Chapter 17
Food Allergy and Intolerance: Diagnosis and Nutritional Management

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Key Points

- Food hypersensitivity is categorized as reactions that are either immune-mediated (food allergy) or nonimmune-mediated (food intolerances).
- Diagnosis of food allergy consists of clinical history combined with diagnostic testing (through skin prick testing or serum-specific immunoglobulin E [IgE] testing) or oral food challenge.
- Nutritional management of food allergy involves avoidance of exposure to the allergen and establishing through oral food challenges (OFC) whether baked forms of the allergen are tolerated.
- Food intolerance is diagnosed with an elimination diet and OFC.
- Treatment of food intolerance does not usually require complete avoidance, but determining lower amounts that can be tolerated.

Keywords Food allergy • Food intolerance • Non-allergic hypersensitivity • IgE tests • Oral food challenge • Elimination diet

Introduction

Adverse reactions to food may develop at any age and to any food [1]. They are classified as non-toxic (food hypersensitivity [FHS]), toxic (e.g., food poisoning), or psychologically based (food aversion) [1]. This chapter focuses on non-toxic FHS, which include FHS causing an immune response (food allergy; FA) and FHS where the immune system is not involved (food intolerance or non-allergic food hypersensitivity) (Fig. 17.1) [1–4].

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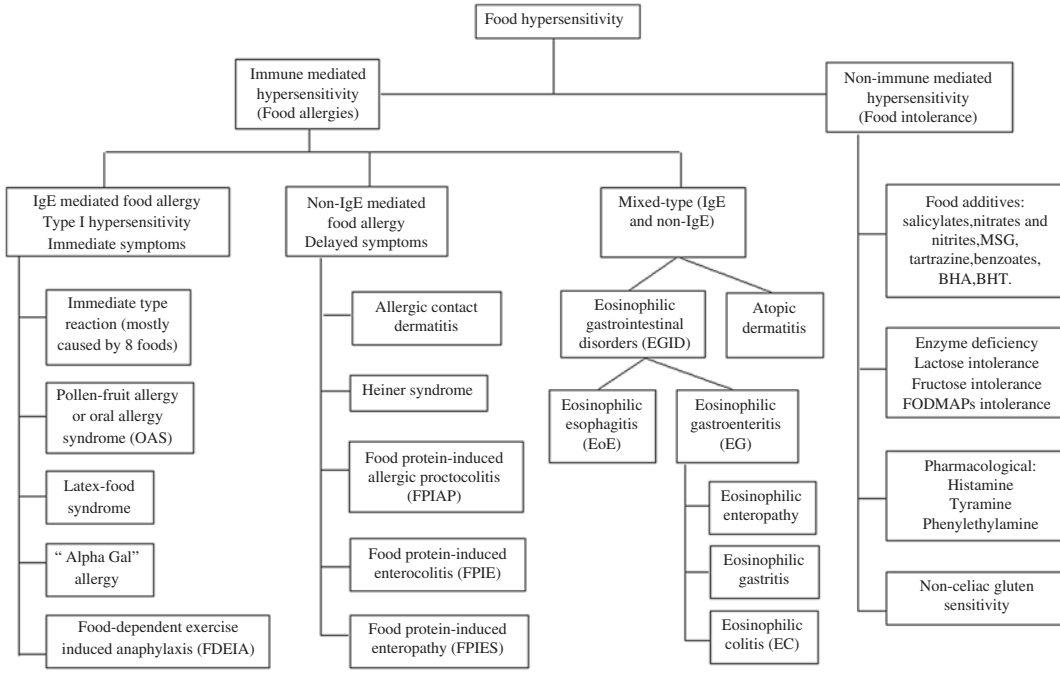

Fig. 17.1 Classification of food allergy and intolerances

The prevalence of FA and food intolerances has substantially increased over the past two decades and are a growing public health concern worldwide. In the United States (US), the prevalence of FA almost doubled in children from 1997 to 2011 [5]. It is estimated that 8% of children and 4% of adults in the US have FA [5]. The prevalence of FA in pre-school children in developed countries is estimated to be around 10% [6], while the prevalence of food intolerance ranges between 15% and 20% [7].

While elimination diets of causative food can be successful in managing these conditions, it can be cumbersome and lead to unnecessary food avoidance and nutritional inadequacies. It is important that the physician identifies these conditions in primary care, follows correct diagnostic procedures, and refers the patient to a dietitian or allergy specialist when necessary.

Food Allergy

FA develop due to an adverse immune response towards one or more proteins or other molecules (allergens) in food and are classified based on the underlying immunology as immunoglobulin E (IgE)-mediated, non-IgE-mediated, or mixed type (overlap between IgE and non-IgE mechanisms) [1, 2]. The distinct symptoms of each are illustrated in Table 17.1. The symptoms may range from mild to severe and involve one or several organ systems [2].

