Should Avoidance of Foods be Strict in Prevention and Treatment of Food Allergy?

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Posted: 09/07/2010; Curr Opin Allergy Clin Immunol © 2010 Lippincott Williams & Wilkins

Abstract and Introduction

Abstract

Purpose of review To discuss whether strict allergen avoidance is the most appropriate strategy for managing or preventing food allergy.

Recent findings The standard of care for the management of food allergy has been strict allergen avoidance. This advice is based upon the suppositions that exposure could result in allergic reactions and avoidance may speed recovery. Recent studies challenge these assumptions. Studies now demonstrate that most children with milk and egg allergy tolerate extensively heated forms of these foods. Moreover, clinical trials of oral immunotherapy show that oral exposure can lead to desensitization. Additionally, recent epidemiologic studies fail to support the notion that delaying introduction of highly allergenic foods to infants and young children prevents the development of food allergy. In fact, the data suggest that delays may increase risks.

Summary Recent data indicate that strict allergen avoidance is not always necessary for treatment. Exposure may be therapeutic, and extended delay in introduction of food allergens to the diet of young children may increase allergy risks. However, in many circumstances strict avoidance is clearly necessary for treatment. Additional studies are needed to determine the risks and benefits of exposure to tolerated allergens, including identification of biomarkers to identify patients who may benefit.

Introduction

The prevalence of food allergy has increased significantly among children in the last 10–15 years, particularly in developed countries such as the United States. Currently, treatment consists of strict avoidance and use of emergency medications in the event of inadvertent ingestion. Implementing strict avoidance is a difficult and burdensome task, particularly because common food allergens, such as milk, egg, and peanut, are ubiquitous in the diet. Reports of accidental exposure with allergic reactions are common.

The vigilance required for strict avoidance coupled with the ever-present risk of an accidental exposure results in impaired quality of life of affected patients and their families. Nevertheless, strict avoidance has been the cornerstone of therapy for food allergy for decades. The advice is practical because the amount of allergen necessary to induce an allergic reaction varies among patients affected by food allergy and the severity of reactions is unpredictable. Additionally, there has been a notion that strict avoidance would hasten recovery; however, there are limited data to support this concept. Finally, delayed introduction of food allergens to infants and young children at risk for atopy has been suggested to reduce atopy risks. The following is a review of recent literature addressing the issue of whether strict avoidance is the best approach to treatment and prevention, with emphasis primarily on children.

Does Strict Avoidance Speed Recovery?

That strict avoidance is necessary to speed the development tolerance has been suggested. This notion is based upon the theory that lack of exposure will result in deletion of immunologic memory. Specific clinical support for this idea is limited, although most children do indeed outgrow their food allergies when instructed to avoid the allergen for practical reasons. In a study of 23 adults with allergies to a variety of foods who underwent baseline double-blind, placebo-controlled food challenges, 10 patients had positive challenges for 13 foods. These
patients were placed on strict dietary avoidance of the offending food for 1-2 years and then re-challenged. Five (38%) of the 13 previously offending foods were well tolerated. This particular study supports the conclusion that strict avoidance may have helped tolerance development in a subset of these adult patients with food allergy.

As a corollary to the dictum that avoidance speeds recovery, there is a concern that accidental ingestions can delay or prevent tolerance development. In practice, we see some children who rapidly outgrow their food allergies without strict avoidance and others who fail to lose their allergies even with the most stringent diet. Additionally, children who fail a medically supervised oral food challenge often go on to tolerate the food in subsequent feeding tests. Allen et al. [16] recently reported the results of questionnaires from 167 families with children having egg allergy. Despite the majority of participants (84%) being advised to avoid all forms of egg, only 68% reported adherence and 47% recounted an accidental exposure. This study found that neither strict avoidance of egg nor accidental ingestion of egg was associated with outgrowing egg allergy. Of the 84 children who underwent open egg food challenges, equal proportions (approximately 1/3) of challenge-positive and challenge-negative children did not avoid egg all the time. Thus, exposure did not influence outcomes.

**Tolerance of Baked Forms of Milk or Egg as a Counter-example of Strict Avoidance**

That some children who react to milk or egg can tolerate extensively heated forms is becoming clear. [17*-18,19*] Nowak-Wegrzyn et al. [17*] challenged children (ages 2-17 years) with milk allergy with heated milk products (e.g. muffin and waffle baked with milk). Those who tolerated the heated milk products were then challenged with unheated milk (e.g. milk or yogurt). The majority (68 of 91, 75%) of children with milk allergy were able to tolerate the baked milk products but not unheated milk. At baseline, heated milk-reactive children had significantly larger skin prick test (SPT) mean wheal diameters and greater specific IgE concentrations to milk, β-lactoglobulin, and casein compared with unheated and unheated milk-tolerant children. Heated milk-tolerant, unheated milk-reactive children ingested heated milk products for 3 months and were then re-evaluated. At 3 months, children ingesting heated milk products had significantly smaller SPT wheals and higher casein-IgG4 compared with baseline, a result often seen with immunotherapy. Milk-specific and casein-specific IgE levels were not significantly different from baseline. Shreffler et al. [18] found that heated milk-tolerant children had a higher percentage of milk-reactive T regulatory cells compared with those who reacted to heated milk.

