

# Early Interventions in Allergic Diseases

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## Introduction

Atopy has been defined as the genetic predisposition to develop IgE antibody responses to a variety of common environmental allergens. Clinically, atopy is expressed by asthma, allergic rhinoconjunctivitis and atopic dermatitis. It has been recognized that the “atopic march” evolves from food allergy and atopic dermatitis in the first 2 years of life, followed by asthma and allergic rhinitis. Over the past 30 years, the prevalence of allergies and asthma has increased significantly in developed countries, and asthma is one of the most common chronic diseases in children. Evidence indicates that environmental factors acting early in life, including respiratory viral infections, exposure to pets and microbial products, day-care attendance, breast feeding, and exposure to allergens, tobacco smoke and other pollutants, are key events for establishment of sensitization and development of chronic, persistent symptoms of allergic diseases [1]. It is thought that gene–environment interactions play a crucial role in these processes. Therefore, attempts to successfully prevent development of allergic diseases should be a priority.

At present, there are no genetic markers for atopy or asthma which could be used routinely in clinical practice and family history of atopy has been used to identify children genetically at-risk of developing allergic diseases. These children from high-risk families have been the focus of most of the intervention studies.

In this chapter, we discuss risk factors for development of sensitization and allergic disease, focussing on preventive strategies for allergies and asthma at an early age.

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## Risk Factors for Allergies and Asthma

### *Respiratory Viruses, Wheezing, Allergen Sensitization and Asthma*

Infections with respiratory viruses, particularly human rhinovirus (HRV) and respiratory syncytial virus (RSV) are leading causes of lower respiratory tract (LRT) illnesses associated with wheezing in children. Although acute wheezing episodes may be severe enough to require hospitalization, majority of children presenting wheezing illnesses early in life will no longer wheeze by the age of 6 [2]. However, in a proportion of these children, early-life-wheezing is a clinical manifestation of asthma. Respiratory viral infections have been implicated in the pathogenesis of asthma in several ways: during infancy, certain viruses have been linked to inception of the asthma phenotype; in children with established asthma, viral respiratory infections play a significant role in triggering acute exacerbations that might lead to hospitalizations and frequent outpatient visits; in children with repeated infections due to day-care attendance or contact with older siblings, respiratory viruses may have a paradoxical effect of reducing long-term risk of allergy and asthma, through alterations of cytokine response profiles.

In the first 3 years of life, most LRT illnesses with wheezing are associated with infection by RSV. In the northern hemisphere, RSV accounts for 60–80% of wheezing episodes in children younger than 2 years of age [3]. It has been shown that children who wheeze with RSV infection in early life have lower level of lung function prior to infection [2]. Most children have serum RSV antibody by the age of 2, yet reinfections are common. Although risk of subsequent wheezing after RSV may decrease significantly with age, recurrent episodes of wheezing due to active RSV infections may occur throughout childhood. Transmission requires close contact, and occurs either by large-particle aerosols or by contamination of hands and inoculation into the eye or nose, with an average incubation period of 2–8 days [4].

More recently, the role of HRVs in causing acute wheezing has been appreciated. HRVs are small, nonenveloped, positive-strand RNA viruses in the family *Picornaviridae*, with over 100 identified serotypes with minimal cross-antigenicity [5]. HRV infects only higher primates, and causes illness only in humans, with replication restricted to the respiratory epithelium [6]. In temperate climates, HRV has been estimated to cause up to 80% of autumn colds [5, 7]. In tropical countries, available evidence indicates that HRV is frequently associated with acute respiratory illnesses (ARI). HRV transmission requires close exposure and occurs mainly by hand-to-hand contact, followed by self-inoculation into the eye or nose. It can also be transmitted by airborne spread. Once HRV reaches the nasal cavity, infection occurs in virtually 100% of susceptible subjects; and approximately 75% of those infected develop illness after 1–2 days incubation [5]. Sensitive PCR-based assays have established the importance of HRV as the cause of LRT illnesses, in addition to upper respiratory tract symptoms. A recent study with *in situ* hybridization applied to lower airway biopsy specimens has demonstrated presence of HRV in the LTR of 45% of a group of children 3–26 months of age with recurrent respiratory symptoms [8].

Other viruses have also been associated with wheezing LRT illnesses in children at lower frequencies, including influenza, human parainfluenza viruses, human coronavirus, adenovirus, human metapneumovirus, and the recently identified human bocaviruses (HBoV) – however at a lower frequency [9].

In keeping with observations made in temperate climates, it has been shown that infection with respiratory viruses and family history of allergy, were independently associated with wheezing among infants [10]. Results of this case-control study carried out in Ribeirão Preto, a city in southeast Brazil, revealed that, in the group of children under 2 years of age, respiratory viruses were detected in 60.8% of wheezing infants versus 13.3% of controls, and RSV was detected in 39% wheezing children and none of the controls. Rhinovirus RNA was found in 20.2 and 10% of the wheezing and control children, respectively, though this difference was not significant ( $p=0.21$ ). The frequency of RSV was lower than that reported in temperate regions (39% versus 60–80%). However, considering the subgroup of infants 0–6 months-old, 61% tested positive for RSV antigen. RSV infections were predominantly found in the months of February to May, corresponding to late summer and early to midfall, indicating that the virus occurs in a different seasonal pattern as compared to that of the northern hemisphere. In the group of children 2–12 years of age, respiratory viruses were not significantly associated with wheezing [10]. In the United States, Heymann et al have shown that viral infections, especially HRV, were the dominant risk factor for wheezing among children hospitalized before the age of 3 [11]. In their study, 84% of wheezing children  $p=3$  years-old were positive for virus, compared to 54% of controls ( $p<0.001$ ); RSV was the dominant pathogen in the winter months among children 2 years-old or younger; however, rhinovirus was detected more often among wheezing children hospitalized in the other months of the year (58%) as compared to controls (26%,  $p<0.04$ ) [11].

