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Atopy, anamnesis and allergy testing

There has been a dramatic increase in the incidence of allergic disorders, which have trebled over the last 20 years. This is highlighted in the International Study on Allergic Diseases in Childhood (ISAAC) Phase I and III data collected on 13- to 14-year-old children from the UK which now shows high prevalence of asthma (32%), hay fever and allergic rhinitis (40%) and eczema (9%) (Asher et al., 2006).

The GP curriculum

Although no single GP curriculum statement covers the presentation, investigation and management of allergy in primary care, it is highly relevant to several GP curriculum statements:

- *Statement 15.4: ENT and facial problems*—lists allergic rhinitis as an important condition in its knowledge base and requires GPs to understand the likely outcomes of tests done to investigate rhinitis. This includes allergy testing.
- *Statement 15.5: eye problems*—lists allergic conjunctivitis as an important condition in its knowledge base. It requires GPs to demonstrate a reasoned approach to the diagnosis of eye symptoms including the use of investigations such as allergy testing.
- *Statement 15.8: respiratory conditions*—lists allergy and anaphylaxis as important conditions in its knowledge base. In addition it requires GPs to understand and implement the key national guidelines that influence health care provision for respiratory problems. The 2008 British Thoracic Society guidelines suggest allergy testing for patients for whom there is uncertainty over the diagnosis of asthma.
- *Statement 15.10: skin problems*—requires GPs to demonstrate a reasoned approach to the diagnosis of skin symptoms using history, examination, incremental investigations and referral. This includes investigation of allergic skin conditions such as eczema.

Most allergic disorders are dealt with in primary care without secondary tier referral. These allergies include reactions to common inhalant aero-allergens (house dust mite, grass and tree pollens, cat, dog and horse dander and mould spores) and food allergens (cow's milk, hen's egg, codfish, shellfish, wheat, soy, peanuts, tree nuts, sesame and kiwi) which are particularly prevalent in children. Allergy testing in atopic families with a personal medical history (*anamnesis*) suggestive of allergy plays an integral role in the effective management of childhood asthma, chronic rhinitis and infantile eczema.

Defining the problem

Allergy is an exaggerated immune response to a specific protein allergen in the environment. Atopic individuals manufacture an abundance of immunoglobulin E (IgE) on initial allergen exposure. On subsequent exposure, this IgE binds to the allergen causing tissue-bound mast cells to degranulate with the release of histamine plus other pro-inflammatory mediators (type 1 immediate hypersensitivity reaction). Histamine then generates pruritus, erythema, excess mucus production and smooth muscle contraction which are so typical of the allergic reaction. When multiple organ systems such as skin, respiratory and cardiovascular become involved in a more generalized allergic reaction, this is termed anaphylaxis which may be life threatening.

Atopy is the predisposition of certain allergy-prone families to produce specific IgE antibodies to environmental allergens and manifest with childhood asthma, allergic rhinitis and infantile eczema. Maternal atopy is a particularly significant risk factor for the onset of childhood asthma and also recurrent wheezing that persists throughout childhood.

Atopic or allergic individuals also tend to produce an age-related excess of serum total IgE (usually greater than 70 ku/l in adult atopics) with associated blood eosinophilia (equal to or greater than 4%) and a TH2 subtype immune regulation.

When diagnosing allergies, the detailed medical history or *anamnesis* is crucial and allergy tests merely confirm the involvement of a suspected allergen. It cannot be over-emphasized that the allergy history provides 85% of the

information and the diagnostic tests should only be interpreted in the light of this history. Allergy testing in isolation (as occurs at the local pharmacy, supermarket or health food store) is not helpful as there is a tendency for false-positive and -negative results to confuse the issue. However, once an allergy is strongly suspected …

Anamnesis …'is detailed information gained by a physician by asking specific questions with the aim of obtaining information useful in formulating the diagnosis and providing medical care to the patient' … synonym *medical history*. (Source: Wikipedia)

Allergy testing is used to diagnose immediate hypersensitivity reactions to pollens, pets, mites and foods in addition to insect venom, latex, occupational allergens and some drugs. Testing may be undertaken using skin prick testing (SPT) with standardized allergen extracts or blood testing for specific IgE antibodies (RAST test). Patch testing may also be performed to identify delayed hypersensitivity reactions to metals, rubber, dyes and preservatives. Allergy testing will then pinpoint or rule out a particular allergen as the cause of a specific allergy causing asthma, rhinitis, eczema, urticaria or angioedema.

