BMJ Best Practice

Food allergy

Straight to the point of care

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Summary

Food allergy is an adverse immune response to food proteins. Most reactions are from peanut, tree nuts, milk, egg, fish, shellfish, wheat, and soya. Symptoms usually appear within 20 minutes of ingestion and nearly always within 2 hours.

Symptoms and signs may vary from pruritus and mild cutaneous eruption to severe anaphylactic respiratory, gastrointestinal, or cardiovascular (e.g., hypotensive) manifestations.

Epinephrine (adrenaline) given by intramuscular injection is the treatment of choice for severe systemic symptoms (anaphylaxis); lesser reactions are managed with a range of therapies from simple withdrawal of suspected food allergen to oral antihistamines.

Patients should be encouraged to obtain medical identification jewellery, be knowledgeable of the incipient signs and symptoms of an allergic reaction, be trained how to use an epinephrine (adrenaline) auto-injector, and know how to activate emergency response services.

Definition

Food allergy is an adverse immune response to food proteins.

Reactions may be either immunoglobulin (Ig) E-mediated, non-IgE-mediated, or mixed IgE-mediated/non-IgE-mediated reactions. IgE-mediated reactions to food are primarily considered here.

THEORY

Epidemiology

The prevalence of immunoglobulin E-mediated food allergy in the population varies between 2% and 10%.[3] [4] [5] In one cross-sectional survey of US adults, almost 19% self-reported a food allergy.[6] However, only 10.8% had a convincing food allergy.

Food allergy is greater in the paediatric population than in adults, with estimates of 6% to 8% in children under 5 years and 3% to 4% in adults.[7] [8] [9] [10] [11] [12] It is seen more often in people with atopic dermatitis, certain pollen sensitivities, or latex sensitivity. The most common food allergens in young children in the US general population are cows' milk (2.5%), egg (1.3%), peanut (0.8%), wheat (approximately 0.4%), soya (approximately 0.4%), tree nuts (0.2%), fish (0.1%), and shellfish (0.1%).[1] Among US adults, the most commonly reported food allergens are shellfish (2.9%), milk (1.9%), peanut (1.8%), tree nut (1.2%), and fin fish (0.9%).[6]

Globally, prevalent allergens differ. For example, there is a higher incidence of sesame seed allergy in Israel, and of mustard allergy in France, and a lower incidence of peanut allergy in China.[2] [13] [14]

Aetiology

Food allergy is likely to develop as a result of both genetic and environmental factors. With regard to genetic determinants:

- Peanut allergy is 7 times more likely to occur in a child with a sibling who is peanut-allergic than in the general population[15]
- Specific genes contributing to food allergy development have not been identified.

Environmental factors hypothesised to contribute to the development of allergy include:[16]

- Reduced exposures to bacteria and infections (the hygiene hypothesis)
- A rise in consumption of omega-3 polyunsaturated fatty acids
- Reduced dietary antioxidants
- Excess or deficiency of vitamin D
- Possible cutaneous exposure[17]

While sensitisation to food proteins is the most common form of allergy to foods of both plant and animal origin, sensitisation to carbohydrate epitopes leading to allergic reaction to mammalian meat has been described. This form of food allergy involves sensitisation to the carbohydrate epitope galactose-alpha-1,3-galactose (alpha-gal). Alpha-gal is a carbohydrate moiety that is present on cells and tissues of all mammals except the higher order primates (including humans). Tick bites can lead to sensitisation of humans to alpha-gal, and subsequent ingestion of meat (e.g., beef, pork, lamb) leads to a delayed allergic reaction. The reaction typically occurs 3 to 6 hours after ingestion. Cross-reactivity with cetuximab has been reported (alpha-gal is present on the Fab portion of the cetuximab heavy chain).[18]

Pathophysiology

Immunoglobulin (Ig) E-mediated food allergy reactions are rapid in onset (usually within minutes to 2 hours of ingestion) and are the manifestation of a cascade of events.[19]

- IgE antibodies to specific epitopes in the food allergen are produced by a patient with atopic disease.

- These antibodies then bind to IgE receptors on mast cells and basophils found in the respiratory tract, gastrointestinal tract, and skin.
- On exposure to the food allergen, the IgE antibodies are cross-linked, resulting in mediator release from the mast cells and basophils.
- Cytokines, chemokines, histamine, prostaglandins, and leukotrienes are released, resulting in vasodilation, smooth muscle contraction, and mucus secretion.

Reactions may be generalised or localised to a specific organ system. Symptoms are believed to be related to mediator release from tissue mast cells and circulating basophils resulting in reactions such as urticaria and angio-oedema, rhinoconjunctivitis, gastrointestinal anaphylaxis, and generalised anaphylaxis. Non-IgE-mediated food allergies present with more chronic or subacute symptoms usually isolated to the gastrointestinal tract. IgE antibody-associated/cell-mediated food allergies may relate to homing of food-responsive T cells to the skin in the case of atopic dermatitis, or to mediators that home and activate eosinophils in the case of eosinophilic gastroenteropathies.[16]

Classification

Clinical classification by immune response[1]

IgE-mediated reactions. Presentations include:

- Urticaria
- Angio-oedema
- Morbilliform rash
- Acute rhinoconjunctivitis
- Acute asthma
- Anaphylaxis
- Food-associated exercise-induced anaphylaxis.

Non-IgE-mediated reactions. Presentations include:

- Contact dermatitis
- Dermatitis herpetiformis
- Food protein-induced enterocolitis syndrome
- Coeliac disease
- Heiner's syndrome.

Mixed IgE-mediated/non-IgE-mediated reactions. Presentations include:

- Atopic dermatitis
- Eosinophilic oesophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis.

THEORY

Case history

Case history #1

An 18-month-old boy is brought by his mother to the paediatrician following an apparent adverse reaction to food. His mother relates that the boy developed a hoarse cry; hives on his face, neck, and trunk; lip swelling; and projectile vomiting 3 minutes after taking one bite of a cracker with peanut butter on it. His mother gave him antihistamine syrup immediately afterwards. Further questioning reveals that the child has also experienced facial hives and vomiting within 10 minutes of ingesting a scrambled egg at 12 months of age. Medical history is significant for wheezing with viral infections during the first year of life and mild atopic dermatitis controlled with frequent emollient use.

Case history #2

A 2-year-old girl is taken to her paediatrician for evaluation of chronic dry skin with frequent episodes of inflammation at bilateral antecubital creases and posterior popliteal fossae. The paediatrician diagnoses atopic dermatitis and learns that the mother has been applying emollients twice daily but is hesitant to use a topical corticosteroid preparation prescribed by another physician 4 months earlier. The mother is particularly concerned that foods are contributing to the child's rash, and has noticed that the child's atopic dermatitis lesions seem to flare up after eating eggs.

Other presentations

Reactions may be either immunoglobulin (Ig) E-mediated, non-IgE-mediated, or mixed IgE-mediated/non-IgE-mediated reactions. IgE-mediated reactions typically include symptoms such as urticaria, angio-oedema, vomiting, diarrhoea, asthma, or stridor. Non-IgE-mediated reactions are thought to be cell-mediated and may include contact dermatitis, food protein-induced enterocolitis syndrome, dermatitis herpetiformis, coeliac disease, or Heiner's syndrome (recurrent pneumonia associated with pulmonary infiltrates, haemosiderosis, gastrointestinal blood loss, iron deficiency anaemia, and failure to thrive).[2] Mixed IgE-mediated/non-IgE-mediated reactions include atopic dermatitis, eosinophilic oesophagitis, and allergic eosinophilic gastroenteritis.[1]

