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Asthma Frequently Asked Questions

Question 6: What is the use of allergy testing in children with asthma?

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Educational aims

The reader will be able to:

- Describe the relationship between childhood asthma and allergies
- Discuss the available options to diagnose an inhalant allergy
- Describe a number of asthma management options in relationship to allergy testing
- Summarize the use of allergy testing in childhood asthma

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ABSTRACT

Disagreement exists between asthma guidelines on the routine use of allergy testing in the diagnostic work-up of a child with persistent asthma, although the important role of inhalant allergy in the pathophysiology of asthma and allergic rhinitis is undisputed. The usefulness of screening for inhalant allergies in asthma is connected to the efficacy of allergen reduction measures and specific immunotherapy, both of which appear to be more effective in children than in adults. Allergen-specific exposure reduction recommendations are therefore an essential part of childhood asthma management. Such recommendations should be guided by appropriate diagnosis of inhalant allergy, based on a structured allergy history and results of sensitization tests. Specific IgE testing and skin prick testing show comparable results in identifying clinically important sensitizations. Although a therapeutic medication trial can be started pragmatically in children with asthma without diagnosing their inhalant allergy, we recommend making or excluding an accurate diagnosis of inhalant allergy.

INTRODUCTION

Making a diagnosis of persistent asthma in a child prompts the physician to start treatment, following the recommendations of national or international asthma guidelines. These guidelines are in agreement about many facets of asthma management, such as the prescription of daily controller and reliever therapy and the self-management training of parents and children [1–3]. Disagreement between guidelines exists, however, about the routine use of allergy testing in the diagnostic work-up of a child with persistent asthma. Whilst the US National Heart, Lung, and Blood Institute asthma guideline strongly recommends such tests, the GINA and NICE asthma guidelines provide only a short and non-committal suggestion about allergy testing [1–3]. Because physicians' non-adherence to asthma guidelines in general is common, guideline recommendations may not reflect actual daily practice. Studies suggest that allergy tests are performed in less than half of children with asthma in US primary care [4–6]. Apparently, not only guidelines but also physicians disagree on the value of allergy testing.

In this review, we discuss the role of allergy testing in the diagnosis and management of childhood asthma. We start by considering the strong relationship between childhood asthma and allergies. Subsequently, we discuss the available options to diagnose an inhalant allergy. In the final section of this paper, we describe a number of asthma management options in relation to (the results of) allergy testing.

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THE RELATIONSHIP OF ASTHMA TO INHALANT ALLERGY

Childhood asthma is an atopic disease (in most children)

For many decades, childhood asthma has been regarded as part of the 'atopic march', preceded by atopic dermatitis and food allergy, and followed by allergic rhinoconjunctivitis [7,8]. Systematic reviews of long-term follow-up studies and large-scale prospective birth cohort studies have shown that only 1 in 3 children with atopic dermatitis will develop asthma during later childhood, and more than half of 6-year-old children with asthma had no atopic dermatitis as an infant [7–11]. Consequently, the current view on atopic diseases is that they share a genetic predisposition to become sensitized to common allergens that non-atopic people do not react to [8,12]. Sensitization to inhalant allergens is, therefore, the hallmark of atopic airway diseases (Fig. 1). In cross-sectional cohort studies, about 70–80 % of children with asthma are atopic, i.e. sensitized to one or more common inhalant allergens, with higher rates of atopy in patients with more severe asthma [13–17].

Sensitization is a weak predictor of allergic diseases

Sensitization does not necessarily imply the presence of an immunologically mediated allergic reaction or allergic disease, as sensitization may be asymptomatic [12]. The development of IgE antibodies to airborne allergens is obviously not the only step required to develop an allergic disease like allergic rhinitis, and most sensitized individuals do not develop allergic diseases. Whether or not a sensitized individual develops a symptomatic atopic disease is dependent on the complex interplay between genetic predisposition and exposure to environmental stimuli like

