

Review article

The role of allergy in childhood asthma

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Prevalence of asthma

Over the last 20–30 years, the prevalence of atopic diseases in childhood (including asthma) has increased considerably in Western industrialized countries. In population-based studies using identical methods of ascertainment at intervals of 10–15 years, an increase in doctor-diagnosed current asthma from around 4% to 7–10% has been reported (1–3). The steering committee of the International Study on Asthma and Allergies in Childhood (ISAAC) recently reported on the world-wide variation in the prevalence of asthma (4). Based on standardized simple questionnaire surveys conducted among representative samples of schoolchildren from centers in most regions of the world, marked variations in the prevalence of asthma symptoms (12-month prevalence) were reported. Up to 15-fold differences were found between countries, ranging from 4.1% to 32.1% in the younger age group and 2.1% to 32.2% in the older age group (6–7 years and 13–14 years, respectively). The prevalence of asthma was particularly high in English-speaking countries and Latin America. These results suggest that the use of the term “asthma” and the translation of the word “wheezing” into other languages may produce results that cannot easily be compared, and methodological variations may, at least in part, explain the differences in the reported prevalence of asthma. A recent critical review of repeated cross-sectional

surveys, published later than 1982, of the occurrence of asthma among children and young adults found that changes in the labeling of asthma and information bias (increased professional and public awareness) had probably occurred and could explain the reported trends (3). Other authors have concluded that there is evidence of a real increase in the prevalence of asthma in children, although there is some evidence that changes in the diagnostic approach and/or parental awareness may account for a part of the reported increase.

Definition of asthma and allergy

In spite of many efforts, strict and correct classification of asthma is difficult in surveys by postal questionnaires. Certainly, not all that wheezes is asthma. Asthma is best defined as a condition of variable airflow limitation that alters over short periods of time, either spontaneously or under the influence of treatment (5). Thus, the diagnosis of asthma must be clinically confirmed by a doctor (doctor-diagnosed asthma). Although bronchial hyperresponsiveness (BHR) is common in asthma, BHR and diagnosed asthma are not synonymous (for review, see ref. 6). The term “atopy” was previously applied to allergic conditions that occur in families (hay fever, asthma, and atopic dermatitis). But since the discovery of IgE (7, 8), we consider atopy to be

characterized by the production of specific IgE in response to common environmental allergens; i.e., type-I IgE-mediated allergic disease (9).

Natural course and phenotypes of asthma

The development and phenotypic expression of asthma (and other allergic diseases) depend on an interaction between genetic factors, environmental exposure to allergens, and nonspecific adjuvant factors (e.g., tobacco smoke, air pollution, and infections). Our understanding of the inheritance of asthma is still incomplete. At present, it is estimated that genetic factors account for about 50% of asthma and allergy. It is unlikely that a change in genetic factors can explain the increased prevalence of asthma seen during the last decades. It is evident that environmental factors play a major role in the development of asthma. The first months of life seem to be an especially vulnerable period, and there is evidence that sensitization is related to the level of allergen exposure during early life. An evaluation of the influence of genetic factors and the influence of early exposure to allergens on the development of asthma is beyond the scope of this review. These topics are covered in detail by other authors in *Allergy Review Series VI* "The immunology of fetuses and infants".

Up to 90% of asthmatic children have been reported to be atopic with a high frequency of positive family history of atopic disease and associated positive skin prick test to common inhalant and/or food allergens (10). There is some evidence that the reported increase in the prevalence of asthma is particularly due to an increase in nonatopic asthma, a finding which indicates that the causes of asthma may have changed (11, 12). These results emphasize the well-known fact that childhood wheezing illnesses may have different causes and varying prognoses, particularly in young children, where different groups can be identified, such as "transient wheezers" with diminished lung function in early life (associated with maternal smoking during pregnancy), "persistent wheezers", or "late-onset wheezers" (13). Table 1 shows the distribution of these different kinds of wheezers, as reported by Martinez et al. (13). Among children with recurrent wheezing during infancy and early childhood, 30–50% have been reported to develop persistent asthma later in childhood (13, 14). However, the reported prevalences of "recurrent wheezing"/asthma in infancy and early childhood vary widely due to differences in study design, particularly diagnostic criteria and selection of patients. Thus, in prospective studies, 21–34% of subjects have been reported to suffer from recurrent wheezing during early childhood (13, 15).