Relevance to GP practice

Most allergy testing could be conveniently performed at the patient's local surgery without referral, using SPTs, IgE blood tests or allergen patch tests. In atopic individuals, food allergies and infantile eczema predominate in the first few years of life. The natural history is for these conditions to resolve or at least improve, but asthma becomes a problem in the mid-childhood years. As the asthma prevalence reduces in the pre-teens, hay fever and allergic rhinitis become health issues in later childhood and teenage years. Hay fever then peaks in the 20s and may be associated with localized fruit-related 'oral allergy syndrome' and as this wanes, the asthma tends to recur again in middle age. This chronological progression from one allergic manifestation to the next over time is referred to as the 'Allergic March' and is more common in atopic families (see Fig. 1).

New primary care guidelines for the management of asthma, rhinitis, eczema and anaphylaxis are now recommending allergy testing as part of the workup of the atopic child. For example, the current BTS Asthma guidelines recommend allergy testing as part of the workup of atopic children with asthma (Box 1).

Allergy testing to the common inhalant, food and occupational allergens will help guide the GP to identify eczematous and wheezy children at risk for going on to develop asthma, allergic rhinitis and food-related anaphylaxis.

Although the recent Cochrane review and meta-analyses of current allergen avoidance strategies were disappointing, better quality studies are now awaited. Allergy testing to identify the causative allergen in patients with a poor response to standard allergy medication may facilitate the option of treatment by desensitization immunotherapy. Sublingual and particularly systemic immunotherapies have

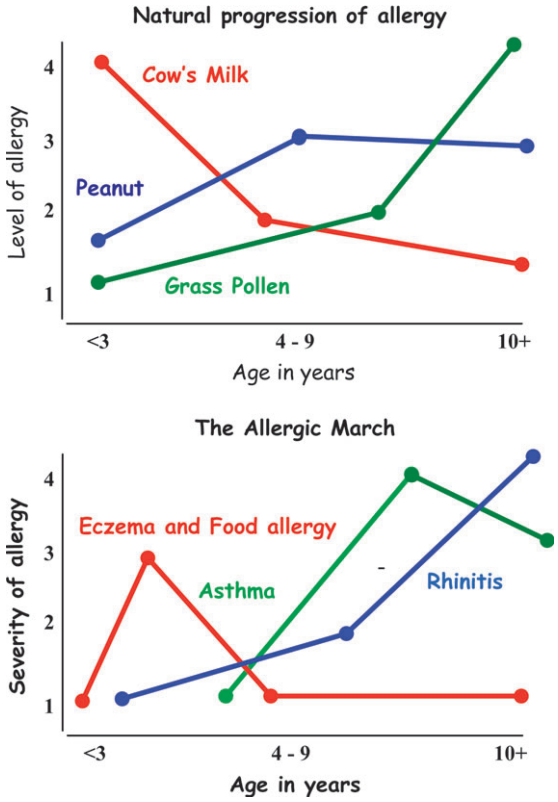


Figure 1. *Allergy March chart illustrations.*

been shown to be effective for inhalant desensitization ; the newer vehicles seem to be effective and less likely to cause side effects or adverse reactions. Studies suggest that successful immunotherapy may actually 'cure' the allergy or at least reduce the need for anti-allergy medication.

Group general practices might consider training a lead member of staff to perform SPTs in-house. These tests are cheap, readily accessible and simple to perform in primary care. The skin test results are also immediately available for interpretation and expedite the allergy management plan. Conversely, a practice may elect to utilize blood testing for allergen-specific IgE antibodies, using our national network of NHS and private

Box 1. BTS 2008

A history of other atopic conditions such as eczema and rhinitis increases the probability of asthma. Positive tests for atopy in a wheezing child also increase the likelihood of asthma. A raised specific IgE to wheat, egg white or inhalant allergens such as house dust mite and cat dander predicts later childhood asthma.

Other markers of allergic disease at presentation, such as positive skin prick tests and a raised blood eosinophil count, are related to the severity of current asthma and persistence through childhood …. British Thoracic Society 2008

pathology laboratories which are able to test up to 400 individual inhalant, food and occupational allergens in this way.

Allergy testing will assist with identifying those patients with asthma and rhinitis who fail to respond to treatment but who might benefit from immunotherapy to grass pollen, house dust mite or pet allergens.

