LOW PREVALENCE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN PEDIATRIC SKIN AND SOFT TISSUE INFECTIONS IN THAILAND

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Abstract. Skin and soft tissue infection (SSTIs) due to methicillin-resistant *Staphylococcus aureus* (MRSA) are an important public health problem among children. We aimed to determine the prevalence of MRSA among children with SSTIs who presented to King Chulalongkorn Memorial Hospital in order to inform empiric treatment. We conducted a prospective study among children aged <15 years who presented during June 2015 to March 2016 with a SSTI. In each subject a swab for culture and sensitivity was obtained from the skin lesion, normal skin, and the anterior nares. A total of 102 patients were included in this study. Forty-seven percent of subjects had a history of atopic dermatitis (AD). Sixty-one patients (60%) had a positive culture. *Staphylococcus aureus* was the most common organism isolated (85%), followed by coagulase-negative *Staphylococcus* (6%), *Streptococcus pyogenes* (5%), *Escherichia coli* (2%) and *Pseudomonas* spp (2%). MRSA was found in 3 patients from the skin lesions, 1 patient from normal skin, and 4 patients from the anterior nares. All patients with MRSA infection had moderately severe AD. All MRSA isolates were susceptible to trimethoprim-sulfamethoxazole, gentamicin, ciprofloxacin, fusidic acid, moxifloxacin and doxycycline. We found a lower prevalence of MRSA among study subjects. Effective antibiotics included trimethoprim-sulfamethoxazole and fusidic acid. Among children aged ≥ 12 years, ciprofloxacin and doxycycline are also treatment options. However our findings suggest empiric coverage for MRSA among our study population with SSTIs is not necessary for initial treatment.

Keywords: *Staphylococcus aureus,* methicillin-resistant, skin and soft tissue infection, children, atopic dermatitis

INTRODUCTION

Staphylococcus aureus (SA) is a common cause of skin and soft tissue infections (SSTIs) in children. The incidence of community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) SSTIs is increasing in some western countries up to 76-85% of SA SSTIs (Hoeger, 2004; Guzik *et al*, 2005; Moran *et al*, 2006; Chung *et al*, 2008; Suh *et al*, 2008). However, one report of MRSA SSTIs from China states it is still uncommon there (Liu *et al*, 2009). A study of the incidence of MRSA SSTIs

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among Thai children with atopic dermatitis (AD) during 2009- 2011reported it to comprise 44% of MRSA SSTIs (Chatproedprai *et al*, 2016). Non-lesional skin and nasal mucosa are important reservoirs of SA among patients with recurring SSTIs (Chiu *et al,* 2010). It is important to know the incidence of MRSA and the pattern of antimicrobial susceptibility among MRSA cases to guide empiric therapy, but data about Thai pediatric patients with MRSA SSTIs is limited. One study reported a declining proportion of MRSA to methicillin-sensitive *Staphylococcus aureus* (MSSA) cases from the US (Ray *et al*, 2013a).

The aims of the present study were to determine the incidence of MRSA among Thai children with SSTIs and the prevalence of MRSA colonizing normal skin and the anterior nares. We also aimed to determine antimicrobial susceptibilities of MRSA in order to inform empiric therapy decision making for the treatment of SSTIs.

MATERIALS AND METHODS

We conducted a cross sectional prospective study from June 2015 to March 2016 among all children aged < 15 years who presented at King Chulalongkorn Memorial Hospital with a SSTI. We excluded patients from the study who had received systemic or topical antibiotics during the 4 weeks prior to being included in the study. Informed consent was obtained from the guardians of all subjects prior to inclusion in the study. Data obtained from each subject included sex, age, history of underlying disease, history of atopy and history of previous treatment. An examination was conducted to determine the severity of disease using the Scoring Atopic Dermatitis (SCORAD) index among subjects with AD. Subjects with a SCORAD index <15 were considered to have mild AD, those with an index of 15-40 were considered to have moderate AD and those with an index >40 were considered to have severe AD (Anonymous, 1993; Wolkerstorfer *et al*, 1999).

