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The role of environmental allergen control in the management of asthma

Omer Kalayci, MD[a]*, Michael Miligkos, MD[b], César Fireth Pozo Beltrán, MD[c], Zeinab A. El-Sayed, MD, PhD[d], René Maximiliano Gómez, PhD[e], Elham Hossny, MD, PhD[d], Peter Le Souef, MD[f], Antonio Nieto, MD[g], Wanda Phipatanakul, MD[h], Paulo Marcio Pitrez, MD[i], Paraskevi Xepapadaki, MD[j], Wang Jiu-Yao, MD[k,l] and Nikolaos G. Papadopoulos, MD, PhD[j,m]

ABSTRACT

Allergen exposure may exacerbate asthma symptoms in sensitized patients. Allergen reduction or avoidance measures have been widely utilized; however, there is ongoing controversy on the effectiveness of specific allergen control measures in the management of children with asthma. Often, allergen avoidance strategies are not recommended by guidelines because they can be complex or burdensome, although individual patients may benefit. Here we explore the potential for intervention against exposure to the major allergens implicated in asthma (ie, house dust mites, indoor molds, rodents, cockroaches, furry pets, and outdoor molds and pollens), and subsequent effects on asthma symptoms. We critically assess the available evidence regarding the clinical benefits of specific environmental control measures for each allergen. Finally, we underscore the need for standardized and multifaceted approaches in research and real-life settings, which would result in the identification of more personalized and beneficial prevention strategies.

Keywords: Asthma, Allergy, Allergen, Mites, Cockroach, Molds, Children

"Intellectuals solve problems, geniuses prevent them."

Albert Einstein

INTRODUCTION

Allergic diseases, due to their high prevalence and the resulting social and economic consequences and their effect on individual wellbeing, have been a major target for designing preventive strategies.

With respect to and specific for allergic diseases, "primary prevention" means prevention of immunological sensitization or, in other words, preventing the formation of specific IgE antibodies. "Secondary prevention" is prevention of diseases following the development of allergic sensitization. An excellent example for this is prevention of the "atopic march" in an infant with atopic dermatitis, and prevention of allergic rhinitis and asthma. Following the publication of the LEAP study,[1] which demonstrated that early introduction of peanuts prevents the development of peanut allergy in children with atopic dermatitis and egg sensitization, prevention of allergic diseases has assumed a new dimension.[2]

Tertiary prevention is a long-term approach to treatment, producing long-term effects. Every

[a]Pediatric Allergy and Asthma, Hacettepe University, School of Medicine, Ankara, Turkey
*Corresponding author. E-mail: okalayci63@gmail.com
Full list of author information is available at the end of the article

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physician taking care of patients with allergic rhinitis or asthma clearly knows that there are certain patients who exclusively have symptoms during a specific pollen season or only upon contacting a specific allergen, such as cat. Environmental allergen control has not achieved such drastic changes as the experiment of nature mentioned above. At the same time, however, it also suggests that allergen control in the environment, if it can be achieved to the level of perfection, may have a substantial effect on disease symptoms.

Successful environmental control is very difficult to achieve because patients often react to a variety of allergens and other stimuli that are very difficult or impossible to avoid. Therefore, a single intervention is unlikely to lead to major clinical outcomes and the studies regarding the control of asthma symptoms through allergen reduction have produced conflicting results.[3]

This paper reviews the available evidence on the effect of environmental control in the treatment of allergic asthma. The major allergens that are implicated in asthma are covered, including house dust mites, pets, cockroaches, rodents, indoor and outdoor molds, and pollens (Fig. 1). Environmental measures for allergen control are summarized in Table 1.

To facilitate reading, the link between each allergen and asthma outcomes is examined in 4 steps:

1. Clinical evidence showing the link between allergen exposure and asthma symptoms
2. What are possible control measures? Are they effective in decreasing the level of allergen in the environment?
3. Are these measures clinically effective? What are the data?
4. Future perspectives.

HOUSE DUST MITES

The role of House dust mites (HDMs) as a potential indoor allergenic source was identified in 1967[4] and unequivocal evidence has accumulated