Table 17.1 Symptoms and diagnosis of food allergies and intolerance

IgE	Non-IgE and mixed-type	Food intolerance
Symptom onset		
• Rapid within minutes to 2 h of ingestion • Acute reactions • Can result in multi-system manifestations • Symptoms recur every time when exposed to food • Severity of symptoms may change over time	Immediate to delayed onset (see Tables 17.2 and 17.3)	• Delayed onset • Prolonged symptomatic phase • Symptoms often dependent on dose of causative food, with small doses being tolerated
Symptoms		
Dermatological symptoms Urticaria/hives, flushing, angioedema, pruritus, atopic dermatitis, exacerbation of existing eczema *Oral and orbital* Itching of mouth, tongue, lips Swelling of lips/tongue Eye itching, redness and watering Periorbital edema *Gastrointestinal symptoms* Throat discomfort, reflux, nausea, vomiting, abdominal cramps, diarrhea *Respiratory symptoms* Nasal itching, rhinorrhea and nasal obstruction, sneezing, laryngospasm, cough, chest tightness, dyspnea, wheezing, asthma *Systemic* Hypotension, arrhythmia, vascular collapse *Oral allergy syndrome* Mild symptoms affecting lip, mouth and throat. Immediate urticarial, itching, tingling of lips, tongue and throat. Angioedema/blistering occasionally. Symptoms are worse during high pollen season. Anaphylaxis can occur, but rare	*Dermatological* Contact dermatitis, atopic dermatitis/eczema *Gastrointestinal* Abdominal pain, nausea, vomiting Diarrhea Malabsorption Constipation Rectal bleed with mucus in a healthy neonate, bloody stools. Ascites Chronic diarrhea/steatorrhea Dysphagia Food impaction Heartburn *Other* Mostly absence of systemic symptoms Failure to thrive Feeding difficulties Irritability Weight loss Anemia Growth failure	*Dermatological symptoms* Urticaria/hives, flushing, angioedema, pruritus, eczema *Gastrointestinal upset* Bloating Flatulence Vomiting Abdominal cramps Diarrhea *Respiratory symptoms* Nasal obstruction, runny nose, asthma, shortness of breath *Other symptoms* (some fall within spectrum of common medically unexplained symptoms) Headaches and migraine Fatigue Musculoskeletal problems Behavioral changes Dizziness Balance problems Visual disturbances
Diagnosis		
1. Clinical history and physical examination 2. IgE testing: SPT or sIgE 3. Oral food challenges (OFC) 4. Elimination diets	1. Clinical history and physical examination 2. Elimination diets and OFC 3. SPT or IgE testing mostly not helpful 4. Endoscopic evaluation and GI biopsies	1. Clinical history and physical examination 2. Fructose and lactose breath testing 3. Elimination diets 4. OFC

Sources: Refs. [1–4, 7–9, 11–13]

Types of Food Allergies

IgE-Mediated FA

About 90% of all FA are caused by eight "major" food allergens including cow's milk (CM), egg, peanuts, tree nuts, soy, wheat, fish, and shellfish [1, 8]. In infants, the most common allergies are to CM and egg. Allergies to peanuts, tree nuts, seafood, CM, and eggs are usually observed in older children, while

adults are more prone to peanuts, tree nuts, seafood, and pollen allergies causing cross-reactive FA [1]. The "major" food allergens mostly cause Type I hypersensitivity reactions, which occur when the immune system that naturally reacts to parasites/pathogens targets food allergens [1]. The consequent food-specific IgE antibodies that are produced bind to mast cells or basophils, which are now sensitized to the allergen (IgE sensitization). During subsequent exposure, the food allergen binds to the specific IgE antibodies resulting in degranulation of the mast cells or basophils to release mediators, such as histamine, leukotrienes, and prostaglandins, which induce immediate hypersensitivity reactions [1].

Oral allergy syndrome (OAS) is an allergic reaction to certain fruit, vegetables, and nuts that develops due to cross-reactivity (e.g., the same IgE antibody recognizes distinct antigens found in common pollens, or house dust mite and in fruit, vegetables and nuts). Almost all patients with OAS first develop IgE sensitization to the aeroallergen; this often presents as seasonal rhinitis if pollen is the aeroallergen. The subsequent ingestion of fruit or vegetables that have proteins with homologue epitopes to the aeroallergen results in an immune reaction and allergy symptoms. Examples of common overlapping antigens in OAS include [1, 4]:

- Birch pollen with apple, peach, plum, cherry, apricot, almond, carrot, celery, parsley, or hazelnut.
- Ragweed pollen with melon, watermelon, cantaloupe, cucumber, zucchini, banana, or kiwi.
- Mugwort pollen with celery, carrot, parsley, peppers, mustard, cauliflower, broccoli, garlic, or onion.
- Orchard grass with melon, peanut, potato, or tomato.
- Timothy grass with Swiss chard or orange.
- Chironomidae (house dust mite) with shellfish.

Latex-food syndrome refers to an allergic reaction to certain fruit and vegetables that develop in more than half of individuals with latex allergies due to cross-reactivity. The food involved include avocado, kiwi fruit, chestnut, papaya, banana, mango, papaya, passion fruit, tomato, and potato [1].

Food-dependent exercise-induced anaphylaxis (FDEIA) refers to the presence of signs and symptoms of anaphylaxis during or soon after exercise and within 2–4 h after ingestion of a food allergen. Symptoms should be absent when the food is consumed without exercise or when vigorous exercise is performed alone. IgE sensitization to the food should be evident through skin prick testing (SPT) or serum immunoglobulin E (sIgE testing) [2].

Non-IgE-Mediated and Mixed-Type FA

The underlying mechanisms involved in non-IgE-mediated FA are not well-understood [1]. They occur mostly in children and are usually outgrown. The classification of these FA is illustrated in Fig. 17.1 and the main symptoms, diagnostic procedures, and treatment recommendations for some of these are briefly summarized in Tables 17.2 and 17.3.

