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Original Article

Antibiotic resistance of *Staphylococcus aureus* colonized in children with staphylococcal scalded skin syndrome

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Objectives: Systemic antibiotic therapy with semisynthetic penicillinase-resistant penicillin or vancomycin and clindamycin are recommended for the treatment of staphylococcal scalded skin syndrome (SSSS). This study assessed the rate of antibiotic resistance of *Staphylococcus aureus* isolated from the anterior nares or skin of children diagnosed with SSSS.

Methods: A retrospective review of the medical records of 25 patients with SSSS between July 2010 and October 2014 was conducted. The clinical characteristics of patients were collected and the antibiotic susceptibility of *S. aureus* were analyzed using automated systems.

Results: The median age of the patients was 22 months (range: 2-95). Ninety-two percent of patients were less than 5 years of age. Nasal swab samples of all patients and skin swab samples of 17 patients were cultured to isolate *S. aureus*. Twenty-one (84%) of 25 patients were colonized with methicillin-resistant *S. aureus* (MRSA). The results of swab samples of the other four patients were no growth or isolation of bacteria other than *S. aureus*. Among 20 strains isolated from the anterior nares, 1 strain (5%) was methicillin-susceptible *S. aureus*. All 15 strains isolated from the skin were MRSA. All 21 strains isolated from anterior nares or skin were found to be resistant to clindamycin upon evaluation using automated systems.

Conclusions: The rates of methicillin and clindamycin resistance in *S. aureus* colonized in children with SSSS were very high. Further studies evaluating proper antibiotic regimens and the effectiveness of systemic antibiotic therapy are needed.

Key Words: Bacterial, Child, Colonization, Drug resistance, Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome (SSSS) collectively refers to a group of diseases characterized by superficial blistering of the skin caused by exfoliative toxins released by *Staphylococcus aureus*, including Ritter disease, ranging from bullous impetigo to general epidermal exfoliation.[1] Only about 3-4% of *S. aureus* strains are known to release exfoliative toxins.[2,3] There are two types of exfoliative toxins, A and B, and exfoliative toxin B is generally identified in *S. aureus* strains isolated from children with SSSS in Korea.[4]

The reported rates of *S. aureus* nasal colonization were 38.3% in preschool-aged children in childcare centers and 32.1% in children presenting to a tertiary healthcare institution.[5,6] The proportions of methicillin-resistant *S. aureus* (MRSA) strains in the colonized S. aureus from the above studies were 24.4% and 18.9%, respectively.

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However, the proportion of MRSA strains in skin-colonized *S. aureus* was very high (96.2–100%) in a study of pediatric patients with SSSS.[7,8]

Semisynthetic penicillinase-resistant penicillin or vancomycin and clindamycin are recommended for the treatment of pediatric patients with SSSS;[9] however, many cases involving MRSA strains show improvement even without the use of susceptible antibiotics, such as vancomycin.[4,7]

This study investigates the rates of oxacillin and clindamycin (a key recommended medication) resistance in nasal- and skin-colonized *S. aureus* strains in pediatric patients with SSSS.

MATERIALS AND METHODS

Subjects

We retrospectively analyzed the medical records of 25 pediatric patients diagnosed with SSSS based on symptoms, including erythema, epidermal exfoliation, and blistering, at our pediatrics department between July 2010 and October 2014. This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (2017-11-010).

Methods

1) Clinical features

We examined medical records to identify patient sex, age, and the presence of fever and skin lesions with discharge. We also analyzed hospitalization status, length of hospital stays, empirical antibiotic administration, and finally selected antibiotics after antibiotic sensitivity testing.

2) Nasal and skin *S. aureus* colonization

In the research facility, the anterior nares of patients diagnosed with SSSS were swabbed with a cotton swab and the sample was cultured to identify *S. aureus* strains colonized in the nasal cavity. For patients with skin lesions with discharge, the lesions were swabbed for bacterial culture.