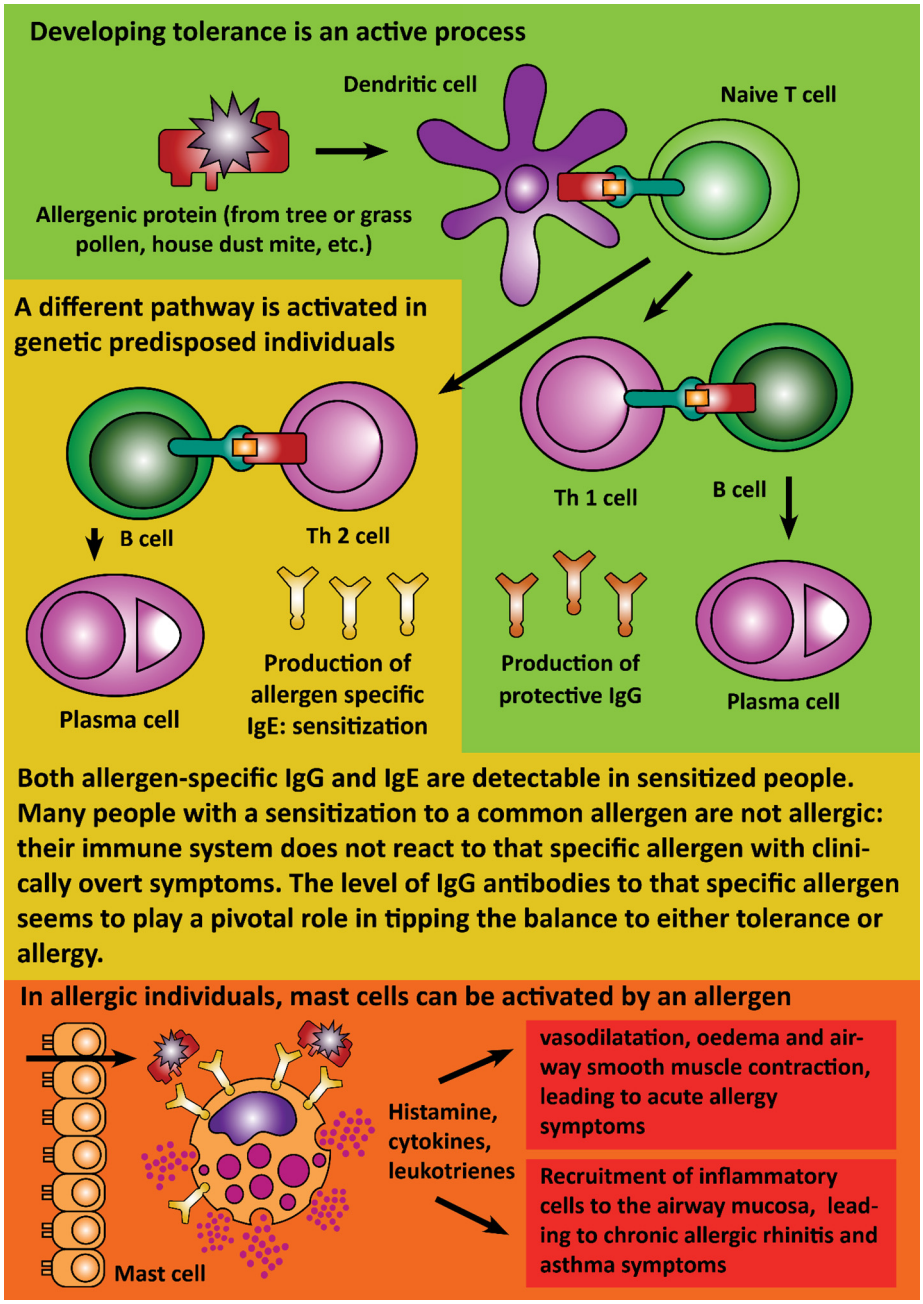

Fig. 1. Neuro-inflammatory and immunological interactions in the development of atopic sensitization.

inhalant allergens and parental smoking, with different effects of specific environmental exposures amongst individuals with different genetic predispositions [18]. The complexity is further increased by the finding that similar to asthma, 'atopic sensitization' is heterogeneous, and that there are several distinct subgroups of sensitization, differing in their risk factors and associations with asthma progression [12]. Patterns of sensitization are mainly determined by the age of onset and types of sensitization, including mono-sensitization to dust mite and multiple sensitization to food and inhalant allergens [12,19]. There is increasing evidence that the risk of asthma is significantly higher among children who are sensitized early in life, or sensitized to multiple allergens [12]. However, in the absence of mechanistic knowledge, it is difficult to identify the role of sensitization in the development of asthma. While sensitization in general does not predict asthma very well, looking for specific sensitization patterns may be helpful to identify children at risk to be or to become asthmatic. But even in children with early, multiple sensitizations, the diagnosis of asthma is primarily based on a history of recurrent wheezing, breathlessness and cough, supported by lung function tests.

