
Review article

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Clinical update on peanut allergy

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Background: Peanut allergy is common, potentially severe, and there has been a recent surge in clinical investigation of this important food allergen.

Objective: To provide the reader with a clinically oriented update on peanut allergy.

Data Sources: English language articles were selected from PubMed searches (search terms: peanut allergy, food allergy, anaphylaxis) and selected abstracts with a bias toward recent (3 years) studies judged to have immediate, practical clinical implications.

Results: Peanut allergy is an increasing problem in western diets that include this food. Both genetic and environmental factors influences the expression of this allergy. The at-risk subject is an atopic individual, with heightened risk for those with atopic dermatitis and/or other food allergies. The allergy is long-lived for most, may increase slightly in severity over time, but approximately 20% of young children will develop tolerance. Parameters that may identify the subset likely to achieve tolerance have been identified. Several large studies have determined laboratory parameters (skin tests, peanut-specific serum immunoglobulin E concentrations) with excellent predictive value (>95%) to diagnose current clinical reactivity or tolerance, although oral food challenges are necessary for a definitive diagnosis. Numerous practical lessons concerning management (avoidance, treatment, and prevention) have been identified.

Conclusions: Recent studies provide the clinician with an armament of improved diagnostic and treatment modalities for peanut allergy. Studies are underway that are likely to provide more definitive therapies in the near future.

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INTRODUCTION

Physicians and allergy-sufferers have long appreciated peanut (*Arachis hypogaea*) as a potent allergen, but the past decade has witnessed an explosion in attention to the allergic potential of this legume. An apparent increase in the prevalence of peanut allergy,^{1,2} in concert with the particularly severe reactions it can elicit^{3–5} and its ubiquity in the diet, has sparked a surge in re-

search. The implications of peanut allergy extend beyond the concerned physician, affected patients and their families. This food allergy in particular has impacted the educational system, the food industry, and public policy. The cost to individuals and families in terms of quality of life can be significant,^{6,7} as this diagnosis can mean a “life sentence” of dietary restriction and fear. The aim of this review is to provide a clinically oriented update on peanut allergy with particular attention to studies that have practical implications for diagnosis and management.

PREVALENCE

It is customary to include prevalence data in a review article, but one might balk at its relevance for the individual patient. However, recent studies are in-

triguing in that there are potential explanation for an increase in prevalence that may, in turn, have implications for prevention. Epidemiologic studies also frame the parameters that identify an individual at risk for this allergy. Finally, it has become apparent that the prevalence is such that a typical school, social gathering, sporting event, public transportation vehicle, restaurant, etc, is likely to have one or several identifiable peanut-allergic patients and this has self-evident implications.

A study on the population prevalence of peanut and allergy in children was performed on a cohort of 1,218 newborns followed to age 4 years on the Isle of Wight, United Kingdom.⁸ The study found positive tests for immunoglobulin (Ig)E antibody to peanut in 13 children (1.1%) followed to age 4 years. Because sensitization (a positive skin test or radioallergosorbent test [RAST]) does not equate with clinical reactivity, it is not surprising that only 6 of the 13 sensitized (0.5% of the cohort) experienced a clinical reaction to peanut. We administered a nationwide, cross-sectional, random-digit dial telephone survey to determine the prevalence of peanut allergy in the US population.¹ Adult surrogates from 4,374 households were interviewed, providing information for 12,032 individuals. Peanut allergy was reported for 0.4% of children and 0.7% of adults. In another population-based study of 2000 representative households in the United Kingdom,⁹ the prevalence of reported allergy was 0.61% in children aged 0 to 14 years, 0.53% in individuals aged 15 to 44 years, and 0.3% in those older than 44 years. Taken together, these studies indicate that approximately 1 in 150 to

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200 individuals has a peanut allergy in these countries.

Case series of anaphylaxis in these selfsame countries indicate that peanut is a major offender: among anaphylactic reactions attributed to foods, 23 to 47% are attributed to peanut.¹⁰⁻¹² Perhaps because of eating patterns or other factors, the proportion of food-induced anaphylaxis attributed to peanut is less in some other countries: 2% in a study of children in Italy¹³ and none in Singapore.¹⁴

From the clinician's perspective, it is helpful to be familiar with epidemiologic features that identify persons, particularly children, at risk for developing peanut allergy. In US children with moderate to severe atopic dermatitis evaluated for food allergy, 22 to 46% had peanut allergy. In Australian children with cow's milk allergy followed prospectively, 55% were reported with peanut allergy.¹⁵ Egg allergy is apparently an even stronger marker for subsequent peanut allergy as 70% of a referral group of children in the United States with peanut allergy had previous egg allergy.¹⁶ Numerous studies indicate that those with peanut allergy are likely to have had (or to develop) atopic diseases.^{1,9,16-19}

There is a clear clinical impression that peanut allergy has increased in prevalence,^{2,20} but the magnitude of the rise has not been determined. It remains unclear as to whether the apparent increase is merely a reflection of the recent rise in atopic diseases, or attributable to peanut-specific factors, such as increased peanut consumption, use of peanut-containing nonfood products,^{21,22} breast-feeding with maternal peanut consumption,¹⁹ the early introduction of foods with potentially cross-reacting proteins as in soy or carob,²³ or other factors. An intriguing observation is that peanut allergy is rare in China,²⁴ where the quantity consumed is not different from that in the United States. One explanation may be the generally lower rate of atopic disease in China, but another possibility is the difference in preparation methods. In China, peanut is boiled or fried whereas in the United

States it is dry roasted. In comparison to frying or boiling, the roasting process seems to enhance the allergenic potential of the major peanut allergens.^{25,26} The absolute impact of cooking methods on the prevalence of peanut allergy remains to be investigated.

