



## MANAGEMENT OF FOOD ALLERGY IN CHILDREN

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### Introduction

Food allergy (FA) is an atopic disorder that affects all age groups, and includes potentially fatal anaphylactic reactions. As there is currently no cure for FA, sensitive individuals must manage their FA through avoidance of foods containing the allergen. FA sufferers experience great stress and difficulty in managing their daily activities, and it changes quality of life in a profoundly negative way. Clear food labeling regarding food allergens is essential to help allergic consumers manage their condition. The majority of FA is mediated by immunoglobulin E (IgE), but sensitization to a specific food as revealed by skin prick or serologic testing does not always imply clinical reactivity. It is well known that children at risk of developing allergic diseases follow an 'atopy march'. These children first manifest FA and eczema during infancy which 'marched' later into airway allergies of asthma and allergic rhinitis.

### Epidemiology

Because of the lack of reliable diagnostic tests, estimates of FA prevalence are generally imprecise. In the 1990s, FA was estimated to affect 6% of American children younger than 3 years of age.<sup>1</sup> The 1995 Manitoba Birth Cohort found 4.2% of Canadian children to have FA.<sup>2</sup> The prevalence also appears to be increasing. In the European Community Respiratory Health Survey, the prevalence of self-reported FA varied from 4.6% in Spain to 12% in United States to 19.1% in Australia.<sup>3</sup> A meta-analysis of published studies found that the incidence of self-reported FA ranged between 3% and 35%. The incidence was lower (2-5%) in studies where subjects were also tested for food sensitization. The few studies that used diagnostic oral challenge procedures found that 1-4% of individuals suffer from FA. The reasons accounting for this marked heterogeneity include wide differences in

response rates, problems in reliability and consistency of diagnosis across studies and poor clinical specificity of skin tests and food-specific IgE measurement.

In contrast to these Caucasian data, the epidemiology of FA has not been well studied in Asian countries. Limited data suggested that the prevalence rates of parent- or self-reported FA were 1.2-6.5%.<sup>4-7</sup> Until very recently, the prevalence of FA in Chinese children has not been investigated. In my population study in 21 nurseries and kindergartens, 8.1% of local preschool children suffered from parent-reported FA. About 11% of them suffered from three or more adverse food reactions in the past 12 months. Many more parents suspected that their children had FA, and 11.5% of these young children were avoiding some kind of foods. The occurrence of parent-reported FA was strongly associated with other atopic comorbidities such as current wheeze, rhinoconjunctivitis and flexural dermatitis (odds ratios 2.22-8.62) (submitted manuscript).

In the United States, 31 fatal cases were identified between 2001 and 2006.<sup>8</sup> These individuals ranged from 5 to 50 years of age. Peanut accounted for 17 deaths, tree nuts for 8, milk for 4, and shrimp for 2. All subjects for whom there were data had asthma, and the lack of readily accessible epinephrine remained an important risk factor for food fatalities with only 4 appearing to have had epinephrine administered in a timely manner. The known locations where the deaths occurred included schools (3; including colleges), homes (12; including homes of friends), restaurants (8), work/office setting (4), and camp (2).

### Clinical Spectrum

The major food allergens identified as causing problems following ingestion are water-soluble glycoproteins 10 to 70 kd in size that are stable to heat, acid, and proteases. Examples include proteins in milk (caseins), peanut

(vicillins), and egg (ovomuroid) and nonspecific lipid transfer proteins found in apple (Mal d 3) or corn (Zea m 14).<sup>9,10</sup> Birch pollen Bet v 1 is an example of an allergen that can induce sensitization through the respiratory route and result in oral symptoms of pruritis to homologous allergens in raw apple or carrot.

