REVIEW

The Role of Inhalant Allergens in Allergic Airways Disease

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Abstract

Immunoglobulin (Ig) E–mediated sensitization to domestic inhalant allergens (eg, dust mite, cockroach, cat, and dog) is the most important risk factor for asthma. The severity of asthma increases among atopic patients exposed to high levels of sensitizing allergen. In addition, synergism between high allergen exposure and respiratory virus infection increases the risk of asthma exacerbation. However, opinions on the role of allergen avoidance in the management of asthma are diverse, partly because most currently used allergen avoidance measures are usually tested in highly artificial experimental conditions, often with no assessment of their effect on personal inhaled allergen exposure or their clinical effectiveness. While there is little evidence for the clinical benefits of single avoidance measures (eg, bedding encasings, vacuum cleaners, and air filters), multifaceted intervention in carefully selected patients may be of benefit. Until conclusive evidence is available, a pragmatic approach in clinical practice should involve the following: *(a)* interventions tailored to the patient's sensitization and allergen exposure (if exposure cannot be estimated, specific IgE antibody level or the results of skin testing can be used as a marker); *(b)* a multifaceted allergen avoidance regime, based on removal of the accumulating allergen; *(c)* initiation of the intervention as early as possible. Currently, no evidence-based advice on the use of allergen avoidance for prevention of allergic disease can be given; however, it is increasingly clear that no single strategy will be applicable to all children, only to those with specific genetic susceptibility.

Key words: Allergens. Asthma. Allergen avoidance. Dust mite. Cat. Dog. Primary prevention.

Resumen

La sensibilización frente a alérgenos inhalantes domésticos mediada por IgE (ej: ácaros, cucaracha, gato, perro) constituye el factor de riesgo más importante para el asma. La severidad del asma se incrementa en aquellos pacientes atópicos expuestos a niveles elevados de alérgenos sensibilizantes. Además, existe un sinergismo entre la exposición elevada del alérgeno y la infección respiratoria por virus sobre el aumento del riesgo de exacerbaciones asmáticas. Sin embargo, hay una diversidad de opiniones sobre el papel de la evitación del alérgeno en el manejo del asma, en parte, debido al hecho de que las medidas de evitación del alérgeno más comunmentes adoptadas están habitualmente ensayadas en condiciones experimentales altamente artificiales, a menudo sin la valoración de sus efectos sobre la propia exposición a alérgenos inhalados o su efectividad clínica. Mientras existe una pequeña evidencia de los beneficios clínicos de las medidas de evitación individuales (ej: forros de colchón, aspiradores, filtros de aire), la intervención multifacética en pacientes cuidadosamente seleccionados puede ser beneficiosa. Hasta que la evidencia sea concluyente, el acercamiento pragmático en la práctica clínica debería ser guiada de la siguiente manera: (1) Aplicar una intervención a la medida de las sensibilizaciones y a la exposición del alérgeno del paciente (si no es posible estimar la exposición, aplicar el nivel de anticuerpos IgE específicos o el tamaño de la prueba prick como marcadores); (2) Utilizar un régimen de evitación multifacetaria del alérgeno, eliminando la acumulación del alérgeno; (3) Iniciar la intervención tan pronto como sea posible. Hasta el momento, no existe una recomendación basada en la evidencia sobre el uso de la evitación del alérgeno para la prevención de la enfermedad alérgica; sin embargo parece cada vez más claro que no debe aplicarse una única estrategia de forma generalizada a todos los niños, sino únicamente a aquellos con una suceptibilidad genética específica.

Palabras clave: Alérgenos. Asma. Evitación del alérgeno. Ácaros. Gato. Perro. Prevención primaria.

