

Biomarkers of Th2 polarity are predictive of staphylococcal colonization in subjects with atopic dermatitis

J.A. Warner,* L.Y. McGirt* and L.A. Beck*†

*Department of Dermatology, Johns Hopkins Medical Institution, Baltimore, MD 21224, U.S.A.

†Department of Dermatology, 601 Elmwood Ave., Box 697, University of Rochester Medical Center, Rochester, NY 14642, U.S.A.

Summary

Correspondence

Lisa A. Beck.

E-mail: Lisa_Beck@URMC.Rochester.edu

Accepted for publication

19 August 2008

Key words

atopic dermatitis, eosinophils, IgE, *Staphylococcus aureus*

Conflicts of interest

None declared.

DOI 10.1111/j.1365-2133.2008.08905.x

Background Staphylococcal colonization of the skin is commonly observed in subjects with atopic dermatitis (AD) and correlates with disease severity. Little is known about whether the degree of T-helper 2 (Th2) polarity in these subjects can also affect the frequency of bacterial colonization in this disease.

Objectives To determine if there is a correlation between markers of Th2 polarity [serum total IgE, eosinophilia and presence of another atopic disease (allergic rhinitis)] and skin colonization with *Staphylococcus aureus* in subjects with AD.

Methods A retrospective chart review was performed of an academic dermatology clinic focused on the treatment of AD with a single provider.

Results *Staphylococcus aureus* colonization was more commonly observed in subjects with AD who had peripheral eosinophilia, elevated serum IgE levels, and/or a history of or active allergic rhinitis.

Conclusions Results suggest that Th2 polarity may enhance subjects' risk for bacterial colonization.

Cutaneous colonization with *Staphylococcus aureus* is a common feature of atopic dermatitis (AD), present on the lesional skin of 80–100% of subjects with AD compared with 5–30% of healthy controls.¹ *Staphylococcus aureus* colonization has been shown to correlate with AD severity as assessed by the subjective scoring system, SCORAD (SCORing Atopic Dermatitis).² Some 30–60% of *S. aureus* strains isolated from patients with AD are able to produce exotoxins with superantigenic properties, such as staphylococcal enterotoxins A, B, C and D and toxic shock syndrome toxin-1. IgE antibodies to these toxins have also been shown to correlate with disease severity.³ Subjects with severe AD are thought to be more susceptible to *S. aureus* colonization and infection because they have both innate immune defects (e.g. dysfunctional epithelial barrier, reduced production of antimicrobial peptides, and defects in toll-like receptor signalling) and adaptive defects (e.g. T-helper 2 (Th2) polarity).^{4–6} We have recently shown that Th2 cytokines can further exacerbate barrier function by reducing filaggrin expression from keratinocytes.⁴ This is in line with the evidence that interleukin (IL)-4 and IL-13 inhibit the release of antimicrobial peptides from keratinocytes, suggesting that adaptive immune responses can adversely affect innate immune responses.^{5,7}

To investigate whether biomarkers of Th2 polarity, namely total IgE and peripheral eosinophilia, are predictive of *S. aureus* colonization, we performed a retrospective study of subjects with AD seen in two university-based dermatology clinics.

Previous studies have suggested that these biomarkers of Th2 polarity and the presence of other atopic diseases such as allergic rhinitis (AR) are also predictive of AD severity.^{2,8,9} With this in mind, we postulated that if elevated biomarkers of atopy, comorbid AR and *S. aureus* colonization are all associated with more severe AD, then perhaps a direct correlation exists between *S. aureus* colonization and biomarkers of Th2 polarity and/or AR. Such a relationship would provide further support that the cutaneous colonization characteristic of AD is secondary to the adaptive immune response to allergens, namely Th2 cytokines.

Materials and methods

We performed a retrospective chart review of subjects with AD seen at Johns Hopkins Bayview Medical Center Dermatology Clinic from July 2001 to April 2006, and at University of Rochester Medical Center Dermatology Clinic from October 2006 to March 2007. We identified 257 subjects with AD diagnosed by a single provider (L.A.B.) based on the Pediatric Consensus guidelines.¹⁰ Data on age, sex and history of AR were collected on all subjects. Serum total IgE levels, total eosinophil counts and bacterial cultures were obtained on a subset of these subjects. The following were considered to be threshold levels indicative of significant Th2 polarity: serum total IgE ≥ 100 kU L⁻¹ and total eosinophil count ≥ 300 cells mm⁻³.

