

# Peanut Allergy: An Overview

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Peanut allergies have been increasing in prevalence in most industrialized countries. Onset is typically in early childhood, with a trend towards earlier ages of presentation. The allergy is lifelong in most affected children, although 15–22% will outgrow their peanut allergy, usually before their teenage years. Manifestations of peanut allergy range from mild to severe, and risk factors predisposing to severe reactions are discussed. However, even in the absence of risk factors, peanut allergic individuals may still experience life-threatening anaphylactic reactions. Approaches to investigation and treatment, patterns of cross-reactivity and possible causes of rising prevalence are discussed.

**Key words:** peanut, allergy, anaphylaxis, nuts

Food allergy is a common problem encountered by primary care physicians. It is estimated to affect 4 to 8% of children and 1 to 2% of adults and is considered a major cause of life-threatening hypersensitivity reactions.<sup>1–3</sup> Eight foods are responsible for more than 90% of food allergies: cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish.<sup>4</sup> Among those foods, peanut has attracted considerable attention for several reasons. Peanut allergy is common, typically with onset in the first few years of life. Allergy to peanut usually is lifelong and accounts for most of the food-induced severe and fatal allergic reactions.<sup>5</sup> Hence, the diagnosis of peanut allergy carries with it considerable medical and emotional significance.<sup>6</sup>

## Prevalence

The prevalence of anaphylaxis from all causes is rising, but food-induced anaphylaxis is causing a disproportionate increase in the rates of anaphylaxis.<sup>7</sup> A recent study in the United States assessed the prevalence of peanut allergy by random telephone survey. The prevalence of peanut allergy was estimated to affect 0.8% of children and 0.6% of adults,<sup>8</sup> showing a twofold increase over a 5-year period.<sup>9</sup> In the Isle of Wight, United Kingdom, a study was conducted on a birth cohort of 3- and 4-year-old children born between 1994 and 1996, and the results were compared with those of a cohort born in 1989. There was a documented twofold increase in reported peanut allergy (0.5–1.0%) and a threefold increase in sensitization, and after further analysis that included oral

challenges, the total estimate for clinical peanut allergy was 1.5% of 3- to 4-year-old children.<sup>10</sup> The results from those two studies are suggestive of an overall increase in the prevalence of peanut allergy among children. Another study estimated the prevalence of peanut allergy to be 1.34% among primary school children in a Canadian province.<sup>11</sup>

## Clinical Reactions to Peanuts

Allergies to peanut have a spectrum of clinical presentations ranging from cutaneous manifestations to life-threatening systemic reactions. Symptoms usually develop within minutes after ingestion of even a trace amount of peanut and may involve cutaneous, cardiovascular, gastrointestinal, genitourinary, and/or respiratory systems. Progressive upper or lower respiratory symptoms, hypotension, and arrhythmias typically develop in fatal and near-fatal cases.<sup>12</sup> Factors that appear to contribute to a fatal outcome include a concomitant diagnosis of asthma, a delay in the administration of epinephrine, previous severe allergic reactions to peanut, and not recognizing the presence of peanut in the meal. Initial reactions occur at the first apparent exposure in 72% of patients, with a median age of 24 months, and most reactions occur in the home.<sup>13</sup> In this study, 89% of initial reactions involved the skin, 52% the respiratory tract, and 34% the gastrointestinal tract. Two organ systems were affected in 31% of reactions, and all three systems were affected in 21%. Moreover, subsequent accidental reactions occurred in 55% of peanut-allergic patients over a median period of 5.5 years with similar symptoms. This illustrates the difficulty of strict avoidance of this ubiquitous food product even in those patients compliant with the recommendations made by treating physicians. Patients with isolated cutaneous manifestations had lower serum peanut-specific IgE levels than the group with respiratory and/or gastrointestinal symptoms, with a median of 1.25 kUA/L versus 11.65 kUA/L.<sup>14</sup> However, despite this, there was no threshold level below which only skin manifestations appeared to occur.

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## Diagnosis

The evaluation of a child with suspected allergy to peanut should include a careful history taking, skin-prick testing, measurement of serum-specific IgE, and, possibly, an oral food challenge.<sup>12</sup> The use of ImmunoCAP, a serologic test, can be both diagnostic and prognostic as a peanut-specific serum IgE level of 15 kUA/L or higher has a 95% predictive value for an allergic reaction on ingestion of peanut.<sup>15</sup> Patients developing typical allergic symptoms after the isolated ingestion of peanut protein who have evidence of peanut-specific IgE antibodies, that is, by a positive skin-prick test and/or ImmunoCAP, do not need to undergo a confirmatory oral challenge.

