Molecular Epidemiology of \textit{Staphylococcus aureus} in Skin and Soft Tissue Infections and Bone and Joint Infections in Korean Children

Seul Gi Park, Hyun Seung Lee, Ji Young Park, and Hyunju Lee

\textsuperscript{1}Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea
\textsuperscript{2}Department of Pediatrics, Seoul National University Hospital, Seoul, Korea

Abstract

\textbf{Background:} Community acquired-methicillin resistant \textit{Staphylococcus aureus} (MRSA) clones, including ST1, ST8, and ST30 are reported worldwide. However, data among Korean children are limited. Thus, we investigated the molecular characteristics of \textit{S. aureus} among children in Korea.

\textbf{Methods:} \textit{S. aureus} isolated from Korean children diagnosed with skin and soft tissue infection (SSTI) or bone and joint infection due to \textit{S. aureus} infection at Seoul National University Bundang Hospital, from August 2010 to November 2016, were analyzed for multilocus sequence type (ST) and SCC\textit{mec} typing. Polymerase chain reaction of Panton-Valentine leukocidin (PVL), \textit{qac} A/B, \textit{smr} and \textit{mup} A genes were also performed. Electronic medical records were reviewed for clinical data and antibiotic susceptibility results. Cases were classified into three groups: health care-associated community-onset (HACO) infections, hospital-onset (HO) infections, and community-acquired (CA) infections.

\textbf{Results:} A total of 67 strains from children with SSTI (41/67, 61.2\%) and bone and joint infection (26/67, 38.8\%) were included. Among all isolates, 29.9\% (20/67) were MRSA, and 70\% (14/20) were classified as CA, 20\% (4/20) as HACO and 10\% (2/20) as HO infections. MRSA rate according to disease was 34.1\% (14/41) for SSTI and 23.1\% (6/26) for bone and joint infection. MRSA strains included ST72-SCC\textit{mec} IV (14/20, 70.0\%), ST5-SCC\textit{mec} II (3/20, 15.0\%) and ST1-SCC\textit{mec} IV (2/20, 10.0\%). ST30 was the most common cause of SSTI and bone and joint infections and 96.6\% (28/29) were methicillin-susceptible \textit{Staphylococcus aureus} (MSSA).

\textbf{Conclusion:} Molecular epidemiology of \textit{S. aureus} in Korean children with SSTI and bone and joint infections showed that ST30 was predominant and mostly MSSA. Among MRSA, ST72-SCC\textit{mec} type IV was the most common strain.

\textbf{Keywords:} \textit{Staphylococcus aureus}; Molecular Typing; Antibiotic Resistance

\section*{Introduction}

\textit{Staphylococcus aureus} is a common pathogen of skin and soft tissue infection (SSTI) and bone and joint infection in children and also one of the most common organisms in hospital-acquired infections.\textsuperscript{1} History of recent hospitalization, recent surgery, older age, and
possession of central catheter are known as major risk factors associated with *S. aureus* bacteremia. Thus, empiric antibiotic therapy of these clinical syndromes should consider risk factors and should be based on local antibiotic susceptibility patterns.

In many countries, community acquired-methicillin resistant *S. aureus* (CA-MRSA) has shown an increase in prevalence since the early 2000s. A number of studies from the US suggested that this lead not only to an increase in antibiotic resistance, but also an actual increase in the incidence of SSTI and hospitalization due to methicillin resistant *S. aureus* (MRSA) in children. The increase in MRSA infection was reported to be attributed by the increase in the clone USA300, otherwise classified as multilocus sequence type (ST), ST8-SCC*mecc* IV which almost always has the Panton-Valentine leukocidin (PVL) toxin.

The increase in virulence and spread of CA-MRSA strains contributes largely to the presence of PVL, a cytotoxin which leads to formation of pores and causes neutrophil lysis and cell death. PVL strains have been reported to be more strongly associated with SSTIs than other forms of invasive diseases, such as pneumonia, musculoskeletal diseases, and bacteremia.

Major CA-MRSA clones have been reported worldwide including ST1 in Asia, Europe, US, ST8 in Europe and US and ST30 in Australia, Europe and South America. PVL-positive ST30-SCC*mecc* IV has been reported as an important CA-MRSA in Singapore, Japan and Latin America. Although the first report of PVL-positive-ST30 MRSA infection was reported in 2013, reports of the distribution of strains in Korean children are limited. The molecular distribution of strains is important as they are closely related with changes in the antibiotic susceptibility and also changes in clinical epidemiology such as incidence of SSTI.