Diagnosis

The diagnosis of FA requires evidence of immune system sensitization as well as reproducible symptoms after exposure to the allergen. The first-line diagnostic approach is a thorough clinical examination and history of the patient's experiences with the suspected food [3]. If the clinical history suggests FA, further tests are necessary to confirm sensitization. The second-line approach involves either *in vivo* (SPT) or *in vitro* food-specific sIgE testing of the suspected food(s) identified through the clinical history [3]. The third-line approach is to carry out elimination diets and oral food challenges (OFC) to establish clinical relevance of SPT or sIgE results, if necessary to confirm the diagnosis or to establish tolerability levels [1].

Table 17.2 Features of non-IgE-mediated food allergy (FA)

	Food protein-induced enterocolitis syndrome (FPIES)	Food protein-induced allergic proctocolitis (FPIAP)	Food protein-induced enteropathy (FPIE)
Age of onset	Infants <9 months, usually within first few weeks of life	Newborn or first few weeks of life	Infants or toddlers 0–24 months of age
	Delayed in breastfed infants to >5 months		
Primary FA	Infants: cow's milk (CM), soy	Infants: CM	Primarily: CM
	Older children/ adults (>1 solid food): rice, oats, barley, meat, chicken, eggs, orange vegetables, fruit, fish, shellfish	Breastfed infants: CM, soy or egg in mother's diet.	Other: soy, egg, rice, poultry, fish, shellfish
Symptoms onset	Infants: around 2 h after ingestion, resolve within 6–12 h	Delayed, 48–72 h after ingestion	Gradual onset within few weeks after intro of causal food
	Older children/adults: delayed onset of reaction		
Symptoms	Infants: severe form with protracted vomiting 1–3 h after feeding, (bloody) diarrhea, hypotension, severe dehydration	Stools with fresh blood and mucus; infant is otherwise healthy	Chronic diarrhoea, steatorrhea, failure to thrive
	Other: irritability, anemia, abdominal distention, failure-to-thrive	Stools may be more frequent but diarrhoea is absent	Also anemia, hypoalbuminemia
	Older children/adults: mild chronic form with nausea, abdominal cramps, lethargy vomiting, hypoproteinemia		
Diagnosis	Presence of symptoms with improvement after elimination	Disappearance of bloody stools with causal food exclusion and reappearance after OFC	Clinical history
	Supervised OFC to confirm diagnosis if needed	SPT/sIgE not recommended	Often confirmed with endoscopy and biopsy
	SPT or sIgE usually negative and not recommended (however, 25% have raised sIgE to causative food)	Colonoscopy and biopsies usually not necessary and only used if symptoms persist after trial elimination diets	SPT and sIgE not recommended
Treatment	Completely eliminate causal food	With breastfeeding mothers, test the exclusion of CM first, then soy, then egg	Completely eliminate causal food
	Avoid potentially cross-reactive food if not yet been introduced	With other infants, change to elemental formula	
	Avoid breastfeeding if it causes symptoms in child		
Symptom resolution	Symptoms improve within 24 h	Symptoms resolve within 48–72 h	Symptoms resolve within 1–3 weeks
Natural course	90% develop tolerance by age 3 years	Tolerance in most at age 1 year	Tolerance in most by age 2–3 years
	FPIES to solid food tend to resolve at older age		

Sources: Refs. [1, 2, 4, 8]

Clinical History and Examination

The clinical history aims to identify the possible presence of FA, trigger food, and the underlying immunological mechanism (e.g., IgE, non-IgE, or mixed). It is recommended that structured questions be used to obtain information on [2, 3, 8]:

Table 17.3 Features of mixed-type IgE and non-IgE food allergy (FA)

	Eosinophilic esophagitis (EoE)	Eosinophilic gastroenteritis (EG)	Atopic dermatitis (AD)
Age of onset	Any age	Any age	Early infancy, can also present in children/adults
Primary causal food	Cow's milk (CM), soy, egg, wheat	CM, egg	Associated with FA in 35% of children with moderate to severe AD. Major food allergens: CM, egg, peanut
Symptoms onset	Gastrointestinal (GI) tract symptoms occur after eating but are chronic	Can be after intake but mostly delayed and chronic	Symptoms can be a combination of immediate within 2 h or delayed, 6–48 h after OFC
Symptoms	Symptoms after eating: reflux, vomiting, dysphagia, abdominal pain, food impaction, cough, chest pain Young children: reflux, feeding difficulties, failure-to-thrive, irritability Adolescents and adults: dysphagia, food impaction, heartburn 50% have other atopic diseases (asthma, allergic rhinitis, eczema)	Can affect any part of GI tract from esophagus to colon, e.g., • Eosinophilic gastritis • Eosinophilic enteropathy • Eosinophilic colitis Symptoms (depend on site affected): ascites, nausea, vomiting, diarrhoea, malabsorption, edema, obstruction, anemia, abdominal pain, weight loss Infants: projectile vomiting Eosinophilic colitis: abdominal pain, bloody stools, diarrhea 50% have other atopic diseases	In general, extreme pruritic, erythematous, morbilliform rash Immediate symptoms: urticaria, angioedema, flush, and pruritus Delayed symptoms: eczema flares with typical distribution at specific sites
Diagnosis	• Diagnosis is challenging. SPT/sIgE indicate sensitization to multiple food and aeroallergens, can sometimes be helpful to indicate role of FA • Diagnosis is confirmed with elimination diet (choose between a targeted one-food or six-food, four-food or total elimination diet) for 2–6 weeks, followed by symptom improvement and OFC of one food at a time • Endoscopy with multiple biopsies often performed and repeated after OFC to confirm histologic remission		• Clinical history • Children <5 years with moderate to severe AD should be evaluated for major allergens with • SPT/sIgE testing • Elimination diet, symptom improvement and, if necessary, an OFC to confirm diagnosis
Dietary treatment	Completely eliminate causal food	Completely eliminate causal food	Eliminate causal food. Whether strict avoidance is always necessary is still being debated
Symptom resolution	2–6 weeks	2–6 weeks	2–6 weeks
Natural course	Likely persistent Often poor response to anti-reflux drugs	Some resolve before age 5 years In many patients, EG is persistent at 5 years follow-up	AD usually resolves during childhood; however, if peanut or tree nut FA is the cause, it is more likely to be persistent