Recently, in an ISAAC-phase II cross-sectional study in schoolchildren aged 5–7 years and 9–11 years, respectively, von Mutius et al. (16) found that different wheezing phenotypes exist within the "asthma

Table 1. Childhood wheeze and atopy (skin prick test [SPT] >2 mm) caused by inhalant allergens (house-dust mite, *Alternaria*, grass, weed, mesquite, mulberry, olive). Follow-up from 0 to 6 years, $n=826$ children

Wheeze	Period (years)	n (%)	Not tested	Positive SPT
No wheeze	0–6	425 (51.5)	317	33.8%
Transient early	0–3	164 (19.9)	125	38.4%
Late-onset	3–6	124 (15.0)	97	55.7%
Persistent	0–6	113 (13.7)	90	51.1%

From Martinez et al. (13), prospective study.

syndrome", one group of asthma children exhibiting a triggering or inducing of asthma symptoms through repeated early childhood infections ("infectious asthma"), and another group exhibiting "atopic asthma". The former had a better prognosis (16). Similar findings have been reported by other investigators (17). Non-atopic asthma seems to have a better prognosis (16, 17). A recent study, using nonbronchoscopic lavage, has found some evidence of differences in airways inflammatory mechanisms between children with "atopic asthma" (increase in eosinophils and mast cells) and nonatopic asthmatics with virus-induced wheezing (18). Many follow-up studies of asthma have shown that 50–70% of children lose their symptoms before adulthood (19). The variation in reported frequencies of recovery from childhood asthma is mainly due to differences in study design, such as diagnostic criteria, age at inclusion, and differences in definition of the recovery from asthma. A recent prospective study reported that only 25% of children with asthma outgrew their disorder before the age of 42 years (20). Many studies have identified risk factors for persistence of asthma, the most important being verified allergy, other atopic manifestations (hay fever, atopic dermatitis), exposure to tobacco smoke, BHR, impaired lung function, severity of disease, and sometimes male sex (especially in early childhood) (19–24).

Frequency of allergic sensitization

Allergic sensitization does not necessarily imply allergic airways inflammation, an almost invariable feature of asthma although not exclusive to asthma. Thus, up to about 20–40% of nonasthmatics can be shown to be atopic if this is defined as a positive skin prick test and/or positive specific serum IgE to at least one food allergen or airborne allergen in population-based studies, compared to about 90% of asthmatic children (25). The results of investigations of the prevalence of sensitization are highly influenced by methodological factors, such as the quality of extracts for skin prick test, the assay used to determine specific IgE, and the chosen cutoff level for positivity. Data from recent studies using well-described and generally accepted methods to determine specific IgE by skin prick test or determination of

specific serum IgE to relevant allergens in childhood asthma have improved our knowledge of the frequency of sensitization both in unselected children without asthma/atopic disease and among young children with recurrent wheezing/asthma, as well as in older children.

Asymptomatic children

There are few valid data on sensitization in unselected children without asthma/atopic disease. In a recent Swedish study investigating 7–8-year-old schoolchildren ($n = 2149$), 12% of children without asthma or any atopic disease had at least one positive skin prick test out of 10 tested airborne allergens, compared to 49% of the 6% of the children with physician-diagnosed asthma (26). From our own series (27), a prospective study of a 1-year birth cohort ($n = 276$) of unselected infants chosen at random and followed up to 10 years of age, data on sensitization to food allergens, as well as inhalant allergens (birch, grass, mugwort, dog, cat, house-dust mites, *Alternaria alternata*, *Cladosporium herbarum*, egg, and cow's milk), were determined by specific IgE (Pharmacia CAP). The frequencies of sensitization to any allergen were 7%, 23%, and 21% at the ages of 18 months, 5 years, and 10 years, respectively, among children without asthma or any atopic disease when RAST class 1 (0.35 kUA/l) was used as the cutoff level. When RAST class 2 (0.7 kUA/l) was used as the cutoff level, the frequencies of sensitization at the same ages were 3%, 10%, and 12%, respectively. The well-known pattern of sensitization was the same as in allergic children with sensitization to food allergens in infancy. In such children, the sensitization decreased with age and was replaced by sensitization to inhalant allergens later in childhood.

Unselected subjects

In our 1-year birth cohort of unselected infants chosen at random and followed from birth to 10 years of age, the following frequencies of specific IgE, as measured by Pharmacia CAP to airborne allergens and food allergens, were found: 7% at 18 months, 27% at 5 years, and 25% at 10 years when RAST class 1 (0.35 kUA/l) was used as cutoff level, compared to 3%, 14%, and 16%, respectively, when RAST class 2 (0.7 kUA/l) was used as cutoff level (27). In a similar German study (the Multicenter Allergy Study [MAS]) of 216 children of a prospective birth cohort, a complete follow-up of specific IgE measurements to nine food and inhalant allergens was available at 1, 2, 3, 5, and 6 years of age; on the basis of these measurements, sensitization rates were estimated for the reference population of 4082 children by weighted analysis. From this study, point prevalences of allergic sensitization to at least one of the nine tested allergens (Pharmacia CAP at least 0.7 kUA/l) – hen's egg, cow's milk, soy, wheat, mixed grasses, birch pollen, house-dust mites, cat, and dog (the latter only at 3, 5,

and 6 years of age) – increased from 11% at 1 year to 30% at 6 years. The point prevalence of sensitization to inhalant allergens was 1.5% at 1 year, increasing to 26% at 6 years of age, whereas sensitization to food allergens remained stable during the first 6 years of life (10%). A higher frequency of sensitization than in our study was reported at around 5–6 years of age. However, the studies are not completely comparable due to different study designs. Furthermore, in the latter study, the subsample investigated by specific IgE had an overrepresentation of predisposed children, although adjustment for this skewness via weighted analysis was reported. It is evident that a high frequency of sensitization will be found among symptomatic atopic children in such unselected series.

