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ORIGINAL ARTICLE

Change in Antimicrobial Susceptibility of Skin-Colonizing *Staphylococcus aureus* in Korean Patients with Atopic Dermatitis during Ten-Year Period

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Background: A small subset of adolescents atopic dermatitis (AD) tends to persist. This also leads to get more antibiotics exposure with advancing years. Antibiotic resistance has been regarded as a serious problem during *Staphylococcus aureus* treatment, especially methicillin-resistant *S. aureus* (MRSA). **Objective:** It was investigated the *S. aureus* colonization frequency in the skin lesions and anterior nares of adolescent AD patients and evaluated the changes in *S. aureus* antimicrobial susceptibility for years. **Methods:** Patients who visited our clinic from September 2003 to August 2005 were classified into group A, and patients who visited from August 2010 to March 2012 were classified into group B. To investigate the differences with regard to patients' age and disease duration, the patients were subdivided into groups according to age. Lesional and nasal specimens were examined. **Results:** Among the 295 AD patients, the total *S. aureus* colonization rate in skin lesions was 66.9% (95/142) for group A and 78.4% (120/153) for group B. No significant changes in the systemic antimicrobial susceptibilities of *S. aureus* strains isolated from adolescent AD patients were observed during about 10-year period. The increased trend of MRSA isolation in recent adolescent AD outpatients suggest that the community including school could be the source of *S. aureus* antibiotic resistance and higher fusidic acid resistance rates provides evidence of imprudent topical use. **Conclusion:** Relatively high MRSA isolation and fusidic acid resistance rates in recent AD patients suggest that the community harbors antibiotic-resistant *S. aureus*. **(Ann Dermatol 28(4) 470~478, 2016)**

-Keywords-
Anti-bacterial agent, Antimicrobial resistance, Antimicrobial susceptibility, Atopic dermatitis, *Staphylococcus aureus*

INTRODUCTION

Atopic dermatitis (AD) is a genetically determined, chronically relapsing inflammatory skin disease with multiple pathogenic factors. While AD occurs most commonly during infancy and children, a smaller subset of adolescents has persistent or new-onset AD. The association between *Staphylococcus aureus* infection and AD is well demonstrated by many investigators[1,2]. *S. aureus* can be found from dermatitic lesions of more than 90% of patients with AD, but also from approximately 70% taken from unaffected areas[1-3]. *S. aureus* plays an important role as a triggering factor[3,4]. The relationship between AD and exacerbation mechanism by *S. aureus* is mainly due to the superantigens (sAgs) and sAgs-specific immunoglobulin E that stimulate various numbers of different T-cell clones

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and cytokine secretion. It has been often proposed that bacterial skin infections are uncommon in AD, while AD patients are commonly colonized with *S. aureus*. Recently lesional *S. aureus* colonization correlates positively with AD clinical severity, and anti-staphylococcal antibiotic therapy can reduce the severity of AD characteristic inflammation[5,6] .

The anterior nares are an important *S. aureus* colonization reservoir. High rate (75%～90%) of nasal carriage of *S. aureus* has been reported in adults and children with AD. In contrast, nasal colonization has ranged from 10% to 50% in normal controls. Thus *S. aureus* carriage in the nose should be targeted for decolonization[7,8].

Antibiotic resistance is increasing around the world to date and has been regarded as an important issue during *S. aureus* treatment since a long time ago, especially methicillin-resistant *S. aureus* (MRSA). MRSA is more difficult to treat because it is resistant to a number of widely used antibiotics. The increasing incidence of community-acquired MRSA (CA-MRSA) in skin infections presents major challenges in the treatment direction. It also raises concerns that the eczematous skin lesions of AD patients might be favorable CA-MRSA reservoirs[9,10]. Topical fusidic acid and mupirocin have been commonly prescribed to eradicate different skin infections via over-the-counter pharmacy in Korea. Although many Asian countries have high MRSA infection rates, there have been no publications about changes in the prevalence of antibiotic-resistant *S. aureus*, including CA-MRSA, in AD patients. Moreover, few studies have dealt with adolescent AD about *S. aureus* colonization and its susceptibilities to various antibiotics.