Source: [1, 2, 4, 8]

1. Causative food: type (probe regarding the eight major food allergens or certain fruit and vegetables if suspecting oral allergy syndrome (OAS)), amount ingested that cause a reaction and form of food (processed, raw, baked, heated, dried), route of exposure (oral, inhalation, skin).
2. Symptoms: reaction type, duration and severity of symptoms, reproducibility of symptoms, frequency of symptoms, time frame involved from exposure to symptom onset, age when symptoms started.

3. Co-factors that may augment FA reaction: alcohol, exercise, NSAID, fever, and acute infection.
4. Socio-demographic factors: age, geographic location, and ethnic dietary habits of the patient; these may all give clues regarding trigger food.
5. Other factors: known risk factors (exposure at school, work, home), family history of allergies, any other coexisting medical problems or allergic diseases (e.g., asthma, allergic rhinitis, atopic dermatitis); if a child, the duration of breastfeeding.
6. Treatment: details on how symptoms were treated.

The clinical examination may reveal acute or chronic signs of asthma, allergic rhinitis, or atopic dermatitis, although this is not necessarily important for FA diagnostic purposes [8].

A dietary history, preferably performed by a dietitian, should include evaluation of nutritional status, including growth monitoring in children and dietary intake. A review of food labels and detailed food diaries may assist in identifying possible causative food, hidden ingredients, or pattern of reactions [3].

Diagnostic Test for IgE Sensitization

Both SPT and sIgE tests (Table 17.4) are reliable and validated to detect IgE-mediated sensitization to food allergens, but cannot be used as the sole tests for clinical allergy diagnosis [9]. One reason for this is false positives. This refers to positive SPT or sIgE test results, but where there are no symptoms or signs of FA when exposed to the specific food allergen. Such individuals do not have FA and it is therefore recommended that the clinical history should always guide diagnostic testing. Testing for large panels of food allergens should be discouraged as false positive SPT or sIgE results may lead to unnecessary dietary elimination and nutritional inadequacies [2, 3]. False negative results are another problem. Accordingly, negative SPT or sIgE results combined with a strong clinical history suggesting FA should be interpreted with caution and warrant further investigation [8]. False negative SPT or sIgE results may, for instance, be possible due to the commercial test extract not containing the relevant allergen found in the raw food [8]. SPT tests are often preferred over sIgE tests due to their lower costs and near instant results [8]. SIgE testing should be used when SPT is contraindicated or ineffective [3].

Promising Diagnostic Tests

Technological advancement in tests, such as component-resolved diagnosis (CRD), make it possible to detect IgE sensitization in specific proteins or protein components instead of the whole food extract, which results in a low misclassification rate and a high sensitivity and specificity [1, 2]. The basophil activation test (BAT) has been used to effectively discriminate between sensitization to some allergens and clinical allergy [3, 8, 9]. However, further research is necessary before these tests can be used for routine diagnosis of FA [3, 8, 9].

Elimination Diets

Elimination diets cannot confirm FA diagnosis on their own, but can help to identify causative food in IgE and non-IgE-mediated FA [3]. These diets are also effective in reversing the clinical severity of mixed-type FA such as eosinophilic gastrointestinal disorders (EGIDs) [2]. The clinical history, allergy-focused diet history, and SPT or sIgE testing should guide which food should be eliminated [8]. There are several different types of elimination diets that can be used including the allergy-directed diet

Table 17.4 Characteristics of skin prick tests and serum-specific IgE tests for diagnosis of food allergy