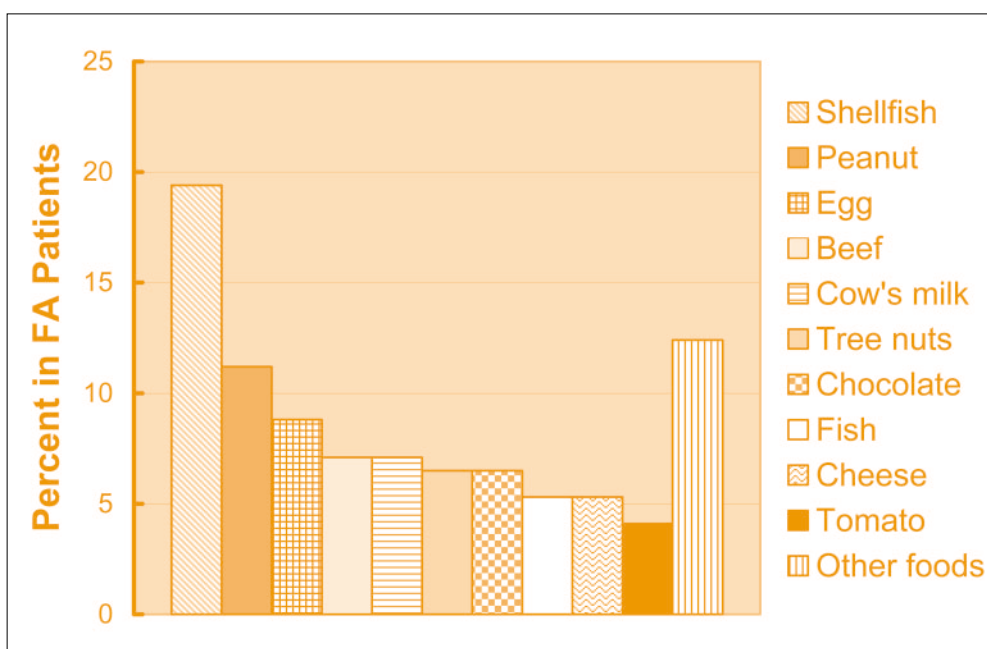
The Food Allergy and Anaphylaxis Network identifies cow's milk, egg, peanut, tree nuts, fish, shellfish, soy and wheat as the most common food allergens in the Caucasian population. Although local data is lacking, it has been a common belief that peanut allergy is rare in Chinese. Nonetheless, my local study as described above found similar prevalence rates of FA in Chinese when compared with the Caucasians. The most important foods in our preschoolers were crustacean shellfish, peanut, egg, beef, cow's milk, tree nuts, chocolate, fish and cheese, each affected at least 5% of our food-allergic children (Figure 1).

Specifically, Sicherer et al reported that the prevalence rates of self-reported FA to peanut and tree nuts in the United States were 0.6% and 0.5%, respectively.<sup>11</sup> These figures were in fact comparable to the local data of 0.65% and 0.41% as found in preschoolers from my recent study. Besides, up to one-fifth of our children with parent-reported FA were allergic to crustacean shellfish, and the prevalence rate of this FA was estimated to be 0.90-1.28%. This figure was lower than the published data of 1.9-2.5% among Caucasians with self-reported FA.<sup>12</sup> In the contrary, allergies to some foods are unique in Asian subjects. Beef, chocolate and cheese seem to be important foods causing FA in our children. Among Singaporeans,

bird's nest and crustacean seafood were the most important foods for anaphylactic reactions. Another study reported shellfish sensitization to be present in two-fifths of the food allergic children.<sup>13</sup> Sesame was second only to cow's milk as foods causing anaphylaxis among Israeli.<sup>5</sup> These findings highlight the importance of accurate food labeling to include items appropriate to our population.

## Diagnosis

Double-blind, placebo-controlled food challenges (DBPCFC) represent the 'gold standard' for diagnosing FA, as none of the above investigations can accurately predict tolerance. However, this procedure is time-consuming, expensive and troublesome for the patient, involving the risk of severe systemic reactions. In clinical practice, the diagnostic work-up of suspected FA includes the patients' history, skin prick tests (SPT), quantification of serum food-specific IgE levels, and more recently atopy patch test (APT).<sup>14</sup> While a positive SPT seems to reflect early reactions (e.g. urticaria) to food challenges, APT has shown diagnostic efficacy for late phase clinical reactions (e.g. exacerbation of eczema). Although sensitization to a specific food as revealed by SPT or serologic testing does not always imply clinical reactivity, recent data suggested various diagnostic 'cut-off' values for SPT reactions or serum specific IgE concentrations that would differentiate 'true positives' from 'false positives' (Table 1). Thus, these simple *in vivo* or *in vitro* tests may be used to accurately diagnose FA, rendering oral food challenges unnecessary in many patients.



**Figure 1.** Clinical spectrum of food allergic reactions in 298 local preschool children with parent-reported food allergy. This chart includes only foods that caused problems in 4% or more of these patients.

**Table 1.** Diagnostic decision points of skin prick tests and serum specific IgE levels for clinical food reactivity in different populations

Study population	Age	Allergen	Cut-off level (mm for SPT; kIU/l for specific IgE)	Predicted probability for positive reaction (%)	Reference
<b>Skin prick tests</b>					
Australian	≤2	Cow's milk	6	100	15,16
		Egg	5	100	
		Peanut	4	100	
Australian	≤16	Cow's milk	8	100	15,16
		Egg	7	100	
		Peanut	8	100	
Spanish	≤2	Egg	3	91	17
French	≤16	Peanut	16	100	18
<b>Serum food-specific IgE levels</b>					
US	≤14	Cow's milk	32	95	19
		Egg	6	95	
		Peanut	15	95	
German	≤16	Egg	13	95	20
	≤1	Egg	11	95	
Spanish	≤1	Cow's milk	5	95	21
French	≤16	Peanut	57	100	22

For serum specific IgE, diagnostic decision points have been established to predict symptomatic FA.<sup>17,19-24</sup> These values serve both to provide the predicted probability (in %) for a given specific IgE value, as well as provide the required IgE level for a chosen probability. For egg, the 95% decision point in the German population (13.0 kU/l) was comparable with the US level (7.0 kU/l).<sup>23</sup> For cow's milk, Sampson described in Americans a 95% predicted probability of 15 kU/l<sup>23</sup> whereas a Spanish group found 5 kU/l to be useful in their infants.<sup>20</sup> Despite these results, decision points have to be studied for each food allergen separately. They are not established for many foods so far and vary among populations.

