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SPECIAL REPORTS AND REVIEWS

Gastrointestinal Food Allergy: New Insights Into Pathophysiology and Clinical Perspectives

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Adverse reactions to food that result in gastrointestinal symptoms are common in the general population; while only a minority of such individuals will have symptoms due to immunologic reactions to foods, gastrointestinal food allergies do exist in both children and adults. These immune reactions are mediated by immunoglobulin E–dependent and –independent mechanisms involving mast cells, eosinophils, and other immune cells, but the complexity of the underlying mechanisms of pathogenesis have yet to be fully defined. Knowledge of the spectrum of adverse reactions to foods that affect the digestive system, including gastrointestinal food allergy, is essential to correctly diagnose and manage the subset of patients with immunologically mediated adverse reactions to foods. Potentially fatal reactions to food necessitate careful instruction and monitoring on the part of health care workers involved in the care of individuals at risk of anaphylaxis. New methods of diagnosis and novel strategies for treatment, including immunologic modulation and the development of hypoallergenic foods, are exciting developments in the field of food allergy.

Allergic reactions are of concern to both medical care providers and the general population because of a rapidly increasing prevalence during the past few decades.[1–3] Approximately 20% of the population has been reported to experience adverse reactions to food (ARF) in industrialized nations such as the United States, the United Kingdom, and Germany, with nuts, fruits, and milk among the most common triggers.[4–9] Epidemiologic data indicate that such reactions are caused by different mechanisms, with only about one third of the reactions in children and one tenth of those in adults due to actual food allergy in which there is an abnormal immunologic reaction to food.[4,6,10,11] It has been recognized for some time now that perceived food allergy is often not substantiated when evaluated by double-blind placebo-controlled food challenge, the gold standard for diagnosing food allergy. Nonetheless, true food allergies are believed to affect up to 6%–8% of children younger than 10 years of age and 1%–4% of the adult population,[4–6,12] a frequency that should result in most medical practitioners seeing cases of food allergy on a regular basis. The majority of ARF are nonimmunologic in origin, with lactose intolerance the most common type worldwide.

It is likely that, along with allergic reactions of a more general nature, allergic reactions to food are increasing in prevalence as well; however, except for peanut allergy,[13,14] clear data confirming this are lacking. The reasons for the increase of allergic diseases are not entirely apparent as yet, although recent epidemiologic studies suggest that the greater level of hygiene in urbanized populations in industrialized countries might play a central role.[15–17] The symptoms of allergy range from slight inconveniences to life-threatening shock reactions.[18] Food allergy can involve different organ systems such as the oral cavity and digestive tract, the skin, the respiratory tract, and the cardiovascular system. While dermatologic, respiratory, and systemic manifestations of food allergy are well recognized, those reactions manifesting primarily in the digestive tract can be difficult to recognize, diagnose, and treat. This relates to the protean ways food can cause gastrointestinal (GI) symptoms, the relatively poorly understood pathophysiologic mechanisms, and the limited diagnostic methods available to objectively identify afflicted individuals. These deficiencies are, in part, a consequence of the difficulty accessing the GI tract to es-

Abbreviations used in this paper: ARF, adverse reactions to food; GI, gastrointestinal; IFN, interferon; IL, interleukin; sIgA, secretory immunoglobulin A; TGF, transforming growth factor; Th, T-helper cell; TNF, tumor necrosis factor.

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tablish mechanisms of disease and develop methods to diagnose and treat food allergy.[19,20]

Food allergies and other types of ARF manifest primarily with GI symptoms in up to 50% of patients; therefore, many afflicted patients consult specialists in gastroenterology who are, as a group, largely unprepared to meet the challenge of dealing with such cases.[21,22] Often, patients of this nature become classified as being psychosomatic, being functional, or having irritable bowel syndrome without defining the real problem. It has been recognized for some time now that irritable bowel syndrome is often associated with ARF and, in some instances, food allergy might be a mechanism for symptoms in a subgroup of afflicted patients.[23–27] The issue of dealing with food allergy becomes even more important now that food allergy has become the most common cause of life-threatening anaphylaxis in industrialized countries.[18,28,29] It is clear that confirmed food allergy is treated most successfully by avoidance of food allergens, the mainstay of treatment of food allergy, but supportive medical treatment with epinephrine, antihistamines, and corticosteroids can be beneficial for severe reactions. Despite a substantial understanding of the field, there are unanswered questions. What causes and what prevents food allergy? What are the underlying mechanisms? How does one confirm the diagnosis on an objective basis? Are there alternatives to food antigen avoidance?

The focus of this review is on food allergy manifesting in the digestive system and, in particular, the underlying mechanisms. The best characterized abnormal immunologic reaction to food is immediate immunoglobulin (Ig) E–mediated hypersensitivity to food, also termed a type I reaction, involved in the pathogenesis of many cases of asthma, rhinitis, urticaria, and atopic eczema as well as GI ARF. Delayed reactions following immediate IgE-mediated hypersensitivity occur in selected individuals and are characterized by an enhanced cell infiltration of the tissue with inflammatory cells and subsequent tissue damage. These and other cell-mediated immune reactions to food antigens may also operate in the GI tract and are believed to play a role in milk and soy protein enteropathies and in celiac disease.[15,30,31] Immunologic reactions to foods can also involve "mixed IgE- and non–IgE-mediated" and other mechanisms than classic immediate or delayed hypersensitivity. The development of food allergy is dependent on the presence of several risk factors to be discussed (Table 1). This report, which emphasizes new information reported since the topic of GI food allergy was last reviewed in GASTROENTEROLOGY 13 years ago,[32] also examines the clinical aspects of food allergy affecting the gut.

Table 1. Risk Factors for the Development of Food Allergy

Immature mucosal immune system
Early introduction of solid food
Hereditary increase in mucosal permeability
IgA deficiency or delayed IgA production
Inadequate challenge of the intestinal immune system with commensal flora
Genetically determined bias toward a Th2 environment
Polymorphisms of Th2 cytokine or IgE receptor genes
Impaired enteric nervous system
Immune alterations (eg, low levels of TGF-β)
Gastrointestinal infections

Pathophysiology

Regulation of the Intestinal Immune Response

The innate mucosal defense system. The intestinal mucosa is perpetually exposed to potentially harmful nutrients, microbes, and toxins. On the one hand, absorption of nutrients and controlled uptake of antigens is crucial for life and for development of the mucosal immune system; on the other hand, the host must protect itself against pathogens and allergens.[33] Innate immune mechanisms and other nonspecific defense systems are critical to meet this challenge. These include gastric acid, bicarbonate, and mucus secretion, an intact epithelial layer forming tight junctions, digestive enzymes, peristaltic movement, alternative complement pathways, phagocytes, and more recently defined antimicrobial peptides such as defensins and cathelicidins.[34–36] Such mechanisms are involved in the prevention of infection, control of invasion, and replication of pathogens and possibly allergen exposure within the GI tract. For example, increased sensitization to food antigens has been shown in humans and animal models treated with proton pump inhibitors and with other antisecretory drugs, likely due to less effective gastric proteolysis at neutral pH.[37] Macrophages and neutrophils have been suggested to be the most important effector cells of the innate immune system, but evidence exists that other cells such as mast cells and eosinophils are also involved.[38,39] These cells recognize conserved bacterial structures through "pattern recognition receptors," including the recently identified Toll-like receptor family.[40] The function of the innate immune system is supported by the specific immune system.

Permeability and uptake of allergens. The notion that undigested macromolecules such as food allergens pass through the intestinal barrier as intact proteins, interacting with the local intestinal immune system and being transported to other body sites such as the skin or the lung, was questioned for many years.

However, several studies indicate that macromolecules such as ovalbumin are taken up by the intestinal mucosa and can be detected in peripheral blood.[41,42] This process was named "persorption" and seems to occur at limited rates under normal conditions that might be of importance for the development of tolerance. However, in infants with an intestinal mucosa not fully matured or in adults with an impaired barrier, increased uptake of macromolecules occurs that may have clinical consequences. The amount of absorbed undigested protein is dependent on genetic factors and variables such as dietary intake, maturity of digestive processes, and the presence of structural or functional abnormalities of the GI tract. Intestinal permeability is increased in patients with food allergy, suggesting that the uptake of food antigens is elevated in food-allergic patients.[32,43] This may be secondary, caused at least in part by secondary inflammatory events such as infection, reduced perfusion, malnutrition, and extraintestinal inflammation.

Antigen presentation and adaptive immune responses in the gut. Antigen-presenting cells in the intestinal mucosa differ from other antigen-presenting cells regarding their low expression of costimulatory molecules such as CD80 (B7-1) and CD86 (B7-2), interacting with CD28 and other counterreceptors on T cells.[44] This contributes to the usual hyporesponsive state of the GI immune system, because antigen presentation through major histocompatibility complex class II proteins without further costimulatory signals preferentially induces T-cell anergy or deletion. In contrast, the up-regulation of costimulatory molecules, which is a characteristic feature of uncontrolled inflammation, could drive an inappropriate immune response.[44,45] The immune response is regulated by the form of costimulation (CD80/CD28 interactions favor a T-helper cell [Th] 1–type response, CD86/CD28 interactions favor a Th2-type response), the type of dendritic cells (plasmacytoid/lymphoid dendritic cells generate Th2-type responses, myeloid dendritic cells generate Th1-type responses), and the cytoplasmic milieu (eg, prostaglandin E_2 induces the development of plasmacytoid dendritic cells, interferon [IFN]-γ induces interleukin [IL]-12–producing myeloid dendritic cells).[46–50] The Th1/Th2 balance is further regulated by more recently characterized T-cell subtypes down-regulating both types of immune responses by secreting transforming growth factor (TGF)-β (Th3 cells) and IL-10 (Tr1 cells). TGF-β and IL-10 are relevant cytokines promoting the isotype switch cells from IgM to IgA production in B cells and antigen-specific anergy in T cells, respectively.[51–53]

Mucosal tolerance. Gut homeostasis is achieved not only by the regulation of barrier function but also by down-regulating the normal immune response to bacteria and food antigens. This phenomenon was termed "oral tolerance" because it is induced following oral challenge with particular antigens. This phenomenon, primarily described in the rodent system, also exists in humans and confers not only a local but also a systemic tolerance against orally administered antigen.[54–56] Active down-regulatory mechanisms comprise different nonspecific (gastric acid, mucus, epithelial barrier) and specific immunologic systems (secretory IgA [sIgA]- and secretory IgM–producing plasma cells, tolerogenic antigen-presenting cells and immunosuppressive T cells, T-cell anergy and apoptosis). Such mechanisms, which have been described in detail elsewhere, are crucial to developing tolerance to dietary antigens.[53,57] The typical hyporesponsiveness of the intestinal immune system seems to be impaired in intestinal inflammatory diseases such as inflammatory bowel disease and also food allergy.[11,30,58] Moreover, the immaturity or breakdown of such mechanisms may increase the risk of sensitization to dietary proteins and subsequently of developing food allergy.

