Concise report

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Exploring *Staphylococcus epidermidis* in atopic eczema: friend or foe?

K. L. Hon,[1] Y. C. K. Tsang,[1] N. H. Pong,[1] T. F. Leung[1] and M. Ip[2]

[1]*Department of Paediatrics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China; and* [2]*Department of Microbiology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China*

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Summary

Background. *Staphylococcus aureus* (SA) colonization/infection is important in the pathophysiology of childhood atopic dermatitis (AD), but the role of *Staphylococcus epidermidis* (SE) is unknown.

Aim. To evaluate if SE co-infects with SA and is associated with more severe disease.

Methods. Associations between bacteriological culture results of skin swabs (taken from the most severely affected area and at the antecubital fossa) and SCORing Atopic Dermatitis (SCORAD) score, skin hydration, transepidermal water loss (TEWL) and quality of life (QoL) were evaluated.

Results. In 100 consecutive patients with AD (aged 12.4 ± 4.8 years), SE was present in 28% and 32% of the swabs taken from the most severe area and the flexural area (antecubital fossa), respectively, whereas SA was present in 69% and 55%, respectively. Binomial logistic regression showed that SE was inversely associated with SA growth in the most severely affected skin site [adjusted odds ratio (aOR) = 0.42, 95% CI 0.22–0.81; $P = 0.01$], frequency of emollient usage (aOR = 0.50, 95% CI 0.29–0.87; $P = 0.01$) and frequency of oral antihistamine usage (aOR = 0.81, 95% CI 0.65–0.10, $P < 0.05$), but positively associated with objective SCORAD (aOR = 1.04, 95% CI 1.00–1.02; $P < 0.05$). SE in the antecubital fossa was not associated with SA growth, disease severity, QoL or any clinical parameters.

Conclusions. SE may not be just a commensal bystander in the skin microbiota. The organism amensalistically displaces SA and is associated with more severe disease.

Introduction

Atopic dermatitis (AD) is a common, chronic, relapsing skin disease, which is estimated to affect about 15% of children.[1–4] Bacterial colonization/infection by *Staphylococcus aureus (*SA*)* is considered an important factor in the pathophysiology of AD.[5–9] A physician caring for patients with severe AD or with acute exacerbation has to decide if the symptomatology is due to SA colonization/infection. Swabs may have to be taken for bacteriology tests, and an empirical course of antibiotics prescribed pending bacteriology results for these patients.[5–8] Treatment targeted at reducing SA colonization/infection may improve quality of life (QoL) for these patients, and ameliorate disease severity and intensity.[9–11] However, antistaphylococcal and antiseptic treatments are not the mainstay of treatment even for moderate to severe disease, because AD is a complex immune disease with factors other than SA infection. The role of *Staphylococcus epidermidis* (SE) is less distinct, and this organism is often considered a commensal bystander in the skin microbiota.[12] There are two different strains of SE, one (SE strain JK16) that inhibits biofilm formation by SA (inhibitory type), and one (SE strain JK11) that does not (noninhibitory

Correspondence: Dr Kam-lun Ellis Hon, Department of Paediatrics, Chinese University of Hong Kong, 6/F, Clinical Science Building, Prince of Wales Hospital, Shatin, Hong Kong SAR, China
E-mail: ehon@hotmail.com

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type).[13–15] An amensalistic relationship may exist between SA and the inhibitory strain of SE.[16]

In the current study, we evaluated if SE plays a synergistic, neutral or antagonistic role with SA, and if there is any association with disease severity or QoL.

Methods

This review was approved by the Clinical Research Ethics Committee of the University. As it was a review of patient data, informed consent from individual patients was not required.

Patients

In total, 100 consecutive patients with AD aged 12.4 ± 4.8 years, managed at the paediatric dermatology service of a university teaching hospital over a 3-year period between January 2012 and February 2015, were reviewed. Patients were excluded from the study if they had other inflammatory dermatitides (such as psoriasis, seborrhoeic dermatitis or ichthyosis) or had been treated with systemic antibiotics (such as cloxacillin or erythromycin) during the previous 4 weeks.