Allergy tests

Allergen skin prick tests

SPT is probably the most popular and accurate allergy test performed on a global scale. These tests measure immediate (IgE) sensitivity to various allergen extracts when applied by pricking the skin. SPT is very useful to determine the exact cause of an inhalant allergy such as occurs in childhood asthma, allergic rhinitis, hay fever and eczema.

Crude skin testing was first performed by Dr Charles Blackley, a Manchester GP, in 1865, when he diagnosed grass pollen as the cause of his hay fever. Today, with purer allergen extracts and lancets which are highly standardized, the accuracy of this technique for diagnosing immediate IgE-mediated allergies is accepted universally.

Foods can also be tested in this manner by applying a droplet of commercial or fresh food extract onto the skin. Fresh food extracts tend to give more accurate results than using commercially prepared extracts. When using a fresh sample of suspected food, the prick-to-prick method should be employed (by pricking the food and then transferring allergen by pricking the skin with the lancet). Up to 25 different food and inhalant allergens may be tested on the skin in this manner during a single consultation. See Box 2 for factors that affect the accuracy of SPTs and Box 3 for contraindications to SPT.

Method of SPT

Droplets of the specific standardized extracts are applied onto the volar aspect of the forearm or back at 3-cm intervals. The skin is then pricked through the droplet at 90 degrees for 1 second using a standardized 1-mm lancet with a shoulder so as not to cause excess skin trauma. A positive (histamine 10 mg/ml) control and a negative (saline/glycerol) control should always be applied for comparison.

After 15 minutes, each allergen-induced 'wheal and flare' reaction's diameter is measured in millimetres. Any wheal diameter which is 3 mm larger than the negative control is considered a positive result. The greater the wheal size, the higher the level of allergen-specific IgE produced by that person. However, it should be noted that the size of the wheal need not necessarily predict the intensity of a suspected allergic reaction. But negative SPTs to specific allergens are good indicators that no IgE-mediated allergy exists in that individual.

Patients should avoid all anti-histamine and tricyclic antidepressant medication for at least 48 hours prior to testing. SPT is very safe in primary care and can be reliably performed on children from 4 months of age. However, the patient should then be monitored in the surgery for 30 minutes after a skin test, and it is recommended that adrenalin be available because of the theoretical risk of an allergic reaction following testing. Caution should be exercised when treating SPT individuals with documented anaphylaxis to specific allergens such as nuts, latex and horse hair and in these cases, blood tests would be preferable. SPT although safe is not yet recommended in pregnancy. SPT kit solutions are usually standardized glycerol-based extracts and are marketed in the UK by ALK-Abello, Allergy Therapeutics, Diagenics (Allergopharma) and Stallergenes. Skin test solutions should be stored in a refrigerator between 2 and 8°C and usually have a 2-year shelf life.

Studies in children with food allergies to egg, milk and peanut have suggested that a wheal over a certain size may reliably predict the presence of a food allergy without the need for oral challenge testing. However, the severity of an allergic reaction cannot be accurately predicted by the size of the wheal alone. For example, some patients with anaphylactic sensitivity to insect venom, latex or antibiotics may have wheal size as small as 3–5 mm while others may conversely have wheals of 10 mm or greater to inhalant allergens but manifest with only mild asthma or rhinitis when challenged.

For IgE-mediated food allergy in children, Sampson and Hill have introduced cut-off points for positive SPTs above which food allergy has a 95% probability of existing. Predictive values for age less than 2 years and greater than 2 years have been drawn up (Table 1). These probabilities have been reproduced in the UK by Roberts and Lack using 'likelihood ratios'.

Negative predictive values (NPVs) approach 95%, meaning a negative skin test provides good evidence that no IgE-mediated food or inhalant allergy exists.

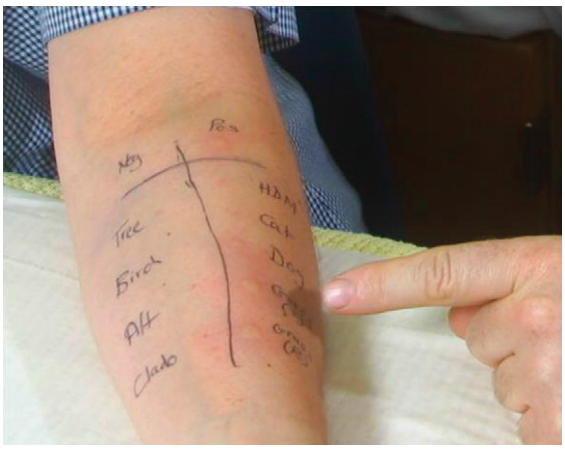
Box 2. Factors that reduce the accuracy of SPT

