

# Food allergy: a practical update from the gastroenterological viewpoint

Cristina Targa Ferreira,<sup>1</sup> Ernest Seidman<sup>2</sup>

## Abstract

**Objective:** To present an up-to-date and critical review regarding food allergies, focusing mainly on treatment and prevention.

**Sources:** Review of published literature searched on MEDLINE database; those data which were the most up-to-date and representative were selected (2000-2006). The search included the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP).

**Summary of the findings:** The prevalence of allergic diseases has increased over the last decades, and food allergy seems to be part of this increase. Food allergy is much more common in pediatrics and has a significant medical, financial and social impact on young children and their families. Treatment and prevention of food allergy is a major challenge for public health, scientific and medical communities. There is a lot of misinformation and the medical management of this condition is still discussable. We present and discuss the guidelines regarding criteria for the prevention of food allergy and atopic diseases published by the Nutrition Committees of ESPGHAN jointly with the European Society for Pediatric Allergy and Clinical Immunology (ESPACI) and AAP.

**Conclusion:** The overdiagnosis of food allergy is quite prevalent. There is a need for standardization of definitions and diagnostic procedures. The primary goal of therapy should be to first establish effective means of preventing food allergies. There is a need for accurate diagnostic methods to confirm or rule out the diagnosis. Patients need appropriate treatment by eliminating foods that cause symptoms, while avoiding the nutritional side effects and the cost of inappropriate diets.

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1. Gastroenterologista e endoscopista pediátrica. Mestre, Fundação Faculdade Federal de Ciências Médicas de Porto Alegre (FFCMPA), Porto Alegre, RS. Doutora, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brasil.
2. Canada Research Chair, Immune-Mediated Gastrointestinal Disorders, Division of Gastroenterology, Montreal Children's Hospital, Montreal, Quebec, Canada. Professor, McGill University Health Center, Montreal, Quebec, Canada.

**Conflict of interest:** Dr. Cristina Targa Ferreira has delivered scientific lectures and participated in satellite symposia and courses sponsored by Nestlé. Currently, she is conducting a multicenter study on probiotics and atopic dermatitis.

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## Introduction

The prevalence of allergic diseases has increased dramatically in children and young adults over the past few decades, and food allergies (FA) constitute a part of this increase.<sup>1,2</sup> Food allergies have become a major health concern worldwide over the past two decades and are associated with a significant negative impact on the quality of life.<sup>3</sup> Risks to well being increase as the foods consumed in a population are increasingly likely to be processed and complex, with inadequate labeling.<sup>4</sup> FA are much more common in the pediatric age group than in adults and has significant medical, financial and social impact on young

children and their families.<sup>2,5</sup> Surveys suggest that between 5 and 25% of adults believe that they or their children are affected.<sup>6</sup>

The true prevalence of FA in children remains unclear because various studies apply different inclusion criteria, diagnostic definitions and methods. There is a need for standardization of definitions, diagnostic procedures, test methods and careful categorization of cases for a more homogeneous description of patients and comparison of clinical outcomes. Comparative data need to be interpreted with caution, and there is a necessity to differentiate between diagnoses made by self-reporting, by measurements of sensitization using IgE antibody-based criteria and by carefully conducted clinical challenges.<sup>5</sup>

Overestimation of FA by patients and their families is well documented.<sup>2,5,6</sup> Adult patients often misjudge their own FA because of confusion between true allergy as opposed to food intolerances.<sup>2,7</sup> Similarly, parents commonly overestimate FA in their children. In a cohort of 520 consecutive newborn babies investigated over the first 3 years of life, only 6% of children reacted to suspected foods in a double-blind placebo-controlled oral food challenge. In contrast, parents believed their child to be food-allergic in 28% of cases.<sup>8</sup>

Recent studies have shown that as much as one fourth of U.S. households report the perception of a family member having a food allergy,<sup>9</sup> while in Spain about 1/6 of parents attribute minor symptoms or changes in their infant's behavior to cow's milk allergy.<sup>10</sup> Much of the controversy surrounding this subject has stemmed from loosely labeling any untoward reaction to food as an allergy, when in fact many clinical responses are food intolerance reactions, rather than FA.<sup>2</sup> This review updates published information about FA, focusing mainly on its treatment and prevention.

### **Terminology**

FA, defined as an adverse immune response to food allergens, affects as much as 6-8% of young children and 3-4% of adults.<sup>6,8,11</sup> Other non-immune-mediated adverse reactions to food can be caused by a variety of mechanisms, including digestive enzyme deficiencies (as in the case of lactose intolerance) or toxins (staphylococcal food poisoning), as well as psychological aversions. However, food hypersensitivity (often used synonymously with FA) may be defined as a reproducible adverse clinical reaction following the ingestion of dietary protein allergens, mediated by an abnormal immune response.<sup>1,11,12</sup>

The World Allergy Organization proposed a new nomenclature for the definitions of allergy in 2003.<sup>13,14</sup> Hypersensitivity should be used to describe reproducible symptoms or signs initiated by exposure to a definite

stimulus at a dose tolerated by normal persons. In contrast, intolerance was suggested to describe an abnormal physiological response to an agent which is non-immune-mediated. The term atopy was suggested as referring to a characteristic that makes one susceptible to develop various allergies, while allergy is a hypersensitivity reaction initiated by specific immunological mechanisms. Food allergy refers to a group of disorders with an abnormal or exaggerated immunological response to specific food proteins that may be IgE or non-IgE-mediated. When other mechanisms can be proven, the term non-allergic hypersensitivity is recommended.<sup>13,14</sup>