Swabs

Body swabs (COPAN Innovation, Brescia, Italy) were taken by either one of the two staff at the clinic, by rubbing the swab for 5 seconds on a typical flexure (right antecubital fossa)[7] and on the worst affected skin area (defined as acute lesional skin with erythema, papulation, excoriation, oozing or crusting). Bacterial cultures of the swabs were prepared by standard laboratory techniques, and sensitivity to common antibiotics was examined. SA growth was classified as scanty [$< 10^4$ colony-forming units (CFU) per mL], moderate (10^4–10^5 CFU/mL), or heavy ($> 10^5$ CFU/mL). We defined moderate to heavy growth as significant growth, and scanty or no growth as negative.[7]

Disease severity, quality of life, skin hydration and transepidermal water loss

AD severity was routinely assessed by a clinician using SCORAD.[17,18] Long-term disease severity (Nottingham Eczema Severity Score, NESS),[19,20] QoL (Children's Dermatology Life Quality Index, CDLQI)[21,22] and biophysiological parameters [skin hydration (SH) and transepidermal water loss (TEWL)][23] were also recorded.

Statistical analysis

Kruskal–Wallis *H*-test and Mann–Whitney *U*-test were used to analyse quantitative traits, and χ^2 test was used to compare proportions between groups. Binomial logistic regression was performed using IBM SPSS software (v20.0; IBM Inc., Armonk, NY, USA). All comparisons were two-sided, and $P < 0.05$ was considered statistically significant.

Binomial logistic regression analyses were performed to ascertain the effects of SA growth, objective SCORAD, usage frequency of topical emollients, oral antihistamines and topical antibiotics, based on the likelihood that patients had any concomitant SE colonization at their most severely affected skin site and their right antecubital fossa.

Results

SE was present in 28% and 32% of the swabs from the most severe area and the flexural area (antecubital fossa), respectively, whereas SA was present in 69% and 55%, respectively.

Binomial logistic regression showed that SE in the most severely affected skin site was inversely associated with SA growth [adjusted odds ratio (aOR) = 0.42, 95% CI 0.22–0.81; $P = 0.01$], frequency of emollient usage (aOR = 0.50, 95% CI 0.29–0.87; $P = 0.01$) and frequency of oral antihistamine usage (aOR = 0.81, 95% CI 0.65–0.10, $P < 0.05$), but positively associated with objective SCORAD (aOR = 1.04, 95% CI 1.00–1.02; $P < 0.05$). SE in the antecubital fossa was not associated with SA growth, disease severity, QoL or any clinical parameter (Table 1).

Discussion

As demonstrated in many previous studies, SA is the most important pathogen associated with severe AD.[5–7] However, the role of SE is less clear. A physician caring for a patient with moderate to severe or chronic AD has to make a number of clinical decisions, including (i) if routine management with topical emollient and corticosteroid and patient adherence is optimal; (ii) whether superimposed or secondary SA colonization/infection is present, which may account for the moderate to severe disease; (iii) if further investigations such as skin swabs for bacteriology and antimicrobial sensitivity need to be taken; (iv) from which sites the swabs are to be taken; and (v) what antibiotic and escalation of treatment is to be prescribed. It takes 48–72 h for culture results to be available. Clinical

Table 1 Comparison of clinical features between patients with atopic dermatitis with and without growth of *Staphylococcus epidermidis* at the most severely affected skin site ($n = 100$) and in the right antecubital fossa ($n = 100$).

