

Bacterial immunotherapy in bronchial asthma

A. Oehling

Department of Allergology and Clinical Immunology, University Clinic, Faculty of Medicine, University of Navarra, Pamplona, Spain

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SUMMARY

Nowadays, bacterial etiology is probably the least considered and most controversial in the etiopathogenesis of bronchial asthma. It was in the first decades of this century when several authors insisted on the close relation between infection and asthmatic response. This is why, since antibiotics have appeared, many renowned authors insist on the basic treatment of the infection with antibiotics. Also, the need of immunotherapy with bacterial antigens is being emphasized, considering the importance of this factor in bronchial asthma. Nevertheless, there are some detractors who, in our opinion, do not base their criteria on experience or precise data which support the rejection of the bacterial infectious factor as a causal triggering factor. It has been in the last decade when several authors, Norn among them, confirm the importance of the bacterial antigen, and especially its potentiating role on the inhalant allergens. On the other hand, in the last decade the symptomatic treatment of asthma by means of bronchodilators and corticosteroids is being fomented. That is, the maintenance of the asthmatic patient is being fomented instead of his consequent treatment, fighting the infection. According to our long experience and the positive number of cases obtained, again we insist on the need to treat bronchial asthma with bacterial immunotherapy. Therefore, it is necessary to study this aspect more in depth in order to reach a real knowledge of all of the above.

Key words: Bacterial immunotherapy - Bacterial infectious asthma - Bacterial antigen potentiation - Dendritic cells and bacterial infection - ECP and bacterial infection

Bacterial immunotherapy as treatment of bronchial asthma of infectious origin was started many decades ago, and although it had some defenders, Blatt and others (1, 2), it has also had some detractors. One of the most controversial aspects in the etiopathogenesis of bronchial asthma has always been the causal importance of the bacterial factor. Some authors still insist on

the importance and exclusivity of the viral factor in the asthmatic response. Nevertheless, we must consider that, although in the first phase of the infection the virus can play a role, it is the bacterial infection which will finally prevail. In a study we performed in a group of asthmatic children, the serologic examinations carried out at the beginning of the asthmatic crisis, and 8 days after in a second study, showed that only in 13.5% of the cases antibodies against different viruses could be detected (3, 4). Therefore, we consider that it is extremely risky to give so much importance to the viral etiopathogenesis in bronchial asthma. We think that the studies performed up to now lack the necessary scientific rigour.

Thanks to modern immunopathology, better knowledge of the specificity of the different bacterial antigens has been reached, in both *in vitro* diagnoses or provocation tests. The number of authors who consider and argue very positively the role of the hyperergic response against the bacterial antigen in bronchial asthma is growing everyday. In several papers we have already explained our criteria and experience (5-11), as well as those of many other authors (12-18) in relation to the problem created in bronchial asthma by the presence of a sensitization to bacterial antigens. In this sense, Norn and other colleagues (20-22) show in several studies the importance of bacterial antigenicity in bronchial asthma. In several of their works they prove that, in patients with bronchial asthma and sensitization to *Dermatophagoides pteronyssinus* or birch pollen, with positive histamine release tests against these antigens, the addition of bacterial antigen potentiated the histamine release, increasing almost three fold when both antigens acted. This is how they reached the conclusion that sensitization to inhalant allergens is potentiated when a rhinosinubronchial bacterial infectious process takes place at the same time. Following their criteria, we could also demonstrate that the *Staphylococcus aureus* bacterial antigen potentiates histamine release in a very important way when a *Dermatophagoides pteronyssinus*