Similarly, studies in children with egg allergy suggest that some can tolerate egg in the heated/baked foods but not in the less heated forms. [19*] Among 91 children (ages 1-18 years) with egg allergy, most (70%) were able to tolerate heated egg in waffles/muffins but not to regular egg (e.g. scrambled or in French toast). At baseline, those tolerating heated egg had smaller SPT wheal diameters and lower specific IgE levels to egg white, ovalbumin, and ovomucoid compared with reactive children. Heated egg-tolerant children incorporated heated egg into their diets and were re-evaluated at 3, 6, and 12 months. Among these children, egg white SPT wheal diameters decreased significantly, and ovalbumin and ovomucoid-specific IgE4 levels increased from baseline at 3 months and were maintained thereafter. Egg white-specific IgE levels did not differ from baseline at any of the follow-up intervals.

These studies demonstrate that the majority of children with milk and egg allergy can tolerate extensively heated forms of these foods. Whether continued ingestion of baked products enables the immune system to develop tolerance (to unheated forms of these foods) remains to be seen. In one retrospective study, [16] a higher percentage of those who outgrew egg allergy (compared with those with persistent egg allergy) reported ingestion of cooked egg (as in cakes and biscuits) as part of their diet, but this difference did not achieve statistical significance. Prospective studies are currently underway.

**Avoidance may Trigger Increased Reactivity**

That avoidance of a food from the diet after it has previously been ingested without acute reactions could result in the occurrence of anaphylaxis upon re-exposure has been observed. [24-27] Prescribing an elimination diet based on positive test results despite a history of tolerance may induce severe acute allergic reactions upon accidental
ingestion.\(^{26,27}\) For example, there is a study of seven children who tolerated fish but were instructed to avoid fish based upon positive tests.\(^{26}\) After a period of avoidance (over 2 years), re-introduction induced acute reactions (skin symptoms in all seven cases, digestive in five, respiratory in four, and anaphylaxis in two). An adolescent girl died from anaphylaxis to milk proteins presumably due to a loss of tolerance after an exclusion diet.\(^{27}\) Late-onset peanut allergy has been reported in adults,\(^{28}\) sometimes associated with avoidance based upon a positive IgE test to peanut. For example, a 50-year-old woman was told to avoid peanut despite a history of consuming peanut products regularly for many years.\(^{29}\) This recommendation was based on a positive skin test to peanut and a peanut-specific IgE level of 0.69 kUA/L. Peanuts were strictly avoided for 3 years before she underwent a food challenge, during which she experienced lower respiratory tract symptoms. Similarly, recurrence of peanut allergy is estimated to be as high as 8% but disproportionately affecting patients who continue to avoid peanut even after resolution of their allergy.\(^{30,31}\)

**Therapeutic Exposure to Allergen: Oral Immunotherapy**

Oral immunotherapy (OIT), the gradual monitored administration of an allergen over months and years for the purpose of treatment, challenge the conventional wisdom of strict avoidance. Several studies have shown encouraging results using oral immunotherapy to milk,\(^{32,35}\) egg,\(^{34,36}\) and peanut\(^ {37}\) and sublingual immunotherapy to hazelnut\(^ {38}\) as treatments for food allergy.

Skredek et al.\(^ {39-1}\) enrolled 20 participants in the first randomized, double-blind, placebo-controlled study of cow's milk OIT in children. The regimen consisted of an initial escalation day (goal, 50 mg of milk protein), eight weekly dose increases (maximum 500 mg milk protein or 15 ml milk), and then maintenance for 3-4 months. The median milk threshold dose increased from 40 to 5140 mg in the treatment group, whereas there was no change within the placebo group. Reactions were common but mild; nearly 90% required no treatment. Milk-specific IgG (but not IgE) levels increased significantly with treatment.

Results of the subsequent open-label phase of the study have also been published.\(^ {40}\) Over the follow-up period, milk-specific IgE decreased, whereas IgG4 increased, and skin test reactivity resolved in most. Adverse reactions were common and largely unpredictable, with several systemic reactions occurring at previously tolerated doses, often in the setting of exercise or viral illness. However, the overall rate of reactions decreased over time, even as milk doses increased. In one participant, apparent clinical reactivity to milk recurred, primarily with gastrointestinal symptoms, suggesting eosinophilic gastrointestinal disease.