	Most severely affected area				Right antecubital fossa			
	All ($n = 100$)	No growth of SE ($n = 72$)	Growth of SE ($n = 28$)	*P*	All ($n = 100$)	No growth of SE ($n = 68$)	Growth of SE ($n = 32$)	*P*
Male, *n* (%)	59 (59.0)	43 (59.7)	16 (57.1)	0.81	59 (59.0)	38 (55.9)	21 (65.6)	0.36
Age, years	12.4 ± 4.8	12.4 ± 4.8	12.5 ± 4.9	0.78	12.4 ± 4.8	11.9 ± 5.1	13.5 ± 4.0	0.14
BMI, kg/m^2	19.0 ± 4.0	18.8 ± 3.8	19.5 ± 4.5	0.43	19.0 ± 4.0	18.6 ± 3.8	20.0 ± 4.3	0.08
Use of topical treatments, days/week								
Corticosteroids	3.9 ± 2.8	3.7 ± 2.7	4.6 ± 2.8	0.13	3.9 ± 2.8	3.9 ± 2.7	4.0 ± 2.9	0.89
Antibiotics	1.4 ± 2.4	1.5 ± 2.5	1.0 ± 2.2	0.33	1.4 ± 2.4	1.6 ± 2.6	0.9 ± 2.0	0.14
Immunomodulators	1.2 ± 2.1	1.2 ± 2.1	1.0 ± 2.3	0.28	1.2 ± 2.1	1.2 ± 2.1	1.1 ± 2.2	0.53
Use of oral antihistamines, days/week	2.5 ± 2.8	2.8 ± 2.8	1.7 ± 2.5	0.07	2.5 ± 2.8	2.7 ± 2.8	2.1 ± 2.7	0.26
Topical emollient use, times/day, *n* (%)								
< 1	4 (4.0)	0 (0.0)	4 (14.3)	0.01	4 (4.0)	0 (0.0)	4 (12.5)	0.03
1	12 (12.0)	8 (11.1)	4 (14.3)		12 (12.0)	10 (14.7)	2 (6.2)	
2	25 (25.0)	18 (25.0)	7 (25.0)		25 (25.0)	18 (26.5)	7 (21.9)	
≥ 3	59 (59.0)	46 (63.9)	13 (46.4)		59 (59.0)	40 (58.8)	19 (59.4)	
S. aureus growth, *n* (%)								
None	31 (31.0)	20 (27.8)	11 (39.3)	0.06	45 (45.0)	29 (42.6)	16 (50.0)	0.68
Scanty	39 (39.0)	25 (34.7)	14 (50.0)		40 (40.0)	29 (42.6)	11 (34.4)	
Moderate	21 (21.0)	18 (25.0)	3 (10.7)		13 (13.0)	8 (11.8)	5 (15.6)	
Severe	9 (9.0)	9 (12.5)	0 (0.0)		2 (2.0)	2 (2.9)	0 (0.0)	
Skin hydration, AU	32.9 ± 13.4	32.1 ± 13.7	35.2 ± 12.4	0.19	32.9 ± 13.4	32.9 ± 13.5	32.9 ± 13.2	0.89
TEWL, g/h/m^2	11.3 ± 2.4	11.3 ± 2.4	11.3 ± 2.5	0.98	11.3 ± 2.4	11.2 ± 2.7	11.4 ± 1.6	0.41
Objective SCORAD	35.6 ± 15.5	35.7 ± 15.5	35.3 ± 15.7	0.93	35.6 ± 15.5	36.1 ± 16.3	34.5 ± 13.8	0.63
Extent, % body surface area	42.3 ± 21.0	42.0 ± 20.7	43.2 ± 22.3	0.61	42.3 ± 21.0	42.9 ± 21.2	41.0 ± 21.0	0.81
Intensity	7.7 ± 3.3	7.8 ± 3.4	7.6 ± 3.3	0.92	7.7 ± 3.3	7.9 ± 3.5	7.5 ± 2.9	0.64
Erythema	1.1 ± 0.7	1.1 ± 0.7	1.1 ± 0.7	0.48	1.1 ± 0.7	1.1 ± 0.7	1.0 ± 0.7	0.51
Oedema/papulation	1.6 ± 0.7	1.6 ± 0.6	1.6 ± 0.8	0.83	1.6 ± 0.7	1.6 ± 0.7	1.6 ± 0.6	0.74
Oozing/crusting	0.9 ± 0.9	1.0 ± 0.9	0.8 ± 1.0	0.30	0.9 ± 0.9	0.9 ± 0.9	0.9 ± 0.9	0.75
Excoriation	1.6 ± 0.6	1.6 ± 0.6	1.5 ± 0.7	0.85	1.6 ± 0.6	1.6 ± 0.7	1.6 ± 0.6	0.75
Lichenification	1.3 ± 0.7	1.2 ± 0.7	1.3 ± 0.7	0.70	1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.7	0.89
Dryness	1.3 ± 0.7	1.3 ± 0.6	1.3 ± 0.8	0.97	1.3 ± 0.7	1.3 ± 0.7	1.2 ± 0.6	0.43
Pruritus	6.3 ± 2.0	6.2 ± 2.1	6.6 ± 1.8	0.24	6.3 ± 2.0	6.3 ± 2.1	6.3 ± 2.0	0.88
Sleep loss	4.8 ± 3.2	4.9 ± 3.3	4.5 ± 3.0	0.52	4.8 ± 3.2	5.0 ± 3.2	4.3 ± 3.3	0.34
NESS	12.2 ± 2.2	12.3 ± 2.1	12.2 ± 2.5	0.96	12.2 ± 2.2	12.3 ± 2.0	12.1 ± 2.5	0.93
CDLQI	9.7 ± 6.1 ($n = 89$)	9.3 ± 5.5 ($n = 64$)	10.5 ± 7.4 ($n = 25$)	0.73	9.7 ± 6.1 ($n = 89$)	10.0 ± 6.2 ($n = 59$)	8.9 ± 5.8 ($n = 30$)	0.48

