Academy of Medicine, Singapore

Management of Food Allergy

AMS-MOH Clinical Practice Guidelines 2/2010

College of Paediatrics and Child Health, Singapore

College of Family Physicians, Singapore

MINISTRY OF HEALTH
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Asthma and Allergy Association

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Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Management of Food Allergy

AMS-MOH Clinical Practice Guidelines 2/2010

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

Foreword

Food allergy is an adverse immune response to food allergens and can cause a myriad of symptoms including anaphylaxis, which is life-threatening. Food allergy has been recognised as a major paediatric health problem in Western countries, due to the severity of reactions and a dramatic increase in prevalence over recent decades.[*]

In Singapore, a large population-based survey of Singaporean children estimated the prevalence of food allergy in children to be between 4-5%;[†] however, this is likely to be significantly overestimated as there tends to be considerable discrepancy between self-reported food allergy and confirmed diagnoses of food allergy. For example, food intolerances such as lactose intolerance may be mistaken as food allergy.

Established diagnostic tests for food allergy are available but unproven tests are widely used in Singapore. The correct diagnosis and management of food allergy is important as it prevents the unnecessary restriction of food, which could lead to malnutrition in children and adversely affect health-related quality of life.

These guidelines incorporate the best available evidence from the scientific literature and local expert opinion. I hope these guidelines will assist all healthcare professionals in Singapore in the management of food allergy.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

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[*] National Institute for Health and Clinical Excellence. Food allergy in children and young people: draft scope for consultation. [Online]. 2010 Jan [cited 2010 Mar 2]. Available from: URL: http://www.nice.org.uk/nicemedia/pdf/FoodAllergyDraftScope.pdf

[†] Lee BW, Chew FT, Goh DYT. Changing prevalence of childhood allergic diseases in Singapore. In 5th West-Pacific Allergy Symposium & 7th Korea-Japan Joint Allergy Symposium. 1997:17-22

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

IgE-mediated food allergy

D Patients with food-induced anaphylaxis should be observed in an appropriate medical facility (hospital, accident and emergency department, or clinic) for a minimum of 6 hours post onset of reaction (pg 19).

Grade D, Level 4

GPP Patients with food-induced anaphylaxis should be referred to a specialist experienced in treating food allergies so that a detailed evaluation can be carried out. This evaluation should include diagnostic confirmation, assessment of cross-reacting foods (especially in nut and fish allergy), education on prevention of further episodes, such as avoiding hidden sources of food allergens, and emergency treatment in case of accidental exposure (pg 19).

GPP

B Chronic urticaria and chronic angioedema are rare, if at all, manifestations of food allergy, but is commonly suspected by the patient. Food allergy evaluation is therefore rarely indicated in chronic urticaria and angioedema (pg 20).

Grade B, Level 2+

GPP Without associated gastrointestinal, dermatologic, or systemic symptoms, rhinitis is a very rare manifestation of food allergy. Therefore, there is no role for routine investigation for food allergy in patients with rhinitis (pg 20).

GPP

D To reduce the likelihood of a false negative result, patients have to stop using antihistamines before skin testing. The length of time of withdrawal depends on the nature of the antihistamine. For example, long-acting antihistamines like loratadine and cetirizine should be avoided for 10 days and short-acting ones like chlorpheniramine and diphenhydramine for 3 days before the test (pg 21).

Grade D, Level 4

GPP The choice of the specific test to order for IgE-mediated food allergy must be directed by the clinical history (pg 24).

GPP

GPP The practitioner should not order a large number of specific IgE tests to screen for allergy when the diagnosis of IgE-mediated food allergy has not been established (pg 24).

GPP

GPP The attending medical practitioner must take into account the context in which he or she practices and the patient's condition when choosing between skin testing and in vitro specific IgE testing (pg 24).

GPP

B Children with moderate to severe atopic dermatitis may benefit from investigations to assess for food allergy. The investigations must be interpreted in context and confirmed with food challenges and, if necessary, food avoidance. In most situations, these tests should be carried out by specialists experienced in treating food allergies (see also Chapter 5) (pg 24).

Grade B, Level 2+

GPP After an IgE-mediated reaction, it is reasonable to wait 4-6 weeks before ordering the specific IgE test to reduce the chance of a false negative result (pg 25).

GPP

C Oral food challenges can be considered for the following purposes:-

- To identify foods causing acute reactions for initial diagnosis of food allergy.
- To determine if the patient has outgrown his/her food allergy.
- To expand the diet in persons with multiple dietary restrictions, because of subjective complaints such as headaches or hyperactive behaviour.
- To assess the status of tolerance to cross-reactive foods.
- To determine whether food allergens associated with chronic conditions such as atopic dermatitis or allergic eosinophilic esophagitis will cause immediate reactions.

(pg 25) **Grade C, Level 2+**

GPP Defer oral food challenges if there is a high likelihood of allergic reaction as predicted by food reaction history (pg 26).

GPP

D To prepare for the oral food challenges, suspected food allergens should be eliminated for 1 to 2 weeks prior to the food challenge for IgE-mediated allergies, and antihistamines stopped for the appropriate period of time to promote a normal histamine response (pg 28).

Grade D, Level 2+

D The total amount of challenge protein used for IgE-mediated allergies, is 0.15 to 0.3 g protein per kg body weight with a maximum of 10 g of the dry food (double for wet foods such as meat and fish, or 200 ml milk). The total amount of challenge protein must be given in sequentially increasing doses with approximately 15 minutes interval for each dose as shown in Table 3 (pg 28).

Table 3 Example of incremental challenge protein doses with their serving time

Time (minutes)	Dose / Percentage of total protein	Dry weight of challenge protein (g)	Cumulative dry weight of challenge protein (g)
0	1%	0.1	0.1
5	4%	0.4	0.5
20	10%	1	1.5
35	20%	2	3.5
50	20%	2	5.5
65	20%	2	7.5
80	25%	2.5	10

Grade D, Level 2+

D The medical practitioner or health care professional needs to record the dose of challenge protein given, the time of administration, vital signs, and any subjective symptoms or objective signs that arise during the challenge. Assess frequently for symptoms or signs that affect the skin, gastrointestinal tract, and/or cardiovascular system (pg 29).

Grade D, Level 2+

C Significant reactions can occur with oral food challenges in high risk patients. Therefore, oral food challenges for these patients are best performed by specialists experienced in treating food allergies and immunologists, and carried out in clinical settings equipped with resuscitation facilities and staffed with trained allied health personnel (pg 29).

Grade C, Level 2+

GPP A physician-supervised oral food challenge is recommended to confirm or refute allergy to this food in patients who present with histories of convincing immediate allergic reactions to a food (within 2 hours), or who present with histories of anaphylaxis to the food in question in isolation or in a mixed meal, even in the setting of negative laboratory and skin tests, provided the benefits of a food challenge outweigh the risks, and with the patient's/parent's informed consent (pg 29).

GPP

GPP Patients with negative skin tests, undetectable serum food-specific IgE levels, and no history of convincing symptoms of immediate food allergies (e.g. symptoms limited to behavioral changes or delayed/chronic gastrointestinal symptoms) can undergo gradual home introduction of the food in question (pg 29).

GPP

D Patients should be monitored for 1 to 2 hours before discharge for home if they tolerate the challenge. However, for those who have allergic reactions during the oral food challenges, they should be observed for 2 to 4 hours after symptoms have resolved with treatment (pg 30).

Grade D, Level 2+

B Patients who have undergone and passed their oral food challenges should be instructed to introduce the challenge foods into their diet (pg 30).

Grade B, Level 2++

B Patients who fail their oral food challenges should be provided emergency treatment plans for allergic reactions, education regarding food avoidance, dietary implications of food avoidance, and recommendations for follow-up visits and evaluations (pg 30).

Grade B, Level 2++

GPP Patients with food allergies should be advised on:

1) Cross-reacting allergens in other foods (Refer to Table 4 on page 44).
2) Hidden food allergens, and should be aware about the importance of reading food labels carefully and having a knowledge of some scientific names (e.g. casein, and whey for cow's milk and ovalbumin for chicken's egg).
3) High risk situations, and therefore the need to enquire at restaurants or parties etc (wherever cooked food is served or offered), and to take other measures to prevent inadvertent exposure to known or suspected allergens or contamination in children with high risk of anaphylaxis.
   (pg 32)

GPP

B In specific foods, re-evaluation of patients with food allergy may be important to determine if food allergy has been lost over time. A food challenge should be recommended when the skin prick test or the IgE specific test is negative or shows a decrease to low levels (guide in Figure 3) on follow up (pg 33).

Grade B, Level 2++

D If there is a history of suspected or proven IgE-mediated anaphylactic reactions to foods, injectable epinephrine should be given to patients and/or caregivers to carry with them and they should be instructed in its use (pg 35).

Grade D, Level 4

GPP A written Food Allergy Anaphylaxis Action Plan (see Annex A) should accompany each patient prescribed with an epinephrine auto-injector (pg 35).

GPP

B In the event of a life threatening anaphylaxis event, the use of self injectable intramuscular epinephrine 0.01mg/kg (maximum dose of 0.5mg) is advised as the first-line treatment. Epinephrine can be administered every 5-15 minutes intramuscularly as necessary to maintain blood pressure and control symptoms (pg 35).

Grade B, Level 2+

B Intramuscular epinephrine should be administered to the anterior-lateral thigh as this has been shown in non-anaphylactic children to lead to peak plasma concentrations attained more quickly with more absorption as compared with subcutaneous administration (pg 35).

Grade B, Level 2+

D Prophylactic medications have not been shown to be effective in managing life-threatening reactions to foods, therefore, oral antihistamines and steroids are used mainly for the cutaneous manifestations, but not as first line medications in the event of anaphylaxis (pg 35).

Grade D, Level 4

D Corticosteroids may be used to alleviate late phase biphasic anaphylactic reactions in high risk individuals (pg 35).

Grade D, Level 4

D There are no firm guidelines for the recommendation of an epinephrine autoinjector but the guidelines adapted from ASCIA (2009), outlined below, can be used:

Epinephrine Autoinjector Prescription Guidelines

RECOMMENDED

- History of anaphylaxis (if patient is considered to be at continuing risk)

MAY BE RECOMMENDED

History of a generalised allergic reaction with one or more of the following:

- Asthma - concurrent or past history
- Age - Adolescents and young adults have greater risk of fatal food anaphylaxis. Most recorded fatal reactions to foods (~90%) occur in children over the age of 5 years.
- Adults have a greater risk of fatal stinging insect anaphylaxis than children.

Specific allergic triggers

- Nut allergy (to peanuts or other nuts) - Most deaths from food anaphylaxis occur from nuts. Generalised allergic reactions can be triggered by exposure to trace or small amounts of nuts, which can be difficult to avoid. Subsequent allergic reactions to nuts may be unpredictable.
- Stinging insect allergy (bees, wasps, jumper ants) in adults

NOT NORMALLY RECOMMENDED

- Asthma - in patients with asthma without anaphylaxis or generalised allergic reactions
- Elevated specific IgE only (positive food allergen IgE and/or skin test) without a history of clinical reactions. Positive test results alone do not necessarily mean there is allergic disease. These patients may be referred to allergy specialists for assessment of allergy and anaphylaxis risk. This may include further investigations such as challenge testing.
- Family (rather than personal) history of anaphylaxis or allergy. Whilst the risk for allergic disease is inherited, anaphylaxis is not inherited.
- Local reactions to insect stings in adults and children. Generalised skin rash (only) to bee or wasp stings in children.
- Resolved food allergy

Dose recommendation for epinephrine autoinjector Epipen® **Prescription**

Epinephrine autoinjector/Junior (0.15mg)	0-6 years or < 20kg
Epinephrine autoinjector/Adult (0.3mg)	Over 7 years or > 20kg

Advice to patients for care of Epinephrine autoinjector

1. Carry the pen with them at all times.
2. Protect the pen from heat and light.
3. Check expiry date and get replacement from doctor ahead of time.
4. After the autoinjector has been used, the needle remains protruding out so *it needs to be carefully disposed of. Although there is fluid left it cannot be re-used. Get* replacement autoinjector from doctor.

B Medical practitioners should not prescribe goat or sheep's milk to cow's milk allergic individuals as these milks cross-react with cow's milk (pg 38).

Grade B, Level 2++

GPP Management of IgE-mediated cow's milk allergy with or without anaphylaxis in infants will generally involve formula replacement with a soy-based formula and if not tolerated, an extensively hydrolysed formula (eHF) or amino acid based formula (pg 38).

GPP

B MMR vaccine is not contraindicated in egg allergy and can be safely given in the normal manner. Medical practitioners should be aware that anaphylaxis can happen after any vaccination, therefore all vaccinations should be performed in a setting equipped to deal with such emergencies (pg 39).

Grade B, Level 2++

D Patients with egg allergy who need the influenza vaccine should be referred to a clinical facility experienced in the management of anaphylaxis. A 2 dose, split protocol (e.g. 1/10 dose followed by 9/10 30 minutes later) can be considered in those with a history of anaphylaxis to egg or uncontrolled asthma (pg 39).

Grade D, Level 4

D A severe reaction to egg is a contraindication to influenza immunization. Individuals with reactions less than severe anaphylaxis can be immunised with the influenza vaccine if skin prick and intradermal tests with the vaccine are negative (pg 39).

Grade D, Level 3

C Patients with peanut allergy can generally tolerate other beans (95%), even soy. Avoidance of all legumes is unwarranted (pg 40).

Grade C, Level 2+

D It is appropriate to eliminate all other tree nuts from the diet if the child with tree nut allergy has never consumed other nuts (pg 41).

Grade D, Level 3

D Patients with fish allergy should avoiding eating all other species of fish. On the rare occasion that a fish-allergic patient has eaten another species of fish without reaction, he can continue eating that species (pg 41).

