Original Article

Carriage of antibiotic-resistant *Staphylococcus aureus* in atopic dermatitis children attending paediatric outpatient clinics

門診異位性皮膚炎患童中抗藥性金黃色葡萄球菌的帶菌狀況

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Children with atopic dermatitis (AD) are commonly colonized with *Staphylococcus aureus*. Antibiotics frequently used for AD may increase antibiotic resistance. There is an increasing incidence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) cutaneous infections in the general population. We evaluated the skin colonisation by *S. aureus* in AD patients and controls at the paediatric clinics. The antibiotic susceptibility patterns of *S. aureus* isolates were compared and risk factors for carriage of *S. aureus* of antibiotic resistance were studied. *S. aureus* was isolated in swabs from 142 AD patients (71.4%) and 52 control patients (40.9%) (p<0.001). CA-MRSA having unique microbiological features was not detected in our study. The antimicrobial susceptibility testing in patients with AD group revealed that 23.4% of *S. aureus* were resistant to erythromycin, 19.7% resistant to tetracycline and 2.8% resistant to fusidic acid. No significant differences in antibiotic resistance and risk factors were observed between the AD and controls. We conclude that no CA-MRSA has yet been identified in our paediatric clinics. AD does not currently appear to be a risk factor for carriage of *S. aureus* with higher antibiotic resistance.

異位性皮膚炎的病童很常有移生金黃色葡萄球菌；而頻繁使用抗生素可能令其抗藥性增加。現時，在總人群中的社區性抗甲氧西林金黃色葡萄球菌皮膚感染發生率正在上升。我們就兒科門診中的異位性皮膚炎與對照組患者的金黃色葡萄球菌皮膚移生狀況進行評估，比較培養出的金黃色葡萄球菌株的耐藥性特性，並研究當中抗藥性金黃色葡萄球菌的帶菌危險因子。我們從一百四十二名

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異位性皮膚炎患者（百分之七十一點四）及五十二名對照組患者（百分之四十點九）的拭抹樣本中分離出金黃色葡萄球菌，當中並未有發現含有獨特微生物特徵的社區性抗甲氧西林金黃色葡萄球菌株；而耐藥性測試揭示當中分別有百分之二十三點四、百分之十九點七及百分之二點八的金黃色葡萄球菌株對紅黴素、四環素及夫西地酸呈抗藥性。此外，異位性皮膚炎與對照組患者的帶菌抗藥性及其危險因子並無重大分別。總括來説，我們的兒科門診病患中並未有發現社區性抗甲氧西林金黃色葡萄球菌；而現階段亦不能把異位性皮膚炎視為高抗藥性金黃色葡萄球菌帶菌的危險因子。

Introduction

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disorder with a genetic predisposition. The incidence of atopic dermatitis is increasing over the past 3 decades affecting about 20% of schoolchildren aged seven years or older.[1] *Staphylococcus aureus* are bacteria commonly carried on the skin or in the nose of healthy people.[2] Approximately 25% to 30% of the population is colonised in the anterior nares with *S. aureus*. Sites that are commonly colonised by *S. aureus* include the anterior nares (30%), axillae (10%) and the perineum (10-20%).[3] In patients with AD, *S. aureus* carriage rates are known to be substantially higher than the normal population, ranging from 70% to 100%.[4,5] The colonisation correlates with the severity of AD via the effects of superantigens and bacterial toxins.[5,6] Colonisation with antibiotic-resistant *S. aureus* is an increasing clinical problem in the hospital and community.[7] The colonisation heralds the deterioration in control of atopic dermatitis and thus imposes significant impacts on the management of AD. Antibiotics are often prescribed for exacerbation of AD complicated by secondary infections mostly involved *S. aureus*.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of *S. aureus* that is resistant to antibiotics called beta-lactams. Beta-lactam antibiotics include methicillin and other more common antibiotics such as penicillin and cephalosporins. Since the discovery of the first clinical isolates in 1960, MRSA has remained a major hospital pathogen throughout the world. However, recent reports suggest that it becomes increasingly prevalent even in the community since the 1990s.[7,8] Now, the MRSA strains designated community-acquired or community-associated MRSA (CA-MRSA) are increasingly discovered in healthy individuals without conventional risk factors for MRSA colonisation. Characteristic features of the CA-MRSA strains include fewer resistance to the non-β-lactam antibiotics, presence of the Panton-Valentine Leukocin (PVL) gene and one of the newer SCC*mec* elements (types IV or V); and they belong to genetic lineages which are different from those of health care-associated MRSA isolates (HA-MRSA).[9,10]

