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Review Article

The application of allergy tests in childhood allergy

兒童變應性疾病中變應原的測試

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The prevalence of allergic diseases in childhood has increased considerably in developed nations in the last 2-3 decades, and accordingly the need of allergy testing has increased steadily. Hong Kong is also facing similar challenge. Allergy testing is an important prerequisite for both early identification of infants at increased risk of allergic disease and for specific allergy treatments. In this review, we shall discuss the allergy tests currently practised in Hong Kong. We have made practical recommendations to local practitioner for testing allergy related dermatological problems. It is desirable to strengthen the co-operation between the specialist sector/hospitals and general practitioners in order to let the right children get the right tests at the right time.

在過去二、三十年中，發達國家的兒童變應性疾病的患病率有相當可觀的增長，對變應原測試的需求亦相應增加。香港亦面對相同的挑戰。變應原測試對早期診斷有變應性疾病風險增加的嬰兒與及治療變應性疾病均為先決條件。本文將討論本地進行的變應原測試。我們就與變應疾病有關的皮膚問題對本地行醫者作出實用的建議。但願醫院專科醫生與普通科醫生之間能加強合作，令合適的患兒在合適的時間接受合適的測試。

Keywords: Allergy testing, CAP-FEIA, IgE, patch test, radioallergosorbent test

關鍵詞：變應原測試， CAP 螢光酶免疫測定， E 型免疫球蛋白，斑貼試驗，放射變應原吸咐試驗

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Introduction

The prevalence of allergic diseases in childhood (atopic eczema, asthma, allergic rhinitis/conjunctivitis, and food allergy) has increased considerably in developed nations in the last 2-3 decades, and accordingly the need of allergy testing has increased steadily. In population-based studies of Hong Kong,[1-3] the estimated prevalence of allergic diseases in school age children was 25-30%. Atopic eczema was found in 8-10% and the prevalence of asthma, food allergy, allergic

rhinitis and conjunctivitis was 7-10%, 2-4% and 20-30% respectively. Many of these children suffered from co-morbidities of these allergic disorders (Figure 1). In the setting of an university affiliated referral allergy clinic for children; we have been seeing a four-fold increase in demand on allergy testing during the last 5 years. In an analysis of the presenting complaints of 300 consecutive patients (unpublished data from author), they mainly fell into these categories: 1) suspected IgE-mediated food allergy (47%); 2) poorly controlled eczema (30%); 3) recurrent angioedema/chronic urticaria (15%); 4) poorly controlled rhinitis/asthma (4%); 5) drug/latex allergy (3%) and 6) suspected anaphylaxis (1%). Although they were undoubtedly subjected to referral bias, they might partly reflect health seeking behaviour of patients and their parents, and perhaps, to a lesser degree, the genuine increase in disease burden. Among these referrals, most were made by general practitioners, family physicians and paediatricians in both private and public sectors but fewer than 3% were actually made by dermatologists. One in five referrals from the private sector already had some allergy tests done in one form or the other. In this review, we shall focus on the allergy tests currently practised in Hong Kong. We try to make practical recommendations that are relevant to local practitioners with special interest in allergy related dermatological problems.

Difference between atopy and allergy

The word allergy was coined in the 19th century from Greek words 'allon argon' and it meant "to react differently". Atopy is also derived from Greek. 'Topos' means a place and 'atopos' means out of place. In allergy scientific literature, atopy is generally defined as the genetic trait that confers an increased risk of sensitization to common environmental allergens. Currently, atopy is assessed by looking for evidence of allergic sensitization which literally means the subject has detectable IgE directed against relevant allergens, but that may not always imply allergy disease. In this review, allergy is defined as hypersensitivity initiated by immunological mechanism which can be antibody or cell-mediated.[4] In most patients, the antibody typically responsible for an allergic reaction belongs to the IgE isotype, and is thus called IgE-mediated allergy. In non-IgE mediated allergy, different mechanisms may be responsible (e.g. IgG, immune complexes, cell mediated, etc.). In patients with IgE-mediated allergic disease, upon exposure to a provoking allergen, a biphasic response would develop. The early response occurs within 20 minutes, being characterised by classic IgE-mediated immediate type hypersensitivity, and is followed by the late phase response after 3-6 hours. This late response is characterised by involvement of eosinophilic inflammation and is associated with prolonged symptoms and hyper-reactivity. In