In each subject, a sterile cotton culture swab specimen was obtained from skin lesions, non-lesional skin and the anterior nares. Culture swab specimens were immediately cultured on blood agar. In cases where the culture was positive for SA, the presence of MRSA was determined using the disc diffusion method with a cefoxitin disc (30 μg) on Mueller-Hinton agar (Skov *et al*, 2003). Having MRSA was defined as finding MRSA from at least one body site.

This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University and adheres to the provisions outlined in the Declaration of Helsinki (IRB No 568/57).

RESULTS

Demographic data

A total of 102 subjects were included in the study. The female to male ratio was 1.3:1. The mean [standard deviation, (SD)] age of the study subjects was 6.1 (±5.0) months (range: 1 month -15 years). AD was the most common underlying skin disease found in the study subjects, present in 48 subjects (47.1%), of which 45 had moderate and 3 had severe AD. Other skin diseases diagnosed were nummular eczema in 6 patients (5.9%) and infantile seborrheic dermatitis in 5 patients (4.9%) (Table 1). Seventy-nine point four percent of subjects had eczema or some other underlying skin diseases. SSTIs diagnosed included impetigo (13.7%), skin abrasion (2.9%), folliculitis (2%), ecthyma (1%) and paronychia (1%) (Table 2).

Table 1
Demographic data and associated skin diseases of patients with skin and soft tissue infections (SSTIs).

Characteristic	*n* (%)
Total SSTIs	102 (100)
Gender	
Female	58 (56.9)
Male	44 (43.1)
Age (years)	
< 5	42 (41.2)
5-10	29 (28.4)
11-15	31 (30.4)
Associated skin diseases	
Atopic dermatitis	48 (47.1)
Nummular eczema	6 (5.9)
Infantile seborrheic dermatitis	5 (4.9)
Frictional lichenoid dermatitis	3 (2.9)
Xerotic eczema	2 (1.9)
Eczema (non-specific)	2 (1.9)
Ulcerated hemangioma	2 (1.9)
Irritant contact dermatitis	2 (1.9)
Other skin diseases	10 (10.0)
No skin disease	22 (21.6)

Treatment of the SSTIs

In this study, topical antibiotics were most commonly prescribed treatment for SSTIs. Mupirocin was the most commonly prescribed topical antimicrobial (80 patients, 78.4%) followed by fusidic acid (16 patients, 15.6%). Other medications prescribed included cloxacillin (2 cases), cloxacillin and fusidic acid (2 cases), cloxacillin and sulfadiazine (1 case), and sulfadiazine (1 case) (data not shown).

Organisms cultured from skin lesion, normal skin and anterior nares

Skin lesion cultures were positive in 61 patients (60%); SA was the most common organism isolated (50.9%) followed by MRSA (6%). Other organisms cultured included coagulase-negative *Staphylococcus* (3.9%), *Streptococcus pyogenes* (3%), *Escherichia coli* (1%), and *Pseudomonas* spp (1%) (Table 3).

Table 2
Type of skin and soft tissue infection.

Type of infection	Total *N* = 102 *n* (%)
Secondary bacterial infection	81 (79.4)
Impetigo	14 (13.7)
Abrasion wound	3 (2.9)
Folliculitis	2 (2.0)
Ecthyma	1 (1.0)
Paronychia	1 (1.0)

Normal skin cultures were positive in 25 patients (24.5%); SA was the most common bacteria isolated (14.7%), followed by coagulase-negative *Staphylococcus* (5.8%), *Streptococcus pyogenes* (2%), and *Enterobacter* spp (1%). MRSA was found in one of the 16 patients with positive cultures for SA from normal skin (Table 3).

Anterior nares cultures were positive in 48 patients (47.1%); SA was the most common bacteria isolated (34.3%), followed by coagulase-negative *Staphylococcus* (2.9%), *Corynebacterium* spp (2.0%), *Streptococcus pyogenes* (1.0%), *Klebsiella pneumoniae* (1.0%), *Acinetobacter baumannii* (1.0%), and *Acinetobacter lwoffii* (1.0%). MRSA was found in 4 patients of the 39 patients with positive cultures for SA from the anterior nares (Table 3).

