Food allergy and the gut

Anna Nowak-Wegrzyn[1], Hania Szajewska[2] and Gideon Lack[3]

Abstract | Food allergy develops as a consequence of a failure in oral tolerance, which is a default immune response by the gut-associated lymphoid tissues to ingested antigens that is modified by the gut microbiota. Food allergy is classified on the basis of the involvement of IgE antibodies in allergic pathophysiology, either as classic IgE, mixed pathophysiology or non-IgE-mediated food allergy. Gastrointestinal manifestations of food allergy include emesis, nausea, diarrhoea, abdominal pain, dysphagia, food impaction, protein-losing enteropathy and failure to thrive. Childhood food allergy has a generally favourable prognosis, whereas natural history in adults is not as well known. Elimination of the offending foods from the diet is the current standard of care; however, future therapies focus on gradual reintroduction of foods via oral, sublingual or epicutaneous food immunotherapy. Vaccines, modified hypoallergenic foods and modification of the gut microbiota represent additional approaches to treatment of food allergy.

[1]*Jaffe Food Allergy Institute, Department of Pediatrics, Division of Allergy and Immunology, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, New York 10029, USA.*
[2]*The Medical University of Warsaw, Department of Paediatrics, Zwirki i Wigury 63A, 02091 Warsaw, Poland.*
[3]*King's College London Academic Paediatric Allergy Service, Guy's & St Thomas' NHS Foundation Trust Children's Allergies Department, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK.*

Correspondence to A. N.-W.
anna.nowak-wegrzyn@mssm.edu

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Food allergy is an adverse reaction to food protein mediated by the immune system[1–3]. The gastrointestinal tract is the major route of exposure to food allergens. Nausea, vomiting, diarrhoea, abdominal pain, food refusal, early satiety, dysphagia, food impaction, haematochezia and dysmotility (regurgitation and constipation) are common manifestations of allergic reactions to ingested foods. The expression of food allergy ranges from immediate, IgE-mediated anaphylaxis, chronic eosinophilic gastrointestinal disorders to cell-mediated, delayed-onset disorders such as food-protein-induced enterocolitis syndrome (FPIES) (TABLE 1). Both coeliac disease and dermatitis herpetiformis fulfil the definition of an adverse reaction to a food protein (in this context, to gluten and related prolamines) by an immune-mediated mechanism. However, both diseases are proven autoimmune disorders with an identified autoantigen (tissue transglutaminase) that require certain HLA types for manifestations. Coeliac disease should be distinguished from food allergy, particularly from cell-mediated wheat allergy, and is consequently not included in this Review[3]. In addition to the classic food allergic disorders (such as anaphylaxis, acute urticaria and oral allergy syndrome), immune reactions to foods can contribute to expression of GERD, IBS, constipation in young children and infantile colic. In this Review we discuss diverse aspects of food allergy, focusing on the gastrointestinal tract.

Epidemiology of food allergy

Food allergy is most common in the first few years of life, with an estimated prevalence of ~6–8% in childhood[4–6]. Cow's milk, egg, soybean, wheat, peanut, tree nuts (for example, almond, cashew, hazelnut and walnut), fish and shellfish collectively cause >90% of food allergy in children, worldwide[7]. Most allergies to cow's milk, egg, soybean and wheat are outgrown, whereas most allergies to peanut, tree nuts, seeds and seafood persist into adulthood[8]. Presence of IgE sensitization is a risk factor for more persistent food allergy in infants; infantile non-IgE-mediated gastrointestinal food allergic disorders usually resolve by age 1–3 years, whereas in IgE-mediated food allergy, high levels of IgE antibodies to cow's milk, egg white, wheat and soy are associated with persistent food allergy[8]. In addition to nuts and seafood, oral allergy to raw plant foods is common in adults with pollen allergic rhinitis, with an overall estimate of adult food allergy of ~4% in developed countries. Peanut allergy prevalence has increased considerably over the past two decades, affecting up to 1–4% of children in societies with westernized lifestyles, such as the USA, UK, Canada and Australia[9]. Food allergy is also on the rise globally, including in developing countries[5], presumably owing to the adoption of a more Western lifestyle in these countries. Food allergy has a high prevalence in patients with certain atopic conditions; an estimated 35% of children with moderate to severe persistent atopic dermatitis have IgE-mediated food allergy[1]. Among patients with eosinophilic oesophagitis (EoE), most have food-responsive disease in which symptoms and histological changes improve or resolve with elimination of the offending food[10].

Pathophysiology of food allergy

Oral tolerance

Gut-associated intestinal lymphoid tissue is the largest secondary lymphoid organ in the human body. This tissue constantly samples ingested foreign antigens and

Key points

- Food allergy affects 6–8% of children <5 years old and 3–4% of the general population in developed countries; incidence of peanut allergy has increased considerably over the past decade
- Food allergy results from a lack of oral tolerance, a state of systemic unresponsiveness to ingested soluble antigens mediated mainly by regulatory T cells in the gastrointestinal tract
- Food reactions can have IgE-mediated, non-IgE-mediated or a combination of IgE-mediated and non-IgE-mediated pathophysiology involving the skin, gastrointestinal tract, respiratory tract and/or cardiovascular system
- Double-blind, placebo-controlled food challenge remains the gold standard for diagnosing food allergy
- Dietary elimination of offending foods is the current standard of care; future therapies focus on specific food immunotherapy via oral, sublingual and epicutaneous routes
- Most childhood food allergies resolve with age, with the exception of peanut and tree nut allergies that tend to be lifelong

has evolved to discriminate between potentially harmful pathogens and nonharmful antigens to either mount a protective immune response or to actively ignore benign antigens, such as food or commensal bacteria[11]. The state of active systemic unresponsiveness to ingested food antigens is referred to as oral tolerance and is the default immune response in the gut. As an example of this tolerance, induction of an IgE-mediated immune response in mice is very difficult after parenteral immunization with antigens (such as ovalbumin, cow's milk proteins or peanut) present in the diet[11]. Tolerance can be transferred to naive animals through the transfer of regulatory T cells, which are pivotal cells in oral tolerance (BOX 1). Anergy and deletion of reactive effector T cells have been identified as potential additional mechanisms of oral tolerance in animal models[12].

Oral tolerance is a phenomenally efficient default response to ingested food antigens, as demonstrated by the fact that most humans have no food allergy despite ingesting several tonnes of food over an average human lifespan. However, when oral tolerance fails, food allergy develops. Food allergy is most common in infants and young children, as a result of the immaturity of the gut barrier and the immune system in these age groups[12,13]. Immune deficiencies — including selective IgA deficiency, common variable immunodeficiency and IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) — are associated with an increased prevalence of food allergy[14]. Treatment with PPIs increases the risk of IgE sensitization to food owing to increased pH in the stomach and impaired digestion of proteins[15]. Additional genetic and environmental risk factors for food allergy can include male sex, African ancestry, *IL10* and *IL13* gene polymorphisms, lack of microbial exposure (including *Helicobacter pylori* infection) in early life, Caesarean section, low vitamin D levels, *n*-3 polyunsuturated fatty acids and westernized diet low in fibre[16].

Dietary changes affect the gut microbiota, leading to changes in bacterial metabolites (such as short-chain fatty acids) that are pivotal for maintaining mucosal integrity and promoting oral tolerance by epigenetic effects on regulatory T cells[17]. Limited evidence exists for altered gut microbiota in children with food allergy. *In vitro* alterations in gut microflora might change Toll-like receptor signalling and integrity of intestinal epithelial cells in children with food allergy[18]. In a gnotobiotic mouse model, selective colonization of the gut with Clostridia-containing microbiota protects from food allergy via activation of innate lymphoid cells, IL-22 production and enhancement of intestinal permeability[19]. Adults from the USA with self-reported nut and seasonal pollen allergy have low phylogenetic diversity of the gut microbiota, characterized by reduced relative abundance of Clostridiales and increased relative abundance of Bacteroidales in their gut microbiota[20]. Whether supplementation with probiotic bacteria can correct the underlying alterations in gut flora in children with food allergy remains to be determined[21].

Initial exposure to food through the impaired skin barrier in infants with atopic dermatitis could predispose these individuals to the development of IgE sensitization prior to first ingestion of food. Additionally, early-life exposure to topical creams containing peanut oil or to peanut dust in the home environment is a risk factor for peanut allergy, particularly in children with atopic dermatitis, whereas early introduction of peanuts at weaning is associated with a decreased risk of peanut allergy among these high-risk infants with atopy[22–26]. In mouse models of egg and peanut allergy, skin exposure to these foods promotes development of specific IgE sensitization to ovalbumin and peanut, whereas an oral exposure promotes oral tolerance[27,28]. Cutaneous exposure to food antigens induces thymic stromal lymphopoietin production, activation of basophils that produce IL-4, production of type 2 T-helper-cell cytokines and accumulation of mast cells in the gut[29]. Mutations in genes encoding proteins that determine the integrity of the skin barrier, such as *FLG* encoding filaggrin, are independent risk factors for peanut allergy[30]. FIG. 1 illustrates differential immune responses to food protein in the gut and skin, with oral tolerance being the default response in the gut.

