



What is new in managing patients with food allergy? Almost everything

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Purpose of review

This review aims to describe current concepts in managing patients with food allergy. There have been many recent advances in the management of patients with IgE-mediated reactions to food, including diagnosis, prevention, management, and ongoing research in the field. Food allergy is increasing in prevalence and may be life threatening. This review aims to highlight changes in recommended practice when diagnosing and managing patients with food allergy.

Recent findings

Early introduction of highly allergenic foods, particularly peanut, has been shown to decrease the risk for development of food allergy in patients who are at elevated risk. Avoidance of foods without a clinical history of food allergy may increase the risk of subsequent allergy. Epinephrine remains the first line therapy for anaphylaxis, and patients and families need to be instructed on indications and technique for use. Promising research is ongoing in areas of immunotherapy to food allergens.

Summary

Food allergy is a potentially life-threatening condition that may persist throughout adulthood. Practitioners should be aware of changes to recommendations for the diagnosis, prevention, and management of patients with food allergy.

Keywords

anaphylaxis, epinephrine, food allergy, immunotherapy

INTRODUCTION

Recent advances regarding IgE-mediated food anaphylaxis or food allergy have changed what we know about prevention, diagnosis, and even treatment of patients with food allergy. Along with new answers, such as recommendations to introduce peanut in infancy, come many new questions, including the safety of the use of injectable epinephrine devices in infants. This review will highlight recent advances that have significantly changed the recommended management of patients with food allergy.

PREVALENCE

It is generally accepted that 8% of children in the United States suffer from food allergy, and that prevalence has been increasing over the past few decades [1]. The eight most common food allergens in the pediatric population include milk, egg, peanut, tree nuts, wheat, fish, shellfish, and soy but other food allergens such as sesame seed are becoming more common [2]. Further research into the many factors contributing to the increasing rates of food allergy is necessary.

WHEN TO INTRODUCE HIGH-RISK FOODS

One potential factor to the increased prevalence of food allergy may be delayed introduction of high-risk foods. The American Academy of Pediatrics previously recommended delayed introduction of peanut and other allergenic foods in high-risk children [3]. Subsequently in 2015, the Learning Early About Peanut (LEAP) Trial showed that delayed introduction of peanut in high-risk children was associated with an increased risk for developing peanut allergy [4]. This data suggested that food avoidance may actually increase the risk of becoming allergic to that food. A 1-year follow-up study showed that the patients in the early introduction

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KEY POINTS

- New evidence is strong that children who are at high risk for developing food allergy should have high-risk foods introduced early with the goal of preventing clinical food allergy.
- Diagnosis of food allergy should be based on clinical history of typical symptoms soon after ingestion of food, and targeted SPT or sIgE testing should be done only to foods suspected to have caused those symptoms.
- Current treatment focuses on avoidance of the food allergen, teaching patients how to recognize and respond to accidental ingestion, and helping them navigate the nutritional and psychosocial aspects of living with food allergy.
- Studies are ongoing which show the benefits and the risks of using food immunotherapy to prevent reactions and possibly induce tolerance. Further research is needed before these therapies are available on a routine basis.

arm maintained tolerance to peanut while consuming peanut ad lib [5].

A systematic review found that early introduction of egg or peanut was associated with reduced risk of allergy to the respective food [6]. Data for other foods are less conclusive. In a population at low risk for development of food allergy, the early introduction of other allergenic foods, namely milk, egg, peanut, wheat, fish, and sesame, resulted in similar rates of food allergy compared with the delayed introduction group [7¹¹]. Though food allergy was not decreased in this population, there was no increased risk of food allergy development with early introduction. Furthermore, the same study showed no effect on rates of breastfeeding in the study population. Recently published National Institute of Allergy and Infectious Diseases (NIAID) addendum guidelines recommend early introduction of peanut between the ages of 4 and 11 months in patients at increased risk for peanut allergy, defined by the presence of atopic dermatitis and/or previously diagnosed egg allergy, after appropriate skin prick tests (SPT) or serum-specific IgE to peanut (sIgE) before introduction [8¹²]. This guideline states that screening is unnecessary for children considered to be low risk.

DIAGNOSIS OF FOOD ALLERGY

Food allergy may be overdiagnosed, given the availability of SPT and in-vitro screening testing, both of which have a high rate of false positives. Positive results on sIgE tests must be evaluated in the context

of clinical history, symptoms, and risk to determine clinical relevance. For diagnosis of food allergy and monitoring for resolution of clinical reactivity, food challenges remain the gold standard.