Introduction

NA large body of evidence from epidemiological studies has demonstrated that immunoglobulin (Ig) E–mediated sensitization to inhalant allergens is an important risk factor for asthma [1,2], particularly in childhood and in developed countries. Of note, recent studies from developing countries have reported similar patterns [3,4], with a strong association between asthma and sensitization to the inhalant allergen (dust mite), but not to carbohydrate allergen galactose-α-1,3-galactose [5]. However, although atopic sensitization increases the risk of asthma, most atopic individuals (ie, those producing IgE antibodies towards common inhalant and food allergens) do not have asthma [6]. One of the difficulties when trying to elucidate the role of allergens in asthma arises from the fact that asthma may not be a single disease [7,8], but rather a complex of several diseases with different etiologies and different environmental and genetic risk factors [7,9] that present with the same or similar symptoms [9-14]. In addition, the phenotypic heterogeneity recognized in asthma may also be observed in atopy. The common definition of atopy used in clinical practice and epidemiology (a positive skin prick test result, usually a wheal diameter ≥3 mm; or a positive allergen-specific serum IgE determination, usually >0.35 kU_A/L to common allergens) is based on the presence of allergen-specific IgE and not on symptoms of allergic disease [15]. A number of studies have demonstrated that allergen-specific IgE level and wheal diameter offer more useful clinical information in suspected respiratory allergy than a positive result in an allergy test, both in children [16-18] and in adults [19]. Among young children with a history of wheezing, quantification of atopy may help identify those at increased risk of subsequent persistent asthma [20]. A recent study suggested that atopy can include several different phenotypes, only 1 of which (affecting one-quarter to one-third of children with positive IgE or skin test results) increased the risk of asthma [21], thus providing a novel conceptual framework for understanding inconsistencies in the results of studies investigating the association between allergy and asthma.

Allergen Exposure, Asthma Severity, and Exacerbation

Attempts to identify clinical biomarkers for predicting the risk of severe asthma or asthma exacerbation have failed. Several cross-sectional studies have reported that the severity of asthma increases in sensitized patients who are exposed to high levels of sensitizing allergen [22-28]. For example, variability in bronchial hyperreactivity and peak expiratory flow rate in mite-sensitized asthmatics increases with exposure to mite allergens [22], and patients with severe brittle asthma are more often sensitized and highly exposed than those with mild disease [27]. In the case of atopic asthmatics, indicators of airway inflammation are much higher in those who are exposed than those who are not exposed to the sensitizing allergen [23-26]. Respiratory virus infection (in particular rhinovirus) is considered a major cause of asthma exacerbation [29,30], and potential mechanisms of virus-induced exacerbations have been identified [31]. These data have been interpreted as proof that viral infection, rather than allergen exposure, causes asthma exacerbations. It has also been suggested that persistent respiratory infections play an important role in the development of intrinsic asthma [32]. However, patients are often exposed to both viruses and allergens simultaneously, and it is likely that, rather than being mutually exclusive, viruses and allergens interact in increasing the risk of asthma exacerbation [33]. In sensitized asthmatics, the synergistic effect of high allergen exposure and respiratory virus infection increases the risk of acute severe asthma exacerbations requiring hospital admission, both in adults [34] and in children [35]. A recent study showing that anti-IgE treatment (omalizumab) reduces seasonal exacerbations of asthma during the autumn and spring (presumed to be caused by viral infections) provides further indirect evidence of this interaction between allergens [36]. The question that remains unanswered is whether allergen avoidance programs could reduce virus-induced severe asthma exacerbations, eg, in children admitted to hospital with a proven viral exacerbation of asthma [37]. If so, such a finding would be a major advance in the management of asthma [37].

Allergen Avoidance as a Component of Asthma Treatment

Allergen avoidance plays an important role in the management of patients with allergy, especially food allergy. However, opinions on allergen avoidance are diverse, and recommendations vary considerably depending on the guidelines consulted (for details, please see the recent review by Tovey and Marks [38]). For example, the US National Heart, Lung and Blood Institute Guidelines (http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.html) recommend evaluation and identification of relevant allergens and explicit advice on specific measures to reduce exposure to allergens to which patients are sensitive. In contrast, the Global Initiative for Asthma Guidelines (http://www.ginasthma.org/guidelines-gina-report-global-strategy-for-asthma.html) and British guidelines on the management of asthma (http://www.sign.ac.uk/pdf/sign101.pdf) are more cautious and recommend that measures should be taken to avoid allergens where possible. However, they also note that that avoiding allergens completely is often impractical and restrictive and that simple single measures have limited or no benefit.

