



# Clinical Management of Childhood Food Allergy

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## Childhood Food Allergy

There is an upsurge in demand of clinical service in the management of childhood food allergy in almost every developed place. Certainly, Hong Kong is of no immunity. Is food allergy a growing problem or is it just a diagnostic fashion? I believe that we are looking at a combination of 1) increased rates of sensitisation 2) increased likelihood of sensitisation progressing to disease 3) increased recognition of food allergy 4) increased use of medical services or a change of health seeking behaviour. Food allergy is a huge subject. There are vast diversities in pathogenesis, clinical presentations, cultural and racial variations and many unresolved controversies. In this review, I will try to focus only on some of the core knowledge that we would apply in our daily clinical care.

### Key Concepts

- The prevalence is greatest in the first few years of life. (5% to 8% of children in their first year of life).
- Relative few foods account for about 90% of food allergy (milk, egg, peanut, nuts, soy, wheat, and fish).
- Milk allergy at 1 year of age is a risk factor for additional food allergies in later childhood.
- Food hypersensitivity in early life is found to be a risk factor for atopic dermatitis, and later asthma.
- Food allergy should be differentiated from adverse reactions to food due to non-immunological mechanism

### Case Scenario

Tom, a 14-month-old boy was born after an uneventful pregnancy and delivery. He was exclusively breast fed for 5 months. The mother had unrestricted diet. Eczema developed from 6 to 8 weeks of age. His mother noted at the age of 9 months egg caused a local urticarial reaction on the face and at the age of 10 months less than a quarter of teaspoon of peanut butter produced immediate angioedema of the face. There was no associated vomiting or wheeze. The angioedema resolved after antihistamine when the mother brought her to the private practitioner. Mother wondered whether the ingestion of cow milk in the past had caused mild eczema flares and for this reason he was maintained on soy milk. Mother and the family physician concerned about possible contraindication to MMR and influenza vaccine. In the last few weeks, his eczema has been under good control. He

Provisional diagnosis and problem list:  
Atopic child with following clinical allergy:

- 1) Mild atopic dermatitis
- 2) Food allergy: IgE mediated (Immediate / hypersensitivity) to egg and peanut. Skin test correlated well with history
- 3) Sensitisation to cow milk but of doubtful clinical relevance, which will require formal challenge for evaluation.
- 4) Early onset asthma associated with environmental tobacco exposure and early house dust mite sensitisation

#### Management:

He continues with soy containing diet. Usual care of atopic dermatitis was advised. He was advised to remain off peanut and egg. Detailed discussion with the parents about strategies to reduce environmental tobacco was made. Household avoidance measures of dust mite should be instituted.

also developed bouts of asthma and mostly were viral induced and was started on inhaled steroid and bronchodilator.

#### Family history:

Father : current smoker with personal history of childhood asthma in remission  
Mother : current allergy to shellfish and personal history of childhood atopic dermatitis in remission  
Brother 5: older - mild episodic asthma

#### Physical examination:

Weight and height were along the 25<sup>th</sup> percentile. He looked well apart from patches of eczema distributed over flexural surfaces on both knees, on the nape of the neck and on the face.

#### Investigations:

|  |
|--|
| RAST (Radioallergosorbent tests) Specific IgE KU./L<br>• Milk 1.3, egg 33, peanut, 25                            |
| Skin Prick Test ( positive result: wheal size > 3mm)<br>• Milk 3mm, egg 7mm, peanut 10mm, soy 2mm, dust mite 3mm |
| Total IgE 300 (u/L) ( normal < 100)  |

He was given MMR at community care without adverse reaction. He was advised not to be given influenza vaccine in view of his egg allergy.

EpiPen Jr was prescribed together with an action plan in case of anaphylaxis.

Subsequent hospital-based formal challenge of cow's milk at age of 3 found he was tolerant.