In present study, it was investigated the *S. aureus* colonization frequency in the skin lesions and anterior nares of AD patients and evaluated the changes in *S. aureus* antimicrobial susceptibility for years. Differences were also analyzed with regard to patient age and disease duration. Also, we investigated the prevalence of topical fusidic acid- and mupirocin-resistant *S. aureus* in adolescent AD.

MATERIALS AND METHODS

Patients

Adolescent AD patients with no evidence of skin infection, who visited the outpatient clinic of the Department of Dermatology, Pusan National University Hospital (Busan, Korea), were enrolled in the study. AD was diagnosed according to the Hanifin and Rajka diagnostic criteria[11]. Total 295 patients who initially visited our clinic from September 2003 to August 2005 were classified into group A, and patients who initially visited from August 2010 to March 2012 were classified into group B. To investigate the differences with regard to patient age and disease duration, the patients were subdivided into groups according to age (younger than 18 years and older than 18 years) and disease duration (less than 1 year, 1～5 years, and more than 5 years). At the first visit, the patient age and disease duration were estimated and AD severity was assessed according to the SCORing Atopic Dermatitis (SCORAD) index[12]. The exclusion criteria were the presence of other skin or allergic diseases; a recent (within 4 weeks) history of inpatient hospital admission; recent (within 4 weeks) treatment with antibiotics, systemic corticosteroids, or immunosuppressants; and treatment with topical antibiotics in the previous 2 weeks.

Methods

The study protocol was approved by the Pusan National University Hospital Institutional Review Board (IRB no. 1409-012-035). Lesional skin specimens were obtained by rolling sterile cotton-tipped swab sticks (transport medium swab; Micromedia Co., Seoul, Korea) over the most affected skin areas twice for at least 5 seconds each. Nasal swabs were obtained by reaching upward toward the top of both anterior nares with sterile cotton-tipped swab stick, followed by a 360° twist to sweep the entire vestibule. The swab specimens were immediately placed in Amie's medium (Micromedia Co.) and were streaked on sheep blood agar plates (Asan Medical Co., Seoul, Korea), incubated at 35°C, and examined at 24 and 48 hours. Colonies were identified in a blind manner by other investigator. In some selected samples of two groups, antibiotic susceptibility tests were performed with the same Vitek 2 system (BioMérieux, Durham, NC, USA) according to the manufacturer's instructions.

For group A, a panel of 8 antibiotics (clindamycin, erythromycin, habekacin, oxacillin, gentamicin, penicillin, bactrim, and vancomycin) was used to test for gram-positive bacteria. For group B, a panel of 11 antibiotics or combinations (ciprofloxacin, fusidic acid, rifampin, teicoplanin, tetracycline, nitrofurantoin, quinupristin/dalfopristin, linezolid, telithromycin, mupirocin, and tigecycline) was added to the previous panel.

Statistical analysis

The Shapiro-Wilk normality test was performed to evaluate differences between the groups with regard to patient age, disease duration, and severity, using the Predictive Analytics Software package (PASW for Windows; IBM Co., Armonk, NY, USA). The chi-square and Fisher's exact tests were performed to estimate differences in the colonization rates between groups that were subdivided ac-

cording to time period, age, and disease duration. Statistical significance was defined as a p-value of <0.05.

RESULTS

Clinical and demographic data

The clinical and demographic data for groups A and B are presented in Table 1. Overall, 142 and 153 patients were enrolled in groups A and B, respectively. The mean patient age in group A was 13.7 years, and the mean disease duration was 7.3 years. The mean patient age in group B was 18.3 years, and the mean disease duration was 10.0 years. The difference in clinical severity according to the SCORAD index was not significant between the 2 groups.