Therefore, in this study, we investigated the antimicrobial resistance and molecular characteristics of *S. aureus* among children in Korea in two important clinical entities, SSTI and bone and joint infection which are common forms of *S. aureus* infections.

### METHODS

#### Study design

*S. aureus* previously isolated from children under 18 years of age diagnosed with SSTI and bone and joint infection at Seoul National University Bundang Hospital from August 2010 to November 2016 were included in the analysis. Demographic information of the patients and details of their underlying diseases and clinical diagnoses were collected from medical records. Electronic medical records were reviewed for clinical data and antibiotic susceptibility results. Cases were classified as health care-associated community-onset (HACO) infections when culture was obtained ≤ 3 days after admission and/or prior year hospitalization, surgery, or central vascular catheter presence ≤ 2 days before culture. Hospital-onset (HO) infections were designated when culture was obtained > 3 days after admission, and cases were defined as community-acquired (CA) infections if no other criteria were met.

#### Bacterial isolation, identification and antimicrobial susceptibility tests

Isolates from children with SSTI and bone and joint infection due to *S. aureus* were collected during the study period and stored at −80°C until analysis. Isolates related to outbreaks were excluded. Isolation of *S. aureus* and antimicrobial susceptibility tests were performed in the clinical microbiology laboratory using an automatic system (MicroScan Walk-Away;
Siemens Healthcare Diagnostics, Deerfield, MA, USA). Antimicrobial susceptibility testing data of 9 antimicrobial agents were obtained: oxacillin, penicillin, gentamicin, ciprofloxacin, clindamycin, erythromycin, rifampicin, trimethoprim/sulfamethoxazole, and vancomycin. Confirmatory tests for MRSA isolates were done by \textit{mecA} gene polymerase chain reaction (PCR) during SCC\textit{mec} typing.\textsuperscript{15} Resistance to antibiotics for each isolate was defined according to the Clinical and Laboratory Standards Institute guidelines published in 2019.

**Multiplex PCR assays for MRSA and molecular typing**
Multilocus sequence typing (MLST) was done by PCR amplification and sequencing of seven housekeeping genes (\textit{arcC}, \textit{aroE}, \textit{glpF}, \textit{gmk}, \textit{pta}, \textit{tpi}, \textit{yqiL}) using the primer pairs as described previously.\textsuperscript{16} Each sequence was submitted to the MLST database website (https://pubmlst.org/) for assignment of an allelic profile and ST. The molecular features of the MRSA strains were analyzed by SCC\textit{mec} typing and subtyping.\textsuperscript{15} PCR was done for the PVL gene,\textsuperscript{17} \textit{qac}/A/B,\textsuperscript{18} \textit{smr},\textsuperscript{19} and \textit{mupA}\textsuperscript{20} genes.

**Ethics statement**
Our study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-1903-529-303). Requirement for informed consent was waived due to the retrospective design of our study.

**RESULTS**

**Patient characteristics**
A total of 67 \textit{S. aureus} clones isolated from SSTI (41/67, 61.2\%) and bone and joint infection (26/67, 38.8\%) were included in the study. The median age of the subjects was 18 months (range 3 days–18 years). Male subjects accounted for 50.7\% (34/67). There were 15 children (22.4\%) with underlying diseases and recent use of hospital care, including prematurity (n = 3), post-operation infection (n = 5), neurologic disease (n = 2), malignancy (n = 2) and others (n = 3).

**Antibiotic resistant rate**
Among the 67 isolates from children with SSTI or bone and joint infection, 20 (29.9\%) were MRSA (Table 1). According to diagnosis, MRSA rate was 34.1\% (14/41) in SSTI and 23.1\% (6/26) in children with bone and joint infection. Among all isolates, 74.6\% (50/67) were CA, 16.4\% (11/67) were HACO infections and 9.0\% (6/67) were HO infections. Among MRSA isolates, 70\% (14/20) were CA, 20\% (4/20) were HACO and 10.0\% were HO infections (Table 1). Regardless of SSTI or bone and joint infection, 53.3\% (8/15) of the children with underlying disease were MRSA. After excluding these cases, among children < 1 month of age, 100.0\% (5/5) were MRSA whereas in children ≥ 1 months of age, 15.4\% (4/26) of SSTI, and 14.3\% (3/21) of bone and joint infection were MRSA.

