Severity of Peanut Allergy and the Unmet Gaps in Care: A Call to Action

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ABSTRACT

Peanut allergy is one of the most common food allergies in children, with a prevalence that has been increasing over the past several decades. The allergy is a type I, immunoglobulin E (IgE)-mediated reaction that commonly presents in childhood and can be associated with an anaphylactic response. There are many theories that attempt to explain the increasing prevalence, including dietary changes, improvements in hygiene, and intentional allergen avoidance. Diagnosis is made through a combination of a thorough patient history, peanut-specific serum-specific IgE levels, peanut skin-prick test, and, if necessary, an oral food challenge. Guidelines based on the landmark 2015 Learning Early About Peanut Allergy trial suggest that peanuts should be introduced into the diet as early as 4 to 6 months of age in infants who are at highest risk of developing peanut allergy. It is important for providers to recognize risk factors for the development of peanut allergy, identify associated clinical symptoms, and provide an accurate diagnosis of patients to effectively manage them and their families and prevent future reactions.

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For author information and disclosures, see end of text.

Peanut allergies, once considered a rare occurrence, are now one of the most common food allergies among children and can be severe and potentially fatal.[1] Several studies by Sicherer and colleagues have found that the prevalence of peanut allergy in children increased from 0.4% in 1997 to 0.8% in 2002 to 1.4% in 2008, as determined by a random digit telephone survey. This increase represents a 3.5-fold increase within an 11-year period.[2-4] A recent survey study conducted between 2015 and 2016 estimates the prevalence of peanut allergies in children in the United States to be 2.5%, suggesting that the prevalence of peanut allergy continues to increase.[5]

Peanut allergies are different from other common food allergies. Egg and milk allergies are usually outgrown in most patients; however, a smaller percentage of children are expected to outgrow their peanut allergy. In a study by Ho and colleagues, 21.4% of study participants achieved a resolution of their peanut allergy by age 5 years, and Kaplan-Meier curves suggest that 34.2% will achieve resolution by age 7 years, with no additional increase in resolution beyond that age.[6] A more rigorous Australian study supports these numbers, showing that 22% of 1-year-old children with challenge-proven peanut allergy outgrew their allergy by age 4 years.[7]

Food-related allergic reactions lead to an emergency department visit approximately once every 3 minutes in the United States.[8] A retrospective cohort study conducted at 37 children's hospitals between 2007 and 2012 found that peanuts were the allergen responsible for 37% of food allergy anaphylaxis cases and for 35% of hospital admissions due to anaphylaxis.[9] An examination of a case series of deaths due to food allergies in the United States found that peanut was the single most common suspected culprit.[10]

Development of a peanut allergy significantly impacts not only the patient, but also the entire family. Food allergies can have a significant psychosocial effect on patients and their families, particularly considering the effect of a food allergy on a family's daily activities and the stress of allergen avoidance.[11] Another significant concern for children with food allergies is the potential for bullying or harassment. Lieberman and colleagues conducted a survey of children and their caregivers with food allergies

(81.3% reported a peanut allergy) and found that 24.1% of individuals with food allergies reported being bullied, teased, or harassed because of their food allergy. When excluding children younger than 5 years, the percentage increased to 35.2%.[12] A recent study by Stensgaard and colleagues found that in patients with food allergies, health-related quality of life was significantly negatively impacted by the risk of accidental food allergen ingestion, as well as by limitations placed on the child or family's social life due to the food allergy.[13]

Pathophysiology

Peanut allergy is an immunoglobulin E (IgE)-mediated type I hypersensitivity reaction.[14,15] In these reactions, the initial exposure to an allergenic peanut protein in a susceptible individual leads to the production of protein-specific IgE, which can then bind to high-affinity IgE receptors on mast cells and/or basophils.[16] When re-exposure to the antigen occurs, the peanut allergen binds to the peanut-specific IgE on mast cells and basophils, cross linking cell-bound IgE triggering degranulation of mast cells and/or basophils, causing them to release preformed allergic mediators, such as histamine. In addition, it leads to production of other inflammatory mediators, such as prostaglandins and leukotrienes. Finally, activation of these cells induces transcription and increased production of multiple cytokines (such as interleukins IL-4 and IL-13) and chemokines, which can initiate a late-phase allergic response by attracting eosinophils, lymphocytes, and monocytes to release additional inflammatory mediators and cytokines.[14,15] These combined effects lead to the clinical symptoms of allergy and sometimes anaphylaxis.[16]