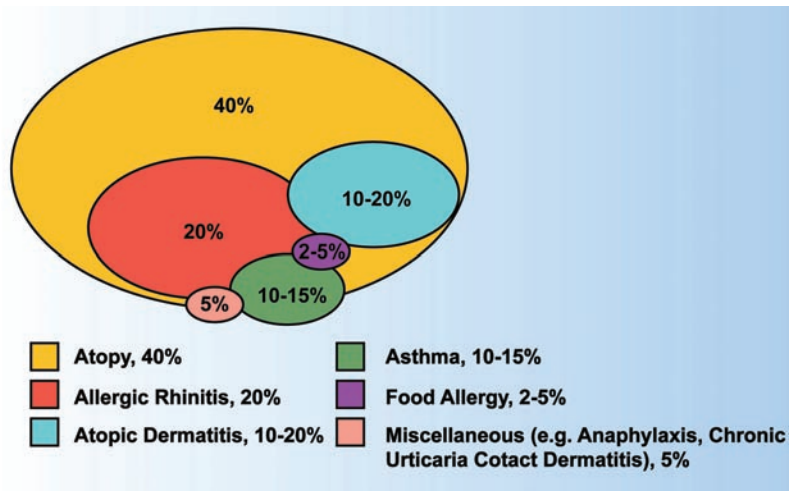

Figure 1. The phenotypic heterogeneity of atopy. The outer box represents a general population: approximately 40% is atopic as defined by skin test positivity. Allergic rhinitis has a population prevalence of 20%. There is a considerable overlap between asthma and rhinitis; however, not all asthmatics are atopic. Atopic eczema has also an overlap with asthma and allergic rhinitis. Please note that figures are estimations for a population of children and adults.

case of daily exposure to allergen, persistent inflammation causes functional and structural changes. The relationship between atopy and allergy is thus a good example of gene-environment interactions.

Allergy march

Various manifestations of atopy/allergy disease often present in a characteristic sequence, referred to as the 'atopic march'. Allergic manifestations are rare during the first month of life. The initial signs of allergic disease are atopic eczema and food allergies, which typically peaks during the first 2 years of life. The development of food allergy closely parallels the pattern of atopic eczema, with the highest rates of food sensitization also noted in the first 2 years of life. The peak incidence of food allergy is 4% to 8% at one year of age, followed by a gradual decrease to 1-2% through adulthood. Correspondingly, specific immunoglobulin E (IgE) antibodies against milk and egg are most frequently detected during the first 1-2 years of life. The development of allergic sensitization to inhalant allergens begins to rise at 3 years of age and is often accompanied by allergic respiratory diseases. Most children with asthma experience disease onset during the first 5 years of life, whereas IgE against inhalant allergen is predominant in school age children. Interestingly, IgE antibodies to allergens (hen's egg white, cow's milk) in infants predict sensitization to inhalant allergen and allergy before 7 years of age.[5]

Biology of immunoglobulin E

Normally present at very low level in plasma, IgE antibodies are produced primarily by plasma cells in mucosa-associated lymphoid tissue and their levels are commonly elevated in patients suffering from atopic condition like asthma, allergic rhinitis and atopic eczema. Production of allergen-specific IgE in atopic individuals is driven by genetic predisposition as well as by environmental factors, including chronic allergen exposure. The lineage commitment by B cells to produce IgE involves irreversible genetic changes at the immunoglobulin heavy chain gene locus and is very tightly regulated. It requires both cytokine signals (interleukin (IL)-4, IL-13) and interaction of B cells CD40 with its ligand on activated T cells.

IgE antibodies exert their biologic functions via the high-affinity IgE receptor, FcεRI, and the low-affinity receptor, CD23. In the classic 'immediate hypersensitivity' reaction, the interaction of polyvalent allergens with IgE bound to mast cells via FcεRI triggers receptor aggregation, which initiates a series of signals that result in the release of various vasoactive and chemotactic mediators. In addition, IgE antibodies have a number of immunomodulatory functions. These include up-regulation of IgE receptors, enhancement of allergen uptake by B cells for antigen presentation, induction of Th2 cytokine expression by mast cells and these may all collaborate to amplify and perpetuate allergic response in susceptible individuals. Thus blockade of IgE effect, using novel anti-IgE therapies, may ultimately prove to have a broad effect.[6]

Why we need allergy testing?

Allergy testing is a very important prerequisite for specific allergy treatment. It is useful for early identifications of infants at risk for later development of allergic diseases and specific allergy treatment. The latter includes specific allergen avoidance measures (e.g. dust mite allergen-prove cover, food avoidance), relevant pharmacotherapy (e.g. autoinjectable adrenaline-EpiPen®) and immunotherapy (conventional subcutaneous or novel sublingual desensitisation).[7]

Who should be tested for allergy?

Generally, all individuals with severe, persisting or recurrent possible allergic symptoms and individuals with need for continuous prophylactic

treatment should be tested for specific allergy irrespective of the age of the child (Table 1). The range of allergy tests typically depends on age of the child, positive family history and symptoms such as possible seasonal or diurnal variations.

Asthma. Allergy testing should be performed, where an early intervention (elimination of relevant allergens/treatments) may improve disease control and prevent progression of disease.

Atopic eczema. Symptoms not under good control by topical steroids or when food allergy is suspected should also be tested.

Urticaria is rarely caused by allergy except in cases with close relation to intake of specific food or exposure to specific allergens.

Insect sting reactions. Virtually non-existing in local children but occasional happens in expatriate children. Children should only be tested for allergy to insect venoms (bee or wasp) in case of severe systemic reactions. Local reaction and urticaria are not indication for testing.

Allergy to drugs. Allergy testing should be conducted for symptoms such as itchy skin reactions, urticaria, angioedema, asthma or anaphylaxis. Maculopapular exanthema is not an indication for testing.

