

Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis

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Background: The skin of patients with atopic dermatitis exhibits a striking susceptibility to colonization and infection with *Staphylococcus aureus*. In this context it has been previously shown that *S aureus*-derived superantigens could function as classic allergens, inducing production of functionally relevant specific IgE antibodies.

Objective: The aim of this study was to determine the prevalence and the role of circulating staphylococcal enterotoxin A (SEA)- and staphylococcal enterotoxin B (SEB)-specific IgE antibodies in children with atopic dermatitis.

Methods: In a cross-sectional study of 58 children with atopic dermatitis, the presence of IgE antibodies to SEA and SEB was correlated with the severity of the disease and the total and other unrelated allergen-specific IgE titers and density of colonization with *S aureus* strains on atopic skin and episodes of superficial *S aureus* skin infections.

Results: Twenty of 58 children (34%) were sensitized to superantigens (45% to SEB, 10% to SEA, 45% to SEA and SEB). In this group, severity of atopic dermatitis and levels of specific IgE to food and air allergens were significantly higher. The degree of disease severity correlated to a higher extent with the presence of SEA/SEB-specific antibodies than with total serum IgE levels. Density of colonization with superantigen-secreting *S aureus* strains was higher in the superantigen IgE-positive group. Sixty-three percent of these children experienced repeated episodes of superficial *S aureus* skin infections.

Conclusions: Sensitization to *S aureus*-derived superantigens may be involved in disease exacerbation. The presence of SEA/SEB-specific antibodies had additional explanatory value for disease severity and therefore may be helpful in the characterization of children with severe atopic dermatitis.

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Key words: Atopic dermatitis, *S aureus* colonization density, superficial *S aureus* skin infection, staphylococcal enterotoxins, total serum IgE, specific IgE to SEA/SEB, severity of AD risk factors for sensitization to SEB/SEA

Abbreviations used

AD:	Atopic dermatitis
SE:	Staphylococcal enterotoxin
SEA:	Staphylococcal enterotoxin A
SEB:	Staphylococcal enterotoxin B
TSST-1:	Toxic shock syndrome toxin-1

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease often associated with a family history of atopy¹ and diagnosed by a combination of characteristic clinical findings.^{2,3} More than 80% of patients with AD have elevated total serum IgE levels, and many show positive immediate-type skin test responses to food and air allergens.⁴⁻⁶ Several studies have demonstrated that exposure to food and air allergens can exacerbate the disease in a subset of patients with AD.⁶⁻¹²

Another well-known disease-promoting agent is *Staphylococcus aureus*.^{13,14} The skin of patients with AD exhibits a striking susceptibility to colonization and infection with this bacterium, which can be isolated from acute exudative lesions and from chronic lichenified plaques.¹³⁻¹⁹ *S aureus* strains isolated from AD skin have been shown to secrete a variety of exotoxins, including staphylococcal enterotoxins A, B, and C (SEA, SEB, SEC, respectively) and toxic shock syndrome toxin-1 (TSST-1) with superantigen activity.¹⁷⁻²¹ These exotoxins may contribute to the immunopathogenesis of AD in several ways. Directly interacting with the T-cell receptor, they can cause profound T-cell activation.²²⁻²⁴ It has been shown that direct application of superantigens on intact skin induces an inflammatory reaction in subjects with and without AD.²⁰ In addition, *S aureus*-derived exotoxins may act as conventional allergens, stimulating the production of specific IgE antibodies. Leung et al²¹ detected circulating IgE antibodies to SEA, SEB, and TSST-1 in almost one half of patients with AD, and Tada et al²⁵ found specific IgE antibodies to SEB and SEA in 80 of 96 adult patients with AD. These antibodies are of functional relevance because they can trigger mediator release from sensitized basophils after the IgE antibodies have been crosslinked with the appropriate antigens.²¹

The aim of this study was to determine the prevalence and role of circulating IgE antibodies with specificity to SEA and SEB in children with AD. For this purpose the presence of the respective IgE antibodies was correlated