Peanuts are legumes and are classified under the scientific name *Arachis hypogaea*.[16] Allergenic peanut proteins can be identified due to their ability to bind to IgE in the serum of an allergic individual.[17] In total, 17 peanut allergens have been identified to date, named Ara h 1 to Ara h 17, with varying degrees of allergenicity.[18] Although all of these peanut proteins can bind to IgE in sensitized patients, some appear to be more clinically relevant than others. For example, using in vitro assays, Ara h 2 and Ara h 6 appear to be more potent in causing mast cell degranulation as compared with Ara h 1 and Ara h 3, whereas Ara h 8 protein sensitivity may indicate lack of clinical allergy.[19,20]

Peanuts usually undergo some type of thermal processing before they are consumed, depending on the region and culture.[21] Commonly, peanuts are either boiled, fried, or roasted, and the choice of preparation method seems to have an impact on the prevalence of peanut allergy.[21] In fact, peanut sensitization patterns differ among various geographic locations in the world.[22] A lower incidence of peanut allergy has been reported in Asian countries, such as China, where peanuts are often consumed after boiling, versus the United States, where peanuts are typically roasted.[23] Boiling peanuts before consumption appears to decrease the IgE binding capacity of Ara h 1, Ara h 2, and Ara h 3 versus roasting the peanuts, which is likely due to a transfer of allergens into the boiling water.[23,24] In contrast, roasting peanuts appears to increase the allergenicity of peanuts and the IgE binding capacity of peanut allergens.[23] The Maillard reaction, a glycosylation reaction that occurs during the dry roasting process, increases the IgE binding capacity of peanut allergens and is thought to contribute to the effect.[21]

Multiple theories exist to explain the rise in food allergies, including peanut allergies, over the last several decades, although none have been verified through randomized controlled trials. The hygiene hypothesis suggests that the decrease in natural microbial exposure, found especially in Western societies, shifts the body's immune response toward IgE production and allergy when presented with a potential allergen.[25] The allergen avoidance hypothesis suggests that earlier recommendations to delay introduction of allergenic foods may have led to an increase in allergy to those foods.[26] The nutritional hypothesis suggests that there may be dietary factors that have affected the risk of food allergies, such as an increased incidence of low vitamin D levels in children.[26] The dual allergen exposure hypothesis suggests that sensitizing skin exposure (through dust or particles in the air) can override potential tolerizing oral exposure, especially when oral exposure is delayed, and lead to food allergies.[26,27]

Clinical Presentation

Symptoms of peanut allergy may develop very quickly, within seconds, or up to 2 hours after ingestion of even trace amounts of peanut protein in a sensitized person (1 peanut contains approximately 300 mg of peanut protein).[28] The symptoms of peanut allergy may involve several organ systems, most commonly the skin, gastrointestinal (GI) tract, respiratory system, and cardiovascular (CV) system. Skin symptoms include acute urticaria, angioedema, or a pruritic erythematous skin rash. GI symptoms may include vomiting, abdominal pain, and diarrhea. Respiratory symptoms may include both the upper and lower airway, including wheezing, stridor, cough, dyspnea, throat tightness, rhinorrhea, and/or nasal congestion.[14,28] CV symptoms, which are typically associated with anaphylaxis, include hypotension and dysrhythmia.[28] The frequency of involvement of the various systems on initial peanut reaction (based on self-report) were studied by Sicherer and colleagues and are listed in **Table 1**.[29]

Patients do not typically have fatal reactions on their first known ingestion of peanuts.[28] Approximately 20% to 30% of patients can also experience a biphasic, or secondary, late-phase reaction, in which allergic symptoms recur 1 to 8 hours after the initial symptoms resolve.[14,28] Patients who have fatal or near-fatal reactions often have a history of asthma, food allergy, and atopy, and are more commonly adolescents or adults.[28,30]

