ORIGINAL ARTICLE

The Association of Skin and Nasal Colonisations of *Staphylococcus aureus* in Children with Atopic Dermatitis with Disease Severity and Its Impact on Quality of Life

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Abstract

Background

Atopic dermatitis (AD) is a chronic, recurrent, pruritic inflammatory skin disease that causes significant burden to affected children. *Staphylococcus aureus* plays a vital role in AD, and its resistance to current topical antibiotics is worrying. This study aims to determine the frequency of *Staphylococcus aureus* colonisation and its resistance pattern. It further assesses the association between *Staphylococcus aureus* colonisation and disease severity; as well as its impact on quality of life.

Methods

A cross-sectional study was conducted among 153 children with AD. Skin and nasal swabs were collected. Antibiotic sensitivity to penicillin, cefoxitin, erythromycin, methicillin, clindamycin, gentamicin, trimethoprim/sulfamethoxazole, tetracycline, rifampicin, fusidic acid and linezolid were tested. Clinical evaluation was performed using the SCORing Atopic Dermatitis index (SCORAD). Quality of life was assessed with the Dermatological Life Quality Index (DLQI).

Results

Twenty-nine patients had positive skin swab results. One patient had methicillin-resistant *Staphylococcus aureus* isolated from nasal swab. Skin colonisation with *Staphylococcus aureus* (p=0.03) and DLQI (p<0.01) were significantly associated with disease severity. The resistant rate is highest in penicillin, followed by fusidic acid, tetracycline, and erythromycin.

Conclusion

Skin colonisation with *Staphylococcus aureus* is an indicator of disease severity in children with AD. Patients with severe disease have lower quality of life. Clinicians need to be aware of high resistance rates towards penicillin and fusidic acid and be prudent in the choice of antibiotics. Antiseptic wash can be considered in patients with *Staphylococcus aureus* colonisation.

Key words: *Staphylococcus aureus, Atopic dermatitis, Dermatological life quality index*

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent, pruritic inflammatory skin disease with estimated prevalence of 10-30% in children and up to 2-5% in adults.[1,2] The incidence of AD appears to be increasing. A systematic review of epidemiologic studies performed between 1990 and 2010 in several regions found increasing trends in incidence

and prevalence of AD.[2] In addition, AD is the most significant contributor to the global burden of disease among skin diseases.[3]

Severe AD causes significant distress to the affected children and their parents.[4,5,6,7] Children with AD often have behavioural problems such as increased dependency, fearfulness, and sleep difficulties.[8] A holistic approach to patient care can be developed after recognising the impact of the disease. Clinicians will be more confident in judging the benefits of therapeutic interventions and ensuring compliance with therapy.

Skin is the biggest organ of the body and it interfaces with the environment. It has a complex ecosystem colonised by many microorganisms (that are either pathogen or mutualist), coexisting in a balance. Atopic dermatitis is well known to be associated with altered skin microbiota, with high prevalence of *Staphylococcus aureus* colonisation and superinfection. The AD skin has a favourable environment for colonisation and proliferation of *Staphylococcus aureus*. The bacteria is frequently found on the skin of AD patients (carriage rates of 30% to 100% depending on the study methodology), whereas in healthy subjects, the prevalence is about 10 to 20%.[9] The prevalence of nasal colonisation by *S. aureus* varies between 10 and 30%.[10,11]

Staphylococci can be mutualist or pathogen depending on its species. The dominant group of skin colonists is the coagulase-negatives, the most prominent of which, is *S. epidermidis*. The bacteria can be an opportunistic pathogen in the context of immunosuppression; it functions predominantly as a mutualist.

Skin-resident *Staphylococcus* species engage in microbe-microbe interactions that are beneficial to the host.[9,12] For example, *S. epidermidis* and *S. hominis* have been shown to secrete antimicrobial peptides that kill *S. aureus*, and transplantation of these species onto the skin of patients with atopic dermatitis led to decreased colonisation by *S. aureus*.[13] However, an association between *S. aureus* colonisation and AD severity is still inconclusive.[14,15,16]

It is not uncommon for children who present with AD to be treated with antibiotics and antiseptic, as this could lead to increased antibiotic resistance.[17] Many studies were done to establish the current antimicrobial resistances and susceptibilities to first-line antibiotic therapy.[18,19,20] With the rapid emergence of resistant bacteria worldwide, rationale use of antibiotics needs to be advocated.

