# The role of allergens in asthma and allergic rhinitis

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**Respiratory allergy manifested as asthma and allergic rhinitis is commonly encountered in clinical medicine. The identification of relevant inhalant allergens with subsequent allergen avoidance and specific immunotherapy in selected patients is an important part of the management of respiratory allergic disorders. This article presents an overview of the relationship between allergen sensitisation and clinical manifestations, the relevant inhalant allergens and their avoidance, and the effectiveness of allergen-specific immunotherapy.**

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## The epidemiology of asthma and allergic rhinitis

Asthma and allergic rhinitis rank among the most common health problems. Data from the United States show that in 1990, there were more than 10 million asthmatics and the cost of illness related to asthma was estimated to be US$6.2 billion (HK$48.4 billion), while reduced productivity represented the largest single indirect cost, approaching US$1 billion (HK$7.8 billion).[1] In 1975, allergic rhinitis caused 2 million lost school days, 6 million bedridden days, and up to US$500 million (HK$3.9 billion) in medical expenses. Asthma affected around 1.4 million Australians in 1991, with the total cost to the community estimated to be in the range of A$585 to A$720 million (HK$3.3 to HK$4.03 billion).[2]

Asthma and allergic disease in both adults and children has been increasing in many Western and developing countries in recent years.[3,4] Compared with its neighbours, Hong Kong has one of the highest prevalence rates for asthma and allergic disease in schoolchildren.[5,6] Using identical methods, schoolchildren in various Asian countries with mean ages of 14 to 16 years, were studied in 1992. We found that the prevalence rates for asthma, hayfever, and eczema (6.6%, 15.7%, 20.1%, respectively) were highest in Hong Kong, intermediate in Kota Kinabalu, Malaysia (3.3%, 11.2%, 7.6% prevalences, respectively), and lowest in San Bu, Guangzhou, China (1.6%, 2.1%, 7.2% prevalences, respectively).[5] In 1989 and again in 1994, 1610 secondary school students and 1573 university students were studied and a significant increase in the prevalence of recent wheeze from 4.6% to 7.6%, diagnosed asthma from 4.8% to 7.2%, eczema from 17% to 32%, rhinitis from 24% to 38%, were also noted.[6] This parallel increase in asthma, allergic rhinitis, and eczema suggests a broadly-based increase in allergic disease, presumably due to increased exposure to allergens and other environmental factors.

## Inhalant allergens in asthma and allergic rhinitis

### *House dust mites*

The house dust mite (*Dermatophagoides pteronyssinus*) is the most prevalent indoor allergen and has been linked with asthma, bronchial hyperreactivity, and allergic rhinitis in many countries.[7-10] Its major allergen, *Der p* 1, is present in the faecal pellets and is often found in carpet and mattress dust. The activity, distribution, and growth of mites is dominated by the need to maintain body water, and an indoor absolute humidity of 7 g of water vapour/kg of dry air is believed to be critical for mite growth.[11] Recent changes in housing styles in many Western countries may have led to conditions which favour increased allergen levels. Houses tend to have less ventilation, making them more humid, and there has been widespread introduction of carpeted floors which provide an ideal habitat for mites.

The perennially high humidity and warm temperatures in many parts of southeast Asia also favour mite growth. In Hong Kong, dust mite sensitivity is present

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in 55.5% of schoolchildren and is the commonest allergen to which atopic schoolchildren are sensitised.[5,12] Mite allergy is strongly associated with bronchial asthma. All of a group of 90 adults[13] and 78.9% of children[14] with extrinsic asthma reacted to *D. pteronyssinus* extract. Gabriel et al identified large numbers of dust mites in dust samples collected from quilts, pillows, and blankets in the homes of 20 patients with mite-sensitive rhinitis.[15] In another study, young adults who were bronchially hyperresponsive to inhaled histamine, a hallmark of asthma, were found to have higher levels of specific IgE to dust mite than did controls.[16]

