 35°C for 18–24 hours, small pink colonies were selected for gram staining. For screening MSSA colonization, clustered gram-positive cocci were tested with a MicroScan PBC 28 for identification and susceptibility testing.

2.4. Molecular analysis of colonizing and clinical isolates

For the cases with concomitant clinical and colonizing *S aureus* isolates obtained from March to December 2014, molecular analysis including multilocus sequence typing (MLST), SCCmec typing, and identification of the Pantone-Valentine leukocidin (PVL) genes by PCR was conducted as described by Lee et al.^[12] *Staphylococcus aureus* genotypes were designated by their ST and their SCCmec type, as proposed by Enright et al.^[15]

3. Results

3.1. Patient characteristics

During the study period, a total of 548 cases of *S aureus* infection were reported in children ≤ 18 years old (Fig. 1). After excluding isolates obtained from eye discharge, urine, and simple surveillance cultures, 126 patients with clinically significant *S aureus* infections were enrolled. Nasal swab culture was performed on 113 of the 126 enrolled children, and 46.0% (52/113) were confirmed as having *S aureus* colonization of the nares (MRSA colonization, $n=46$; and MSSA colonization, $n=6$). Of 113 *S aureus* infections, 96 (85.0%) and 17 (15.0%) were HA-SA and CA-SA infections, of which 45.8% (44/96) and 47.1% (8/17) cases occurred in conjunction with *S aureus* colonization, respectively.

The demographic characteristics of the total of 52 *S aureus* cases with concurrent nasal colonization are shown in Table 1. Median age was 26 months (range, 1–216 months), and 44 cases were HA-SA infections. The most common underlying medical condition of the patients with HA-SA infections was congenital heart disease (11/44, 25%), followed by prematurity (7/44, 15.9%), chronic lung diseases (6/44, 13.6%), and hematologic diseases (4/44, 9.1%). The most common source of the HA-SA isolates was respiratory specimens (25/44, 56.8%) including endotracheal sputum and bronchial aspirates obtained

