

Evaluation of the relationship between IgE level and skin superinfection in children with atopic dermatitis

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ABSTRACT

Increased Th2 polarity weakens the innate immune response and predisposes children with atopic dermatitis (AD) to skin superinfection. This study was designed to evaluate the relationship between IgE level and bacterial superinfection in children with AD. A medical chart review was performed on 103 children with AD to assess the association between IgE level and skin superinfection. A multivariable logistic regression model was used to assess the relationship between categorized IgE level and the presence of bacterial superinfection after adjusting for confounding variables including allergic rhinitis, asthma, and food allergy. A Wilcoxon signed-rank test was used to compare pre- and postskin superinfection median IgE levels in a subset of patients. Compared with children with an IgE level of <300 IU/mL, children with an IgE level of >1001 IU/mL were 66.00 times more likely to have a skin superinfection ($p = 0.003$) and children with an IgE level between 301 and 1000 IU/mL were 12.38 times more likely to have a skin superinfection ($p < 0.001$). After controlling for confounding variables including asthma, allergic rhinitis, and food allergy, children with an IgE level of >1001 IU/mL were 71.89 times more likely to have a skin superinfection ($p = 0.018$) and children with an IgE level between 301 and 1000 IU/mL were 8.79 times more likely to have a skin superinfection ($p < 0.001$) when compared with children with an IgE level of <300 IU/mL. There was a significant increase in IgE levels from baseline in 13 children treated for a skin superinfection ($p = 0.001$). IgE level is associated with *Staphylococcus aureus* superinfection in children with AD.

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Key words: Allergic rhinitis, asthma, atopic dermatitis, dust-mite allergen, food allergy, IgE level, peanut allergy, skin superinfection, *Staphylococcus aureus*, steroid cream

Atopic dermatitis (AD) is a pruritic, inflammatory process that disrupts the superficial skin barrier and predisposes children to bacterial superinfection.¹ Over 93% of children with AD are colonized with *Staphylococcus aureus*,^{2,3} up to 65% produce exotoxins with superantigenic properties,⁴ and 40–66% of these patients experience significant *Staphylococcus* infections during their lifetimes.⁵ Subjects with severe AD are thought to be more susceptible to *S. aureus* colonization and infection because of a polarized Th2 cytokine profile^{2,6–8} that disrupts the function of the innate immune system and predisposes to infection.^{9–11} Furthermore, *S. aureus* colonization has been associated with increased disease severity and glucocorticoid resistance.^{6–8} Up to 65% of children with AD also produce *S. aureus* exotoxin. Exposure to *S. aureus* superantigen has been shown to skew the immune response toward a Th2 profile leading to increased inflammation and elevated IgE levels.

The Th2 cytokine profile disrupts the skin barrier by reducing filaggrin^{12,13} and attenuates the innate im-

mune system. Macrophages have a decreased capacity to make interferon γ , and there is defective Toll-like receptor signaling.^{2,14,15} The predominance of IL-4, IL-5, and IL-13 up-regulated in AD prevents the mobilization of antimicrobial peptides, human β -defensin 3, and cathelicidins^{16–18} from reaching the surface for effective killing of *S. aureus*.^{19–21}

The IgE level is a significant predictor for AD.²² Previous studies have shown an association between increased IgE levels and increased eczema severity.²³ IgE level has also been used as a biomarker for Th2 polarity to study the association between AD and increased susceptibility to *S. aureus* colonization and herpetic eczematicum superinfection.^{5,24,25} We reviewed the medical records of children treated for AD in a university-based tertiary care clinic to determine (1) whether total IgE is a clinically useful biomarker for Th2 polarity and (2) whether IgE is predictive of bacterial superinfection when skin is refractory to topical steroid creams and responsive to oral antibiotics.

METHODS

We performed a retrospective chart review of subjects with AD seen at Alfred I. duPont Hospital for Children from January 1990 to November 2008. We used EPIC (EPIC Systems Corp., Verona, WI), our central computerized patient database, to attain all de-

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mographic, clinical, and historical information. This information included outpatient and emergency department records, prescribed medications including systemic antibiotics and steroids, laboratory tests, and results of appropriate procedures. In accordance with the accepted standards for research involving human subjects, approval for this study was granted by our institutional review board. Given the retrospective nature of our study, the institutional review board waived the need for informed consent.