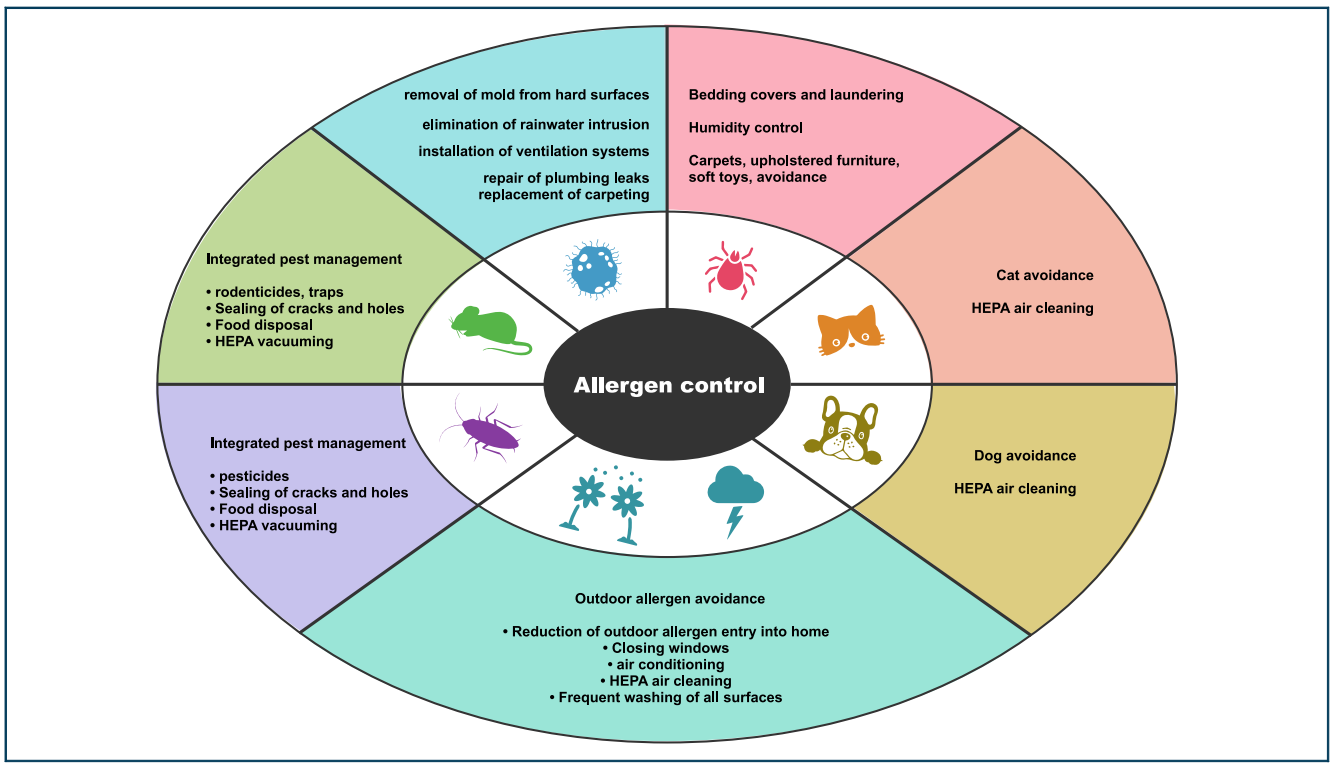

Fig. 1 Allergen control measures

Allergenic Proteins	Dust Mites Der p 1 Der f 1	Cockroach Bla g 1 Bla g 2	Mouse Mus m 1 Mus m 2	Cat Fel d 1	Dog Can f 1	Mold Alt n 1 Asp f 1
Information	• Requires moisture for survival • Feeds off dead skin cells and micro-organisms	• Bla g 1 is in feces • Bla g 2 is an aspartic protease • Infestation associated with inner-cities, low SES, populated areas	• Allergen found in mouse urine, dander, hair follicles • Infestation associated with inner-cities, low SES, populated areas	• Allergen found in saliva, skin and fur • Allergen carried on small particles, remains airborne and adherent to surfaces • After removal, the decline in Fel d 1 is slow	• Allergen found in saliva, fur, and dander • Reservoirs include bedding, furniture, and carpeting	• Wide variety of indoor and outdoor molds • Common indoor molds are *Aspergillus* and *Penicillium* species • Common outdoor molds are *Cladosporium*, *Alternaria*, *Epicoccum* • Depends on moisture for growth
Control Measures	• Encase mattresses, pillows, and box springs • Wash bedding in hot water and dry in high heat every 1–2 weeks • Remove reservoirs such as stuffed toys, carpets, and upholstered furniture • Vacuum carpets with HEPA filtration regularly • Keep indoor humidity levels below 50% → use of a humidity gauge is helpful	• Home extermination of occupant and neighbors, but not effective alone • IPM → combined use of insecticide, professional cleaning, occupant education • Remove reservoirs such as carpeting, bedding, or other areas containing allergen	• Home extermination of occupant and neighbors, but not effective alone • IPM → combined use of insecticide, professional cleaning, occupant education • Remove reservoirs such as carpeting, bedding, or other areas containing allergen • Mouse traps	• First line → removal of cat, followed by cleaning to remove reservoirs If unwilling to remove: • Keep cat out of bedroom • Encase mattress and pillows • HEPA air filter, esp. in the bedroom • Remove carpeting • Cat immersion washing, must be frequent to be effective • No scientific evidence to	• First line → removal of dog, followed by cleaning to remove reservoirs If unwilling to remove: • Keep dog out of bedroom • Encase mattress and pillows • HEPA air filter, esp. in the bedroom • Remove carpeting • Dog immersion washing, must be frequent to be effective • No scientific evidence to	• Use of air conditioner in the summer • Use of dehumidifier in the basement • Repair of leaks • Removal of water-damaged materials • Run vent in bathroom and kitchen • Clean moldy areas with a fungicide → cleaning agents containing hypochlorite are effective

(continued)

