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Health Professional's Guide *to* Nutrition Management of Food Allergies

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Scott H. Sicherer, MD

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Preface

We first conceived of this textbook in 2008 after assessing the food allergy educational needs of dietitians in the United States and again in 2014 when we expanded this assessment to dietitians in other parts of the world. The results indicated that dietitians manage food allergy for a substantial patient base although they do not report a high level of expertise in many of the important aspects of food allergy management. Knowing that dietitians want expert-level knowledge, and each patient deserves the most up-to-date, informed, and safe guidance, we developed this textbook to teach dietitians and other healthcare professionals around the world about food allergies. Each chapter of this textbook was coauthored by both physicians and dietitians to ensure a comprehensive text and to address the interests of not only dietitians but also physicians, researchers, nurses, and all other medical professionals who are managing food allergy.

Over the past few decades, the prevalence of food allergies has risen, yet the number of healthcare professionals with expertise to assist in the management of food allergies is still insufficient. The role of the dietitian is also growing beyond food allergy management, with dietitians now playing a crucial role in the prevention and treatment of food allergies. Our initial research provided valuable information for developing targeted food allergy education for dietitians across the globe. Additionally, we bring unique expertise in the overall management of patients with food allergy. As dietitians who have spent their careers in academic food allergy centers, we have had the opportunity to collaborate with clinicians, physician scientists, nurses, psychologists, feeding therapists, basic scientists and other healthcare professionals on research, food allergy guidelines development, unique educational endeavors, and the clinical care of patients with food allergy. In these roles, we have been grateful to have developed profound expertise in all areas of food allergy. As thought leaders, we have each been honored to serve multiple times on expert panels on food allergy topics for the National Institutes of Health.

In developing and editing this textbook, we were joined by two world renowned and generous physicians: Scott H. Sicherer, MD and John James, MD. Sicherer, an academic physician scientist, brought his clear vision and decades of expert allergy/immunology science and clinical, research and educational expertise to the text. Sicherer is a world leader in food allergy and his name is synonymous with food allergy science. James is a retired allergist with over 30 years of experience in private clinical practice. He has trained and collaborated with some of the world's most acclaimed allergists, and he currently works as a consultant in food allergy education.

This entire book is built on the world-wide expertise of the 27 authors and 17 reviewers. Indeed, each chapter was written and reviewed by leading experts in the topic area. The chapters were written to stand alone so if you are interested in a specific food allergy disorder such as immunoglobulin E(IgE)-mediated food allergy to specific foods, non IgE-mediated food allergies such as food protein induced allergic proctocolitis (FPIAP), food protein induced enterocolitis syndrome (FPIES), eosinophilic esophagitis (EoE), or breastfeeding and formula feeding with food allergies, then you can skip right to that chapter. If you are new to food allergies, the book progresses from defining food allergy, food intolerance, and food allergic disorders before moving on to more complicated themes of diagnosis and oral food challenges and finally onward to the practical aspects of avoidance diets and dietary management. We round off the book with two topics that are of great interest in modern food allergy: nutritional interventions to prevent food allergy and oral immunotherapy to foods.

We are so grateful to all the experts who have given of their time and expertise and who have surely made this textbook the valuable resource we know it will be as you aim to improve the lives of patients living with food allergy.

There is still much work to be done in food allergy science and we need your help! We would like to invite you to join the International Network for Diet and Nutrition in Allergy (INDANA; www.indana-allergynetwork.org), an organization in which we are both past chairs and a home for food allergy dietitians worldwide.

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CHAPTER

1

Adverse Reactions to Foods

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CHAPTER OBJECTIVES

- Review the categorization of disorders within adverse reactions to foods.
- Discuss the prevalence, clinical manifestations, diagnosis, and management of immune-mediated food-induced allergic disorders.
- Examine what is known about immunologic mechanisms involved in the development of immune-mediated food-induced allergic disorders and the acquisition of tolerance.
- Discuss the prevalence, clinical manifestations, diagnosis, and management of food-induced allergic disorders that are not immune-mediated.

OVERVIEW

Adverse reactions to foods are broadly distinguished by those that are immune-mediated and those that are not immune-mediated. This chapter reviews the various diagnoses and their pathophysiology within each category of adverse reactions to foods. The section on Immune Mechanisms of Adverse Food Reactions presents more advanced immunology as a supplement to the main discussion of adverse food reactions.

The Spectrum of Adverse Food Reactions

The ability of a food to provoke symptoms only in specific individuals is what separates toxic reactions to foods—which affect anyone who eats that food—from nontoxic reactions.[1] The National Institute of Allergy and Infectious Diseases (NIAID) defines a nontoxic reaction to food as a reproducible adverse health effect, rather than a hypersensitivity reaction as has been proposed by other nomenclature committees.[2,3] NIAID guidelines propose that nontoxic adverse food reactions, which are immune-mediated, include immunoglobulin E (IgE)-mediated, non–IgE-mediated, mixed IgE-mediated and non–IgE-mediated, and cell-mediated conditions such as celiac disease (see Figure 1.1 and Box 1.1 on page 3). Non–immune-mediated conditions—including metabolic, pharmacologic, and toxic conditions, as well as conditions described as other, idiopathic, or undefined—are often collectively called food intolerances. Recently, experts have proposed that the term *intolerance* needs to be much better defined.[4]

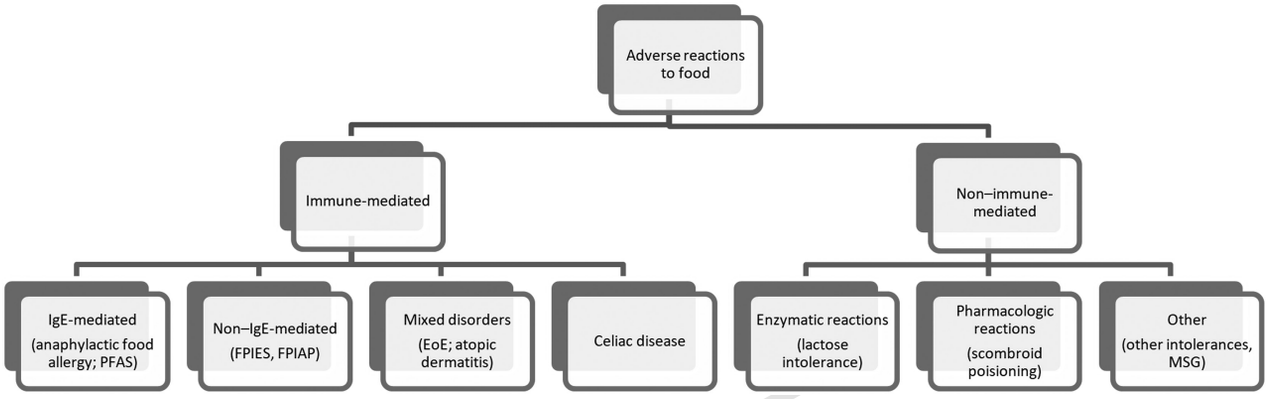
Immune-Mediated Adverse Food Reactions

Conditions Mediated by Immunoglobulin E

Classic Food Allergy and Food-Induced Anaphylaxis

Epidemiology IgE-mediated food allergies are characterized by rapid onset of symptoms following ingestion of a food allergen. Symptoms can range from mild, isolated cutaneous or gastrointestinal (GI) symptoms to multisystem involvement, as seen in anaphylaxis.[5,6] Studies have reported that IgE-mediated food allergies occurs in up to 10% of children[7,8] and 8% of adults.[8] Interestingly, a small number of foods account for the majority of cases—namely, cow's milk, hen's egg, wheat, soy, peanut, tree nuts, fish, crustacean shellfish, and

FIGURE 1.1 Categorization of adverse reactions to foods into immune-mediated and non–immune-mediated disorders



Abbreviations: EoE, eosinophilic esophagitis; FPIAP, food protein–induced allergic proctocolitis; FPIES, food protein–induced enterocolitis syndrome; IgE, immunoglobulin E; MSG, monosodium glutamate; PFAS, pollen food allergy syndrome.

BOX 1.1

Clinical Manifestations and Tests to Help Differentiate Various Immune-Mediated Adverse Food Reactions

Immunoglobulin E (IgE)–mediated

Classic food allergy or food-induced anaphylaxis

Clinical history	Immediate and reproducible symptoms, such as hives, vomiting, or wheezing, within 2 h of ingestion of the food allergen
Supportive testing	Skin prick test or specific IgE test for sensitization to food of concern
	Oral food challenge, when clinically indicated

Pollen food allergy syndrome (previously called oral allergy syndrome)

Clinical history	Isolated oral itching or tingling after eating raw fruits or vegetables, legumes, tree nuts
Supportive testing	Skin prick test or specific IgE test for sensitization to pollens that cross-react with protein in the food

Galactose-α-1,3-galactose (alpha-gal) syndrome

Clinical history	Delayed (3-6 h after ingestion) systemic reaction to mammalian meat, such as beef, pork, lamb, venison, and their organ meats
	Occurs most often in the southeastern United States
	Reaction to milk from these mammals, in some patients

Box continues

BOX 1.1 (CONTINUED)

Supportive testing	Specific IgE test for sensitization to alpha-gal; history of tick bites (eg, a Lone Star tick bite)

Non–IgE-mediated

Food protein–induced enterocolitis syndrome

Clinical history	Delayed (1-4 h after ingestion) and protracted vomiting, often with lethargy and pallor, after ingestion of a trigger food
Supportive testing	Clinical history

Food protein–induced proctocolitis

Clinical history	Blood-tinged stools in an otherwise healthy and thriving infant that are, in most cases, secondary to ingestion of cow's milk protein
Supportive testing	Guaiac test for occult blood in stool

Other forms of non–IgE-mediated food allergies (eg, food protein–induced enteropathies)

Clinical history	Varied presentation
Supportive testing	Clinical history
	Endoscopy, depending on the presentation

Mixed conditions

Eosinophilic esophagitis

Clinical history	Feeding difficulties and poor weight gain in young children
	Dysphagia and food impaction in adolescents or adults
Supportive testing	Histological evidence of esophageal eosinophilia on endoscopy