While 25% to 30% of the population is colonised with *S. aureus*, 1% or less is colonised with methicillin-resistant strains.[11] In children with AD, overseas studies suggest that carriage of MRSA and strains with resistance to other antibiotics may be higher.[12,13] In view of the increased colonisation of *S. aureus* in AD patients and the frequent practice of antibiotic prescription to control acute flare of AD, patients with AD may represent a potential reservoir for antibiotic-resistant *S. aureus*, including MRSA. Arkwright et al have shown that the prevalence of fusidic acid and methicillin resistance *S. aureus* strains on AD skin tripled from infancy to adolescence in United Kingdom.[14]

This study aimed to evaluate the colonisation rate of *S. aureus* and define the antimicrobial

susceptibility of *S. aureus* carried by children with AD attending paediatric clinics in Hong Kong; and to investigate the prevalence of MRSA carriage in AD characterised by high carriage rate of *S. aureus*. Since community-acquired MRSA are known to possess unique microbiological features, MRSA strains were studied for their SCCmec types and the PVL gene.

Patients and methods

In our study, we compared the rates of antibiotic resistance (for MRSA, macrolide and fusidic acid) among isolates in the AD group with that of the non-AD group followed up in the paediatric outpatient clinics.

We investigated whether identifiable risk factors such as severe AD, previous hospital admissions, and multiple antibiotic use were present in children with antibiotic-resistant *S. aureus* (MRSA or resistance to ≥2 antibiotic classes). Patient-to-patient transfer of antibiotic-*resistant S. aureus* in the AD group was also assessed by the epidemiological method using the pulsed-field gel electrophoresis. Patients' medical records were reviewed for basic demographics, previous antibiotic uses and hospital admission histories (Table I).

The study population was children aged between 3 months and 15 years and were attending paediatric dermatology or general paediatric clinics at Queen Mary Hospital. Diagnosis of AD was defined by Hanifan and Rajka's criteria.[15] In order to distinguish the resistance pattern of isolates in outpatients from those acquired as inpatients, children who have been admitted to the hospital within the last 12 months were excluded from this study Children with airway hyper-reactivity, asthma, and allergic rhinitis were not excluded. A comparable number of children without AD (non-AD group) were recruited as control.

Written consent from the parents or guardians was sought for recruitment into the study and the study was approved by the local ethics committee. Patients completed questionnaires on several demographic data and potential predisposing factors for carriage of antibiotic-resistant strains. The severity of their AD was assessed by the two clinicians according to the Three Item Severity Score (TIS score) based on the evaluation of erythema, oedema / papule and excoriation on a scale from 0 to 3. The range of the TIS score lies between 0 and 9.[16] The TIS scoring system is a quick system to use and suitable for epidemiological study.

Two culture specimens from the anterior nares and the most active eczematous lesions or axillae were obtained from the subjects using commercial swab sticks with transport jelly (Medical Wire & Equipment Co., Ltd., Corsham, United Kingdom).

