Community-acquired methicillin-resistant
Staphylococcus aureus in Taiwan

Chih-Jung Chen, Yhu-Chering Huang

Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children’s Hospital, Taoyuan, Taiwan

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Staphylococcus aureus is a major cause of infections in both hospitals and communities, and is exhibiting increasing resistance to methicillin (methicillin-resistant S. aureus, MRSA) and related β-lactams. MRSA is usually considered a nosocomial pathogen, but increasingly it is acquired in the community. In Taiwan, MRSA was colonized in a substantial proportion of healthy children and accounted for 25% to 75% of childhood community-acquired (CA) S. aureus infections. From the preliminary data, the isolates of sequence type (ST) 59 by multi locus sequence typing method appeared to be the major clone of CA-MRSA in northern Taiwan. Compared with those reported from the US and other countries, CA-MRSA isolates in Taiwan did not always harbor type IV staphylococcal cassette chromosome (SCCmec) and were resistant to multiple non-β-lactam antibiotics, including clindamycin and macrolides. Molecular evidence suggested transmission of the community strain of MRSA into the hospital setting, and that the community strain had became a health care-associated pathogen. The treatment of putative CA S. aureus infection should be stratified according to the severity and the disease entity.

Key words: Community-acquired infections, methicillin resistance, review, Staphylococcus aureus, Taiwan

Emergence of Community-acquired Methicillin-resistant Staphylococcus aureus

Staphylococcus aureus is a major cause of infections in both hospitals and communities, causing diseases ranging from mild skin infections to fulminant septicemia, and has become increasingly resistant to methicillin (oxacillin). Methicillin-resistant S. aureus (MRSA) was first reported in the early 1960s and rapidly increased and spread in 1980s [1]. Nowadays, MRSA is endemic in most hospitals in the world and accounts for 40-60% of all nosocomial S. aureus infections [2]. In Taiwan, MRSA was first documented in the early 1980s and rapidly increased in the 1990s [3]. In 2000, methicillin resistance had been identified in 53-83% of all S. aureus isolates in 12 major hospitals of Taiwan [4].

Although MRSA infections in the community were not uncommon, they were traditionally confined to individuals with health care-associated risk factors such as residence in long-term care facility, recent hospitalization or surgery, indwelling catheter or hemodialysis [5,6]. The changing epidemiology of MRSA became evident in the 1990s when MRSA infections occurred in previously healthy children without established risk factors for MRSA acquisition [7-11]. These infections were acquired in the community and have been referred to as community-acquired or community-associated (CA) MRSA infections. CA-MRSA has been recognized as a novel pathogen genetically different from nosocomial MRSA [10,12, 13]. Community-acquired strains were characterized by limited antibiotic resistance (except to β-lactams), with cellulitis and abscess the major clinical manifestations. They have a common pulsed-gel electrophoresis (PFGE) pattern, which is distinct from the major pandemic clones of hospital-acquired (HA) isolates [14], possess different exotoxin gene profiles (e.g., Panton-Valentine leukocidin, PVL), and may represent a new acquisition of type IV staphylococcal cassette chromosome mec (SCCmec) DNA in a previously susceptible S. aureus strain [12,15-17]. SCCmec is the genetic element that carries the methicillin-resistant gene, mecA, and integrates in the S. aureus genome in a site-specific manner. There are at least 5 SCCmec types identified at present (Table 1) [18-20].

The CA-MRSA appeared to be an epidemiologically successful clone which had spread rapidly and
predominated over methicillin-susceptible *S. aureus* (MSSA) in certain populations such as a rural midwestern American Indian community [21]. In the Texas Children’s Hospital, 76.4% of CA *S. aureus* isolates were methicillin resistant in 2004 [22]. Recent studies further demonstrated a remarkable success of CA-MRSA strains in replacing other MRSA strains in some hospitals [23-25]. In addition, the virulence of CA-MRSA seemed to parallel its epidemiologic success. Although skin and soft tissue infections remained the most common clinical syndromes, invasive CA-MRSA infections and even death did occur increasingly in apparently healthy pediatric patients [26-28]. With the emergence of a virulent MRSA in the community, an understanding of the epidemiology of MRSA in the local community is crucial for physicians to appropriately manage their patients with putative CA *S. aureus* infections.

