
Efficacy and safety of allergen immunotherapy in children

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Objective: To determine the efficacy and safety of immunotherapy in children with allergic rhinitis and allergic asthma.

Data Sources: Current Contents database for 1967 to 2005.

Study Selection: The expert opinion of the author was used to select studies for inclusion in this review.

Results: Meta-analyses have confirmed the clinical effectiveness of allergen immunotherapy in patients with allergic rhinitis and asthma; however, most studies involved immunotherapy with a single allergen. Special considerations of safety regarding immunotherapy in children are also necessary, since fatalities have been reported. Fatal reactions occur primarily in patients with asthma and particularly those whose asthma is not well controlled. There is probably increased risk during the build-up phase and with the first injection from a new vial. Injections at home or in clinics without adequate supervision also constitute an increased risk of a fatal outcome.

Conclusions: Specific immunotherapy has been demonstrated to have some protective effect against the development of additional sensitivities in the monosensitized child and to reduce the risk of developing asthma in children with allergic rhinitis. Because of the modification of the underlying immune process, the beneficial effects of immunotherapy persist for a long but not yet fully determined period after the cessation of treatment. This persisting effect makes immunotherapy an attractive supplement to symptomatic treatment of children with allergic asthma and allergic rhinitis. The treatment is not without risk, however, especially in the child with asthma, so it should be administered with caution.

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INTRODUCTION

Allergen immunotherapy with inhalant allergens is indicated for the treatment of allergic rhinitis and allergic asthma. The indications for instituting allergen immunotherapy for allergic rhinitis depend on the severity and duration of the symptoms and the response to symptomatic treatment. However, additional considerations are the impact that immunotherapy can have on the underlying immune mechanisms and on the progression of rhinitis to bronchial asthma. Allergen immunotherapy can only be effective in treating asthma to the extent that an allergic reaction is contributory to the symptoms. It is generally believed that the allergic component in asthma is most important and the prospects for a response to immunotherapy are greatest in school-age children.¹ Indeed, compelling evidence exists that allergy is an important contributor to the occurrence and severity of asthma in this age group. The evidence for this important role is 3-fold: (1) in children sensitization to indoor allergens and outdoor fungi increases the risk of asthma, (2) in sensitized children the severity is related to the level of exposure, and (3) in sensitized children reduction of exposure improves asthma symptoms and pulmonary function and reduces bronchial hyper-responsiveness. This article reviews this evidence to determine the efficacy and safety of immunotherapy in children with allergic rhinitis and allergic asthma. The Current Contents database was searched for articles published between 1967 and 2005, and the author's expert opinion was used to select studies for inclusion in this review.

THE RELATION OF ALLERGY TO ASTHMA

Sensitization as a Risk Factor for Asthma

A number of studies have examined the presence of immediate skin test reactions to inhalant allergens as a risk factor for the presence of asthma in school-age children (Table 1). Whether the studies were conducted in the United States, Japan, New Zealand, or Australia, the pattern was remarkably similar. Sensitization to indoor allergens, especially house dust mite and animal danders, and to the seasonal outdoor fungus *Alternaria* constitutes a risk for the presence of asthma in these children, whereas sensitization to pollens does not. The lack of an association between sensitization to pollens and asthma is important, since it indicates that the relationship between asthma and sensitization to indoor allergens and *Alternaria* is not apt to be just a genetic linkage but rather causal. In a survey of unselected schoolchildren in Sydney, Australia, sensitivity by skin prick testing to house dust mite correlated with the presence of asthma.⁵ Furthermore, the size of the skin prick test reaction to house dust mite extract correlated with specific asthma manifestations, including the presence of frequent wheeze, recent use of asthma medication, regular asthma symptoms, urgent visits for asthma treatment, and the degree of bronchial sensitivity to methacholine.

Severity of Asthma and Level of Allergen Exposure

In children who are sensitized to indoor allergens or *Alternaria*, the severity of asthma is related to their exposure to those allergens (Table 2). Thus, in children sensitized to house dust mites, the level of exposure correlated with asthma symptoms and peak expiratory flow measurements.^{9,10}

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Table 1. Sensitization as a Risk Factor for Development of Asthma in Children

Source, y	Country	Significant sensitizations	Pollen sensitization
Sears et al, ² 1989	New Zealand	House dust mites, cat, dog, <i>Aspergillus</i>	Grasses, no
Shibasaki et al, ³ 1990	Japan	House dust mites	Grasses, no
Cookson et al, ⁴ 1991	Australia	House dust mites, fungi	Grasses, no
Peat et al, ⁵ 1994	Australia	House dust mite, <i>Alternaria</i>	Grasses, yes and no
Duffy et al, ⁶ 1998	Australia	House dust, cat, <i>Alternaria</i>	Pollens, no
Henderson et al, ⁷ 1995	North Carolina	House dust mite, cat, <i>Alternaria</i>	Pollens, no
Gergen and Turkeltaub, ⁸ 1992	United States	House dust, <i>Alternaria</i>	Grasses and ragweed, no