The objectives of this study are to evaluate the frequency of skin and nasal colonisation by *Staphylococcus aureus* in children with atopic dermatitis. In addition, it aims to identify antimicrobial sensitivity, as well as establish the association between colonisation of *S. aureus* and disease severity, and its impact on psychosocial wellbeing of the children.

Materials and Methods

A cross-sectional study was conducted. A total number of 153 children (age below 18 years old) with confirmed diagnosis of atopic dermatitis by dermatologists were recruited between January 2020 and April 2020 from the Dermatology outpatient clinic of Hospital Sultanah Aminah, Johor Bahru, a tertiary hospital in Malaysia.

The estimated sample size was based on a study by Rezaei M, *et al*.[21] Sample size estimation was calculated using two population proportion formulae.[22] A minimum sample size of 153 samples per group is needed to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Pearson's Chi-square test for independence will be used to evaluate this null hypothesis. Exclusion criteria were patients who received oral or topical antibiotic four weeks before the study, patients who have coexisting inflammatory skin diseases, clinical evidence of cutaneous bacterial, viral or fungal infection and upper respiratory infection within four weeks.

A predesigned clinical research form for recording demographic data, medical history, clinical examination, and disease severity using SCORing Atopic Dermatitis (SCORAD) index was completed during the visit. By using the SCORAD index, the severity of eczema was scored in each patient as mild (<25), moderate (25-50) or severe (>50).[23,24] All patients and their parents were required to fill up a validated and licensed Dermatological Life Quality Index (DLQI) form according to the children's age

group. The DLQI stratifies the quality of life into five categories: no effect at all on patient's life (0-1), a small effect on patient's life (2-5), moderate effect on patient's life (6-10), very large effect on patient's life (11-20) and extremely large effect on patient's life (21-30).[25,26]

Skin and nasal swabs were collected from subjects using Micro Science Microbiology Transport Swab with Medium Amies with Charcoal. The skin swab was taken from an eczematous lesion. Levine method was used for obtaining the skin swab. Nasal swab was taken from both nostrils by using the same swab. Specimens were sent to the Department of Microbiology of Hospital Sultanah Aminah within 24 hours for processing.

The nasal sample was inoculated onto 10% sheep blood agar plates, whereas the skin sample was inoculated onto 10% sheep blood agar and MacConkey's medium. After 24 hours inoculation at 37°C, the agars were reviewed. *S. aureus* isolates were identified by a coagulase test (to differentiate *S. aureus* and *Staph spp.*) and catalase test (to differentiate *Strep spp.* and *Staph spp.*). *S. aureus* colony was cultured on the *Staphylococcus* panel including Cefoxitin disk (FOX-disk) for another 24 hours to test for methicillin resistance. The antibiotic sensitivity test is done according to the Clinical and Laboratory Standards Institute (CLSI, 2019). The tested antibiotics included penicillin, cefoxitin, erythromycin, methicillin, clindamycin, gentamicin, trimethoprim/sulfamethoxazole, tetracycline, rifampicin, fusidic acid and linezolid. The interpretation of the susceptibility was given as sensitive (S), intermediate susceptible (IS), or resistant (R) following standard recommendation.

The data analysis was done using the Statistical Package of the Social Science (SPSS) version 22 (IBM Corporation, CA). Descriptive analysis was performed and was presented as frequency and percentage. Association was analysed using Chi-square or Fisher's exact test. A value of $p<0.05$ is considered statistically significant. A graphical presentation was used to illustrate the antibiotic susceptibility. Ethics approval was obtained from the National Medical Research Registry, Malaysia (NMRR-19-3254-53344).

Results

From January 2020 through April 2020, a total of 153 patients with Atopic Dermatitis were screened and all were recruited. There were 111 preschool children (72.5%), 26 primary school children (17%) and 16 secondary school participants (10.5%). Eighty two participants (53.6%) were male. A hundred and twenty participants (78.4%) were Malay, 25 participants (16.3%) were Chinese and seven participants (4.6%) were Indian. Ninety six participants (62.8%) had normal body mass index (BMI), 25 participants (16.3%) were underweight, nine participants (5.9%) were overweight and 23 participants (15%) were obese. A hundred and thirty eight participants (90%) had family history of atopy. Seventy one participants (46%) had personal history of another atopy (Table 1). The SCORAD Index showed 30.7% mild, 53.6% moderate and 15.7% severe. For quality of life, six participants (3%) reported no effect at all, 40 participants (26.2%) reported a small effect, 51 participants (33%) reported moderate effect, 46 participants (30%) reported very large effect and ten participants (6%) reported extremely large effect (Table 2).