One important issue would be whether infections with respiratory viruses particularly RSV and HRV occurring early in life could function as triggers or “adjuvants” for subsequent development of sensitization and persistent symptoms of allergic diseases. The rationale for this hypothesis would be the potential of these infections to induce significant damage to the airways which might facilitate penetration of allergen(s) and/or trigger events related to airway remodeling. RSV enters the cell by fusion of the viral envelope with the cell membrane, and causes syncytia formation as a result of fusion of the infected cells to adjacent ones. Replication in the bronchiolar epithelium causes necrosis of ciliated cells, peribronchiolar inflammation with abundant lymphocytes and macrophages, and impairment of secretion clearance, resulting in small airway obstruction and the hyperinflation characteristic of bronchiolitis. Clinically, involvement of the LRT is characterized by tachypnea, dyspnea, cough, expiratory wheezing, air trapping, hyperaeration of the lungs on chest X-rays, and intercostal muscle retractions and cyanosis [4]. The pathogenesis of HRV infection is based on the release of cytokines, chemokines, and inflammatory mediators triggered by productive viral replication in a limited number of cells. A number of chemokines, particularly CXCL8 (IL-8), CCL3 (macrophage inflammatory protein 1 $\alpha$ ) and CCL5 (RANTES) are major mediators released during respiratory viral infections, which could recruit virus-specific T-cells as well as allergen-specific T-cells that in turn could augment

any ongoing allergic response in the lung [12, 13]. It has been speculated that the contemporaneous occurrence of cycles of viral-induced and allergen-induced inflammation in the airways during the period of rapid lung growth and remodeling in infancy interacts synergistically to disrupt underlying tissue differentiation programs. This interaction could result in deleterious changes in ensuing respiratory functions, which may then manifest as persistent wheeze and/or asthma [14].

Studies have shown association of RSV bronchiolitis and other early respiratory tract infections with recurrent wheezing or symptomatic asthma during the first 4–7 years of life [15,16]. A long-term study carried out in Tucson, Arizona, revealed an association of LTR infection caused by RSV early in life with persistent wheezing at 3 and 6 years of age; however, this effect was lost at age 13 [17, 18]. Besides RSV, HRV [19] may be potentially implicated in the subsequent development of childhood asthma. Lemanske et al. have shown that, in a group of 285 children at high risk of asthma, studied during the first 3 years of life, infection with HRV in the first year was the greatest risk factor for persistent wheezing in the third year [20]. The authors showed that 63% of children who wheezed during rhinovirus season continued to wheeze in the third year, as compared to only 20% of all other infants (OR=6.6). A study in Finland revealed that infants hospitalized for rhinovirus-induced wheezing presented a fourfold higher risk of asthma in school age, as compared to wheezing infants from whom no rhinovirus was identified. Children with atopic dermatitis were especially likely to develop wheezing during HRV infections [21]. These studies highlight the previously unrecognized potential role of rhinovirus infection occurring in early life in the onset of asthma.

Follow-up of children 0–2 years of age who participated in the emergency room study in Brazil [22] revealed that, after 2 years, 52% presented persistent wheezing. In contrast to studies carried out in temperate regions, viral infections were not a risk factor for persistent wheezing. On the other hand, early sensitization particularly to mites and cockroach, at 2–4 years of age, and exposure to high levels of cockroach allergen in the home in the first 2 years of life were both strong and independent risk factors for persistence of wheezing. It has been consistently shown that early allergen sensitization becomes a major risk factor for wheezing exacerbations and hospitalizations for wheezing after age 3 [17, 22–25]. It is thought that IgE-mediated inflammation found in most children with persistent symptoms of asthma is a key factor in causing lung function impairment and airway remodeling. Previous studies in Brazil have shown that day-care centers and schools, in addition to homes, are sources of significant exposure to mite and cockroach allergens, which might contribute to sensitization [26, 27]. Heymann et al have demonstrated that sensitization to house dust mites and other aeroallergens was an important risk factor for hospital admissions for wheezing and adverse responses to viral infections, particularly those caused by rhinovirus, in 3–18 years old children [11], highlighting the synergistic effect of sensitization, allergen exposure, and concomitant viral infection in augmenting inflammatory responses in the airways [28]. The possibility that viral and atopy-associated inflammation may interact synergistically to drive asthma pathogenesis has been raised recently by Kusel et al. [14]. Results of this community-based cohort, involving 198 children followed from

birth to 5 years, revealed that acute LTR infection caused by rhinovirus or RSV in the first year of life interacted with atopy in infancy (sensitization  $\leq 2$  years-old) to promote later asthma [14].

It is well recognized that exacerbations of asthma, in patients with established disease, are often triggered by respiratory viral infections, particularly those caused by rhinovirus. In asthmatic patients, persistence of HRV up to 6 weeks following infection or exacerbation of asthma, has been reported [29, 30], suggesting that an aberrant immune response to HRV may be involved in the development of acute exacerbations in atopic individuals with asthma. Also, coexistence of atopy enhances the clinical effect of HRV infection, increasing intensity and duration of bronchial hyperreactivity [31].

Finally, it has been suggested that repetitive viral infections might confer protection to development of asthma, based on their ability to skew the immune system away from the Th2-type response [13, 15]. Day-care attendance and/or siblings significantly increased the likelihood of occurrence of RSV or rhinovirus infections, and increased the risk of rhinovirus-induced wheezing at an early age. Neonatal interferon (IFN)- $\gamma$  responses were lower in infants with high frequency of respiratory infections; conversely, frequent infections were associated with a smaller decline of IFN- $\gamma$  responses during the first year of life, indicating that pre-existing immunologic factors may influence the expression of viral infections in infancy [15].

