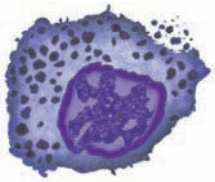


1. Diagnosis, treatment and prevention of allergic disease: the basics

Jo A Douglass and Robyn E O'Hehir

ABSTRACT

- Allergy is defined as an immune-mediated inflammatory response to common environmental allergens that are otherwise harmless.
- The diagnosis of allergy is dependent on a history of symptoms on exposure to an allergen together with the detection of allergen-specific IgE.
- The detection of allergen-specfic IgE may be reliably performed by blood specific testing or skin prick testing.
- Skin prick testing is not without its attendant risks, and appropriate precautions need to be taken. A doctor should be present for safety and test interpretation.
- Accurate diagnosis of allergies opens up therapeutic options that are otherwise not appropriate, such as allergen immunotherapy and allergen avoidance.
- Allergen immunotherapy is an effective treatment for stinging insect allergy, allergic rhinitis and asthma.
- The most effective methods for primary prevention of allergic disease in children that can currently be recommended are breastfeeding and ceasing smoking.
- Emerging trends in allergen treatment include sublingual immunotherapy.

MJA 2006; 185: 228–233

SERIES EDITORS: Andrew Kemp, Raymond Mullins, John Weiner

Allergic diseases are common and increasing in prevalence in Western countries, resulting in morbidity and mortality in all age groups. Drug therapy offers the opportunity for effective treatment, and a clear understanding of the spectrum of allergic diseases and the accurate identification of environmental triggers can enable the doctor to recommend optimal allergen-specific treatment, thereby minimising morbidity and mortality. To give general practitioners and non-allergy specialists a framework on which to base the clinical assessment of patients with allergic disease, we outline here the general principles of diagnosis, treatment and prevention.

Making the diagnosis

Is it allergy?

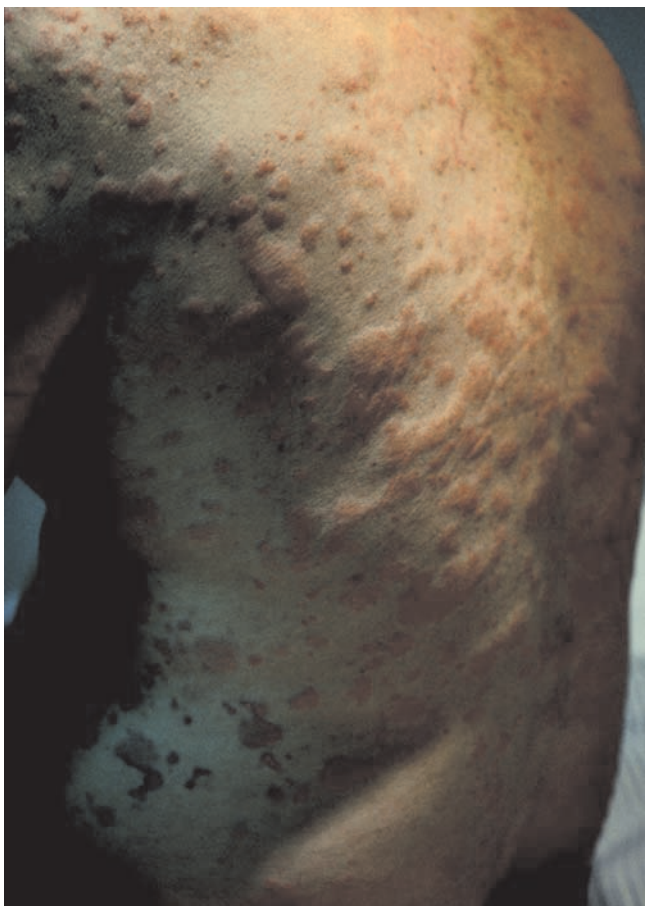
Allergy can be defined as a detrimental immune-mediated hypersensitivity response to common environmental substances. While the word "allergy" can mean many things to the lay person, the clinician needs to keep in mind that diagnosis of allergies is critically dependent on identifying the immune processes involved in the allergic response.