Hygiene hypothesis. Adequate challenge of the intestinal immune system with commensal microorganisms and other stimuli is required for full maturation of the adaptive immune system and, in particular, the sIgA defense system. It has been suggested that reduced stimulatory reinforcement of the developing mucosal immune system in individuals residing in states of enhanced cleanliness might contribute to the increased frequency of allergy and autoimmune disorders in industrialized countries.[16,59,60] This "hygiene hypothesis" is supported by the findings that probiotics such as lactobacilli and bifidobacteria strains can enhance sIgA responses in a T-cell–dependent manner and that nonenteropathogenic *Escherichia coli* or *Lactobacillus GG* reduce infection and protect against the development of food-induced atopic dermatitis.[60,61] In this respect, it is interesting to note that breast-feeding may protect against infection and atopy, likely because of the delivery of sIgA and other protective molecules such as TGF-β and IL-10 through breast milk.[62–64]

Allergic Inflammation

Allergen-specific T-cell responses. Allergic inflammation of the gut requires a sufficient load of triggering allergen into the gut lumen and a hyperresponsive mucosal immune system. Enhanced antigen exposure may result from genetically determined alterations of key molecules comprising the GI barrier, immaturity, or acquired disturbances of the GI defense system such as enteric infection or a combination thereof. Genetic and environmental factors regulating gut permeability and

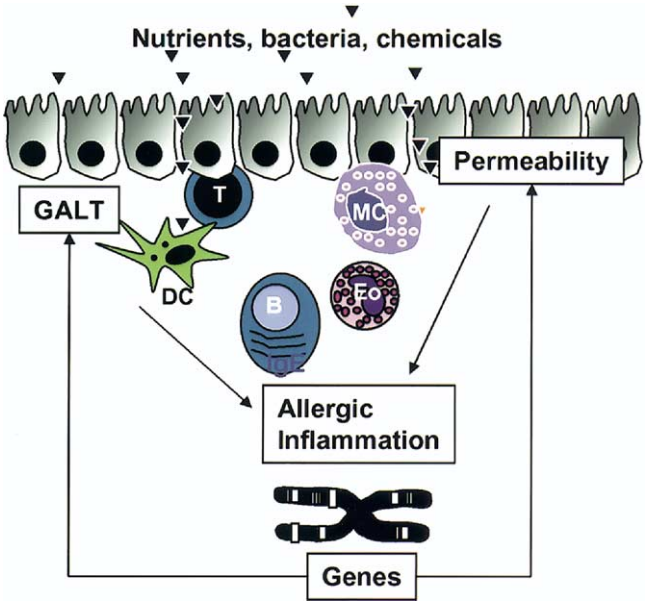

Figure 1. Factors affecting the development and outcome of allergic inflammation in the GI tract. Various environmental factors, including bacteria, nutrients, and other agents, gain access to the cells comprising the gut-associated lymphoid tissue (GALT) through the epithelial barrier via transcellular or paracellular pathways. Whether immune tolerance or allergic sensitization results from exposure to antigenic stimulation depends in part on host genes that regulate the immune response; the nature of the antigen-presenting cells that include macrophages, dendritic cells (DC), and perhaps even epithelial cells; and the cytokine production from the helper T lymphocytes (T). The consequence of the immune response that results from these various factors can lead to stimulation of B lymphocytes (B) and activation of other effector cells, including mast cells (MC) and eosinophils (Eo), that result in allergic inflammation.

the gut-associated lymphoid tissue act together in the pathophysiology of food allergy and other forms of gut inflammation (Figure 1). Nonspecific inflammation induced by bacteria, viruses, or toxins can predispose to a loss of tolerance and subsequent development of immunologic hypersensitivity. Dendritic cells lose their hyporesponsiveness by expressing costimulatory molecules, epithelial cells also start to express costimulatory molecules, and eventually both cell types become capable of priming naive lymphocytes for cytokine-producing Th2 effector cells or IgE-producing plasma cells. Allergen-specific T cells can be isolated from blood, skin, and mucosal sites in patients with food allergy and, characteristically, they express a Th2 cell phenotype releasing IL-4, IL-5, and IL-13.[65] Such cytokines play a central role in the induction and maintenance of allergic responses by regulating IgE synthesis (IL-4, IL-13) and chemoattraction of inflammatory cells such as mast cells (IL-4) and eosinophils (IL-5).[66–69] In addition to the cytokine milieu, the biochemical properties of the triggering antigen influence the type of immune response. In general, soluble proteins are more tolerogenic than particulate or globular antigens.[30] Other biochemical characteristics of food allergens affect their absorption and their stability. For example, the peanut protein Ara h1 was recently shown to resist degradation because of the formation of stable homotrimers.[70] Dose of antigen is of relevance for the subsequent immunologic response with activation of regulatory T cells (Th3) by low doses of antigen, whereas high doses induce anergy or apoptosis.[30]

Allergen-specific B-cell responses and the role of IgE. The regulation of mucosal IgA production by B cells is dependent on genetic and environmental factors, thereby explaining the large individual variations. Any delayed development of the IgA system in the postnatal phase or an enhanced switch to IgE-producing Bε cells is associated with an increased risk of developing allergic disease. The major inducer of IgA synthesis, apart from external triggers, is TGF-β derived from Th3 cells, whereas the switch to IgE synthesis is dependent on CD40L, IL-4, and IL-13 derived from Th2 cells and inflammatory cells such as mast cells or basophils.[30,54] In contrast, Th1 cytokines such as IFN-γ inhibit the action of Th2 cells, and thereby Th1-driven immune responses believed to be the default GI response that can be enhanced by bacterial antigens may prevent the production of IgE.[68] This explains why, under normal conditions, low Th2 cytokine levels and undetectable IgE production are characteristic of the GI mucosa. Such mechanisms further argue for the hygiene hypothesis, which proposes that an overly "clean" environment with reduced microbial challenge is a risk factor for atopy, defined as an enhanced Th2 milieu and subsequent IgE-mediated allergy. Clinical studies strongly suggest that IgE is also produced locally in the respiratory and GI mucosa,[71] providing an explanation for the fact that serum IgE measurements and skin tests do not correlate well with mucosal allergic responses in the intestine.[19] In atopic individuals, elevated IgE levels are closely correlated with IL-13, a gene subject to polymorphisms that are linked to atopy.[72]

Sensitization and effector phases of allergic inflammation. The IgE-mediated allergic immune response can be divided into 3 phases: the sensitization phase, the effector phase consisting of an acute-phase and a facultative late-phase reaction, and a chronic phase that may be the result of repetitive late-phase reactions. The sensitization phase is dependent on the uptake and processing of the antigen by antigen-presenting cells such as dendritic cells, macrophages, or B cells and the subsequent presentation of antigenic peptides to naive $CD4^+$ T cells. Under the influence of particular cytokines such as IL-4 and IL-13, the naive Th0 cells are transformed to

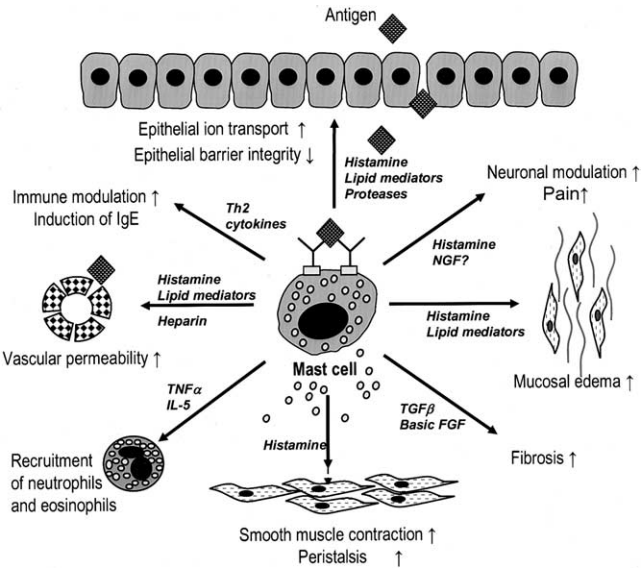

Figure 2. Versatile functions of human GI mast cells. With cross-linking of IgE, mast cells release a number of mediators, including histamine, lipid mediators, proteases, cytokines, and growth factors such as TNF-α, IL-5, fibroblast growth factor (FGF), and nerve growth factor (NGF). By releasing such mediators, mast cells are believed to regulate epithelial ion transport, vascular permeability, smooth muscle contraction and peristalsis, fibrogenesis, and enteric nerve function. Moreover, mast cells contribute to the recruitment of inflammatory cells such as neutrophils and eosinophils and to edema formation, typical features of allergic inflammation.

Th2-type lymphocytes required for B-cell switch to plasma cells producing larger amounts of specific IgE directed against particular food antigens. Once mast cells and basophils expressing the high-affinity IgE receptor have bound sufficient specific IgE, recurrent antigen exposure may induce an effector phase by cross-linking of surface IgE molecules. This "acute phase" causes activation of mast cells and basophils with release of histamine, leukotrienes, and other mediators known to be responsible for a number of effects in the GI tract (Figure 2). Acute reactions occurring within seconds to minutes may be followed by a "late-phase reaction" starting within 2–24 hours after allergen challenge and characterized by a cellular infiltration of the tissue with granulocytes (basophils, eosinophils) and lymphocytes (mainly Th2 cells).[73] These phases have been studied less extensively in the GI tract, but there is some evidence suggesting that they occur in a similar fashion as described previously in other organs.[19,74] Interestingly, the chronic phase, believed to be a result of repetitive late phases, is not necessarily Th2 dominated, because Th1-type lymphocytes are also found as described for chronic airways disease or Crohn's disease of the gut. The pathology of such a chronic inflammation typically consists of a mixture of Th2- and Th1-type cytokines and cells accompanied by arteriolar dilatation, increased vascular permeability, stimulation of sensory nerves, and impaired GI function. The ongoing inflammation induces a permanent up-regulation of adhesion molecules and the release of chemokines causing persistent infiltration of all types of granulocytes, macrophages, and lymphocytes and finally structural changes such as fibrosis and organ dysfunction.