3) Antibiotic susceptibility of *S. aureus*

To determine the bacterial strains and antibiotic susceptibilities, a Phoenix 100 automated system (BD Diagnostics, Sparks, USA) was mainly used with the aid of a Vitek 2 (bioMérieux, Marcy l'Etoile, France) instrument. In *S. aureus* strains isolated after 2013, D-zone tests were performed for strains with erythromycin resistance and clindamycin susceptibility, with inducible clindamycin resistance being considered clindamycin-resistant.

4) Statistical analysis

The distributions of descriptive statistics were examined using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Medians and ranges were computed for continuous variables with non-normal distributions.

RESULTS

Table 1. Clinical characteristics of 25 children diagnosed with staphylococcal scalded skin syndrome

Variables	n (%)
Sex	
Male	14 (56)
Female	11 (44)
Age (months), median (range)	22 (2 - 95)
< 24	15 (60)
24-60	8 (32)
≥ 60	2 (8)
Fever	7 (28)
Admission	24 (96)
Hospital days, median (range)	7 (3 - 12)
Involved location	
Head and neck	25 (100)
Extremities	18 (72)
Trunk	22 (88)
Associated disease	
Atopic dermatitis	1 (4)
Acute otitis media	2 (8)
Hand foot mouth disease	1 (4)
Leukocytosis (≥ 15,000/㎣)	7/23 (30.4)
Eosinophilia (≥ 500/㎣)	3/23 (13)

Clinical features

Among 25 patients diagnosed with SSSS during the study period, 14 were male (56%) (Table 1). The median age was 22 months, with age ranging from two months to 7 years and 11 months. Ninety-two percent of the study population was children aged 60 months or younger, with children aged 24 months or younger accounting for 60% of the study population. Seven patients (28%) had an accompanying fever, which lasted less than two days in six of them (85.7%). Twenty-four (96%) patients were hospitalized and one patient (4%) was treated as an outpatient. The median length of hospital stay was seven days, ranging from 3-12 days.

All patients had head and neck lesions at admission, 72% had extremities, and 88% had trunk lesions. The accompanying diseases were atopic dermatitis, otitis media, and hand-foot-mouth disease. Laboratory tests were performed in 23 patients. Seven patients had leukocytosis and three patients had eosinophilia. SSSS mainly occurred in autumn and 56% of patients were diagnosed in September-November (Fig. 1).

Results of bacterial culture from nasal and skin samples

Bacterial culture was performed for all patients diagnosed with SSSS to determine nasal *S. aureus* colonization. In addition, culture of skin lesions

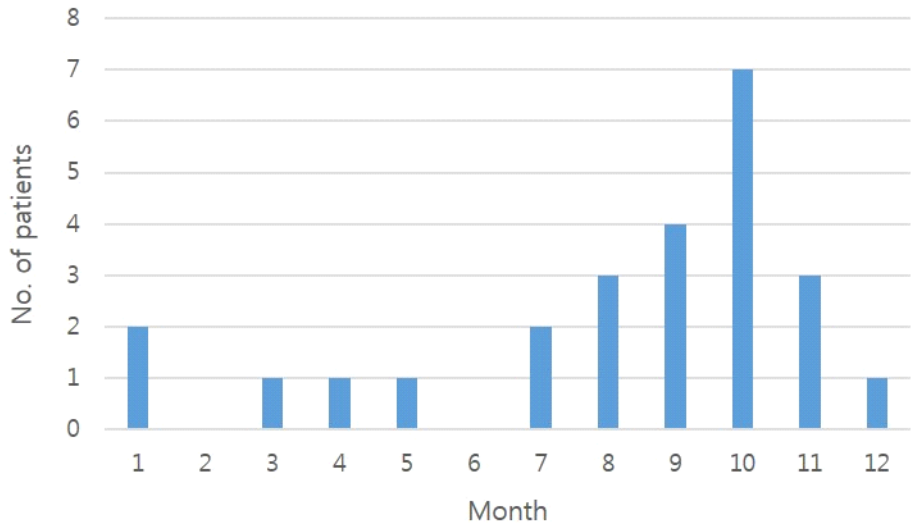

Fig. 1. Monthly distribution of staphylococcal scalded skin syndrome.