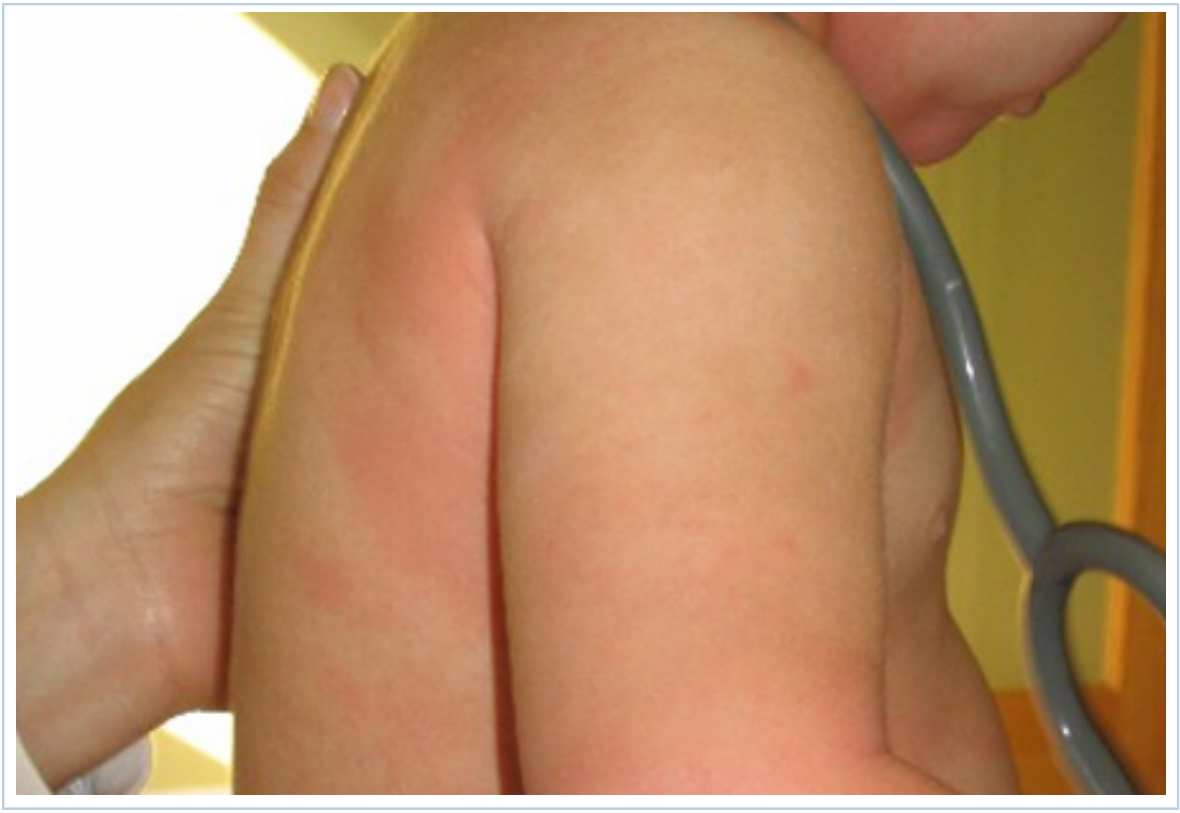
Approach

The initial task in assessment of a patient with suspected food allergy is to separate atopic from non-atopic disease, and to distinguish symptoms and signs of minor adverse immune reactions from more severe concerns of anaphylactic response. It should also aim to identify, if possible, a culprit food. Testing for food allergens should be based on and interpreted in the context of the historical and physical findings.

History and examination

Evaluation should begin with detailing the specific signs and symptoms reported by patient or parent, with particular focus on dermatological, respiratory, gastrointestinal, ophthalmic, and severe cardiac or systemic manifestations. Findings that support the diagnosis of a food allergy include:

- Pruritus, flushing, urticaria, and angio-oedema of the skin



Typical cutaneous findings in food allergy at 30 minutes after ingestion of peanuts

From the collection of Duke University Medical Center; used with permission

- Sneezing, rhinorrhoea, nasal congestion, metallic taste, hoarseness, stridor, a sense of choking, laryngeal oedema, dyspnoea, tachypnoea, wheezing, coughing, or cyanosis
- Nausea, vomiting, abdominal cramping, bloating, and diarrhoea
- Conjunctival injection, lacrimation, periorbital oedema
- In severe cases, conduction disturbances, tachycardia, bradycardia, arrhythmias, hypotension, and cardiac arrest.

Pertinent clues that support the clinical impression of atopic disease include a family member with food allergy, presence of other allergic disease (e.g., atopic dermatitis, allergic rhinitis, asthma), perinatal transdermal food exposure (e.g., peanut oil), dietary excess or diminished vitamin D, omega-3 polyunsaturated fatty acids or antioxidants, and a paucity of exposure to bacteria and infection. Studies in the UK have shown that if a first-degree family member has peanut allergy, the risk of peanut allergy

increases 7 times.[15] Monozygotic twins have been reported to have a 64% concordance rate for food allergy compared with 6.8% among dizygotic twins.[20] Patients with atopic dermatitis, asthma, and allergic rhinitis are more likely to have a food allergy. The presence of asthma is a risk factor for a fatal reaction.[36] Two-thirds of children with atopic dermatitis and food allergy are reactive to egg.[37]

Ninety percent of reactions are caused by milk, egg, peanut, tree nuts, wheat, soya, fish, and shellfish in children, and by peanut, tree nuts, shellfish, fish, and vegetables in adults.[1] [38] [39] The causative food may often be revealed with careful questioning and consideration of the patient's response.

- Has the suspected food allergen been ingested, inhaled, or touched? A specific suspect food should produce symptoms reproducibly nearly every time it is ingested.
- How much of the food was ingested at the time of the reaction? IgE-mediated reactions may be triggered by minute amounts, whereas other disorders may require larger amounts.
- How soon after exposure to the suspected food allergen did the symptoms occur? IgE-mediated reactions usually occur within 20 minutes of exposure and almost always within 2 hours.
- How long did it take for the symptoms to resolve in the past and how was the reaction treated? IgE-mediated symptoms typically resolve within 4 to 12 hours. Reactions may resolve spontaneously or may respond to medical interventions.
- Has exercise been associated with the development of symptoms? Food-dependent, exercise-induced anaphylaxis may occur if the food is eaten within 2 to 4 hours before or after exercise.[37]
- Were any medications or alcohol ingested in proximity to the reaction? Medications and alcohol are believed to increase the rate of allergen absorption.[40] [41] [42]

Testing modalities for food allergy

If the initial evaluation is suggestive of food allergy, diagnostic testing should be performed. Testing may begin with either in vitro immunoglobulin (Ig) E immunoassays or skin prick testing. If the assessment is negative (e.g., the patient tolerates the food regularly and has no related symptoms), then diagnostic testing does not need to be performed and food allergy may be ruled out as a cause of the symptoms.[43] If a food has been tolerated in large quantities many times before, it is not likely a relevant allergen, even with a positive test. Commercially prepared extracts of fruits and vegetables are not as predictive because of the lability of the protein. Fresh fruits and vegetables should be used for skin testing.[44]

High sensitivity and low specificity of skin prick and IgE testing for food allergy can yield false positive results, which may lead to elimination diets that are potentially harmful to patients.[43] Effects such as progression to immediate-type allergy, including anaphylactic reactions have been reported.[43] [45] [46] [47] Testing should be performed by an allergy specialist trained in the treatment of rare but potentially life-threatening events. If specific testing falls below values predictive of a reaction by immunoassay testing and by skin testing, or the diagnosis is in question, then a food challenge may be performed. Negative skin tests to foods early in life do not preclude the subsequent development of specific IgE hypersensitivity in later childhood.[22]

Double-blind placebo-controlled food challenges are considered the key test in diagnosing food allergy.[48] These challenges are graded, and there should be an equivalent number of placebo and food steps. If the patient passes this challenge, then an open feeding is performed. If this is tolerated, then food allergy has been excluded.

Investigational studies

Purified or recombinant allergens are used to identify specific IgE sensitisation to proteins within an individual food allergen in component-resolved diagnostics. Some studies have shown an increased ability to predict the likelihood of having a severe allergic reaction to foods like peanut, soy, or hazelnut; however, geographical pollen sensitisation patterns may affect results, and further studies are needed to generalise interpretability.[49] [50] The role of component testing continues to evolve.[51]

Atopy patch testing is typically used to identify allergens that cause reactions through delayed contact hypersensitivity where T cells play a major role. Allergenic extract is occluded against intact skin for 48 hours; it is available for investigational use only.[52] Patch testing is well validated for contact dermatitis but not food allergy in general.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Strong risk factors include a family member with atopic disease and prior atopic dermatitis.

milk, egg, nut, fish, shellfish, wheat, or soya ingestion (common)

- Ninety percent of reactions are caused by milk, egg, peanut, tree nuts, wheat, soya, fish, and shellfish in children, and by peanut, tree nuts, shellfish, fish, and vegetables in adults.[1] [38] [39] All foods ingested before a reaction should be noted, including hidden ingredients found in salad dressings, desserts, sauces, or beverages.

reproducible symptoms (common)

- Reaction with every ingestion, although there may be differences based on the amount ingested.

flushing, urticaria, or angio-oedema of the skin (common)

- Result of immunoglobulin E-mediated reactions.

sneezing, rhinorrhoea, or nasal congestion (common)

- Most often seen in conjunction with other organ system involvement.
- Rarely the only presenting sign of food allergy.

dyspnoea, tachypnoea, wheezing, coughing, or cyanosis (common)

- Result of immunoglobulin E-mediated reactions.

hoarseness, stridor, or sense of choking (common)

- Cellular mediators released during an allergic reaction trigger inflammatory response.

nausea and vomiting (common)

- Minutes to 2 hours after ingestion.
- Characteristic of gastrointestinal anaphylaxis. Often accompanied by allergic manifestations in other target organs.

abdominal cramping or bloating (common)

- Characteristic of gastrointestinal anaphylaxis. Often accompanied by allergic manifestations in other target organs.

diarrhoea (common)

- Minutes to 2 hours after ingestion.
- Characteristic of gastrointestinal anaphylaxis.

conjunctival injection or lacrimation (common)

- Results from immunoglobulin E-mediated reactions.

periorbital oedema (common)

- Results from immunoglobulin E-mediated reactions.

abrupt onset of symptoms (common)

- Reaction occurs within seconds to minutes of ingestion, and rarely beyond 2 hours. Symptoms typically resolve within 4 to 12 hours spontaneously or may respond to epinephrine (adrenaline), antihistamines.

reaction caused by small amount of food (common)

- Reaction caused by very small amounts of food protein.

presence of other allergic disease (common)

- Patients with atopic dermatitis, asthma, and allergic rhinitis are more likely to have a food allergy.

laryngeal oedema (uncommon)

- Results from immunoglobulin E-mediated reactions.

