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Differentiating Food Allergies from Food Intolerances

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Abstract Adverse reactions to foods are extremely common, and generally they are attributed to allergy. However, clinical manifestations of various degrees of severity related to ingestion of foods can arise as a result of a number of disorders, only some of which can be defined as allergic, implying an immune mechanism. Recent epidemiological data in North America showed that the prevalence of food allergy in children has increased. The most common food allergens in the United States include egg, milk, peanut, tree nuts, wheat, crustacean shellfish, and soy. This review examines the various forms of food intolerances (immunoglobulin E [IgE] and non–IgE mediated), including celiac disease and gluten sensitivity.

- Immune mediated reactions can be either IgE mediated or non-IgE mediated. Among the first group, Immediate GI hypersensitivity and oral allergy syndrome are the best described.
- Often, but not always, IgE-mediated food allergies are entities such as eosinophilic esophagitis and eosinophilic gastroenteropathy.
- Non IgE-mediated immune mediated food reactions include celiac disease and gluten sensitivity, two increasingly recognized disorders.
- Finally, non–immune mediated reactions encompass different categories such as disorders of digestion and absorption, inborn errors of metabolism, as well as pharmacological and toxic reactions.

Keywords Food allergy · Food intolerance · Food sensitivity · Celiac disease · Eosinophilic esophagitis · Eosinophilic gastroenteritis

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Purpose of Review

This review is timely: a recent major evidence-based consensus document has been recently published [1••], providing guidelines for the diagnosis and management of food allergy in the United States: a report from the National Institute of Allergy and Infectious Diseases-sponsored expert panel. In addition, all immune-mediated food intolerances are on the rise, making increasing awareness of these conditions an important and extremely relevant element of medical education. The purpose of this review is to report in a concise analysis the current state of knowledge on major forms of food allergies and intolerances, and to provide a succinct guide to a proper diagnostic approach, avoiding common pitfalls. Current evidence for treatment and prevention options will be reviewed as appropriate.

Introduction

Adverse reactions to foods are extremely common, and generally they are attributed to allergy. However, clinical manifestations of various degrees of severity related to ingestion of foods can arise as a result of a number of

disorders, only some of which can be defined as allergic. A food allergy is defined as "adverse immune response that occurs reproducibly on exposure to a given food and is distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions" [1••]. Other conditions causing adverse reactions to food include congenital or acquired disorders of digestive-absorptive processes, toxic reactions, or autoimmune reactions. Until an adverse reaction to food is proven to be of an immune-mediated nature, the generic, non-committed term of "food intolerance" should be used, encompassing all forms of adverse reactions due to ingested food (Table 1).

The National Institute of Allergy and Infectious Diseases (NIAID), which is part of the National Institutes of Health, recently published a set of guidelines for the diagnosis and management of food allergies based on a comprehensive review of scientific and clinical literature. This, along with the recent policy statement by the American Academy of Pediatrics (AAP) regarding the effects of early nutritional interventions on the development of atopic disease [2••] are two influential documents in the clinician's approach to food allergies and intolerances and provide key points that will be discussed throughout this article.

Adverse food reactions can be classified as immune mediated or non-immune mediated. Immune mediated reactions can be further broken down into immunoglobulin E (IgE) mediated and non-IgE mediated reactions. Non-immune mediated food reactions encompass disorders of digestion and absorption such as disaccharidase deficiencies, inborn errors of metabolism such as galactosemia, and phenylketonuria, and pharmacological and idiosyncratic reactions. These reactions can also be classified as food intolerances, as they are not true food allergies. Celiac disease is an autoimmune-based adverse food reaction, increasing in diagnosis and incidence [3, 4]; a distinct entity is gluten sensitivity, possibly also of immune nature but whose pathogenesis is presently unknown.

Food Allergy

Epidemiology

Recent epidemiological data in North America showed that the prevalence of food allergy in children has increased.