The immune processes of allergy usually rely on the production of IgE antibodies specific to common allergens. Allergic diseases are caused by the activation of mast cells and basophils through cell-surface-bound IgE. This causes the release of histamine and other mediators, leading to allergic inflammation. Chronic allergic inflammation characteristically involves a cellular tissue infiltrate of eosinophils and lymphocytes associated with chronic tissue damage. This definition of allergy is intentionally restrictive and, for the purposes of this article, excludes cutaneous contact allergy, which is mediated by T cells rather than IgE.

In the community, diverse symptoms are often attributed to "allergy". A useful test for the clinician is to ask whether the symptoms are, or could be, IgE-mediated (IgE-mediated symptoms include asthma, rhinitis, urticaria, eczema, food hypersensitivity and anaphylaxis). If not, then the symptoms are unlikely to be the result of true allergy.

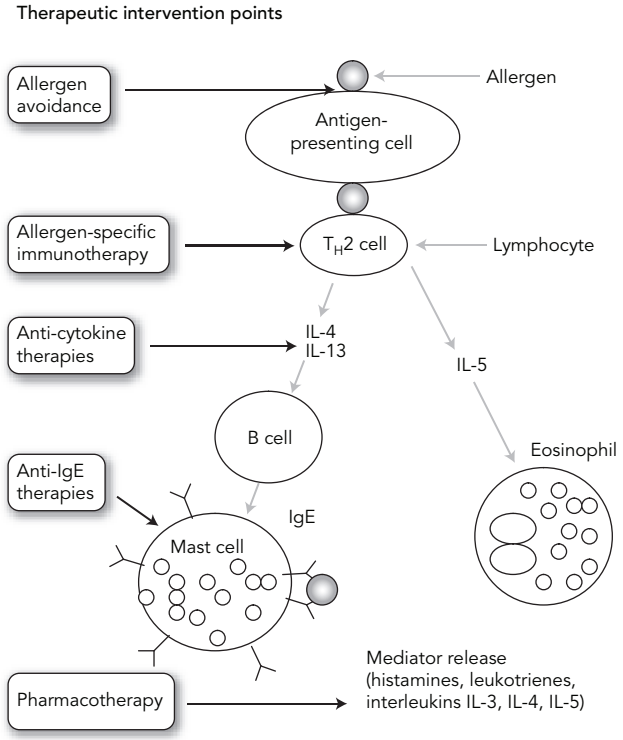
IgE is produced by B lymphocytes directed by cytokine release from T helper (T_H) lymphocytes (Box 1). In people with allergies, the T_H lymphocytes secrete cytokines that stimulate the production of IgE antibodies to allergens. The condition of secreting IgE in response to common environmental allergens is called "atopy". Predisposition to atopy is determined by both genetic and environ-

Urticaria



One cause of urticaria can be IgE-mediated allergy. Other IgE-mediated symptoms include asthma, food allergies, eczema and allergic rhinitis. ◆

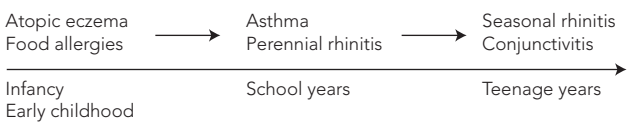
1 The allergic cascade



In people with allergies, the T helper (T_H) lymphocytes secrete cytokines, which predominantly stimulate B lymphocytes to produce IgE antibodies to allergens and also help to stimulate other pro-inflammatory cells, such as eosinophils. Cross-linking of IgE molecules by the allergen leads to mast cell degranulation and the secretion of mediators responsible for allergic inflammation. The points in the allergic cascade at which therapy may interrupt the process are indicated.

