Food intolerances and allergens: immunological mechanism, clinical manifestations and dietary management strategies

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Abstract. Adverse reactions to food represent a growing public health concern worldwide, encompassing a heterogeneous spectrum of conditions ranging from non- immune-mediated food intolerances to potentially life-threatening IgE-mediated allergic responses. This review provides a comprehensive and mechanistically oriented analysis of the principal categories of food intolerance including lactose intolerance, fructose malabsorption, and non-celiac gluten sensitivity alongside the immunological pathways underpinning celiac disease and IgE-mediated food allergies. Particular attention is given to the biochemical basis of allergenicity, the role of food processing in modifying allergenic potential, and the clinical spectrum from localized oral allergy syndrome to systemic anaphylaxis. The review also examines the epidemiology of the major regulated allergens under EU Regulation (EU) No 1169/2011, summarizes current diagnostic approaches including skin prick testing, specific IgE assays, and double-blind placebo-controlled food challenges (DBPCFC), and discusses emerging immunotherapeutic strategies such as oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT). Finally, the review addresses the practical implications of cross-reactivity phenomena, including latex-fruit syndrome and pollen-food allergy syndrome, for clinical management and dietary counselling.
Keywords: food allergy, food intolerance, IgE, anaphylaxis, celiac disease, lactose intolerance, oral immunotherapy, allergen labelling, cross-reactivity, food hypersensitivity.

Introduction. Adverse reactions to food affect an estimated 15–20% of the global population at some point during their lifetime, yet the underlying mechanisms, severity, and management strategies differ substantially depending on whether the reaction is immunologically mediated (Sicherer & Sampson, 2018; Cianferoni & Spergel, 2009). The dichotomy between food *allergy* defined as an aberrant immune response to specific food proteins and food *intolerance* encompassing metabolic, pharmacological, or undefined non-immune mechanisms is clinically fundamental but frequently misunderstood by patients and healthcare professionals alike (Johansson et al., 2004).

In Europe, the prevalence of self-reported food hypersensitivity reaches approximately 20%, while objectively confirmed food allergy affects roughly 3–4% of adults and 6–8% of children (Nwaru et al., 2014). The economic burden of food allergies encompassing medical costs, dietary substitution, reduced quality of life, and occupational restrictions is substantial and rising, driven in part by increasing sensitization rates in Westernized populations and by the hygiene hypothesis positing that reduced early microbial exposure dysregulates immune tolerance mechanisms (Sicherer & Sampson, 2018).

This review aims to: (i) characterize the immunological and biochemical basis of the principal food intolerances and allergies; (ii) describe the clinical spectrum from mild intolerance symptoms to anaphylaxis; (iii) analyze allergen properties and the impact of food processing on allergenic potential; (iv) summarize the EU regulatory framework for allergen labelling; and (v) evaluate current and emerging diagnostic and therapeutic approaches.

Food Intolerances: Non-Immune Adverse Reactions

Lactose intolerance: enzymatic basis and clinical variability. Lactose intolerance is the most prevalent form of food intolerance globally, resulting from a deficiency of intestinal lactase-phlorizin hydrolase (LPH), the brush border enzyme responsible for hydrolyzing dietary lactose into glucose and galactose prior to absorption. The condition can be classified into three subtypes: *primary* (adult-type hypolactasia), which is an autosomal recessive trait affecting 65–75% of the world population reflecting evolutionary loss of lactase persistence after weaning; *secondary*, caused by intestinal mucosal damage due to gastroenteritis, celiac disease, or Crohn's disease; and *congenital*, an extremely rare autosomal recessive disorder presenting in newborns (Swagerty et al., 2002).

Undigested lactose reaching the colon is fermented by resident microbiota, producing short-chain fatty acids, hydrogen, carbon dioxide and methane gases responsible for the hallmark symptoms of bloating, flatulence, abdominal cramping, and osmotic diarrhea. The threshold for symptom onset varies widely between individuals (typically 12–18 g lactose, equivalent to 240 mL milk) and is influenced by intestinal transit rate, colonic microbiota composition, and psychological factors (Shaukat et al., 2010). Critically, many lactose-intolerant individuals can tolerate moderate dairy consumption particularly fermented products such as yoghurt and hard cheeses with reduced lactose content without significant symptoms (Figures 1-2).