Table 1 Classification of food intolerances with gastrointestinal manifestations

Type	Pathogenesis	Main Clinical Entities
Immune- mediated (Food Allergy)	IgE mediated	Immediate GI hypersensitivity
		Oral allergy syndrome
	Non-IgE mediated	Food protein-induced Enterocolitis (FPIES)
		Proctocolitis
		Enteropathy
	Occasionally IgE mediated	Eosinophilic esophagitis
		Eosinophilic gastroenteropathy
Possibly Immune-mediated	Pathogenesis unknown	Gluten Sensitivity
Autoimmune	Innate as well as adaptive immunity	Celiac disease
Nonimmune mediated	Disorders of digestive-absorptive processes	Glucose-galactose malabsorption
		Lactase deficiency
		Sucrase-isomaltase deficiency
		Enterokinase deficiency
	Toxic or Pharmacologic reactions	Food poisoning
		Tyramine (aged cheeses)
		Histamine (strawberries, caffeine)
		Theobromine (chocolate, tea)
	Idiosyncratic reactions	Food additives
		Food colorants

In the United States, the prevalence of reported food allergy in fact increased 18% from 1997 through 2007 in children less than 18 years of age ($P<0.01$), while outpatient visits due to allergy tripled between 1993 and 2006 ($P<0.01$). In 2007, almost 4% of US children <18 years of age had reported food allergy [5]. Peanut allergy appears to have been particularly increasing, with self-reported rates in children going from 0.6% to 1.4% between 1997 and 2008 [6, 7]. Various theories have been proposed to explain the rise in food allergies during the past few decades: namely the hygiene hypothesis, the dietary fat hypothesis, the antioxidant hypothesis, and the vitamin D hypotheses. An alternative hypothesis has also been recently proposed [8•] suggesting that sensitization to allergen occurs through environmental exposure to allergen through the skin and that consumption of food allergen induces oral tolerance.

IgE Mediated Reactions

The most common food allergens in the United States include egg, milk, peanut, tree nuts, wheat, crustacean shellfish, and soy. Cow's milk proteins are the most common cause of food allergy during infancy with soybean proteins ranking second. Egg protein intolerance is most common in school-aged children [9]. Allergen-specific IgE (sIgE) antibodies to foods typically appear within the first 2 years of life and most children will eventually tolerate the allergy inducing foods including milk [10], egg [11], soy [12] and wheat [13•], although in a significant minority of patients, wheat allergy may persist into adolescence [14]. Allergies to peanuts and tree nuts are less likely to resolve, although it is now known that about 20% and 10%, respectively, of young patients outgrow peanut and tree nut allergies [15]. It appears that achieving tolerance is associated with increasing circulating T regulatory cells and reduced production of allergen-specific IgE. It is well known that family history of atopy and atopic dermatitis are risk factors for the development of IgE mediated food allergies with the coexistence of asthma being the most commonly identified factor for severe reactions. The severity of the allergic reactions can not be predicted by allergy testing including sIgE level, wheal size from skin prick testing (SPT) or by past reactions.

Clinical Presentations

IgE mediated reactions typically have a rapid onset within minutes to two hours from the time of ingestion of the offending agent. Symptoms can involve many organ systems including the skin, lungs, gastrointestinal tract, and heart. The most common presentation in children (50% to 80%) is with gastrointestinal symptoms such as nausea, abdominal pain, vomiting and diarrhea followed by skin involvement (20% to 40%) such as erythema, itching, and urticaria. Respiratory symptoms such as cough, wheezing, and rhinorrhea are present in about 4% to 25% of children [16].

The NIAID Expert Panel (EP) recommends that food allergies should be considered if symptoms occur within minutes to hours of ingesting food or if a patient presents with anaphylaxis. Infants and children should also be suspected of having food allergies if they are diagnosed with moderate to severe atopic dermatitis, eosinophilic esophagitis, enterocolitis, enteropathy, and allergic proctocolitis.

Diagnosis

There is not a well accepted set of criteria for the diagnosis of food allergies [17•]. Diagnosis is further complicated by the observation that detection of food-specific IgE implies sensitization, but does not necessarily indicate clinical allergy. Therefore, diagnosis requires a careful medical history, laboratory studies, and, in many cases, an oral food challenge to confirm a diagnosis [16]. The NIAID guidelines in fact specifically recommend ***against*** using intradermal testing and total serum IgE levels as methods of diagnosis. They do state that skin prick tests and sIgE testing may be useful to assist in identifying foods that provoke an IgE-mediated food reaction but can not be used alone to diagnose food allergies. These tests have indeed very high sensitivity but poor specificity and must be interpreted along with clinical presentation and possible food challenge [18, 19]. Oral food challenges can be used to diagnose food allergies and the double-blind placebo controlled food challenge remains the gold standard; however, it is expensive, time consuming and rarely acceptable in clinical practice. Single-blind and open food challenges are diagnostic only if no symptoms are elicited indicating no food allergy, or if objective symptoms correlate with medical history and are supported by laboratory testing which would then indicate a positive food allergy.