IL = interleukin. ◆

2 The atopic march*



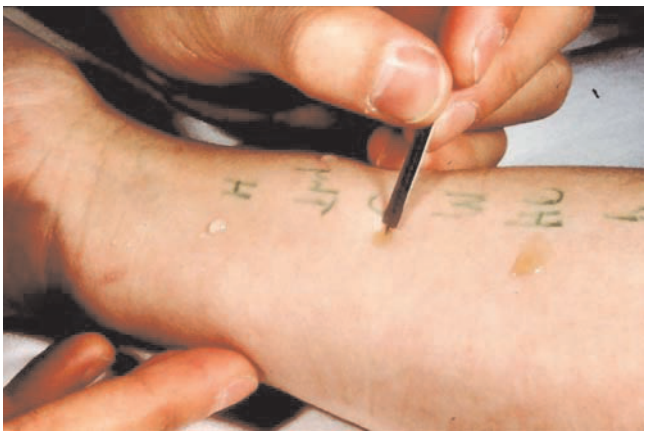
*Modified from Spergel.[1] ◆

mental influences, particularly in infancy, when immune responses to allergens are maturing, and T lymphocyte cytokine production is influenced by environmental exposures.

Allergic diseases include allergic rhinitis and asthma; food and stinging insect allergies leading to anaphylaxis; and allergic dermatitis. The diagnosis of allergic disease depends on identifying both the symptoms on allergen exposure and the relevant allergen-specific IgE. For example, an individual who develops rhinitis in early spring may be sensitive to grass pollen, and identifying IgE specific to rye grass pollen confirms the likely aetiology. However, identification of house dust mite-specific IgE in the same individual in the absence of rye grass pollen-specific IgE may suggest it is not an allergic process, as house dust mite is a perennial (year-round) allergen, and seasonal exacerbation of symptoms is unlikely to be related to exposure to this agent.

The manifestation of allergic diseases changes throughout life: food allergies and eczema are most likely to develop in infants, asthma in young children, and rhinitis in older children and adults (Box 2).[1] There is increasing evidence that appropriate treatment of allergies can prevent and alter the natural history of allergic diseases. Optimal treatment requires accurate determination of allergic triggers. Moreover, if an allergen avoidance strategy is to be pursued in relation to food or aeroallergens, it is critical to minimise the inconvenience of this strategy by making a correct diagnosis as early as possible.

3 Skin prick testing



Skin prick testing is usually performed on the forearm with standardised allergens. The technique, allergens and lancet used are purpose designed to provide consistent results. ◆

Detecting allergen-specific IgE

Accurate diagnosis of allergic disease and the relevant allergens helps to determine appropriate treatment options. Allergen-specific IgE can be detected by skin prick testing and by blood specific IgE testing (ie, serum allergen-specific IgE testing [as distinct from total IgE testing]).

Skin prick testing

Skin prick testing relies on the introduction of a very small amount of allergen extract into the epidermis using a standardised method to ensure reproducibility and comparability of results (Box 3). The results of skin prick testing are read at 10 minutes (for the positive control [histamine dihydrochloride or codeine]) and 15 minutes (for the allergen), and the diameter of the resulting weal is recorded in two dimensions. By convention, a positive test is one in which the mean of the two weal diameters is at least 3 mm greater than the negative control (saline), although if the reaction is as small as this, the relevance of the response is in question. Positive and negative controls are critical to enable interpretation of test results.[2]

When performed correctly, skin prick testing with aeroallergens (eg, house dust mite allergen, pollens, domestic pet allergens) shows good correlation with blood specific IgE testing in a semi-quantitative manner.[3] However, careful patient selection for skin prick testing is critical for both safety and interpretation: absolute and relative contraindications to skin prick testing are listed in Box 4.

Although very rare, systemic reactions to skin prick testing, and even fatalities, have been reported, and therefore equipment and

4 Skin prick testing

Patient selection

- Patients should be > 2 years of age. (Due to difficulties in interpretation of results of allergy testing in children under 2 years, as well as concerns about safety, such testing is best done by specialist allergists.)

Absolute contraindications

Skin prick testing is contraindicated if:

- A diffuse dermatological condition is present. Testing must be performed on normal healthy skin.
- Severe dermatographism is present.
- Patient cooperation is poor.
- The patient is unable to stop using drugs that may interfere with the test result.