### **Pathogenesis**

Although significant advances have been made in our understanding of the mucosal immune system, the precise pathogenesis of most food hypersensitivity reactions remain incompletely understood. Several factors clearly play important roles, including genetics, host's intestinal flora, the timing, dosage, and frequency of exposure to various dietary allergens, as well as the allergenicity of various food proteins.<sup>2,15</sup> Immaturity of the intestinal mucosal barrier has been suggested as one mechanism that may explain the higher incidence of food allergy in infants and children.<sup>12</sup> However, despite the fact that macromolecular uptake is increased in preterm infants, this is not necessarily associated with an increased incidence of food allergy.<sup>2,16</sup> Abnormalities in the induction or maintenance of oral tolerance have been suggested to play a role in the development of food hypersensitivity reactions. Experimental studies suggest a key role of the bacterial flora in the development of allergy and tolerance.<sup>17</sup> However, despite the explosion of information providing new insights into the mechanisms of oral tolerance in mice, relatively little is known about the ontogeny of oral tolerance mechanisms and the key roles of dendritic and T regulatory cells in humans.<sup>18</sup>

The production of allergen-specific IgE antibodies has been shown to play an essential role in immediate, type I hypersensitivity reactions. In other forms of food hypersensitivity, such as protein-induced enterocolitis, non-IgE type IV immune mechanisms are thought to predominate.<sup>2</sup> There is evidence to suggest that eosinophilic diseases of the gastrointestinal tract may be caused by abnormal Th2 cytokine response (IL-4, 5) and chemokine production, resulting in eosinophil activation and recruitment.<sup>19,20</sup> However, little of this information has translated into more specific or sensitive clinical approaches for the diagnosis and management of FA. Given the complexity of the mucosal immune response to dietary antigens and the multiple immunological mechanisms

involved, much more research is necessary before a better understanding of the pathogenesis of these conditions can be achieved.

### Clinical presentations

As reviewed above, FA can be broadly classified as IgE or non-IgE-mediated. The disorders mediated by IgE antibodies generally have an acute onset of signs and symptoms after ingestion. This reaction activates tissue mast cells and blood basophils resulting in sensitization. After a subsequent exposure, the causal food allergens bind to IgE-specific molecules and trigger the release of mediators that cause symptoms.<sup>21</sup> Non-IgE-mediated FA present with subacute or chronic symptoms and are thought to be primarily mediated by T cells. A third group of chronic disorders attributed to FA appears to be a mixed reaction of both IgE and T cell-mediated responses. Tables 1 and 2 illustrate the major clinical features of FA, the types of immunological reactions and the different organ systems involved. The subset of infants presenting with colic, symptoms suggestive of gastroesophageal reflux, or chronic constipation, pose particular diagnostic dilemmas. Although these symptoms are often attributed to FA, usually implying immune reactions to cow's milk, an immunological basis for these conditions is not usually established.<sup>22</sup>

### Diagnosis

An accurate diagnosis is essential to the correct management of FA. As reviewed above, a diagnosis of FA on the basis of the parent's history is inaccurate in a sizeable proportion of cases.<sup>23</sup> An accurate history is important in order to ascertain the delay in timing of ingestion and the onset of symptoms, the type of symptoms, the food allergens likely to be causing the problem, and the risk of atopy. Although essential for planning the necessary clinical evaluation and investigations, the clinical history alone corresponds to a positive double-blind placebo-controlled challenge in about 30-40% of cases.<sup>6</sup>

The elimination of a putative offending antigen for a couple of weeks is often utilized in clinical practice to assist in the diagnosis of FA. However, a favorable clinical response to an elimination diet is often unreliable, and may simply be a coincidence. Hence, there is a need for reliable diagnostic tests for FA.<sup>23</sup>

IgE-mediated food allergy is by far the most studied type of disease; there is good general knowledge of the mechanisms, reliable diagnostic tools, but no proactive treatment. Skin testing or the detection of circulating allergen-specific IgE antibodies is an accurate diagnostic tool for patients with IgE-mediated milk allergy.<sup>23,24</sup> Although false positives are problematic in children with atopic dermatitis, false negative skin prick tests are

**Table 1** - Classification of immune-mediated reactions to foods and the target organ systems involved

Organ system involvement	IgE-mediated /Acute onset	IgE/Cell-mediated /Delayed onset	Cell-mediated /Delayed onset
Gastrointestinal tract	Oral allergy syndrome, gastro-enteropathy	Eosinophilic esophagitis, gastroenteritis	Proctitis, proctocolitis, enterocolitis, celiac disease
Skin	Urticaria, angioedema, anaphylaxis	Atopic dermatitis	Dermatitis herpetiformis
Respiratory	Rhinitis, conjunctivitis Bronchospasm (asthma)	Asthma	Hemosiderosis (associated with milk-specific IgG)

uncommon. Food challenges in such cases do not warrant the risk. Tests for food specific IgE antibodies include percutaneous skin tests (prick/puncture) and serum assays. They are highly sensitive (> 90%), but only modestly specific (50%), and are well suited for use when suspicion of a particular food is high. They are not effective for the purpose of screening.<sup>22</sup> Both techniques - skin prick test and serum assays for specific IgE- merely detect the presence of antibody (sensitization) and do not necessarily indicate that ingestion would result in clinical reactions. The results of these tests are more valuable when they are negative, since the high sensitivity makes them approximately 95% accurate for ruling out IgE-mediated reactions. However, a positive test result is associated with true clinical reactions in only 50% of the time.<sup>22</sup> In addition, the test results may also remain positive some time after

clinical reactivity has resolved. In general, studies show that strongly positive skin tests, confirmed by allergen-specific serum IgE assays, have a positive predictive value of 95% in infants with IgE-mediated FA.<sup>6,25</sup>