Treatment

The mainstay of treatment for IgE-mediated food allergies is to avoid ingesting the causative allergens. Epinephrine, antihistamines and steroids may be used to treat allergic reactions if the allergen is inadvertently ingested. NIAID guidelines do not recommend the use of allergen-specific immunotherapy or with cross-reactive allergens. However, the possibility of favoring acquisition of tolerance in children with food protein allergy by controlled exposure

to the allergens (desensitization) that was originally suggested 70 years ago, [20] has recently been re-proposed [21••, 22–25]. In addition, there is evidence that the addition of baked milk to the diet of children tolerating such foods appears to accelerate the development of unheated milk tolerance compared with strict avoidance [26]. At present, there is agreement that oral desensitization treatment for food allergy in children appears as an exciting development, but more studies are needed before this practice can be standardized and proper recommendations on its use be made [27•].

Prevention of Food Allergy

Prevention of food allergies through allergen avoidance during pregnancy, breastfeeding, and infancy has been seen as an effective health policy, but in reality there is little epidemiological data to support this recommendation. On the contrary, there are now studies suggesting that early oral exposure may result in the induction of tolerance. New strategies to prevent food allergy in infants need to be put to test in randomized controlled interventional studies. The AAP issued a new policy statement in January 2008 re-examining the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods and hydrolyzed formulas on the development of atopic disease in infants and children [2••]. Outlined below are the key points of this statement in regards to preventing food allergies. Of interest, all statements are also supported by the NIAID guidelines. The definition of "at risk" patients includes those with a first degree relative who has existing or a history of food allergy, atopic dermatitis, asthma, or allergic rhinitis. The policy statement also includes information regarding the development of atopic dermatitis and wheezing which is beyond the scope of this article.

Maternal Dietary Restriction

According to previous recommendations by the AAP, mothers should avoid peanuts during pregnancy and breast-feeding and additional allergens during lactation [28]. Recently however, both the AAP and the section on Paediatrics of the European Academy of Allergology and Clinical Immunology have changed their position, acknowledging that we do not know whether certain aspects of avoidance prevent allergies, and recommendations about avoidance of specific food allergens have been replaced by comments about the lack of current evidence on these topics [2••, 29]. Many food antigens can be found in human milk, however it is unlikely that these contribute to the development of food allergies in the infant. Therefore, at this time, there are no recommendations for maternal dietary restrictions during pregnancy or lactation to prevent infant food allergies.

Breastfeeding

The World Health Organization promotes exclusive breastfeeding during the first 6 months of life, and delaying weaning to solids and milk formulas after that age [30] in order to prevent development of food allergies. However, there is no convincing evidence that exclusive breastfeeding beyond 4 months of age has any effect on reducing atopic disease. On the other hand, exclusive breast feeding for four months when compared to feeding with intact cow milk protein formula in infants at high risk of developing atopic disease has been shown to decrease the incidence of cow milk allergy and atopic dermatitis in the first two years of life [2••].

Timing and Introduction of Complementary Foods

The AAP had previously recommended that families with an infant at increased risk of atopy based on family history should avoid peanuts in the infant's diet during the first 3 years of life and common food allergens until the first (milk), second (egg), or third (tree nuts and fish) years of life [28]. While there is solid evidence that very early (ie during the first 2–3 months of life) introduction of potential allergens poses an increased risk to infants at risk, there is no convincing evidence that delaying the introduction of solid foods beyond 4 to 6 months of age has any protective effect on the development of food allergy. Even for foods that are considered highly allergenic such as fish, eggs, and peanut proteins, there appears to be little evidence that a delayed introduction is beneficial.