### *Moulds*

Mould spores are prevalent indoor and outdoor aeroallergens, which have been suspected of causing respiratory allergies since as early as 1873. Epidemics of bronchial asthma have been associated with high concentrations of mould spores[17] and sensitisation to *Alternaria* spp. has been associated with a 200-fold increase in the risk of respiratory arrest in children and young adults with asthma.[18] In Hong Kong, the predominant indoor moulds identified on settled plates, in descending order of abundance, are *Cladosporium*, *Penicillium*, *Aspergillus*, and *Alternaria* spp. (C Lam, personal communication). Sensitisation to various species of house mould is present in 23.4% of Hong Kong schoolchildren.[12]

### *Cockroaches*

Cockroaches were first recognised as an indoor allergen in the 1960s and have since been associated with inhalant allergy.[19] Sensitisation to cockroaches causing occupational allergy among laboratory workers has also been reported.[20] Cockroach hypersensitivity is frequently encountered in crowded, multi-family dwellings with heavy infestation. Twenty-six and 36% of unselected schoolchildren in Hong Kong and southern China, respectively,[5] and approximately half of the urban atopic population with asthma and allergic rhinitis in Taiwan had positive skin reactions to cockroach extracts.[21] The combination of sensitisation and exposure to cockroach and other indoor allergens is a major risk factor for asthma, particularly among lower income populations, which have the highest hospital admission rates and mortality for asthma.[22]

### *Domestic pets*

Cats are popular pets in Western countries and at least one cat is found in 28% of homes in the United States.[23] The reported prevalence of sensitisation to cat allergen is variable, but it is at least 2% of the general population and up to 50% of asthmatic children.[24] Clinically, the most important cat allergen, *Fel d* 1, is located in the salivary gland and the pelt of a cat. This allergen has been detected in carpet dust of houses where cats have never been present, suggesting it can be carried into cat-free buildings on the clothing of people exposed to cats.[25] Sensitisation to cat dander at the age of 3 years has been found to be an independent risk factor for the development of asthma at the age of 13.[26] Dogs are common domestic pets and dog allergens have been detected in up to 60% of homes in the Baltimore area.[27] A positive skin test to dog dander was found in 14% of a random sample of Finnish adolescents[28] and 40% of asthmatic children.[29] The main sources of dog allergens are found in the hair and dander. Cross-reactivity between dog and cat allergens has been shown, suggesting the presence of identical immunological determinants in both allergens.

### *Pollen*

Pollen grains of rye, couch, and other temperate zone pasture grasses are common outdoor allergens in spring and summer and are frequently associated with seasonal rhinitis and asthma in Australia and the West Coast of the United States. Various species of ragweeds (*Ambrosia* spp.) are distributed throughout different parts of North America and contribute significantly to morbidity associated with pollinosis there. Increased exposure to pollen allergens during the pollen season has been shown to increase bronchial hyperresponsiveness and asthma symptoms in pollen-sensitive subjects. Rye grass pollen can precipitate acute asthma in sensitive subjects by releasing large quantities of major pollen grain allergens, which rupture osmotically on encountering rainwater during the pollen season.[30] Allergic rhintis has also been associated with sagebrush (*Artemisia* spp.) pollen in Beijing, castor bean, and plane tree (*Platinus* spp.) pollen in Shanghai.[31]

## The relationship between allergen exposure and allergic disease

There is a spectrum of sensitivity to environmental allergens in any population, ranging from those who do not become sensitised irrespective of the level and duration of exposure, to those who show extensive sensitisation to low levels of multiple allergens. This ability to respond to allergens, or atopic tendency, is genetically determined. There are two stages to the development of asthma and allergic rhinitis in predisposed individuals: there must be sufficient aeroallergen exposure to cause sensitisation; and continued aeroallergen exposure of a sensitised individual is needed to give rise to clinical manifestations.