The radioallergosorbent (RAST) test and similar semi-quantitative *in vitro* assays that provide evidence of IgE-mediated food-allergy are being replaced by more quantitative measurements of food specific IgE antibodies. Notably, the CAP system-fluorescent enzyme immunoassay has been shown to be more predictive of symptomatic IgE-mediated FA.<sup>6</sup> The use of such quantitative food-specific IgE antibody levels has greatly increased the positive predictive value of the studies and has eliminated the need to carry out food allergen challenges in approximately 50% of cases.<sup>6</sup>

**Table 2** - Type of immune-mediated reactions to food and related gastrointestinal symptoms

Type of reaction	Symptoms/signs/characteristics
IgE-mediated Acute onset of symptoms Immediate gastrointestinal tract reaction	Acute onset of nausea, vomiting, abdominal pain, diarrhea. Any age group (more frequent in pediatric patients). Various food antigens implicated.
IgE associated/cell-mediated Delayed-onset/chronic Eosinophilic gastroenteropathies	Chronic relapsing; symptoms vary with respect to site, depth and severity of eosinophilic infiltration. Multiple food antigens may be involved. Clinical course is variable and may require treatment with corticosteroids.
Cell-mediated Delayed-onset/chronic Proctitis Proctocolitis/enterocolitis Enteropathy	Allergic proctitis/colitis occurs more often in infants, while enterocolitis is seen more often in children. <b>Infants:</b> hematochezia with or without diarrhea; vomiting, poor weight gain, irritability. May occur with exclusive maternal milk. Most frequent dietary allergen: cow's milk. Usually resolves within 1 year. Infants & young children: malabsorption, diarrhea, failure to thrive. Most frequent food implicated: cow's milk, eggs, soy. May be accompanied by atopic dermatitis. Usually resolves by the age of 2-3 years.
Celiac disease	<b>Toddlers and young children:</b> "classical" presentation -malabsorption, diarrhea, failure to thrive, abdominal distention. Older age: "irritable bowel like" symptoms, abdominal pain, constipation, anemia, diarrhea, short stature, pubertal delay, osteoporosis. HLA-DQ2 or DQ8-associated. Food implicated: gluten. Permanent.

The relationship between atopic dermatitis and FA deserves particular mention. About 1/3 of the cases of atopic dermatitis have cow's milk allergy, while almost 1/2 of milk-allergic infants have atopic dermatitis. The implication is that skin tests are less reliable in patients with atopic dermatitis, with as much as 24% of false positives reported.<sup>26</sup> Even in breastfed infants positive skin prick tests to foods, particularly to egg white, are very common if these infants have moderate to severe generalized atopic dermatitis.<sup>27</sup> The use of assays for allergen-specific serum IgE is helpful in such circumstances.<sup>24</sup>

Because of the low and variable predictive accuracy and lack of standardized approach to testing, the patch test is also not currently indicated for routine use.<sup>22</sup> Other unapproved and useless tests include provocation-neutralization cytotoxic tests, IgG antibody assays to specific foods, and hair analyses.<sup>25</sup>

Recent advances in technology have enabled mapping the IgE-binding regions of many major food allergens. It was found that both conformational and sequential epitopes cause allergic reactions. Allergic patients who possess IgE antibodies primarily to conformational epitopes appear to tolerate small amounts of processed foods (extensive heating or partial hydrolysis) because these epitopes are significantly modified or destroyed, whereas those with IgE antibodies to sequential epitopes react to the food in any form.<sup>6,28</sup> Furthermore, it has been shown that egg and milk-allergic patients with IgE antibodies reacting against sequential epitopes tend to have persistent allergy, whereas those with IgE antibodies primarily to conformational epitopes tend to develop clinical tolerance.<sup>6,28</sup> Thus, while double-blind placebo-controlled tests still constitute the gold standard for the definitive diagnosis of FA, these recent technical advances are improving the value of laboratory tests.

Skin tests are unable to detect the majority of non-IgE, primarily gastrointestinal food-induced enteropathies or colitis. In the latter scenario, intestinal biopsies revealing primarily eosinophilic infiltration of the mucosa may be helpful, if positive.<sup>22,25</sup> However, the mucosal lesions in food allergic enteropathies are characteristically focal. Thus, sampling error results in negative biopsies in many cases. Colonic biopsies are more often helpful in cases with allergic (eosinophilic) colitis, usually seen in infants with FA-induced hematochezia. Our recent experience with wireless capsule endoscopy supports the use of this technique to examine the entire small bowel for areas of focal villous edema or atrophy in cases of FA.<sup>29</sup>

The measurement of inflammatory markers in blood and stool that accurately predict reaction to foods would be

convenient, but has met with mixed success. When the history and testing indicate that a non-IgE-mediated (cell-mediated) adverse immune response to food is possible, ancillary tests may be needed to confirm the diagnosis of food intolerance or immune reactions to foods, such as breath hydrogen tests for lactose intolerance or gastrointestinal biopsy to determine eosinophilic inflammation or atrophic villi.<sup>22</sup> In the case of IgE-negative food allergies, double-blind, placebo-controlled challenges still remain the gold standard in terms of diagnosis.<sup>12,23,30,31</sup>