Colonization of *S. aureus*

Among the 295 AD patients, the total *S. aureus* colonization rate in skin lesions was 66.9% (95/142) for group A and 78.4% (120/153) for group B ($p=0.03$). In group A, 142 samples were taken from the nares. In group B, 97 sampling were done in the nares. In the nasal swabs, *S. aureus* was found to colonize 64.1% (91/142) of the group A patients and 63.9% (62/97) of the group B patients ($p=0.05$). To analyze antibiotics sensitivity, 64 samples and 57 samples were used at the lesion and nares in group A. One hundred and six samples and 23 samples were used in each of group B.

In group A, 2 of 64 (3.1%) and 4 of 57 (7.0%) patients carried MRSA in the lesional skin and the anterior nares, respectively, whereas in group B, 11 of 106 (10.4%) and 3 of 23 (13.0%) patients carried MRSA in the lesional skin and the anterior nares, respectively ($p>0.05$; Table 2).

Changes in *S. aureus* antimicrobial susceptibility

Changes in *S. aureus* antimicrobial susceptibility in adolescent AD patients over time are shown in Table 3. In lesional skin, the rates of *S. aureus* susceptibility to clindamycin and erythromycin increased significantly in group B when compared with those in group A. The rates of susceptibility of *S. aureus* in lesional skin to fusidic acid and mupirocin, which are the main topical agents used to treat AD skin infections, were 67.0% and 95.3%, respectively in group B. The susceptibility rates of *S. aureus* in the anterior nares to fusidic acid and mupirocin were 60.9% and 91.3%, respectively. The rate of susceptibility of *S. aureus* in nasal swabs to erythromycin increased significantly during about 10-year period. For samples of both lesional skin and anterior nares, the penicillin susceptibility rate increased over time but remained much lower than those for other antibiotics.

The MRSA colonization rates did not significantly differ between groups A and B ($p>0.05$). All isolated MRSA strains were susceptible to habekacin, bactrim, and vancomycin (Table 4).

S. aureus antimicrobial susceptibility was also analyzed according to the patient age (younger than 18 years versus older than 18 years; Table 5). In patients older than 18 years, *S. aureus* in samples of both the lesional skin and anterior nares was significantly more susceptible to erythromycin, compared to the susceptibility in patients younger than 18 years. Low susceptibility rates to penicillin and fusidic acid were observed regardless of the patient age.

Table 6 shows the antimicrobial susceptibility of *S. aureus* with regard to the disease duration. For lesional skin samples, erythromycin susceptibility rate was significantly lower in patients with disease duration of less than 5 years than in those with disease duration of more than 5 years.

Table 1. Demographics of atopic dermatitis patients

Demographics	Group A (n=142)	Group B (n=153)	Total (n=295)
Male:female	72:70	92:61	164:131
Age (yr)	13.7±9.6	18.3±9.5	16.1±9.9
≤18	95 (66.9)	81 (52.9)	176 (59.7)
>18	47 (33.1)	72 (47.1)	119 (40.3)
Disease duration (yr)	7.3±6.6	10.0±7.7	8.7±7.3
≤1	23 (16.2)	22 (14.4)	45 (15.3)
1~5	54 (38.0)	30 (19.6)	84 (28.5)
>5	65 (45.8)	101 (66.0)	166 (56.3)
SCORing atopic dermatitis index	38.4±1.7	36.9±2.0	37.6±1.9

Values are presented as number only, mean±standard deviation, or number (%).

Table 2. Total colonization rates (%) of *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) in lesional skin and anterior nares

Colonization	Lesional skin			Anterior nares		
	Group A	Group B	p-value	Group A	Group B	p-value
S. aureus	66.9 (95/142)	78.4 (120/153)	0.03	64.1 (91/142)	63.9 (62/97)	0.05
MRSA	3.1 (2/64)	10.4 (11/106)	>0.05	7.0 (4/57)	13.0 (3/23)	>0.05

Values are presented as percentage (number/total number).

