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Community-acquired methicillin-resistant *Staphylococcus aureus* in children in northern Taiwan

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Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is a well-recognized nosocomial infection of increasing incidence. Recent reports have also revealed an increment of community-acquired MRSA (CA-MRSA) infections in people without any risk factors. We reviewed the medical charts of 464 children with *S. aureus* infections presenting between January 1997 and August 2001, in order to understand the occurrence of CA-MRSA infections in children without any risk factors and to define the spectrum of disease. MRSA made up 74% of community-acquired *S. aureus* infections (59/80). Among them, patients without identifiable risk factors comprised 29 CA-MRSA infections (36%). The number of patients with CA-MRSA disease increased from 11 of 172 (6%) *S. aureus* infections between January 1997 and April 1999 to 48 of 292 (16%) between May 1999 and July 2001. Skin and soft tissue infections were the most common presentations of community-acquired *S. aureus* infections. Bacteremia was the major manifestation of nosocomial *S. aureus* infections, and osteomyelitis and bacteremia were not infrequently seen in patients with CA-MSSA infections. Only 13 out of 29 patients (45%) with CA-MRSA infections without risk factors received effective antibiotic therapy, while 16 cases were cured by either antibiotics without in vitro activity, or surgical drainage, or both. CA-MRSA isolates were more likely to be susceptible to minocycline, gentamicin, and trimethoprim-sulfamethoxazole, compared to hospital-acquired MRSA isolates. Our data suggest an increasing role of MRSA as a community pathogen in previously healthy children. Infection control strategies for both hospital and community should be re-evaluated.

Key words: Antibiotic susceptibility, cellulitis, community-acquired infection, methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection first emerged in early 1961 [1,2], and has increased its prevalence steadily since. Most documented MRSA infections are acquired nosocomially, and community-acquired cases were restricted to patients residing in long-term care facilities and to intravenous drug users. Other risk factors for community-acquired MRSA (CA-MRSA) infections include recent hospitalization, transfer from another hospital, prior antimicrobial use, endotracheal intubation, in-dwelling catheters, invasive procedures, and underlying diseases such as chronic liver, lung, and vascular disease, or malignancies [3-5]. Recently, CA-MRSA infections without any predisposing factors have been seen in many reports in adults and children [6-16].

The increase in MRSA infections in the community raises considerable concern since this type of *S. aureus* would cause infections difficult to treat in an outpatient setting and markedly increase the need for vancomycin therapy. In Taiwan, the prevalence of MRSA infection increased from 16.3% in 1993 to 82% in 1998 in the nosocomial setting [17,18]. Only a few reports described CA-MRSA infections in children in Taiwan [15]. The aim of this study is to analyze the trend of CA-MRSA infections in children without risk factors, and the clinical spectrum of the disease.

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Materials and Methods

National Taiwan University Hospital is a university-affiliated medical center in northern Taiwan with a total of 2000 beds, including 221 pediatric beds. We analyzed *S. aureus* isolates from patients younger than 18 years old between January 1997 and August 2001. Specimens from the respiratory tract were excluded, except those from pleural effusion or lung parenchyma. All available medical records were reviewed, including demographics, medical risk factors, sites of cultured specimens,

antibiotic susceptibility, modalities of treatment including initial and effective antibiotic therapy, surgical intervention, clinical responses, and duration of hospitalization. We also contacted enrolled patients to confirm whether they had been admitted to any other healthcare facility within one year of sample collection.

A community-acquired *S. aureus* isolate was defined as one obtained in an outpatient setting, or within 72 hours of admission, including cases within 96 hours of admission, from which cultures were delayed but obtained from relevant and aseptic sites. A hospital-acquired isolate was one obtained beyond that time span.

A disease-associated isolate was defined as one responsible for a clinical syndrome as determined from physical examination, relevant clinical data, and the site where *S. aureus* was isolated [19]. Colonizing isolates were excluded. We also excluded patients who had been hospitalized, including the baby room, within 12 months prior to admission, or were in residence in a long-term care facility [9,10].

Risk factors for MRSA infections were defined as the presence of any of the following: previous antimicrobial therapy or outpatient clinic visit within 6 months from the date of MRSA isolation [6,8,9,11,20]; a history of surgery or admission to an intensive care unit; presence of in-dwelling vascular or urinary catheters; and underlying chronic diseases such as congenital heart diseases, chronic skin diseases, and malignancies. All other patients without any of the above-mentioned conditions were classified as "without identified risk".