The severity of an allergic reaction cannot be predicted based on the severity of past reactions or lab values.[30] Severity can vary based

TABLE 1. Characteristics of Initial Reaction to Peanut[29]

Organ System Involved	Percentage of Patients Affected
Skin	
Urticaria, erythema, angioedema	89
Respiratory	
Wheezing, stridor, cough, dyspnea, throat tightness, nasal congestion	42
Gastrointestinal	
Vomiting, diarrhea, abdominal pain	26
Cardiovascular	
Hypotension, dysrhythmia, cardiac arrest	4
1 organ system	54
2 organ systems	32
3 organ systems	13
4 organ systems	1

Adapted from Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol*. 2001;108(1):128-132.

on the amount ingested, the form of peanut ingested (raw, roasted, boiled), and co-ingestion of other foods.[30] The severity may also be influenced by the age of the patient, the degree of sensitization when ingestion occurs, and how quickly the peanut is absorbed. Absorption can be influenced by factors such as whether the peanut is ingested on an empty stomach and whether exercise occurred around the time of ingestion.[30]

A recent large database study (N = 1070) of children with potential peanut allergy conducted by Leickly and colleagues found that 33.9% of patients diagnosed with a peanut allergy self-reported an episode of anaphylaxis on a subsequent peanut exposure, and 81.6% of these patients did not have a prior history of anaphylaxis.[31] Reactions of greater severity than the initial presenting reaction occurred in 27.7% of patients; these more severe reactions were more common in children who had a skin reaction as their initial peanut reaction.[31] The study also found that 33.3% of children with a history of anaphylaxis experienced anaphylaxis during a subsequent exposure. **Table 2** compares the initial peanut reaction with subsequent exposure with and without anaphylaxis.[31]

Diagnosis

Diagnosis of peanut allergy should always begin with a thorough medical history and physical examination.[30] The medical history can provide important information to estimate a prior probability of peanut allergy.[32] The history should include assessment of symptoms, timing between peanut ingestion and initiation of symptoms, the type and consistency of symptoms (skin, GI, respiratory), the amount of peanut protein ingested, whether symptoms occur after eating similar foods, and any cofactors that may be related, such as exercise, alcohol use, medications, and any comorbid conditions.[16,28,30,32] Critical questions to ask patients presenting with possible peanut allergy are listed in **Table 3**.[30]

The physical examination can also provide evidence to suspect a peanut allergy and help focus the evaluation, although its findings alone are not sufficient evidence to be diagnostic for a peanut allergy.[30] The presence of physical symptoms can verify the presence of an atopic disorder, such as urticaria or atopic dermatitis, and can also reveal symptoms that may be more suggestive of a nonallergic disorder and point to further evaluation and testing.[30]

It is important to note that self-reported symptoms have a low positive predictive value for peanut allergy, with multiple studies demonstrating that 50% to 90% of presumed food allergies of all types are not allergies on further examination.[30] Therefore, although the medical history and physical symptoms are critical components of the diagnostic process, they alone do not provide enough information to be diagnostic.[30]

The most common subsequent steps in the diagnosis of peanut allergy include an evaluation of peanut-specific IgE by means of skin-prick testing or serum testing. These can help the clinician decide whether it is reasonable to perform an oral food challenge with peanuts.[28] A skin-prick test is a safe, convenient, and inexpensive test used to elicit a localized IgE-mediated allergic reaction.[14,30] A positive skin-prick test correlates with the presence of serum-specific IgE (sIgE) levels bound to the surface of cutaneous mast cells.[30] To perform the test, a drop of peanut extract is typically placed on the forearm or back, and the skin is pricked with some form of skin-prick device, such as a lancet. This is an epicutaneous test and does not penetrate the epidermal/dermal junction. Negative (saline) and positive (histamine) controls are also placed at the same time. Results of the test are read 15 minutes after placing the test; a result is considered positive when the wheal from the extract has a mean diameter of 3 mm greater than the negative (saline) control, with a larger wheal diameter more suggestive of a clinically relevant allergy, although not necessarily a more severe reaction. In general, a skin-prick test has a high sensitivity and high negative predictive value, but low specificity and positive predictive value, compared with an oral food challenge.[14,28,30] Therefore, the use of skin-prick tests alone can lead to over-diagnosis of peanut allergy; it is important to remember that a significant number of patients may have a positive skin-prick test but no clinical allergy.[1]