### ***Breast Feeding***

Exclusive breast feeding for at least 4 months has been associated with protection against development of asthma or atopic diseases [32, 33], but other studies have failed to demonstrate protection by breast milk [34]. Bottcher et al. [35] found no relationship in levels of cytokines (IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, IFN- $\gamma$ , TGF- $\beta$ 1, TGF- $\beta$ 2), chemokines (RANTES, eotaxin) or secretory IgA in breast milk, and development of sensitization or allergic symptoms, or levels of salivary IgA during the first 2 years of life.

### ***Endotoxin***

Endotoxin is a constituent of the outer membrane of gram-negative bacteria, found ubiquitously in nature, being present in most indoor environments as a component of house dust. Endotoxin stimulates the release of potent proinflammatory cytokines. Exposure to high levels of endotoxin in dust is associated with induction of asthma in sensitive patients [36, 37].

It has been demonstrated that bacterial endotoxin is capable of producing Th1-associated cytokines, IFN- $\gamma$ , and IL-12 and therefore, has the potential to decrease

allergen sensitization. Chronic endotoxin exposure, before polarized T-cell responses are established, might be expected to protect against allergen sensitization by continuously enhancing Th1-type lymphocyte development [38]. This assumption has been partially confirmed by studies in humans showing that exposure to high levels of endotoxin in early life was associated with protection against allergic sensitization [39, 40].

An experimental study with pregnant BALB/c mice has shown that combined exposure to endotoxin during prenatal and postnatal phases suppressed allergen-specific sensitization (IgE production), eosinophilic airway inflammation (reduced numbers of eosinophils in bronchoalveolar lavage fluids), and in vivo airway reactivity in response to methacholine. The suppression of allergen-mediated inflammatory responses was associated with increased Toll-like receptor and T-bet expression by lung tissues and a shift toward predominantly Th1 immune responses [41]. Similar results were observed by Wang and McCusker [42].

The relationship of exposure to microbial agents (endotoxin, fungal agents, and other microbial contaminants) early in life (3 months of age) and the development of atopic sensitization and physician-diagnosed asthma and wheeze in the first 4 years of life, in children of atopic mothers, was investigated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. A significant reduction in the development of asthma was associated with early exposure to these substances [43].

Children who were born and raised in a farm environment and exposed to poultry and livestock were reported to have lower prevalence of asthma and/or allergic diseases in comparison to those living in urban area [44, 45]. Until recently, exposure to high levels of endotoxin was associated with exposure to farm animals, presence of pets in home, number of people living in the house, and cleaning habits [46]. However, results of a study carried out on children from rural areas in Europe, evaluating farm-related exposures and health outcomes, revealed that levels of endotoxin and extracellular polysaccharides were associated with health outcomes independent of farm exposures [47].

It has recently been shown by Simpson et al. that the impact of endotoxin may be genetically determined [48]. In the setting of a birth cohort study, increasing endotoxin exposure was associated with reduced risk of allergic sensitization and eczema, and increased risk of nonatopic wheeze, only in children with the CC genotype at -159 of the CD14 gene [48].

### ***Pet Ownership***

Several prospective birth cohort studies have raised the issue of whether keeping of pets, particularly keeping of dogs or cats, might decrease the risk of developing sensitization to those allergens and have confirm these results in part [49–51]. A systematic review of the scientific literature concerning keeping of pets within the first 2 years of life and prevalence of asthma has shown that exposure to pets

was associated with increased risk of asthma and wheezing in children older than 6 years of age and a tendency for protection in those aged below 6 years [52].

In a recent study, a protective effect of early exposure to cat was documented [53]; however it hasn't happened unanimously and some bias of selection may have accounted for the results. So, the protective effect observed might be attributable to allergen or other exposures associated with pet ownership (eg. Endotoxin), but may in part be due to the prior removal of pets in families where children are sensitized or symptomatic or in families with a positive history for atopy at the time the child was born [49].

Platts-Mills and colleagues [54] while evaluating the immune response among 226 children, 47 of whom had asthma and airway hyperresponsiveness, have demonstrated that increasing the exposure to house dust mites was associated with an increase in frequency of sensitization to dust mite allergen. The highest category of exposure to cat allergen though was associated with decreased frequency of sensitization and higher prevalence of IgG antibody to Fel d 1. However, the occurrence of sensitization to dust mite or cat allergens was the strongest independent risk factor for asthma (mite OR=4.2; cat OR=6.1).

### ***Tobacco Smoke***

Maternal tobacco smoking during gestation is an important avoidable risk factor associated with elevated levels of IgE in cord blood, subsequent asthma and allergic diseases in childhood [55–57], and reduction of pulmonary function in children [58]. Increased production of IL-13 by cord blood cells has been found in newborns whose mothers had smoked during gestation as compared with those who never smoked [56]. Macaubas et al. [59] reported a direct relationship of maternal tobacco smoking with both low concentrations of IL-4 and IFN- $\gamma$  in cord blood and increased risk of wheezing by age 6 years. A recent experimental study on BALB/c mice has shown that daily in utero exposure to maternal tobacco smoking was associated with exacerbation of subsequent adult responses to initial allergen exposure [60].

There is a strong body of evidence to support the role of exposure of children to environmental tobacco smoke (ETS) in increasing the incidence of asthma, wheeze, cough, bronchitis, bronchiolitis, pneumonia, and impaired pulmonary function. ETS increases both the prevalence and severity of asthma, as judged by increases in the frequency of attacks, the number of emergency room visits, and the risk of intubation [55, 57]. The risk associated with parental smoking seems to be greater at younger ages. Although a dose–response relationship between ETS exposure and respiratory outcomes has been demonstrated, at present there is no threshold dose of ETS exposure below which an effect will not occur, and therefore active intervention measures and policies to reduce or eliminate children's exposure to ETS should be strongly encouraged [55].