FEATURES OF CLINICAL REACTIONS

Compared with other food allergens, peanut is particularly capable of eliciting severe and potentially deadly allergic reactions. In reviews of fatal, food-induced anaphylaxis in the United States, 7 of 13 deaths were attributable to peanut.^{3,5} In a registry of fatal food-induced anaphylaxis, 63% of the 32 fatalities were caused by peanut.⁴ Our population-based study¹ confirmed that reactions to peanut can be severe: 81% reported respiratory or multiorgan system reactions. Additional characteristics of severe peanut-induced anaphylaxis were recently reviewed.²⁷

Reactions to peanut include the full spectrum of allergic responses. Rancé et al¹⁷ reported the clinical characteristics of food allergy in 544 children aged 0 to 15 years evaluated with oral food challenges upon referral to their medical center in France. In this selected group, 24% had peanut allergy. Clinical symptoms attributed to peanut allergy included atopic dermatitis (46%), urticaria/angioedema (32%), asthma (15%), generalized anaphylaxis (5%), and gastrointestinal symptoms (3%).

To further define the clinical characteristics of peanut allergy, we have established a registry of peanut (and tree nut)-allergic individuals.¹⁸ Analysis of the first 4,685 with peanut allergy provides a number of clinical observations, but it must be appreciated that 89% of the registrants were children entered by their parents. The median age of a first reaction to peanut was 14 months with the following distribution of organ systems affected: skin 89%, respiratory 42%, gastrointestinal 26%, and cardiovascular 4%. Nearly half of the reactions involved multiple organ systems. Registrants with asthma were more likely than

those without to experience severe reactions (33% vs 21%, $P < 0.001$). Reaction severity increased slightly with subsequent reactions (28% at 14 months, 35% at a median age of 3 years, and 40% at 4 years), but this may have been accounted for in part by increased verbalization in the older children (eg, the ability to complain of throat tightness). An increase in severity was noted previously in very young children with sustained peanut allergy,²⁸ but not in slightly older children.¹⁶

Reactions to peanut frequently occur (>74%) on what is considered to be the first known exposure.^{16,18,29} The onset of symptoms is prompt, within 5 minutes for the majority and >30 minutes for only 7%. For young patients, first reactions typically occur at home (approximately 70%) whereas subsequent reactions generally occur outside the home (approximately 70%) in locations such as schools, restaurants/food establishments, and relatives'/friends' homes.¹⁸ Accidental exposures are unfortunately common; in the registry, 23% had experienced two accidental ingestions by a median age of 4 years. In our referral population of peanut-allergic children, 55% experienced a reaction to accidental exposure by a median of 5.5 years with an average of two accidents.¹⁶ In a longitudinal study with up to 10 years of followup, 75% experienced accidental exposures with reactions.²⁸

The quantity of peanut capable of eliciting a reaction seems to be small, with some subjects indicating reactions to casual exposures from skin contact or inhalation.^{18,30-32} Overall, it seems far more likely/common that ingestion rather than skin contact or inhalation, can elicit severe reactions. In formal challenge studies, as little as 100 μ g of ingested peanut has elicited subjective symptoms,³³ but the more typical doses that trigger reactions in patients undergoing challenge (biased perhaps by exclusion of the most sensitive patients) is generally in the range of 100 to 1,000 mg.^{34,35} For reference, one peanut kernel is approximately 800 mg.

GENETIC BASIS

As with any human disease, the phenotype of peanut allergy is dependent upon genetic and environmental factors. From a broad perspective, a family history of atopic disease is perhaps the best predictor of atopy in any given individual; this general predisposition extends to peanut allergy.^{1,16,19} We³⁶ and others¹⁹ have observed that 7% of siblings of probands with peanut allergy share this allergy. Because the population prevalence is approximately 0.5%, the relative risk for this allergy in a sibling is approximately 14. This magnitude of relative risk among siblings is relatively high for a complex trait (greater than 10 is favorable for successful gene identification).³⁷