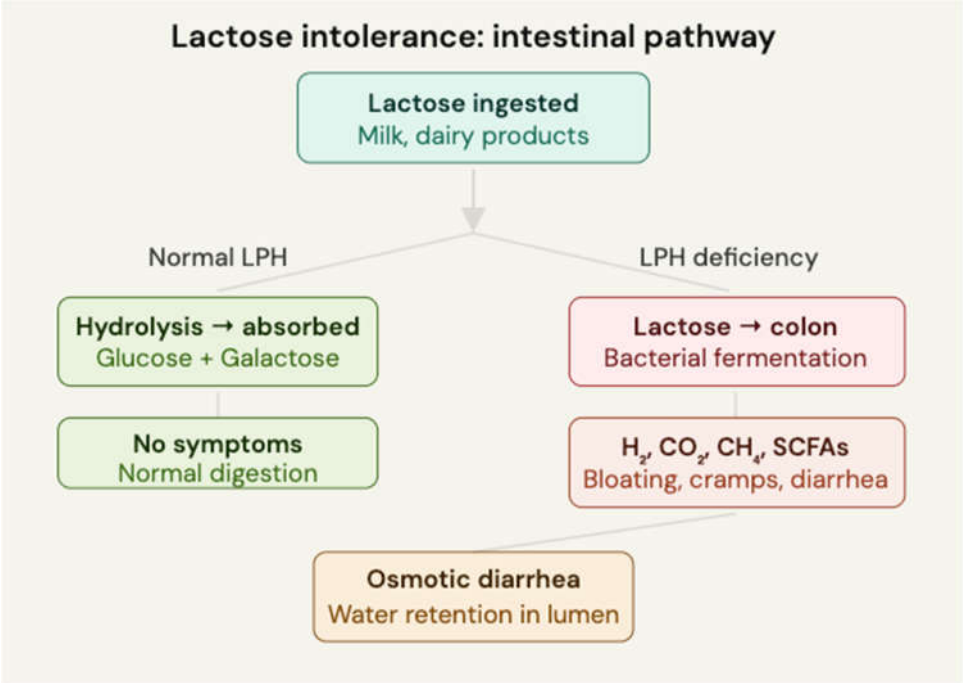

Figure 1. Intestinal pathway of lactose digestion in individuals with normal and deficient lactase-phlorizin hydrolase (LPH) activity.

Fructose malabsorption and histamine intolerance. Dietary fructose malabsorption arises from saturation or impaired expression of the intestinal GLUT5 transporter, resulting in colonic fermentation of unabsorbed fructose analogous to lactose intolerance. It is distinct from hereditary fructose intolerance (HFI), a rare but life-threatening autosomal recessive enzymatic disorder caused by aldolase B deficiency, in which fructose-1-phosphate accumulates to toxic levels in hepatocytes, causing acute liver failure upon fructose ingestion (Schnedl et al., 2025; Rao, 2026). Histamine intolerance, by contrast, results from reduced activity of the intestinal enzyme diamine oxidase (DAO), impairing the catabolism of dietary histamine found in fermented, aged, and processed foods including wine, aged cheeses, cured meats, and certain fish species. Symptoms mimic

allergic reactions urticaria, rhinorrhea, headache and gastrointestinal discomfort complicating differential diagnosis (Maintz & Novak, 2007).

Non-celiac gluten sensitivity (NCGS) is a clinical entity characterized by gastrointestinal and extraintestinal symptoms triggered by gluten ingestion in individuals in whom celiac disease and wheat allergy have been excluded by appropriate testing. The pathophysiology of NCGS remains incompletely understood; current evidence implicates innate immune activation (rather than the adaptive Th1/Th17 response of celiac disease), increased intestinal permeability and possible contributions from fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) co-present in wheat (Catassi et al., 2013). The absence of specific biomarkers renders diagnosis challenging and is currently based on symptom improvement following a gluten-free diet after exclusion of other diagnoses.