Allergenic Proteins	Dust Mites Der p 1 Der f 1	Cockroach Bla g 1 Bla g 2	Mouse Mus m 1 Mus m 2	Cat Fel d 1	Dog Can f 1	Mold Alt n 1 Asp f 1
	• Acaricides, tannic acid and air filters with limited or unproven benefit	• Roach traps • Repair holes in walls and points of entry • Eliminate food sources, wash dirty dishes, cover trash cans, close food containers	• Repair holes in walls and points of entry • Eliminate food sources, wash dirty dishes, cover trash cans, close food containers	support "hypoallergenic" pets	support "hypoallergenic" pets	

Table 1. Environmental control of allergens and mold. *SES: Socioeconomic Status; IPM: Integrated Pest Management; HEPA: High Efficiency Particulate Arrestance*

that demonstrate the role of HDM allergens on the development of and as triggers of symptoms in several allergic diseases.[5] Up to 40%–85% of patients with allergic asthma all over the world are sensitized to HDM and this trend is widely present.[6] The effect of innate immune responses to HDM allergen and airway inflammation has been reviewed in detail.[7,8] Mite allergens may also have a synergistic effect with other triggers of disease such as viral, for example.[9] Additionally, some studies demonstrate a potent tertiary preventive effect when children with asthma are moved to high-altitude settings where the exposure to HDM is negligible.[10]

An effective reduction of the exposure to HDM allergens is based on the following measures.[11,12]

1) The materials used for covering pillows and mattresses: In general, fine woven fabrics with a pore size less than 6–10 µm are appropriate for pillow and mattress covers.[13] All other materials in the bed should be suitable for regular washing with a hot cycle followed by a dryer which can kill virtually all mites. The use of detergent, bleach, and repeated washing may also be critical.[14,15]

2) Humidity control: A relative humidity of 45–50% is generally considered to be the threshold to achieve control.

3) Vacuum cleaners: Vacuum cleaners must be equipped with a high-efficiency particulate air (HEPA) filter. However, they are not able to remove live mites from a carpet. Since vacuum cleaners can disturb room dust, patients are recommended to wear a mask during cleaning and leave the room for 20 min afterwards.[11,16]

4) Room air cleaners: Most types of electrostatic cleaners are not advisable as they produce ozone. The potential role of air conditioning is controversial. Even though theoretically advisable, as it could reduce the environmental humidity and also filter the air, some authors warn about the possibility that its filters can contain relevant amounts of HDM allergens that could be released to the room air.[17]

5) Carpets and upholstered furniture: Many studies have shown that carpet and upholstered supplies are important sources of HDM allergen. Thus, carpets should be kept to a minimum, and if possible,

taken up to be cleaned and dried in the sun. The use of benzyl benzoate/tannic acid has only showed modest and transient effects in reducing mite concentration and the question about their use as a potential prophylactic tool remain unanswered.[18,19] For all other sites of possible mite growth, the general principle is to keep upholstered material to a minimum if humidity cannot be controlled.[11]

It is generally agreed that the greatest clinical benefit would be obtained from a multifaceted and comprehensive approach to HDM avoidance including education about the allergen, implementing strategies like the encasings, removing HDM reservoirs, and more (Table 1). Multifaceted, individualized, home-based, comprehensive avoidance measures have consistently demonstrated a significant reduction of HDM allergens,[20,21] and this correlated with reduced complications of asthma.[21-23] However, maintaining this practice over time is of great importance in achieving success.[22,24]

The real effect of the HDM avoidance measures on clinical outcomes has been controversial. In fact, some meta-analyses concluded that it would be difficult to offer any definitive recommendation because trials are generally small and of poor methodological quality.[25] However, these meta-analyses have been questioned on the basis that this statistical approach would be inappropriate because of difficulties in standardizing multifaceted and personalized allergen avoidance protocols.[11,23] Nevertheless, well-designed randomized controlled trials in children demonstrate the efficacy of avoidance measures on several clinical outcomes.[22,26]

In the future, more efficient HDM avoidance measures may be identified.

Towards this goal, we need to better understand the physical nature of chronic aeroallergen exposure. Clinically more relevant HDM allergens and their potential differential response to specific avoidance measures must be identified. The interactions between allergen exposure, innate immune modulators and other asthma triggers especially viruses at different disease stages should be investigated.

Furthermore, we may be able to identify individuals who would benefit from different avoidance measures. In all cases, large and well-designed trials as well as real-life studies in children will be needed.

INDOOR MOLDS

Fungal exposure can result either from outdoor fungi such as *Alternaria* and *Cladosporium*, while fungi more commonly associated with indoor dampness and water damage include *Penicillium* and *Aspergillus*.[27] "Dampness" is defined as any visible, measurable, or perceived excess moisture in buildings, such as visible mold, leaks, mold odor, or directly measured excess moisture.