Grade D, Level 3

D Patients who are allergic to one type of crustacean should avoid eating other types of crustaceans. A referral to a specialist experienced in treating food allergies may be appropriate to define the precise types of crustacean to avoid (pg 42).

Grade D, Level 2+

Non-IgE and mixed-IgE / Non-IgE-mediated gastrointestinal food allergies

D Allergic eosinophilic esophagitis should be considered in infants and children with gastro-esophageal reflux-like symptoms and/or feeding problems who do not respond to gastric acid suppression, particularly if there are associated atopic manifestations (pg 48).

Grade D, Level 3

D Skin prick testing for food and environmental allergens could be considered in patients with allergic eosinophilic esophagitis so that potential allergens and the atopic status of these patients can be identified (pg 48).

Grade D, Level 3

D Endoscopy and biopsy of the lower esophagus (>15 eosinophils/hpf) is diagnostic in the appropriate clinical setting, and should be performed to confirm the diagnosis of allergic eosinophilic esophagitis (pg 48).

Grade D, Level 3

D Gastric acid suppression should be considered as co-therapy for allergic eosinophilic esophagitis (pg 49).

Grade D, Level 3

D Elimination diet (exclusion of the 5 common allergenic foods: Milk, Soy, Egg, Wheat & Peanut) should be considered in all children diagnosed with allergic eosinophilic esophagitis (pg 49).

Grade D, Level 3

D There is limited benefit for the use of other pharmacoogical agents in the treatment of allergic eosinophilic esophagitis. Systemic corticosteroids, topical corticosteroids, leukotriene-receptor antagonists and cromolyn sodium may be tried (pg 49).

Grade D, Level 3

D Biopsy of the gut to demonstrate presence of eosinophils should be done for diagnosis of allergic eosinophilic gastroenterocolitis (pg 50).

Grade D, Level 3

D Skin prick testing and patch testing to food allergens may be done to identify IgE-mediated and cell-mediated food allergies (pg 51).

Grade D, Level 3

D In allergic eosinophilic gastroenterocolitis, the elimination of the implicated food and the use of an amino-acid based formula is recommended (pg 51).

Grade D, Level 3

D In the treatment of allergic eosinophilic gastroenterocolitis, corticosteroids, sodium cromoglycate and montelukast can be used as alternative treatments, but symptoms can recur on weaning the systemic corticosteroids (pg 51).

Grade D, Level 3

GPP Skin prick test and serum food-IgE levels may be used to delineate concomitant IgE-mediated food allergy but are not useful for diagnosis of food protein-induced enterocolitis syndrome (pg 52).

GPP

D Treat Food Protein-Induced Enterocolitis Syndrome with food allergen elimination (pg 52).

Grade D, Level 3

D In patients with reactions to cow's milk and/or soy milk formulas in Food Protein-Induced Enterocolitis Syndrome, which often coexist, an extensively hydrolysed milk formula is recommended. In those who do not tolerate these hydrolysates, an amino acid-based formula is recommended (pg 52).

Grade D, Level 3

D In Food Protein-Induced Enterocolitis Syndrome, food challenges should be conducted under medical practitioner supervision in a hospital setting with resuscitation medications available (pg 53).

Grade D, Level 3

GPP Food patch testing is not recommended for the evaluation of allergic enteropathy (pg 53).

GPP

GPP Endoscopy and biopsy of the small bowel is recommended for the diagnosis of allergic enteropathy (pg 54).

GPP

GPP Eliminate the food allergen in patients with allergic enteropathy. This leads to the clearing of gastrointestinal symptoms within 3 to 21 days (pg 54).

GPP

D In allergic enteropathy, a graded home food challenge can be tried following discussion with the patient. If still sensitised, symptoms may recur within days or up to several weeks. Most patients outgrow their hypersensitivity at between the ages of 1-3 years (pg 54).

Grade D, Level 4

GPP For the diagnosis of allergic protocolitis, skin prick test and serum food-specific IgE levels are not required. Endoscopic examination is also not needed for diagnostic purposes. However, if symptoms fail to respond to elimination of suspected food allergen (cow's milk in most cases), then endoscopic examination with histological diagnosis is recommended (pg 55).

GPP

D In allergic proctocolitis, treatment by elimination of the food allergen is indicated if significant blood loss is present. Mild cases can resolve spontaneously (pg 55).

Grade D, Level 3

D In allergic proctocolitis, eliminate cow's milk from the mother's diet if the mother is breastfeeding (pg 55).

Grade D, Level 3

D In allergic proctocolitis, for cow's milk formula or soy milk fed infants, an extensively hydrolysed milk formula is recommended, due to the high rates (up to 30%) of concomitant cow's milk protein and soy protein allergy. Only in rare instances is an amino-acid based formula required. Clearance of symptoms typically occurs within 48-72 hours (pg 56).

Grade D, Level 3

D In allergic proctocolitis, a gradual food introduction at home can be attempted after the age of 1 year as tolerance of the allergen is usually attained by that age (pg 56).

Grade D, Level 3

Atopic eczema dermatitis syndrome and food allergy

GPP Consider evaluating for food allergy in young children with moderate to severe atopic dermatitis eczema syndrome who do not respond to optimized topical treatment, and in those with a history suggestive of IgE-mediated reactions. Foods commonly involved are hen's egg, cow's milk and soy (the role of wheat is far less clear) (pg 59).

GPP

GPP In young children with moderate to severe atopic dermatitis eczema syndrome, a trial of limited food allergen (e.g. cow's milk and eggs) elimination for a limited period (up to one month to monitor for response) may be considered as long as the nutrition is not affected (pg 59).

GPP

Unproven and disproved allergy tests

B Medical practitioners should not order unproven and disproved allergy tests because they do not have scientific basis and do not provide objective and reliable diagnosis of allergy (pg 63).

Grade B, Level 2++

B Patients who are found to have positive test results with one or more of the unproven or disproved tests should not be told that they have food allergy but they should be re-evaluated so that a precise diagnosis may be offered (pg 63).

Grade B, Level 2++

Primary prevention of food allergy

A Allergen avoidance during pregnancy to prevent allergy in the offspring is not recommended as it has not been shown to be effective, and more importantly, it may adversely affect maternal and/or fetal nutrition (pg 65).

Grade A, Level 1+

B Breast feeding is highly recommended for all infants irrespective of atopic heredity. The most striking results on primary prevention have been shown for exclusive breast feeding for at least 4-6 months (pg 65).

Grade B, Level 2++

B Maternal dietary modification while breastfeeding is not recommended for the prevention of food allergy in the offspring (pg 65).

Grade B, Level 2++

A Breastfeeding is also highly recommended for high-risk infants, as exclusive breastfeeding is more protective than hydrolyzed formula. However, a hydrolyzed formula can be recommended for high-risk infants who cannot be completely breastfed (pg 66).

Grade A, Level 1++

C Cow's-milk based formula should be avoided in the first 5 days of life as the administration of cow's milk-based formula during the first 5 days in the newborn nursery increases the risk of specific sensitization (pg 66).

Grade C, Level 2+

B Weaning to semisolid foods should be delayed for at least 4-6 months for all infants (pg 67).

Grade B, Level 1+

B It is unnecessary to delay introduction of solid food after 4-6 months of age as there is no evidence that it is useful to prevent food allergy. In fact, delayed introduction of solids beyond 6 months may increase the risk of food allergy (pg 67).

Grade B, Level 2++

1 Introduction

1.1 Objectives and scope of guideline

Food allergy, whether true or perceived, is a common clinical problem. The guidelines are not to be viewed as a protocol, but it aims to provide consensus on the diagnostic approach to food allergy as well as to debunk misconceptions that may lead to unnecessary use of disproven and invalidated tests.

1.2 Epidemiology

The prevalence of true food allergy tends to be overestimated due to over-reporting and subjective bias by patients. Other forms of food intolerances, which include lactose intolerance and pharmacological effects, such as palpitations induced by caffeine in beverages and migraine induced by tyramine in cheese, may be mistaken as food allergy.

Nonetheless, a global increase in the prevalence of IgE-mediated food allergy in children has been observed in recent years, and appears to follow the epidemics of childhood asthma and other allergic diseases. These increases have been greatest in populations with affluent and westernized lifestyle. Peanut allergy has increased dramatically in the western world, with more recent studies showing prevalence figures of more than 1% in children.[1, 2] In contrast, peanut allergy in a Singapore schoolchildren survey was estimated to be not more than 0.6%.[3] The prevalence of true food allergy in Singapore is unknown. It has been reported to affect approximately 4-5% of Singaporean schoolchildren.[4]

1.3 Target group

The target groups of these guidelines are all medical practitioners and other healthcare professionals involved in the management of patients with food allergy. The layman's version is an educational resource for food allergy sufferers and parents with children with food allergy, as well as other professions such as teachers and food caterers, who are in contact with and care for or serve individuals with food allergy.

1.4 Guideline development

These guidelines have been produced by a committee comprising paediatricians and an internist, with an interest in either allergy, gastroenterology and developmental paediatrics; a general practitioner, dieticians and patient representatives appointed by the Ministry of Health Singapore and Academy of Medicine Singapore. They were developed using the best available current evidence and expert opinion.

1.5 Review of guidelines

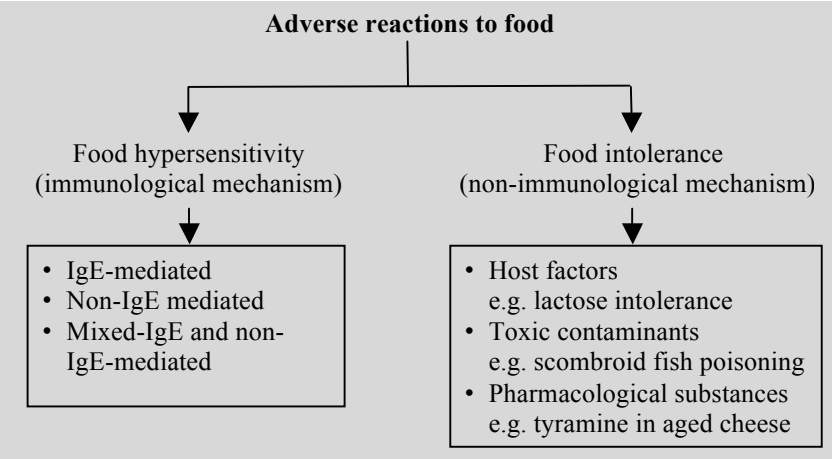
Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Definition and Classification

2.1 Definition

Food allergy or hypersensitivity is a subcategory of adverse reactions to food. Figure 1 illustrates the classification of adverse food reactions. Food allergy or hypersensitivity is defined as an adverse reaction to food where an immunological mechanism has been demonstrated. The term IgE-mediated food allergy is used when IgE is involved in the reaction; and non-IgE-mediated food allergy is used when other immunological mechanisms are implicated.[5]

Figure 1 Classification of adverse reactions to food



2.2 Classification

Food allergy may be classified based on:

i. The underlying immunological mechanism
   - IgE-mediated
   - Non-IgE-mediated

ii. Onset of symptoms following exposure
   - Immediate (usually within 2 hours)
   - Delayed

3 IgE-mediated food allergy

3.1 Clinical features

IgE-mediated food reactions are characterized by a close temporal relationship between the reaction and prior exposure to a specific food allergen. These reactions can be sudden, unexpected, severe, and life-threatening.

The characteristic features are as follows:

1) rapid onset of symptoms following ingestion or exposure to the food allergen (often within minutes and usually by 2 hours),
2) small amounts of food may elicit severe reactions, and
3) reactions usually recur with re-exposure.

Classification of severity:

The severity of IgE-mediated food allergic reactions is assessed by the presence or absence of anaphylaxis. The clinical features of food allergic reactions may include:

- Upper and lower respiratory - rhinoconjunctivitis, laryngeal edema, and wheezing
- Cardiovascular - hypotension* and shock
- Cutaneous - flushing, urticaria and angioedema often with pruritis,
- Gastrointestinal - vomiting, abdominal cramps and diarrhoea

Features of respiratory and/or cardiovascular compromise are prerequisites for the diagnosis of anaphylaxis. **Anaphylaxis is therefore diagnosed when there is the presence of respiratory compromise and/or hypotension.** It should be appreciated, however, that anaphylaxis may present without cutaneous symptoms. The presence of anaphylaxis is regarded as life threatening and warrants immediate emergency management. The definitive pharmacotherapy for anaphyalxis is intramuscular epinephrine (0.01mL of 1:1000 dilution/kg every 5-15 minutes as needed; maximum 0.5mL per dose). Detailed management of anaphylaxis is clearly described in Miles et al (2005). [6]

* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [12 x age]) from 1 to 10 years, and less than 90- mm Hg from 11 to 17 years

Anaphylaxis often occurs in the acute form, but although uncommon in our population, biphasic reactions may occur. Biphasic reactions typically occur up to 8 hours but have been reported as late as 24hrs after the first reaction.[7] The frequency of these reactions have been reported to vary between 5-20% in paediatric series, and slightly higher in adult series.[7-9] Although the biphasic reaction can be milder, there may be considerable risk of intractable hypotension resulting in mortality.

D Patients with food-induced anaphylaxis should be observed in an appropriate medical facility (hospital, accident and emergency department, or clinic) for a minimum of 6 hours[10] post onset of reaction.

Grade D, Level 4

Recognition of the variable and different presentations of anaphylaxis is therefore critical to providing effective therapy with epinephrine and reducing inappropriate use of antihistamines and glucocorticoids as first line therapy.[11]

GPP Patients with food-induced anaphylaxis should be referred to a specialist experienced in treating food allergies so that a detailed evaluation can be carried out. This evaluation should include diagnostic confirmation, assessment of cross-reacting foods (especially in nut and fish allergy), education on prevention of further episodes, such as avoiding hidden sources of food allergens, and emergency treatment in case of accidental exposure.