Atopic dermatitis

Clinical history	Relapsing erythematous and pruritic skin condition with a clear and consistent food trigger that is recalcitrant to appropriate skin care management
Supportive testing	Clinical history and exam

sesame.[5] However, culprit foods may differ depending on a person's age: milk, egg, peanut, tree nuts, and crustacean shellfish are most common in children, and crustacean shellfish, fish, peanut, and tree nuts are most common in adults.[9] Knowledge of the natural history of IgE-mediated food allergies is required for the long-term management of these conditions. In general, allergies to milk, egg, wheat, and soy are outgrown, whereas allergies to peanut, tree nuts, and sesame seeds tend to be persistent.[10,11]

Diagnosis using clinical history A patient's clinical history is the most important element in the diagnosis of an IgE-mediated food allergy (see also Chapters 2 and 3).[3] Symptoms involved in IgE-mediated reactions to foods can include, but are not limited to, cutaneous

(urticaria, angioedema), respiratory (wheezing, coughing, sneezing, rhinorrhea, congestion), GI (vomiting, abdominal pain), cardiovascular (hypotension), and miscellaneous (eg, a sense of impending doom) symptoms.[5] These typically develop within 30 minutes of eating a trigger food, and nearly all reactions occur within 2 hours; however, some factors are believed to delay digestion and absorption of the allergens (eg, very high fat foods, possibly baked milk and egg). Symptoms should subside promptly with treatment, assuming the food is not being continuously ingested, unless the individual experiences biphasic or protracted anaphylaxis, which is rare.[10,12] Similarly, while the exact symptomatology may differ with each ingestion, clinical symptoms should be reproducible with each ingestion of a food allergen outside of specific situations in which an augmenting factor is required, such as food-dependent exercise-induced anaphylaxis (see Chapter 2).[3] Thus, knowledge of the allergenicity and natural history of the food allergen in question is essential.

Diagnosis using food allergy testing Routinely available testing methods to assist in the diagnosis of IgE-mediated food allergies include skin prick testing (SPT) and a type of blood test called a specific IgE (sIgE) test, which measures the level of IgE antibodies in response to an individual (ie, specific) allergen. A positive test result, however, indicates sensitization (a measurable immune response) and is not, in isolation, diagnostic of a food allergy. Many people with a positive test (i.e., who are sensitized) are able to eat the food with no symptoms. Although larger wheal sizes on a SPT and higher serum sIgE levels are associated with an increased likelihood of allergy, no result can indicate a diagnosis of IgE-mediated food allergy with 100% certainty.[13] Furthermore, a convincing clinical history alone is not sufficient to diagnose a food allergy, given that more than half of self-reported food allergies cannot be reproduced.[3] To make the diagnosis of IgE-mediated food allergy, a combination of positive test results for markers of sensitization and reproducible symptoms upon ingestion of the suspected food is required. Therefore, allergy testing should only be performed for specific foods of concern based on the patient's clinical history, and broad panel testing (testing for reactions to multiple foods) should be avoided, as this can lead to the overdiagnosis of food allergies and inappropriate food avoidance.[13]

When a patient's clinical history is inconclusive, an oral food challenge can be pursued to assess oral tolerance to a specific food. An oral food challenge is a procedure conducted by an allergist-immunologist during which the patient eats a specific food under medical supervision for the purpose of making an accurate diagnosis of adverse food reaction.[14,15] Food challenges are often used to assess for acquired tolerance of a food, when clinically appropriate.[5] They can vary in regard to starting dose, escalation of dosing, intervals between doses, and length of observation period, depending on the clinical situation. Although it is not typically done in clinical practice, a double-blind, placebo-controlled oral food challenge is the gold standard for the diagnosis of IgE-mediated food allergies. Open challenges are more commonly used outside of research settings. Oral food challenges are discussed in more detail in Chapter 4.[3]

Molecular diagnostics, also called component-resolved diagnostics, evaluate IgE binding to specific component proteins within a food as opposed to a mixture. This can be beneficial in the diagnosis of allergies to some foods.[13,16] For example, peanut has at least nine component proteins, which have been well described and are relevant to food allergies. Ara h1, Ara h 2 (high homology with Ara h 6 and Ara h 7), and Ara h 3 (Ara h 4 isoform) are heat-resistant seed-storage proteins, and they are considered the major, clinically relevant allergens. Ara h 5, Ara h 8, and Ara h 9 have homology with plant allergens; most notably, Ara h 8 is a Bet v 1 (birch pollen) homologue.[16] Ara h 2 has the strongest association with IgE-mediated, systemic allergic reactions to peanut[17] and has the best diagnostic accuracy compared to any other clinically available test. Meanwhile, patients who are monosensitized to Ara h 8 may have no symptoms with peanut ingestion or experience mild symptoms consistent with pollen food allergy syndrome, which is discussed in more detail

shortly.[16] Component-resolved diagnostic testing for many foods is available and is discussed in Chapter 3.

Management and potential therapies Once an IgE-mediated food allergy is diagnosed, the mainstay of treatment is individualized avoidance of the food allergen (see Chapters 5 and 6) and patient education in how to manage future reactions.[5] Skin prick testing and sIgE testing do not accurately predict the severity of an allergy. In the United States, experts recommend that all patients with IgE-mediated allergies to foods that could elicit severe reactions be prescribed an epinephrine auto-injector, regardless of the severity of the initial clinical reaction,[3] and guidelines from Europe recommend an epinephrine auto-injector prescription for those with a history of a severe allergic reaction.[18]

Treatment options for food allergies, such as oral immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy, are promising.[13,19,20] They are discussed in Chapter 11.

Cross-reactive foods Consideration of potentially cross-reactive foods is a common concern. For example, a patient who has a clinical history of reacting to shrimp has a high likelihood of being allergic to other crustacean shellfish.[21] Alternatively, a patient who reacts to peanut has a low likelihood of being clinically allergic to other legumes but has a high likelihood of testing positive (ie, cosensitization) to some legumes, such as lupine or fenugreek.[5,21] Thus, the decision to test for allergies to other related foods not already tolerated should be based on knowledge of the likelihood of a clinically relevant coallergy vs cosensitization.[3]

Pollen Food Allergy Syndrome

The pollen food allergy syndrome (PFAS), previously called oral allergy syndrome, is a localized, IgE-mediated hypersensitivity with symptoms such as tingling, itching, or swelling of the lips, tongue, mouth, or throat on ingestion of raw fruits and vegetables or other plant foods such as peanut and tree nuts.[5] The prevalence varies widely based on the geographic area studied and rates of pollen sensitization, but studies suggest that up to 48% of children and 70% of adults with pollen allergies experience PFAS, and the prevalence among the general adult population could be 2% or more.[22-26] PFAS is caused by food proteins that cross-react with pollen antigens to which the patient is sensitized; for example, eating a raw apple may provoke symptoms in people sensitized to birch pollen (Bet v 1), but eating apple sauce will not.[21] This is because the particular proteins (PR-10 proteins and profilins) in raw plant foods that cross-react with Bet v 1 are sensitive to heat and gastric digestion and so are not recognized once the food is heated or digested.[27,28] Commonly implicated pollens and corresponding foods include but are not limited to: birch tree pollen with apple, carrot, pear, almond, soybean, peanut, hazelnut; ragweed with cantaloupe, cucumber, and banana; mugwort with celery, carrot, and multiple spices; grass pollen with wheat (see Box 1.2).[21]

Symptoms of PFAS can occur in people who have no clinical history of allergic rhinitis but who are sensitized (ie, have positive allergy skin or blood test results) to pollens. Any child or adult who is sensitized or allergic to pollen can have positive sIgE test results for cross-reactive foods, especially peanut or tree nuts that bear similar proteins. Therefore, knowledge of a patient's pollen sensitization profile is essential when evaluating reported reactions to plant foods, as pollen-sensitized individuals may have positive test results to peanut and tree nuts, which may not be clinically relevant. Conversely, testing to commercially available fruit, vegetable, and soybean extracts is not always helpful because the labile allergens are degraded in extract preparation or lose potency over time.[5] Thus, although SPTs to raw fruits or vegetables or soy milk have not been standardized, these tests may be more useful than using commercial allergen extracts.[27,29] Although symptoms are typically limited to the oropharynx, anaphylaxis can occur in up to 9% of cases.[22,30,31] Thus, while it

BOX 1.2

Pollens and Foods Involved in Pollen Food Allergy Syndrome[21]

Pollen	Allergens	Potential food triggers
Silver birch (*Betula verrucosa*)	PR-10 allergens (Bet v 1 homologues)	Apple, pear, cherry, peach, nectarine, apricot, plum, damson, greengage, strawberry, kiwifruit, hazelnut, walnut, almond, Brazil nut, peanut, celery, carrot, potato, soy, fig, bean sprouts, mange-tout
Timothy grass (*Phleum pratense*)	Profilins	Melon, watermelon, orange, tomato, eggplant, sweet pepper, chili or cayenne pepper, potato, peanut, Swiss chard
Common mugwort (*Artemisia vulgaris*)	Profilins	Celery, celeriac, carrot, parsnip, dill, parsley, coriander, cumin, fennel, aniseed, caraway, angelica, chervil, sunflower seed, honey
Common ragweed (*Ambrosia artemisiifolia*)	Profilins	Watermelon, melon, banana, zucchini, cucumber, vegetable marrow, squash, pumpkin

is not standard treatment for all patients with PFAS, the prescription of an epinephrine auto-injector should be considered for patients with a history of laryngeal swelling or respiratory compromise.[5]

Alpha-Gal Syndrome

Galactose-α-1,3-galactose (alpha-gal) is an oligosaccharide found in most mammals. Alpha-gal syndrome is a condition characterized by delayed, systemic reactions to the consumption of mammalian (red) meat, such as beef, pork, lamb, venison, and rabbit.[5] Reactions typically occur 2 to 6 hours after food ingestion. Specific IgE testing to galactose-α-1,3-galactose (alpha-gal) is diagnostically useful as results of skin prick testing to mammalian meats are often negative. Treatment consists of avoiding the offending food or foods and a prescription for an epinephrine auto-injector device. Interestingly, a tick bite—primarily a bite from the Lone Star tick (*Amblyomma americanum*) found in the southeastern United States—is responsible for this condition (see also Box 1.1).[32,33]

Conditions Not Mediated by Immunoglobulin E

Food Protein–Induced Enterocolitis Syndrome

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy characterized mainly by delayed and repetitive vomiting.[34] This condition is covered in detail in Chapter 7. FPIES typically starts in the first year of life, although later onset has been reported.[34] Cumulative incidence ranges from 0.015% to 0.7%[35] while a US population-based study published in 2019 reported a prevalence of 0.51%.[36]

