

Review

Food allergy

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Food allergy encompasses a range of disorders that result from adverse immune responses to dietary antigens. This group of conditions includes acute, potentially fatal reactions, and a host of chronic diseases that mainly affect the skin and gastrointestinal tract. Tools for diagnosis and management have not changed much in the past two decades, and include the clinical history, physical examination, tests for specific IgE antibody to suspected foods, elimination diets, oral food challenges, and provision of medications such as epinephrine for emergency treatment. However, much research in the past few years has enhanced our understanding of the clinical, epidemiological, and immunological aspects of these disorders. In this review I will discuss these advances and incorporate them into an improved diagnostic and management scheme. Additionally, emergent diagnostic, treatment, and prevention strategies are reviewed.

Food allergy is defined as an adverse immunological (hypersensitivity) response to food,¹ and as such it is not a single disease, nor is it caused by one pathophysiologic disturbance. Wheat allergy is a prime example of the amazing plurality of food hypersensitivity. Dependent on various factors, an individual with wheat allergy could have one of several disorders such as atopic dermatitis, isolated urticaria, anaphylaxis (in some cases only when exercise follows ingestion), so-called baker's asthma induced by inhalation of wheat antigens, or coeliac disease caused by gluten.

Food allergic disorders can be broadly divided into those that are mediated by IgE antibodies and those that are not. Disorders with acute onset of symptoms after ingestion are usually mediated by IgE, which arms tissue mast cells and blood basophils, to result in a state termed sensitisation. Upon re-exposure, the causal food proteins bind to the IgE molecules specific for them and trigger the release of mediators, such as histamine, that cause symptoms. Another group of food hypersensitivity disorders are subacute or chronic, and are mediated mainly by T cells.² A third group of chronic disorders attributed to food allergy are variably associated with measurable IgE (IgE-associated or cell-mediated disorders). Table 1 shows features of a range of food allergic disorders categorised by pathophysiology. The list is not comprehensive, and various other disorders (recalcitrant childhood gastro-oesophageal reflux,³ constipation,⁴ irritable bowel syndrome,⁵ and occult gastrointestinal blood loss) are sometimes attributed to food allergy.

IgE-dependent food-allergic reactions affect one or more target organs: the skin (urticaria, angio-oedema), respiratory tract (rhinitis, asthma), gastrointestinal tract (pain, emesis, diarrhoea), and cardiovascular system (anaphylactic shock). Reactions can be triggered by direct exposure of the involved organ system to the food or by systemic

distribution of proteins after ingestion. Examples of reactions from direct exposure are isolated gastrointestinal reactions, asthma and rhinitis after inhalation of food in aerosols from cooking or industrial processing, local (contact) urticaria, such as that seen on the faces of children during sloppy eating, and the oral allergy syndrome, or pollen-food syndrome, described in panel 1.^{6–10} An immediate, systemic reaction mediated by IgE is called anaphylaxis irrespective of severity,¹¹ but colloquially the term anaphylaxis is applied to severe, potentially fatal allergic reactions. Features of food-induced anaphylaxis are shown in panel 2.^{12–17}

Subacute and chronic food allergic disorders typically affect the gastrointestinal tract¹⁸ or skin,¹⁹ with a propensity to affect infants and children. Eosinophilic gastroenteropathies (eosinophilic oesophagitis, gastroenteritis, and gastritis) are food-responsive in some patients.^{18,20,21} In addition to the symptoms described in table 1, the diagnosis requires a biopsy sample with eosinophilic infiltrate, and elimination of alternative diagnoses (eg, parasites, inflammatory bowel disease). Several gastrointestinal disorders mainly affect infants and are usually associated with hypersensitivity to cow's milk or soya. The least problematic is dietary protein-induced proctitis or proctocolitis. Infants with this disorder have small amounts of blood mixed with mucus in their stools.²² Coeliac disease and the related skin disorder dermatitis herpetiformis²³ can be classed as food allergies because a hypersensitivity response to gluten is responsible. Enteropathy induced by dietary (food) protein is another malabsorption syndrome, but unlike coeliac disease, it is usually due to cow's milk, is transient, and is not associated with malignancy or dermatitis.²⁴ The most serious form of gastrointestinal food allergy in infants is food protein-induced enterocolitis syndrome,^{25,26} which has a symptom complex of profuse

Search strategy and selection criteria

I did Medline searches, using the terms food allergy, food intolerance, and related terms—eg, celiac, genetics, atopic dermatitis, food anaphylaxis, etc—and major allergy textbooks to identify articles and materials. Published work was then selected for inclusion on the basis of importance, pertinence, timeliness, accessibility, appeal to readers from various areas of medical practice and geographical location, and for further reading potential.