An alternative pathway of allergic sensitization to food could occur in the airways. In adults working in the food industry and exposed to wheat and egg white proteins via inhalation of the food dust, asthmatic responses to the inhaled food allergens can occur (for example, in baker's asthma); in some individuals this response is followed by a breach in the oral tolerance to the previously tolerated wheat and egg-white protein, as these individuals develop immediate allergic reactions upon ingestion of these foods[31]. Additionally, systemic reactions to ingested egg can occur in adults exposed to pet bird dander via inhalation[32]. Whether primary sensitization via the airways occurs in infants (for example, through microaspiration of the gastric content in infants with GERD) is unknown.

Characteristics of food allergens

The majority of food allergens are proteins. Class I food allergens are 10–70 kDa animal or plant glycoproteins that are resistant to processing and enzymatic

digestion and are capable of inducing IgE sensitization via ingestion, such as casein and whey protein in cow's milk, ovalbumin and ovomucoid in egg and storage seed proteins in nuts[1]. Class II food allergens are pollen-homologous proteins that are very unstable when subjected to heating or enzymatic digestion, such as in apple (Mal d 1), carrot (Dau c 1) and celery (Api g 1). Owing to their susceptibility to digestion, class II food allergens are considered incapable of inducing primary IgE sensitization via ingestion[1,33]. However, when inhalation of pollen leads to expression of pollen-specific IgE antibodies in the oropharyngeal mucosa, cross-reactive reactions to foods occur, mainly via a form of contact urticaria known as oral allergy syndrome. Rarely, complex carbohydrates cause food allergy. One example is galactose-α-1,3-galactose (also known as alpha-gal), which can induce delayed anaphylactic reactions after its ingestion via mammalian meat. In the USA, the lone star tick (*Amblyomma americanum*) bite predisposes individuals to generation of IgE antibodies against alpha-gal[34].

Gastrointestinal manifestations

Immediate IgE-mediated food allergy

Oral allergy syndrome. Pollen-associated food allergy, known as oral allergy syndrome, usually manifests as transient itching in the oropharynx, sometimes accompanied by mild to moderate lip swelling or blisters in the mouth, within minutes of raw plant-food ingestion (such as fruits, vegetables, legumes and nuts) in individuals with pollen allergy[35]. In rare patients, severe symptoms of dysphagia, nausea and abdominal pain can be elicited by ingestion or contact of raw plant foods with oral mucosa[35]. Oral allergy syndrome is generally mild and self-limiting; cooked or baked forms of plant foods are well tolerated. Pollen-specific subcutaneous immunotherapy with a high dose of birch pollen extract can ameliorate or resolve oral allergy syndrome symptoms to apple in a subset of patients[35]. Oral symptoms identical to oral allergy syndrome can also be an initial manifestation of a systemic reaction to non-pollen-related foods, such as milk or egg, in patients with food allergy[1]. Oral symptoms in patients with a known systemic food allergy must be observed closely and can warrant immediate treatment.

Anaphylaxis. Reaction to an allergen can result in anaphylaxis, an immediate, potentially fatal multisystemic allergic reaction; nausea, vomiting, diarrhoea and abdominal cramps start within minutes to 1–2 h following food ingestion. Symptoms improve with intramuscular adrenaline and/or antihistamines and resolve within minutes to hours. Gastrointestinal symptoms are usually accompanied by pruritus, urticaria, angioedema, flushing, cough, wheezing, shortness of breath, tachycardia or hypotension. Teenage men and young athletic adult women (aged 20–40 years) can manifest anaphylactic symptoms if they exercise within 2–4 h following food ingestion, which is referred to as food-dependent, exercise-induced anaphylaxis[36] (TABLE 1).

Mixed pathophysiology IgE disorders

Eosinophilic gastrointestinal disorders. The heterogeneous group of diseases known as eosinophilic gastrointestinal disorders are chronic inflammatory conditions of the gastrointestinal tract that include EoE, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis and eosinophilic colitis[37]. In infants and young children with mucosal eosinophilic gastroenteritis, a trial of an elemental diet for 2–4 weeks can be warranted. Non-IgE-mediated cow's milk allergy can be associated with increased numbers of mucosal eosinophils in the stomach, small intestine and colon. However, in patients with evidence of transmural (muscular or serosal) involvement, elimination diets are generally not successful[38,39]. Transmural involvement usually occurs in adults and can present with intestinal pseudo-obstruction or ascites. Treatment relies on systemic corticosteroids and other immune-modulating agents[38,39].

EoE predominantly affects white men, with an onset from school age to midlife and is increasingly seen during infancy through adolescence[40,41]. The prevalence of EoE was estimated as between one and six per 10,000 persons in the USA and Europe in 2014 (REFS 42,43). EoE is found in up to 54% of patients with food impaction[41]. A personal or family history of atopic disorders (including asthma, atopic dermatitis, rhinitis and anaphylactic food allergy) is common. Family history of EoE is also frequently reported, predominantly in male relatives, suggesting a 2% heritability risk[41]. Genetic variants in thymic stromal lymphopoietin, C-C motif chemokine 26 (also known as eotaxin-3), and calpain-14 are associated with an increased risk of EoE[44–47].

EoE typically manifests with symptoms resembling GERD, intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance and failure to respond to conventional reflux medications. In infants and young children, symptoms are unspecific, with refusal of solid foods and failure to thrive being most common; in adolescents and adults, abdominal discomfort, dysphagia, oesophageal strictures and food impaction are typical symptoms. Patients can exhibit compensatory behaviours, such as eating slowly, chewing carefully, cutting food into small pieces, drinking liquids to dilute foods and avoiding hard foods that could cause dysphagia (for example, meats and breads).

EoE is a food-allergen-responsive disease (meaning that elimination of the offending food resolves inflammation) in both children and adults. The immune responses to food proteins in EoE are non-IgE-mediated (driven by eosinophils and mast cells), despite a high frequency of associated IgE sensitization to multiple foods in these patients[48]. In children, response rates to dietary management vary from 98% on an amino-acid-based diet to 81% on an empiric six-food elimination diet (which includes cow's milk, wheat, egg, soy, nuts and seafood)[49]. In adults, response to amino-acid-based diet is 88% and to empiric six-food elimination diet is 74%[50,51]. No statistically significant difference exists in response rates to elimination diets between children and adults[50].

Eosinophilic gastroenteritis is a rare disease, estimated to affect 8.1 in 100,000 people in the USA[52]. Diagnosis of eosinophilic gastroenteritis is based on clinical symptoms (including abdominal pain, diarrhoea, eosinophilic ascites, protein-losing enteropathy and nausea and/or vomiting) in combination with gastric, small intestinal and/or large intestinal eosinophilia above the normally reported numbers[53].

Non-IgE disorders

Several gastrointestinal disorders are thought to result from cell-mediated hypersensitivities, such as FPIES, food protein-induced proctocolitis (FPIAP) and food protein-induced enteropathy (FPE). T-cell-mediated pathophysiology has been determined in FPE, however, direct evidence is lacking in FPIES and FPIAP (TABLE 1).

Table 1 | **Classification of gastrointestinal food allergic disorders on the basis of IgE antibody involvement in pathophysiology**

Disorder	Age groups	Food triggers	Symptoms	Diagnosis	Prognosis and natural history
IgE-mediated food allergic disorders					
Oral allergy syndrome	• Any • Most common in young adults (age 20–50 years) with pollen allergy • 50% of adults with birch pollen allergic rhinitis report oral allergy syndrome to apple	• Raw plant foods, fruits, vegetables, legumes and nuts • Common pollen-food cross-reactivities include: birch allergy (apple, peach, carrot, celery, peanut, soy and hazelnut); ragweed allergy (melon, banana and cucumber); mugwort allergy (cabbage, mustard, fennel, carrot and celery)	Immediate symptoms on contact of raw food with oral mucosa: pruritus, tingling, erythema or angioedema of the lips, tongue or oropharynx; throat pruritus or tightness; and rarely nausea, abdominal pain, rhinorrhea and blisters in the mouth	• History, positive skin-prick test with raw fruits or vegetables • Oral food challenge positive with raw plant food, negative with cooked food	• Severity of symptoms fluctuates with pollen season • Oral allergy syndrome can improve in a subset of patients with pollen immunotherapy
Anaphylaxis	Any	Any, most common triggers in severe anaphylaxis include peanut and tree nuts	• Onset of minutes to 2 h, with nausea, abdominal pain, emesis and diarrhoea • Typically in conjunction with cutaneous and/or respiratory symptoms	• History, positive skin-prick test and/or serum food-IgE level • Confirmatory physician-supervised oral food challenge	Favourable in infants and young children; those with peak lifetime food-specific IgE antibody levels >50 kU_A/l tend to have a more persistent food allergy
Food-dependent, exercise-induced anaphylaxis	• Any • Most common in teenage men and young athletic women (age 20–50 years)	Any, most common triggers are wheat, cow's milk, celery, fish and shellfish	• Exercise within 2–4 h after food ingestion yields symptoms of anaphylaxis • Food well tolerated if no exercise	• History, positive skin-prick test and/or serum food-IgE level • Confirmatory oral food challenge	• Natural history unknown • Severity can increase during or after pollen season in pollen-allergic patients
Mixed, IgE and cell-mediated gastrointestinal food allergy					
Eosinophilic oesophagitis	Any	Any, most common triggers are cow's milk, wheat, egg, soy, seafood and nuts	• Infants and children: chronic or intermittent emesis, gastro-oesophageal reflux, abdominal pain, poor appetite and failure to thrive • Adolescents and adults: chronic intermittent dysphagia, food impaction, abdominal pain and early satiety	• Endoscopy and biopsy >15 eos/hpf) provides conclusive diagnosis and information about treatment response • History, positive skin-prick test and/or food-IgE level in up to 50%, but poor correlation with clinical symptoms • Elimination diet and oral food challenge	• Chronic, relapsing course • Uncontrolled inflammation yields a risk of fibrosis and oesophageal narrowing with time
Eosinophilic gastroenteritis	Any	• Children with mucosal form of eosinophilic gastroenteritis: any food, most commonly cow's milk • Adults, especially those with serosal or muscular involvement: the disease is usually not responsive to dietary elimination	Chronic or intermittent abdominal pain, emesis, irritability, poor appetite, failure to thrive, weight loss, anaemia and protein-losing gastroenteropathy	• Endoscopy or biopsy provides conclusive diagnosis and information about treatment response • History, positive skin-prick test, and/or food-IgE level in up to 50% of patients, but poor correlation with clinical symptoms, elimination diet, and oral food challenge[50,112]	Variable, can be transient, persistent or chronic intermittent