- Oral anti-histamines, anti-emetics and tricyclic antidepressants in previous 48 hours
- Oral ranitidine, beta blockers and mast cell stabilizers reduce wheal size
- Topical anti-histamines, corticosteroids and immunomodulators on test site
- Aged atrophic skin is more likely to bleed and is less reactive
- Pigmented skin difficult to read reaction

Box 3. Contraindications to SPT

- Extensive atopic eczema with no clear area of skin to test
- Dermatographia with wheal development on pressure
- Severe allergic reaction to nuts, horse hair, latex or food allergen
- Fear of needles
- Pregnancy
- Incorrectly stored allergen solutions
- Inexperienced operator

SPT application.



SPT result.

Blood tests for IgE

RAST blood test

Shortly after the discovery of the IgE antibody by Johansson and Ishikara in 1967, allergy blood tests became widely available. The RAST (**R**adio-**A**llergo-**S**orbent **T**est) was the first commercial allergy blood test developed in 1974 and now 90% of NHS pathology laboratories utilize the similar but more refined ImmunoCAP system.

The ImmunoCAP consists of a standardized allergen in a small container (cap) which then latches onto the patients' serum-specific IgE. After which a fluorescent enzyme 'labelled' anti-IgE is added, and the amount of allergen-specific IgE can then be accurately quantified. A large range of inhalant, food and occupational allergens can be tested in this way. The ImmunoCAP results are graded from negative 0 (<0.35 ku/l) to positive Grade 1 (>0.35 ku/l) up to Grade 6 (>100 ku/l). Levels above 3.5 ku/l (Grade 2) are usually clinically relevant and the higher the level, the greater it's significance.

Total serum IgE (a combination of specific and non-specific IgE) was the test of choice but high total IgE levels may occur in certain non-allergic conditions such as in extensive eczema or parasite infections. Even though the 'older' total serum IgE blood test is less sensitive in allergy, raised levels of total IgE are frequently associated with atopy and thus if present increase the likelihood of an individual having allergies. However, allergen-specific IgE remains the current blood test of choice when attempting to identify a specific allergy with a sensitivity approaching 75% and specificity of 95% and positive predictive value (PPV) close to 100%.

Table 1. SPT: 100% Positive Predictive Value (PPV) for food allergy

Food allergen	100% PPV < 2 years (wheal diameter), mm	100% PPV > 2 years (wheal diameter), mm
Cow's milk	6	>8
Hen's egg	5	>7
Peanut	4	>8

Source: Sampson *et al.*, 2000.

Allergy screening panels

ImmunoCAP (Phadia) provide allergy screening panels for testing IgE in blood to common groups of allergens. About 3 ml of fresh clotted blood is required to test a limited panel of allergens.

The Phadiatop inhalant allergy panel includes house dust mite, cat, dog, grass, weed and tree pollen mixes and mould spores, while the paediatric food allergy panel (also called fx5) includes cow's milk, hen's egg, wheat, soy, codfish and peanut. These panels are useful for screening if no one particular allergen is suspected. Studies show that raised IgE titres (>3.5 ku/l) for both Phadiatop and fx5 have strong predictive values (97.4%) for the presence or development of allergic diseases such as asthma, allergic rhinitis and eczema.

Remember that not all children sensitized to allergens will develop allergies and many may remain relatively symptom free. However, once sensitized, they have a greater likelihood of developing clinical allergies at some stage, but this may not occur until adulthood. Quantification and monitoring of specific IgE levels over time may be useful in predicting whether an allergy will persist or whether it will resolve. Children who experience food anaphylaxis but have low food allergen-specific IgE tend to outgrow their disease and this has been documented in 20% of peanut allergic children.

Other food allergy panels include the fx1 nut allergen panel (peanut, Brazil nut, almond, hazelnut, coconut), fx2 seafood panel (cod, tuna, shrimp, blue mussel, salmon) and fx3 cereal panel (wheat, oat, maize, sesame, buckwheat).

Over 400 individual allergens can be tested using ImmunoCAP technology, including environmental inhalant allergens, food allergens, insect venom, antibiotics and occupational allergens. They are also particularly useful when a SPT is not available, when the patient is unable to stop taking anti-histamine medication, during pregnancy or for those with extensive eczema which makes skin testing difficult. See Box 4 for advantages and disadvantages of IgE-specific blood tests.