The following sections address some of the reasons for such discrepancies and provide a pragmatic approach to allergen avoidance for practicing allergists.

Allergen Control Measures

Knowledge of the aerodynamic characteristics and distribution of different allergens and how and when personal allergen exposure occurs is essential when designing effective methods to reduce personal exposure [39]. The aerodynamic characteristics of the allergen-carrying particles of major inhalant allergens vary considerably [40]: whereas most mite (and cockroach) allergens are carried on relatively large particles (>10 mm in diameter) [41,42], a significant portion of airborne cat allergen [43] and dog allergen [44] is carried on small particles (<5 mm in diameter), thus increasing the likelihood of deposition in the lower airways. Consequently, asthmatic individuals who are sensitized to mite and cockroach rarely appreciate the temporal relationship between exposure to allergens and symptoms, whereas individuals who are allergic to cat or dog usually develop wheezing within minutes of contact with a pet. Furthermore, the fact that exposure to domestic allergens can occur outside the home [45-47] has to be taken into account when designing measures to reduce overall personal allergen exposure. Unfortunately, our understanding of what represents personal exposure does not result from precise measurement of the nature or sources of exposure, but from assumptions and extrapolations [38]. One such assumption (based on the observation that mite allergen concentration is usually high in mattress dust) is that exposure to dust mite allergens occurs predominantly overnight in bed. Another assumption is that the concentrations of allergens in dust collected from reservoirs within the home (eg, mattresses or carpets) or from a static air sampler in the room are good markers of personal exposure. Moreover, the effectiveness of strategies to reduce exposure is measured by proxy, and the assumption is made that, for example, the reduction in the amount of allergen or dust recovered by vacuuming the mattress equates to a similar reduction in personal inhaled allergen exposure.

Most currently recommended allergen avoidance measures were assessed using highly artificial experimental conditions, which were designed to differentiate between consumer products using indirect measures of exposure [38]. Although the effect of most interventions on personal inhaled allergen exposure is unknown [38], products are often advertised directly to patients, with no clinical evidence of their effectiveness. In a recent review on mite allergen avoidance, Tovey and Marks [38] reported that almost one-third of the 50 websites of various asthma foundations and consumer groups promoted proprietary products for allergen avoidance and that some even had their own certification programs. Only 2 websites conveyed uncertainty with respect to the clinical effectiveness of the featured products [38].

Measures for Reducing Exposure to Dust Mite Allergen

As outlined above, the effect of these measures on personal exposure to aeroallergens is mostly unknown. A series of measures for reducing exposure to dust mite allergens in the home are listed below (see reference [39] for a review):

1. Encase mattress, duvet, and pillows with mite allergen–impermeable covers.

2. Wash bedding regularly (a temperature >55°C is needed to kill mites).

Of note, data on the effectiveness of different laundry procedures are lacking.

3. Replace carpet with hard flooring (eg, wood or linoleum).

The effect of removing the carpet on airborne allergens is unknown; factors relevant to particle aerosolization (eg, electrostatic charge, cleaning frequency, and type of floor) may be important.

4. If carpets remain in place, expose them to sunlight, use steam cleaners, use acaricides or tannic acid, and freeze with liquid nitrogen.

All of these methods are only partially effective in reducing reservoir levels; the frequency with which they need to be applied is unknown, and the effect on personal exposure is likely to be minimal.

5. Use vacuum cleaners with built-in high-efficiency particulate arrest (HEPA) filters and double-thickness bags.

Vacuum cleaners do not leak allergens in an experimental chamber [48]. However, when an operator vacuums carpets in a domestic setting while wearing intra-nasal air samplers (which monitor personal exposure), the amount of allergens inhaled during vacuum-cleaning increases [49]. Therefore, based on data obtained solely from experimental chamber studies, it remains unclear whether these vacuum cleaners are safe and effective for allergy sufferers.

