

Determinants of systemic manifestations of food allergy

Scott H. Sicherer, MD *New York, NY*

The myriad of systemic manifestations induced by food hypersensitivity responses is testament to the ability of localized exposure to foods in the gastrointestinal tract to result in symptoms in distal target organs. Cow's milk protein, for example, may induce hives (urticaria), atopic dermatitis, isolated gastrointestinal symptoms, or severe generalized anaphylaxis in different individuals or in the same person at different times. These diverse manifestations are the result of complex interactions among the causal food protein, gut, immune system, and target organs. The dynamic state of these interactions is demonstrated by the development of food tolerance in most subjects and by the ability to experience the development of new allergies in some subjects. This review explores the variety of clinical manifestations of food hypersensitivity disorders in the context of the question: What determines the local or systemic expression of food allergy in a given individual at a particular time? Evidence is provided for both systemic and local immune activation. The role of food-protein chemistry, absorption and processing of ingested allergen, immune responses (type, degree, and specificity), and target organ hyperreactivity are considered as determinants in the expression of food allergic disorders. (*J Allergy Clin Immunol* 2000;106:S251-7.)

Key words: *Anaphylaxis, asthma, atopic dermatitis, food allergens, food challenge, food hypersensitivity*

Food allergy is defined as an adverse immunologic response to foods.¹ However, food allergy is not a single disease, nor is it caused by a solitary pathophysiologic disturbance. It is nothing less than amazing to consider that a single food protein can cause hives in 1 individual, atopic dermatitis in another, severe gastrointestinal disease in yet another, and no symptom in a fourth individual, unless that person ingests the food just before exercise! Interestingly, particular food proteins (ie, peanuts, tree nuts, seafood) are more likely to cause severe systemic anaphylactic reactions,^{2,3} whereas others more commonly cause gastrointestinal disease (eg, gluten in celiac disease).⁴ Clearly, the diversity in the systemic manifestations of food allergic diseases is the result of a complex series of events that involve the immune system,

Abbreviations used

AD: Atopic dermatitis
CLA: Cutaneous lymphocyte antigen
DBPCFC: Double-blind, placebo-controlled oral food challenge
OAS: Oral allergy syndrome

the intrinsic characteristics of ingested food proteins, and the features of the target organs. The varied clinical manifestations of food allergic disease are reviewed herein, with emphasis on the complex interplay of the determinants that influence the final local or systemic manifestations of these disorders.

CLINICAL MANIFESTATIONS OF FOOD HYPERSENSITIVITY

Although food initially contacts the gastrointestinal mucosa, allergic manifestations frequently occur outside of the gastrointestinal tract, with symptoms or diseases affecting a variety of target sites alone or in combination (Table I).⁵⁻⁷ In a series of 544 children and adolescents with confirmed food allergies,⁸ food allergy was associated with a wide range of clinical disorders, the distribution of which varied with age (Fig 1). Studies that used double-blind, placebo-controlled oral food challenges (DBPCFCs) have also demonstrated the variety of organ systems affected during food allergic reactions in children with atopic dermatitis. In a study by Sampson and Ho,⁹ 227 positive DBPCFCs were reported in 196 children with atopic dermatitis. Although 71% of the challenges resulted in gastrointestinal symptoms, an even greater proportion involved distal organ sites, with 86% resulting in skin symptoms and 38% in respiratory tract symptoms. In several recent series of oral food challenges in children with atopic dermatitis,^{10,11} the skin was the most commonly affected organ. Additionally, multiple organ system involvement was demonstrated in approximately 40% of children. Although atopic dermatitis is not commonly linked to food allergy in adults,^{12,13} acute, multisystem reactions (anaphylaxis) are common systemic manifestations.¹⁴

Skin responses

There are several distinct manifestations of skin reactions caused by food allergy. Most of these disorders are mediated by food-specific IgE antibody that is bound to high affinity IgE receptors on mast cells. A typical skin reaction after food ingestion is urticaria and angioedema.

From The Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine.

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Reprint requests: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, New York 10029-6574.

