IgE to *Staphylococcus aureus* enterotoxins in serum is related to severity of asthma

To the Editor:

Staphylococcus aureus–derived enterotoxins (SAEs) are a group of high-molecular-weight superantigens that possesses an extremely potent stimulatory activity for T lymphocytes by cross-linking the V_{β}-chain of the T-cell receptor with MHC class II molecules on accessory or target T cells, outside the peptide-binding groove area.[1] The SAEs are a family of structurally related, heat-stable proteins comprising several major serologic types; among these are the 5 prototypic SAEs (types A through E) and toxic shock syndrome toxin 1 (TSST-1).

Although *S aureus* is often found as part of the normal microflora of the upper respiratory tract, especially the vestibulum nasi, there is a marked paucity of studies documenting an association between SAEs and airway disease, particularly rhinitis, sinusitis, and asthma. Studies in animals have shown that SAE-B triggers airway recruitment of several pro-inflammatory cell types, including T cells, eosinophils, neutrophils, and macrophages, and the release of cytokines, associated with increased airway responsiveness in these animals.[2] There is circumstantial evidence that SAEs might trigger T-cell activation in poorly controlled asthma in human beings,[3] as the expression of corresponding TCR-Vβ8 on T cells in bronchoalveolar lavage is significantly increased in comparison with controls. We have recently provided evidence that SAEs are related to eosinophilic inflammation in nasal polyposis, a chronic eosinophilic inflammation located in the sinuses, which often is associated with severe asthma and aspirin hypersensitivity.[4] In approximately 50% of the polyp homogenates, IgE antibodies specific to SAE-A and/or SAE-B could be demonstrated; these were linked to high total tissue IgE and a local multiclonal IgE antibody formation against various inhalant allergens. In SAE-specific IgE antibody–positive polyp samples versus controls, the eosinophilic inflammation was significantly more pronounced in terms of synthesis of IL-5, eotaxin, eosinophil cationic protein (ECP), and cysteinyl-leukotrienes, and most of these patients also had asthma and aspirin hypersensitivity.[4]

It was therefore tempting to investigate the potential role of SAEs in lower airway disease, using IgE antibodies specific to enterotoxins as a marker. To allow screening of sera from asthmatic patients, we characterized the patterns of IgE antibody responses specific to SAEs in nasal polyps and established a mix consisting of 3 SAEs (SAE-A, SAE-C, and TSST-1) coupled to the ImmunoCAP solid phase (Pharmacia Diagnostic, Uppsala, Sweden), which proved to be both more sensitive than the single allergens and highly specific (cutoff, 0.1 kU/L). No nonspecific IgE reactivity to SAE mix/ImmunoCAP was found for non–antibody-active IgE (E myeloma) at concentrations up to 1000 kU/L. Samples positive for IgE antibody to SAE mix tested negative to a control ImmunCAP without allergen.

Presence of IgE antibody to SAE mix was studied in the following groups: (a) 15 healthy controls (10 female, 5 male; mean age, 33 years), who had no symptoms compatible with asthma; (b) 34 patients with mild asthma (16 female, 18 male; mean age, 27 years), who had a resting FEV_1 of >80% predicted and received only the inhaled short-acting β-agonist salbutamol as on-demand therapy; and (c) 21 patients with severe asthma (11 females, 10 males; mean age, 45 years), as defined by the need for regular high-dose inhaled corticosteroid therapy and (despite this treatment) persistently impaired lung function (FEV_1 < 80%). All of the patients with severe asthma were receiving high-dose inhaled corticosteroid therapy (≥800 μg BDP or the equivalent), as well as additional asthma medication (mostly 4 different asthma therapies); 4 of these patients were also receiving long-term oral corticosteroid therapy. None of the asthmatic patients had active disease or could recall having had atopic dermatitis previously. We measured total IgE, IgE antibodies specific to a mixture of inhalant allergens (Phadiatop), IgE antibodies specific to SAE mix, and ECP (Pharmacia Diagnostic) in serum.

Severity of asthma was reflected not only in FEV_1 percent and medication but also in increased serum ECP concentrations (Table I). IgE antibodies to SAE mix were found more often in serum from asthmatic patients than in serum from controls (49% vs 13%; $P = .03$) and, within the group of asthmatic patients, more often in those with severe asthma than in those with mild asthma (62% vs 41%; $P = .224$), with a statistical significant difference between patients with severe asthma and controls (62% vs 13%; $P = .01$; χ^2 test). These data suggest a relation between the presence of IgE antibody to SAE mix and the severity of asthma (in terms of spirometry and need for medication) as well as eosinophilic inflammation, as previously identified in nasal polyposis, a disease closely related to asthma. Furthermore, the data support a link between enterotoxins and steroid insensitivity in airway disease, as was demonstrated previously in human mononuclear cells.[5]

Inasmuch as most of the asthmatic patients—certainly those with severe asthma—also had rhinitis symptoms, we could speculate that the source of SAEs might also be the nose and sinuses and that droplets from the nose containing SAEs would be inhaled. However, further research needs to be done to clarify the pathophysiologic link between SAE-specific IgE and bronchial inflammation.