Inhalant allergy is closely related to asthma control

It is undisputed that allergic sensitization can develop into an inhalant allergy, and exposure to that specific allergen can result in a pulmonary allergic reaction. This relationship between inhalant allergy and asthma symptoms is very well illustrated in asthmatic children with an animal dander allergy, experiencing acute asthma symptoms after exposure to that specific animal [20]. The significant role of inhalant allergy is also obvious in children with a pollen allergy and a strict seasonal pattern of asthma symptoms.

The effect of an inhalant allergy on asthma control, however, is usually not so obvious. Many children with asthma have perennial symptoms, with a broad range of stimuli such as viral infections, exercise and exposure to inhaled allergens. In these patients, the contribution of the inhalant allergy to asthma symptoms may remain unclear. This is particularly a problem in patients with chronic exposure to an allergen, such as patients with a house dust mite allergy or pet owners with a pet allergy [20]. Identification of the role of allergen exposure in determining asthma control is even more complex because there is some evidence that asthma stimuli may interact: children with higher allergen exposure may have more severe asthma symptoms during viral infections [21].

The sometimes-complex assessment of the role of inhalant allergy in individual patients, however, does not imply that inhalant allergies have a minor role in asthma outcomes. Studies have shown that children with asthma who are sensitized and exposed to indoor allergens, including dust mite, rodent, cockroach, and pet allergens, have worse asthma control and lung function and greater airway inflammation and morbidity than those who are either not sensitized or not exposed to these allergens [20,22]. Asthma symptoms, pulmonary function, and need for medication in mite-sensitive asthma patients correlate with the level of house-dust mite exposure [22]. The impact of inhalant allergy on asthma control is further illustrated by high sensitization rates among children visiting specialized outpatient asthma clinics, and among hospitalized children with asthma, where sensitization rates of up to 90% have been described [16,17]. Therefore, it can be concluded that inhalant allergy affects asthma control in different ways, and in many more cases than suspected when relying only on an allergy history.

Asthma and allergic rhinitis: united airway disease

Different manifestations of atopic disease may co-exist in patients, or develop at different times [7]. Patterns of co-incidence can be identified among the four main atopic diseases: atopic dermatitis, food allergy, asthma and allergic rhinitis. Food allergy, for example, is mainly diagnosed in children with eczema, a co-incidence which is thought to be caused by a disrupted skin barrier facilitating transcutaneous allergen presentation to the immune system, making a person more likely to develop sensitization to the specific allergen [23]. Asthma and allergic rhinitis also have high rates of co-incidence [7,24]. Allergic rhinitis is the most common atopic airway disease in school-aged children and adults, and is often the single expression of atopy in these patients [25]. Up to 85% of school-aged children and adults with atopic asthma have concomitant allergic rhinitis [7,24,25]. These two diseases not only often co-exist, but appear to share the pathophysiology of an evolving, inflammatory reaction, sustained and amplified by interconnected neuro-inflammatory mechanisms [26]. Therefore, inhalant allergy affects asthma control also by an indirect route after nasal exposure [26]. The shared pathophysiology has clinical relevance: treatment of rhinitis leads to better control of asthma [17,25]. Allergic rhinitis and asthma therefore require an integrated diagnostic and therapeutic approach to achieve disease control [24,27].

HOW TO DIAGNOSE INHALANT ALLERGY

From the above it follows that identifying sensitization in a patient does not equate with clinical allergy [28]. In other words, allergy sensitization tests show a high false-positive rate. A structured allergy history alone also carries high false positive and false negative rates [29]. This is in particular the case in patients with perennial respiratory symptoms and for indoor allergens with chronic exposure. For a reliable diagnosis of a specific allergy, the structured allergy history needs to be considered alongside results of allergy tests of each patient.

