

Diagnosis and Management of Food Allergy



Roxanne Carbonell Oriel, MD, Julie Wang, MD*

KEYWORDS

- Food allergy • Diagnosis • Skin prick test • Allergen-specific serum IgE
- Oral food challenge • Disease management • Anaphylaxis • Prevention

KEY POINTS

- Accurately diagnosing food allergy is critical because significant dietary restrictions and impairment in quality of life for patients and their families can occur.
- Diagnosis requires a compelling clinical history, positive skin prick testing, positive allergen-specific serum immunoglobulin E, and/or oral food challenge.
- Management of food allergies includes allergen avoidance, recognition of signs and symptoms of allergic reactions, and readily available emergency medications to treat reactions.
- There are emerging diagnostic and treatment modalities for food allergies that are very promising.

INTRODUCTION

Food allergy is a growing public health concern given its increasing incidence in infants and children in the last few decades worldwide, particularly in industrialized countries.¹ The most common food allergens are milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish.^{2,3} Seeds, with sesame being the most common, are also increasingly identified as allergens.⁴

Definitions

An adverse food reaction is defined as any abnormal clinical response associated with ingestion of a food. This definition includes both immune-mediated (allergic) and non-immune-mediated mechanisms. Food allergy is defined as an adverse health effect that is caused by a specific immune response and occurs reproducibly on exposure

This article originally appeared in *The Pediatric Clinics of North America*, Volume 66, Issue 5, October 2019.

Disclosure: The authors have nothing to disclose.

Department of Pediatrics, Division of Allergy & Immunology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1198, New York, NY 10029, USA

* Corresponding author.

E-mail address: julie.wang@mssm.edu

Immunol Allergy Clin N Am 41 (2021) 571–585

<https://doi.org/10.1016/j.iac.2021.07.012>

0889-8561/21/© 2021 Elsevier Inc. All rights reserved.

immunology.theclinics.com

to a given food.³ Although different conditions come under the term food allergy, the unifying mechanism in the diagnosis is the failure of tolerance to an otherwise benign exposure to food. **Fig. 1** shows a classification of adverse food reactions based on mechanism.

Food allergy may be categorized in the following way:

- Immunoglobulin (Ig) E mediated: acute urticaria, oral allergy syndrome, anaphylaxis, food-dependent exercise-induced anaphylaxis
- Non-IgE mediated: atopic dermatitis, food protein-induced enterocolitis syndrome, food protein-induced allergic proctocolitis, food protein-induced enteropathy, allergic contact dermatitis, food-induced pulmonary hemosiderosis (Heiner syndrome)
- Mixed IgE mediated and non-IgE mediated: eosinophilic esophagitis or other eosinophilic gastrointestinal disease

For the purposes of this article, food allergy refers to IgE-mediated mechanisms.

Pathophysiology

IgE-mediated allergy to food entails allergen binding to specific IgE antibodies leading to cross-linking of IgE receptors on mast cells and basophils, which trigger the release of preformed mediators, including histamine, tryptase, and chymase, as well as de novo synthesis of leukotrienes, prostaglandins, and platelet-activating factor. These mediators and others are responsible for the symptoms that arise in an allergic reaction: vasodilation leading to erythema, increased permeability of the vasculature yielding swelling, nociceptive nerve activation that is responsible for itching, and smooth muscle constriction that results in bronchoconstriction and abdominal pain.

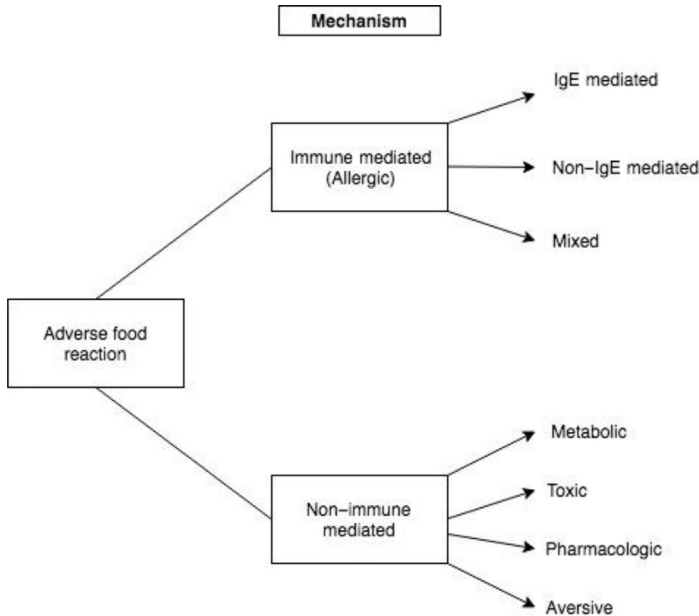


Fig. 1. Classification of adverse food reactions.