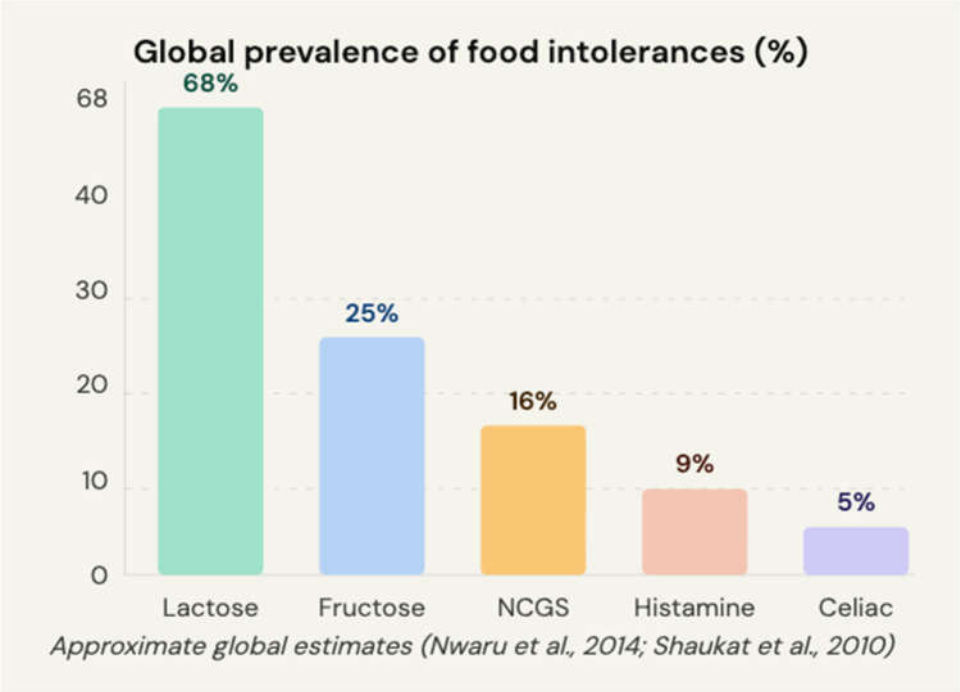

Figure 2. Approximate global prevalence of the main food intolerance conditions.

Celiac Disease: Autoimmune Enteropathy. Celiac disease (CD) is a chronic, immune-mediated enteropathy triggered by dietary gluten in genetically predisposed individuals, affecting approximately 1% of the global population with a female-to-male ratio of approximately 2:1 (Fasano & Catassi, 2012). It is strongly associated with HLA-DQ2 (present in ~90% of patients) and HLA-DQ8 haplotypes, which present deamidated gliadin peptides generated by tissue transglutaminase 2 (tTG2) to CD4+ T helper cells in the intestinal lamina propria (Figure 3).

The resulting Th1/Th17 immune response triggers local inflammation and villous atrophy through cytotoxic (CD8+) intraepithelial lymphocytes, crypt hyperplasia, and increased intestinal permeability a constellation described histologically using the Marsh classification (grades 0–3). The autoimmune character is evidenced by the production of autoantibodies against tTG2 itself (anti-tTG IgA), which serve as the primary serological screening marker, with sensitivity exceeding 95% (Husby et al., 2012). Clinical manifestations range from classical malabsorption (steatorrhoea, weight loss, iron-deficiency anaemia) to atypical presentations including osteoporosis, infertility, neurological symptoms (gluten ataxia, peripheral neuropathy), and dermatitis herpetiformis. Currently, strict lifelong adherence to a gluten-free diet (GFD) remains the only effective treatment.