Other diagnostic factors

tachycardia or bradycardia (common)

- May be present in severe cases.

reaction exacerbated by exercise or exertion (uncommon)

- In some patients, allergic reactions to foods may only occur after activity or may worsen with exertion.

alcohol or medication ingestion before reaction (uncommon)

- Alcohol or medication ingestion is believed to increase the rate of allergen absorption.

cardiac arrhythmia (uncommon)

- May be present in severe cases.

hypotension (uncommon)

- May be present in severe cases.

Risk factors

Strong

family history of food allergy

- Studies in the UK have shown that peanut allergy is 7 times more likely to occur in a child with a sibling who is peanut-allergic than in the general population.[15] Monozygotic twins have been reported to have a 64% concordance rate for food allergy compared with 6.8% among dizygotic twins.[20]

atopic dermatitis

- One third of children with refractory, moderate to severe atopic dermatitis have IgE-mediated clinical reactivity to food proteins. The prevalence of food allergy in this population is significantly higher than that in the general population.[21] Children with early-onset and severe atopic dermatitis are much more likely to have food allergy.[22]
- The National Institute of Allergy and Infectious Diseases notes that infants with severe eczema, egg allergy, or both, are at high risk for the development of peanut allergy.[23]

Weak

newborn

- Newborns, particularly those genetically predisposed to atopic disease, are considered at an increased risk secondary to the immune system being biased towards an allergic or Th2 response, increased gut permeability, and other aspects of digestive immaturity that may promote sensitisation.[24] Th2 refers to an allergic phenotype and the cytokines released, including interleukin (IL)-4, IL-5, and IL-13, which all promote allergic disease.

perinatal peanut oil exposure

- One study showed that children topically exposed to peanut-based oils in the perinatal period had an increased risk of peanut allergy.[25]

Investigations

1st test to order

Test	Result
in vitro IgE-specific immunoassay • Normative results available for CAP fluorescent enzyme immunoassay (CAP-FEIA) system; 95% positive predictive values in patients with a history of a reaction.[53] • Higher concentrations of food-specific IgE correlate to increased likelihood of a reaction on ingestion.[54] [55] [56] • It is important to recognise that IgE values below the predictive values are still relevant. With an IgE level of 2 kUA/L for peanut, milk, and egg the patient still has a 50% chance of having food allergy. • Food challenge may not be necessary if CAP IgE values exceed predictive levels.[54] [55] [56] Values obtained from other testing systems are not interchangeable.[57]	**egg: ≥7 kUA/L (≥2 kUA/L if ≤2 years old); milk: ≥15 kUA/L (≥5 kUA/L if ≤2 years old); peanut: 14 kUA/L; tree nuts: approximately 15 kUA/L; fish: 20 kUA/L**
skin prick testing • Highly reproducible and less costly to perform than in vitro tests. • Sensitivity >90%, specificity approximately 50%.[3] • The larger the wheal, the greater the likelihood of clinical allergy, with a wheal diameter >8 to 10 mm indicating a greater likelihood of having a clinical reaction.[58] • Negative predictive accuracy is >95% for most foods (wheal diameter <3mm greater than the negative control) and is helpful for excluding IgE-mediated allergic reactivity.[56] • 90% to 95% positive predictive accuracy for most foods in most patients. Accuracy may be <90% in young infants.[2] [55] • Minimal patient discomfort. • Results within 15 minutes. • Safely performed in patients of any age.	**wheal diameter 3 mm greater than control**

Other tests to consider

Test	Result
food challenges • Food challenge performed by giving increasing amounts of suspected allergen over time. • Setting equipped with the necessary medications, equipment, and staff to treat anaphylaxis is mandatory. • Patient is challenged with an initial dose for the test food that is unlikely to produce a reaction, then progressing to a dose that should trigger a reaction. • Double-blind placebo-controlled food challenges are considered the key test in diagnosing food allergy.[48] Open challenges are prone to bias. • Challenges are graded; there should be an equivalent number of placebo and food steps. • If patient passes challenge, then an open feeding is performed. If open feeding is tolerated, then food allergy is excluded.	**allergic reaction**
component-resolved diagnostics • Purified or recombinant allergens are used to identify specific IgE sensitisation to proteins within an individual food allergen. • Some studies have shown an increased ability to predict the likelihood of having a severe allergic reaction to foods like peanut or hazelnut; however, geographic pollen sensitisation patterns may affect results, and additional studies are needed to justify the use of component-resolved diagnostics for foods other than peanut and hazelnut.[49] [50] • The role of component testing continues to evolve.[51]	**positive**

Emerging tests

Test	Result
atopy patch testing • Identifies allergens that cause reactions through delayed contact hypersensitivity where T cells play a major role.[52] • Allergenic extract is occluded against intact skin for 48 hours. • Standardisation of extracts and interpretation method needed before this can be incorporated into clinical practice.[52] • For investigational use only. Patch testing is well validated for contact dermatitis but not food allergy in general.	**erythema and induration**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Atopic dermatitis	• Pruritic, morbilliform, or maculopapular eruptions.	• Selected allergens evaluated for specific IgE based on history. • Rash in the predilection sites for atopic dermatitis within 1 hour of an oral challenge.[59]
Urticaria	• Appearance not necessarily related to food ingestion (e.g., penicillins, sulfonamides, muscle relaxants, diuretics, non-steroidal anti-inflammatories). • Erythematous oedematous lesions on any part of the body. • Typically pruritic, although occasionally painful or burning sensation reported. • Dissipates within 24 hours leaving no residual markings. • Up to 40% of cases of urticaria have associated angio-oedema (swelling of the deeper layers of the subdermis). • Foods are not the cause of chronic urticaria (lasting >6 weeks).	• Lack of response to in vitro IgE testing or skin prick testing. • Foods are not the cause of chronic urticaria (lasting >6 weeks).
Auriculotemporal syndrome	• Recurrent episodes of facial flushing, sweating along the distribution of the auriculotemporal nerve. • Occurs in response to gustatory stimuli.[60]	• Diagnosis is clinical.
Acute asthma exacerbation in children	• Fatigue, dyspnoea, exercise intolerance, aesthete body type, and wheezing, but seldom the only symptoms and signs.[61]	• Pulmonary function testing with diminished FEV1. • Greater likelihood of progression to irreversible obstructive airway disease.
Acute asthma exacerbation in adults	• Dyspnoea; may be precipitated by allergens, cold, or exercise; wheezing reversible on administration of bronchodilators.	• Pulmonary function testing with diminished FEV1. • Greater likelihood of progression to irreversible obstructive airway disease.

Condition	Differentiating signs / symptoms	Differentiating tests
Food-induced pulmonary haemosiderosis (Heiner's syndrome)	• Recurrent pneumonia associated with pulmonary infiltrates, haemosiderosis, gastrointestinal blood loss, iron deficiency anaemia, and failure to thrive.[2] • In infants, most often caused by non-IgE-mediated hypersensitivity to cows' milk.	• High titres of precipitating IgG antibodies to bovine milk proteins.[19] • Chest x-ray with pulmonary infiltrates.[19] • Symptoms improve with removal of cows' milk from the diet.
Tracheo-oesophageal fistula	• Neonates. • Regurgitation of feeding. • Aspiration and pneumonia.	• Chest x-ray with air-distended oesophageal atretic pouch; the nasogastric tube coiled in this pouch. • Also, excessive dilation of stomach as a result of fistula communication.[62]
Pollen food syndrome (oral allergy syndrome)	• Oropharyngeal pruritus and angio-oedema of the lips, oral mucosa, and soft palate.[63] • Symptoms not likely to progress to systemic anaphylaxis.	• Double-blind placebo-controlled food challenge. • Skin prick testing or in vitro assays with suspected fresh fruit or vegetable. • Causative allergens in fruits and vegetables have homologous proteins to pollens of grasses, trees, and weeds.[63]
Food protein-induced enterocolitis syndrome	• Manifests in the first few months of life. Projectile vomiting, diarrhoea, and failure to thrive.[19] • Associated with ingestion of cows' milk or soya protein. • Similar syndrome presents in older infants and children as a result of egg, wheat, rice, oat, peanut, nuts, chicken, turkey, and fish sensitivity. Shellfish sensitivity may be causative in adults.	• Oral food challenge will lead to vomiting within 1 to 4 hours after ingestion (caution: may cause severe hypotension). • Elevation in peripheral blood neutrophils.[37]
Food protein-induced colitis	• Presents in first few months of life.[19] • Infants with isolated finding of blood in the stool.	• Stool positive for blood in infants.
Eosinophilic oesophagitis/ gastroenteritis	• Postprandial nausea, gastro-oesophageal reflux, vomiting, abdominal pain, and early satiety. Weight	• Oesophageal or gastric biopsy shows dense eosinophilic infiltrates.[19]

