Allergy 2000: 55: 214–218
Printed in UK. All rights reserved

Copyright © Munksgaard 2000
ALLERGY
ISSN 0105-4538

Review article

Bacterial vaccines: anything but placebo

H.-J. Malling
Allergy Unit, National University Hospital, Copenhagen, Denmark

Key words: asthma; bacterial allergy; bacterial immunotherapy; clinical efficacy; cytokines; immunostimulation; T-cell responses.

Hans-Jørgen Malling
Allergy Unit 7551
National University Hospital
Blegdamsvej 9
DK-2100 Copenhagen
Denmark

Accepted for publication 28 September 1999

Background

The frequent observation of bacterial infections in patients with acute exacerbation of asthma has led to the hypothesis that such infections play a crucial role in the induction and exacerbation of asthma (bronchial asthma of infectious origin). Consequently, the attempt to modify the course of the disease by immunologic intervention in bacterial infections seems logical. In the 1940s and '50s, the success (partly inspired by the lack of effective antiasthma pharmacologic treatment) of immunotherapy (desensitization; hyposensitization) with inhalant allergens suggested that the clinical outcome of asthma treatment could be improved by injecting bacterial antigens (1, 2). Several – mostly open studies – have evaluated the beneficial effect of bacterial immunotherapy in patients with bronchial asthma (3). The clinical effect has recently been questioned, and international recommendations clearly state that bacterial vaccines have no role in modern asthma treatment (4–6). This review focuses on the importance of bacterial infections in asthma and the clinical documentation of the efficacy of bacterial vaccines. On the basis of current immunologic knowledge of the pathophysiologic mechanisms of the allergic response, a possible role for bacterial antigens in the treatment strategy is proposed.

Importance of respiratory tract infections in asthma

In discussing the role of respiratory tract infections in asthmatic patients, distinguishing between viral and bacterial infections is the first crucial point. Secondly, it is important to distinguish between infections playing a major pathogenic role in acute exacerbation and those being a bystander phenomenon secondary to the inflammatory reactions in the bronchial mucosa involved in acute asthma. In such a discussion, the clinical importance and the role of IgE sensitization to bacteria (bacterial allergy) should be carefully analyzed. Does antibacterial IgE play a causative role in allergic asthma? Is the potentiating role of bacteria in the releasability of mediators simply an *in vitro* phenomenon, or does it have a major impact on the *in vivo* manifestations of the disease? The role of bacterial infections in directing the immature immune response from the original fetal Th-2-dominated to the normal mature Th-1-dominated nonallergic response and the role of inducing/suppressing the IgE response in allergic asthma may have a major impact on future immunomodulating interventions (7).

Viruses versus bacteria

The role of respiratory infections in asthma exacerbation varies according to the age group investigated. In infants and small children, most acute bronchospastic episodes are related to upper and lower airways infections. The viruses most often associated with exacerbation of asthma are rhinoviruses (8). Experimental rhinovirus infections enhance airway responsiveness and the risk of developing a delayed allergic reaction after bronchial allergen challenge. By the technique of bronchoscopy and segmental allergen

challenge, it was found that rhinovirus infections promoted mast-cell releasability and the recruitment of eosinophils to the airways (9). The conclusion of these experiments was that rhinovirus infections may promote allergic inflammation and consequently increase both the likelihood of asthma exacerbation and the severity of bronchospastic episodes.

Recent developments in the diagnostic tests for respiratory viral infections, such as the PCR technique, have permitted studies investigating the role of viral infections in asthma exacerbation (10). Several studies have confirmed the importance of rhinoviruses in bronchospastic episodes in children (11) and that rhinoviruses can replicate in the lower airways, suggesting that virus-induced asthma exacerbations are the result of a spread of viruses from the upper to the lower airways. The role of *Clamydia pneumoniae* respiratory tract infections was investigated in 163 adult patients with acute wheezing illnesses or chronic asthma (12). In a subgroup of 20 patients diagnosed as having *C. pneumoniae* infection, 50% developed wheeze for the first time, and five of them subsequently developed chronic asthma, indicating that acute *C. pneumoniae* respiratory tract infections in previously unexposed, nonasthmatic individuals can result in chronic asthma. Chronic *C. pneumoniae* infection was seen in 10 patients already diagnosed as having chronic asthma.