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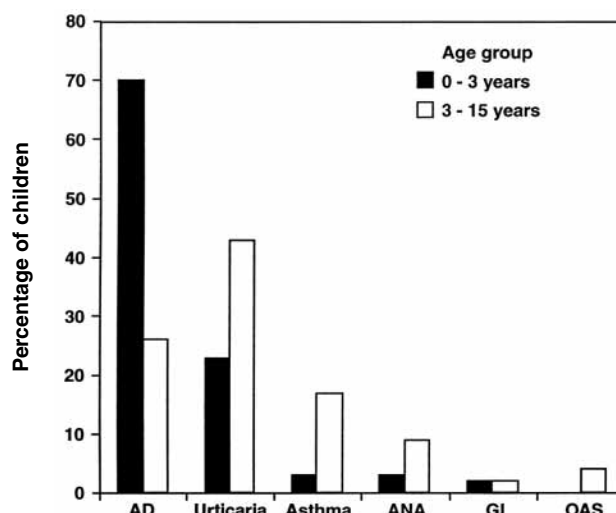


FIG 1. The percentage of children with food allergies demonstrates various clinical symptoms/diseases, by age group. *AD*, atopic dermatitis; *ANA*, anaphylaxis; *GI*, vomiting/diarrhea; *OAS*, oral allergy syndrome.

TABLE I. Clinical examples of local and systemic symptoms/disorders attributed to food hypersensitivity

Allergen exposure	Symptom/disorder
Local reactions (elicited by direct contact with food)	
Skin	Contact urticaria (hives)
Respiratory	Asthma or rhinitis after inhalation of food particles
Gastrointestinal	OAS, proctocolitis, vomiting/diarrhea, enterocolitis, allergic enteropathy, celiac disease
Systemic reactions (after ingestion)	
Skin	AD, urticaria, dermatitis herpetiformis
Respiratory	Asthma, rhinitis, food-induced pulmonary hemosiderosis, laryngeal edema
Cardiovascular	Shock
Other	Uterine contractions

Food allergy accounts for approximately 20% of acute urticaria.¹⁵ Atopic dermatitis (AD), a chronic condition that involves ongoing local T-cell responses to the ingested protein, is also associated with food-specific IgE antibody.^{16,17} AD is associated with food allergy in children in particular; one third of children with moderate-to-severe AD demonstrate food allergy.^{18,19} The variety of systemic manifestations of food allergy in the skin is further demonstrated by dermatitis herpetiformis, a chronic papulovesicular skin disorder in which lesions are distributed over the extensor surfaces of the elbows, knees, and buttocks.²⁰ Like celiac disease, this disorder is associated with a specific immune sensitivity to gluten without involvement of IgE antibody.

Gastrointestinal tract

Although allergic reactions confined to the gastrointestinal system after food ingestion could be considered "non-systemic," many gastrointestinal allergic disorders include a systemic component. One example is cow's milk or soy-induced enterocolitis syndrome. This is a T-cell-mediated food allergic disorder that occurs in infancy with profuse

vomiting and diarrhea.^{21,22} These symptoms may progress to lethargy, dehydration, and hypotension (often mimicking bacterial sepsis) and may be complicated by acidosis and methemoglobinemia.²³ Although symptoms may be limited to the gastrointestinal tract, the systemic nature of the syndrome is demonstrated by a characteristic increase in the peripheral blood polymorphonuclear leukocyte count during a reaction.²⁴

Even when symptoms are limited to the gastrointestinal tract, the broad variety of manifestations speaks to a variety of underlying immunopathophysiologic processes. For example, oral allergy syndrome (OAS) is a local contact reaction mediated by specific IgE antibody and characterized by isolated oral pruritus and edema.²⁵⁻²⁸ The symptoms are triggered by particular fresh, uncooked fruits and vegetables whose proteins cross-react with common pollen allergens. However, acute IgE-mediated reactions to foods may also trigger reactions in the lower gastrointestinal tract that result in severe vomiting and diarrhea ("gastrointestinal anaphylaxis"). Among disorders that are non-IgE-mediated, immunologic and clinical responses are varied as evi-

denced by the type of triggering foods, longevity of allergy, and location of gut involvement. For example, celiac disease²⁹ is a persistent disorder attributed to gluten hypersensitivity that is characterized by damage to intestinal villi, whereas enteropathy caused by cow's milk protein is a clinically similar but transient disorder of infancy.³⁰ Similarly, proctocolitis of infancy is typically caused by milk protein and is characterized by an eosinophilic infiltration of the distal colon/rectum, leading to bloody stools.^{31,32} In contrast to this disorder, the eosinophilic infiltration of allergic eosinophilic gastroenteritis is persistent, is caused by multiple foods, and may occur in various regions of the gastrointestinal tract, leading to pain, vomiting, and obstruction.^{33,34}