#### Comment:

We are going to review his food allergy problem in 1-2 yearly. 80-90% of children will grow out of egg allergy by age of 8. Peanut allergy is usually persistent. Recent literature reported 10-20% of children may eventually outgrow of the condition. The timing of peanut challenge could be guided by skin test activity or RAST levels. Good asthma control is vital to prevent life threatening food related hypersensitivity.

### Prevalence of Food Allergy in Young Children

| Food      | Young children |           |        |        |       | Adult |
|-----------|----------------|-----------|--------|--------|-------|-------|
|           | USA            | Australia | France | Norway | China |       |
| Milk      | 2.5%           | 2.0%      | 1.1%   | 3.2%   | 1.7%  | 0.3%  |
| Egg       | 1.3%           | 3.2%      | 0.8%   | 2.0%   | 3.0%  | 0.2%  |
| Peanut    | 0.8%           | 1.9%      | 0.7%   | -      | 0.3%  | 0.6%  |
| Tree Nut  | 0.2%           | 0.3%      | 0.7%   | -      | -     | 0.5%  |
| Fish      | 0.1%           | 0.07%     | -      | -      | 0.3%  | 0.4%  |
| Shellfish | 0.1%           | -         | 1.4%   | -      | -     | 2.0%  |
| Overall   | 6%             | -         | 6%     | -      | 5.2%  | 3.7%  |

(Source: Dr. DJ Hill, presented in an invited symposium AAAAI 2006)

### Natural History

Most children become tolerant or seem to "outgrow" their food allergies to milk, soy, and egg within a few years. 85% of children with milk allergy become tolerant by age of 3 years. 70% of children with egg allergy become tolerant by age of 5 years. Loss of clinical hyperactivity to peanut, though less common, occurs in 20% of peanut allergic children by age of 7 years. Older children and adults with food allergies are less likely to become tolerant. Allergies to other nuts, fish, and shellfish are believed to be more persistent.

### Evaluation and Management

In evaluating adverse food reactions, the work-up



depends on the age at onset of the disease (Table 2), on differentiating food intolerance from food hypersensitivity (Table 3), and on differentiating the food hypersensitivity is IgE or non-IgE mediated (Table 4). IgE-mediated allergy typically provokes and on symptoms within minutes to hours. Non-IgE mediated allergy induces symptoms from hours to days. The patient's history not only suggests the type of food hypersensitivity and causative food allergen but also provides information necessary to design an appropriate food challenge for confirming the diagnosis.

Negative prick skin tests is an excellent means of excluding IgE-mediated food allergy.

The majority of children with positive skin tests to foods will not experience allergic symptoms when ingesting that food. The weal size of skin prick and level of food-specific serum IgE help to predict the clinical reactivity upon challenge but not the severity.

Some forms of oral food challenge are necessary to establish the diagnosis of food hypersensitivity. Prescribing a food elimination diet is no different from prescribing any medication and must be based on a firm diagnosis of specific food allergy.

## Skin Testing

Skin testing with allergenic extracts is the favoured method of in-vivo testing for IgE-mediated sensitivity. Positive skin test results are useful for demonstrating sensitivity to the patient and the patient's family, and for improving compliance. Skin testing alone is not diagnostic. Skin test results should be correlated with the patient's clinical history. With standardised allergen reagent and technique, the weal sizes of skin prick test correlates with clinical sensitivity but not severity. The larger the skin reaction size, the more likelihood of clinical reaction upon exposure but the size per se could not predict how severe the reaction will be.

### Methods of skin testing (Diagram 1)

Percutaneous /epicutaneous(prick or puncture),

- Preferred
- Safer
- Easy to perform
- Less painful
- Less sensitive but more specific than intradermal / intracutaneous

### Intradermal/intracutaneous testing

- Reserved for weak extracts such as testing for drug allergy.
- When the prick/puncture test is negative to allergens that are strongly suggested by the patient's history or exposure
- Not used in testing food allergens

### Patch Test

Takes a few hours to 3 days

To evaluate delay hypersensitivity (e.g., atopic dermatitis due to food, contact dermatitis due to chemicals)

The size of the skin test reactions depends on 1) amount of specific IgE, 2)binding affinity of the IgE antibody, 3)releasability of the patient's mast cell, 4)reactivity of the patients' skin to histamine, 5)area of body used for testing, with the back being more reactive than the arms 6)age (baby younger than 4 months may have false negative results)

## Laboratory Test

### Allergen-specific IgE antibody

This is the most important analyte measured in the clinical immunology laboratory for diagnosis of allergic disease. It is performed as a confirmatory test to support a clinical history. Quantitative IgE levels to selected foods (milk, egg, fish, and peanut) if above a pre-defined IgE antibody threshold may eliminate the need for food challenges.