SPT has been used for decades to prove or exclude sensitization to allergens. A Caucasian report suggested that the 'cut-off' values of SPT wheal sizes exceeding the upper 95% confidence interval of responses in tolerant subjects: 5 mm for cow's milk, 4 mm for egg, 6 mm for peanut and 3 mm for wheat and soy.<sup>25</sup> Another study reported higher 'cut-off' levels for the diagnostic capacity of children with FA: 8 mm for cow's milk, 7 mm for egg, and 8 mm for peanut.<sup>15</sup> These 'cut-off' values may be lower in children younger than 2 years of age. Differences in SPT decision values between authors may be due to different patient populations.

## Management

The mainstay of treatment for FA is to avoid the causal food or foods. Accurate food labels are essential to indicate the presence of major food allergens, but using simple terms (e.g. "milk" instead of "casein"). Patients with FA and their caregivers should be encouraged to obtain medical identification cards or bracelets, taught to

recognize symptoms, and instructed on using self-injectable epinephrine and activating emergency services. Comprehensive educational materials are available through organizations such as the Food Allergy and Anaphylaxis Network.

Drug treatments can provide symptomatic relief for food-induced disorders. Antihistamines partially ameliorate oral allergy syndrome and IgE-mediated skin symptoms. Anti-inflammatory therapies might be beneficial for allergic eosinophilic gastroenteritis.<sup>26</sup> Novel therapies for IgE-mediated FA include anti-IgE antibody for treatment of peanut allergy, traditional Chinese herbal medicine and immunotherapy. Anti-IgE treatment increased the average amount of peanut tolerated, and hopefully lowers the risk of severe food reactions in patients accidentally exposed to peanut. However, about one-quarter of the subjects did not respond.<sup>27</sup> Traditional Chinese herbs showed efficacy in a murine model of peanut-induced anaphylaxis,<sup>28</sup> but its clinical efficacy is currently unknown. Standard immunotherapy for pollen-induced rhinitis may also improve pollen-food allergy syndrome.<sup>29</sup> On the other hand, peanut immunotherapy using standardized desensitization protocol as a means to treat peanut allergy had been performed with variable success.<sup>30-32</sup> However, the occurrence of severe adverse reactions even during maintenance phase precludes the clinical use of immunotherapy in treating FA.

The indications and timing of food re-challenges are still controversial. Although remission has been reported in one-fifth of patients, allergies to peanuts and tree nuts are usually responsible for long-lasting allergic symptoms on re-exposure. Allergies to some foods such as cow's milk and egg have a good prognosis in childhood.<sup>33</sup> Up to three-quarters of these FA patients will outgrow their

allergies by 5 years of age. In order to minimize the deleterious effects of unnecessary elimination diets on growth and nutrition, it would be useful to re-challenge patients with these foods at intervals of 12-18 months especially for those patients with initially mild adverse food reactions. This time interval for re-challenge would be much longer for some potent allergens such as peanut, tree nuts and shellfish. There is also data suggesting that changes in food-specific IgE levels may predict the development of clinical tolerance, although this issue is still under debate. Thus, controlled oral food challenges are still the only measure to establish clinical tolerance after some time of food avoidance.

### Prevention

Approaches to delay or prevent FA through dietary manipulation have been the subject of several reviews.<sup>34,35</sup> Exclusive breast-feeding during the first 3 to 6 months of life, and supplementation of hypoallergenic formula for those whom breastfeeding is not possible, in infants at high risk for atopic disease may be beneficial. There is no evidence that supports the FA preventive effect of hypoallergenic formulae in the general population, and neither is there any conclusive study indicating

that manipulation of the mother's diet during pregnancy or breastfeeding or the restriction of allergenic foods from infant's diet will prevent FA development.<sup>34,36</sup> On the other hand, these measures may jeopardize infant's growth and nutrition. The American Academy of Pediatrics recommends a conservative approach, including that mothers of high-risk infants avoid allergens, such as peanuts and nuts, during lactation and that major food allergens, such as peanuts, tree nuts and seafood, be introduced only after 3 years of age.<sup>35</sup>

### Useful Links

1. The Food Allergy and Anaphylaxis Network: <http://www.foodallergy.org>.
2. American Academy of Allergy, Asthma and Immunology: [http://www.aaaai.org/members/resources/practice\\_guidelines/food\\_allergy.asp](http://www.aaaai.org/members/resources/practice_guidelines/food_allergy.asp).
3. National Institute of Allergy and Infectious Diseases: <http://www3.niaid.nih.gov/topics/foodAllergy/default.htm>.
4. Anaphylaxis Network of Canada: <http://www.anaphylaxis.org>.

(References cited in this article are available from the author upon request.)