### **Management of FA**

Three modalities are generally employed for the management of food allergic disorders: elimination and avoidance of specific allergens, pharmacological therapies, and preventive measures.<sup>21</sup> Once a definitive diagnosis of FA is made, strict avoidance of the causal food or foods is the treatment and is of paramount importance. Complete exclusion of the offending food is the only proven form of prophylactic management currently available. This is not always an easy task, especially if the food is ubiquitous and thus difficult to avoid, such as milk products. Labeling may be misleading, small amounts of the food allergen may be present in tolerated foods and there may also be hidden contamination of foods considered safe.<sup>22</sup>

As is true of other chronic conditions, management requires a multidisciplinary approach. Consultation with a dietician is essential to properly educate the parents with the information required to make safe and appropriate dietary choices for the child. Their input is valuable for follow-up and prevention of nutritional deficiencies and subsequent growth impairment. Since elimination diets may lead to malnutrition or other adverse effects, every effort should be made to ensure that the dietary needs of the patient are met and that the patient and/or caregiver are fully educated in dietary management.<sup>32</sup>

A recent study pointed out that most parents are unable to identify common allergic food ingredients.<sup>33</sup> Improved labeling is much needed, as is diligent and extensive education of the parents, children and other caregivers to carefully read all product labels. Requesting information about specific ingredients outside the home is essential to avoid accidental exposure to offending allergens. Cross-contamination and errors in packaged foods in shops and restaurants are additional obstacles.

Infant formulas that are most often employed in cow's milk-allergic infants consist of hydrolyzed casein, whey or soy protein. Extensively hydrolyzed cow's milk protein-based formulas (eHPF) are almost always effective (97%) in infants with cow's milk protein allergy of immediate or delayed onset.<sup>2,34</sup> However, none of the hydrolyzed

formulas are completely allergen-free, and rare severe reactions to eHPF have been described.<sup>30</sup> In severe cases resistant to eHPF therapy or in patients with multiple food allergies, amino acid-based formulas are necessary.

The use of soy protein-based formulas for cow's milk allergy is somewhat controversial. In general, it is not advisable to introduce a new food, such as soy, to patients with an actively inflamed and damaged, hyperpermeable mucosal barrier for at least 1 month, so as not to "sensitize" them to another potent allergen. Moreover, concomitant soy and cow's milk protein allergies may be present in an individual despite the fact that no "cross reactivity" exists. The prevalence of concomitant soy intolerance in infants with cow's milk allergy ranges widely (0-60%) in different studies, depending upon the criteria employed (whether placebo-controlled challenges were performed or not).<sup>2</sup> In a study that employed placebo-controlled challenges, 14% of infants with type I (IgE+) cow's milk allergy were documented to have soy allergy.<sup>35</sup> A higher probability has been observed in non-IgE-mediated enterocolitis.<sup>36</sup> A recent prospective, randomized trial of 170 infants with documented cow's milk allergy addressed these issues.<sup>37</sup> Infants were assigned to a standard soy protein, or a cow's milk-based eHPF. The outcome was that 10% reacted to soy, whereas only 2.2% reacted to the hydrolysate formula. The incidence of allergic problems was the same in IgE positive and negative patients. The authors noted that the development of IgE antibodies to soy was rare.<sup>37</sup> On the basis of this and other studies, the use of soy-based formulas is generally recommended only for soy naïve, IgE positive cow's milk allergy. When the high cost limits the use of eHPF, the use of soy-based formulas can be tried in less severe, non-IgE-mediated cow's milk allergy, bearing in mind the risk of inducing soy allergy as noted above.

The duration of treatment depends upon the type of allergy. Unlike allergy to nuts, which is usually permanent, cow's milk allergy usually resolves within the three first years of life in the majority of patients. A study found that the percentages of cow's milk protein intolerant infants who became milk tolerant after 1, 2, and 3 years of an exclusion diet were 30%, 54%, and 70%, respectively.<sup>38</sup> Persistent allergy was associated with positive IgE tests for milk proteins. The period of elimination generally recommended is at least 1 year. Infants who present with allergic colitis, usually within the first 6 months of age, can be challenged earlier, usually after 6 to 8 months of an exclusion diet. Rarely, these patients may be IgE positive, in which case challenges are dangerous and should be delayed.

Pharmacological therapies such as antihistamines and mast cell stabilizers generally play little role in the treatment of gastrointestinal manifestations of FA.

However, corticosteroids may be necessary for exceptional cases with pronounced gastrointestinal manifestations refractory to dietary exclusion alone. These may include systemic steroids for allergic enteritis, colitis, or eosinophilic gastroenteropathy. Recently, topical therapies such as fluticasone and montelukast have been reported to be effective for the treatment of eosinophilic esophagitis.<sup>39,40</sup>

For patients with more severe symptoms of anaphylaxis, or with respiratory or cardiovascular symptoms, additional treatment is needed. Adrenaline is the mainstay of management of severe reactions of immediate-type food allergies and of anaphylaxis.<sup>21</sup>

### Prevention of FA

The increasing incidence of allergic disorders in industrialized nations of the world has been attributed to the lack of exposure to microbial infections early in life, or the so-called "hygiene hypothesis".<sup>41</sup> There are some data suggesting an increasing prevalence of asthma and allergic diseases in Brazil.<sup>42</sup>