The safety of peanut OIT was also explored in a study at Duke\(^ {41}\) enrolling 28 children with peanut allergy, but without a history of anaphylaxis or severe or poorly controlled asthma. The protocol included an: initial escalation day (up to 60 mg), build-up phase (maximum 300 mg, equivalent to less than 1/4 tsp of peanut butter), and home dosing/maintenance phase. Reactions were most frequent during the initial escalation day with 26 children (93%) experiencing some symptoms; four received epinephrine. Doses were better tolerated during build-up (46% risk of reaction) and reactions were generally mild, none requiring epinephrine. Finally, home doses were associated with an estimated 3.5% risk of reaction; two children received epinephrine after one home dose each, one of which was associated with pneumonia. Children with asthma (affecting 68% of this study population) were particularly at risk of developing chest symptoms during OIT.

Evaluation of immunologic changes throughout peanut OIT\(^ {42-44}\) suggests that desensitization develops by 6 months and is followed by down-regulation of the TH2 response to peanut. Over 6-12 months, secretion of IL-10 as well as inflammatory cytokines (IL-5, IFN-γ, and TNF-α) from PBMCs increased. Peanut-specific FoxP3 T cells increased until 12 months and then decreased thereafter. By 12-18 months, peanut-specific IgE decreased, whereas IgG4 increased. In addition, T-cell microarrays showed down-regulation of genes in apoptotic pathways, suggesting a novel mechanism of OIT.

Oral immunotherapy can be effective in desensitizing at least a subset of children with IgE-mediated food allergy.
but it is not clear whether tolerance would be maintained without regular intake. Staden et al. \cite{35} randomly assigned 45 children with milk or egg allergy to either treatment (OIT) or strict elimination (control). Food challenges were performed after a median of 21 months. Children in the treatment group received a secondary elimination diet for 2 months prior to their follow-up challenges to assess persistence of induced oral tolerance. At the follow-up challenge, the same percentage of patients in each group (35%) was shown to have developed tolerance. This may be illustrative of OIT as a means to desensitize but not necessarily to promote tolerance.

**Additional Examples of Allowable Exposure to Allergens and Situations when Strict Avoidance is Prudent**

There are exceptions when strict avoidance is not necessarily prescribed. For example, in pollen-food allergy syndrome (oral allergy syndrome), heat, acid, and proteases eliminate the effects of the unstable allergen, allowing ingestion of heated and processed forms without symptoms, whereas raw forms elicit mild reactions. (Oral allergy syndrome is reviewed by Connie Katala in this issue.) Allergists often allow patients with pollen-food-related syndrome to ingest the food if symptoms are mild.\cite{43}

Strict avoidance is, however, necessary for most patients in whom exposure to small amounts of food proteins can elicit allergic reactions. In a recent meta-analysis,\cite{44} the lowest dose predicted to provoke reactions in 10% of the peanut-allergic population (ED10) was estimated to be 11 mg whole peanut (or approximately 1/100 of a peanut). Establishing the threshold dose in individuals outside of the research setting, however, is impractical, thereby making patient-specific recommendations unfeasible for less-than-strict levels of avoidance.\cite{45,47} There is no consensus for permitting patients who tolerate some small amounts of allergen (e.g., small amounts of peanut) to ingest up to their threshold dose because doing so is risky and the immune consequences are unknown.

Moreover, patients can react severely even to foods that some can tolerate, such as extensively heated forms of milk\cite{17-1} and egg.\cite{19-1} In fact, heated milk-reactive children had more severe symptoms during heated milk challenges (35% given epinephrine) than heated milk-tolerant children experienced during their unheated milk challenges (0% requiring epinephrine). Therefore, strict avoidance is often the most practical approach.

**Prevention**

Extended avoidance of allergens has been previously suggested for otherwise healthy infants and young children with a family history of atopy to reduce the risk of atopic disease (e.g., no milk until age 1, egg until age 2, and peanut, nuts and fish to age 3 years).\cite{14,49} However, in 2008 the American Academy of Pediatrics (AAP) published a summary report\cite{49} that stated there is 'no current convincing evidence' to support any dietary restrictions beyond 4-6 months of age, which is in accord with other professional societies.\cite{50,52} The European Society for Pediatric Gastroenterology, Hepatology and Nutrition committee\cite{51} recommended that complementary foods be introduced after 17 weeks (~4 months) but no later than 28 weeks (~6 months). These conclusions were made based upon studies showing protective effects of fish\cite{53} and possible detrimental effects of delayed introduction of wheat\cite{51,54} or other solids.\cite{55} Indeed, there exist various reports that show a lack of evidence for protection or decreased risk of atopy associated with delaying solid foods beyond 6 months.\cite{53,54} Most recently, Nwaru et al.\cite{60} suggest that late introduction of solid foods is associated with increased risk of allergic sensitization to food allergens; clinical food allergy was not used as an outcome.