Latex allergy. Allergy testing is primarily indicated for at risk children group, e.g. spina bifida, urogenital malformation with recurrent catheter insertions, early major surgery, atopic subjects or other patients who have clinical symptoms upon exposure to latex.

Anaphylaxis. Patients with anaphylaxis need a thorough, comprehensive allergy-immunology evaluation to diagnose the specific aetiology. It aims at preventing exposure to the allergens and providing strategies for dealing with episodes of

Table 1. Indications for allergy testing

Gastrointestinal symptoms: vomiting, diarrhoea, colic, failure to thrive	Persisting or intermittent symptoms without any other known reason
Atopic eczema	Persisting symptoms or allergen related symptoms, particularly in case of other concurrent atopic symptoms
Acute urticaria/angioedema	Severe cases and/or suspicion of specific allergy
Children <3 years of age with recurrent wheezing/asthma	Persisting severe symptoms and need daily treatment Children with long lasting cough/wheeze/dyspnoea, particularly during play/physical activity and during the night Children with reduced level of activity or frequent pneumoniae without other known causes should be allergy tested
Children >3 years with asthma	Should always receive allergy testing for relevant allergen Should be investigated for rhinitis
Rhinitis	Treatment resistant cases Should be investigated for concurrent asthma
Conjunctivitis	Treatment resistant cases
Insect sting reaction	Only severe systemic reactions should be tested
Anaphylaxis	Should always be evaluated for allergy under special observation
Contact dermatitis	Treatment resistant dermatitis, hand dermatitis, unusual distribution (consider patch testing)

allergic anaphylaxis. The physician and family need to implement a written action plan detailing the early recognition of signs and symptoms of anaphylaxis and the use of an epinephrine auto-injector for self-administration as pre-hospital treatment. Because fatal anaphylaxis occurs despite timely and appropriate treatment, successful avoidance strategies and education remains the mainstay of management.[8,9]

How do we select allergen panels?

In rank order, house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and cockroach are the commonest inhalant allergens in Hong Kong.[10-12] Pets (dog and cat dander) should be tested according to exposure. Common food allergens are not much different from those of Western data, with cow's milk common in infants. Hen's egg, codfish and peanuts are common in preschoolers. Shellfish is relative common in adolescents or young adults.[13] Other foods like wheat and tree nuts are quite uncommon and should only be tested when there is a relevant history. In Table 2, proposals of relevant allergens testing at different ages are described. When children are tested according to age for specific allergy diagnosis, additional testing might be considered for assessment of sensitization reflecting the atopic constitution.

Children less than 3 years

In early infancy, food allergy with manifestations from skin, gastrointestinal or respiratory tract is relative common. Atopic eczema and recurrent wheezing are the common presenting symptoms. Children with long-lasting cough/wheeze/dyspnoea, particularly during play/physical activity and during night and children with reduced level of activity or frequent pneumonia without other known causes should be allergy tested. Children with food allergy almost always show symptoms from two or more organ systems concomitantly, but in some cases, e.g. atopic eczema, the children may only show one severe persisting symptom. Cow's milk allergy is the most common food allergy in young children followed by allergy to hen's egg, peanut and fish. A few children are sensitized to indoor inhalant allergens already during the first 1-2 years of life and in case of persisting asthmatic symptom, allergy testing for relevant indoor allergens such as mite and cat may be useful.

Children above 3 years

With increasing age, allergy to inhalant allergens develops, including indoor allergens (house dust mites, pets, cockroaches) and outdoor allergens (pollen and moulds). During childhood a high frequency of sensitization is seen in individuals with asthma, rhinitis or conjunctivitis. A great proportion of asthmatics (>70%) also suffers from rhinitis, and a great proportion of individuals with rhinitis also suffers from asthma, though frequently not detected. Typical hay fever is seldom seen in Hong Kong. We rarely need to test patients on pollens. Mold/fungi allergy is also infrequent in local children.

Cross-reactivities

Cross-reactivities occur when two or more allergens share epitopes, or in some cases have very similar epitopes, and therefore bind to the same IgE-antibodies. Thus, patients sensitized to one of the allergens may also react to the other without previous exposure and sensitization. The knowledge about cross-reactivities is important when evaluating the need and extent of allergy testing (Table 3).

Practical pearls

Although positive skin prick test (SPT) and/or positive specific IgE in serum indicate that a person has antigen-specific IgE, these findings do not prove that exposure to the allergen in question causes clinical allergic symptoms. Theoretically, only controlled allergen challenge can confirm the cause-effect relationship. However, in daily clinical practice, it is common to use a positive SPT and or/presence in serum of specific IgE to relevant environmental allergens and a suggestive clinical

Table 2. Allergy testing according to age and disease/symptoms. The allergen panel should be adjusted according to allergen related symptoms and local allergen exposure, indoor as well as outdoor (in Hong Kong we seldom has positive tests to outdoor allergens)