Skin testing is generally relied on for diagnosis. A wheal 3 mm greater than the negative control is considered a positive reaction.<sup>16</sup> Overall, a negative skin-prick test to peanut has a negative predictive value of more than 95%.<sup>15</sup> The positive predictive value, however, is significantly lower, reaching only 60% in patients with a convincing history of an allergic reaction.<sup>17</sup> A recent study showed that a positive skin-prick test with a wheal diameter of 8 mm or more had a predictive value of 95% (95% confidence interval 76.2–99.9) for a positive challenge.<sup>18</sup>

For acute allergic reactions, the diagnosis is based on clinical symptoms, a history of exposure to relevant allergen, and supportive skin-prick tests and/or ImmunoCAP test. Serum  $\beta$ -tryptase level, considered the hallmark of mast cell activation, may not be helpful since it can be normal in patients with food-induced anaphylaxis.<sup>19</sup>

The three major allergenic proteins in peanut are Ara h1, h2, and h3.<sup>20</sup>

## Cross-Reactivity with Other Foods

Peanut belongs to the plant family Leguminosae. The legume family also includes soybeans, peas, lima beans, green beans, other beans, chickpeas, and lentils. The fact that they are low in fat, contain no cholesterol, and are high in protein, folate, potassium, iron, and magnesium has contributed to their widespread consumption in the North American diet.

Barnett and colleagues demonstrated a high rate of cross-reactivity between peanut and legumes when they screened sera from 40 patients with peanut allergy against 10 other legumes.<sup>21</sup> There was demonstrable IgE binding to multiple legumes in 38% of patients. However, clinical cross-reactions are uncommon. In a study of 32 children with peanut allergy confirmed by a double-blinded, placebo-controlled oral food challenge, 10 (31%) had a positive skin-prick test response to soy, but only 1 (3%) had a clinical reaction to soy and another 1 to pea.<sup>22</sup>

Cosensitization to tree nuts is also common, although the cross-reacting proteins are not yet known. The rate of co-allergy varies from 2.5% in one survey<sup>9</sup> to as high as approximately one-third of peanut-allergic patients.<sup>13</sup> There is a high degree of cosensitization with seeds.<sup>23</sup>

## Theories on Why the Prevalence of Peanut Allergy Is Increasing

It remains unclear why the prevalence of peanut allergy is rising in the Western world. Multiple theories have tried to explain the overall increase in the prevalence of allergic diseases in the Western world over the last decade, mainly describing an imbalance between the T-helper 1 (Th1)/T-helper 2 (Th2)-biased cellular responses in early life.<sup>24</sup> Other theories have been advanced to explain the rise of peanut allergy. The major peanut allergens have been detected in the breast milk of lactating women.<sup>25</sup> This occult exposure through breast milk from mothers ingesting peanut during lactation may sensitize the infants to peanut and thus explain the occurrence of allergic reactions to peanut on first exposure in the majority of children.<sup>13</sup> Alternatively, exposure of infants to peanut protein via breast milk in the perinatal period may aid in the development of immunologic tolerance in some infants.

The methods by which peanuts are prepared may contribute to the increase prevalence of peanut allergy in the Western hemisphere. Peanuts are prepared mainly by dry roasting, including peanuts that are made into peanut butter. Roasting has been shown to alter both the structure and the allergenicity of peanut.<sup>26</sup> Dry roasting also induces functional alterations by causing a 3.6-fold increase in the function of Ara h2, which acts as a trypsin inhibitor protecting Ara h1 from proteolytic digestion.<sup>26</sup> Lack and colleagues found an association between peanut allergy in preschool-age children and a family history of peanut allergy, consumption of soy during infancy, early onset of eczema, other rashes with oozing and crusting, and exposure to topical preparations containing peanut oil.<sup>27</sup> The latter are present in the form of emollients for the treatment of diaper rash, eczema, dry skin, and inflammatory cutaneous conditions during infancy.

## Other Names and Common Sources of Hidden Peanut Products

Warnings and educational brochures about allergy to peanuts are distributed by the Canadian Food Inspection Agency (<http://www.inspection.gc.ca>). Peanuts may be manufactured under other names, including arachis oil, beer nuts, cacahouette, goober nuts or peas, ground nuts, mandelonas, nu-nuts, nut meats, and valencias.<sup>24</sup>