Relative contraindications

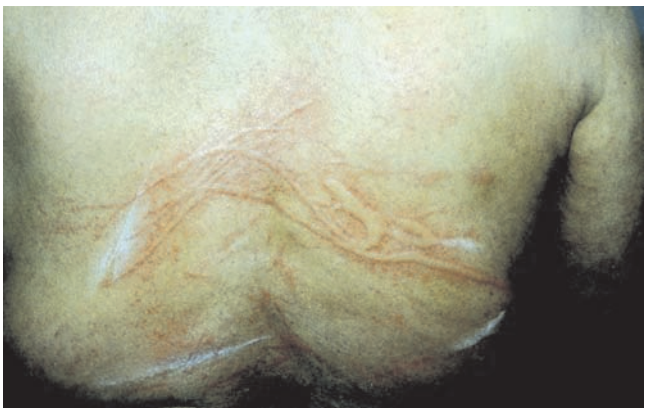
Skin prick testing is inadvisable if:

- Persistent severe or unstable asthma is present.
- There is a severe initial reaction (anaphylaxis).
- The patient is pregnant.
- The patient is taking certain types of drugs:
  - Antihistamines, tricyclic antidepressants, some antinauseants, and topical steroids (but not oral steroids) can interfere with results;
  - β-blockers and angiotensin-converting enzyme inhibitors should be used with caution. ◆

supplies for treating anaphylaxis (including oxygen and adrenaline) should be available at the testing site. Systemic reactions to skin prick testing are more common in infants or in cases where the reaction being investigated is systemic (as in true food allergies or allergies to latex or stinging insects). In these cases, skin prick tests should be performed with particular caution or avoided in favour of blood specific IgE testing.

Commercially prepared allergens for skin prick testing are usually standardised against either laboratory controls or by in vivo methods to ensure comparability between tests and reagents.

Dermatographism



Dermatographism is a skin condition in which wealing occurs after stroking of the skin. When present, it is a contraindication to skin prick testing, as the tests will be very difficult to interpret due to formation of weals in all tests. ◆

5 Case scenario*

A 24-year-old man presented complaining of food allergies involving many foods. He reported long-standing seasonal rhinitis, which had been a particular problem when he lived in Europe as a teenager, but had been less troublesome since his return to Australia 3 years previously.

He had been aware for many years of oral tingling and minor throat swelling on eating apricots, and generally avoided them. He had had no systemic or gastrointestinal symptoms on eating apricots, and had not experienced anaphylaxis after eating any foods. However, he had noticed more recently that bananas, raw apples, kiwifruit and hazelnut chocolates were giving him similar symptoms to apricots and was concerned that these would get worse.

He was otherwise well. He had moved into a new housing estate 2 years previously, and had a cat in the house. On questioning, he recalled having antihistamine treatment for hay fever in August and September of the past year.

Skin prick testing revealed reactions to grass pollens (4 mm) and house dust mite (8 mm), as well as a strong reaction to birch pollen (17 mm).

The patient's history of rhinitis and the skin prick test result strongly suggest birch pollen allergy. He would have acquired this while growing up in Europe, and it had probably been exacerbated by living in his new house, which was situated in an estate liberally planted with birch trees. This would explain the recurrence of his hay fever in the pollination season for birch pollen.

Food sensitivities are a common complication of birch pollen allergy. Described as "oral allergy syndrome", the condition is thought to be due to cross-reactivity. Foods such as apples, hazelnuts, apricots and other stone fruits cross-react with IgE antibodies to birch pollen, giving rise to oral symptoms but rarely anaphylaxis.

The best current treatment is avoidance, if possible, but immunotherapy to birch pollen offers promise of both treating allergic rhinitis and relieving (but probably not curing) oral allergy symptoms.

* This is a fictional case scenario based on similar real-life cases. ◆

Tests using mixes of foods or inhalant allergens are not recommended, as they can give results that are difficult to interpret. Where standardised reagents are not available, crude allergens can be used for testing, but the results require interpretation by an allergy specialist.