Bacterial cultures were performed by rubbing rayon-tipped swabs over excoriated or eroded lesional skin in subjects whose disease had been refractory to treatment, or whose examination was notable for numerous excoriations indicating severely pruritic disease. Subjects with clinically obvious infections such as impetigo, furuncles or cellulitis were excluded from the study. Swabs were plated and incubated for 24–72 h in CO₂ at 35 °C. *Staphylococcus aureus* colonies were identified by Staphaurex® rapid latex-agglutination assay (Murex Diagnostics Ltd, Dartford, U.K.). Data points were compared with Fisher's exact test and the Mann–Whitney U-test (Statview, 1998; SAS, Cary, NC, U.S.A.).

Results

Of the 257 subjects with AD, 66 (26%) underwent lesional skin cultures. The mean $\pm$ SEM age of these 66 subjects was 33.1 ± 2.2 years, and the female/male ratio was 2.5 : 1. The demographics of the total AD population were similar to our cultured subpopulation with respect to sex and age.

Of the 66 subjects from whom cultures were taken, 51 (77%) had *S. aureus*, consistent with AD colonization rates reported in previous studies.¹ Eight subjects (12%) had methicillin-resistant *S. aureus* (MRSA), which is 10-fold higher than rates of MRSA colonization in the community (1–3%),¹¹ but comparable with the incidence of MRSA seen among subjects with AD (6–19%).¹² These MRSA isolates had antimicrobial susceptibilities typical of community-acquired MRSA.¹³

Among the subjects from whom cultures were taken, 54 (82%) had eosinophil counts measured and 53 (80%) had serum IgE levels measured. In patients with *S. aureus* colonization, there was a significantly higher IgE level than in those without colonization (mean $\pm$ SEM 1720 ± 1458 vs. 158 ± 153 kU L⁻¹, $P = 0.05$; Fig. 1). Likewise, in patients with *S. aureus* colonization, there was a significantly higher number of eosinophils than in those without colonization (mean $\pm$ SEM 500 ± 91 vs. 139 ± 164 cells mm⁻³, $P = 0.002$; Fig. 2). Finally, subjects with a history of and/or active AR were significantly more likely than subjects without a history of AR to be colonized with *S. aureus* (86% vs. 64%, respectively; $P = 0.04$).

Discussion

Although limited by small sample size and retrospective design, this study supports several important conclusions. While *S. aureus* colonization is known to correlate with clinical disease severity, our findings confirm that this association also exists with biomarkers of Th2 polarity. High total IgE and peripheral eosinophilia are markers of Th2 polarity and suggest that Th2 cytokines may predispose subjects with AD to *S. aureus* colonization. It is widely recognized that Th2 cytokines, such as IL-4 and IL-13, are involved in pathways which suppress the innate and possibly even the adaptive immune response and may thereby increase the susceptibility of subjects with AD to *S. aureus* and other cutaneous microbes.^{5,7} The

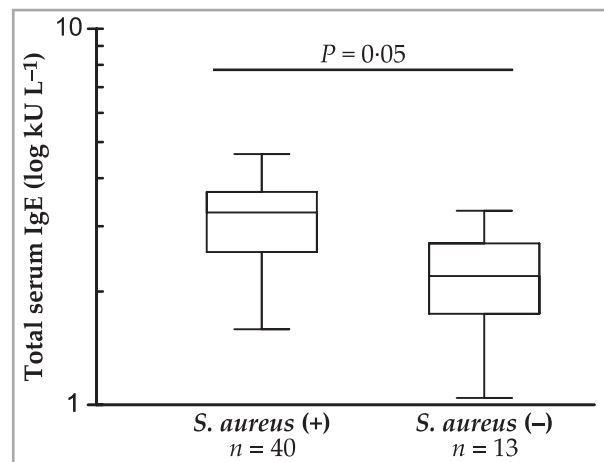


Fig 1. Serum total IgE levels in *Staphylococcus aureus*-positive ($n = 40$) and negative ($n = 13$) subjects with atopic dermatitis. Values ≥ 100 kU L⁻¹ were considered elevated. The box illustrates median and interquartile range, and the whiskers show range of values obtained.

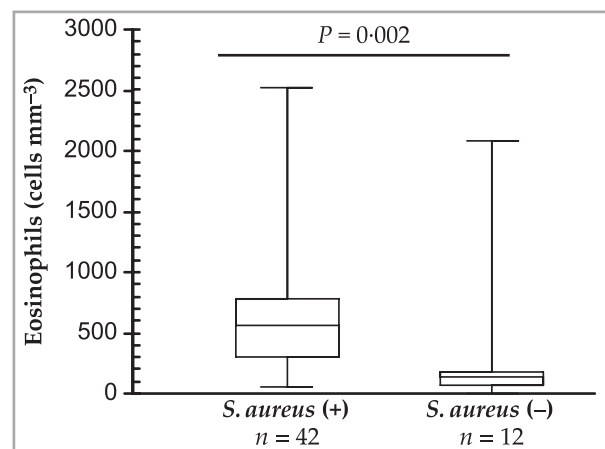


Fig 2. Eosinophilia in *Staphylococcus aureus*-positive ($n = 42$) and negative ($n = 12$) subjects with atopic dermatitis. Values ≥ 300 cells mm⁻³ were considered elevated. The box illustrates median and interquartile range, and the whiskers show range of values obtained.