Table 3. Change in *Staphylococcus aureus* antimicrobial susceptibility

Antibiotics	Lesional skin			Anterior nares		
	Group A	Group B	*p*-value	Group A	Group B	*p*-value
Clindamycin	52 (81.3)	100 (94.3)	0.007	50 (87.7)	21 (91.3)	1.0
Erythromycin	38 (59.4)	97 (91.5)	<0.001	36 (63.2)	21 (91.3)	0.012
Habekacin	64 (100.0)	106 (100.0)	-	55 (96.5)	23 (100.0)	1.0
Oxacillin	62 (96.9)	95 (89.6)	0.134	53 (93.0)	20 (87.0)	0.218
Gentamicin	52 (81.3)	92 (86.8)	0.331	48 (84.2)	18 (78.3)	0.530
Penicillin	9 (14.1)	22 (20.8)	0.274	8 (14.0)	6 (26.1)	0.210
Bactrim	64 (100.0)	106 (100.0)	-	57 (100.0)	23 (100.0)	-
Vancomycin	64 (100.0)	106 (100.0)	-	57 (100.0)	23 (100.0)	-
Ciprofloxacin	-	105 (99.1)	-	-	22 (95.7)	-
Fusidic acid	-	71 (67.0)	-	-	14 (60.9)	-
Rifampin	-	106 (100.0)	-	-	23 (100.0)	-
Teicoplanin	-	105 (99.1)	-	-	23 (100.0)	-
Tetracycline	-	98 (92.5)	-	-	23 (100.0)	-
Quinupristin/dafopristin	-	106 (100.0)	-	-	23 (100.0)	-
Nitrofurantoin	-	105 (99.1)	-	-	23 (100.0)	-
Linezolid	-	106 (100.0)	-	-	23 (100.0)	-
Telithromycin	-	106 (100.0)	-	-	22 (95.7)	-
Mupirocin	-	101 (95.3)	-	-	21 (91.3)	-
Tigecycline	-	106 (100.0)	-	-	23 (100.0)	-
Total	64 (100.0)	106 (100.0)		57 (100.0)	23 (100.0)	

Values are presented as number (%).

Table 4. Change in methicillin-resistant *Staphylococcus aureus* antimicrobial susceptibility

Antibiotics	Lesional skin		Anterior nares	
	Group A	Group B	Group A	Group B
Clindamycin	2 (100.0)	9 (81.8)	3 (75.0)	2 (66.7)
Erythromycin	1 (50.0)	9 (81.8)	2 (50.0)	2 (66.7)
Habekacin	2 (100.0)	11 (100.0)	4 (100.0)	3 (100.0)
Gentamicin	2 (100.0)	9 (81.8)	3 (75.0)	2 (66.7)
Penicillin	0	0	0	0
Bactrim	2 (100.0)	11 (100.0)	4 (100.0)	3 (100.0)
Vancomycin	2 (100.0)	11 (100.0)	4 (100.0)	3 (100.0)
Ciprofloxacin	-	10 (90.9)	-	3 (100.0)
Fusidic acid	-	11 (100.0)	-	3 (100.0)
Rifampin	-	11 (100.0)	-	3 (100.0)
Teicoplanin	-	11 (100.0)	-	3 (100.0)
Tetracycline	-	9 (81.8)	-	3 (100.0)
Quinupristin/dafopristin	-	11 (100.0)	-	3 (100.0)
Nitrofurantoin	-	11 (100.0)	-	3 (100.0)
Linezolid	-	11 (100.0)	-	3 (100.0)
Telithromycin	-	10 (90.9)	-	2 (66.7)
Mupirocin	-	9 (81.8)	-	2 (66.7)
Tigecycline	-	11 (100.0)	-	3 (100.0)
Total	2 (100.0)	11 (100.0)	4 (100.0)	3 (100.0)

Values are presented as number (%).

Low susceptibility rates to penicillin and fusidic acid were observed regardless of the disease duration.