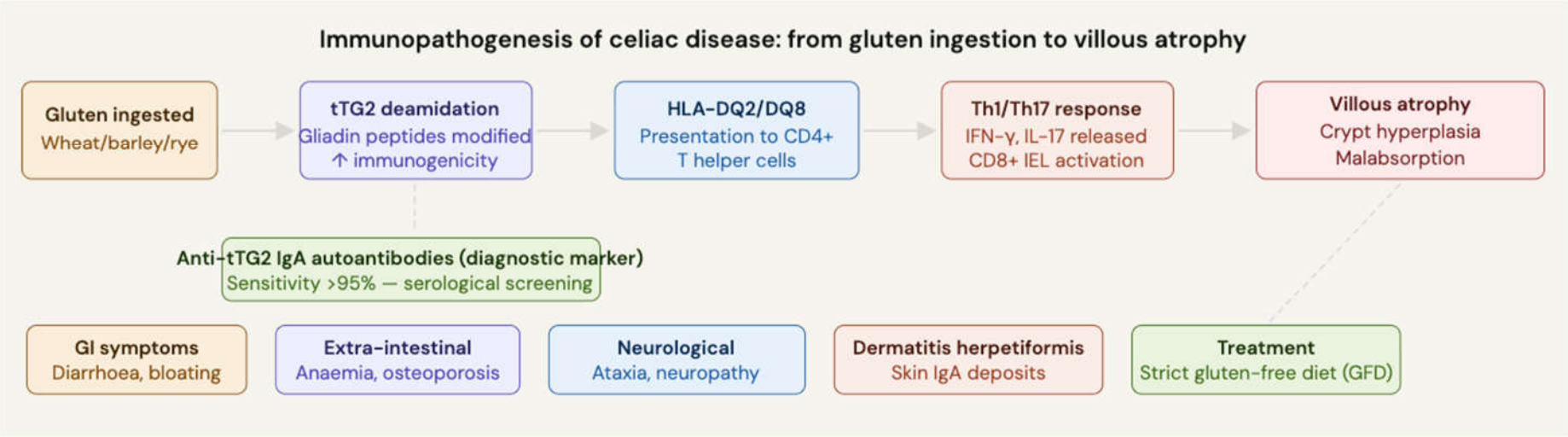

Figure 3. Immunopathogenic cascade of celiac disease from gluten ingestion through HLA-DQ2/DQ8- mediated T cell activation to villous atrophy and clinical manifestations (adapted from Fasano & Catassi, 2012; Husby et al., 2012).

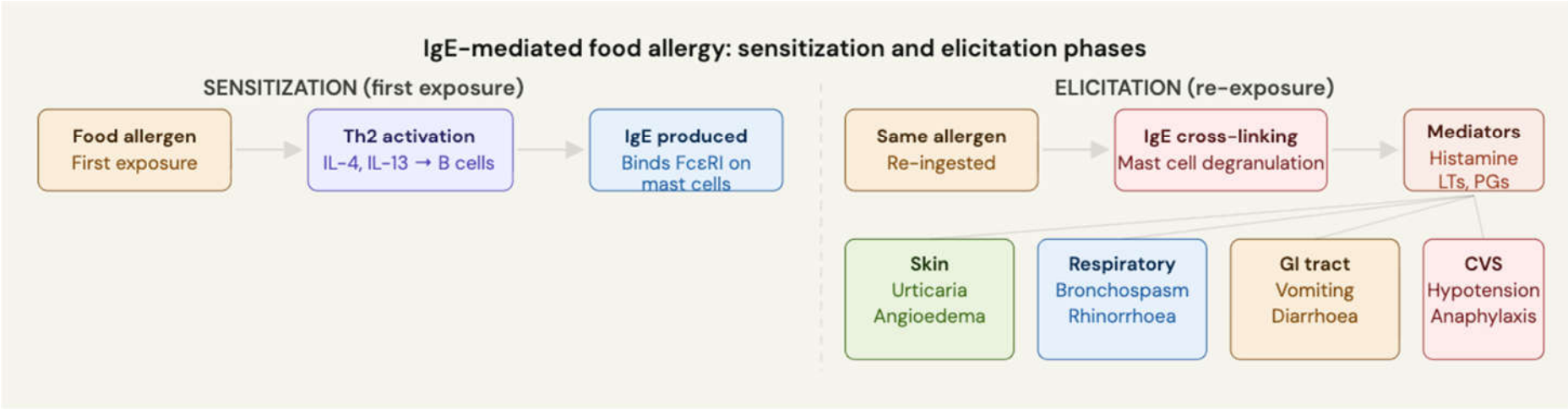

Figure 4. Two-phase mechanism of IgE-mediated food allergy: sensitization leads to mast cell-bound IgE and elicitation upon re-exposure triggers mediator release and multi-organ clinical manifestations including anaphylaxis (adapted from Sicherer & Sampson, 2018; Sampson et al., 2006).