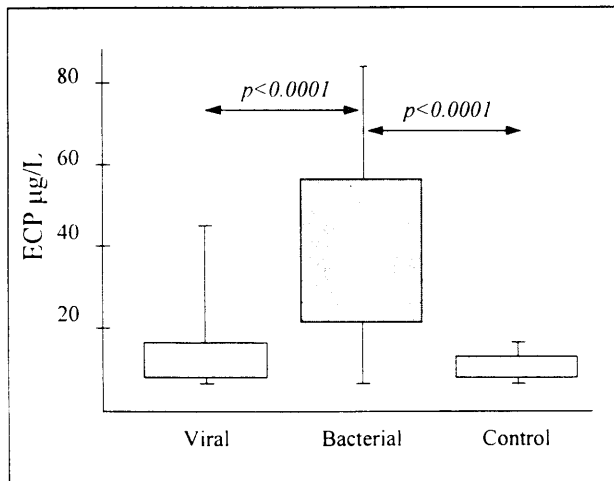


Fig. 1. Serum levels of ECP in subjects with acute viral or bacterial infections and in healthy controls. Karawajczyk, M. *et al.* Clin Exp Allergy 1995, 25: 713-719.

antigen is associated in patients with sensitization to this mite (23). In favour of this, we also have the studies by Pauwells (24) in relation to the presence of antigen-specific IgE antibodies to bacteria in patients with infectious bronchial asthma. From the point of view of dynamics in the allergic inflammatory response, the TH1 lymphocytes are the ones involved in the case of bacterial infection.

Lastly, as far as the inflammatory response is concerned, to which more attention is being paid in recent years although it has always been considered essential in the asthmatic response since ancient times, in depth study of the mediators of substances responsible for the inflammatory response has also been possible. Of these substances, the eosinophil cationic protein (ECP) is probably the most studied, whose importance we have already highlighted (25). Recently, Karawajczyk *et al.* (26) could follow the levels of ECP in sera in the course of acute bacterial and viral infections. In the controls

(Fig. 1) the mean values were 8.8 µg/l. In patients with viral infection, 10.4 µg/l, and in those with bacterial infection 24.3 µg/l. Therefore, ECP values in the subsequent inflammatory response are higher in the case of bacterial infection. All this indicates that the eosinophilic response is much more superior in the bacterial infection than in the viral, and that the inflammation compromise is also greater.

According to some recent studies performed by Holt *et al.* (27, 28), the inhalation of bacterial lipopolysaccharide led to a quick accumulation of dendritic cells in the airways epithelium, and after a 24 hour aerosol challenge, the density of the resulting dendritic cells was near 200% of that found at basal state. According to these authors, bystander infections in the respiratory tract which occur concomitantly with exposure to inhalant allergen could, by stimulating the migration of activated IFN α /IL-12-secreting phagocytes from infected airway tissue into the regional lymph nodes, directly influence the outcome of the TH-1/TH-2 selection process occurring within the evolving allergen-specific primary immune response, favouring the outgrowth of TH-1 cells (Fig. 2). That is, bystander respiratory bacterial infections can directly modulate TH-1/TH-2 selection in the immune response to inhalant allergens (Fig. 3).

RECOMMENDATIONS AND METHODS

In general, bacterial hyposensitizations have been performed with extracts which do not have an optimal germ concentration, or suitable dilutions, from lower to higher concentration, in order to reach a hyposensitization such as Besredka envisaged (29).

This is why we consider that, in order to follow the appropriate method in immunotherapy, the following factors are necessary:

- A hyposensitization dose schedule (Table I), following Besredka criteria (29), as we do with pollinic, mite, or other antigens.