Patient Population

We identified 103 subjects, aged 1–18.5 years, diagnosed with AD according to the diagnostic criteria as defined by Hanifin and Rajka.²⁶ Demographic information including race, sex, chronological age, age at the time IgE was drawn, history of food allergy, asthma, and aeroallergen sensitization was collected on all patients.

Exclusion Criteria

Several diseases that may be related to AD in children and also make them more susceptible to skin superinfection were excluded from the study. Children who have other known immunodeficiencies such as Wiskott-Aldrich syndrome, hyper-IgE syndrome (as defined by elevated total serum IgE, eczematoid skin lesions, cold abscesses, recurrent pneumonias, osteopenia/osteoporosis, and characteristic facies), human immunodeficiency virus, malignancy, and chronic granulomatous disease were excluded from the study.

Outcome Variable

The presence of a skin superinfection was established indirectly. The following criteria were used as a proxy for skin superinfection: pain on palpation, erythema, tenderness, crusting/oozing, pustules, and/or regional adenopathy for which the patient was not adequately controlled with topical steroid preparation and resolved with oral antibiotics as prescribed by dermatology or allergy and immunology. Routine skin cultures were not attained because they are known to be positive for *S. aureus* in 70–80% of children with AD, even when their skin is not inflamed.²

Predictor and Other Controlled Variables

The predictor variable, IgE, was collected quantitatively and then recoded into three categories: an IgE level of <300 IU/mL, an IgE level between 301 and 1000 IU/mL, and an IgE level of >1001 IU/mL. The other included study variables are sex (male or female), race (white, black, or other, which includes Hispanic, Asian, or Indian), chronological age in years, presence of asthma (yes or no), family history of atopy (yes or no), and other atopic features that may have elevated the total IgE level including sensitization to specific aeroallergens and foods

as defined by skin test value of 3 mm greater than the negative control. Skin testing was performed by the skin-prick method using the Greer Pick (Greer Labs, Lenoir, NC) and the commercial extract (Hollister-Stier Laboratories, LLC, Spokane, WA). The skin-prick tests were considered positive when the wheal diameter was 3 mm and 50% larger than the negative control. All children with histories suggestive of allergic rhinitis or AD had been skin tested to the same panel of aeroallergens. Data were recorded in a Microsoft Excel file and were later transferred to an SPSS data set (Version 17.0; SPSS, Chicago, IL).

Statistical Analysis

Categorical variables were described using frequency and percentages while continuous variables were summarized using mean, standard deviation, median, minimum, and maximum. Pearson chi-square statistic was used to examine the distribution of study characteristics in the three groups (IgE of <300 IU/mL, IgE of 301–1000 IU/mL, and IgE of >1001 IU/mL). An univariable logistic regression model was used to examine the association between the presence of skin superinfection and IgE level. A multivariable logistic regression model was used to examine the association between presence of skin superinfection and IgE level after adjusting for statistically/clinically significant covariates. Moreover, a Wilcoxon signed-rank test was used to compare pre- and postinfection median IgE levels in 13 children who had levels drawn at baseline and during a superinfection. All analyses were two tailed at the value of $p < 0.05$ significance level. All analyses were performed using the statistical package SSPS Version 17.0.

RESULTS

Description of Variables

Of the 103 children with AD, 46 (44.7%) had an IgE of <300 IU/mL, 25 (24.3%) had an IgE level between 301 and 1000 IU/mL, and 32 (31%) had an IgE of >1001 IU/mL. A majority of the children were boys (63.1%) and white (63.1%) with an even distribution between all three groups categorized by IgE level (Table 1). The mean age was 6.74 years with a range from 1 to 18.5 years. A majority of the children in the study had associated atopic features including specific food and aeroallergen sensitization and asthma (70.9%). Groups categorized by higher IgE levels had a significant association with asthma ($p < 0.040$) when compared with the group with an IgE level of <300 IU/mL. Children with higher IgE levels were also more likely to be sensitized to dust mites ($p < 0.001$), cats ($p = 0.028$), mold mix ($p = 0.011$), trees ($p = 0.005$), peanuts ($p = 0.002$), and wheat ($p = 0.026$).