DISCUSSION

S. aureus may not be of primary importance in AD pathogenesis but is an important triggering and/or aggravating factor in cutaneous AD inflammation due to *S. aureus* sAgs[13]. *S. aureus* colonization rate is significantly higher in AD patients than in normal controls because the stratum corneum of AD patients is highly susceptible to colonization by various bacteria including *S. aureus*[10,14]. Also, several studies have showed that AD keratinocytes produce lower amounts of antimicrobial peptides and this may increase the colonization and infection with *S. aureus*[15]. This study revealed the increasing prevalence of *S. aureus* colonization in adolescent AD skin (from 66.9% to 78.4% [p=0.03]) during about 10-year period. This is consistent with the increased *S. aureus* colonization rates over time that were previously described in cross-sectional studies[10,16]. The increased *S. aureus* colonization rate indicates the importance of determining the antibiotic susceptibility of *S. aureus* and controlling AD inflammations effectively.

Prolonged or imprudent antibiotic use may induce the development of antibiotic-resistant *S. aureus* strains[13,17].

Table 5. *Staphylococcus aureus* antimicrobial susceptibility with respect to age in patients with atopic dermatitis

Antibiotics	Lesional skin			Anterior nares		
	≤18 yr	>18 yr	*p*-value	≤18 yr	>18 yr	*p*-value
Clindamycin	85 (85.9)	67 (94.4)	0.075	40 (88.9)	31 (88.6)	1.0
Erythromycin	70 (70.7)	65 (91.5)	0.001	27 (60.0)	30 (85.7)	0.012
Habekacin	99 (100.0)	71 (100.0)	-	45 (100.0)	33 (94.3)	0.188
Oxacillin	90 (90.9)	67 (94.4)	0.403	39 (86.7)	34 (97.1)	0.129
Gentamicin	86 (86.9)	58 (81.7)	0.355	38 (84.4)	28 (80.0)	0.604
Penicillin	17 (17.2)	14 (19.7)	0.672	6 (13.3)	8 (22.9)	0.266
Bactrim	99 (100.0)	71 (100.0)	-	45 (100.0)	35 (100.0)	-
Vancomycin	99 (100.0)	71 (100.0)	-	45 (100.0)	35 (100.0)	-
Total	99 (100.0)	71 (100.0)		45 (100.0)	35 (100.0)	
Ciprofloxacin	57 (98.3)	48 (100.0)	1.0	7 (100.0)	15 (93.8)	1.0
Fusidic acid	38 (65.5)	33 (68.8)	0.725	4 (57.1)	10 (62.5)	1.0
Rifampin	58 (100.0)	48 (100.0)	-	7 (100.0)	16 (100.0)	-
Teicoplanin	58 (100.0)	48 (100.0)	-	7 (100.0)	16 (100.0)	-
Tetracycline	53 (91.4)	45 (93.8)	0.726	7 (100.0)	16 (100.0)	-
Quinupristin/dafopristin	58 (100.0)	48 (100.0)	-	7 (100.0)	16 (100.0)	-
Nitrofurantoin	57 (98.3)	48 (100.0)	1.0	7 (100.0)	16 (100.0)	-
Linezolid	58 (100.0)	48 (100.0)	-	7 (100.0)	16 (100.0)	-
Telithromycin	57 (98.3)	48 (100.0)	1.0	6 (85.7)	16 (100.0)	0.304
Mupirocin	55 (94.8)	46 (95.8)	1.0	6 (85.7)	15 (93.8)	0.526
Tigecycline	58 (100.0)	48 (100.0)	-	7 (100.0)	16 (100.0)	-
Total	58 (100.0)	48 (100.0)		7 (100.0)	16 (100.0)	

Values are presented as number (%).