Intradermal allergy testing (in which a small amount of diluted allergen is injected into the dermis) has a very high non-specific reaction rate, but is useful in specific protocols for investigating drug and stinging insect allergy. Its use should be restricted to specialist clinics. Other methods of skin testing such as "scratch" testing are no longer used, owing to inconsistency of results.

Doctors wishing to conduct skin prick testing should refer to specific guidelines for conducting skin prick tests.[2] Standardised conduct of testing is critical to identifying the relevant allergens, and interpretation of the results is equally critical. Where feasible, the requesting doctor should observe the patient's skin prick tests to aid interpretation.

Blood specific IgE testing

Blood specific IgE testing to a wide range of allergens detects and quantifies allergen-specific IgE. It can be used to diagnose all types of allergies, but is generally less sensitive than skin prick testing. Blood specific IgE testing is particularly useful when anaphylaxis is

6 Evidence-based practice tips*

- Allergen immunotherapy is an effective treatment for stinging insect allergy, allergic rhinitis and asthma (Level I).
- Avoidance of house dust mites cannot be currently recommended to improve asthma or rhinitis (Level I).
- Stopping smoking in the home and when pregnant is an effective way of reducing respiratory disease in children (Level II).

*Based on National Health and Medical Research Council levels of evidence.[4] ◆

being investigated, as testing carries no associated risk of anaphylaxis and there are very few contraindications. Blood specific IgE testing can be performed in patients who are taking antihistamines or other drugs that are contraindicated in skin prick testing, and in patients whose risk of an adverse reaction to skin prick testing is high (eg, those with unstable asthma or anaphylaxis).

Generally, a blood specific IgE grading of ≥ 2 (a ratio of specific to non-specific binding) denotes a specific response to an allergen. Blood specific IgE testing can be difficult to interpret in patients who have very high levels of total IgE (> 1000 kU/L) (eg, patients with eczema), as they may have low-grade reactions to many allergens.

Although blood specific levels of IgG antibodies, especially to food allergens, can be measured, such testing should not be requested, as there is no evidence that it is relevant to allergy diagnosis.

Management of allergic disease

Accurate diagnosis of the allergens responsible for allergic disease presents therapeutic opportunities for allergen-specific therapies such as allergen avoidance and immunotherapy (Box 5 and Box 6).

Allergen avoidance

Careful avoidance of the specific allergens responsible for allergic disease should always be the first consideration in managing patients with allergies. This is the primary form of treatment for food allergies and some stinging insect allergies, as avoidance can be a very effective strategy if patients are well educated about precautionary measures. For example, a person allergic to jumper-ant venom can minimise the chances of being stung by wearing shoes and long-sleeved shirts when outdoors and gloves when gardening. Accurate diagnosis of food allergies can enable patients to minimise the disruption to their lives caused by an unnecessarily restrictive diet.

However, allergen avoidance is particularly contentious when applied to the area of aeroallergens and respiratory allergic disease. People who are clearly allergic to animal allergens (eg, cat allergens) are generally not troubled by the allergy unless they encounter the animal, providing a strong case for allergen avoidance. Similarly, to give an example from the health care environment, avoidance of powdered latex gloves has been effective in reducing symptomatic latex allergy and the incidence of new cases in hospital staff.[5] But the situation is less clear with respect to house dust mite allergen, the most common domestic allergen in Australia. While older trials of allergen avoidance suggested that it reduced asthma symptoms, bronchial reactivity and eczema, two recent studies in patients with asthma[6] and rhinitis,[7] confirmed by a meta-analysis,[8] question these benefits and suggest that further studies of secondary treatment of asthma by allergen avoidance are unlikely to prove that the method is effective.

So, what should the treating doctor recommend? The evidence suggests that house dust mite avoidance should be recommended cautiously, if at all, and certainly only in people with clear sensitivity to house dust mite allergen. In symptomatic animal allergy, there is some evidence that removal from the home of a pet to which a person is allergic significantly reduces allergic symptoms and medication requirements.[9] Although it is intuitively reasonable to reduce relevant allergen exposure in people with allergic symptoms, recent studies challenge the effectiveness of universal allergen avoidance strategies for allergies to domestic allergens.