Condition	Differentiating signs / symptoms	Differentiating tests
	loss and failure to thrive in children.[19]	
Gastroenteritis in children	• Persistent diarrhoea lasting from 1 to 8 days. • Usually accompanied by fever.	• Presence of faecal lymphocytes. • Microscopy and stool culture positive for causative organisms. • Elevated WBC if sepsis; blood cultures positive for causative organisms. • *Clostridium difficile* toxin present (i.e., in patients with recent prolonged antibiotic use).
Gastroenteritis in adults	• Persistent diarrhoea lasting from 1 to 8 days. Usually accompanied by fever.	• Presence of faecal lymphocytes. • Microscopy and stool culture positive for causative organisms. • Elevated WBC if sepsis; blood cultures positive for causative organisms. • *Clostridium difficile* toxin present (i.e., in patients with recent prolonged antibiotic use).
Irritable bowel syndrome	• Recurrent abdominal pain or discomfort that is associated with a change in stool frequency or form. • Mild and poorly localised tenderness in the right lower quadrant and/or left lower quadrant.	• Diagnosis is clinical and by exclusion of other causes (e.g., Crohn's disease, ulcerative colitis).
Crohn's disease	• Family history of Crohn's disease; more common in white people than in black or Asian people; age 15 to 40 years or 60 to 80 years. • Crampy or constant abdominal pain with non-bloody, intermittent diarrhoea. • Perianal lesions (e.g., skin tags, fistulae, abscesses, scarring) may be present.	• Abdominal radiography with small bowel or colonic dilation; calcification; sacroiliitis; intra-abdominal abscesses. • CT and MRI with skip lesions, bowel wall thickening, surrounding inflammation, abscess, fistulae. • Bowel biopsy histology demonstrates transmural non-caseating granulomas.
Ulcerative colitis	• Diarrhoea and haematochezia. • Cramps, anorexia, weight loss, mild anaemia, malaise,	• Abdominal radiography with dilated colon, intra-abdominal free air, perforation.

Condition	Differentiating signs / symptoms	Differentiating tests
	and low-grade or intermittent fever.[64]	• Colonic biopsy histology of acute and chronic inflammation with polymorphonuclear leukocytes infiltrating the submucosa.[64]
Hiatal hernia	• Intolerance to spicy or acidic foods, particularly with recumbency and after retiring for the evening. • Mid-epigastric to lower thoracic discomfort relieved with prolonged sitting position or elevation of head of bed. • Specific lack of cutaneous or respiratory symptoms.	• Diagnosis is primarily clinical. • Upper gastrointestinal series with gastric cardia herniated 2 cm above the hiatus.
Pyloric stenosis	• Vomiting, failure to thrive. • Pyloric mass.[65]	• Abdominal ultrasound with pyloric thickness >4 mm or an overall pyloric length >14 mm.[65]
Hirschsprung's disease	• Abdominal distension and stool retention. • Toxic megacolon, peritonitis, perforation.	• Barium enema demonstrates segmental narrowing with ballooning of the proximal part of the bowel. • Rectal/colon biopsy absence of ganglion cells.
Pancreatic insufficiency (e.g., cystic fibrosis)	• Chronic diarrhoea. • Steatorrhoea.	• Elevated sweat chloride levels (>60 mmol/L) in cystic fibrosis.
Gastro-oesophageal reflux disease	• Heartburn. • Hiatal hernia and advancing age. • Acidic reflux into oral cavity. • Absence of cutaneous or respiratory involvement.	• Diagnosis is clinical. • A therapeutic trial of a proton-pump inhibitor can serve for both diagnosis and initial treatment.
Cholecystitis	• Right upper quadrant or epigastric abdominal pain.[66] Pain may radiate to the right shoulder or back and is usually steady and severe. • Associated symptoms: nausea, vomiting, and anorexia. • Often a history of fatty food ingestion about 1 hour or more before initial onset of pain.	• Elevated leukocytes with a left shift on FBC. • Ultrasound or cholescintigraphy may be needed to confirm the diagnosis.[66]

Condition	Differentiating signs / symptoms	Differentiating tests
Coeliac disease	• Persistent diarrhoea with gluten ingestion. • Presence of dermatitis herpetiformis.	• Low Hb and microcytic red cells on FBC. • Immunoglobulin A-tissue transglutaminase (IgA-tTG) titre above normal for laboratory. • Endomysial antibody titre elevated. • Biopsy of the small bowel helpful when positive, but a negative result does not rule out the disease. • Human leukocyte antigen DQ2DQ8 testing is highly sensitive (90% to 95%) for coeliac disease but not very specific.
Food poisoning (e.g., Clostridium botulinum, Staphylococcus aureus, Escherichia coli)	• Abdominal pain, nausea, vomiting. • Fever may appear from 1 to 72 hours after ingestion.[65]	• Faecal leukocytes present and stool culture grows organism. • Blood cultures grow organism.
Alcohol overdose	• In early acute intoxication, euphoria, giddiness, and loss of inhibitions.[52] Nausea, vomiting, abdominal pain, facial flushing, ataxia, and diminished reflexes. • In late acute intoxication, central nervous system depression becomes generalised, leading to ataxia, nystagmus, slurred speech, and sedation. May progress to coma, loss of protective airway reflexes, autonomic dysfunction, hypothermia, death.	• With acute intoxication an elevated blood alcohol level is detectable.
Lactose intolerance	• Typically 8 to 15 years of age. • Crampy abdominal pain, bloating, and acidic diarrhoea.[67]	• Trial elimination diet therapeutic. • Positive hydrogen breath test, defined as a rise in breath hydrogen >20 ppm within 90 minutes of ingestion of 50 g of lactose.[67]
Toxic reactions (e.g., scombroid poisoning, ciguatera poisoning, saxitoxin)	• Cutaneous symptoms of prolonged flush in the absence of urticaria.	• Normal serum tryptase and elevated histamine.[19] • May have normal serum tryptase and histamine in IgE-mediated responses.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Several people dining from the same meal may experience symptoms.[19]	
Accidental contamination (pesticide or antibiotics)	• Excessive salivation, lacrimation, bronchorrhoea, urinary and faecal incontinence, and vomiting.[68]	• Atropine (1 to 2 mg intravenously as a single dose) is given as a therapeutic trial in all suspected cases or when diagnosis is in doubt. Lack of anticholinergic response is a positive test. • Plasma cholinesterase and red blood cell cholinesterase used to confirm diagnosis. • Specific IgE may be present with inadvertent allergy to antibiotic ingested.
Fungal toxins (e.g., aflatoxins, trichothecenes, ergots)	• Fever, malaise, vomiting, and jaundice.[69]	• Absence of specific IgE.
Caffeine overdose	• Overdose may lead to agitation, vasoconstriction, tremor, and hypertension.[68]	• Diagnosis is clinical.
Theobromine (e.g., tea, chocolate) intoxication	• Nausea, vomiting, anxiety, nervousness, and insomnia are evident in mild intoxication. Seizures occur in severe poisonings.[68]	• Diagnosis is clinical.
Serotonin (e.g., banana, tomato) overdose	• Diarrhoea, headache, and fatigue if ingested in large amounts.[70]	• Diagnosis is clinical.
Food phobias/aversions	• May mimic adverse food reactions.	• Absence of specific IgE. • Double-blind placebo-controlled food challenge (DBPCFC). • Symptoms are not reproducible with DBPCFC.[19]

Approach

Treatment of many allergic diseases is well established; however, treatment of food allergy still relies heavily on avoiding food allergens and reversing immune responses with epinephrine (adrenaline). Food allergy education for patients and carers is vital to help the successful implementation of these strategies. It is important that patients and carers are at all times alert for an allergic reaction caused by accidental ingestion. Reports of accidental exposure to the causative allergen range from 7% to 75% following diagnosis.[71]
An individualised written allergy action plan may be beneficial to patients, parents/carers, and healthcare providers in preparing for treatment of an allergic reaction to food.[72] [AAP: allergy and anaphylaxis emergency plan] (https://publications.aap.org/pediatrics/article/139/3/e20164005/53741/Guidance-on-Completing-a-Written-Allergy-and?_ga=2.210811421.945634437.1666173539-1410774310.1666173538)

Treatment of accidental ingestion of food allergens

Management of an accidental reaction to foods includes antihistamines for milder reactions and then epinephrine (adrenaline), antihistamines, and other treatment modalities for more severe reactions.
The management of acute anaphylaxis requires immediate intervention with supportive and specific care.[73] [74] [75] The sudden onset of respiratory or cardiovascular compromise, usually with a history of allergen exposure (in presumably sensitised patients), with skin rash, wheezing and inspiratory stridor, hypotension, anxiety, nausea, and vomiting, should prompt immediate treatment.