Mast cells and eosinophils. Inflammatory mediators produced by mast cells and eosinophils are responsible for the clinical symptoms and the organ dysfunction that occurs during allergic reactions (Figure 2). Elevated levels of histamine and its metabolite, methylhistamine, tryptase, eosinophil cationic protein, eosinophil-derived protein X, IL-5, and tumor necrosis factor (TNF)-α have been measured in serum, urine, gut lavage fluid, and stool from patients with food allergy.[75–81] Further evidence of activation of mast cells and eosinophils are histologic studies showing degranulation, cytokine production by these cell types, and enhanced levels of proinflammatory mediators after allergen provocation tests.[74] Mast cells, eosinophils, and basophils are now recognized not only as effector cells of allergic inflammation but also as immunoregulatory cells contributing to the maintenance of GI homeostasis and are also involved in defense mechanisms (eg, against bacteria and parasites).[39,79,82–84] Human mast cells produce TNF-α causing neutrophil recruitment at sites of bacterial infection; IL-5, promoting eosinophil accumulation; and many other cytokines. IL-4 is not produced by human mast cells under normal conditions, but it acts as a central regulator of mast cell cytokine production.[67,85] Allergens that cross-link IgE are not the only triggers of mast cell activation because bacterial and viral products activate mast cells through Toll-like receptors and viral receptors such as gp120, respectively.[86–89] Similar observations have been made for eosinophils.[79,83] The mechanisms regulating control of inflammation and loss of tolerance with subsequent activation of mast cells and eosinophils in the course of food hypersensitivity are summarized in Figure 3.

Neuroimmune interactions in the GI tract. The enteric nervous system acts, to a large extent, independently of higher control centers in the central nervous system and regulates many important gut functions such as blood supply, smooth muscle activity, and coordinated peristaltic movements as well as immune and epithelial function. This is achieved in part through a branching network of neural fibers throughout the gut wall. In recent years, it has become evident that the enteric nervous system regulates key cells involved in allergic inflammation such as lymphocytes, mast cells, and eosinophils. The morphologic and functional associations between immune cells and nerves were first recognized

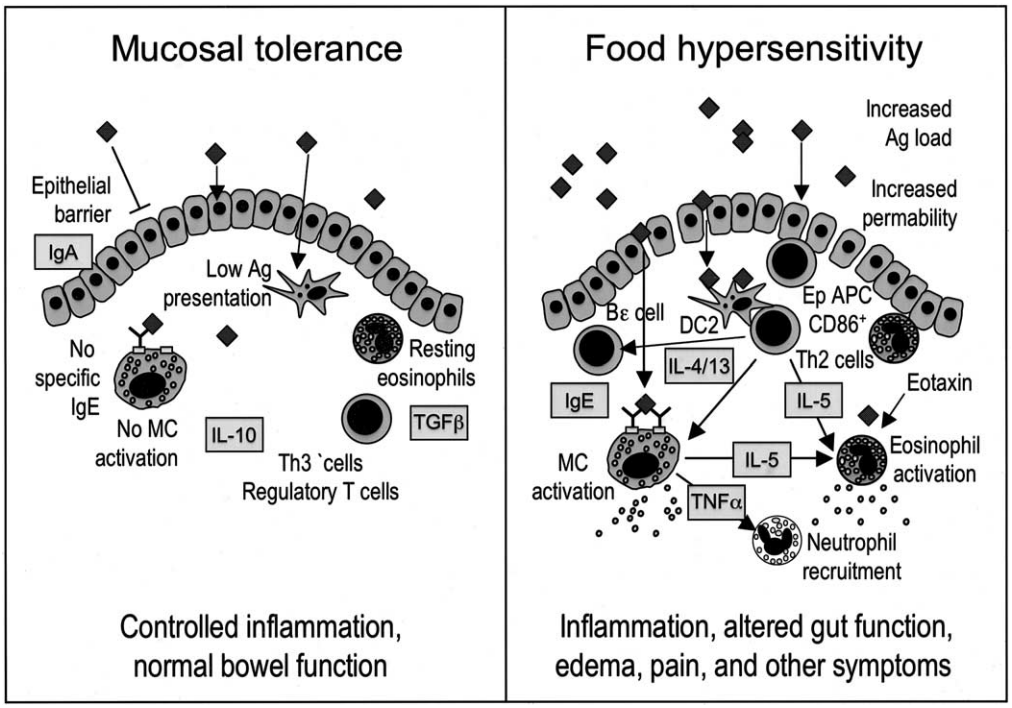

Figure 3. Mechanisms leading to mucosal tolerance or hypersensitivity to food antigens in the GI tract. In the normal setting (*left panel*), lower antigen (Ag) exposure results from an intact epithelial barrier, sIgA production, and other innate immune defense mechanisms. In this setting, a Th3 predominates with secretion of IL-10 and TGF-β. No specific IgE is produced, and eosinophils and mast cells (MC) remain in a resting state. This results in a state of controlled inflammation that characterizes the normal gut mucosa. In contrast, altered epithelial permeability (*right panel*) leads to an increased antigen load and certain forms of antigen-presenting cells (APC), including epithelial (Ep) $CD86^+$ cells and dendritic cell type 2 (DC2), result in activation of B lymphocytes producing IgE (Bε cell) and a bias toward a Th2 form of immune response with IL-4, IL-5, and IL-13 production. Mast cell (MC) activation leads to the release of various factors, including TNF-α, and secondary recruitment and activation of eosinophils and neutrophils. Together, these events lead to altered gut function, inflammation, and clinical manifestations of GI food allergy.

for mast cells in the skin, lung, intestine, and lymphoid and synovial tissues of animals and humans.[90] The extent to which eosinophils are in such close proximity to nerves in different tissues has been studied less extensively.[91,92] Of particular interest is the finding that gut-associated lymphoid tissue is innervated and, in turn, the enteric nervous system is also modulated by mediators derived from immune and inflammatory cells. Such enteric neuroimmune interactions provide a potential mechanism for the reported psychological or functional aspects of allergic responses.[93]

Neurotrophins and neuropeptides in allergy. The mechanisms underlying the close anatomic and functional association of immunocytes and nerves in mucosal tissues are unclear. Among the relevant mediators, nerve growth factor deserves note because it increases mast cell numbers in tissues of neonatal rats, promotes growth and differentiation of murine and human mast cells in vitro, and exerts chemotactic effects on rat peritoneal mast cells.[94,95] Similar effects were also reported for human eosinophils, whose differentiation and survival were enhanced by nerve growth factor.[96] It is worth noting that certain findings in the rodent system cannot always apply to humans. For example, substance P is a potent secretagogue in rat peritoneal and human skin mast cells but not in human intestinal mast cells.[97,98] Acetylcholine enhances antigen-induced histamine release from human lung tissue and mediates mast cell degranulation following electrical stimulation of parasympathetic nerves, whereas disruption of the parasympathetic nerve supply results in reduced mast cell density and tissue histamine content in animals and humans.[99,100] Catecholamines, however, have inhibitory effects on mast cell function. The physiologic consequence of mast cell/nerve interactions has been documented in animal models of GI hypersensitivity. In such models, antigen challenge results in mast cell degranulation, decreased mucosal histamine content, and increased epithelial ion secretion and enhanced mucosal permeability, thus indicating a relationship between mast cell activation and mucosal function.[32,101,102] Further confirmation of nerve/mast cell interactions includes studies using inhibitors of mast cell products, mast cell–stabilizing agents, or mast cell–deficient mice[103] and, later, human GI tissues.[104] Taken together, the studies clearly show that the enteric nervous system is involved in the pathophysiology of allergic reactions of the gut.

Table 2. Genetic Findings in Allergic Disorders

Gene	Alleles/mutations	Allergic association	Reference
HLA class II	DR4 and/or DR7	Birch pollen and apple	126
HLA class II	DRB1*08/*12	Peanut allergy/carrot allergy	124, 125
HLA class II	DRB1*08/12tyr16	Peanut allergy	124
HLA class II	DQ7	Cow's milk allergy	122
HLA class II	DQB1*04/+0301	Peanut allergy/grass pollen allergy	124, 125
HLA class II	DPB1*0301	Peanut allergy	124
IgE heavy chain	VH, VH5	Peanut and mite allergy	123
IgE receptor β chain	Mutations on chr11q13	Asthma, pollen, and mite allergy	121, 127
IL-4 receptor α subunit	1902 G/A (R576)	Elevated total serum IgE, atopy	129
IL-13	Arg130Gln	Elevated total serum IgE	133
STAT6	G allele	Nut allergy	131
STAT6	2964A + 13-GT repeat	Asthma, allergy	132
IL-10 promoter	571 C/A	Elevated total serum IgE	130
TNF-β promoter	509 C/T	Elevated total serum IgE	130

Animal Models of GI Allergy

Animal models, despite their individual limitations, have been useful tools for the study of allergic diseases in vivo.[32,105,106] They have been instrumental in advancing our understanding of the underlying pathophysiologic mechanisms, assessing the allergenicity of food products, and evaluating new therapeutic strategies.[107–110] Animal models offer the ability to study sensitization, studies that are not possible in humans for obvious ethical reasons. Animal models vary in terms of animal used (mouse, rat, guinea pig, pig, dog), sensitization protocols (type of food allergen, dose, route of administration, use of adjuvants), and the methods used to assay the allergic response after antigen challenge (measurement of inflammatory mediators, functional assays of gut function, morphologic studies). It is also important to consider the genetic background of the animal in eliciting an immune response. For example, Brown Norway rats and Balb/c mice are good IgE responders, whereas other mouse strains such as C3H/HeJ mice vary in IgE production although they have been used in establishing good models of food allergy.[111,112] This may be related to the recent observation that this mouse strain has a point mutation in Toll-like receptors preventing lipopolysaccharide responses by peritoneal macrophages that might be necessary to elicit a full IgE response.[105] Smaller laboratory animals also offer the potential for genetic manipulation in which specific effector cells of inflammation (mast cells, eosinophils) or mechanisms of antigen recognition (IgE, antigen-specific T-cell receptors) are manipulated. Examples include mast cell–deficient mice[102,113] and ovalbumin-specific T-cell receptor transgenic mice.[114] Larger animals such as pigs and dogs have been used as models that might better approximate responses that occur in humans.[115–117] Despite the benefits of animal models of food allergy, there are limitations. To date, there is no animal model that can identify known food allergens, predict the allergic potential of novel food proteins, or mimic the human food-allergic sensitization and allergic responses.[105]

Genetics of Allergic Disorders

During the past few years, substantial progress has been made in our understanding of the genetics of allergic diseases.[118–120] It was clear from sibling and family studies that allergy had a genetic background and that the risk of allergy was substantially increased if first-degree relatives were afflicted. Now these observations can be related to several gene polymorphisms associated with allergic diseases (Table 2). Recent studies describe several associations with HLA class II genotypes, mutations in the genes encoding for IgE, and the β-chain of its high-affinity receptor FcεRI.[121–127] Although the mutations found in allergic individuals do not necessarily impair the function of the receptor, they are closely associated with dust mite and pollen allergy and also with pollen-associated food allergy.[128] Cytokines and their receptors and signaling molecules have also been examined regarding polymorphisms associated with allergy. One of the most intriguing findings was the linkage of atopy with distinct mutations in the genes encoding for the β-chain of the IL-4 receptor and STAT6 gene. Other cytokines have been examined as well, including IL-13, which is critically involved in IgE regulation, IL-10, and TGF-β.[129–133]