Disease/symptoms	**What to test in relation to age**	
Eczema	<3 years of age Foods (for IgE food allergy associated eczema) • cow's milk (most common <1 year) • egg white • peanut, cod fish, • if with suggestive history test: wheat, nuts, soy inhalant allergen (to test the atopic risk) • house dust mites • cat, dog and cockroach	>3 years of age Foods (in case with severe persisting eczema) • cow's milk • egg white • peanut • if with suggestive history test: wheat, nuts, fish, shellfish, soy inhalant allergen (allergen-associated eczema) • house dust mites • cat, dog and cockroach
Persistent and intermittent runny and stuffy nose and/or wheezing	For allergen-specific diagnosis • house dust mites • cat, dog and cockroach • +/-molds • +/-pollen	

Table 3. Cross-reactivities between allergens

Symptom related allergens	**Frequently cross-reactive allergens**
Cow's milk	Goat's milk, sheep's milk, beef
Peanut	Tree nuts, soy beans, green beans
Shrimp	Other shellfish e.g. clams, crabs, lobsters
Dust mites	Shellfish (with tropomysin)
Grass	Potato, tomato, wheat , peanut
Birch	Apple, apricot, plum, peach, hazelnut, carrot, potato, celery, cherry, pear
Latex	Kiwifruit, mango, papaya, avocado, banana, chestnut
Lentils	Peanut, soy

history as proof of allergy induced disease. The higher the specific IgE antibodies, the stronger the association with clinical disease. SPT and *in vitro* tests may differ in their accuracy (sensitivity, specificity and reproducibility) to detect sensitization depending on the quality of the extracts used and the methodology. Patients referred to tertiary centre and/or specialists tend to have a higher prevalence of sensitization, multiple sensitization and more severe clinical symptoms. Thus, extrapolating the data directly from tertiary centre without due consideration of local setting is not very desirable. In community practice, where a low level of mono-sensitization without a suggestive clinical history may be encountered, the clinical relevance may be limited.

Allergy testing includes the following elements:

- Case history
- Determination of IgE-sensitization
  - ♦ SPT
  - ♦ Total and specific IgE in serum

- Allergen challenge
  - Food allergy (in particular)
- Other optional tests (e.g. basophil histamine release assay, environmental investigations). These tests are mainly for research purposes or in the hands of specialists

Skin prick test

Percutanous/epicutaneous (prick or puncture) with allergen extracts is the favoured method of *in vivo* testing for IgE-mediated sensitivity. It is safe, not painful and easy to perform. It is less sensitive but more specific than intradermal route. Intradermal skin test for food allergy is now considered inappropriate due to higher risk of systemic reaction. It is, however, reserved for evaluation of drug allergy because haptens of drugs are weak allergens.

There is no age limit for doing skin test in children but the number of skin tests should be kept to the minimum, especially for younger children. The prerequisite is avoid short and long acting antihistamine for 3 and 7 days prior the test respectively. Potent topical steroid and calcineurin inhibitors over the tested area should also be avoided for 1-2 weeks. Positive control (histamine, 10 mg/ml) and negative control (glycerated saline) solutions are used. SPT are performed on the back in infants and on the forearm in older children. The skin wheal diameter is measured between 10 to 15 minutes later. Irregular shapes are recorded as the mean of two perpendicular diameters. Attention should be paid to the quality of extracts and the characteristics of the device used. The results should be documented in a quantitative manner that can be interpreted by other practitioners. We prefer to use single head lancet than multi-adaptors. The lancet gives clearer result, whilst multi-adaptor is easier to perform in case of a non-cooperative child. However it tends to give more false positives due to its larger grid which inflicts a bigger trauma to skin.

Positive skin test results are also useful for education purposes to the patient and the patient's family, and may improve treatment compliance. A positive response is often referred to as a wheal of 3 mm or larger. SPT is most informative when negative because the negative predictive value (NPV) of the test is very high (>95%). Conversely, the positive predictive value (PPV) is between 30% and 50%. Thus positive skin tests must be correlated with clinical history and food challenges. The size of wheal depends on many factors such as level of specific IgE, binding affinity of the IgE antibody, releasability of the patients' mast cell, reactivity of patients' skin to histamine, area of body used for testing (with back being more reactive than the arm) and sometimes age (baby younger than 4 months may have false negative results).

With standardised allergen reagent and technique, the diameter of wheals in SPT correlates with clinical sensitivity but not severity, i.e. the larger the wheal , the more likely clinical reaction would develop upon exposure but it does not predict how severe the reaction will be.[14-20] In the analysis of fruit allergy, we sometimes need to apply prick-by-prick technique with fresh fruit as "testing reagent" because some of the fruit proteins are quite labile and their allergic potential readily lose after even brief storage and processing.

Total IgE

It is used as an indicator of atopy but not by itself a diagnostic marker for allergic disease. There is a wide overlap in the total serum IgE levels between atopic and non-atopic populations (e.g. parasitic infestation, skin diseases other than eczema, drug induced conditions, graft versus host disease, Hyper IgE syndrome etc.).