Soy and Hydrolyzed Formulas

Feeding with soy-based infant formula has not been shown to prevent food allergies. Feeding with extensively or partially hydrolyzed formulas compared with cow milk formula in the first 4 to 6 months in infants with high risk of developing atopic disease has been shown to delay or prevent atopic dermatitis. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed formulas in prevention of atopic disease. It is unclear if these benefits continue on into late childhood, although a recent large epidemiological investigation on almost 6,000 children in Germany suggests that this is indeed the case until the age of 6 [31••].

Immune, Non-IgE Mediated

The non-IgE mediated food allergies present in a more subacute or chronic nature and more commonly affect only the gastrointestinal tract. The primary disorders in this category include food protein-induced enterocolitis (FPIES), food protein-induced proctitis and enteropathy, and celiac disease. There are no medications currently recommended by the NIAID to prevent non-IgE mediated reactions.

Food Protein-induced Enterocolitis Syndrome

FPIES is an allergic syndrome that occurs in the infant population in response mostly to cow's milk and, to a lesser extent, soy; although rice, oat, and poultry have been identified as causative agents [32]. It is thought that the intestinal inflammatory response is largely determined by the cytokine release triggered by the pathologic mechanism, with a deficit in TGF-β1 response and an excessive TNF-α response likely pathogenetic factors [33]. Humoral immune response may also be involved in the pathophysiology of FPIES with an increase of specific IgA and a decrease in specific IgG4 antibodies. The presentation is typically in the first month of life and consists of profuse vomiting, diarrhea, and melena or hematochezia. Although endoscopy is rarely performed, changes in the duodenal mucosa (several degrees of villous flattening and inflammatory infiltration) and in the colon (crypt abscesses, colitis) have been reported [34]. This condition is diagnosed mostly by history; a food challenge may also be performed to confirm it, but if there is a history of a hypotensive episode, multiple reactions to the same food and absence of symptoms when the causative food is eliminated, then the diagnosis can be made without a food challenge [1••]. Treatment is based on eliminating the offending food, and recent evidence showed that most children presenting FPIES will eventually become tolerant of the offending food by the age of 3 [35].

Food Protein-induced Proctocolitis

Food protein-induced proctocolitis is another cell-mediated reaction to cow's milk, soybean, and egg proteins (occasionally corn has been implicated too) that often presents in the first month of life and is the most common cause of low-grade rectal bleeding in young infants [36]. Unlike FPIES, it is a benign condition that tends to occur in exclusively breast fed infants, in response to food allergens ingested by mom and appearing in her breast milk. Blood loss is usual minimal and anemia is uncommon, but can occur. Diagnosis is made clinically and treatment is again avoidance of the inciting allergen. This entity even if untreated usually resolves in six months to two years.

Food Protein-induced Enteropathy

Food protein-induced enteropathy presents in infants and young children as chronic osmotic diarrhea and failure to thrive, and may clinically appear very similar to celiac disease. It is also a cell-mediated reaction to cow's milk and soy protein that causes inflammation in the small intestine with distortion of villous architecture similar if not indistinguishable from celiac disease, but typically displaying a patchy distribution at the duodenal biopsies. The differentiation from celiac disease is based mostly on the negative serologies, especially the highly specific anti-tissue transglutaminase or deamidated gliadin peptides. Treatment is avoidance of the offending allergen, in most cases milk protein.

Eosinophilic Gastrointestinal Diseases (Eosinophilic Esophagitis, Gastroenteropathy)

Eosinophilic gastrointestinal disorders are characterized by eosinophilic infiltration of segments of the intestinal tract on mucosal biopsy in conjunction with clinical symptomatology [37]. Although eosinophilic gastrointestinal diseases are typically listed under non-IgE food reactions, approximately 50% of cases are caused by IgE mediated responses. These disorders present with a myriad of gastrointestinal symptoms depending on the location and extent of involvement and can include difficulty or pain with swallowing, abdominal pain, nausea, vomiting, and weight loss, among others. Food specific IgE tests in addition to SPTs may be used to identify foods associated with EoE but alone are not sufficient to make the diagnosis and if negative do not rule out the possibility of eosinophilic gastroenteropathies [1••, 38••]. Upper or lower endoscopies, depending on the presentation, to obtain mucosal biopsies are necessary for diagnosis in conjunction with the patient's clinical presentation. The diagnosis is difficult due to the lack of strictly defined diagnostic criteria.