FA is a complex trait influenced not only by polygenetic inheritance, but also by environmental factors. Like other medical conditions, both genetic and environmental factors influence the phenotypic expression of FA.<sup>22</sup> In regard to genetic influences, male children appear to be at increased risk for atopic disease. Genetic studies of food allergy are few.<sup>22</sup> Most epidemiological studies have examined asthma, atopic dermatitis and allergic rhinitis rather than FA. For peanut allergy, the influence of HLA class II genes has been demonstrated.<sup>22</sup> A family history of atopy, or FA in particular, appears to be the best screening test currently available.<sup>2,22,43</sup> A positive family history entails atopic parents, or one or more siblings with atopic dermatitis, asthma, allergic rhinitis or FA. The rate of observed FA in children born to families with a strong parental or biparental history of atopy was approximately fourfold higher when compared with an unselected population.<sup>44</sup> For peanut allergy, a significantly higher concordance rate for this allergy exists among monozygotic (64%) compared with dizygotic twins (7%). The risk of allergy in a sibling of an affected person is approximately tenfold higher than that of the general population.<sup>22,45</sup>

The majority of preventive studies to date have focused on infants with a positive family history of allergy. However, it has been questioned whether this usual selection criterion is sensitive or specific enough. Calculations demonstrate that similar numbers of so-called non-risk infants eventually develop symptoms of allergic disease as well.<sup>46</sup> Of those infants termed "no-risk" (70% of all newborns), there is nevertheless a 15% residual allergic risk and

11/100 newborn infants will develop an allergy at a later age. Among "intermediate-risk" infants with one atopic parent or sibling (approximately 25% of all newborns), there is a 20- 40% risk of developing allergies and 8/100 will develop allergy at a later age. Finally, among the high-risk infants with biparental atopy or allergic history (5% of all newborns), there is a 50- 80% risk of allergies and 3/100 infants will develop an allergy at a later age. Thus, calculations based on the data show identical absolute numbers of infants with and without allergic risk (11/100) who are likely to develop allergies.<sup>46</sup> Therefore, it has been questioned whether allergy prevention programs should be directed towards the newborn population as a whole, as opposed to focusing only on known, at-risk infants.<sup>46</sup>

FA risk is also influenced by environmental factors that have been identified to influence atopic disease in children investigated primarily for respiratory disease. These include a protective effect of breastfeeding and detrimental effect of exposure to tobacco smoke. In regard to FA, numerous possible risk factors have been investigated, with controversial results.<sup>22</sup> Factors under consideration include maternal diet during pregnancy and breastfeeding, age at introduction of solid foods and allergenic foods, exposure to pollutants, cesarian section, maternal age, etc.

Microbial agents may also have an important effect on atopic sensitization and induction of tolerance.<sup>22</sup> The use of probiotic therapy to prevent allergic disease has been investigated in neonates, demonstrating a long-term reduction in atopic dermatitis.<sup>47</sup> The normal interaction between the newborn's mucosal immune system and microbes is thought to be compromised in industrialized nations, particularly in bottle-fed infants, resulting in a reduction of bifidobacteria and an increase in clostridial species in the intestinal flora.<sup>47</sup> Infants with milk allergy and atopic eczema have exhibited milder symptoms and fewer markers of intestinal inflammation when their cow's milk formula was fortified with lactobacilli, supporting a favorable effect of adding probiotics to infant formulas.<sup>22</sup>

At the present time food allergen avoidance is the only way to treat and prevent FA. In the near future, food manipulation with molecular and immunological engineering will hopefully deliver more promising and enduring strategies in the prevention of allergic diseases.

Avoidance can be presently instituted at any of the three stages of allergy prevention, termed primary, secondary or tertiary prevention. Primary prevention attempts to decrease the likelihood of the initial sensitization and onset of symptoms in at-risk, as yet unsensitized individuals. Primary prevention blocks immunologic sensitization to foods, particularly due to IgE antibodies. It has been

suggested that a critical period exists prior to or early after birth during which the genetically programmed, atopy-prone child may be at increased risk of becoming sensitized to the encountered allergens.<sup>22</sup> The challenge is to promptly identify at-risk infants and to institute preventive measures that are cost-effective, realistic, and acceptable.<sup>2</sup> Secondary prevention is directed towards already sensitized individuals, in order to suppress disease expression after sensitization. Tertiary prevention tries to limit symptoms and additional problems in subjects already suffering from chronic allergy.<sup>22</sup> Tertiary prevention is the stage of treatment in which there is an attempt to avoid recurrence of symptoms and susceptibility to other potential antigenic proteins.

Primary allergy prevention has focused on two major objectives: the prevention of sensitization to milk and other food allergens, and the prevention of early atopic dermatitis, a disease marker highly predictive of the so called "allergic career".<sup>48</sup> Several risk factors have been identified as potentially contributing to the identification of infants at high risk for FA, including genetic linkage, cord blood or neonatal IgE levels, allergen-specific IgE levels, and Th1/Th2 cytokine profiles (IFN- $\gamma$ /IL-4 ratios). However, none of these markers has greater predictive value than a family history of atopy.<sup>35</sup>

Several challenges still exist towards recommending criteria for the prevention of FA. The scientific advisory committees of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN),<sup>15</sup> along with the European Society for Pediatric Allergy and Clinical Immunology (ESPACI) and the American Academy of Pediatrics (AAP)<sup>49</sup> have published recommendations for the primary and tertiary prevention of FA, summarized in Tables 3 and 4. These recommendations are similar, but do have some minor differences. These recommendations are based upon the best evidence from existing, updated data. However, they do not indicate the absolute or the standard of care because several unanswered questions remain in this topic. Each patient must be considered individually, in the context of his or her unique family history, social and epidemiological setting.<sup>15,43,49</sup>