- An airway should be established and maintained. Patients with severe airway obstruction may require intubation.
- Oxygen should be given and saturation monitored with pulse oximetry.
- Epinephrine (adrenaline) should be given intramuscularly every 5 to 15 minutes, in appropriate doses as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control and prevent progression to respiratory distress, hypotension, shock, and unconsciousness.[76] [77] In refractory anaphylaxis with progressing systemic signs, treatment may best be facilitated by intravenous infusion of epinephrine (adrenaline). For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine (adrenaline) and prolonged resuscitation efforts are encouraged, if necessary.[78]
- The patient should be placed in a recumbent position and the lower extremities elevated.
- Venous access for giving medication intravenously should be established.
- Intravenous normal saline for fluid replacement and treatment of vasogenic shock should be instituted.

Specific measures to consider after epinephrine (adrenaline) administration include:[78] [79][80]

- H1- and H2-antagonists for cutaneous and gastric symptoms
- Nebulised beta-2 agonist for bronchospasm resistant to epinephrine (adrenaline)
- Systemic corticosteroids
- Vasopressors for persistent hypotension
- Glucagon for patients taking beta-blockers
- Atropine for symptomatic bradycardia
- Transportation to an emergency department or an intensive care facility.

For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine (adrenaline) and prolonged resuscitation efforts are encouraged, if necessary.[78] Patients with severe airway obstruction may require intubation.

For rhinoconjunctivitis and symptoms from accidental ingestion limited to localised urticaria or pruritus, treatment with an oral antihistamine may be sufficient. Additional at-home management may consist of non-emergent therapy comprising:

- Bronchodilator
    - Relaxes bronchial smooth muscle by action on beta-2 receptors with little effect on heart rate
    - Effective when wheezing is present, and may be given in a nebulised form with supplemental oxygen if needed
- H2 antagonists
    - Work by competitive inhibition of histamine at H2 receptors of the gastric parietal cells, which inhibits gastric acid secretion and reduces gastric volume and hydrogen ion concentration
    - Reported to be more effective management of cutaneous symptoms than treatment with H1 antagonist (antihistamine) alone
- Epinephrine (adrenaline) portable auto-injectors for self-injection.

For purposes of differentiating local versus systemic reactions, anaphylaxis herein is defined as an acute, severe, life-threatening allergic reaction in pre-sensitised people, leading to a systemic response caused by the release of immune and inflammatory mediators from basophils and mast cells.

A prescription for two epinephrine (adrenaline) auto-injectors must be given after any episode of anaphylaxis.[81] [82] The patient or carer should carry both at all times and be familiar with their use.[77] For children at risk of anaphylaxis, the epinephrine (adrenaline) auto-injectors should be prescribed in conjunction with a personalised written emergency plan.[72][77] [AAP: allergy and anaphylaxis emergency plan] (https://publications.aap.org/pediatrics/article/139/3/e20164005/53741/Guidance-on-Completing-a-Written-Allergy-and?_ga=2.210811421.945634437.1666173539-1410774310.1666173538)

Avoidance of food allergens

Patients should be educated regarding strict avoidance of the causative food allergen. Involvement of a dietician in this process is often very helpful, as poorly prepared elimination diets may lead to malnutrition. Successful avoidance relies on specific identification of the causative food allergen in the patient; recognition of cross-reacting foods; education of the patient and/or carer about avoidance measures, with emphasis on hidden food allergens or additives; and a willingness of the educated patient and/or carer to read labels carefully and give particular attention to hidden ingredients when eating at restaurants in order to prevent accidental exposures.[3]

US food labelling laws passed in January 2006 now require manufacturers to list the names of major allergens as ingredients in common terms; however, vigilance by the patient and carer is paramount in successful avoidance.[1] [3] Those ingredients that must be listed are milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, and soyabeans. Food labelling laws in the European Union have gone even further. In addition to the foods mentioned above, sesame, gluten-containing grains (rye, barley, oats) and wheat, mustard, celery, molluscs, lupin, and sulphites (used as preservative) must be identified separately.[83]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
anaphylactic reaction		
	1st	airway management and oxygen
	plus	epinephrine (adrenaline)
	plus	intravenous fluids
	adjunct	corticosteroid
	adjunct	vasopressor
	adjunct	glucagon
	adjunct	atropine
	adjunct	cardiopulmonary resuscitation
cutaneous symptoms		
	1st	antihistamine + H2 antagonist
bronchospasm		
	1st	bronchodilator
rhinoconjunctivitis		
	1st	antihistamine

Ongoing (summary)		
following stabilisation		
	1st	avoidance and allergy action plan
■ with anaphylactic episode	plus	portable epinephrine (adrenaline) auto-injectors for home use

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

anaphylactic reaction

1st **airway management and oxygen**

» Airway management and oxygenation supersedes all other aspects of management.

» Endotracheal intubation may be necessary in severe cases of upper airway obstruction.

plus **epinephrine (adrenaline)**

Treatment recommended for ALL patients in selected patient group

Primary options

» adrenaline (epinephrine): children: 0.01 mg/kg (1:1000 solution) intramuscularly every 5 minutes; adults: 0.3 to 0.5 mg (1:1000 solution) intramuscularly every 10-15 minutes

» Epinephrine (adrenaline) given by intramuscular injection in the lateral thigh is the treatment of choice for significant systemic symptoms.

» Any symptoms of anaphylaxis, such as systemic reaction of pruritus, erythema, urticaria, and angio-oedema alone, and any other systemic symptom including those not involving vital organs, should be treated immediately and as necessary with appropriate doses of intramuscular epinephrine (adrenaline) in an attempt to prevent more severe anaphylaxis from occurring.[76][77]

» Confusion, syncope, hypotension, and shock necessitate laying the person flat with their legs elevated.

plus **intravenous fluids**

Treatment recommended for ALL patients in selected patient group

» Appropriate venous access is required to allow high-volume fluid resuscitation (e.g., lactated Ringer solution or isotonic saline) of shock and bolus intravenous administration of medication.

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Acute

Primary options

» methylprednisolone: children and adults: 1-2 mg/kg/day intravenously

» Use of corticosteroids to limit biphasic anaphylaxis is controversial; evidence to support their use is lacking.[78][79]

adjunct **vasopressor**

Treatment recommended for SOME patients in selected patient group

» Vasopressors may be required to treat persistent hypotension associated with anaphylaxis.[79] Seek advice from critical care specialists.

» Consult specialist for guidance on choice of regimen and dose.

adjunct **glucagon**

Treatment recommended for SOME patients in selected patient group

Primary options

» glucagon: see local protocol for dosing guidelines

» Used in patients taking beta-blockers and not responsive to epinephrine (adrenaline).[79]

» Glucagon is thought to reverse refractory hypotension and bronchospasm by activating adenylate cyclase independent of the beta-receptor; however, the occurrence and importance of this mechanism of action in anaphylaxis is unproved.

» Airway protection must be ensured because glucagon frequently causes emesis.[80]

adjunct **atropine**

Treatment recommended for SOME patients in selected patient group

Primary options

» atropine: children: 0.02 mg/kg intravenously every 5 minutes when required, maximum 1 mg/total dose; adults: 0.5 to 1 mg intravenously every 5 minutes when required, maximum 2 mg/total dose

» Blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and the central nervous

Acute

system; increases cardiac output, dries secretions.

» Atropine reverses the muscarinic effects of cholinergic poisoning. The primary goal in cholinergic poisonings is reversal of bronchorrhoea and bronchoconstriction.

» Atropine has no effect on the nicotinic receptors responsible for muscle weakness, fasciculations, and paralysis.

» In patients with anaphylaxis it may be used to treat symptomatic bradycardia.[79]

adjunct **cardiopulmonary resuscitation**

Treatment recommended for SOME patients in selected patient group

» For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine (adrenaline) and prolonged resuscitation efforts are encouraged, if necessary.[78]

cutaneous symptoms

1st **antihistamine + H2 antagonist**

Primary options

» diphenhydramine: children: 5 mg/kg/day orally/intravenously given in divided doses every 6-8 hours, maximum 300 mg/day; adults: 25-50 mg orally/intravenously every 6-8 hours when required, maximum 400 mg/day
-and-
» cimetidine: children: consult specialist for guidance on dose; adults: 300 mg intravenously as a single dose

» Diphenhydramine, an antihistamine, competes with histamine for H1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Oral antihistamines may not be effective in more severe allergic reactions because they are relatively slow to act and principally relieve cutaneous symptoms rather than the cardiorespiratory problems that make anaphylaxis a life-threatening emergency.[78]

» H2 antagonists (e.g., cimetidine) work by competitive inhibition of histamine at H2-receptors of the gastric parietal cells, which inhibits gastric acid secretion and reduces gastric volume and hydrogen ion concentration. Do not affect pepsin secretion, pentagastrin-stimulated intrinsic factor secretion, or serum gastrin.