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	Age-group	Key symptoms/signs/features	Course
IgE-dependent, acute onset			
Urticaria/angio-oedema	Any	Wheal and flare, oedema. Ingestion or by direct skin contact. Food commonly causes acute (20%) but rarely chronic (2%) urticaria.	Variable by food
Immediate gastrointestinal reaction	Any	Acute onset nausea, emesis, pain. Diarrhoea may follow.	Variable by food
Oral allergy syndrome (pollen-related)	Children/adult	Pruritus, mild oedema confined to oral cavity. See panel 1.	Wax/wane
Rhinitis	Any	Congestion/rhinorrhoea after ingestion or inhalation. Rarely an isolated symptom. Variable by food	
Asthma	Any	Bronchospasm after ingestion or inhalation. Isolated chronic asthma is usually not due to food allergy.	Variable by food
Anaphylaxis	Any	Multiple organ system reaction can include cardiovascular collapse. Most frequent cause for outpatient anaphylaxis. See panel 2.	Variable by food
Food-associated, exercise-induced anaphylaxis	Any	Food triggers anaphylaxis only if ingestion is followed temporally by exercise. Causes: wheat and celery most described.	Unclear
IgE-associated/cell-mediated, delayed-onset/chronic			
Atopic dermatitis	Infant/child	Chronic/relapsing pruritic dermatitis, xerosis, atopic history. 35% of children with moderate-severe disease have food allergy, but rarely a trigger for adults. Common causes: cow's milk, egg, soya and wheat.	Resolves: early childhood
Eosinophilic gastroenteropathies	Any	Symptoms vary with respect to site(s)/degree of eosinophilic inflammation. Oesophageal: dysphagia, pain. Generalised: ascites, weight loss, oedema, obstruction. Causes: multiple foods.	Variable
Cell-mediated, delayed-onset/chronic			
Dietary protein enterocolitis	Infants	Chronic exposure: emesis, diarrhoea, poor growth, lethargy. Re-exposure after restriction: emesis, diarrhoea, hypotension (15%) 2 h after ingestion. Common causes: cow's milk, soya, grains	Resolves: 1–3 years
Dietary protein proctitis	Infants	Mucousy, bloody stools. Common cause: cow's milk via breastfeeding	Resolves: 1 year
Dietary protein enteropathy	Infant/child	Malabsorption, oedema, emesis, poor growth. Common cause: cow's milk	Resolves: 1–2 years
Coeliac disease	Any	Malabsorption, diarrhoea, HLA-DQ2-associated. Cause: gluten	Permanent
Dermatitis herpetiformis	Any	Papulovesicular skin lesions, acral distribution. Cause: gluten	Permanent
Associated with precipitating milk-specific IgG			
Pulmonary haemosiderosis	Infant	Anaemia, pulmonary infiltrates, poor growth. Cause: cow's milk	Unclear

Table 1: Features of some food-allergic disorders categorised by pathophysiology^{1,2,18,39–48}

vomiting and diarrhoea, and potentially a sepsis-like clinical picture with dehydration, acidaemia, methaemoglobinemia, raised blood neutrophil counts, and shock. Table 1 shows other chronic disorders caused by food allergy.

Epidemiology

Atopic disease is increasingly common worldwide, and food allergy seems to be a part of this rise. In the European Community Respiratory Health Survey administered to 17 280 adults in 15 countries,²⁷ 12% of respondents reported a food allergy or intolerance, ranging from 4·6% in Spain to 19·1% in Australia. The foods most commonly causing breathlessness were hazelnut in Norway, Sweden, and Germany, fruits in Iceland, Belgium, Ireland, and Italy, and peanut in the USA. This variation in causal foods could be due to different eating patterns, cultural and environmental influences, and genetic factors, and to inclusion of non-immunological reactions. A population-based study of 33 110 people in France defined food allergy on the basis of self-report of typical allergic symptoms only, and found a rate of 3·5%.²⁸ The main foods responsible in childhood were egg and milk, with atopic dermatitis a frequent manifestation. In adulthood, seafood, fruits, and vegetables were the most common causes, with angioedema or urticaria, or both, as the most frequent symptoms.

Oral food challenges are more definitive than self-report for diagnosis of food allergy, and the double-blind, placebo-controlled oral food challenge is the gold standard. The application of this technique shows that patients often overestimate their own food allergies. In a population-based study of 20 000 people in the UK, 20% of adults thought that they had a food allergy or intolerance.²⁹ However, the results of oral food challenges in a small subset of these patients with eight selected foods

showed that the derived overall prevalence of food allergy was 1·8%. This rate is probably an underestimate because half of the implicated foods were not formally assessed, but clearly adult patients often avoid foods because of false concerns about allergy or intolerance. Similarly, 28% of parents of 520 consecutive newborn babies investigated over the first 3 years of life in a health clinic in the USA believed their child to be food-allergic.³⁰ However, in double-blind, placebo-controlled oral food challenges, only 6% of children reacted to suspected foods. These results show not only that food allergy affects many children and adults, but also that physician assessment is needed to discount food allergy in many individuals with false notions. By contrast with the relatively high rate of allergy to foods, results of a population-based study of reactions to food additives, such as colours and preservatives, showed a prevalence of only 0·23%.³¹