Clinical Manifestations

IgE-mediated food allergy reactions manifest with acute symptoms involving skin, respiratory tract, gastrointestinal tract, and/or the cardiovascular system, usually minutes to a few hours after ingestion of the culprit food protein. **Table 1** lists symptoms suggestive of an IgE-mediated reaction. A diagnosis of food allergy should be suspected if allergic symptoms occur shortly after ingesting a food, particularly if symptoms have reproducibly followed ingestion of the given food on more than 1 occasion. One noteworthy exception is alpha-gal allergy, which is an IgE-mediated reaction to meats following sensitization to a carbohydrate antigen from a tick bite. In this type of allergy, symptoms are usually delayed and occur 4 to 6 hours after ingestion.

Epidemiology

The prevalence of food allergy differs in various parts of the world and varies depending on the allergen in question. Prevalence estimates are difficult to ascertain because the gold standard for determining diagnosis is a double-blind, placebo-controlled oral food challenge (DBPCFC), but many epidemiologic studies estimate prevalence based on self-reported food allergy or sensitization only (ie, positive skin prick test [SPT] and/or allergen-specific serum IgE [sIgE]).

In the population-based HealthNuts study conducted in Australia, infants underwent skin prick testing and an oral food challenge if the wheal size was greater than or equal to 1 mm to raw egg, peanut, and/or sesame. More than 10% of infants showed food challenge–confirmed allergies at age 1 year to 1 or more foods.⁵ In a follow-up study with additional recruitment of subjects, the prevalence of challenge-confirmed food allergy to any food at age 4 years was 3.8%, with resolution of egg allergy largely responsible for the decrease in prevalence.⁶ In the EuroPrevall birth cohort, the prevalence of challenge-proven food allergy in the first 2 years of life was 0.59% for milk and 1.23% for egg.^{7,8} **Table 2** lists prevalence data from around the world based on challenge-proven food allergy.

In contrast with studies performed in other industrialized nations, the US food allergy prevalence data evaluated broader age ranges but relied on self-report or sensitization, which likely overestimate true prevalence. Using several surveys, including the National Health Interview Survey and the National Health and Nutrition Examination Survey, Branum and Lukacs⁹ suggest that approximately 5% of children less than 5 years of age and 4% of adolescents and adults are affected by food allergy.

Table 1
Symptoms of an immunoglobulin E-mediated allergic reaction

Cutaneous	Urticaria, angioedema, pruritus, flushing, morbilliform rash
Respiratory	Upper airway: rhinorrhea, nasal pruritus, nasal congestion, sneezing, hoarseness, stridor
	Lower airway: cough, wheeze, dyspnea, cyanosis
Cardiovascular	Increased heart rate, low blood pressure, pallor, dizziness, shock, loss of consciousness
Gastrointestinal	Swelling of lips/tongue/uvula, nausea, vomiting, abdominal cramps, diarrhea
Neurologic	Anxiety, headache, seizure, altered mental status, feeling of impending doom
Ocular	Conjunctival erythema and tearing

Table 2 Prevalence of challenge-proven food allergy				
	Peanut (%)	Egg (%)	Sesame (%)	Milk (%)
<i>HealthNuts (Australia)</i>				
Peters et al ⁶ Age 1 y	3.1	9.5	0.6	—
Peters et al ⁶ Age 4 y	1.9	1.2	0.4	—
<i>EuroPrevall (Europe)</i>				
Schoemaker et al ⁷ Up to age 2 y	—	—	—	0.59
Xepapadaki et al ⁸ Up to age 2 y	—	1.23	—	—
<i>South Africa</i>				
Botha et al ⁶⁶ 1–3 y	0.8	1.9	—	0.1
<i>China</i>				
Chen et al ⁶⁷ 0–12 mo	—	2.5	—	1.3

In a more recent study using a population-based survey completed via Web or telephone between 2015 and 2016, food allergy prevalence in children in the United States was estimated at 7.6%.¹⁰ A study conducted by the same group found that food allergy prevalence in children was 8.0% based on an electronic survey distributed between 2009 and 2010.¹¹ The investigators note that a direct comparison between the 2 studies cannot be drawn given stricter criteria used in the diagnosis of food allergy in the more recent study.

Natural History

Although many with food allergy outgrow this condition, the natural course of the disease differs depending on the allergen, with most outgrowing milk, egg, wheat, and/or soy allergies and those with peanut, tree nut, fish, and/or shellfish allergies tending to have lifelong allergy.¹² Predictors of persistent food allergy include more severe initial reaction characteristics, presence of other food allergy or other allergic conditions (atopic dermatitis, asthma, or allergic rhinitis), increased severity of comorbid conditions, earlier age at diagnosis, lower eliciting dose for reaction, larger SPT wheal size, and higher allergen-specific sIgE level.^{13–17} The rate of decline in SPT wheal size and sIgE level over time is informative in assessing food allergy resolution.