Specific in-vitro IgE immunoassays may be preferable to skin testing for patients who :

- Have severe dermatographism, ichthyosis, or generalised eczema
- Use long-acting antihistamines or tricyclic antidepressants
- Are at undue risk if their medications are discontinued
- Refuse skin testing or cannot cooperate with testing
- Have a clinical history suggesting a higher risk of anaphylaxis with skin testing to a particular allergen.

### Total serum IgE

This is a diagnostic marker for allergic diseases, but its limitation lies in its wide overlap in the total serum IgE levels between atopic and non-atopic populations such as in parasitic diseases, skin diseases, other than eczema, drug induced conditions, hyper-IgE syndrome, etc.

### Mast cell tryptase

This is a marker of mast cell activation during anaphylaxis. Elevated levels, (>10 µg/L) are detectable 1 to 4 hours after the onset of systemic anaphylaxis with hypotension.

## Provocation Test

The provocation test or challenge is recognised as the gold standard against all other in-vivo or in-vitro tests. Food challenge is the most common procedure carried out in the paediatric allergy service under the supervision of trained medical personnel. Food challenge procedures 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. This gives parents or families a scientific structure and a plan for the future and the safety of knowing that any reaction will occur within a setting with resuscitative facilities.

### Open challenge

Scientifically less vigour

Useful in situation to refute the suspected history where the chance of allergy is low.

Useful for infants and young children 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 provides an excellent diagnostic aid in confirming or refuting histories of hypersensitivity reactions, in particular circumstances where patients opinions or concerns may influence the outcome.



### Double-Blind-Placebo-Controlled Challenge (Diagram 2) 'Gold standard'

Designed to reproduce the individual's signs and symptoms

Tedious and time-consuming, may take days to complete

#### Clinical features of food allergy in children (Table 1)

|                                   |   |
|-----------------------------------|---|
| <b>Cutaneous reactions</b>        |   |
| IgE mediated                      | Atopic dermatitis<br>Urticaria<br>Angioedema  |
| Non-IgE Mediated                  | Contact rash<br>Atopic dermatitis (some forms)  |
| <b>Gastrointestinal reactions</b> |   |
| IgE mediated                      | Immediate gastrointestinal hypersensitivity (e.g., nausea, vomiting, diarrhoea)<br>Oral allergy syndrome<br>Colic |
| Non-IgE mediated                  | Allergic eosinophilic oesophagitis, gastritis, or gastroenteritis<br>Dietary protein colitis, enteropathy         |
| <b>Respiratory reactions</b>      |   |
| IgE mediated                      | Rhinoconjunctivitis<br>Asthma<br>Laryngeal oedema<br>Food-dependent exercise-induced asthma                       |
| Non-IgE mediated                  | Pulmonary haemosiderosis (Heiner's syndrome [rare])   |
| <b>Systemic anaphylaxis</b>       |   |

#### Age at onset of food allergy (Table 2)

|          |   |
|----------|---|
| Age (yr) | Food  |
| 0-1      | Milk, egg   |
| 1-2      | Fish, peanut  |
| >2       | Fruits, vegetables                                      |
| >3       | Pollen-related cross-reactivity (oral allergy syndrome) |