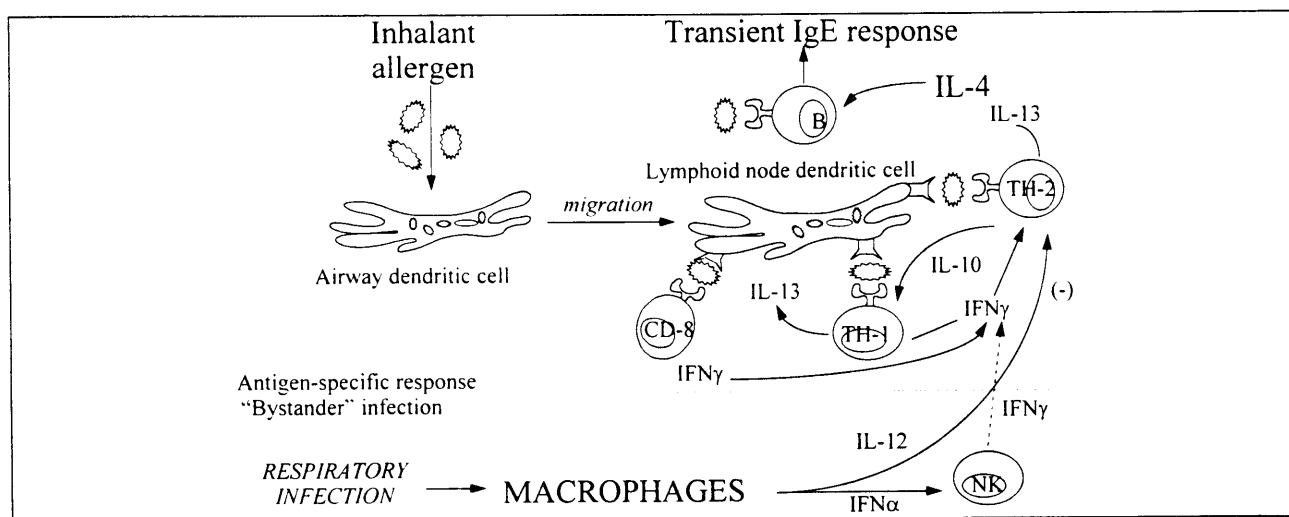


Fig. 2. Primary immune response to inhaled allergens. Holt, P.G. Pediatr Allergy Immunol 1995, 6: 1-10.

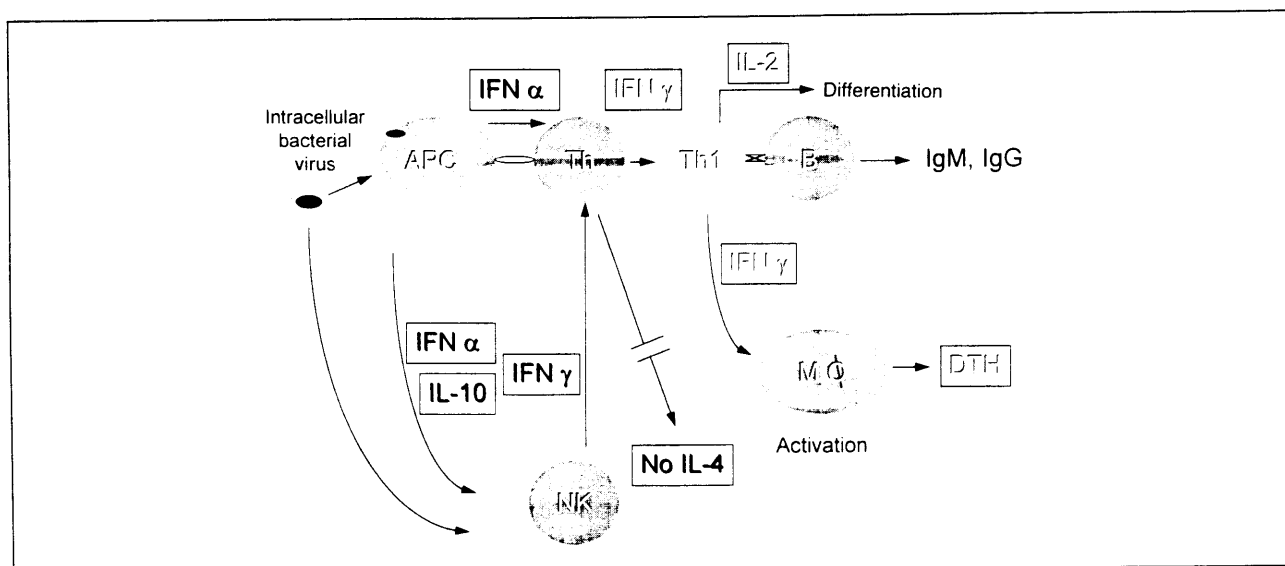


Fig. 3. Immunological mechanisms in infective asthma: Th1 induces humoral and DTH responses.