IgE-Mediated Food Allergy and Anaphylaxis

Sensitization and effector mechanisms. IgE-mediated food allergy involves two distinct phases: an initial *sensitization phase*, during which allergen-specific IgE antibodies are produced and bound to high-affinity FcRI receptors on mast cells and basophils; and an *elicitation phase*, occurring upon re-exposure, when cross-linking of receptor-bound IgE by multivalent allergen triggers cellular degranulation and release of preformed mediators (histamine, tryptase, heparin) alongside de novo synthesis of prostaglandins, leukotrienes, and platelet-activating factor (Sicherer & Sampson, 2018). The clinical consequences of this mediator release range from localized urticaria and angioedema to systemic anaphylaxis, characterized by the simultaneous involvement of two or more organ systems skin, respiratory, cardiovascular, and gastrointestinal with cardiovascular collapse representing the life-threatening extreme (Sampson et al., 2006) (Figure 4).

The major food allergens responsible for >90% of severe allergic reactions in Europe include cow's milk, hen's egg, wheat, peanuts, tree nuts, fish, crustaceans, soybeans, sesame, celery, mustard, lupin, molluscs, and sulfite compounds all mandatorily declared under EU Regulation (EU) No 1169/2011 (EFSA, 2014) (Table 1). The structural basis of allergenicity is associated with several protein superfamilies: the prolamin superfamily (2S albumins in peanuts and tree nuts), the cupins (vicilins and legumins), the Bet v 1 homologues (PR-10 proteins mediating pollen-food syndromes), and the non-specific lipid transfer proteins (nsLTPs), the latter being among the most heat-stable food allergens (Breiteneder & Radauer, 2004).

Cross-reactivity phenomena. Cross-reactivity between structurally homologous allergens from different biological sources is a clinically important phenomenon that complicates dietary management. The *pollen-food allergy syndrome* (PFAS), also termed oral allergy syndrome (OAS), arises from IgE cross-reactivity between labile Bet v 1-homologous proteins in plant foods (apple, carrot, celery, stone fruits, hazelnuts) and birch pollen Bet v 1, typically producing localized oropharyngeal symptoms rapidly resolving upon removal of the food (Kleine-Tebbe & Jakob, 2015). In contrast, the *latex-fruit syndrome* involves sensitization to Hev b proteins in natural rubber latex, with cross-reactivity to class I chitinases and thaumatin-like proteins in fruits such as avocado, banana, kiwi, and chestnut (Brehler et al., 1997). Unlike PFAS, latex-fruit reactions are frequently systemic and can trigger anaphylaxis, as the responsible proteins are heat-stable and resist digestion.

Allergen Properties, Processing and Eu Labelling. The allergenic potential of food proteins is influenced by their biochemical stability, resistance to gastrointestinal proteolysis and ability to penetrate the intestinal mucosal barrier in immunologically intact form. Proteins such as Ara h 2 (2S albumin of peanut) and Cor a 9 (11S legumin of hazelnut) are highly stable to heat and digestion, explaining the systemic severity of reactions they trigger. In contrast, the Bet v 1-homologous proteins responsible for PFAS are labile, rapidly denatured by cooking, and digested in the stomach which is why many apple-allergic patients can safely consume cooked apple products (Breiteneder & Radauer, 2004).

Thermal processing generally reduces allergenicity of labile proteins but may paradoxically increase it for stable ones: the Maillard reaction between peanut proteins and reducing sugars during roasting increases the IgE-binding capacity of Ara h 1 and Ara h 2 compared to raw peanuts, potentially explaining the higher peanut allergy prevalence in populations consuming roasted rather than boiled peanuts (Maleki et al., 2000). High-pressure processing (HPP), enzymatic hydrolysis, and fermentation are emerging food processing strategies that show promise in reducing allergenicity of milk, wheat and soy proteins, though regulatory approval of hypoallergenic food products requires rigorous clinical validation.