Polymorphisms in the proinflammatory cytokine genes tumor necrosis factor- $\alpha$  (TNF) and lymphotoxin- $\alpha$  (LTA) have been associated with asthma and atopy in some

studies. Secondhand smoke and ozone both stimulate TNF production. In a recent study, Wu et al. genotyping six tagging single nucleotide polymorphisms (SNPs) in TNF and LTA have observed that genetic variation in TNF may contribute to childhood asthma and that association may be modified by parental smoking [61].

A home-based, individualized, intervention study [62] carried out among inner city children with atopic asthma which included education and remediation for exposure to both allergens and ETS, resulted in reduction of asthma associated morbidity.

## **Therapeutic and Preventive Strategies**

### ***Perspectives of Treatment and Prevention of Respiratory Viral Infections***

Few specific interventions are available to reduce the impact of respiratory viruses. No vaccine is currently available for RSV prophylaxis. The disease enhancement caused by formalin-inactivated vaccine in the 1960s plus results of more recent unsuccessful trials of live-attenuated vaccines, have significantly slowed progress toward an RSV vaccine. Passive immunization/immunoprophylaxis with monthly infusions of RSV immunoglobulin or monthly intramuscular injections of humanized monoclonal antibody, during the RSV season, reduced the incidence and severity of RSV infections in high-risk children including those preterm babies less than 6 months-old, children with congenital heart disease, and children less than 2 years with bronchopulmonary dysplasia [4]. The large number of HRV serotypes with minimal cross-antigenicity has hampered the development of an HRV vaccine. It may be possible to reduce exposure to HRV by washing of hands after contact with a cold sufferer or after handling objects that may have been contaminated with respiratory secretions [5]. Immunization with formalin-inactivated or live-attenuated multivalent influenza virus vaccines and chemoprophylaxis for influenza virus A are the methods available for preventing influenza. Influenza vaccine is used prior to the influenza season. The inactivated vaccine has an approximate 70–90% efficacy in preventing illness in healthy children and adults.

In summary, there are virtually no effective strategies targeted at the respiratory viruses for treatment or prevention of viral-induced wheezing illnesses in children. However, evidence indicates that treatment of lung inflammation with inhaled corticosteroids or blocking viral-induced overproduction of leukotrienes with leukotriene-receptor antagonist Montelukast may be effective in decreasing severity and frequency of viral-induced wheezing in young children with recurrent or persistent symptoms [63, 64]. A double-blind, controlled trial (PREVIA study) investigated the effect of treatment with Montelukast for 12 months in 2–5 years-old children with intermittent asthma. Approximately half of these children were positive for at least one respiratory virus, including HRV, coronavirus, and RSV in their nasal



aspirates during exacerbations of symptoms. The results showed that Montelukast had a beneficial effect, decreasing frequency of exacerbations, increasing time between acute wheezing episodes, and reducing the need for inhaled corticosteroids during exacerbations [64].

### ***Environmental Interventions in Genetically Predisposed Infants***

Preventive strategies have focused on manipulating the environment of high-risk individuals as an attempt to reduce the prevalence of allergies and asthma in children. At present, six primary prevention controlled studies are in progress [65]. The longest follow-up reported has been from the Isle of Wight study [66]. In this randomized, controlled study, a group of 120 high-risk infants was recruited prenatally, and development of allergic diseases and sensitization to common allergens was assessed at ages 1, 2, 4 and 8 years. Intervention included strict elimination of common food allergens (dairy products, egg, wheat, nuts, fish, and soy) to the age of 12 months. Lactating mothers followed the same restriction diet (except wheat) for the duration of breast feeding. Extensively hydrolyzed formula was given as a supplement to the child from birth, or when breast feeding was discontinued before 9 months. Stringent allergen avoidance measures were also instituted at birth, aimed at reducing exposure to house dust mites. Repeated measurement analysis showed a sustained preventive effect of allergen avoidance on asthma, atopic dermatitis, and sensitization to allergens over the period of the first 8 years of life, and on allergic rhinitis at age 8 [67]. Therefore, the conclusion was that stringent avoidance of mite and food allergens applied to high-risk children in infancy were beneficial and resulted in reduction of allergic sensitization and clinical manifestations of allergy, beyond the period of avoidance [67]. Likewise, outcome of the Canadian Primary Prevention Study on high risk infants has been reported at age 7 years, showing that intervention during the first year of life, comprising avoidance of mite, pet allergens and ETS, as well as dietary regimen, resulted in reduction of asthma symptoms and asthma diagnosed by a pediatric allergist in the intervention group. In the Canadian study, no significant effect of intervention was observed for bronchial hyperreactivity, allergic sensitization, allergic rhinitis, or atopic dermatitis at age 7 years [68]. Initial results from other cohorts look promising; however further follow-up will be necessary before any recommendations can be made [65]. Results of the Manchester Asthma and Allergy Study (MAAS) have been reported up to the age of 3, and showed that stringent mite and pet allergen avoidance measures starting during gestation, resulted in decrease in severe wheezing and exercise induced wheezing at age 1, and improved pulmonary function in the intervention group at age 3. However sensitization to mites was increased at 3 years of age [69]. In the Study of Prevention of Allergy in Children in Europe (SPACE), environmental control measures aimed at reducing exposure to dust mite allergens at birth and education failed to prevent sensitization at age 2 [70]. Another study looking at the effects of mite avoidance measures during gestation and education. The PIAMA study, showed a modest benefit

of reduction of cough apart from colds at 2 years of age [71]. The results of the Childhood Asthma Prevention Study (CAPS), carried out in Australia, revealed that house dust mite allergen avoidance in conjunction with supplementation of diet with omega-3 fatty acids (abundant in fish and canola-based oils), applied to children with high risk of asthma, resulted in decrease in cough and sensitization to mites at 3 years of age, with no significant differences in wheeze [72].