We undertook a study to estimate the heritability of peanut allergy (the variance in a phenotype that is genetically determined). We studied the frequency of shared disease between mono- and dizygotic twin pairs in whom at least one of the pair had peanut allergy.³⁶ The procedure is predicated on the fact that monozygotic (identical) twins have all their genes in common, whereas dizygotic (fraternal) twins share on average only half of their genes. A greater similarity between identical versus fraternal twins is attributed to accumulated effects of several genes. Heritability of 100% would indicate complete genetic influence and 0% would indicate solely an environmental influence.³⁸ We found that 7% of fraternal twins shared peanut allergy, but among monozygotic twins 64% shared the allergy. Heritability of peanut allergy was estimated to be 81.6% (95% confidence interval [CI], 41.6% to 99.7%). This result was similar to that found in other atopic disorders (asthma [87%],³⁹ atopic dermatitis [74%],³⁸ and allergic rhinitis [74 to 82%]⁴⁰) and shows a strong genetic influence on peanut allergy. There are numerous potential candidate genes for peanut allergy and among them human leukocyte antigen class II genes have already proven to be important.^{41,42} At this point, the take-home message from genetic studies on peanut allergy is simply that a child born

into a family with other atopic diseases is at risk for peanut allergy, and if a sibling has peanut allergy, there is a 7% chance of peanut allergy in other siblings.

CROSS-REACTIVITY AND CO-ALLERGY

Legumes

Peanut shares homologous proteins with other beans. Indeed, several studies have demonstrated that individuals with clinical reactions to a single legume often (38 to 79%) show IgE binding (positive skin test/RAST) to a variety of legumes.^{43,44} However, the majority do not show clinical reactions to the other legumes. One might expect that soybean, in particular, would be problematic for those with peanut allergy as it is a major allergen itself, yet clinical evaluations with blinded oral food challenges shown a surprisingly low rate of co-reactivity. For example, among 113 children with atopic dermatitis, only one (0.8%) had allergy to both foods,⁴⁵ a low rate that was confirmed in a similar population [3 of 165 children (1.8%)].⁴⁶ Bock and Atkins⁴⁷ studied 32 children with peanut allergy confirmed by double-blind, placebo-controlled, oral food challenges and found that 10 had a positive skin test to soy, but only 1 (3%) had a clinical reaction upon ingestion of soy.

In a study of 69 children with peanut allergy that evaluated allergy to soy and other legumes (pea, string bean, lima) by blinded food challenges, Bernhisel-Broadbent and Sampson⁴⁸ found that 6.5% with severe peanut allergy had reactions to soy. Overall, only 2 of 41 with any one positive challenge reacted to more than one legume (5%). The two peanut-allergic patients with co-allergy lost their soy sensitivity after 3 years and were also able to consume other legumes. Taken together, the authors concluded that elimination of all legumes in individuals with clinical reactions to one, was unwarranted.

Recent studies^{49,50} have rekindled concerns about multiple legume allergy. Lupine, not a common food in the United States, is one bean in par-

ticular that seems to warrant caution for those with peanut allergy.^{49,51} In an evaluation of children with peanut allergy in France,⁵¹ 11 of 24 (44%) had positive skin tests to lupine and of 8 subjects who underwent double-blind, placebo-controlled oral food challenges (6 children) or labial challenges (2 children) to lupine, 7 reacted. In vitro studies in this group of patients showed the potential causal protein to be a common allergen (43 kD) that has not been recognized as a major peanut allergen. Complicating issues include the possibility that lupine pollen causes sensitization in this geographic region, and more studies in a variety of geographic settings are needed to more specifically identify the risks.

Also unsettling was a report on fatal anaphylaxis to foods in Sweden that argued that peanut-allergic individuals may react to soy with severe consequences.⁵² These investigators reviewed the medical records of fatal reactions over a 3-year period. Two deaths caused by peanuts and four deaths presumably caused by soy were evaluated. These subjects were aged 9 to 18 years and all had previously diagnosed severe peanut allergy, underlying asthma, but no reaction to previous soy ingestion. In the four fatal reactions attributed to soy in peanut-allergic individuals, the causal foods were hamburger in three cases (2.2 to 3% soy), and kebab in one case (7% soy). However, a number of questions have been raised about the verification of soy as the causal allergen,⁵³ and severe reactions to soy have not been noted at this time in the United States. It seems prudent for clinicians to be aware of potential reactivity to multiple legumes in a small subset of patients with peanut allergy and to individualize diets based upon the allergy evaluation (which may require oral food challenges).

Tree Nuts

Should peanut-allergic patients avoid nuts from trees (walnut, Brazil nut, cashew, etc)? Peanut does not share significant homologous proteins with tree nuts. However, several studies of

highly atopic individuals referred for evaluation of peanut or tree nut allergy indicate that co-allergy to peanut and tree nuts is a strong possibility: 41% of 62 patients,²⁰ 28% of 122,¹⁶ and 49.5% of 622¹⁹ reported allergy to both. In contrast to studies in referred populations, our recent epidemiologic study¹ showed a lower rate (2.5%) of co-allergy to peanut and tree nuts. These findings suggest that co-allergy to these foods in highly atopic children is attributable to atopic disposition in the host, rather than to cross-reacting proteins. We evaluated 111 serum samples from children with peanut and/or tree nut allergies and found no strong correlation between peanut-specific IgE concentration and tree nut-specific IgE concentration for seven nuts.¹⁶

There are conflicting views on whether patients with peanut allergy should avoid tree nuts. Although it may be overly restrictive, we¹⁶ and others¹⁹ advise complete avoidance of tree nuts by young peanut-allergic children, except for particular tree nuts that were previously tolerated and eaten in isolation. Reasons for this recommendation include the concern that tree nut sensitivity appears to be severe and long-lived, that there is a potential for cross contamination of tree nut products with peanut, and it is difficult to identify specific nuts in various processed foods.⁵⁴ Further studies will be needed to evaluate the best course of management for children, particularly to determine what dietary advice is appropriate as they get older. For adults with peanut allergy who tolerate tree nuts, there does not seem to be a reason to restrict tolerated nuts; however, caution about cross-contamination with peanut in various products must be emphasized.