	Skin prick testing (SPT)	sIgE
Advantages	• Near instant results (within 15 min) • High sensitivity (>90%) • High negative predictive value accuracy, e.g., a negative SPT correctly indicates absence of IgE-mediated allergy in 90–95% of cases • Can be performed on all age groups (even infants) • Causes minimal discomfort • Suspected food samples can be tested even if no commercial tests or food extracts are available	• No risk of anaphylaxis • Order from physician's office without specialist referral • Can be used when SPT is contraindicated or ineffective: – Pregnant women – Significant anaphylaxis risk – Severe skin disease (dermographism, extended or severe atopic dermatitis) – Unable to stop using B-blockers or antihistamine for testing purposes
Disadvantages	• Moderately specific (≈50%) • Moderate positive predictive value (50%), e.g., a positive results indicate sensitization but not allergy • Cannot be used as a screening tool • Cannot predict prognosis • Cannot predict severity of future reactions • Requires referral to specialist/allergy clinic	• High chance of false positive results (e.g., the individual is not allergic) • Lower sensitivity (e.g., it may miss 10–25% of true allergies) • Cannot predict prognosis • Cannot predict severity of future reactions
Procedure (short summary)	• Apply small drop of commercially prepared food extract on skin of the forearm or upper back • 3 cm between drops • One drop with positive control (histamine) and one with negative control (physiological glycerine) • Prick (1 mm) each drop with a new sterile lancet • Hold for 3 s to avoid bleeding • Remove allergen with blotting paper • If the individual is sensitive to the food IgE antibodies, a wheal will develop on the skin. • Measure wheal diameter after 15 min *Prick-to-prick method:* • To establish sensitization to: – fresh food such as fruit and vegetables – food for which commercial extracts are not available • Method: prick the fresh fruit or vegetable and then the patient's skin with the same lancet, followed by usual SPT protocol	• Phlebotomy required • Analyses of the blood sample for food sIgE antibodies using standardized assays in certified laboratories. – Fluorescence enzyme immunoassay (FEIA) tests such a ImmunoCap® – Radioallergosorbent test (RAST®) • Results available depending on laboratory schedule, usually the next day

(continued)

Table 17.4 (continued)

	Skin prick testing (SPT)	sIgE
Diagnosis of sensitization to a food	• In general, a positive SPT result is defined by a wheal diameter ≥3 mm measured after 15 min • Different wheal diameter cut-offs have been defined for egg, milk, and peanut FA in children [9]	• Food-specific diagnostic cut-offs for sIgE results where clinical symptoms are associated with a PPV >95% have been identified for several of the major food allergens • A high total IgE level is often associated with multiple false-positive food sIgE levels and this is particularly important to consider in patients with severe eczema

Source: Refs. [1–3, 8, 9]

(elimination of specific food(s)), the oligo-antigenic diet, the extensively-hydrolyzed or amino acid-based elemental diet, the six-food group elimination diet, the four-food group elimination diet, the gluten-free diet, and the milk-elimination diet [2, 3]. In order to achieve symptom relief, the elimination diet should be followed for a period of 2–4 weeks if suspecting IgE-mediated FA, or for up to 6 weeks for non-IgE-mediated FA [8]. The elimination phase is then followed by a well-planned reintroduction phase of eliminated allergens according to specified guidelines [8].

Oral Food Challenges (OFC)

The double-blind placebo-controlled oral food challenge is the gold standard procedure for objective diagnosis of FA [2, 3, 9]. As this test is expensive, labor intensive, and time-consuming [3, 8], open or single-blinded OFC are often used in clinical practice [10]. When open or single-blinded OFC cause an objective unequivocal reaction, it is deemed sufficient to diagnose a FA [8], while the double-blind challenge is recommended when symptoms are subjective.

Food challenges are usually performed in a specialist practice where emergency treatment is available for severe allergic reactions [8, 9]. Protocols for performing OFC exist and involve re-introduction to one food allergen at a time, in specific dosages that increase in a stepwise manner over several hours while monitoring reactions [2, 8].

Alternative Tests

Alternative tests are often used by the public, but should not be advised or used for the diagnosis of FA or food intolerances as they lack evidence to support their use in clinical practice [1, 8, 11]. Examples are as follows:

- Electrodermal tests
- Hair analyses
- Applied kinesiology
- IgG and food-specific IgG4 levels
- Iridology
- Lymphocyte stimulation
- Facial thermography
- Gastric juice analyses
- Endoscopic allergen provocation
- Cytotoxicity assays
- Mediator relapse test
- Pulse test

Furthermore, intradermal testing to food and atopy patch tests are not validated and standardized and thus not routinely recommended for investigating FA [3].

Monitoring for Tolerance

As about 70–80% of children outgrow FA to egg, CM, wheat, and soy by adolescence, regular monitoring is important to identify when tolerance has been reached in order to avoid unnecessary dietary eliminations. Peanut and tree-nut allergies most often continue into adulthood [12]. Favorable factors associated with outgrowing FA include younger age, type of allergy (e.g., CM, egg, soy, wheat), lower sIgE levels, mild symptoms, and absence of other FA. A decline in IgE sensitization indicates that the patient is likely outgrowing the FA and may help in deciding when an oral food challenge (OFC) is warranted [10]. It is recommended that diagnostic tests (SPT or sIgE) be repeated every 12–18 months in children <5 year old and every 2–4 years in those >5 year old to establish change in sensitization [10]. An OFC is the gold standard procedure to confirm that FA is no longer present [10].

Nutritional Management

General Dietary Recommendations for FA

Dietary elimination of the food allergen(s) is key in the management of FA [8]. However, exposure to the food allergen may occur through the skin, the lungs, or by oral intake. Oral intake may result in mild to severe reactions when ingesting a very small amount of the allergenic food, by ingesting food that is cross-contaminated with the allergen, or due to cross-reactivity [10]. Self-elimination of food or food groups can cause nutritional deficiencies, significant stress, poor quality of life, and impact negatively on family life. It is therefore important that referral to a dietitian is made to ensure effective dietary management of FA. During dietetic consultations, education and practical advice on any of the following (applicable to the patient or caregiver) can be provided [13]:

- Diet sheet indicating food allowed and restricted/eliminated as well as alternatives for these.
- Well-planned nutritionally balanced avoidance diet [8].
- Supplementation if necessary.
- Reading labels and examples of terms used in the ingredient list that refer to the causative allergen (by law in most countries food labels must indicate if the food contains the eight major food allergens).
- Commercial food products and available brands that can be used instead of the usual product that contains the allergen (e.g., imitation cheese instead of regular cheeses or yoghurt not made from CM).
- Recipe adaptations. Provide example recipes and alternatives that can be used instead of CM, egg, flour, etc.
- High-risk situations where cross-contamination is likely and how to deal with this, e.g., ice cream parlors, ethnic restaurants, bakeries (peanut, egg, CM, and tree nuts), and buffets (all food) [10].
- Eating in restaurants: order plain food, be careful of fried food, sauces, condiments, pastries, bakery items, desserts.
- Tips for travelling abroad as this can be particularly challenging. Translated information may be necessary on food products and emergency treatment [14].
- Special occasions such as children's birthday parties. There may be a need to inform the host of the FA and take own food.

- School food environment: ideas for lunch boxes and arrangements with school canteen.
- Importance of education for all caregivers: teachers, grandparents, friends' parents.
- Cross-reactive food. Cross-reactivity often occurs between the following food and exclusion of the other food in the same group may be necessary [1]:
  - Peanuts with other tree nuts and sesame
  - CM with goat's milk
  - All fish species
  - Chicken eggs with eggs of other species such as turkey, duck, and goose.
- Contamination of food during preparation, serving, and storage. Provide designated areas in fridge and storage area. Label dishes, cutlery, crockery, and cutting boards that are used solely for allergen-free food preparation.
- Breastfeeding. Although food allergens are detected in breastmilk, breastfeeding remains the first choice milk for infants with FA. In rare cases, however, it might be necessary for the mother to follow an allergen-elimination diet [1, 8].
- Milk choice for infants with cow's milk protein allergy (CMPA) that are formula fed [1, 8]:
  - Partially hydrolyzed formula milk is inappropriate for CMPA and should not be recommended.
  - Extensively hydrolyzed milk is the first choice for mild to moderate CMPA.
  - Amino acid-based formula is indicated for a subgroup of infants; usually those with severe CMPA.
  - Plant-based milks (rice and oat milk) are not suitable as a sole infant formula, but might be used in older children, adolescents, and adults.
  - Goat, sheep, and other mammalian milks are not suitable due to high cross-reactivity (e.g., 95% of children with CMPA react to goat's milk).
- Food reintroduction and "milk ladder" [15].
- Tolerance to baked CM and egg (see below).

Managing Oral Allergy Syndrome

Patients with OAS must avoid the raw trigger fruit and vegetables [1]. However, they may eat the trigger fruit and vegetable when cooked or processed as structural changes in the proteins occur which reduce the binding capacity to IgE antibodies [1, 2]. In some instances, peeling the trigger fruit or vegetable may also be effective as the epitopes are often in the skin [1].

Ingestion of Baked Cow's Milk or Egg

Results from various studies indicate that about 69–83% or 63–84% of children with CM or egg allergy, respectively, can tolerate baked CM or egg as the extensive heating modifies certain CM or egg proteins to be less allergenic and interactions with a food matrix, such as wheat, during baking decrease IgE recognition. Adding baked CM and egg to the diet of a child with CM or egg allergy generally improves quality of life, variety of food choices, and nutritional content. Furthermore, children who regularly consumed the baked forms were more likely to outgrow their CM or egg allergy compared to those who never or infrequently consumed baked CM or egg. It is therefore recommended that tolerance to baked egg and CM should be established and those who can tolerate the baked forms should regularly consume these [16].

Although most studies indicate that higher sIgE and SPT levels are associated with intolerance to baked egg or CM, no definite cut-points have been defined. Therefore, to diagnose tolerance to baked CM or egg, physician-led OFCs according to standardized protocols are recommended as anaphylaxis to baked CM or egg have been reported. Those tolerant to baked egg or CM should still eliminate all fresh CM, other dairy products, raw egg and eggs that are not extensively heated for a long duration such as stove-top egg preparations [17].

Peanut Allergy

Some individuals are highly sensitive to peanut allergens and may react to an environment or mucosa that has been contaminated with peanuts. The peanut antigen has been detected 110 days after peanut butter was smeared onto a table [1]. While normal dishwashing liquid is not sufficient to remove the antigen from cutlery, a disinfectant wipe can be used to clean surfaces to eliminate the allergen [1].

The severity of symptoms that develop due to accidental peanut exposure may change over time, e.g., a child may initially only present with hives to peanut exposure, but in subsequent exposures may develop anaphylaxis. It is thus important that care-givers do not become at ease to exposure of small amounts of the allergen if reactions are initially mild [10]. Furthermore, FA and eczema in early life (<2 years of age) may progress into asthma and allergic rhinitis, known as the atopic march [18].