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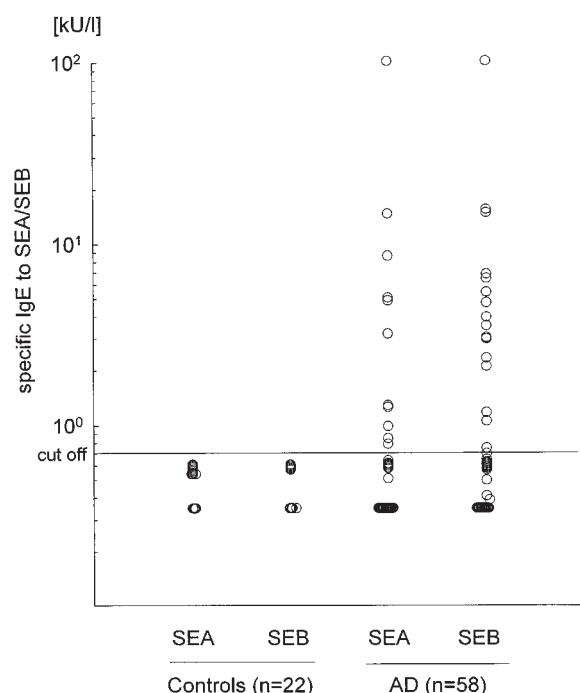


FIG 1. Levels of IgE antibodies to SEA and SEB in nonatopic healthy control patients compared with patients with AD. Cut off, 0.7 KU/L.

with severity of disease, total IgE, and the presence of IgE antibodies against food and air allergens and the presence of exotoxin-producing strains of *S aureus* on the skin.

METHODS

Study populations

From May 1996 to May 1997, 58 children who were hospitalized because of AD (median age, 30 months; range, 6 months to 184 months) and 22 healthy control children (median age, 73 months; range, 3 months to 110 months) were enrolled in a cross-sectional study. Only patients who fulfilled the criteria of Hanifin and Rajka² as modified by Sampson and who had not used topical or systemic antimicrobial drugs for at least 14 days before investigation were included in the study. Severity of AD was determined according to the SCORAD index.²⁶

Isolation of *S aureus* from skin and nose

For the isolation of *S aureus*, contact samples from both unaffected and eczematous skin were obtained. Neck, wrist, elbow, and erosive-eczematous lesions were investigated with Rodac blood-agar plates (diameter, 5.6 cm) that were incubated for 48 hours at 32°C. *S aureus* was identified by testing typical colonies for coagulase activity.²⁷ Colonization was quantified by an estimation of the number of colony-forming units per agar plate and subsequent calculation of colonies per square centimeter. Nasal carriers were identified by the incubation of standardized samples that were obtained from both nares by sterile cotton tips on blood and mannitol agar for 48 hours at 32°C.

Detection of *S aureus*-derived exotoxins

To identify the production of exotoxins, a defined inoculum of *S aureus* (10 colonies of a 24-hour subculture on blood agar) was

incubated in RPMI-1640 (Gibco, Grand Island, NY) protein-free cell culture medium for 18 hours at 37°C.

The filter-sterilized supernatants (0.45 µm) were tested for the presence of exotoxins with the TSST- and SET-RPLAR latex agglutination test (Unipath, Hampshire, UK) according to the manufacturer's instructions.

Determination of superficial and invasive *S aureus* infection

Superficial *S aureus* skin infections were characterized by small pustules, crusting, pus and increased pruritus,^{13,14} and the presence of *S aureus*, as determined by contact sampling and culture. Invasive *S aureus* infections, such as cutaneous abscesses, septicemia, and osteomyelitis, were diagnosed by the isolation of *S aureus* in blood culture or drained or aspirated tissue lesions. All children with superficial or invasive *S aureus* infection received systemic antimicrobial treatment after samples had been taken.

Determination of total and allergen-specific serum IgE

Blood samples were taken on admission, and levels of total IgE and IgE specific for cow's milk, egg, soybean, wheat, mite, cat, grass, and birch were determined by use of the Pharmacia CAP assay (Pharmacia and Upjohn, Upsala, Sweden), according to the manufacturer's instructions. IgE antibodies against SEA and SEB were measured by the use of AlaSTAT assay (DPC Biemann, Bad Nauheim, Germany), which is a liquid-phase enzyme immunoassay for allergen-specific IgE antibody determination.²⁸ Specificity was demonstrated by inhibition experiments with SEA, SEB, and TSST-1 (personal communication, Dr E Unver, DPC, Los Angeles, Calif).