Clinical Presentation

Classification of Food Allergy

Food allergies are often categorized by the organ systems they affect and by the immune mechanisms

Table 3. End-Organ Effects of Food Allergy

Organ	Disease	IgE mediated	Afflicted age group
GI tract	Immediate GI hypersensitivity	+++	All
	Oral allergy syndrome	+++	Children, adults
	Eosinophilic gastroenteropathies	+	All
	Eosinophilic esophagitis	+	Infants, children
	Eosinophilic gastritis	+	All
	Eosinophilic enterocolitis	+	All
	Eosinophilic proctitis	+	Infants, children
	Dietary protein enterocolitis and proctitis	−	Infants
	Chronic constipation	−	Children
	Dietary protein enteropathy	−	Infants
	Celiac disease	−	Children, adults
	Irritable bowel syndrome	?	Adults
Respiratory	Rhinitis	++	All
	Asthma	++	All
	Alveolitis	+	All
Skin	Urticaria and angioedema	++	All
	Atopic eczema	+	Infants, children
	Dermatitis herpetiformis	−	Children, adults
Cardiovascular	Vasculitis	+	All
	Systemic anaphlyaxis	+++	All

Role for IgE: +++, significant; ++, moderate; +, minor; ?, unknown; −, none.

involved.[10] Although the dermatologic and respiratory tract manifestations of food allergy are often better recognized, the GI tract can be affected by food allergies in various ways (Table 3). Typical manifestations of food allergy in infants and young children are food (dietary) protein–induced proctitis or proctocolitis, food protein–induced enteropathy, and atopic dermatitis.[21,134,135] More recently, eosinophilic esophagitis and allergic constipation have been described.[25,136,137] In older children and adults, the most common manifestation of food allergy is the so-called oral allergy syndrome.[19,134] However, other GI manifestations of immunologic ARF do occur in adults, such as eosinophilic gastroenteropathies and celiac disease.[79,138,139]

While it is beyond the scope of this review to discuss the extragastrointestinal manifestations of food allergy in detail, a variety of dermatologic and respiratory conditions result from immunologic reactions to foods. These include atopic dermatitis associated with increased gut permeability and urticaria.[140] It is unclear as to what extent urticaria is attributable to food allergy because there are many other causes.[140] A variety of foods are associated with urticaria that occurs in association with food-dependent exercise-induced anaphylaxis.[51] Dermatitis herpetiformis is well recognized to occur in association with gluten-sensitive enteropathy, and the skin lesions are effectively treated by a gluten-free diet alone. Respiratory manifestations of food allergy include airway hyperresponsiveness, asthma, rhinitis, and possibly serous otitis media.[141] Although asthma is commonly believed to be due to inhalant allergens, a recent study indicates that food allergy is a major risk for life-threatening asthma in children along with the expected risk factor of poorly controlled asthma.[142] Other potential non-GI manifestations of food allergy include joint diseases, recurrent edema, migraine headaches and chronic fatigue syndrome, and psychiatric and behavioral problems; however, because their association with abnormal immunologic reactions to foods is not established, these presentations will not be discussed in detail here.

The most important manifestation of food allergy is systemic anaphylaxis. It is now recognized that food allergy is the major cause of anaphylactic reactions in industrialized societies, including the United States, Australia, and Europe.[143–145] The prevalence of peanut allergy (0.5%–7% of adults in the United States and the United Kingdom)[8] and its potentially fatal consequences has had significant effect on the operational policies of groups ranging from school districts[146] to the airline industry.[147] Fatal anaphylaxis can result from exposure to minute amounts of antigen such as that imparted by a kiss.[148–150] Food-associated exercise-induced anaphylaxis is a rare type of anaphylaxis in which the food only elicits an anaphylactic reaction when the subject exercises within several hours of ingesting that food.[51] A recent study suggests that wheat-dependent exercise-induced anaphylaxis due to the major allergen ω-5 gliadin (Tri a 19) may result from exercise-induced activation of tissue transglutaminase in the intestinal mucosa, leading to cross-linking of ω-5 gliadin–derived peptides forming larger allergen complexes capable of eliciting an anaphylactic response.[151] Acetylsalicylates and other nonsteroi-

dal anti-inflammatory drugs can also augment type I allergic symptoms when combined with food and exercise in individuals with food-dependent exercise-induced anaphylaxis.[152,153]

GI Manifestations of Immune-Mediated Food Allergy

Oral allergy syndrome. The oral allergy syndrome is the most common manifestation of food allergy in adults. The most relevant triggering allergens are plant proteins that cross-react with certain inhalant antigens, particularly birch, ragweed, and mugwort. Exposure to the cross-reacting foods may lead to pruritus, tingling, and/or swelling of the tongue, lips, palate, or oropharynx and occasionally to bronchospasm or more systemic reactions occurring a few minutes after ingestion of the allergen. Because these reactions are almost all mediated by IgE, the diagnosis can be confirmed by skin prick tests or measurement of specific IgE levels.[21,154]

Latex-food allergy syndrome. Latex-food allergy syndrome, also referred to as the latex-fruit syndrome, is a specific form of food allergy showing increasing prevalence throughout the world and a frequency of associated food allergy that varies from 21% to 58%.[155,156] One of the more recent studies indicates that 8.6% of medical workers in Taiwan had latex allergy, with 26.9% of them having the latex-fruit syndrome.[157] Worldwide, banana, avocado, chestnut, and kiwi are the most common causes of food-induced symptoms associated with latex allergy. In latex-sensitive individuals, exposure to these foods can result in the same symptoms as if exposed to latex, including pruritus, eczema, oral-facial swelling, asthma, GI symptoms, and anaphylaxis.

GI food allergy/anaphylaxis. Typically the GI symptoms of food-allergic reactions (nausea, vomiting, abdominal pain, and diarrhea) occur in conjunction with allergic manifestations in other target organs. The foods primarily responsible for this type of GI food allergy include cow's milk, eggs, peanuts, seafood, and fish, depending on the local eating habits. Of interest to GI/hepatology specialists are recent reports of food allergy arising in the post–liver transplantation setting. In some reports, food-induced reactions have occurred in tacrolimus-immunosuppressed pediatric liver transplant recipients.[158–161] In another report, a 60-year-old nonallergic male recipient of a liver from a 15-year-old boy who died of anaphylaxis after eating peanuts developed anaphylaxis to cashews 25 days posttransplantation. The recipient was found to react to peanut, cashew, and sesame, and it was then established that the donor had IgE to these 3 food antigens.[162]

Food protein enteropathy and food protein enterocolitis/proctitis. Food protein enteropathy is a disease of infants characterized by protracted diarrhea and vomiting with resulting malabsorption. Protein-losing enteropathy may lead to edema, abdominal distention, diarrhea, vomiting, and anemia. The differential diagnosis includes other causes such as infectious and metabolic disorders, lymphangiectasia, celiac disease, and so on. The underlying mechanisms involve immune complex mechanisms and/or abnormal T-cell immune responses most commonly against cow's milk, soy, and other foods. These other foods range from egg, fish, and grains (rice, oats, barley) to vegetables (sweet peas, squash, string beans, peas) and meats (chicken, turkey).[21] Usually these conditions are not associated with induction of specific IgE. Diagnosis is based on endoscopy/biopsy findings (increased intraepithelial lymphocytes and eosinophils, villous injury similar to that seen in celiac disease), elimination diets, and rechallenges. Although certain features are shared with celiac disease, most other food protein enteropathies are different because resolution generally occurs in 1–2 years and there is no increased risk of future malignancy. The symptoms of food protein enterocolitis/proctitis typically seen in the first few months of life are similar to but more severe than those observed in food protein enteropathies.[135,163–167]

Celiac disease. Recent studies in Europe and the United States indicate that celiac disease may occur in up to 1% of the population, making this form of food allergy much more common in adults than previously appreciated.[168] Dietary ingestion of gliadin found in wheat, hordelein in rye, and secalin on barley induces an enteropathy in genetically susceptible individuals. Removal of the offending grains from the diet restores normal small bowel function and appearance, with improvement in symptoms that can range from diarrhea, weight loss, and failure to thrive to the more common but less often recognized symptoms of fatigue, dyspepsia, neurologic dysfunction, and musculoskeletal problems. As with other immune-mediated ARF, elimination of the offending food substance (gluten) is the primary method of management in celiac disease. However, unlike most other food protein–induced enteropathies, gluten must be eliminated from the diet on a lifelong basis in celiac disease.[169]

Eosinophilic esophagitis and gastroesophageal reflux disease. Studies on cow's milk elimination in infants have shown that a subset (about one third) of reflux diseases is attributable to cow's milk allergy.[21,136,170] In those infants and children, symptoms of esophagitis may not improve following standard treatment for acid reflux