FPIES. Onset of FPIES is usually in the first 6 months of life, and the syndrome manifests as protracted vomiting, lethargy, pallor and diarrhoea[39]. Prevalence of cow's milk FPIES was reported as 0.34% of infants younger than 12 months in an unselected Israeli birth cohort[54]. Repetitive vomiting usually occurs 1–4 h after feeding; continued exposure leads to diarrhoea, anaemia, abdominal distension and failure to thrive (chronic FPIES). Cow's milk and soy-protein-based formulas are the most common triggers in infants; rice, oatmeal, egg, wheat, oat, peanut, nuts, chicken, turkey and fish are triggers in older infants and children. In adults, shellfish sensitivity can provoke a similar syndrome, with symptoms of severe nausea, abdominal cramps and protracted vomiting[55,56].

FPIAP. Usually, FPIAP manifests in the first few months of life and is predominantly caused by cow's milk or soy. The majority of cases occur in breastfeeding infants that seem well, have normally formed or loose stools and are discovered because of the presence of blood (gross or occult) mixed with mucus in their stools[57,58]. Blood loss is usually minor but occasionally can cause

Table 1 (cont.) | **Classification of gastrointestinal food allergic disorders on the basis of IgE antibody involvement in pathophysiology**

Disorder	Age groups	Food triggers	Symptoms	Diagnosis	Prognosis and natural history
Non-IgE, presumed cell-mediated gastrointestinal food allergy					
Food-protein-induced enterocolitis syndrome	• Majority onset in the first 12 months of life • New onset rarely occurs in older children or adults	• Infants: cow's milk, soy, rice, oat, egg, fish, poultry, fruits and vegetables • Older children and adults: fish, shellfish and egg	• Chronic: emesis, diarrhoea, failure to thrive on chronic exposure to cow's milk or soy-infant formula • Acute: repetitive emesis within 1–4 h post food ingestion, dehydration (15% shock), leukocytosis and thrombocytosis on repeat exposure after elimination period	• History, response to dietary restriction • Physician-supervised oral food challenge • Jejunal biopsies: flattened villi, oedema, and increased numbers of lymphocytes, eosinophils and mast cells[113,114]	• Avoidance of the offending food in the diet • Most have resolution by 3–5 years; rarely persists into adulthood
Food-protein-induced allergic proctocolitis	Young infants (<6 months old) who are frequently breastfed	Cow's milk or soy in infant formula; cow's milk, egg, wheat or corn in maternal breast milk	Blood-streaked or haeme-positive stools; otherwise healthy appearing	• History, prompt response (resolution of gross blood in 48 h) to allergen elimination; biopsy would be conclusive but is not necessary for most patients • Sigmoidoscopy: areas of patchy mucosal injection to severe friability with small, aphthoid ulcerations and bleeding • Colonic biopsy: prominent eosinophilic infiltrate in the surface and crypt epithelia and the lamina propria; neutrophils are prominent in severe lesions with crypt destruction	• Avoidance of the offending food in the maternal diet or substitution with a hypoallergenic formula; • Most patients able to tolerate cow's milk or soy by 1–2 years of age, reintroduction of the offending food at home
Food-protein-induced enteropathy	Young infants; incidence has decreased since the 1970's	Cow's milk, soy, egg, wheat	Osmotic diarrhoea resulting from secondary lactose intolerance; secretory diarrhoea resulting from loss of villus surface, fat malabsorption and protein losing enteropathy; emesis, failure to thrive and anaemia in 40% of patients	• History, endoscopy and biopsy • Response to dietary restriction • Clinical symptoms resolve within a few weeks • Recovery of villi can take up to 6 months	• Avoidance of the offending food in the diet • Most patients have resolution in 1–2 years • Reintroduction of the offending food at home • In contrast to coeliac disease, wheat food protein-induced enteropathy is a self-limiting condition; coeliac serology is negative, genetic markers are absent and wheat food-protein-induced enteropathy is commonly associated with additional food sensitivities

eos/hpf, eosinophils per high power field.

Box 1 | **FOXP3$^+$CD4$^+$ T_{reg} cells are central to the maintenance of immune homeostasis and tolerance**

- FOXP3$^+$ CD4$^+$ T regulatory (T_{reg}) cells are present in every organ of the body and constitute ~10% of the total CD4$^+$ T cell population. In the intestinal lamina propria, they constitute a much higher proportion: >30% of CD4$^+$ T cells in the colonic lamina propria and ~20% in the small intestinal lamina propria[105].
- Intestinal FOXP3$^+$ T_{reg} cells regulate mucosal immune responses at multiple cellular levels through various molecular mechanisms. They constitutively express CTLA4, inducible T cell co-stimulator (ICOS), IL-10, TGFβ and IL-35, and inhibit bystander T cells to maintain immune tolerance to dietary components and intestinal microbiota.
- A subset of T_{reg} cells controlls expansion of T follicular helper cell populations.
- T_{reg} cells suppress immunopathology mediated by effector T cells. Mice with low numbers or reduced suppressive activity of colonic T_{reg} cells have an increased susceptiblity to infection and mucosal injury.
- FOXP3$^+$ induced T_{reg} cells are required for oral tolerance and their depletion results in defective oral tolerance in mice[106,107].

Consequence of FOXP3$^+$ T cell deficiency

- Lack of FOXP3$^+$ T cells leads to enteropathy, eczema and elevated IgE in both mice and humans (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome). Severe food allergy occurs as one manifestation of *FOXP3* mutations in humans[108].

Role of FOXP3$^+$ T cells in resolution of food allergy

- Natural development of oral tolerance on food-allergic children is associated with increased FOXP3$^+$ T cells.
- Resolution of cow's milk allergy in children is associated with an increased frequency of peripheral blood CD4$^+$ CD25$^+$ T_{reg} cells after an oral milk challenge and reduced proliferation of milk-specific T cells[109,110]. Depletion of CD4$^+$ CD25$^+$ T_{reg} cells restores the *in vitro* proliferative response in milk-tolerant individuals[109].
- In children with egg and peanut tolerance, stimulation of the peripheral mononuclear cells with the relevant allergen resulted in markedly increased numbers of IL-10-expressing CD25$^+$ CD127^{lo} cells (type 1 T_{reg} cells), FOXP3$^+$ cells and CD4$^+$ cells compared with children who have persistent egg and peanut allergies[111].

anaemia. However, in many breast-fed infants with proctocolitis, the resolution of bloody stools occurs spontaneously over few weeks, without maternal dietary food elimination[57,58].

FPE. Manifestation of FPE usually takes place in the first several months of life, with protracted diarrhoea, vomiting, failure to thrive, malabsorption, anaemia (40%) and/or protein loss. Cow's milk is the most frequent cause of FPE, but other causes include soy, egg, wheat, rice, chicken and fish. In contrast to coeliac disease, wheat-FPE is mostly not a life-long condition and autoantibodies specific for coeliac disease are negative. Additionally, wheat-FPE can be associated with allergies to other foods.