| Clinical diagnosis | Overall (n = 67) | MRSA (n = 20) |
|--------------------|-----------------|---------------|
|                     | MSSA            | MRSA          | Total     | Community-associated | Healthcare-associated | Hospital-onset | Total |
| SSTI               | 27 (65.9)       | 14 (34.1)     | 41        | 9 (45.0)            | 4 (20.0)             | 1 (5.0)       | 14    |
| BJ                  | 20 (76.9)       | 6 (23.1)      | 26        | 5 (25.0)            | 0 (0.0)              | 1 (5.0)       | 6     |
| Total              | 47 (70.1)       | 20 (29.9)     | 67        | 14 (70.0)           | 4 (20.0)             | 2 (10.0)      | 2     |

Data are presented as number (%). SSTI = skin and soft tissue infection, BJ = bone and joint infection, MSSA = methicillin-susceptible \textit{Staphylococcus aureus}, MRSA = methicillin-resistant \textit{S. aureus}.

https://jkms.org

https://doi.org/10.3346/jkms.2019.34.e315
As for other antibiotics, the resistant rate among all strains was 9.0% (6/67) for clindamycin, 4.5% (3/67) for ciprofloxacin, 52.2% (35/67) for erythromycin and none of the isolates had resistance against trimethoprim/sulfamethoxazole (Table 2). Among the 20 MRSA strains, 15.0% (3/20) were resistant to clindamycin, and 20.0% (4/20) were clindamycin susceptible and also erythromycin resistant suggesting inducible clindamycin resistance.

### Molecular analysis

Among all isolates, ST30 was the most common clone among SSTI and bone and joint infection, followed by ST72 and ST5 (Table 3). Among methicillin-susceptible *Staphylococcus aureus* (MSSA) strains, ST30 (28/47, 59.6%) was the predominant clone and among all ST30, 96.6% (28/29) were MSSA. MRSA strains included ST72-SCCmec IV (14/20, 70.0%), ST5-SCCmec II (3/20, 15.0%), ST1-SCCmec IV (2/20, 10.0%) and ST30-SCCmec IV (1/20, 5.0%). PVL was detected in 3 strains which were all ST30 (3.8%, ST30-SCCmec IV N=1, MSSA ST30 n = 2). *qacA/B* was detected in 3 strains (MRSA = 3), *smr* in 3 strains (MSSA = 1, MRSA = 2) and *mupA* in 7 strains (MSSA = 2, MRSA = 5).

### Table 2. Antibiotic resistance rate according to clinical diagnosis

| Variables | SSTI (n = 41) | BJI (n = 26) | Total (n = 67) |
|-----------|---------------|--------------|----------------|
| Oxacillin  | 14 (34.1)     | 6 (23.1)     | 20 (29.0)      |
| Clindamycin| 4 (9.8)       | 2 (7.7)      | 6 (9.0)        |
| Ciprofloxacin | 2 (4.9)       | 1 (3.8)      | 3 (4.5)        |
| Erythromycin| 22 (53.7)     | 13 (50.0)    | 35 (52.2)      |
| Gentamicin  | 8 (19.5)      | 2 (7.7)      | 10 (14.9)      |
| Penicillin  | 39 (95.1)     | 26 (100.0)   | 65 (97.0)      |
| Rifampin    | 0 (0.0)       | 0 (0.0)      | 0 (0.0)        |
| TMP/SMX     | 0 (0.0)       | 0 (0.0)      | 0 (0.0)        |
| Vancomycin  | 0 (0.0)       | 0 (0.0)      | 0 (0.0)        |

Data are presented as number (%). Among MRSA strains (n = 20): clindamycin-R (n = 3, 15%), TMP/SMX-R (n = 0, 0%), clindamycin-R/erythromycin-R (n = 3, 15%), clindamycin-S/erythromycin-R (n = 4, 20%). SSTI = skin and soft tissue infection, BJI = bone and joint infection, TMP/SMX = trimethoprim/sulfamethoxazole, MRSA = methicillin resistant *Staphylococcus aureus*.