Bacterial allergy, as indicated by the demonstration of IgE antibodies specific for bacterial antigens, has been observed. In a study of 190 adult patients with asthma, IgE antibodies to *Haemophilus influenzae* and *Streptococcus pneumoniae* (frequently associated with acute airways obstruction in asthmatic patients) were observed in 29% of the patients (13). Moreoever, the study showed significantly higher levels of antibacterial IgE antibodies in patients with IgE antibodies to various inhalant allergens, but also found IgE-antibodies to bacteria in 22% of patients without demonstrable IgE-mediated hypersensitivity. The direct causative role of antibacterial IgE antibodies in acute bronchospastic episodes was not elucidated, but the authors concluded that immediate hypersensitivity to bacteria may play a role in the infectious exacerbation of bronchial asthma. IgE antibodies directed against bacterial antigens seem rather unusual. A study performed in 100 atopic patients and 100 healthy controls colonized with *Neisseria flavescens* in pharyngeal exudates found positive skin tests in 8% of atopic patients and 3% of normal controls (14). Detection of serum IgE anti-*Neisseria* antibodies was observed in 6% of atopic patients and 1% of normals. The study reasonably concluded that bacterial allergy to *Neisseria* does not seem to play an important role in rhinitis/asthma. These figures are in striking contrast to the postulated importance of the bacterial factor in asthma, asserted to represent almost 70% of asthmatic patients (3).

Another aspect in the discussion of the importance of bacterial infections in exacerbation of asthma is the potentiating role of bacterial substances on the release of mediators (15). A study in 36 asthmatic patients sensitized to *Dermatophagoides pteronyssinus* showed more than 10% histamine release only at the highest concentration (200 μg/ml) of *Staphylococcus aureus* extract and a significantly higher histamine release in patients with positive nasal culture of *S. aureus* (16). Coincubation of *D. pteronyssinus* and *S. aureus* extract resulted in a significantly higher histamine release than observed with the individual antigens; i.e., a potentiating effect of *S. aureus* on the histamine release induced by *D. pteronyssinus*. An important question in relation to the clinical relevance of these observations is whether this phenomenon is a strictly *in vitro* phenomenon, or also takes place *in vivo* and consequently plays a pathophysiologic role in allergic asthma. This question is related to the level of bacterial antigens in the bronchial mucosa – are the concentrations needed to induce and potentiate histamine release physiologically relevant? The conclusion of the authors that their findings support the important role of bacterial infections in the etiopathogenesis of bronchial asthma and the importance of a treatment against this infection has not been substantiated by clinical studies. In any event, the rational approach to the problem is antibiotic treatment rather than attempts to modulate the microbial defense system immunologically.

Clinical documentation of the effect of bacterial vaccines in asthma

Most studies investigating the clinical efficacy of bacterial vaccines in asthma are out of date and noncontrolled. Two different sets of outcomes have been explored: the reduction in bacterial infections and improvement in the clinical severity of asthma. The anti-infectious capacity of bacterial vaccines has been investigated in a double-blind, placebo-controlled (DBPC) study in children treated with an oral bacterial vaccine (Broncho-Vaxom) (17). The incidence and duration of infectious rhinosinusitis episodes and the number and duration of concomitant antibiotic treatments decreased significantly with active treatment. In an open study investigating 3008 children, the effect of a corresponding bacterial vaccine (Biostim) on recurrent ENT infections was considered good by the investigator in 76% of the cases (18). Three out of four children had no or only one infection during the 3-month follow-up period. Compared with 6.27 ± 3.04 episodes during the previous year, the effect seems rather modest. An open study investigating the anti-infectious capacity of nonspecific immunomodulation using bacterial lysate in 332 patients with recurrent respiratory tract infections showed improvement in about 2/3 of the patients

(19). A controlled, double-blind, randomized study in 40 patients with chronic bronchitis compared the standard regimen (3 months) of oral bacterial vaccine (RU 41740) with long-term treatment (6 months) (20). Both treatment schedules reduced the number and duration of infectious exacerbations compared with a corresponding period of the previous year, with no difference between the standard and long-term treatment.