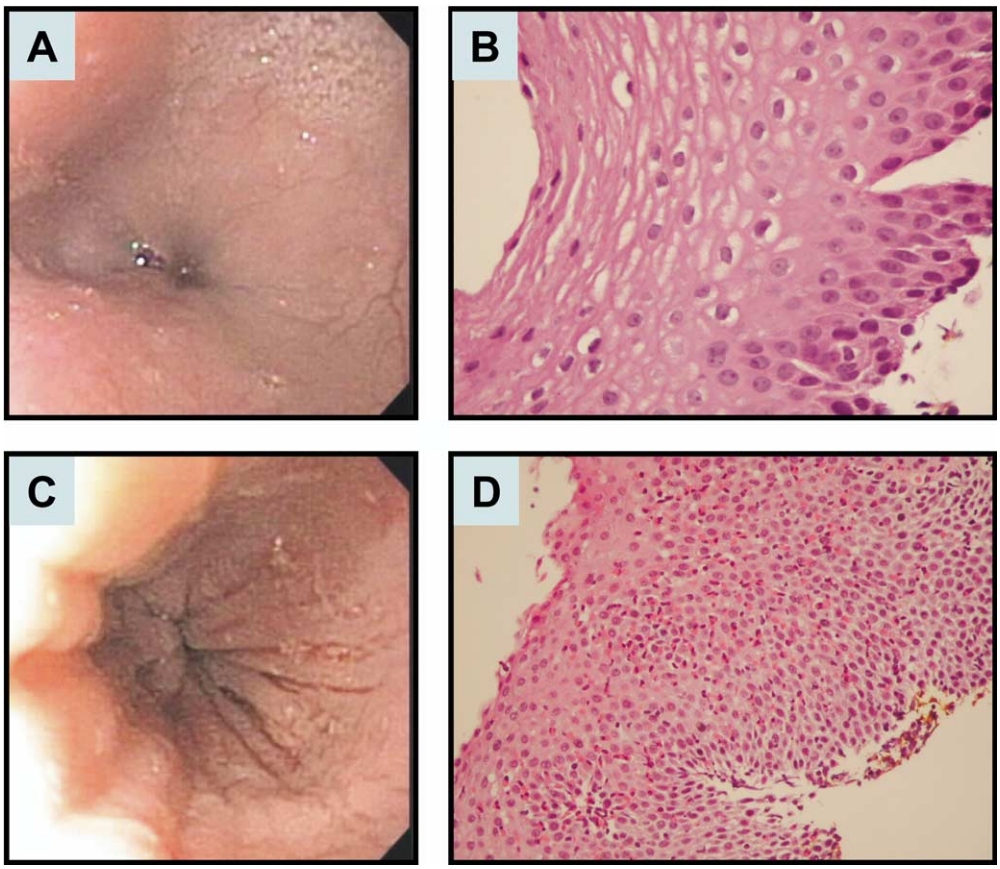

Figure 4. Eosinophilic esophagitis. (*A* and *B*) Normal esophagus. (*C* and *D*) Eosinophilic esophagitis (distal esophagus). (*A* and *C*) Endoscopic and (*C* and *D*) histologic (H&E stain) aspects are shown. Photographs are courtesy of Marc Rothenberg, Phil Putnam, Margaret Collins, and Richard Noel (Children's Hospital, University of Cincinnati, Cincinnati, OH).

and examination of the esophageal mucosa reveals a dense infiltration with eosinophils, giving rise to the label of eosinophilic esophagitis (Figure 4). This condition differs from esophageal inflammation due to gastroesophageal reflux, because treatment strategies such as food elimination (if food allergy can be confirmed as causative) or corticosteroids (if the triggering agent[s] remain unclear) are beneficial rather than measures to inhibit gastroesophageal reflux. Presenting symptoms include vomiting, pain, and dysphagia, and some affected individuals present with food impactions and strictures. Allergy, particularly food allergy, is an associated finding in most patients, and many have concomitant asthma or other chronic respiratory disease. A subtle granularity with furrows or rings has been identified as the endoscopic marker of histologic eosinophilic esophagitis. Histologic characteristics include peripapillary or juxtaluminal eosinophil clustering in some cases. This condition occurs in association with eosinophilic gastroenteritis, but not commonly. Interestingly, recent studies suggest that this disease entity is not restricted to infants and children but can affect adults to an as yet unknown degree.[171]

Eosinophilic gastroenteritis. Eosinophilic gastroenteritis is a heterogeneous and uncommon disorder characterized by eosinophilic inflammation of the GI tissues. The location and depth of infiltration determine the varied manifestations of this condition, and the latter is also the basis for the classification into mucosal, muscular, and serosal forms of eosinophilic gastroenteritis. Abdominal pain, vomiting, and diarrhea occur together in nearly 50% of cases, and peripheral eosinophilia is seen in up to two thirds of patients with eosinophilic gastroenteritis. The differential diagnosis of eosinophilic gastroenteritis in children includes parasitic infections, inflammatory bowel disease, connective tissue diseases, some malignancies, and adverse effects of drugs. Eosinophilic gastroenteritis itself has been strongly associated with food allergies, and concomitant atopic diseases or a family history of allergies is elicited in 50%–70% of cases. The gold standard for diagnosis, usually demonstrated on endoscopic biopsy specimens, is prominent tissue eosinophilia with a mild mastocytosis (Figure 5). However, the diagnosis may be obscured by the patchy nature of the disease and is more difficult to establish in the muscular and serosal subtypes of eosinophilic gastroenteritis. In the latter cases, full-thickness biopsies are indicated for a definitive diagnosis. There are many reports of successful treatment of eosinophilic gastroenteritis in children using a variety of treatment regimens, including elimination diets. Corticosteroids remain the

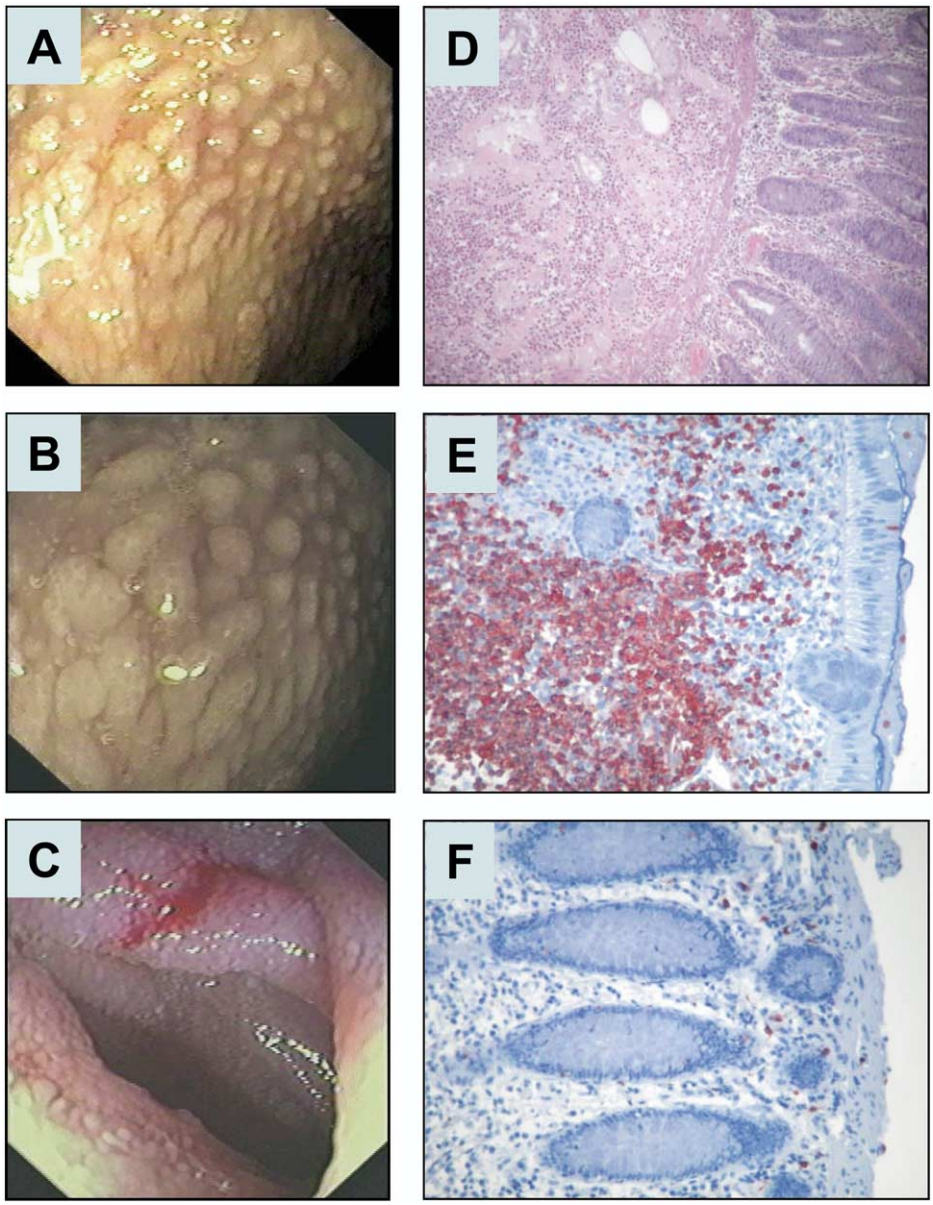

Figure 5. Eosinophilic enterocolitis. *A–C* show different endoscopic examples of eosinophilic ileitis, and *D–F* show tissue sections from a case of severe eosinophilic colitis presenting with abdominal pain and diarrhea. (*D*) H&E staining. (*E*) Immunohistochemical staining using EG2 monoclonal antibody against eosinophil cationic protein. (*F*) Immunohistochemistry using a monoclonal antibody against human mast cell tryptase. (Original magnification: *D*, 100×; *E* and *F*, 200×.)

most effective agents for controlling symptoms, but unfortunately the relapsing nature of the disease often necessitates prolonged corticosteroid use.[138,172]

Other GI disorders associated with ARF. There are many studies that have examined the role of diet in inflammatory bowel disease, but there is no evidence that specific immune-mediated reactions to food play a role in most patients with either Crohn's disease or ulcerative colitis.[19] Patients in remission should be encouraged to eat a nutritionally balanced diet without restrictions unless they experience intolerance to specific foods. It is common for patients with inflammatory bowel disease to be instructed to avoid dairy products, but this is unnecessary apart from those with symptomatic lactose intolerance or rare instances of cow's milk protein allergy, particularly because such foods are good sources of calcium in a population at increased risk for osteoporosis. Even in the absence of a history of food intolerance, it is commonplace for patients with GI disorders to believe that something in their diet has caused their condition and to seek dietary advice from various sources, including GI specialists.[20] A significant number of GI conditions are associated with ARF, but food plays a causal role in only some of these disorders (Table 4). In particular, there is no clear role for hypoallergenic diets in irritable bowel syndrome, although a few studies report benefit from such diets[27,173,174] and, in some instances, such measures may be needed to convince a patient that specific dietary factors are not the cause of his or her illness.

Table 4. GI Disorders Associated With ARF

Immune mediated (food allergy)
GI food allergy/anaphylaxis
Oral allergy syndrome
Food protein enteropathy
Food protein enterocolitis/proctitis
Celiac disease
Eosinophilic esophagitis
Eosinophilic gastroenterocolitis
Non–immune mediated (food intolerance)
Food toxicity (microorganisms, bacterial toxins)
Pseudoallergic reactions (eg, nonimmune mast cell activation by strawberries, chocolate, egg white, pork, cinnamon, pineapple, papaya, legumes, shellfish, tomatoes, herbs, white wine, and additives such as salicylates, benzoates, and tartrazine)
Pharmacologic reactions (eg, histamine found in cheeses, scombroid fish such as tuna, salmon, fresh shellfish, tomato, spinach, meat, pig's liver, tinned foods; tyramine found in chocolate, herrings, tinned fish, brewer's yeast, red wine, and cheese such as Roquefort, cheddar, gruyere, brie; and additives such as sulfites, tartrazine, and monosodium glutamate and other amines)
Metabolic reactions (eg, lactose intolerance)
Psychological food intolerance
Physiologic reactions (eg, starches found in legumes serve as substrate for gas production by colonic flora, and favoring histamine synthesis by fermentation)
Other GI conditions where adverse reactions to foods are implicated
Gastroesophageal reflux disease
Nonulcer dyspepsia
Inflammatory bowel disease
Irritable bowel syndrome

Nonimmune ARF

Food toxicity. The vast majority of ARF are not immunologic in origin but, by virtue of their prevalence, are worthy of consideration. Food toxicity or food poisoning results from microbial contamination of food causing primarily GI manifestations due to preformed toxins (eg, staphylococcal enterotoxin) or replication of enteric pathogens (*Campylobacter*, *Salmonella*, *Shigella*, *E coli*). These reactions can be distinguished from other ARF because they usually do not recur and have fairly characteristic presentations. Occasionally, a self-limited infection may result in a postinfectious irritable bowel syndrome. Patients with recurrent infectious GI illnesses should be evaluated for immunodeficiencies such as IgA deficiency, which occurs at a frequency of approximately one in 500–600, the most common form of inherited immunodeficiency.