### *Exposure and sensitisation*

There is increasing evidence to suggest that sensitisation to allergens is dose-dependent among genetically predisposed individuals. Charpin et al found the prevalence of positive skin prick tests to house dust mites to be 27.5% in Marseilles, a Mediterranean city where mite allergen level is high (15.8 μg of *Der p* 1/g of dust), compared with 10.2% in Briancon, an alpine city located at an altitude of 1350 m, where mite allergen level is low (0.36 μg of *Der p* 1/g of dust).[32] The concept of threshold levels for indoor allergens has been developed in recent years to indicate significant exposure. It was proposed by an International Workshop on dust mites that exposure to ≥2 μg of *Der p* 1/g of dust (equivalent to 100 mites/g of dust) is a risk factor for sensitisation to dust mite and that exposure to ≥10 μg of *Der p* 1/g of dust (equivalent to 500 mites/g of dust) increases the risk for overt allergy.[33] The threshold risk levels of exposure to major allergens of cat and cockroach for sensitisation and asthma have not yet been as well defined.

### *Sensitisation and clinical allergy*

Peat et al[34] studied 3581 schoolchildren in different climatic areas of New South Wales, Australia, and found that sensitisation to one or more aeroallergens was significantly associated with recent asthma, hay fever, eczema, and bronchial hyperreactivity. Among the indoor and outdoor allergens, sensitivity to house dust mite had the strongest independent association with current asthma in all areas. Case-controlled studies in the United States found that adults who presented to the emergency room with acute attacks of asthma, had specific IgE antibody levels to one or more inhalants (dust mite, cat, cockroach, grass pollen, and ragweed pollen) that were 4 to 20 times those of non-asthmatic controls.[22]

In a prospective study of 67 children aged from 1 to 11 years in England, Sporik et al found a trend towards increasing sensitisation at age 11 years, with greater dust mite exposure at the age of one year.[35] The relative risk for asthma at age 11 years was 4.8 for those children who were exposed to ≥10 μg of *Der p* 1/g of dust at the age of 1 year. Approximately 60% of children with acute asthma attacks were found to be both sensitised and exposed to high levels of mite allergens.

## Critical period of sensitisation

Recently, there has been considerable interest in allergen exposure during the first year of life, with infants being particularly susceptible to sensitisation. Studies from Sweden show that rates of sensitisation to birch pollen are 25% higher among those children born during the birch pollen season, compared with those born after this season who were not exposed until they were 9 months old.[36] Early exposure to potent allergens such as cow's milk protein, pollens, or house dust mite[35] are risk factors for sensitisation in later life in predisposed individuals. Dietary modification of the breast-feeding mother as well as the infant diet from the age of 6 to 12 months have resulted in a lower incidence of eczema and atopy.[37] These observations suggest that early exposure during infancy leading to subsequent sensitisation to allergens are often important in the development of clinical allergy in later life.

## Diagnosis of asthma and allergic rhinitis

The diagnosis of allergen-sensitive asthma and rhinitis requires a careful history of seasonal patterns and precipitants. House dust mite-sensitive asthma and rhinitis tends to be perennial, with an inclination towards worsening in autumn following the increased summer humidity that promotes mite growth. Mite exposure is likely if the patient's domestic environment contains items such as carpets, woollen blankets, and soft furnishings, which are particularly conducive to mite infestation. Pollen-sensitive asthma and rhinitis have a seasonal pattern, with onset of symptoms varying with the type of pollen to which the patient is sensitive. Grass pollens are released in spring and early summer, whereas trees and certain weeds pollinate in late summer or early autumn. A history of pet ownership, cockroach infestation, or mould and dampness in the house, with a story of symptoms on exposure, should alert one to the possibility of allergen sensitisation and the relevance of antigens in causing disease.

Skin prick tests to a range of aeroallergens should be performed. Positive results indicate sensitisation, and suggest a disease association. Together with a history of symptoms on exposure, a positive skin prick test provides confirmation that a particular allergen is involved. The size of the skin test reaction reflects the degree of sensitisation and correlates strongly with asthma morbidity, including disturbed sleep, missed school days, and emergency room visits for acute attacks.[7] Radioallergosorbent tests (RASTs), although less sensitive than skin tests, are a useful adjunct if skin tests are invalidated because the patient is taking antihistamines. These tests should also be performed as confirmation, prior to the commencement of desensitisation immunotherapy. In exceptional cases, an in-

halation or intra-nasal challenge with allergen may also be performed if there is doubt about the clinical relevance of a particular allergen.