DIAGNOSIS

Given the potential social and nutritional impact of food avoidances, correctly diagnosing patients with food allergy is paramount. Establishing a diagnosis of food allergy involves a careful clinical history, evidence of allergen-specific IgE by skin and/or blood testing, and in some cases an oral food challenge. Although new diagnostic tools are being developed, such as the basophil activation test, these approaches will require validation and standardization before they become available for use in routine clinical practice.

Clinical History

The most important tool in establishing a diagnosis of IgE-mediated food allergy is an accurate allergy-focused clinical history. However, history alone is not enough to establish a definitive diagnosis of food allergy and this can only be confirmed by a positive DBPCFC in approximately 30% to 40% of individuals.^{3,18,19} Specific inquiry should be undertaken for foods ingested with specific characteristics (raw vs heated), amount of food ingested, time course between ingestion and symptom onset, manifested symptoms, outcomes of prior exposure to the food, and possible potentiating factors (ie, alcohol, exercise). Whether the patient has had the food following initial reaction with recurrence of symptoms should also be noted. If subsequent exposure has occurred without symptoms, then an alternative culprit food or diagnosis should be sought. Other questions for the patient and caregiver include the treatment following reaction and the length of time that has elapsed since ingestion with or without allergic reaction. Careful history taking allows the health care provider to discern whether the clinical picture is concerning for an IgE-mediated reaction.

Comorbid atopic conditions should also be noted, including atopic dermatitis, asthma, allergic rhinitis, and eosinophilic gastrointestinal disease. Children with atopic dermatitis are at greatest risk for food allergy.^{20,21} Particular attention should be given to the presence or absence of atopic dermatitis, with age of onset and severity noted, because more than 50% of infants developing severe eczema in the first few months of life develop IgE-mediated allergy to foods.²²

Skin Prick Test

SPTs with commercially available extracts provide an immediate method to screen patients for the presence of food-specific IgE antibodies bound to mast cells in the skin. The technique is a simple, inexpensive, and reproducible *in vivo* test that involves a drop of allergen to the volar surface of the arm followed by a small skin prick using a skin prick testing device (multiple types are commercially available). After 10 to 15 minutes, the wheal site is measured. Important considerations when evaluating skin test results include that commercial extracts and methods of performing and recording SPT results lack standardization. Furthermore, variations between devices have been shown, with increased histamine concentrations required for less sensitive devices and mean wheal diameters differing depending on device used.²³

A wheal of 3 mm or greater than the negative control is considered positive. Although SPT has a poor positive predictive value, it has a high negative predictive value. Therefore, SPT is useful for ruling out food allergy.¹⁹ The size of the SPT wheal correlates with the likelihood of food allergy, with larger sizes indicating a higher risk of clinical allergy.^{17,24} Specifically, with cow's milk, hen's egg, or peanut, wheal diameters greater than 8 mm were greater than 95% predictive of clinical reactivity to the specific food.²⁵ Multiple studies have shown that there is no reliable correlation between wheal size and severity of reaction.²⁰

Positive SPT represents food sensitization, so a positive test in the absence of a clinical history suggestive of allergy is not diagnostic, thus testing should be pursued in the context of high clinical suspicion for allergy.

If the clinical history is suggestive of a food allergy, but the diagnostic testing is negative, then oral food challenge may need to be performed to definitively diagnose or eliminate the diagnosis. False-negative skin test results can occur in cases in which the allergen is not present in sufficient quantities in the commercial extract. In these cases, skin-prick testing with fresh foods may be helpful, in particular with fruits and vegetables because the extract manufacturing process can denature the relevant

allergens. This technique is not standardized and irritant reactions to the fresh food may occur.²⁶

Allergen-specific Serum Immunoglobulin E Test

slgE testing is an in vitro immunoassay in which allergen is covalently coupled to a solid phase and binds with the specific IgE in the patient's serum sample. Results are typically reported in allergen-specific kilounits (kU_A) per liter. Like SPT, a positive test indicates sensitization to a food, but in itself is not diagnostic of clinical allergy. In addition, slgE may be undetectable to a food that triggers clinical allergy, so a compelling history and a negative slgE warrants further evaluation. In cases such as these, additional evaluation with SPT and/or oral food challenge can be informative.

Similar to SPT, increasing concentration of food-specific IgE correlates with an increased risk of clinical allergy, but the level of slgE does not accurately predict the severity of allergic reactions that can be triggered by the allergen.³ Clinical decision points have been published for some major food allergens and these can be found in **Table 3**. Considerations when applying these positive predictive values to clinical practice include age, population studied, comorbid conditions, and clinical history.^{27–32}

Periodic testing with SPT and/or slgE should be performed to reevaluate food allergy status because some individuals have transient allergy.