Frequency of allergic sensitization in asthmatic children

The allergens associated with asthma depend on the age of the asthmatics; climatic, seasonal, and social factors; and housing conditions. In temperate and humid regions, allergy to house-dust mites shows the strongest association with asthma, followed by allergy to furred pets (especially cats). In arid regions of the USA, allergy to the fungus *Alternaria* is important; in urban communities, allergy to cockroach may be important, especially in the inner city. These relationships have been reviewed by Platts-Mills et al. (29). Characteristically, sensitization evolves in the following order of exposure: food, and indoor allergens, and outdoor allergens. These characteristics concerning sensitization to airborne allergens were clearly demonstrated in an Italian study (30) (Table 2).

Infancy and early childhood

Around 30% of children with recurrent wheezing, aged 4–60 months, were sensitized to cow's milk protein before 12 months, around 15% at 12–24 months, 10% at 24–48 months, and a very low percentage after that age. In comparison, an increasing frequency of sensitization to house-dust mites (positive skin prick test and positive RAST class 2 or greater) from 40% before 12 months to 70–80% at 4–5 years of age was reported (31). Similar results have been reported among asthmatic children below 3 years of age (32). In children with asthma and

Table 2. Sensitization (skin prick test ≥ 3 mm) to airborne allergens (house-dust mite, pollen, pets, molds) in children with respiratory symptoms ($n = 564$; aged 5 months–17 years, outpatient clinic)

	<i>n</i>	Sensitization	House-dust mite	Pollen
5 months–4 years	181	29.8%	84.5%	42.6%
4–7 years	201	55.2%	87.4%	42.3%
7–10 years	96	68.8%	89.4%	60.6%
10–17 years	86	84.9%	78.1%	79.5%

From Silvestri et al. (30).

wheezing up to 6 years of age, Martinez et al. (13) reported at least one positive skin prick test in 33% of nonwheezing children, 38% of children with transient early wheezing during the first 3 years of life, 55% of so-called late-onset wheezers, and 51% of persistent wheezers (Table 1). Similar results have been reported by other investigators (21), although a lower frequency of sensitization among nonwheezing children up to 4 years of age was reported (15.6% *vs* 33%). The reported differences in allergic sensitization may be due to many factors, such as different number and quality of extracts investigated, and different selection and diagnostic criteria.

Later childhood

A comprehensive study (929 children under 18 years of age) has confirmed the strong association between indoor allergen sensitization and asthma, while finding exclusive sensitization to pollens to be associated primarily with rhinitis. Sensitization was more prevalent for indoor allergens than for outdoor allergens in all groups determined according to diagnosis or age. The prevalence and degree of sensitization were shown to peak in young adults regardless of the allergen, and to diminish with adult age (33). Among patients with severe asthma, a very high frequency of sensitization to indoor allergens has been reported; up to 94% to house-dust mites and up to 71% to cat (34). In conclusion, the majority of asthmatic children (doctor-diagnosed asthma) are atopic with IgE-mediated sensitivity to common inhalant allergens, particularly house-dust mite, cat, dog, and cockroach, depending on the local distribution and magnitude of exposure to allergens.

Clinical significance of sensitization

Although true positive skin prick tests and/or positive specific IgE in serum indicate that a patient has antigen-specific IgE, these findings do not prove that exposure to the allergen in question causes significant clinical allergic symptoms. Only controlled allergen challenge can confirm the cause-effect relationship between allergen exposure and clinical symptoms. However, in daily allergy testing, there is a good correlation between a "significant" positive skin prick test (mean wheal diameter at least 3 mm greater than the negative control) and/or high levels of specific IgE ($\geq$ class 2) to relevant environmental allergens and clinical disease. Performers of allergy testing should always be aware of the diagnostic capacity of the applied allergy-testing methods. Low levels of specific IgE to several allergens – food allergens as well as inhalant allergens – are a normal phenomenon, especially in early childhood, and has no clinical significance (35). It has been disputed whether the higher frequency of atopy (specific IgE to environmental allergens) in asthmatic children is merely

a sign of the atopic status of these children, or whether the specific allergy causes the development and persistence of bronchial inflammation and severity of disease. The proven dose-response relationship between allergen exposure and severity of asthma in several studies (29, 34, 36, 37) indicates that sensitization precedes and causes the allergic inflammation leading to clinical symptoms. Likewise, in high-risk infants, the early manifestations of atopic disease, atopic dermatitis, and gastrointestinal symptoms are often caused by food allergy, whereas asthmatic symptoms in these infants most often develop later in relation to (after) sensitization to environmental inhalant allergens (38, 39). This allergy march has been described in many prospective studies (40), and early allergic sensitization, as demonstrated by specific IgE to food (cow's milk protein and egg protein) and house-dust mites, predicts the later development of asthma (35, 38–44).