FPIES is a clinical diagnosis. Acute FPIES is defined by a clinical presentation of the major criterion—namely, vomiting in the period from 1 to 4 hours after ingestion of the suspected food and the absence of classic skin or respiratory symptoms associated with IgE-mediated allergy—and three or more minor criteria. The minor criteria are: a second (or more) episode of repetitive vomiting after eating the same suspect food, a repetitive

vomiting episode 1 to 4 hours after eating a different food, extreme lethargy with any suspected reaction, marked pallor with any suspected reaction, the need for an emergency department visit with any suspect reaction, the need for intravenous fluids with any suspected reaction, diarrhea in 24 hours, hypotension, and hypothermia.[34] When the diagnosis is not clear, an oral food challenge should be considered, particularly because viral gastroenteritis with similar symptomatology is common in infants.[34]

Chronic FPIES can occur when the trigger food is ingested on a regular basis (eg, cow's milk–based formula). Patients with chronic FPIES do not have acute symptoms but rather intermittent and progressive GI symptoms and growth faltering. Essential components in the diagnosis of the chronic condition include resolution of symptoms within days of avoiding the offending food and acute symptoms with reintroduction of the food.[34] As FPIES is a non–IgE-mediated condition, there is little utility in performing IgE testing to foods of concern when the clinical history is clear.[34] An exception to this is when atypical FPIES is a possibility. Atypical cases are characterized by the development of sensitization (ie, a positive sIgE or SPT) to a food avoided for FPIES.[34] The frequency of this varies, ranging from 5% to 30% of children with FPIES, and it occurs most often in FPIES triggered by cow's milk.[35-37]

The most common triggers of acute FPIES in infants are rice, oats, cow's milk, soy, and select fruits and vegetables, such as sweet potatoes and bananas.[34] However, triggers can vary with geographic location and infant feeding practices; for example, fish is a more common trigger in Spain and Italy.[38,39] Fish and shellfish are the most common food triggers in older children and adults.[34]

Management of FPIES includes instructing patients to avoid the culprit food or foods and educating them about the risk for dehydration in FPIES and the fact that traditional therapies for IgE-mediated food allergies (ie, epinephrine and antihistamines) have no role.[34] The natural history of FPIES is generally favorable in that most patients will outgrow it by school age[34]; therefore, assessing for acquisition of tolerance through an oral food challenge (Chapter 4) is essential for long-term management. Caregivers of infants with FPIES require guidance on complementary feeding. See Chapter 7 for more details on dietary and nutrition management of FPIES.

The pathophysiology of FPIES has not been fully elucidated. However, FPIES is believed to be secondary to intestinal inflammation after food-antigen exposure and T-cell activation, which leads to increased permeability of the gut and fluid shifting into the intestinal lumen.[34] Neutrophilia has also been observed in patients with acute FPIES and constitutes one of the minor diagnostic criteria for a positive FPIES oral food challenge result; however, routine laboratory testing is not recommended or necessary for FPIES. The immune mechanisms that underlie FPIES are complex, involve many different cells and mediators of the immune system, and are not fully understood.[40-42]

Food Protein–Induced Allergic Proctocolitis

Food protein–induced allergic proctocolitis (FPIAP) is a non–IgE-mediated adverse food reaction typically presenting in the first few months of life with GI symptoms, specifically blood in the stool, in an otherwise growing and thriving infant.[43,44] The exact prevalence of FPIAP is unknown, but it is thought to be more common than FPIES.[43]

FPIAP can occur in breastfed or formula-fed infants. Cases in breastfed infants occur through maternal ingestion of the food antigen; cow's milk is the most common culprit, and soy, egg, and wheat are others.[44] Cases in formula-fed infants are typically caused by cow's milk–based or soy-based formulas. Treatment involves maternal avoidance of the allergen in breastfed infants or transition to a hypoallergenic formula in formula-fed infants. More recently, a "watch and wait" approach has also been proposed (see Chapter 7).[44] As this is a non–IgE-mediated food allergy, there is little role for SPT or sIgE testing in the effort to

identify triggers. Fortunately, FPIAP is typically a self-limited condition, with the majority of patients outgrowing it by age 1 year.[44]

Mixed IgE-Mediated and Non–IgE-Mediated Conditions

Some immune-mediated adverse food reactions are mixed in nature in that they involve both IgE-mediated and non–IgE-mediated mechanisms.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil predominant inflammation.[45] (This disorder is also extensively reviewed in Chapter 8). The prevalence of EoE in Western countries is estimated to be 0.4% among children and adults.[46] Patients with EoE are more often male than female, and they frequently have comorbid atopic conditions, such as IgE-mediated food allergies, atopic dermatitis, asthma, or allergic rhinitis.[46] Symptoms differ depending on the age of the patient. Common presenting symptoms in children include feeding difficulties, vomiting, and abdominal pain, whereas adolescents and adults typically present with dysphagia and food impactions.[46] In addition to clinical symptoms, pathological evidence on endoscopy is also required for diagnosis, with the threshold for diagnosis being at least 15 eosinophils per high-powered field in the esophageal mucosa after ruling out other causes of esophageal eosinophilia.[45,46] Long-term complications of untreated EoE include malnutrition, esophageal stricture formation, and food impaction.[46]

Treatment for EoE can include medications, dietary therapy, and esophageal dilation. Although esophageal dilation alleviates esophageal narrowing, it does not treat the underlying inflammatory process. Thus, it is not recommended as monotherapy, as EoE is a chronic disease.[46] Medications include proton pump inhibitors and having patients swallow steroids that are in formulations that are normally inhaled from metered dose inhalers ("asthma puffer") or nebulizer machines to treat asthma..[45,47] To swallow the steroids that are normally used for asthma, patients may be instructed to spray the puffs from a fluticasone metered-dose inhaler (but swallow rather than inhale), or a viscous preparation of liquid budesonide (used in nebulizer machines) might be mixed with an agent to increase viscosity and make it easier for young children to swallow. These and other treatments are often used off-label in the treatment of EoE, despite currently lacking US Food and Drug Administration approval for this use.[46]

Dietary therapy is an additional treatment option for patients with EoE (see Chapter 8). Standard elimination diets including elemental, testing-directed, and empiric elimination diets are used.[48] In general, 30% to 50% of patients have one food that causes their disease, 30% have two, and the remainder have three or more offending foods.[49] The elemental diet consists of exclusively feeding the patient with an amino acid–based formula; it has high success rates—up to 90% in children and 94% in adults[50]—but is highly restrictive and often unpalatable, thus limiting its practical use in routine cases of EoE.[48]

Although the role of IgE in EoE has not yet been fully characterized, the predominant mechanism seems to be non–IgE-mediated.[46] Thus, testing-directed diets, in which foods are removed based on traditional allergy testing (SPT, serum sIgE test), has not been highly successful.[48] The atopy patch test was proposed as a diagnostic test because a positive test might reflect a non-IgE response but similarly demonstrated mixed results.[48] A systematic review of testing-directed dietary therapy reported success in 48% of children and 32% of adults.[50]

A registered dietitian nutritionist (RDN) plays a crucial role in implementing dietary avoidance in patients with EoE. The RDN can also assess whether the prescribed dietary therapy is feasible. Empiric elimination diets consist of avoiding foods that are the most causative food allergens in EoE without actually doing allergy testing.[48] Commonly recommended empiric elimination diets are:

- the six-food elimination diet, which eliminates (1) cow's milk, (2) wheat, (3) egg, (4) soy, (5) peanut and tree nuts, and (6) fish and crustacean shellfish;
- the four-food elimination diet, which eliminates (1) cow's milk, (2) egg, (3) wheat, and (4) soy and legumes;
- the two-food elimination diet, which eliminates (1) cow's milk and (2) wheat; and
- the one-food elimination diet, which eliminates cow's milk.

In general, the more restrictive the diet, the more successful it will be[48]; however, this must be balanced against quality of life, nutrition needs, and the need for an increased number of endoscopies with subsequent food reintroductions. Overall, the choice of treatment approach is based on a discussion between the treating physician and the patient (and the family or caregiver) of the risks and benefits of each approach.

Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory skin condition characterized by pruritus, scratching, and relapsing eczematous lesions.[51,52] It often presents in infancy and affects 10% to 20% of children and 1% to 3% of adults.[51] It is often the first manifestation in the "atopic march," with many patients later developing IgE-mediated food allergies, asthma, or allergic rhinitis.[51] The diagnosis is clinical, based on characteristic clinical history and exam findings. Skin care is the first-line treatment; this includes regular bathing, frequent use of moisturizing creams, and topical steroids as needed for flares.[51]

Although atopic dermatitis is very rarely due to an underlying or undiagnosed food allergy, patients with early onset and severe atopic dermatitis are at the greatest risk for developing food allergies.[53] Patients with atopic dermatitis can also have an elevated total IgE level, which can lead to nonspecific binding and multiple elevated food-specific IgEs.[51] Much of the sensitization may not be clinically relevant, leading to unnecessary food avoidances and the risk for negative psychosocial, developmental, and nutritional effects.[54] Furthermore, removing a previously tolerated food from the diet of a child for whom there were only concerns of worsening atopic dermatitis can lead to the development of a true clinical IgE-mediated food allergy after a period of avoidance.[55] Thus, current guidelines for the evaluation of food allergies in patients with atopic dermatitis recommend testing only in patients with a suggestive clinical history of an IgE-mediated food allergy to the food of concern or in patients with moderate to severe atopic dermatitis that is recalcitrant to optimized therapeutic skin care management. The guidelines specifically recommend against food avoidances based on SPT or sIgE testing alone (see Chapters 2 and 3).[51,52,56,57]

Celiac Disease

Celiac disease is categorized by the NIAID 2010 guidelines as an immune-mediated adverse reaction to a food.[3] The condition is defined by a chronic, small-intestinal, immune-mediated enteropathy precipitated by exposure to dietary gluten.[58] Glutens are alcohol-soluble proteins in cereals, which include gliadins in wheat, hordeins in barley, and secalins in rye. The response to ingested gluten involves the recognition of gliadin peptides bound to antigen-presenting cells by T cells in the lining of the GI tract.[59] This binding is enhanced

by tissue transglutaminase (an enzyme), which also deamidates these peptides, increasing their immunogenicity.[59,60] This provokes damage to the GI tract, resulting in consequent malabsorption. The estimated prevalence of celiac disease is between 1% and 1.5% worldwide and is largely driven by genetic factors, with the vast majority of people with this disease having the class II human leukocyte antigen (HLA)-DQ2 haplotype or HLA-DQ8 haplotype (or both).[61]

Classic symptoms include diarrhea, steatorrhea, weight loss, and mild, nonspecific GI symptoms, such as abdominal pain. Isolated growth failure presents in a minority of children.[62,63] Celiac disease also presents in adult life, with a nonclassic presentation and no family history being more prevalent in males and older people.[64] Dermatitis herpetiformis, a chronic skin condition triggered by gluten ingestion can be an important sign of celiac disease in 10% to 15% of individuals, most of whom will have no GI symptoms.[65] In addition, celiac disease can manifest with other symptoms, such as delayed puberty, fatigue, iron deficiency anemia, oral ulcers, dental enamel hypoplasia, low bone mineral density, and osteoporosis. The nonspecific nature of these symptoms may cause diagnostic delay, especially if GI symptoms are not predominant, leading to a low level of diagnostic accuracy in some primary care settings.[66,67] Neurological symptoms such as neuropathy and ataxia may precede a diagnosis of celiac disease.[68] Nutritional deficiencies are often associated with undiagnosed celiac disease, especially iron deficiency and suboptimal levels of vitamin D, folate, vitamin B12, vitamin B6, and zinc.[69] Individuals with such deficiencies are, therefore, at high nutritional risk and would benefit from early intervention by an RDN.