#### Food intolerance: adverse reaction to foods (Table 3)

|                          |                          |
|--------------------------|--------------------------|
| Toxic/pharmacologic      | Nontoxic/intolerance     |
| Bacterial food poisoning | Lactase deficiency       |
| Heavy metal poisoning    | Galatosaemia             |
| Scombroid fish poisoning | Pancreatic insufficiency |
| Caffeine                 | Hepatobiliary disease    |
| Tyramine                 | Reflux/hiatal hernia     |
| Histamine                | Anorexia nervosa         |

#### Food allergy spectrum (Table 4)

|                       |  |   |
|-----------------------|--|---|
| IgE-mediated          | →  | Non-IgE mediated  |
| Oral Allergy Syndrome |  |   |
| Anaphylaxis           |  |   |
| Urticaria             |  |   |
|                       | Eosinophilic oesophagitis<br>Eosinophilic gastritis<br>Atopic dermatitis | Protein-induced enteritis<br>Protein-induced enteropathy<br>Coeliac disease |

## Food Allergy in Asia

Food allergy is increasing in prevalence in Western population, but little is known about it in Asia. The perception is that the prevalence in this region is low, but is likely to increase with the global increase in allergy. Asia is unique because of the many different cultures and eating habits, with the resulting occurrence of unique food allergens (Table 5). The lack of availability of epinephrine auto-injectors in many countries is an important issue that needs to be addressed. Large, well designed epidemiological studies

are needed so that the scale of the problem can be understood. The labelling of packaged food manufactured in Asia is another area that needs to be improved.

#### Unique food allergen in Asia (Table 5)

| Food        | Forms/origin                            | Reported in Country           | Allergen identified           | Incidence  | Remarks   |
|-------------|---|-------------------------------|-------------------------------|--|---|
| Birds nest  | Chinese delicacy/the saliva of swiftlet | Singapore<br>Hong Kong<br>SAR | A 66 KDa glycoprotein         | Most common cause of anaphylaxis in Singaporean children                           | May outgrow in adulthood                                  |
| Buckwheat   | Noodles, cakes/grain                    | China<br>Japan<br>Korea       | Yes                           | Ranked fourth in Japan   |   |
| Chestnut    | Desserts/ tree nut                      | Korea                         | At least nine major allergens | Most common food allergen in Korea   | Cross react with avocado, peach, apple and mugwort pollen |
| Chickpea    | Staple food/legume                      | India                         | Under study                   | 1 in 4 of patients diagnosed of food allergy in India are patients of food allergy |   |
| Royal jelly | Health tonic/bees                       | Hong Kong<br>Australia        | Under study                   | Reports of asthma exacerbations  |   |
| Sesame      | Seasoning/grains                        | Israel<br>Australia           | Under study                   | Third most common food allergen in Israel  |   |

## Food Anaphylaxis

Anaphylaxis is a potentially fatal multi-system syndrome resulting from 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. These symptoms often have an explosive onset, occurring within seconds to minutes of exposure to the triggering agent, but can also be delayed for several hours after the initial exposure. The acute anaphylactic event can be followed by a late-phase or biphasic reaction occurring 3 to 8 hours after the initial reaction. Biphasic anaphylaxis occurs in 5% to 20% of anaphylactic reactions. Half of fatal anaphylaxis occurs within the first hour.

In our practice, the common triggers are cow milk, egg, fish and peanut. According to Western data, peanut and tree nut are the most common causes of fatal anaphylaxis in children. Idiopathic anaphylaxis is relative uncommon in children. Anaphylactoid (non-IgE-mediated) reaction may occur on the first exposure, whereas IgE-mediated and immunological mediated anaphylactic reactions require sensitisation from a previous exposure unless there is cross-reactivity. Sensitisation is possible through in-utero placental transfer of allergens. This explains why some infants have reaction upon first exposure of foods like cow milk, hen's egg and peanut.

#### Epinephrine

Epinephrine is universally recommended as the drug of choice in the treatment of acute anaphylaxis and the preferred route of administration in children is intramuscular. Epinephrine is a potent catecholamine with both  $\alpha$ -adrenergic and  $\beta$ -adrenergic properties.