association between biomarkers of Th2 polarity and susceptibility to herpes simplex infections in subjects with AD has also been noted.^{7,14,15} Two groups have demonstrated that subjects with AD who developed eczema herpeticum (EH) had higher total serum IgE levels than subjects with AD who did not develop such infections.^{14,15} Additionally, serum levels of the type 1 interferon, interferon- β , were significantly lower in subjects with AD who had EH, providing further evidence of a Th1/Th2 imbalance.¹⁵ Likewise, concomitant AR and asthma were more frequently present in subjects with EH, although the association was not significant.¹⁴ In our cohort of subjects with AD with a history of EH, we confirmed the association of serum IgE levels and noted an association with peripheral

eosinophilia and the presence of other atopic diseases (food allergy, asthma and AR).¹⁶ Furthermore, we found that subjects with EH reported a history of *S. aureus* and human papillomavirus infections more commonly than subjects with AD who had no history of EH.¹⁶ Collectively, these studies support the hypothesis that Th2 polarity and the presence of other atopic disorders enhance susceptibility of subjects with AD to a variety of cutaneous microbial infections.

In summary, AD disease severity and markers of Th2 polarity seem to predict *S. aureus* colonization in outpatients with AD. Therapies which inhibit the production of Th2 cytokines (IL-4 and IL-13) may improve AD in part by reducing *S. aureus* colonization.

Acknowledgments

We acknowledge the help of Ms Judith Warson, RN, whose compassionate care of these patients is appreciated by all. Funding: NO1 AI40029 (L.A.B.).

References

- Breuer K, Haussler S, Kapp A, Werfel T. *Staphylococcus aureus*: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol* 2002; **147**:55–61.
- Gilani SJ, Gonzalez M, Hussain I *et al.* *Staphylococcus aureus* re-colonization in atopic dermatitis: beyond the skin. *Clin Exp Dermatol* 2005; **30**:10–13.
- Breuer K, Wittmann M, Bösch B *et al.* Severe atopic dermatitis is associated with sensitization to staphylococcal enterotoxin B (SEB). *Allergy* 2000; **55**:551–5.
- Howell MD, Kim BE, Gao P *et al.* Cytokine modulation of AD filaggrin skin expression. *J Allergy Clin Immunol* 2007; **120**:150–5.
- McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol* 2006; **118**:202–8.
- Hasannejad H, Takahashi R, Kimishima M *et al.* Selective impairment of toll-like receptor 2-mediated proinflammatory cytokine production by monocytes from patients with atopic dermatitis. *J Allergy Clin Immunol* 2007; **120**:69–75.
- Howell MD, Wollenberg A, Gallo RL *et al.* Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol* 2006; **117**:836–41.
- Schäfer T, Heinrich J, Wjst M *et al.* Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol* 1999; **104**:1280–4.
- Salt BH, Boguniewicz M, Leung DY. Severe refractory atopic dermatitis in adults is highly atopic. *J Allergy Clin Immunol* 2007; **119**:508–9.
- Eichenfield LF. Consensus guidelines in diagnosis and treatment of atopic dermatitis. *Allergy* 2004; **59** (Suppl. 78):86–92.
- Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clin Infect Dis* 2003; **36**:131–9.
- Arkwright PD, Daniel TO, Sanyal D *et al.* Age-related prevalence and antibiotic resistance of pathogenic staphylococci and streptococci in children with infected atopic dermatitis at a single-specialty center. *Arch Dermatol* 2002; **138**:939–41.
- Kowalski TJ, Berbari EF, Osmon DR. Epidemiology, treatment, and prevention of community-acquired methicillin-resistant *Staphylococcus aureus* infections. *Mayo Clin Proc* 2005; **80**:1201–7.
- Wollenberg A, Zoch C, Wetzel S *et al.* Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. *J Am Acad Dermatol* 2003; **49**:198–205.
- Eis-Hubinger A-M, Novak N. Risk factors of atopic dermatitis patients for eczema herpeticum. *J Invest Dermatol* 2007; **127**:1261–3.
- Beck LA, Latchney LR, Zaccaro D, Leung DY. Disease severity and biomarkers of Th2 polarity are predictive of atopic dermatitis subjects risk for eczema herpeticum. *J Invest Dermatol* 2007; **127**:748A.