In February 2011, the Journal of Allergy and Clinical Immunology published updated consensus recommendations for eosinophilic esophagitis in children and adults. According to this review, treatment involves dietary therapy of three possible regimens: strict use of amino acid-based formula, dietary restriction based on allergy testing, or dietary restriction based on eliminating the most likely food antigens. The committee also recommended that topical

steroids should be considered for both initial and maintenance therapy. Treatment with cromolyn sodium, leukotriene receptor antagonists, and immunosuppressive agents was not recommended [38••].

Possibly Immune-Mediated

Recently, another form of intolerance to gluten, a storage protein contained in wheat, barley and rye, has been defined, as distinguished from celiac disease: gluten sensitivity. This clinical entity whose prevalence is currently unknown but thought to be at least as common as celiac disease, and likely much more commonly seen in adults than in children, is defined as an adverse reaction occurring upon ingestion of gluten in patients who do not have celiac disease or wheat allergy and whose symptoms subside after gluten withdrawal. The definition is necessarily broad, as many clinical manifestations are attributed to gluten sensitivity, ranging from strictly gastrointestinal to extra-intestinal such as fatigue, headaches, joint pain. Gastrointestinal manifestations however appear to be the most common complaint of affected individuals, to the point that looking for gluten sensitivity (in addition to celiac disease [39]) has been recommended in patients with irritable bowel syndrome [40]. Two very recent studies [41, 42] showed the gluten-dependency of symptoms in such patients, and also supported the notion that so far, no clear-cut biological markers useful for diagnosis are available. Thus, diagnosis is essentially a clinical one [43•] and rests, at present, on exclusion of celiac disease (see below) and wheat allergy.

Autoimmune Food Intolerance

Celiac Disease

The most common genetically induced food intolerance, celiac disease (CD) is an autoimmune disorder affecting about 1% of the population and occurring in individuals of all ages, from infancy to the elderly, expressing the HLA-Class II haplotypes DQ2 and/or DQ8. It is triggered by the ingestion of gluten and related prolamins found in wheat, barley, and rye. This condition is now considered a systemic disorder, originating in the intestine and affecting primarily the small intestine, where it progressively leads to flattening of the mucosa through a combined action of adaptive as well as innate immunity [44]. Along with the intestinal damage, specific autoantibodies are produced that can be detected in the serum of patients as they eat gluten: anti-tissue transglutaminase antibodies (TTG), anti-Endomysium antibodies (EMA) and more recently, anti-Deamidated Gliadin Peptides (DGP). Signs and symptoms can vary greatly between patients, and is thought that the majority of affected individuals will actually be asymptomatic.

Schematically, four possible presentations of CD are in fact recognized: 1) typical, characterized mostly by gastrointestinal signs and symptoms; 2) atypical or extra-intestinal, noted by minimal or absent gastrointestinal signs/symptoms; 3) various extra-intestinal, characterized by present manifestations, ranging from short stature to iron-deficient anemia, and from dermatitis Herpetiformis to female infertility; 3) silent, where the small intestinal mucosa is damaged and CD autoimmunity can be detected by serology, but there are minimal or no symptoms (silent celiac is commonly found in patients that come to be diagnosed by screening, often belonging to high-risk groups [Table 2], such as relatives of celiacs or because of the coexistence of other autoimmune conditions); and 4) potential, in which mucosa morphology is normal. These individuals have genetic compatibility with CD (ie, they are HLA-Class II DQ2 and/or DQ8 positive) and also show positive autoimmune serology; they may or may not show signs and symptoms consistent with celiac disease [45]. There is recent evidence both in children and in adults that full-blown CD may ensue at a later time in a high proportion of these individuals if they continue to eat gluten [46, 47], and that this outcome can be predicted on the basis of the presence of TTG in the duodenal biopsies [48].

CD can be effectively screened by checking blood levels of the very sensitive and specific TTG, EMA or DGP, and the diagnosis is then typically confirmed by the histological changes of the duodenal mucosa bioptic samples obtained via an upper endoscopy. There is currently no cure for CD, but the prompt institution and a strict adherence to a life-long gluten-free diet results in the complete remission of the intestinal damage and of symptoms in the vast majority of the patients.