Performing a structured allergy history

Questions to be asked to assess the exposure to specific aeroallergens and the risk of having an allergy are given in Table 1. This may result in a clear diagnosis. If a patient only reports symptoms of asthma in the summer, and the results of allergy tests are positive for tree or grass pollen, the trigger for the asthma symptoms is likely to be grass pollen allergy because the pollination period of trees occurs in early spring. More challenging is the assessment of multiple inhalation allergies or perennial indoor allergies, because patients have chronic symptoms, which are difficult to relate to direct exposure [30]. If the patient is sensitized to house dust mites or animal danders, the likelihood that house-dust mite or animal dander allergy contributes to asthma symptoms increases with more affirmative answers to the questions listed in Table 1. It is helpful to be aware of existing pests, because in inner-city areas mouse allergen and cockroach allergen are the most important indoor allergens children are exposed to [31]. However, absence of positive responses does not exclude a contribution of exposure to house-dust mite or animal dander to the patient's symptoms. Given the evidence that exposure to cat allergens can be significant in homes, schools, and offices in the absence of animals, the issue of allergen exposure in sites without animals has become more relevant. A Swedish study showed an increase of asthma symptoms in children after summer holidays, particularly in children from school classes with many cat owners [32], suggesting that children with cat allergy may be affected by indirect cat exposure at school. In a study in inner-city school-aged children with asthma, exposure to mouse allergen at schools was associated with increased asthma symptoms and decreased lung function [31].

Table 1
Structured allergy history.

Questions to be asked to patients with perennial symptoms
Animals
• Exposure: Are there any pets kept indoors? What type? Does the child visit family of friends with pets?
• Symptoms if a pet is kept indoors:
o Do nasal or chest symptoms improve when the child is away from home for a week or longer, and stays in a place with no exposure to animal related allergens?
o Do the patient's symptoms worsen during the first 24 hours after returning home?
o Do symptoms increase after physical contact with the animal?
House-dust mite (and moulds)
• Exposure: Assume exposure to house-dust mites unless patient lives in a semiarid region. High exposure:
o Is the child living in an older house, with many carpets, or a low housekeeping frequency?
o Is there moisture, dampness or visible moulds in any room of the home?
o What does the child's bed look like (Covers, teddy bears, etc.)?
• Symptoms:
o Does playing in a dusty place (e.g. the attic, at a friend's with a less well-cleaned house) cause nasal, eye or chest symptoms?
o Does the child sneeze repeatedly in the morning?
o Does the patient have increased symptoms during vacuuming in the house?
o Has the patient noticed a change of symptoms when away from home on vacation (e.g. increase in dusty hostels or hotels and sleeping on an old mattress)?
o Do nasal, eye, or chest symptoms appear when the patient is in a carpeted or recently vacuumed room?
Pests
• Exposure: Have the caregivers seen cockroaches or rodents in the child's home in the past month? Is the patient living in inner-city conditions?
• Symptoms
o Does the patient have increased symptoms during vacuuming of the house?
o Has the patient noticed a decrease of symptoms when away from home on vacation?
Questions to be asked to patients with a seasonal symptom pattern
Pollen (early spring - trees, late spring - grasses, late summer to autumn - weeds and Alternaria)
• Nasal, eye or chest symptoms in a specific season?
• Do symptoms increase when the patient is outside in general or doing outdoor activities in green spaces such as parks with grass and trees?
Mite or animal dander
• Symptoms late autumn and early winter may be related to mite or animal dander allergy, ask questions as suggested above for patients with perennial symptoms.

Performing allergy tests: choice of inhalant allergens

In taking a history, it can be difficult to associate clinical allergy with allergen exposure. This is particularly true for perennial allergies and exposure to allergens such as house dust mite or cockroaches in the living environment. In contrast, certain pollen allergies may be clinically diagnosed more easily if allergy symptoms coincide with or clearly exacerbate in a particular pollen season. However, patients sensitized to seasonal pollen may also have mild persistent symptoms caused by chronic up-regulation of inflammatory cells and mediators in the mucosa, leading to increased sensitivity to allergens and non-specific irritants [33,34]. While those sensitized to perennial allergens may experience intermittent symptoms that worsen during autumn and winter caused by increased exposure [35]. Therefore, in many patients with a mono-sensitization to pollen or house dust mite allergy, a seasonal variability of the symptoms is detectable [35].