Of the 102 subjects, 48 had AD. All 48 presented with eczema and a secondary bacterial infection, 24 had a positive culture for SA, and 3 had a positive culture for MRSA. Nine subjects had normal skin cultures positive for SA, of which 1 had MRSA. Twenty subjects had anterior nares cultures positive for SA, 4 had MRSA. All subjects with a positive culture for MRSA

Table 3
Organisms found on the skin lesion, normal skin and anterior nares.

Organisms	Total *N*=102		
	Skin lesion *n* (%)	Normal skin *n* (%)	Anterior nares *n* (%)
No growth	41 (40.2)	77 (75.5)	54 (52.9)
Culture positive			
MRSA	3 (2.9)	1 (1.0)	4 (3.9)
Staphylococcus aureus	49 (48.0)	15 (14.7)	35 (34.3)
Coagulase-negative *Staphylococcus*	4 (3.9)	6 (5.8)	3 (2.9)
Streptococcus pyogenes (group A)	3 (3.0)	2 (2.0)	1 (1.0)
Corynebacterium spp	-	-	2 (2.0)
Gram-negative			
Escherichia coli	1 (1.0%)	-	-
Pseudomonas spp	1 (1.0%)	-	
Enterobacter spp	-	1 (1.0)	
Klebsiella pneumoniae	-	-	1 (1.0)
Acinetobacter baumannii	-	-	1 (1.0)
Acinetobacter lwoffii	-	-	1 (1.0)
Total culture positive	61 (60)	25 (24.5)	48 (47.1)

MRSA, methicillin-resistant *Staphylococcus aureus.*

Table 4
Demographic data of patients with MRSA infection.

Variable	007	015	017	018
Sex	Male	Male	Male	Female
Age in years	11.4	1.3	8.3	4.8
Underlying disease	AD	AD	AD	AD
SCORAD	19	32	20	34
SSTIs	Secondary bacterial infection	Secondary bacterial infection	Secondary bacterial infection	Secondary bacterial infection
Treatment	Topical fusidic acid	Topical mupirocin	Topical fusidic acid	Topical mupirocin
Lesion organism	*Staphylococcus aureus*	MRSA	MRSA	MRSA
Normal skin organism	*Staphylococcus aureus*	MRSA	NG	NG
Nasal organism	MRSA	MRSA	MRSA	MRSA

AD, atopic dermatitis; SCORAD, Scoring atopic dermatitis; SSTIs, skin and soft tissue infections; MRSA, methicillin-resistant *Staphylococcus aureus;* NG, no growth.

Table 5
Antimicrobial susceptibilities of MRSA.

Site of positive culture	Susceptibility antibiotics								
	Clindamycin	Erythromycin	Trimethoprim/ sulfamethoxazole	Gentamicin	Ciprofloxacin	Fusidic acid	Moxifloxacin	Doxycycline	Cefoxitin
Lesion, *n* (%) (3 cases)	2 (66.7)	2 (66.7)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	0 (0)
Normal skin, *n* (%) (1 case)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0)
Nasal, *n* (%) (4 cases)	2 (50.0)	2 (50.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	0 (0)

MRSA, methicillin-resistant *Staphylococcus aureus*.

had moderately severe AD, with a mean SCORAD index of 26.25 (range, 19-34). Demographic data of 4 patients with MRSA are shown in Table 4.

Drug sensitivities of MRSA isolates

All MRSA isolates were resistant to cefoxitin, but were all susceptible to trimethoprim-sulfamethoxazole, gentamicin, ciprofloxacin, fusidic acid, moxifloxacin, and doxycycline. Sixty-six point seven percent of MRSA isolates cultured from lesions and 50% of MRSA isolates cultured from the anterior nares were susceptible to clindamycin and erythromycin. None of the MRSA isolates cultured from normal skin were resistant to clindamycin or erythromycin (Table 5).