Quantification of serum allergen-specific IgE

This is the most important analyte measured in the clinical immunology laboratory for diagnosis

of allergic disease. It is synonymous with radioallergosorbent test (RAST). Classically it is a two-stage non-competitive radioimmunoassay. Allergen-specific antibodies are bound to an allergosorbent. Bound IgE antibodies are detected with radio-iodinated anti-human IgE. An analysis against a standard calibration curve is performed in each assay to quantify the allergen-specific IgE. Now after several generations of modification, most practising allergists and accredited laboratories favoured the use of a FDA-approved system, namely CAP-FEIA or ImmunoCap (Phadia, Pharmacia, Uppsala, Sweden). It is in fact widely validated in different clinical settings and ethnic populations. Quantitative IgE levels to selected foods (milk, egg, fish, and peanut), if above a pre-defined IgE antibody threshold (Table 4), may eliminate the need for food challenges.[21-24] It is interchangeable with SPT for inhalant allergen in most of the circumstances.

Specific *in vitro* IgE immunoassays may be preferable to skin testing for patients and their families who: 1) have severe dermographism, or generalised eczema, 2) unable to stop antihistamines, 3) refuse skin testing or cannot cooperate with testing and 4) have a clinical history suggestive of a higher risk of anaphylaxis with skin testing to a particular allergen. However, RAST is rather expensive and of limited availability. In general, we preferred SPT than RAST in daily clinical practice.

Multi-allergen test

This is a quantitative *in vitro* measurement of a panel of common food or inhalant allergens (e.g. Phadiatop®, Phadiatop infant®, fx5®). It is often applied to young infants as screening of atopic constitution.[25] Generally, we think it is a better tool than total IgE as an indicator of atopy. Prediction of asthma development at age of 4-5 years has been made by utilising the sum of IgE antibodies level in combination with the number of allergens that elicit positive tests results. It may represent a more efficient diagnostic tool and its wider application is being actively sought. One recent study suggested it might be used as an alternative to SPT in the epidemiological setting to diagnose atopy.[26] The results of the tests were: sensitivity 85.0% (95%CI 82.2-87.8%), specificity 85.5% (95%CI 82.7-88.3%), positive predictive value 72.7% (95%CI 69.0-76.1%), negative predictive value 92.7% (95%CI 90.6-94.7%) and accuracy 85.3% (95%CI 82.3-88.0%); with better performance among the symptomatic groups. New emerging commercial blot kits, which could screen out a large number of allergens with minute amount of blood, are in fact not well studied.

Table 4. Diagnosis decision points of skin tests and serum specific IgE levels for clinical food reactivity

Study population	Age (year)	Food	Cut-off level*
Skin prick tests			Wheal size (mm)
Australian	≦2	Cow's milk	6
		Egg	5
		Peanut	4
Australian	≦16	Cow's milk	8
		Egg	7
		Peanut	8
Serum food-specific IgE#			KUa/L
USA	≦14	Cow's milk	32
		Egg	6
		Peanut	15

*95% positive predictive value of positive food challenge, it varies with study population and currently no Asian data
#by (Pharmacia-CAP-FEIA)

Patch test

Clinical features may be insufficient to distinguish allergic from irritant contact dermatitis and endogenous eczema. Patch tests are used in delayed hypersensitivity reactions (i.e. allergic contact dermatitis). Patch testing is indicated in patient with treatment-resistant dermatitis, hand dermatitis, stasis dermatitis, suspected allergy to topical medicaments (e.g. otitis externa) and suspected occupational exposure. Eczema with unusual distribution should preferably seek specialist (e.g. dermatologist) opinion prior to performing such test. Three important considerations before we coin the diagnosis of contact dermatitis: a) the index case has the clinical feature of contact dermatitis, b) the index cases have environmental exposure to the allergen in consideration and c) the allergen identified by patch test explains the clinical feature and course. Unselected patch testing in people with eczema can have many caveats.

The test involves placing a series of allergens on the skin and leaving them in place for 48 hours. The precise technique varies between different centres but experience is essential for correct interpretation. Allergen is applied in aluminium Finn chambers (a disc with a rim), usually on the back. Allergen can be applied in an inert vehicle such as petroleum jelly or in an aqueous solution. Substances in petroleum jelly are applied directly to the disc solution or on filter paper. The chambers are held in place with non-allergenic tape (Micropore® or equivalent) and are left for 48 hours. During this time the patient is instructed to keep the area dry and not to remove or tamper with the tests. Bathing and showering should be avoided until after the final reading. Some would re-examine the skin at 72 and 96 hours if there is no reaction at 48 hours. It gives semi-quantitative scale which is usually reported on a three point scale (+, ++, +++). Toxic/irritant reactions and questionable results should be documented. Most centres use a standard series of the most frequent allergens for all patients and add on other allergens according to patient's clinical history and likely exposure.

Data on patch test findings in Hong Kong are scarce. In a retrospective analysis of all patch tests performed on patients with suspected allergic contact dermatitis in the Social Hygiene Service, a total of 2585 patients were patch tested with the European standard series from January 1995 to December 1999.[27] One or more positive responses were noted in 55% of subjects. The most common allergens were nickel sulfate (24.4%), fragrance mix (13.7%), cobalt chloride (8.7%), p-phenylenediamine (6.0%) and balsam of Peru (5.7%). Nickel sensitivity was more common in female patients and dichromate sensitivity was more common in male patients. A positive atopy history was a significant risk factor for contact allergic sensitivity. We should be cautious about the fact that some atopic subjects may have false negative result due to skin anergy.