The actions of epinephrine reverse all the pathophysiological features of anaphylaxis. Hypotension, peripheral vasodilatation, increased permeability, urticaria, angioedema are all reversed by the  $\alpha$ -adrenergic stimulation from epinephrine. The success of cardiopulmonary resuscitation is often dependent upon restoration of aortic diastolic pressure. Increased aortic pressure enhances myocardial perfusion and cerebral perfusion is improved by increased carotid arterial pressure, both of which are results of arterial vasoconstriction and selective redistribution of cardiac output from the  $\alpha$ -adrenergic effects of epinephrine. The  $\beta$ -agonist properties of epinephrine have positive inotropic and chronotropic effects on cardiac muscle, cause bronchodilation, and increase the production of intracellular cyclic AMP, thereby inhibiting mast cell mediator release.

The current recommendation of epinephrine dosage is 0.01ml/kg every 10 to 20 minutes up to a maximum of 0.3 to 0.5ml of 1:1000 w/v dilution. Epinephrine is available for out-patient use by parents and patient in a user friendly pre-loaded autoinjector, EpiPen® and EpiPen Jr®. This is a single-use device. EpiPen® dispenses one 0.3mg/dose of 1:1000w/v aqueous epinephrine solution and EpiPenJr® dispenses one 0.15mg /dose. The EpiPen dose is appropriate for a 30kg person, and EpiPen Jr dose is appropriate for a child 15 kg. The autoinjectors are administered intramuscularly into the vastus lateralis muscle of the thigh. (Diagram 3)

Antihistamine, systemic corticosteroids, and bronchodilators are secondary medications to be given after epinephrine has been administered. Pretreatment with corticosteroids and antihistamines is often ineffective in preventing biphasic anaphylaxis.

Patients with anaphylaxis need a thorough, comprehensive allergy-immunology evaluation to diagnose the specific aetiology. It aims to prevent contact with the allergens that will induce anaphylaxis in susceptible individuals, and to provide strategies for dealing with episodes of 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 for pre-hospital treatment. Because fatal anaphylaxis occurs despite timely and appropriate treatment, successful avoidance strategies and education remain the mainstay of management.

### Frequently asked questions:

What can I do during pregnancy to reduce the chance of my child developing allergies?

- Ensuring the baby's mattress and bedding is free from mite allergen
- Reducing animal allergens
- Reducing dampness in the house
- Developing a smoke-free environment
- Preparing to breast feed
- Does not justify putting pregnant woman on special diet

When is it safe to start to give peanut butter to children?

- for children with atopic parents, it is probably best to avoid it completely before age of 6 months and arguably, the longer you delay the less likely the child is to become allergic to peanut.

- most of the sensitisation of peanut seems occur before age of 2years.

What is the current advice regarding egg allergy and MMR?

- Egg allergy is not a contraindication to MMR (measles, mumps, rubella) vaccination.
- for those children who have experienced a very severe allergic reaction to egg, the vaccination should be given in a hospital setting, where the vaccine can be given by someone trained and equipped to deal with the very small chance of a reaction.
- where the allergy is mild the vaccination may be given in the community.