Our microbiology laboratory confirmed oxacillin resistance by the standard disk-diffusion method as recommended by the National Committee for Clinical Laboratory Standards [21]. The antimicrobial agents tested included penicillin, oxacillin, clindamycin, erythromycin, vancomycin, minocycline, gentamicin, and trimethoprim-sulfamethoxazole.

All clinical data were analyzed using a 2-tailed chi-squared test; $p<0.05$ was considered statistically significant.

Results

There were 464 children with *S. aureus* infections, from our outpatient clinic, emergency department, and hospital wards, between January 1997 and August 2001 (Table 1). Eighty cases (17%) fulfilled our inclusion criteria of community-acquired *S. aureus* infections. Of these, 59 (74%) had MRSA and 21 (26%) had methicillin-susceptible *S. aureus* (MSSA) infections. Among them, 29 out of 59 CA-MRSA infections had no identifiable risk factors. The number and proportion of patients with CA-MRSA infections increased from 11 out of 172 *S. aureus* infections (6%) between January 1997 and April 1999 to 48 out of 292 cases (16%) between May 1999 and July 2001.

Clinical characteristics of CA-MRSA infections without risk factors

Of 29 patients with CA-MRSA infections without identified risk factors, 14 patients (48%) needed hospitalization, and all received beta-lactam antibiotics initially, including oxacillin, cefazolin, or amoxicillin-clavulanic acid. Eight patients (57%) later received effective antimicrobial agents, including vancomycin or trimethoprim-sulfamethoxazole, and 6 of these 8 patients also underwent incision and drainage. Twenty-five patients (86%) had skin and soft tissue infections. There was 1 case of bacterial tracheitis, 1 case of pneumonia with empyema, and 1 case of pyomyositis, osteomyelitis and bacteremia. Six of the 14 hospitalized patients improved after being treated with ineffective antibiotics with only 1 patient undergoing incision and drainage. These infections comprised cellulitis, abscess, folliculitis,

Table 1. Distribution of *S. aureus* infections from January 1997 to August 2001

Source of isolates	No. of isolates in hospitalized patients	No. of isolates in OPD or ER patients	Total
MRSA			
Community-acquired without RF	14	15	29
Community-acquired with RF	17	13	30
Hospital-acquired	314	0	314
MSSA			
Community-acquired	13	8	21
Hospital-acquired	70	0	70
Total	428	36	464

Abbreviations: RF = risk factors; OPD = outpatient clinics; ER = emergency room; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*

and surgical scarlet fever. One patient with pneumonia and empyema was treated in an intensive care unit. No complications or mortalities were seen among the cases.

Of the remaining 15 outpatients, 5 were cured by effective antibiotics after positive cultures of MRSA, and 2 underwent incision and drainage. However, 10 patients with soft tissue infections were treated with antibiotics ineffective against MRSA, although 7 patients received incisions and drainage. Most were cellulitis or abscess cases, and there was also 1 conjunctivitis case and 1 acute otitis externa case.

The clinical features of CA-MRSA without risk factors and CA-MRSA with risk factors are similar.

CA-MRSA vs CA-MSSA

The risk factors and clinical spectrum data are depicted in Table 2. CA-MRSA infections tended to occur at younger ages (8 years vs 11 years, p=0.01). There was no gender difference in the CA-MRSA group, but boys dominated the CA-MSSA group. Skin and soft tissue infections were the most common infections in both groups (92% vs 71%, p=0.022), in contrast to the HA-MRSA group, in which bacteremia and skin and soft tissue infections were equally common (30% and 37%). However, compared with the CA-MRSA group, the CA-MSSA group had a greater incidence of bacteremia (33% vs 7%, p=0.004) and osteomyelitis (24% vs 3%, p=0.002). Thirty-two out of 59 (54%) cases in the CA-MRSA group required hospitalization, compared to 13/21 (62%) in the CA-MSSA group. One patient in each group needed intensive care. The duration of hospitalization for CA-MRSA infections was 9 days on average, but the duration was longer in the MSSA group which had an average of 14 days (p=0.01).