Studies of the prevalence of allergy to specific foods in a population provide additional insights. Workers who did population-based investigations of cow's milk allergy, confirmed by challenge in infants and young children, recorded a prevalence of 1·9–3·2%.^{32–35} Egg is another common allergen in childhood, with an estimated cumulative prevalence of 2·6% by age 2·5 years.³⁶ Population-based questionnaire studies in the USA and UK estimate peanut allergy in 0·5–0·6% of individuals^{37,38} and tree nut (eg, hazel, walnut) allergy in 0·5%.³⁷ Overall, the typical allergens of infancy and early childhood are egg, milk, peanut, wheat, and soya, whereas allergens responsible for severe reactions in older children and adults are mainly caused by peanut, tree nuts, and seafood. Allergy to fruits and vegetables is common, but usually not severe.^{7–9} Consideration of the rate at which food allergy is responsible for particular disease presentations can be clinically helpful (table 1).^{39–48}

Panel 1: Pollen-food syndrome (oral allergy syndrome)^{6–10}

Pathophysiology	Initial respiratory exposure to pollens results in IgE antibody directed to proteins homologous to those in particular fruits or vegetables
Risk group	Individuals with seasonal allergic rhinitis (~50%)
Symptoms	Pruritus, erythema, oedema localised to the oral cavity
Nuances of syndrome	Heating the foods denatures proteins sufficiently to avoid symptoms Symptoms can be more prominent after the associated pollen season (priming) Causal proteins are concentrated in the peel of some fruits Reactions beyond the oral mucosa (~9%) and severe systemic reactions (~2%) can occur Reaction to all related foods is unlikely but sensitivity to more than one type is common Allergy tests with fresh antigens are most sensitive for diagnosis
Pollen-food associations	Birch pollen–apple, peach, pear, almond, hazelnut, potato, carrot Ragweed pollen–melons, banana, gourd family Mugwort pollen–celery, carrot, spices Grass pollen–tomato

Food allergy is one of the first manifestations of the so-called atopic march; young children generally outgrow food allergy and atopic dermatitis as they develop respiratory allergies, asthma, and allergic rhinitis.⁴⁹ The genes linked to allergic inflammation (T helper type 2 [Th-2] responses) might also be partly responsible for food allergy, and include those involved in the expression of cytokines, chemokines, IgE antibody, and T-cell receptors.^{50,51} A strong genetic influence on peanut allergy has been recorded; the concordance rate is 64% in identical twins but only 7% in fraternal twins.⁵² HLA class II might, in part, influence specific allergies,⁵³ but additional genes are involved in the overall expression of food allergy and are under investigation.

Pathophysiology*Immune mechanisms*

Food hypersensitivity is born out of a malfunction of the normal immune responses to dietary proteins. Healthy gastrointestinal immune responses need mechanisms by which to recognise but ignore harmless dietary antigens and commensal bacteria, and to simultaneously identify and protect against harmful pathogens. The process by which the gastrointestinal immune system avoids attacking harmless antigens is termed oral tolerance.^{54,55} These mechanisms have been investigated mostly in animal models, and the induction of T-cell anergy, deletion of reactive T cells, and generation of suppressor T cells are implicated. Concomitantly, active immunity—such as the production of IgA—curtails infection. To co-ordinate these events, soluble antigens must be differentiated from particulate antigens, which are more likely to be

Panel 2: Severe/fatal, food-induced anaphylaxis^{12–17}

Pathophysiology	IgE-dependent mechanism, massive release of mediators
Risk group	Previously-identified, food-allergic (particularly to peanut, tree nuts, and seafood) adolescents with underlying asthma seem to be at highest risk of death
Symptoms/signs	Mild: mouth tingle, itch, odd taste, flushing, urticaria, abdominal pain, nausea, vomiting, diarrhoea, uterine contractions Severe: throat tightness, hoarse voice, stridor, wheezing, hypotension, cyanosis, feeling of impending doom
Nuances	Time course usually prompt (minutes, within 1 h) after ingestion Can follow biphasic pattern (recurrence of severe anaphylaxis 1–2 h later) Can lack skin symptoms in severe reactions Typical triggers are peanut, nuts, and seafood but any food possible Aspirin, exercise, or alcohol can increase risk

pathogenic. This distinction is accomplished, in part, by differential processing of luminal contents. The follicle-associated epithelium (M cells) overlying Peyer's patch is thought to be mainly responsible for sampling particulate antigens where macrophages and regulatory T cells induce the requisite IgA responses;⁵⁶ soluble antigens are sampled by intestinal epithelial cells,⁵⁶ and immune processing by antigen-presenting cells, and intraepithelial and lamina-propria lymphocytes, results in tolerance. Although luminal contents meet various physiological barriers at the intestinal wall (epithelial cells, glycocalyx, and enzymes) a small portion of ingested antigen penetrates the gut barrier and has the potential to stimulate systemic immune responses. Feeding of new antigens to healthy adults results in T-cell tolerance but antibody responses (IgG) proceed and are apparently physiological.^{57,58}

The gastrointestinal cytokine milieu includes transforming growth factor β , which induces T-cell suppression, promotes B-cell switching to IgA production, and preserves epithelial barrier function.^{59,60} Additional cytokines representing non-allergic T-helper-cell profiles, Th1-type (interferon-gamma and interleukin-2),⁶¹ and Th2 (interleukin-4)⁵⁹ take part in these processes. A Th2 profile seems dominant in early development;⁶² with exposure to ingestants and the influence of gut flora, the normal result is controlled or physiological inflammation. Presumably, alterations in the immunological response (among Th1, Th2, and abrogation of tolerance) result in disease.