### Table 3. Multilocus sequence typing distribution according to diagnosis and methicillin susceptibility

| ST     | Clinical diagnosis | Methicillin susceptibility | Total |
|--------|--------------------|----------------------------|-------|
|        | SSTI               | BJI                        | MSSA  | MRSA |
| ST30   | 20 (48.8)          | 9 (34.6)                   | 28 (66.6) | 1 (3.4) | 29 |
| ST72   | 12 (29.3)          | 7 (26.9)                   | 5 (26.3) | 14 (73.7) | 19 |
| ST5    | 3 (7.3)            | 2 (7.7)                    | 2 (40.0) | 3 (60.0)   | 5 |
| ST188  | 1 (2.4)            | 2 (7.7)                    | 3 (100.0) | 0 (0.0)   | 3 |
| ST1    | 1 (2.4)            | 1 (3.8)                    | 0 (0.0)  | 2 (100.0)  | 2 |
| ST15   | 2 (4.9)            | 0 (0.0)                    | 2 (100.0) | 0 (0.0)   | 2 |
| ST6    | 0 (0.0)            | 2 (7.7)                    | 2 (100.0) | 0 (0.0)   | 2 |
| ST121  | 0 (0.0)            | 1 (3.8)                    | 1 (100.0) | 0 (0.0)   | 1 |
| ST1486 | 1 (2.4)            | 0 (0.0)                    | 1 (100.0) | 0 (0.0)   | 1 |
| ST291  | 1 (2.4)            | 0 (0.0)                    | 1 (100.0) | 0 (0.0)   | 1 |
| ST398  | 0 (0.0)            | 1 (3.8)                    | 1 (100.0) | 0 (0.0)   | 1 |
| ST7    | 0 (0.0)            | 1 (3.8)                    | 1 (100.0) | 0 (0.0)   | 1 |
| Total  | 41                 | 26                         | 47     | 20      | 67 |

Data are presented as number (%).

ST = sequence type, SSTI = skin and soft tissue infection, BJI = bone and joint infection, MSSA = methicillin-susceptible *Staphylococcus aureus*, MRSA = methicillin-resistant *S. aureus*. 

https://jkms.org

https://doi.org/10.3346/jkms.2019.34.e315

4/8
DISCUSSION

In this study, we analyzed the antibiotic resistant rate and molecular epidemiology of SSTI and bone and joint infection due to *S. aureus* among children in Korea. MRSA accounted for 34.1% in SSTI and 23.1% in bone and joint infection in children. When excluding children with underlying diseases, all cases in children under 1 month of age were MRSA and among children 1 month and older, 15.4% in SSTI and 14.3% in bone and joint infection were found to be MRSA. Although there is no definite cutoff as to what percentage of CA-MRSA should include coverage of MRSA for empirical antibiotics, neonates and children with underlying diseases may need coverage for MRSA in SSTI or bone and joint infection pending microbiologic culture results. Children over 1 month of age with no underlying diseases need judicious antibiotic choice based on the clinical manifestations, age, other risk factors and antibiotic resistant rates.

The MRSA rate of 23.1% in this study might suggest an increase in MRSA on bone and joint infection in children, compared to a previous report in Korea during 2003–2009, which showed that among cases due to *S. aureus*, 12.7% were MRSA. In this study, 70% (14/20) of the MRSA strains were CA which may suggest an increase of MRSA in the community. Increase in MRSA has been seen recently in many countries. In studies done at a large children’s hospital in the US, by 2004, more than 70% of all CA *S. aureus* (CA-S) infections, almost 60% of invasive CA-S infections were MRSA, of which > 90% were USA300. However, interestingly, recent reports showed that the CA-MRSA rate is decreasing again. Compared with 2007, invasive CA-MRSA infections decreased from 61.0% to 33.8% in 2014. Such changes in epidemiology emphasize the importance of continuous monitoring on antibiotic resistance rates in the community.

Clindamycin and trimethoprim/sulfamethoxazole are feasible options for treatment in SSTI or in limited cases of bone and joint infection. Clindamycin may be considered for empirical treatment in children with SSTI or bone and joint infection when clindamycin resistance rate is < 10%. Thus, considering the overall resistant rate for clindamycin in this study of 9.0%, clindamycin may be an option in empirical treatment in Korean children. The clindamycin resistance rate is higher compared with a previous study of children with MRSA nasal carriage, where clindamycin resistance was 2.5%. Direct comparison between the studies is difficult, however continuous monitoring on clindamycin resistance is warranted. Trimethoprim/sulfamethoxazole also showed to be comparable in a randomized controlled trial to clindamycin in uncomplicated SSTIs. None of the strains in this study was resistant to trimethoprim/sulfamethoxazole.