Evaluation of peanut-specific IgE in vitro can also assist in determining the likelihood of peanut allergy. Skin-prick testing and sIgE evaluation both identify the presence of allergen-specific antibodies, although, because sIgE measures the serum and skin-prick testing reflects IgE bound to cutaneous mast cells, the results may not correlate.[30] Serum testing can be especially useful when

skin-prick testing cannot be done (ie, if the patient has extensive skin conditions or is actively taking antihistamines).[14,30] In this assay, peanut-specific IgE results are measured quantitatively, with a range of less than 0.35 kUA/L to greater than 100 kUA/L (although some labs report down to 0.10 kUA/L), with higher levels correlating with a higher probability of clinical reactivity but not severity of reaction.[14,28] Data suggest that approximately 95% of patients will react during a peanut challenge if their peanut-specific IgE level is equal to 15 kUA/L or greater.[14] However, the presence of sIgE represents an allergic sensitization and not always a true clinical allergy.[30] Compared to skin-prick testing, sIgE measurement has a similar sensitivity but may have a greater positive predictive value.[14,30] Therefore, serum sIgE represents an additional tool that may be useful in the diagnosis of peanut allergy, but it is not a diagnostic test alone for food allergy. Future research is being conducted to evaluate IgE binding to specific peanut proteins (such as Ara h 2) in distinct populations and may provide a more specific and accurate diagnostic test in certain populations.[32,33]

Oral food challenge is considered the gold standard for diagnosis of peanut allergy.[28,34] Before initiating a food challenge, the suspected food should be fully eliminated from the diet for several weeks.[30] The double-blind, placebo-controlled food challenge is the most rigorous and typically used in research settings.[28,30] This process involves the patient ingesting incremental portions of peanut or placebo, hidden in a masking vehicle, at 15- to 30-minute intervals. Any signs and symptoms of an allergic reaction should be documented throughout the challenge, and, if a reaction occurs, the challenge should be stopped and patient symptoms should be managed.[35] However, this process can be both labor and time intensive in a clinical setting, so an open oral food challenge is commonly done instead, although this introduces the risk of patient and physician bias.[34]

Studies suggest that some infants with allergic reactions to peanuts will outgrow their allergy, especially if they have low levels of sIgE.[7,28,36] These children should be evaluated again by school age (4-6 years) to determine whether the allergy has been outgrown, although their skin-prick test and sIgE levels may remain positive for years even if they have outgrown their allergy. Therefore, an evaluation every 1 to 2 years may be appropriate.[28]

Prevention of Peanut Allergy

Previous clinical practice guidelines from organizations including the American Academy of Pediatrics have recommended delaying introduction of peanuts, especially in children considered high-risk for peanut allergy, for at least the first year of life or longer.[37] In 2010, the "Guidelines for the diagnosis and management of food allergy in the United States" were published by an expert panel and coordinating committee that was convened by the National Institute of Allergy and Infectious Diseases (NIAID).[30] These guidelines did not present a strategy for the prevention of peanut allergy because of a lack of definitive studies available. The guidelines differed from previous recommendations, however, by stating that "insufficient evidence exists for delaying introduction of solid foods, including potentially allergenic foods, beyond 4 to 6 months of age, even in infants at risk of developing allergic disease."[30]

In 2015, the *New England Journal of Medicine* published the landmark results of the Learning Early About Peanut Allergy (LEAP) trial.[38] The trial was based on a previous study by Du Toit and colleagues that was published in 2008, which found that the prevalence of peanut allergy was 10-fold higher among Jewish children in London compared with Jewish children in Tel Aviv, with the difference not accounted for by differences in atopy, social class, genetic background, or peanut allergenicity. In Israel, foods that contain peanuts are introduced into the diet in high quantities during the