A recent DBPC study has investigated the efficacy of oral immunotherapy with an immunomodulating bacterial extract in hemodialysis patients suffering from several immune defects making them prone to develop bacterial respiratory tract infections (21). The trial was conducted for 24 weeks in the endemic season. During the first 12 weeks of treatment, no difference between the bacterial extract and the placebo group was seen, but during the last half of the observation period, the number of respiratory tract infections and antibiotic treatment courses was significantly lower in the bacterial group. Immunomodulating bacterial extracts had no effect on nonrespiratory infections. The study concluded that immunomodulation with selected bacterial extracts constitutes a promising approach for the prevention of bacterial airway infections in risk groups. The advantages, cost-effectiveness, and long-term effects of the immunologic therapy compared with antibiotic treatment were not investigated.

The effect of bacterial vaccine immunotherapy on asthma symptoms shows a clear discrepancy between the controlled studies with minimal or no effect and a high success rate in the noncontrolled studies. Bacterial immunotherapy has been used widely for many decades, but now has a very limited use. Some negative studies including double-blind design (22–25) are claimed to have used insufficient concentration of bacteria and too short a treatment duration (26). The only positive DBPC study is 30 years old (27). This study showed a reduction in the number of infections and in the severity of asthma symptoms. Most studies on bacterial immunotherapy in bronchial asthma have been performed by Oehling's group. A questionnaire study investigating the results after 3 years of treatment in 120 patients (aged 7–73 years) showed a success rate of 75% (91% in small children) in an open study in patients with symptoms exclusively of bacterial origin (28). From the same group, a study in children (aged 2–10 years) showed that only 14% did not respond favorably to bacterial immunotherapy (29). A study comparing the effect of standard bacterial vaccine and bacterial ribosomal antigens in 150 children with bacterial bronchial asthma showed a better clinical response in patients treated with bacterial ribosomal antigens after 1 year of therapy, but no difference between the two groups after 3 years of treatment (30). Furthermore, both treatments induced a significant increase in IgG levels in IgG-deficient patients.

A prospective controlled trial investigated the outcome of "minor" allergic respiratory diseases in 261 children (31). A total of 103 children received nonspecific immunotherapy and were treated with bacterial vaccine aerosols plus Fusafungin spray and ketotifen. Sixty-four children were included in a specific immunotherapy program to receive *D. pteronyssinus*, and these two protocols were compared with a control group of 67 children. The patients were followed for 1–4 years (mean 2 years), and the results showed that the group receiving allergen-specific immunotherapy with house-dust mites had a significantly higher improvement rate (84%) than the nonspecific immunotherapy group (improvement 52%) and the control group (improvement 16%). The study also found a preventive capacity of allergen-specific immunotherapy, as this treatment prevented the progression to asthma in 94% of subjects, in contrast to 77% in the bacterial vaccine group and 63% in the control group. The conclusion was that allergen-specific immunotherapy in IgE-sensitized children has better efficacy than nonspecific bacterial immunotherapy in nonatopic children with minor respiratory diseases, but that the nonspecific treatment is better than no treatment!

Relation between infections and the development of Th-cell cytokine profiles

Recent research indicates that the clinical response to airborne environmental allergens is determined by the underlying cytokine balance within the respective allergen-specific Th-memory cell populations. In nonatopic individuals, the Th-cell response is typically dominated by Th-1 cytokines such as IFN-γ. In atopic individuals, the response is polarized toward the Th-2 cytokine profile, IL-4, IL-5, and IL-13 being predominant (32). The allergic phenotype is primarily determined by genetic factors, but current knowledge indicates that environmental factors may modulate the genetic response. The demonstration of putative allergen-specific T cells in cord blood suggests transplacental priming (33, 34). The *in utero* Th-2-skewed Th-2 cytokine phenotype represents a preferential suppression of Th-1 cells to protect the placenta from the toxic effects of Th-1 cytokines (35). After birth, genetic and environmental factors in most children result in the maturation of the nonallergic Th-1 phenotype. The maturational deficiency in Th-1 function is more pronounced in children with the atopic genotype, as demonstrated by a deficiency in IFN-γ production in cord blood and during infancy (36). The transient delayed maturational defect in Th-1 cytokine-producing capacity during infancy and early childhood may be responsible for the development of allergic diseases later in life. The immune deviation toward downregulation of the fetal, primed, low-level, allergen-