Possible hidden sources of peanut exposure include almond

and hazelnut paste, icing, glazes, marzipan, and nougat; artificial nuts (peanuts that have been altered to look and taste like almonds, pecans, and walnuts); baked goods (cakes, cookies, doughnuts, pastries); cereals; chili; cross-contamination (containers, foods deep fried in oil, utensils); desserts (frozen desserts, frozen yogurts, ice cream, sundae toppings); dried salad dressing, soup mix; ethnic foods (including sauces and soups); fried foods; gravy; hydrolyzed plant protein/vegetable protein; peanut oil; snack foods (candy, chocolate, dried fruits, energy/granola bars, mixed nuts, popcorn, potato chips, trail mixes); and vegetarian meat substitutes. Nonfood sources containing peanut protein include ant baits, bird feed, mouse traps, and pet food; cosmetics; sunscreens; craft materials; medications; vitamins; mushroom-growing medium; and stuffing in toys.<sup>28</sup>

### Outgrowing Peanut Allergy

In comparison to allergy to milk and egg, it was traditionally thought that allergy to peanut is rarely outgrown. However, one study has shown that peanut allergy can be outgrown in as many as 21.5% of patients.<sup>29</sup> In another study, patients with a history of peanut allergy could successfully pass their oral challenge with peanut according to their serum peanut-specific IgE level. More specifically, 55% of children with a peanut-specific IgE of 5 kUA/L or less, 63% with a peanut-specific IgE of 2 kUA/L or less, and 73% with an undetectable peanut-specific IgE passed an oral challenge with peanut.<sup>30</sup> These data suggest that patients with a history of peanut allergy and a peanut-specific IgE level of 5 or less have at least a 50% chance of outgrowing their allergy. This information, along with the details of previous clinical reactions and the results of ongoing allergic evaluation, can then be used to stratify current risk and prognosticate. Also, parents and patients need to know that there is a possibility of re-sensitization after a negative prick skin test (PST) and negative challenge, especially in the absence of regular intake.<sup>31</sup>

### Management

Management of peanut allergy is based mainly on

1. Educating patients and families to avoid peanuts and peanut-containing products
2. Awareness of early signs of an allergic reaction resulting from accidental exposure
3. Education on the proper use of self-injectable epinephrine (eg, Twinject or EpiPen autoinjectors)

Patients and caregivers of a child with peanut allergy, including parents, teachers, babysitters, daycare workers, and other family members, must be instructed to carefully read all in-

**Table 1.** Online Resources for Families and Patients in Need of Further Information about Peanut Allergy

Name of Organization	Website
Anaphylaxis Canada	<a href="http://www.anaphylaxis.ca">http://www.anaphylaxis.ca</a>
Allergy Asthma Information Association	<a href="http://www.aaia.ca">http://www.aaia.ca</a>
The Food Allergy and Anaphylaxis Network	<a href="http://www.foodallergy.org">http://www.foodallergy.org</a>
American College of Allergy, Asthma and Immunology	<a href="http://www.acaai.org">http://www.acaai.org</a>
American Academy of Allergy, Asthma and Immunology	<a href="http://www.acaai.org">http://www.acaai.org</a>
Food You Can Eat	<a href="http://www.foodyoucaneat.com">http://www.foodyoucaneat.com</a>
Association Québécoise des Allergies Alimentaires	<a href="http://www.aqaa.qc.ca">http://www.aqaa.qc.ca</a>

redient labels when purchasing prepackaged foods, inform the school authorities about the presence of allergy to peanuts, and develop an action plan to be implemented in the event of an allergic emergency. There are multiple reliable online resources for families and patients in need of further information, some of which are included in Table 1.

In the acute setting, patients and family members are advised to inject epinephrine early during the course of the reaction as this has been shown not only to reduce the risk of a fatal outcome<sup>32</sup> but also to reduce the likelihood of a biphasic reaction.<sup>33</sup> Asthma, especially when poorly controlled, is a recognized risk factor for near-fatal or fatal anaphylaxis.<sup>34</sup> In individuals at risk for anaphylaxis, it is crucial to stress the need to ensure that asthma remains well controlled at all times. Patients and parents are always instructed to go to the nearest emergency department if they or their child develops a systemic reaction and/or need to use injectable epinephrine.

### Therapies under Investigation

Some therapeutic modalities are currently under investigation and show considerable promise. These include monoclonal anti-IgE, oral peanut desensitization and immunotherapy, Chinese herbal formulas, probiotics, and heat-killed *Listeria monocytogenes* (HKL).

#### Anti-IgE

Allergic reactions are mediated by antigen-specific IgE bound to high-affinity receptors (FcεRI) on mast cells and basophils.<sup>35</sup> TNX-901 is a humanized IgG1 monoclonal antibody against IgE that binds with high affinity to an epitope in the CH<sub>3</sub> domain, masking a region responsible for binding to FcεRI. Leung and colleagues divided 84 patients with peanut allergy into four groups: a placebo arm and three active treatment groups receiving either 150, 300, or 450 mg of TNX-901 subcutaneously every 4 weeks for four doses.<sup>36</sup> Several

weeks after completing the study, patients on the higher dose of anti-IgE therapy had a significant increase in the threshold of sensitivity to peanut by oral food challenge, from one peanut (178 mg) to almost nine peanuts (2,805 mg). Despite the short duration of the study, one would predict that indefinite administration of anti-IgE is needed to maintain a state of relative tolerance.