Among children with SSTI and bone and joint infection, ST30 was the most common type and the majority was MSSA (96.6%). PVL toxin was found in 3 strains (4.8%) which were all ST30 and among them, one strain was MRSA. Among MRSA isolates in this study, ST72-SCC*me*c type IV was most common. These results coincide with previous reports in Korea where ST72-SCC*me*c type IV strains have been reported as the most prevalent molecular type in CA-MRSA. A study among adults reported ST72-SCC*me*c type IV the most prevalent strain in 2005 and another study in children during 2006–2010 with MRSA infection showed ST72-SCC*me*c type IV to be most common. In that study, 10% (4/40) of the CA-MRSA strains were PVL positive, including three strains ST8-SCC*me*c type IV-related (2 ST and 1 isolate ST931, a SLV of ST8) and 1 ST30-SCC*me*c type IV. Overall, the molecular distribution of CA-MRSA in Korea does not seem to have changed greatly since 2005.
In this study, \textit{qac A/B}, \textit{smr} and \textit{mupA} genes were included in the analysis. \textit{qac} A/B and \textit{smr} genes encode multidrug efflux pumps which are associated with higher minimum bactericidal concentrations of chlorhexidine and various antiseptics used in hospital settings.\textsuperscript{19} \textit{mupA} gene is known to be related with mupirocin resistance,\textsuperscript{20} a widely used topical antimicrobial agent used for skin infections due to gram-positive pathogens, including \textit{S. aureus}. This majority of isolates were community-associated, and \textit{qac} A/B, \textit{smr} and \textit{mupA} genes were detected in a limited number of isolates in this study. A need for further wide-scale studies on healthcare-associated infections is essential.

Data in this report may not be applied to other regions in the country, as strains were obtained from subjects of a single tertiary hospital. Park et al.\textsuperscript{30} reported the molecular characteristics of CA-MRSA from children with skin infections in Busan, Korea. Among \textit{S. aureus} isolates, 40.6\% (28/69) were MRSA and among 28 CA-MRSA isolates, two major clones were identified as staphylocoagulase (SC) type Vb ST72 SCC\textit{mec}IV and SC type 1 ST89 SCC\textit{mec}II variant. The results of these studies will give us a glimpse into the antibiotic resistance and molecular epidemiology of \textit{S. aureus} isolated from SSTI and bone and joint infection in children in Korea.

Although many CA-MRSA strains have been reported to be disseminating worldwide, ST72 has not been widely reported. Interestingly, ST72 does not contain the PVL gene and Chen et al.\textsuperscript{31} reported that the whole genome analysis of PVL-negative ST72 showed no additional virulence determinants, such as other leukotoxins, to substitute the absence of PVL. This finding suggests that the virulence of such strain may be dependent on the gene regulatory adaptations that enhance the expression of core-encoded virulence determinants, rather than the acquisition of other virulence factors such as PVL.\textsuperscript{31}

Among CA-MRSA strains, ST30 has been reported to be a dominant strain in many countries.\textsuperscript{32-34} However, although ST30 was the most prevalent in this study, the majority of the strains were MSSA. Continuous monitoring on the molecular distribution and antimicrobial resistance patterns of this strain in Korea might be warranted. In conclusion, \textit{S. aureus} is a major pathogen in SSTI and bone and joint infection in children. In children ≥ 1 month with no underlying diseases, MRSA accounted for approximately 15\% in SSTI and bone and joint infection; whereas, MRSA was the dominant strain in children < 1 month of age. Among children with SSTI and bone and joint infection, ST30 was the predominant strain, and the majority was MSSA. Among MRSA isolates, ST72-SCC\textit{mec}IV type IV was the most common in SSTI and bone and joint infection. No strains of the USA300 trait were found in this study, and PVL toxin was found in limited cases. The antibiotic resistance rate and molecular epidemiology among staphylococcal infections in Korean children should be monitored continuously for guidance on appropriate empirical antibiotics.