specific Th-2 responses is deficient, and consequently does not result in the generation of a Th-1 polarized immunologic memory (36, 37). In the protected *in utero* environment, the fetus is not dependent upon a functional Th-1 immune response for protection against infections, an immune response which is essential for survival after birth.

Holt et al. (38) have proposed the hypothesis of the importance of microbial stimulation via the respiratory and gastrointestinal mucosa during early childhood for the postnatal maturation of a Th-1 deviated immune response. The mechanism of Th-1 polarization could be initiated by microbial products such as bacterial lipopolysaccharides or specific immunostimulatory sequences (ISS) in bacterial DNA. This will stimulate upregulation of IL-12 production of immature antigen-presenting cells and result in a deviation of the Th-cell immune response toward the Th-1 cytokine phenotype (39, 40). Interestingly, a comparison of the effect of steroids with that of ISS in the mouse model showed that both treatments inhibited IL-5 production, but only ISS treatment induced IFN-γ production, suggesting that only the ISS treatment resulted in modification of the underlying immune process. Likewise, in experimental animals, BCG immunization may protect against the development of allergic responses by preventing airway hyperresponsiveness, reducing eosinophil influx into the airway lumen, reducing IL-4 and IL-5 levels, and increasing IFN-γ production (41). Heat-killed *Listeria monocytogenes* as an adjuvant during immunization successfully biases the development of Ag-specific cytokine synthesis toward Th-1 cytokine production (42). *In vitro*, the adjuvant effect of bacterial derived, cross-linked, crystalline surface-layer proteins conjugated to recombinant Bet v 1 (the major birch-pollen allergen) induced IFN-γ production in rBet v 1-induced T-cell lines from the peripheral blood of birch-pollen-allergic patients (43). In cultures of peripheral blood mononuclear cells, both bacterial surface-layer proteins and Bet v 1 conjugated to bacterial surface-layer proteins (but not Bet v 1 alone) stimulated the production of high levels of IL-12, a central inducer of the Th-1 response. The effect could be reversed by neutralizing anti-IL-12 monoclonal antibodies.

Conclusion

The importance of infections in exacerbation of asthma is predominantly related to viral infections, rhinoviruses being the main cause. Both primary and secondary bacterial infections may also play an important role. Although IgE antibodies to bacterial antigens have been demonstrated, their relative importance compared with other specific and nonspecific stimuli is unknown. Likewise, the impact of the demonstrated potentiating role of bacterial products on mediator release is far from elucidated. With respect to antibacterial IgE antibodies and the role of bacteria in asthma exacerbations, the limited and in most cases uncontrolled effect of bacterial immunotherapy does not, on a scientific evidence-based foundation, justify the routine use of this therapeutic principle in modern asthma treatment strategy. The insufficient documentation of a beneficial effect does not rule out the possibility that bacterial immunotherapy might be beneficial for the asthmatic patient. The possible advantages, taking the expense and time consumption into consideration, compared with antibiotic treatment in patients with obvious signs of a bacterial infection requiring treatment, should be elucidated in carefully designed controlled studies. These studies should be placebo-controlled and double-blind, and should, in both arms, include optimally antibiotic treatment based on the documentation of a bacterial infection necessitating antibiotic treatment as well as antiasthma treatment.

The prospects for future intervention strategy both to prevent the development of asthma and to interfere with the progression of mild asthma might take into account the possible adjuvantic role of bacterial infections in modifying the Th-2-skewed T-cell response in infants predisposed to atopy. Bacterial products might be useful as adjuvants in optimizing the clinical efficacy of allergen-specific immunotherapy by a preferential induction of a Th-1 response.