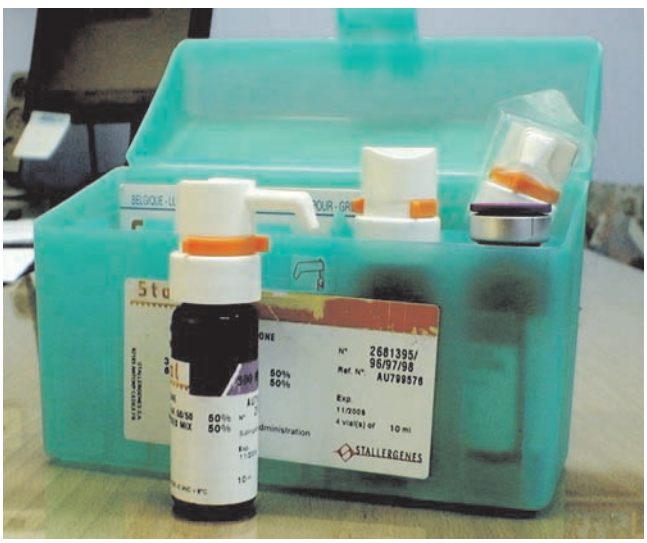
Allergen immunotherapy

Allergen-specific immunotherapy involves administration of increasing doses of allergen to a patient to achieve clinical and immunological tolerance over time. Allergen injection immunotherapy induces T cell tolerance by several methods, including decreased allergen-induced proliferation, alteration of secreted cytokines, stimulation of apoptosis, and the production of T regulatory cells. This results in a reduction in inflammatory cells and mediators in the affected tissues, the production of blocking antibodies, and the suppression of IgE.[10]

The only absolute indication for immunotherapy is in patients who develop systemic reactions to insect venom, in whom incremental subcutaneous doses of venom can achieve tolerance to insect stings in 80%–90% of cases.[11] However, immunotherapy for stinging insect sensitivity needs to be continued for at least 5 years to achieve durable tolerance.[12] Conventional (subcutaneous) immunotherapy for allergic respiratory disease is clearly effective compared with placebo and requires 3 or more years of treatment to obtain durable efficacy.

Subcutaneous immunotherapy is very effective for seasonal allergic rhinitis caused by grass pollens. It has been shown in some

Sublingual immunotherapy kit



Immunotherapy is an effective way of inducing physiological and immunological tolerance to allergens such as house dust mite allergen and grass pollens. Increasing evidence supports the effectiveness of the sublingual route of administration. ◆

studies to reduce symptoms by over 60%.[13] While not first-line treatment for asthma, allergen immunotherapy has been shown to be effective in reducing airway responsiveness and exacerbation rates.[14] Although the benefits of subcutaneous immunotherapy are apparent in both asthma and allergic rhinitis, the use of immunotherapy needs to be balanced against the inconvenience of its delivery and the risks associated with anaphylaxis due to allergen administration.

More recently, allergen immunotherapy for aeroallergens has been delivered by sublingual/swallow immunotherapy (SLIT). Meta-analysis of the many trials of this form of treatment confirms its safety and efficacy,[15] but there are insufficient trials comparing sublingual immunotherapy with subcutaneous immunotherapy to compare similar dosing regimens. Moreover, efficacy with some allergens and in children is still under debate. However, if its efficacy for a broad range of allergens is proven, sublingual immunotherapy offers treatment that is probably more acceptable to patients and parents than subcutaneous immunotherapy. The major current drawback of sublingual immunotherapy is cost, as allergen doses required for effective treatment are at least 100-fold greater than those needed for subcutaneous immunotherapy. This translates into medication costs at least three times higher than for subcutaneous therapy. Poor patient adherence to prolonged courses of sublingual treatment may also be a factor reducing effectiveness.