Birth cohorts including high-risk infants showed a two-fold increase of infant wheeze and childhood asthma associated with exposure to species of *Penicillium* and *Aspergillus*.[28] In a Swedish birth cohort, exposure to mold or dampness during infancy increased the risk of asthma and rhinitis up to 16 years of age, while early exposure was particularly associated with persistence of asthma through adolescence.[29] In a cohort of Northern Chinese patients, mold sensitivity was positively correlated with increased asthma severity.[30] Data from large cross-sectional studies confirm significant and consistent associations between current mold exposure and wheeze morbidity, irrespective of atopy (OR 1.58; 95% CI 1.4–1.79).[31] A recent systematic review concluded that there is convincing evidence of a causal relationship between indoor mold exposure with the development and exacerbations of asthma in children.[32]

Contrary to reported visible dampness, evidence for a relationship of asthma exacerbations with quantifiable sources of indoor mold is less conclusive. However, a Canadian study showed that high mold levels ($\geq$30 000 CFU/m2) in vacuumed dust samples from indoor play areas and mattresses were significantly associated with current asthma.[33]

Molds at home are also significant determinants of rhinitis, allergic rhinitis, and rhinoconjunctivitis, with associations being strongest with mildew/musty odor.[34] Allergic rhinitis with mold allergy have a greater predisposition for asthma and

high concentration of FeNO.[35] Fungus exposure is also associated with allergic bronchopulmonary mycoses, allergic fungal sinusitis, and hypersensitivity pneumonitis.[27]

Interventions for reducing indoor fungal exposure are integral components of asthma management in sensitized patients. These include removal of mold from hard surfaces, elimination of rainwater intrusion, installation of ventilation systems, and repair of plumbing leaks and water extravasation by sealing cracks and gaps around the foundation, cleaning out exterior guttering, and sloping soil away from the foundation.[36] Caution should be exercised while using chlorine-based bleach products that kill mold spores, due to their potential hazardous effects on lungs. The US National Institute of Occupational Safety and Health (NIOSH) recommends use of an N-95 mask, at minimum, when removing visible mold while the US Environmental Protection Agency (EPA) recommends an experienced contractor for mold removal (https://www.epa.gov/mold/mold-cleanup-your-home). To minimize fungal spore transportation indoors, the use of a central heating, ventilation, and air conditioning (HVAC) system is recommended. Extensively mold-contaminated building materials should be replaced. Even though frequent vacuuming can reduce fungal spore levels in the dust, replacement of carpeting with other types of flooring appears to be more effective.[37]

It has been consistently shown that interventions used in homes significantly decrease the levels of fungi up to 75%.[38] Adgate et al demonstrated a significant decrease in fungi spores following simple cleaning and education interventions that was comparable to expensive, difficult- to –sustain allergen control maneuvers.[39] In parallel, a significant decrease in HDM levels was also observed which was attributed to the lower humidity.[40]

Regarding the effect of the above measures on asthma symptoms, an earlier study evaluated a multifaceted approach for reduction of fungal levels over a period of 12 months in the homes of children with a history of troublesome asthma. The study showed a significant increase in asthma symptom free days (SFDs) and a lower incidence of exacerbations compared to controls.[41] Of importance, these effects were attributed solely to the reduction of fungal allergen exposure. In line with this, increased ventilation and decreased mold were associated with improvements in asthma outcomes and medication use in adults.[42] Subsequent interventional studies on fungi reduction failed to show a strong beneficial effect on allergy-associated outcomes. However, a Cochrane systematic review combining 12 studies with more than 8000 participants concluded that measures aiming at reducing fungal exposure result in less asthma-related symptoms and respiratory infections in adults. Such interventions at school environments were associated with significantly fewer emergency visits for respiratory symptoms in children, although data were of low quality.[43] In a wider context, a randomized controlled trial in children with atopic asthma that investigated the effect of multifaceted environmental interventions for reducing several allergens including mold as well as tobacco smoke exposure at home, showed significant declines in dust mite and cockroach levels and subsequently reduced asthma morbidity.[22] From another perspective, when children with asthma were moved into an "Easy Breath Home", designed with structural characteristics that prevent moisture accumulation, a significant decrease in asthma symptom days and acute healthcare utilization was observed after 12 months.[44]

To design effective strategies that aim at reducing health effects related to fungi, it is essential to standardize the methods used to measure exposure to fungal allergens, since it is well accepted that airborne spore counts correlate very poorly with fungal allergens in settled dust. Specific control measures should consistently be used in studies for data to be comparable. Improved and standardized reagents for testing sensitization to fungi are essential, since currently used extracts show differences as they derive from highly diverse source materials and some include germinating spores that release allergens prone to proteolytic degradation. Finally, studies assessing the sole impact of fungal exposure on asthma and rhinitis morbidity, excluding the concurrent decrease of other substances, such as dust mites,

cockroach, endotoxins, and non-allergenic fungal products, are awaited.