Acute

» Treatment with a combination of an antihistamine H1 and H2 antagonist has been reported to be more effective in lessening the cutaneous manifestations of anaphylaxis than treatment with antihistamines alone.[80]

bronchospasm

1st **bronchodilator**

Primary options

» salbutamol inhaled: (100 micrograms/dose metered dose inhaler) children and adults: 400-800 micrograms (4-8 puffs) every 20 minutes for 3 doses, then every 4-6 hours when required

OR

» salbutamol inhaled: children: 0.15 mg/kg nebulised every 20 minutes for 3 doses, then every 1-4 hours when required; adults: 2.5-5 mg nebulised every 20 minutes for 3 doses, then every 1-4 hours when required

» Bronchodilators are effective when wheezing is present, and may be given in a nebulised form with supplemental oxygen if needed.[79]

» Relaxes bronchial smooth muscle by action on beta-2 receptors with little effect on heart rate.

» For purposes of differentiating local versus systemic reactions, anaphylaxis herein is defined as an acute, severe, life-threatening allergic reaction in pre-sensitised people, leading to a systemic response caused by the release of immune and inflammatory mediators from basophils and mast cells.

rhinoconjunctivitis

1st **antihistamine**

Primary options

» diphenhydramine: children: 5 mg/kg/day orally/intravenously given in divided doses every 6-8 hours, maximum 300 mg/day; adults: 25-50 mg orally/intravenously every 6-8 hours when required, maximum 400 mg/day

» Treatment with oral antihistamine is sufficient.

Ongoing

following stabilisation

following stabilisation — **1st** — **avoidance and allergy action plan**

» Ingestion of hidden ingredients is a particular concern. For example, milk may be variously listed as casein, whey, caseinate, or lactalbumin. Food allergy education for patients and carers is vital.

» Intervention at the first sign of a severe allergic reaction offers the best chance of resolution. The most common manifestations of an allergic reaction involve cutaneous, respiratory, and gastrointestinal symptoms.

» At minimum, patients and carers should know where to locate and how to activate public emergency notification systems.

» An individualised written allergy action plan may be beneficial to patients, parents/carers, and healthcare providers in preparing for treatment of an allergic reaction to food.[72] [AAP: allergy and anaphylaxis emergency plan] (https://publications.aap.org/pediatrics/article/139/3/e20164005/53741/Guidance-on-Completing-a-Written-Allergy-and?_ga=2.210811421.945634437.1666173539-1410774310.1666

with anaphylactic episode — **plus** — **portable epinephrine (adrenaline) auto-injectors for home use**

Treatment recommended for ALL patients in selected patient group

Primary options

» adrenaline (epinephrine): children <30 kg body weight: 0.15 mg intramuscularly as a single dose; children ≥30 kg body weight and adults: 0.3 mg intramuscularly as a single dose
Dose refers to Epipen brand.

» A prescription for two epinephrine (adrenaline) auto-injectors must be given after any episode of anaphylaxis.[81] [84] The patient or carer should carry both at all times and be familiar with their use.[77]

Emerging

Sublingual immunotherapy

Gradual oral exposure to native food proteins induces regulatory T cells early in treatment and results in immune deviation towards non-allergic Th1 responses later in therapy.[16] In one study, patients taking hazelnut sublingual immunotherapy (SLIT) were able to increase the mean threshold dose eliciting a reaction, although 50% of the patients' symptoms were limited to oral allergy syndrome at enrolment.[85] A double-blind, placebo-controlled study of peanut SLIT showed that those receiving peanut SLIT were able to tolerate 20 times more peanut protein than the placebo group.[86] A significant decrease in skin prick test wheal diameter, decreased basophil responsiveness, and significant changes in both peanut-specific immunoglobulin (Ig) E and IgG4 were detected in the treatment group compared with the placebo group. Studies investigating the utility of SLIT for other foods are ongoing, and its use is still considered investigational.

Oral immunotherapy

A food allergen is given in increasing amounts over a period of months to increase the triggering dose threshold for food-allergic patients. A number of oral immunotherapy (OIT) trials have focused on treatment of peanut allergy and have shown that the majority of children with peanut allergy can be desensitised using OIT. In one phase III trial, children and adolescents who were highly allergic to peanut were randomised to receive OIT with a peanut-derived OIT, or placebo. Children who received peanut-derived OIT were able to ingest higher doses of peanut protein without dose-limiting symptoms compared with the placebo group, and had lower symptom severity during peanut exposure at the exit food challenge.[87] Peanut (Arachis hypogaea) allergen powder is an OIT that is approved for use in patients, aged 4 to 17 years, with a confirmed diagnosis of peanut allergy. However, one systematic review and meta-analysis of OIT for peanut allergy showed that, despite effectively inducing desensitisation, peanut OIT regimes considerably increased allergic and anaphylactic reactions compared with avoidance or placebo.[88] It is important to note that most reactions experienced during OIT are mild and do not prevent participants from continuing on therapy; sustained immunological remission has not been convincingly proven when OIT is discontinued or continued at a reduced dose.[89] [90] [91] The latter is an important limitation of OIT since the majority of peanut-allergic individuals receiving OIT will need to ingest peanut indefinitely to maintain the protective benefit of OIT. Further research will focus on reducing adverse effects associated with therapy, and the development of surrogate biomarkers to better characterise allergic patients who will respond favourably to therapy, and those for whom other treatment options or strict allergen avoidance would be preferable. OIT to other foods, such as milk and egg, has also shown promise.[92] [93] [94] For example, ADP101, an IgE-mediated multi-food oral immunotherapy, has been granted fast-track designation by the Food and Drug Administration (FDA) for the treatment of single or multiple food allergies, including almonds, cashews, chicken egg, codfish, cow milk, hazelnut, peanut, pecan, pistachio, salmon, sesame seed, shrimp, soya, walnut, and wheat. One multicentre, randomised, double-blind, placebo phase I/II trial demonstrated that ADP101 has a dose-dependent, clinically meaningful desensitisation response for paediatric patients with some food allergies.[95]

Peptide immunotherapy

Numerous small peptides are presented to T-cell epitopes without IgE crosslinking. Efficacy has been shown in murine models, but translation to humans has been difficult.[16]

Chinese herbal medicine

The herbal compound (Food Allergy Herbal Formula-2 or FAHF-2) has been proven safe in adolescents and adults; however, the ability to improve tolerance to food allergens has not been demonstrated.[96] Ongoing trials are investigating the potential of FAHF-2 to improve the safety of OIT when used in combination with multi-food OIT.[97]

Omalizumab

Omalizumab, an anti-IgE monoclonal antibody, is approved by the FDA for IgE-mediated food allergy in children 1 year or older and adults for the reduction of allergic reactions (including anaphylaxis) due to accidental exposure to one or more foods. It should be used in conjunction with food allergen avoidance. Omalizumab has also been demonstrated to improve the safety of milk oral immunotherapy without affecting efficacy.[98] An ongoing clinical trial is investigating the potential of omalizumab to increase the dose-triggering threshold for a number of food allergens in multi-food allergic individuals, and to improve the safety of multi-food OIT.[99]

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT) involves prolonged exposure to an allergen to the skin via an epicutaneous patch. One phase III trial reported a statistically significant response to EPIT (35.3% vs 13.6% in the placebo arm) peanut-allergic children aged 4 to 11 years.[100] However, the prespecified lower bound of the confidence interval criterion for a positive result was not met.[100] Ongoing trials are investigating the efficacy of milk EPIT in milk-allergic children and peanut EPIT in peanut-allergic children 1 to 3 years of age.[101] [102]

Primary prevention

Current evidence does not support an antigen avoidance diet for high-risk women during pregnancy.[26] [27]

Maternal antigen avoidance during lactation may reduce the likelihood of an infant developing eczema, or reduce the severity of eczema should it develop, but larger studies are necessary.[27]

Ante- and perinatal maternal supplementation with omega-3 polyunsaturated fatty acids (n-3 PUFA) may reduce prevalence of sensitisation to egg in children up to 12 months old; however, postnatal supplementation with n-3 PUFA has not been shown to prevent allergic disease.[28] [29] [30]