In terms of diagnosis, relevant history includes having a first-degree relative with celiac disease or a family history of type 1 diabetes mellitus, autoimmune thyroid or liver disease, or Down syndrome.[66] Diagnostic tests with a high specificity and sensitivity are immunoglobulin A (IgA) antibodies against tissue transglutaminase (anti-TG2) and endomysium (anti-EMA).[70] However the avoidance of gluten can confound the result, so for those in this category or who are in an at-risk group and have negative test results, the analysis of HLA type is very useful, given that testing negative for class II HLA types DQ2 and DQ8 has a predictive value of more than 99%.[70] A positive test result, whether anti-TG2, anti-EMA, or a specific genetic test, indicates the need to perform a duodenal biopsy, but when this is not possible, guidelines suggest that the diagnosis of celiac disease can be confirmed in those who are symptomatic and also have a high level of IgA anti-TG2 (more than 10 times the upper limit), a positive anti-EMA test result, and the HLA-DQ2 haplotype.[71,72]

It is vital to ensure a correct diagnosis, as the only way to facilitate mucosal healing and effective absorption of nutrients is a lifelong exclusion of dietary gluten.[66] This includes strict avoidance of wheat, rye, and barley; there are similar proteins (avenins) in oats, but most people with celiac disease can tolerate oats provided they are certified as gluten-free (meaning not contaminated with gluten from other cereals).[73] No more than 50 mg contaminating gluten should be ingested per day to prevent the exacerbation of symptoms and consequent enteropathy.[74] Around 90% of individuals with celiac disease demonstrate long-term adherence to a gluten-free diet, especially if they presented with classic symptoms of diarrhea and weight loss or have been diagnosed by biopsy.[75,76]

Managing a gluten-free diet can be challenging. Patients have concerns about which products to choose, the healthiness of a gluten-free diet, unexpected contamination of supposedly gluten-free foods, the limited availability or choice of gluten-free foods, and the effect that a strict diet may have on their social life.[77,78] Cross-contamination can be a major issue for some types of food preparation.[79] Avoidance of gluten-containing cereals can affect energy intakes in children and lead to a reduced intake of carbohydrates, dietary fiber, and micronutrients, including iron, calcium, zinc, and folate.[80] Gluten-free diets may be low

in these nutrients, and patients strictly adhering to a gluten-free diet for some years are especially at risk of a folate deficiency.[81] Specialized gluten-free products, frequently made from rice-, corn-, or potato-based starches, often contain lower levels of protein and other nutrients than their gluten-containing equivalents.[82] Naturally gluten-free grains (eg, amaranth, millet, buckwheat, sorghum, quinoa, and teff) and other naturally gluten-free foods (eg, nuts, seeds, and legumes) are more nutrient-dense substitutes. Thus, the dietary management of celiac disease requires an individualized approach, incorporating advice from a qualified RDN, in order to optimize the nutritional quality of the gluten-free diet.[83] Patients whose disease is not entirely responsive to a gluten-free diet may have other forms of food intolerance, such as lactose or fructose intolerance, or poor digestion of foods naturally high in histamine.[84]

Trends in Immune-Mediated Adverse Food Reactions: The Increasing Prevalence of Food Allergies

Estimates of food allergy prevalence are difficult to verify. Two systematic reviews were unable to estimate prevalence because of the variations in study design among the included studies or differences between populations.[85,86] Studies of self-reported food allergies in children estimate prevalence to be in the range of 6.5% to 8% in the United States and 6.5% to 28.7% in Europe, whereas the figures for probable food allergies were much lower—only 1.9% to 5.5% among children in the United States and 1.45% to 3.8% among children in Europe.[7,87-89] The prevalence of probable food allergies in European adults is lower than it is for children, ranging from 0.3% to 5.6%.[90] A systematic review of European studies reported the point prevalence of self-reported food allergies in all age groups to be 5.9%, whereas the point prevalence of food allergies confirmed by food challenge was 0.9%.[91]

While these data show great variability in reported vs actual prevalence, it remains unclear whether there is an upward trend in food allergies. Estimates of self-reported food allergies and allergen sensitization are likely to grossly overestimate the prevalence of IgE-mediated allergies. In US adults, the prevalence of self-reported food allergies increased from 9.1% in 2001 to 13% in 2010, whereas the prevalence of physician-diagnosed food allergies remained essentially stable over the same time period (5.3% in 2001 vs 6.5% in 2010).[92] A more recent survey (2019) reported that 19% of adults believed they had at least one current food allergy, but only 10.8% actually had a physician-diagnosed allergy.[8] An analysis of results from two birth cohorts studied on the Isle of Wight (IOW) recruited 12 years apart found that the prevalence of challenge-confirmed food allergies in 10-year-olds had slightly increased—from 2.3% in the IOW 1989 cohort to 3.6% in the IOW Food allergy and intolerance research (FAIR) 2001 birth cohort.[93] However, a subanalysis found no significant difference in the prevalence of peanut allergy at any time points.[94]

When trying to establish whether food allergies are on the rise, it is important to take into account age, race, diet, and regional or country-specific changes. Although it seems that the prevalence of confirmed food allergies may vary from country to country, the rate may also vary by age, with one systematic review reporting the rate of challenge-proven food allergies in 1-year-olds to be 10%.[95]

Non–Immune-Mediated Adverse Food Reactions

Adverse food reaction that are not immune mediated are linked to insufficient digestive enzymes, pharmacologic reactions, and other dietary substances, including various types of food additives. Box 1.3 summarizes non-immune-mediated reactions and common examples.

BOX 1.3

Non-Immune-Mediated Adverse Reactions to Foods and Common Examples

Enzymatic reactions

Diagnosis is made by clinical history and, if needed, a hydrogen breath test.

Example: Lactase deficiency or lactose intolerance

Pharmacologic reactions

Pharmacologic reactions can be provoked by high levels of vasoactive amines in food or a sensitivity to naturally occurring substances in foods, such as caffeine, theobromine, and salicylates.

Example: Scombroid poisoning. This is an adverse reaction to ingesting large amounts of dietary histamine in improperly preserved fish (eg, tuna, mahi-mahi, and others). Typical symptoms include flushing, pruritus, urticaria, and bronchospasm.

Other types of non–immune-mediated adverse food reactions

Functional gut disorders secondary to reactions to lactose, fructose, or histamine

Reactions to chemical food additives or food colorings

Reactions to food preservatives (eg, sulfites and benzoates)

Reactions to monosodium glutamate

Enzymatic Reactions

Many people around the world experience digestive discomfort after ingesting milk, a condition caused by a deficiency of the enzyme lactase that hydrolyzes lactose (the disaccharide in milk).[96] Congenital lactase deficiency is extremely rare; rather, symptoms are usually the result of a natural decline in lactase activity after weaning. Lactose intolerance may develop from early childhood onward and affects up to 80% of the populations, with the prevalence depending on ethnicity.[96] Up to 95% of adults in Caucasian populations retain a high level of lactase sufficiency, compared to only 30% to 40% of adults in Indian, South American, or African populations, and just 10% of adults from Southeast Asia.[97] Temporary lactose intolerance can occur later in life if GI illness damages the brush border of the small intestine.[96] The inability of the gut to hydrolyze lactose increases the osmotic load and accelerates transit in the small intestine, leading to fermentation by colonic bacteria, which yields short-chain fatty acids and hydrogen gas. Thus, abdominal pain, bloating, diarrhea, and flatulence are common symptoms, although occasionally nausea and vomiting are predominant.[98]

A diagnosis can often be made using clinical symptom history alone, but pretest symptoms have been shown to be poor predictors of lactose intolerance, especially if milk is not habitually consumed. Currently, the most reliable diagnostic tool is the measurement of breath hydrogen and methane levels over a period of 3 to 6 hours, before and after the consumption of a standard dose of lactose. The hydrogen breath test, which has good sensitivity and specificity, is considered to yield a positive result when the amount of hydrogen in the breath is 20 ppm or more above the baseline level or the amount of methane is 15 ppm or more above baseline, or both.[99] It is important to measure both hydrogen and methane because approximately 20% of individuals will produce methane rather than hydrogen due to particular populations of bacteria in the gut.[100] The hydrogen breath test is a useful

diagnostic tool, as a high percentage of patients with chronic GI symptoms or irritable bowel syndrome have a positive test result.[101,102] This suggests that investigations for lactose intolerance should be considered as a first-line approach in those with irritable bowel syndrome or nonspecific GI symptoms, with an assessment of the efficacy of a lactose-free diet being undertaken if hydrogen breath testing is not available. Fructose intolerance may occur in patients who are already lactose intolerant, so it should be considered if symptoms persist despite eliminating lactose from the diet or if the results of a lactose hydrogen breath test are negative.[103]

Following a positive breath test result, patients should eliminate lactose from their diet for 4 weeks to confirm the diagnosis and then reintroduce foods containing small amounts of lactose to see how well this is tolerated. Some lactose-intolerant patients may tolerate up to 15 g lactose throughout the day, and this might also help to decrease symptom severity.[98] A reduction in dairy products may affect the calcium intake of the diet and increase the potential for bone loss and osteoporosis. However, patients who are intolerant to lactose are not at greater risk for changes in bone density, probably because lactose-free milk products still contain calcium and plant-based substitutes are often fortified with calcium and vitamin D.[104,105] The dietary elimination or reduction of lactose can be complicated by the addition of lactose to nondairy products, including baked goods, breakfast cereals, and processed meats. Under allergen-labeling laws, any form of cow's milk present in a product must be listed in the ingredients list on the food label.[106] However, many foods containing milk proteins may not actually contain clinically relevant amounts of lactose, and milk as a minor ingredient is rarely problematic for people with lactose intolerance. RDNs can greatly assist patients with a lactose or fructose intolerance, especially patients who are already excluding other foods or who have an existing IgE-mediated food allergy.