Table 6. *Staphylococcus aureus* antimicrobial susceptibility with respect to disease duration in patients with atopic dermatitis

Antibiotics	Lesional skin				Anterior nares			
	≤1 yr	1~5 yr	>5 yr	*p*-value	≤1 yr	1~5 yr	>5 yr	*p*-value
Clindamycin	18 (81.8)	41 (89.1)	93 (91.2)	0.567	10 (100.0)	23 (92.0)	38 (84.4)	0.407
Erythromycin	16 (72.7)	31 (67.4)	88 (86.3)	0.023	5 (50.0)	16 (64.0)	36 (80.0)	0.108
Habekacin	22 (100.0)	46 (100.0)	101 (99.0)	1.0	10 (100.0)	24 (96.0)	44 (97.8)	0.783
Oxacillin	19 (86.4)	40 (87.0)	98 (96.1)	0.053	8 (80.0)	23 (92.0)	42 (93.3)	0.409
Gentamicin	18 (81.8)	40 (87.0)	86 (84.3)	0.824	9 (90.0)	22 (88.0)	35 (77.8)	0.582
Penicillin	3 (13.6)	6 (13.0)	22 (21.6)	0.408	1 (10.0)	5 (20.0)	8 (17.8)	0.919
Bactrim	22 (100.0)	46 (100.0)	102 (100.0)	-	10 (100.0)	25 (100.0)	45 (100.0)	-
Vancomycin	22 (100.0)	46 (100.0)	102 (100.0)	-	10 (100.0)	25 (100.0)	45 (100.0)	-
Total	22 (100.0)	46 (100.0)	102 (100.0)		10 (100.0)	25 (100.0)	45 (100.0)	
Ciprofloxacin	12 (100.0)	23 (100.0)	70 (98.6)	1.0	1 (50.0)	4 (100.0)	17 (100.0)	0.087
Fusidic acid	7 (58.3)	15 (65.2)	49 (69.0)	0.700	1 (50.0)	4 (100.0)	9 (52.9)	0.825
Rifampin	12 (100.0)	23 (100.0)	71 (100.0)	-	2 (100.0)	4 (100.0)	17 (100.0)	-
Teicoplanin	12 (100.0)	23 (100.0)	71 (100.0)	-	2 (100.0)	4 (100.0)	17 (100.0)	-
Tetracycline	10 (83.3)	20 (87.0)	68 (95.8)	0.104	2 (100.0)	4 (100.0)	17 (100.0)	-
Quinupristin /dafopristin	12 (100.0)	23 (100.0)	71 (100.0)	-	2 (100.0)	4 (100.0)	17 (100.0)	-
Nitrofurantoin	12 (100.0)	23 (100.0)	70 (98.6)	1.0	2 (100.0)	4 (100.0)	17 (100.0)	-
Linezolid	12 (100.0)	23 (100.0)	71 (100.0)	-	2 (100.0)	4 (100.0)	17 (100.0)	-
Telithromycin	12 (100.0)	23 (100.0)	70 (98.6)	1.0	2 (100.0)	3 (75.0)	17 (100.0)	0.261
Mupirocin	11 (91.7)	23 (100.0)	67 (94.4)	0.353	2 (100.0)	3 (75.0)	16 (94.1)	0.462
Tigecycline	12 (100.0)	23 (100.0)	71 (100.0)	-	2 (100.0)	4 (100.0)	17 (100.0)	-
Total	12 (100.0)	23 (100.0)	71 (100.0)		2 (100.0)	4 (100.0)	17 (100.0)	

Values are presented as number (%).

Although careful antibiotic use has been often suggested, to our knowledge, no reports have investigated changes in antibiotics susceptibility only in adolescent AD patients. Diamantis et al.[18] reported a comparison of antibiotic resistance patterns in pediatric dermatology patients infected by *S. aureus* in 2005～2007 (66% of children with AD) versus 2008～2009 (72.4% with AD). They found an increase in *S. aureus* antibiotic resistance except to methicillin, which surprisingly decreased. Other pediatric dermatology clinic in North Carolina also conducted the antibiotic susceptibility profiles in *S. aureus* cutaneous infections between 2005 and 2007[19]. The subjects of study included 66% of AD patients, and they demonstrated the following resistance patterns: penicillin (86%), erythromycin (46%), methicillin (32%), clindamycin (22%), gentamicin (3%), vancomycin (0%), and trimethoprim-sulfamethoxazole (0%).