Nasal and pulmonary responses

Although numerous studies have shown that ingested food proteins can elicit responses in the upper and lower airway, isolated nasal symptoms are an uncommon (<1%) manifestation of food-allergic reactions. Nevertheless, 25% to 80% of patients who experience generalized reactions during oral food challenges experience concomitant nasal symptoms.³⁵ Analysis of nasal lavage fluid or secretions collected during positive oral food challenges demonstrate a significant elevation in allergic mediators, including histamine and eosinophil products.³⁵

Asthma is not common as an isolated manifestation of food allergy but is often triggered during multiorgan allergic reactions. In a study by James et al³⁶ of 320 children with AD who underwent DBPCFCs for the evaluation of food hypersensitivity, 205 children (64%) had reactions in at least 1 organ system during the challenges. Overall, 34 of the 205 children (17%) with positive challenges experienced wheezing, and all but 3 children had a history of asthma. Pulmonary function was measured in 88 patients to more closely monitor respiratory changes. Of these 88 patients, 13 (15%) experienced lower airway symptoms, but only 6 had significant obstruction with a greater than 20% decrease in FEV₁. Bock³⁷ also used DBPCFCs to evaluate 279 asthmatic children with a history of food-induced asthma and found that 67 of the children (24%) experienced wheezing. In a separate study of 140 otherwise unselected asthmatic children who ranged in age from 2 to 9 years, food-related asthma was observed in 8 children (6%).³⁸ Last, in a study conducted by Onorato et al³⁹ with 300 consecutive asthma patients (age, 7 months–80 years), 25 patients (8%) were suspected of having food-related asthma, but only 6 patients (2%) had asthmatic responses to DBPCFCs. Interestingly, the 6 patients were all children who ranged in age from 4 to 17 years.

Food allergy may induce increased airway hyperreactivity to account for those patients who experience food-related asthma. In a study by James et al,⁴⁰ changes in airway hyperresponsiveness to methacholine challenge were assessed before and after DBPCFCs. Twelve of 22 patients (55%) with positive DBPCFCs experienced mild chest symptoms (ie, cough and/or wheezing with no significant change in FEV₁). Of the 12 patients, 7 (58%)

demonstrated significant increases in airway hyperactivity. The authors concluded that food-induced allergic reactions increase airway reactivity in a subset of food-allergic patients. Overall, these studies indicated that ingested food allergens can elicit both airway hyperreactivity and acute asthma symptoms in children.

The airway reactions described earlier were mediated by food (protein)-specific IgE antibodies. A different immunologic mechanism is responsible for Heiner's syndrome; this uncommon syndrome of infancy is characterized by an immune reaction to cow's milk proteins.⁴¹ The syndrome is associated with precipitating antibodies (IgG) to milk protein that result in pulmonary infiltrates, pulmonary hemosiderosis, anemia, recurrent pneumonia, and failure to thrive.

SYSTEMIC ASPECTS OF FOOD ALLERGY Laboratory evidence for systemic reactivity

Laboratory evaluations performed in humans and in animal models of food hypersensitivity provide evidence of systemic immune activation. Sampson and Jolie⁴² monitored plasma histamine levels in a DBPCFC study of 33 children with AD. Positive responses were associated with a mean increase in plasma histamine from 296 ± 80 pg/mL to 1055 ± 356 pg/mL ($P < .001$), compared with no change evoked by placebo challenges or by foods that did not elicit allergic symptoms. Acute reactions after oral food challenges have also been associated with an increase in serum tryptase concentration.⁴³ In addition to acute changes in allergy mediator levels during challenges, baseline differences in cellular activity have been demonstrated in children with AD who were chronically ingesting foods to which they were allergic. These children exhibited high "spontaneous" basophil histamine release (in vitro) from peripheral blood basophils, compared with patients with AD and with no food allergy or with normal control subjects (mean, $35.1\% \pm 3.9\%$ vs $1.8\% \pm 0.2\%$ vs $2.3\% \pm 0.2\%$, respectively; $P < .001$).⁴⁴ When the children with food allergy were placed on an appropriate elimination diet, they experienced improvement of their eczema and a significant reduction in spontaneous basophil histamine release ($38.0\% \pm 9.6\%$ to $4.3\% \pm 2.1\%$; $P < .01$). Peripheral blood mononuclear cells from subjects with food allergy and with high spontaneous basophil histamine release were found to elaborate cytokines (eg, histamine-releasing factors) that could activate basophils from children who were food sensitive, but not children who were food insensitive.