The conclusion of these prospective studies so far is that environmental measures taken to decrease exposure to dust mite allergens, even if started during gestation, appear to have limited beneficial effects. However, dust mite avoidance in conjunction with stringent dietary avoidance measures applied to high-risk infants of highly motivated families, may result in prevention of sensitization and clinical manifestations of allergy up to 8 years. Follow-up of some of the studies is still too short to allow more definitive recommendations.

### *Pharmacological Treatment*

The prophylactic treatment with an antihistamine, ketotifen, in atopic dermatitis patients was followed by a fourfold reduction in incidence of asthma related symptoms, mainly in those with high levels of serum total IgE [73]. Similar results were observed among children with high risk of developing asthma. The incidence of asthma in preasthmatic patients treated with ketotifen was 9% versus 31% in the placebo group [74].

Warner et al. have evaluated long-term treatment with cetirizine as a preventive tool for the onset of asthma in children aged less than 2 years with atopic dermatitis and without asthma, in a double-blind, randomized, placebo-controlled trial (the Early Treatment of the Atopic Child, ETAC study). At the end of 18 months of active treatment, they observed a significant reduction in the onset of asthma among grass pollen-sensitized infants and dust mite-sensitized infants. These differences were sustained only for the grass pollen-sensitized infants after 18 months of treatment interruption. They concluded that cetirizine truly delays or, in some cases, prevents the development of asthma in a subgroup of infants with atopic dermatitis sensitized to grass pollen and, to a lesser extent, to house dust mite [75]. More recently, preliminary results of the Early Prevention of Asthma in Atopic Children (EPAAC) study, shows that the use of levocetirizine daily for 18 months was safe among atopic children 12–24 months of age [76]. On the whole, these studies indicate that the antihistamines ketotifen, cetirizine, and levocetirizine are safe for use in very young atopic children, and that they may have a role in preventing development of asthma in some of these children, particularly those with atopic dermatitis, and those allergic to house dust mite and grass pollen at an early age [76].

The hypothesis that early introduction of inhaled corticosteroids in young children at high risk of developing asthma could change the natural history of the disease has been investigated. A recent study in preschool children at high risk of asthma revealed that 2 years of treatment with inhaled corticosteroid was highly effective in reducing symptoms and asthma exacerbations, though the benefit was

no longer present during a third treatment-free year, indicating that corticosteroids may not have disease modifying effects [63]. In this trial, the Prevention of Early Asthma in Kids (PEAK), 285 children aged 2–3 years were randomized to receive either 88 mcg Fluticasone twice daily for 2 years or placebo, and at the end of the second year, treatments were interrupted. Clinical and functional differences favoring the children treated with inhaled Fluticasone disappeared a few weeks after discontinuation of regular treatment. Recently, two other studies carried out in the United Kingdom and Denmark [77, 78] reached similar conclusions as the PEAK trial: very early treatment of asthma with inhaled corticosteroids, even before the persistent form of the disease has become evident, does not change the natural clinical course of the disease, and does not seem to affect the level of lung function attained at the end of follow-up, despite the fact that this form of treatment is very effective in controlling asthma symptoms while in use [79].

### *Allergen-Specific Immunotherapy*

Specific immunotherapy (SIT) administered by the subcutaneous route is an efficient treatment for IgE-mediated disease to defined allergens [80]. Beneficial effects of SIT in children have been demonstrated in preventing new sensitizations in children monosensitized to mites [81, 82] and in slowing the progression to asthma in those with seasonal allergic rhinitis, sensitized to pollen allergens (the PAT study) [83]. Follow-up of children with allergic rhinitis sensitized to birch or grass pollens, who underwent SIT for 3 years [83] showed that the effect of SIT in preventing development of asthma was still evident 2 years after SIT was discontinued [84]. Concerns regarding the use of SIT in asthma include the possibility of severe anaphylaxis; however guidelines have been developed to minimize risks of reaction [80]. Sublingual immunotherapy (SLIT) is increasingly being regarded as an efficient tool for the treatment of patients with asthma and/or rhinitis, as indicated by results of meta-analysis of studies carried out in children and adults [85]. The increased safety and ease of administration of SLIT makes this strategy very attractive as a form of early intervention in young children with IgE-mediated disorders, which could modify the natural course of allergic diseases. Studies addressing the use of SLIT in young children however have not been reported. Issues including standardization of the vaccines, establishment of effective doses and schedules for administration, compliance, and better understanding of mechanisms of action and magnitude of efficacy need further research [85].