Table 1 Study variables characterized by IgE levels

Variable	IgE of <300 IU/mL n (%)	IgE of 301–1000 IU/mL n (%)	IgE of >1001 IU/mL n (%)	Total (IU/mL) n (%)	p Value
Total no. of children in each category	46 (44.7)	25 (24.3)	32 (31.0)	103	
Gender					
Male	27 (58.7)	16 (64.0)	22 (68.8)	65 (63.1)	0.660
Female	19 (41.3)	9 (36.0)	10 (31.2)	38 (36.9)	
Race					
White	33 (71.7)	13 (52.0)	19 (59.4)	65 (63.1)	0.438
Black	8 (17.4)	9 (36.0)	8 (25.0)	25 (24.3)	
Hispanic, Asian, or Indian	5 (10.9)	3 (12.0)	5 (15.6)	13 (12.6)	
Chronological age (yr)					
Mean (SD)	7.19 (3.37)	8.14 (4.16)	5.67 (3.51)	6.74 (3.75)	
Median	7.25	7.00	6.00	7.00	
Minimum–maximum	2–17	2–17	1–14	1–17	
Presence of asthma					
Yes	27 (58.7)	19 (76.0)	27 (84.4)	73 (70.8)	0.040
No	19 (41.3)	6 (24.0)	5 (15.6)	30 (29.1)	
Family history of atopy					
Yes	40 (86.9)	23 (92.0)	32 (100.0)	95 (92.2)	0.106
No	6 (13.1)	2 (8.0)	0 (0.00)	8 (77.7)	
Sensitization to significant allergens					
Mold mix					
Yes	6 (13.0)	11 (44.0)	11 (34.4)	28 (27.2)	0.011
No	40 (87.0)	14 (56.0)	21 (65.6)	75 (72.8)	
Tree mix					
Yes	32 (69.6)	14 (56.0)	18 (56.2)	64 (62.1)	0.005
No	37 (80.4)	19 (76.0)	15 (46.9)	71 (68.9)	
Cat					
Yes	15 (32.6)	13 (52.0)	20 (62.5)	48 (46.6)	0.028
No	31 (67.4)	12 (48.0)	12 (37.5)	55 (53.4)	
Dog					
Yes	14 (30.4)	11 (44.0)	14 (43.8)	39 (37.9)	0.377
No	32 (69.6)	14 (56.0)	18 (56.2)	64 (62.1)	
Dust mite					
Yes	9 (19.6)	11 (44.0)	26 (81.3)	46 (44.7)	<0.001
No	37 (80.4)	14 (56.0)	6 (18.7)	57 (55.3)	
Wheat					
Yes	1 (2.2)	5 (20.0)	6 (18.8)	12 (11.7)	0.026
No	45 (97.8)	20 (80.0)	26 (81.2)	91 (88.3)	
Peanut					
Yes	12 (26.0)	11 (44.0)	21 (65.6)	44 (42.7)	0.002
No	34 (74.0)	14 (56.0)	11 (34.4)	59 (57.3)	

Note: *p*-value is generated from a chi-square statistic.

IgE Levels and Outcome Variables

There was also an increased frequency of skin infections over time in the groups with higher IgE levels when compared with children with an IgE level of <300 IU/mL. Of the pediatric AD patients with IgE levels of >1000 IU/mL, 75% had one or more skin superinfections, whereas only 36% of pediatric AD patients with IgE level between 301 and 1000 IU/mL

had a skin superinfection. Only 4.3% of pediatric AD patients with an IgE level less than 301 IU/mL had at least one skin superinfection. Higher IgE levels were associated with increased number of infections ($p < 0.001$), as shown in Table 2.