GPP

Other manifestations of IgE-mediated food allergy:

- Local allergic manifestations such as acute contact urticaria are less common.
- Atopic eczema associated with IgE-associated food reactions triggering are more difficult to discern by history alone and may occur hours after food ingestion (see chapter 5 on atopic dermatitis eczema syndrome).
- Oral allergy syndrome, also known as pollen-food syndrome,[12] occurs in individuals who have pollen allergy. As a result of cross reactive allergens, the ingestion of raw food and vegetables causes localized

symptoms that include oropharyngeal pruritis and mild oedema that is confined to the oral cavity, including lip angioedema. Anaphylaxis, however, has also been described with this syndrome. Since it is related to pollen allergy, it is uncommon in those living in tropical climates such as Singapore's.

- Food-dependent, exercise-induced anaphylaxis is an uncommon condition that occurs when food triggers anaphylaxis only if ingestion is followed temporally by exercise. Wheat and shellfish have been most commonly associated in older children and younger adults.

B Chronic urticaria and chronic angioedema are rare, if at all, manifestations of food allergy, but is commonly suspected by the patient. Food allergy evaluation is therefore rarely indicated in chronic urticaria and angioedema.[13, 14]

Grade B, Level 2++

GPP Without associated gastrointestinal, dermatologic, or systemic symptoms, rhinitis is a very rare manifestation of food allergy. Therefore, there is no role for routine investigation for food allergy in patients with rhinitis.[15, 16]

GPP

3.2 Diagnostic tests

The approach to the diagnosis of IgE-mediated food allergy is summarised in Figure 2 (on page 31).

3.2.1 Investigations in food allergy

History taking is very important in the evaluation of IgE-mediated food allergy. The diagnosis of IgE-mediated food allergy is almost always based on the history; investigations only provide confirmation that the suspected foods are responsible. Further confirmation of the role of the suspected foods requires food challenges or elimination diets.

Skin tests and *in vitro* specific IgE tests are similar in many ways. They show that the patient harbours IgE antibodies directed

against the food allergen, which is the same as saying that he or she is sensitized.

Sensitization must precede the development of an allergic illness but is not sufficient in itself to justify a diagnosis of food allergy. Therefore, specific IgE testing helps to confirm a diagnosis of allergy to a specific food, but is of limited utility if interpreted without or in an inappropriate clinical context. Positive tests in the absence of disease are known as false positive results.[11, 17]

In clinics where skin test panels and protocols have been set up, skin tests are often preferred to blood testing because skin tests are cheaper (especially when many foods have to be tested), they provide the answer in 20 minutes and they offer a visual cue to the patient. Serum IgE testing is preferred over cutaneous testing when:

- The patient does not have healthy skin for testing (e.g. severe atopic dermatitis or dermographism);
- The patient's reaction was anaphylactic and the doctor is not willing to risk even a skin test; and
- The patient cannot stop using antihistamines.[18]

3.2.2 Skin tests in food allergy

Studies on aeroallergens showed that skin tests are generally more sensitive than in vitro specific IgE tests[19, 20] though a study on cow's milk and egg allergy in children showed good correlation between the two.[21] A review that used American healthcare costs and data from inhalant and venom allergy studies concluded that either skin testing or specific IgE test may be offered as first-line tests provided trained technicians and validated reagents and equipment are available.[22] In the chapter titled "Unproven and Disproved Allergy Tests" we shall discuss why only the prick skin test (also known as the puncture or epicutaneous test) but not the intradermal skin test should be accepted.

D To reduce the likelihood of a false negative result, patients have to stop using antihistamines before skin testing. The length of time of withdrawal depends on the nature of the antihistamine. For example, long-acting antihistamines like loratadine and cetirizine should be avoided for 10 days and short-acting ones like

chlorpheniramine and diphenhydramine for 3 days before the test.[23]

Grade D, Level 4

Skin test reagents are commercially available for many common food allergens. Another advantage of skin test is its flexibility. When prepared reagents are not available for local or unusual foods, aqueous food extracts may be freshly prepared, or the prick-prick technique used. The test material is placed on the skin (usually the volar aspect of the forearm or the back in children) and the skin is pricked through the reagent, just penetrating the dermis, without drawing blood. The skin response is read in 15 to 20 minutes. Positive histamine and negative controls are always included in the test.

3.2.3 Measurement of allergen-specific IgE

Quantifying the concentration of allergen-specific IgE in the serum of allergic patients is a standard method of establishing that allergen sensitization has occurred. Radioallergosorbent test (RAST) was the usual way of performing this test, but enzyme methods (for example, fluorescent enzyme immunoassay, FEIA) are more commonly used now. All commercial methods make use of allergens bound (or absorbed) on to a solid phase. Standards for IgE testing are laid down in a position paper.[24]

The classical teaching, albeit not well supported by evidence, is to wait for 4 to 6 weeks to elapse after an IgE-mediated hypersensitivity reaction before assaying the specific IgE concentration because the IgE is consumed during the reaction, and the test may be falsely negative. Recently, this assertion has been challenged.[25] Fifteen patients with anaphylaxis due to suxamethonium were studied. However, with no comparable data in food-allergic patients, it is still advisable to wait a certain period after a reaction before ordering the IgE test.

3.2.4 Interpretation of results

In the skin test, the wheal (swelling) and flare (redness) responses in 15 or 20 minutes are recorded. For the skin test to be interpretable, the positive control must show a strong response and the negative control minimal or no response. Most practitioners accept a wheal of greater than 3 mm and flare greater than 10 mm as a positive test.[26]

Skin prick tests for food allergens generally have better negative predictive value than positive predictive value. In other words, when the skin test is negative, we are 90% confident that the patient is not allergic to that particular food. When the test is positive, the confidence is lower, which is why this result has to be followed by food challenge, in the appropriate clinical context.[26]

The concentration of specific IgE is traditionally reported in terms of classes, even though modern equipment are capable of providing a precise quantitative result. Table 1 shows the seven classes and quantitative IgE levels of one commonly used form of the test.[27]

Table 1 The correlation of the class of the result, the units and the general interpretation.

Please note that the kU/L is an arbitrary unit of the equipment manufacturer, in this case, Phadia, Uppsala, Sweden.

Class	IgE kU/L	Interpretation
0	<0.35	Negative
1	0.35-0.70	Equivocal
2	0.71-3.5	Positive
3	3.51-17.5	Positive
4	17.6-50.0	Strongly positive
5	50.1-100.0	Strongly positive
6	>100.0	Strongly positive

Though results of class 2 and above are labelled as positive, it is better to know the quantitative IgE concentration as well.

Generally, patients with higher specific serum IgE concentrations are more likely to be allergic to the food than those with lower levels. For example, only 37% of patients with concentration of milk-specific IgE below 0.35 kU/l developed a reaction in a food challenge, while 79% of those with concentration above 3.0 kU/l did so.[27] Some experts have shown that, in children, if the history is consistent and the food-specific IgE level exceeds a certain threshold, a diagnosis of food allergy may be made without need for food challenge.[28, 29] However, this has not been demonstrated in different population groups and the methodology to establish these thresholds is not accepted by all.[30] It was also shown that decreasing IgE levels in children with cow's milk and hen's egg allergy, especially those below four years old, correlated with the development of tolerance.[31]

GPP The choice of the specific test to order for IgE-mediated food allergy must be directed by the clinical history.

GPP

GPP The practitioner should not order a large number of specific IgE tests to screen for allergy when the diagnosis of IgE-mediated food allergy has not been established.

GPP

GPP The attending medical practitioner must take into account the context in which he or she practices and the patient's condition when choosing between skin testing and in vitro specific IgE testing.

GPP

B Children with moderate to severe atopic dermatitis may benefit from investigations to assess for food allergy. The investigations must be interpreted in context and confirmed with food challenges and, if necessary, food avoidance. In most situations, these tests should be carried out by specialists experienced in treating food allergies. (see also Chapter 5)

Grade B, Level 2+

GPP After an IgE-mediated reaction, it is reasonable to wait 4-6 weeks before ordering the specific IgE test to reduce the chance of a false negative result.

GPP

3.2.5 Oral food challenges

Oral food challenges are needed to either confirm or rule out food allergy whenever the clinical diagnosis is in doubt. This procedure is important because it helps prevent unnecessary food restrictions. Avoiding highly nutritious, widely used food such as eggs, milk and soy products may have adverse effects on patients' nutrition status and growth, as well as restrict their food choices. Challenges may be done with the food unhidden (open), disguised but known by the medical practitioner to contain the challenge food (single-blind), or double-blind and placebo-controlled.[32-35] Refer to Figure 2 (page 31) and Figure 3 (page 34) for flowcharts of the diagnosis and evaluation of a child with food allergy.

3.2.5.1 Indications for oral food challenges

The decision to conduct oral food challenges for a patient is based on the patient's medical history, age, past adverse food restrictions, skin prick test (SPT) and serum food-specific IgE test results, and concomitant food allergies. The decision is also influenced by the importance of the food to the patient because of its nutritional value, commonly used in ethnic diets, and the patient's and family's preferences.[35]

C Oral food challenges can be considered for the following purposes:- [34, 35]

- To identify foods causing acute reactions for initial diagnosis of food allergy.
- To determine if the patient has outgrown his/her food allergy.
- To expand the diet in persons with multiple dietary restrictions, because of subjective complaints such as headaches or hyperactive behaviour.
- To assess the status of tolerance to cross-reactive foods.

- To determine whether food allergens associated with chronic conditions such as atopic dermatitis or allergic eosinophilic esophagitis will cause immediate reactions.

Grade C, Level 2+

3.2.5.2 Deferring oral food challenges

GPP Defer oral food challenges if there is a high likelihood of allergic reaction as predicted by food reaction history.

GPP

The levels of serum food-specific IgE antibody and/or size of skin prick test results may also be used as a guide to decide when to perform a food challenge. The 95% positive predictive values for age for various food specific IgE levels are shown in Table 2 on pg 27).[35] However, these levels may differ from study to study as well as the brand of diagnostic kit used.[36] Given these concerns with the published positive predictive decision points, careful interpretation of the serologic levels of IgE antibody should be made within the context of the patient's clinical history.

Table 2 Positive and negative allergen-specific IgE values predicting outcomes of oral food challenges in children[28, 37-39]

Food	Specific IgE levels (kIU/L)		SPT wheal (mm)	
	≈ 95% Positive predictive value	**≈ 50% Negative predictive value***	**≈ 95% Positive predictive value**	**≈ 50% Negative predictive value***
Cow's milk	≥ 15	≤ 2	≥ 8	-
	≥5 if younger than 1 year	-	-	-
Egg white	≥ 7	≤ 2	≥ 7	≤ 3
	≥2 if younger than 2 years	-	-	-
Peanut	≥ 14	≤ 2 with and ≤ 5 without history of peanut reaction	≥ 8	≤ 3
Fish	≥ 20	-	-	-

It should be noted that a subset of patients with undetectable serum food-specific IgE antibody and negative SPT has been reported to have objective reactions confirmed by oral food challenges.

These predictive levels are only a guide as these values have been performed on mainly Caucasian population. There is limited data from Asia (Japan) to determine if these levels will be applicable to our Singaporean children. However, serum levels of food-specific IgE antibodies and SPT wheal sizes are not absolute indications to performing an oral food challenges. Laboratory test results have to be interpreted in the context of clinical history.

3.2.5.3 Procedure for oral food challenges

There are published guidelines by the Americans, Europeans and Japanese on oral food challenges but the procedures are not internationally standardized.[32, 34, 40]

D To prepare for the oral food challenges, suspected food allergens should be eliminated for 1 to 2 weeks prior to the food challenge for IgE-mediated allergies, and antihistamines stopped for the appropriate period of time to promote a normal histamine response. [34]

Grade D, Level 2+

D The total amount of challenge protein used for IgE-mediated allergies, is 0.15 to 0.3 g protein per kg body weight with a maximum of 10 g of the dry food (double for wet foods such as meat and fish, or 200 ml milk). The total amount of challenge protein must be given in sequentially increasing doses with approximately 15 minutes interval for each dose as shown in Table 3.[34, 40]

Table 3 Example of incremental challenge protein doses with their serving time

Time (minutes)	Dose / Percentage of total protein	Dry weight of challenge protein (g)	Cumulative dry weight of challenge protein (g)
0	1%	0.1	0.1
5	4%	0.4	0.5
20	10%	1	1.5
35	20%	2	3.5
50	20%	2	5.5
65	20%	2	7.5
80	25%	2.5	10

Grade D, Level 2+

D The medical practitioner or health care professional needs to record the dose of challenge protein given, the time of administration, vital signs, and any subjective symptoms or objective signs that arise during the challenge. Assess frequently for symptoms or signs that affect the skin, gastrointestinal tract, and/or cardiovascular system.

Grade D, Level 2+

C Significant reactions can occur with oral food challenges in high risk patients. Therefore, oral food challenges for these patients are best performed by specialists experienced in treating food allergies and immunologists, and carried out in clinical settings equipped with resuscitation facilities and staffed with trained allied health personnel.[32-35]

Grade C, Level 2+

GPP A physician-supervised oral food challenge is recommended to confirm or refute allergy to this food in patients who present with histories of convincing immediate allergic reactions to a food (within 2 hours), or who present with histories of anaphylaxis to the food in question in isolation or in a mixed meal, even in the setting of negative laboratory and skin tests, provided the benefits of a food challenge outweigh the risks, and with the patient's/parent's informed consent.