When T helper type 2 responses dominate, food hypersensitivity associated with IgE-mediated mechanisms can ensue. The most remarkable conundrum is that food-specific IgE is often present (sensitisation) without clinical reactivity, although the concentration of specific IgE correlates positively with risk of reactions.⁶³ Several other variables seem to influence the clinical response. Target-organ reactivity is one such variable; patients with asthma are more likely than those without to have respiratory reactions during anaphylaxis.^{12,64} Food absorption can also affect responses. Increased absorption might explain why infants, who have leakier gut barriers than older people,

	Risk of allergy to >1 member (approximate)	Features
Food family		
Legumes	5%	Main causes of reactions are peanut, soya, lentil, lupine, and garbonzo Reactions are often severe
Tree nuts (eg, hazel, walnut, brazil)	35%	
Fish	50%	Reactions can be severe
Shellfish	75%	Reactions can be severe
Grains	20%	
Mammalian milks	90%	Cow's milk is highly cross-reactive with goat's or sheep's milk (92%) but not with mare's (4%)
Rosaceae (rock) fruits	55%	Risk of reactions to more than three related foods is very low (<10%)
Latex-food	35%	For individuals allergic to latex, banana, kiwi, and avocado are the main causes of reactions

Table 2: **Clinical implications of cross-reactive proteins in IgE-mediated allergy**⁷⁹

frequently have food allergy. In experimental models, sensitisation (IgE) itself enhances transepithelial transport in the intestine.⁶⁵ Alcohol, aspirin, and exercise are important co-factors in food-induced anaphylaxis, probably through facilitation of increased absorption.^{15,16,28}

The immune mechanisms underlying disorders that are not dependent on IgE have been partly elucidated. For example, the skin might be targeted in food-responsive atopic dermatitis by food-specific T cells that express the skin homing molecule cutaneous lymphocyte antigen.^{66,67} The immune process that causes food protein-induced enterocolitis syndrome results partly from elaboration of the cytokine tumour necrosis factor α by milk-responsive T cells.^{68,69} Results of tests in murine models show that allergen exposure must be distributed simultaneously to the respiratory and gastrointestinal tract to induce eosinophilic oesophagitis; this process is centrally affected by the cytokine interleukin-5 and the chemokine eotaxin, which provides an eosinophil homing signal.⁷⁰ In some cases of isolated gastrointestinal allergy without measurable serum IgE, localised gut IgE is thought to mediate the response.⁷¹ The most extensively studied gastrointestinal allergy is probably coeliac disease.⁷² This disorder is caused by gliadin-specific T-cell responses

enhanced by deamidated gliadin, which is produced by tissue transglutaminase. Antigen presentation is an important factor, since more than 95% of patients are positive for HLA DQ2.

Food biochemistry

Potent food allergens are usually water-soluble glycoproteins with molecular weights of 10–60 kD that are stable at low pH. Cooking can reduce the allergenicity of certain food proteins, as shown with fruits and vegetables in oral allergy syndrome, and with cooked versus raw or undercooked egg and fish.^{73,74} Conversely, heating can increase the allergenicity of certain proteins through the induction of covalent modifications that lead to new antigens or improved stability.⁵ In peanuts, for example, the roasting process produces end-products with greater resistance to digestion and heightened allergenicity compared with those produced by frying or boiling.^{75,76} This finding might partly account for the low prevalence of peanut allergy in China where peanut is widely consumed but not roasted.

Concerns have been raised about the allergenicity of genetically modified foods.⁷⁷ Genetic modifications can introduce a known allergenic protein, create new allergens, or upregulate the expression of potential allergens. These concerns have led to increasing study of the products of genetic manipulations and regulation in manufacture.

The conservation of proteins across species wreaks havoc for those with food allergy.⁷⁸ Many so-called pan-allergens have been described: profilins in birch pollen, hazelnut, and apple; class 1 chitinases in avocado, banana, and latex; lipid transfer proteins in apple and peach; and tropomyosin in insects and shellfish. Cross-reacting IgE antibodies reactive with related foods can often be detected in people who are allergic to a member of these food groups (usually >50%), but clinical reactions are uncommon (table 2).⁷⁹