It has been hypothesized that the airway inflammation in asthma might precede the development of sensitization to environmental allergens. This does not seem to be the normal course in the development of atopy and asthma considering the above-mentioned course of the allergy march in high-risk infants and the documented power of early sensitization to food and airborne allergens to predict the development of allergic asthma. Nor is there any convincing evidence of such a hypothesis in the group of so-called nonatopic asthmatics with asthma symptoms caused by viral infections, as described in recent studies (16, 18). Therefore, in future studies on asthma in childhood, efforts should be made to describe the clinical, immunologic, and inflammatory type of asthma, as well as the genotype. Furthermore, it is very important that future studies concentrate on prospective, longitudinal studies in order to obtain valuable information on the natural course of the different types of asthma and insight into optimal (and different?) therapeutic approaches to them.

Characteristics of allergic asthma

In nonatopic asthma, wheezing episodes are mainly related to viral respiratory infections, whereas allergy to environmental allergens does not play a major role. In contrast, in atopic asthma, exposure to major indoor allergens is an important risk factor for asthma symptoms in most parts of the world, and allergen exposure is related to the severity of asthma, as shown by correlation between objective indices of asthma severity (e.g., BHR, variability in peak expiratory flow rate) and level of allergen exposure (29, 34, 36, 37). There is no generally accepted criterion for threshold levels of allergens inducing sensitization or allergic symptoms, although there seems to be a correlation between exposure levels and sensitization, as well as a correlation between exposure levels and severity of asthma (for

review, see ref. 45). Other studies have confirmed a correlation with skin prick reactivity to indoor allergens as a marker of asthma severity (10, 46–51). Furthermore, there is evidence of a correlation between allergy and prolonged BHR and persistence of asthma symptoms into adolescence (52, 53).

Inhalation challenge of allergic asthmatics with specific allergy evokes a biphasic response (54). The early asthmatic response develops after exposure to allergen within 20 min, and is characterized by bronchospasm due to classical immediate-type hypersensitivity, triggered through allergen-induced cross-linking of specific IgE antibody bound to mast cells through high-affinity receptors. The released mediators are mainly histamine and leukotrienes, which are responsible for the immediate symptoms, and which contribute to some aspects of the late-phase reaction. In addition, mast cells release various chemokines and cytokines, which induce recruitment and activation of secondary effectors; in particular, eosinophils, one of the hallmarks of the late-phase of allergic reactions. This late-phase response is driven by activated Th2 cells. Beside eosinophils, monocytes, neutrophils, and platelets are involved in the late-phase response (55). The clinical late-phase response appears at 3–6 h after allergen exposure, and this prolonged reaction increases BHR for days to weeks after allergen challenge/exposure (6), and daily allergen exposure may lead to the development of persistent inflammation in the airway wall, resulting in structural and functional changes responsible for chronic asthma symptoms. Thus, in atopic asthma, allergen exposure may lead to development of BHR, reversible airflow obstruction, and airways inflammation, which may become persistent. Therefore, avoiding exposure to relevant allergens is the logical way to treat allergic asthma when the offending allergen can be identified and effective avoidance is feasible.

Specific allergy treatment

Avoidance

For establishment of a cause-effect relationship, avoidance measures should be able both to reduce the allergen level and achieve a clinical effect.

The effectiveness of allergen reduction was first suggested by studies in which patients were removed from their homes to a “low-allergen environment”, and later by allergen-reducing measures in the homes of the asthmatics. High-altitude studies have shown that asthma control and markers of inflammation improve after asthmatics allergic to house-dust mite move to high altitudes with low levels of humidity and house-dust mites (56–59). Other studies (60–62) demonstrated that increased ventilation in homes in temperate regions resulted in decreased humidity, decreased exposure to house-dust mite, and improved asthma control in

asthmatics with allergy to house-dust mite. Several studies on different measures for environmental control have been performed (for review, see refs. 63 and 64). Studies investigating avoidance measures should describe diagnostic criteria and include only patients with proven disease and specific allergy – preferably documented by bronchial allergen challenge. The patients included should not have other clinically important allergies to allergens to which they are exposed during the study period, and the follow-up period should be sufficiently long to allow a reduction in airway inflammation. Moreover, pharmacologic treatment should be monitored carefully and continuously adjusted to the lowest effective dose to avoid “over-treatment” that may hide a possible effect of environmental measures.

As reviewed by Tovey & Marks (63) and Custovic et al. (64), several controlled, randomized studies have demonstrated that some avoidance measures, especially those for allergens of house-dust mite, have proven to be effective in reducing the level of allergens and improving disease control. For elimination of allergens of house-dust mite, encasing of mattresses has been shown to be effective, significantly reducing allergen level, BHR, inflammation markers, and symptoms (65–72). Other effective measures were washing of pillows, duvets, and blankets at least every 4 months (>55°C) and washing of soft toys and other mite reservoirs (for review, see refs. 63 and 64). As regards pets, the only effective method is removal of the pet. Even after removal of the pet, it may take many months before the reservoir of allergens is reduced sufficiently, and it may take 6–12 months before the full benefit is achieved (73).

Thus, environmental avoidance measures have been proven effective as a specific treatment of a specific allergy under the right conditions – and thereby have also documented a cause-effect relationship between exposure to allergens and symptoms in allergic asthma.