## General approach to the management of patients allergic to inhalant allergens

### *Dust mite-sensitive asthma and rhinitis*

The first line of management in mite-sensitive asthma and rhinitis involves the standard anti-inflammatory drugs and bronchodilators used for asthma, as well as anti-histamines and intra-nasal steroids for allergic rhinitis. In addition, specific measures should be directed towards avoiding allergen exposure. In those not improved by these therapies, consideration should be given to specific immunotherapy. The aims of reduction in allergen exposure are threefold: eradication or reduction of mite counts; treatment and removal of allergen; and prevention of mite re-colonisation. Currently available methods include both physical and acaricidal procedures (Table).

### *Removal of mite habitat*

One of the initial procedures is to provide fewer habitats in which mites can live and breed. The removal of soft toys and furnishings from the bedroom is generally recommended. Carpets, irrespective of type, have higher concentrations of mites than do smooth floors, and are also more difficult to keep mite-free. Where possible, carpets should also be removed from the bedroom.[38]

### *Washing*

Routine domestic laundry procedures effectively kill mites, if a minimum water temperature of 55°C is used.[39] The use of a variety of commercial washing powders does not enhance mite killing at lower water temperatures. However, dust mite allergen is water soluble and washing with water alone will significantly reduce allergen levels. Hence, a cold laundry cycle with or without laundry powder does not remove the live mites from bedding, but will reduce allergen concentration by more than 90%. Dry cleaning, conversely, kills most, if not all mites, but does not reduce allergen concentration. Therefore, hot washing of bedding, usually every two weeks, is recommended to both kill mites and remove allergen.[38]

### *Bedcovers*

The use of occlusive bedcovers provides both a physical barrier between the dust mite allergen reservoir and the patient, and also prevents re-colonisation by house dust mites. Studies in which mites were vacuumed from mattress covers showed a 30- to 100-fold reduction, compared with those in dust from the mattresses.[40] The *Der p* 1 level from mattresses covered with polyurethane-coated fabric has also been found to be about 1% of levels found in uncovered mattresses.[41] Hence, this is an effective measure and should always be recommended to dust mite-sensitive patients. However, mattresses that are heavily infested should be chemically treated or replaced before covering.

### *Vacuuming*

Less than 10% of the live mites present on the surface of a mattress or carpet are removed by vacuuming. Even with expert use of an efficient vacuum cleaner,

**Table. Mite eradication and allergen avoidance procedures**

| Most useful | Possibly useful | Of little use |
|---|---|---|
| Removal of soft furnishings and carpet from bedroom | Vacuuming | Air filtration |
| Instal occlusive mattress and pillow covers | Dry cleaning and cold washing | Air ionisers |
| Hot washing of bedding (water temperature >55°C) | Acaricidal and tannic acid treatment | Electrostatic precipitators |
| | Humidity control achieved by better housing design and ventilation<br>Air conditioning<br>Electric blankets | |

clinical efficacy of vacuuming appears limited, as the mites rapidly migrate back into the bedding and carpets. Moreover, a limited study measuring airborne allergen levels showed that conventional vacuum cleaning actually increased airborne levels of *Der p* 1.[42] Hence, vacuum cleaning in isolation cannot be recommended for house dust mite control.

### *Humidity control*

Since mites thrive in conditions of high humidity, an alternative approach is the reduction of indoor humidity to make it less conducive to mite colonisation. Indeed, it has been advocated in Scandinavia as the treatment of choice for eradicating dust mite populations.[43] However, in Scandinavian countries, outdoor humidity is so low during winter months that increasing ventilation alone will effectively reduce indoor humidity below 7 g/kg. This is not a practical option for many areas of the world, including Hong Kong, where the humidity is generally high throughout the year. Reduction of indoor humidity by housing design relevant to local climatic conditions is currently under investigation.