Table 1. Clinical characteristics of patients with atopic dermatitis and controls attending the paediatric outpatients

	AD (n=199)	**Control (n=127)**	**P value**
Age	8.1±4.3	9.1±4.6	0.08
Male gender	115 (57.8%)	70 (55.1%)	0.63
Asthma	62 (33.2%)	20 (15.7%)	0.10
Allergic rhinitis	41 (21.9%)	11 (8.6%)	0.08
Antibiotics use in 3 months	44 (22.1%)	28 (22.0%)	0.98
Antibiotics use in household members	24 (12.1%)	26 (20.5%)	0.06
Prior admission 1 year before	61 (30.7%)	41 (32.3%)	0.45
No. of siblings	1±1	1±1	0.90
No. of household members	4.2±1.2	4.3±1.2	0.21

AD: atopic dermatitis

The samples were transported back to the microbiology laboratory at Queen Mary Hospital, University of Hong Kong and processed on the same day.

Laboratory investigation

Bacterial isolation and identification

The specimens were inoculated into a selective medium (mannitol salt broth) for enrichment of *S. aureus* and incubated for 24 to 48 hours at 35°C in room air.[17] Samples that yield a positive growth (yellow) were sub-cultured onto blood agar with and without oxacillin (6 μg/ml) and incubated for 24 hours. Colonies that grew on the agar plates with morphology suggestive of *S. aureus* were investigated further by slide agglutination test, tube coagulase and DNAse. All strains were kept at -70°C in commercial bacterial preservation system (Microbank) for further analysis.

Antibiotic susceptibility testing

Susceptibility of all strains of *S. aureus* to the following 12 antibiotics was determined by the disc diffusion test: cefoxitin, erythromycin, clindamycin, tetracycline, minocycline, gentamicin, levofloxacin, cotrimoxazole, chloramphenicol, fusidic acid, rifampicin and vancomycin. Resistance to cefoxitin disc was used as a screening test for MRSA. All tentative MRSA strains were confirmed by PCR for presence of the *mecA* gene. All results were interpreted according to the CLSI (NCCLS) (Clinical and Laboratory Standards Institute, 2005). Quality control strains (*Staphylococcus aureus* ATCC 29213) were included with each run.

Molecular typing

Chromosomal DNAs were extracted from cells that had been cultured overnight by the phenol-chloroform extraction methods described previously.[17] Detection of the PVL gene, *mecA* gene and typing of the SCC*mec* elements were carried out by PCR.[18] To determine the genetic lineage of the MRSA strains, we sequenced the polymorphic X region of the protein A gene (*spa*) and compared it to our national database.[9,10,17,18]

Statistical analysis

The group of AD children with antibiotic-resistant S aureus was compared against their counterparts. Potential variables will be identified by univariate and multiple logistic analyses using SPSS. A χ^2 analysis was used for hypothesis testing, with statistical significance set at $p < 0.05$ and 95% confidence interval.

Results

Patients and bacterial isolates

A total of 326 swabs from 199 AD children (115 males and 84 females) and 127 control children (70 males and 57 females) were collected over 6 months from April 2006 to September 2006. *S. aureus* was isolated in 142 AD patients (71.4%) and 52 control patients (40.9%). The difference in isolation rate of *S. aureus* was statistically significant ($p < 0.001$). In AD group, there is a statistically significant difference in AD severity by TIS score between *S. aureus* carriers and non-*S. aureus* carriers with the mean TIS score of 4.1 and 2.3, respectively ($p < 0.001$).

MRSA was uncommon and isolated only in 2 patients in the AD group (1.0%) and the carriage in both AD patients was related to health-care exposure. One patient carrying MRSA was a child of a health care worker , the other was receiving long-term institutional care. Both MRSA isolates belonged to spa type *t701* which is a HA-MRSA lineage in our region. The two isolates had SCCmec type V and were PVL negative. In AD group, 82 (57.7%) of 142 patients carrying *S. aureus* were male and their mean age was 8.6+/-4.1 years. In the control group, the male to female ratio of 52 patients carrying *S. aureus* was 1:1 and their mean age was 8.5+/-4.4 years. None of the patients in the control group were positive for MRSA.