Specific immunotherapy

Immunotherapy has been shown in many studies to be an effective treatment for patients with seasonal allergic rhinoconjunctivitis (74). Its efficacy in allergic asthma has previously been questioned, but recent controlled trials of specific immunotherapy (subcutaneous injections) have documented its effect in allergic asthma (75–77). A meta-analysis of 30 randomized, controlled trials of allergen immunotherapy in asthma has shown that subjects treated with immunotherapy had a significant reduction in asthma symptoms and medication, an overall reduction in nonspecific BHR, and a significant reduction in allergen-specific BHR. These effects were most marked for immunotherapy with extracts of house-dust mite, pollen, and animal dander (especially cat). It is emphasized that these clinically useful outcomes were homogeneous (74–76).

Recently, specific immunotherapy with house-dust mites in pediatric asthma patients achieved a significant reduction of bronchial responsiveness (as measured by cold, dry air challenge) compared to controls (75). In allergic asthma patients with chronic airways inflammation, BHR is a consequence of this inflammation. As measured by cold air challenge, BHR appears to be a more relevant and physiologic marker of airways inflammation than previously used pharmacologic methods. Furthermore, preliminary controlled studies have indicated a preventive effect of specific immunotherapy on the development of asthma in children with hay fever and allergy to pollen (birch, grass) (78).

Conclusion

In prospective studies, 21–34% of subjects have been reported to suffer from recurrent wheezing during early childhood. Childhood wheezing illnesses may have different causes and varying prognoses, particularly in young children where different groups can be identified, such as transient wheezers with diminished lung function in early life, persistent wheezers, or late-onset wheezers. Among children with recurrent wheezing during infancy and early childhood, 30–50% have been reported to develop persistent asthma later in childhood, where at least two different wheezing phenotypes have been identified within the asthma syndrome, one group with “infectious asthma” and another group with “atopic asthma”. Over the last 20 years, the prevalence of doctor-diagnosed asthma among schoolchildren seems to have increased from around 4% to 7–10%. The recovery rate from childhood asthma before adulthood has previously been reported to be 50–70%, but recent studies indicate a worse prognosis with a recovery rate of around 25% before the age of 42. The identified risk factors for persistence of asthma are verified allergy, other atopic manifestations, exposure to tobacco smoke, BHR, impaired lung function, severity of disease, and, in early childhood, also male sex.

The frequency of sensitization to environmental allergens depends on the age of the asthmatics; climatic, seasonal, and social factors; and housing conditions. Characteristically, sensitization evolves in the order of exposure, food, indoor allergens, outdoor allergens. In early infancy, 30–60% of recurrent wheezers are sensitized to relevant environmental allergens compared to a sensitization rate of 3–10% among asymptomatics in prospective studies. In asthmatic children of school age, up to 70–90% are sensitized mainly to indoor inhalant allergens, as compared to a sensitization rate of 12–20% among asymptomatic controls (Table 3). Low levels of specific IgE to environmental allergens, food as well as inhalant, are normal findings in early childhood and may be without clinical significance, whereas high levels (mean wheal diameter ≥ 3 mm or specific serum

Table 3. Prevalence of recurrent wheezing (RW)/asthma (A) and allergic sensitization in childhood

Age	RW/A	Sensitization ¹	
		Children with RW/A	Asymptomatics
Early childhood	21–34% ²	30–60% ³	3–10% ²
School age	7–10% ⁴	70–90%	12–20% ²

¹ Sensitization defined as positive skin prick test (mean wheal diameter ≥ 3 mm) or specific serum IgE $\geq$ class 2.

² Data from prospective studies (see text).

³ Data from prospective studies (see text); results depend on selection of patients and severity of disease.

⁴ Data from repeated cross-sectional studies (see text); current doctor-diagnosed asthma.

IgE $\geq$ class 2) is predictive of later development of asthma, as well as being significant for sensitization and clinical relevance in asthmatics, although only controlled allergen challenge can confirm the cause-effect relationship between allergen exposure and clinical symptoms. There are no generally accepted criteria for threshold levels of allergens inducing sensitization or allergic symptoms, although there is a correlation between exposure level and sensitization, as well as a correlation between exposure levels and severity of asthma. Inhalation challenge of allergic asthmatics with specific allergy evokes a biphasic response, the early response within 20 min being characterized by bronchospasm due to classical IgE-mediated immediate-type hypersensitivity, and followed by the late-phase response after 3–6 h, which is characterized by involvement of eosinophil inflammation in the airway wall. This leads to prolonged BHR and, in the case of daily exposure to allergen, per-sistent inflammation resulting in structural and functional changes that cause chronic asthma symptoms.

Avoiding exposure to relevant allergens is the logical way to manage allergic asthma when the offending allergen can be identified and effective avoidance is feasible. Several controlled, randomized studies have demonstrated that avoidance measures, especially against allergens of house-dust mite and animal dander, have proven effective both in reducing the level of allergens and improving disease control. Recently, specific immunotherapy with subcutaneous injections has been shown to be effective in allergic asthma in randomized, controlled trials with extracts of house-dust mite, pollen, and animal dander (especially cat). A significant reduction in asthma symptoms and medication, and a reduction in both nonspecific and allergen-specific hyperresponsiveness has been documented.