One may expect that pet allergy can be relatively easily identified by asking the patient if he or she experiences allergy or asthma symptoms when exposed to the pet. However, the large majority (78%) of patients with a positive bronchial provocation test to cat allergen did not think that cat exposure was a trigger of their allergic symptoms [30]. We therefore recommend screening children with asthma for inhalant allergy sensitization, at least testing for common indoor allergens including house dust mite and cat and dog dander. Allergy testing for dander of specific types of pets or horses are only relevant for those who have a history of exposure. Screening for cockroach, rodent and moulds is indicated when exposure to these allergens is likely, which depends on the geographic location and the living environment. Screening for tree and grass pollen sensitization may also be relevant because sensitization to specific pollen may be a target for high-dose oral immunotherapy [36].

Skin prick test (SPT) or specific IgE (sIgE)

Serum IgE testing and allergy skin testing show comparable results in identifying clinically important sensitizations, and there is no lower age limit for either of these tests [28,30]. Disagreement between the two tests is common in children. In two small paediatric studies of children with multiple inhalant allergen sensitization, only half of the sensitized patients showed both a positive skin prick test and elevated sIgE to the same allergen [30]. In two studies including children with asthma, discordance between SPT and IgE testing was 10–20% [37,38]. When a SPT shows no sensitization despite a very suggestive positive allergy history, performing sIgE testing should be considered (and vice versa). The choice of skin prick test or serum IgE may be based on availability and the specific advantages of the tests. A skin prick test has the advantage that results are visible to the patient within ten minutes and an official report can be provided accordingly. This may encourage adherence to environmental control measures. The risk of severe allergic reactions in skin prick testing in children is too low to be a clinically relevant consideration in the choice of allergy testing. Testing serum IgE has the advantage that it does not require specific skills or allergen extracts, and that the test can be performed on patients who are taking medications that suppress the immediate skin test response (antihistamines). The cost of specific IgE sensitization screening is considerably higher than that of skin prick testing, however, and results are not immediately available.

Interpretation of test results

To add precision to diagnosing allergy, the level of sensitization to a specific allergen should be taken into consideration, because the risk of having a symptomatic inhalant allergy increases with higher levels of sIgE [39]. In an adult cohort, approximately 2/3 of patients with slightly elevated specific IgE to house dust mite

or cat did not report any symptoms suggestive of a house dust mite or cat dander allergy, compared to over 95% of patients with high level grass pollen IgE levels reporting symptoms in the grass pollen season [39]. We were unable to find similar paediatric studies. Although the risk of symptomatic allergy increases with the degree of sensitization, even highly sensitized patients may be completely asymptomatic, as illustrated by the finding that almost a quarter of adults with high house dust mite specific IgE levels did not report symptoms suggestive of a dust mite allergy [38]. In polysensitized patients with high sensitization levels to specific allergens, low sIgE levels to other inhalant allergens are usually of no clinical relevance [19].

THE CASE FOR AND AGAINST DIAGNOSING INHALANT ALLERGY IN CHILDREN WITH ASTHMA

Considering the strong relationship between inhalant allergy and asthma control as outlined above, it is remarkable that guidelines are inconsistent about testing for inhalant sensitizations. This inconsistency is related to a persistent disagreement on the effectiveness and the potential role of avoidance of allergens in the management of asthma, in particular the avoidance of house dust mite allergens. Some recent reviews and guidelines have concluded that dust mite avoidance interventions have no role in asthma management [2,3,21]. This conclusion is disputed in two articles, by summarizing potential flaws of these reviews [21,39]. Among several limitations addressed in these papers is the combined analyses of data for adults and children. House dust mite exposure measures may have increased effectiveness in children with asthma, compared to adults. It has been suggested that this may be related to chronic inflammation and remodelling of airways in adults and to greater allergen exposure in children, because of their proximity to the floor (including playing on the floor), and longer sleeping time [21,40].