with discharge was performed in 17 (68%) patients (Table 2). Nasal *S. aureus* colonization was confirmed in 20 (80%) patients, and *S. aureus* was cultured in the skin sample from 15 (88%) patients for whom additional skin culture was performed. The presence of *S. aureus* was confirmed in the nasal cavity or skin in 21 patients (84%), all of whom had strains of MRSA. One of these patients had a methicillin-resistant strain in the skin but a methicillin-susceptible strain in the nasal cavity.

Antibiotics resistance of colonized *S. aureus*

Nineteen of 20 (95%) nasal-colonized *S. aureus* strains were methicillin-resistant; the remaining strain was susceptible to methicillin (Table 3). The strain with methicillin susceptibility was also susceptible to penicillin. Eighteen of 20 strains were tested for clindamycin susceptibility and 18 were resistant to clindamycin. Two of these clindamycin-resistant strains were resistant to erythromycin but sensitive to clindamycin but were found to have inducible clindamycin resistance in the D-zone test. All of the strains were susceptible to ciprofloxacin, rifampin, vancomycin, and trimethoprim/sulfamethoxazole.

All 15 *S. aureus* strains isolated from the skin cultures were methicillin-resistant. The clindamycin susceptibility results were reported for 14 of the isolates, 13 of which were clindamycin-resistant; for the remaining strain, clindamycin susceptibility could not be verified because the strain was resistant to erythromycin and susceptible to clindamycin but a D-zone test was not performed. Thus, all 13 strains in which clindamycin susceptibility was assessed were resistant to clindamycin. One strain (6.7%) was susceptible to erythromycin, and all of the strains were susceptible to ciprofloxacin, rifampin, vancomycin, and trimethoprim/sulfamethoxazole.

Antimicrobials used for treatment and treatment outcomes

Table 2. Results of bacterial cultures using swab specimens from the anterior nares and skin

	Nasal swab (N = 25)	Skin swab (N = 17)
Isolation of *S. aureus*	20 (80)	15 (88)
MRSA	19 (76)	15 (88)
MSSA	1 (4)	0 (0)
No growth or isolation of bacteria other than *S. aureus*	5 (20)	2 (12)

Data are presented n (%).
Abbreviations: MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-seusceptible *Staphylococcus aureus*

Table 3. Antimicrobial susceptibility of Staphylococcus aureus isolates by colonization sites

Antibiotics	n (%)	
	Anterior nares (N = 20)	Skin (N = 15)
Penicillin	1 (5)	0 (0)
Oxacillin	1 (5)	0 (0)
Clindamycin	0 (0)*	0 (0)†
Erythromycin	0 (0)	1 (6.7)
Gentamicin	2 (10)	0 (0)
Ciprofloxacin	20 (100)	15 (100)
Rifampin	20 (100)	15 (100)
Vancomycin	20 (100)	15 (100)
Trimethoprim/sulfamethoxazole	20 (100)	15 (100)

*N = 18. The results of two isolates were not reported.
†N = 13. The result of one isolate was not reported. The other was erythromycin-resistant and clindamycin-susceptible strain, but the double-disk diffusion test was not conducted.

Cefazolin and clindamycin were used as the initial empiric antibiotics in 20 patients (80%). Cefazolin alone was used for two patients (8%), oral trimethoprim/sulfamethoxazole for two patients (8%), and oral clindamycin for the remaining patient.

A total of eight patients (40%) were administered vancomycin at least once during the course of treatment for a methicillin-resistant strain in the nasal cavity or skin; six of these patients (62.5%) were infants aged 12 months or younger. Four patients (16%) continued to use cefazolin until discharge. Although three of these patients were confirmed to have MRSA, the antibiotic was not changed. A total of 16 patients (64%) were prescribed trimethoprim/sulfamethoxazole at discharge.