Other gastrointestinal disorders

Food allergy can contribute to the dysmotility underlying the pathophysiology of GERD (especially in the infants with severe and persistent regurgitations, food aversions, failure to thrive and atopic dermatitis), infantile colic, IBS and constipation in a subset of patients. The exact pathomechanism of dysmotility induced by food allergens remains poorly understood[59–61]. A direct interaction between the enteric nervous system and inflammatory cells (such as mast cells and eosinophils) and pro-inflammatory cytokine secretion is possible[62–67]. Stimulation of afferent nerve circuits via the brainstem during allergic reaction might influence sphincter tone and trigger gastrointestinal symptoms[68]. Large and well-designed studies are needed for a better understanding of the role of food proteins and to delineate the immunological mechanisms at work in these disorders.

Diagnosis of food allergy

Diagnosis of food allergy is based on clinical features, physical examination and the results of supportive laboratory tests[1–3] (FIG. 2). The initial assessment should include details about the specific signs and symptoms, the timing of symptom onset from food ingestion, and the presence of potential co-factors that might increase reaction severity (such as exercise, alcohol, NSAIDs or histamine H2 receptor blockers). Medical history and physical examination guide the selection of the laboratory tests. History can be useful in diagnosing food allergy in acute events such as systemic anaphylaxis after isolated ingestion of peanut, but alone should never be used to make a definitive diagnosis, as <50% of reported food-allergic reactions could be verified by double-blinded, placebo-controlled food challenges[1]. In chronic disorders (for example, atopic dermatitis, EoE and non-IgE-mediated gastrointestinal food allergy) the history is often an unreliable indicator of the offending allergen[1]. Although history alone is insufficient, it is critical when combined with other assessments for establishing whether reported symptoms are consistent with an IgE-mediated (for example, urticaria or anaphylaxis within minutes to 1–2 h) or non-IgE-mediated immune mechanism (for example, bloating and abdominal discomfort after drinking milk in a patient who tolerates small amounts of dairy and cheese, suggestive of lactose intolerance). When history suggests that an immune mechanism is unlikely, testing for food allergy is discouraged because it could yield false-positive results, lead to unnecessary dietary restrictions and delay accurate diagnosis. The differential diagnosis of food allergy is extensive, as summarized in TABLES 2 & 3.

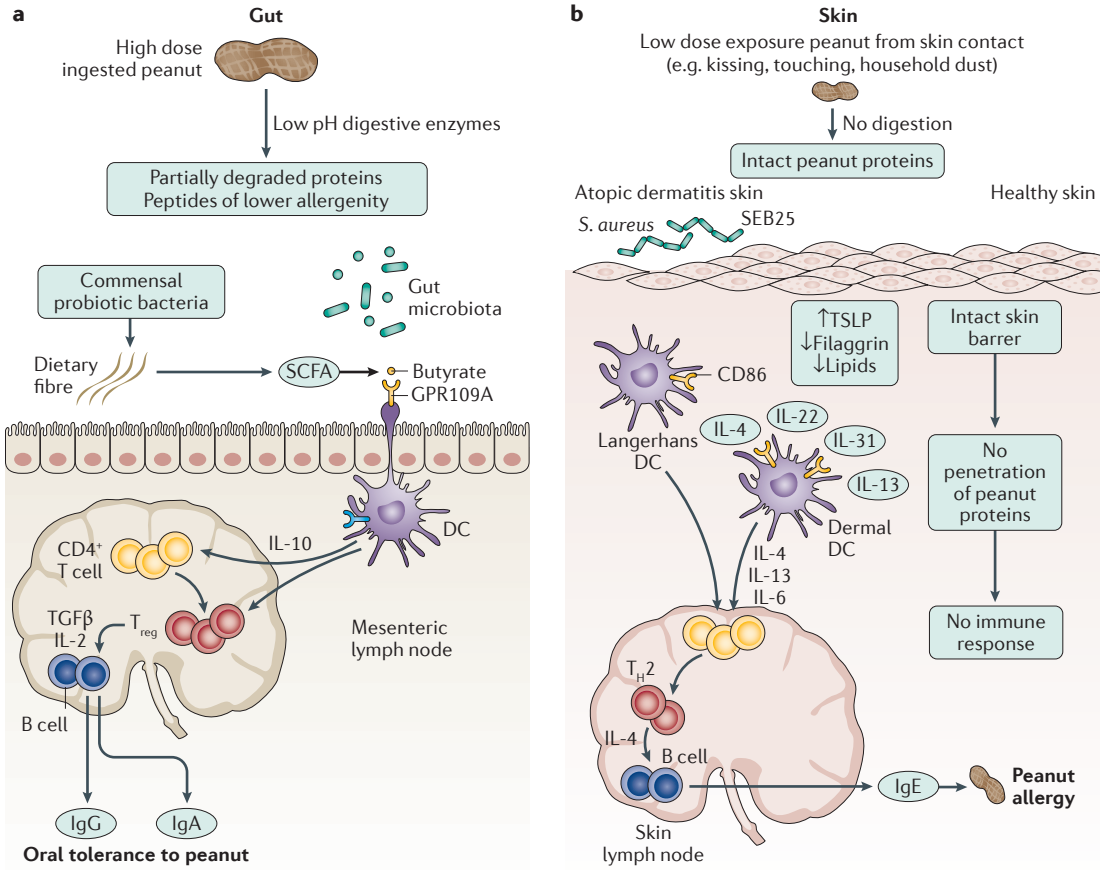

Figure 1 | **Differential immune responses in the gut (oral tolerance) and skin (IgE sensitization and food allergy) using peanut allergy as an example.** Oral ingestion of peanut has an increased likelihood of inducing oral tolerance in the majority of children at a high-risk of peanut allergy with atopic dermatitis, compared with epicutaneous exposure to peanut protein in children with atopic dermatitis and impaired skin barrier, which has an increased likelihood of allergic IgE sensitization. **a** | In the induction of oral tolerance, dietary fibre is digested by probiotic bacteria to release short-chain fatty acids (SCFA; for example butyrate, which acts via GPR109A) that then stimulate dendritic cells (DC) to produce IL-10 and to induce regulatory T cells (T_{reg}). **b** | Conversely, *S. aureus* and its toxins (for example, staphylococcal enterotoxin B; SEB25) can lead to inflammation by inducing T-cell-independent expansion of B cells, which initiates the production of thymic stromal lymphopoietin (TSLP) from keratinocytes, and stimulates mast cell degranulation, resulting in type 2 T helper cell (T_H2) skewing. *S. aureus* also disrupts proteolytic balance in the skin by inducing multiple metalloproteases in dermal fibroblasts. DCs secrete IL-4, IL-13 and IL-6 that stimulate generation of T_H2 skewed effector T cells. T_H2 $CD4^+$ T cells secrete IL-4 that induces IgE production by B cells. Failure to develop oral tolerance can be influenced by lack of ingestion of regular doses of peanut, combined with intermittent exposure to trace amounts in the diet, inflammation in the gastrointestinal tract, high gastric pH, low levels of digestive enzymes, gut dysbiosis and increased intestinal permeability or immune defects resulting in deficiency of FOXP3 (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; see BOX 1) or IgA (selective IgA deficiency, common variable deficiency). TGFβ, transforming growth factor β.

Diet diaries can be used as an adjunct to history; patients keep a chronological record of all foods ingested and any symptoms experienced over a specified period. Diet diaries should be recorded prospectively to minimize recall bias and provide very detailed information about foods eaten (such as amount, specific foods and food brands) and temporal association with symptoms. Additionally, elimination diets are commonly used in the diagnosis of food allergy. Suspected foods are completely eliminated from the diet for ~2 weeks in atopic dermatitis and up to 4–8 weeks in EoE and chronic non-IgE-mediated gastrointestinal food allergy[1–3]. The resolution of symptoms with an elimination diet supports the diagnosis of food allergy; however, elimination of cow's milk and dairy products will also improve symptoms of primary and secondary lactose intolerance. Although avoidance of suspected food allergens is recommended before oral food challenge, results from elimination diets alone are rarely diagnostic of food allergy, especially in chronic disorders such as atopic dermatitis, EoE and non-IgE-mediated gastrointestinal food allergy. A trial of diagnostic elimination diet that resulted in resolution or improvement of symptoms should be followed by a rechallenge. In IgE-mediated food allergy and in FPIES, the oral food challenge should be conducted under physician supervision owing to risks of a severe reaction. Double-blinded, placebo-controlled food challenge remains the gold

standard in the diagnosis of IgE-mediated food allergy; however, open oral food challenge is considered a useful screening tool. A positive oral food challenge with mild objective or subjective symptoms should be confirmed by a double-blinded, placebo-controlled food challenge. In non-IgE mediated gastrointestinal food allergy, such as EoE, FPIAP or FPE, challenge to the suspected food can be done at home and symptoms recorded with a symptom diary.