When interpreting testing in order to make a diagnosis of food allergy, the pretest probability of clinical reaction may be affected by many factors. A review of racial effects on diagnosis of food allergy found that, when compared with non-Hispanic white patients, black patients had higher risk for food allergy to wheat, soy, corn, fish, and shellfish, and Hispanic patients had higher risk of food allergy to corn, fish, and shellfish [9]. Panjari *et al.* [10] found that children born in Australia to parents who immigrated from Asian countries were more likely to have peanut and tree nut allergies compared with children born in their country of lineage. Finally, the LEAP study showed that non-Hispanic black patients had more positive sIgE to peanut than SPT, suggesting that screening black children for food allergies with sIgE testing may lead to more false positives [4].

Given the impact of a food allergy diagnosis on a patient and family, testing in evaluation of possible food allergens should be carefully selected. Stukus *et al.* [11] reviewed food allergy in-vitro testing at a tertiary care children's hospital. They found that when primary care physicians ordered sIgE tests for foods, extensive panels were used 45% of the time, compared with allergist evaluation whereas a general panel was used just 1.2% of the time. Many of the panels contained foods that are unlikely causes of food allergy, such as strawberry, corn, chocolate and rice, and the investigators also found a 48% increase in the cost when food panels were ordered.

SPECIAL CONSIDERATIONS

Atopic dermatitis

Children with eczema present a dilemma when making a diagnosis of food allergy.

While children with eczema are at a higher risk for developing food allergy compared with the general population, their frequently elevated total serum IgE leads to more false-positive sIgE and SPT to foods. Recent evidence shows that the common practice of testing for and avoiding foods as a way to improve eczema may come with drawbacks. In a longitudinal study monitoring for the safety of pimecrolimus in infants and children with mild-to-moderate eczema, sensitization to foods and development of clinical allergy were monitored [12]. The investigators found that sIgE to foods, even at very high levels, were not useful as a screening test to

determine which children with eczema were food allergic.

More recent evidence suggests that avoidance of food as an adjunct to other eczema treatments may come with the risk of promoting the development of anaphylaxis to the avoided food. Chang *et al.* [13[¶]] performed a retrospective review of 298 patients at an academic center who avoided previously tolerated foods in an effort to treat eczema. They found that when the foods were reintroduced, 19% of children had symptoms of acute IgE reactions, of which 70% were isolated cutaneous reactions and 30% were classified as anaphylaxis. This data demonstrates that avoidance of tolerated food as a treatment for eczema may lead to food allergy. The authors advise that if a food is avoided to treat eczema, the patient and parents should be advised of the potential increased risk of developing food allergy. If no improvement in eczema is noted with food elimination, the food should be quickly reintroduced in an attempt to avoid development of food allergy, and if the food was avoided for a prolonged time the clinician should consider reintroducing the food in a supervised setting.

Siblings

Many families who have one child with food allergy will ask if siblings need to be evaluated for food allergy. Gupta *et al.* [14] reviewed data from 478 index patients with food allergy and their siblings and found that the rate of clinical food allergy was only slightly increased compared with the general population. Given this data, the authors recommend against screening of siblings if no other risk factors are present.

Social concerns of a food allergy diagnosis

A recent review found that food allergy has significant effects on both quality of life and finances of patients and their families. In addition, avoidance of food allergens can lead to nutritional deficits and growth restriction [15]. Many factors that may lead to increased anxiety associated with a food allergy diagnosis, including the number of food allergens, severity of past reactions, ease of avoidance, presence of bullying, and age of diagnosis. Gupta *et al.* [16] found evidence of significant financial burdens on patients and family with food allergy, including direct medical costs and the increased cost of allergen-free foods. Beck *et al.* [17] found that kids with persistent food allergy are especially at risk for reduced height and weight by 4 years old. It has also been shown that bullying of children with food allergy is prevalent, and can involve both verbal

harassment and intentional physical exposure to their allergens, which is often not perceived by teachers or parents [18]. Because of these issues, the management of children with food allergy should involve frequent evaluation of both medical and psychosocial aspects of the diagnosis with the patient and their families. In a recent review, Herbert *et al.* provide guidance on discussion and counseling regarding issues of fear of a potential reaction, interactions in social settings, and bullying [19[¶]]. The authors offer suggestions for how clinicians can help their patients with food allergy address these issues.