Antimicrobial susceptibility

The 2 cases of MRSA were susceptible to vancomycin, fusidic acid and rifampicin. In patients with AD, 76.6% of *S. aureus* were sensitive

to erythromycin, 100% to cotrimoxazole, but 19.7% of *S. aureus* were resistant to tetracycline. 7.0% of the strains were resistant to clindamycin, 6% to gentamicin and 2.8% to fusidic acid.

In the control group, no MRSA was detected. A higher proportion of *S. aureus* were resistant to erythromycin (45.1%). 3.8% of *S. aureus* were resistant to clindamycin and fusidic acid. 98.1% of *S. aureus* were sensitive to cotrimoxazole. The susceptibilities to tetracycline were 91%, 98% for levofloxacin and 98% for gentamicin. The multidrug resistance isolates were present in 5.6% in AD group and 5.7% in control group. No statistically significant difference in the resistance rate of *S. aureus* to individual antibiotics between the two groups except erythromycin (*p*=0.006) (Table 2). There was no significant correlation between the severity of AD and the antibiotic resistance of *S. aureus* in the AD group. The mean TIS scores were 4.6 in non-resistant group and 3.9 in group whose isolates resistant to at least 1 antibiotic (*p*=0.103).

Prior antibiotic use within 3 months was noted in 44 AD patients (22%) and 28 control patients (22%), respectively. Sixty-one AD patients (31%) and 41 control patients (32%) had never been admitted to the hospitals. Twenty-four AD patients (12.1%) and 26 control patients (20.5%) had

household members receiving antibiotics in the last 3 months, respectively. Hospitalisation 12 months or longer preceding sampling was not a significant predictor of carriage of antibiotic-resistant strains in both groups. The use of antibiotics in the past 3 months was not a significant predictor of carriage of antibiotic-resistant strains. No statistically significant differences in antibiotic resistance and risk factors were observed between the AD and control groups apart from the erythromycin resistance rate. No significant correlation was found between the antibiotic resistance and studied risk factors.

Discussion

The colonisation of skin by *S. aureus* in patients with AD and its correlation to eczema severity have been well documented.[5,6] In our study, *S. aureus* colonisation was noted on skin of 71.4% of pediatric AD patients with MRSA accounting for 1.4% of *S. aureus* isolates. The level of colonisation in our AD patients has taken into account of the use of antibiotics and topical corticosteroids in the studied population; the findings are more representative of the typical outpatient setting.

All the MRSA were not community-acquired by molecular methods. The MRSA isolates were

Table 2. Comparison of the resistance to antibiotics of 194 *Staphylococcus aureus* isolates from patients with atopic dermatitis and controls

	AD	**Control**	**P value**
S. aureus isolates	142 (71.4%)	52 (40.9%)	<0.01
Oxacillin	2 (1.4%)	0 (0%)	0.99
Erythromycin	33 (23.4%)	23 (45.1%)	<0.01
Clindamycin	10 (7.0%)	2 (3.8%)	0.52
Fusidic acid	4 (2.8%)	2 (3.8%)	0.66
Cotrimoxazole	0 (0%)	1 (1.8%)	0.28
Tetracycline	28 (19.7%)	5 (9.6%)	0.13
Levofloxacin	8 (5.6%)	1 (1.9%)	0.45
Chloramphenicol	5 (9.6%)	3 (5.7%)	0.69
Gentamicin	8 (5.6%)	1 (1.9%)	0.45
MDR	8 (5.6%)	3 (5.7%)	0.99

AD: atopic dermatitis. Multidrug resistance (MDR) was defined by co-resistance to ≥2 antibiotics.