There are also promising reports of sublingual immunotherapy for food allergies. While this approach needs to be further confirmed in extensive studies, and will need to be performed in specialist centres because of its high risk, this is a promising avenue of treatment for food allergy — an area in which current treatment relies on long-term avoidance for secondary prevention.[16]

Can allergy be prevented?

Primary prevention

"What can I do to prevent allergic diseases in my children?" This is a very common question asked by parents. Although there has been much conjecture on how to influence the infantile immune response to reduce the likelihood of allergen sensitisation and subsequent allergic disease, effective specific preventive therapies have not yet been developed. Nevertheless, the following recommendations all have some evidence of efficacy in preventing either allergen sensitisation or disease such as wheeze or eczema, or both, especially in children born to high-risk families.[17]

- Exclusive breastfeeding to 4–6 months of age;
- Use of hydrolysed milk formulas for babies unable to be breastfed; and
- Quitting smoking.

Maternal avoidance of certain foods during pregnancy and lactation has not been effective in preventing the onset of allergic disease, and cannot be recommended. As there is conflicting evidence for the effectiveness of avoidance of house dust mites or pets in infancy for preventing subsequent allergic sensitisation, no recommendations can be made at this time regarding these initiatives.

More relevant to primary prevention are large trials of multifactorial interventions, such as the Canadian Childhood Asthma Primary Prevention Study[18] and the Australian Childhood Asthma Prevention Study.[19] The Canadian study, which has now been going for 7 years, shows a significant odds ratio (0.39) for the prevention of current asthma in a cohort of high-risk children as a result of a multifaceted intervention that has included encouragement of breastfeeding and avoidance of house dust, pets and tobacco smoke. The results of other similar trials, and data demonstrating the durability of benefits, will be needed to formulate public health measures in this direction.

Secondary prevention

In addition to allergen avoidance in the presence of established disease, allergen-specific treatments can be used to reduce the development of allergic disease in sensitised individuals. Subcutaneous allergen immunotherapy has been shown to halve the rate of subsequent development of asthma in children with seasonal allergic rhinitis, indicating that allergen immunotherapy may have particular benefits in these children.[20] Sublingual immunotherapy may also offer promise in reducing asthma onset in children with both perennial and seasonal rhinitis and asthma.[21] Also, daily antihistamine treatment of children with eczema has been shown to reduce rates of asthma in those with grass pollen allergy.[22]

What's on the horizon?

Researchers into allergen immunotherapy continue to seek safer and more convenient allergy "vaccines".[23] Peptide therapies based on the T lymphocyte epitopes of allergens offer hope in this area, but their clinical utility is yet to be demonstrated for all but cat allergy.[24] Other approaches to allergic disease have been the development of humanised monoclonal anti-IgE antibodies, which have been found to have some efficacy in treating asthma[25] and food allergies.[26] Anti-IgE treatments may offer therapeutic opportunities for people with multiple sensitivities. Anti-cytokine therapies have also been investigated to treat asthma. Anti-interleukin-5 therapy has produced some reduction in inflammation, but has failed to improve bronchial hyper-responsiveness.[27] Early trials of tumour necrosis factor alpha (TNF-α) blocking have shown some success, but further work is needed on specific blockers in inflammatory pathways.[28]

Future options for treating allergic disease will focus on allergen-specific routes, including further development of immunotherapy and targeting of specific mediators — an area with a great deal of promise, especially in people with refractory disease.

Fact or fiction — true or false?

1. Nearly all true allergic reactions are mediated by IgE (T/F)
2. A positive skin prick test always indicates an allergy (T/F)
3. Allergen immunotherapy is an effective method of treating and preventing asthma (T/F)
4. Avoidance of house dust mites is always indicated in childhood asthma (T/F)

1. True.
2. False. A diagnosis of allergy depends on identifying both the symptoms on allergen exposure and the relevant allergen-specific IgE.
3. True. There is extensive evidence that allergen immunotherapy is effective in asthma treatment,[14] and emerging evidence suggests that it may prevent the development of asthma in children with rhinitis.
4. False. Not all children with asthma are allergic to house dust mite allergen, and allergen avoidance is only indicated if allergy to a specific allergen is clearly identified; moreover, current evidence does not support house dust mite avoidance as an effective treatment for asthma. ◆

Competing interests

Jo Douglass and Robyn O'Hehir have received funding from GlaxoSmith-Kline and AstraZeneca to attend international meetings.