None of the patients required a change of antibiotics due to worsened symptoms prior to confirming the antibiotic susceptibility of the nasal- or skin-colonized *S. aureus* strains. Furthermore,

none of the patients developed complications or died during the course of treatment.

DISCUSSION

This study aimed to confirm the colonization of *S. aureus* strains in the nasal cavity or skin of pediatric patients diagnosed with SSSS and to examine the proportions of antibiotic resistance, particularly to oxacillin and clindamycin, in the isolated strains.

SSSS may develop in adults, but it generally affects infants and young children.[10] General blistering and skin exfoliation are usually present in children, presumably because children are less able to excrete toxins and have a lower concentration of antibodies that can neutralize toxins.[11] The majority of our study sample was children under 5 years of age. The prognosis of SSSS is relatively good in children;[12] as anticipated, most patients in our study were discharged within 10 days.

Nasal or skin *S. aureus* colonization was confirmed in 84% of our patients, all of whom had MRSA. Previous Korean studies have reported that a substantial proportion of colonized *S. aureus* strains in SSSS patients are methicillin-resistant.[4,7,8] The proportion of MRSA is very high among patients with SSSS compared to that in patients with general nasal *S. aureus* colonization[5] or invasive diseases,[13] but the reason for this observation has yet to be elucidated.

Because SSSS is a toxin-induced disease, guidelines suggest the additional use of clindamycin to suppress toxin formation.[9] In the present study, all of the nasal- or skin-colonized strains with verified antibiotic susceptibility were resistant to clindamycin. Although clindamycin may suppress the production of exfoliative toxins by *S. aureus*,[14] it was difficult to find data directly supporting clindamycin's capability to suppress exfoliative toxin release in clindamycin-resistant strains. However, Schlievert et al.[15] reported that clindamycin can suppress the production of toxic shock syndrome toxins even in clindamycin-resistant strains. Because clindamycin was used as an early intervention for most patients in this study, it was difficult to analyze its clinical efficacy in suppressing toxin production.

All of the MRSA isolates in this study were susceptible to ciprofloxacin, rifampin, vancomycin, and trimethoprim/sulfamethoxazole. Similar results were found in previous studies with regard to the isolated strains and skin- or nasal-colonized *S. aureus* strains in children with SSSS.[8]

SSSS is characterized by toxin-induced blistering; in many cases, the primary lesions are improved or cannot be examined by the time the patient presents to a hospital. Therefore, there may be doubts as to whether antibiotics must be used; in fact, in clinical practice, patients with MRSA have shown improvement of symptoms even without the administration of antibiotics to which the MRSA isolates are susceptible.[4,7] Similarly, in our study, cefazolin (beta-lactam)

and clindamycin were used as early empiric antibiotics in most patients, but none of the patients required a change of antibiotics due to worsening symptoms prior to receiving the culture results. No study has directly analyzed antibiotic efficacy in patients with SSSS or compared patients in whom drugs to which the MRSA were susceptible were used and those to whom the conventionally recommended beta-lactams and clindamycin were administered.

The present retrospective review of medical records computed the proportions of isolates with methicillin and clindamycin resistance based on the automated analysis of antibiotic resistance of *S. aureus* isolates obtained from patients with SSSS. We could not perform genetic analysis of the staphylococcal cassette chromosome *mec* gene and toxin gene and susceptibility testing by disc diffusion method on Mueller Hinton agar or E-test. However, unlike previous SSSS studies that only performed cultures with skin samples, we cultured samples from the nasal cavity, a major source of *S. aureus* in all patients diagnosed with SSSS, and confirmed that most patients had MRSA strains. Furthermore, we examined and discussed the proportion of isolates with clindamycin resistance and presented topics in need of additional research.

Most *S. aureus* strains in patients with SSSS were MRSA, and all of these strains were also resistant to clindamycin. Considering these resistance rates, additional research is needed to substantiate the efficacy of the current recommendation of beta-lactams and clindamycin therapy.

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