Pharmacologic Reactions

Pharmacologic reactions to foods include reactions provoked by a high level of vasoactive amines in a food and sensitivities to naturally occurring substances in foods, such as caffeine, theobromine, and salicylates.

Vasoactive or biogenic amines occur in foods as a result of bacterial degradation during fermentation, storage, or decay, and they can be either monoamines, such as tyramine, or diamines, such as histamine.[107] Reaction to ingesting a large amount of dietary histamine is known as scombroid poisoning, the symptoms of which can include flushing, pruritus, urticaria, tachycardia, bronchospasm, arrhythmia, and life-threatening hypotension, occurring immediately or up to 2 hours after eating.[108] Certain species of fish may, if improperly preserved, contain excessive amounts of histamine due to the bacterial decarboxylation of histidine by marine bacteria; this can be the case even though the fish look and smell fresh.[107] One-third of restaurant-associated, single-food foodborne disease outbreaks in the United States are caused by fish consumption, with the vast majority of these being attributable to scombroid toxin.[109] Tuna, which belong to the Scombridae family, can cause symptoms when fresh or canned in oil; other fish frequently involved in scombroid poisoning incidents are other members of the Scombridae family (eg, mackerels) and species of the Scomberesocidae family, all of which generally contain high levels of histidine, the precursor of histamine.[110] Still others include mahi-mahi, sardine, anchovy, bluefish, marlin, and tilapia.[111] Although most people will react on exposure to very high levels of histamine in foods, some may be sensitive to smaller amounts, especially people who also suffer from urticaria, functional gut symptoms, or migraine.[112-114] Although there are putative diagnostic tests for the measurement of diamine oxidase, the enzyme that catabolizes histamine, such tests are not recommended for the diagnosis of histamine intolerance.[115] When considering the likelihood of histamine intolerance, experts recommended practitioners take a focused

diet and clinical history and conduct a trial exclusion of foods high in vasoactive amines, such as seafood, hard cheeses, red wine, pork products, aged meats, and fermented foods.[116]

Foods naturally high in salicylic acid, a signaling molecule widely distributed in plant foods, can also provoke adverse pharmacologic reactions.[116] Aspirin (acetylsalicylic acid) is a synthetic derivative of salicylic acid, and aspirin-exacerbated respiratory disease is thought to affect 20% of individuals with asthma and up to 40% of people with nasal polyps.[117] Some experts have proposed that dietary salicylates could adversely affect a considerable number of people, not only those with aspirin-exacerbated respiratory disease but also those with inflammatory bowel disease, irritable bowel syndrome, and food allergies.[116,118] However, based on the substantial variation in the salicylic acid content of plant foods and the lack of any large controlled studies evaluating the effects of a reduced intake of dietary salicylic acid, it is currently not possible to recommend the dietary exclusion of foods high in salicylic acid.[116,118] Rarely, pharmacologic reactions (eg, migraine, anxiety, disordered sleep) to dietary methylxanthines—such as caffeine, which is found in tea, coffee, caffeinated soft drinks, and some cola drinks—and theobromine, which is found in chocolate, have been reported.[116]

Other Non–Immune-Mediated Reactions to Foods

Functional gut disorders often involve reactions to lactose, fructose, or histamine, although many respond to the exclusion of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs).[119] Reactions to foods can also involve a sensitivity to food additives, although the prevalence of this is low and such reactions may only occur in conjunction with comorbidities, such as urticaria or asthma.[120] It is well accepted that natural food colorings that have proteins, such as carmine (cochineal) or annatto, can provoke IgE-mediated food-induced allergic reactions. In contrast, synthetic colorants that are chemicals and not proteins have been linked to adverse reactions that include rashes or other symptoms, but the evidence is less compelling for them and the mechanisms often unknown.[120] The other main group of additives linked to reactions to foods are preservatives such as sulfites, which prevent enzymatic and nonenzymatic browning of foods, control oxidation, and inhibit bacterial growth in alcoholic drinks, dried fruits, fruit juices, fruit cordials, frozen cooked shrimp, frozen raw potato products, and some meat products.[116] Sulfite-containing foods affect up to 10% of people with asthma, especially those with severe persistent asthma who regularly take corticosteroids.[121] Another added food preservative, benzoate, also occurs naturally in cinnamon, cloves, tea, plums, raspberries, and cranberries. A cinnamon-free and benzoate-free diet has been shown to reduce symptoms in patients suffering from orofacial granulomatosis.[122] The flavor enhancer monosodium glutamate (MSG) occurs naturally in some foods, including mushrooms and spinach, and is frequently added to processed savory foods.[116] Although MSG has been associated with asthma, headache, urticaria, angioedema, rhinitis, psychiatric disorders, and convulsions, evidence of a causal connection from controlled research investigations is weak.[123]

Immune Mechanisms of Adverse Food Reactions

This section is presented as a supplement to the main discussion of adverse food reactions and presents advanced immunology as additional background for the reader.

The immunologic mechanisms involved in the development of IgE-mediated and non–IgE-mediated food allergies from an initial state of tolerance in utero are complex and involve a variety of cellular and molecular pathways that, in some cases, overlap.[3,124] The primary difference between IgE-mediated and non–IgE-mediated food allergies is the presence

or absence of IgE antibodies. Immune pathways that lead to the production of IgE, and those involved in the production of inflammatory responses, were highlighted earlier in this chapter.

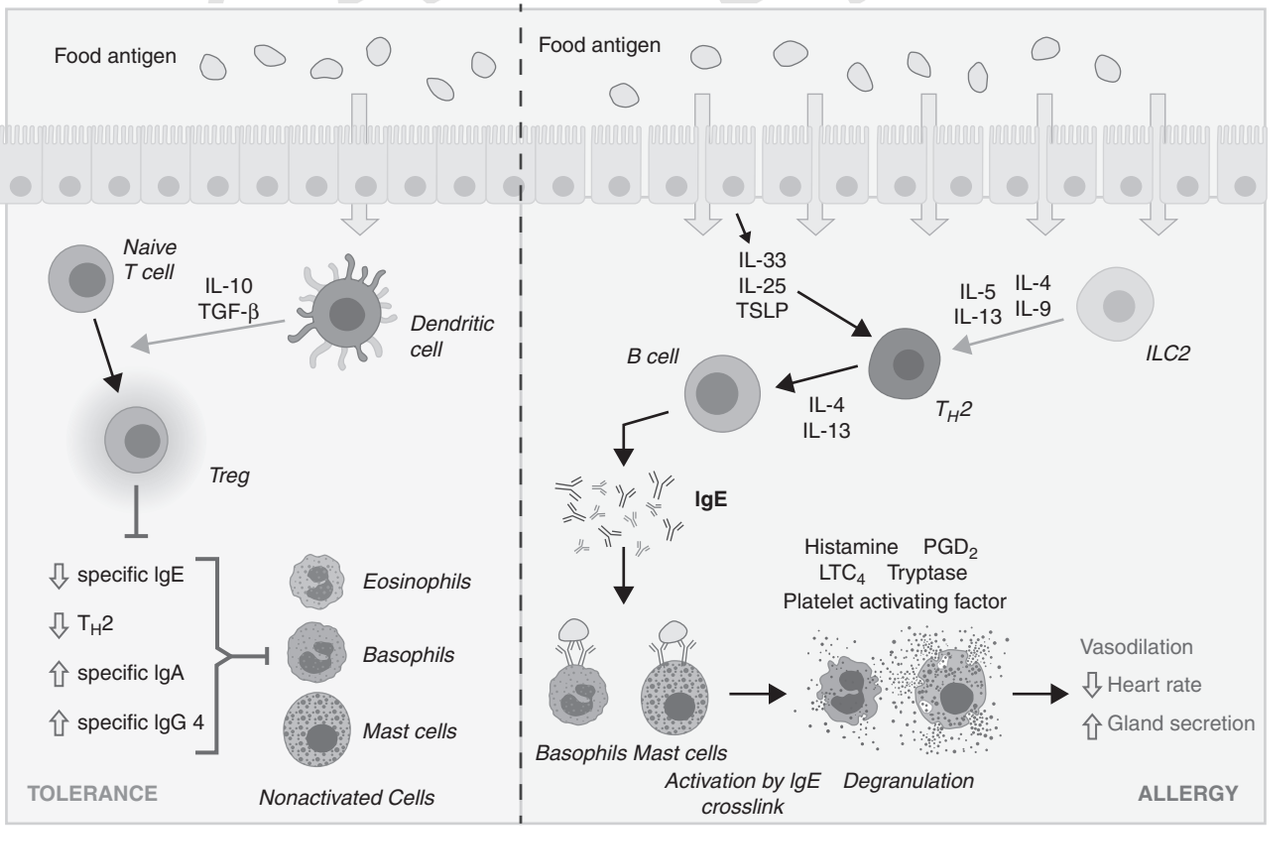
Immune Cells and Their Roles in IgE-Mediated and Non–IgE-Mediated Immune Responses

There are similarities between the immunological mechanisms involved in the development of IgE-mediated and non–IgE-mediated food allergies, as evidenced by diseases with features of both mechanisms, such as EoE and atopic dermatitis. Key components of the immune system are involved in the development of food tolerance and food sensitization or allergies. These are the epithelium, antigen presenting cells, T cells, B cells, and, finally, the effector cells of the allergic response: mast cells, basophils, eosinophils, and neutrophils (Figure 1.2).