Diagnosis

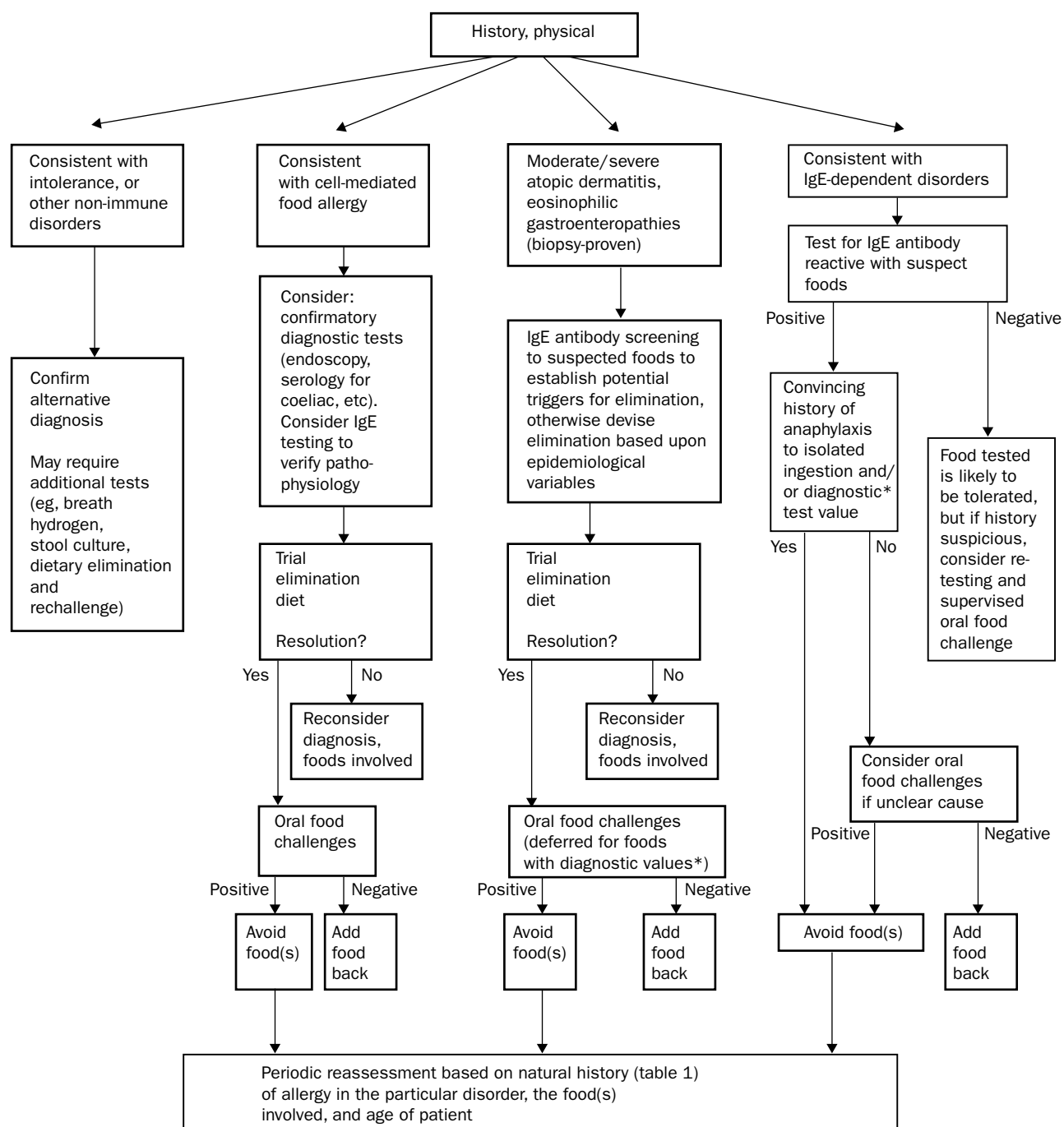
General considerations

Assessment of food allergy begins with a thorough history and physical examination to consider a potentially broad differential diagnosis (panel 3). When food allergy has been identified as a likely cause of symptoms, confirmation of diagnosis and identification of implicated foods can proceed. A general scheme for the diagnosis of food allergy is shown in the figure. An initial step is to identify the most likely mechanism of the disorder (IgE-dependent, IgE-associated, or non-IgE-mediated) and suspected food or foods. The identification of suspect foods is difficult because food is ingested throughout the day, and symptoms that arise soon after an ingestion might be wrongly attributed to food allergy, or attributed to the wrong food. For acute reactions, a food that is ingested infrequently is more probably responsible for a reaction than one that has previously been tolerated. Additionally, reactions are more often caused by unintentional exposure to previously identified allergens than they are by a new sensitivity. Much investigation is needed to identify possible allergens in processed foods and in restaurant meals.

For chronic disorders, suspicions about particular foods are notoriously inaccurate and are only verified in about 30% of cases. Diet records and symptom diaries are helpful but rarely diagnostic. In some cases, invasive tests such as endoscopy are needed, but usually diagnosis is dependent on identification of food-specific IgE (or confirmation of its absence), results of elimination diets, and responses to oral food challenges.^{80,81}

Panel 3: Examples of non-immunological adverse reactions to food and masqueraders of food allergy

- Intolerance (lactase deficiency)
- Infection (bacterial, viral, parasitic)
- Pharmacological effects (caffeine, histamine, tyramine)
- Anatomical (pyloric stenosis)
- Digestive (gallbladder disease, pancreatic insufficiency)
- Metabolic disorders (galactosaemia)
- Toxins (bacterial contamination, scombroid fish poisoning)
- Non-food allergy (reactions to pollen, mould, dust mite, dander)
- Neurological (gustatory rhinitis from spicy foods, facial flush from tart foods)
- Factitious (Munchausen's syndrome/ Munchausen's syndrome by proxy)
- Psychological (panic disorder)



General scheme for diagnosis of food allergy

See text for specific advice at each stage. *In some cases, positive test results for IgE specific for particular foods may indicate a high probability of clinical allergy (see text).