**ACKNOWLEDGMENTS**

The authors would like to thank Eun Seong Lee for her excellent technical support.

**REFERENCES**

1. Kaplan SL. \textit{Staphylococcus aureus} infections in children: the implications of changing trends. \textit{Pediatrics} 2016;137(4):c20160101. [PUBMED] [CROSSREF]
2. Heo ST, Peck KR, Ryu SY, Kwon KT, Ko KS, Oh WS, et al. Analysis of methicillin resistance among *Staphylococcus aureus* blood isolates in an emergency department. *J Korean Med Sci* 2007;22(4):682-6. 

3. Moran GI, Krishnadasan A, Gorwitz RJ, Fusheime GE, McDougalLK, Carey RB, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006;355(7):666-74. 

4. Edelsberg J, Tanega C, Zervos M, Haque N, Moore C, Reyes K, et al. Trends in US hospital admissions for skin and soft tissue infections. *Emerg Infect Dis* 2009;15(9):1516-8. 

5. Klein EY, Mojica N, Jiang W, Cosgrove SE, Septimus E, Morgan DJ, et al. Trends in methicillin-resistant *Staphylococcus aureus* hospitalizations in the United States, 2010–2014. *Clin Infect Dis* 2017;65(11):1921-3. 

6. Gerber JS, Coffin SE, Smathers SA, Zaoutis TE. Trends in the incidence of methicillin-resistant *Staphylococcus aureus* infection in children’s hospitals in the United States. *Clin Infect Dis* 2009;49(1):65-71. 

7. Diekema DJ, Richter SS, Heilmann KP, Dohrn CL, Riahi F, Tendolkar S, et al. Continued emergence of USA300 methicillin-resistant *Staphylococcus aureus* in the United States: results from a nationwide surveillance study. *Infect Control Hosp Epidemiol* 2014;35(3):285-92. 

8. Lee AS, de Lencastre H, Garau J, Kluytmans J, Malhotra-Kumar S, Peschel A, et al. Methicillin-resistant *Staphylococcus aureus*. *Nat Rev Dis Primers* 2018;4:18033. 

9. Shallcross LJ, Fragaszy E, Johnson AM, Hayward AC. The role of the Panton-Valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;13(1):43-54. 

10. Deurenberg RH, Stobberingh EE. The evolution of *Staphylococcus aureus*. *Infect Genet Evol* 2008;8(6):747-63. 

11. Liu Y, Xu Z, Yang Z, Sun J, Ma L. Characterization of community-associated *Staphylococcus aureus* from skin and soft-tissue infections: a multicenter study in China. *Emerg Microbes Infect* 2016;5(12):e127. 

12. Chen CJ, Huang YC. New epidemiology of *Staphylococcus aureus* infection in Asia. *Clin Microbiol Infect* 2014;20(7):605-23. 

13. Ko J, Chung DR, Park SY, Baek JY, Kim SH, Kang CI, et al. First imported case of skin infection caused by PVL-positive ST30 community-associated methicillin-resistant *Staphylococcus aureus* clone in a returning Korean traveler from the Philippines. *J Korean Med Sci* 2013;28(7):1100-2. 

14. Johnson JK, Khoei T, Shurland S, Kreisel K, Stine OC, Roghmann MC. Skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus* USA300 clone. *Emerg Infect Dis* 2007;13(8):1195-200. 

15. Milheiriço C, Oliveira DC, de Lencastre H. Multiplex PCR strategy for subtyping the staphylococcal cassette chromosome mec type IV in methicillin-resistant *Staphylococcus aureus*: ‘SCCmec IV multiplex’. *J Antimicrob Chemother* 2007;60(1):42-8. 

16. Enright MC, Day NP, Davies CE, Peacock SI, Spratt BG. Multi locus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. *J Clin Microbiol* 2000;38(3):1008-15. 

17. Lina G, Piémont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V, et al. Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis* 1999;29(5):1128-32. 

18. Noguchi N, Suwa J, Narui K, Sasatsu M, Ito T, Hiramatsu K, et al. Susceptibilities to antiseptic agents and distribution of antiseptic-resistance genes gacA/B and smr of methicillin-resistant *Staphylococcus aureus* isolated in Asia during 1998 and 1999. *J Med Microbiol* 2005;54(Pt 6):557-65. 

