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Changes in molecular epidemiology of community-associated and health care–associated methicillin-resistant *Staphylococcus aureus* in Korean children☆,☆☆,★

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ABSTRACT

Widespread emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has changed the epidemiology of *S. aureus* infections. We examined the molecular types and antibiotic susceptibility of CA-MRSA and health care–associated MRSA (HA-MRSA) among Korean children. MRSA isolates were obtained from patients admitted to university-affiliated tertiary hospitals in Korea, between 2006 and 2010. Molecular studies including multilocus sequence typing, SCC*mec* typing, and polymerase chain reaction amplification of *PVL* genes and antibiotic susceptibility tests were performed. SCC*mec* type IV was most frequently found for both CA-MRSA (80.0%) and HA-MRSA (56.4%). ST72-MRSA-SCC*mec* type IV and its single-locus variants were the most prevalent MRSA clones in the Korean pediatric population, both in community and in health care settings. The *PVL* genes were detected in 10% (4/40) of CA-MRSA isolates. Most of the clinical MRSA isolates showed vancomycin MIC ≥ 1.0 μg/mL. In conclusion, the molecular characteristics of HA-MRSA have been changing and CA-MRSA genotype overtook HA-MRSA genotype in health care settings.
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1. Introduction

Staphylococcus aureus is both a human commensal and a leading cause of human bacterial infections. *S. aureus* has outstanding ability to acquire resistance to antibiotics. Methicillin-resistant *S aureus* (MRSA) was first reported in 1961, 2 years after the antibiotic was introduced to treat the penicillin-resistant strain (Jevons et al., 1961). MRSA isolates spread worldwide over the next several decades and are now endemic in most hospitals and health care facilities in industrialized countries (Deleo et al., 2010). For the past 15 years, widespread emergence of community-associated MRSA (CA-MRSA) has changed the previous epidemiology of *S. aureus* infections. In contrast with health care–associated MRSA (HA-MRSA) infections, for which there are usually predisposing risk factors or illness, community-associated MRSA (CA-MRSA) infections can occur in otherwise healthy individuals (Herold et al., 1998). Outbreaks of CA-MRSA infections have been reported worldwide, although the prevalence of CA-MRSA varies geographically (Boucher & Corey, 2008). The incidence rates of CA- and HA-MRSA in Korean children were rarely reported; more than half of the *S. aureus* isolates associated with clinical infections showed methicillin resistance, and 12.4% and 87.6% of the MRSA isolates were CA- and HA-MRSA in origin, respectively, in our institute, during a recent 4-year period (Choe et al., 2009).

In Korea, previous surveys showed that most CA-MRSA strains were sequence type (ST) 72 clones carrying SCC*mec* type IV, and they did not contain *PVL* genes (Kim, 2007; Kim et al., 2007; Lee et al., 2007; Park et al., 2007). Most Korean HA-MRSA strains were ST5 or ST239 clones carrying SCC*mec* type II or III (Cha et al., 2005; Ko et al., 2005). In the past, many MRSA strains isolated in the Korean community were reported to show typical HA-MRSA genotypes, a finding that suggests the spread of HA-MRSA isolates from hospitals into the community (Jeong et al., 2007; Ma et al., 2005). However, there have been recent studies showing the prevalence of CA-MRSA strains in health care environments (Park et al., 2009; Yoo et al., 2011), and community genotypes emerged as significant causes of HA infections, which seems to be a worldwide phenomenon (Gonzalez et al., 2006; Klevens et al., 2006; Nichol et al., 2011). Furthermore, community genotype strains caused not only community-onset HA-MRSA infections but also hospital-onset HA-MRSA infections (Park et al., 2009).

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CA-MRSA isolates obtained from Korean children revealed a unique evolutionary history from other countries (Ma et al., 2005; Peck et al., 2008). Although outbreaks of CA-MRSA infections among children and adolescent have not yet been detected except in clustered cases of staphylococcal scaled-skin syndromes in the Kyungsangnam-do Province of Korea (Ma et al., 2005), CA-MRSA is an important pathogen among Korean children (Choe et al., 2009). It is known that children have higher persistent *S. aureus* carriage rates than adults (Armstrong-Esther, 1976; Cunliffe, 1949; Noble et al., 1967), and CA-MRSA infections are more likely to occur in younger individuals (Naimi et al., 2003). Therefore, children comprise a major reservoir of MRSA infections, especially CA-MRSA, and we may more easily observe epidemiologic change of MRSA in children compared to adults. However, studies focusing on the molecular epidemiology including genotyping of MRSA infections among childhood rarely reported in Korean children.

In this study, we examined the molecular epidemiology and antibiotic susceptibility including the vancomycin MIC of CA-MRSA and HA-MRSA isolates collected from pediatric patients at tertiary hospitals in Korea and compared our results to our previous data evaluating CA-MRSA as a nasal colonizer in Korean children (Lee et al., 2011).

2. Materials and methods

2.1. Study sample

The study sample consisted of children younger than 18 years with culture-confirmed MRSA infections who were admitted to Seoul National University Children's Hospital or Seoul National University Bundang Hospital during the study period from January 2006 to December 2010. The institutes concerned are university-affiliated tertiary hospitals located in Seoul and Seongnam, South Korea, respectively. Clinical data including demographic profiles, primary sites of infection, underlying diseases, and health care–associated risk factors were retrospectively collected by reviewing medical records.