6. Control humidity throughout the dwelling [50].

Reducing indoor air humidity does not necessarily reduce humidity in mite microhabitats, which are often deep within the pile of the carpet or the mattress [51]. This approach also depends to a large extent on local climate and housing design [52,53]. The effect of reducing air humidity on the dynamics of airborne particles has received little attention.

A major reduction in dust mite allergen levels in homes can only be achieved by a comprehensive strategy combining the most appropriate measures applicable to individual households and a specific geographical area [54]; simple, single measures are unlikely to be effective. A comprehensive environmental control regime combining a number of the measures listed above has been shown to achieve and maintain low allergen levels in dust reservoirs over a prolonged period [55]; however, its effect on long-term personal aeroallergen exposure is unknown. In addition, mite-sensitive asthmatics are often sensitized to other allergens, raising the question of whether focusing only on 1 allergen is the right approach to allergen control.

Pet Allergen Avoidance Measures

Pet removal is the only way for allergic patients to effectively reduce exposure to domestic pet allergens [39]. Patients should be informed that after removal of a pet from the home, it can take many months for allergen levels in the dust reservoirs to fall [56].

Various measures have been suggested to control pet allergen levels with pets in situ, including the use of high-efficiency vacuum cleaners [57] (see previous section), air cleaning units [58], and pet washing [59].

Air filtration: Air cleaners with HEPA filters can reduce the airborne concentration of cat and dog allergens [58] in homes with pets. However, while measurements under experimental conditions suggest substantial reductions in airborne allergen levels, the results of field studies measuring exposure to inhaled allergen are less convincing [60].

Pet washing: Washing pets reduces allergen levels in fur and dander samples, but the effect is short lived (2-3 days) [61]; it is highly unlikely that a modest reduction in allergen recovered from pet fur translates into a clinical benefit.

Allergen Avoidance: Clinical Studies

Complete absence of exposure to sensitizing allergen usually results in complete remission (eg, patients with seasonal allergic rhinitis and seasonal asthma are asymptomatic outside the pollen season) [62]. However, avoidance of domestic allergens (eg, dust mites and domestic pets) involves several unresolved practical issues, namely, reducing personal inhaled allergen exposure in daily life and identifying patients who can benefit from an effective intervention [62].

Mite Avoidance in Asthma and Rhinitis

The effectiveness of mite impermeable bed covers has been tested in well-designed, large, randomized, double-blind, placebo-controlled trials in asthma [63] and in allergic rhinitis [64]. The findings of both trials demonstrated that a single intervention with encasings was ineffective. In the asthma study [63], post hoc analysis of the subgroup of 130 participants with high mite-specific IgE levels who were exposed to high levels of mite allergen at baseline revealed no differences in outcomes between the active and the placebo groups. In contrast, a small study of 60 mite-sensitized asthmatic children who were exposed to high levels of mite allergen in their beds reported that inhaled corticosteroid use was safely reduced by approximately 50% of patients in the intervention group (polyurethane mattress and pillow encasings); no effect was observed in the control group [65]. These data suggest a differential response to allergen avoidance between adults and children.

A recent update of the Cochrane meta-analysis concluded that current chemical and physical methods aimed at reducing exposure to dust mite allergens cannot be recommended in patients with mite-sensitive asthma [66]. The analysis comprised 54 trials with a total of more than 3000 patients (36 assessed physical methods, 10 chemical methods, and 8 a combination of chemical and physical methods). One plausible explanation for the lack of clinical benefit is that the allergen control measures used did not sufficiently reduce personal aeroallergen exposure.

A Cochrane review of trials analyzing mite avoidance measures in the management of rhinitis carried out in 2011 (9 trials; 501 participants) concluded that most studies published by that date were small and of poor methodological quality, making it difficult to provide definitive recommendations [67].