GPP

GPP Patients with negative skin tests, undetectable serum food-specific IgE levels, and no history of convincing symptoms of immediate food allergies (e.g. symptoms limited to behavioral changes or delayed/chronic gastrointestinal symptoms) can undergo gradual home introduction of the food in question.

GPP

3.2.5.4 Outcome of oral food challenges

Food allergies are considered outgrown or ruled-out if patients tolerate the entire oral food challenges, including the masked and open portions of a blinded oral food challenge and observation period.

D Patients should be monitored for 1 to 2 hours before discharge for home if they tolerate the challenge. However, for those who have allergic reactions during the oral food challenges, they should be observed for 2 to 4 hours after symptoms have resolved with treatment.[35]

Grade D, Level 2+

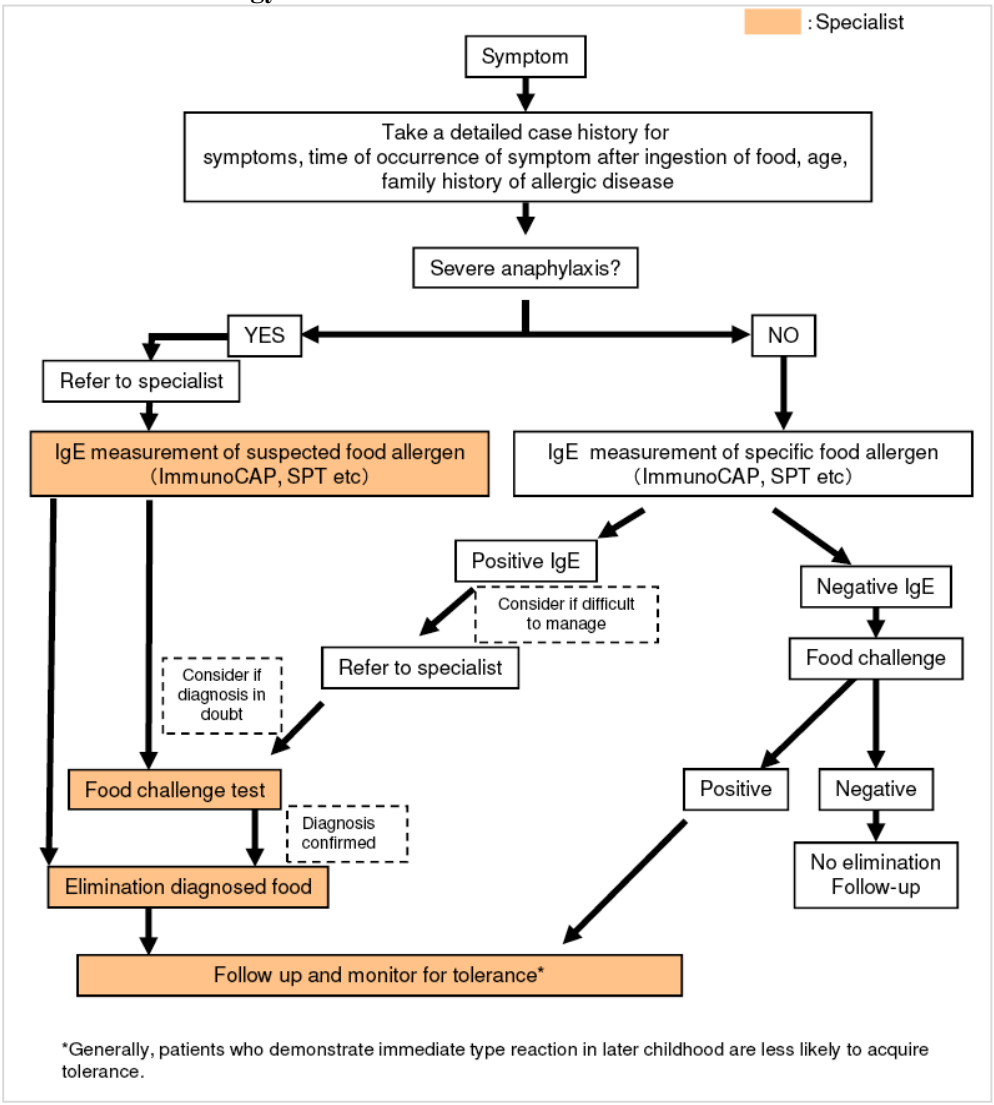
B Patients who have undergone and passed their oral food challenges should be instructed to introduce the challenge foods into their diet. [32, 33, 35]

Grade B, Level 2++

B Patients who fail their oral food challenges should be provided emergency treatment plans for allergic reactions, education regarding food avoidance, dietary implications of food avoidance, and recommendations for follow-up visits and evaluations.[32, 33, 35]

Grade B, Level 2++

Figure 2 **Approach to management of IgE-mediated food allergy**[‡]



[‡] Adapted from: Motohiro Ebisawa Management of Food Allergy in Japan "Food Allergy Management Guideline 2008 (Revision from 2005)" and "Guidelines for the Treatment of Allergic Diseases in Schools". Allergology International. 2009;58:475-483

3.3 Long term management and treatment

The key management of patients with food allergy is avoidance of foods known to have or suspected of having caused a reaction. Elimination diets should only be advised based on a positive history with confirmatory skin prick test or specific IgE test. Prolonged elimination of multiple food products may lead to malnutrition or other serious adverse effects (e.g., feeding difficulties), thus every effort should be made to ensure that the dietary needs of the patient are met and that the patient and/or caregiver(s) are fully educated in dietary management. Once the diagnosis of food allergy is confirmed, the patient should be advised to avoid eating the food.

In case of accidental exposure to food allergens, a written management plan (Annex A on page 70) containing instructions for the emergency treatment of anaphylaxis should be provided. Parents and caregivers should be well versed at recognizing and managing early stages of an allergic reaction (e.g. use of self-injectable epinephrine where appropriate).

3.3.1 Advice on food avoidance

GPP Patients with food allergies should be advised on:

1) Cross-reacting allergens in other foods (Refer to Table 4 on page 44).
2) Hidden food allergens, and should be aware about the importance of reading food labels carefully and having a knowledge of some scientific names (e.g. casein, and whey for cow's milk and ovalbumin for chicken's egg).
3) High risk situations, and therefore the need to enquire at restaurants or parties etc (wherever cooked food is served or offered), and to take other measures to prevent inadvertent exposure to known or suspected allergens or contamination in children with high risk of anaphylaxis.

GPP

Although uncommon, patients who are exquisitely allergic may react to trace amounts of exposure, for example through contact and inhalational exposure[41, 42] and kissing.[43]

There are no labelling laws in majority of Asian countries which makes the risk of exposure to (hidden) ingredients high. Labeling laws in North America[44] requires 8 common allergens, whilst in Europe[45] 12 common food allergens need to be included in the labels of all processed foods. In Asia, only Japan[46] has in place labeling laws that includes the top 5 allergenic foods namely: hen's egg, cow's milk, wheat, buckwheat and peanuts with the recent addition of shrimp and crab to their food guidelines. These laws determine that the common allergenic components are clearly stated in all product labels that are exported or imported into the country.

3.3.1.1 "May contain traces" of Allergens in Statements on Food Labels

These statements are used by manufacturers to indicate that the product may be contaminated with the most common allergenic proteins (which differ according to the country that the product is exported from) through processing and packaging. At present these statements are voluntary and there are no clear guidelines for companies regarding how and when to use them. The wording of the statements further limits food choices for people with food allergy. A product that does not contain the statement may be no safer than a product that does.

In general, people with a history of severe or anaphylactic reactions for specific food should avoid products with these statements for that specific food.[47]

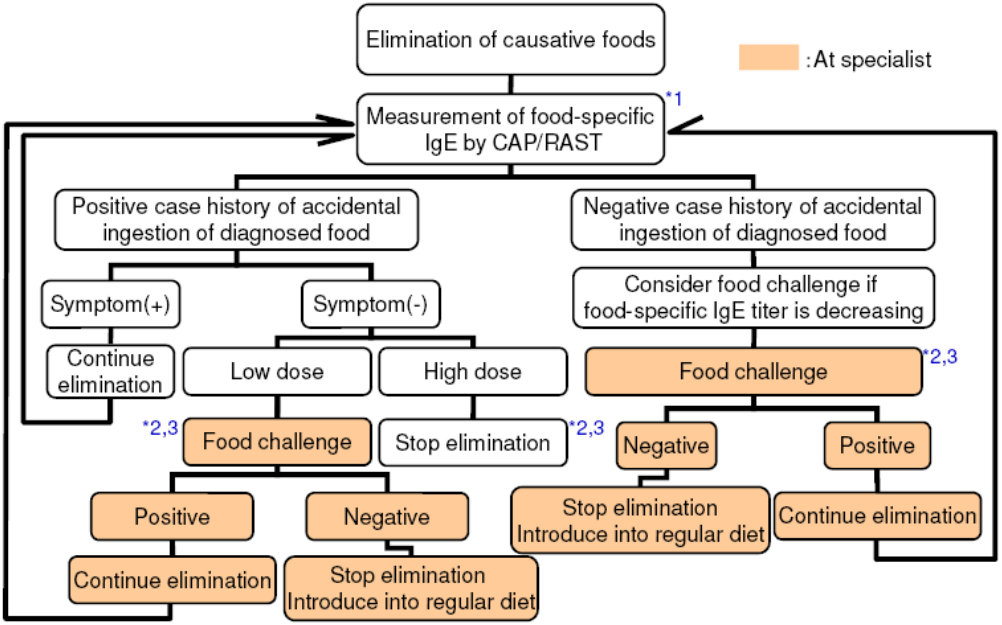
3.3.2 Monitoring food allergy *(see also Chapter 3.4 for specific food allergies)*

The monitoring and follow up of IgE-mediated food allergy is summarised in Figure 2.

B In specific foods, re-evaluation of patients with food allergy may be important to determine if food allergy has been lost over time. A food challenge should be recommended when the skin prick test or the specific IgE test is negative or shows a decrease to low levels (guide in Figure 3 on page 34) on follow up.[28, 29]

Grade B, Level 2++

Figure 3 Follow-up management of IgE-mediated food allergy[§]



* Guideline on Timing of examinations

	Below 3 yrs.	3-5 yrs.	Over 6 yrs.
*1: Food-specific IgE	Every 6 months	0.5 – 1 yr.	1 yr. or more
2: Food challenge test	0.5 – 1 yr.	1 – 2 yrs.	2 – 3 yrs.
*3: Methods of food challenge test	Open	Open, single-blind, double-blind	Open, single-blind, double-blind

[§] Adapted from: Motohiro Ebisawa Management of Food Allergy in Japan "Food Allergy Management Guideline 2008 (Revision from 2005) " and "Guidelines for the Treatment of Allergic Diseases in Schools"Allergology International. 2009;58:475-483

3.3.3 Treatment of an acute food allergic reaction in the field

D If there is a history of suspected or proven IgE-mediated anaphylactic reactions to foods, injectable epinephrine should be given to patients and/or caregivers to carry with them and they should be instructed in its use.[48]

Grade D, Level 4

GPP A written Food Allergy Anaphylaxis Action Plan (see Annex A on pg 70) should accompany each patient prescribed with an epinephrine auto-injector.

GPP

B In the event of a life threatening anaphylaxis event, the use of self injectable intramuscular epinephrine 0.01mg/kg (maximum dose of 0.5mg) is advised as the first line. Epinephrine can be administered every 5-15 minutes intramuscularly as necessary to maintain blood pressure and control symptoms.[49]

Grade B, Level 2+

B Intramuscular epinephrine should be administered to the anterior-lateral thigh as this has been shown in non-anaphylactic children to lead to peak plasma concentrations more quickly compared with subcutaneous administration.[50, 51]

Grade B, Level 2+

D Prophylactic medications have not been shown to be effective in managing life-threatening reactions to foods, therefore, oral antihistamines and steroids are used mainly for the cutaneous manifestations, but not as first line medications in the event of anaphylaxis.[52]

Grade D, Level 4

D Corticosteroids may be used to alleviate late phase biphasic anaphylactic reactions in high-risk individuals.[53-55]

Grade D, Level 4

Food allergens are a frequent cause of severe anaphylaxis, particularly in patients with concomitant asthma and allergy to peanut, tree nut, or seafood. Such reactions may be biphasic or protracted.

3.3.4 Tips on prescribing epinephrine autoinjectors

D There are no firm guidelines for the recommendation of an epinephrine autoinjector but the guidelines adapted from ASCIA (2009),[56] outlined below, can be used:

Epinephrine Autoinjector Prescription Guidelines

RECOMMENDED

- History of anaphylaxis (if patient is considered to be at continuing risk).

MAY BE RECOMMENDED

History of a generalised allergic reaction with one or more of the following:

- Asthma - concurrent or past history
- Age - Adolescents and young adults have greater risk of fatal food anaphylaxis. Most recorded fatal reactions to foods (~90%) occur in children over the age of 5 years.
- Adults have a greater risk of fatal stinging insect anaphylaxis than children.

Specific allergic triggers

- Nut allergy (to peanuts or other nuts) - Most deaths from food anaphylaxis occur from nuts. Generalised allergic reactions can be triggered by exposure to trace or small amounts of nuts, which can be difficult to avoid. Subsequent allergic reactions to nuts may be unpredictable.
- Stinging insect allergy (bees, wasps, jumper ants) in adults.