Recent findings specifically raise the question of whether early introduction of peanut during infancy, rather than avoidance, will prevent the development of peanut allergy. It has been observed that Jewish children in the UK have a prevalence of peanut allergy that is 10-fold higher than that of Jewish children in Israel.\cite{59} DuToit et al.\cite{56} reported that this difference was not accounted for by differences in atopy, social class, genetic background, or peanut allergenicity. Rather, Israeli infants consume peanut in the first year of life, whereas UK infants avoid peanuts. Randomized controlled trials (such as the Learning Early About Peanut Allergy Study)\cite{61} are underway
to test whether high doses of peanut protein in high-risk infants are more effective at preventing peanut allergy than avoidance therapy.

**Conclusion**

Currently, it is not known if practicing strict avoidance speeds or hinders recovery from a food allergy or represents effective primary prevention of allergy for infants (Table 1). Studies described herein suggest that exposure may be a means of treatment or at least may improve quality of life by allowing an expanded diet. However, there are clear risks to allowing ingestion of a food which in a larger dose or a different form may induce an allergic reaction. Much more study is needed with regard to determining the safety, utility, and efficacy of these approaches. In many cases, strict avoidance is a necessity. OIT may allow an increase in the threshold dose (desensitization) for allergic reactions and a reduction of risk of severe reactions after inadvertent ingestion of the allergen. What remains to be determined is whether permanent tolerance can be successfully and safely induced by these or other treatments. Additional studies to inform the best time to introduce allergens to ‘at risk’ infants are underway.

**Table 1. Factors supporting/refuting the need to prescribe strict allergen avoidance**

<table>
<thead>
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<th>Against</th>
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<tr>
<td>Lack of evidence that accidental ingestions delay or prevent tolerance</td>
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<td>Lack of evidence that supervised ingestion resulting in an allergic reaction (e.g. a failed oral food challenge) reduces the chance of achieving tolerance</td>
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<td>Some children who react to milk or egg being able to tolerate extensively heated forms</td>
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<td>Avoidance of a food from the diet after it has previously been tolerated resulting in allergic reaction upon re-exposure</td>
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<td>Oral immunotherapy shown to be effective in desensitizing at least a subset of children with IgE-mediated food allergy</td>
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<td>Allergists often allowing patients with pollen-food-related syndrome to ingest the food if symptoms are mild</td>
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<td>In favor of</td>
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<td>Limited evidence from observational studies that tolerance develops after a period of avoidance</td>
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<tr>
<td>Strict avoidance necessary for patients in whom exposure to small amounts of food proteins can elicit allergic reactions</td>
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<td>Difficult/impractical to give patient-specific recommendations regarding less-than-strict avoidance</td>
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<tr>
<td>Without performing challenges, cannot predict who will react severely to foods that some can tolerate, such as extensively heated forms of milk and egg</td>
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<td>To be determined</td>
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<tr>
<td>If ingestion of extensively heated foods can hasten induction of tolerance of unheated forms of these foods</td>
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<tr>
<td>Whether oral immunotherapy can induce permanent tolerance (e.g. without regular intake to maintain desensitization)</td>
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*a*See text for details of context and circumstance.

**References**
   ** Most children with milk allergy in this study were able to tolerate extensively heated milk. Immunologic changes associated with heated milk ingestion for 3 months included a small decrease in milk SPT wheal diameter and increased caseinspecific IgG4 levels.
   ** Most children with egg allergy could tolerate extensively heated forms of egg. Immunologic changes associated with heated egg ingestion for 3 months included a small decrease egg SPT wheal diameter and ovalbumin-specific IgE and increased ovalbumin and ovomucoid-specific IgG4 levels.


When compared with placebo, milk OIT was shown to induce desensitization of varying degrees in all participants.


When compared with placebo, OIT induced clinical desensitization to peanut. Associated immunologic changes after 6 months of OIT included down-regulation of genes in apoptotic pathways in T cells.

43. Ma S, Sicherer SH, Nowak-Wegrzyn A. A survey on the management of pollen-food allergy syndrome in


Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 270).

Acknowledgement
Funding disclosures: S.H.S. is a consultant for Food Allergy Initiative, New York and receives grant support from the NIH-NIAID.

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