In the patients with CA-MRSA infections, traditional MRSA risk factors are absent and resistance is usually limited to β-lactam antibiotics[16]. Following the first report in 1961 in England, the incidence of MRSA has increased progressively[20]. Recently, MRSA infections have been described in patients without established risk factors who are living in the community, especially AD patient. In a previous report, 4.2% of those obtained from the general outpatient pediatric population showed methicillin resistance and in our study, the frequency of CA-MRSA-positive skin samples was 10.4% despite smaller samples[21,22].

This agrees with earlier findings that the CA-MRSA prevalence was 7.4% to 18.4% of skin cultures from AD patients[9,10]. In our study, increased trend of MRSA isolation rates were observed in both skin lesions and anterior nares although these increases were statistically insignificant. Moreover, MRSA colonization rates in healthy individuals were reported as 0%～9% in previous studies, and these rates are comparable with those of AD patients[21-23]. Since *S. aureus* has a predilection for damaged skin and AD patients are frequently exposed to antimicrobials, the relatively lower rate of MRSA colonization observed in our study might be meaningful. But, increased caution during MRSA infection management is required in AD patients, as they can be sources of CA-MRSA. All MRSA strains in this study were susceptible to vancomycin, the treatment of choice for MRSA infections. However, vancomycin use should be reserved for MRSA infections which is based by culture.

The present study verified the low rates of *S. aureus* penicillin susceptibility in adolescent AD outpatients (14.0%～26.1%), regardless of the time period, age, or disease duration. This finding is consistent with a previous study, which reported that 13% of AD patients were sensitive to penicillin[16]. The penicillin susceptibility rate remains much lower than that of other antibiotics, even though penicillin usage is restricted in AD patients in Korea. This is because the rates of declining resistance appear to be slower than that of emerging resistance and appear to vary with different agent classes[24].

Fusidic acid has been widely used as topical antimicrobial to treat bacterial superinfections in AD patients until now. In our study, relatively low susceptibility rates (60.9%～67.0%) to fusidic acid were observed regardless of the patient age and disease duration. In Korea, topical fusidic acid antimicrobial has been classified over-the counter drug and its low susceptibility provides evidence of imprudent topical use. Our results suggest that another agent should be used for the treatment of adolescent AD patients with suspected *S. aureus* infections. In a British study published in 2009, 41% of *S. aureus* isolates from dermatology patients were fusidic acid-resistant, compared with a 50% resistance rate in 2001, due to usage restrictions and a significant decrease in the use of topical fusidic acid[25,26]. The authors supposed that a lag period might occur before fusidic acid resistance is absent from the community. Topical fusidic acid use should be restricted due to the current high level of resistance. A relatively high susceptibility (91.3%～95.3%) to mupirocin was demonstrated in our study, regardless of the time period, patient age, and disease duration. This finding was consistent with previous results, which suggested that 4% of isolates from AD patients were mupirocin-resistant[27]. These results indicate that topical fusidic acid has been used more extensively than mupirocin. However, the potential for the development of bacterial resistance to mupirocin ointment should not be ignored, and thus caution regarding its use is needed to retain the high antimicrobial effects[28,29].

Despite the concerns of many dermatologists, there were no significant changes in *S. aureus* antimicrobial susceptibility in AD, except for erythromycin and clindamycin, during the recent 10-year period. In the 1990s, erythromycin was the first-line treatment for bacterial infections in AD patients, but its use has decreased after reports of high erythromycin resistance rates in *S. aureus* and recommended usage restrictions[30,31]. According to our data, the erythromycin susceptibility rate increased significantly during the period from 59.4% to 91.5% for the lesional skin samples and from 63.2% to 91.3% for the anterior nare samples. Previous reports conducted in the USA, Europe, and Asia indicated that 51%～76% of *S. aureus* strains were erythromycin-susceptible in 1999[32-34]. Hoeger's study[35] of antimicrobial susceptibility, which was published in 2004, revealed that the rate of *S. aureus* eryth-

romycin resistance remained low in 82% of AD patients. Thus, erythromycin should no longer be recommended as a therapeutic agent for *S. aureus*-infected AD patients.