In infants at high risk for developing allergy, there is no need to avoid complementary food introduction beyond 4 months of life.[31] In 2017, a US National Institute of Allergy and Infectious Diseases expert panel published revised guidance for preventing peanut allergy in infants at high risk (i.e., those with severe eczema, egg allergy, or both).[23] The expert panel concluded that, subsequent to the findings of the LEAP (Learning Early About Peanut allergy) study, age-appropriate peanut-containing foods can be introduced to the diet of these infants as early as 4 to 6 months of age (with the caveat that peanut-specific IgE measurement, skin prick test, or both be strongly considered before introducing peanut to determine if it should be introduced and, if so, the preferred method of introduction).[23] LEAP, a randomised trial that investigated strategies for preventing peanut allergy in infants with severe atopic dermatitis or egg allergy (i.e., infants at high risk for developing peanut allergy), found that 1.9% of those who had peanut introduced in the first 4 to 11 months of life developed peanut allergy, compared with 13.7% of those who avoided peanut during the first 60 months of life.[32] A 12-month follow-up study (LEAP-ON) found the benefits of early peanut consumption to be long-lasting.[33]

In the EAT (Enquiring about Tolerance) study, the introduction of peanut and egg into the diet of exclusively breastfed infants from the general population (i.e., not selected based on risk of developing food allergy) between 3 and 6 months of age was shown to be protective against the development of peanut and egg allergy in those who adhered to the diet.[34] The early introduction of cows' milk, sesame, whitefish, or wheat was not protective. Adherence to each of the six allergenic food-containing diets proved difficult in the study.[34]

UK guidance recommends that infants should be exclusively breastfed up to 6 months of age, after which complementary foods (including peanut and egg) can be introduced, alongside continued breastfeeding, in an age-appropriate form, and when convenient for infant and family.[35]

Secondary prevention

There is evidence that breastfeeding for at least 4 months, compared with feeding formula made with intact cows' milk protein, prevents or delays the occurrence of atopic dermatitis, cows' milk allergy, and wheezing

in early childhood. However, there are no apparent advantages to exclusive breastfeeding beyond 3 to 4 months for prevention of atopic disease.[26]

In studies of infants at high risk of atopy (and who were not exclusively breastfed for 4 to 6 months), there is a lack of evidence that the onset of atopic disease may be prevented by the use of hydrolysed formulas compared with intact cows' milk formula.[26] [31] [105]

World Allergy Organization (WAO) guidelines make no recommendation regarding the use of probiotic therapy for food allergy prevention, noting that there are very few studies in this clinical setting.[106] WAO guidelines suggest that prebiotics may be used in non-exclusively breastfed infants for food allergy prevention, but not in exclusively breastfed infants.[107] However, these recommendations are based on limited evidence. European guidelines have concluded that there is no evidence to support the use of prebiotics or probiotics for food allergy prevention.[31]

Patient discussions

Food allergy education for patients and their carers is critical to the success of its management, which relies on allergen avoidance and a readiness to recognise and treat allergic reactions.[103]

For children with food allergies, each stage of their development produces different safety and psychosocial issues, as well as changing roles for the child in their own self-management.[103] Therefore, there is a need for ongoing education that is tailored to the child's and family's needs at every developmental stage.[3] [103] To meet this need the American Academy of Allergy, Asthma and Immunology (AAAAI) has developed a range of age-specific, evidence-based, patient education handouts with practical recommendations for managing and coping with food allergies in everyday life.[103] These handouts could be used as an educational resource during healthcare visits, and directly accessed online by families. [AAAAI: food allergy stages handouts] (https://www.aaaai.org/Tools-for-the-Public/Conditions-Library/Allergies/Food-Allergy-Stages-Handouts)

The Food Allergy Research and Education (FARE), Allergy UK, and AAAAI websites may also be useful information sources for patients. [FARE: food allergy research and education] (https://www.foodallergy.org) [AAAAI: allergy asthma and immunology resources] (https://www.aaaai.org) [Allergy UK: supporting people living with allergy] (https://www.allergyuk.org)

Specific discussions with patients and carers may include that they should carefully read food labels and take special precautions in restaurants to prevent accidental ingestion. Patients should also obtain medical identification jewellery, be able to identify symptoms of an allergic reaction (e.g., difficulty breathing, raised splotches on the skin), know how to use their epinephrine (adrenaline) auto-injectors, and be able to activate emergency response services. Individualised written allergy action plans are often helpful for families in preparing for treatment of an allergic reaction to food.[72] [AAP: allergy and anaphylaxis emergency plan] (https://publications.aap.org/pediatrics/article/139/3/e20164005/53741/Guidance-on-Completing-a-Written-Allergy-and?_ga=2.210811421.945634437.1666173539-1410774310.1666173538) Patients should notify their primary care physician about allergic episodes and obtain prompt follow-up with an allergist when they occur. Parents of children with life-threatening food allergies should inform the child's school of the child's allergy history and provide the school with a copy of a written anaphylaxis action plan prepared by the child's doctor.[104]

Monitoring

Monitoring

Patients should be followed up at regular intervals to determine when they might have outgrown the food allergy, with either in vitro immunoglobulin (Ig) E testing or skin prick testing. If sensitivity to the allergen is lost, then a food challenge may be considered before reintroduction into the diet. It is important to recognise that a patient may have outgrown the food allergy and still have evidence of IgE by either skin prick testing or in vitro IgE. In patients with severe symptoms and anaphylaxis, because of the possibility of a biphasic reaction or recurrence after resolution of the initial presentation, monitoring as an inpatient is indicated for 24 hours.

Complications

Complications	Timeframe	Likelihood
death	**short term**	**low**
Occurs following cardiovascular shock or cardiac arrest if giving intramuscular epinephrine (adrenaline) is delayed. Previous episodes of anaphylaxis with the same food put the patient at increased risk of a fatal reaction.[36]		
myocardial infarction	**short term**	**low**
Although myocardial infarction during anaphylaxis is uncommon, it will become more frequent as the general population ages and allergic reactions of senescence become more prevalent. Cardiac ischaemia may be triggered by hypotension associated with anaphylaxis or the hypertension and tachycardia that often follows the administration of epinephrine (adrenaline). If the diagnosis is made early and the appropriate management is initiated promptly, the outcome of cardiac arrest in this population may be better. However, serious sequelae of inadequate brain perfusion may occur and prognosis depends mainly on comorbidities and patient age.		
growth retardation	**long term**	**low**
Patients eliminating many foods may have nutritional deficits leading to growth failure. Involvement of a dietician in this process is often very helpful because elimination diets may lead to malnutrition.		
anaphylaxis recurrence	**variable**	**high**
Patients with previous allergic and anaphylactic reactions are at higher risk for recurrence. However, the severity of a previous reaction does not necessarily predict the severity of a subsequent one.		

FOLLOW UP

Prognosis

Natural course

Living with food allergies can be challenging, and no therapies are available to alter their natural course. The outlook will depend on the success of immunotherapy, allergen avoidance, and compliance with carrying both epinephrine (adrenaline) auto-injectors at all times.[81]

Co-existing atopic illness

Patients with asthma, lack of readily accessible epinephrine (adrenaline), or peanut, tree nut, or shellfish allergy, and adolescents or young adults are at increased risk of having a fatal allergic reaction.[36] Particular attention should be paid to these patients.

Spontaneous desensitisation

Allergies to milk, egg, soya, and wheat will resolve by school age in approximately 60% of young children.[1] Peanut, tree nut, and seafood allergies are more likely to persist.

Diagnostic guidelines

United Kingdom

BSACI guidelines for the management of egg allergy (https://www.bsaci.org/guidelines/bsaci-guidelines)

Published by: British Society for Allergy and Clinical Immunology **Last published:** 2021

BSACI guideline for the diagnosis and management of peanut and tree nut allergy (https://www.bsaci.org/guidelines/bsaci-guidelines)

Published by: British Society for Allergy and Clinical Immunology **Last published:** 2017

BSACI guideline for the diagnosis and management of cow's milk allergy (https://www.bsaci.org/guidelines/bsaci-guidelines)

Published by: British Society for Allergy and Clinical Immunology **Last published:** 2014

Europe

Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology (https://hub.eaaci.org/resources/guidelines)

Published by: European Academy of Allergy and Clinical Immunology **Last published:** 2021

North America

Diagnosis and management of celiac disease (https://gi.org/guidelines)

Published by: American College of Gastroenterology **Last published:** 2023

Anaphylaxis - a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis (2020) (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology **Last published:** 2020

Anaphylaxis - a 2023 practice parameter (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology **Last published:** 2023

Peanut allergy diagnosis: a 2020 practice parameter update, systematic review, and GRADE analysis (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology **Last published:** 2020

Addendum guidelines for the prevention of peanut allergy in the United States (2017 addendum to guidelines for the diagnosis and management of food allergy in the United States, 2010) (https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy)

Published by: National Institute of Allergy and Infectious Diseases **Last published:** 2017

Food allergy: a practice parameter update - 2014 (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology **Last published:** 2014

Guidelines for the diagnosis and management of food allergy in the United States (https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy)

Published by: National Institute of Allergy and Infectious Diseases **Last published:** 2010