Laboratory tests for food allergy

Diagnosis of IgE-mediated food allergy. Skin-prick tests are an inexpensive, reproducible method that can be used to screen patients for IgE-mediated food allergy[69]. Glycerinated food extracts and appropriate positive histamine and negative saline controls are applied by the prick or puncture technique. Results are available within 10–15 min. A positive skin-prick test (indicated by wheal and flare) indicates the

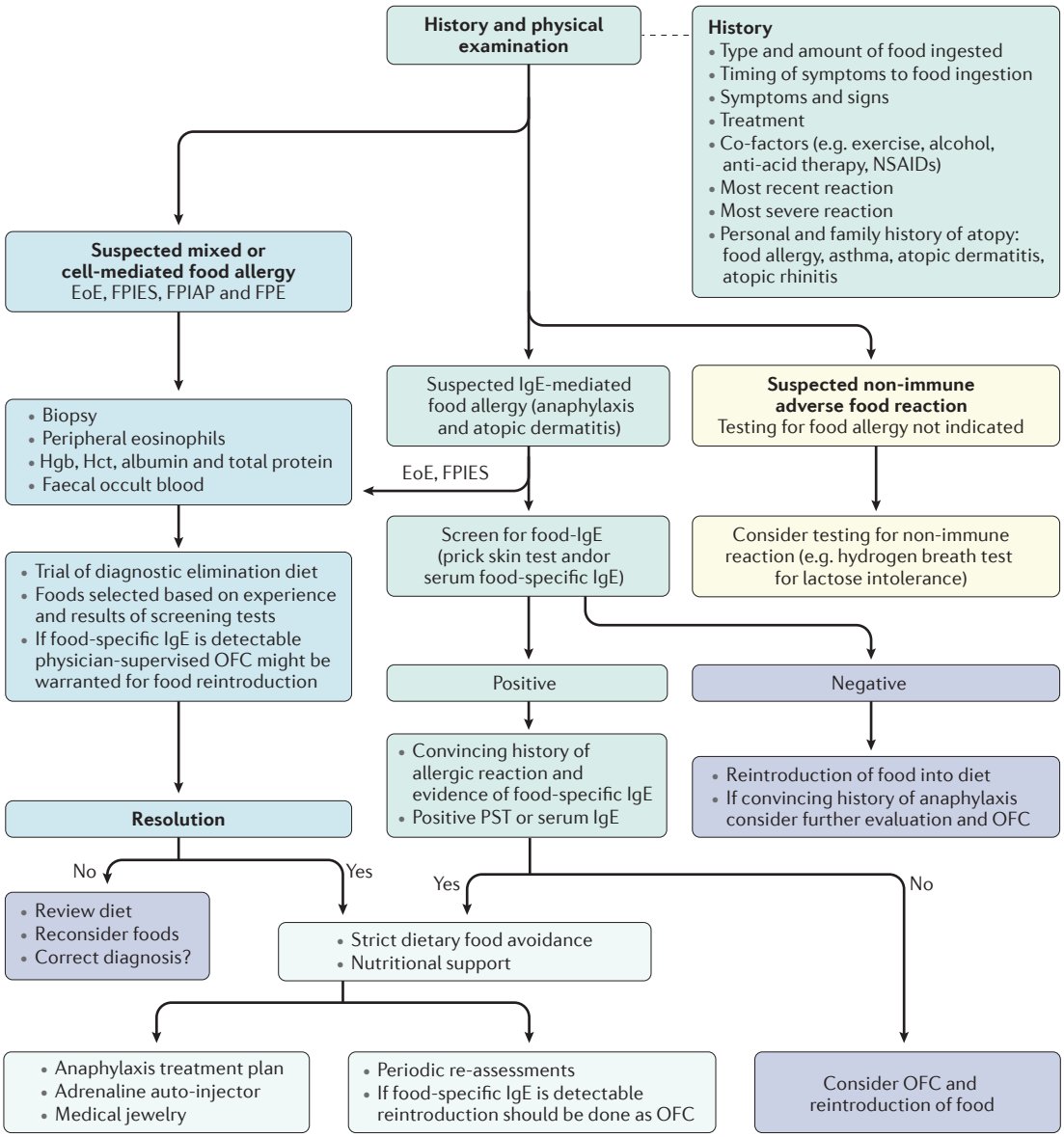

Figure 2 | **Approach to diagnosis and management of food allergy.** In eosinophilic oesophagitis (EoE) and food protein-induced enterocolitis syndrome (FPIES) food-specific IgE can be detectable in a subset of patients. In EoE, patients with detectable food-specific IgE could be at risk of immediate, anaphylactic-type reactions to foods upon reintroduction following a period of elimination. Consequently, evaluation of food-specific IgE is recommended before food reintroduction in EoE; if positive, supervised oral food challenge (OFC) might be warranted; if negative, food reintroduction can be done at home. In FPIES, especially as a result of cow's milk, ~25% of patients develop detectable cow's-milk-specific IgE (a condition known as atypical FPIES) over time. Of these patients, ~1 in 3 can progress to immediate-type symptoms, including anaphylaxis. In FPIES, the offending food reintroduction should be done during a supervised OFC (not at home) regardless of IgE positivity, owing to the risk of severe reactions with hypotension. When food-specific IgE is detected, OFC protocol is modified to account for the possibility of anaphylaxis. FPE, food protein-induced enteropathy; FPIAP, food protein-induced allergic proctocolitis; Hct, haematocrit; Hgb, haemoglobin; PST, prick skin test.

Table 2 | **Differential diagnosis of food allergy**

Condition	Pathomechanism	Symptoms
Enzyme deficiencies		
Lactose intolerance	Lactase deficiency can be primary (congenital and hypolactasia) or secondary (coeliac disease, infectious enteritis, radiation, graft versus host disease or enteropathy resulting from other causes)	Bloating, abdominal pain, diarrhoea (dose-dependent) and borborygmi
Hereditary fructose intolerance	Hereditary deficiency of fructose aldolase B; uncommon	Emesis, poor feeding, hypoglycaemia, seizures, jaundice and chronic liver disease with hepatomegaly
Sucrase-isomaltase deficiency	• Sucrase-isomaltase deficiency • Can be congenital, resulting from genetic mutations: both parents must carry the mutated gene for the child to have the disease	The majority of infants present in the first year of life with severe diarrhoea, abdominal bloating, perianal excoriation and growth failure after the introduction of sucrose and starch-containing foods
Alcohol intolerance	• Polymorphism of the gene encoding aldehyde dehydrogenase causing deficiency of the enzyme, which metabolizes alcohol in the liver • Common in people of Asian descent	Nasal congestion, flushing and vomiting within minutes of ingesting alcohol
Exocrine pancreatic insufficiency	Deficiency of pancreatic enzymes, which can be acquired or congenital (such as in cystic fibrosis and Shwachman–Diamond syndrome)	• Diarrhoea and/or steatorrhoea with weight loss and/or growth failure • Other symptoms can be caused by deficiencies in fat-soluble vitamins
Chronic liver disease or cholestasis	Deficiency of bile acids	• Diarrhoea and/or steatorrhoea with weight loss and/or growth failure • Other symptoms can be caused by deficiencies in fat-soluble vitamins
Gastrointestinal disorders		
Very-early-onset IBD	• 25% of patients have underlying immunodeficiency • Can be caused by mutations in *IL10*, *IL10R*, *NCF2*, *XIAP*, *LRBA* or *TTC7*	• Increased probability of manifestation as colitis compared with patients with late-onset IBD, with blood and mucus in the stool • Onset younger than 6 years; infantile IBD-onset younger than 2 years • Patients frequently resistant to IBD therapies • Associated with a very strong family history of IBD (at least one 1st degree family member with IBD)
Fructose malabsorption	• Deficiency of fructose carrier GLUT5 in the small intestine enterocytes • Prevalence 10% in Asia, up to 30% in Western Europe and Africa	Bloating, abdominal pain, diarrhoea (dose-dependent)
GERD	Symptoms related to erosive or nonerosive oesophagitis by acid GERD	Nausea, emesis, heartburn, refusal to feed, acid regurgitation, dysphagia and failure to thrive
Peptic ulcer disease	Ulcer of the gastrointestinal tract (commonly duodenum)	Abdominal pain, anorexia, nausea, weight loss and melaena
Pylorus hypertrophy	Hypertrophy of the pylorus muscle	Severe, projectile non-bilious vomiting in the first 3 months of life; rare case reports described eosinophilic infiltrates in pylorus and reported resolution of muscle hypertrophy with hypoallergenic formula or steroids
Hirschsprung disease	Failure of the neural crest cells to migrate completely during fetal development of the intestine resulting in agangliosis, usually affecting the short segment of the distal colon	Delayed passage of meconium, severe constipation and/or inability to pass bowel movement spontaneously (distal obstruction syndrome), ileus, emesis and abdominal distension
Tracheo-oesophageal fistula	• Congenital: failed fusion of the tracheosophageal ridges during the third week of embryological development • Acquired: a surgical complication for example, laryngectomy	Prominent salivation, choking, coughing, vomiting, and cyanosis associated with the onset of feeding in newborn babies and young infants, recurrent pneumonia, if not recognized and treated
Gastrointestinal infections		
Viral, bacterial or parasitic enteritis	Virus (for example, norovirus, rotavirus, enteric adenovirus), bacteria (for example, *Salmonella* spp, Campylobacter spp, Shigella spp, Yersinia spp), or parasites (for example, Giardia intestinalis, *Cryptosporidium parvum*)	Pain, fever, nausea, emesis and diarrhoea
Neurologic disorders		
Gustatory rhinitis	Neurogenic reflex	Profuse watery rhinorrhoea associated with spicy foods
Frey syndrome (auriculo-temporal syndrome)	Neurogenic reflex, can be associated with traumatic delivery and injury to trigeminal nerve (for example, forceps delivery)	Facial flush in trigeminal nerve distribution associated with spicy foods