Component-resolved Diagnostics

Component-resolved diagnostics (CRD) refers to slgE testing that is directed toward specific food antigens or epitopes. Testing for specific epitopes can increase specificity by distinguishing clinically relevant IgE from IgE directed at nonallergic components. This approach is in contrast with conventional testing, which measures IgE to whole food extracts that contain multiple proteins. An example of the potential benefit of CRD is in patients with birch pollen allergy who may have detectable IgE to whole peanut extract because of cross-reactivity (Bet v 1 of birch pollen is homologous with Ara h 8 of peanut). Monosensitization to Ara h 8 predicts tolerance to peanut.³³ Ara h 2 and Ara h 6, other peanut allergens, not only have the highest diagnostic accuracy for peanut allergy but also can help approximate the severity of allergy. In a prospective study in peanut-allergic patients aged 6 to 18 years, sensitization to the most potent peanut allergens Ara h 2 or Ara h 6 was 100% sensitive for moderate or severe peanut allergy, with Ara h 6 the best marker for moderate or severe allergy.³⁴ Furthermore, polysensitization to Ara h 1, Ara h 2, and Ara h 3 was 100% specific for moderate or severe peanut allergy.³⁴ CRD for several major food allergens are commercially available (**Table 4**); however, questions remain regarding clinically relevant cutoff values and cost-effectiveness of additional diagnostic testing.³⁵

Oral Food Challenge

This procedure is the most definitive means to diagnose a food allergy. Oral food challenges entail supervised ingestion of increasing amounts of the suspected food allergen over a defined period of time with subsequent monitoring in an office or hospital setting with personnel equipped to treat an allergic reaction. The gold standard for diagnosis is a DBPCFC. Because this is a time-consuming and resource-intensive procedure, open food challenge or a single-blind challenge may be considered instead. When no symptoms occur during challenge, it is referred to as a negative challenge and recommendations to incorporate the food into the diet are advised. When objective or persistent subjective symptoms are observed, this is referred to as a positive challenge and confirms a diagnosis of allergy.

Table 3
Predictive values for food allergen-specific immunoglobulin E (kU_A/L) and skin prick test wheal size (millimeters)

	Milk	Egg	Soy	Wheat	Peanut	Tree Nuts	Fish
Likely Reactive if $\geq$	15 (95%) ≤ 2 y: 5 (95%) SPT: ≥ 8 (95%) ²⁰	7 (98%) ≤ 2 y: 2 (95%) SPT: ≥ 7 (95%) ²⁰	65	80	14 (100%) 1 y: 34 (95%) 4 y: 2.1 SPT: ≥ 8 (95%) ^{20,65}	15 (95%)	20 (100%)
Possibly Reactive	—	SPT ≤ 3 (50%) ²⁰	30 (73%)	26 (74%)	SPT ≤ 3 (50%) ²⁰	—	—
Unlikely Reactive if $<$	0.35	0.35	0.35	0.35	0.35	0.35	0.35

Positive predictive values are indicated in parentheses.

Adapted from Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. JACI 2001;107:891-6. Other references are noted in the table or text.

Table 4 Major food allergens and their component proteins		
Food	Component Protein	Clinical Relevance
Cow's milk	Bos d8 (casein)	Increased levels of casein indicate increased likelihood of reactivity to extensively heated milk
Egg	Gal d1 (ovomucoid)	Increased levels of ovomucoid indicate increased likelihood of reactivity to extensively heated egg
Peanut	Ara h1	Associated with systemic reactivity
	Ara h2	Associated with systemic reactivity
	Ara h3	Associated with systemic reactivity
	Ara h6	Associated with systemic reactivity
	Ara h8	Cross-reactive with Bet v1 (birch pollen). In absence of other component proteins or if predominant component, usually indicates clinical tolerance or predictive of only mild oral allergy symptoms
	Ara h9	Associated with systemic reactivity (Mediterranean populations)
Hazelnut	Cor a1	Cross-reactive with Bet v1 (birch pollen). In absence of other component proteins or if predominant component, usually indicates clinical tolerance or predictive of only mild oral allergy symptoms
	Cor a8	Associated with systemic reactivity (Mediterranean populations)
	Cor a9	Associated with systemic reactivity
	Cor a14	Associated with systemic reactivity
Cashew	Ana o3	Associated with systemic reactivity
Walnut	Jug r1	Associated with systemic reactivity

Different protocols for performing oral food challenges are available and may vary based on age of the patient, food (raw, cooked, or baked), dosing amounts, and time intervals between doses.^{36,37}

Testing that Has No Proven Utility

A multitude of tests are available and purported to aid in diagnosis of food allergy. However, the following tests have no proven benefit: IgG testing, applied kinesiology, hair analysis, electrodermal test, facial thermography, gastric juice analysis, endoscopic allergen provocation.³⁸