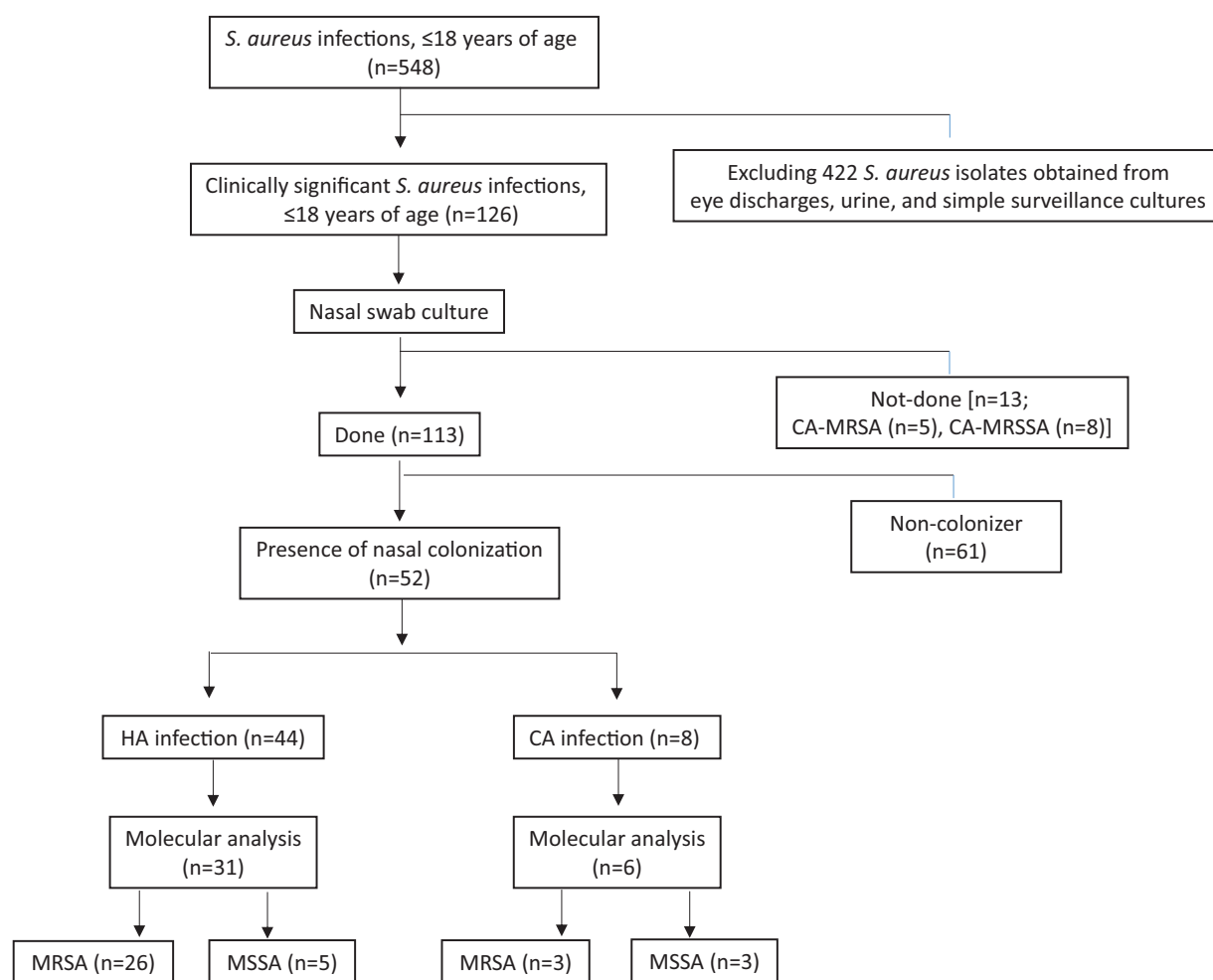


Figure 1. Flow-chart of the study. CA=community-associated, HA=healthcare-associated, MR=methicillin-resistant, MS=methicillin-susceptible, SA=*S. aureus*.

from children with pneumonia, followed by blood (12/44, 27.3%). The 8 CA-SA cases presented with diagnoses of SSTI (n=6) and deep-seated abscess (n=2). There were no fatal cases related to *S. aureus* infection during the study period.

3.2. Molecular characterization of the *S. aureus* isolates

From among the 52 *S. aureus* cases with concurrent nasal colonization, 37 pairs of clinical and colonizing *S. aureus* isolates could be submitted to molecular analysis of MLST, and SCCmec typing (Fig. 1). STs associated with the indicated clinical diseases were shown in Table 1.

Among the total of 74 isolates, the most common ST was ST72 (n=36), followed by ST5 (n=16) and ST1 (n=13) (Table 2). Among the total of 58 clinical and colonizing MRSA isolates obtained from the 3 cases of CA-MRSA and the 26 of HA-MRSA, the most common genotype was ST72-SCCmec type IV (n=30), followed by ST5-SCCmec type II (n=13), and ST1-SCCmec type IV (n=8). The STs of the 8 clinical and 5 colonizing MSSA isolates were: ST1 (n=5), ST72 (n=4), ST5 (n=2), and ST15 (n=2). The 3 discordant pairs of HA-MSSA infections with nasal MRSA were as follows: 1 case of ST1-MSSA bacteremia with nasal ST72-SCCmec type IV-MRSA, and 2 cases of respiratory infections caused by either ST5-MSSA with nasal

ST5-SCCmec type II-MRSA or ST5-MSSA with nasal ST72-SCCmec type IV, respectively.

The PVL genes were detected in 2 CA-MRSA infections involving an ST714-SCCmec type IV and an ST30-SCCmec type IV strain, respectively; these isolates were both obtained from patients with SSTIs.