Systemic aspects of food hypersensitivity reactions have also been reported in a mouse model of cow's milk hypersensitivity.⁴⁵ C3H/HeJ mice were sensitized orally to cow's milk protein, with the addition of cholera toxin to abrogate tolerance induction and induce a T_H2-cell response. These mice developed an increase in cow's milk-specific IgE antibody. In comparison with control mice, when challenged orally with cow's milk, the sensitized mice developed symptoms that included rapid onset of scratching, edema, wheezing, cyanosis, and death.

Histologic examination of the skin revealed mast-cell degranulation, whereas the lung revealed marked inflammation with eosinophilia and mucus production. In the gut, histologic review showed vascular congestion, edema of the lamina propria, and sloughing of enterocytes at the villi tips. Interestingly, there was evidence of increased intestinal permeability because serum casein concentrations in sensitized mice were significantly higher than in sham-sensitized mice after the challenge. These experiments demonstrated that ingested allergen may elicit systemic reactions by distribution through the circulation to target sites.

Factors that determine clinical expression of food allergy

A variety of factors determine the clinical expression of food allergy (Fig 2). Many of these factors have important implications regarding systemic versus local manifestations. Two hypotheses are proposed to account for the systemic and local manifestations of food allergy: absorption-deposition hypothesis, and immune-response hypothesis.

Absorption-deposition hypothesis. Certain features of systemic food-allergic reactions can be explained by the gastrointestinal absorption and random deposition of immunologically intact food proteins to target organs through the circulation. Deposition of triggering allergen subsequently leads to the release of mast-cell products and clinical manifestations. This mechanism is referred to as the "absorption-deposition hypothesis," the features of which are summarized in Table II. Indeed, this process was demonstrated in human subjects through a classic series of experiments by Brunner and Walzer⁴⁶ and Wilson and Walzer⁴⁷ performed over 60 years ago. Sixty-five normal adult volunteers were passively sensitized by intracutaneous injection of serum from a patient with severe fish allergy.⁴⁶ Within 90 minutes of ingesting fish the following day, 61 of 65 volunteers (94%) experienced a wheal and flare reaction at the sensitized site. Similar results were found in children who were sensitized to egg protein.⁴⁷ In its simplest form, this hypothesis can account for food-induced anaphylaxis, with its multisystem manifestations in the sensitized host. However, for this hypothesis to be a tenable explanation for a number of other systemic manifestations of food allergy, additional characteristics of the allergic host and food protein must be considered.

With the absorption-deposition hypothesis, target organ hyperreactivity is a key factor in determining the observed clinical reactions. For example, individuals with underlying asthma/airway hyperreactivity are also most at-risk for severe anaphylaxis with respiratory compromise during food-induced anaphylaxis.² Further, children undergoing supervised food challenges who experience lower respiratory symptoms are usually those with a history of asthma.^{36,37} Similarly, individuals with AD have skin that is particularly sensitive to irritants and other triggers of itch that lead to scratching and dermatitis.⁴⁸ These individuals, when sensitized to food, are like-

ly to experience pruritus (also with overt hives and/or morbiliform eruptions) and flaring of the dermatitis after the ingestion of the causal food.

The absorption-deposition hypothesis also requires consideration for the biochemical characteristics of food allergens and their absorption. Although virtually any food protein can elicit reactions, a rather short list (egg, cow's milk, soybean, wheat, seafood, peanut, tree nuts) accounts for most of the observed allergies.^{11,16} Indeed, food allergens share a number of characteristics; they are generally low molecular weight (10 to 60 kd) water-soluble glycoproteins that are stable at low pH. Protein conformation may also play a role in protein stability. For example, the peanut protein, Ara h 1, was recently shown to resist degradation because of the formation of stable homo-trimers.⁴⁹ Conversely, protein lability may effect clinical outcomes. This feature was demonstrated by individuals who reacted to fish prepared in the usual manner (eg, grilled), but not when the fish was highly processed (eg, canned, lyophilized).⁵⁰ The OAS may also be explained by the lability of the implicated proteins that elicit only local reactions because of protein breakdown in the upper gastrointestinal tract or cooking method.