Pseudoallergic and pharmacologic reactions. Anaphylactoid or pseudoallergic reactions to food result from foods that mimic the effects of mast cell degranulation but do not involve IgE antibodies.[31,175] As with true food allergy, patients exhibiting such reactions should be instructed to avoid the offending food substance if identifiable. Pharmacologic reactions to food or food additives represent a relatively common type of ARF, although most of these reactions cause symptoms outside of the GI tract. Histamine found in certain foods can cause headaches and diffuse erythema of the skin. Certain individuals develop migraine headaches to various foodstuffs, including those rich in amines. Sulfites, tartrazine, and monosodium glutamate have all been associated with asthma, and glutamate can cause a characteristic syndrome consisting of a burning or warm sensation, chest tightness, headache, and gastric discomfort shortly after its ingestion (Table 4).

Lactose intolerance. Globally, this disorder is the most common adverse reaction to a specific food, with most cases due to declining levels of intestinal lactase activity in later childhood and adult life (metabolic food intolerance), although rare congenital deficiencies can occur. Symptoms of lactase insufficiency are usually dose related and include bloating, flatulence, and diarrhea. Secondary lactase deficiency can result from viral gastroenteritis, radiation enteritis, Crohn's disease, and celiac sprue. It is important from a management standpoint to understand that individuals with lactose intolerance (1) do not experience severe and potential life-threatening complications of ingesting lactose and (2) are able to consume naturally low-lactose dairy products, including most cheeses and yogurts. This contrasts with cow's milk–allergic individuals, who may experience anaphylactic or asthmatic reactions to dairy products and must avoid all foods containing the culprit cow's milk protein, usually casein or β-lactoglobulin.

Psychological intolerance. In certain individuals, reactions to food may be psychological.[93,176] This is a difficult type of ARF to diagnose because the mechanisms giving rise to such reactions are poorly understood. Some studies suggest individuals reporting ARF without confirmation by food challenge had higher rates of hypochondria, hysteria, somatization, and anxiety than those with ARF confirmed by food challenge,[93,109] while other studies suggest there is no increase of psychological disturbance in those who perceive they have ARF than other populations.[177–179] An individual who experienced a severe food poisoning reaction may avoid the culprit food for fear of further reactions. Children forced to eat certain foods under adverse circumstances (ie, as a form of child abuse) may experience symptoms of anxiety or fear when ingesting the food later in life. There is also some evidence that hypersensitivity reactions to food may be triggered through central neural mechanisms so that, eventually, just the thought of ingesting the food can trigger allergic symptoms in the absence of antigen. Laboratory studies in animal models show that Pavlovian conditioning to food antigens can

trigger mast cell degranulation and mucosal pathophysiology in the absence of specific antigen provocation.[100,180] Similar findings have been shown for inhalant allergen provocation in the upper respiratory tract of humans[181,182] and in isolated cases of human food-allergic reactions in the GI tract.[32] Given the extensive neural networks connecting the central nervous system, the enteric nervous system, and various immunocytes, it is quite conceivable that psychological reactions to foods may be much more common than currently appreciated. Food allergy itself may lead to psychologic distress. Studies of food-allergic subjects report an altered quality of life for the individual and his or her family, and severe manifestations such as anaphylaxis can result in a posttraumatic stress situation.[93,183,184]

Physiologic food intolerance. Perhaps the most common form of ARF results from physiologic reactions to food components or additives. For example, it is well known that starches found in legumes serve as a substrate for gas production by colonic flora. Many other foods are associated with "gas," including cabbage, bran fiber, and other vegetables and grains. Other foods and food additives affect the lower esophageal sphincter, while foods high in fat delay gastric emptying, all with the potential to cause symptoms of heartburn and dyspepsia. Physiologic reactions to foods are often noted by patients with functional bowel disease, many of whom exhibit heightened endocrine, motor, and sensory responses to normal digestive events. It is important to determine whether specific food intolerances exist in this group of patients, because elimination of the offending food(s) can provide some benefit. A survey of patients in a gastroenterology clinic in the United Kingdom showed that those with functional diagnoses were most likely to report adverse reactions to foods and drugs, with foods reported to worsen GI symptoms.[185]

Food Allergens

Among thousands of food proteins, only a relatively small number seem to induce IgE-dependent allergic reactions. The structural and biochemical properties of a given molecule required for allergenicity are still unclear.[186] This issue is of particular interest with the advent of genetically modified foods that raise the question of how to predict or test allergenicity.[187] The spectrum of allergens that may cause allergic reactions in the digestive tracts is not necessarily restricted to food, because it has been shown that inhalant allergens such as pollens are also swallowed in substantial amounts and can even be detected in fecal samples. Here, they must be considered in the differential diagnosis of parasite infections because pollen share morphologic features with certain parasite eggs.[19] The list of foods inducing allergic reactions is dependent on the cultural habits of eating different kind of foods and therefore varies somewhat among different countries. For example, peanut allergy is a particular issue in North America, while sesame allergy is more common in the Middle East.[188] The relative importance of particular food allergens also changes depending on the age of afflicted individuals; allergies to cow's milk, eggs, and wheat are more common in infants and children, whereas seafood allergies are more common in adults. Of particular interest is the cross-reactivity among foods belonging to the same botanical group of foods and between foods and other types of allergens such as pollens, mites, or latex (Table 5).[189,190] Knowledge of such cross-reactivity focuses the history of possible foods and other substances inducing allergic symptoms, enhances the accuracy of dietary elimination advice, and allows new insights into the molecular structures of typical allergens.

Table 5. Cross-reactivity Between Foods and Other Types of Allergens

Apple, hazelnut	Betulaceae
Tomato, peach, apricot	Betulaceae, grass pollen
Celery, carrot, spices	Compositae (mugwort)
Melon, banana	Compositae (ambrosiae)
Tomato, pears	Grass pollen
Egg yolk	Bird's feathers (bird-egg syndrome)
Kiwi, chestnut, banana, avocado, walnut, spinach, melon, passion fruit	Natural rubber latex
Snail	Mites

During the past decade, so-called major allergen epitopes have been identified and characterized on a molecular level. Such major epitopes are found in allergens belonging to the same group of allergens or even in different types of allergens such as pollens and foods. They explain on a molecular basis the well-known phenomenon of cross-reactivity between allergens. The first major proteins identified were Bet v1 and Bet v2 (profilin) found in birch pollen and a number of food allergens such as fruits and celery.[191] Most specific IgE in patients experiencing allergy to birch pollen and foods is directed against Bet v1, emphasizing the importance of this protein as a major B-cell epitope and cross-linking agent of mast cells in sensitized individuals. Since then, more than 1000 epitopes, of which about 50–100 are major epitopes, have been cloned and sequenced (for details on recombinant allergen epitopes, see http://www.allergome.org).

The availability of recombinant food antigens offers a number of new possibilities both for the diagnosis and

the treatment of food allergy. Firstly, recombinant allergens may be used for skin testing and in vitro laboratory tests such as measurement of specific IgE or mediator release assays, in place of allergen extracts that are known to contain low amounts of allergen of limited stability and unknown immunologic activity.[192–194] However, better standardization of allergen extracts has only been achieved for inhalant allergens, which, unlike food antigens, also have the potential to be used for immunotherapy. Secondly, recombinant allergens can be modified so they will be recognized by T cells but not by B cells and thus offer the potential for safe and effective desensitization in patients with food allergy.[195,196] For example, the cloned peanut allergen Ara h3 can be modified to a hypoallergenic molecule that binds less efficiently to IgE but retains the ability to stimulate T-cell activation in peripheral blood mononuclear cells from Ara h3–allergic donors. Such an engineered allergen variant displays 2 characteristics essential for recombinant allergen immunotherapy and might therefore be suitable for clinical tests.[197]

Diagnostic Approach

General Approach to Patients Reporting ARF

Guidelines for the evaluation of food allergies have recently been published as a medical position statement by the American Gastroenterological Association.[198] As shown in Figure 6, the evaluation of suspected GI food allergy begins with a careful history correlating symptoms with specific foods. Most immediate hypersensitivity reactions to food include a set of symptoms that consistently occur minutes to hours after ingesting certain foods. In some individuals, other factors such as medications or exercise may modulate the reaction to a specific food. Specificity of the reaction does not always imply a food allergy because patients with anaphylactoid reactions or lactose intolerance report defined reactions to specific foods. If a specific food or group of foods cannot be identified by the initial history, the patient should keep a diet diary for several weeks in an attempt to correlate foods with GI and other symptoms. After certain foods are identified as possible culprits by history or a diet diary, these items should be eliminated from the diet for several weeks to determine the effect on symptoms. If a benefit is seen, the patient may reintroduce the putative allergen(s) in an attempt to prove the association. Such open food challenges are subject to bias and should be corroborated by another more objective method before permanent elimination from the diet, particularly if the patient is young and the foods in question represent a major component of the diet such as eggs, milk, or wheat. If specific foods are not identified by the clinical history or by a diet diary, a hypoallergenic diet (Table 6) may be tried for 2–3 weeks. In cases where a benefit is seen, new foods are gradually introduced in an attempt to identify specific foods that may contribute to the illness.[154,199]

