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The importance of reducing risk in peanut allergy: Current and future therapies

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Clinical Problem: Peanut Allergy

The prevalence of peanut allergy has steadily increased during the past 10 years, especially in children. A 2009 to 2010 survey of more than 40,000 children (aged 0–17 years) in the United States found that peanut allergy was the most common food allergy, affecting 2% (1.5 million) of children nationwide.[1] Data from a 2014 meta-analysis of 29 studies from multiple European countries using various reporting methods estimated the occurrence of peanut allergy to be 0.3% (by positive food challenge result) to 4.1% (by peanut specific IgE positivity) in children aged 2 to 5 years and 0.4% (by self-reporting) to 9.8% (by peanut specific IgE positivity) in children aged 6 to 17 years.[2]

The burden of peanut allergy has a significant effect on the daily lives of patients, parents, and other caregivers. Allergic reactions to peanut vary and are unpredictable, ranging from skin manifestations to life-threatening systemic reactions.[3] In certain regional and national data, peanut allergy has been reported to be a leading attributed cause of food allergy–related emergency department visits and cases of anaphylaxis in children[4]; it is also a common cause of fatal food allergic reactions in assembled reports of known fatalities.[5]

As a consequence of their allergies, patients, their families, and other caregivers can experience psychosocial issues and anxiety, including the fear of ingesting even trace amounts of peanut. The variability of allergic reactions and uncertainty regarding the risk of future reactions are major contributors to patient and caregiver fear.[6] The unpredictable nature of reactions is noted in a Canadian study of 252 children 4 years or older who were diagnosed with peanut allergy and observed for 244 patient-years. During that time, the annual incidence of unintentional peanut exposure was 14.3%, and the severity of the initial reactions did not predict the severity of reactions to subsequent unintentional exposures.[7]

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The cornerstone of management for peanut allergic patients is strict elimination of peanut products from the diet. This elimination has been made somewhat easier in recent years because content labels on most packaged foods now list the most common food allergens.[8] Although the food industry is collectively working to minimize cross-contact of peanut, packaged foods occasionally contain unintended allergen residue, prompting voluntary precautionary allergen labeling (PAL) by food manufacturers.[9] Despite widespread use of these labels, the lack of transparency and uniformity of use because of their voluntary nature has resulted in frustration because allergic consumers may unnecessarily limit their food choice or quality of life (QoL) to avoid all packaged foods that have a PAL statement or choose to ignore some or all PAL statements and possibly increase their risk of reactions by consuming the products.[9] Furthermore, perceived risk is heightened in food service establishments, where the opportunity for allergen cross-contact can be high, because food is prepared out of sight of customers and ingredients may be unknown, adding yet another challenge to the lives of peanut allergic patients and their parents and caregivers. Thus, patients and caregivers have limited information to assess the risk of unintentional exposure, and that risk is real.

Strategies and Evidence

Current Guideline-Based Management of Food Allergy

There is no currently approved option for the prevention or treatment of peanut allergy.[10,11] Current standards of care are restricted to avoidance of peanut products and immediate symptom management with epinephrine to treat anaphylaxis associated with unintentional exposure.[10,11] On the basis of collective clinical experience and published research, if treatment were available, the primary objective of most patients and caregivers would be protection from the consequences of unintentional exposure to peanuts, rather than ad lib ingestion.[12] Consequently, for most, the main goal of peanut allergy immunotherapy (in lieu of an obtainable cure) is to safely increase an individual's reactivity threshold (desensitization) to reduce the risk of allergic reactions attributable to unintentional exposure.[13] Such therapy is preventive as opposed to an abortive treatment (eg, epinephrine) or avoidance.

The allergy field is anticipating upcoming approvals from the US Food and Drug Administration (FDA) of 2 first-time treatments for peanut allergy. There are currently 2 peanut immunotherapy strategies, epicutaneous immunotherapy and oral immunotherapy, in phase 3 development that could lead to registration in the near future.[14,15] Sublingual immunotherapy, another mucosally targeted immunotherapeutic approach for peanut allergy, is also under investigation and has shown promise in phase 1 and early phase 2 trials.[16]

Relative Risk Reduction: How Much Do You Need?