Inner-city children in the United States who were sensitized to cockroach had increased asthma symptoms, more missed school days, and more hospitalizations with increasing exposure to cockroach allergens.¹¹ In surveys of a number of Australian communities, the prevalence of current asthma in schoolchildren doubled with each doubling of the levels of house dust mites in the homes.¹² House dust mite exposure in early childhood was also found to be a risk factor for asthma in patients aged 11 years in a study in England of children at genetic risk of asthma.¹³

Reduction of Exposure and Asthma Improvement

The most impressive examples of reduction in allergen exposure come from the studies of children sensitized to house dust mites who are hospitalized in asthma treatment centers in mountainous regions free of house dust mites. Asthmatic Italian children with house dust mite sensitivity who were hospitalized in the Dolomites had rapid improvement in symptoms, pulmonary function, bronchial hyperresponsiveness, and evidence of airway inflammation.¹⁴ Similar improvement has been reported in Dutch children with house dust mite sensitivity who were hospitalized in Switzerland.¹⁵ Nine young adults in the United Kingdom who were sensitive to house dust mites agreed to use a virtually mite allergen-free hospital room as their living and sleeping room while otherwise continuing their normal daily activities. As in the Italian and Dutch children, several months of strict avoidance of indoor allergens resulted in a marked decrease in bronchial hyperresponsiveness and improvement in morning peak flows in the face of discontinuation of their inhaled anti-inflammatory therapy.¹⁶

ALLERGEN IMMUNOTHERAPY IN CHILDHOOD

How Early Should Immunotherapy Be Considered?

Allergy society guidelines of England¹⁷ and Canada¹⁸ recommend that immunotherapy not be given to children younger than 5 years. The arguments for not giving immunotherapy to younger children are as follows: difficulty in explaining the purpose to the child, thus potentially instilling a fear of health care practitioners; difficulty in recognizing the early symptoms of a systemic reaction; and the possibility that the child may continue to develop additional sensitivities while receiving the treatment, requiring further immunotherapy at a later time. Although these continue to be valid arguments against early institution of immunotherapy, several studies have suggested that there are unique opportunities associated with the early institution of immunotherapy, including preventing both new sensitizations and the development of asthma in children who only have rhinitis.

Prevention of Further Sensitization

Several studies have now demonstrated that the institution of immunotherapy in a child with only a single sensitivity (monosensitized) decreases the number of additional sensitivities that develop in the child over time,^{19–21} not only during the duration of immunotherapy but also for at least 3 years after it is discontinued.^{19,20} Two of these studies^{19,20} treated children sensitized only to house dust mites, with the control being those children whose parents choose not to accept immunotherapy for their children. The ages of the children at the initiation of immunotherapy were 4 to 6 years¹⁹ and 5 to 8 years.²⁰ The number of children developing

Table 2. Importance of Allergen Exposure in Childhood Asthma

Source, y	Allergen	Country	Correlation
Sensitized children			
Zock et al, ⁹ 1994	House dust mites	Netherlands	Asthma symptoms and peak expiratory flows
Chan-Yeung et al, ¹⁰ 1995	House dust mites	Canada	Asthma symptoms and peak expiratory flows
Rosenstreich et al, ¹¹ 1997	Cockroaches	United States	Correlation with asthma symptoms, hospitalization, and missed school days
All children			
Peat et al, ¹² 1996	House dust mites	Australia	Current asthma prevalence doubled with doubling of the levels of house dust mites in the community
Sporik et al, ¹³ 1990	House dust mites	England	Exposure to >10 µg/g of Der p 1 in house dust during the first year of life increased risk of asthma at age 11 years by 4.8

additional positive skin prick test results was reduced from 100% to 45%¹⁹ and 68% to 25%²⁰ in the 2 studies. In a study of older children and young adults, patients who were mono-sensitized to various inhalant allergens received immunotherapy for 4 years and were followed up for 3 additional years.²¹ New skin prick test reactions developed in 77% of the controls and only 27% of those who had received immunotherapy. No reports show that this protection against the development of additional positive skin prick test results applies to children who already have multiple positive skin prick test results at the initiation of immunotherapy.