3.3. Antibiotic susceptibility profiles

The antimicrobial susceptibility patterns of the 37 clinical isolates included in the molecular analysis are presented in Table 3. All the 29 MRSA isolates were fully susceptible to vancomycin and trimethoprim/sulfamethoxazole. The double-disk diffusion test was positive in 43.8% (7/16) of the erythromycin-resistant and clindamycin-susceptible MRSA isolates; all 7 of these isolates had MLS_B-inducible phenotypes. Considering both inducible and constitutive phenotypes, 48.3% of the MRSA isolates were clindamycin-resistant.

3.4. Concordance between colonizing and clinical isolates by genotype and methicillin susceptibility

The overall concordance rate by methicillin susceptibility was 94.2% (49/52); all 3 discordant cases were HA-MSSA cases with

Table 1**Demographic and clinical characteristics of 52 *S aureus* infections with concurrent nasal colonization.**

Characteristic	Community-associated <i>S aureus</i> (n=8)	Healthcare-associated <i>S aureus</i> (n=44)
Sex, M/F	3/5	24/20
Median age, months, range	20 (1–111)	27 (1–216)
Presence of underlying diseases *	0 (0)	43 (97.7%)
Clinical diagnosis		
Bacteremia, n=12	0	12; ST1 (n=2), ST5 (n=3), ST72 (n=7)
Lower respiratory tract infections, † n=25	0	25; ST1 (n=3), ST5 (n=4), ST72 (n=5), ST1863 (n=1)
Skin and soft tissue infection, n=12	6; ST1 (n=1), ST15 (n=1), ST30 (n=1), ST714 (n=1)	6; ST1 (n=1), ST5 (n=1), ST72 (n=2), ST2779 (n=1)
Deep-seated abscess, n=2‡	2; ST72 (n=2)	0
CAPD peritonitis, n=1	0	1; ST72 (n=1)
No. of MRSA, %§	4 (50%)	42 (95.5%)
SCCmec type II	0% (0/3)	28.6% (8/26)
SCCmec type IV	100% (3/3)	64.3% (18/26)
PVL-positive§	2	0
Sequence type, ST§		
ST72, n=17	2	15
ST5, n=8	0	8
ST1, n=7	1	6
Others, n=5	3	2

CAPD=continuous ambulatory peritoneal dialysis, PVL=Panton–Valentine Leucocidin.

* Underlying medical conditions included congenital heart disease (n=11), prematurity (n=8), chronic lung diseases (n=6), hemato-oncologic disease (n=4), chronic renal diseases (n=3), metabolic diseases (n=3), neurologic diseases (n=2), liver disease (n=2), congenital diaphragmatic hernia (n=1), and Hirschsprung disease (n=1).

† Lower respiratory tract infections were diagnosed based on the presence of any respiratory symptoms and infiltration on chest radiography with concomitant isolation of *S aureus* from lower respiratory specimens including endotracheal aspirates (n=19), induced sputum (n=5), and bronchial aspirates (n=1).

‡ Including osteomyelitis (n=1) and liver abscess (n=1).

§ From the 52 *S aureus* cases with concurrent nasal colonization, 37 pairs of clinical and colonized *S aureus* isolates were included for molecular analysis including MLST, SCCmec typing, and PVL PCR. STs associated with the indicated clinical diseases were shown.

|| Other STs included ST1863, ST2779, ST15, ST30, and ST714.

nasal MRSA (Table 2). Of the 31 pairs of HA-SA cases and 6 pairs of CA-SA infections, the concordance rates by methicillin susceptibility were 90.3% (28/31) and 100% (6/6), respectively.

Of the 29 pairs of colonizing and clinical MRSA isolates, 27 (93.1%) were concordant by both ST and SCCmec type; the concordance rates in HA-MRSA and CA-MRSA cases were

92.3% (24/26) and 100% (3/3), respectively. Of the 8 MSSA cases, the concordance rates by ST in HA-MSSA and CA-MSSA cases were 60% (3/5) and 100% (3/3), respectively.