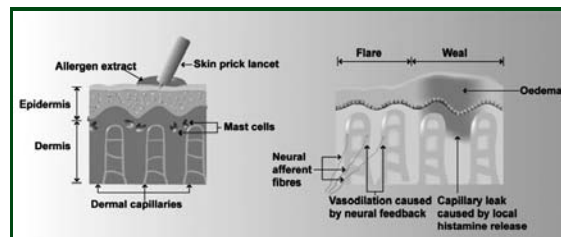


Diagram 1a. Patho-physiology of skin weal response

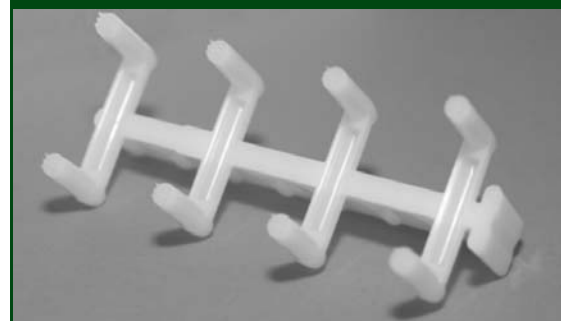
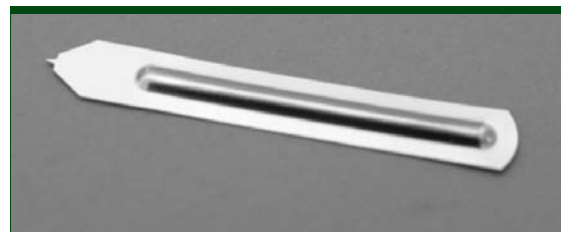


Diagram 1b. Different SPT devices (single head lancet vs. multi-test adaptor)

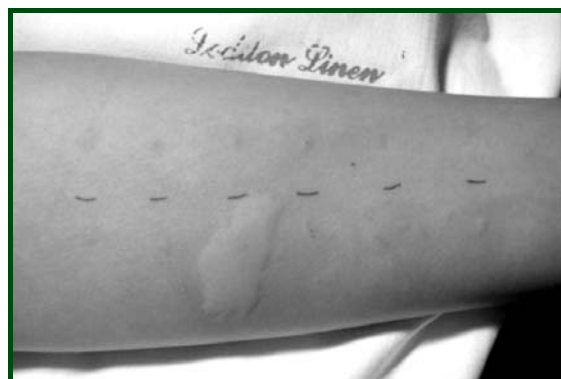


Diagram 1c. A child with peanut allergy shows strong skin reaction to peanut extract

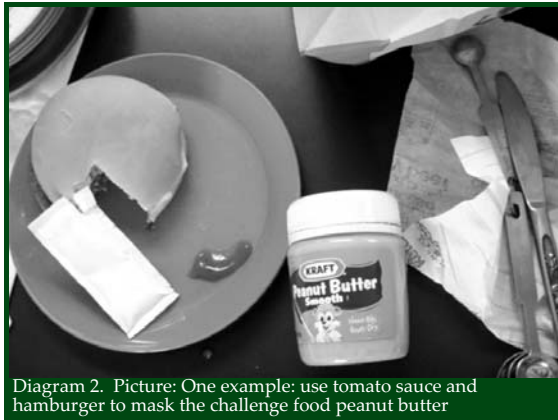


Diagram 2. Picture: One example: use tomato sauce and hamburger to mask the challenge food peanut butter



**SAMPLE Action plan for Anaphylaxis**

Label here

Name: \_\_\_\_\_

Date of Birth: \_\_\_\_\_

Known severe allergies: \_\_\_\_\_

Parent /carer name (s): \_\_\_\_\_

Work Phone: \_\_\_\_\_

Home Phone: \_\_\_\_\_

Mobile Phone: \_\_\_\_\_

Plan Doctor: \_\_\_\_\_

Doctor In-Charge: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**MILD TO MODERATE ALLERGIC REACTION**

→ swelling of lips, face, eyes  
→ hives (urticaria)  
→ abdominal pain, vomiting

**ACTION**

→ stay with child and call for help  
→ give medications (if prescribed)  
→ locate EpiPen® or EpiPen® Jr  
→ contact parent/carer

**Watch for signs of Anaphylaxis**

**ANAPHYLAXIS (SEVERE ALLERGIC REACTION)**

→ difficulty/hoarse breathing  
→ swelling of tongue  
→ swelling/tightness in throat  
→ difficulty talking and/or hoarse voice  
→ wheeze or persistent cough  
→ loss of consciousness and/or collapse  
→ pale and floppy (young children)

**ACTION**

→ Give EpiPen® or EpiPen® Jr  
→ Call ambulance, Telephone: 999  
→ Contact parent/carer  
If in doubt, give EpiPen® or EpiPen® Jr

Additional Instructions \_\_\_\_\_

**How to give EpiPen® or EpiPen® Jr**

Diagram 3. EpiPen®

**Suggested reading:**

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