Table 1

Dose schedule for hyposensitization with bacterial vaccine.

I	II	III
1st dose 0.05 cc	7th dose 0.1 cc	12th dose 0.1 cc
2nd dose 0.1 cc	8th dose 0.3 cc	13th dose 0.2 cc
3rd dose 0.3 cc	9th dose 0.5 cc	14th dose 0.3 cc
4th dose 0.5 cc	10th dose 0.8 cc	15th dose 0.4 cc
5th dose 0.8 cc	11th dose 1.0 cc	16th dose 0.5 cc
6th dose 1.0 cc		17th dose 0.6 cc
		18th dose 0.7 cc
		19th dose 0.8 cc
		20th dose 1.0 cc

Bottle I: Concentration 7.5 million/cc. Bottle II: Concentration 75 million/cc. Bottle III: Concentration 750 million/cc.

- b) Immunotherapy length of at least three years, as we do with other antigens.
- c) Efficient antibiotic treatment for the recurrent infections, in order to eradicate the infectious focus, and thus obtain a better response to immunotherapy.

These three points are basic and must be considered in the treatment of bronchial asthma and asthmatic bronchitis of bacterial etiology. As in the sensitizations to inhalants, and in the case of immunotherapy with professional or pollen antigens, we try to remove the patient from his/her environment or to start a pre-seasonal treatment. From here the antibiotic treatment in these patients is important. It would be really naive to think that only bacterial immunotherapy, with no other treatment against the bacterial focus, would be enough to achieve spectacular results.

Dose schedules and results in bacterial immunotherapy

Considering all of the above and the evidence of the importance of the bacterial factor in bronchial asthma,

Table 2

Composition of standard bacterial vaccine.

	Millions
<i>Neisseria catarrhalis</i>	100
<i>Klebsiella pneumoniae</i> (Friedländer)	50
<i>Diplococcus pneumoniae</i> (Type I, II, III)	200
<i>Hemophilus influenzae</i>	150
<i>Streptococcus</i> (hemolytic and viridans)	100
<i>Staphylococcus aureus</i>	100
<i>Staphylococcus albus</i>	50

which represents almost 70% of the asthmatic patients, we have been using immunotherapy with bacterial antigens for almost 25 years as we have referred to in several works. In one of them, by means of lyophilized bacterial antigen solutions, 70.9% of positive results was already obtained (30). Subsequently, using a pool with the main germs involved in the respiratory infection (Table 2), and following a hyposensitization schedule with different germ contents, that is 7.5, 75 and 750 million/cc (5-7, 31) with a study period of at least three years, the results obtained in these studies with 120 adult patients and 80 children, were also quite satisfactory. In Table 1, the dosage schedule followed is shown. In adult patients, and as can be seen in Table 3, after three years, 75% of the asthmatic symptomatology had disappeared. That is, there was no symptomatology and only a minimum relapse of bacterial colds, without bronchospasm.

As can be seen in Table 4, in the group of asthmatic children where the evolution of the disease was shorter, the results are even more satisfactory, obtaining complete disappearance of the asthmatic symptomatology in 90.4% of the cases (6). Among the studies performed in recent years in relation to this problem, the ones by Müller and Lanz (32) probably reflect an experience

Table 3

Clinical results after three years of immunotherapy with bacterial vaccine.