TABLE 2. Anaphylaxis With Second Exposure to Peanut[31]

Initial Peanut Reaction	Second Exposure With Anaphylaxis (n = 38)	Second Exposure Without Anaphylaxis (n = 74)
Anaphylaxis	7	14
Contact urticaria	12	20
Urticaria	12	9
Angioedema	3	1
Gastrointestinal symptoms	2	1
Oral allergy syndrome	1	2
Other symptoms	1	27

Adapted from Leickly FE, Kloepfer KM, Slaven JE, Vitalpur G. Peanut allergy: an epidemiologic analysis of a large database. *J Pediatr*. 2018;192:223-228.e1.

TABLE 3. Questions to Assist in Obtaining a Thorough Medical History[30]

- What symptoms are concerning to you?
- Did the ingestion of peanuts precipitate the symptoms?
- Have you experienced these symptoms following the ingestion of peanuts more than once?
- What quantity of peanuts was ingested when the symptoms occurred?
- What form was the peanut in (cooked, raw, boiled, roasted, etc)?
- When did the symptoms occur in relation to exposure to the peanut?
- Have peanuts ever been eaten without the symptoms occurring?
- Were any other factors involved, such as exercise, alcohol, or use of aspirin or nonsteroidal anti-inflammatory drugs?
- Have the symptoms been present at times other than after exposure to peanuts?
- What treatment was given, and how long did the symptoms last?

Adapted from Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(suppl 6):S1-S58.

first year of life, while in the United Kingdom, children did not typically consume any peanuts during the first year of life. The findings raised the question of whether introduction of peanuts early in the first year of life would prevent the development of peanut allergy versus the standard practice of avoidance in many Western countries.[39]

The LEAP trial randomized 640 children aged 4 to 11 months with severe eczema, egg allergy, or both to either consume or avoid peanut-containing foods until age 60 months.[38] At that time, a peanut oral food challenge was administered to determine the prevalence of peanut allergy. Patients in the LEAP trial were stratified upon study entry into 2 separate cohorts based on preexisting sensitivity to peanut extract, which was determined by skin-prick testing. One cohort consisted of infants with no measurable skin test wheal to peanut and the other consisted of infants who developed a wheal measuring 1 to 4 mm in diameter. Infants with a wheal measurement 5 mm or greater in diameter were not included in the study because these infants were presumed to be allergic to peanut. Among the 530 patients in the intent-to-treat population with a negative baseline skin-prick test, the prevalence of peanut allergy at age 60 months was 13.7% in the peanut avoidance group and 1.9% in the peanut consumption group (P <.001), equating to an 86.1% relative risk reduction in the prevalence of peanut allergy. Among the 98 patients with a positive skin-prick test result, the prevalence of peanut allergy at age 60 months was 35.3% in the peanut avoidance group and 10.6% in the peanut consumption group (P = .004), equating to a 70% relative risk reduction in the prevalence of peanut allergy.[38]

In 2016, the Enquiring about Tolerance trial was published, examining the effects of early introduction (at age 3 months) of several allergenic foods in the diet of breastfed infants on the development of food allergy in the general population. The results of the per protocol analysis were consistent with the LEAP trial and found the prevalence of peanut allergy between age 1 and 3 years to be 0% in the early introduction group versus 2.5% in the standard introduction group (P = .003).[40]

The LEAP study was the first randomized trial to study the use of early peanut introduction as a preventive strategy. Considering these data, the NIAID published an addendum to its 2010 guidelines in 2017 entitled, "Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel."[41] The addendum provides 3 separate guidelines for infants in varying risk categories for development of peanut allergy. A summary of the guidelines is illustrated in **Table 4**.[41] The guidelines recommend evaluation of patients with severe eczema, egg allergy, or both with peanut sIgE, a skin-prick test, or both before introduction of peanuts to determine if peanut should be introduced. For these children, the guidelines recommend introduction of age-appropriate foods containing peanuts as early as age 4 to 6 months, after other solid foods have been introduced, to reduce the risk of peanut allergy.[41]