Diagnostic tests for IgE

Skin prick tests are commonly used by allergy specialists to detect food-specific IgE. While the patient is off antihistamines for an appropriate length of time, a device such as a bifurcated needle, lancet, plastic probe, or tip of a small gauge needle is pressed through a commercial extract of a food into the epidermis. This almost painless procedure allows the test protein to interact with food-specific IgE on the surface of skin mast cells. If the antibody is present, mast cells degranulate and release mediators that cause localised angio-oedema, vasodilation, and a wheal and flare, within 15 min. Positive (histamine) and negative (saline-

glycerine) controls are used to establish that the immune response is not blocked and to show whether there is dermographism, a response to local trauma that causes the same symptoms as a positive response. Even infants can be tested. Some workers prefer to use fresh extracts, especially when testing for sensitivity to fruits and vegetables that are prone to degradation.⁹ Skin prick tests are judged positive if there is a mean wheal diameter of 3 mm or greater, after subtraction of the saline control, since this diameter provides acceptable sensitivity (75–95%) and specificity (30–60%).^{63,82} Intradermal allergy skin tests with food extracts should not be used because they give an

unacceptably high false-positive rate and can elicit systemic reactions (rarely an issue for skin prick tests).⁸³

Another way to detect food-specific IgE that is more widely available to the general practitioner is the radioallergosorbent test (RAST). The allergen of interest is bound to a solid matrix and exposed to the patient's serum. IgE antibody specific for the allergen binds to the protein-matrix and is detected by use of a secondary labelled antibody specific for IgE. Manufacturers and substrates vary, and results can be reported as classes (class one to five or six), counts, percentages, or arbitrary units of concentration.

As discussed, skin prick tests and RASTs detect sensitisation (the presence of food-specific IgE) but because sensitisation can exist without clinical reactions, the tests generally cannot be used to diagnose food allergy without consideration of the clinical history. Panels of food allergy tests should not be done without obtaining a clinical history because there could be many irrelevant positive results. The results are most valuable when they are negative, since the tests' high sensitivity makes them about 95% accurate for discounting IgE-mediated reactions.⁸⁴ However, in chronic disorders a positive test is associated with true clinical reactions only in about 50% of cases.⁸⁰⁻⁸⁵ Indeed, tests sometimes remain positive for some time after clinical reactivity has resolved. RAST is generally less sensitive than skin prick tests. Neither the size of the skin prick test nor level of IgE by RAST usefully predicts the type or severity of reaction.^{63,86}

Findings of studies with children lend support to the notion that especially high concentrations of food-specific IgE are associated with a very high likelihood of reactions.^{63,86,87} The concentration of specific IgE measured with a particular method (CAP System FEIA, or UniCap [Pharmacia and UpJohn Diagnostics, Uppsala, Sweden], which measures in arbitrary units, kU_A/L) was compared to outcomes of double-blind placebo-controlled food challenges in children with atopic dermatitis assessed at mean age 5 years.⁶³ Specific-IgE concentrations of 6 kU_A/L or greater for egg, 32 kU_A/L or greater for milk, 15 kU_A/L or greater for peanut, and 20 kU_A/L or greater for codfish were 95% predictive of a reaction. Such cutoff concentrations have not been determined for other foods, allergic disorders, or age groups. Results of a prospective study of children not selected for atopic dermatitis (only 61% with the disorder) showed the 95% diagnostic cutoff point to be slightly lower for milk (15 kU_A/L).⁸⁶ Other investigators showed that concentrations of specific-IgE with high predictive capacity are lower in younger infants or children.^{85,88,89} Findings of one study with skin prick tests showed that all young children with especially large wheals (≥ 8 mm for milk and peanut and ≥ 7 mm for egg) had clinical reactions⁸⁷ but other studies had different results.⁸⁵ Overall, the evidence indicates that skin prick test and RAST are invaluable aids to confirm suspected acute reactions, exclude particular foods from having caused an acute reaction, and for screening (if done in a judicious manner) to determine whether foods are causing a chronic IgE-mediated disorder.

Many tests have been suggested for the diagnosis of food allergy, but have never proved useful in masked studies. Such tests include measurement of IgG₄ antibody, provocation-neutralisation (extracts placed under the tongue or injected to diagnose and treat various symptoms), electrodermal tests, leukocyte cytotoxicity, and applied kinesiology (muscle-strength testing).⁹⁰

Elimination diets

The amelioration of symptoms during dietary elimination of suspected foods provides presumptive evidence of causality.