MANAGEMENT OF PATIENTS WITH FOOD ALLERGY

Avoidance

As with all allergies, the first treatment of food allergy is allergen avoidance. Parents should be instructed on reading labels, avoidance of cross contamination when preparing foods, and the risk of exposure when eating outside the home and at restaurants. The Food and Drug Administration (FDA) requires food manufacturers to clearly label food which contain the eight most common food allergens. Precautionary labels such as 'May Contain' or 'Manufactured in a facility...' are not regulated by the FDA and are left to the discretion of the food manufacturers. A recent peanut allergen threshold study found that half of patients with food allergy consumes foods with precautionary labels, that have been shown to contain enough food to cause reactions [20]. Because of the risk for a reaction, guidelines recommend that patients avoid foods with precautionary labels.

Treatment of reactions

After identification of food allergens and undergoing instruction on avoidance measures, all patients and caregivers should be taught how to recognize and treat food allergy reactions. Widely available food allergy action plans are useful to assist patients and families to recognize reactions and when to use epinephrine.

Epinephrine

Epinephrine causes vasoconstriction and bronchodilation, decreases upper airway mucosal edema, and prevents further release of mediators of reactions. Epinephrine auto-injectors (EAI) are the primary treatment used to manage anaphylaxis. There are four available brands of EAI, and the choice

between them often depends on availability, insurance coverage, and ease of use. Up to 19% of pediatric patients treated with epinephrine for anaphylaxis will need a second dose; therefore, two EAI should always be available [21[¶]].

Published guidelines recommend using the 0.15 mg EAI for patients weighing 7.5–15 kg. Whereas the label for EAI lists 30 kg as the weight to increase to the higher dose, expert opinion suggests switching at a weight of 25 kg [22–27].

Epinephrine auto-injectors are often used incorrectly even with provider education, and each EAI has different instructions for use. A study by Brown *et al.* [28] found that improper administration of EAI was associated with lacerations and embedded needles, especially in pediatric patients. They found that a major contributing factor to EAI-associated injuries was uncooperative children. They recommend parents immobilize the leg during administration, hold the auto-injector against the leg, and then compress. They advocate against the ‘swing and firmly push’ maneuver listed on the label.

Parish *et al.* reviewed published studies on effects of temperature excursions above or below the recommended storage temperatures of 15–30 °C (59–86 °F) and concluded that temperature excursions may be permissible, especially for colder temperatures [29]. The usual expiration dating for epinephrine auto-injectors is 18–20 months, but injectors up to 24 months past expiration have been found to contain 90% of the expected epinephrine dose [30].

Antihistamines

Antihistamines are not optimal in the management of food allergy because of slow onset of action, lack of effect on respiratory symptoms [21[¶],31] and use for anaphylaxis is not FDA approved. Overall, antihistamines may be used as an adjunctive therapy to prevent and alleviate skin reactions. One study compared cetirizine, a long-acting nonsedating antihistamine, to diphenhydramine for management of food allergy, and found the median time to resolution of urticaria and pruritus was similar with a nonsignificant trend toward less sedation in the cetirizine group (17.1 and 28.6%, $P = \text{NS}$). The authors concluded that cetirizine may be a reasonable alternative to diphenhydramine for acute food allergy reactions [32].

Steroids

Emergency Department Anaphylaxis Practice Parameters found little evidence for use of oral steroids to treat anaphylaxis [33]. The studies reviewed in the parameter demonstrated that steroids need 4–6 h to

work, indicating no role in managing acute symptoms. They also found no evidence that antihistamines or steroids are necessary after the patient leaves the emergency department.

Monitoring for resolution

Although, it is known that most children with food allergy to milk and egg will outgrow their food allergy, few outgrow allergies to peanut and tree nuts. A review looked into the clinical and laboratory predictors of outgrowing a food allergy to the most common foods including milk, egg, and peanut [34]. Common predictors of outgrowing these foods include lower size of the SPT or lower sIgE at diagnosis, and the rate of change of the SPT or sIgE. Children with food allergy should be followed at regular intervals to assess for possible resolution, as reintroduction of the food has important psychosocial and nutritional benefits. Follow-up visits allow for risk assessment and provide opportunity to reemphasize avoidance and treatment strategies. It many cases clinical reactivity to an allergen may resolve despite persistence of reactivity on skin or in vitro testing.

TREATMENT OF FOOD ALLERGY

There is currently no FDA-approved intervention for the treatment of food allergy. Current clinical research has focused on food allergen-specific immunotherapy. Immunotherapy relies on the delivery of increasing doses of allergen to induce desensitization, defined as temporary antigen hyporesponsiveness, which is reliant on regular allergen exposure. Some studies have evaluated for tolerance, also referred to as sustained unresponsiveness, that is defined as the ability to ingest the allergen without symptoms despite irregular intake [35^{¶¶}]. Current immunotherapy modalities under study use oral immunotherapy (OIT), sublingual immunotherapy (SLIT), or epicutaneous immunotherapy (EPIT) routes.