Compared to other FA, a lower percentage of children (20–25%) outgrow peanut and tree nut allergies [4, 19]. SPT and sIgE cut-points that predict persistence of peanut allergy after age 4 years have been published [19]. However, children who outgrow peanut allergy can at a later stage re-acquire the allergy, especially if peanuts have been avoided [4]. Recently, the results of the Learning Early About Peanut Allergy (LEAP) randomized controlled trial indicated that "high risk" infants who were introduced to peanuts early in life (between 4 and 11 months of age) and consumed 6 g peanut protein (equal to 24 g peanuts or three teaspoons peanut butter) per week for 5 years had a relative risk reduction of 80% for development of peanut allergy by age 5 years compared to the group who avoided peanut consumption during the first 5 years of life [20]. Consequently, various allergy associations have published an interim guideline that recommends the early introduction of peanuts in the diets of "high-risk" infants [21]. It is suggested that infants with severe early onset eczema or egg allergy in the first 4–6 months of life be referred to an allergist to perform SPT and possibly peanut OFC (if SPT is <4 mm) and to provide a recommendation regarding the implementation of these guidelines. The recommendation for infants or children with a SPT wheal diameter >5 mm to peanuts is to avoid peanuts and follow-up SPTs should be done on an annual basis [21]. Further research is necessary to establish the effect of sporadic peanut intake, alternative peanut dosages, early discontinuation of peanut intake, and minimum time necessary to induce risk reduction [21].

Prevention

The avoidance of major allergenic food during pregnancy, breastfeeding, and infancy is not recommended for allergy prevention. Exclusive breastfeeding for the first 6 months of life is widely recommended for various health benefits, but whether it protects against FA is unclear due to conflicting results from various studies [22].

In the past decade, several studies have indicated that the delayed introduction of the major allergenic food is not protective against the development of FA [22]. Early introduction and regular consumption of peanuts have actually been associated with FA prevention [20]. However, it is unknown whether early introduction of the other major allergenic food prevents FA; research in this regard is ongoing [22]. Detailed practical guidelines on the introduction of complementary food, including the

major allergenic food, from 4 to 6 months of age are outlined elsewhere [22]. Once allergenic food have been introduced and shown to be well-tolerated, regular consumption is advised so as to maintain tolerance, although the appropriate amount and frequency is not known [22].

Food Intolerance

Food intolerance is a non-allergic reaction to food with the immune system not being involved (Fig. 17.1) [1]. The differences and similarities in symptoms between FA and food intolerance are summarized in Table 17.1.

Types of Food Intolerance

Enzymatic Deficiencies or Transport Defects

The majority of reported food intolerance is caused by either enzymatic deficiencies or transport defects in the gastrointestinal (GI) tract, which leads to incomplete digestion or absorption of food that contain substances collectively termed FODMAPs (fermentable oligo-, di-, mono-saccharides, and polyols). These substances are short-chain carbohydrates that consequently enter the colon where bacteria will ferment them and produce gas. This gives rise to symptoms of food intolerance in some individuals such as abdominal distention, cramping, bloating, and flatulence. Nausea, vomiting, and osmotic diarrhea may also occur as increased water in the lumen is needed to dilute the osmotic load [1, 11]. FODMAPs include lactose (disaccharide), fructose (monosaccharide), fructans and galactans (oligosaccharides), and polyols such as sorbitol, mannitol, and xylitol [11]. Individuals may have a food intolerance to one of these FODMAPs (e.g., most notably lactose or fructose intolerance) or a combination of different ones.

The enzyme lactase digests lactose in the GI tract to glucose and galactose, which can then be absorbed [7, 11]. Newborns have the highest concentration of lactase, which declines during childhood to <10% of pre-weaning levels [7]. Lactase deficiency may lead to lactose malabsorption (no symptoms) or lactose intolerance (malabsorption with symptoms). There are three types of lactase deficiencies, namely congenital, primary late onset, or secondary. The majority of lactose intolerance seen today is due to primary late-onset hypolactasia, i.e., a gradual decrease of lactase activity from age 2 years with symptoms manifesting from age of 5–6 years, but in the majority of cases only during adolescence or adulthood [7].

The capacity for fructose absorption in the GI tract is limited. Fructose malabsorption occurs when the absorption process is incomplete, when the total fructose intake or load is too high, or when too much "free fructose" food (that have high fructose and low glucose content) are consumed [1].

Humans lack enzymes to completely digest food with fructans (branched fructose polymers) and galactans (galactose polymers). Polyols are passively absorbed in the GI tract, but the rate of absorption may vary between individuals and consequently cause a laxative effect [1, 23].

Reactions to Pharmacological Agents in Food

Some individuals are sensitive to certain pharmacological agents in food such as vasoactive or biogenic amines (e.g., histamine, tyramine, and phenylethylamine). Histamine intolerance occurs mostly due to enzyme deficiencies, while a drug–food interaction between tyramine in food and monoamine

oxidase inhibitors leads to majority of cases of tyramine intolerance. Symptoms range from migraine headaches and dizziness to urticaria, eczema, nausea, and vomiting [11].

Reactions to Food Additives

Intolerance to specific food additives such as salicylates, nitrates and nitrites, glutamates (e.g., monosodium glutamate), artificial colorants (e.g., tartrazine), benzoates, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) can also cause adverse reactions manifesting in a variety of symptoms such as hives, asthma, angioedema, migraine, and GI tract symptoms. Underlying mechanisms have been proposed, but the pathophysiology is, in general, poorly understood [11].

Noncoeliac Gluten Sensitivity

Noncoeliac gluten sensitivity (NCGS) is a relatively new term that describes individuals who develop GI tract symptoms to gluten exposure, but do not have coeliac disease or wheat allergy [1, 11]. These individuals report that dietary gluten elimination results in improvement of a wide array of symptoms; however, clinical studies are inconsistent and unreliable to confirm NCGS [11]. The underlying mechanism is unclear, but it is possible that it overlaps with IBS [1].