Future of Diagnostics

The basophil histamine release/activation test (BAT) has the potential to discriminate patients with clinical reactivity versus sensitization to foods by mimicking what occurs in vivo. As mentioned, a food allergic reaction occurs when an ingested food antigen interacts with IgE and its high-affinity Fc receptor (FcεRI) on the surface membrane of mast cells in mucosal tissues and on circulating basophils. Subsequent FcεRI cross-linking leads to release of histamine and other preformed mediators. The BAT measures markers of basophil activation, cluster of differentiation (CD) 63 and CD203c expression, by flow cytometry following allergen stimulation of a patient's basophils in vitro. This testing might be useful in the future as an intermediate step before proceeding with an oral food challenge if the SPT and sIgE are equivocal.^{39,40}

The mast cell activation test is another promising diagnostic tool currently used in research. A patient's allergen-specific IgE antibodies are used to elicit mast cell

degranulation. This test may also prove useful as an intermediate step to differentiate allergy versus sensitization. Recent studies have shown increased specificity when using this test to diagnose peanut allergy.^{41,42}

MANAGEMENT

The current management recommendations for individuals with food allergy remain strict avoidance of the allergen and preparation to manage allergic reactions in case of accidental exposures. Successful food allergen avoidance entails reading ingredient labels and knowledge of cross-contact/cross-contamination issues. However, allergen avoidance is not always infallible and allergic reactions can occur that are unpredictable, ranging from mild to severe. Therefore, patients are prescribed epinephrine autoinjectors to have emergency medication available at all times.

Age and developmentally appropriate management guidance should be provided to families. Management of infants and young children with food allergy is particularly difficult because they are unable to recognize or verbalize allergy symptoms. In addition, infants and young children explore the world using their mouths. As such, they frequently place objects such as toys and hands in their mouths, which can lead to allergen exposure outside of mealtimes. Adolescents are at particularly high risk for allergic reactions because of nonadherence to recommended strategies for avoidance and riskier behaviors, including intentional exposures and not having an epinephrine autoinjector readily available.^{43–45}

Allergen Labeling

Several countries have enacted legislation mandating allergen labeling on packaged goods for the most common food allergens to improve safety for food allergy consumers.⁴⁶ In 2004, the US Congress passed the Food Allergen Labeling and Consumer Protection Act, which required listing milk, egg, soy, wheat, peanut, tree nuts, fish, and crustacean shellfish on packaged goods. This legislative action also required that the allergen be listed in unambiguous terms (ie, label must include milk in addition to casein, whey). Similar legislation passed in Europe in 2014 and required the following allergens to be listed: milk, egg, gluten, lupine, soy, peanut, tree nuts, sesame seed, mustard seed, fish, crustacean and mollusk shellfish, celery and celeriac, and sulfur dioxide and sulfites. Several other countries have allergen labeling legislation as well, with variations in terms of which allergens are covered (<https://farrp.unl.edu/IRChart>).

Precautionary advisory labeling (PAL) uses phrases that include “may contain [allergen],” “processed in a facility that manufactures [allergen],” or “manufactured on shared equipment with [allergen]” and appears on 17% of manufactured products in the United States and on 65% of products in Australia.^{47,48} Patients should be educated that PAL is unregulated and not mandated by law, but is pervasive on packaged goods. PAL often leads to consumer confusion because these labels do not reliably correspond with the presence or absence of detectable allergenic proteins.⁴⁹

Anaphylaxis

Management of anaphylaxis entails prompt recognition and management. Studies have shown that early use of epinephrine leads to improved anaphylaxis outcomes (both morbidity and mortality).^{50,51} When counseling patients, it is key to discuss that reaction severity and the threshold dose of allergen to trigger allergic reactions is unpredictable and although cutaneous manifestations such as urticaria and pruritus are common, these symptoms may be absent in up to 20% of patients who have

anaphylaxis.⁵² Patients should be provided prescriptions for epinephrine autoinjectors and trained on how the devices should be used. In addition, written allergy and anaphylaxis emergency plans that outline signs and symptoms of allergic reactions and indications for use of emergency medications should be provided (www.aap.org/anaphylaxis) and updated at least annually or whenever medical changes occur.⁵³