19. McNeil JC, Kok EY, Vallejo JG, Campbell JR, Hulten KG, Mason EO, et al. Clinical and molecular features of decreased chlorhexidine susceptibility among nosocomial *Staphylococcus aureus* isolates at Texas children’s hospital. *Antimicrob Agents Chemother* 2015;60(2):1121-8.
20. Warren DK, Prager M, Munigala S, Wallace MA, Kennedy CR, Bommarito KM, et al. Prevalence of qacA/B genes and mupirocin resistance among methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in the setting of chlorhexidine bathing without mupirocin. *Infect Control Hosp Epidemiol* 2016;37(5):590-7.

21. Choi JH, Choe YJ, Hong KB, Lee J, Yoo WJ, Kim HS, et al. The etiology and clinical features of acute osteoarthritis in children; 2003–2009. *Korean J Pediatr Infect Dis* 2011;18(1):31-9.

22. Kaplan SL, Hulten KG, Gonzalez BE, Hammerman WA, Lamberth L, Versalovic J, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. *Clin Infect Dis* 2005;40(12):1785-91.

23. Mishaan AM, Mason EO Jr, Martinez-Aguilar G, Hammerman W, Propst JJ, Lupski JR, et al. Emergence of a predominant clone of community-acquired *Staphylococcus aureus* among children in Houston, Texas. *Pediatr Infect Dis J* 2005;24(3):201-6.

24. Hultén KG, Mason EO, Lamberth LB, Forbes AR, Revell PA, Kaplan SL. Analysis of invasive community-acquired methicillin-susceptible *Staphylococcus aureus* infections during a period of declining community acquired methicillin-resistant *Staphylococcus aureus* infections at a large children’s hospital. *Pediatr Infect Dis J* 2018;37(3):235-41.

25. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52(3):e18-55.

26. Lee J, Sung JY, Kim YM, Oh CE, Kim HB, Choi EH, et al. Molecular characterization of methicillin-resistant *Staphylococcus aureus* obtained from the anterior nares of healthy Korean children attending daycare centers. *Int J Infect Dis* 2011;15(8):e558-63.

27. Miller LG, Daum RS, Creech CB, Young D, Downing MD, Eells SJ, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. *N Engl J Med* 2015;372(12):1093-103.

28. Kim ES, Lee HJ, Chung GT, Lee YS, Shin DH, Jung SI, et al. Molecular characterization of methicillin-resistant *Staphylococcus aureus* isolates in Korea. *J Clin Microbiol* 2011;49(5):1979-82.

29. Sung JY, Lee J, Choi EH, Lee HJ. Changes in molecular epidemiology of community-associated and health care-associated methicillin-resistant *Staphylococcus aureus* in Korean children. *Diagn Microbiol Infect Dis* 2012;74(1):28-33.

30. Park SH, Kim KJ, Kim BK, Hwang SM. Molecular characterization of community-associated methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* isolates from children with skin infections in Busan, Korea. *J Bacteriol Virology* 2015;45(2):104-11.

31. Chen Y, Chatterjee SS, Porcella SF, Yu YS, Otto M. Complete genome sequence of a Pantón-Valentine leukocidin-negative community-associated methicillin-resistant *Staphylococcus aureus* strain of sequence type 72 from Korea. *PLoS One* 2013;8(8):e72803.

32. Fernandez S, de Vedia L, Lopez Forst MJ, Gardella N, Di Gregorio S, Ganaha MC, et al. Methicillin-resistant *Staphylococcus aureus* ST30-SCCmec IVc clone as the major cause of community-acquired invasive infections in Argentina. *Infect Genet Evol* 2013;14:401-5.

33. Isobe H, Takano T, Nishiyama A, Hung WC, Kuniyuki S, Shibuya Y, et al. Evolution and virulence of Panton-Valentine leukocidin-positive ST30 methicillin-resistant *Staphylococcus aureus* in the past 30 years in Japan. *Biomed Res* 2012;33(2):97-109.

34. Hsu LY, Koh YL, Chlebicza NL, Tan TY, Krishnan P, Lin RT, et al. Establishment of ST30 as the predominant clonal type among community-associated methicillin-resistant *Staphylococcus aureus* isolates in Singapore. *J Clin Microbiol* 2006;44(3):1090-3.