Table 2 (cont.) | **Differential diagnosis of food allergy**

Condition	Pathomechanism	Symptoms
Psychiatric disorders		
Panic disorder	An anxiety disorder in children and adults; usually leads to extensive medical testing; can be controlled with medication	Subjective reactions, fainting upon smelling or seeing the food, tachycardia, perspiration, dyspnoea, shivers and uncontrollable fear (fear of dying)
Anorexia nervosa	Psychiatric disorder, predominantly affecting young women (age 20–40 years)	Extreme dietary restrictions, distorted body image, untreated can lead to death owing to electrolyte abnormalities and bradycardia
Bulimia	Psychiatric disorder	Binge eating followed by vomiting, weight fluctuations, enamel erosions

possibility of a symptomatic IgE-mediated food allergy, whereas negative results confirm the absence of IgE-mediated food allergy (negative predictive accuracy ≥95%) if good-quality food extracts are used from a reliable source[1–3]. In oral allergy syndrome, fresh foods can be used. The skin-prick test can be an excellent means of excluding IgE-mediated food allergy but it can only suggest the presence of clinical food allergy. The skin-prick test is of limited or no utility in EoE and other cell-mediated food allergic disorders[1].

Intradermal skin testing is a more sensitive and less specific diagnostic method than the skin-prick test, but increases the risk of a systemic reaction compared with skin-prick testing; therefore, this test is not recommended for diagnosis of food allergy[1]. Atopy patch tests have also been evaluated for the diagnosis of food allergic disorders with proven or suspected T cell involvement, such as atopic dermatitis, EoE or FPIES, with conflicting results. However, the lack of standardized reagents limits the utility of this approach; therefore, atopy patch tests are not recommended for routine diagnosis of food allergy[1,2].

The quantitative measurement of serum food-specific IgE antibodies (using an enzyme immunoassay) is more predictive of symptomatic IgE-mediated food allergy than other methods[1,3]. Food-specific IgE levels exceeding the diagnostic values indicate >95% likelihood of an allergic reaction following food ingestion: for example, serum peanut-IgE levels >14 kU_A/l (allergen-specific units of IgE per litre)[70]. Food-specific IgE levels can be monitored, and if they fall to serum levels <2 kU_A/l for egg, milk, or peanut, patients without severe reactions in the past 1–2 years should be rechallenged to evaluate for resolution of IgE-mediated food allergy[71].

Molecular diagnosis is based on purified individual natural or recombinant allergens and potentially offers superior specificity owing to the purity of the allergens compared with whole food extracts. Molecular diagnosis is particularly useful in diagnosis of peanut and hazelnut allergy in patients with birch pollen allergy, as these nuts are the most studied and are cross-reactive with birch pollen. Patients with IgE antibodies directed exclusively against birch Bet v 1 cross-reactive allergens in peanut (Ara h 8) and hazelnut (Cor a 1) are at low risk of systemic reaction to peanut and hazelnut[1–3]. Many individuals can ingest these nuts without any allergic symptoms and consequently such patients are excellent candidates for supervised oral food challenge. By contrast, patients with IgE directed against Ara h 2 or Cor a 9 and/or 14 are at high risk of systemic reactions[72]. Basophil activation tests rely on detection of the expression of surface markers (CD63) on basophils during degranulation in an allergic reaction, measured by flow cytometry. In one study, basophil activation was more accurate than food-specific IgE detection for diagnosis of symptomatic peanut allergy in children[73].

Diagnosis of mixed or non-IgE mediated food allergy. No reliable laboratory tests exist for mixed and non-IgE-mediated food allergy, as food-specific IgE are either not detected or, as in the case of EoE, have poor diagnostic accuracy in identifying the triggering foods. Peripheral blood eosinophilia, increased intestinal permeability, faecal presence of eosinophil-derived neurotoxin, presence of faecal reducing substances or presence of blood, mucus and/or leukocytes in stool smear support the diagnosis of food allergy but are non-specific and can be present in many other diseases. Diagnosis of EoE is based on a constellation of clinical symptoms and supporting findings on endoscopy and in biopsy samples. Endoscopy can show white specks (eosinophilic exudates), linear furrows, mucosal oedema, oesophageal rings and strictures. With few exceptions, 15 eosinophils per high-power field (peak value) in one biopsy specimen are considered a minimum threshold for a diagnosis of EoE[40,74,75]. Patients with suspected EoE should be treated with high-dose PPIs for 8 weeks to exclude GERD or PPI-responsive oesophageal eosinophilia, with the responses assessed clinically and by repeat biopsy[40,76]. A trial of a diagnostic elimination diet followed by an oral food challenge is utilized to identify the offending foods in EoE and other cell-mediated food allergy[1,2,77] (FIG. 2).

In FPIES, after an acute reaction, a prominent increase in the number of peripheral blood neutrophils occurs, peaking at 4–6 h from the onset of symptoms[78,79]. Stools often contain occult blood, neutrophils, eosinophils and Charcot–Leyden crystals. Skin-prick test results for the suspected foods are usually negative, but a small subset of patients can develop IgE sensitization to the FPIES food (known as atypical FPIES), which is associated with a protracted reaction course.

Diagnosis can be established when elimination of the responsible allergen leads to resolution of vomiting within several hours (although diarrhoea can persist up to 72 h) and oral food challenge induces symptoms of repetitive vomiting within 1–4 h. Because ~50% of oral food challenges lead to profuse vomiting, dehydration

and hypotension, these tests must be performed under medical supervision[1]. FPIES is a clinical diagnosis that is based on a constellation of symptoms, and oral food challenges are usually not necessary for an initial diagnosis of FPIES in infants with repeated reactions to the same food, episodes of hypotension and resolution of symptoms with food elimination. Oral food challenges are routinely performed to monitor for resolution of FPIES, usually at 12–18 month intervals[1].

The diagnosis of FPIAP can be established when food elimination leads to resolution of gross blood or haematochezia, usually with dramatic improvement observed within 72 h; complete clearance and resolution of mucosal lesions can take up to 1 month. Reintroduction of the allergen leads to recurrence of symptoms within several hours to days. Lesions are usually confined to the distal large bowel. Cow's milk and soy FPIAP usually resolve within 6 months to 2 years of allergen avoidance, but occasional refractory cases exist[39].

Diagnosis of FPE requires the identification and elimination of the responsible allergen from the diet, with resolution of symptoms within days to weeks. On endoscopy, a patchy villous atrophy is found; biopsy samples exhibit a prominent mononuclear cell infiltrate and a small number of eosinophils in the lamina propria, which are similar to, but less extensive than, those observed in coeliac disease[80].

Histological improvement usually occurs within 4–6 weeks of allergen avoidance, but complete resolution of the intestinal lesions can require 6–18 months in a subset of patients[81]. Unlike coeliac disease, loss of clinical reactivity frequently occurs in FPE, but the natural history of this disorder has not been well studied[39].

Unproven diagnostic tests. No controlled trials currently support the diagnostic value of current commercially marketed tests for food-specific IgG or IgG_4 antibody levels, food antigen–antibody complexes, evidence of lymphocyte activation (for example, uptake of 3H-tagged food protein, IL-2 production or leukocyte inhibitory factor production), or sublingual or intracutaneous provocation in IgE-mediated and non-IgE-mediated food allergy[1,2]. Use of the IgG and IgG_4-based tests, for example, could result in considerable overdiagnosis of allergy, as they mostly reflect exposure to a given food in the diet.