(continued on next page)

Epinephrine Autoinjector Prescription Guidelines *(continued)*

NOT NORMALLY RECOMMENDED

- Asthma - in patients with asthma without anaphylaxis or generalised allergic reactions
- Elevated specific IgE only (positive food allergen IgE and/or skin test) without a history of clinical reactions. Positive test results alone do not necessarily mean there is allergic disease. These patients may be referred to allergy specialists for assessment of allergy and anaphylaxis risk. This may include further investigations such as challenge testing.
- Family (rather than personal) history of anaphylaxis or allergy. Whilst the risk for allergic disease is inherited, anaphylaxis is not inherited.
- Local reactions to insect stings in adults and children. Generalised skin rash (only) to bee or wasp stings in children.
- Resolved food allergy

Dose recommendation for epinephrine autoinjector Epipen® **Prescription**

Epinephrine autoinjector/Junior (0.15mg)	0-6 years or < 20kg
Epinephrine autoinjector/Adult (0.3mg)	Over 7 years or > 20kg

Advice to patients for care of Epinephrine autoinjector

5. Carry the pen with them at all times.
6. Protect the pen from heat and light.
7. Check expiry date and get a replacement from doctor ahead of time.
8. After the autoinjector has been used, the needle remains protruding out so *it needs to be carefully disposed of. Although there is fluid left it cannot be re-used. Get* a replacement autoinjector from the doctor

Grade D, Level 4

3.4 Specific food allergies

Food allergens are commonly glycoproteins. Any food could potentially cause an IgE-mediated reaction, but some common foods are more allergenic and therefore responsible for the most food allergic reactions. In infants and young children, these are cow's milk, hen's egg, peanut, tree nuts, soybeans, and wheat, whereas the adult counterparts are peanuts, tree nuts, fish, crustaceans, and mollusks. Although sensitivity to most food allergens, such as milk, egg and wheat, tend to remit in late childhood, other food allergens, such as, peanut, tree nut (walnut,

cashew, Brazil nut, pistachio), and crustaceans, mollusks, are more persistent and may continue throughout the patient's life.

Food additives are widely perceived by the general population to be implicated in food allergic reactions. However, only a small number of these additives, such as antioxidants, flavouring and colouring substances, preservatives, sweeteners, thickeners have been implicated in food allergy. In fact, many reported allergic adverse reactions to additives and spices have been anecdotal and/or based on poorly controlled challenge procedures.[57, 58] One better documented food adverse reaction is sulphite hypersensitivity, which results in wheeze and asthma.[59]

3.4.1 Cow's milk

Cow's milk allergy is one of the most common food allergy in infants and young children, affecting 2% to 3% of the general population[60-63] Tolerance is often achieved (approximately 80%) by the age of 3 to 5 years.[60, 64] About 90% of cow's milk allergic patients will react to goat and/or sheep's milk due to a high-degree of cross-reactivity.[65-68]

B Medical practitioners should not prescribe goat or sheep's milk to cow's milk allergic individuals as these milks cross-react with cow's milk.

Grade B, Level 2++

GPP Management of IgE-mediated cow's milk allergy with or without anaphylaxis in infants will generally involve formula replacement with a soy-based formula and if not tolerated, an extensively hydrolysed formula (eHF) or amino acid based formula.[69, 70]

GPP

3.4.2 Egg

Egg allergy is a very common cause of food allergy in young children.[71] Approximately two-thirds of egg allergic children outgrow their egg allergy by 5 yrs of age.[72] Individuals can be allergic to egg white and/or egg yolk as both contain different allergens; however, egg white allergy is more common.[73] Cooking

and gastric digestion reduces the allergenicity of egg protein, thus explaining why some children react to uncooked but not to cooked egg, and some to contact but not ingestion.[74, 75]

B MMR vaccine is not contraindicated in egg allergy and can be safely given in the normal manner.[76, 77] Medical practitioners should be aware that anaphylaxis can happen after any vaccination, therefore all vaccinations should be performed in a setting equipped to deal with such emergencies.

Grade B, Level 2++

Egg-free influenza vaccine if available can be used safely.

D Patients with egg allergy who need the influenza vaccine should be referred to a clinical facility experienced in the management of anaphylaxis. A 2 dose, split protocol (e.g. 1/10 dose followed by 9/10 30 minutes later) can be considered in those with a history of anaphylaxis to egg or uncontrolled asthma.[78, 79]

Grade D, Level 4

D A severe reaction to egg is a contraindication to influenza immunization. Individuals with reactions less than severe anaphylaxis can be immunised with the influenza vaccine if skin prick and intradermal tests with the vaccine are negative. [78]

Grade D, Level 3

3.4.3 Peanut

Peanut allergy appears to be on the increase around the world in developed countries.[1, 2, 80, 81] In Singapore, there has been an increase in the number of children presenting with food related allergic manifestations with peanut allergy presenting as the 3rd most common food allergen sensitization in a population of children with food allergies presenting to an Allergy service in Singapore.[71]

Peanuts are legumes, a plant family that includes soybeans, green beans, and lentils. It is common to find positive test responses for IgE to several beans in individuals who are clinically reactive to one type. Despite the high rate of cross-sensitisation, clinical

cross-reactions are uncommon (5% at most), as shown by studies of allergenic legumes, such as peanut[65] and soy. These studies did not include several different legumes, and it may be that particular types are more allergenic or cross-reactive. Introduction of soy formula does not increase the risk of peanut sensitization in children.[82]

It appears that approximately 20% of children with peanut sensitization/allergy may eventually tolerate peanut ingestion. [80, 83] However, for a great majority, peanut allergy is typically life long, often with severe reactions and potentially fatal on exposure to peanuts.[84, 85] Peanut and tree nuts account for most fatal and near-fatal food allergic reactions in North America, Europe and Australia.

Highly refined peanut oil or highly processed peanut oil – oils that do not contain peanut protein – may be tolerated by peanut allergic individuals and is generally safe.[86, 87] Cold-pressed or extracted peanut oils do contain peanut protein and could induce an allergic reaction. As the degree of processing of commercial peanut oil especially locally maybe difficult to determine, avoidance is prudent for most peanut allergic individuals.

C Patients with peanut allergy can generally tolerate other beans (95%), even soy. Avoidance of all legumes is unwarranted.[88]

Grade C, Level 2+

3.4.4 Tree nuts

Allergy to tree nuts (walnut, cashew nut, hazelnut (filbert), Brazil nut, pecan, almond, pistachio) can be severe and potentially fatal. The allergy is usually long-lived. Sensitization (the presence of specific IgE) and clinical allergy to tree nuts is common amongst children with peanut allergy, with 30-50% of peanut allergic children having sensitization to tree nuts and 21% reporting clinical allergy.[89, 90] Hence, it is advised at present for avoidance of all tree nuts for persons with peanut allergy or any single tree nut allergy. Individualization of the avoidance plan is advocated in cases when nuts known to be tolerated are eaten without possible contamination by other nuts with proven clinical

sensitivity.[90, 91] Evaluation of young children by skin prick testing or specific IgE may reduce avoidance of tree nuts in young children. Evaluation of these patients should be performed by specialists experienced in treating food allergies, with resuscitation equipment available.

Evaluation of cross-reactivity among tree nuts (walnut, hazelnut, Brazil nut, pecan, pistachio) is characterized by shared allergens among tree nuts. Clinical reactions to tree nuts can be severe and potentially fatal and can occur at the first exposure to tree nuts and a history of previous avoidance.

D It is appropriate to eliminate all other tree nuts from the diet if the child with tree nut allergy has never consumed other nuts.[92, 93]

Grade D, Level 3

3.4.5 Fish

Fish allergy is uncommon in Singapore. There is significant cross-reaction between different species of fish, including salt and fresh water. Most patients with fish allergy would therefore not tolerate all or multiple fish. Rare individuals are monosensitized and react to one particular species of fish only.[94-96]

D Patients with fish allergy should avoiding eating all other species of fish. On the rare occasion that a fish-allergic patient has eaten another species of fish without reaction, he can continue eating that species.

Grade D, Level 3

3.4.6 Crustacean shellfish

Common crustacean seafood in Singapore includes crabs, crayfish, lobsters, shrimps and prawns. As a group, crustacean shellfish is among the commonest causes of food allergy in this country, especially the IgE-mediated reactions, constituting a third of the implicated foods in local series.[94, 97, 98] Crustacean seafood can be serious and is a common cause of food-induced anaphylaxis.[95] The similarity of tropomyosin found in the flesh of these creatures is believed to be the reason why there is a high degree of cross-reaction (estimated to be 75%) in allergic patients.[65, 96] The cross-reaction between the tropomyosin of

crustaceans and that of mollusks (such as scallop, oyster and clam) and arachnids (house dust mites) is suspected and is being studied.[99]

D Patients who are allergic to one type of crustacean should avoid eating other types of crustaceans. A referral to a specialist experienced in treating food allergies may be appropriate to define the precise types of crustacean to avoid.

Grade D, Level 2+

3.4.7 Soy

Soy allergy is an uncommon allergy, and a prevalence rate of 0.3 to 0.4% has been quoted.[33] Prevalence is likely dependent on local feeding habits and exposure.[100] Although sensitization to soy may be common with 3% of Singapore children showing sensitization to soy from skin prick test in a previous study,[71] true soy allergy is likely to be much lower.

Soy allergy is of particular importance because soy products are commonly introduced into the diets of Singaporean children in the first 2 years of life.[101] Furthermore, soybeans are widely used in processed foods, cosmetics and pharmaceutical products and, therefore, represent a particularly insidious source of hidden allergens.[100, 102]

It is fortunate that patients with soy allergy are less likely to have severe allergic reactions to traces of soy in processed foods compared to peanut allergic patients.[102] It has been reported that soy allergy appears to affect 6% of atopic children, 14% of children with cow's milk allergy[100] and, up to 50% in group of patients with non IgE-mediated cow's milk protein-induced enterocolitis[103] (see chapter 4 on non-IgE-mediated allergy).

3.4.8 Wheat

Wheat allergy is not common in our population. Wheat allergy reactions are typically limited to the seed storage proteins of wheat. There are some people who have reactions that are restricted to wheat proteins, while others can react across many varieties of seeds and other plant tissues.

There are many allergenic components in wheat, for example serine proteinase inhibitors, glutelins and prolamins and different responses are often attributed to different proteins.

The most severe response is exercise or aspirin induced anaphylaxis attributed to one-omega gliadin, a relative of the protein that causes coeliac disease.[104]

In patients who have wheat allergy, false positive tests to other grains are common. However clinical cross reactivity between grains is rare.

3.4.9 Unique local food allergens

Allergy to edible Bird's Nest from swiftlets has been described in the Chinese population in Singapore, Malaysia, Indonesia and Hong Kong. It is the commonest cause of anaphylaxis in Singapore children. The natural history of bird's nest allergy has not been described. There is no known cross reacting food allergen and hence avoidance of other foods is not necessary.[105]

Royal Jelly, another food supplement very popular amongst the Chinese, has also been reported to trigger asthma and anaphylaxis in Hong Kong and ethnic Chinese in Australia.[106, 107] Buckwheat which is used to make noodles in some Asian countries have been observed to cause anaphylaxis in Japan, Korea and China.[108, 109]

The clinical characteristics of the more common food allergies are summarised in Table 4 on page 44.

3.4.10 Allergens from dust mite contamination of wheat flour

In the tropical climates like Singapore, wheat flour stored at room temperature may result in dust mite contamination.[110] Ingestion of dust mite contaminated flour could result in severe anaphylactic reactions in dust mite allergic individuals.[111] This possibility should be considered in patients whose food allergen trigger for anaphylaxis is not obvious.

Table 4 Specific food allergens: presentation, prognosis, cross reactive food allergens

Specific Food Allergen	Age of onset	Risk of anaphylaxis	Prognosis	Examples of cross reacting Foods	Risk of clinical cross reactivity
Cow's milk[49-51]	< 2 years old	Possible	80% likely to outgrow by 4 years old	Goat's milk Sheep's milk	90% 90%
Hen's eggs[93]	< 2 years old	Low	80% likely to outgrow by 4 years old	Avian Eggs	Unclear
Peanut[63, 66]	< 2 years old	High	Only 20% likely to outgrow by 5 years old; 80% with persistent peanut allergy	All Tree Nuts (e.g. Hazelnut [Filbert], Walnut, Cashew Nut)	5% 32% sensitization 21% clinical allergy
Soybean [27,85,94]	< 2 years old	Low	Most children outgrow soy allergy by 3 years old	Legume	Uncommon
Fish[78]	All ages	Possible	Tends to persist	All fish (Cod, Mackerel, Herring, Plaice, Salmon, Trout, Perch, Carp, Eel)	Unclear
Crustaceans[48,79,95]	Older children and adults	High	Tends to persist	All Crustaceans (e.g. shrimp, Crab, Lobster) All Mollusks (e.g. Limpets, Abalone, Mussel, Oyster, Scallop, Squid)	Above 75% for other forms of crustaceans Moderate to high
Tree Nuts[76,96]	Older children and adults	High	Tends to persist	Peanut, walnut, cashew nut, hazelnut (Filbert),brazil nut, pecan, almond, pistachio	Severe and potentially fatal
Bird's Nest[88]	Older children and adults	High	Unclear	None	None documented
Wheat[87,93,97]	All ages	Possible	Unclear	Other grains (but unlikely to occur)	Unlikely, unnecessary to eliminate from diet

4 Non-IgE and mixed-IgE / non-IgE-mediated gastrointestinal food allergies

Gastrointestinal food allergies are disorders that encompass various immunopathologies that span from IgE-mediated (chapter 3), mixed-IgE/non-IgE involving eosinophilic inflammation, to non-IgE involving other cell-mediated reactions[112] (Table 5). In this chapter, the following mixed-IgE/non-IgE and non-IgE-mediated food allergies are discussed:

- Allergic Eosinophilic Esophagitis
- Allergic Eosinophilic Gastroenterocolitis
- Food Protein Induced Enterocolitis Syndrome
- Allergic Enteropathy
- Allergic Protocolitis

Table 5 Classification of gastrointestinal hypersensitivity syndromes

IgE-mediated ➔	Mixed non-IgE/IgE-mediated ➔	Non-IgE-mediated
Immediate gastrointestinal hypersensitivity Oral Allergy Syndrome	Allergic eosinophilic esophagitis Allergic eosinophilic gastritis Allergic eosinophilic gastroenterocolitis	Food protein induced enterocolitis syndrome Allergic enteropathy Allergic proctocolitis Coeliac disease

Coeliac disease (gluten-sensitive enteropathy) is not discussed in this pathway as it is uncommon in our population although more common in those of European descent. This disorder is caused by gliadin-specific T cell responses triggered by mostly wheat gluten and sometimes other glutens like rye and barley in the diet, and results in inflammatory injury to the small bowel mucosa. Exclusion of gluten from the diet results in amelioration of the disease.