If an anaphylactic reaction is suspected but uncertainty remains, such as occurs while undergoing anaesthesia or at cot

death, serum tryptase levels can be measured up to 6 hours after the event. A raised serum tryptase level is pathognomonic of anaphylaxis and can be used for forensic purposes.

The NPV of skin and RAST testing is very helpful in excluding an immediate IgE-mediated allergy, but the PPV is less sensitive. About 80% of individuals who test positive to allergen-specific IgE will have an allergic disease caused by that allergen. This further endorses the importance of a clear and detailed allergy history and compounds the fact that allergy testing alone may not be in the patients' best interest.

The higher the measure of serum-specific IgE in a patients' blood, the greater the likelihood is of that individual having a clinically relevant allergic disease. The World Allergy Organization have published ImmunoCAP RAST 'decision points' for food-specific IgE above which there is a 90% probability of a food allergy being present (Table 2).

No food challenge testing is necessary if the food-specific IgE concentration is equal to or greater than the above decision point. Also of diagnostic value is that negative results (less than 0.35 ku/l) have a NPV approaching 95% that no IgE-mediated allergy exists. Box 5 outlines tests accuracy criteria.

Box 4. Advantages and disadvantages of IgE specific blood tests

Advantages:
- Unaffected by medication
- No potential for inducing allergic reaction
- Independent of operators training or technique
- No need to stock large repertoire of SPT allergens

Disadvantages:
- More invasive than SPT (need at least 3 ml venous blood)
- Test results not immediately available (have to be processed elsewhere)
- False-positive results more likely than with SPTs
- More costly per allergen when compared to SPTs (£8 versus 50 p per allergen)

Box 5. How accurate is that test?

- PPV—likelihood of a truly positive test among those testing positive to an allergy
- Sensitivity—proportion with positive results among patients with disease
- NPV—likelihood of a truly negative test in all those with negative to allergy tests
- Specificity—proportion of negative results among unaffected patients

Other tests to determine allergic hypersensitivity

The hallmark of an accurate allergy diagnosis is a comprehensive and clear allergy history implicating an allergen which is then confirmed by performing a limited range of IgE allergen-specific blood (RAST) or Skin prick tests (SPT).

ImmunoCAP multichannel blood analyser. Reproduced with permission from Phadia UK.

Atopy patch testing

Atopy patch testing (APT) is similar to the patch test originally used to detect contact allergen sensitization in allergic contact dermatitis but may be employed to detect delayed hypersensitivity reactions to foods and inhalants. Allergens are applied to the skin for 48 hours inside plastic or aluminium Finn chambers under occlusive micropore. These are then removed and the skin reaction is 'read' after a further 24 hours. Reactions are graded 0 (no reaction) to 3+ (erythema with blistering) for each allergen. This is particularly

Table 2. Using specific IgE levels to predict food allergy

Food-specific IgE concentration (ku/l) clinical decision points						
	Egg	**Milk**	**Peanut**	**Fish**	**Soya**	**Wheat**
Reactive if equal to or greater than:	7	15	14	20	65	80

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useful if used together with SPT and improves the predictive value of SPTs in food-induced eczema and where a delayed hypersensitivity to a food or other allergen is suspected.

Intradermal skin tests

Dilute allergen extract (0.05 ml of 1:100) is injected intradermally and a positive reaction is a 5-mm or greater wheal developing over 15 minutes. It is about 100 times more sensitive than SPT but more likely to induce a systemic allergic reaction. Positive (histamine) and negative (saline) controls should also be performed. Intradermal testing may be used if a SPT is negative, but an allergic reaction is still strongly suspected as occurs in drug allergy to antibiotics, anaesthetic agents or insect venom allergy.

Nasal eosinophil smear

Eosinophil counts on nasal mucus smears are a good indicator of allergic rhinitis if more than 10% of the stained cells are eosinophils. The nasal mucus specimen should be collected on a glass rod and assessed under light microscopy after application of Hansel's stain (a combination of eosin and methylene blue stains).

When is it appropriate to consider referral to specialist allergy unit?

It is appropriate to consider referral to a specialist allergy unit if

- You are uncertain of allergy diagnosis
- Tests needed are not available in primary care
- There is a risk of adverse reaction if the patient is skin tested in primary care
- There is difficulty interpreting test results
- Complex or multiple allergies are suspected
- The patient has anaphylaxis, severe angioedema or anaesthetic and drug-related allergies
- Respiratory and/or food challenge testing is needed

The British Society for Allergy and Clinical Immunology provides an extensive list of NHS allergy clinics around the UK on the website www.bsaci.org. Box 6 gives contact details for allergy test distributors in the UK.