4. Discussion

In this prospective study, we found a high concordance rate between colonizing and clinical *S aureus* isolates from both healthcare and community settings in Korea where ST72 is the predominant clone: the infecting strain in 94.2% and 86.5% of the patients was concordant with the colonizing strain by methicillin susceptibility and genotype, respectively. Active surveillance showed that at least 46.5% of the pediatric patients with clinically significant *S aureus* infections had nasal *S aureus* colonization.

Table 2**Concordance between colonizing and clinical isolates by genotype* and methicillin-susceptibility†.**

Clinical infection	Clinical isolate	Colonizing isolate	No. of cases
HA-MRSA, n=26	ST72-SCCmec type IV	ST72-SCCmec type IV	14
	ST5-SCCmec type II	ST5-SCCmec type II	6
	ST1-SCCmec type IV	ST1-SCCmec type IV	4
	ST5-SCCmec type II	ST1863-SCCmec type II	1
	ST2779-SCCmec type II	ST2779-SCCmec type IV	1
HA-MSSA, n=5	ST1	ST1	1
	ST72	ST72	1
	ST1	ST72-SCCmec type IV	1
	ST5	ST5-SCCmec type II	1
	ST5	ST72-SCCmec type IV	1
CA-MRSA, n=3	ST72-SCCmec type IV	ST72-SCCmec type IV	1
	ST714-SCCmec type IV	ST714-SCCmec type IV	1
	ST30-SCCmec type IV	ST30-SCCmec type IV	1
CA-MSSA, n=3	ST1	ST1	1
	ST72	ST72	1
	ST15	ST15	1

CA-SA=community-associated *S aureus*, HA-SA=healthcare-associated *S aureus*.

* Of the 37 pairs of colonizing and clinical *S aureus* isolates, 32 (86.5%) were concordant by MLST and SCCmec typing; the concordance rates in HA-MRSA and HA-MSSA cases were 92.3% (24/26) and 40.0% (2/5), respectively.

† The overall concordance rate by methicillin susceptibility was 94.2% (49/52); all 3 discordant cases were HA-MSSA cases with nasal MRSA whose genotypes were ST72-SCCmec type IV (n=2) and ST5-SCCmec type II (n=1).

Table 3**Antibiotic resistance of clinical *S aureus* isolates.**

Antibiotic	MRSA (n=29)	MSSA (n=8)
Clindamycin*	48.3% (14/29)	12.5% (1/8)
Erythromycin	48.3% (14/29)	12.5% (1/8)
Amoxicillin/clavulanate	100% (29/29)	25% (2/8)
Azithromycin	40% (10/25)	14.3% (1/7)
Ciprofloxacin	34.5% (10/29)	25% (2/8)
Levofloxacin	34.5% (10/29)	12.5% (1/8)
Gentamycin	48.3% (14/29)	50% (4/8)
Mupirocin	13.8% (4/29)	37.5% (3/8)
Rifampin	6.9% (2/29)	0% (0/8)
Trimethoprim/sulfamethoxazole	0% (0/29)	0% (0/8)
Daptomycin	0% (0/20)	0% (0/5)
Linezolid	0% (0/29)	0% (0/8)
Vancomycin	0% (0/29)	0% (0/8)

* MLS_B-inducible resistance cases are included (n=7).