Prevention of Progression From Rhinitis to Asthma

The one airway concept visualizes allergic rhinitis and allergic asthma as a single inflammatory disease process that involves a common respiratory mucosa, which, however, has certain regional differences.²² Patients with allergic rhinitis often have asymptomatic lower airway inflammation and bronchial hyperresponsiveness. Furthermore, the presence of rhinitis is a risk factor for the development of asthma. A multicenter study was undertaken in children with rhinitis due to birch or timothy pollen and no diagnosis of asthma.²³ Children 7 to 13 years of age were enrolled to receive 3 years of specific immunotherapy. The principal outcome was the development of asthma, but bronchial sensitivity to methacholine was also monitored in and out of season. Children who received immunotherapy became progressively less sensitive to inhaled methacholine both in and out of season, with changes from baseline being significant in all instances except for the first in-season study. Only minor and inconsistent changes in bronchial sensitivity occurred in the control group. At the end of 3 years of immunotherapy, 32 (44%) of 72 controls had developed asthma compared with only 19 (28%) of 69 children who had received immunotherapy.

Multiple Allergen Immunotherapy in Children

Meta-analyses have confirmed the clinical effectiveness of allergen immunotherapy in patients with allergic rhinitis²⁴ and asthma.^{25,26} In an analysis of 64 randomized controlled trials published between 1954 and 1998, Abramson et al²⁶ included 13 studies that were performed exclusively in children and 24 others that included both children and adults. Overall, the analysis demonstrated that there was a significant reduction in both symptoms and medication use with immunotherapy. However, most studies involved immunotherapy with a single allergen. Indeed, it is difficult to find studies that include the multiple allergen mixes regularly administered in allergy practice in the United States. One study that closely reflects clinical practice was conducted a half century ago by Johnstone and Dutton.²⁷ Every child with perennial bronchial asthma and positive skin test results referred to the pediatric allergy clinic of Strong Memorial Hospital in Rochester, NY, between August 1953 and January 1955 was entered into the study. The children were randomly assigned to receive injections of saline, a dilute extract (10^{-7}), an extract that at maintenance had each allergen at a 1:5,000 (wt/vol) concen-

Table 3. The Value of Hyposensitization Therapy for Bronchial Asthma in Children: A 14-Year Study²⁷

Therapy	Children, %
Free of asthma after 4 y	
Placebo and 10^{-7}	18
1:5,000 (wt/vol) maintenance	58
1:250 (wt/vol) maintenance	81
Free of asthma at end of study (age 16 y)	
Placebo and 10^{-7}	22
1:5,000 (wt/vol) maintenance	66
1:250 (wt/vol) maintenance	78

tration or one in which each allergen at was 1:250 (wt/vol) in the maintenance vial. Extracts contained all of the inhalant allergens to which the children reacted on skin prick testing. Parents and children did not know they were in a study, and those evaluating the patients were unaware of to which group the child was assigned. Thus, the study may be considered double-blind although not conducted with the formality typical of today's studies. A total of 230 children were enrolled in the study; 173 completed 4 years of participation and 130 continued in the study until they reached the age of 16 years. Similar numbers of children dropped out of each of the treatment groups. The results of the study are shown in Table 3. No difference occurred in outcome between the placebo group and those receiving the dilute extract, so their results were combined. Those who received a maximum dose of 1:5,000 (wt/vol) clearly benefited but not to the extent of those who received the highest dose (1:250 [wt/vol]). In addition to a decrease in the number reporting any wheeze, the 2 higher doses were associated with a shift toward milder asthma in those still wheezing.

Safety of Immunotherapy in Children

In addition to the special considerations of safety of immunotherapy in children younger than 5 years, the usual cautions that apply to patients of all ages apply as well to children. The 2 most recent reports of fatalities associated with immunotherapy include occurrences in children.^{28,29} In the compilation of fatalities between 1985 and 1989, 4 of the 17 patients were between 10 and 18 years of age.²⁸ In the survey for 1990 to 2001, 17 additional fatal reactions were reported, 1 in a child 5 years of age.²⁹ There are several recurring themes in these reports. Fatal reactions occur primarily in patients with asthma and particularly those whose asthma is not well controlled. There is probably increased risk during the build-up phase and with the first injection from a new vial. Injections at home or in clinics without adequate supervision also constitute an increased risk of a fatal outcome.

CONCLUSIONS

Allergy is often an important contributing factor in childhood asthma. Therefore, to the extent that avoidance is not practical, immunotherapy is a viable option. In addition, specific immunotherapy has been demonstrated to have some protective effect against the development of additional sensitivities

in the monosensitized child and to reduce the risk of developing asthma in children with allergic rhinitis. Because of the modification of the underlying immune reprocess, the beneficial effects of immunotherapy persist for a long but not yet fully determined period after the cessation of treatment. This persisting effect makes immunotherapy an attractive supplement to symptomatic treatment for not only children with allergic asthma but also those with significant allergic rhinitis. The treatment is not without risk, however, especially in the child with asthma, so it should be administered with caution.

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