Oral immunotherapy involves ingestion of gradually increasing doses of allergen. Once maintenance dosing is reached, the patient remains on this daily dose. The majority of patients who undergo OIT achieve desensitization, with reported ranges of 35–100% [35^{¶¶}]. However, OIT has been limited by the frequency of adverse reactions, that can range from gastrointestinal upset to anaphylaxis, and can occur at any point during the treatment course. A commercial OIT product for peanut (AR101 by Aimmune Therapeutics; Brisbane, California, USA) is in phase III clinical trials. Most studies with OIT have utilized desensitization as a final endpoint but a

recent publication demonstrated that peanut OIT in preschool children was more likely to induce tolerance than in studies of older patients, and was generally regarded as well tolerated [36[■]]. Additional research has been published on OIT for egg [37], milk [38], and for multiple simultaneous foods [39].

Studies of peanut EPIT demonstrate a 10-fold increase in the tolerated dose but had no effect on tolerance [40]. A commercial EPIT product is currently in phase III clinical trials (Viaskin Peanut by DBV Technologies; Montrouge, France). Though data indicate that OIT is more efficacious in achieving tolerance than SLIT or EPIT, both of these latter therapies continue to be under investigation due to their favorable adverse event profiles.

CONCLUSION

In the past few years studies have provided radically new information about diagnosis and prevention of food allergy, though much work remains. Future directions in food allergy will likely be focused on applying new knowledge and working toward potential food allergy treatment that can allow patients to eat their food allergen safely again.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Sicherer S, Sampson H. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol* 2014; 133:291–307.
2. Patel A, Bahna SL. Hypersensitivities to sesame and other common edible seeds. *Allergy* 2016; 71:1405–1413.
3. Baker SS, Cochran WJ, Greer FR, *et al.* American Academy of Pediatrics Committee on nutrition: hypoallergenic infant formulas. *Pediatrics* 2000; 106:346–349.
4. Du Toit G, Roberts G, Sayre P, Bahnson HT. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; 372:803–813.
5. Du Toit G, Roberts G, Sayre P, Sever M, *et al.* Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016; 374:1435–1443.
6. Lerodiakonou D, Garcia-Larsen V, Logan A, Groome A, *et al.* Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease; a systematic review and meta-analysis. *J Am Med Assoc* 2016; 316:1181–1192.
7. Perkin M, Logan K, Mars T, Radulovic S, *et al.*, Enquiring about tolerance ■ (EAT) study. Feasibility of an early allergenic food introduction regimen. *J Allergy Clin Immunol* 2016; 137:1477–1486.

A study demonstrating that early introduction of allergenic food is feasible, does not cause harm, and does not decrease breastfeeding rates.