### ***Intervention strategy during pregnancy***

Although some studies showed a beneficial effect of maternal adherence to a milk-free diet during late pregnancy and lactation, it is unclear whether the benefits were due to maternal dietary restrictions, to lactation, or both. Furthermore, other studies failed to show a benefit of a restricted diet during pregnancy, and this was confirmed by a meta-analysis.<sup>50</sup> In addition to these negative findings,

**Table 3** - Recommendations for primary prevention of food allergies

Parameter	AAP, 2000 <sup>49</sup>	ESPGHAN, 1999 <sup>15</sup>	Comment
High-risk infants	Biparental; parent and sibling	Parent or sibling	Prevention is limited to high-risk infants
Diet during pregnancy	Not recommended	Not recommended	Studies fail to show benefit from cow's milk and egg avoidance – could affect maternal nutrition
Exclusive breastfeeding	6 months	4-6 months	Studies confirm beneficial preventive effect
Maternal diet during lactation	Consider eliminating cow's milk, eggs, fish, peanuts and other nuts	Not recommended	Conflicting studies exist. AAP eliminates peanuts and nuts
Supplementation of Ca and vitamins during periods of restricted diet	Recommended	Not discussed	Need to prevent possible micronutrient deficiencies
Avoid soy formulas	Recommended	Recommended	Studies fail to show benefit from soy formula in primary prevention
Hypoallergenic formulas for bottle-fed infants	eHF or pHF	eHF or pHF	There is support for the use of formulas with reduced allergenicity – pHF may be particularly suitable in view of equivalent efficacy, lower cost and improved palatability
Hypoallergenic formulas for supplementation in breastfed infants	eHF or pHF	eHF or pHF	There is greater support for eHF, but in view of its higher cost, it may replace the use of pHF
Delayed introduction of solid foods	6 months - least allergenic first Cow's milk - 12 months Eggs - 24 months Nuts and fish - 36 months	5 months	ESPGHAN recommendations are more liberal, based on studies in which CMA was prevented even when cow's milk formulas were introduced at 5 months

AAP = American Academy of Pediatrics; CMA = cow's milk allergy; eHF = extensive hydrolyzed formulas; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology and Nutrition; pHF = partially hydrolyzed formulas.



maternal weight gain was compromised by the restriction of cow's milk and eggs, considered key foods during pregnancy.<sup>43</sup> Currently, the consensus is that there is no scientific basis for recommending a restricted diet during late pregnancy.<sup>15,43,49</sup>

### ***Intervention strategy during breastfeeding for the newborn***

It has long been held that breastfeeding affords passive immunity against infections, and may also actively stimulate the infant's immune system, providing multiple

**Table 4** - Recommendations for tertiary prevention of food allergy symptoms and complications

<b>Parameter</b>	<b>AAP, 2000<sup>49</sup></b>	<b>ESPGHAN, 1999<sup>15</sup></b>	<b>Comment</b>
Infants with FA (confirmed)	Complete exclusion	Complete exclusion	Exclusion is the only way to avoid symptoms and may lead to earlier tolerance
Exclusive breastfeeding	Trial of maternal exclusion of cow's milk. Possible trial of egg, fish, nuts, peanuts	Trial of maternal exclusion of cow's milk	Properly conducted studies with food challenges confirm that infants develop symptoms from food proteins found in breastmilk (CM protein)
Formula-fed infants	Use of hypoallergenic formulas (eHF)- 95% of resolution-Amino acid based formula may be necessary in selected casesSoy formula in IgE-mediated allergy.Benefit of exclusion should be seen within 2-4 weeks	Use of hypoallergenic formulas (eHF)- 95% of resolution-Amino acid-based formula may be necessary in selected cases	AAP suggests that a trial of soy formula in infants with IgE-mediated CMA can be considered.The need for an amino acid based formula is rare and should be reserved for specific situations
Avoid partially-hydrolyzed formulas (pHF)	Yes	Yes	These formulas have intact proteins and should be used only in primary prevention, never as treatment
Avoid other proteins (goat, sheep, red meat)	Yes	Yes	Some homology exists between CM and these other proteins
Infants with malabsorptive enteropathy	Use of a hypoallergenic formula – eHF or amino acid based if symptoms persist	Use of a hypoallergenic formula – eHF or amino acid based formula - lactose-free and with medium chain triglycerides until normal absorptive function returns	The formula must be selected according to each patient's condition when there is a significant intestinal injury

AAP = American Academy of Pediatrics; CM = cow's milk; CMA = cow's milk allergy; eHF = extensive hydrolyzed formulas; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology and Nutrition; pHF = partially hydrolyzed formulas.