A summary of the key distinguishing clinical features of each is listed in Table 6.

Table 6 Clinical features helpful to distinguish dietary protein-induced protocolitis, enteropathy, enterocolitis and eosinophilic esophagitis*

	Vomiting	Diarrhea	Growth	Foods	Other	Onset
Food Protein Induced Enterocolitis Syndrome	Prominent	Prominent	Poor	Milk/Soy/ Others	Reexposure: severe, subacute symptoms	Days to 1 year
Allergic Eosinophilic Esophagitis	Common	Minimal	May be affected	Milk/Soy/ Egg/Wheat/ Peanut	Reflux-type symptoms Abdominal pain	Any age
Allergic Eosinophilic Gastroentero -colits	Prominent	Prominent	Poor	Milk/soy/ egg/ wheat/fish	Strictures, dysmotility, ascites, anemia, GI bleed	Any age
Allergic Enteropathy	Variable	Moderate	Poor	Milk/Soy	Hypoalbumin aemia, Edema	2 to 24 months
Allergic Protocolitis	Absent	Minimal, bloody	Normal	Breast milk/soy	-	Days to 6 month

* Adapted from Sicherer SH. Enterocolitis, proctolitis, and enteropathy. Paediatric allergy: Mosby; 2003[113]

4.1 Allergic eosinophilic esophagitis

Allergic eosinophilic esophagitis is a primary clinicopathologic disorder of the esophagus.[114] It is characterized by esophageal and/or upper gastrointestinal tract symptoms, associated with eosinophilic inflammation on mucosal biopsy specimens containing > 15 intraepithelial eosinophils per HPF, and the absence of pathologic gastro-esophageal reflux (GERD) as evidenced by a normal pH monitoring of the distal esophagus.

4.1.1 Clinical features

The age of onset is variable.[114] Sixteen studies identified 754 children (66% male), with a mean age of 8.6 years (range 0.5-21.1 years) at presentation. The symptoms include those similar to gastro-esophageal reflux (GERD) (vomiting, heartburn, chest pain), dysphagia, feeding intolerance and abdominal pain. Symptoms may also depend on age at presentation; with feed refusal, regurgitation and reflux, which fails to respond to pharmacotherapy, in infants and young children. Vomiting (8-100%) and abdominal pain (5-68%) are also commonly reported.[114] Additional symptoms in older children include dysphagia and food impaction. Failure to thrive (5-19%) has also been reported.

Allergic responses as the etiology of allergic eosinophilic esophagitis are based on the observation that 50-80% of patients with allergic eosinophilic esophagitis have other atopic conditions such as atopic dermatitis, allergic rhinitis and asthma.[115] 71-78% of children with allergic eosinophilic esophagitis have elevated total IgE.[114] In addition, two thirds of patients have positive skin tests to at least one food allergen. The mean number of positive skin tests to foods varied from 2.7 ±3.3 to 6 ±4.2. The most common foods reported to be positive by skin prick tests include common food allergens – peanuts, eggs, soy, cow milk and wheat. Moreover, patients are seen to improve on an allergen-free diet, even in the absence of skin prick test results.

Allergic eosinophilic esophagitis tends to be a chronic disease with persistent or relapsing symptoms.[115] The majority of children in the largest longitudinal study of children with allergic eosinophilic esophagitis relapsed following discontinuation of medical treatment. On the other hand, dietary treatment with restriction or an amino-acid based formula was highly effective in inducing and maintaining remission. The natural history of allergic eosinophilic esophagitis is not well established. There are no clear predictors as to which children may develop long-term complications (such as esophageal strictures). Esophageal metaplasia has not been reported. Periodic assessments with repeat endoscopies and/or barium studies have been recommended, but the optimal interval for such surveillance is unclear.

4.1.2 Diagnosis and investigations of Allergic Eosinophilic Esophagitis

D Allergic Eosinophilic Esophagitis should be considered in infants and children with gastro-esophageal-reflux-like symptoms and/or feeding problems who do not respond to gastric acid suppression, particularly if there are associated atopic manifestations.

Grade D, Level 3

There are no positive or negative predictive values for food-specific IgE level testing in Allergic Eosinophilic Esophagitis. Studies using empiric elemental formula or empiric elimination diet in children without any allergy testing documented a 77-98% disease improvement.[116-118]

D Skin prick testing for food and environmental allergens could be considered in patients with Allergic Eosinophilic Esophagitis so that potential allergens and the atopic status of these patients can be identified.

Grade D, Level 3

D Endoscopy and biopsy of the lower esophagus (> 15 eosinophils /hpf) is diagnostic in the appropriate clinical setting, and should be performed to confirm the diagnosis of Allergic Eosinophilic Esophagitis.

Grade D, Level 3

Esophageal eosinophilia is not pathognomonic of Allergic Eosinophilic Esophagitis. It is also seen in association with gastro-esophageal reflux, Crohn's disease, collagen vascular disease and infectious esophagitis.

4.1.3 Treatment of Allergic Eosinophilic Esophagitis

Acid suppression is useful as part of the diagnostic criteria for Allergic Eosinophilic Esophagitis. Acid suppression should not be considered as primary treatment for Allergic Eosinophilic Esophagitis. However, it may be considered as co-therapy because it sometimes can alleviate symptoms as part of Allergic Eosinophilic Esophagitis. There is speculation that patients with

Allergic Eosinophilic Esophagitis may have enhanced esophageal sensitivity to acid even in the absence of pathologic reflux.

D Gastric acid suppression should be considered as co-therapy for Allergic Eosinophilic Esophagitis.

Grade D, Level 3

Dietary therapy should be considered in all children diagnosed with Allergic Eosinophilic Esophagitis. This could be in the form of specific antigen removal (5 common allergenic foods mentioned above), an elemental diet or an amino acid based diet. The patient's lifestyle and family resources need to be considered. Elimination diet is best done in conjunction with a dietician to ensure proper calories/vitamins.

D Elimination diet (exclusion of the 5 common allergenic foods: Milk, Soy, Egg, Wheat & Peanut) should be considered in all children diagnosed with Allergic Eosinophilic Esophagitis.

Grade D, Level 3

There is limited benefit for the use of other pharmacological agents in the treatment of Allergic Eosinophilic Esophagitis. These include systemic corticosteroids, topical corticosteroids, leukotriene-receptor antagonists and cromolyn sodium. Systemic and topical steroids may be considered when urgent relief of symptoms is required, such as severe dysphagia requiring hospitalization, dehydration because of swallowing dysfunction and strictures.[119] However, symptoms generally recur when medications are discontinued.

D There is limited benefit for the use of other pharmacoogical agents in the treatment of Allergic Eosinophilic Esophagitis. Systemic corticosteriods, topical corticosteriods, leukotriene-receptor antagonists and cromolyn sodium may be tried.

Grade D, Level 3

4.2 Allergic Eosinophilic Gastroenterocolitis

Allergic eosinophilic gastroenterocolitis is characterized by eosinophilic infiltration of the gastrointestinal tissues. Involvement of the mucosa causes pain, nausea, vomiting and diarrhoea.[120, 121] Involvement of the muscular layer causes strictures and dysmotility.[122, 123] Serosal inflammation may lead to ascites. Protein-losing enteropathy have been reported.[103] Other features of severe disease include gastrointestinal bleeding, iron-deficiency anemia and growth failure.[124]

4.2.1 Clinical features of Allergic Eosinophilic Gastroenterocolitis

Allergic eosinophilic gastroenterocolitis can present at any age. Males are more commonly affected. There is evidence that allergic eosinophilic gastroenterocolitis arise secondary to the interplay of genetic and environmental factors. Approximately 10% of patients have an immediate family member afflicted with the disorder,[125, 126] and 75% are atopic.[127, 128]

Cow's milk, soy, egg, wheat and fish are most commonly implicated.

Improvement in symptoms has been seen with removal of the offending food if known and the use of amino acid formulas.[129] When restricted diet fails, steroids have been used.[130] Other treatment strategies include the use of sodium cromoglycate[131] and montelukast.[132]

4.2.2 Investigations

Diagnosis requires confirmation of an eosinophilic infiltration on gut biopsy. Peripheral eosinophilia or raised IgE may be present. Other causes of peripheral eosinophilia have to be excluded.

D Biopsy of the gut to demonstrate presence of eosinophils should be done for diagnosis of allergic eosinophilic gastroenterocolitis.

Grade D, Level 3

D Skin prick testing and patch testing to food allergens may be done to identify IgE-mediated and cell-mediated food allergies.

Grade D, Level 3

4.2.3 Treatment

D In allergic eosinophilic gastroenterocolitis, the elimination of the implicated food and the use of an amino-acid based formula is recommended.

Grade D, Level 3

D In the treatment of allergic eosinophilic gastroenterocolitis, corticosteroids, sodium cromoglycate and montelukast can be used as alternative treatments, but symptoms can recur on weaning the corticosteroids.

Grade D, Level 3

4.3 Food Protein-Induced Enterocolitis Syndrome (FPIES)

Food Protein-Induced Enterocolitis Syndrome is an uncommon, paediatric non-IgE-mediated disorder triggered by ingestion of certain food proteins. The pathophysiology is not clear but appears to be mediated by T-cell elaboration of the cytokine tumor necrosis factor (TNF)-alpha.[133]

Most children present during the first 6 weeks of life about 2 hours after ingesting the food protein with profuse vomiting and/or diarrhoea. Other associated features include pallor, lethargy, cyanosis, metabolic acidosis and neutrophilia.[133-135] Most children show rapid recovery within a few hours but up to 20% of children require fluid resuscitation for hypovolemic shock.[133, 136-138] There is no sex predilection and may be associated with atopic disease or IgE-mediated food allergy.[138]

Causative foods associated with Food Protein-Induced Enterocolitis Syndrome were cow's milk and soy in very young infants, and rice, oats, sweet potato, banana, fish, chicken and lamb anytime after weaning to semi solids.[138] In an Australian series, rice was one of the most common triggers of Food Protein-Induced Enterocolitis Syndrome.[139]

4.3.1 Clinical features of Food Protein-Induced Enterocolitis Syndrome

The diagnosis of Food Protein-Induced Enterocolitis Syndrome remains a clinical one. It can be based on the criteria proposed by Sicherer and co-workers[133, 137] which are:

1) repeated exposure to the incriminated food elicited repetitive vomiting and/or diarrhoea within 24 hours without any other cause for the symptoms.
2) symptoms were limited to the gastrointestinal tract.
3) removal of the offending protein from the diet resulted in resolution of symptoms and/or food challenge elicited vomiting and/or diarrhoea within 24 hours after administration.

4.3.2 Investigations

GPP Skin prick test and serum food-IgE levels may be used to delineate concomitant IgE-mediated food allergy but are not useful for diagnosis of Food Protein-Induced Enterocolitis Syndrome.

GPP

4.3.3 Treatment

D Treat Food Protein-Induced Enterocolitis Syndrome with food allergen elimination.

Grade D, Level 3

D In patients with reactions to cow's milk and/or soy milk formulas in Food Protein-Induced Enterocolitis Syndrome, which often coexist, an extensively hydrolysed milk formula is recommended. In those who do not tolerate these hydrolysates, an amino acid-based formula is recommended.

Grade D, Level 3

Tolerance of the allergen is usually attained by 3 years of age.[136-138]

D In Food Protein-Induced Enterocolitis Syndrome, food challenges should be conducted under medical practitioner supervision in a hospital setting with resuscitation medications available.[140]

Grade D, Level 3

4.4 Food Protein Allergic Enteropathy

Allergic enteropathy is characterized by protracted diarrhoea (not infrequently steatorrhea), vomiting, malabsorption, and failure to thrive. The immune mechanism appears to involve a mixture of T cell responses and eosinophilic infiltration. Additional features may include abdominal distention, early satiety, occult blood in stools, anaemia, protein-losing enteropathy, hypoalbuminaemia and edema.[113]

4.4.1 Clinical features

Symptoms usually begin in the first few months of life, but can occur at any age through adolescence. Allergic enteropathy appears to occur more commonly in infants taking formula, rather than infants who are breast-fed.

Allergic enteropathy is most commonly caused by an immune response to cow's milk protein, but soy, cereal grains, egg, and seafood have all been implicated.[113]

This enteropathy generally resolves in 1-3 years. Unlike gluten-sensitive enteropathy (Celiac disease), there is no increased threat of future malignancy.[113]

4.4.2 Investigations

Food patch testing has been found to be positive in some research studies, but will require further validation before it can be recommended for use in clinical management of patients.[103]

GPP Food patch testing is not recommended for the evaluation of allergic enteropathy.