References

1. Blatt H. Microbial allergy. Acta Allergol 1959;**13**:279–285.
2. Blatt H. Microbial allergy. Ann Allergy 1961;**19**:1037–1055.
3. Oehling A. Bacterial immunotherapy in bronchial asthma. J Investig Allergol Clin Immunol 1997;**7**:14–19.
4. Global strategy for asthma management and prevention. WHO/NHLBI workshop report. National Institutes of Health, National Heart, Lung, and Blood Institute, Publication no. 95–3659, 1995.
5. Malling H-J, Weeke B, editors. Immunotherapy. EAACI position paper. Allergy 1993;**48 Suppl 14**:9–45.
6. Bousquet J, Lockey RF, Malling H-J, editors. Allergen immunotherapy: therapeutic vaccines for allergic diseases. WHO position paper. Allergy 1998;**53 Suppl 44**:1–42.
7. Martinez FD. Role of respiratory infections in onset of asthma and chronic obstructive pulmonary disease. Clin Exp Allergy 1999;**29 Suppl 2**:53–58.
8. Gern JE, Busse WW. Association of rhinovirus infections with asthma. Clin Microbiol Rev 1999;**12**:9–18.

9. Busse WW, Gern JE, Dick EC. The role of respiratory viruses in asthma. Ciba Found Symp 1997;**206**:208–213.
10. Gern JE, Galagan DM, Jarjour NN, Dick EC, Busse WW. Detection of rhinovirus RNA in lower airway cells during experimentally induced infection. Am J Respir Crit Care Med 1997;**155**:1159–1161.
11. Johnston SL. The role of viral and atypical bacterial pathogens in asthma pathogenesis. Pediatr Pulmonol Suppl 1999;**18**:141–143.
12. Hahn DL, McDonald R. Can acute *Clamydia pneumoniae* respiratory tract infections initiate chronic asthma? Ann Allergy Asthma Immunol 1998;**81**:339–344.
13. Pauwels R, Verschraegen G, van der Straeten M. IgE antibodies to bacteria in patients with bronchial asthma. Allergy 1980;**35**:665–669.
14. Olonso A, Rodriguez SM, Marino GA, Scavini LM, Pionetti CH, Lewkowicz JF. IgE antibodies against *Neisseria flavescens*. J Investig Allergol Clin Immunol 1992;**2**:33–35.
15. Norn S, Baek L, Jensen C. Influence of bacterial endotoxins on basophil histamine release. Potentiation of antigen and bacterial-induced histamine release. Allergy 1986;**41**:125–130.
16. Oehling A, Aguila de la Coba R, Fernandez M, Leyva J, Sanz ML, Resano A. Potentiation of histamine release against inhalant allergens (*Dermatophagoides pteronyssinus*) with bacterial antigens in bronchial asthma. J Investig Allergol Clin Immunol 1997;**7**:211–216.
17. Zagar S, Lofler-Badzek D. Broncho-Vaxom in children with rhinosinusitis: a double-blind clinical trial. ORL J Otorhinolaryngol Relat Spec 1988;**50**:397–404.
18. Bellon G, Ounis I. The preventive treatment of recurrent respiratory infections using RU 41740 in 3,008 children. Ann Pediatr (Paris) 1990;**37**:535–540.
19. Palma-Carlos AG, Palma-Carlos ML. Non-specific immunomodulation in respiratory infections. Allerg Immunol (Paris) 1990;**22**:181–185.
20. Fietta AM, Merlini C, Uccelli M, Gialdroni Grassi G, Grassi C. Immunological and clinical effect of long-term oral treatment with RU 41740 in patients with chronic bronchitis: double-blind trial long-term versus standard dose regimen. Respiration 1992;**59**:253–258.
21. Tielemans C, Gastaldello K, Husson C, et al. Efficacy of oral immunotherapy on respiratory infections in hemodialysis patients: a double-blind, placebo-controlled study. Clin Nephrol 1999;**51**:153–160.
22. Frankland AW, Hughes WH, Gorrild RH. Autolog bacterial vaccine in the treatment of asthma. BMJ 1955;**2**:941.
23. Helander C. Bacterial vaccines in the treatment of bronchial asthma. Acta Allergol 1959;**13**:47.