RODENTS

Mouse allergen is ubiquitous and more prevalent in urban environments, with multiple studies identifying up to 95% of homes and apartments affected in the United States, whereas the estimated respective proportion in Europe and Central America is around 50–60%.[45–48] While often co-existing with cockroach,[45] evidence suggests that in some cities, mouse allergen is the major allergen in urban cities.[49–51] Moreover, a nationally representative survey of homes in the United States found detectable levels of mouse allergen in 82% of homes;[52] mouse allergen was also prevalent in homes of suburban, middle-class children with asthma.[53] Mouse sensitization and exposure has been associated with increased acute care visits and decreased FEV1/FVC percentage values, independent of cockroach allergen,[49] and at-risk school aged children demonstrate higher asthma severity scores and require higher treatment steps.[54] Sensitized and exposed preschool children to Mus m 1 levels greater than 0.5 μg/g had 50% more asthma symptom days, 80% more days of β-agonist use, and more health care related visits.[55] While less prevalent than mouse allergen, rat allergen was found in 33% of inner-city homes and sensitized and exposed urban children to rat allergen have increased number of hospitalizations and medical visits as well as more days with slowed activity due to asthma.[56] While most of these studies have focused on homes and highlighted its importance, the School Inner-City Asthma study[57] focused on comprehensively identifying school/classroom exposure risk factors for asthma morbidity, adjusting for exposure at home. This prospective study found that students had exposure to higher levels of mouse allergen in their classrooms than homes[58] and this exposure was linked to a dose-response relationship with increased asthma symptoms and decreased lung function, independent of allergic sensitization and home exposure.[59]

Reduction of rodent allergens is most successful through integrated pest management (IPM). IPM includes: removal of factors, such as food, that lead to rodent infestation; thorough cleaning; blocking pathways of rodent entry; and removal of rodents using traps and rodenticides.[60] The IPM approaches have been found effective in reducing allergen levels.[61]

A randomized controlled trial in a subset of patients from the Inner-City Asthma Study evaluating the effectiveness of a rodent-specific environmental intervention demonstrated that reducing bedroom floor mouse allergen levels led to less missed school, sleep disruption, and caretaker burden; however, the study was not powered to detect a statistically significant change in symptoms or medical utilization.[62] In New York City, a multi-trigger intervention approach targeted towards dust mites, furry animals, mold, and pests reduced exposures. Dust mites, mouse, and cockroach allergens were also reduced in the control homes. Overall, the study did not demonstrate a reduction in the primary outcome of treatment step requirement, except in those where mouse allergen levels were reduced, regardless of treatment arm.[63] The Mouse Allergen and Asthma Intervention Trial (MAAIT) randomized 361 mouse sensitized and exposed children and adolescents with asthma to receive IPM plus pest management education or pest management education alone and found no significant difference in maximal symptom days between the 2 groups. However, both treatment and control groups had substantial reductions in mouse allergen levels. In this study, a 90% reduction in mouse allergen level, regardless of treatment arm, was associated with 0.8 fewer acute care visits and 0.07 fewer hospitalizations per person-year.[64] These reductions in morbidity are similar to what has been seen in the Childhood Asthma Management Program using inhaled corticosteroids.[65] The MAAIT study also demonstrated that children who had 75% reduction in mouse allergen exposure have a significantly larger projection in lung growth, suggesting that environment intervention may provide long-lasting benefit.[66]

Interventions against rodent allergens appear effective in reducing exposure, although sometimes there are different health effects depending on how the intervention arm compares to control. Most of the work has focused on homes. Furthering our understanding of risk factors and

comprehensively understanding the complexities of the microbiome and its impact on the mix of exposures from those sensitized are needed. Work on areas outside of the home, such as schools, are needed. Results of a school-based environmental IPM and HEPA filter study recently identified that school IPM reduced asthma symptoms by 63% compared to control, but only in the early fall/winter during the season of peak exacerbations and the benefit was not sustained. Classroom HEPA filters were successful in significantly reducing airborne particles and allergens compared to sham (an air filtration system without a filter), but this reduction was not enough to improve health. Further work to sustain benefit and comprehensively support improvements in home, school, and other environments, while costly, may be needed.[67]

COCKROACH

Over 2 decades ago, the National Cooperative Inner City Asthma Study (NCICAS) identified that cockroach allergen was highly prevalent in urban homes,[68] particularly among those with highly dense population, lower socioeconomic status, less maternal education, and black or Hispanic race/ethnicity.[69] Almost half of the low-income urban homes have detectable levels of cockroach allergen. Cockroach exposure, particularly exposure to Bla g 1 levels greater than 1 U/g in the kitchen, is associated with increased cockroach sensitization and asthma morbidity, while levels more than 2 U/g were detected in 15% of kitchen floor in US homes.[68,70,71] This study highlighted the importance of unique exposures in home environments in urban children with asthma and stemmed a line of investigation in this area, confirming the importance of sensitization and exposure to cockroach in contributing to more hospitalizations and unscheduled medical visits for asthma[72] and decline in lung function.[73] Of importance, sensitization to cockroach has been reported in as high as 60–80% of asthmatic children living in urban areas, while respective rates in suburban population was 21%.[70,74] Nevertheless, data from certain populations challenge the importance of sensitization/exposure to cockroach as opposed to mouse allergen.[49] While less common, cockroach allergen was also shown to be prevalent in suburban middle-class homes.[70]