In order to institute proper treatment of childhood asthma, the clinical and immunologic type of asthma should be defined in all asthmatic children with persistent or recurrent symptoms and need of prophylactic treatment. Allergy testing is a prerequisite for proper classification and specific treatment of allergic asthmatics, in whom avoidance of relevant – mainly

indoor – allergens may greatly improve disease control and the prognosis of asthma. Furthermore, subcutaneous specific immunotherapy may be a valuable

complementary treatment in allergic asthmatics where prophylactic medical treatment and/or allergen-avoidance measures have been ineffective.

References

- BURR ML. Epidemiology of asthma. In: *Epidemiology of clinical allergy*. Monogr Allergy 1993;**31**:80–102.
- BURR ML, BUTLAND BK, KING S, VAUGHAN-WILLIAMS E. Changes in asthma prevalence: two surveys fifteen years apart. *Arch Dis Child* 1989;**64**:1452–1456.
- MAGNUS P, JAAKKOLA JKK. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross-sectional surveys. *BMJ* 1997;**314**:1795–1799.
- International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: ISAAC. *Eur Respir J* 1998;**12**:315–335.
- CIBA Foundation Study Group. Identification of asthma. Edinburgh: Churchill Livingstone, 1971:38.
- WARNER JO. Bronchial hyperresponsiveness, atopy, airway inflammation, and asthma. *Pediatr Allergy Immunol* 1998;**9**:56–60.
- JOHANSSON SG, BENNICHT H. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology* 1967;**13**:381–394.
- ISHIZAKA K. The identification and significance of gamma E. In: DIXON FJ, FISHER DW, editors. *The biology of immunologic diseases*. Sunderland: Sinauer Associated, 1983:13–23.
- JARVIS D, BURNEY P. The epidemiology of allergic disease. *BMJ* 1998;**316**:607–610.
- SEARS MR, BURROWS B, HERBISON GP, HEWITT CJ, HOLDAWAY MD. Atopy in childhood. II. Relationship to airway responsiveness, hay fever and asthma. *Clin Exp Allergy* 1993;**23**:949–956.
- NYSTAD W, MAGNUS P, GULSVIK A. Increasing risk of asthma without other atopic diseases in schoolchildren: a repeated cross-sectional study after 13 years. *Eur J Epidemiol* 1998;**14**:247–252.
- PEAT JK, VAN DEN BERGH RH, GREEN WF, et al. Changing prevalence of asthma in Australian children. *BMJ* 1994;**308**:1591–1596.
- MARTINEZ MD, WRIGHT AL, TAUSSIG LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;**332**:133–138.
- WENNERGREN G, ÅMARK M, ÅMARK K, ÖSKARSDÓTTIR S, STEN G, REDFORS S. Wheezing bronchitis reinvestigated at the age of 10 years. *Acta Paediatr* 1997;**86**:351–355.
- HALKEN S, HØST A, HUSBY S, HANSEN LG, ØSTERBALLE O, NYBOE J. Recurrent wheezing in relation to environmental risk factors in infancy. A prospective study of 276 infants. *Allergy* 1991;**46**:507–514.
- VON MUTIUS E, ILLI S, HIRSCH T, et al. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 1999;**14**:4–11.
- STEIN RT, SHERRILL D, MORGAN WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;**354**:541–545.
- STEVENSON EC, TURNER G, HEANEY LG, et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997;**9**:1027–1035.
- GROL MH, GERRITSEN J, POSTMA DS. Asthma: from childhood to adulthood. *Allergy* 1996;**51**:855–869.
- GROL MH, GERRITSEN J, VONK JM, et al. Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. *Am J Respir Crit Care Med* 1999;**160**:1830–1837.
- TARIQ SM, MATTHEWS SM, HAKIM EA, et al. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;**101**:587–593.
- HALONEN M, STERN DA, WRIGHT AL, TAUSSIG LM, MARTINEZ FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;**155**:1356–1361.
- MARTIN AJ, MCLENNAN LA, LANDAU LI, PHELAN PD. The natural history of childhood asthma to adult life. *BMJ* 1980;**280**:1397–1400.
- KELLY WJW, HUDSON I, PHELAN PD, PAIN MCF, OLINSKY A. Childhood asthma in adult life: a further study of 28 years of age. *BMJ* 1987;**294**:1059–1062.
- PEARCE N, PEKKANEN J, BEASLEY R. How much asthma is really attributable to atopy? *Thorax* 1999;**54**:268–272.
- RÖNMARK E, LUNDBÄCK B, JÖNSSON E, PLATTS-MILLS TAE. Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in northern Sweden: prevalence rates and risk factor pattern. *Respir Med* 1998;**92**:316–324.
- JACOBSEN HP, MORTENEN S, ESTMANN A, HØST A, HALKEN S. Sensitization in a birth cohort of unselected Danish children from birth to 10 years of age. *Allergy* 1999;**(Suppl)**:5.
- KULIG M, BERGMANN R, KLETTKE U, WAHN V, TACKE U, WAHN U, and Multicenter Allergy Study Group. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;**103**:1173–1179.
- PLATTS-MILLS TAE, VERVOLET D, THOMAS WR, et al. Indoor allergens and asthma: report of the Third International Workshop. *J Allergy Clin Immunol* 1997;**100**:S1–S24.
- SILVESTRI M, ODDERA S, ROSSA GA, CRIMI P. Sensitization to airborne allergens in children with respiratory symptoms. *Ann Asthma Immunol* 1996;**76**:239–244.
- TRINDADE JC. The importance of diagnosis of allergy in early wheezing. *Pediatr Allergy Immunol* 1998;**9**:23–29.
- SONG CH. Skin sensitization in asthmatic children less than 36 months of age. *Ann Allergy Asthma Immunol* 1997;**79**:273–276.
- BOULET L-P, TURCOTTE H, LAPRISE C, et al. Comparative degree and type of sensitization to common indoor allergens in subjects with allergic rhinitis and/or asthma. *Clin Exp Allergy* 1995;**27**:52–59.
- SPORIK R, HOLGATE ST, PLATTS-MILLS TAE, COGSWELL JJ. Exposure to house dust mite allergen (Der p 1) and the development of asthma in childhood: a prospective study. *N Engl J Med* 1990;**323**:502–507.
- HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Clinical symptoms and IgE responses to common food protein and inhalants in the first 7 years of life. *Clin Allergy* 1987;**17**:571–580.
- PEAT J, TOVEY E, TOELLE BG, et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Care Med* 1996;**153**:141–146.