PREVENTION

Given the increasing prevalence of food allergy in infants and children, strategies for prevention have been explored. In the Learning Early About Peanut (LEAP) trial, investigators found that, among infants at high risk for allergy, sustained consumption of peanut resulted in an 81% lower rate of peanut allergy.⁵⁴ In the follow-up Persistence of Oral Tolerance to Peanut (LEAP-On) study, peanut tolerance caused by early peanut consumption was maintained despite peanut avoidance for 12 months.⁵⁵ These landmark studies led a transformational shift to now encouraging and supporting early peanut introduction into the diets of high-risk infants. The National Institute of Allergy and Infectious Diseases–sponsored expert panel published guidelines on recommendations for patients with severe eczema, egg allergy, or both.⁵⁶ Patients with peanut IgE level less than 0.35 kU_A/L and/or peanut SPT of 0 to 2 mm should either introduce peanut at home or have a supervised feeding in office. Peanut IgE level greater than or equal to 0.35 kU_A/L should have further evaluation by an allergist. For patients with peanut SPT of 3 to 7 mm, a supervised feeding in office or graded oral food challenge should be offered. In addition, for patients with SPT greater than or equal to 8 mm, current recommendations are to strictly avoid peanut because of likely peanut allergy. For lower risk infants, those with mild to moderate eczema, peanut-containing foods should be introduced around 6 months of age. For infants without eczema or any food allergy, the current recommendation is to introduce peanut-containing foods when age appropriate and in line with family preferences. In a meta-analysis evaluating the effect of early introduction of egg between the ages of 4 and 6 months, introduction to the diet was associated with lower risk of egg allergy.⁵⁷ Other ongoing studies are examining the potential benefits of early introduction of other highly allergenic foods.

Other approaches are being investigated for prevention. Atopic dermatitis is frequently found as a comorbid condition in children with food allergy and there is evidence to support that food allergen exposure through the impaired skin barrier rather than through oral exposure leads to a failure of tolerance in the gastrointestinal tract.⁵⁸ In an ongoing clinical trial in the United Kingdom (Barrier Enhancement for Eczema Prevention [BEEP] study), investigators are assessing the effect of daily application of emollients in the first year of life and risk of development of atopic dermatitis.⁵⁹ In another study currently enrolling patients, conducted by the Immune Tolerance Network and sponsored by the National Institute of Allergy and Infectious Diseases, investigators are seeking to assess the early influence of vaginal microbiome exposure in cesarean section infants and risk of allergen sensitization at 1 year of age ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT03567707).

TREATMENTS FOR FOOD ALLERGY

Several treatment approaches are currently being explored for food allergies, with recent clinical trials focusing on oral, epicutaneous, and sublingual immunotherapies. Clinical trials have focused on desensitization, which refers to increasing the threshold dose of allergen to trigger allergic reactions while on therapy. Few studies have

assessed for sustained unresponsiveness, which is defined as a lack of responsiveness to a food after immunotherapy has been discontinued.

Oral immunotherapy (OIT) entails incremental ingestion of increasing doses of allergen, with the aim of desensitization to protect allergic individuals from accidental allergen exposure. This daily treatment approach has been most extensively studied for peanut. The largest study to date show that 67.2% of children and adolescents aged 4 to 17 years who are highly allergic to peanut (ie, dose-limiting symptoms of 100 mg or less of peanut protein) who received an investigational oral immunotherapy drug were able to ingest 600 mg of protein or more when maintained on 300 mg of peanut protein for 6 months.⁶⁰ Side effects of OIT include allergic reactions, ranging from mild to severe, as well as persistent gastrointestinal symptoms, which have raised concerns for eosinophilic esophagitis. Areas requiring further investigation include whether sustained unresponsiveness is possible, long-term outcomes of OIT, and biomarkers to identify patients who would benefit from OIT. Ongoing studies are examining OIT for other allergens as well as a combination of allergens.

Epicutaneous immunotherapy (EPIT) has been studied for peanut and milk allergy. EPIT involves exposure of the cutaneous immune system to the allergen, with the goal of offering protection against accidental allergen exposures. Based on outcomes reported to date, there seems to be minimal risk to patients with this approach; only mild skin irritation at the patch site has been noted in most subjects in clinical trials. In a recently completed phase 3 trial in children 4 to 11 years of age evaluating the efficacy of a 250- μ g transdermal peanut patch, 35.6% in the active group versus 13.6% in the placebo group were responders ($P<.0001$).⁶¹ Responders were defined as tolerating greater than or equal to 300 mg of the eliciting dose (ED) with baseline ED less than or equal to 10 mg, or an ED greater than or equal to 1000 mg.

Sublingual immunotherapy (SLIT) requires administration of food allergen extract under the tongue, with doses ranging from 2 to 7 mg of protein. With this approach, desensitization can be achieved after 1 year of treatment.^{62,63} However, note that these were small clinical trials evaluating the efficacy of SLIT. This approach has a favorable safety profile, with side effects primarily limited to oropharyngeal itching and tingling.