long-term benefits. Grulee & Sanford<sup>51</sup> reported more than 70 years ago that breastfeeding compared with a cow's milk-based diet reduced by sevenfold the development of eczema at 9 months in a cohort of approximately 20,000 infants. As noted above, the principal risk factors for the development of FA are a family history of atopy and early exposure to milk proteins. Since one cannot alter genes, efforts at prevention have focused on controlling the environment. The delivery of trace amounts of food allergens via breastmilk may contribute to tolerance induction. On the other hand, even exclusively breastfed infants can present with allergic reactions to milk proteins and to other proteins. A recent study suggested that low levels of total and cow's milk specific IgA in breastmilk contributes to the risk of developing cow's milk allergy.<sup>52</sup> Several studies have shown that exclusive breastfeeding for the first 4 to 6 months of life, along with the delayed introduction of solid foods until after 5 months, reduces the incidence of atopic dermatitis and respiratory allergies.<sup>53</sup> Advisory committees strongly recommend exclusive breastfeeding for the primary prevention of FA on the basis of existing data, only differing in duration – the AAP<sup>49</sup> recommends at least 6 months and ESPGHAN<sup>15</sup> 4 to 6 months. The AAP<sup>49</sup> recommends continuing breastfeeding, although not exclusively, to at least 12 months of age.<sup>43,49</sup> The Brazilian Health Ministry recommends continuing breastfeeding until 2 years of age, although this is more for socioeconomic reasons than for allergy prevention.<sup>54</sup> These recommendations are the same for all newborns, whether at risk for atopy or not. The safety of exclusive breastfeeding for 6 months has already been demonstrated by a meta-analysis.<sup>55</sup> This recommendation reduces infant illnesses at the community level and can potentially reduce the overall cost of health services.<sup>43</sup>

#### ***Intervention strategy during breastfeeding for the mother***

In the general, not-at risk population, the prevalence of FA in exclusively breastfed infants ranges from 0.04% to 0.5%.<sup>43,56</sup> Beta-lactoglobulin, casein, gammaglobulin, ovalbumin, gliadin and peanut antigens have been detected in small quantities in breastmilk 1 to 6 hours after the consumption of these foods, irrespective of maternal status of atopy. The concentrations of food allergens in breastmilk are thus theoretically sufficient to trigger reactions in allergic infants. The molecular size of these food antigens in maternal milk is similar to their respective allergens, thus confirming, although not proving their potential for sensitization.<sup>43,57</sup>

Some studies have therefore evaluated the utility of maternal food allergen avoidance diets during lactation for preventing atopic disease in high-risk infants.<sup>58-60</sup> Two

prospective controlled studies evaluated whether maternal diet for the first 3 months of lactation and avoidance of soy and peanuts for the entire lactation period affected atopy in high-risk infants placed on a relatively hypoallergenic dietary regimen during infancy. These studies noted significant reductions of atopic eczema in the maternal diet groups by ages 3, 6 and 18 months. However, at 10 years of age the rates of allergies were the same between the children in both groups.<sup>59,60</sup> A meta-analysis of these studies concluded that a food allergen avoidance diet of the mothers during lactation may transiently reduce the development of eczema in early childhood.<sup>50</sup> The authors also noted that methodological limitations of the reported studies suggest caution before implementing the findings. Moreover, other studies conflict with the above findings. For this reason advisory committees are more prudent on this point and suggest implementing a restrictive maternal diet during lactation only after evaluation of each family's atopic risk and individual circumstances.<sup>43</sup> The AAP<sup>49</sup> recommends avoidance of peanuts because it is not an essential food and peanut allergy is very common in the USA. In mothers following dietary restrictions, the AAP<sup>49</sup> suggests supplemental calcium and a multivitamin preparation.

#### ***Intervention strategy in formula-fed infants***

It has been shown that exposure to even a small amount of cow's milk formula during the first days after birth can increase the likelihood of cow's milk protein allergy.<sup>56</sup> Both hydrolyzed formula and breastmilk have been reported to protect against cow's milk allergy, compared to the use of routine, cow's milk-based infant formula.<sup>61</sup> Despite the fact that eHPF have been shown to help prevent milk allergy, issues concerning their cost and palatability resulted in the creation of less extensive, so-called partially hydrolyzed formulas (pHPF).<sup>2</sup> The aim of developing this type of product was to try to prevent primary sensitization of infants while fostering oral tolerance to milk antigens. Other potential advantages of pHPF over eHPF are their better organoleptic properties, as well as lower cost.<sup>2</sup> However, the peptides in pHPF retain antigenicity and are thus contraindicated in established milk allergy. The evidence from numerous studies supports the use of pHPF for the prevention of allergy in infants at high risk.<sup>62</sup> A meta-analysis of 15 prospective, controlled studies in infants at high risk showed that pHPF and breastmilk were protective, compared to cow's milk formula.<sup>63</sup> Thus, both pHPF and eHPF, compared to cow's milk or soy formulas, have been shown to reduce atopic dermatitis, cow's milk allergy, milk allergen specific IgE, and asthma. Outcomes were similar to exclusive breastfeeding, with benefits that persisted for 5 years. In terms of which is best, eHPF or pHPF, there is no clear-cut answer.<sup>2</sup>