For infants, elimination simply involves a change in formula, but the procedure is more complicated in breastfed infants, for whom maternal diet must be restricted, and in older children and adults.⁸⁰ Elimination diets can be undertaken by removal of foods that are thought to cause symptoms, by removal of all but a defined group of foods that are rarely allergenic (oligoantigenic diet), or by giving an elemental diet of only a hypoallergenic, extensively hydrolysed formula or a non-allergenic aminoacid-based formula. The elemental diet provides the most definitive trial but can be difficult to undertake. The type of elimination diet selected is dependent on the clinical scenario, a priori reasoning about offending foods derived from epidemiological data, and the results of tests for IgE. The length of trial is dependent on the type of symptoms, but 1–6 weeks is usually the range needed. These diets are difficult to manage and the expert advice of allergists and dieticians is needed to ensure nutritional adequacy, accurate avoidance, and correct interpretation of the results. When a food to which the patient is sensitised is removed from the diet during a chronic disorder, reintroduction can induce severe reactions.⁹¹ When an elimination diet is successful, a potential placebo effect should be considered, and the relation between the food and the symptoms should be confirmed, where indicated, with oral food challenges.

Oral food challenges

The oral food challenge is done by feeding gradually increasing amounts of the suspected food under observation by a physician over hours or days.⁸⁰ Oral food challenges are done either openly, or masked by camouflaging the test food in a carrier food or in opaque capsules. The double-blind, placebo-controlled food challenge is the method least prone to bias. Oral food challenges can be used to assess any type of suspected adverse response to foods. The procedure is most often needed when several foods are under consideration, tests for specific IgE are positive, and elimination has resulted in resolution of symptoms. The challenge setting also provides a safe forum in which to introduce foods that are strongly suspected of causing severe reactions despite negative skin tests or RASTs. For non-IgE-mediated reactions, oral food challenges are usually the only means of diagnosis. They are also required to monitor patients likely to become tolerant.

Oral food challenges, particularly for acute IgE-mediated reactions, severe atopic dermatitis, and enterocolitis syndrome, can induce severe reactions. As a general rule, such challenges should never be done at home.⁹¹ The supervising clinician, usually an allergist, should have drugs and supplies for resuscitation immediately available to manage reactions. Challenges can be optional or contraindicated in certain circumstances, and risks of the challenge must be weighed against the social and nutritional deficits of continued avoidance. Recent and severe anaphylaxis after an isolated ingestion with a positive test for specific IgE to the causal food is one example of a relative contraindication, because this scenario represents a convincing history. The false negative rate of double-blind, placebo-controlled trials is about 3%, so negative challenges should always be followed by a supervised open feeding of a relevant portion of the tested food in its commonly prepared state.⁹²

Management

Medications

Antihistamines are sometimes the only medication needed to reduce itching and rash. However, for patients with more severe symptoms of anaphylaxis, or with respiratory or cardiovascular symptoms, additional treatment is needed.¹¹

A complete review of treatment of such patients is beyond the scope of this paper, but includes cardiopulmonary resuscitation, administration of epinephrine, antihistamines, corticosteroids, oxygen, intravenous fluids, inhaled bronchodilators, and medications to support blood pressure.

Epinephrine is the mainstay of treatment for anaphylaxis.¹¹ Intramuscular injection allows more efficient absorption than the subcutaneous route.⁹³ The dose is 0.01 mL/kg of 1:1000 dilution of aqueous epinephrine intramuscularly (maximum dose 0.3–0.5 mL, 0.3–0.5 mg). Premeasured doses of epinephrine for self-injection allow prompt administration by patients. Guidelines to determine who should have access to this medication are under scrutiny; candidates include food-allergic patients with previous severe reactions, those with allergy to foods that commonly cause severe reactions, and those with underlying asthma. Indications for administration of drugs generally include signs of respiratory or cardiovascular allergic symptoms after a known or possible exposure, but patients with a history of severe reactions might warrant treatment after ingestion of causal food even when there are no symptoms. The indications and technique of administration of self-injectable epinephrine should be periodically reviewed because mistakes are common.⁹⁴ Patients should be instructed that, after they have taken the drug, they should seek prompt transportation to an emergency facility with prolonged observation (>4 h) since recurrence of severe symptoms is possible.¹² Patients should obtain medical emergency bracelets to identify their allergy, and should be reminded to update expired and expended epinephrine injectors. Important components of management of food allergy in schools are to have a clear emergency plan in place, medications readily available, and school personnel trained in recognition and treatment of reactions.⁹⁵

Diet

Dietary management of food allergy is fraught with nutritional and other pitfalls. In most countries, shortcomings on the parts of manufacturers and in labelling make it very difficult to identify allergens in commercial food products. Cross contamination and errors in packaged food shops and restaurants are an additional obstacle. For children, dietary management in schools can be difficult since food sharing, school projects with foods, parties, lack of on-site medical personnel, and other issues arise.⁹⁶ Families can obtain helpful information from support groups such as the Anaphylaxis Campaign, UK (www.Anaphylaxis.org.uk) and the Food Allergy and Anaphylaxis Network, USA (www.foodallergy.org).