Table 2. Comparison between MRSA and MSSA infections in the community

Clinical presentations	CA-MRSA n = 59 (%)	CA-MSSA n = 21 (%)	p
Age (years) [mean (SD)]	8 ± 5.7	11 ± 4.4	0.01
Gender (M/F)	29/30	17/4	0.011
Site of infection			
Soft tissue and skin infections	54 (92)	15 (71)	0.022
Osteomyelitis/arthritis	2 (3)	5 (24)	0.004
Bacteremia	4 (7)	7 (33)	0.002
Pneumonia	1 (2)	1 (5)	NS
Bacterial tracheitis	1 (2)	0	NS
Infective endocarditis	0	1 (5)	NS
Meningoencephalitis	0	1 (5)	NS
Preceding events			
Previous surgery	5 (8)	0	NS
Previous antimicrobial use	14 (24)	5 (24)	NS
Previous clinic visit	31 (52)	8 (38)	NS
Underlying diseases			
Chronic skin disease (eczema)	9 (15)	2 (10)	NS
Chronic respiratory disease (asthma)	7 (12)	2 (10)	NS
Others (CHD, CP, hemophilia)	3 (5)	2 (10)	NS
Clinical course			
Hospitalization	32 (54)	13 (62)	NS
Hospital days (range)	9 (2-114)	14 (2-56)	0.01
Surgical intervention	32 (54)	14 (62)	NS
Admission to intensive care unit	1 (2)	1 (5)	NS

Abbreviations: CA-MRSA = community-acquired methicillin-resistant *S. aureus*; CA-MSSA = community-acquired methicillin-susceptible *S. aureus*; SD = standard deviation; NS = no significance; CHD = congenital heart disease; CP = cerebral palsy

With regard to risk factors, 5 of 59 patients in the CA-MRSA group underwent surgery, compared with none in the CA-MSSA group (p=0.168). However, there were no statistically significant differences between the 2 groups in exposure to antimicrobials and visits to outpatient clinics or emergency departments within 6 months.

CA-MRSA vs HA-MRSA

As shown in Table 3, antimicrobial susceptibility patterns of HA-MRSA demonstrated multi-drug resistance including beta-lactam antibiotics. However, most CA-MRSA isolates showed greater susceptibility than HA-MRSA to some non-beta-lactam antibiotics, such as minocycline (93% vs 48%, p<0.05), gentamicin (66% vs 14%, p<0.05), and trimethoprim-sulfamethoxazole (97% vs 28%, p<0.05). No isolates showed resistance to vancomycin.

There was no statistical difference in the patterns of antimicrobial susceptibility between CA-MRSA with and without risk factors.

Discussion

In this study, we demonstrated a marked increase in prevalence of CA-MRSA infections in children (Fig. 1). The isolation of MRSA is no longer limited to those with predisposing factors [3-5]. CA-MRSA comprised 74% of community-acquired *S. aureus* infections in our study, higher than previous reports (25% to 59%) [6-9,15,22]. Meanwhile, CA-MRSA infection in patients without identified risk factors made up 36% of community-acquired *S. aureus* infections.

There could be an overestimation of the occurrence of true CA-MRSA infections in our study because this

Table 3. Antibiotic susceptibilities of MRSA and MSSA isolates to six non-beta-lactam agents

	No. (%) of MRSA isolates			No. (%) of MSSA isolates		
	CA (n = 59)		HA (n = 314)	CA (n = 21)		HA (n = 70)
	RF(+)	RF(-)		RF(+)	RF(-)	
Erythromycin	1 (3)	1 (3)	7 (2)	4 (44)	3 (25)	43 (61)
Clindamycin	1 (3)	1 (3)	40 (13)	4 (44)	7 (58)	51 (73)
Vancomycin	30 (100)	29 (100)	314 (100)	9 (100)	12 (100)	70 (100)
Minocycline	29 (97)[a]	27 (93)[a]	151 (48)[a]	9 (100)	12 (100)	66 (94)
Gentamicin	24 (80)[a]	19 (66)[a]	43 (14)[a]	9 (100)	9 (75)	66 (94)
Trimethoprim-sulfamethoxazole	28 (93)[a]	18 (97)[a]	89 (28)[a]	9 (100)	12 (100)	67 (96)

Abbreviations: CA = community-acquired, HA = hospital-acquired; RF = risk factors

[a]Statistically significant differences between CA-MRSA and HA-MRSA.

is a hospital-based retrospective review, and therefore may lack important information in the medical charts, as well as having inadequate numbers of cases. Further prospective community-based studies are warranted.

It is well known that the colonization of MRSA may be persistent, and even last up to 40 months [23]. In a report from Finland [24], the proportion of CA-MRSA was 21% if the definition of community acquisition covered a 2-year time period without healthcare facility contact before the MRSA isolation, but this increased to 26% if the cut-off period was 1 year.

Here, we defined true "CA-MRSA" as a patient without previous hospitalization within 1 year, including the absence of antimicrobials or treatment clinical visits within the prior 6 months. The original source of acquisition cannot be known with certainty and could have been hospitalization or exposure to a healthcare facility in the remote past. Therefore, it is possible that we overestimated the occurrence of "true" MRSA infections acquired in the community. A more strict definition of CA-MRSA may be needed in further studies.