Asia

Japanese guidelines for food allergy 2017 (http://www.sciencedirect.com/science/article/pii/S1323893017300059)

Published by: Committee for Japanese Pediatric Guideline for Food Allergy; The Japanese Society of Pediatric Allergy and Clinical Immunology; The Japanese Society of Allergology **Last published:** 2017

Treatment guidelines

United Kingdom

BSACI guidelines for the management of egg allergy (https://www.bsaci.org/guidelines/bsaci-guidelines)

Published by: British Society for Allergy and Clinical Immunology **Last published:** 2021

BSACI guideline for the diagnosis and management of peanut and tree nut allergy (https://www.bsaci.org/guidelines/bsaci-guidelines)

Published by: British Society for Allergy and Clinical Immunology **Last published:** 2017

BSACI guideline for the diagnosis and management of cow's milk allergy (https://www.bsaci.org/guidelines/bsaci-guidelines)

Published by: British Society for Allergy and Clinical Immunology **Last published:** 2014

Europe

Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology (https://hub.eaaci.org/resources/guidelines)

Published by: European Academy of Allergy and Clinical Immunology **Last published:** 2021

Guidelines on the management of IgE-mediated food allergies (https://link.springer.com/journal/40629/24/7/page/1)

Published by: German Association of Scientific Medical Societies **Last published:** 2015

EAACI food allergy and anaphylaxis guidelines (https://hub.eaaci.org/resources/guidelines)

Published by: European Academy of Allergy and Clinical Immunology **Last published:** 2014

North America

Diagnosis and management of celiac disease (https://gi.org/guidelines)

Published by: American College of Gastroenterology **Last published:** 2023

A consensus approach to the primary prevention of food allergy through nutrition: guidance (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology **Last published:** 2021

The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. (https://pediatrics.aappublications.org/content/143/4)

Published by: American Academy of Pediatrics **Last published:** 2019

Addendum guidelines for the prevention of peanut allergy in the United States (2017 addendum to guidelines for the diagnosis and management of food allergy in the United States, 2010) (https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy)

Published by: National Institute of Allergy and Infectious Diseases **Last published:** 2017

Anaphylaxis - a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis (2020) (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology **Last published:** 2020

Anaphylaxis - a 2023 practice parameter (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology **Last published:** 2023

Food allergy: a practice parameter update - 2014 (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters/Practice-Parameters-Guidelines)

Published by: American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology **Last published:** 2014

North America

Guidelines for the diagnosis and management of food allergy in the United States (https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy)

Published by: National Institute of Allergy and Infectious Diseases **Last published:** 2010

Asia

Japanese guidelines for food allergy 2017 (http://www.sciencedirect.com/science/article/pii/S1323893017300059)

Published by: Committee for Japanese Pediatric Guideline for Food Allergy; The Japanese Society of Pediatric Allergy and Clinical Immunology; The Japanese Society of Allergology **Last published:** 2017

Online resources

1. AAP: allergy and anaphylaxis emergency plan (https://publications.aap.org/pediatrics/article/139/3/e20164005/53741/Guidance-on-Completing-a-Written-Allergy-and?_ga=2.210811421.945634437.1666173539-1410774310.1666173538) *(external link)*

2. AAAAI: food allergy stages handouts (https://www.aaaai.org/Tools-for-the-Public/Conditions-Library/Allergies/Food-Allergy-Stages-Handouts) *(external link)*

3. FARE: food allergy research and education (https://www.foodallergy.org) *(external link)*

4. AAAAI: allergy asthma and immunology resources (https://www.aaaai.org) *(external link)*

5. Allergy UK: supporting people living with allergy (https://www.allergyuk.org) *(external link)*

Key articles

- Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010 May 12;303(18):1848-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20460624?tool=bestpractice.bmj.com)
- Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. Annu Rev Med. 2009 Feb;60:261-77. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18729729?tool=bestpractice.bmj.com)
- Greer FR, Sicherer SH, Burks AW, et al. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. Pediatrics. 2019 Apr;143(4):e20190281. Full text (https://pediatrics.aappublications.org/content/143/4/e20190281.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30886111?tool=bestpractice.bmj.com)
- Muraro A, Halken S, Arshad SH, et al. EAACI food allergy and anaphylaxis guidelines: primary prevention of food allergy. Allergy. 2014 May;69(5):590-601. Full text (http://onlinelibrary.wiley.com/doi/10.1111/all.12398/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24697491?tool=bestpractice.bmj.com)
- Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012 Dec;130(6):1260-74. Full text (http://www.jacionline.org/article/S0091-6749%2812%2901663-6/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23195525?tool=bestpractice.bmj.com)
- Heyman MB. American Academy of Pediatrics, Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. Pediatrics. 2006 Sep;118(3):1279-86. Full text (http://pediatrics.aappublications.org/content/118/3/1279.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16951027?tool=bestpractice.bmj.com)

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2. Dalal I, Binson I, Levine A, et al. The pattern of sesame sensitivity among infants and children. Pediatr Allergy Immunol. 2003 Aug;14(4):312-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12911511?tool=bestpractice.bmj.com)
3. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update - 2014. J Allergy Clin Immunol. 2014 Nov;134(5):1016-25;e43. Full text (https://www.jacionline.org/article/

S0091-6749(14)00672-1/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25174862?tool=bestpractice.bmj.com)

4. Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2008. J Allergy Clin Immunol. 2009 Feb;123(2):319-27. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19203656?tool=bestpractice.bmj.com)

5. Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010 May 12;303(18):1848-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20460624?tool=bestpractice.bmj.com)

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Images

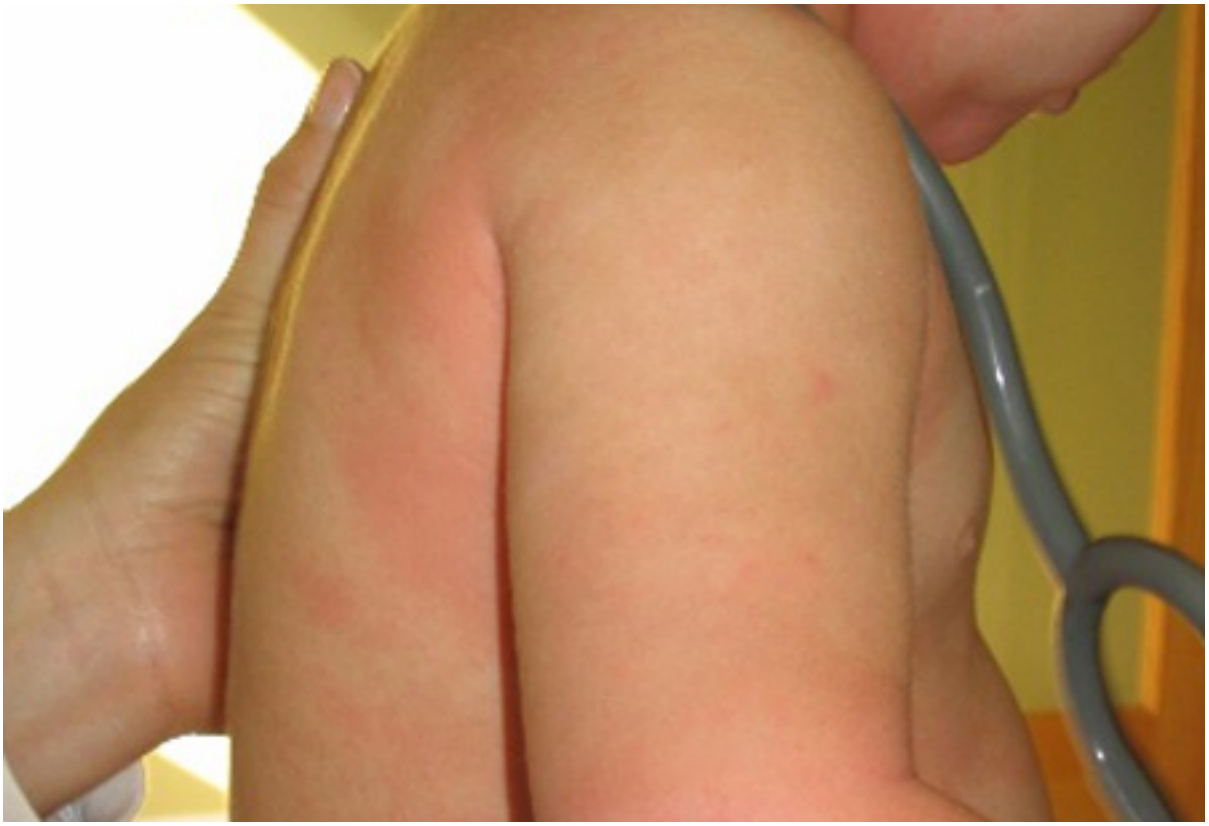

Figure 1: Typical cutaneous findings in food allergy at 30 minutes after ingestion of peanuts

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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