

IgE Antibodies to Bacteria in Patients with Bronchial Asthma

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Bacterial respiratory infections, especially with *Haemophilus influenzae* and *Streptococcus pneumoniae*, are frequently associated with an increase of airways obstruction in patients with bronchial asthma. The possible involvement of immediate hypersensitivity in this phenomenon was studied. IgE antibodies to *Haemophilus influenzae* (HI) and *Streptococcus pneumoniae* (SPn) were investigated in the serum of 190 adult patients with bronchial asthma. The IgE antibodies were measured using a solid phase radioimmunoassay method. Living bacteria were used as solid phase. A correction of the non-specific binding of IgE was necessary. IgE antibodies to one or both bacteria were present in 55 of the 190 patients (29%).

Eighteen patients were sensitive to HI, 33 to SPn and four to both bacteria. Significantly more IgE antibodies to bacteria were found in patients with demonstrable IgE antibodies to various inhalant allergens. However, the IgE antibodies to one or both bacteria were also present in 22% of patients with no other demonstrable IgE mediated hypersensitivity. The total serum IgE level in patients with IgE antibodies to bacteria was not significantly higher than in patients without hypersensitivity to these bacteria. From these data we concluded that immediate hypersensitivity to bacteria may play a role in the infectious exacerbations of bronchial asthma.

Key words: bacteria; bronchial asthma; IgE; immediate hypersensitivity

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An increased frequency of respiratory infections is observed in patients with bronchial asthma (9, 10). Both viral and bacterial infections of the respiratory tract are frequently associated with an increase of the airways obstruction. The mechanisms involved in this increase of airway resistance during a bacterial respiratory tract infection are not clear. Several explanations are possible. An increase in the amount and the viscosity of the sputum may certainly play a role. However, during acute infectious exacerbations, most patients with bronchial asthma show a severe degree of bronchospasm. The bronchoconstriction may be due to the action of non-

specific products such as endotoxin, bacterial enzymes or the histamine sensitizing factor (15). Immunological phenomena leading to the release of bronchoconstrictory mediators have also been postulated (7, 12, 18).

The present investigation was started in order to look for an immediate type hypersensitivity in bacterial exacerbations of bronchial asthma. *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most common bacterial species associated with an acute infectious exacerbation of bronchial asthma. IgE antibodies to these bacteria were assayed in the serum of patients with bronchial asthma.

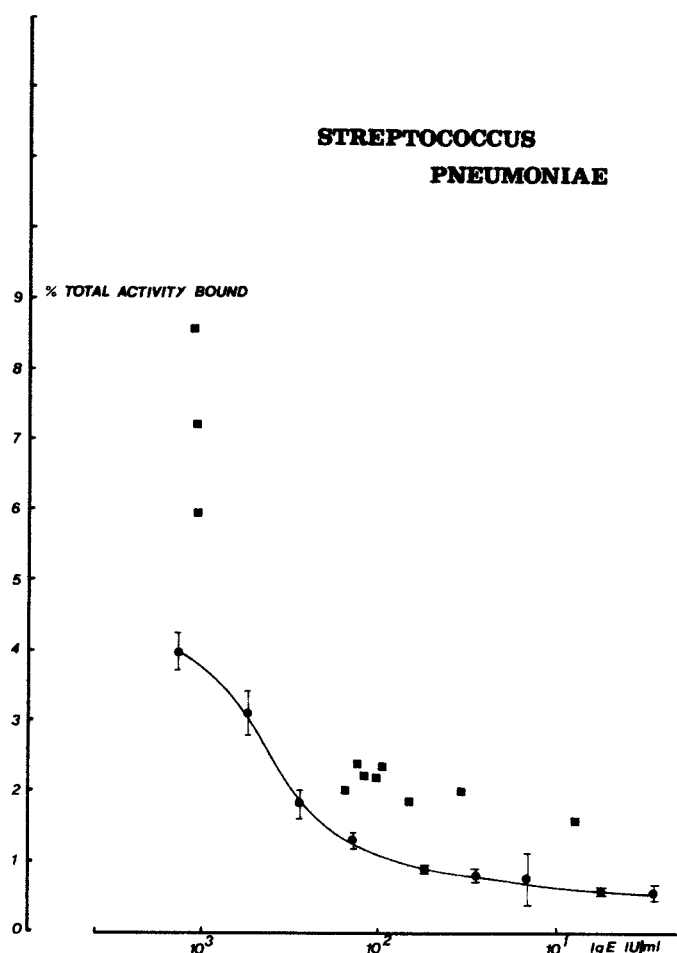


Fig. 1. Radioimmunoassay for IgE antibodies to *Streptococcus pneumoniae*. The curve illustrates the binding of normal and myeloma IgE (mean ± 2 s.d.) to the bacteria. Square signs illustrate positive patient sera.