GPP

GPP Endoscopy and biopsy of the small bowel is recommended for the diagnosis of allergic enteropathy.[103]

GPP

Biopsy reveals patchy small bowel villous injury, increased crypt length, intraepithelial lymphocytes, and few eosinophilis.[113]

GPP Eliminate the food allergen in patients with allergic enteropathy. This leads to the clearing of gastrointestinal symptoms within 3 to 21 days.[112]

GPP

D In allergic enteropathy, a graded home food challenge can be tried following discussion with the patient. If still sensitised, symptoms may recur within days or up to several weeks. Most patients outgrow their hypersensitivity at between the ages of 1-3 years.[113]

Grade D, Level 4

4.5 Allergic Protocolitis

This disorder of infancy is characterized by the presence of mucous, bloody stools in an otherwise well-appearing infant caused by an immune response directed, most commonly, against cow's milk protein.[113]

4.5.1 Clinical features

Allergic protocolitis typically presents in the first few weeks to 6 months of life.[141] Parents typically note a gradual onset of bloody stools which increases in frequency unless the casual allergen is removed.[141] Occasionally there is associated colic or increased frequency of bowel movements, but failure to thrive is absent. Examination of the abdomen is benign. Additional observations in a minority of infants include anaemia. Peripheral blood eosinophilia, and mild hypoalbuminemia rarely occur. Markers of atopy such as atopic dermatitis or positive family history for atopy are not significantly increased compared with general population.[142]

Allergic protocolitis usually occurs in breast-fed infants (up to 60%), where the immune response results from maternal ingestion of the food allergen, usually cow's milk, which is passed in immunologically recognizable form into the breast milk. Cow's milk and soy milk are the causative foods in the majority of the remaining formula fed infants. Allergic protocolitis has rarely been described in infants fed protein hydrolysate formulas.

4.5.2 Diagnosis

Diagnosis is usually made through clinical history and response to an elimination diet. The bleeding is often mistakenly attributed to perianal fissures, but other differentials include infection, necrotising enterocolitis, or intussusception.

GPP For the diagnosis of allergic protocolitis, skin prick test and serum food-specific IgE levels are not required. Endoscopic examination is also not needed for diagnostic purposes. However, if symptoms fail to respond to elimination of the suspected food allergen (cow's milk in most cases), then endoscopic examination with histological diagnosis is recommended.

GPP

4.5.3 Treatment

D In allergic proctocolitis, treatment by elimination of the food allergen is indicated if significant blood loss is present. Mild cases can resolve spontaneously.[103]

Grade D, Level 3

D In allergic proctocolitis, eliminate cow's milk from the mother's diet if the mother is breastfeeding.[103]

Grade D, Level 3

D In allergic proctocolitis, for cow's milk formula or soy milk fed infants, an extensively hydrolysed milk formula is recommended,[69] due to the high rates (up to 30%) of concomitant cow's milk protein and soy protein allergy. Only in rare instances is an amino-acid based formula required. Clearance of symptoms typically occurs within 48-72 hours.

Grade D, Level 3

D In allergic proctocolitis, a gradual food introduction at home can be attempted after the age of 1 year as tolerance of the allergen is usually attained by that age.[112]

Grade D, Level 3

5 Atopic eczema dermatitis syndrome and food allergy

Although food allergy may trigger atopic dermatitis eczema syndrome, especially in young children, the majority of children with atopic dermatitis eczema syndrome do not have food allergy. Moreover, adult atopic dermatitis eczema syndrome is unlikely to be associated with food allergy. It is merely in young children with severe persistent atopic dermatitis eczema syndrome, who are not responding well to topical treatment, that food allergy can be involved as a trigger or maintenance factor of atopic dermatitis eczema syndrome.

It should be noted that the predictive value of a history of an adverse reaction to food (i.e. worsening of the atopic dermatitis eczema syndrome) is lower than that for food-induced immediate reactions.[143, 144] In other words, a history of food triggered atopic dermatitis eczema syndrome is less reliable than in cases of acute allergy (such as urticaria). Therefore, elimination of food, followed by a rechallenge may be necessary to clarify the involvement of foods in atopic dermatitis eczema syndrome.

5.1 Prevalence of food allergy in children with eczema

The prevalence of food allergy in children with eczema ranges from 33-63%.[145] Both IgE-mediated reactions and independent T-cell mediated responses appear to be involved in eczema. Several studies have shown that in the majority of eczematous children, only a limited number of foods allergens are involved, such as cow's milk, hen's egg, and soy.[145-148] The role of wheat in eczema is far less clear, especially in Singaporean children. Food allergy may also present as IgE-mediated immediate allergy with acute urticaria and/or angioedema, on top of existing eczema lesions.[149]

5.2 IgE-mediated hypersensitivity and eczema

A large number of children with atopic eczema dermatitis syndrome have signs of other allergic diseases, such as asthma, rhinitis or food allergy (i.e. urticaria, angioedema).[150] About 30% of all children with atopic eczema dermatitis syndrome will develop asthma, and when considering severe atopic eczema

dermatitis syndrome the prevalence is even higher, reaching 60% to 80%.[151] Immediate IgE-mediated food allergy may often co-exist independently in individuals with eczema. Increased total serum IgE has been recorded in about 80% of patients (less in infants). In addition, there is a correlation between total serum IgE and severity of atopic eczema dermatitis syndrome (also in infants).[152] Allergen sensitization as reflected by skin prick and *in-vitro* specific IgE tests to a number of inhaled allergens and food allergens are commonly found in patients with moderate to severe eczema.[11]

Allergen sensitization (i.e. positive allergy testing), however, does not always indicate clinical relevance, and does not mean that the underlying eczema is necessarily exacerbated by a particular food allergen (i.e. false positive result). A positive skin prick test corresponds to a clinically detectable allergy (by a provocation test) in only about 25% of atopic eczema dermatitis syndrome patients.[11, 153] Threshold discriminatory levels of specific IgE to food may assist in the decision to proceed with food challenge testing. [29, 154, 155]

Taken together, personal history, food specific IgE or skin prick testing are not sufficiently reliable for identification of clinically relevant foods in eczema. Therefore, food challenge may still be necessary to make an appropriate diagnosis of food allergy in eczema. Elimination diets based on *in vitro* or skin prick testing are inadequate. A trial of food allergen elimination can be the first step for patients strongly sensitized food allergens, provided nutritional adequacy is ensured. A negative elimination and re-challenge may confirm the absence of food allergy but long term dietary restrictions should be based on a positive food challenge.

5.3 Non-IgE-mediated food triggers

The determinations of specific IgE may also yield false negative results. A possible explanation for the false negative results is the presence of non-IgE-dependent mechanisms, such as T-cell mediated responses. Currently there are no standardized in-*vitro* tests to evaluate non-IgE-mediated food triggers of eczema. The atopy patch test is available for research purposes but further studies are needed before it can be used routinely.[143, 145]

GPP Consider evaluating for food allergy in young children with moderate to severe atopic dermatitis eczema syndrome who do not respond to optimized topical treatment, and in those with a history suggestive of IgE-mediated reactions. Foods commonly involved are hen's egg, cow's milk and soy (the role of wheat is far less clear).

GPP

5.4 The food challenge test (also refer to Chapter 2)

Food challenge is considered a useful tool to evaluate food allergy as a trigger of eczema. There are strict scientific criteria for challenge tests and the best design is the double-blind placebo-controlled test, assessing immediate and late (2 to 24 hours post-challenge) eczematous reactions.[40, 145] Evaluation is often made after a period (2 to 3 weeks) of food allergen elimination, and when skin lesions have been managed optimally with topical therapy. A double-blind placebo controlled challenge with a placebo administration arm is considered when the role of possible underlying psychological factors is assessed to be important, otherwise open challenges may be considered for practical reasons. Provocation testing should be performed in a facility where close monitoring is available. In view that delayed reactions may occur as late as 24 hours post challenge, a review the next day may be necessary.

Based on studies carried out in US and Europe, the most common food allergens triggering positive provocation tests are: cow's milk, eggs, soy, wheat, seafood, peanuts and treenuts.[156, 157] A food challenge test provides the most reliable means of the diagnosis of food allergen triggered eczema, as the clinical history and allergen specific IgE to common foods may not be reliable.[158]

GPP In young children with moderate to severe atopic dermatitis eczema syndrome, a trial of limited food allergen (e.g. cow's milk and eggs) elimination for a limited period (up to one month to monitor for response) may be considered as long as the nutrition is not affected.

GPP

6 Unproven and disproved allergy tests

Many tests that are not in accordance with generally accepted scientific principles are purported to detect allergy, especially food allergy. Persons with symptoms atypical of food allergy, such as lethargy, hyperactivity or poor concentration, are sometimes diagnosed to be suffering from this condition based on the results of these tests.[159]

Unproven tests are those that lack a sound scientific basis and have not been subjected to proper studies to evaluate their effectiveness. Unproven tests can be divided into those that have no diagnostic utility in any medical conditions, and those that may be useful for the management of certain medical problems but have not been evaluated for allergy.[160] Disproved tests are those that have been shown to produce results no better than by chance in controlled studies. It must be mentioned that, on the whole, there have not been many studies designed to discredit these tests, which is one reason why they continue to flourish.

These tests tend to produce false positive results, leading to misdiagnosis of food allergy. It is unfair to patients if they are told they are allergic to food when they are not because eating is important for social interaction and daily pleasure.[161]

Currently, direct-to-consumer food allergy testing is available, so the family physician has to be able to review the results critically to provide an accurate assessment.

Table 7 Unproven tests

Tests	Short description	Comments
Food-specific IgG[162-164]	This is similar to testing for specific IgE to foods, except that IgG is detected.	No clinical correlation has been found between food allergy and food-specific IgG. Such IgG is found in people without evidence of allergy.
Food-specific IgG4[164-166]	IgG4 was thought to act in a similar way to IgE in causing allergic reactions.	After examining the evidence, a position statement issued by the American Academy stated that IgG4 had no proven role in the diagnosis of allergy.
Chemical analysis of body fluids and tissues[24]	Samples of blood, hair, fat and urine are tested for various substances such as organic solvent, heavy metals, pesticides, minerals and cytokines.	This is motivated by the unsupported theory that chemicals accumulate in the body, damage the immune system and predispose to allergy. There is no evidence that the levels of chemicals in the tissues of people with and without allergy are different.

Table 8 Disproved tests

Tests	Short description	Comments
Intradermal skin tests[167, 168]	Skin tests for IgE-mediated reaction using the intradermal route of administration of allergen.	Intradermal administration of allergens remains a valid test for evaluating drug and insect venom allergies. However, it is not indicated for food and environmental allergens because of the high rates of false positive results and risk of systemic reactions.
Skin end-point titration[167, 169]	Increasing 5-fold serial concentrations of allergens are injected intradermally. As many as nine injections for each allergen are administered, and multiple allergens are studied each time.	Allergy practitioners feel that the number of injections is excessive for the purpose of establishing allergy. Reactions, even those not typically thought of as allergic in origin, constitute positive responses.
Provocation-neutralization[170, 171]	This is a method to test for and treat allergy and is an extension of the above. Increasing concentrations of the allergen are administered subcutaneously, intradermally or sublingually. Any kind of response is considered positive. Further injections are given until a neutralizing dose is found, which may be higher or lower than the provoking dose. This dose is thought to lead to the disappearance of provoked symptoms.	The neutralizing doses are very dilute and are different from those used in conventional subcutaneous immunotherapy.
Electrodermal testing[24, 172]	Skin resistance is measured while the patient is exposed to the food by means of sealed tubes containing the allergen placed in the electric circuit.	There is no scientific evidence that skin resistance is related to allergy and the test has been disproved in controlled studies.
Applied kinesiology[24, 171, 173, 174]	The patient holds stoppered bottles containing food allergens in one hand. The strength of the other arm is tested. When there is a decrease in muscle power, the test is considered positive.	It is inexplicable how holding bottles containing allergens can lead to fall in muscle power and how this relates to food allergy. One study each showed that the responses to food allergens and to insect venom were not reproducible.
Cytotoxic testing (the commercial ALCAT test is based on this)[159, 160, 162, 171, 175, 176]	Leucocytes are mixed with serum and water and placed on glass slides containing dried food extracts. The slides are reviewed repeatedly and reported as positive when neutrophils become less motile, turn round, develop vacuoles, flatten, fragment or disintegrate.	This test was based on the erroneous belief that leucopaenia develops during symptomatic pollen allergy. Studies indicate that test results do not correlate with symptoms due to food.

B Medical practitioners should not order unproven and disproved allergy tests because they do not have scientific basis and do not provide objective and reliable diagnosis of allergy.

Grade B, Level 2++

B Patients who are found to have positive test results with one or more of the unproven or disproved tests should not be told that they have food allergy but they should be re-evaluated so that a precise diagnosis may be offered.

Grade B, Level 2++

7 Primary prevention of food allergy

The optimal approach to allergies is to prevent them from becoming clinically expressed. Preventing allergy or prevention of allergic sensitization in a healthy infant is referred to as primary prevention. A number of primary preventive measures for food allergy, in large part without clear scientific validation, have been applied during the last decades. Most of them constitute avoidance of food allergens in early life, by using hypoallergenic formulae or delayed introduction of allergenic foods, assuming that this may reduce the risk of food allergy.[177] However, despite these so-called preventive measures, the prevalence of food allergy has steadily increased worldwide, resulting in an increase of the incidence of childhood food sensitization to allergens such as peanut, an increase in specialist consultations for food allergy, and an increase in hospitalizations for food-related anaphylaxis.[177]

Interventions of primary prevention can be divided into: interventions during pregnancy (prenatally) and interventions during early life (postnatally). Both types of interventions have been reviewed recently in the literature.[178, 179] Most studies have been performed on postnatal primary prevention, while only a few intervention studies during pregnancy were published.