The ease in which potential allergy-triggering proteins are absorbed is affected by several variables. Factors such as the total quantity of protein ingested, or alterations in absorption caused by dilution by other stomach contents, likely play a role. Variation in absorption may also account for food-associated, exercise-induced anaphylaxis.⁵¹ This disorder occurs in sensitized individuals who experience anaphylaxis to the causal food only when ingestion is followed shortly thereafter by exercise. Alcohol consumption is another factor that may allow increased absorption of coingested food allergens and result in a greater likelihood for systemic reactions in the sensitized host.

The absorption-deposition hypothesis can potentially explain the development of tolerance to some food proteins with the passage of time. For instance, although an adult may still test positive for food-specific IgE antibody, the mature gut may restrict the absorption of the triggering food protein. However, the absorption-deposition hypothesis neglects a number of immunologic features of food allergy and, therefore, cannot solely account for the diversity of systemic manifestations.

Immune-response hypothesis. All manifestations of food allergy ultimately depend on specific immune responses; the role of immunologic factors in the systemic manifestation of food allergy will be termed the *immune-response hypothesis* (Table II). This hypothesis proposes that the specific type of immune response (primarily T-cell response vs the additional production of food-specific IgE antibody) determines or modulates the systemic manifestation of the allergy, as described previously for specific disorders. This hypothesis also considers that other factors (T-cell homing to specific target organs, spectrum of immune activation [type/degree of cellular reactivity or antibody response], route of sensitization) play a role in the manifestations of food allergy.

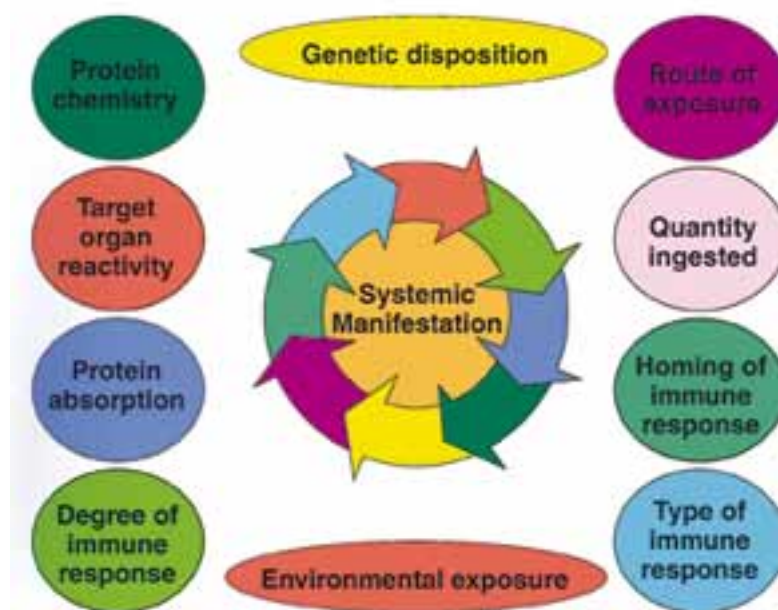


FIG 2. A schematic drawing shows the factors that determine the systemic manifestation of food allergy.

AD is a disorder of the skin associated with systemic immune involvement. Systemic involvement is evidenced by circulating food-specific lymphocytes,⁵² gastrointestinal malabsorption,⁵³ and the presence of allergic inflammatory markers (eg, eosinophil cationic protein) in the stool.⁵⁴ The factor determining skin involvement in this process may include the homing of food-specific T cells to the skin, mediated by “cutaneous lymphocyte antigen” (CLA), the T-cell homing receptor that interacts with E-selectin.⁵⁵ In a study of patients with cow’s milk-induced AD,⁵⁶ the expression of CLA on peripheral blood lymphocytes after in vitro stimulation with casein was significantly higher than the expression in subjects without AD and in nonatopic control subjects. Similarly, in a group of 17 adults with birch-pollen allergy who experienced exacerbation of their AD after DBPCFCs with birch-pollen-related foods, there was a significantly higher increase in the proportion of blood lymphocytes that expressed CLA compared with 20 adults with birch-pollen allergy who did not experience AD after food challenges.⁵⁷