Because exposure to even a small amount of peanut can elicit a reaction in some patients, desensitization that protects against a reaction to unintentional exposure to peanut could significantly increase safety for individual patients on a daily basis.[13] With new immunotherapy options likely forthcoming, assessing the level of protection provided is important. The increase in threshold reactivity from baseline to the end of immunotherapy treatment—assuming the threshold increase is sufficient to reduce the number of reactions—is key in evaluating the effect of risk reduction for each patient. Determining the final eliciting dose (ED; the amount of allergen needed to trigger symptoms) is necessary for quantitatively measuring this effect.[13] Whether an allergic reaction has occurred in response to a discrete threshold dose of peanut or because of the cumulative dose an individual consumed at the time of reaction is an important consideration.[17] Therefore, despite known limitations, such as cofactors, including general state of health and activity that may introduce day-to-day variability, reporting changes in a patient's sensitivity to the allergen provides additional information on how much a peanut allergic individual is able to tolerate before reacting. That is why in clinical trials the degree of treatment efficacy is evaluated by the change in ED after a double-blind, placebo-controlled food challenge.[13]

Treatment benefit is a function of pretreatment risk and risk reduction attributable to therapy (ie, absolute risk reduction). According to proceedings of the FDA Allergenic Products Advisory Committee, attaining a degree of protection that reduces the rate of reactions attributable to unintentional peanut exposure at the individual level is a clinically meaningful end point for trials evaluating peanut allergy immunotherapy.[13] To date, the clinical utility of primary outcomes in food immunotherapy trials has been unknown. Furthermore, until recently, little was known about the risk reduction associated with a patient's increase in threshold that signifies the ability to minimize risks associated with unintentional ingestion in daily life, such as with trace amounts of peanut. The Quantitative Risk Assessment (QRA) model developed by the Food Allergy Research and Resource Program provides a probabilistic approach to assess the benefit of increasing a peanut allergic individual's threshold during immunotherapy.[18] This work demonstrated the level of protection provided by immunotherapy against allergic reactions to unintentional ingestion of food products that contain trace amounts of peanut. The recently published QRA modeling approach, which matched modeled exposure to peanut protein with individual threshold levels, allowed for assessment of the potential risk reduction achieved for each peanut allergic individual.[18] The QRA model compares the threshold dose of a peanut allergic individual to a diversity of exposure doses (based on an analysis of dietary data recorded in the 2003–2010 National Health and Nutrition Examination Surveys and a range of peanut protein concentrations that could be present in packaged foods) to determine the potential for a reaction on exposure to peanut protein residue. The QRA model results showed that increasing a peanut allergic individual's baseline ED threshold of peanut protein from 100 mg or less to 300 mg (equivalent to approximately 1 peanut kernel) corresponds to a 94.9% to 99.9% decrease in the risk of allergic reaction associated with unintentional exposure to trace amounts of peanut (up to 1,000 ppm) for that individual (Fig 1). Further increasing the threshold to 1,000 mg of peanut protein had an additional quantitative benefit in risk reduction for patients reacting to 300 mg or less at baseline (specifically, >98.6% risk reduction for ice cream consumption).[18] The clinical relevance of increasing an allergic individual's peanut sensitivity threshold has also been characterized in a European population using the same QRA approach with European consumption data, with similar results.[19] These 2 studies are based on estimated concentrations of unintended peanut protein residue detected in packaged foods (eg, cookies, ice cream, donuts, snack cakes, croissants, snack chip mixes, salty snacks) based on published retail product surveys.[17,20–26] The products did not contain peanut as an ingredient but may have declared the potential presence of peanut residue via a voluntary PAL statement on the package label. Nonetheless, the 300-mg peanut protein threshold dose is clinically relevant, and achieving this level through immunotherapy provides a margin of safety for peanut allergic individuals who may encounter trace levels of peanut (Fig 1).[18]

Although achieving an individual threshold dose of 300 mg of peanut protein is predicted to provide a level of protection, standard precautions for peanut avoidance should remain in practice because patients undergoing peanut immunotherapy may still be