Author details

Jo A Douglass, MD, FRACP, Physician,[1] Associate Professor[2]
Robyn E O'Hehir, FRACP, PhD, FRCPath, Director,[1] Professor[2]
1 Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, VIC.
2 Department of Medicine, Monash University, Melbourne, VIC.
Correspondence: j.douglass@alfred.org.au

References

1 Spergel JM. Atopic march: link to upper airways. *Curr Opin Allergy Clin Immunol* 2005; 5: 17-21.
2 Skin tests used in type I allergy testing. Position paper. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. *Allergy* 1989; 44 Suppl 10: 1-59.
3 Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. *J Allergy Clin Immunol* 1999; 103 (5 Pt 1): 773-779.
4 National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC, 2000. http://www.nhmrc.gov.au/publications/_files/cp69.pdf (accessed Jul 2006).
5 Latza U, Haamann F, Baur X. Effectiveness of a nationwide interdisciplinary preventive programme for latex allergy. *Int Arch Occup Environ Health* 2005; 78: 394-402.
6 Woodcock A, Forster L, Matthews E, et al; Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003; 349: 225-236.
7 Terreehorst I, Hak E, Oosting AJ, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med* 2003; 349: 237-246.
8 Gøtzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2004; (4): CD001187.
9 Shirai T, Matsui T, Suzuki K, Chida K. Effect of pet removal on pet allergic asthma. *Chest* 2005; 127: 1565-1571.
10 Gardner LM, Thien FC, Douglass JA, et al. Induction of T "regulatory" cells by standardized house dust mite immunotherapy: an increase in CD4+ CD25+ interleukin-10+ T cells expressing peripheral tissue trafficking markers. *Clin Exp Allergy* 2004; 34:1209-1219.
11 Westall GP, Thien FCK, Czarny D, et al. Adverse events associated with rush Hymenoptera venom immunotherapy. *Med J Aust* 2001; 174: 227-230.
12 Moffitt JE, Golden DB, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol* 2004; 114: 869-886.
13 Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med* 2005; 353: 1934-1944.
14 Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003; (4): CD001186.
15 Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; 60: 4-12.
16 Enrique E, Pineda F, Malek T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005; 116: 1073-1079.
17 Prescott SL, Tang MLK. The Australasian Society of Clinical Immunology and Allergy position statement: summary of allergy prevention in children. *Med J Aust* 2005; 182: 464-467.
18 Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005; 116: 49-55.
19 Peat JK, Mihrshahi S, Kemp AS, et al. Childhood Asthma Prevention Study. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2004; 114: 807-813.
20 Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109: 251-256.
21 Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114: 851-857.
22 Warner JO; ETAC Study Group. Early treatment of the atopic child. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. *J Allergy Clin Immunol* 2001; 108: 929-937.
23 Gardner L, O'Hehir RE, Rolland JM. T-cell targeted allergen derivatives for improved efficacy and safety of specific immunotherapy for allergic disease. *Curr Med Chem* 2003; 2: 351-365.
24 Alexander C, Tarzi M, Larche M, Kay AB. The effect of Fel d 1-derived T-cell peptides on upper and lower airway outcome measurements in cat-allergic subjects. *Allergy* 2005; 60: 1269-1274.
25 Niebauer K, Dewilde S, Fox-Rushby J, Revicki DA. Impact of omalizumab on quality-of-life outcomes in patients with moderate-to-severe allergic asthma. *Ann Allergy Asthma Immunol* 2006; 96: 316-326.
26 Leung DY, Sampson HA, Yunginger JW, et al; Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003; 348: 986-993.
27 Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest* 2003; 112: 1029-1036.
28 Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006; 354: 697-708.

(Received 10 Mar 2006, accepted 29 Jun 2006) ❑