Epithelial Barrier

The epithelial barrier (epithelium) plays a major role in defense against pathogens. In the context of IgE-mediated food allergies, the epithelium prevents unnecessary entry of antigens. An intact epithelial barrier is important in the maintenance of tolerance, as it prevents

FIGURE 1.2 Immune mechanisms of IgE-mediated food allergies and immune tolerance



Abbreviations: Ig, immunoglobulin; IL, interleukin; ILC2, type 2 innate lymphoid cell; LTC_4, leukotriene C_4; PGD_2, prostaglandin D_2; TGF-β, transforming growth factor β; T_H2, type 2 helper T cell; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin

the entry of danger signals and subsequently prevents the production of inflammatory cytokines, following exposure to food antigens. Antigens cannot freely pass through an intact epithelium, such as a mature intestinal lining or intact skin. Instead, with an intact epithelium, antigens are often transported with cellular mechanisms. This is a complicated process to maintain the integrity of the epithelial barrier[125] and promote the development of tolerance.[126-128] When this process is disrupted, food sensitization and food allergies can occur.[129,130]

Antigen-Presenting Cells and Innate Lymphoid Cells

Antigen-presenting cells are the most upstream mediators of allergic responses. They can mediate tolerance or the expression of allergies. Macrophages and dendritic cells produce the anti-inflammatory regulatory cytokine interleukin (IL)-10 and promote the development of regulatory T cells to cause tolerance.[127,131] Conversely, the breakdown of tolerance due to a compromised epithelial barrier causes macrophages, dendritic cells, and innate lymphoid cells to promote allergic responses.[129-132] Type 2 innate lymphoid cells have also been shown to play a critical role in the specific induction of food allergies,[133] producing IL-5, IL-13, IL-4, and IL-9, which promote food allergies.[134-136] These cytokines enhance mucosal mast cell activation and contribute to the clinical expression of food allergies.[133]

T Cells and B Cells

The appropriate influence of cytokines and innate cell mediators promotes the development of allergies by encouraging the transformation of naive T cells to type 2 helper T (T_H2) cells. Naive T cells reside in the draining lymph nodes and wait for the upstream signals; then, in combination with the presented antigens, they promote either allergies through T_H2 cells or tolerance through the development of regulatory T cells, transforming growth factor β, retinoic acid, or IL-10[126-128] through their suppressive activity.[137-139] T_H2 differentiated cells migrate out of the draining lymph nodes to promote production of eosinophils and basophils. IL-4 produced by T_H2 cells causes B-cell class switching, which produces IgE. T_H9 cells also contribute to the development of the allergic response by secreting IL-9, which promotes the accumulation of tissue-resident mast cells.[140] IgE is recognized by receptors on effector cells: mast cells, basophils, and eosinphils.[141]

Effector Cells (Mast Cells, Basophils, and Eosinophils)

Tissue residing mast cells, eosinophils, and circulating basophils are important in the allergic process. Food antigen-specific IgE binds to the receptors on mast cells and basophils. Upon exposure to the antigen, cross-linking of IgE and the IgE receptors occurs on the surface of mast cells and basophils, resulting in the release of mediators responsible for food allergy symptoms. These mediators—histamine, tryptase, platelet activating factor (PAF), prostaglandins, and leukotrienes—cause anaphylactic symptoms,[142] including vasodilation, increased vascular permeability, increased heart rate, increased cardiac contraction, and increased glandular secretion.

Tryptase is a preformed mast cell mediator[143] whose levels peak at 60 to 90 minutes after the onset of anaphylaxis.[144] In anaphylaxis, it causes angioedema by the activation of the contact (kallikrein-kinin) system. PAF is also a potent mediator of anaphylaxis, causing bronchoconstriction, increased vascular permeability, chemotaxis, and degranulation of eosinophils and neutrophils. Prostaglandin D_2 (PGD_2) is produced by mast cells and enhances the release of histamine from basophils. Leukotrienes have a slow onset of action, resulting in smooth-muscle contraction, mucus secretion, and increased vascular

permeability. Effector cells release tryptase, histamine, PAF, PGD_2, and leukotrienes, which are key targets for future therapeutic agents.

Immune Tolerance Development

The development of tolerance to food antigens is influenced by many immunologic components, including dendritic cells, epithelial cells in the gut, and the gut microbiome (see Figure 1.2). Dendritic cells capable of inducing regulatory T cells that express anti-inflammatory cytokines cause development of anergic T cells. These contribute to oral tolerance by reducing the number of effector cells. The human microbiome is also an essential mediator in the induction of oral tolerance or food allergies. Although the immune mechanisms mediating the development of natural tolerance in individuals with food allergies are not completely understood, the mechanisms mediating tolerance development with the early introduction of foods and immunotherapy have been described.[145] The prevention of food allergies is discussed in Chapter 10.

Conclusion

Adverse reactions to food comprise a wide range of disorders that differ in their clinical manifestations and underlying pathophysiology. These disorders may be immune-mediated (ie, allergies) or not immune-mediated; the clinical features of the adverse reaction suggest which is the case. Immune-mediated conditions are categorized into IgE-mediated, non–IgE-mediated, or mixed. Again, the clinical features of the adverse reactions suggest which of these three categories apply. Conditions that are not immune-mediated include metabolic, pharmacologic, and toxic conditions, as well as diagnoses described as other, idiopathic, or undefined.[3] People with non–immune-mediated disorders frequently seek medical attention from allergists and immunologists because of the relationship between food ingestion and the adverse clinical symptoms. Unfortunately, outside of select examples, such as the hydrogen breath test for lactose intolerance, validated testing to confirm a diagnosis of a non–immune-mediated condition is lacking; however, characteristics of the history often reveal the likely diagnosis.

An understanding of these differing disorders and the methods for evaluating them is essential because patients may use the term *allergy* to describe these diagnoses interchangeably or incorrectly. Obtaining a careful and detailed clinical history is paramount in every case. Practitioners need to be aware that specific diagnostic allergy testing has certain limitations in the overall assessment of adverse reactions to foods and must be used in concert with the clinical history. This clinical reasoning needs to be shared with patients so that they are aware of their diagnoses and understand the recommended management. Finally, the role of RDNs in the care of these patients needs to be considered and their skills utilized appropriately.

References

1. Bruijnzeel-Koomen C, Ortolani C, Aas K, et al. Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. *Allergy*. 1995;50(8):623-635. doi:10.1111/j.1398-9995.1995.tb02579.x
2. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113(5):832-836.
3. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol*. 2010;126(6):1105-1118.

4. Dreborg S. Debates in allergy medicine: food intolerance does not exist. *World Allergy Organ J.* 2015;8:37.
5. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update—2014. *J Allergy Clin Immunol.* 2014;134(5):1016-1025.e43.
6. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food allergy from infancy through adulthood. *J Allergy Clin Immunol Pract.* 2020;8(6):1854-1864.
7. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics.* 2011;128(1):e9-e17.
8. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open*. 2019;2(1):e185630.
9. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract.* 2016;4(2):196-203; quiz 204.
10. Grimshaw KE, King RM, Nordlee JA, Hefle SL, Warner JO, Hourihane JO. Presentation of allergen in different food preparations affects the nature of the allergic reaction—a case series. *Clin Exp Allergy.* 2003;33(11):1581-1585. doi:10.1046/j.1365-2222.2003.01795.x
11. Anvari S, Miller J, Yeh CY, Davis CM. IgE-mediated food allergy. *Clin Rev Allergy Immunol*. 2019;57(2):244-260.
12. Yonkof JR, Mikhail IJ, Prince BT, Stukus D. Delayed and severe reactions to baked egg and baked milk challenges. *J Allergy Clin Immunol Pract.* 2021;9(1):283-289.e2. doi:10.1016/j.jaip.2020.09.059
13. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol.* 2018;141(1):41-58.
14. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. *J Allergy Clin Immunol.* 2009;123(6 suppl):S365-S383.
15. Bird JA, Leonard S, Groetch M, et al. Conducting an oral food challenge: an update to the 2009 Adverse Reactions to Foods Committee Work Group report. *J Allergy Clin Immunol Pract*. 2020;8(1):75-90.e17.
16. Tuano KS, Davis CM. Utility of component-resolved diagnostics in food allergy. *Curr Allergy Asthma Rep*. 2015;15(6):32.
17. Greenhawt M, Shaker M, Wang J, et al. Peanut allergy diagnosis: a 2020 practice parameter update, systematic review, and GRADE analysis. *J Allergy Clin Immunol.* 2020;146(6):1302-1334.
18. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69(8):1026-1045.
19. Vickery BP, Vereda A, Casale TB, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med.* 2018;379(21):1991-2001.
20. Kim EH, Burks AW. Food allergy immunotherapy: oral immunotherapy and epicutaneous immunotherapy. *Allergy*. 2020;75(6):1337-1346. doi:10.1111/all.14220
21. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol.* 2001;108(6):881-890.
22. Carlson G, Coop C. Pollen food allergy syndrome (PFAS): a review of current available literature. *Ann Allergy Asthma Immunol*. 2019;123(4):359-365.
23. Blankestijn MA, Knulst AC, Knol EF, et al. Sensitization to PR-10 proteins is indicative of distinctive sensitization patterns in adults with a suspected food allergy. *Clin Transl Allergy*. 2017;7:42.
24. Skypala IJ, Bull S, Deegan K, et al. The prevalence of PFS and prevalence and characteristics of reported food allergy; a survey of UK adults aged 18-75 incorporating a validated PFS diagnostic questionnaire. *Clin Exp Allergy*. 2013;43(8):928-940.
25. Skypala IJ, Calderon MA, Leeds AR, Emery P, Till SJ, Durham SR. Development and validation of a structured questionnaire for the diagnosis of oral allergy syndrome in subjects with seasonal allergic rhinitis during the UK birch pollen season. *Clin Exp Allergy*. 2011;41(7):1001-1011.
26. Baek HS, Jeong JW, Lee HB, Kwon JW. Molecular sensitization patterns in birch pollen-sensitized Korean children according to the presence of oral allergy syndrome. *Medicine (Baltimore)*. 2020;99(10):e19469.
27. Werfel T, Asero R, Ballmer-Weber BK, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy*. 2015;70(9):1079-1090.
28. Faber MA, Van Gasse AL, Decuyper, II, et al. Cross-reactive aeroallergens: which need to cross our mind in food allergy diagnosis? *J Allergy Clin Immunol Pract*. 2018;6(6):1813-1823.
29. Rancé F, Juchet A, Brémont F, Dutau G. Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. *Allergy.* 1997;52(10):1031-1035.
30. Skypala IJ. Can patients with oral allergy syndrome be at risk of anaphylaxis? *Curr Opin Allergy Clin Immunol*. 2020;20(5):459-464. doi:10.1097/ACI.0000000000000679
31. Guvenir H, Dibek Misirlioglu E, Buyuktiryaki B, et al. Frequency and clinical features of pollen-food syndrome in children. *Allergol Immunopathol (Madr)*. 2020;48(1):78-83.
32. Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM. Diagnosis and management of patients with the α-Gal syndrome. *J Allergy Clin Immunol Pract.* 2020;8(1):15-23.e11.
33. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. *J Allergy Clin Immunol*. 2011;127(5):1286-1293.e1286.

34. Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: executive summary—workgroup report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol.* 2017;139(4): 1111-1126.e1114.
35. Nowak-Wegrzyn A, Berin MC, Mehr S. Food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol Pract.* 2020;8(1):24-35.
36. Nowak-Wegrzyn A, Warren CM, Brown-Whitehorn T, Cianferoni A, Schultz-Matney F, Gupta RS. Food protein–induced enterocolitis syndrome in the US population-based study. *J Allergy Clin Immunol*. 2019;144(4):1128-1130.
37. Caubet JC, Ford LS, Sickles L, et al. Clinical features and resolution of food protein–induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol.* 2014;134(2):382-389.
38. González-Delgado P, Caparrós E, Moreno MV, et al. Clinical and immunological characteristics of a pediatric population with food protein–induced enterocolitis syndrome (FPIES) to fish. *Pediatr Allergy Immunol.* 2016;27(3):269-275.
39. Díaz JJ, Espín B, Segarra O, et al. Food protein–induced enterocolitis syndrome: data from a multicenter retrospective study in Spain. *J Pediatr Gastroenterol Nutr.* 2019;68(2):232-236.
40. Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Węgrzyn A, Berin MC. Systemic innate immune activation in food protein–induced enterocolitis syndrome. *J Allergy Clin Immunol.* 2017;139(6):1885-1896.e1889.
41. Mehr S, Lee E, Hsu P, et al. Innate immune activation occurs in acute food protein–induced enterocolitis syndrome reactions. *J Allergy Clin Immunol.* 2019;144(2):600-602.e602.
42. Lee E, Campbell DE, Barnes EH, Mehr SS. Resolution of acute food protein–induced enterocolitis syndrome in children. *J Allergy Clin Immunol Pract.* 2017;5(2): 486-488.e481.
43. Nowak-Węgrzyn A. Food protein–induced enterocolitis syndrome and allergic proctocolitis. *Allergy Asthma Proc.* 2015;36(3):172-184.
44. Meyer R, Chebar Lozinsky A, Fleischer DM, et al. Diagnosis and management of non-IgE gastrointestinal allergies in breastfed infants—an EAACI position paper. *Allergy.* 2020;75(1):14-32.
45. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128(1):3-20.e26; quiz 21-22.
46. Furuta GT, Katzka DA. Eosinophilic esophagitis. *N Engl J Med.* 2015;373(17):1640-1648.
47. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE Conference. *Gastroenterology.* 2018;155(4):1022-1033.e1010.
48. Chehade M, Brown S. Elimination diets for eosinophilic esophagitis: making the best choice. *Expert Rev Clin Immunol.* 2020;16(7):679-687.
49. Spergel J, Aceves SS. Allergic components of eosinophilic esophagitis. *J Allergy Clin Immunol.* 2018;142(1):1-8.
50. Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146(7):1639-1648.
51. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol.* 2013;131(2):295-299.e291-227.
52. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol.* 2018;120(1):10-22.e2. doi:10.1016/j.anai.2017.10.039
53. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases–sponsored expert panel. *J Allergy Clin Immunol.* 2017;139(1):29-44.
54. Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr.* 2011;158(4):578-583.e571.
55. Chang A, Robison R, Cai M, Singh AM. Natural history of food-triggered atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract.* 2016;4(2):229-236.e221.
56. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014;70(2):338-351.
57. Graham F, Eigenmann PA. Atopic dermatitis and its relation to food allergy. *Curr Opin Allergy Clin Immunol*. 2020;20(3):305-310.
58. Ludvigsson JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut.* 2014;63(8):1210-1228.
59. van de Wal Y, Kooy YM, Drijfhout JW, Amons R, Koning F. Peptide binding characteristics of the coeliac disease-associated DQ(α1*0501, β1*0201) molecule. *Immunogenetics*. 1996;44(4):246-253.
60. Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med*. 1997;3(7):797-801.
61. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16(6):823-836.e822.
62. Bishop J, Ravikumara M. Coeliac disease in childhood: an overview. *J Paediatr Child Health*. 2020;56(11):1685-1693.
63. Riznik P, De Leo L, Dolinsek J, et al. Clinical presentation in children with coeliac disease in Central Europe. *J Pediatr Gastroenterol Nutr*. 2021;72(4):546-551. doi:10.1097/MPG.0000000000003015
64. Tan IL, Withoff S, Kolkman JJ, Wijmenga C, Weersma RK, Visschedijk MC. Non-classical clinical presentation at diagnosis by male celiac disease patients of older age. *Eur J Intern Med.* 2021; 83:28-33.

65. Salmi TT. Dermatitis herpetiformis. *Clin Exp Dermatol.* 2019;44(7):728-731. doi:10.1111/ced.13992
66. Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. *Gastroenterology*. 2015;148(6):1175-1186.
67. Fueyo-Díaz R, Magallón-Botaya R, Masluk B, et al. Prevalence of celiac disease in primary care: the need for its own code. *BMC Health Serv Res*. 2019;19(1):578.
68. Shen TC, Lebwohl B, Verma H, et al. Peripheral neuropathic symptoms in celiac disease and inflammatory bowel disease. *J Clin Neuromuscul Dis*. 2012;13(3):137-145.
69. Wierdsma NJ, van Bokhorst-de van der Schueren MA, Berkenpas M, Mulder CJ, van Bodegraven AA. Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. *Nutrients*. 2013;5(10):3975-3992.
70. Husby S, Murray JA, Katzka DA. AGA Clinical practice update on diagnosis and monitoring of celiac disease—changing utility of serology and histologic measures: expert review. *Gastroenterology*. 2019;156(4):885-889.
71. Sugai E, Moreno ML, Hwang HJ, et al. Celiac disease serology in patients with different pretest probabilities: is biopsy avoidable? *World J Gastroenterol*. 2010;16(25):3144-3152.
72. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society [for] Paediatric Gastroenterology, Hepatology and Nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70(1):141-156.
73. Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. *J Pediatr Gastroenterol Nutr*. 2009;48(5):559-565.
74. Catassi C, Fabiani E, Iacono G, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *Am J Clin Nutr*. 2007;85(1):160-166.
75. Schiepatti A, Maimaris S, Nicolardi ML, et al. Determinants and trends of adherence to a gluten-free diet in adult celiac patients on a long-term follow-up (2000-2020). *Clin Gastroenterol Hepatol.* 2022;20(4):e741-e749. doi:10.1016/j.cgh.2020.12.015
76. Pedoto D, Troncone R, Massitti M, Greco L, Auricchio R. Adherence to gluten-free diet in coeliac paediatric patients assessed through a questionnaire positively influences growth and quality of life. *Nutrients*. 2020;12(12):3802. doi:10.3390/nu12123802
77. Garnweidner-Holme L, Sende K, Hellmann M, et al. Experiences of managing a gluten-free diet on multiple levels of society: a qualitative study. *BMC Nutr.* 2020;6(1):65.
78. Shah S, Akbari M, Vanga R, et al. Patient perception of treatment burden is high in celiac disease compared with other common conditions. *Am J Gastroenterol.* 2014;109(9):1304-1311.
79. Parsons K, Brown L, Clark H, et al. Gluten cross-contact from common food practices and preparations. *Clin Nutr.* 2021;40(5):3279-3287. doi:10.1016/j.clnu.2020.10.053
80. Penagini F, Dilillo D, Meneghin F, Mameli C, Fabiano V, Zuccotti GV. Gluten-free diet in children: an approach to a nutritionally adequate and balanced diet. *Nutrients.* 2013;5(11):4553-4565.
81. Hallert C, Grant C, Grehn S, et al. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. *Aliment Pharmacol Ther.* 2002;16(7):1333-1339.
82. Wu JH, Neal B, Trevena H, et al. Are gluten-free foods healthier than non-gluten-free foods? An evaluation of supermarket products in Australia. *Br J Nutr.* 2015;114(3):448-454.
83. Thompson T, Dennis M, Higgins LA, Lee AR, Sharrett MK. Gluten-free diet survey: are Americans with coeliac disease consuming recommended amounts of fibre, iron, calcium and grain foods? *J Hum Nutr Diet.* 2005;18(3):163-169.
84. Schnedl WJ, Mangge H, Schenk M, Enko D. Non-responsive celiac disease may coincide with additional food intolerance/malabsorption, including histamine intolerance. *Med Hypotheses.* 2020:110404.
85. Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. *Ann Allergy Asthma Immunol.* 2014;112(3):222-229.e223.
86. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol.* 2007;120(3):638-646.
87. McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. *J Allergy Clin Immunol.* 2013;132(5):1216-1219.e1215.
88. Lyons SA, Clausen M, Knulst AC, et al. Prevalence of food sensitization and food allergy in children across Europe. *J Allergy Clin Immunol Pract*. 2020;8(8):2736-2746.e2739.
89. Grabenhenrich L, Trendelenburg V, Bellach J, et al. Frequency of food allergy in school-aged children in eight European countries—the EuroPrevall-iFAAM birth cohort. *Allergy*. 2020;75(9):2294-2308.
90. Lyons SA, Burney PGJ, Ballmer-Weber BK, et al. Food allergy in adults: substantial variation in prevalence and causative foods across Europe. *J Allergy Clin Immunol Pract.* 2019;7(6):1920-1928.e1911.
91. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69(1):62-75.
92. Verrill L, Bruns R, Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. *Allergy Asthma Proc*. 2015;36(6):458-467.
93. Venkataraman D, Erlewyn-Lajeunesse M, Kurukulaaratchy RJ, et al. Prevalence and longitudinal trends of food allergy during childhood and adolescence: results of the Isle of Wight Birth Cohort study. *Clin Exp Allergy*. 2018;48(4):394-402.
94. Venter C, Maslin K, Patil V, et al. The prevalence, natural history and time trends of peanut allergy over the first 10 years of life in two cohorts born in the same geographical location 12 years apart. *Pediatr Allergy Immunol.* 2016;27(8):804-811.

95. Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127(3):668-676.e661-662.
96. Misselwitz B, Pohl D, Frühauf H, Fried M, Vavricka SR, Fox M. Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment. *United European Gastroenterol J*. 2013;1(3):151-159.
97. Itan Y, Jones BL, Ingram CJ, Swallow DM, Thomas MG. A worldwide correlation of lactase persistence phenotype and genotypes. *BMC Evol Biol*. 2010;10:36.
98. Lomer MC, Parkes GC, Sanderson JD. Review article: lactose intolerance in clinical practice—myths and realities. *Aliment Pharmacol Ther*. 2008;27(2): 93-103.
99. Amieva-Balmori M, Coss-Adame E, Rao NS, Dávalos-Pantoja BM, Rao SSC. Diagnostic utility of carbohydrate breath tests for SIBO, fructose, and lactose intolerance. *Dig Dis Sci*. 2020;65(5): 1405-1413.
100. Vernia P, Camillo MD, Marinaro V, Caprilli R. Effect of predominant methanogenic flora on the outcome of lactose breath test in irritable bowel syndrome patients. *Eur J Clin Nutr*. 2003;57(9):1116-1119.
101. Viswanathan L, Rao SSC, Kennedy K, Sharma A, Yan Y, Jimenez E. Prevalence of disaccharidase deficiency in adults with unexplained gastrointestinal symptoms. *J Neurogastroenterol Motil.* 2020;26(3):384-390.
102. Catanzaro R, Sciuto M, Singh B, Pathak S, Marotta F. Irritable bowel syndrome and lactose intolerance: the importance of differential diagnosis. A monocentric study. *Minerva Gastroenterol Dietol (Torino)*. 2021;67(1):72-78. doi:10.23736/S2724 -5985.20.02734-8
103. Schnedl WJ, Meier-Allard N, Lackner S, Enko D, Mangge H, Holasek SJ. Increasing expiratory hydrogen in lactose intolerance is associated with additional food intolerance/malabsorption. *Nutrients*. 2020;12(12):3690. doi:10.3390/nu12123690
104. Ratajczak AE, Rychter AM, Zawada A, Dobrowolska A, Krela-Kaźmierczak I. Lactose intolerance in patients with inflammatory bowel diseases and dietary management in prevention of osteoporosis. *Nutrition*. 2020;82:111043.
105. Hamilton NK, Ojo O, Adegboye ARA. The effect of self-reported lactose intolerance and dairy consumption on bone mineral density among American hip arthroplasty patients: a cross-sectional study. *Int J Environ Res Public Health.* 2020;17(19):7182. doi:10.3390/ijerph17197182
106. Facioni MS, Raspini B, Pivari F, Dogliotti E, Cena H. Nutritional management of lactose intolerance: the importance of diet and food labelling. *J Transl Med.* 2020;18(1):260.
107. Bodmer S, Imark C, Kneubühl M. Biogenic amines in foods: histamine and food processing. *Inflamm Res*. 1999;48(6):296-300.
108. Maintz L, Novak N. Histamine and histamine intolerance. *Am J Clin Nutr.* 2007;85(5):1185-1196.
109. Angelo KM, Nisler AL, Hall AJ, Brown LG, Gould LH. Epidemiology of restaurant-associated foodborne disease outbreaks, United States, 1998-2013. *Epidemiol Infect*. 2017;145(3):523-534.
110. Hungerford JM. Scombroid poisoning: a review. *Toxicon*. 2010;56(2):231-243. doi:10.1016 /j.toxicon.2010.02.006
111. Colombo FM, Cattaneo P, Confalonieri E, Bernardi C. Histamine food poisonings: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2018;58(7):1131-1151.
112. Son JH, Chung BY, Kim HO, Park CW. A histamine-free diet is helpful for treatment of adult patients with chronic spontaneous urticaria. *Ann Dermatol.* 2018;30(2):164-172.
113. Comas-Basté O, Sánchez-Pérez S, Veciana-Nogués MT, Latorre-Moratalla M, Vidal-Carou MDC. Histamine intolerance: the current state of the art. *Biomolecules*. 2020;10(8)):1181. doi:10.3390 /biom10081181
114. Izquierdo-Casas J, Comas-Basté O, Latorre-Moratalla ML, et al. Diamine oxidase (DAO) supplement reduces headache in episodic migraine patients with DAO deficiency: a randomized double-blind trial. *Clin Nutr*. 2019;38(1):152-158.
115. Reese I, Ballmer-Weber B, Beyer K, et al. German guideline for the management of adverse reactions to ingested histamine: guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Association of Allergologists (AeDA), and the Swiss Society for Allergology and Immunology (SGAI). *Allergo J Int.* 2017;26(2):72-79.
116. Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. *Clin Transl Allergy.* 2015;5:34.
117. Stevens WW, Jerschow E, Baptist AP, et al. The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: a Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol*. 2021;147(3):827-844. doi:10.1016/j.jaci.2020 .10.043
118. Mitchell JE, Skypala I. Aspirin and salicylate in respiratory disease. *Rhinology*. 2013;51(3): 195-205.
119. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: the FODMAP approach. *J Gastroenterol Hepatol.* 2010;25(2):252-258.
120. Valluzzi RL, Fierro V, Arasi S, Mennini M, Pecora V, Fiocchi A. Allergy to food additives. *Curr Opin Allergy Clin Immunol*. 2019;19(3):256-262.
121. Vally H, Misso NL. Adverse reactions to the sulphite additives. *Gastroenterol Hepatol Bed Bench*. 2012;5(1):16-23.

122. Campbell HE, Escudier MP, Patel P, Challacombe SJ, Sanderson JD, Lomer MC. Review article: cinnamon- and benzoate-free diet as a primary treatment for orofacial granulomatosis. *Aliment Pharmacol Ther*. 2011;34(7):687-701.
123. Henry-Unaeze HN. Update on food safety of monosodium L-glutamate (MSG). *Pathophysiology.* 2017;24(4):243-249.
124. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. *J Allergy Clin Immunol*. 2018;141(1):11-19.
125. Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis—filaggrin and other polymorphisms. *Clin Rev Allergy Immunol*. 2016;51(3):315-328.
126. Mazzini E, Massimiliano L, Penna G, Rescigno M. Oral tolerance can be established via gap junction transfer of fed antigens from $CX3CR1^+$ macrophages to $CD103^+$ dendritic cells. *Immunity*. 2014;40(2):248-261.
127. Coombes JL, Siddiqui KR, Arancibia-Cárcamo CV, et al. A functionally specialized population of mucosal $CD103^+$ DCs induces $Foxp3^+$ regulatory T cells via a TGF-β– and retinoic acid–dependent mechanism. *J Exp Med.* 2007;204(8):1757-1764.
128. Hadis U, Wahl B, Schulz O, et al. Intestinal tolerance requires gut homing and expansion of $FoxP3^+$ regulatory T cells in the lamina propria. *Immunity.* 2011;34(2):237-246.
129. Paul WE, Zhu J. How are T_H2-type immune responses initiated and amplified? *Nat Rev Immunol.* 2010;10(4):225-235.
130. Divekar R, Kita H. Recent advances in epithelium-derived cytokines (IL-33, IL-25, and thymic stromal lymphopoietin) and allergic inflammation. *Curr Opin Allergy Clin Immunol*. 2015;15(1):98-103.
131. Steinbach EC, Plevy SE. The role of macrophages and dendritic cells in the initiation of inflammation in IBD. *Inflamm Bowel Dis*. 2014;20(1):166-175.
132. Blázquez AB, Berin MC. Gastrointestinal dendritic cells promote Th2 skewing via OX40L. *J Immunol*. 2008;180(7):4441-4450.
133. Noval Rivas M, Burton OT, Oettgen HC, Chatila T. IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function. *J Allergy Clin Immunol.* 2016;138(3):801-811.e809.
134. Mjösberg J, Bernink J, Golebski K, et al. The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. *Immunity*. 2012;37(4):649-659.
135. Saenz SA, Siracusa MC, Monticelli LA, et al. IL-25 simultaneously elicits distinct populations of innate lymphoid cells and multipotent progenitor type 2 (MPP^{type2}) cells. *J Exp Med.* 2013;210(9):1823-1837.
136. Halim TY, Steer CA, Mathä L, et al. Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity.* 2014;40(3):425-435.
137. Bakdash G, Vogelpoel LT, van Capel TM, Kapsenberg ML, de Jong EC. Retinoic acid primes human dendritic cells to induce gut-homing, IL-10-producing regulatory T cells. *Mucosal Immunol.* 2015;8(2):265-278.
138. Evans TI, Reeves RK. All-*trans*-retinoic acid imprints expression of the gut-homing marker α4β7 while suppressing lymph node homing of dendritic cells. *Clin Vaccine Immunol.* 2013;20(10):1642-1646.
139. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell*. 2008;133(5):775-787.
140. Sehra S, Yao W, Nguyen ET, et al. T_H9 cells are required for tissue mast cell accumulation during allergic inflammation. *J Allergy Clin Immunol.* 2015;136(2): 433-440.e431.
141. Sugimoto M, Kamemura N, Nagao M, et al. Differential response in allergen-specific IgE, IgGs, and IgA levels for predicting outcome of oral immunotherapy. *Pediatr Allergy Immunol.* 2016;27(3):276-282.
142. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol.* 2010;125(2 suppl 2):S73-S80.
143. Pereira PJ, Bergner A, Macedo-Ribeiro S, et al. Human β-tryptase is a ring-like tetramer with active sites facing a central pore. *Nature*. 1998;392(6673):306-311.
144. Molinari JF, Scuri M, Moore WR, Clark J, Tanaka R, Abraham WM. Inhaled tryptase causes bronchoconstriction in sheep via histamine release. *Am J Respir Crit Care Med.* 1996;154(3 pt 1):649-653.
145. Rachid R, Umetsu DT. Immunological mechanisms for desensitization and tolerance in food allergy. *Semin Immunopathol*. 2012;34(5):689-702.