Table 3 examines the relationship between IgE levels and presence of skin superinfection in children with AD. Compared with children with an IgE level of <300

Table 2 Number of children with a skin superinfection and the no. of documented skin infections in these children categorized by IgE level

Variable	IgE of <300 IU/mL n (%)	IgE of 301–1000 IU/mL n (%)	IgE of >1001 IU/mL n (%)	Total (IU/mL) n (%)	p Value
Presence of infection					
Yes	2 (4.3)	9 (36.0)	24 (75.0)	35 (34.0)	
No. of infections					
0	44 (95.7)	16 (64.0)	8 (25.0)		
1	0 (0.0)	4 (16.0)	8 (25.0)		
2	2 (4.3)	3 (12.0)	4 (12.4)		
3–4	0 (0.0)	2 (8.0)	6 (18.8)		
>5	0 (0.0)	0 (0.0)	6 (18.8)		

The *p* value is from chi-square statistic.

Table 3 Univariate logistic regression model evaluating the association between IgE level and the presence of a skin superinfection

Groups Based on IgE Levels	Odds Ratio	p Value	95% Confidence Interval
IgE of <300 IU/mL	Reference	Reference	Reference
IgE of 301–1000 IU/mL	12.38	0.003	2.41–63.51
IgE of >1001 IU/mL	66.00	<0.001	12.97–335.97

IU/mL, pediatric AD patients with an IgE level of >1000 IU/mL were 66.00 times more likely to have a skin superinfection ($p < 0.001$), and children with an IgE level between 301 and 1000 IU/mL were 12.38 times more likely to have a skin superinfection ($p = 0.003$). After adjusting for statistically/clinically significant covariates such as gender; race; presence of asthma; chronological age; and sensitization to mold mix, tree mix, cats, dust mites, wheat, and peanuts, children with an IgE level of 301–1000 IU/mL were 8.79 times more likely to have a skin superinfection and those with an IgE level of >1001 IU/mL were 71.89 times more likely to have a skin superinfection when compared with children with an IgE level of <300 IU/mL (Table 4).

In 13 children with IgE levels drawn at baseline and during a bacterial skin superinfection, there was a significant increase in the median IgE value ($p = 0.001$) before treatment for a skin superinfection. The median IgE level was 14,518 IU/mL during an infection and only 5015 IU/mL at baseline (Table 5).

DISCUSSION

Our study looked at the association between IgE levels and skin superinfection in subjects with AD who have mean IgE levels above age-expected norms. We used an IgE level of <300 IU/mL as our control group to compare with the two other groups with an IgE level of >301–1000 IU/mL and >1001 IU/mL, respectively. It is well known that IgE levels vary in the general population and are not

reliable in diagnosing atopic disease. The normal range found in the general population is 0.6–424 IU/mL or 2–100 IU/L.²⁷ Although IgE levels can overlap between atopic and nonatopic subjects,²⁷ higher IgE levels in atopic patients have been associated with increased inflammation and propensity to infection.^{23–25} In the current study, all 13 children who had IgE levels drawn at baseline and during a skin superinfection, the IgE level increased significantly during a superinfection (see Table 5). Previous studies suggest subjects with severe AD are thought to be more susceptible to *S. aureus* colonization and infection^{5–7} because of a polarized Th2 cytokine profile.^{2,9} This study suggests that total IgE level may be a good clinical biomarker for Th2 polarization to predict when children will benefit from more aggressive topical antibiotic therapy.

Interestingly, our data also support findings in the literature that suggests an association between dust-mite allergy and higher total IgE levels.²⁸ Significantly more pediatric AD patients categorized with higher IgE levels had sensitization to dust when compared with pediatric AD patients with an IgE level of <300 IU/mL ($p < 0.001$).²⁸

Although many studies suggest that targeting the Th2 cytokine profile with anti-IL-4 therapy may improve AD skin lesions, a more recent study in murine animals suggests that this may alter the balance of other cytokines including IL-17 and lead to increased hyperresponsiveness and neutrophilic inflammation.²⁹ However, this study did not evaluate the impact IL-17 has on increased

Table 4 Multivariable logistic regression model evaluating the association between IgE level and the presence of a skin superinfection after adjusting for covariates