Statistical analysis

Statistical analysis was performed with the chi-squared test, Fisher's exact test, and Wilcoxon's test for independent samples. The interdependence of the SCORAD score on total serum IgE, specific IgE to air and food allergens, and specific IgE to SEA and/or SEB was demonstrated by classic multiple regression.

RESULTS

Prevalence of serum IgE with specificity to SEA and/or SEB in children with severe AD

The presence of serum-IgE antibodies to *S aureus*-derived exotoxins (SEA/SEB) was analyzed in 58 children with AD and 22 healthy control children. In the control group, concentrations of SEA-specific IgE ranged from 0.03 to 0.6 KU/L (median, 0.57 KU/L), and concentrations of SEB-specific IgE ranged from 0.07 to 0.61 KU/L (median, 0.59 KU/L). Twenty of the 58 children (34%) with AD demonstrated sensitization to SEA and/or SEB (45% to SEB, 10% to SEA, 45% to SEA and SEB). Eleven children were sensitized to SEA and had a median IgE of 1.3 KU/L; 18 children were sensitized to SEB and had median IgE levels of 3.0 KU/L. Sensitization was defined as specific IgE concentrations higher than 0.7 KU/L (Fig 1).

Prevalence of skin colonization and superficial/invasive infections with *S aureus* in sensitized versus nonsensitized children

All SEA/SEB-sensitized children were colonized with *S aureus* on admission, compared with 71% of nonsensitized children with AD ($P < .01$) and only 18% ($n = 4$) of

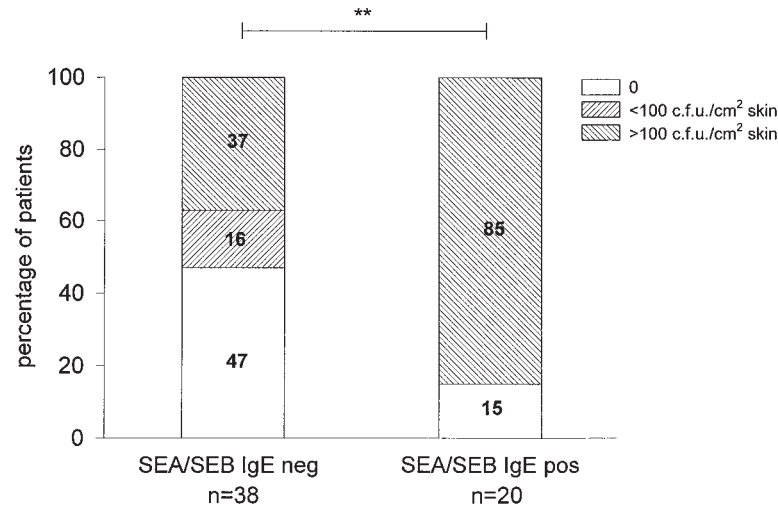


FIG 2. Density of *S aureus* colonization of the most severely affected skin site (erosive-eczematous areas) in sensitized versus nonsensitized children with AD. Columns represent the median colony-forming units per square centimeters of the tested skin. **Pearson test, $P < .01$.

TABLE I. Characterization of children who have AD with and without IgE antibodies against SEA and/or SEB

	Superantigen IgE negative* (n = 38)	Superantigen IgE positive* (n = 20)
Sex (F:M)	11:27	9:11
Age (mo)		
Median,	19†	57†
Minimum-maximum	6-184	9-153
No. of children colonized by <i>S aureus</i> (%)	27 (71)‡	20 (100)‡
No. of children colonized by SEA-positive strains of <i>S aureus</i> (%)	4 (11)	5 (25)
No. of children colonized by SEB-positive strains of <i>S aureus</i> (%)	0‡	5 (25)‡
History of antimicrobial therapy		
No. of children with no antimicrobial therapy (%)	30 (79)§	4 (20)§
No. of children with antimicrobial therapy/superficial <i>S aureus</i> infection (%)	7 (18)§	8 (40)§
No. of children with antimicrobial therapy/superficial and invasive <i>S aureus</i> infection (%)	1 (3)§	8 (40)§

*SEA- and/or SEB-sensitized grouped together.

†Wilcoxon 2-sample test, $P < .05$.

‡Fisher's exact test, $P < .01$.

§Pearson test, $P < .0001$.