Management

Management of IgE-mediated food allergy relies on dietary avoidance, prompt recognition and treatment of acute reactions, attention to the nutritional risks of elimination diets and potential feeding difficulties in infants[1–3,77]. In mixed and non-IgE-mediated food allergy, empirical dietary elimination is common

Table 3 | **Physiological effects of the active substances in foods**

Substance	Source	Symptoms
Tyramine	A natural monoamine derived from tyrosine that acts as a catecholamine-releasing agent; found in pickled, aged, smoked, fermented or marinated foods; e.g. tofu, sauerkraut, hard cheeses and fava beans	Migraine
Histamine	• Naturally occurring in fermented foods and beverages; e.g. fish and sauerkraut owing to a conversion from histidine to histamine performed by fermenting bacteria or yeasts • Sake contains histamine in the 20–40 mg/l range; wines contain it in the 2–10 mg/l range	Flushing, headache and nausea
Serotonin	• A neurotransmitter derived from tryptophan found in nuts, mushrooms, fruits and vegetables • The highest values of 25–400 mg/kg have been found in nuts of the walnut and hickory genera • Concentrations of 3–30 mg/kg have been found in plantain, pineapple, banana, kiwi, plums and tomatoes	Flushing, palpitations, diarrhoea
Theobromine	Bitter alkaloid in cocoa bean and tea leaves	Anxiety, tremors, restlessness, sleeplessness, increased urination, loss of appetite, nausea and vomiting
Caffeine	• Xanthine alkaloid (natural pesticide in plants) that acts as a stimulant drug • Found in coffee, tea and drinks containing products derived from the kola nut, yerba mate, guarana berries and guayusa	Tremors, cramps and diarrhoea
Sodium metabisulfite	Antioxidant and preservative in food, E223	Rare reports of bronchospasm in sensitive individuals
Monosodium glutamate (MSG)	Naturally occurring non-essential amino acid, flavour enhancer; double-blinded, placebo-controlled food challenges confirmed objective reactions to MSG in 2 of 130 (1.65%) self-reported MSG-reactive adults	• So-called Chinese restaurant syndrome begins 15–20 minutes after the meal and lasts ~2 h • Symptoms: numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and palpitations

Table 4 | **Management of food allergy**

Disorder	Dietary food allergen avoidance	Emergency management of acute reactions	Comments
IgE-mediated food allergy			
Anaphylaxis	• Strict dietary avoidance, as well as avoidance of skin or mucosal contact (e.g. kissing) and inhalation (e.g. steaming milk or boiling fish) exposures • Annual allergy re-testing and periodic oral food challenges are recommended to evaluate for resolution	• Educate patients on how to recognize and treat anaphylaxis • Provide written emergency treatment plan • Prescribe adrenaline auto-injector device	Dietitian consultation recommended for patients with anaphylaxis to trace amounts of foods or multiple food allergy
Milder forms of systemic immediate milk and egg allergy[115]	• Majority of children with milder cow's milk and egg allergy tolerate extensively heated (baked) products with cow's milk and egg • Baked cow's milk and egg diet seems to accelerate development of tolerance to regular non-baked cow's milk and egg • Annual allergy re-testing and periodic oral food challenges are recommended to evaluate for resolution	• Educate patients on how to recognize and treat anaphylaxis • Provide written emergency treatment plan • Prescribe adrenaline auto-injector device	Children reactive to baked cow's milk have higher risk of anaphylaxis and more persistent cow's milk allergy than individuals tolerant of baked cow's milk
Food-dependent, exercise-induced anaphylaxis	Avoid exercise for 2–4 h after ingestion of the offending food	• Educate patients how to recognize and treat anaphylaxis and not exercise alone • Provide written emergency treatment plan • Prescribe adrenalin auto-injector device	• In some patients ingestion of any food can trigger allergic reactions if followed by exercise • Exercise transiently increases intestinal permeability and inflammation • Natural history is unknown
OAS	• Strictness of avoidance of the triggering raw food depends on the severity of the objective symptoms • Strict avoidance is recommended for patients reporting throat discomfort or worsening symptoms • Patients with mild oral symptoms can eat raw foods as tolerated • Baked, cooked, microwaved or pasteurized foods are usually well tolerated	Prescribe adrenaline auto-injector device for patients with pharyngeal swelling and discomfort	• OAS usually develops following major pollen allergy to raw plant foods that have been previously well tolerated • Pollen immunotherapy can improve OAS symptoms in some patients • Severity of OAS fluctuates and usually increases during or following pollen season
Mixed pathophysiology gastrointestinal food allergic disorders			
Eosinophilic oesophagitis*	• Elemental (amino-acid-based formula) or oligoallergenic diet can be used with strict avoidance of all forms of the eliminated foods • A subset of patients can tolerate baked milk • With regular ingestion of food allergens, acute symptoms are uncommon but following several weeks of food avoidance, anaphylactic reactions can ensue in patients with IgE-sensitization to foods; therefore, reintroduction of the suspected foods should be done under physician supervision	For patients with evidence of IgE-sensitization to foods and with risk factors for anaphylaxis: educate how to recognize and treat anaphylaxis, provide a written emergency treatment plan and prescribe an adrenaline auto-injector device	• Long-term adherence to diet is suboptimal • Dietitian consultation is recommended for all patients to educate about the principles of food avoidance and to compose a nutritionally adequate and tasty elimination diet
Eosinophilic gastroenteritis	• Rare published reports of avoidance of cow's milk or elemental diet • Improvement with elimination diet within 6–8 weeks	For patients with evidence of IgE sensitization to foods and risk factors for anaphylaxis: educate how to recognize and treat anaphylaxis, provide a written emergency treatment plan and prescribe an adrenaline auto-injector device	• Long-term adherence to diet is suboptimal • Dietitian consultation is recommended for all patients to educate about the principles of food avoidance and to compose a nutritionally adequate and tasty elimination diet • Most effective treatment is oral steroids
Cell-mediated disorders			
FPIES	• Majority of patients react to a single food, usually cow's milk, soy or rice • Strict avoidance of the offending food in the patient diet is recommended • Breastfeeding infants are usually asymptomatic and maternal dietary restrictions are not indicated unless acute of chronic symptoms occur • Periodic oral food challenges are recommended to evaluate for resolution • In cow's milk FPIES, testing for cow's milk IgE is recommended; ~25% develop cow's milk IgE positivity over time and of those, 33% can shift to immediate IgE cow's milk allergy	• Provide emergency treatment plan in writing emphasizing intravenous rehydration in severe reactions; in milder reactions oral rehydration can suffice • Intravenous or intramuscular ondansetron can be useful to manage vomiting • A single dose of intravenous methylprednisolone can be used	• Children with multiple food FPIES or those exclusively breastfed are at risk of deficiencies of calories, vitamin D and iron • Delayed introduction of solids is a risk factor for food refusal and feeding difficulties

Table 4 (cont.) | **Management of food allergy**

Disorder	Dietary food allergen avoidance	Emergency management of acute reactions	Comments
Cell-mediated disorders (cont.)			
Food-protein-induced allergic proctocolitis	Usually strict avoidance of cow's milk and soy formula or proteins in maternal breast milk is necessary for symptom resolution	No risk of acute reactions	Natural history is favourable, resolution occurs by age 1–2 years; reintroduction of the offending food is done gradually at home
Food-protein-induced enteropathy	Strict avoidance of the offending foods, usually cow's milk, soy wheat, egg	No risk of acute reactions	Natural history is favourable, resolution occurs by age 2–3 years; reintroduction of the offending food is done gradually at home

*Management of eosinophilic oesophagitis is discussed in more detail in TABLE 5. FPIES, food protein-induced enterocolitis syndrome; OAS, oral allergy syndrome.

as no reliable *in vitro* testing is currently available. For diagnostic purposes, this dietary elimination must be strict to draw correct conclusions. In children, nutritional management by an experienced dietitian and close monitoring of growth parameters are essential. The principles of food allergy management are presented in TABLE 4.

Management of EoE includes elimination diet (with targeted, empiric or amino-acid-based formula), medications and dilatation[41,82] (TABLE 5). Although EoE is driven by food allergens, implementation of amino-acid-based formula is limited by its high cost, poor adherence by patients to hypoallergenic formulas (owing to bitter taste) and negative effects on quality of life (if a patient is unable to eat normal foods and must drink hypoallergenic formulas). Pollen exposure in the sensitized individuals can trigger seasonal EoE flares. Food elimination can shift the chronic food allergy phenotype to anaphylaxis in patients with food IgE sensitization; allergy evaluation and supervised oral food challenge can be necessary prior to food reintroduction[1]. A number of cases reported resolution of eosinophilic gastroenteritis with empirical milk elimination; a limited trial of amino-acid-based or elimination diet can also be considered, but oral corticosteroids are considered the mainstay of therapy[83,84].

Natural history

Natural history of food allergy varies by food, age of onset and pathophysiology. Infantile IgE-mediated food allergy to cow's milk, egg, soy and wheat usually resolves by school age; peak food-specific, lifetime serum IgE antibody concentrations exceeding 50 kUA/l are associated with the persistence of food allergy into adolescence[8]. Allergy to peanut, tree nuts and seafood tends to be lifelong. EoE is a chronic relapsing disease, but infantile forms of EoE can have a more favourable prognosis. Regarding non-IgE gastrointestinal food allergy, resolution of FPIAP usually occurs by age 12 months, and FPE by age 1–3 years. FPIES usually resolves be age 3–5 years; however, development of IgE to the offending food is associated with a protracted allergy course[39]. The natural history of adult-onset food allergy is not well known, which is due in part to the lower frequency of food allergy in adults compared with infantile food allergy.

Prevention

Infants with at least one first degree relative (parent or sibling) with an atopic condition are considered at risk of atopy. In infants who are at risk and who cannot be exclusively breastfed during the first 4–6 months of life, hypoallergenic formulas (such as extensively hydrolyzed casein and partially or extensively hydrolyzed whey) were shown to protect against development of atopic dermatitis at 1, 6, 10 and 15 years, compared with conventional cow's milk formula[85–88]. A meta-analysis published in 2016 questioned the use of hydrolyzed formula to prevent allergic disease in infants at a high-risk of atopy[89]. Currently, official guidelines recommend substituting hypoallergenic formulas in infants who are at risk of atopy and who cannot be breastfed[90–92].