Out of 153 patients, 29 of them had positive skin swab. All of those with positive yield cultured methicillin susceptible *Staphyloccocus aureus* (MSSA). One patient had *Streptococcus dysgalactiae* in addition to MSSA. No patient had methicillin-resistant *Staphyloccocus aureus* (MRSA) from the skin swab. Only one patient was a MRSA carrier from the nasal swab. This patient's skin swab had no growth (Table 3).

There was a significant association between positive skin swab and disease severity ($p=0.03$) (Table 4). Out of the 29 patients with positive skin swab, 89.7% with positive skin swab had moderate to severe disease. Three participants (10.3%) had mild SCORAD index, 20 participants (69%) had moderate SCORAD index and six participants (20.7%) had severe SCORAD index. Majority of patients with mild SCORAD index had negative skin swab. Of those with mild SCORAD index, 44 patients had negative skin swab and only three had positive skin swab. Of those with negative skin swab, 44 participants (35.5%) had mild SCORAD index, 62 (50%) had moderate SCORAD index and 18 (14.5%) had severe SCORAD index. There is no significant association between nasal swab

colonisation and disease severity. Only one patient with moderate disease was an MRSA carrier.

There was a highly significant association between disease severity and quality of life (p<0.001). Among patients with DLQI score >20 (extremely large effect), six patients (60%) had severe disease, three patients (30%) had moderate disease and only one patient (10%) had mild disease. All patients who reported no effect at all on DLQI assessment had mild disease. The DLQI score for most of the patients with mild disease were in small effect (44.7%) and moderate effect (25.5%) categories. The DLQI score for most of the patients with moderate disease were in moderate effect (36.6%) and very large effect (36.6%) categories. The DLQI score for most of the patients with severe disease were in moderate effect (37.5%) and very large effect (37.5%) categories. The mean DLQI score for patients with had no effect at all was 2; for patients with small effect was 13.3; for patients with moderate effect was 17; for patients with very large effect was 15.3 and for patients with extremely large effect was 3.3. Majority of participants had moderate disease (53.6%), resulting in higher mean DLQI score from small effect to very large effect categories.

Penicillin (86.2%) was found to have the highest resistant rate followed by fusidic acid (34.5%), tetracycline (17.2%), erythromycin (3.4%) and gentamycin (3.4%) (Figure 1). The most susceptible antibiotics (100% sensitivity) were cefoxitin, methicillin, trimethoprim/sulfamethoxazole, and rifampicin.

Table 1. Demographic characteristics

Demographic		n (%)
Age (years)	Preschool (less than 7) Primary school (7 to 12) Secondary school (13 to 17)	111 (72.5) 26 (17.0) 16 (10.5)
Gender	Male Female	82 (53.6) 71 (46.4)
Ethnicity	Malay Chinese Indian Others	120 (78.4) 25 (16.3) 7 (4.6) 1 (0.7)
BMI	Underweight (≤5th percentile) Normal (5th to ≤ 85th percentile)) Overweight (85th to ≤95th percentile) Obese (≥95th percentile)	25 (16.3) 96 (62.8) 9 (5.9) 23 (15.0)
Age at diagnosed	Preschooler (less than 7) Primary school (7 to 12) Secondary school (13 to 17)	136 (88.9) 15 (9.8) 2 (1.3)
Family history of atopy	Yes No	138 (90.2) 15 (9.8)
Personal history of another atopy	Yes No	71 (46.4) 82 (53.6)

BMI, Body mass index

Table 2. DLQI and SCORAD index

DLQI and SCORAD Index		n (%)
DLQI	No effect Small effect Moderate effect Very large effect Extremely large effect	6 (3.9) 40 (26.2) 51 (33.3) 46 (30.1) 10 (6.5)
SCORAD index	Mild Moderate Severe	47 (30.7) 82 (53.6) 24 (15.7)

DLQI, Dermatological life quality index; SCORAD, SCORing Atopic dermatitis

Table 3. Skin (lesional) and nasal (non-lesional) swab yields for *Staphylococcus aureus*