Specialist allergy tests

Eosinophil cationic protein, urinary histamine and basophil histamine release can be measured in allergic inflammation as well as exhaled nitric oxide (FENO) and induced sputum differential cell counts. These tests, used mainly for research purposes, are usually limited to academic centres for asthma, rhinitis and urticaria and are beyond the scope of this article.

Allergen provocation tests

For respiratory allergies, patients may be referred to specialist centres for direct allergen or histamine and methacholine challenges on nasal, conjunctiva or bronchial mucosal surfaces.

The 'gold standard' in food allergy testing is the double-blind placebo-controlled food challenge test. This involves oral challenges with a suspected allergen concealed in food or in a capsule but must be undertaken in a hospital environment with full resuscitation facilities. Neither the patient nor tester is aware which 'broth' or capsule contains active ingredient and which contains placebo. To prevent any subjective bias, this information is only made available after the test. However, challenge testing in severe allergy is dangerous and should not be considered in the primary care setting.

Tests of no proven value

Testing for IgG4 antibodies to diagnose food intolerances is best avoided. According to UK and European allergy opinion leaders, IgG responses to food are a normal physiologic phenomenon and raised food-specific IgG has no predictive role for food allergies or intolerances. Another pseudo-scientific testing modality called blood leucocytotoxic testing (marketed as Nutron or Allergy Leucocyte Cellular Activation Test (ALCAT) test) has been available since 1956 but has no proven diagnostic value in allergy. There are a number of tests used by complementary and alternative practitioners such as chiropractors and homeopaths to diagnose so-called 'allergy and intolerances'. These include the VEGetative electro-Acupuncture test (VEGA) testing for electromagnetic fields in acupuncture meridians, applied kinesiology (a muscle strength test), hair and nail sample analysis and iridology all of which have been shown to have no diagnostic value in allergy or food intolerance.

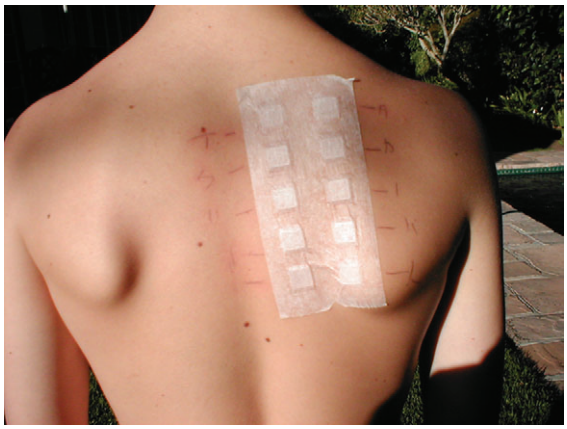
Box 6. Contact details for allergy test distributors in the UK

SPT kits:
Alk Abello (UK): www.alk-abello.com/UK
Telephone: 01488 686 016
Diagenics (UK): www.diagenics.co.uk
Telephone: 01908 376376
Allergy Therapeutics: www.allergytherapeutics.com
Telephone: 01903 844700
Stallergenes (UK): www.stallergenes.com

IgE blood tests:
Phadia (ImmunoCAP test): www.phadia.co.uk
Telephone: 01908 847034

Finally

Conventional allergy testing plays an integral role in confirming the allergy diagnosis, facilitating treatment and allergen avoidance measures. But a family history of atopy, the individual's recollection of the allergic event including a specific medical and allergy history, age group and geographic location remain pivotal to the allergy diagnostic



Atopy patch test.

process. Allergy testing in isolation without a good clinical allergy history should be avoided as this is often not helpful and may even be misleading.

Key points

- The incidence of allergic diseases has trebled over the last 20 years
- Allergic diseases commonly present as asthma, rhinitis, infantile eczema, acute urticaria and anaphylaxis
- Allergy testing forms an integral part of the investigation of an atopic child
- Common aero-allergens include house dust mites, pet dander, pollens and mould spores
- Common food allergens in children include cow's milk, egg, wheat, soy, codfish and peanut, while shellfish, nut and fruit allergies are more common in adults
- Tests detecting immediate IgE allergy with reliable accuracy include SPT and blood tests for specific IgE antibodies (RAST)
- Atopy patch testing may be of use for delayed hypersensitivity.

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