2.2. Definitions

Based on the epidemiologic definition, CA-MRSA infection was defined as MRSA infection occurring in the community or <48 h after hospital admission in patients with no health care–associated risk factors (Klevens et al., 2006, 2007). Health care–associated risk factors were presence of an invasive device (e.g., vascular catheter, gastric feeding tube) at time of admission or evaluation, and a history of MRSA infection or colonization, surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding culture (Klevens et al., 2006, 2007). Health care–associated infections, in turn, were classified as either community-onset (cases with a health care risk factor but with a culture obtained ≤48 h after hospital admission) or hospital-onset (cases with culture obtained >48 h after admission, regardless of whether they also had other health care risk factors) (Klevens et al., 2006, 2007).

Persistent bacteremia was defined as MRSA growth >72 h after the onset of appropriate antimicrobial therapy such as glycopeptides (Mermel et al., 2009), and recurrent MRSA infection was defined as a case of MRSA regrowth with at least 4 weeks of culture-negative period (Klevens et al., 2007).

2.3. Bacterial isolates

Since 2006, MRSA isolates obtained from only normally sterile body fluids such as blood and pleural fluid were collected during the study period and stored at −70 °C. Since the end of 2007, however, all MRSA isolates irrespective of specimen were retained at −70 °C at our institutes. Collected MRSA isolates were classified as either CA-MRSA or HA-MRSA using the epidemiologic definition (Klevens et al., 2006, 2007). Among 221 pathogenic MRSA isolates, CA-MRSA was 18.1% ($n = 40$) and HA-MRSA was 81.9% ($n = 181$) which consisted of community-onset (32.6%, $n = 59$) and hospital-onset (67.4%, $n = 122$) MRSA isolates.

All CA-MRSA isolates with clinical significance, regardless of isolation site, were included in this study. Among the CA-MRSA isolates, those isolated from urine, nasal aspirates/swabs, or from neonates staying in neonatal intensive care units (NICU) were excluded. For comparing CA- and HA-MRSA molecular characteristics, HA-MRSA isolated from blood only excluding those collected at the NICU were selected during the same study period, and the numbers were comparable to those of CA-MRSA isolates. Only 1 isolate from each episode was included in this study.

2.4. Antimicrobial susceptibility testing

Identification of MRSA and antimicrobial susceptibility tests were performed on the MicroScan Pos Breakpoint Combo Panel Type 28 (PBC28) (Siemens, Illinois, USA). Antimicrobial susceptibility testing data of 10 antimicrobial agents were obtained: oxacillin, penicillin, gentamicin, ciprofloxacin, clindamycin, erythromycin, rifampicin, tetracycline, trimethoprim/sulfamethoxazole, and vancomycin. Detection of inducible clindamycin resistance (macrolide-lincosamide-streptogramin–inducible phenotypes) was achieved using the disc approximation D-zone test (double-disc diffusion test) (Zelazny et al., 2005). Vancomycin MIC was determined by E-test in accordance with the Clinical and Laboratory Standards Institute recommendation (CLSI, 2010). The susceptibility breakpoint for vancomycin was ≤2 μg/mL. Isolates were classified as multidrug resistant (MDR) if they were resistant to 3 or more different classes of non–β-lactam antimicrobial based on susceptibility to gentamicin, erythromycin, clindamycin, ciprofloxacin, rifampicin, tetracycline, and trimethoprim/sulfamethoxazole. *S. aureus* ATCC 29213 was used as a control strain (Pillar et al., 2008).

2.5. Molecular characterization

The molecular types of all the MRSA isolates were determined by multilocus sequence typing (MLST), carried out by polymerase chain reaction (PCR) amplification and sequencing of 7 housekeeping genes (*arcC, aroE, glpF, gmk, pta, tpi,* and *yqiL*) using the primer pairs as described previously (Enright et al., 2000). Each sequence was submitted to the MLST database website (http://saureus.mlst.net) for assignment of an allelic profile and sequence type (ST).

SCC*mec* typing was performed by multiplex PCR as described by Milheirico et al. (2007). Control strains for SCC*mec* types I, II, III, IV, V, and IV were as follows: type I, COL (Milheirico et al., 2007); type II, BK2464 (Oliveira & de Lencastre, 2002); type III, ANS46 (Milheirico et al., 2007); type IV, MW2 (Milheirico et al., 2007); type V, WIS (Milheirico et al., 2007); type VI, HDE288 (Milheirico et al., 2007).

PCR amplification of genes encoding for *PVL* was performed on all MRSA isolates as described by Lina et al. (1999).

3. Results

3.1. Patient characteristics

From 2006 to 2010, a total of 40 CA-MRSA and 39 HA-MRSA isolates available for testing were included in the present study. HA-MRSA infections were further classified based on the onset of infection: 17.9% (7/39) were community-onset HA-MRSA infections and 82.1% (32/39) were hospital-onset HA-MRSA infections. Demographic data showed similar sex ratios for both CA-MRSA and HA-MRSA. Also, the age distributions were similar between CA-MRSA and HA-MRSA. The patients with HA-MRSA infections were mainly associated with intravascular catheter infection (29/39, 74.4%); the remaining 10 patients consisted of primary bacteremia without

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