7.1 Recommendations during pregnancy

Only a limited number of studies were published on cow's milk and egg avoidance during pregnancy and no beneficial effect was shown. In contrast, increased sensitization in the offspring was found in a number of them.[178] There have been contradictory results on the role of peanut avoidance during pregnancy. In one study from South Africa, high consumption of peanuts by the pregnant woman was associated with an increased risk to develop peanut allergy in the child, while studies from UK showed that reduction of peanut exposure during pregnancy resulted in higher prevalence of peanut allergy in the children.[180, 181] A recent Cochrane review concluded that *the prescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her child's risk of atopic diseases, and such a diet may adversely affect maternal and/or fetal nutrition.*[182]

A Allergen avoidance during pregnancy to prevent allergy in the offspring is not recommended as it has not been shown to be effective, and more importantly, it may adversely affect maternal and/or fetal nutrition.

Grade A, Level 1+

7.2 Recommendations regarding breastfeeding

Breastfeeding is beneficial for the child's health and may prevent or decrease allergic sensitization in infancy. However, there is no clear benefit on the development of inhalant allergies later in childhood. Moreover the effect of breastfeeding on food allergy is difficult to study, as most studies are non-controlled and not blinded, leading to potentially biased results. A review of the few studies looking at this has shown that exclusive breastfeeding for at least 4 months in at-risk babies resulted in a lower incidence of cow's milk allergy until 18 months of age.[183] However, a Cochrane review showed no significant reduction on subsequent food allergy among those exclusively breastfed.[182] It is difficult to draw firm conclusions at this point in time as there are too few studies with too many variations including length and exclusivity of breastfeeding.

B Breast feeding is highly recommended for all infants irrespective of atopic heredity. The most striking results on primary prevention have been shown for exclusive breast feeding for at least 4-6 months.[182]

Grade B, Level 2++

B Maternal dietary modification while breastfeeding is not recommended for the prevention of food allergy in the offspring.[184, 185]

Grade B, Level 2++

Birth cohort studies from Denmark suggested that daily intake of cow's milk (by the mother) via breast milk may be beneficial and facilitate tolerance induction to cow's milk.[186]

7.3 Recommendations regarding formula feeding

Studies on preventing cow's milk allergy and usage of hydrolyzed formula feeding for primary prevention of allergy have been reviewed recently.[187] Taken together, the greatest impact of using hydrolyzed formulae (i.e. extensive and partial hydrolysate) has been found on the prevention of cow's milk allergy and on atopic eczema. However, a large variation of potential efficacy was reported, mostly in relation to specific features of the formula, with extensively hydrolyzed, casein-based formula being the most effective in one study.[188]

A recent Cochrane review examining the role of formula on subsequent allergy found some evidence for a protective effect on the development of cow's milk allergy with hypoallergenic formula in high risk infants. This effect was similar for both partially and extensively hydrolysed formula.[189]

At the moment, due to contradictory results, it is not clear from primary prevention studies whether extensively hydrolysed formula is more effective than partially hydrolysed formula in the prevention of cow's milk allergy despite the greatly differing content of cow's milk allergen.[177]

In high risk infants who are unable to be completely breastfed, there is evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy.

A Breastfeeding is also highly recommended for high-risk infants, as exclusive breastfeeding is more protective than hydrolyzed formula. However, a hydrolyzed formula can be recommended for high-risk infants who cannot be completely breastfed..[189]

Grade A, Level 1++

C Cow's-milk based formula should be avoided in the first 5 days of life as the administration of cow's milk-based formula during the first 5 days in the newborn nursery increases the risk of specific sensitization.[190]

Grade C, Level 2+

7.4 Regarding weaning to solids

Studies have shown that the introduction of solid foods before 4 months of age increases the risk of developing allergic disease such as atopic eczema and food allergy.[191, 192] One hypothesis for this is that the infant gut is immature and therefore more permeable to food allergens in early life and that avoidance of allergenic foods would prevent food allergy and atopic disease.

The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for at least 4 to 6 months, followed by the gradual introduction of solid foods in the second half of the first year.[193]

Recently, there has been a suggestion that excessive delay in weaning to solids may have a paradoxical effect of increasing the risk of asthma and allergies. One study showed that delay in exposure to cereal grains until after 6 months increased the risk of developing wheat allergy.[194] In another study, prolonged exclusive breastfeeding increased the risk of atopic eczema and food hypersensitivity at 5 and 11 years.[195]

B Weaning to semisolid foods should be delayed for at least 4-6 months for all infants.[196]

Grade B, Level 1+

B It is unnecessary to delay introduction of solid food after 4-6 months of age as there is no evidence that it is useful to prevent food allergy. In fact, delayed introduction of solids beyond 6 months may increase the risk of food allergy.[193]

Grade B, Level 2++

8 Clinical quality improvement

The following clinical quality improvement parameters, based on recommendations in this guideline, are proposed:

1. Proportion of patients discharged with auto-injectable adrenaline after hospital (inpatient or accident and emergency) discharge and clinic visit for food-induced anaphylaxis. (pg 35)

2. Proportion of patients given a written action plan after diagnosis of food-induced anaphylaxis (in- and out-patient). (pg 35)

3. Proportion of patients and caregivers who can demonstrate the correct use of self-injectable adrenaline. (pg 35)

9 Cost-effectiveness issues

A review of the literature illustrated the lack of information and clear methodology for assessing costs of food allergy. No studies investigating the cost of food allergies were found. Two studies[196, 197] concluded that there is a need for a more structured research programme to generate data essential for future evaluation of procedures and technologies for the diagnosis, treatment and management of food allergy.

Annex A Example of written action plan**

ACTION PLAN FOR ANAPHYLAXIS

Name: _____

Date of Birth: _____

Substance (allergens) to be avoided:

_____

_____

Family/ carer name and contact:

_____

Picture

MILD TO MODERATE ALLERGIC REACTION

- Itching and swelling of lips, face, eyes
- Hives or welts
- Tingling mouth
- Vomiting, diarrhea

ACTION

- Stay with the person and call for help
- Give medications (if any) _____
  _____
- Locate EpiPen® or EpiPen Jr®
- Contact family/carer

Watch for any one of the following signs of ANAPHYLAXIS

ANAPHYLAXIS (SEVERE ALLERGIC REACTION)

- Swelling of tongue
- Swelling/tightness in throat
- Difficulty talking and/or hoarse voice
- Wheeze or persistent hacking cough
- Difficult noisy breathing
- Loss of consciousness and/or collapse
- Pale and floppy (young children)
- Severe abdominal colic(older child/adults)

ACTION

- Give EpiPen® or EpiPen Jr®
- Give medications (if any)
- Call Ambulance telephone # 995
- Lay patient flat and elevate legs. If breathing is difficult, allow to sit but do not stand
- Contact family/carer
- Further EpiPen® doses may be given if no response after five 5minutes

If in doubt, Give EpiPen® or EpiPen Jr®

How to Give EpiPen®

1. Form fist around EpiPen® and Pull Off grey cap

2. Place black end against outer mid-thigh (with or without clothing).

3. Push down hard until a click is heard or felt and hold in place for 10 seconds.

4. Remove EpiPen® and be careful not to touch the needle.

Plan prepared by:

Dr. _____ Date: _____

Name and Signature

** Adapted (with permission) from the Australasian Society of Clinical Immunology and Allergy (ASCIA) action plans for anaphylaxis(www.allergy.org.au)

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://smj.sma.org.sg/cme/smj/index.html *(the link will only be available once the July 2010 issue of the SMJ becomes available).* The answers will be published in the SMJ September 2010 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Indicate whether each statement is True or False.

		True	False
1.	IgE-mediated reaction to food		
	A) typically occurs days to weeks after exposure to the food.	☐	☐
	B) is the mechanism through which anaphylaxis occurs.	☐	☐
	C) can present as vomiting and abdominal pain.	☐	☐
	D) may play a role in childhood eczema.	☐	☐
2.	In anaphylaxis,		
	A) injectable epinephrine is first-line treatment and should be administered first before anti-histamines and corticosteroids.	☐	☐
	B) this is diagnosed when a patient has life-threatening features of allergy such as cardiovascular collapse or breathing difficulties.	☐	☐
	C) patients are usually stable after epinephrine and no further medical care needed.	☐	☐
	D) epinephrine should be administered via the IV route if possible.	☐	☐

		True	False
3.	Regarding diagnostic tests in food allergy,		
	A) skin prick tests measure the presence of IgE antibodies.	☐	☐
	B) skin prick tests and *in vitro* measurement of specific IgE antibodies are validated for certain food allergens and can both be used to assess the presence of sensitization.	☐	☐
	C) skin prick tests are preferred when the patient has dermatographism.	☐	☐
	D) antihistamines affect skin prick tests and should be stopped for at least 1 month before that.	☐	☐
4.	Regarding food allergens,		
	A) goat's milk is safe in patients with cow's milk allergy as the level of cross-reactivity is low.	☐	☐
	B) hen's egg allergy is rarely outgrown.	☐	☐
	C) shellfish allergy tends to persist.	☐	☐
	D) detectable levels of IgE antibodies or a positive skin prick test indicate definite clinical allergy.	☐	☐
5.	In infants with food allergy,		
	A) soy-based formula is recommended in infants with cow's milk allergy.	☐	☐
	B) MMR vaccination is contraindicated if the infant develops urticaria to egg.	☐	☐
	C) peanut allergy is mild and outgrown in the majority.	☐	☐
	D) injectable epinephrine should never be used in anaphylaxis as there is no appropriate dose for children who weigh < 10kg.	☐	☐

		True	False
6.	Please state if the following statements are true or false:		
	A) Lethargy, arthritis, autism and hyperactivity are due to food allergy and tests should be performed to identify the provoking allergen.	☐	☐
	B) No correlation has been found between the presence of food-specific IgG and food allergy.	☐	☐
	C) Intradermal tests are recommended in food allergy when skin prick tests are negative as they are more sensitive.	☐	☐
	D) Non-IgE based alternative allergy tests such as ALCAT, applied kinesiology and measurement of food-specific IgG must be scientifically sound since they are available commercially.	☐	☐
7.	The following should be done when treatment for a 12-month infant suspected of having allergic eosinophilic esophagitis?		
	A) Recommending a switch to total breast feeding	☐	☐
	B) Eliminating cow's milk, soy, peanut, eggs and wheat from his diet	☐	☐
	C) Commencing the child on acid suppression (e.g. ranitidine)	☐	☐
	D) Use of a leukotriene-receptor antagonist as first line therapy if there is peripheral eosinophilia	☐	☐
8.	The following features are consistent with a diagnosis of cow's milk induced protocolitis in an infant?		
	A) Presence of blood specks and mucous in stool	☐	☐
	B) Presence of atopic eczema	☐	☐
	C) Presence of poor weight gain	☐	☐
	D) Presence of anaemia	☐	☐

		True	False
9.	On eczema in children		
	A) The best test for diagnosing food allergy in eczema is a skin prick test	☐	☐
	B) Food allergy is often involved in older children with eczema	☐	☐
	C) The most common food allergy in infants with eczema is egg	☐	☐
	D) The atopy patch test is useful in the assessment of eczema	☐	☐
10.	On primary prevention		
	A) HA-formula's containing probiotics are useful in primary prevention of asthma	☐	☐
	B) Late introduction of solid foods (> 1 year) is advised to prevent allergy	☐	☐
	C) Allergen avoidance (diet) during pregnancy can prevent allergy	☐	☐
	D) Allergen avoidance during breast feeding can reduce the incidence of eczema	☐	☐

Workgroup members

The members of the workgroup, who were appointed in their personal professional capacity, are:

Chairperson

Dr Lee Bee Wah
Adjunct Professor
Department of Paediatrics
University Children's Medical Institute
National University Health System.

Members

Prof Marion Aw
Senior Consultant
Paediatric Gastroenterology, Hepatology and Nutrition Service
Department of Paediatrics
University Children's Medical Institute
National University Health System

Dr Chiang Wen Chin
Consultant
Allergy Service
Department of Pediatrics
KK Women's and Children's Hospital

Mrs Grace Mary George
Parent representative

Dr Anne Goh Eng Neo
Senior Consultant
Head, Allergy Service,
Department of Pediatrics
KK Women's and Children's Hospital

Dr Han Wee Meng
Senior Dietitian
Department of Nutrition & Dietetics
KK Women's and Children's Hospital

Dr Jean-Jasmin Lee Mi-Li
Family Doctor
Ang Mo Kio Polyclinic
National Healthcare Group Polyclinics

Dr Leong Khai Pang
Senior Consultant
Department of Rheumatology, Allergy and Immunology
Tan Tock Seng Hospital

Dr Liew Woei Kang
Consultant
Allergy Service,
Rheumatology and Immunology Service,
Department of Pediatrics
KK Women's and Children's Hospital

Members

Adj A/Prof Mary Daniel
Adjunct Associate Professor
Duke-NUS Graduate Medical School

Ms Phuah Kar Yin
Senior Dietitian
Department of Nutrition & Dietetics
KK Women's and Children's Hospital

Dr Lynette Shek
Associate Professor and Senior Consultant
Department of Paediatrics
University Children's Medical Institute
National University Health System

Prof Hugo Van Bever
Senior Consultant
Department of Paediatrics
University Children's Medical Institute
National University Health System

Subsidiary editors:

Dr Pwee Keng Ho
Deputy Director (Health Technology Assessment)
Health Services Research & Evaluation Division
Ministry of Health

Mr Raymond Huang
Assistant Manager (Health Technology Assessment)
Health Services Research & Evaluation Division
Ministry of Health

Acknowledgement:

Dr Edwin Chan Shih-Yen
Head, Epidemiology
Singapore Clinical Research Institute
Assoc Professor, Duke-NUS Graduate Medical School, Singapore
Director, Singapore Branch, Australasian Cochrane Centre;
Head (Evidence-based Medicine)
Health Services Research & Evaluation Division
Ministry of Health