Pet Avoidance in Asthma

The advice to pet-sensitized pet owners with asthma to remove the pet from the home is based on common sense, rather than on the results of a rigorous trial, since a double-blind, randomized study of pet removal from the home is not feasible. One small nonrandomized, nonblinded observational study indicated that pet removal reduces airway responsiveness more than optimal pharmacotherapy alone in a group of pet-allergic asthmatics [68].

A Cochrane Airways Group systematic review on the effect of cat and dog allergen avoidance with pets in the home emphasized the paucity of evidence and concluded that no meta-analysis was possible [69].

Multifaceted Interventions

Several studies of multifaceted interventions tailored to patients' individual needs provide evidence of improvement in asthma control [70,71]. A large US study by the Inner-City Asthma Study Group adopted a comprehensive environmental intervention [71] in children with poorly controlled asthma and at least 1 positive skin test result. The intervention was tailored to the child's sensitization and exposure status, mattress and pillow encasings and high-filtration vacuum cleaners were supplied to all homes, and HEPA air filters were also provided if necessary. Children in the intervention group had significantly fewer days with asthma symptoms than the controls, and the effect was sustained throughout the 2-year period. A recent study of environmental control using nocturnal temperature–controlled laminar airflow treatment reported that this device (which displaces aeroallergens from the breathing zone by distributing a filtered cooled laminar airflow descending from an overhead position) improves quality of life and reduces airway inflammation in adults and children with atopic asthma [72].

The Role of Allergen Exposure in the Development of Asthma

Our understanding of the role of allergen exposure in the development of sensitization and asthma has changed and evolved over the last 25 years [38,39,73-75]. Allergen exposure was initially considered to be a major factor in the development of both sensitization and asthma in a simple dose-response manner [76], and in utero exposure was thought to prime the T-cell system even before birth [77,78]. However, subsequent evidence has proven that the relationship between allergen exposure and allergen-specific immune responses [79], sensitization, and asthma is much more complex. Although the longitudinal study by Lau et al [80] demonstrated a linear dose-response relationship between early exposure to mite and cat allergens and the development of specific sensitizations during childhood, other studies failed to confirm this finding [81]. In fact, some studies reported that high exposure to cat allergen protected against cat sensitization [54,82,83], suggesting that the dose-response relationship between allergen exposure and sensitization may differ between allergens (for example, it may be linear for dust mite and cockroach and bell-shaped for cat) [84,85]. Only 1 longitudinal study reported a significant relationship between early mite allergen exposure and increased risk of asthma [76], whilst most others did not find such an association [80,81,86].

Simpson et al [87] reported a complex relationship between a genetic variant in *CD14*, exposure to dust mite allergen, and endotoxin, suggesting that although greater mite allergen exposure increased the risk of sensitization, this effect was modulated by endotoxin exposure among children with a specific genotype (CC homozygotes at position on –159 on *CD14*). Consequently, allergen-specific sensitization could be influenced not only by allergen exposure, but also by other environmental exposures (including endotoxin). Genetic predisposition is also very important. The complex interaction between environmental exposure and genotype was recently disussed by Custovic et al [88], who observed the opposite effect of early day care attendance on the development of asthma between children with different variants in the *TLR2* gene. In fact, Bisgaard et al [89] found that cat ownership can increase the risk of eczema in children with filaggrin loss-of-function variants, but not in those without [89]. Extrapolation of these data to the context of allergen avoidance would indicate that the effects of allergen control could vary considerably between individuals with different genetic predispositions, suggesting that only individuals with particular genetic susceptibility can benefit from a specific environmental intervention; the caveat is that the same intervention in individuals with different genetic susceptibility may be harmful [88,90].

The Role of Allergen Avoidance in the Prevention of Asthma

The role of allergen avoidance has been the subject of several review articles [91-94]. It is worth noting that primary prevention studies investigating the effect of allergen avoidance on the development of allergic diseases are long-term by design; consequently, it will take many years to report definitive findings. At least 7 such ongoing studies have published results to date. While all the studies have focused on children at high risk of developing allergic disease, the definition of what constitutes high risk differed between studies. Furthermore, although the interventions started at birth (or before birth), several studies used different environmental control approaches and designs and different definitions of primary outcomes. In addition, the patients assessed were of different ages. Therefore, the results cannot be compared.