DIAGNOSIS

The tools used to diagnose peanut allergy are no different from those used for other food allergies: history, physical examination, appropriate laboratory tests, and oral food challenges.^{55,56} When an individual has experienced an acute allergic reaction to peanut with typical symptoms, other potential trig-

gers are excluded, and there is evidence of peanut-specific IgE antibody (prick skin test or RAST), then the diagnosis is essentially secured and no further testing (such as an oral food challenge) is warranted. It is impossible to discuss every eventuality in this review, but the clinician must keep in mind the possibility of alternative diagnoses and the fact that a positive test for IgE antibody does not, in isolation, prove clinical allergy.

The clinical example mentioned above is straightforward. However, with the surge in atopic disease and a high rate of sensitization to peanut,⁵⁷ there are a number of increasingly common scenarios that are quite challenging to evaluate. The clinician may be faced with a patient who has tested positive to peanut without a known ingestion/reaction, one who avoided peanut because of their family history, or who demonstrated an unexplained aversion to eating peanut. In all of these situations, the clinician must make a risk evaluation to determine a course of action that generally boils down to continued avoidance or an oral provocation test.

Tests for IgE antibody are helpful in the risk evaluation, but no test in medicine is perfect. It must be ever appreciated that the history (age, time since last reaction, diet, social issues, type of reaction, possible alternative diagnoses, etc) must factor in the decisions. In essence, the test results assist in defining a spectrum of risk. A number of recent studies have considered the diagnostic value of prick skin tests and determination of serum peanut-specific IgE antibody concentrations.^{58–61} The predictive value of a test result can vary depending upon the population studied (age, history, type of atopic disposition) and the relative prevalence in the population to which the test is applied. For skin tests in particular, the variety of devices used and reagents can also affect the results. Table 1 includes several representative studies that have recently explored the diagnostic efficiency of tests. Several nuances must be kept in mind. For example, it is likely that for a particular

degree of positive test, a younger patient is more likely to react than an older one. The clinician must consider various issues when considering the application of these study results to their patient.

Properly performed negative skin tests/RASTs are highly likely to indicate a lack of clinical reactivity. When these tests are negative, unless there is a history of a previous reaction or suspicion of one, the clinician could expect that peanut would be tolerated. If there is any suspicion of clinical reactivity from the history despite negative tests (which would be prudent to repeat if this were the case), introduction of peanut should be undertaken under a physician's supervision. As indicated in Table 1, when skin tests are particularly large or serum peanut-specific IgE concentration particularly high, then clinical reactivity becomes increasingly likely; in many cases clinical reactivity assumed and avoidance continued. The feature of tests that must be emphasized is that a negative results does not guarantee tolerance and a positive one does not, in isolation, prove clinical reactivity. One may argue that some situations (eg, an older child who never had a reaction but was followed with positive tests) may warrant an oral food challenge, even if the risk of reaction is somewhat high, as the burden of a lifetime of unnecessary avoidance also carries risk. For those with an unclear reaction history, or a long period of time since the reaction and with indeterminate test results, a physician-supervised oral food challenge may be warranted (again, within the context of the factors mentioned previously).

A variety of oral challenge procedures with variations in doses, timing, and blinding have been suggested.^{35,56,58,61–63} Challenges must be undertaken with appropriate provision to treat reactions. A number of workers begin with a small smear of peanut placed in the inner lip or on the buccal mucosa, and most aim for 8 to 10 g of peanut as a cumulative dose in blinded challenges. In general, patients are considered to be tolerant if they openly consume a serving size portion of peanut in an open oral food challenge. A

Table 1. Representative Recent Studies on the Efficacy of Skin Prick Test/RAST to Predict Peanut Allergy