37. CHAN-YEUNG M, MANFREDI J, DIMICH-WARD H, et al. Mite and cat allergen levels in homes and severity of asthma. *Am J Respir Crit Care Med* 1995;**152**:1805–1811.
38. HØST A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol* 1994;**5**(Suppl):5–36.
39. SASAI K, FURUKAWA S, MUTO T, BABA M, YABUTA K, FUKUWUTARI Y. Early detection of specific IgE antibody against house dust mite in children at risk of allergic disease. *J Pediatr* 1996;**128**:834–840.
40. ZEIGER RS, HELLES S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomised study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;**95**:1179–1190.
41. BERGMANN RL, EDENHARTER G, BERGMANN KE, et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998;**28**:965–970.
42. BURR ML, MERRITT TG, DUSTAN FDJ, MAGUIRE MJ. The development of allergy in high risk children. *Clin Exp Allergy* 1997;**24**:1247–1253.
43. DELACOURT C, LABBE D, VASSAULT A, BRUNET-LANGOT D, DE BLIC J, SCHEINMANN P. Sensitization to inhalant allergens in wheezing infants is predictive of the development of infantile asthma. *Allergy* 1994;**49**:843–847.
44. NICKEL R, KULIG M, FORSTER J, et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;**99**:613–617.
45. CUSTOVIC A, SIMPSON A, CHAPMAN MD, WOODCOCK A. Allergen avoidance in the treatment of asthma and atopic disorders. *Thorax* 1998;**53**:63–72.
46. ZIMMERMANN B, FEANNY S, REISMAN J, et al. Allergy in asthma. The dose relationship of allergy to severity of childhood asthma. *J Allergy Clin Immunol* 1988;**81**:63–70.
47. KUEHR J, FRISCHER T, MEINERT R, et al. Sensitization to mite allergens is a risk factor for early and late onset of asthma and for persistence of asthmatic signs in children. *J Allergy Clin Immunol* 1995;**95**:655–662.
48. SARPONG SB, KARISSON T. Skin test reactivity to indoor allergens as a marker of asthma severity in children with asthma. *Ann Allergy Asthma Immunol* 1998;**80**:303–308.
49. SEARS MR, BURROWS B, LANNERY EM, HERBISON GP, HOLDAWAYS MD. Atopy in childhood. I. Gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy* 1993;**23**:941–948.
50. BURROWS B, SEARS MR, FLANNERY EM, HERBISON GP, HOLDAWAY MD, SILVA PA. Relation of the course of bronchial responsiveness from age 9 to age 15 to allergy. *Am J Respir Crit Care Med* 1995;**152**:1302–1308.
51. NELSON R, DINICOLA R, FERNÁNDEZ-CALDAS E, SELEZNICK MJ, LOCKEY RF, GOOD RA. Allergen-specific IgE levels and mite allergen exposure in children with acute asthma first seen in an emergency department and in nonasthmatic control subjects. *J Allergy Clin Immunol* 1996;**98**:258–263.
52. PEAT JK, SALOMNE CM, WOODCOCK AJ. Longitudinal changes in atopy during a 4 year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990;**85**:65–74.
53. GERRITSEN J, KOETER GH, POSTMAN DS, SCHOUTEN JP, VAN AALDEREN WMC, KNOL K. Airway responsiveness in childhood as a predictor of the outcome of asthma in adulthood. *Am Rev Respir Dis* 1991;**143**:1468–1469.
54. O'BYRNE PM, DOLOVICH J, HARGREAVE FE. Late asthmatic responses. *Am Rev Dis* 1987;**136**:540–551.
55. HOLT PG, MACANBAS C, STUMBLES PA, SLY PD. The role of allergy in the development of asthma. *Nature* 1999;**402S**:B12–B17.
56. BONER AL, NIERO E, ANTOLINI I, VALETTA EA, GABURRO D. Pulmonary function and bronchial hyperactivity in asthmatic children with house dust mite allergy during prolonged stay in the Italian Alps (Misurini 1756 m). *Ann Allergy* 1985;**54**:42–45.
57. PIACENTINI GL, VINCENTINI L, MAZZI P, CHILOSI M, MARTINATI L, BONER AL. Mite-antigen avoidance can reduce bronchial epithelial shedding in allergic asthmatic children. *Clin Exp Allergy* 1998;**28**:561–567.