Skin Swab Result	n (%)
No growth MSSA MSSA + Streptococcus dysgalactiae	124 (81) 28 (18.3) 1 (0.7)
Nasal Swab Result	**n (%)**
No MRSA MRSA	152 (99.3) 1 (0.7)

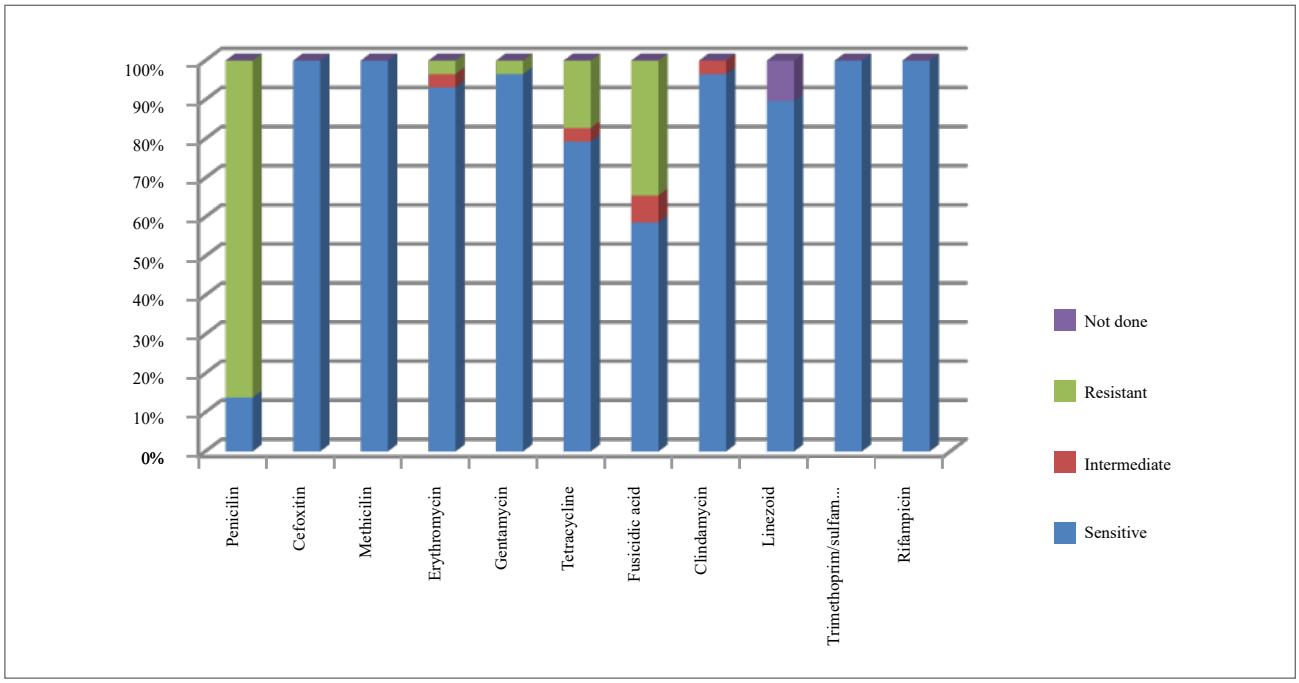
MSSA, methicillin susceptible Staphyloccocus aureus; MRSA, methicillin-resistant Staphyloccocus aureus

Table 4. Association between disease severity (SCORAD) and growth (skin and nasal) and quality of life (DLQI)

	SCORAD Index n (%)			*p*-value
	Mild	Moderate	Severe	
Skin swab				0.030[a]
Growth No growth	3 (10.3) 44 (35.5)	20 (69) 62 (50)	6 (20.7) 18 (14.5)	
Nasal swab				1.000[b]
MRSA No MRSA	0 (0) 47(30.9)	1 (100) 81 (53.3)	0 (0) 24 (15.8)	
DLQI				<0.001[b]
No effect Small effect Moderate effect Very large effect Extremely large effect	6 (100) 21 (52.5) 12 (23.5) 7 (15.2) 1 (10)	0 (0) 19 (47.5) 30 (58.9) 30 (65.2) 3 (30)	0 (0) 0 (0) 9 (17.6) 9 (19.6) 6 (60)	