Diagnosis

Food Exclusion, Symptom Improvement, and Food Challenge

The most reliable method for diagnosing food intolerance is exclusion or reduced intake of possible trigger food followed by symptom improvement, as well as gradual reintroduction of the food followed by symptom induction. If the diet history points to one specific food or food component (e.g., lactose), the food exclusion and challenge can be executed based on the elimination of all food that contain lactose. However, it is often difficult to identify specific trigger food or it is possible that more than one food intolerance contributes to the symptoms. It is then recommended that the low FODMAP (fermentable oligo-, di-, mono-saccharides, and polyols) diet be followed for 3–4 weeks followed by the reintroduction of food using a specific food challenge process under expert guidance to identify trigger food and individual tolerance thresholds to these food [11].

Breath Tests

Hydrogen and/or methane breath testing can be used to assess lactose or fructose malabsorption in the GI tract as these products are produced by bacterial fermentation of the undigested lactose or fructose, rapidly absorbed, and expelled through the lungs. Various protocols exist with most involving either 50 g of lactose or 25–35 g of fructose that must be ingested after an overnight fast. Breath hydrogen or methane is measured at baseline and every 15 or 30 min for 3–5 h depending on the protocol used. Malabsorption is indicated by a 10–20 ppm increase in breath hydrogen or methane above baseline on two consecutive measurements [11]. These tests should not be used alone for diagnostic purposes as the results only indicate malabsorption; many patients with a positive test may not experience any symptoms and are therefore not intolerant. Breath tests for sorbitol, mannitol, fructans, and galactans are not useful for identifying malabsorption and are therefore not recommended [11].

Other Tests

The lactose tolerance blood test, which measures change in blood glucose levels following a lactose load, is less sensitive than breath tests and is not recommended for diagnostic purposes [7]. No further objective tests currently exist that can identify food intolerance. Confocal laser endomicroscopy is a novel technique that explores the real-time effect of food antigens on the GI tract. It may be useful in future to diagnose food intolerance, but more research is necessary to validate the procedure and usefulness in clinical practice [11].

Nutritional Management

Food sources of lactose include milk produced by cows, sheep, and goats and products from these such as yoghurt, ice-cream, custard, buttermilk, and soft cheeses. It is unnecessary to completely eliminate lactose from the diet as the majority of lactose-intolerant individuals can consume about 12–15 g (250–320 mL) of milk daily, or even higher amounts, without any symptoms [1, 7, 11]. The tolerance threshold is dependent on several factors and should be individually determined [11]. It is recommended that intakes should be spread throughout the day [11]. Fermented products such as yoghurt and buttermilk are better tolerated [11]. Lactose-free milk is also available in food stores. It is important to advise patients regarding the benefits of still including a tolerable amount of lactose in their diet as dairy food provide several essential nutrients, such as calcium and vitamin B_{12}. An additional reason for milk ingestion is to help build up tolerance to lactose. Although lactase supplements can be prescribed, this is expensive and unnecessary for the majority of patients. It is controversial whether hypolactasia causes infantile colic; lactose-free formulas are not recommended, while breastfeeding remains the preferred option [7].

Fructose is naturally found in fruit, sugarcane, and honey. It is also added as a sweetener to sugar-sweetened beverages (SSBs) and other food, often as high-fructose corn syrup (HFCS). Dietary recommendations include limiting the total fructose content of a meal/snack to <3 g. Food that usually contain >3 g fructose per standard serving include dried fruit, fruit bars, two or more fresh fruits, fruit juice, fruit concentrate, fortified wines (sherry), food sweetened with HFCS, SSBs, and indulgent quantities of confectionaries. The intake of "free fructose" food should be limited [23].

Food high in fructans include wheat products, vegetables (e.g., artichoke, garlic, leeks, onion), and other food (added as fructo-oligosaccharides (FOS), inulin, oligofructose). Galactans are found in human milk, legumes, some grains, and nuts. Polyols are found naturally in higher amounts in certain fruit (apricots, peaches, cherries, apples, pears) and vegetables (mushrooms and cauliflower), but are also added as artificial sweeteners to food products. It is advised to restrict FODMAPs globally using a low FODMAP diet rather than restricting individual FODMAPs, unless only lactose or fructose intolerance is diagnosed [23].

Food additives and pharmacological agents are widely spread in food and elimination may lead to nutritional inadequacies; careful planning of such elimination diets are necessary [11].

Conclusion

The prevalence of food allergies and intolerances is increasing world-wide. The underlying mechanisms involved in food allergies (FA) and food intolerances are different; an immune response is only triggered in FA. However, a variety of symptoms caused by food intolerances are similar to those caused by FA. The adverse reactions of food intolerance are less severe and small tolerable amounts of the offending food/substance might still be allowed. FA, by contrast, may cause life-threatening

anaphylaxes; complete dietary elimination of the allergen is necessary to prevent symptoms. It is therefore important to rule out FA through clinical history, diagnostic testing, and oral food challenges. Referral to a dietitian is necessary to help educate patients and plan nutritionally balanced and individualized elimination diets.

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Suggested Further Reading

American Academy of Allergy, Asthma, and Immunology. www.aaaai.org.
Asthma and Allergy Foundation of American. www.aafa.org and www.kidswithfoodallergies.org.

European Academy of Allergy and Clinical Immunology. http://www.eaaci.org/resources/position-papers.html.
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