8. Togias A, Cooper S, Acebal M, Assa'ad A, *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; 139:29–44.
- NIAID expert panel guidelines that provide recommendation on the early introduction of peanut. The authors divide patients by risk for the development of peanut allergy to determine the necessity of preintroduction screening and the appropriate age to first offer peanut-containing foods.
9. Mahdavinia M, Fox SR, Smith BM, James C, *et al.* Racial differences in food allergy phenotype and healthcare utilization among US Children. *J Allergy Clin Immunol Pract* 2017; 5:352–357.
10. Panjari M, Koplin JJ, Dharmage SC, Peters RL, *et al.* Nut allergy prevalence and differences between Asian-born children and Australian-born children of Asian descent: a state-wide survey of children at primary school entry in Victoria, Australia. *Clin Exp Allergy* 2016; 46:602–609.
11. Stukus DR, Kempe E, Leber A, Thornton D, *et al.* Use of food allergy panels by pediatric care providers compared with allergists. *Pediatrics* 2016; 138:1–7.
12. Spergel JM, Boguniewicz M, Schneider L, Hanifin J, *et al.* Food allergy in infants with atopic dermatitis: limitations of food-specific IgE measurements. *Pediatrics* 2015; 136:e1530–e1538.
13. Chang A, Robison R, Cai M, Singh AM. Natural history of food-triggered ■ atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract* 2016; 4:229–236.
- Study that demonstrated that 19% of patients with food-triggered atopic dermatitis and no previous history of immediate reactions developed new immediate food reactions after initiation of an elimination diet.
14. Gupta RS, Walkner MW, Greenhawt M, Lau C, *et al.* Food allergy sensitization and presentation in siblings of food allergic children. *J Allergy Clin Immunol Pract* 2016; 4:956–962.
15. Patel N, Herbert L, Green TD. The emotional, social, and financial burden of food allergies on children and their families. *Allergy Asthma Proc* 2017; 38:88–91.
16. Gupta R, Holdford D, Bilaver L, Dyer A, *et al.* The economic impact of childhood food allergy in the United States. *J Am Med Assoc Pediatr* 2013; 167:1026–1031.
17. Beck C, Koplin J, Dharmage S, Wake M, *et al.* Persistent food allergy and food allergy coexistent with eczema is associated with reduced growth in the first 4 years of life. *J Allergy Clin Immunol Pract* 2016; 4:248–256.
18. Egan M, Sicherer S. Doctor, my child is bullied: food allergy management in schools. *Curr Opin Allergy Clin Immunol* 2016; 16:291–296.
19. Herbert L, Shemesh E, Bender B. Clinical management of psychosocial ■ concerns related to food allergy. *J Allergy Clin Immunol Pract* 2016; 4: 205–213.
- A thorough overview of common psychosocial concerns among children with food allergy and their families. This review also provides guidance to medical providers regarding the identification and treatment of food allergy-related psychosocial challenges.
20. Hourihane JO'B, Allen KJ, Shreffler WG, Dunngalvin G, *et al.* Peanut Allergen Threshold Study (PATS): novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J Allergy Clin Immunol* 2017. [Epub ahead of print]
21. Sicherer SH, Simons FE. Epinephrine for first-aid management of anaphylaxis. ■ *Pediatrics* 2017; 139:e1–e10.
- An update on the 2007 clinical report from the American Academy of Pediatrics. It provides information regarding identification of patients at risk for anaphylaxis, and includes information about epinephrine auto injectors including their appropriate use.
22. Sicherer SH, Simons FE. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics* 2007; 119:638–646.
23. EpiPen and EpiPen Jr [package insert], Morgantown, WV; Mylan Specialty, L.P.; May 2016.
24. Epinephrine injection, USP auto-injector [package insert], Morgantown, WV; Mylan Specialty, L.P.; February 2017.
25. Adrenaclick [package insert], Horsham, PA; Amedra Pharmaceuticals, LLC; April 2013.
26. Epinephrine injection, USP auto-injector [package insert], Washington, PA; Lineage Therapeutics, Inc.; May 2016.
27. Auvi-Q [package insert], Richmond, VA; Kaleo, Inc.; May 2016.
28. Brown JC, Tuuri RE, Akhter S, Guerra L, *et al.* Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann Emerg Med* 2016; 67:307–315.
29. Parish HG, Bowser CS, Morton JR, Brown JC. A systematic review of epinephrine degradation with exposure to excessive heat or cold. *Ann Allergy Asthma Immunol* 2016; 117:79–87.
30. Rachid O, Simons ER, Wein MB, Rawas-Qalaji M, *et al.* Epinephrine doses contained in outdated epinephrine auto-injectors collected in a Florida allergy practice. *Ann Allergy Asthma Immunol* 2015; 114:354–356.
31. Simons FE. Advances in H1-antihistamines. *N Engl J Med* 2004; 351: 2203–2217.
32. Park JH, Godbold JH, Chung D, Sampson H, *et al.* Comparison of cetirizine and diphenhydramine in the treatment of acute food-induced allergic reactions. *J Allergy Clin Immunol* 2011; 128:1127–1128.

33. Cambell RL. Emergency Department diagnosis and treatment of anaphylaxis: a practice parameter. *Ann Allergy Asthma Immunol* 2014; 113:599–608.
34. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract* 2016; 4:196–203.
35. Gernez Y, Nowak- Węgrzyn A. Immunotherapy for food allergy: are we there yet? *J Allergy Clin Immunol Pract* 2017; 5:250–272.
A review of currently studied modes of food allergen immunotherapy.
36. Vickery BP, Berglund JP, Burk CM, Fine J, *et al.* Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017; 139:173–181.e8.
A randomized study demonstrating that oral immunotherapy with peanut in preschool children is well-tolerated and effective, with higher rates of sustained unresponsiveness compared to prior OIT studies.
37. Jones SM, Burks AW, Keet C, Vickery B, *et al.* Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016; 137:1117.e10–1127.e10.
38. Elizur A, Appel MY, Goldberg MR, Yitchie T, *et al.* Clinical and laboratory 2-year outcome of oral immunotherapy in patients with cow's milk allergy. *Allergy* 2016; 71:275–278.
39. Begin P, Winterroth LC, Dominguez T, Wilson S, *et al.* Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy Asthma Clin Immunol* 2014; 10:1–8.
40. Jones SM, Sicherer SH, Burks WA, *et al.* Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol* 2017; 139:1242–1252.