### Immunotherapy and DNA Immunization

Oppenheimer and colleagues conducted a trial of rush injection immunotherapy for the treatment of anaphylactic sensitivity to peanut.<sup>37</sup> Patients in the treatment group were able to tolerate increased amounts of peanut in food challenges after treatment. Unfortunately, there was a high rate of adverse systemic reactions, including a case of fatal anaphylaxis, associated with the treatment group compared with the group receiving placebo.

Another approach makes use of deoxyribonucleic acid (DNA) immunization. DNA immunization employs the subcutaneous injection of a plasmid DNA vector encoding a specific allergenic protein. After uptake and processing by antigen-presenting cells, it is presented to T cells in the context of the major histocompatibility complex. This approach is thought to induce a Th1 phenotypic response with upregulation of interferon (IFN)- $\gamma$ , an increase in IgG2a, and suppression of allergen-specific IgE production.<sup>38</sup> This approach has thus far been used in murine models and has yet to be applied to human subjects.

### Chinese Herbal Formula

A herbal formula called Food Allergy Herbal Formula (FAHF)-1 was previously reported to block systemic anaphylactic in mice sensitized to peanut protein. It does so by reducing mast cell degranulation and histamine release, peanut-specific serum IgE level, and Th2 cytokine secretion.<sup>39</sup> A subsequent report used a refined herbal formula, FAHF-2, produced after exclusion of two herbs from the original formula. Peanut-sensitized mice pretreated with FAHF-2 for 7 weeks had no signs of anaphylaxis following peanut challenge 1, 3, and 5 weeks posttherapy. It was concluded that FAHF-2 treatment protected against active anaphylaxis in peanut-allergic mice.<sup>40</sup> However, this herbal formula has not yet been studied in humans for safety and efficacy.

### Probiotics

Probiotics are bacterial components that enhance the host's intestinal microbial balance. Kalliomaki and colleagues con-

ducted a prospective study dividing newborn infants into two groups receiving either the probiotic *Lactobacillus rhamnosus* strain GG (ATCC 53103) or placebo.<sup>41</sup> At 4 years of age, there was a significant decrease in the prevalence of atopic dermatitis (AD) in the *Lactobacillus* treatment group, suggesting a role for probiotics in the prevention of the development of AD. However, the number of children with allergic rhinitis and asthma did not differ between the two groups, although the concentration of exhaled nitric oxide, considered a marker of bronchial inflammation, was significantly greater in children receiving placebo than in those receiving *Lactobacillus*. When added in vitro, probiotics resulted in enhanced production of IFN- $\gamma$ , interleukin (IL)-10, and tumour necrosis factor  $\alpha$ . However, oral administration of probiotics to children with food allergy, some of whom were allergic to peanut, is associated with a decrease in IgE production in vitro.<sup>41</sup> This may support a role for probiotics in protecting against or ameliorating the allergy to peanut, although this is still experimental.

### Heat-Killed *Listeria*

HKL is a potent stimulator of the innate immune system. Yeung and colleagues found that mice immunized with keyhole-limpet hemocyanin (KLH) mixed with HKL developed a reversion of the established immune responses dominated by the production of Th2 cytokines and high levels of KLH-specific IgE.<sup>42</sup> Treatment with HKL induced a Th1-type response with high levels of IFN- $\gamma$  and IgG2a and low KHL levels of IgE and IL-4. These results suggest that use of HKL as an adjuvant during immunization can successfully bias the development of antigen-specific cytokine synthesis toward Th1 cytokine production even in the setting of an ongoing Th2-dominated response. Frick and colleagues found KHL subcutaneous vaccination with peanut allergen and HKL increased the threshold for peanut allergen-induced skin reactions and symptoms in peanut-allergic dogs.<sup>43</sup> Similar data have not yet been developed in humans, and the safety of this approach in human remains unclear.

### Summary

Peanut allergy continues to be a major health-related issue worldwide, with many theories advanced to explain this apparent rise in prevalence. Manifestations of peanut allergy may be life-threatening and require an aggressive approach to risk factor modification and management, with emphasis on prevention and the early use of injectable epinephrine. Multiple novel therapeutic options are under investigation with considerable prospects for successful modification of a common, potentially fatal condition.

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