PATIENTS AND METHODS

Patients and controls

190 patients with bronchial asthma (1), 94 females and 96 males were involved in the study. Their age varied from 14 to 52 years. Patients with atopic eczema were excluded from the study. The controls were healthy persons employed at the department of chest diseases. The human myeloma IgE was a gift of J. P. Vaerman, Brussels.

Measurement of antibacterial IgE

A solid phase radioimmunoassay method with living bacteria as solid phase was used for the detection of bacteria-specific IgE (13). Bacteria were grown on liquid culture medium and washed extensively in saline before use in the assay in order to eliminate contamination

from the culture medium. The bacteria were taken at random from positive sputum cultures. No serotyping was performed. Approximately 10^9 bacteria were incubated with 100 μ l undiluted serum during 3 h by continuous shaking. The bacteria were then washed four times with saline. Afterwards 100 μ l of radioiodinated anti-human IgE serum (Pharmacia, Sweden) was added to the bacteria. After an incubation of 18 h, the bacterial suspension was again washed four times. The remaining radioactivity was then counted in a gammacounter (Berthold MAG 310). Tubes containing the same amount of bacteria but with the addition of saline instead of serum during the first step were used as controls. The radioactivity of the control tubes was subtracted before the analysis of the test material.

For the interpretation of the results, we had to take into account the non-specific binding of IgE to the bacteria. Myeloma IgE and 20 control sera, negative for IgE antibodies to bacteria, were assayed using the same solid phase method. Fig. 1 shows the amount of radioactivity bound. The amount of radioactivity bound increased with higher IgE levels. The control sera and the myeloma IgE gave similar results.

The results of individual patient sera were expressed as positive or negative for IgE antibodies to *Haemophilus influenzae* or *Streptococcus pneumoniae*. A serum was regarded as positive when the amount of radioactivity bound exceeded the mean plus two standard deviations of the bound radioactivity for the corresponding IgE value of the standard serum pool of control sera. The square signs in Fig. 1 indicate positive sera. The same principle was applied for the test with *Streptococcus pneumoniae* or *Haemophilus influenzae*. The non-specific IgE binding was higher for *Haemophilus influenzae* than for *Streptococcus pneumoniae*.

Total serum IgE and radioallergosorbent technique

Total serum IgE levels and specific IgE-antibodies to 18 different allergens (house dust

Table 1

Frequency of IgE antibodies to bacteria in patients with bronchial asthma

Patients	n	<i>Haemophilus influenzae</i>	<i>Streptococcus pneumoniae</i>	Total
Total group	190	22	37	55
RAST+	91	18	17	33
RAST-	99	4	20	22

mite, grass pollen, birch pollen, beech pollen, oak pollen, marguerite pollen, mugwort pollen, dandelion pollen, cat dander, dog dander, horse dander, egg white, milk, codfish, *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria tenuis*) were measured using the methods previously described (11).

RESULTS

Using the above technique, we demonstrated the presence of IgE antibodies to one or both bacteria in 55 of the 190 patients with bronchial asthma. The frequency of IgE antibodies to the specific bacteria was different. Nine percent of the patients had IgE antibodies to *Haemophilus* alone, 17% had only specific IgE antibodies to *Streptococcus pneumoniae* and four patients had demonstrable IgE to both species.

When we divided the patients with bronchial asthma in two groups, one group with demonstrable IgE antibodies to inhalant allergens, the so-called extrinsic asthmatics, and a second group with no IgE antibodies to inhalant allergens, the so-called intrinsic asthmatics, we found IgE antibodies to bacteria in both groups. The frequency of anti-bacterial IgE was significantly higher in the extrinsic asthma group (Table 1). As may be expected, the total serum IgE level was increased in patients with IgE antibodies to one or more inhalant allergens. The presence or absence of antibacterial IgE had no significant influence on the total serum IgE level.

In the history of the patients with IgE

Table 2

Frequency of history of acute bacterial exacerbations in patients with bronchial asthma. Relation with the presence of anti-bacterial IgE (Bact. +) or IgE to inhalant allergens (RAST +).