A robust pipeline of other food allergy therapies are undergoing study, including use of biologics, vaccines using modified proteins or DNA, probiotics, Chinese herbal formulas, and combination therapies.^{64,65}

SUMMARY

IgE-mediated food allergy is a global health problem affecting multiple facets of these patients' lives. Therefore, correctly diagnosing these patients is paramount. The diagnostic approach includes a detailed clinical history, SPT, sIgE, and/or oral food challenge, and management involves strict avoidance of foods as well as preparedness to treat allergic reactions. The field of food allergy is rapidly advancing because many emerging diagnostic tools and potential treatments are on their way to clinical practice. Research is also ongoing to develop preventive strategies for food allergy.

REFERENCES

1. Renz H, Allen KJ, Sicherer SH, et al. Food allergy. *Nat Rev Dis Primers* 2018;4:17098.
2. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol* 2018;141(1):41–58.

3. Boyce J, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;125(6Suppl):S1–58.
4. Patel A, Bahna SL. Hypersensitivities to sesame and other common edible seeds. *Allergy* 2016;71(10):1405–13.
5. Osborne NJ, Koplin JJ, Martin PE, et al, HealthNuts Investigators. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011; 127(3):668–76.
6. Peters RL, Koplin JJ, Gurrin LC, et al, HealthNuts Study. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017;140(1): 145–53.
7. Schoemaker AA, Sprickelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children -EuroPrevall birth cohort. *Allergy* 2015;70:963–72.
8. Xepapadaki P, Fiocchi A, Grabenhenrich L, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life - the EuroPrevall birth cohort study. *Allergy* 2016;71:350–7.
9. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124(6):1549–55.
10. Gupta RS, Warren CM, Smith BM, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics* 2018;142(6): e20181235.
11. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128(1): e9–17.
12. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract* 2016;4:196–203.
13. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 2014;133(2):492–9.
14. Spergel JM, Beausoleil JL, Pawlowski NA. Resolution of childhood peanut allergy. *Ann Allergy Asthma Immunol* 2000;85(6 Pt 1):473–6.
15. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, et al. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;110(2):304–9.
16. Elizur A, Rajuan N, Goldberg MR, et al. Natural course and risk factors for persistence of IgE-mediated cow's milk allergy. *J Pediatr* 2012;161(3):482–7.
17. Savage JH, Matsui EC, Skripak JM, et al. The natural history of egg allergy. *J Allergy Clin Immunol* 2007;120(6):1413–7.
18. Sampson HA, Aceves S, Bock SA, et al. Food allergy. A practice parameter update – 2014. *J Allergy Clin Immunol* 2014;134:1016–25.e43.
19. Sampson HA. Food allergy – accurately identifying clinical reactivity. *Allergy* 2005;60(Suppl. 79):19–24.
20. Genuneit J, Seibold AM, Apfelbacher CJ, et al. Overview of systematic reviews in allergy epidemiology. *Allergy* 2017;72:849–56.
21. Du Toit G, Tsakok T, Lack S, et al. Prevention of food allergy. *J Allergy Clin Immunol* 2016;137:998–1010.
22. Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015; 45:255–64.

23. Tversky JR, Chelladurai Y, McGready J, et al. Performance and pain tolerability of current diagnostic allergy skin prick test devices. *J Allergy Clin Immunol Pract* 2015;3(6):888–93.
24. Peters RL, Gurrin LC, Allen KJ, et al. The predictive value of skin prick testing for challenge-proven food allergy: a systematic review. *Pediatr Allergy Immunol* 2012;23(4):347–52.
25. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30(11):1540–6.
26. Nowak-Wegrzyn A, Burks W, Sampson HA. Chapter 81: reactions to foods. In: Middleton E, Franklin Adkinson N, Busse WW, et al, editors. *Middleton's allergy: principles and practice*, vol. 2, 8th edition. Philadelphia: W B Saunders; 2014. p. 1237–59.
27. Komata T, Soderstrom L, Borres MP, et al. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol* 2007;119(5):1272–4.
28. Maloney JM, Rudengren M, Ahlstedt S, et al. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol* 2008;122:145–51.
29. Perry TT, Matsui EC, Kay Conover-Walker M, et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004;114:144–9.
30. Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy* 2003;33:1041–5.
31. Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, et al. Specific IgE levels in the diagnosis of immediate hypersensitivity to cow's milk protein in the infant. *J Allergy Clin Immunol* 2001;107:185–90.
32. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891–6.
33. Asaranoj A, Nilsson C, Lidholm J, et al. Peanut component Ara h 8 sensitization and tolerance to peanut. *J Allergy Clin Immunol* 2012;130:468–72.
34. Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, et al. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. *Allergy* 2015;70:1239–45.
35. Kim JF, McCleary N, Nwaru BI, et al. Diagnostic accuracy, risk assessment, and cost-effectiveness of component-resolved diagnostics for food allergy: a systematic review. *Allergy* 2018;73(8):1609–21.
36. Bird JA, Groetch M, Allen KJ, et al. Conducting an oral food challenge to peanut in an infant. *J Allergy Clin Immunol Pract* 2017;5(2):301–11.e1.
37. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work group report: oral food challenge testing. adverse reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2009;123(6 Suppl):S365–83.
38. Kelso JM. Unproven diagnostic tests for adverse reactions to foods. *J Allergy Clin Immunol Pract* 2018;6(2):362–5.
39. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015;70(11):1393–405.
40. Koplin JJ, Perrett KP, Sampson HA. Diagnosing peanut allergy with fewer oral food challenges. *J Allergy Clin Immunol Pract* 2019;7(2):375–80.