**Epidemiology in Taiwan**

In Taiwan, CA-MRSA infections have been increasingly reported in pediatric patients since 2000 [29-31]. The reported incidence of CA-MRSA infections in children was discrepant in different retrospective studies with similar designs between 1997 and 2001 [26,32,33]. Of 2 studies conducted in the urban hospitals of northern and central Taiwan, MRSA accounted for 74% and 28%, respectively, of all CA *S. aureus* clinical infections [32,33]. The rate of MRSA was 47% in our previous study of hospitalized children with CA *S. aureus* infections in suburban Taiwan [26]. After pooling these data, the rate of MRSA was estimated to be 44% in pediatric cases of CA *S. aureus* infections. A substantial proportion (35-59%) of the pediatric patients with CA-MRSA infection had no identified risk, although the definition of health care-associated risks varied among different studies.

In addition to the hospital-based studies, several community-based studies [34-36] were conducted to estimate the extent of MRSA in the community. We surveyed the nasal carriage of *S. aureus* and MRSA among 262 school children attending child care centers, elementary schools or junior middle schools and 137 health care workers in a teaching hospital during 2001-2002 [34]. MRSA carriage rate was 1.9% among school children and 13% among health care workers. In a study conducted by Boyle-Vavra et al., 640 healthy children less than 12 years of age who either presented for a well-child health care visit or attended 1 of 3 kindergartens in Taipei near Tri-Service General Hospital (TSGH), were sampled in 2003 and the nasal carriage rate of MRSA in those without designated risk factors for MRSA was 5.3% [36]. We also investigated 66 contacts following a case of severe CA-MRSA disease, and MRSA carriage rate among the contacts was 13.6% [35]. Some contacts were colonized with an indistinguishable MRSA strain as the clinical isolates from the case patient, indicating that MRSA can spread in a school once MRSA emerges in a school child. Nevertheless, more than 50% of the contacts were colonized with MRSA strains of distinct clones, suggesting that not all MRSA isolates from the contacts were related to the case patient and indirectly implying that MRSA was circulating in the community in Taiwan.

In contrast to pediatric cases, CA-MRSA infections were uncommon in adults. In 2 island-wide surveys of representative isolates of *S. aureus* from medical centers and local hospitals in 1998 and 2000, respectively, the rate of MRSA was estimated to be 40% in outpatient

<table>
<thead>
<tr>
<th>SCCmec type</th>
<th>Representative strain</th>
<th>Origin</th>
<th>SCCmec size of the representative strain (bp)</th>
<th>Major determinants in SCCmec</th>
<th>Antibiotic-resistant gene carried by SCCmec</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NCTC10442</td>
<td>HA</td>
<td>34,364</td>
<td>Class B Type 1 (ccrA1, ccrB1)</td>
<td>mecA</td>
</tr>
<tr>
<td>II</td>
<td>N315</td>
<td>HA</td>
<td>53,017</td>
<td>Class A Type 2 (ccrA2, ccrB2)</td>
<td>mecA, aadD, ermA</td>
</tr>
<tr>
<td>III</td>
<td>85/2082</td>
<td>HA</td>
<td>66,896</td>
<td>Class A Type 3 (ccrA3, ccrB3)</td>
<td>mecA, aadD, tetK</td>
</tr>
<tr>
<td>IV</td>
<td>CA05</td>
<td>CA</td>
<td>24,248</td>
<td>Class B Type 2 (ccrA2 variant, ccrB2 variant)</td>
<td>mecA</td>
</tr>
<tr>
<td>V</td>
<td>WIS</td>
<td>CA</td>
<td>27,624</td>
<td>Class C Type 5 (ccrC)</td>
<td>mecA</td>
</tr>
</tbody>
</table>

Abbreviations: ccr = cassette chromosome recombinase; HA = hospital-acquired; CA = community-acquired


b The ccrA and ccrB genes encode putative site-specific recombinases of SCCmec which is responsible for the movement of SCCmec.

c aadD encodes resistance to tobramycin and kanamycin.

d ermA encodes resistance to macrolide-lincosamide-streptogramin antibiotics.

e tetK encodes tetracycline resistance.
CA-MRSA in Taiwan

settings [37,38]. Exposures to the risk factors for MRSA acquisition were not mentioned in these cases. In 2 other studies of CA. S. aureus bloodstream infections, the rates of MRSA were 26% and 33.7%, respectively [39,40]. Almost all of the patients had identified risk factors. These observations suggest that CA-MRSA in adults is still limited and most adult patients have traditional health care-associated risks.