Cockroach allergen reduction measures include: blocking means of entry; eliminating sources of food, water, and shelter; eliminating contaminant sources through traps and insecticides; and eliminating reservoirs through HEPA vacuuming and mattress covers.[75] The most effective intervention, however, is the professional-led intervention, resulting in 80–90% reduction of cockroach exposure.[76] Intervention studies to reduce cockroach have had mixed results. A randomized trial compared occupant education, insecticide bait application, and extensive professional cleaning to no intervention and demonstrated significant reductions in cockroach levels in the intervention group after 6 months.[77] This reduction in cockroach allergen was maintained at 12 months with application of insecticide bait, and control homes treated with insecticide bait alone at month 6 also achieved significant reductions in levels of cockroach.[78] A subsequent three-arm, randomized trial compared placement of insecticide baits by entomologists, commercial pest control, and no intervention in 60 cockroach-infested homes in North Carolina and found significant reductions in Bla g 1 only in those homes treated by professional entomologists.[79] Currently, the use of gel bait insecticides, fipronil or indoxacarb based, has been shown to be the most effective intervention, while sprays should be avoided. The engagement of a pest professional is indicated.[36]

Environmental interventions aimed at decreasing cockroach allergen-associated morbidity have been mixed. The multi-faceted Inner-City Asthma Study (ICAS) intervention by Morgan et al showed that targeting cockroach and dust mite exposure reduced asthma symptoms during the 1-year intervention that persisted even 1 year after the intervention stopped.[22] A substudy of the NCICAS compared professional home extermination with insecticide and education on cockroach allergen removal with a control group and found that there was no significant change between the groups[80] with difficulty in achieving lasting reductions in exposure. Eggleston et al investigated the effects of a comprehensive intervention including home-based education, cockroach and rodent extermination, mattress and pillow encasings, and HEPA filter in a randomized controlled trial. The study

demonstrated significant reductions in $PM_{2.5}$ and PM_{10} levels as well as daytime asthma symptoms; however, there were no significant changes in lung function tests, nighttime symptoms, or emergency department use.[81] A recent unblinded, randomized controlled trial of children in New Orleans evaluated the effectiveness of insecticide bait in homes with cockroaches. Cockroaches were eliminated in homes with insecticidal bait leading to significantly reduced asthma morbidity in children residing in these homes.[76] Of importance, a substantial clinical benefit resulting from reduction in cockroach levels has also been reported in exposed but not sensitized asthmatic children, although to a lesser extent. On the other hand, in a randomized controlled trial of inner city adults and children, environmental control measures decreased significantly the levels of indoor allergens including cockroach, but these measures did not provide any additional benefit on asthma controller medication use compared to the control group.[63] The limitation of this study is that reductions on cockroach allergens were similar in the intervention and control group, potentially resulting in minimal changes in asthma control.

While home environmental interventions have had some success, there have been mixed results overall. Interventions in the school environment have the potential to significantly impact the health of children on a wider, community-based level. Furthering our understanding of the community risk factors is necessary. Ongoing research is needed to determine the effectiveness of intervention in other areas such as school, day cares and work areas in improving asthma morbidity. Our understanding in these areas will help inform future public health policy and strategies to help us care for children vulnerable to these exposures.

CAT

Early cat exposure as an inducer of asthma development is still a matter of debate. Some studies have shown that the exposure to cat's epithelium increases risk of asthma in a dose-dependent manner while others report protective effects of early exposure to pets for asthma or wheezing.[82,83]

However, once asthma is established and sensitization confirmed, substantial evidence correlating cat exposure and asthma morbidity is available. Both sensitization rate and asthma symptoms have been correlated with environmental levels of Fel d1, the major cat allergen. Indeed, no direct exposure seems to be necessary; even indirect exposure in public places or at school demonstrated a significant impact on asthma symptoms.[84,85]

Several studies, mainly in adults, have investigated the direct impact of cat allergen exposure on asthma symptoms, using different challenge techniques.[86–89] In general, cat allergen challenges produced both clinical and biomarker responses, suggesting a potential implication of cat exposure in asthma morbidity.[90,91]

The general current approach is avoidance, ie, taking the cat away from home. The most effective long-term strategy described is to remove the pet from the house; however, once removed it may take months (20–24 weeks) to significantly reduce allergen levels.[92] Studies in asthma have shown that removing pets result in a significant reduction of inhaled corticosteroid consumption.[93]

A major challenge is that exposure in public places, contact with pet owners, or even at school may result in symptoms, as cat allergenes can be found anywhere.[94] In order to support advice given to parents of asthmatic children with cat sensitization, a detailed evaluation of continuous exposure and a well-documented positive correlation with asthma symptoms or exacerbations is required.

The efficiency of reducing airborne cat allergens with the use of HEPA air cleaner was investigated, with positive results.[95] Nonetheless, its practicality and accessibility is debatable, particularly in developing regions.