Variables	Odds Ratio	<i>p</i> Value	95% Confidence Interval
Categorical IgE level			
IgE of <300 IU/mL	Reference	Reference	Reference
IgE of 301–1000 IU/mL	8.79	0.018	1.45–53.42
IgE of >1001 IU/mL	71.89	<0.001	10.35–499.51
Race			
White	Reference	Reference	Reference
Black	0.86	0.83	0.22–3.43
Hispanic, Asian, or Indian	0.80	0.80	0.13–4.74
Gender			
Male	Reference	Reference	Reference
Female	0.88	0.85	0.23–3.34
Presence of asthma			
No	Reference	Reference	Reference
Yes	0.63	0.55	0.14–2.90
Sensitization to tree mix			
No	Reference	Reference	Reference
Yes	0.23	0.06	0.05–1.08
Sensitization to cat allergen			
No	Reference	Reference	Reference
Yes	3.09	0.10	0.80–11.97
Sensitization to mold mix			
No	Reference	Reference	Reference
Yes	1.20	0.80	0.31–4.68
Sensitization to dust mite			
No	Reference	Reference	Reference
Yes	1.92	0.35	0.49–7.56
Sensitization to wheat			
No	Reference	Reference	Reference
Yes	0.77	0.76	0.15–4.00
Sensitization to peanut			
No	Reference	Reference	Reference
Yes	1.42	0.59	0.41–4.97
Chronological age	1.08	0.36	0.91–1.29

Table 5 Comparison of pre- and post-superinfection median IgE levels in 13 children with IgE levels drawn at baseline and during a skin superinfection

	Median	Standard Deviation	Minimum–Maximum	Total	Significance (<i>p</i> Value)
IgE at baseline	5015.54	9617.49	148–34,000	13	*0.001
IgE during a superinfection	14518.31	17938.89	212–54,122	13	

*The *p* value is generated using a Wilcoxon signed-rank test.

susceptibility to infection in children with AD in the presence of IL-4 and IL-13, which are both known to inhibit interferon γ and down-regulate the β -defensins.^{2,14,15–18} A previous study had suggested that the Th2 microenvironment partially inhibits the IL-17–dependent up-regulation of β -defensins, HBD-2, when exposed to

S. aureus–derived superantigen staphylococcal enterotoxin B.³⁰ Thus, this study suggests that Th2 polarization inhibits the function of IL-17 and may account for the high rate of *S. aureus* skin colonization in children with AD.³⁰ More studies are needed to assess the impact of altering the Th2 cytokine profile on other mediators of inflammation.

The weaknesses of our project include the retrospective design. There may have been bias in the recorded symptoms, health care providers' thresholds for treating skin superinfections with oral antibiotics, and in selecting which children should have a total IgE level drawn. We often check IgE levels in children with clinical histories of associated food allergies, environmental allergies, or chronic AD so that we can follow their trend over time. This should not adversely affect our findings because we suspect that these are the children who are more prone to bacterial superinfection. Skin superinfection was also determined by indirect evidence for bacterial infection of the skin. Many of the children were empirically treated with oral antibiotics without a confirmed culture. This should not bias our results because it is well known that 70–80% of children with AD have a positive culture for *S. aureus* even when their skin is not inflamed.²

A future prospective study can focus on the trend in IgE levels at baseline, during treatment for a bacterial superinfection, and during an AD flare to assess whether IgE level is a good clinical biomarker for staphylococcal superinfection. Future studies can focus on the difference in IgE levels before and after 5–10 days of twice-daily topical antibiotic therapy to determine whether prophylactic topical therapy reduces IgE levels, improves skin integrity, and need for oral antibiotic therapy. A therapeutic study could look at the effect immunomodulators favoring the Th1 cytokine profile have on reducing *S. aureus* colonization and superinfection in children with AD.

In summary, IgE level, a clinical biomarker for Th2 polarization, is associated with skin superinfection in an outpatient clinic. We can use this marker in conjunction with our clinical judgment to help determine when patients will improve from an oral antibiotic.

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