Author	Study population/design	Methods	Results
Sampson and Ho ⁵⁹ and Sampson ⁶⁰	N = 41, children with atopic dermatitis, mean age 5.2 yrs, retrospective, diagnosis-43% history, remainder by DBPCFC. Prospective study confirmed findings.	Commercial extract SPT: evaluated positive defined as mean wheal diameter 3 mm greater than negative control. Pharmacia CAP System FEIA in kIU/L	SPT (cut-off 3 mm): Sn-90%, Sp-29% PPV-55, NPV-75% CAP-RAST >0.34 kIU/L: PPV-78%, NPV-85% CAP-RAST cut-off 10.7 kIU/L: PPV-94%, NPV-62% (95% PPV at 15 kIU/L, best NPV = 85% if < 0.35 kIU/L)
Pucar et al ⁶¹	140 challenges, OFC & SBFC, children, median 5.2 yrs, retrospective, challenges at discretion of tertiary care MDs, excluded convincing history with SPT ≥ 5 mm	Commercial extract with positive test defined as above	SPT (cut-off 3 mm): Sn-100%, Sp-62.3% PPV-28.1%, NPV-100% (0 of 16 with wheal 3–4 mm reacted, 11 of 23 with wheal ≥ 8 mm reacted.
Sporik et al ⁵⁸	95 OFC to peanut, median age 4.8 yrs, challenged for suspected allergy	Commercial extract, lancet	SPT (cut-off 3 mm): Sp-71% (Sp-66% for age under 2 yrs) (at wheal ≥ 8 mm, 100% reacted; 3 of 18 with a negative SPT reacted)

SPT—skin prick test, OFC—open oral food challenge, SBFC—single-blind food challenges, DBPCFC—double-blind, placebo-controlled oral food challenge, PPV—positive predictive value, NPV—negative predictive value, Sp—specificity, Sn—sensitivity

variety of considerations concerning oral food challenges have been reviewed.^{56,63}

MANAGEMENT

Once the diagnosis is secured, the treatment is avoidance of the causal food protein and preparedness to treat reactions from accidental ingestions. These apparently simple tenets of treatment are actually quite complex and demand careful patient education. Commercial products will generally indicate the presence of peanut but labeling laws are in a transition period. It has been recognized that labels, particularly on confections and baked goods, may not accurately reflect the presence of peanut in possibly 25% of the cases.⁶⁴ Although trace contamination may not induce reactions in most patients, some very sensitive patients may react.⁶⁵ Some companies have labeled products to indicate a possibility of peanut contamination (eg, “may contain peanut or traces of peanut”), a label that is appreciated with mixed emotions and some confusion among patients. Another point of confusion is the allergic relevance of peanut oil. The processed type of oil most typically does not contain a relevant

amount of peanut protein,^{66–68} and may be tolerated by most peanut-allergic individuals, although unprocessed or gourmet peanut oil does contain peanut protein⁶⁹ and will induce reactions. Many experts advise their peanut-allergic patients to avoid peanut oil in any form to avoid confusion and the low risk of reactions.³⁵ It should be remembered that an accidental ingestion of a product with peanut oil that does not result in a reaction is NOT an indication of peanut tolerance.

As mentioned previously, reactions to peanut can occur essentially anywhere food is eaten, and so for children, schools are a serious concern. We reviewed allergic reactions to peanut occurring in schools and daycare from among registrants in the National Peanut and Tree Nut Registry.³¹ Families of 115 children described reactions in the school setting and 25% of the reactions were severe. A majority occurred in daycare (64%), and for 25% the school reaction was their first. Parents attributed reactions to ingestion (60%), skin contact (24%), and inhalation (16%). However, in the majority of reactions attributable to inhalation, concomitant ingestion/skin contact could

not be ruled out. The primary cause of reactions attributed to skin contact/inhalation was craft projects using peanut (eg, spreading peanut on pinecones to make bird feeders). It can be surmised that the vast majority of peanut-allergic patients do not develop symptoms when near others eating peanut butter in the school setting. Additional trouble areas in school reactions were food sharing and parties/special occasions. Delayed treatment in the school was attributed to failure to recognize symptoms, calling parents rather than initiating treatment, and incorrect technique in using an epinephrine injector device.

Recommendations for managing peanut allergy in the school setting are shown in Table 2 and are based upon the results of this study and recommendations by the Board of Directors of the American Academy of Allergy, Asthma and Immunology.^{31,70} The banning of peanut from entire schools has been the focus of much controversy with arguments on each side summarized in Table 3. It may be that limited bans for young age groups in particular may be helpful, but more research is needed to determine the best management strategies. Whether or not peanut is banned, education about

Table 2. Avoidance and Treatment Strategies for Food Allergy in Schools^{31,70}

Avoidance:

Increased supervision during meals/snacks (perhaps allergy-free table)
 No food, container, or utensil sharing
 Cleaning of tables, toys
 Substitution of causal food during craft, cooking, science projects
 Handwashing before/after food handling and eating
 Avoidance of exposure to food during preparation/cooking
 Provision of safe substitute foods
 Foods brought in should have ingredient labels
 Instruction of staff on issues of
 Careful label reading
 Cross-contamination
 Technical/scientific word(s) for the food(s)

Treatment:

Physician-prescribed treatment protocols in place, periodic review of protocols
 Epinephrine available for potentially life-threatening reactions (readily available, not locked)
 Education of supervising personnel on
 Recognizing signs of an allergic reaction
 Technique of medication administration
 Basic first aid and resuscitation

the allergy should be undertaken and emergency plans developed and reviewed frequently.