DISCUSSION

In this study, eczema with secondary bacterial infection was the most common type of SSTIs. AD was the most common (47%) underlying skin disease. AD patients have skin barrier dysfunction and altered innate and acquired immunity (Bieber, 2008; Boguniewicz and Leung, 2011; Leung, 2013), leading to increased risk for SA infection and colonization in both lesions and non-lesional skin. SA infections and colonization of the skin and anterior nares are important triggers among AD patients (Chiu *et al*, 2010). Skin microbiomes in AD patients have been found to be different from healthy skin (Kong *et al*, 2012). Treatment with emollients helps restore skin barrier function and decreases colonization with SA, decreasing risk of flare ups of AD (Seite *et al*, 2014).

SA was the most common (50.9%) organism isolated among our study subjects, but only 6% had MRSA. All MRSA isolates were found in moderately severe AD patients. The prevalence of MRSA in

our study was low compared to reports from western countries (Moran *et al*, 2006).The prevalence of MRSA varies by country and region, with 54% (range: 15-74%) in the US (Ray *et al*, 2013a), 21% in Israel (Berla-Kerzhner *et al*, 2016) and 1.1% in China (Liu *et al*, 2009). These may be due to genetic susceptibilities or environmental factors. MRSA colonization was 20% from patient swabs obtained on admission to the hospital in Singapore (Kong *et al*, 2016).

In a previous study (Chatproedprai *et al*, 2016), the prevalence of MRSA among AD patients was 44.4% during November 2009 to October 2011. After the study we decreased the use of oral antibiotics and increased the use of topical antibiotics; 84% of the patients in this current study were prescribed topical antibiotics. Other studies have also found a decrease in the prevalence of MRSA (Ray *et al*, 2013b).

In this study, all cultures positive for MRSA were susceptible to trimethoprim-sulfamethoxazole, gentamicin, ciprofloxacin, fusidic acid, moxifloxacin, and doxycycline. Studies from the US reported nearly all MRSA isolates were susceptible to trimethoprim-sulfamethoxazole, 86% of isolates were susceptible to tetracycline and 81% of isolates were susceptible to clindamycin (Moran *et al*, 2006; Walraven *et al*, 2012). In our study 33.3% of MRSA isolates from lesions were resistant to clindamycin and erythromycin and 50% of MRSA isolates from the anterior nares were resistant to clindamycin. This is in contrast to a previous study from the US that found 11% of MRSA isolates were resistant to erythromycin and fusidic acid (Ray *et al*, 2013b). A study from Brazil found 1.1% and 5.9% of isolates were resistant to mupirocin and fusidic acid, respectively (Bessa *et al*, 2016) and a report from The Netherlands found 23% of the nasal isolates and 35% of wound isolates were resistant to fusidic acid (Rijnders *et al*, 2012). Regular monitoring of MRSA susceptibilities needs to be conducted to follow trends in each region.

SA was the most common isolate from SSTIs in our study. The incidence of MRSA was low, so dicloxacillin is still the drug of choice to treat SSTIs in Thailand. For SSTIs unresponsive to dicloxacillin, or in patients with moderate to severe AD or those with a positive culture for MRSA, fusidic acid can be used in patients with a few lesions. However, in cases with widespread infection, trimethoprim-sulfamethoxazole can be used. For children older than 12 years, ciprofloxacin or doxycycline can also be used. The high rates of resistance to clindamycin and erythromycin among MRSA isolates in our study may be due to the overuse of topical clindamycin and erythromycin, which are commonly used for skin infections or to treat acne in Thailand. Thus, clindamycin and erythromycin are not good choices for MRSA treatment in our study population. A limitation of this study was the small sample size, of which only 60% of samples from patients with SSTIs had a positive culture.

In summary, the most common cause of SSTIs in this study was SA.The prevalence of MRSA is still uncommon in SSTIs among our study subjects. Effective antibiotic agents to treat MRSA are trimethoprim-sulfamethoxazole and fusidic acid and among children aged > 12 years are ciprofloxacin and doxycycline.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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