AU, arbitrary unit; BMI, body mass index; CDLQI, Children's Dermatology Life Quality Index; NESS, Nottingham Eczema Severity Score; SCORAD, SCORing Atopic Dermatitis; SE, *Staphylococcus epidermidis*. Data are mean ± SD unless otherwise stated.

features such as disease severity (objective SCORAD) and lesion intensity are associated with moderate to severe SA growth in lesional skin.[5–8] However, in one study, significant isolates of *S. aureus* were found in only approximately one-third of specimens even in the most affected skin areas, implying that SA may not be the sole factor in mediating AD.[7] In the present study, we investigated the hypothesis that SE might be another such factor.

In a number of studies,[7,10] SE was reported as the second most common organism present in the skin swabs of patients with AD. SE is often considered as an innocent or commensal bystander in the skin microbiota, but its role in the pathophysiology of AD is unknown. The present logistic regression study showed that SE in the most severely affected skin site was inversely associated with SA growth, frequency of emollient usage and frequency of oral antihistamine usage, but positively associated with objective SCORAD. Our findings confirm that an amensalistic relationship may exist between SA and the inhibitory strain of SE.[16] Furthermore, presence of SE at the worst eczema site is associated with inadequate emollient and antihistamine usage. Importantly, the observed amensalistic relationship between SE and SA did not translate to a lower objective SCORAD or less severe disease. Rather, it appears that SE may independently and pathophysiologically be associated with more severe disease.

A limitation of this retrospective study is that we did not investigate whether the strain of SE was JK16 (inhibitory) or JK11 (noninhibitory).[13–15] It would be useful to perform a prospective study to evaluate if eradicating SE with antiseptic or antimicrobial treatment would ameliorate disease severity, or if treating the disease with corticosteroids and other immunomodulating agents might reduce disease severity, with resultant eradication of SE. The present study was not designed to confirm the pathogenic role of SE, as no comparison was made between the severity of atopic dermatitis before and after its eradication. In addition, the numbers of patients included were relatively small, and there was no healthy control group.

Knowledge of local bacteriology and antibiotic sensitivity is important, as the physician may need to make a clinical decision based on symptomatology and start a course of oral antibiotic pending bacteriology. We previously reported that our local physicians may consider a course of cloxacillin or equivalent as a therapeutic option when managing a patient with moderate to severe disease and SA colonization/infection. In patients with a history of penicillin allergy, erythromycin, clindamycin and cotrimoxazole may be options. SE is generally sensitive to vancomycin, fucidic acid and mupirocin. Despite disease severity and prevalence of methicillin-resistant SA (MRSA) in other childhood conditions, MRSA in AD is not prevalent in our locality.[7,10,24–26]

Conclusion

SA and SE colonization/infection are important in the pathophysiology of childhood eczema. SE may not be just a commensal bystander in the skin microbiome. The organism amensalistically displaces SA and is associated with more severe disease.

What's known about this topic?

• SA colonization/infection is important in the pathophysiology of childhood AD but the role of SE is unknown.

What does this study add?

• SE may not be just a commensal bystander in the skin microbiota.
• The organism amensalistically displaces SA, and is associated with more severe disease.

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