related to exposure to a health care environment and possessed epidemiological, clinical and biological characteristics distinct from that of CA-MRSA.[19] The findings indicated that the prevalence of MRSA remains low in our population of paediatric AD patients. One of the two AD patients who had colonisation of MRSA was child of a nurse working in a hospital. Our study had not investigated the parental colonisation of *S. aureus* and their resistance pattern. However, Bonness et al demonstrated that there was possible interfamilial transmission of *S. aureus* by showing that 84% of the isolates present in AD children and their parents displayed identical antibiotic resistance profiles, PFGE and enterotoxin patterns.[20] AD is not associated with MRSA colonisation in our study population. This is consistent with the low prevalence of MRSA of less than 1% in our general population, and pediatric AD patients are not at risk of MRSA carriage compared with the general population and children with other paediatric conditions.[21]

Thirty-six percent and 1.9% of school children were colonised with *S. aureus* and MRSA respectively, in a nasal culture survey in northern Taiwan.[22] No risk factors were identified for the nasal carriage of MRSA in this study. In contrast, a recent study from Korea found that the carriage rate of MRSA was high at 18.4% in pediatric AD patients in the background of 5.1% MRSA in the healthy children in community.[23] The authors inferred that, in view of the predisposition of colonisation and infection by *S. aureus* and the frequent use of antibiotics in AD patients, AD children are at risk of carrying *S. aureus* of high antibiotic resistance and developing invasive infections.

The colonisation of *S. aureus* in AD children is also associated with more severe AD as reflected by the higher mean TIS score. The observation is consistent with the deleterious effects of superantigens and bacterial toxins on the course of AD.[3] High rate of erythromycin resistance should be considered (23.4%) when starting antibiotics in children. *S. aureus* resistant to tetracycline (19.9%), clindamycin (7.1%) and fusidic acid (2.8%)

may be related to topical antibiotic use. The finding of resistance to tetracycline was unusual as oral tetracycline was seldom prescribed to children below 12 years of age because of the side effect on dentition. This might be related to the widespread use of topical 3% chlortetracycline (Aureomycin®) ointment for skin infections in our community. The rate of fusidic acid resistance increased from 9.7% to 23.4% during the period 1995 - 2001 while methicillin resistance remained stable at about 0.5% from *S. aureus* isolates from AD inpatients in Netherlands.[24] The authors concluded that prolonged topical use of fusidic acid have probably caused the rising fusidic acid resistant rate. The present finding of low resistance rate to fusidic acid (2.8%) may be related to the practice of limited use of topical and systemic fusidic acid in our centre. Antimicrobial therapy remains an important part of the management of AD, especially during the bouts of the disease. Flucloxacillin and macrolides are often prescribed first-line antibiotics for empirical treatment of *S. aureus* infections in AD. The resistance rate to erythromycin is significant at 23.4% in our study. Thus, macrolides are not recommended for infective exacerbations of AD because of an increased high resistance rate. Hoeger et al studied antibiotic susceptibility in children with AD in Germany, demonstrating comparable rate of erythromycin resistance of *S. aureus* at 18%, fusidic acid at 6%, amoxicillin at 13% and clindamycin at 1%.[25] No MRSA was detected in their study. First generation cephalosporins seem to be a better alternative in this regard. The resistance rate of *S. aureus* to fusidic acid is low at 2.8% in AD group and 3.8% in the control group in comparison to the rising resistance rate of *S. aureus* to fusidic acid in European countries.[24] Therefore, it remains a valuable antibiotic of choice and should be reserved for the treatment of MRSA infections.

S. aureus carriage is common in children with AD. No community-acquired MRSA has yet been identified in children with AD in our paediatric outpatient clinics. This study has suggested that community colonisation with MRSA remains low

in Hong Kong. AD does not appear to be a risk factor for carriage of *S. aureus* with higher antibiotic resistance in Hong Kong. Flucloxacillin and first generation of cephalosporins remain useful antibiotics in the treatment of *S. aureus* infections in AD children. Close surveillance on persistently colonised groups of AD patients is warranted.

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