Efficacy	N° patients		Percentage	
Very good	41	90	34.16	75
Good	49		40.84	
Fair	20	23	16.66	19.16
Poor	3		2.50	
Treatment suspended	7		5.83	
Total	120		100	

Oehling, A., Jerez, J., Neffen, H., Sánchez Palacios, A. *Allergol Immunopathol* 1979, VII: 47.

similar to ours. In Figures 4 and 5, the very positive results obtained in relation to the average number of respiratory infections and evolution in 62 patients with infectious bacterial asthma after treatment with bacterial immunotherapy are reflected, as well as the influence of immunotherapy on the severity of the associated

Table 4

Clinical results after three years of immunotherapy in children with bacterial vaccine.

Efficacy	N° patients		Percentage	
Very good	10	19	47.61	90.47
Good	9		42.86	
Fair	2		9.52	
Poor				
Total	21		100	

Oehling, A., Baena-Cagnani, C.E., Neffen, H. *Allergol Immunopathol* 1980, VIII: 177.

bronchial asthma, before and during treatment with bacterial immunotherapy or placebo. These authors also recommend immunotherapy periods of at least two years.

In view of all of the previously exposed factors, we consider that in recent years the influence of bacterial antigens in the etiopathogenesis of bronchial asthma has

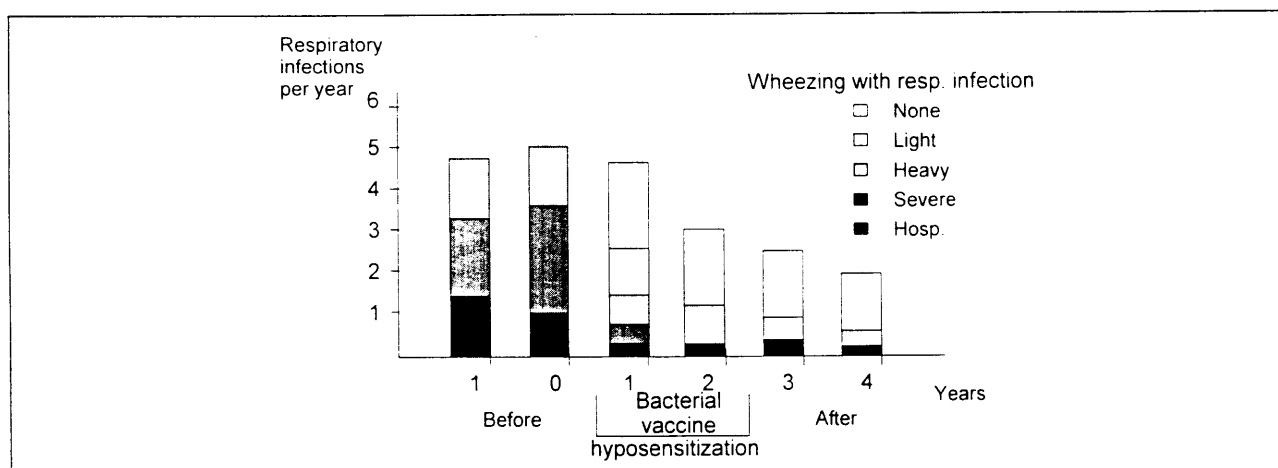


Fig. 4. Average number of respiratory infections and evolution in 62 patients with infectious bacterial asthma after treatment with bacterial vaccine immunotherapy. Müller and Lanz, JAMA 1969.