41. Santos AF, Couto-Francisco N, Bécares N, et al. A novel human mast cell activation test for peanut allergy. *J Allergy Clin Immunol* 2018;142(2):689–91.e9.
42. Bahri R, Custovic A, Korosec P, et al. Mast cell activation test in the diagnosis of allergic disease and anaphylaxis. *J Allergy Clin Immunol* 2018;142(2):485–96.e16.
43. Smith TD, Camacho J, Wang J. Behavioral risks associated with food allergy management in an urban pediatric population. *J Allergy Clin Immunol* 2018;6:680–2.
44. Robinson M, Koplin JJ, Field MJ, et al. Patterns of carriage of prescribed adrenaline autoinjectors in 10- to 14-year-old food-allergic students: a population-based study. *J Allergy Clin Immunol Pract* 2018;7(2):437–43.
45. Macadam C, Barnett J, Roberts G, et al. What factors affect the carriage of epinephrine auto-injectors by teenagers? *Clin Transl Allergy* 2012;2:3.
46. Taylor SL, Hefle SL. Food allergen labeling in the USA and Europe. *Curr Opin Allergy Clin Immunol* 2006;6:186–90.
47. Pieretti MM, Chung D, Pacenza R, et al. Audit of manufactured products: use of allergen advisory labels and identification of labeling ambiguities. *J Allergy Clin Immunol* 2009;124:337–41.
48. Zurzolo GA, Mathai ML, Koplin JJ, et al. Precautionary allergen labeling following new labeling practice in Australia. *J Paediatr Child Health* 2013;49:E306–10.
49. Ford LS, Taylor SL, Pacenza R, et al. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J Allergy Clin Immunol* 2010;126:384–5.
50. Fleming JT, Clark S, Camargo CA Jr, et al. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *J Allergy Clin Immunol Pract* 2015;3(1):57–62.
51. Hochstadter E, Clarke A, De Schryver S, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol Pract* 2016;137(6):1888–90.e4.
52. Arkwright PD, MacMahon J, Koplin J, et al. Severity and threshold of peanut reactivity during hospital-based open oral food challenges: an international multicenter survey. *Pediatr Allergy Immunol* 2018;29(7):754–61.
53. Wang J, Sicherer SH, American Academy of Pediatrics, Section on Allergy and Immunology. Guidance on completing a written allergy and anaphylaxis emergency plan. *Pediatrics* 2017;139(3):e20164005.
54. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372(9):803–13.
55. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016;374:1435–43.
56. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol* 2017;139(1):29–44.
57. Ierodiakonou D, Garcia-Larsen V, Logan 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. *JAMA* 2016;316:1181–92.
58. Brough HA, Liu AH, Sicherer S, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol* 2015;135:164–70.

59. Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomized controlled trial. *Trials* 2017;18:343.
60. Vickery BP, Vereda A, Casale TB, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med* 2018;379(21):1991–2001.
61. Fleischer DM, Sussman GL, Begin P, et al. Effect of epicutaneous immunotherapy on inducing peanut desensitization in peanut-allergic children: topline peanut epicutaneous immunotherapy efficacy and safety (PEPITES) randomized clinical trial results. *J Allergy Clin Immunol* 2018;141(2):AB410.
62. Kim EH, Bird JA, Kulis M, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011;127(3):640–6.e1.
63. Fleischer DM, Burks AW, Vickery BP, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. *J Allergy Clin Immunol* 2013;131(1):119–27.e1-7.
64. Virkud YV, Wang J, Shreffler WG. Enhancing the safety and efficacy of food allergy immunotherapy: a review of adjunctive therapies. *Clin Rev Allergy Immunol* 2018;55(2):172–89.
65. Cook QS, Burks AW. Peptide and recombinant allergen vaccines for food allergy. *Clin Rev Allergy Immunol* 2018;55(2):162–71.
66. Botha M, Basera W, Facey-Thomas HE, et al. Rural and urban food allergy prevalence from the South African Food Allergy (SAFFA) study. *J Allergy Clin Immunol* 2019;143(2):662–8.e2.
67. Chen J, Hu Y, Allen KJ, et al. The prevalence of food allergy in infants in Chongqing, China. *Pediatr Allergy Immunol* 2011;22(4):356–60.