### *Air filters and ionisers*

High efficiency particulate air (HEPA) filters, air ionisers, and electrostatic precipitators have been studied as a means of reducing exposure to inhaled aeroallergen. None of the trials, however, have shown these to produce clinical improvement.[44-47] Consequently, the use of air filters and ionisers cannot be recommended for routine management.

### *Acaricidal/chemical measures*

A range of chemicals with acaricidal activity have been developed. Most of these acaricides show good mite killing activity but only a few have been tested in clinical trials, and there are few data available on long term safety or toxicity. This treatment must be followed by thorough vacuuming to remove the allergen pool of dead mites and their faecal material. Otherwise, large numbers of dead mites remain in the dust, where they gradually disintegrate and generate aerosolisable, allergen-bearing particles.

Of the available acaricides, solidified benzyl benzoate has been the most thoroughly evaluated. It has potent acaricidal activity in laboratory mite cultures, but studies of its effect on allergen levels in mattresses and carpets have yielded conflicting results.[48,49] These studies differed in their duration and frequency of application of chemical acaricides, which may partly explain their differing results. Additional confounding factors were the variable vacuuming and cleaning procedures used after treatment. More studies are needed to define the optimal mode of application and cleaning required for maximal acaricidal activity and efficacy of allergen reduction.

Tannic acid is not acaricidal, but denatures proteins and has been recommended for reducing the allergenic potential of house dust. A 1% solution completely abolishes the allergenicity of house dust.[50] A preparation combining an acaricide (a benzyl derivative) with tannic acid, significantly reduces mite numbers and allergen levels. However, it should be used in combination with occlusive covers as its efficacy, when used alone, lasts for less than four weeks.[51]

### *Pollen-sensitive asthma and rhinitis*

Allergen avoidance is not a practical option in patients sensitive to outdoor allergens such as grass or tree pollen. Seasonal hay fever should be treated symptomatically with appropriate doses of antihistamines, and prophylactically with intranasal steroids. Seasonal exacerbation of pollen-sensitive asthma requires an increase in the dose of maintenance inhaled steroids for the duration of the season, which can then be reduced (or ceased if the asthma is only seasonal) at the end of the pollen season.

### *Other inhalant allergies*

For allergy to animal dander, the treatment of choice is removal of pets from the domestic environment, wherever possible. Nevertheless, allergen levels may persist for four to six months.[52] Washing the cat will markedly decrease the quantity of airborne allergens by 90% and will reduce the rate of allergen production.[50] Weekly washing of the cat in combination with removal of reservoirs such as carpets and upholstered furniture, as well as air filtration, have been proposed as a possible avoidance regimen with the cat remaining indoors.[53] It remains to be seen whether these procedures will be clinically effective in reducing symptoms in cat-allergic patients. The effects of avoidance measures on cockroach allergen levels and asthma symptoms are unknown and further studies are needed.

## Immunotherapy for asthma and allergic rhinitis

Allergen immunotherapy involves the administration of progressively increasing doses of a specific allergen, to reduce reactivity to the allergen on subsequent exposure. It leads to a number of immunologically measurable changes including increased levels of specific IgG-blocking antibody, a fall in specific IgE, decreased histamine release from leukocytes, and the

production of a number of cytokines which inhibit further IgE production. Although the exact mechanism of specific immunotherapy remains unclear, it is useful in cases where attempts at allergen avoidance and pharmacological therapy have failed to control symptoms.

The efficacy of immunotherapy depends on allergen specificity, potency of the allergen extract, total cumulative dose administered, and the duration of treatment. Subcutaneous injection is the preferred route of administration, and no benefit has been shown with low dose injection or sublingual drops of allergen.[54]

Immunotherapy should be directed at single allergens which, based on clinical history and domestic/laboratory challenge, are considered important in disease pathogenesis. Immunotherapy to multiple allergens is not advisable because the dose of each allergen that can be safely delivered per treatment is reduced, thereby prolonging the duration of treatment. Also, there is a potentially greater risk of anaphylaxis when higher doses of multiple allergens are administered in the latter course of treatment. Careful selection of asthma patients for immunotherapy is of utmost importance. Patients with extrinsic or allergic asthma are the only ones to be considered and ideally, they should meet the following criteria: definite worsening of symptoms after exposure to an allergen (this can be elicited from the clinical history and by means of domestic or laboratory-based provocation tests); poor control with, or poor tolerance of, traditional pharmacotherapy; good reversibility of symptoms with bronchodilators or steroids; good understanding of the procedure, and that it will lead to an improvement in symptoms, rather than a cure.