In children, allergic contact dermatitis is relatively uncommon. As an infrequent user, we prefer using a commercial kit (True-test®) for patch testing. There is a standardised reading method according to the manufacturer. The main problem is that the applied test may quite easily slough off. We have solved it by additionally applying Tegaderm® or equivalent over it, providing that the patient has no allergic history to such material.

Atopy patch tests have been used in recent studies[28] for identification of cell mediated reactions to foods, particularly in children with atopic eczema. It uses similar technique as Finn Chamber method with food allergen soaked in a filter paper. A diagnostic algorithm (atopy patch test constitutes part of it) has been proposed by several international working groups (Figure 2).[29] A ready-to-use atopy patch test (Diallertest®) is now available in Hong Kong. It is a commercial kit with standard interpretation defined by the manufacturer. It is used to identify cow's milk delayed hypersensitivity. Patient with positive

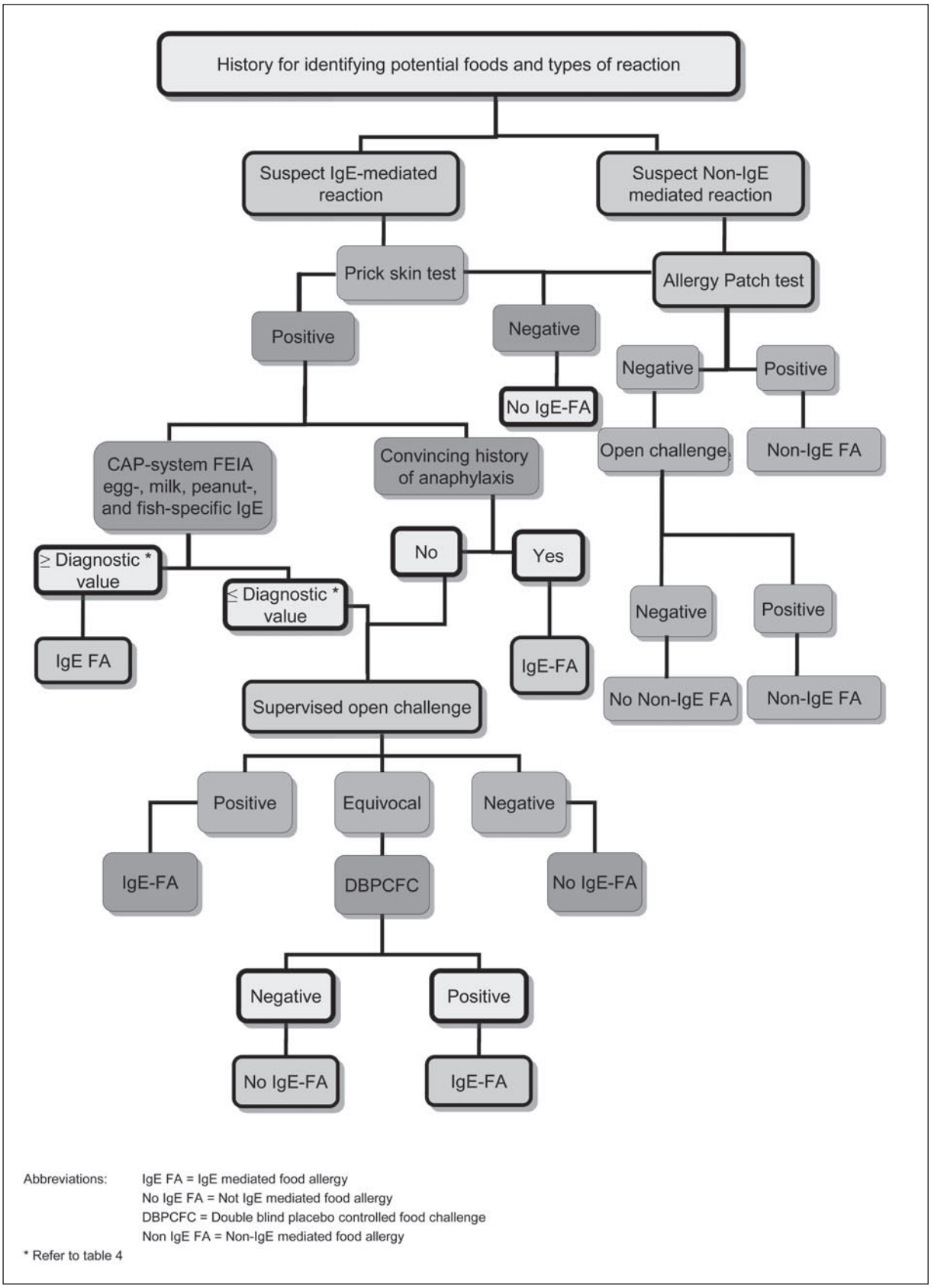

Figure 2. Diagnostic algorithm for food related hypersensitivities.

results is thus recommended to be fed with extensive hydrolysed formula (e.g. Neocate®). The manufacturer of this test is also the manufacturer of the recommended special formula. There is so far only one controlled study sponsored by the company, showing a sensitivity of 76%, a specificity of 90% and 90% PPV in comparing atopy patch test with food challenge.[30] We believe that such test should be properly evaluated in the local population before wide adoption.