Table 1

The 14 major allergens regulated under EU Regulation (EU) No 1169/2011: key proteins, typical clinical reactions and notes on cross-reactivity

Allergen	Major allergenic proteins	Typical reaction severity	Key cross-reactivities
Peanut	Ara h 1, 2, 3, 6 (legumin, 2S albumin)	Severe — frequent anaphylaxis	Tree nuts, legumes (lupine, soy)
Tree nuts	Cor a 9, Jug r 1, Ana o 3	Severe — anaphylaxis	Peanut, other tree nuts
Cow's milk	Caseins, β-lactoglobulin, α-lactalbumin	Moderate–severe; often outgrown	Goat/sheep milk
Hen's egg	Ovomucoid (Gal d 1), ovalbumin	Moderate; often outgrown	Poultry meat (bird-egg syndrome)
Wheat	ω-5 gliadin (Tri a 19), HMW glutenins	Moderate–severe (exercise-induced)	Other cereals, grass pollen
Fish	Parvalbumin (Gad c 1)	Severe; rarely outgrown	Cross-reactive across fish species
Crustaceans	Tropomyosin (Pen a 1)	Severe	Molluscs, dust mites, cockroach
Sesame	Ses i 1 (2S albumin), Ses i 3	Severe; emerging prevalence	Other seeds, peanut
Celery / Mustard	nsLTP, Bet v 1 homologues	Mild (OAS) to severe	Birch pollen, carrot, spices
Lupin	α/β-conglutin (legumin)	Moderate–severe	Peanut (35–50% co-sensitization)

Diagnosis and Emerging Immunotherapy. The gold standard for food allergy diagnosis remains the double-blind placebo-controlled food challenge (DBPCFC), which eliminates both patient and clinician bias and provides objective dose-response data (Bindslev-Jensen et al., 2004). In clinical practice, initial assessment relies on a detailed clinical history supplemented by skin prick testing (SPT) and measurement of allergen-specific serum IgE (sIgE) by ImmunoCAP assay. Component-resolved diagnostics (CRD) measuring IgE to individual purified or recombinant allergen molecules improve prediction of reaction severity and cross-reactivity risk; for example, elevated Ara h 2-specific IgE reliably predicts systemic reactions to peanut, while sensitization limited to Ara h 8 (Bet v 1 homologue) predicts only mild OAS (Kleine-Tebbe & Jakob, 2015).

Oral immunotherapy (OIT) involving gradual escalating doses of the culprit allergen under medical supervision has emerged as a disease-modifying therapeutic approach, with anti-peanut OIT (Palforzia) receiving EMA approval in 2020 as the first licensed food allergy immunotherapy in Europe. OIT induces desensitization (raised reaction threshold) and in a proportion of patients, sustained unresponsiveness, associated mechanistically with decreased basophil reactivity, expansion of regulatory T cells (Tregs), induction of allergen-specific IgG4, and a shift from Th2 to Th1 immune profiles (Vickery et al., 2017). Epicutaneous immunotherapy (EPIT) via skin patch delivery and sublingual immunotherapy (SLIT) represent alternative, potentially safer routes under active clinical investigation.

Conclusions. Food intolerances and food allergies constitute a clinically and mechanistically heterogeneous spectrum of adverse dietary reactions whose accurate differentiation is indispensable for appropriate patient management and nutritional counselling. While intolerances such as lactose maldigestion and fructose malabsorption

are mediated by metabolic deficiencies amenable to dietary adjustment, IgE-mediated food allergies involve sophisticated immunological dysregulation capable of life-threatening systemic responses. Celiac disease occupies an intermediate position as an autoimmune condition driven by both adaptive T cell responses and autoantibody production against a well-characterized tissue enzyme. The structural biology of allergens their stability to heat, acid, and proteolysis is a principal determinant of clinical severity and determines the effect of food processing on allergenic potential. The EU regulatory framework under Regulation (EU) No 1169/2011 provides a critical public health safety net, yet challenges persist in enforcing cross-contamination controls and addressing undeclared allergens in the food chain. Emerging immunotherapeutic strategies, particularly OIT, offer the prospect of transforming food allergy from a condition of strict avoidance to one of active immune modulation, though long-term safety and efficacy data from post-marketing surveillance will be essential to guide their widespread clinical implementation.

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Authors Contributions. Lidia Ioana Hoza contributed to all aspects of the work.

Conflicts of Interest. The author declares that there is no conflict of interest.

Data Availability. The data supporting the findings of this study are available from the author upon reasonable request.

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