Natural history

Fortunately, most children (about 85%) lose their sensitivity to most allergenic foods (egg, milk, wheat, soya) within the first 3–5 years of life (table 1).⁹⁷ Food-specific IgE concentrations generally fall with tolerance.⁹⁸ Even children with multiple, severe allergies usually achieve tolerance.⁹⁹ By contrast, adults with food allergy can have long-lived sensitivity. Unfortunately, persistence of childhood food allergy seems to be increasingly common.¹⁰⁰

Sensitivity to peanut, tree nuts, and seafood is rarely lost. The notion that peanut and tree nut allergy is permanent derives, in part, from the observation that it is an allergy that affects adults,^{37,38} and longitudinal studies of school-age children have not shown resolution.¹⁰¹ However, about 20% of peanut-allergic children younger than 2 years achieve tolerance by school age.^{102,103} Children

who outgrow peanut allergy tend to have small or negative skin prick tests, a long (>3 year) interval since the last reaction, few additional food allergies, and mild reactions.

The mechanisms underlying tolerance are unknown, but might be associated with maturation of the gut with reduced systemic absorption and maturation of immune responses that play a part in tolerance. The specific regions on proteins (epitopes) to which IgE binds could affect the likelihood of resolution.¹⁰⁴ With egg and milk, for example, IgE binding to epitopes that are comprised of sequential aminoacids, compared with epitopes that are dependent on folding conformations, are associated with persistence of allergy.^{105,106}

Prevention

Breastfeeding^{107,108} and delayed introduction of solid foods¹⁰⁹ are associated with a reduction in atopic disease. Expert panels from Europe¹¹⁰ and the USA¹¹¹ made recommendations for allergy prevention through dietary manipulation aimed at infants at high risk of atopic disease. The recommendations differ slightly from each other, but breastfeeding (6–12 months), delayed introduction of solid foods (beyond the 5th month of life) and hypoallergenic formula (not soya) for supplementation, if needed, are shared recommendations.

Maternally ingested foods can pass in immunologically intact form into breastmilk¹¹² and induce reactions in the infant.¹¹³ Several workers have shown that infants from atopic families whose mothers exclude highly allergenic foods from their diets during lactation generally have less atopic dermatitis and food allergy than those whose mothers' diets are unrestricted.^{114–116} However, such differences might not extend beyond early childhood^{115,117,118} so a true effect on long-term prevention is uncertain. Additionally, dietary restrictions during pregnancy generally seem ineffective.¹¹⁹ Ultimately, there are no definitive recommendations on dietary restriction during lactation with regard to allergy prevention. The US recommendations¹¹¹ when one or both parents and siblings are atopic include: elimination of peanut and nuts with consideration of elimination of other foods during breastfeeding, consideration of elimination of peanut during pregnancy, and delayed introduction of allergenic foods (milk to 12 months, egg to 24 months, and peanut, nuts, and fish to 36 months). Although in some studies the point prevalence of food allergy, atopic dermatitis, and food sensitisation was reduced by 30–50% in the first 2 years with such an approach, there was no significant difference in atopic parameters by age 4 and 7 years,^{115,118} so the effect on disease progression is unproven and more studies are needed to validate this approach. To confuse matters further, atopic mothers' breastmilk could contain cytokines that direct immune responses in the infant toward allergic reactions,^{120–122} so further prospective masked studies are needed to identify the best practices in defined groups.

Future directions

Research has renewed our hopes for better diagnostic tests. The identification of informative segments (epitopes) of proteins to which IgE binding correlates with a high risk of clinical reactions might prove useful to enhance the diagnostic value of skin prick tests and RASTs.^{104–106,123} Skin patch tests, similar to those used for delayed hypersensitivity testing, show promise especially for prediction of delayed reactions to foods.^{21,124,125} The measurement in blood and stool of inflammatory markers that predict reaction would be convenient but attempts at such strategies have met with mixed success.^{126–128}

Quantification of IgE-positive cells in the gastrointestinal tract or assessment of gut mucosal responses to allergen instillation during endoscopy might improve diagnostic capability, but are invasive.^{129–131}

Numerous treatment strategies are under investigation. Humanised antibodies against IgE (designed for injection) are able to bind and inactivate unbound IgE in the bloodstream and reduce allergic responses such as those responsible for asthma and allergic rhinitis.¹³² The application of this treatment to food allergy is under investigation and is particularly enticing because it would theoretically reduce or circumvent reactions without concern for the specific food involved. Immunotherapy (so-called allergy shots) is another attractive approach to treatment but has proven impractical because the injection of food protein results in anaphylaxis.¹³³ To bypass this problem, engineered proteins for immunotherapy have been designed; these proteins are altered to remove IgE binding epitopes that trigger anaphylaxis while T-cell epitopes that could induce tolerance are preserved.^{134,135} Another approach to induce tolerance to specific food allergen is vaccination with DNA sequences that code for food allergens,^{136–138} and the use of immune modulators (cytokines, specific DNA sequences) that can direct the immune response away from allergy. Herbal remedies are also under investigation.¹³⁹

Improved strategies for prevention are also likely to emerge. The composition of gut bacterial flora seems to influence atopy.¹⁴⁰ Moderate reduction in atopy is seen when specific, beneficial bacterial strains are introduced to colonise the gut of atopy-prone infants.¹⁴¹ The combination of improved diagnostic methods, proactive methods for prevention, and novel treatments of food allergy are likely to improve the quality of life for patients and their families in the coming years.

Conflict of interest statement

None declared.

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