### **Conclusions**

Evidence suggests that events taking place between 2 and 3 years of age might be crucial determinants in the development of allergies and asthma [86]. Strategies to prevent development of sensitization and progression to disease or to elicit long

**Table 1** Recommendations based on the World Allergy Organization Project Report and Guidelines on Prevention of Allergy and Allergic Asthma – primary prevention*Infants without a special risk for allergic diseases*


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Exclusive breast feeding for 6 months is recommended by the WHO: if a supplement is needed, a conventional cow-milk-based formula is recommended (B)

No special maternal diet during pregnancy or lactation (A)

Avoidance of solid foods until 6 [4] months of age (B)

Avoidance of exposure to tobacco smoke (also during pregnancy) (B)

*Infants with a high risk for allergic diseases*

Exclusive breast feeding for at least 6 months: if a supplement is needed, a documented hypoallergenic formula is recommended for the first 4 months of life; after the age of 4 months, high-risk children can receive the same nutrition as nonhigh-risk children (A)

No special maternal diet during pregnancy or lactation (A)

Avoidance of solid foods until 6 [4] months of age (B)

Environmental measures

Avoidance of tobacco smoke (also during pregnancy) (B)

Reduction of allergen exposure early in life (house dust mites, furred pets, cockroaches) (B)

Avoidance of damp housing conditions (C)

Avoidance of pollutants (C)

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**Table 2** Recommendations based on the World Allergy Organization Project Report and Guidelines on Prevention of Allergy and Allergic Asthma – secondary prevention*Avoidance of tobacco smoke (B)*


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Patients who have perennial asthma, rhinitis, or eczema and who are allergic to house dust mites or animal dander should try to reduce their exposure to the relevant allergens (A, B).

Recommended measures include:

Removal of relevant pets

Reduction of indoor relative humidity below 50% if possible

Encasing of mattresses with documented protective coverings

Washing of pillows in hot water (>55°C) regularly or encasing of pillows with documented protective coverings

Washing of bedding in hot water (>55°C) regularly (every 1–2 weeks)

Removal of carpets in bedroom

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lasting remission of symptoms are strongly desirable. However, current environmental interventions and treatment modalities with pharmacotherapy do not meet these expectations.

According to the recent published World Allergy Organization Project Report and Guidelines on Prevention of Allergy and Allergic Asthma document [87], some evidence-based recommendations can be highlighted (Tables 1 and 2).

**Acknowledgments** Dr. L. Karla Arruda's research on risk factors for asthma in children in Brazil is supported by FAPESP and CNPq, Instituto de Investigação em Imunologia, L.K.A. and D.S. are recipients of CNPq scholarships.

## References

1. Von Mutius E. Influences in allergy: epidemiology and the environment. *J Allergy Clin Immunol* 2004;113:373-9
2. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002;109:362-7
3. Gern J, Busse WW. The role of viral infections in the natural history of asthma. *J Allergy Clin Immunol* 2000;106:201-12
4. Piedra PA, Englund JA, Glezen WP. Respiratory syncytial virus and parainfluenza viruses. In: Richman DD, Whitley RJ, Hayden FG (eds) *Clinical Virology*. ASM Press, Washington, 2002, p763
5. Gwaltney JM Jr, Heinz BA. Rhinovirus. In: Richman DD, Whitley RJ, Hayden FG (eds) *Clinical Virology*. ASM Press, Washington, 2002, p 995.
6. Arruda E, Boyle TR, Winther B, Pevear DC, Gwaltney JM, Hayden FG. Localization of human rhinovirus replication in the upper respiratory tract by in situ hybridization. *J Infect Dis* 1995;171:1329-33
7. Arruda E, Pitkaranta A, Witek TJ Jr, Doyle CA, Hayden FG. Frequency and natural history of rhinovirus infections in adults during autumn. *J Clin Microbiol* 1997;35:2864-8
8. Malmström K, Pitkäranta A, Carpen P, Pelkonen A, Malmberg LP, Turpeinen M, Kajosaari M, Sarna S, Lindahl H, Haahtela T, Mäkelä MJ. Human rhinovirus in bronchial epithelium of infants with recurrent respiratory symptoms. *J Allergy Clin Immunol* 2006;118:591-6
9. Chung JY, Han TH, Kim SW, Kim CK, Hwang ES. Detection of viruses identified recently in children with acute wheezing. *J Med Virol* 2007;79:1238-43
10. Camara AA, Silva JM, Ferriani VPL, Tobias KR, Macedo IS, Padovani MA, Harsi CM, Cardoso MR, Chapman MD, Arruda E, Platts-Mills TA, Arruda LK. Risk factors for acute wheezing among children in a subtropical environment: role of respiratory viruses, IgE antibodies and allergen exposure. *J Allergy Clin Immunol* 2004;113:551-7
11. Heymann PW, Carper HT, Murphy DD, Platts-Mills TAE, Patrie J, McLaughlin AP, Shaker MS, Hellems M, Peerzada J, Hayden FG, Hatley TK, Chamberlain R. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *J Allergy Clin Immunol* 2004;114: 239-47
12. Schaller M, Hogaboam CM, Lukacx N, Kunkel SL. Respiratory viral infections drive chemokine expression and exacerbate the asthmatic response. *J Allergy Clin Immunol* 2006;118:295-302
13. Copenhaver CC, Gern JE, Li Z, Shult PA, Rosenthal LA, Mikus LD, Kirk CJ, Roberg KA, Anderson EL, Tisler CJ, DaSilva DF, Hiemke HJ, Gentile K, Gangnon RE, Lemanske RF. Cytokine response patterns, exposure to viruses, and respiratory infections in the first year of life. *Am J Respir Crit Care Med* 2004;170:175-80
14. Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119:1105-10
15. Lemanske RF Jr. Viral infections and asthma inception. *J Allergy Clin Immunol* 2004;114:1023-26
16. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161:1501-7
17. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541-5
18. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661-75

19. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy – the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111:66–71
20. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, Kirk CJ, Reisdorf E, Roberg KA, Anderson EL, Carlson-Dakes KT, Adler KJ, Gilbertson-White S, Pappas TE, Dasilva DF, Tisler CJ, Gern JE. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;116:571–7
21. Korppi M, Kotaniemi-Syrjänen A, Waris M, Vainionpää R, Reijonen TM. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis* 2004;23:995–9
22. Silva JM, Camara AA, Tobias KR, Macedo IS, Cardoso MR, Arruda E, Chapman MD, Platts-Mills TA, Arruda LK, Ferriani VP. A prospective study of wheezing in young children: the independent effects of cockroach exposure, breast-feeding and allergic sensitization. *Pediatr Allergy Immunol* 2005;16:393–401
23. Platts-Mills TAE, Rakes GP, Heymann PW. The relevance of allergen exposure to the development of asthma in childhood. *J Allergy Clin Immunol* 2000;105:S503–8
24. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;323:502–7
25. Eggleston PA, Rosenstreich D, Lynn H, Gergen P, Baker D, Kattan M, Mortimer KM, Mitchell H, Ownby D, Slavin R, Malveaux F. Relationship of indoor allergen exposure to skin test sensitivity in inner-city children with asthma. *J Allergy Clin Immunol* 1998;102:563–70
26. Tobias KR, Ferriani VP, Chapman MD, Arruda LK. Exposure to indoor allergens in homes of patients with asthma and/or rhinitis in southeast Brazil: effect of mattress and pillow covers on mite allergen levels. *Int Arch Allergy Immunol* 2004; 33:365–70
27. Rullo VE, Rizzo MC, Arruda LK, Sole D, Naspitz CK. Daycare centers and schools as sources of exposure to mites, cockroach, and endotoxin in the city of São Paulo, Brazil. *J Allergy Clin Immunol* 2002;110:582–8
28. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002;324:1–5
29. Jartti T, Lehtinen P, Vuorinen T, Koskenvuo M, Ruuskanen O. Persistence of rhinovirus and enterovirus RNA after acute respiratory illness in children. *J Med Virol* 2004;72:695–9
30. Kling S, Dinninger H, Williams Z, Vermeulen J, Weinberg E, Latiff K, Ghildyal R, Bardin P. Persistence of rhinovirus RNA after asthma exacerbations in children. *Clin Exp Allergy* 2005; 35:672–8
31. Holgate S. Rhinoviruses in the pathogenesis of asthma: the bronchial epithelium as a major disease target. *J Allergy Clin Immunol* 2006;118:587–90
32. Hanson LA, Korotkova M, Telemo E. Breast-feeding, infant formulas, and the immune system. *Ann Allergy Asthma Immunol* 2003;90:59–63
33. Oddy WH. A review of the effects of breastfeeding on respiratory infections, atopy and childhood asthma. *J Asthma* 2004; 41:605–21
34. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Poulton R. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; 360:901–7
35. Bottcher MF, Jenmalm MC, Björkstén B. Cytokine, chemokine and secretory IgA levels in human milk in relation to atopic disease and IgA production in infants. *Pediatr Allergy Immunol* 2003;14:35–41
36. Michel O, Ginanni R, Duchateau J, Vertongen F, Le Bom B, Sergysels R. Domestic endotoxin exposure and clinical severity of asthma. *Clin Exp Allergy* 1991;21:441–8
37. Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, Pauwels R, Sergysels R. Severity of asthma is related to endotoxin in house dust. *Am J Respir Crit Care Med* 1996;154:1641–6

38. Asher I, Dagli E. Environmental influences on asthma and allergy. In: Johansson SGO, Haahtela T (eds) *Prevention of Allergy and Allergic Asthma – World Allergy Organization Project Report and Guidelines*. Karger, Basel, 2004, pp36–101
39. Gereda JE, Leung DYM, Thatayatikom A, Streib JE, Price MR, Klinnert MD, Liu AH. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitization in infants at high risk of asthma. *Lancet* 2000;355:1680–3
40. Gereda JE, Klinnert MD, Price MR, Leung DY, Liu AH. Metropolitan home living conditions associated with indoor endotoxin levels. *J Allergy Clin Immunol* 2001;107:790–6
41. Gerhold K, Avagyan A, Seib C, Frei R, Steinle J, Ahrens B, Dittrich AM, Blumchen K, Lauener R, Hamelmann E. Prenatal initiation of endotoxin airway exposure prevents subsequent allergen-induced sensitization and airway inflammation in mice. *J Allergy Clin Immunol* 2006;118:666–73
42. Wang Y, McCusker C. Neonatal exposure with LPS and/or allergen prevents experimental allergic airway disease: development of tolerance using environmental antigens. *J Allergy Clin Immunol* 2006;118:143–51
43. Douwes J, van Strien R, Doekes G, Smit J, Kerkhof M, Gerritsen J, Postma D, de Jongste J, Travier N, Brunekreef B. Does early indoor microbial exposure reduce the risk of asthma? The Prevention and Incidence of Asthma and Mite Allergy birth cohort study. *J Allergy Clin Immunol* 2006;117:1067–73
44. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grise L, Maisch S, Carr D, Gerlach F, Bufe A, Lauener RP, Schierl R, Renz P, Nowak D, von Mutius E. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; 347: 869–77
45. Waser M, Schierl R, von Mutius E, Maisch S, Carr D, Riedler J, Eder W, Schreuer M, Nowak D, Braun-Fahrlander C; ALEX Study Team. Determinants of endotoxin levels in living environments of farmers' children and their peers from rural areas. *Clin Exp Allergy* 2004;34:389–97
46. Thorne PS, Metwali N, Avol E, McConnel RS. Surface sampling for endotoxin assessment using electrostatic wiping cloths. *Ann Occup Hyg* 2005;49:401–6
47. Ege MJ, Frei R, Bieli C, Schram-Bijkerk D, Waser M, Benz MR, Weiss G, Nyberg F, van Hage M, Pershagen G, Brunekreef B, Riedler J, Lauener R, Braun-Fahrlander C, von Mutius E; PARSIFAL Study team. Not all farming environments protect against the development of asthma and wheeze in children. *J Allergy Clin Immunol* 2007;119:1140–7
48. Simpson A, John SL, Jury F, Niven R, Woodcock A, Ollier WE, Custovic A. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med* 2006;174:386–92
49. von Mutius E, Schmid S; PASTURE Study Group. The PASTURE project: EU support for the improvement of knowledge about risk factors and preventive factors for atopy in Europe. *Allergy* 2006;61:407–13
50. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environmental and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;103:415–20
51. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002;288:963–72
52. Apelberg BJ, Aoki Y, Jaakkola JJ. Systematic review: exposure to pets and risk of asthma-like symptoms. *J Allergy Clin Immunol* 2001;107:455–60
53. Fasce L, Tosca MA, Silvestri M, Olcese R, Pistorio A, Rossi GA. "Early" cat ownership and the risk of sensitization and allergic rhinitis in Ligurian children with respiratory symptoms. *Ann Allergy Asthma Immunol* 2005;94:561–5
54. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;357:752–6
55. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco exposure and children's health. *Pediatrics* 2004;113:1007–15

56. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. *Allergy* 2003;58:1053–8
57. Lannerö E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res* 2006;7:3
58. Gilliland FD, Berhane K, Li YF, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 2003;167:917–24
59. Macaubas C, Klerk NH, Holt BJ, Wee C, Kendall G, Firth M, Sly PD, Holt PG. Association between antenatal cytokine production and the development of atopy and asthma at age 6 years. *Lancet* 2003;362:1192–7
60. Penn AL, Rouse RL, Horohov DW, Kearney MT, Paulsen DB, Lomax L. In utero exposure to environmental tobacco smoke potentiates adult responses to allergen in BALB/c mice. *Environ Health Perspect* 2007;115:548–55
61. Wu H, Romieu I, Sienna-Monge JJ, Rio-Navarro BE, Anderson DM, Dunn EW, Steiner LL, Lara-Sanchez IC, London SJ. Parental smoking modifies the relation between genetic variation in tumor necrosis factor- $\alpha$  (TNF) and childhood asthma. *Environ Health Perspect* 2007;115:616–22
62. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R, Stout J, Malindzak G, Smartt E, Plaut M, Walter M, Vaughn B, Mitchell H; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351:1068–80
63. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, Bacharier LB, Lemanske RF, Strunk RC, Allen DB, Bloomberg GR, Heldt G, Krawiec M, Larsen G, Liu AH, Chinchilli VM, Sorkness CA, Taussig LM, Martinez FD. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985–97
64. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi CA, Polos P. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171:315–22
65. Simpson A, Custovic A. Allergen avoidance in the primary prevention of asthma. *Curr Opin Allergy Clin Immunol* 2004;4:45–51
66. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58:489–93
67. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119:307–13
68. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, Dybuncio A, Becker A. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116:49–55
69. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, Simpson A, Custovic A; NAC Manchester Asthma and Allergy Study Group. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004;170:433–9
70. Horak F, Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, Schwieger A, Forster J; The SPACE study group. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study – 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004;34:1220–5
71. Koopman LP, van Strien RT, Kerkhof M, Wijga A, Smit HA, de Jongste JC, Gerritsen J, Aalberse RC, Brunekreef B, Neijens HJ; Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002;166:307–13



72. Peat JK, Mihrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K, Mellis CM, Leeder SR. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2004;114:807–13
73. Iikura Y, Naspitz CK, Mikawa H, Talaricoficho S, Baba M, Sole D, Nishima S. Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992;68:233–6
74. Bustos GJ, Bustos D, Bustos GJ, Romero O. Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995;25:568–73
75. Warner JO; ETAC Study Group. Early Treatment of the Atopic Child. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol* 2001;108:929–37
76. Simons FE; Early Prevention of Asthma in Atopic Children (EPAAC) Study Group. Safety of levocetirizine treatment in young atopic children: An 18-month study. *Pediatr Allergy Immunol* 2007;18:535–42. Epub 2007 Jun 11
77. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A; IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomized, controlled study. *Lancet* 2006;368:754–62
78. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354:1998–2005
79. Martinez FD. Asthma treatment and asthma prevention: a tale of 2 parallel pathways. *J Allergy Clin Immunol* 2007;119:30–3
80. Bousquet J, Lockey R, Malling HJ, Alvarez-Cuesta E, Canonica GW, Chapman MD, Creticos PJ, Dayer JM, Durham SR, Demoly P, Goldstein RJ, Ishikawa T, Ito K, Kraft D, Lambert PH, Lowenstein H, Muller U, Norman PS, Reisman RE, Valenta R, Valovirta E, Yssel H. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;81:401–5
81. Des Roches A, Paradis L, Menardo J-L, Bouges S, Daurés J-P, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extrat. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99:450–3
82. Pajno GB, Barbeiro G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitization in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six year follow-up study. *Clin Exp Allergy* 2001;31:1392–7
83. Möller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study). *J Allergy Clin Immunol* 2002;109:251–6
84. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Høst A, Koivikko A, Koller D, Norberg LA, Urbanek R, Valovirta E, Wahn U, Möller C; PAT Investigator Group. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 2006;61:855–9
85. Pajno GB. Sublingual immunotherapy: the optimism and the issues. *J Allergy Clin Immunol* 2007;119:796–801
86. Kurukulaaratchy RJ, Matthews S, Arshad SH. Does environment mediate earlier onset of the persistent childhood asthma phenotype? *Pediatrics* 2004;113:345–50
87. Host A, Boner A, Odhiambo J, Custovic A, Lockey R. Preventive measures: early interventions In: Joahansson SGO, Haahela T (eds) *Prevention of Allergy and Allergic Asthma – World Allergy Organization Project Report and Guidelines*. Karger, Basel, 2004, pp135–151