In previous studies conducted in 1997 and 1999, a 91%～97% clindamycin susceptibility rate was demonstrated in Singapore and Europe[36,37]. In 2008, Niebuhr et al.[30] reported that clindamycin has been recommended as a first-line therapy (alternative to cephalexin or cefuroxime) and for staphylococcal skin infections in Germany, and another study conducted in 2005 and 2006 revealed a clindamycin susceptibility rate of 79% for *S. aureus*[35,36]. Interestingly, in our study, the clindamycin susceptibility rate in lesional skin samples increased significantly from 81.3% to 94.3% during the period. In Korea, reports described relatively low *S. aureus* susceptibility rates to clindamycin (48%～82.6%) and recommended clindamycin usage restrictions; our data reflect those efforts[37,38]. Clindamycin acts against a variety of anaerobic bacteria, but broad antibiotic coverage is not required in AD, as *S. aureus* is the most frequent skin infection-inducing microorganism[30]. Therefore, clindamycin should also no longer be suggested as a therapeutic agent for *S. aureus* infections in AD patients.

According to our age-based analysis, for both the lesional skin and nasal cultures, patients younger than 18 years have significantly lower susceptibility rates against erythromycin than do patients older than 18 years. Our results are comparable to those of Arkwright et al.[39], who studied age-related changes in the *S. aureus* prevalence on affected AD skin. The authors found that children older than 5 years had a higher prevalence of erythromycin-resistant *S. aureus* (35%) than did younger children (26%). This discordance of results between the 2 studies might be due to differences in the age groups and distributions. In our study, the group of patients who were younger than 18 years included more group A patients with significantly higher erythromycin resistance rates. According to our disease duration-based analysis, different resistant patterns have shown in various antimicrobials, although we did not find a statistic difference. In our population, patients with disease duration of less than 5 years were less susceptible to erythromycin than patients with disease duration of more than 5 years. It was possible that erythromycin was no more used as a therapeutic agent for *S. aureus*-infected AD patients in different outpatient settings. A previous study by Ewing et al.[40] supported the idea that antibiotic therapy is not helpful in AD patients who do not present signs of bacterial infection. Moreover, the MRSA incidence rate increased after a 4-week systemic antibiotic therapy course. Continuous antibiotic use with the intent to clear *S. aureus* colonization in AD may ultimately result in the failures of these antibiotics to treat severe infections, which are not uncommon in AD[41]. The therapeutic recommendation for bacterial infections in AD patients includes a combination therapy of topical anti-inflammatory drugs and topical/systemic antibiotics during the early stage when clinical signs of a secondary bacterial infection are present[42]. Recently, cephalexin, a first-generation cephalosporin, was found to be a good first-line antibiotic for the treatment of secondary *S. aureus* infections in AD due to its restricted antimicrobial spectrum, which comprises gram-positive bacteria and a limited number of gram-negative strains[30].

In conclusion, despite our concerns, no significant changes in the antimicrobial susceptibilities of *S. aureus* strains isolated from AD patients were observed during a 10-year period. These results indicate that in medical society, a high level of attention is focused on the misuse and abuse of antibiotics. However, the increased trend of MRSA isolation and fusidic acid resistance rates in recent AD outpatients suggest that the community including school could be the source of *S. aureus* antibiotic resistance and its imprudent prescription. To appropriately treat skin infections in adolescent AD, proper antibiotic use through periodic reviews and understandings of changes in microorganisms and antimicrobial sensitivities is necessary to avoid the excessive use of broad-spectrum empiric antibiotics.

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