Molecular epidemiology of CA-MRSA
Our preliminary data disclosed that there were 3 major pulstotypes (designated as PFGE type A, C, and D in our hospital) of MRSA strains simultaneously circulating in the hospitals and communities of Taiwan [26,41-43]. Type IV SCCmec, an epidemiologic marker for CA-MRSA, was identified in 25% and 40% of CA and HA isolates, respectively [26]. We therefore considered that the CA-MRSA isolates in Taiwan, distinct from those reported from US and other countries, were closely associated with the HA isolates. However, Wang et al collected and analyzed 17 consecutive CA-MRSA isolates from children hospitalized at TSGH for skin and soft tissue infections during the 5-year period from September 1997 to August 2002 and disclosed that these CA-MRSA isolates were of a single clone [44]. The pulsotype of these 17 CA-MRSA (similar to type D in our study) isolates was different from 4 nosocomial isolates and the genotype was ST (sequence type) 59 by multilocus sequencing typing (MLST). Only 2 of 16 isolates studied carried type IV SCCmec and 13 isolates carried a newly identified subtype of SCCmec V, called SCCmec V_T [36]. In order to clarify this issue, we recently had some MRSA strains of representative PFGE patterns in our studies genotyped by MLST. The results disclosed that the strains of PFGE type A in our studies were ST239, while the strains of both PFGE types C and D were ST59. ST239 was a Brazilian or Hungarian epidemic MRSA clone, which was among the 6 pandemic clones of HA isolates and has been shown to be the major clone of nosocomial MRSA in Taiwan [45,46]. The strain of ST59 was a clone less commonly reported but was recently identified as a major MSSA genotype causing CA abscess and soft tissue infections among intravenous drug users in the UK [47]. Our previous studies also disclosed that PFGE types C and D (ST59) accounted for 76% of 40 CA-MRSA isolates [26]. Thus, it appeared that the strain of ST59 was a prevalent clone of CA-MRSA in Taiwan. If this was the case, the additional findings in our previous study [26] that the isolates of PFGE types C and D (possibly ST59) accounted for 70% of childhood HA-MRSA isolates may imply that CA-MRSA strains did spread into the hospital and even successfully replaced the original hospital strains (PFGE type A), and became a dominant clone in our pediatric wards. Replacement of nosocomial MRSA strains by CA-MRSA strains had been reported previously in other countries [23,24]. However, these studies were retrospective and thus the interpretation may be misleading. We are now undergoing a comprehensive large-scale prospective study to delineate the molecular epidemiology of CA-MRSA in Taiwan.

Antibiotic resistance of CA-MRSA
The methicillin resistance of S. aureus is due to the acquisition of mecA gene encoding penicillin-binding protein, PBP2a. The mecA gene is carried by a mobile element (SCCmec). This PBP2a protein has low affinity for most β-lactam antibiotics and, therefore, mediates cross-resistance to all of these compounds. In our previous study, mecA gene was identified in all of the 40 CA-MRSA isolates. Wang et al examined the minimal inhibitory concentration (MIC) level of their 17 CA-MRSA isolates, and found that only 6 isolates (35%) had an oxacillin MIC of at least 8 µg/mL [44]. However, most of the colonized isolates in our previous studies had an oxacillin MIC of at least 24 µg/mL [34,35].

The antibiograms of CA-MRSA isolates in Taiwan disclosed a specific pattern which was different from that in the United States. Similar to both nosocomial MRSA isolates and CA-MRSA isolates from children without risk factors, the CA-MRSA isolates from children without risk factors were also resistant to multiple antibiotics, including clindamycin (93-100%), erythromycin (94-100%) and chloramphenicol (57-65%) [26,32,44]. Trimethoprim-sulfamethoxazole (SXT) was the only drug associated with different susceptibility between CA- and HA-MRSA strains, to which CA-MRSA isolates were significantly more susceptible than HA-MRSA isolates [26]. In the studies reported by Wang et al [44] and Fang et al [32], the CA-MRSA isolates were also less resistant to gentamicin (11-34%), ciprofloxacin (0%), fusidic acid (0%) and minocycline (7%) than nosocomial MRSA. Wang et al [32] further examined their 17 CA-MRSA isolates using the double disk diffusion method and polymerase chain reaction for macrolide resistance gene detection, and indicated that all strains had the macrolide-lincosamide-streptogramin (MLS)-constitutive phenotype and the ermB gene.
Virulence of CA-MRSA