Provocation test

The provocation test or challenge test is recognised as the gold standard against all other *in vivo* or *in vitro* tests. Inhalation allergen challenges applied via route of ocular, intra-nasal, respiratory tract are rarely performed nowadays particularly in children. Food and drug challenges are relatively common. Food challenge is by far the most common procedure carried out in the paediatric allergy service under the supervision of trained medical personnel. Food challenge procedure should be properly validated and standardised in administration and documentation. This involves giving a child increasing amounts of a food over a period of about several hours and observing for any objective clinical allergic response within a setting with resuscitative facilities. The different approaches to food challenges are listed in Table 5.

Other tests

Histamine release test

This test measures the histamine release from basophil granulocytes. The results of histamine release test were comparable to the results of SPT and specific IgE-tests. Histamine release test is more complicated for daily clinical practice, but may be a helpful tool in certain cases, e.g. testing for infrequent allergies or drug allergies.

Assessment of indoor allergens

Determination of allergen content in house dust samples (house dust mites, pets) may be useful in order to prove clinically important exposure to the investigated allergens and to monitor avoidance measures.[31] But the main problem of this test is the difficulty in standardising the collection and quantification methodology.

Allergy testing application in clinical scenarios

Atopic dermatitis and food allergy

In our paediatric dermatology clinic, overwhelming majority of cases are being consulted for poorly controlled eczema. Issues concerning food allergy and allergy testing are commonly brought up by parents. Self-initiated avoidance/elimination of a wide range of foods is not uncommonly seen and some may actually render their child with problem of malnutrition and poor growth. From the allergy perspective, literature reports suggested about a third of children with moderate to severe atopic eczema was affected by food allergy, though some recent reports claimed an even higher proportion.[32] The younger the child and the more severe the eczema, the more likely the child is affected by food allergy.[33-36] Egg, milk and peanut allergy account for about 80% of food allergy diagnosed by food challenge in children with eczema and egg allergy is the most common. Appropriate diagnosis of food allergy and elimination of the culprit may lead to significant clearing of eczematous lesions in the majority of food allergy-associated eczema. Infants with eczema and egg allergy are at high risk for developing respiratory allergy.

The diagnosis of food allergy in eczema is complicated by several factors related to the disease: 1) the immediate response to ingestion of causal food is apparently down-regulated with repetitive ingestion, making obvious "cause-effect" relations by history difficult to establish; 2) other environmental trigger factors (other allergen, irritants, infection) may play a role in the waxing and waning of the disease, obscuring the effect of dietary changes and 3) patients have the ability to generate IgE to multiple allergens which may or may not be associated with clinical symptoms,

Table 5. Different approaches of food challenges

Open challenge
- Scientifically less vigor
- Useful in situation to refute the suspected history in which the chance of allergy is low
- Useful for infants and young child in whom subjective symptom is rarely a problem

Single-blind challenge
- Very useful in daily clinical allergy practice
- Less time consuming than double-blind-placebo-controlled challenge
- Often provide an excellent diagnostic aid in confirming or refuting histories of hypersensitivity reactions, in particular circumstances where patient opinions or concerns may influence the outcome.

Double-blind, placebo-controlled challenge
- 'Gold standard'
- Designed to reproduce the individual's signs and symptoms
- Tedious and time consuming, may take days to complete

making diagnosis based solely on laboratory testing impossible.

The best general approach is to screen children suffering from moderate to severe persistent eczema for food sensitization: <1 year to milk and <3 years of age to eggs, cod fish, peanuts by using SPT or RAST, with only additional testing for other suspected food when we obtain the relevant history. If RAST reveals specific IgE to certain foods, then determining the quantity of food-specific IgE antibodies (e.g. CAP-FEIA, Pharmacia) to the positive allergens would indicate whether food challenge are necessary. After this, the best initial treatment is elimination of suspected food from the diet, followed by a food challenge if indicated. Because symptoms are chronic in eczema and often a large number of foods are alleged, it is often necessary to perform diagnostic oral challenge.

Urticaria and angioedema

Causes of acute urticaria can only sometimes be determined and are likely to involve IgE-mediated reactions, viral infections or insect bites and stings. If there is no apparent trigger and temporal relationship with food exposure, the positive yield of doing skin test or RAST is actually quite low. Chronic urticaria (>6 weeks) is typically idiopathic. Physical stimuli (pressure, rubbing, thermal, solar) often contribute to the symptoms. Urticaria must be distinguished from urticarial vaculitis and sometimes skin biopsy may be required. In 40 consecutive local children referred to us for evaluation of chronic urticaria with a median follow up of 26 months, about 60% has a prolonged remission. They have been investigated by a standard panel of allergy test (common inhalation allergen and food allergen screening by SPT or RAST) and autoimmunity screening (ANA, C3 C4, anti-thyroglobulin, anti-microsomal antibody), and fewer than 5% has any positive test of the above panel. C1-inhibitor assay has been studied in 1/3 of patients before seeking our opinion for recurrent angioedema and none actually show positive result. In fact it is quite unnecessary for such test to be done if the case has concomitant urticaria, so called "itchy angioedema". We agree to screen C1-inhibitior in case of painful angioedema, laryngeal oedema, prolonged oedema with poor response to antihistamine and adrenaline and those with positive family history (data from author, manuscript in preparation). C3/4 is an alternative screening test as C1-inhibitor quantification alone may miss a substantial number of those functional deficient cases. Adult studies suggested that contact allergen[37] and food additive[38] seems to be relevant in some of the chronic urticaria