TABLE II. Correlation between sensitization to SEA/SEB and total and specific IgE to food and air allergens

	SEA/SEB IgE negative,*† KU/L, median (min-max)	SEA/SEB IgE positive,*† KU/L, median (min-max)	P value§
Total IgE	116 (2-4290)	3835 (67-42000)	<.0001
Hen's egg	0.46 (0.35-100)	3.6 (0.35-100)	<.01
Cow's milk	0.38 (0.35-100)	2.7 (0.35-100)	<.05
Soybeans	0.35 (0.35-48.3)	4.2 (0.35-81.9)	<.01
Wheat	0.35 (0.35-100)	2.9 (0.35-92.7)	<.01
Birch	0.35 (0.35-100)	17.5 (0.35-100)	<.001
Grass	0.35 (0.35-34.5)	2.8 (0.35-100)	<.01
Mite	0.35 (0.35-94)	2.6 (0.35-100)	<.001
Cat	0.35 (0.35-53.7)	22.6 (0.35-100)	<.0001

*SEA- and/or SEB-sensitized grouped together.

†n = 38.

‡n = 20.

§Wilcoxon 2-sample test.

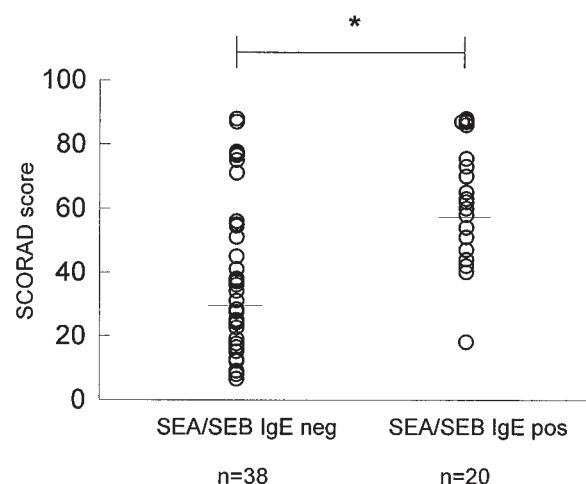


FIG 3. Severity of AD as determined by the SCORAD Score in SEA/SEB sensitized versus nonsensitized children. *Solid lines* represent the median SCORAD scores. *Wilcoxon 2-sample test, $P < .05$.

the healthy control children. Furthermore, nonsensitized children with AD differed significantly from those sensitized to SEA and/or SEB in age (Table I), the degree of colonization with *S aureus* on both affected and nonaffected skin in all skin areas tested (neck, wrist, elbow, most severely affected skin had erosive-eczematous lesions; Fig 2), a higher incidence of *S aureus* infections requiring antimicrobial therapy (Table I), and the prevalence of SEB-producing strains on the skin (Table I).

Sixteen children (80%) of the sensitized group had superficial *S aureus* skin infections (Table I).

S aureus skin colonization (Fig 2) and superficial infection (Table I) were both highly correlated with the presence of IgE antibodies to superantigens SEA/SEB.

Invasive infections in the sensitized group included 5 patients with skin abscesses, 1 patient with lymphadenitis, and 2 patients with septicemia. One patient with osteomyelitis was present in the nonsensitized group.

Correlation between sensitization to SEA/SEB and severity of AD

On the basis of the known association between colonization with *S aureus* and the severity of skin lesions,²⁹ we also investigated the interrelationship between specific sensitization to SEA/SEB and severity of skin disease as quantified by the SCORAD score. Severe dermatitis was significantly more often observed in SEA/SEB-sensitized children (Fig 3).

Serum levels of total and nonrelated allergen-specific IgE in children sensitized to *S aureus*-derived exotoxins

To further characterize SEA/SEB-sensitized patients, we examined the levels of total and specific IgE antibodies to food and air allergens. As demonstrated in Table II, total IgE and serum-levels of IgE with specificity to milk, hen's egg, soybeans, and wheat were significantly higher

TABLE III. Dissociation of total and SEA/SEB-specific IgE antibodies in patients with AD