Restaurants and other food establishments are another common location for exposure to peanut. We reviewed allergic reactions to peanut in these establishments,⁷¹ and found that errors occurred more commonly in

Table 3. Arguments for and against Banning Peanuts from Schools

For:

To reduce the general burden/chance for potential exposure
 Children are likely to share food
 Children may carry food into play areas and cause contamination

Against:

Technically impractical
 May cause undue burden on unaffected
 Slippery slope (ban other foods? All foods?)
 May create a false sense of security
 Not a real world situation

Asian restaurants, bakeries, and ice cream shops. In sit-down restaurants the desserts were the most likely problem. Pitfalls included cross contamination and pure errors. In many cases, peanut was a hidden ingredient in sauces, stews, or dressings. In almost half of the cases of errors, the allergic person/family had not specifically warned the establishment about the reasons for their request (ie, allergy vs a taste preference). The management lessons from the study are listed in Table 4.

In certain settings, avoidance of peanut is quite difficult (eg, in commercial airliners when many individuals open packets of roasted peanut at one time).⁷² Although reactions in that setting are usually not severe, most individuals with peanut allergy should do what they can to minimize such exposure. Although specific laws are under consideration, families may wish to call ahead, request no peanuts be served (may be easier on a morning flight), or that the rows ahead and behind them be peanut-free. It is also prudent to clean seats and tray tables and have medications available.

Fatal outcomes from accidental ingestion of peanut have been attributed, in part, to delayed treatment.^{3,4} This under-

Table 4. Strategies for Dining out with Peanut Allergy⁶⁷

Identify the diet request as a life-threatening allergy, not just a preference
 Avoid Asian restaurants, ice cream shops, and bakeries
 Identify the individual(s) in the restaurant who are responsible for the ingredients
 Remind the restaurant personnel about issues of cross-contamination and hidden peanut
 Avoid buffets
 Be wary of desserts, especially ice creams and baked goods
 Be wary of multi-ingredient, mixed items (stews, sauces dressing, sauces, soups, chili)
 If there is an error, hold the dish and have the management bring a newly prepared order
 If the patron is uncomfortable in trusting the establishment, leave

scores the need to follow the treatment strategies outlined in Table 2.⁷³ The Food Allergy and Anaphylaxis Network (Fairfax, VA; www.foodallergy.org) is a lay organization that is helpful for families with food allergies and can provide additional information on issues of food avoidance.

PREVENTION

Attention has focused toward prevention of this allergy. The Committee on Nutrition of the American Academy of Pediatrics made recommendations on this issue for families at risk defined as "a strong (biparental; parent and sibling) family history of allergy."⁷⁴ The recommendations include a consideration to avoid peanut during pregnancy, to avoid it while breast-feeding, and not to introduce it to the diet until after age 3 years. There are no definitive prospective studies to prove the benefit of these recommendations.

The role of in utero sensitization to peanut was evaluated in a study by Frank et al.⁷⁵ Forty-three children up to age 3 years referred for evaluation of food allergy were selected for participation on the basis of a positive RAST to food. There were 25 peanut-sensitized subjects and 18 control subjects (children sensitized to milk and/or egg but not to peanuts) and further feeding information was obtained by questionnaire. Mothers who consumed peanuts more than once a week during pregnancy were more likely to have a peanut-sensitized child than mothers who consumed peanuts less than once a week ($P = 0.063$; odds ratio = 3.97, 98% CI 0.73 to 24). Interestingly, there was no significant relationship to peanut consumption during lactation with peanut sensitization ($P = 0.47$, odds ratio = 2.09, 95% CI 0.39 to 13.47). Peanuts or peanut butter was introduced into the child's diet from a significantly younger age in the peanut-sensitized subjects ($P < 0.03$). Data were not provided to evaluate confounding variables (for example, earlier feeding of peanut to children of mothers who consumed it more frequently during pregnancy). The study

was based on recall and not blinded. A prospective study seems warranted.

The possibility that maternally ingested peanut can sensitize infants through breast milk has attracted attention. It was recently shown that peanut protein can pass in immunologically intact form into breast milk.⁷⁶ Apparently, not all women are efficient in passing peanut as it was detectable in the breast milk of only 11 of 23 who consumed 50 g and the quantities for those who passed peanut protein were low with a median peak concentration of 200 ng/mL. In any event, sensitization of the infant by this route is at least theoretically possible.

Hourihane et al¹⁹ evaluated a number of parameters among families of 622 persons with peanut allergy, including the possible role of sensitization from breast milk. Peanut allergy was reported with increasing rates through successive generations up to the proband: 0.1% of grandparents, 0.6% of aunts and uncles, 1.6% of parents, and 6.9% of siblings. All forms of atopy were also significantly more common in successive generations. Although the study did not control for recall bias, mothers of younger probands (≤ 5 yrs) were significantly more likely than mothers of older ones ($P < 0.005$) to report eating peanuts regularly while pregnant or breast-feeding. An additional observation was that age of onset correlated inversely with year of birth ($r = -0.6$, $P < 0.001$). These results imply that increasing ingestion of peanut by pregnant or breast-feeding mothers and earlier ingestion by children is partly responsible for the apparently increased prevalence of the allergy. However, the impact of the confounding variables (increased general atopic disease through the generations) is not known.