Table 2 Groups at risk of celiac disease

Condition	Approximate prevalence of celiac disease
Insulin dependent diabetes mellitus	8%–12%
Multiple sclerosis	11%
Thyroiditis	3%–5%
Sjögren syndrome and other connective tissue diseases	3%–4%
Down syndrome	10%–12%
Williams syndrome	5%
Turner syndrome	5%
First degree relatives of celiac patients	8%–10%

Table 3 Diagnostic approach for immune-mediated food intolerances

Condition suspected	Clinical	Food(s) involved	Diagnostic approach
Immediate GI Hypersensitivity	Usually infancy to childhood; reactions to offending food within minutes: vomiting, diarrhea, nausea, pain; also rhinoconjunctivits, skin rash, angioedema	Cows' milk, soy, eggs, peanuts, wheat, shellfish	History+SPT and/or sIgE
Oral Allergy Syndrome	Itching, burning, erythema, or tingling of the lips, tongue, palate or oropharynx.	Fresh fruits and vegetables	History+SPT and/or sIgE
FPIES	Early infancy; vomiting, diarrhea, colitis	Rice, Soy, cow's milk, vegetables and fruits, oats, meats and fish	Clinical criteria±food challenge (Patch test being investigated)
Food protein-induced Proctocolitis	Early infancy: Streaks of blood and mucus in stools in breast-fed, typically healthy babies	Cow's milk, eggs, soy, corn (in mom's diet)	Clinical diagnosis supported by food elimination (in mom's diet)
Food protein-induced enteropathy	Infants and toddlers; Malabsorption syndrome similar to early-onset celiac disease, including hypoalbuminemia	Cow's milk Occasionally soy or egg	Clinical, supported by duodenal biopsies with patchy villous atrophy
Eosinophilic Esophagitis	All ages; From asymptomatic to reflux- or dyspepsia-like symptoms	Cows' milk, soy, eggs, peanuts, wheat, shellfish	Endoscopy with biopsies showing typical changes. SPT, sIgE sometimes useful
Eosinophilic gastroenteropathy	Highly variable symptoms depending on localization and extension of eosinophilic infiltrates	Cows' milk, soy, eggs, peanuts, wheat, shellfish	Endoscopy with biopsies
Gluten sensitivity	Mostly adults with IBS-like symptoms	Gluten	Clinical only: no diagnostic marker available
Celiac Disease	All ages. Strictly limited to HLA-DQ2 and/or DQ8 positive subjects. GI and extra-GI symptoms	Gluten	Specific serology+diagnostic features of duodenal biopsies

SPT Skin prick Test; *sIgE* specific serum IgE

Conclusions

As in all other fields of medicine, a good medical history and a physical examination are the first necessary component of a proper diagnostic process [1••]. The history is in most cases pointing toward the possible offending food, but one has to keep in mind that parent and patient reports of a food intolerance must be confirmed: in fact, multiple studies have shown that 50% to 90% of alleged food allergies are actually not such. Also in children, outside of anaphylactic reactions, simply relying on sIgEs to determine the need for a food elimination diet is not sufficient, especially in atopic dermatitis. In these circumstances, oral food challenges may be indicated to confirm food allergy status [49]. Several diagnostic tests may be of help, and in the previous sections we have indicated some for some specific conditions. Table 3 is a schematic list to suggested diagnostic approaches to immune-mediated food intolerances. Prompted by the limitations of currently available diagnostic tests for many of the conditions due to food allergy, in the past many years a large number of unproven methods of "diagnosing" have appeared and are enjoying an undeserved popularity. The most common of these alleged diagnostic tests are reported in Table 4. As clearly stated in the recently released guidelines however, there is no scientific

Table 4 Tests *not* recommended to diagnose food allergies or intolerances (from ref. [1••])

Test
Basophil histamine release/activation
Lymphocyte stimulation
Facial thermography
Gastric juice analysis
Endoscopic allergen provocation
Hair analysis
Applied kinesiology
Provocation neutralization
Allergen-specific IgG4
Cytotoxicity assays
Electrodermal test
Mediator release assay

validation whatsoever to any of these tests, that therefore should never be utilized in ruling in or out a food allergy, both in children and in adults [1••].

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- • Of importance
- •• Of major importance

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