Recent studies regarding the natural history of CA-MRSA infection disclosed that subjects colonized with CA-MRSA were more likely to develop clinical disease than those colonized with CA-MSSA [48]. Patients with musculoskeletal infections caused by CA-MRSA required longer hospital stays and had more febrile days than did those affected by CA-MSSA [49]. CA-MRSA strains seemed to be more virulent than CA-MSSA strains. Molecular analysis of CA S. aureus strains has shown that CA-MRSA isolates harbor genes encoding superantigen toxins such as enterotoxins [12]. In 1999, 4 children died of fulminant CA-MRSA sepsis [27]. The MRSA isolates accounting for the 4 pediatric deaths were genetically related and the whole genome sequences of 1 isolate (MW2) disclosed a range of virulence genes that were distinct from those displayed on the chromosome of extant S. aureus strains [17]. These genes encoded for several superantigens and leukotoxins such as PVL. PVL had been shown to be associated with necrotizing hemorrhagic pneumonitis and skin abscess [50-53]. Furthermore, PVL gene was seen as a genetic marker of CA-MRSA, since it was infrequently found in HA-MRSA [54]. PVL gene was also identified in the CA-MRSA isolates in Taiwan and may also contribute to severe and even fatal infections in pediatric cases [44,55].

Clinical manifestations of CA-MRSA infections

Skin and soft tissue infections remained the most common manifestations of CA-MRSA infections. Invasive CA-MRSA infections and even death, however, were increasingly reported [30,35,55]. Among 54 episodes of CA-MRSA infections in our pediatric series, 28% were considered to be serious [26]. Some cases even developed sepsis with multiple focal infections, including pneumonia, pyomyositis, arthritis and/or osteomyelitis. Invasive diseases were also noted in 8% of 59 children with CA-MRSA infections in Fang et al’s study [32]. Pulmonary septic embolism secondary to primary sites infection, often bones or joints, was a common and characteristic manifestation in severe pediatric cases [26,31,35].

Therapeutic strategy for CA-MRSA infections

Due to the high rate of multi-resistant MRSA in the community, increasing usage of glycopeptides or linezolid would be inevitably expected. However, the usage of glycopeptides in management of children with CA-MRSA infections did not increase markedly, since the most common manifestation of CA-MRSA infection was skin and soft tissue infections and most skin and superficial soft tissue infections resolved spontaneously or after incision and drainage with and without susceptible antibiotic treatment [26,32,44]. Auto-drainage of the infected site and host defenses may play important roles in these superficial soft tissue infections. Borderline methicillin resistance in some S. aureus isolates may be another consideration [44]. For severe cases, initial non-susceptible antibiotic therapy was not associated with unfavorable outcome in our previous study [26]. However, delayed use of effective antibiotics may have contributed to a fatal outcome in pediatric cases with fulminant CA-MRSA sepsis [55]. The management of CA S. aureus infections, therefore, should be stratified according to the severity and site of disease entity in an area where high prevalence of methicillin resistance was noted such as Taiwan. In Taiwan, we suggest that for skin and superficial soft tissue infections, oral form of SXT can be considered as the first-line regimen. For those with soft tissue infections and systemic symptoms and signs requiring hospitalization and considering the adverse effects of the intravenous form of SXT, we suggest that empiric therapy with intravenous forms of β-lactams such as oxacillin or a first-generation cephalosporin may be used in most cases. Incision and drainage should be attempted and done if possible. Oral SXT can be used as sequential therapy for these patients. If the infection is invasive or located in deep-seated structures, glycopeptides or linezolid should be used empirically and continued as definitive therapy if MRSA is identified subsequently. Clindamycin and macrolides are not suitable for treating children with putative CA S. aureus infections at present in Taiwan.

Conclusion

CA-MRSA with multiple drug resistance has established itself as a prevalent pathogen in the community of Taiwan. Skin and superficial soft tissue infections remain the most common manifestation of CA-MRSA infections and often resolve after auto- or incisional drainage in spite of initial inactive antibiotic treatment. Significant morbidity and even mortality associated with CA-MRSA infection are increasingly reported, especially in pediatric patients. Management of CA S. aureus infections should be stratified according to the site and severity of the disease entity and for severe cases glycopeptides or linezolid should be used
empirically. Further studies should be conducted to elucidate the epidemiology of CA-MRSA in Taiwan.

References
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