The effect of bathing the pet regularly, frequent changing and washing clothes and indoor cleaning measures are questionable.[96] More recently, reducing the major cat allergen (Fel d 1) by a specific neutralizing antibody (anti Fel d 1 IgY) in cat's food, has shown promising results in decreasing exposure load and subsequent

allergic symptoms, but its usefulness on allergic asthmatic patients is still unknown.[97]

Due to the lack of robust and conclusive data about the preventive effect on allergy sensitization and associated asthma development, recommendations on avoidance or early exposure cannot be made with certainty. However, when sensitization and diagnosed asthma are present, all the possibilities on avoidance might be discussed with parents and/or care givers. Recommendations should be personalized, and multifactorial aspects must be considered in each case. Careful follow-up on both direct and indirect exposure and its morbidity correlation needs to be taken.[98]

DOG

Dogs are an important source of indoor allergens that may cause rhinoconjunctivitis, urticaria, and asthma. A population-based study concluded that early exposure to dogs and/or cats is associated with a higher incidence of respective pet allergy during the first 4 years of life.[99] About 44.2% of asthma exacerbations were attributable to the presence of high levels of dog allergens in the bedrooms of dog-sensitive patients.[90] In school and daycare settings, dog and cat allergen prevailed in carpeted and upholstered areas and this was associated with increased asthma morbidity.[100] A cross-sectional study reported that dog ownership is associated with reduced pulmonary function tests without an increased risk of asthma due to exposure to endotoxins abundant in houses of dog owners.[86] Dog and cat allergens are assumed to enhance endotoxin-induced asthma and wheeze.[101]

On the other hand, dog ownership during the first year of life reduced the risk of dog allergy, whereas dog-keeping thereafter had no effect on allergic symptoms.[102] The prevalence of allergic disease in children aged 7–9 years was reduced in a dose-dependent fashion with the number of household dogs and cats during their first year of life,.[103]

It is not always clear whether sensitization to dog allergen points to clinical relevance.[104] A significant percentage of individuals sensitized to dog allergens on skin prick testing do not develop respiratory symptoms after direct dog contact.

Using crude dog dander extract has several limitations due to variation of allergen content and cross-reactivity with allergens from other furry animals.[105,106] In addition, inconsistent and contaminated extracts may conversely identify sensitization to the contaminants.[94] Therefore, nasal provocation tests might clarify the clinical relevance of sensitization.[107] However, they are not well standardized and allergen content is liable to variability.[104]

Identification of distinct dog allergens (Can f 1–7) has improved the diagnostic approach for sensitized patients. Can f 1 showed a higher positive predictive value for dog allergy at 16 years of age than crude dog extract. Can f 5 is an androgen-regulated protein expressed in the prostate and therefore detectable only in male dogs.[108] Can f 5 is a risk factor for human seminal plasma allergy, potentially inducing generalized/anaphylactic reactions in adults.[107]

Although in case of a proven exposure-symptom relationship, the most advisable measure would be to avoid the animal, this is often impossible and associated with a major emotional impact. Furthermore, indirect exposure occurs in apparently pet-free environments. Immunotherapy is emerging as a potential solution, especially if patient education, allergen avoidance, and pharmacotherapy do not efficiently control the symptoms.[109] Benefits of immunotherapy with current crude dog extract are limited.[94] Exploring many clinical aspects such as mono or poly-sensitization and induction of symptoms after exposure should precede prescribing dog allergen immunotherapy. Moreover, detailed information on the possible exposures to other furry animals is mandatory – a procedure commonly neglected in clinical practice. The use of component resolved diagnostics (CRD) could potentially verify the presence of concomitant allergic sensitization to lipocalins and/or albumins belonging to other furry animals.[110]

The concept of "hypoallergenic dog breeds" has been used to market dogs proposed to be less allergenic.[94] The amount of shedding and length of hair were assumed to be influential. However, published data revealed that the levels of

allergen Can f 1 in the hair and coat of dogs as well as floor and airborne dust were comparable between breeds thought to be "hypoallergenic" (Labradoodle, Poodle, Spanish Water Dog, and Airedale Terrier) and those considered non-hypoallergenic.[111]

Molecular-based allergy diagnostics would help in determining primary sensitization to dog allergens and overcome the problem of cross-reactivity. Since dog allergic individuals are not all exclusively allergic to Can f 1, combinations of the appropriate component allergens will be required for optimal therapeutic interventions.[94] In children, multisensitization to dog allergens, particularly to lipocalins, indicates clinically relevant dog allergy and monosensitization to Can f 5 should not be regarded primarily as a marker for dog allergy. Indeed, high-quality randomized controlled trials of allergen immunotherapy are warranted.

OUTDOOR ALLERGENS – POLLENS AND MOLDS

Abundant evidence has linked outdoor allergen exposure to asthma symptoms. Levels of outdoor tree and grass pollens and fungal spores have been associated with increased allergic illnesses including asthma in the community.[112] The likelihood that this relationship is causal in children is further evidenced by pollen levels being directly associated with both emergency department visits for asthma[113] and prescriptions for anti-allergy medications.[114] Although the seasonal nature of asthma coincides with increases in both pollen levels[115] and rhinovirus infections[116] among children with a rhinovirus infection, those with evidence of allergy experience more severe asthma exacerbations than non-allergic children.[116]