In addition to organ-specific homing, the degree and/or type of immunologic response to food determines the clinical manifestation of allergy. This process is illustrated by the immediate (ie, IgE-mediated) and delayed gut reactions (primarily T-cell mediated) described previously. The spectrum and degree of these responses are central to the systemic manifestations observed and to the development of tolerance. For example, the specific repertoire of food protein epitopes to which IgE antibodies are directed may alter the severity or type of clinical reactivity and may reflect the potential for development of tolerance. This was demonstrated by the fact that children who do not outgrow egg hypersensitivity are more likely to have IgE antibody directed to stable linear,

TABLE II. Hypotheses to account for systemic versus local manifestations of food allergy

Hypothesis	Attributes
Absorption-deposition hypothesis	Target organ hyperreactivity Biochemical characteristics of food allergen Efficiency of gastrointestinal absorption
Immune-response hypothesis	IgE versus primarily T-cell response Pattern of epitope recognition T-cell homing Degree of immune response Route of sensitization

rather than to unstable conformational, epitopes of egg proteins.⁵⁸ The same may be true for cow’s milk.⁵⁹ In addition, the magnitude of immune response may also modulate the systemic manifestations of food allergy. For example, in a number of studies, the absolute concentration of food-specific IgE antibodies have been shown to reflect the likelihood of clinical reactivity.^{9,60} Similarly, the reduction in concentration of IgE antibody is associated with resolution of allergy.⁶¹⁻⁶³

In vitro lymphocyte responses to stimulation with food proteins are also representative of systemic features of clinical reactivity. In children with active, non-IgE-mediated, isolated severe gastrointestinal reactions to cow’s milk, TNF- α secretion from PBMCs was elevated compared with control subjects who experienced resolution of this allergy.⁶⁴ Interestingly, a study of the kinetics of TNF- α secretion found that children with primarily

immediate, cutaneous responses had an isolated early peak (day 1 of culture) compared with children with delayed, gastrointestinal reactions who had a second peak in TNF- α secretion (day 5 of culture).⁶⁵

Finally, the route of sensitization may play a role in determining the systemic character of the reaction. Presumably, most food allergy results from sensitization in the gut after ingestion of particular food proteins. Eigenmann et al⁶⁶ showed that, in children with several manifestations (urticaria, AD, wheezing) of IgE-mediated cow's milk allergy, stimulation of PBMCs with the cow's milk protein β -lactoglobulin resulted in a significantly higher expression of the gut mucosal adhesion receptor $\alpha 4\beta 7$ integrin compared with that in atopic control subjects. This indicates that sensitization occurs in the gut and that clinical expression of the allergy involves additional organs. However, sensitization may also occur by alternate routes with potentially different clinical reactions. Kazemi-Shirazi et al⁶⁷ used qualitative immunoblot inhibition to show that, in subjects with OAS, sensitization to pollen was the cause of the syndrome rather than sensitization through ingestion of the implicated food. Although the nonsystemic nature of OAS may primarily relate to features of the proteins themselves, this is a key observation because it differs from other food allergies in which systemic reactions occur after gastrointestinal exposure and sensitization. In contrast, there is evidence that the respiratory route of sensitization may lead to respiratory reactions after ingestion. In a study by van Ree et al,⁶⁸ using RAST inhibition, sensitization to house dust mite resulted in symptomatic food allergic reactions to snails caused by cross-reacting proteins in 28 adults with cosensitization. Interestingly, consumption of snail resulted in symptoms outside of the respiratory tract in 10 of 28 subjects (36%), but all 28 subjects experienced asthma during their reaction to snail consumption. Thus, for this antigen, ingestion resulted primarily in reactions at the site of initial sensitization. In other cases, direct sensitization of foods through the respiratory tract does not lead to systemic reactions, as illustrated in Bakers' asthma.⁶⁹

CONCLUSIONS

Food hypersensitivity reactions result in numerous symptoms in a variety of target organs and, thus, epitomize the systemic aspects of local (gut) allergen exposure. These disorders depend on an atopic disposition (genetic) and environmental exposure to relevant allergens. The particular clinical responses are determined by absorption and distribution of immunologically active proteins, with reactivity modulated by intrinsic characteristics of the protein and absorption by the host. In addition, the immune response modulates the final clinical manifestations. These factors, and possibly a host of others, contribute to the immunologic and clinical responses that characterize the systemic aspects of food hypersensitivity. The challenge for therapy is to interrupt these processes at key points to prevent or reverse these responses.

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