Patients	Total IgE (KU/L)	Specific IgE SEA (KU/L)	Specific IgE SEB (KU/L)
H.D.	67	<0.7	1.06
G.H.	269	<0.7	2.34
B.F.	492	3.18	<0.7
V.F.	930	<0.7	2.11
M.C.	1695	5.04	6.45
H.P.	13700	0.85	3.52
C.B.	36500	<0.7	1.55
H.C.	11330	100	2.98
F.W.	42000	14.52	100
J.K.	29300	8.56	15.32
S.J.	3470	<0.7	<0.7
N.F.	4210	<0.7	<0.7

Cut off <0.7 KU/L.

in SEA/SEB-sensitized children. In addition, SEA/SEB-positive children had higher amounts of specific IgE to birch, grass, mite, and cat allergens. However, as shown in Table III, we identified SEA/SEB-sensitized patients with low levels of total IgE and patients with high levels of total IgE but who were negative for SEA/SEB-specific IgE. In addition, the presence of IgE antibodies to SEA or SEB was independent from each other.

Multiple regression analysis revealed that the presence of SEA/SEB-specific serum-IgE ($R = 0.42$; $R^2 = 0.17$; $P < .001$) has a higher explanatory value for disease severity as total IgE ($R = 0.03$; $R^2 = 0.09$; $P < .05$) or food- and air allergen-specific IgE (not significant).

DISCUSSION

There is strong evidence that *S aureus* contributes to the pathogenesis of AD. More than 80% of patients with AD show *S aureus* colonization of their skin.^{13,14,16,19} In addition, superficial invasion of *S aureus* causes acute inflammation with (micro) abscesses and dermal neutrophil influx.¹³ Furthermore, antistaphylococcal therapy reduces skin inflammation in a subset of patients with AD.¹⁴ Although the clinical evidence is persuasive, the underlying pathomechanisms still remain to be elucidated. Intact bacteria, *S aureus*-derived cell wall products, and exotoxins, including superantigens, can penetrate the skin and directly interact with several immunocompetent cell populations.³⁰⁻³⁶ Campbell and Kemp³⁷ found that peripheral blood mononuclear cells from children with AD demonstrate enhanced proliferation to cells of *S aureus* and SEB.

IgE antibodies against *S aureus* cell wall products have been described particularly in severe cases.²⁹ High levels of such antibodies are also produced by patients with the hyperimmunoglobulin-E syndrome,^{38,39} an immunodeficiency syndrome⁴⁰ associated with recurrent superficial and invasive *S aureus* infections. We demonstrated here that sensitization to *S aureus*-derived exotoxins with superantigen activity like SEA and SEB identifies children with severe AD.

Superantigens have been originally described as potent T-cell activators that modulate T-cell function through unconventional interaction with the T-cell receptor. The presence of IgE antibodies to *S aureus*-derived products like SEA and SEB in patients with AD can be explained in several ways. On the one hand, exotoxins may function as classic antigens through uptake by and presentation on antigen-presenting cells resulting in specific sensitization. Alternatively, some staphylococcal exotoxins have been also described as B-cell superantigens. Staphylococcal enterotoxin appears to function by inducing several of VH-4-expressing IgM B cells, and staphylococcal protein A induced production of IgM by VH-3-expressing B cells.^{41,42} However, to our knowledge, such activity has not been described for the induction of IgE antibodies for SEA or SEB. In addition, the presence of high levels of total IgE in some SEA/SEB nonsensitized patients and specific sensitization without increased total IgE makes it unlikely that superantigen-like binding of SEA/SEB to IgE molecules accounted for our results. The most stringent argument, however, is that none of the healthy control group had specific IgE levels higher than 0.7 KU/L.

What might be the clinical impact of IgE antibodies to *S aureus*-derived superantigens? Leung et al²¹ demonstrated IgE-dependent mediator release from sensitized basophils that were coincubated with superantigens. Crosslinking of mast cell-bound IgE by locally produced superantigens could therefore trigger release of histamine and other mediators. They promote the itch-scratch cycle that, along with mast cell-derived mediators, cytokines, and leucocyte chemotactic factors, may contribute to the late-phase inflammatory response. This is compatible with our observation that such IgE antibodies are present in infants with severe clinical phenotypes and polyvalent sensitizations to air and food allergens.

Our results suggest that sensitization to *S aureus*-derived superantigens may be involved in disease exacerbation. Consequently, the determination of SEA/SEB-specific IgE antibodies provides important additional information in the follow-up of patients with AD.

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