Thunderstorm asthma is relatively rare, but it is responsible for sudden increases in acute severe asthma exacerbations that can overwhelm both adult and pediatric emergency departments.[117] Recent research has shown that grass pollens are the main factor responsible, most likely by triggering rupture of pollen grains, each releasing hundreds of starch granules that are both toxic and small enough (<3 μm) to penetrate and disrupt small airways.[117]

Inhalation of outdoor fungal spores, especially *Alternaria* and *Cladosporium*, has been implicated as a cause of acute asthma admissions in children, but this relationship is still unclear due in part to the lack of routine collection of atmospheric fungal data.[118] Fungi, *Alternaria* in particular, may contribute to thunderstorm asthma, but their role is not well established.[117] A role for mycotoxins as a cause of chronic respiratory or systemic disease has been suggested, but this possibility is not supported by sufficient reliable, non-anecdotal, scientific evidence,[119] especially for outdoor molds.

Control of the levels of outdoor pollens and fungi themselves would be excessively difficult, but exposure can be reduced by spending less time outdoors particularly when counts are high and in the morning.[120] The incursion of outdoor allergens into the indoor environment can be reduced by closing windows, air conditioning, and the use of high-efficiency particulate arrestor filters and frequent washing of all surfaces.[120] Of note, major reductions in allergy symptoms have been noticed during the lockdown, to a large extent attributable to masks,[121] an approach that could be utilized by the allergic patient on specific occasions.

Outdoor allergen avoidance is accepted as a sensible approach to improving clinical outcomes for those with seasonal allergic asthma and obviously is likely to be important for thunderstorm asthma, but the clinical efficacy of this approach to avoidance has not been proven, except in the context of people with seasonal sensitizations having no symptoms outside their respective season. Nevertheless, a recent meta-analysis concluded that there was insufficient evidence to show that avoiding exposure to outdoor allergens was clinically effective.[122] Preventing outdoor allergens from entering the house of allergic asthmatic children also makes sense, but there is little if any evidence for the clinically efficacy of this approach.

Further studies are required to assess the possible clinical benefit of outdoor allergen avoidance, but these will be difficult and expensive to undertake on the necessary scale. The need for these studies is underlined by the likelihood that the relationship between pollens and asthma in

children will intensify in the future with climate change, as pollens linked to heat and humidity are expected to increase globally.[123] In addition, improved measures at both the personal and community levels need to be evaluated. For instance, in 2018, the American Academy of Allergy, Asthma and Immunology (AAAAI) proposed a criterion-based algorithm for the selection of the most appropriate, low-allergenic plants for the allergic patient.[124]

CONCLUSION

While in principle allergen avoidance can be considered as a cornerstone for attenuating clinical symptoms of allergy, in practice, allergen avoidance is challenging, as it requires labour-intensive approaches and often major lifestyle changes. Nevertheless, there is mounting evidence that, if achieved, reduced exposure to allergens in sensitized patients may have tangible clinical benefits. In some cases, such as indoor molds, the impact may extend to non-sensitized individuals as well. The identification and subsequent design of "healthy" environments remain a challenge, particularly public places such as schools. We are now well-aware that excessive avoidance and lack of exposure may increase rather than decrease the risk for allergic sensitization; furthermore, specific immune responses may vary between individuals and communities. Based on such understanding, extensive research efforts are needed to identify and describe balanced environments in which exposures allow the development of tolerance, while avoiding sensitizing, toxic, and other adverse effects.

Abbreviations

LEAP, Learning Early About Peanut Allergy; HDM, House dust mite; HEPA, High-efficiency particulate air; FeNO, Fractional exhaled nitric oxide; NIOSH, National Institute of Occupational Safety and Health; EPA, Environmental Protection Agency; HVAC, Heating, ventilation, and air conditioning; SFD, Symptom free days; IPM, Integrated pest management; MAAIT, Mouse Allergen and Asthma Intervention Trial; NCICAS, National Cooperative Inner City Asthma Study; ICAS, Inner-City Asthma Study; CRD, Component-resolved diagnostics.

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Author details

[a]Pediatric Allergy and Asthma, Hacettepe University, School of Medicine, Ankara, Turkey. [b]First Department of Pediatrics, "Aghia Sophia" Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece. [c]Alergia e Inmunología Clínica Pediátrica, Hospital Infantil de México Federico Gómez, Mexico. [d]Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University, Cairo, Egypt. [e]School of Health Sciences, Catholic University of Salta, Argentina. [f]School of Paediatrics & Child Health, Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Crawley, WA, Australia. [g]Pediatric Pulmonology & Allergy Unit. Health Research Institute. Children's Hospital La Fe, Valencia, Spain. [h]Pediatric Allergy and Immunology, Boston Children's Hospital, Boston, MA, USA. [i]School of Medicine, Pediatric Pulmonary Division, Hospital Moinhos de Vento, Porto Alegre, Brazil. [j]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece. [k]Department of Allergy and Immunology, Children's Hospital, China Medical University, Taichung, Taiwan. [l]Department of Pediatrics, National Cheng Kung University Hospital, Tainan, Taiwan. [m]Division of Infection, Inflammation & Respiratory Medicine, The University of Manchester, Manchester, UK.

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