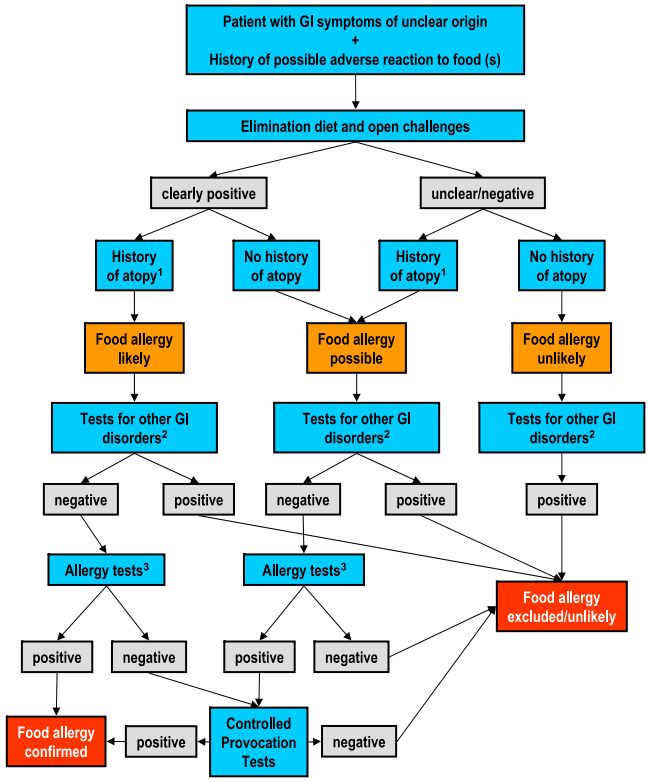

Figure 6. Diagnostic algorithm for evaluating suspected classic food allergy (type I hypersensitivity) manifesting in the GI tract. (1) History of atopy is based on a history of extraintestinal allergy in the patient or first-degree relatives and/or high IgE levels in serum. (2) Tests for other GI disorders include those that exclude other causes of food intolerance (eg, lactose intolerance), other types of immune-mediated GI ARF (eg, celiac disease), and other GI diseases (eg, infection, inflammatory bowel disease, neoplasia). (3) Allergy tests consist of skin tests of allergy and measurement of specific IgE in serum. Controlled provocation tests include oral provocation, preferably performed as a double-blind placebo-controlled food challenge, and local provocation performed by endoscopy (eg, colonoscopic allergen provocation test).

Skin tests. Skin prick testing provides a readily available and relatively inexpensive means to assess a panel of food allergens in both children and adults. The major limitation of skin testing is its poor positive predictive value (many asymptomatic patients exhibit reactions to food allergens), but a negative test result in the absence of antihistamine use strongly suggests that IgE-mediated hypersensitivity is an unlikely mechanism for the patient's food-induced complaints. The value of the classic skin prick test is further limited because of the

Table 6. Elimination Diet

Food category	Allowed	Avoid
Meat and meat alternatives	Lamb	Pork
	Chicken	Beef
	Turkey	Fish
		Eggs
		Milk and milk products
		Seafood
Grains	Rice (barley)	Wheat
		Oats
	Tapioca	Corn
	Arrowroot	Rye
Legumes and nuts		Avoid all dried peas, beans, and nuts
Vegetables	All except corn and peas	
Fruits	All except citrus fruits, strawberries, and tomatoes	
Sweeteners	Sugar (cane or beet)	
	Maple syrup	
	Honey	
Fats and oils	Olive oil	Soy, corn, peanut oils
	Safflower oil	Butter
	Vegetable oil	Margarine
Miscellaneous	White vinegar	Coffee, tea
	Water (ginger ale)	Alcohol
		Chocolate
	Salt (pepper)	Colas
		Spices
	Fruit juices	Chewing gum

NOTE. Also referred to as an exclusion or hypoallergenic diet. Foods in parentheses may cause adverse reactions in some individuals. These may be omitted from the trial elimination diet. If an allowed food is one that has caused a reaction in the past, it should also be omitted. While on the trial elimination diet, symptoms are recorded and a note should be made if there is any change from ones on the previous regular diet. If there are symptoms, determine if there is any relationship to particular foods.

poor standardization and stability of many food allergen extracts, a problem that might be overcome by the use of recombinant food allergens. Skin tests can be improved using native food instead of extracts by performing the prick-to-prick test (first the food is pricked, and then the skin). The recently established epicutaneous patch test allows testing for delayed reactions to food.[200] Conventional patch testing is used to diagnose contact hypersensitivity reactions involving T cells and has been applied to the evaluation of food allergy in the setting of atopic dermatitis and allergic eosinophilic esophagitis, primarily to cow's milk proteins. In a recent study, the sensitivity and specificity of cow's milk atopy patch testing compared with the gold standard of oral challenge were found to be 79% and 91%, respectively.[201] In another study, the combination of patch testing and prick test (or measurement of specific IgE) had the highest positive predictive value for food allergy in children with atopic dermatitis.[202]

Measurement of specific IgE. A radioallergosorbent test or newer nonradioactive tests (eg, Pharmacia [Pharmacia Diagnostics, Kalamazoo, MI] CAP test system) can be used as an alternative to skin testing. The advantages of a radioallergosorbent test compared with skin prick testing are the higher specificity and higher reliability. Moreover, this test has advantages in patients with skin involvement such as atopic dermatitis in which prick tests are not recommended. For selected antigens such as egg, milk, peanut, or fish, high IgE levels may preclude the need to perform provocation testing for confirmation of IgE-mediated food allergy.[11,203] Apparent discrepancies between skin testing or a radioallergosorbent test and the clinical history may be due to local gut levels of food-specific IgE that result in GI hypersensitivity reactions but without a corresponding elevation of serum levels of food-specific IgE. Indeed, older studies showed that IgE concentration in feces and intestinal juice did not correlate with IgE concentration in the blood.[204,205]

Other laboratory tests. The basophil histamine release assay or the more recently established cellular allergen stimulation test (CAST–ELISA), a basophil leukotriene release assay, can also be used to evaluate allergic reactions to food in vitro but are largely reserved for research studies.[206] Another recently reported method for the diagnosis of food allergy is tissue oxygenation provocation, an ex vivo approach, in which intestinal biopsies liberate tryptase, eosinophil cationic protein, and TNF when challenged by specific food allergens. The investigators report a good sensitivity and very high specificity of this evaluation when compared with the results of oral food challenge tests,[207] but this is unlikely to be reproduced in other centers. Diagnostic tests for non–IgE-mediated food allergies include food allergy patch testing, T-cell cytokine assays, and serum measurements of markers of eosinophil activation, including eosinophil cationic protein and eosinophil-derived protein X, also known as eosinophil-derived neurotoxin.[80,208] Laboratory methods have also been developed to measure IgE, TNF-α, and eosinophil-derived mediators in stool samples, making them interesting tools for the assessment of GI allergy and eosinophilic gastroenteropathies, but are not yet established for use in clinical practice.[209–211] Given the limitations of the various diagnostic tests available, the diagnosis of food allergy rests primarily on the clinical history and also the exclusion of other conditions.

Provocation tests. Because reactions to food antigens by a radioallergosorbent test or skin testing are neither specific nor sensitive, a double-blinded placebo-control food challenge in which food antigens are administered by na-

sogastric tube or gelatin capsules should be performed if possible. This technique is considered the gold standard for diagnosing food allergy, but it is not widely available and false negatives do occur.[11,199,212–214] Furthermore, this procedure has several limitations with regard to food allergy manifesting primarily in the GI tract. The readout is by no means standardized or well validated, making the test subjective rather than objective. Secondly, the test does not confirm food allergy but rather food intolerance and thus only confirms the patient's history without insight into the mechanism of the adverse reaction. A number of investigators have performed the GI equivalent of skin testing by injecting the GI mucosa with a panel of antigens and observing for a wheal-and-flare response by endoscopy (Figure 7). This technique was reported as early as the 1930s, with subsequent series describing gastric, duodenal, and most recently colonic mucosal allergen challenge.[74,215] Although these techniques represent an advance in the field of food hypersensitivity, their incorporation into routine clinical practice has been limited. In contrast, endoscopy and mucosal biopsy techniques remain the major diagnostic method to evaluate other GI immune-mediated reactions to food, including celiac disease, food protein gastroenteropathies, and eosinophilic esophagitis and gastroenteritis. A diagnostic approach to patients with GI symptoms attributed to foods is summarized in Figure 6.

Treatment

Established Therapies

Dietary management. The cornerstone of the management of food allergy is avoidance of the offending allergen (Table 6). This is particularly important in cases of food allergies such as peanut allergy where trace amounts of allergen can cause significant reactions. Most fatalities due to food allergy have been due to peanut allergy.[18] Patients with food allergies should learn to read and understand labels for hidden food allergens and to recognize the potential for foods to cross-react with other antigens (Table 5).[154,199] In North America, the Food Allergy and Anaphylaxis Network (1-800-929-4040; http://www.foodallergy.org) is a source of valuable information for those with various types of food allergy. Similarly, it is important for patients with celiac disease to join local celiac disease foundations and support groups that can provide information used to determine sources of gluten-free foods and medications. Dietary restrictions for food allergy associated with anaphylaxis, celiac disease, and most cases of peanut allergy should be maintained on a long-term basis, whereas such measures can be lessened in other types of food allergy that resolve with time, particularly those presenting in early child-

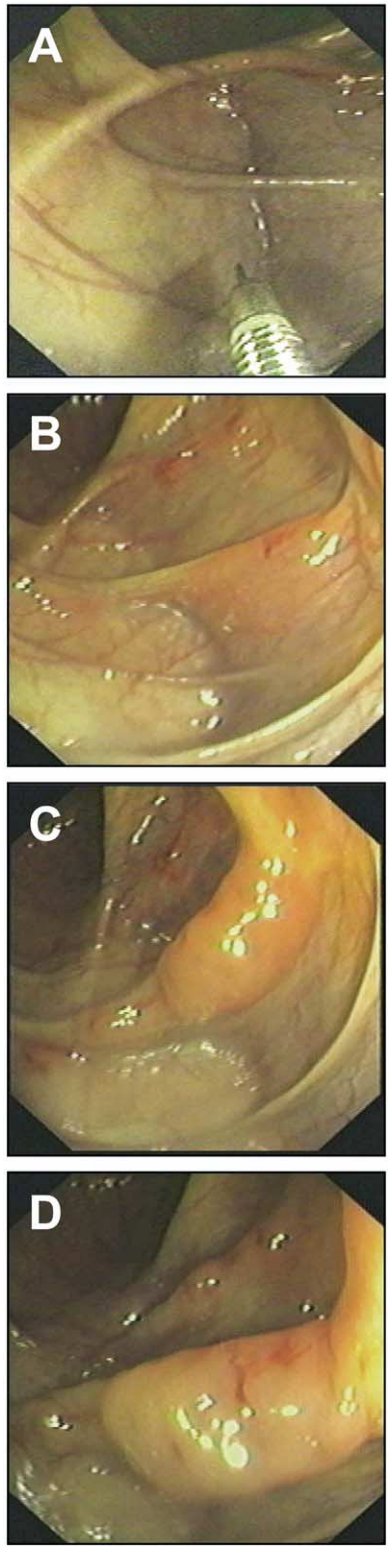

Figure 7. Colonoscopic allergen provocation. (*A*) The cecal mucosa of a suspected food-allergic patient is challenged endoscopically with wheat allergen extract by injection using a fine-gauge needle. A wheal-and-flare reaction starts within 1 minute (*B*), becomes clearly visible after 5 minutes (*C*), and further increases after 15 minutes (*D*). This test is used to confirm diagnosis of GI food allergy in selected individuals and to study underlying mechanisms. Further details on the procedure are described by Bischoff et al.[74]

hood. However, recent studies indicate that a subset of individuals may "outgrow" even peanut allergy.[216]