With the objective of assessing the preventive effect of different hydrolyzed formulas compared with cow's milk formula in infants with a hereditary risk for atopy, the German Infant Nutritional Intervention Program (GINI) enrolled 2,252 infants between 1995 and 1998.<sup>1</sup> Healthy term neonates with at least a unifamilial history of atopic disease were enrolled in this prospective, randomized, government-funded double blind study.<sup>1</sup> Infants were randomized into one of four study formulas if breastmilk was insufficient: routine cow's milk formula; whey-based pHPF, casein-based eHPF, or whey-based eHPF. Solids were introduced after 4 months, and highly allergenic foods were excluded. At 12 months, the incidence of allergic manifestations was significantly lower with the casein-based eHPF than with the conventional formula (9 vs. 16%). The pHPF was almost as effective (11%), whereas the whey-based eHPF did not confer a benefit (14%). The authors suggested that the different preventive benefits between whey- and casein-based extensively-hydrolyzed formulas might be explained by different hydrolyzation processing using different enzymes, rather than by the degree of hydrolyzation or the protein source. They speculated that the hydrolyzation process might influence the remaining epitopes and consequently, the residual antigenicity of a particular hydrolysate.<sup>1</sup> As anticipated, the most frequent allergic manifestation observed during the first year of this study was atopic dermatitis. Both the pHPF and the casein-based eHPF reduced the incidence of atopic dermatitis (9 and 7%) compared to the conventional and whey-based eHPF (15 and 13%, respectively;  $p < 0.05$ ). Taken together, the findings in this study suggest that the degree of hydrolysis is less critical than the tolerogenic properties of the specific formula.<sup>1</sup> The family history was found to be a key determinant of outcome in this study. The benefits of the pHPF and casein-based eHPF were far less impressive if the family history was positive for atopic dermatitis. Atopic dermatitis in first degree family members was found to be a stronger risk factor for the development of allergic manifestations during infancy than the history of any other allergic disease in two members of the family.<sup>1</sup> This is in agreement with epidemiologic studies that showed a genetic influence over atopic dermatitis and is further supported by the genetic linkage of atopic dermatitis to chromosome 3q21.<sup>64,65</sup> Finally, the pHPF was found to yield the lowest incidence of sensitization (IgE antibodies) to cow's milk and egg proteins, as well as to common aeroallergens. They concluded this study by stating that prevention of allergic diseases in the first year of life is feasible by means of dietary intervention, but that outcomes are influenced by a family history of atopic dermatitis. They suggest that the preventive effect of each hydrolyzed formula needs to be clinically evaluated.<sup>1</sup>

A recent revision from Cochrane Systematic Reviews<sup>66</sup> addressed the theme of whether the use of hydrolyzed formulas for infant feeding prevents allergy and food intolerance. Eighteen trials met the inclusion criteria. No eligible trials examined the effects of prolonged hydrolyzed formula feeding on allergy beyond early childhood. They concluded that there is no evidence to support feeding with a hydrolyzed formula for the prevention of allergy in preference to exclusive breastfeeding. However, in high-risk infants unable to be completely breastfed, there is evidence that prolonged feeding with a hydrolyzed compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy. Benefits found from the use of a partially hydrolyzed formula include reduced allergy incidence in infancy and childhood, asthma incidence in childhood, eczema incidence in infancy and prevalence in childhood, food allergy prevalence in childhood and cow's milk allergy prevalence in childhood. The included trials did not find significant differences in allergy incidence in infancy when comparing extensively hydrolyzed to partially hydrolyzed formulas. They suggest future trials to determine if significant clinical benefits persist beyond 5 years of age and if there is any additional benefit from the use of an extensive compared to a partially hydrolyzed formula. The incremental costs of hydrolyzed formulas and the effect of this cost on compliance was not measured in any of the trials.<sup>66</sup>

The final issue is whether there is evidence that an allergen-reduced diet is beneficial for infants in the general population, without particular risk factors. This issue is highly relevant, in view of the rapidly increasing incidence of atopic diseases in many countries. The ZUFF study<sup>46,67</sup> addressed this issue by comparing a treatment (breastfed and/or pHPF, no regular infant formula or solids for 4 months) with a normally fed control group. Although growth was similar in all groups, skin problems were reduced in the treatment compared to freely fed control infants at 2 years (7 vs. 15%,  $p < 0.0001$ ). Feeding a pHPF to partially or non-breastfed infants resulted in the same overall health benefits as exclusive breastfeeding, in contrast to routine formula.<sup>46,67</sup>

### ***Is there a place for soy formulas in primary prevention?***

Soy-based formulas have been used to treat infants with allergy or food intolerance, but according to existing studies there is insufficient evidence to recommend soy formula feeding for primary prevention of FA. Soy protein is immunogenic and allergenic.<sup>42</sup> A low prevalence of soy allergy has been found by double-blind, placebo-controlled food challenge both in children with food allergy and in infants of atopic parents fed soy formula from birth or early

in life.<sup>68-70</sup> Randomized prospective studies of soy versus cow's milk formula feeding in infants, generally from atopic families, have not shown any preventive effect of soy on FA or atopic dermatitis.<sup>42</sup> Both the AAP<sup>49</sup> and ESPGHAN<sup>15</sup> committees agree that there is insufficient evidence to recommend soy formula for primary food allergy prevention (Table 3). According to AAP,<sup>49</sup> there may be a place for soy formula feeding in the secondary prevention of IgE-mediated food allergy.

A recent Cochrane Library review assessed whether feeding infants without clinical evidence of food allergy or intolerance an adapted soy formula compared to human milk, cow's milk formula or a hydrolyzed protein formula prevents allergy or food intolerance.<sup>71</sup> They found only five eligible studies, all enrolling infants at high risk of allergy on the basis of a family history of allergy in a first degree relative. No eligible study enrolled infants fed human milk. Comparing soy to cow's milk formula one study with unclear allocation criteria and 19,5% losses to follow-up reported a reduction in the cumulative incidence of childhood allergy, asthma and allergic rhinitis. It was concluded that soy formula feeding should not be recommended for the prevention of allergy or food intolerance in infants at high risk.<sup>71</sup>

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Correspondence:  
Cristina Targa Ferreira  
Rua Pedro Weingartner, 105/202  
90430-140 – Porto Alegre, RS – Brazil  
Tel.: +55 (51) 3331.3295  
Fax: +55 (51) 3388.4369  
E-mail: cristinatarga@terra.com.br