The Isle of Wight study reported that at age 8 years, sensitization to house dust mite was reduced by more than 50% in the active intervention group, despite only modest reductions in mite allergen levels [95]. Children in the active group were also significantly less likely to have current wheeze, nocturnal cough, wheeze with bronchial hyperresponsiveness, and atopy [95]. However, the study design made it impossible to determine which part of the intervention program was responsible for the effect. In the Canadian Primary Prevention Study (CaPPS), the prevalence of physician-diagnosed asthma at age 7 years was significantly lower in the intervention group than in the control group (14.9% vs 23.0%) [96], but no difference was observed for allergic rhinitis, eczema, atopy, or bronchial hyperresponsiveness. The Study on the Prevention of Allergy in Children in Europe (SPACE) reported no difference between the control and intervention groups for the prevalence of mite sensitization or allergic diseases (asthma, eczema, and rhinitis) [97] in children at age 2 years. In the Australian Childhood Asthma Prevention Study (CAPS), the prevalence of eczema at age 5 years was higher in the active mite avoidance group (26% vs 19%) [98], although the prevalence of asthma, wheezing, and atopy did not differ between the groups. In the Primary Prevention of Asthma in Children Study (PREVACS) in the Netherlands, at 2 years of age, the intervention group appeared to have fewer asthma-like symptoms, including wheezing, shortness of breath, and nighttime cough, than the control group; however, no significant differences in total and specific IgE were found between the groups [99]. In the Prevention and Incidence of Asthma and Mite Allergy Study (PIAMA) in the Netherlands, early intervention with mite-impermeable mattress covers temporarily reduced the risk of asthma symptoms in early life (at age 2 years); however, at age 8 years there was no reduction in risk of wheeze, hay fever, eczema, or allergic sensitization [100].

The most stringent environmental control regime was applied in the Manchester Asthma and Allergy Intervention Study [54,101]. At age 1 year, slightly more atopy was observed in the intervention group than in the control group (17% vs 14%), although the difference was not statistically significant [102]. Asthma-like symptoms were consistently less severe in the intervention group. This difference was statistically significant for attacks of severe wheeze with shortness of breath, medication prescribed for wheeze attacks, and wheeze after playing or exertion. No difference between the groups was seen for eczema. Counterintuitively, at age 3 years, children in the intervention group were significantly more frequently sensitized to dust mite than controls [103]. However, lung function (assessed by the measurement of specific airway resistance) was markedly and significantly better among children in the intervention group [103].

Conclusions

There is little evidence to support the use of simple physical or chemical methods as single interventions to control dust mite or pet allergen levels (eg, mattress encasings, vacuum cleaning, or air filters). Multifaceted intervention in carefully selected patients could have a positive effect. Until conclusive evidence on the effectiveness of allergen avoidance for all age groups and all allergens is available, a pragmatic approach in the clinical setting should be as follows:

- Interventions should be tailored to the patient's sensitization and estimated allergen exposure.
- If the degree of exposure cannot be estimated, the level of allergen-specific IgE antibodies or the size of the wheal on skin testing can be used as a marker.
- A comprehensive allergen control regime should be implemented to achieve complete cessation of exposure or as great a reduction in exposure as possible; additional domestic interventions to remove accumulating allergen (eg, frequent cleaning and laundry) should be considered.
- The intervention should be started as early possible in the natural history of the disease.

No evidence-based recommendations on allergen avoidance as a means of preventing allergic disease can be provided. Long-term follow-up of ongoing studies is required to ensure that interventions are safe before we can confidently provide practical clinical advice.

It is becoming increasingly clear that no single primary prevention strategy will be applicable to all children, but only to those with a particular susceptibility [90,104]. The future of primary prevention will be based on tailored interventions that target individuals with specific genetic susceptibilities.

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