[a]Chi-square tests; [b]Fisher's exact tests; SCORAD, SCORing Atopic dermatitis; MRSA, methicillin-resistant Staphyloccocus aureus; DLQI, Dermatological life quality index

Figure 1. Antibiotic sensitivities of *Staphylococcus aureus*



Discussion

The sample in this study was mainly preschoolers, followed by primary school children and secondary school children. Similar trends were observed for age when AD was first diagnosed. This was in line with the natural course of childhood eczema which mostly manifests AD before the age of two.[27] Most of the affected children have family history of atopy which indicates the genetic role in the pathogenesis of atopic dermatitis. However, it was observed that less than half of the patients have other atopy histories. This could be due to the initial stage of atopic march which begins with atopic dermatitis, and followed by IgE-mediated food allergy, asthma, and allergic rhinitis.[28]

In this study, the percentage of skin (lesional) colonisation by *S. aureus* was only 19%, whereas nasal (non-lesional) colonisation was 0.7%. This was lower than other studies where skin carriage rates among AD patients were reported between 30% and 100%, while the percentage of nasal colonisation by *S. aureus* varies between 10 and 30%.[9,10,11] This discrepancy might be attributed to the significant variation in AD clinical severity in each study. Most of the patients were found to have mild to moderate AD. Other possibilities for such variations are intermittent colonisation by *S.*

aureus resulting in negative detection at the time of examination, hygienic status of patients, sampling technique, and sampling area of skin lesion.[9,29]

From our study, we found that severity of disease was associated with quality of life ($p<0.01$). About 70 % of the patients with mild disease reported small or moderate effect during the DLQI assessment. On the other hand, 73.2% of patients with moderate disease and 75% of patients with severe disease reported moderate to very large effect during the DLQI assessment. The result showed that higher SCORAD index seemed to be associated with worse DLQI. Although most skin diseases are not life-threatening, it could still lead to a significant disability burden. This result was consistent with the study by Holm et al., where AD had a negative impact on the QoL, and was proportional to the disease severity.[30] Children with AD often have behavioural problems such as increased dependency, fearfulness and sleep difficulties.[34] These findings should draw our attention to the long-term effect on children's behaviour and development.

The resistance rate to fusidic acid in this population was found to be higher compared with other studies. Tang (2011) found that fusidic acid resistance was lower than penicillin, erythromycin, clindamycin, tetramycin and gentamycin.[31] Likewise, Hoeger (2004) and Niebuhr (2008) also had lower fusidic acid resistance rate in their findings.[32,20] However more current studies by Jung (2015) and Lee (2016) found that fusidic acid is the second highest resistant antibiotic after penicillin.[11,33] Higher resistance rates towards fusidic acid in recent studies could be due to increased use of topical fusidic acid in treating the patient with infective or inflammatory skin diseases in recent years. In view of this finding, the use of fusidic acid should not be advocated. Besides that, the use of neomycin and bacitracin were not advised as they were nominated as an allergen in 2003 and 2010, respectively.[34] Moreover, the resistance rates to neomycin and bacitracin were high in Bessa *et al.*'s report.[35] Sulphur-based topical treatments have a high risk of hypersensitivity, leading to physicians' hesitancy to use these in the paediatric group. Therefore, mupirocin and retapamulin are the choice of antibiotics if clinically indicated. With the concern of developing resistance to the newer antibiotic, continuous surveillance of antibiotic susceptibility patterns are important.

From our study, we found that 26 patients (89.7%) with *Staphylococus aureus* colonisation and 105 patients (69.1%) with negative skin swab had moderate to severe disease. As patients with *Staphylococcus aureus* colonisation tends to have more severe disease, decolonisation with antiseptic wash such as a diluted bleach bath should be considered. It helps in relieving symptoms of AD and it is better tolerated than topical antibiotics. This approach could potentially reduce antibiotic resistance.[36,37] Decolonisation of MSSA with a topical antibiotic is not recommended as quick recolonisation occurs after discontinuing the antibiotic.[38,39]

Conclusion

Staphylococcus aureus skin colonisation among AD patients is associated with increased disease severity. The severity of the disease has an impact on patient's quality of life. Antiseptic wash should be considered instead of topical antibiotics for *Staphylococcus aureus* decolonisation. Antiseptic wash is better tolerated and can potentially reduce antibiotic resistance.

Conflict of Interest Declaration

The authors declare no conflict of interest.

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