One way to isolate and evaluate the potential of maternal intake to affect allergy in their infants is to manipulate the maternal diet. Maternal dietary avoidance was studied over a long followup period in a group of 115 children in Sweden.⁷⁷⁻⁷⁹ Matched groups of infants with a family history of atopy were treated with or without maternal elimination of egg, milk, and

fish for the first 3 months of lactation. Peanut consumption was not targeted in the intervention. Sensitization rates to the foods originally eliminated were not significantly different, although the total number of positive tests were higher in the nonintervention group (three times greater). Peanut sensitization was greater by skin prick testing but not RAST in the controls; however, an equivalent number of subjects in each group had experienced food-allergic reactions.

Zeiger et al¹⁸⁰⁻⁸² studied a comprehensive dietary intervention program in a randomized, prospective study of 288 subjects with followup until age 7 years. Their program targeted peanut (and many other foods) and included elimination of peanut during the third trimester of pregnancy, through breast-feeding and avoidance of peanut until age 3 years. There were fewer positive food skin test by 24 months (16.5% vs 29.4%; $P = 0.019$), caused primarily by fewer positive milk skin tests (1% vs 12.4%; $P = 0.001$). However, there was no significant difference in the number with positive skin tests to peanut (5 in the treatment vs 7 in the control group) and this lack of difference was maintained to age 7 years.

Our group reviewed the data in the US Peanut and Tree Nut Allergy Registry and found that peanut allergy was reported in 94% of those whose mothers specifically recalled eating peanut during lactation, in 88% that specifically avoided it, and in 90% not breast-fed.⁸³ The modest differences were statistically significant ($P < 0.05$) for the first group compared with the latter two. The study is limited in several ways, including that it is not population-based, is potentially recall-biased, and did not control for age of introduction of foods. Overall, the effect of avoidance during breast-feeding seemed to be modest. Clearly, additional prospective, randomized studies are warranted. It may be prudent to follow the dietary recommendations⁷⁴ mentioned above for many reasons, but it seems that evidence for a long-term protective effect on peanut allergy, if any, is not

overwhelming. Clinicians should be careful to address these uncertainties with families, especially those who consider themselves to have caused the allergy through feeding.

NATURAL HISTORY

The notion that peanut allergy is a permanent affliction was derived from the observation that adults are affected and from a study of 32 children aged 1 to 14 years (mean age 7) followed 2 to 14 years with no resolution of allergy.⁴⁷ It is now clear from several studies that very young peanut-allergic subjects sometimes outgrow their allergy. For example, Spergel et al⁸⁴ documented a young child with a positive physician-supervised challenge reverting to a negative challenge. Zimmerman and Urch⁸⁵ noted that 10% of children with positive skin tests at approximately age 2 1/2 years had negative skin tests to peanut approximately 3 years later. The birth cohort studied by Tariq et al⁸ followed children to age 4 years and found that 2 of the 6 children who reacted to peanut (at ages 9 months and 24 months) lost their clinical reactivity. Thus, this epidemiologic study documented a high sensitization rate (1.1%), a modest reaction rate (0.5%), and the potential for resolution of peanut allergy (33%).

Subsequent reports highlighted the potential for resolution of peanut allergy. Hourihane et al⁸⁶ performed oral challenges to peanut in 120 children with convincing histories of peanut allergy selected from 230 with peanut allergy based upon convincing history. Selection of children for oral challenges were individualized, but included subjects with negative skin tests and possible ingestion without reaction. Twenty-two of the 120 children (18% of the original group) passed the oral challenge; this group experienced a first reaction at a mean of 11 months of age and were challenged at a median of 5 years. Skolnick et al⁶² evaluated children aged 4 to 20 years with a history of peanut allergy and offered oral food challenges to those with serum peanut-specific IgE less than 21 kIU/L. Two-hundred twenty patients

were evaluated, 85 underwent challenges, 41 declined, and 97 did not qualify. Forty-eight (21.5%) passed the challenge. Taking the results of the various studies together, it seems that approximately 20% of young children outgrow peanut allergy. The features that may be helpful in assessing the possibility that a patient outgrew a food allergy are summarized in Table 5. Among children who have a positive skin test to peanut and have avoided the food (perhaps by self-selection from previous mild reactions), approximately half are tolerant based upon challenges.^{61,84,87} Long term followup on individuals who outgrew their peanut allergy has not been published. It does seem that rare patients re-develop this allergy,⁸⁸ and further studies to address this point are needed.

EMERGING THERAPIES

The clinical encounter with peanut-allergic patients can be discouraging for all, as the diagnosis often entails the following discussion: the allergy is usually lifelong, potentially severe, the only management options are avoidance and emergency treatments, and there is a high risk of accidental exposures. It should be emphasized that numerous avenues of research are underway to provide more definitive therapies for this and other food allergies.