### *Immunotherapy for house dust mite allergy*

Immunotherapy for mite-sensitive, perennial rhinitis is effective and may be considered for patients remaining symptomatic after attempting appropriate avoidance measures and drug therapy. For house dust mite asthma many studies of immunotherapy using standardised mite extracts have found significant protection compared with placebo or control groups.[54] A recent meta-analysis of the published randomised, double-blind, placebo-controlled trials of mite immunotherapy in asthma found the combined odds ratio for symptomatic improvement to be 2.7, reduction in medication was 4.2, and reduction in bronchial responsiveness was 13.7.[55] The risk of provoking asthmatic reactions is greater in patients with irreversible airflow obstruction ($FEV_1$ < 70% of predicted value), and immunotherapy should be avoided in these patients. The use of synthetic oligopeptides of major dust mite allergens to render T-cells unresponsive to immunogenic challenge is also currently under investigation.[56] These developments promise newer and effective forms of immunotherapy, with lower risks of allergic reactions or anaphylaxis. These risks are present with current immunotherapy methods using native allergen. The duration of immunotherapy is debatable, but may be as short as 18 months for perennial rhinitis, while monthly maintenance may be necessary for many years, for certain asthma cases.

### *Immunotherapy for pollen allergy*

The efficacy of subcutaneous immunotherapy for allergic rhinitis caused by grass and ragweed pollen has been confirmed by a number of double-blind, placebo-controlled studies.[54] For most other pollen species, however, the data are lacking, and the precise role of desensitisation is unclear. A recent, well-designed, placebo-controlled study in patients with severe grass pollen hay fever showed that specific immunotherapy significantly improves symptoms and decreases the need for medications such as oral corticosteroids.[57] Controlled studies have also shown that immunotherapy is an effective treatment for pollen-sensitive asthma.[54] The optimal duration of immunotherapy is debatable, but at least three years are required, with courses of injections given out of season.

### *Immunotherapy for other inhalant allergies*

There are only limited data on the efficacy of immunotherapy for inhalant allergies other than dust mite and pollen. Immunotherapy for cockroach allergy using an aqueous extract has resulted in significant symptom reduction and medication use in a small number of cockroach-sensitive asthmatics.[58] Of the four double-blind, placebo-controlled trials of cat immunotherapy reported since 1978,[52,59-62] all have reported an improvement in symptoms or bronchial responsiveness. The improvement in provocation dose ranged from as little as 2.8-fold to as great as 11-fold. Thus, immunotherapy seems to be effective and should be considered for patients with intermittent, unavoidable, social exposure.

## Adverse reactions to immunotherapy

In general, adverse reactions increase with potency and dosage; and range from local swelling, to anaphylaxis, and death.[63] Mild local reactions occur with 2% of all injections; systemic reactions occur with 0.1% to 0.5% of all injections, and appear to be more common in people with asthma and when grass pollen or mould allergens are used. Life-threatening reactions almost

invariably occur within 30 to 45 minutes of the injection and all patients must be observed in the clinic during this period. Immunotherapy should not be given unless facilities for resuscitation are present. It is contraindicated during pregnancy, in patients with autoimmune disease, in patients with malignancies in which immune aberrations may be present, and in patients receiving beta-blocker medication.

## Conclusion

There is a clear relationship between exposure to allergens and the development of sensitisation and allergic disease in susceptible individuals. House dust mite is the most common inhaled allergen responsible for allergic respiratory disease in Hong Kong. Allergen avoidance is effective in ameliorating allergic rhinitis and asthma, and should be one of the cornerstones of management in conjunction with appropriate pharmacotherapy. In addition, specific immunotherapy may be beneficial in selected patients when other measures have failed.

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