24. Fontana VJ, Salanitro AS, Wolfe HI, Moreno F. Bacterial vaccine and infectious asthma. JAMA 1965;**193**:895.
25. Koivikko A. Bacterial vaccine in childhood asthma. Acta Allergol 1973;**28**:202–210.
26. Oehling A. Importance of bacterial infection in the etiopathogenesis of bronchial asthma. In: Chanez P, Bousquet J, Michel FB, Godard P, editors. From genetics to quality of life. The optimal treatment and management of asthma. Seattle, WA: Hogrefe & Huber, 1996:119–126.
27. Mueller HL, Lanz M. Hyposensitization with bacterial vaccine in infectious asthma. A double-blind study and a longitudinal study. JAMA 1969;**26**:1379–1383.
28. Oehling A, Jerez J, Neffen H, Sanchez Palacios A. Bacterial immunotherapy in bronchial asthma. Allergol Immunopathol (Madr) 1979;**7**:47–54.
29. Oehling A, Baena-Cagnani CE, Neffen H. Bacterial immunotherapy of childhood bronchial asthma. Allergol Immunopathol (Madr) 1980;**8**:177–184.
30. Sanchez Palacios A, Quintero A, Martin Escudero JC, San Jose Diez J, Sanchez Palacios MA. Immunotherapy with standard bacterial and bacterial ribosomal antigens in childhood bronchial asthma. Allergol Immunopathol (Madr) 1986;**14**:383–391.
31. Rocha EM. Effect of 2 therapeutic protocols in minor forms of respiratory allergy. Allerg Immunol (Paris) 1986;**18**:29–41.
32. Romagnani S. Induction of Th1 and Th2 responses: a key role for the "natural" immune response? Immunol Today 1992;**13**:379–381.
33. Holt PG. Primary allergic sensitisation to environmental antigens: perinatal T cell priming as a determinant of responder phenotype in adulthood. J Exp Med 1996;**183**:1297–1301.
34. Prescott SL, Macaubas C, Holt BJ, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T-cell responses towards the Th-2 cytokine profile. J Immunol 1998;**160**:4730–4737.
35. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a Th-2 phenomenon? Immunol Today 1993;**14**:353–356.
36. Holt PG, Macaubas C. Development of long term tolerance versus sensitisation to environmental allergens during the perinatal period. Curr Opin Immunol 1997;**9**:782–787.
37. Holt PG, Sly PD, Björkstén B. Atopic versus infectious diseases in childhood: a question of balance? Pediatr Allergy Immunol 1997;**8**:53–58.
38. Holt PG, Macaubas C, Prescott SL, Sly PD. Microbial stimulation as an aetiologic factor in atopic disease. Allergy 1999;**55**:12–16.
39. Kline JN, Waldschmidt TJ, Businga TR, et al. Modulation of airway inflammation by CpG oligodeoxynucleotides in a murine model of asthma. J Immunol 1998;**169**:2555–2559.
40. Broide DJ, Schwarze H, Tighe T, et al. Immunostimulatory DNA sequences inhibit IL-5, eosinophilic inflammation, and airway hyperresponsiveness in mice. J Immunol 1998;**161**:7054–7062.
41. Herz UK, Gerhold C, Gruber A, et al. BCG infection suppresses allergic sensitization and development of increased airway reactivity in an animal model. J Allergy Clin Immunol 1998;**102**:867–874.
42. Yeung VP, Gieni RS, Umetsu DT, Dekruyff RH. Heat-killed *Listeria monocytogenes* as an adjuvant converts established murine Th2-dominated immune responses into Th1-dominated responses. J Immunol 1998;**161**:4146–4152.
43. Jahn-Schmid B, Siemann U, Zenker A, et al. Bet v 1, the major birch pollen allergen, conjugated to crystalline bacterial cell surface proteins, expands allergen-specific T cells of the Th1/Th0 phenotype *in vitro* by induction of IL-12. Int Immunol 1997;**9**:1867–1874.