Medical therapy. To date, there is no clear evidence that oral desensitization, injection immunotherapy, prophylactic medication, or similar techniques are beneficial in the prevention or modulation of food allergy, although isolated reports suggest that such approaches may be of benefit.[217] Antihistamines, ketotifen, oral cromolyn, and corticosteroids may modify symptoms to food allergens, but their efficacy is unproven. In addition, there are many other unproven therapeutic and diagnostic approaches being used in the broad field of ARF, including food allergy.[218] In instances where an elimination diet cannot be adhered to (typically with multiple food allergies or allergies to common foods such as cow's milk, wheat, soy, and/or eggs) or when one is unable to identify specific foods, antiallergic medications should be tried. The mast cell–stabilizing agent disodium cromoglycate is available in formulations that act locally in the GI tract and can be tried in such instances, although the studies supporting their use are limited.[23,219,220] In more severe cases of food allergy, therapy with corticosteroids may become necessary. Topical corticosteroids may be helpful in eosinophilic esophagitis.[221] Whether alternately metabolized systemic corticosteroids such as oral budesonide are helpful in GI food allergy has not yet been studied. Because it is often difficult to prevent accidental exposure to food antigens, patients with a history of an anaphylactic reaction should be instructed to carry an epinephrine-containing syringe for emergency administration along with corticosteroids and antihistamines.[222–224] Because reactions may be biphasic in nature, patients must be instructed to go to a local emergency facility after the initial symptoms. Individuals who are at increased risk for anaphylaxis include those (1) with a past history of anaphylaxis; (2) with reactions with respiratory symptoms; (3) with reactions after the ingestion of peanuts, tree nuts, fish, or seafood; and (4) taking beta-blockers or angiotensin-converting enzyme inhibitor therapy.

Prevention of Food Allergy

Common recommendations. The optimum means to prevent the development of allergies in high-risk individuals remains an area of controversy. Recommendations have been made in the United States and in Europe for infants with a strong family history of atopy, but differences exist on both sides of the Atlantic as to the specific suggestions.[225] Common recommendations include the exclusive use of breast-feeding for at least 4–6 months,[226] delayed introduction of solid foods until after 4–6 months of age, particularly allergenic foods such as egg, nuts, and fish,[225,227] avoidance of all cow's milk protein, and, if formula is needed, to use only extensively hydrolyzed or amino acid–based formulas.[228,229] Partially hydrolyzed cow's milk, soy, and goat or sheep milk products are not recommended. Hypoallergenic diets have been recommended during pregnancy and with breast-feeding for atopic mothers to reduce the incidence of food allergy in their offspring, but no consensus has been reached largely because there have been limited numbers of well-conducted studies to support these recommendations.[230] One recent study showed that exclusive breast-feeding had a preventive effect on the early development of allergic disease, including atopic dermatitis, asthma, and allergic rhinitis.[64] Several recent international studies show the benefit of feeding infants at high risk for atopy with hydrolyzed cow's milk–based formulas.[231,232] When compared with soy-based or regular cow's milk–based formulas, the hydrolyzed formulas resulted in lower levels of IgE specific for the food protein and decreased clinical manifestations of eczema, urticaria, and GI symptoms.[229] Another recent multicenter European study showed that avoidance of food antigens and the use of environmental measures to avoid dust mite exposure diminish sensitization rates to egg and milk as well as dust mite antigen.[233] A current report indicates that exposure to food antigens outside of the GI tract may also be an issue in the development of food allergy. In that study, topical application of products containing peanut oil to the inflamed skin of infants was shown to be a predisposing factor in the development of peanut allergy.[234]

Probiotics. Probiotic *Lactobacillus GG* (also called *Lactobacillus rhamnosus* [ATCC 53103]) or placebo was given to pregnant women during the last 4 weeks of pregnancy and during subsequent breast-feeding until infants were 3 months of age. While only 39% of the women completed the study, a benefit was seen in the group of mothers/infants treated with the probiotic. Allergic eczema occurred in 47% of offspring randomized to the placebo group, while only 15% of children whose mothers received probiotics were affected.[235] Similar benefit was observed in another randomized double-blinded study in which *Lactobacillus GG* was administered to pregnant women and during breast-feeding for 6 months.[60,236] Other studies suggest that probiotics may also be beneficial in ameliorating the severity of allergic responses in established food allergy.[237,238] In one study, the use of *Lactobacillus GG* in conjunction with extensively hydrolyzed formula proved to be of benefit over extensively hydrolyzed formula alone in infants with atopic dermatitis and GI symptoms.[239] However, in another study, young adults and teenagers with oral allergy

syndrome to birch pollen and apples who were treated orally with *Lactobacillus GG* experienced no beneficial effect in terms of subsequent symptoms and the use of medications.[240] Given that the underlying rationale for using probiotics in allergic diseases is that normal enteric flora established shortly after birth provides counterregulatory signals against a sustained Th2-skewed immune response,[237] it is not surprising that the greater benefits of probiotics would be observed in very young infants and/or as prophylaxis during pregnancy.

Future Therapeutic Strategies

Hypoallergenic antigens and anti-IgE. Perhaps the most exciting developments in the field of food allergy are new immunomodulatory therapeutic approaches that offer the potential to be applied to food allergy.[241] These include tolerogenic peptides, recombinant proteins, anti-IgE and DNA vaccination, and neutralizing antibodies or receptor antagonists of Th2 cytokines such as IL-4.[241–243] Methods to genetically or chemically modify the antigenic structures of foods to reduce their allergic potential are being developed. For example, it is known that single amino acid substitutions in the IgE binding site of a peanut allergen can lead to the loss of binding to these epitopes.[197,244] Valenta et al showed on a molecular level that such approaches could be extended to virtually all allergens that have been cloned, thereby offering new approaches for a vaccination against type I allergies.[245] Antibodies specific for the portion of the IgE molecule that binds to receptors on mast cells and basophils have been used in animal models and in clinical trials with asthmatic subjects with benefit and have the potential for use in food allergy.[246] The latter therapeutic strategy has recently been used successfully for the treatment of patients with peanut allergy.[247]

Site-directed immunotherapy. New strategies to modulate the immune system include DNA-based immunotherapies, either plasmid DNA-based or oligodeoxynucleotide immunostimulatory sequences of DNA. Whereas classic immunotherapy and oral immunotherapy are still considered for the treatment of food allergy,[241,244] new approaches aiming to direct the antigen more precisely to the gut are under development. For example, Li et al showed that modified recombinant peanut protein administered rectally in heat-killed *E coli* could reverse peanut anaphylaxis in a murine model.[248] DNA vaccination to induce host cell expression of antigenic protein offers promise as a therapy for food allergy as well, as evidenced by a recent study in a mouse model of peanut allergy. Mice vaccinated orally with DNA coding for a major peanut allergen, Ara h2, complexed with a polysaccharide delivery vehicle, were shown to express the food protein in their GI tract and exhibit less immunologic and clinical reactivity to subsequent challenge with antigen when compared with control mice.[249] Another method to induce tolerance involved the treatment of ovalbumin T-cell receptor transgenic mice with the probiotic *Lactobacillus casei*, inducing IL-12 and thereby inhibiting IgE and IgG1 responses.[114] Most recent studies indicate that induction of oral tolerance is not only possible in rodents but also in animal models that might be more relevant to human allergic diseases, such as the IgE high-responder dog model in which tolerance to ovalbumin and prevention of asthma and allergy could be induced by a 28-day treatment with ovalbumin.[117] Oligodeoxynucleotide immunostimulatory sequences from bacteria are known to activate antigen-presenting cells, natural killer cells, and B cells and enhance production of Th1 cytokines such as IFN-γ. Synthetic oligodeoxynucleotide immunostimulatory sequences containing unmethylated CpG motifs have been used in experimental models of allergy. While this strategy has been shown to be beneficial in murine models of asthma and anaphylaxis,[242,250] their potential role in the desensitization of established food allergy remains to be confirmed.

Immune modulation and other new strategies. Other potential strategies to modulate the immune response in food allergy include the administration of Th1-type cytokines such as IL-12 and IFN-γ or strategies to antagonize the actions of Th2 cytokines such as IL-4 and IL-5.[241] IL-12 has been shown to have benefit in a murine model of peanut hypersensitivity.[251] In atopic dermatitis, IFN-γ combined with an elimination diet was shown to be more effective than either treatment alone.[252] Although anti–IL-4 and anti–IL-5 have been evaluated in asthma, anti-Th2 cytokines have not been examined in food allergy. Traditional Chinese medicine (herbal) used for allergic disorders has been shown to modulate the immune response and to block anaphylaxis in a murine model of peanut allergy,[241] suggesting that such treatments may be beneficial in human food allergy. Other experimental therapies are being directed to modifying the intestinal barrier so it is less permeable to food and other types of antigens. Glucagon-like peptide 2 has been shown to decrease transepithelial antigen uptake and diminish immediate- and late-phase hypersensitivity reactions in a mouse model of allergy to horseradish peroxidase.[253] Various cytokines also decrease permeability of the intestine, including TGF-β and IL-10.[254] Another potential approach focuses on slowing down the absorption of ingested foods. In an in vitro model, activated charcoal was shown to bind peanut proteins that bind IgE and IgG, providing a theoretical basis for

slowing or preventing further absorption of a culprit food antigen, although this approach has not been used in vivo where it could also interfere with the absorption of other therapies.[255]

Summary and Conclusions

ARF resulting in GI symptoms are common in the general population and often underestimated, particularly in adults, of whom 1%–4% have symptoms due to food allergy. GI food allergies are mediated by IgE-dependent and IgE-independent mechanisms involving mast cells, eosinophils, and other immune cells and result in a large number of clinical presentations. Despite substantial progress in understanding the underlying mechanisms, many questions in the field of food allergy remain to be answered. The emerging understanding of the role of innate defense systems and the gut microflora has opened exciting new therapeutic strategies such as the use of probiotic bacteria for the treatment and the prevention of food allergy. Developments in the field of recombinant allergens and their modulation by genetic engineering will improve both diagnostic strategies and therapeutic options.

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