In terms of non-peanut-specific therapy, administration of humanized, anti-IgE antibodies that have received attention for the treatment of respiratory allergy also have the potential to treat food allergy and are under evaluation for this indication. Peanut-specific therapy using peanut protein for immunotherapy has been investigated in adults by Nelson et al.⁸⁹ They found increased tolerance to oral ingestion in some of the patients, but IgE-mediated side effects of the immunotherapy were prohibitive. However, this investigation has shown that specific therapy is potentially efficacious. One approach to circumvent the side effects of the immunotherapy with whole protein is to use digests⁹⁰ or engineered proteins where IgE binding sites are mutated.⁹¹

Another method of specific therapy is to introduce DNA encoding particular peanut proteins (plasmid DNA) that would result in endogenous production of the allergenic protein, perhaps resulting in tolerance (and switching from Th2 to Th1 responses). The plasmid DNA construct could be introduced either by injection or orally (associated with polysaccharide particles). This methodology has been tested in a number of systems, including mouse models of peanut allergy.^{92,93} Although prophylactic administration of plasmid

DNA encoding particular peanut proteins gave partial protection from challenge with the particular protein (ara h 2)⁹³ with evidence of Th1 immune responses, these responses to vaccination have been strain dependent.⁹² Additional avenues under investigation include cytokine therapy,⁹⁴ (eg, interleukin 12), the use of immunostimulatory sequences and herbal remedies.⁹⁵

CONCLUSION

Recent clinical studies provide a host of clinically relevant information for the improved diagnosis and management of peanut allergy. More study is needed to prevent the allergy (and to determine who is at risk). Hopefully, emerging therapeutic strategies will provide more definitive treatment options over those now available.

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Table 5. Factors that Are Helpful in Predicting Those Who May Outgrow a Peanut Allergy when Evaluated at School-Age^{47,62,84,86}

Factor	Favorable to have outgrown	Not favorable to have outgrown	Point controversial
Age	Allergy not "proven" by age 4 years	Allergy proven to exist after age 7 years	Long term followup not available for various ages
Skin test	Negative or small	Wheal larger than histamine control or > 6 mm	May be biased by exclusion in studies of larger skin tests
IgE concentration (kIU/L)	< 0.35 kIU/L-73% pass < 2 kIU/L-67% pass < 5 kIU/L-61% pass	Level > 5 kIU/L (Level > 10 kIU/L at any time, ~4% outgrow)	May be biased in studies by exclusion of higher IgE concentrations
Interval since last reaction	> 3 years	≤ 1 year	
Severity of reaction	Mild reactions	Severe reactions	Yes
Atopic history	Fewer atopic diseases, isolated peanut allergy	Multiple atopic disease, multiple food allergy, persistent egg allergy	Yes

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CME Examination

1–5, Sicherer SH. 2002;88:350–361.

CME Test Questions

1. Which of the following has *not* been considered a potential explanation for the apparent recent increase in peanut allergy?
 - a. Increased maternal consumption of peanut while breast-feeding.
 - b. Increased consumption of peanut in the diet.
 - c. Method of peanut preparation (eg, roasting).
 - d. Genetic factors.
 - e. A reflection of the general increase in atopy.
2. Which of the following *is not* a characteristic of peanut allergy in young children?
 - a. First reactions to peanut usually occur on what is perceived to be the first known exposure.
 - b. First reactions to peanut most commonly occur in the home.
 - c. Subsequent reactions to peanut (accidental ingestion) usually occur outside of the home.
 - d. The skin is the most common organ system involved in a reaction.
 - e. Reactions typically begin 20 to 30 minutes after exposure.
3. Which statement is accurate?
 - a. The majority of individuals with peanut allergy are clinically reactive to other legumes.
 - b. The majority of individuals with peanut allergy are clinically reactive to nuts from trees.
 - c. Many peanut-allergic individuals exhibit sensitization to other legumes, but relatively few are clinically reactive.
 - d. Peanut and nuts from trees share numerous clinically relevant homologous proteins that account for a high rate of cross-reactivity.
 - e. Adults with a new onset of confirmed walnut allergy should avoid peanut and all legumes.
4. You are evaluating a 6-year-old with resolved atopic dermatitis and a history of resolved egg allergy who never ingested peanut because he had a positive skin test to peanut at 12 months of age. He has avoided peanut successfully and has no history of reactions. The most reasonable next step would be:
 - a. Suggest continued avoidance of peanut.
 - b. Allow peanut to be ingested at home.
 - c. Perform an open, oral food challenge to peanut under physician supervision.
 - d. Perform a blinded, oral food challenge to peanut under physician supervision.
 - e. Perform a prick skin test to peanut.
5. A 7-year-old had a reaction to peanut at age 15 months and is being evaluated for the possibility of outgrowing a peanut allergy. Which of the following features would be *least* favorable in predicting that he is now tolerant?
 - a. A current prick skin test wheal of 2 mm.
 - b. No history of other food allergies.
 - c. A reaction of mild severity to accidental isolated peanut ingestion at age 6 years.
 - d. Undetectable (<0.35 kIU/L) IgE to peanut by RAST.
 - e. A history of mild, resolved atopic dermatitis.

Answers found on page 394.