patients. However, similar study in children is currently lacking. Our clinical impression is that food additive may not be very relevant. The majority of parents among our paediatric patients have been doing such measures but this seems unhelpful.

Anaphylaxis, systemic mastocytosis and mast cell tryptase

Anaphylaxis is a potentially fatal multi-system syndrome as a result of massive release of inflammatory mediators from mast cells and basophils. Typically, the symptoms can be cutaneous, respiratory, gastrointestinal and/or cardiovascular. Cutaneous symptoms are the most commonly occurring symptoms in acute anaphylaxis but the absence of cutaneous symptoms does not preclude the diagnosis of anaphylaxis. Strictly, quantification of mast cell tryptase is not an allergen test, but rather to differentiate a true anaphylactic event from other medical emergencies.[39] Tryptase is the most abundant protein in mast cells. It is also found in basophils in much smaller amount. Tryptase proforms are continuously released from the mast cells into the bloodstream reflecting the number of mast cells. Elevated baseline tryptase levels serve as a risk marker for certain patients to get into severe anaphylactic reactions, especially after parenteral introduction of substances such as insect venoms and drugs. Pathological increased levels of tryptase proforms reflect the mast burden in certain haematological abnormalities, neoplasms and the severity grade in systemic mastocytosis.[40] Mature tryptase is released into the blood stream during mast cell activation, either by IgE or non-IgE mediated mechanisms. The transiently increased level of mature tryptase (>10 μg/L), detectable 1 to 4 hours after the onset of systemic symptoms with hypotension, serves as a clinical marker confirming anaphylaxis. The biological half-life for tryptase is about 2 hours. The return of baseline should be verified.[40,41] Since the test availability is quite limited, prior consultation should be made with laboratory immunologist.

Should I develop allergy testing service in my office practice?

The primary care sector is in a state of flux at the moment, owing to reposition of health bureau/ Hospital Authority's service target and parallel discussion about the future shape of the healthcare system including building up a children's hospital. Whatever shape the new system takes, we can be sure that there will continue to be a large number of patients with allergic conditions who will want to know more about their condition, the substance to which they are reacting and what they can do to improve matters. Ideally, this advice should be easily accessible to the patient. It should be possible to provide targeted information and recommended care pathway for individual patients and their advisors in the healthcare system. Anyone who is advising on allergen avoidance or other targeted intervention ought really to be offering a diagnostic service to guide their decision-making. We have been training nurses in doing skin testing and many nurses specialising in food allergy and asthma have already received training in skin testing and allergy advice. However the public sectors are reluctant to deploy them in fulfilling this task as there are other calls on their time and no direct reimbursement.

Skin testing is useful and relatively cheap, but may not be an appropriate option for a practice that only tests a few patients each year. Easy access to and sensible use of immunological tests may be a better option for low-volume users (Table 6). Partnership with secondary/tertiary centre with allergy testing service is economically sound. It is recommended to ensure and strengthen co-operation between specialist sector/hospitals, general practitioners and local home carer in order to benefit the individual patient. The shared care covering both primary and secondary/tertiary sectors should ensure that the right children will get the right tests at the right time, along with the best evidence-based treatment of their allergic disease. Specialist referral should be made if the patient failed to respond to standard therapy, or

Table 6. Determination of allergen specific IgE

	Skin testing	Serology
Method	Prick test	RAST
Availability	Limited	Widely
Expense	Cheap	Expensive
Results	Immediate	Delayed
Risk of anaphylaxis	Rare	Nil
	Antihistamine	
Interference	Extensive eczema	High total IgE
	Dermatographism	
Sensitivity	4+	2+
Specificty	4+	2+
PPV	2+	2+
NPV	4+	3+

Abbreviation: RAST=radioallergosorbent test; PPV=positive predictive value; NPV=negative predictive value; ++++ extremely good; +++ very good; ++ good

where there are possible serious clinical or medico-legal issues (e.g. allergic reaction during anaesthesia and potential anaphylactic reaction). High risk drug and food challenge should be carried out in appropriate clinical settings with trained personnel and resuscitative facility as back-up. Specialist advice should also be sought before starting interventions such as immunotherapy that may have a major impact on patients' quality of life.

Conclusions

Allergy testing is an important pre-requisite for both early identification of infants at increased risk of developing allergic disease and for specific allergy treatment. We recommend to strengthen the co-operation between specialist sector/ hospitals and general practitioners so that the right children will get the right tests at the right time, along with the best evidence-based treatment of their allergic disease.

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