Of the 55 patients with asthma, 31 showed increased concentrations of total IgE in serum (>100 kU/L), and 21 of those had IgE antibodies to SAE mix. Consequently, each of 10 subjects had an increased total IgE but no IgE antibodies to SAE mix. Twelve sera had total IgE levels above 500 kU/L, and 9 were positive and 3 negative for IgE antibodies to SAE. These data confirm the specificity of the assay; furthermore, they suggest that in approximately one third of the patients, superantigens other than the ones tested here might also play a role.

In addition, there was a significant though weak correlation between concentrations of total IgE and IgE antibodies to SAE mix ($P = .000$; $r = 0.533$), as well as

TABLE I. Total IgE, IgE antibodies specific to a mixture of inhalant allergens (Phadiatop), IgE antibodies specific to SAE mix, and eosinophil cationic protein in serum of controls, patients with mild asthma, and patients with severe asthma

	Controls (n = 15)	Versus	Mild asthma (n = 34)	Versus	Severe asthma (n = 21)	Versus controls
FEV_1: percent	>80		94 (90-101)		48 (43-57)	
Skin prick test: +/n (%)	(All negative)	$P < .001$	33/34 (97)	$P = .018$	15/21 (71)	$P < .001$
Phadiatop: +/n (%)	3/15 (20)	$P < .001$	33/34 (97)	$P < .001$	9/18 (50)	$P = .155$
SAE mix: +/n (%)	2/15 (13)	$P = .113$	14/34 (41)	$P = .224$	13/21 (62)	$P = .010$
IgE (kU/L)	27 (7-75)	$P < .001$	255 (94-633)	$P = .001$	56 (22-193)	$P = .023$
Eosinophil cationic protein (□g/L)	5.3 (3-8)	$P = .012$	10.4 (6-24)	$P = .290$	16.0 (7-35)	$P = .009$

Skin prick test, Phadiatop, and SAE mix: number of positive cases/total number of cases (percent); statistical analysis, χ^2 test (Yates correction). IgE and eosinophil cationic protein: median (interquartile range); statistical analysis, Mann-Whitney *U* test.

between the concentrations of IgE antibody to SAE mix and IgE antibody to common allergens (Phadiatop; $P = .007$; $r = 0.380$). This would suggest that a multiclonal IgE response due to SAEs could affect not only total IgE concentrations but also IgE antibody concentrations to individual allergens, pointing to a link between (staphylococcal) infection and allergy.

Collectively, we propose a crucial role for SAEs in the pathophysiology of upper an lower airway disease, linked to severity of eosinophilic inflammation, clinical severity, and corticosteroid dependence, to be confirmed in larger population as well as in confirmatory treatment studies.

Claus Bachert, MD, PhD[a]
Philippe Gevaert, MD[a]
Peter Howarth, BSc, DM, FRCP[b]
Gabriele Holtappels[a]
Paul van Cauwenberge, MD, PhD[a]
S. G. O. Johansson, MD, PhD[c]
[a]*Department of Otorhinolaryngology*
Ghent University Hospital
Ghent, Belgium
[b]*Respiratory Cell and Molecular Biology Research Division*
University of Southampton
Southampton, United Kingdom
[c]*Department of Clinical Immunology*
Karolinska Hospital
Stockholm, Sweden

REFERENCES

1. Fleischer B. Superantigens. APMIS 1994;102:3-12.
2. Herz U, Ruckert R, Wollenhaupt K, Tschernig T, Neuhaus-Steinmetz U, Pabst R, et al. Airway exposure to bacterial superantigen (SEB) induces lymphocyte-dependent airway inflammation associated with increased airway responsiveness—a model for non-allergic asthma. Eur J Immunol 1999;29:1021-31.
3. Hauk PJ, Wenzel SE, Trumble AE, Szefler SJ, Leung DY. Increased T-cell receptor vbeta8+ T cells in bronchoalveolar lavage fluid of subjects with poorly controlled asthma: a potential role for microbial superantigens. J Allergy Clin Immunol 1999;104:37-45.
4. Bachert C, Gevaert P, Holtappels G, Johansson SGO, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol 2001;107:607-14.
5. Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PBMCs by microbial superantigens. J Allergy Clin Immunol 2000;105:782-7.

doi:10.1067/mai.2003.1389