In view of the evidence that high allergen exposure can trigger asthma symptoms (as outlined before), and that a low-allergen environment can be achieved in children's homes [41], the real question is not whether allergen avoidance is effective, but how to achieve a sufficiently large reduction in personal allergen exposure in real-life to achieve clinical improvement [21]. This suggests that the effectiveness of home-based allergen-control interventions is determined by the extent to which allergen reduction is achieved. This consideration may help to understand why multicomponent interventions are more effective in improving asthma control (Table 2) [42]. But even single interventions may affect asthma outcomes, as illustrated by a randomized trial of 284 school-aged children with asthma and sensitization to house dust mite. Patients who received dust mite-impermeable bed encasings had a 27% lower risk of severe asthma exacerbations than children with placebo bed covers [43].

These findings provide a convincing rationale for the use of allergen avoidance in asthma management, and allergy testing to guide allergen avoidance in asthma management is a logical choice (Table 3). However, the treatment of allergic asthma and rhinitis always includes pharmacotherapy, which is mainly determined by symptoms and lung function and not by the specific allergies. Because antihistamines and inhaled, nasal and ocular corticosteroids have a very favourable benefit/risk ratio, a case can also be made for an empiric trial of medication as the initial step for patients with a convincing history of allergic rhinitis or asthma, without confirming inhalant allergy by skin prick or sIgE testing. In patients who are comfortable with taking medication, and control of asthma and allergic rhinitis is achieved with low or medium dose of inhaled and nasal corticosteroids, such a pragmatic approach to treatment without allergy diagnosis appears reasonable (Table 3).

Table 3
arguments for and against allergy testing in children with asthma.

Arguments favouring specific allergy testing	Arguments against routine allergy testing
Allergen avoidance measures can be focused on the relevant allergens	Indication of pharmacotherapy irrespective of allergic state
Prevents the application of useless allergen avoidance measures in non-allergic patients	Excellent benefit/risk ratio of pharmacotherapy
Contributes to the identification of possible causes of uncontrolled asthma	Complete avoidance of allergens is impossible
Provides target for specific allergen immunotherapy	Non-allergic stimuli have a significant role in asthma control.

Table 2
allergen specific recommendations to reduce allergen exposure or to reduce respiratory symptoms during exposure.

House-dust mite
- Encase the mattress in an allergen-impermeable cover.
- Encase the pillow in an allergen-impermeable cover or wash it weekly.
- Wash the sheets and duvets/blankets on the patient's bed weekly in hot water. A temperature of >60 °C is necessary for killing house-dust mites. Prolonged exposure to dry heat or freezing can also kill mites but does not remove allergen.
- Reduce indoor humidity to or below 60 percent, ideally between 30 and 50 percent.
- Remove carpets from the home, at least from the bedroom.
- Avoid sleeping or lying on upholstered furniture.
- In children's beds, minimize the number of stuffed toys, and wash them weekly, or put them in a freezer.
- In case of persistent symptoms: consider home visit by dedicated asthma nurse to provide tailored advice about reducing exposure
- In case of expected exposure to high levels of HDM (e.g. school camps with sleeping on old mattresses): take oral antihistamines or SABA in advance.

Animals
- If the patient is allergic to an animal, remove animal from the house.
- If removal of the animal is not acceptable: Keep the pet out of the patient's bedroom. Keep the patient's bedroom door closed. Remove upholstered furniture and carpets from the home, or isolate the pet from these items to the extent possible.
- If the patient is allergic to an animal, don't buy a new pet when the current pet dies.
- In case of expected contact with an animal (e.g. playing with a friend with animals): take oral antihistamines or SABA in advance.
- Cat-allergy and symptoms related to school: take oral antihistamines or SABA in advance.

Pollens
- Start with a nasal steroid 2–4 weeks before the pollination period. Monitor pollen counts online.
- Take oral or ocular antihistamines before going outside. Wear (sun)glasses.
- Keep bedroom windows closed, in particular during periods of peak pollen exposure, usually during the afternoon.
- Undress outside the bedroom, wash hair before going to bed.
- Avoid drying laundry and bed sheets outside during pollination period.