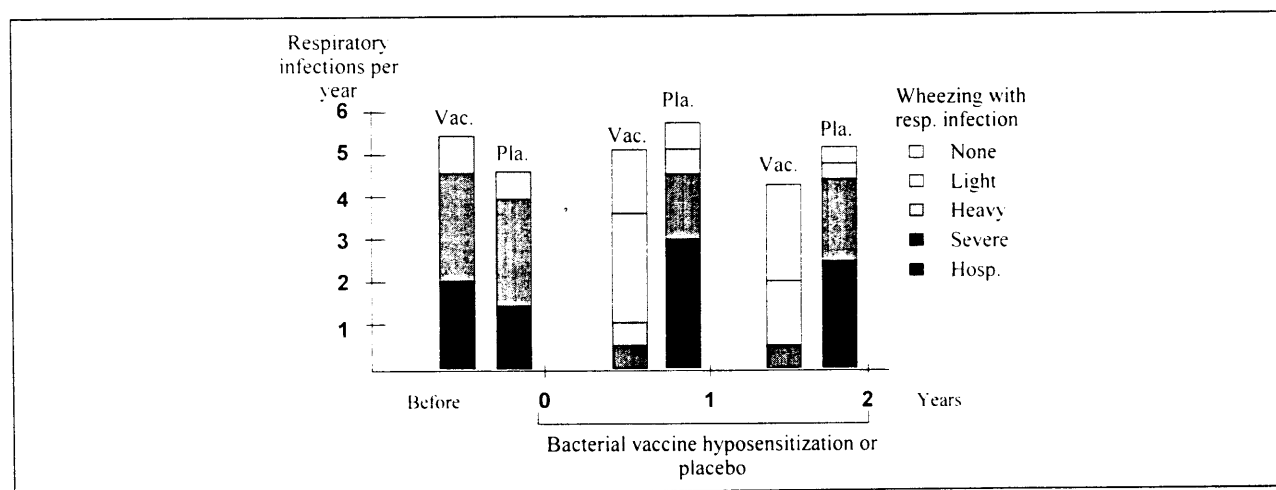


Fig. 5. Average number of respiratory infections per year and severity of associated asthma before and during treatment with bacterial immunotherapy or placebo. Müller and Lanz JAMA 1969 (32).

been very strongly proven, and therefore that not only the corresponding antibiotic treatment is recommended in case of relapses, but also that the indication of immunotherapy with bacterial antigens containing an important number of germs, at suitable concentrations, and followed for at least three to four years, must be seriously considered. In our experience, this is how we can contribute to curing asthmatic patients and not just maintaining them with symptomatic medication. That is, reducing the asthma treatment to bronchodilators and corticosteroids. As far as this last medication is concerned, the number of corticoid-dependent asthmatics driven to a suprarenal insufficiency is very alarming (33).

RESUMEN

En el momento actual tal vez sea, en la etiopatogenia del asma bronquial, la etiología infectivo-bacteriana la menos considerada y más discutida. Es en las primeras décadas de este siglo cuando diversos autores insisten en la estrecha relación entre infección y desencadenamiento de la respuesta asmática. De ahí que, con la llegada de los antibióticos, muy diversos y reconocidos autores insistan en el tratamiento fundamental de la infección con antibioterapia. Igualmente se insiste en la necesidad de llevar a cabo una inmunoterapia con antígenos bacterianos ante la importancia de este factor en el asma bronquial. Sin embargo, también surgen detractores que a nuestro parecer no basan su criterio en experiencias y datos precisos que avalen el rechazo del factor infectivo bacteriano como desencadenante y causa. Es precisamente en la última década cuando diversos autores, y entre ellos Norn confirman la importancia del antígeno bacteriano y muy especialmente el papel potenciador que ejerce sobre los antígenos inhalantes. Por otra parte, en la última década se ha venido fomentando fundamentalmente el tratamiento sintomático del asma mediante medicación broncodilatadora y corticosteroidea; esto es, se ha fomentado el mantenimiento del enfermo asmático y no su tratamiento consecuente, combatiendo la infección. En nuestra larga experiencia quiero insistir aquí de nuevo, ante la positiva casuística obtenida, sobre la necesidad de instaurar inmunoterapia bacteriana en el asma bronquial. Se hace por tanto necesario que se profundice más en este aspecto para conseguir un real conocimiento de cuanto se expone.

Palabras clave: Inmunoterapia bacteriana - Asma infectiva bacteriana - Potenciación antígenos bacterianos - Células dendríticas e infección bacteriana - ECP e infección bacteriana

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Correspondence: Prof. Dr. A. Oehling, Department of Allergology and Clinical Immunology, University Clinic, Apartado 4209, 31080 Pamplona, Spain.