To reduce the risk of peanut allergy in children with mild to moderate eczema, the guidelines recommend introduction of peanut-containing foods around age 6 months, after other solid foods have been introduced and in accordance with family preferences. This introduction can occur at home if the family is comfortable, or the infant may have an in-office supervised feeding if that is preferable. For children without eczema or any other food allergy, the guidelines recommend that peanut-containing foods be introduced in the diet without restriction along with other solid foods in accordance with family preferences.[41]

According to the guidelines, if peanut is introduced into the diet of children with severe eczema, egg allergy, or both, the total amount of peanut protein ingested per week should be approximately 6 to 7 grams over 3 or more feedings.[41] This recommendation is based on data from the LEAP trial where, at evaluations conducted at age 12 and 30 months, 75% of children in the peanut consumption cohort reported eating at least this amount of peanut protein per week according to analysis of their food diary for the 3 days before evaluation.[38] The guidelines recommend that if, after 1 week or more of consuming peanut, the child displays mild allergic symptoms within 2 hours of peanut ingestion, the healthcare provider should be contacted for further evaluation.[41]

TABLE 4. NIAID Guideline Recommendations for Prevention of Peanut Allergy in Infants[41]

Infant Risk Criteria	Recommendations	Age of Peanut Introduction
Severe eczema, egg allergy, or both	Evaluate sIgE, skin-prick test, and/or oral food challenge. Based on result (ie, if patient is not likely already allergic), begin to introduce peanut-containing foods	4-6 months
Mild to moderate eczema	Introduce peanut-containing foods	About 6 months
No eczema or any other food allergy	Introduce peanut-containing foods	When age-appropriate in accordance with family and cultural preferences

NIAID indicates National Institute of Allergy and Infectious Diseases; sIgE, specific immunoglobulin E. Adapted from Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29-44.

Gaps in Care

The new 2017 NIAID guidelines represent a paradigm shift in current thinking on the prevention

of food allergies. This has led to an educational gap for providers, as well as parents and caregivers, because many parents are understandably hesitant to introduce peanuts early to infants, especially those considered high-risk. A recent survey study conducted by Greenhawt and colleagues found that just 31% of new and expecting caregivers with infants younger than 1 year expressed willingness to implement early peanut introduction before or around age 6 months, although 40% expressed willingness to introduce peanut after age 11 months. The study also found that 56.8% of these caregivers were unwilling to allow an in-office oral peanut challenge before age 11 months.[42] Therefore, a significant gap exists in understanding that must be addressed before broad-based implementation of the guidelines can be implemented.

Another area of controversy involves the role of screening younger siblings of children with peanut allergy. The NIAID guidelines do not directly identify this group as a population requiring allergy testing before peanut introduction. Many families are hesitant with early introduction because they are concerned that the development of peanut allergy may have a genetic cause, although this has not been proven.[43] Families should be encouraged to discuss their concerns with providers and to introduce younger siblings to peanuts at around age 6 months with evaluation if necessary.[43]

Finally, the recommendations surrounding peanut exposure in schools are areas of significant debate and variability throughout the country. As of 2017, 49 of 50 states had enacted some sort of law requiring schools to stock epinephrine (with most laws providing for an option to stock epinephrine versus a mandate to stock epinephrine), but fewer than 25% of states have any formal food allergy management guidelines.[44] There are no state guidelines or allergy professional societies that advocate for allergen bans as an effective strategy to accommodate students with peanut allergy, although this is a popular strategy adopted by many caregivers and advocates.[44] Results of a recent study of school nurses in Massachusetts showed that there was no association between "nut-free" schools and a decrease in epinephrine use, although a significant reduction in epinephrine use was found in schools with nut-free tables.[45] Therefore, this important issue is still being debated at community, state, and national levels.

Conclusions

Peanut allergy is one of the most common food allergies in children and can be life-changing for patients and their families to manage. It is critical to recognize and differentiate true food allergies from other conditions and to appropriately introduce peanut-containing foods to infants, especially those at high risk for development of allergy. As the understanding of this food allergy evolves, educating parents and caregivers is essential to ensure that new guidelines are being implemented effectively. ■

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