Colonization pressure is a predictive factor for nosocomial transmission of MRSA,^[16,17] and MRSA colonization is a risk factor for subsequent MRSA infection in children admitted to a pediatric intensive care unit.^[18] In a neonatal care unit where MRSA infection was endemic, colonized infants had a significantly higher rate of MRSA infection than those without colonization, and the genotypes of the clinical and colonizing isolates were indistinguishable in >90% of episodes.^[19] However, among children in a community setting, there was no relationship between baseline *S aureus* household colonization pressure and subsequent SSTI.^[20] The striking difference in the concordance rates of HA and CA cases might be explained by differences in their transmission dynamics. In a hospital setting, most individual contacts are limited to healthcare staff, whereas in the community, routes of transmission are more diverse because the colonizing strain can come not only from within the household but also from external sources.^[20,21]

Compared to the reports from the United States, where the USA 300 strain is the major genotype in SSTI outbreaks, we found relatively diverse genotypes, including ST72, among our CA-SA isolates, but no ST8 strains. Because routine screening is not performed in cases of CA-SA infection in our institute, all the cases that failed to undergo nasal screening were CA infections, irrespective of methicillin susceptibility. Even though only a small number of CA-SA cases could be included in our molecular analysis, the infecting and colonizing isolates in all 6 cases were indistinguishable by ST, SCCmec type, and methicillin susceptibility. Among the 26 HA-MRSA cases, more than 80% were caused by the 2 most common strains, ST72 (54%) and ST5 (27%); colonizing and infecting strains were indistinguishable in 24 of these cases. We suggest that decolonization and taking continuous precautions might be effective in managing and preventing both HA- and CA-SA infections in our setting.

Clinical outcomes and bacterial virulence factors may differ depending on genotype; rapid spread of the USA 300 strain has been reported, which is highly contagious and is now the most common cause of global epidemics.^[22,23] Freitas et al^[23] reported that individuals colonized with USA 300 were more likely to have SSTIs than those colonized with non-USA 300 strains ($P=.02$); however, no significant difference between USA 300 and non-USA 300 strains was observed in other types of clinical infection. The ST72 strain was considered as a community-associated strain, found frequently in Korea; however, it is now the most common genotype in HA-SA infections,^[10,25] replacing ST239-SCCmec type III and ST5-SCCmec type II.^[26,27] Although Uhlemann et al report that the ST72 strain is the most prevalent in the Dominican Republic, its *spa* type seems to be different from the predominant Korean *spa* type.^[28] ST72-SCCmec type IV is associated with lower mortality than ST5-SCCmec type II in adult patients with MRSA bacteremia.^[29] Since the majority of previous studies were conducted on patients with SSTIs in a region where the USA 300 clone was the major genotype,^[21,24] it would be inappropriate to extrapolate the relationship between colonizing and clinical isolates observed in those studies to other clinical manifestations and bacterial genotypes.

PVL is associated with CA infections causing necrotic lesions involving the skin or mucosa, such as pyogenic skin lesions or necrotizing pneumonia.^[30,31] Recently, 10% of pediatric patients with CA-MRSA infections were found to be positive for the PVL gene in Korea.^[11] We found 2 examples of CA infections due to PVL gene positive strains; 1 strain was ST714-SCCmec type IV, a genotype not previously reported in Korea.^[32]

There are several limitations to our study. First, it was based on *S aureus* infections observed in a single tertiary university hospital in Seoul, Korea, and the results cannot be extrapolated to the general pediatric population. Because some patients were already on antibiotic treatment when nasal swabs were obtained, the colonization rate might be underestimated. In addition, significant conclusions regarding the concordance rate among pediatric CA-SA infections and control measures cannot be drawn owing to the paucity of CA-SA cases included in the molecular analysis. Further studies focusing on CA-SA infections would be helpful for understanding the relationship between colonization and clinical infection in non-outbreak settings. Nevertheless, this study could suggest the clinical significance of colonizing *S aureus* isolates in the circumstances where most *S aureus* strains were ST72 clones without PVL genes.

In conclusion, most colonizing and clinical *S aureus* isolates in pediatric *S aureus* infections in Korea where ST72 is the major genotype as an endemic strain in both healthcare and community settings were indistinguishable from each other. Precautions to minimize the transmission, and decolonization, might be useful to reduce *S aureus* infections in Korean children, and their effects should be studied.

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