As part of making a shared decision with parents and children about asthma treatment, allergen avoidance should be discussed, including the uncertainty of its effects. In our experience, many parents are willing to take allergen exposure control measures to try and keep the dose of inhaled and nasal steroids as low as possible. Parents obtain information through the Internet about allergen avoidance, including mite-impermeable mattress encasings, high-efficacy vacuum cleaners, and air filter systems. If parents are asked about what information they have sought on the Internet about allergy control measures, they commonly disclose having found conflicting information, and they express concern about the costs of control measures [44]. Showing an interest in the information that parents have collected themselves will contribute to the confidence parents have in the physician, and hence increase the perceived credibility of the physician as a valuable source of reliable information [45]. Physicians can help parents with a reliable allergy diagnosis for their child, preventing parents from taking useless, and potentially costly, interventions aimed at allergens their asthmatic child is not sensitized or allergic to.

For clinicians in outpatient asthma and allergy clinics, therefore, allergen avoidance education is daily practice (Table 2). This should be based on a combination of data from medical history and allergy sensitization tests, as outlined above. Environmental control strategies are tailored to each potentially relevant indoor exposure, based on knowledge of the patient's allergic sensitivities and relevant indoor exposures.

IMMUNOTHERAPY FOR ALLERGIC RHINITIS AND ASTHMA

In patients with uncontrolled allergic rhinitis, despite the use of nasal steroids and oral antihistamines, allergen specific immunotherapy is a potentially useful treatment option [25,33]. The efficacy of subcutaneous and high-dose oral immunotherapy in children with allergic rhinitis has been established for children with grass and tree pollen allergy, and more for children with house dust mite allergy [33,46]. Both subcutaneous and high-dose oral immunotherapy have side-effects, mainly local reactions at the application site. Immunotherapy carries a substantial risk of mild systemic side effects (up to 22% of patients in RCTs). Life-threatening anaphylaxis is rare, and is mainly associated with multiple allergen-therapy and with subcutaneous immunotherapy [SCIT] [1,2]. The benefits and risks of immunotherapy should be carefully discussed with the child's family before treatment is started, and the diagnosis of the clinically relevant allergy to the specific allergen(s) immunotherapy is targeted at should be firmly established. Because immunotherapy requires long-term treatment at home, particularly when prescribed as high-dose oral immunotherapy, specific attention should be paid to patients' adherence toward medication. The communication strategies associated with high adherence to maintenance medication have been described in detail elsewhere [47].

In contrast to the solid evidence base for immunotherapy in allergic rhinitis, high quality evidence for the beneficial effect of allergen specific immunotherapy in childhood asthma is lacking [48–50]. In adults with asthma, only house dust mite sublingual immunotherapy was associated with a robust improvement in clinically relevant end points [49]. This may be the reason that some guidelines, despite the poor quality of evidence, propose immunotherapy as an option to be considered in the treatment of asthma in children when regular daily controller therapy with inhaled corticosteroids with or without long-acting beta agonists fails to control the disease [2,49]. In our view, immunotherapy is only indicated in children with difficult to control asthma if they have comorbid allergic rhinitis and an unambiguous allergy diagnosis based on the patient's history and sensitization.

CONCLUDING REMARKS

In patients with asthma, allergy to inhalant allergens is common and it may significantly affect asthma control. Although a pragmatic approach with a trial of medication for asthma and allergic rhinitis may be applied to children with a high likelihood of inhalant allergy as a relevant contributing factor to the asthma and rhinitis symptoms, we recommend performing inhalant allergy screening testing in children with persistent asthma, because the results of such testing may help determining the extent to which inhalant allergies contribute to asthma and rhinitis symptoms, have consequences for the counselling on allergen avoidance measures, and affect the indication for specific allergy immunotherapy.

DIRECTIONS FOR FUTURE RESEARCH

- Explore the role of allergen component testing in distinguishing clinically relevant from irrelevant (asymptomatic) aeroallergen sensitization
- Study the relationship between the degree of sensitization to aeroallergens and firmly established inhalant allergies in children with asthma
- Explore the relationship between the degree of sensitization to aeroallergens and the effectiveness of allergen exposure reduction measures

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CONFLICT OF INTEREST

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Practice points

Allergy testing in children with asthma:

- In most children with asthma, inhalant allergy contributes to asthma symptoms
- The diagnosis of an inhalant allergy is based on the allergy history and sensitization
- Serum IgE testing and allergy skin testing show comparable results in identifying clinically important sensitizations
- A reliable diagnosis of specific allergies is important to provide the patient and family with effective recommendations about reduction of allergen exposure

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