58. PIACENTINI GL, MARTINATI L, MINGONI S, BONER AL. Influence of allergen avoidance on the eosinophil phase of airway inflammation in children with allergic asthma. *J Allergy Clin Immunol* 1996;**97**:1079–1084.
59. PIACENTINI GL, MARTINATI L, FORNARI A, et al. Antigen avoidance in a mountain environment: influence on basophil releasability in children with allergic asthma. *J Allergy Clin Immunol* 1993;**92**:644–650.
60. HARVING H, KORSGAARD J, DAHL R. House-dust mites and associated environmental conditions in Danish homes. *Allergy* 1993;**48**:106–109.
61. WICKMAN M, EMEINUS G, EGMAR A-C, AXELSSON G, PERSHAGEN G. Reduced mite allergen levels in dwelling with mechanical exhaust and supply ventilation. *Clin Exp Allergy* 1994;**24**:109–114.
62. HARVING H, KORSGAARD J, DAHL R. Clinical efficacy of reduction in house-dust mite exposure in specially designed, mechanically ventilated "healthy" houses. *Allergy* 1994;**49**:866–870.
63. TOVEY E, MARKS G. Methods and effectiveness of environmental control. *J Allergy Clin Immunol* 1999;**103**:179–191.
64. CUSTOVIC A, SIMPSON A, CHAPMAN MD, WOODCOCK A. Allergen avoidance in the treatment of asthma and atopic disorders. *Thorax* 1998;**53**:63–72.
65. EHNERT B, LAU-SCHADENDORF S, WEBER A, BUETTNER B, SCHOU C, WAHN U. Reducing domestic exposure to dust mite allergen reduces bronchial hyperactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992;**90**:135–138.
66. WEEKS J, OLIVER J, BIRMINGHAM K, CREWES A, CARSWELL F. A combined approach to reduce mite allergen in the bedroom. *Clin Exp Allergy* 1995;**25**:1179–1183.
67. TAN BB, WEALD D, STRICKLAND I, FRIEDMAN PS. Double-blind controlled trial of effect of house-dust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996;**347**:15–18.
68. CARSWELL F, BIRMINGHAM K, OLIVER J, CREWES A, WEEKS J. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children – a double-blind controlled trial. *Clin Exp Allergy* 1996;**26**:386–396.
69. FREDERICK JM, WARNER JO, JESSOP WJ, ENANDER I, WARNER JA. Effect of a bed covering system in children with asthma and house dust mite hypersensitivity. *Eur Respir J* 1997;**10**:361–366.
70. MARKS GB, TOVEY ER, GREEN W, SHEARER M, SALOME CM, WOOLCOCK AJ. House dust mite allergen avoidance: a randomized controlled trial of surface chemical treatment and encasement of bedding. *Clin Exp Allergy* 1994;**24**:1078–1083.
71. MARKS GB, TOVEY ER, GREEN W, SHEARER M, SALOME CM, WOOLCOCK AJ. The effect of changes in house dust mite allergen exposure on the severity of asthma. *Clin Exp Allergy* 1995;**25**:114–118.

72. SHAPIRO GG, WIGHTON TG, CHINN T, et al. House dust mite avoidance for children with asthma in homes of low-income families. *J Allergy Clin Immunol* 1999;**103**:1069–1074.
73. WOOD RA, CHAPMAN MD, ADKINSON NF Jr, EGGLESTON PA. The effect of cat removal on allergen content in household-dust samples. *J Allergy Clin Immunol* 1989;**83**:730–734.
74. BOUSQUET J, LOCKEY RF, MALLING H-J, editors. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;**53**:1–42.
75. ABRAHAMSON MJ, PUY RM, WEIHER JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;**151**:969–974.
76. GRUBER W, EBER E, MILEDER P, et al. Effect of specific immunotherapy with house dust mite extract on the bronchial responsiveness of paediatric asthma patients. *Clin Exp Allergy* 1999;**29**: 176–181.
77. ABRAHAMSON R, PUY R, WEINER JM. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999;**54**: 1022–1041.
78. VALOVIRTA E. Capacity of specific immunotherapy in prevention of allergic asthma in children: the Preventive Allergy Treatment Study (PAT). *J Investig Allergol Clin Immunol* 1997;**7**:369–370.