BACT + : 76%	N.S.
BACT - : 67%	
RAST + : 62%	P < 0.05
RAST - : 83%	

antibodies to bacteria a higher frequency of acute exacerbations of their asthma, associated with purulent sputum, was observed (Table 2). The difference with the patients without bacteria specific IgE was not significant. Patients with IgE antibodies to inhalant allergens had a significantly lower frequency of bacterial exacerbations than the so-called intrinsic asthma group.

DISCUSSION

Several decades ago, bacterial allergy and, more specifically, an immediate type hypersensitivity to bacteria was regarded as an important mechanism in the acute infectious exacerbations of bronchial asthma (3). This concept has lost most of its adepts due to the lack of specificity of the antigens both for skin tests and bronchial challenge (5) and to the ineffectiveness of the bacterial vaccines (8). The increased bronchoconstriction frequently observed in asthmatic patients in association with a bacterial infection (9) was explained by the activity of non-specific bacterial products, such as endotoxin, enzymes and the histamine sensitizing factor on hyperreactive airways (15).

Our results show that IgE antibodies to *Haemophilus influenzae* and/or *Streptococcus pneumoniae* are present in the serum of patients with bronchial asthma. Both extrinsic and intrinsic asthmatics had bacteria specific IgE. Twenty-nine percent of the investigated sera had such antibodies. The IgE antibodies specific for *Streptococcus pneumoniae* were the most frequent. This observation contrasts with the higher frequency of *Haemophilus influenzae*

compared to *Streptococcus pneumoniae* as cause of respiratory infection in obstructive lung disease (9). This discrepancy can possibly be explained by different immunogenic properties of the two bacterial species.

Recently three other papers (13, 16, 17) described IgE antibodies to bacteria. Schopfer et al. (13) demonstrated IgE antibodies to *Staphylococcus aureus* in patients with hyperimmunoglobulinemia E, chronic generalized eczema and severe recurrent staphylococcal infections. They observed some non-specific IgE binding in control patients with high IgE levels. Walsh et al. (17) found anti-staphylococcal IgE in atopic patients with chronic dermatitis with or without recurrent staphylococcal abscesses. The non-specific IgE binding by the bacteria was not taken into account.

Tee (16) used a solid phase radioimmunoassay, different from the technique we used. Whole bacteria were first coupled to CN Br activated sepharose 4B. IgE antibodies to bacteria were demonstrable in patients with bronchial asthma. The frequency of these IgE antibodies to *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae* is not mentioned in the abstract.

The significance of the IgE antibodies to bacteria remains to be elucidated.

Microorganisms may play the role of an allergen and cause an immediate type hypersensitivity leading to an increased bronchoconstriction. In our study, the presence of IgE antibodies to bacteria was not significantly associated with an increased frequency of bacterial exacerbations. Kay et al. (7) measured an increased amount of IgE and eosinophils in the sputum of chronic bronchitics and skin test-negative asthma patients and suggested that an immediate type hypersensitivity may be involved in the pathogenesis. During acute infectious exacerbations in both extrinsic and intrinsic asthmatics, the sputum contains high amounts of histamine (2). IgE antibodies to *Staphylococcus aureus* have been thought to be related to the occurrence of recurrent

staphylococcal infections in patients with hyperimmunoglobulinemia E by their interference with the neutrophilic function (13). A similar mechanism in the recurrence of bacterial infections of the airways can not be excluded.

Viral infections often precede bacterial infections of the bronchi. Recently, the role of viral infections in the induction of immediate type hypersensitivity in children has been demonstrated (4). Viral infections may thus play a role, not only as precipitant of bronchial obstruction, but also as adjuvant for the induction of bacteria-specific IgE.

IgE, including myeloma IgE, binds non-specifically to the surface of *Haemophilus influenzae* and *Streptococcus pneumoniae*. Besides the importance of these findings for the interpretation of the radioimmunoassay results, it can not be excluded that the non-specific adsorption of IgE to bacteria may be relevant. The non-specific binding of bacteria to mastcell-bound IgE may induce mediator release. Concanavallin A has been shown to release mediators from mast cells by non-specific bridging of IgE molecules on the surface of the cells (14). A comparable interaction of polyclonal human IgE with protein A from *Staphylococcus aureus* was recently described (6).

The demonstration of IgE antibodies to bacteria in patients with bronchial asthma, both in the extrinsic and intrinsic asthma group, opens new perspectives for the study of the role of infectious agents in asthma. The non-specific interaction between IgE and bacteria may also be involved.

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