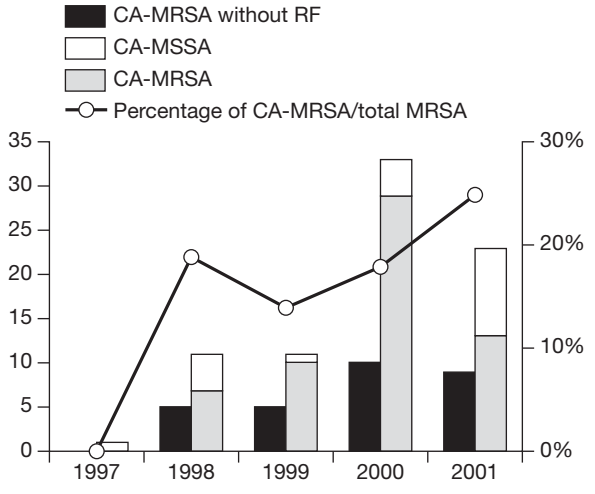

Fig. 1. Annual trend of CA-MRSA infections. CA-MRSA without risk factors (RF) and its percentage of total MRSA has increased markedly every year since 1998. The average percentage of CA-MRSA in community-acquired *S. aureus* infections reached a maximum of 74% during the 4.5-year study period (Jan 1997-Aug 2001).

As in previous reports, skin and soft tissue infections were the most common clinical features in both the CA-MRSA and CA-MSSA groups [6-9,14-16,20,22,25]. However, bacteremia and osteomyelitis were also important presentations in the CA-MSSA group. This is consistent with the experience of Sattler et al [20]; CA-MSSA was 3 times more likely to be associated with deep-seated infections than CA-MRSA, including more bacteremia in the CA-MSSA group. Also, the average duration of hospitalization was longer in the CA-MSSA group, which may have resulted from the greater number of patients with severe infections in the CA-MSSA group in our study.

Although CA-MRSA tended to be associated with superficial infection, more than 30% of severe infections were caused by MRSA isolates in our study, including osteomyelitis, bacteremia, and pneumonia. In addition, 4 fatal cases due to CA-MRSA infections in Minnesota and North Dakota highlight the potential risks of severe infections [26]. The reason why CA-MRSA more commonly causes milder infections is not known. More case numbers of *S. aureus* infections are needed to further clarify this finding.

Comparison of CA-MRSA infections with CA-MSSA in patients with predisposing risk factors showed no statistically significant difference in previous exposure to antibiotics and visits to outpatient clinics or emergency departments within the prior 6 months. This is consistent with several studies, including a recent prospective study by Sattler et al [20].

In the clinical course of CA-MRSA infections without risk factors, we found the majority of cases to be cured without effective antibiotics, with or without surgical intervention. Most of these cases were superficially infected, and included folliculitis, cellulitis, or abscess. Previous studies also demonstrate similar clinical manifestations [11,15]. This shows that the host defense itself plays an important role in overcoming infections. Futhermore, there were possibly heterogeneous MRSA isolates with lower MICs to oxacillin, which accounts for improvement after treatment with only oxacillin or first-generation cephalosporins [27]. Further antibiotic susceptibility of the isolates was not performed in this study.

Previous reports noted that CA-MRSA isolates tended to be more susceptible to non-beta-lactam antibiotics, such as clindamycin, gentamicin, trimethoprim-sulfamethoxazole, or even erythromycin, when compared to HA-MRSA [6-9,14,16,20,22]. In our study, CA-MRSA isolates were more susceptible to minocycline, gentamicin, and trimethoprim-sulfamethoxazole, but not to clindamycin or erythromycin. Overuse of erythromycin and clindamycin in our community explains this inconsistency compared with the experience of other countries [28].

Oxacillin and first-generation cephalosporins can still be used as the first-line antibiotics when treating *S. aureus* infections in a community, because most infections were cured by these antimicrobials alone in our study. Other non-beta-lactam antibiotics are also good alternatives, and surgical intervention is an important adjuvant therapy for those with skin and soft tissue infections. Vancomycin should be reserved for critical infections or infections with poor response to other antibiotic therapy. However, since MRSA infections continue to prevail in the community, it may be prudent to adjust empirical antimicrobial agents, especially for severe *S. aureus* infections. More studies are needed to monitor the epidemiology of MRSA infection and to reassess empirical antimicrobial therapy and prevention strategies for staphylococcal infections.

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