Solid foods should be introduced between 4 and 6 months of age, usually starting from oatmeal or rice cereal, fruits and vegetables, followed by gradual introduction of all food groups, without delaying the introduction of so-called high-risk foods such as peanut, egg, milk or wheat[90–92]. The results of a large randomized clinical trial (the Learning Early About Peanut allergy (LEAP) trial) in infants at risk of peanut allergy who have severe atopic dermatitis and/or egg allergy indicate that early introduction of dietary peanut has a strong protective effect against peanut allergy at 60 months in infants with disrupted skin barrier[25,93] (BOX 2). Another large randomized clinical trial (EAT) including an unselected general population suggested that early introduction of peanut and egg (with consumption of at least 2 g per week) into the diet of a breast-fed infant could be protective against IgE-mediated peanut and egg allergy at age 1–3 years[26]. Infants aged 6–12 months who have known IgE-mediated food allergy should be tested for specific IgE to other high-risk foods and, if positive, these foods should be introduced under medical supervision.

Future therapies

No proven therapies currently exist that accelerate the development of oral tolerance or provide reliable protection from accidental exposures[94]. Ongoing active clinical investigations involve food-allergen-specific immunotherapy via oral, sublingual and epicutaneous routes; hypoallergenic vaccines based on the modified major

peanut allergens with and without adjuvants are under preparation[95]. To date, clinical trials have reported high rates (>50%) of desensitization with food oral immunotherapy but no permanent tolerance. Desensitization is a temporary state of an increased threshold for allergic reactions that requires daily intake of the immunotherapy doses. Interruption of dosing, concurrent febrile illness, exercise, dosing on an empty stomach or menstrual period might cause allergic reactions to the previously tolerated doses[96]. Nevertheless, the patients are protected from unintentional exposures. How long and at what dose food immunotherapy should be given to achieve permanent tolerance is currently unclear. Two studies have suggested that long-term daily dosing could be necessary[97,98]. At this time, oral immunotherapy has been most extensively studied; compared with sublingual and epicutaneous immunotherapy, oral immunotherapy seems to have superior efficacy but an inferior safety

Table 5 | **Principles of EoE management**

Intervention	Mechanism	Efficacy	Pros	Cons
Dietary food protein elimination				
Elemental diet	Amino-acid-based formula is not recognizable as antigen by immune system	After 6–8 weeks complete resolution of eosinophilic inflammation in >90% of children and adults[116]	Prompt control of eosinophilic inflammation and no adverse effects	• Utilization of elemental diet is limited by high cost, poor adherence owing to taste and negative effects on QOL • Must be maintained long-term, reintroduction of foods is gradual, repeated endoscopies and biopsies are required • Recommended consultation with a dietitian to assist with reintroduction of foods
Oligoantigenic diet (empiric)	Elimination of the six most common food allergens: cow's milk, wheat, egg, soy, nuts and seafood	Symptomatic and histologic response rate 53–82% in adults and children[49,51,117]	No adverse effects of medical therapies, possible to maintain a satisfying diet	• High cost, risk of nutritional deficiencies, negative effect on QOL • Must be maintained long-term, reintroduction of foods is gradual, repeated endoscopies and biopsies are required • Recommended consultation with a dietitian to assist with proper dietary elimination and designing a nutritious alternative diet
Oligoantigenic diet based on allergy testing and elimination of cow's milk	Allergy evaluation combination of skin prick and patch testing; cow's milk is the single most common food allergen in EoE at all ages	77% histological success[118,119]	No adverse effects of medical therapies, possible to maintain a satisfying diet	• High cost, risk of nutritional deficiencies, negative effect on quality of life • Must be maintained long-term, reintroduction of foods is gradual, repeated endoscopies and biopsies are required • Recommended consultation with a dietitian to assist with proper dietary elimination and designing a nutritious alternative diet
Pharmacotherapy				
Oral corticosteroids	Decreased inflammation and fibrosis through the reduction of inflammatory cells and IL-13 (REF. 120)	Almost 100% symptomatic and histologic improvement within few weeks	Prompt improvement, inexpensive, regular diet is maintained	High relapse rate upon discontinuation of oral corticosteroids, long-term treatment limited by major systemic adverse effects: adrenal axis suppression, Cushing syndrome, immunosuppression, osteoporosis
Topical swallowed corticosteroids such as fluticasone or viscous liquid budesonide	Decreased inflammation and fibrosis through the reduction of inflammatory cells and IL-13 (REF. 120)	• Clinical and histological efficacy of topical swallowed corticosteroids ranges from 53–95% after 2–12 weeks of treatment[121,122] • Topical glucocorticoids can also reduce the frequency of food impactions	Prompt improvement of symptoms, preservation of an unrestricted diet	• Potential adverse effects include local Candida infection, adrenal axis suppression, bone demineralization and diminished growth • Swallowed topical glucocorticoids undergo first-pass metabolism; therefore, such adverse effects are uncommon
PPIs	Decrease in acid secretion; decrease in cytokine secretion from the oesophageal epithelium	Supportive treatment in co-existent GERD and EoE in a subset of patients	Have a role in the diagnostic evaluation of PPI-responsive oesophageal eosinophilia, inexpensive, usually well tolerated	Effective in a smaller subset of patients compared with diet or corticosteroids
Mechanical or surgical approaches				
Oesophageal dilation	Series of endoscopic dilations over multiple sessions to gradually diminish narrowing	Symptomatic relief of luminal narrowing	Immediate relief of oesophageal strictures, food impactions	Requires a series of procedures, does not address the underlying inflammation, risk of oesophageal perforation ~1%, post-procedure chest pain in 75%

EoE, eosinophilic oesophagitis; QOL, quality of life.

Box 2 | **LEAP Study**

Study design and results

- 640 children at high-risk of peanut allergy were enrolled at age 4–11 months
- Each child was randomly assigned to an avoidance group (complete avoidance of peanut-containing foods) or a consumption group (consume a peanut snack three times a week; 6 g of peanut protein per week)
- Among the 530 children in the intention-to-treat population who initially had negative results on the skin-prick test to peanut, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group ($P<0.001$)
- Among the 98 participants in the intention-to-treat population who initially had positive skin prick test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($P=0.004$)

Clinical implications

- Health-care providers should recommend introducing peanut-containing products into the diets of infants at a high-risk of peanut allergy early on in life (4–11 months of age) in countries where peanut allergy is prevalent, because delaying the introduction of peanut can be associated with an increased risk of peanut allergy[93]

LEAP, Learning Early About Peanut allergy (www.leapstudy.co.uk)[25].

profile. Although severe anaphylactic reactions during oral immunotherapy are uncommon (usually <0.01% of oral immunotherapy doses), mild symptoms are frequent and chronic gastrointestinal manifestations such as abdominal pain, vomiting and diarrhoea are associated with up to 30% of the doses and are the most common reason for discontinuation of oral immunotherapy. EoE has been reported in up to 2% of patients treated with food oral immunotherapy[99]. Oral immunotherapy can be combined with monoclonal anti-IgE antibody to improve safety of the dose escalation phase[100,101]. Multi-food oral immunotherapy has a similar safety profile to single food oral immunotherapy[102]. A randomized clinical trial suggested that co-administration of probiotic (*Lactobacillus rhamnosus* GG, LGG) and peanut oral immunotherapy could enhance development of sustained unresponsiveness; however, the trial did not include placebo arm for peanut oral immunotherapy[103]. Children with cow's milk allergies fed with extensively hydrolyzed casein formula containing LGG had increased rates of cow's milk tolerance acquisition at 12 months, compared with extensively hydrolyzed casein formula without LGG, soy formula, hydrolyzed rice formula or amino-acid formula[104]. LGG-supplemented formula expanded butyrate-producing bacterial strains in cow's milk-allergic infants[21]. These results suggest that targeting gut microbiota could be an effective strategy for treatment of food allergy. However, at present these data have only been shown in patients from Italy and should be confirmed in different patient populations.

Conclusions

The gut serves as a major portal of entry for food allergens. Food allergy develops when oral tolerance, the dominant physiological immune response to ingested food allergens, is not acquired or is breached. Early introduction of peanut is protective against peanut sensitization via disrupted skin barrier in infants at a high-risk for peanut allergy with severe atopic dermatitis or egg allergy. Early introduction of peanut and egg into the diet of breast-fed infants from the beginning of the fifth month of age could have a protective effect against IgE-mediated peanut and egg allergy. Childhood food allergy generally has a favourable prognosis, whereas natural history in adults is largely unknown. Elimination of the offending foods is the current standard of care; however, future therapies for IgE-mediated food allergy focus on gradual reintroduction of foods via specific food immunotherapy. Further research is needed to elucidate the pathophysiology of various IgE and non-IgE food allergic disorders to develop specific non-invasive biomarkers for initial diagnosis and monitoring for resolution. The role of gut microbiota and strategies for modification of gut microbiota in food allergy require assessment.

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