Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management

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This review provides general information to serve as a primer for those embarking on understanding food allergy and also details advances and updates in epidemiology, pathogenesis, diagnosis, and treatment that have occurred over the 4 years since our last comprehensive review. Although firm prevalence data are lacking, there is a strong impression that food allergy has increased, and rates as high as approximately 10% have been documented. Genetic, epigenetic, and environmental risk factors are being elucidated increasingly, creating potential for improved prevention and treatment strategies targeted to those at risk. Insights on pathophysiology reveal a complex interplay of the epithelial barrier, mucosal and systemic immune response, route of exposure, and microbiome among other influences resulting in allergy or tolerance. The diagnosis of food allergy is largely reliant on medical history, tests for sensitization, and oral food challenges, but emerging use of component-resolved diagnostics is improving diagnostic accuracy. Additional novel diagnostics, such as basophil activation tests, determination of epitope binding, DNA methylation signatures, and bioinformatics approaches, will further change the landscape. A number of prevention strategies are under investigation, but early introduction of peanut has been advised as a public health measure based on existing data. Management remains largely based on allergen avoidance, but a panoply of promising treatment strategies are in phase 2 and 3 studies, providing immense hope that better treatment will be imminently and widely available, whereas numerous additional promising treatments are in the preclinical and clinical pipeline. (J Allergy Clin Immunol 2018;141:41-58.)

Key words: *Food allergy, food hypersensitivity, oral tolerance, prevention, gastrointestinal food hypersensitivity, food allergens, anaphylaxis*

This article is an update to our comprehensive review of food allergy published in 2014.[1] We have not published a primer on food allergy since 2006[2] and are also taking this opportunity to provide general information meant to be helpful for those embarking on understanding the diagnosis and management of food allergy. We continue to use pertinent definitions according to a 2010 Expert Panel Report sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), which defined *food allergy* as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" and *food intolerance* as nonimmune reactions that include metabolic, toxic, pharmacologic, and undefined mechanisms.[3] We will emphasize conclusions from recent systematic reviews and meta-analyses, but we also advise the reader to avail themselves of a number of practice parameters, guidelines, clinical reports, workgroup reports, and international consensus papers that emphasize key points in the diagnosis, management, and prevention of food allergy and anaphylaxis in greater detail than possible in this review.[4-16] We also advise the interested reader to review a comprehensive report on food allergy from the National Academies of Sciences, Engineering and Medicine (NAS),[17] which describes numerous aspects of food allergy and provides recommendations to a wide variety of stakeholders for improving management of food allergy and also suggests a comprehensive research agenda.[18] Companion articles in this issue of the *Journal* focus on oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) and additional modalities of treatment under study,[19] mechanisms,[20] "omics,"[21] and prevention,[22] and therefore we will not review these topics in great detail. We highlight recent clinical observations and advances that inform diagnosis and management now and, hopefully, in the near future.

EPIDEMIOLOGY AND NATURAL HISTORY

Prevalence

There are extensive data to suggest that food allergies are common (up to 10% affected),[23] have been increasing in prevalence in the last 2 to 3 decades, appear to disproportionately affect persons in industrialized/westernized regions, and are more common in children compared with adults and that a rather short list of foods account for most of the more serious disease burden, namely peanut, tree nuts, fish, shellfish, egg, milk, wheat, soy, and seeds.[3,17,24] However, the determination of nondisputable prevalence statistics remains elusive because there are many manifestations of food allergy with different severities, and individual

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Abbreviations used
AD: Atopic dermatitis
CoFAR: Consortium for Food Allergy Research
CRD: Component-resolved diagnostics
DC: Dendritic cell
EPIT: Epicutaneous immunotherapy
FDA: US Food and Drug Administration
FPIES: Food protein–induced enterocolitis syndrome
LEAP: Learning Early About Peanut
NAS: National Academies of Sciences, Engineering and Medicine
NIAID: National Institute of Allergy and Infectious Diseases
OFC: Oral food challenge
OIT: Oral immunotherapy
OR: Odds ratio
RR: Relative risk
SPT: Skin prick test
sIgE: Specific IgE
SLIT: Sublingual immunotherapy
Treg: Regulatory T

studies present various allergy definitions, evaluate specific study populations, focus on specific foods, and use different methodologies.

To compound the difficulty in obtaining solid prevalence data, there are geographic variations; diet exposure effects; differences according to age, race, and ethnicity; and myriad other factors influencing prevalence.[17] It is clear that self-reported food allergy rates are substantially higher than those confirmed by medically supervised oral food challenges (OFCs).[25] The NAS report extensively reviewed the global prevalence literature but did not come up with definitive summary statistics, noting the many caveats involved.[17] Nonetheless, individual studies and systematic reviews are informative for producing snapshots of the scope of the problem and insights on variability based on study populations and methods. For example, although limited by self-report, Gupta et al[26] used an electronic US household survey (n = 38,480) in 2009-2010 and estimated that 8% of children have food allergy, 2.4% have multiple food allergies, and about 3% experience severe reactions.

Nwaru et al[25] undertook a systematic review and meta-analysis of food allergy to "common foods" in Europe, compiling 42 studies. They found an overall lifetime self-reported prevalence of 6% (95% CI, 5.7% to 6.4%).

A systematic review and meta-analysis on the prevalence of tree nut allergy[27] included 36 studies, half of them from Europe and 5 from the United States and mostly about children (n = 24). They noted a prevalence rate of less than 2% for OFC-confirmed allergy and between 0.05% and 4.9% for probable allergy (including reported IgE-mediated reactions or a doctor's diagnosis). Hazelnut was the most common tree nut allergy in Europe, and walnut and cashew were the most common in the United States.

A systematic review of fish and shellfish allergy prevalence identified 61 studies and concluded that fish allergy ranged from 0% to 7% and shellfish allergy ranged from 0% to 10.3%.[28]

A EuroPrevall birth cohort study involving 9 countries enrolled 12,049 infants, with 77.5% followed to age 2 years, and included OFCs to confirm diagnoses when possible.[29,30] They found an adjusted mean incidence of egg allergy of 1.23% (95% CI, 0.98% to 1.51%), with the highest rate in the United Kingdom (2.18%) and the lowest in Greece (0.07%).[29] Regarding milk, the rates were lower (0.54%; 95% CI, 0.41% to 0.70%), with the highest rates in The Netherlands and United Kingdom (1%) and the lowest rates in Lithuania, Germany, and Greece (<0.3%).[30]

Some of the highest rates of food allergy are noted in Australia and are obtained from the population-based HealthNuts study, which recruited 5276 children at age 1 year and included OFCs.[23,31] They reported an 11% age 1 prevalence of challenge-proved food allergy only considering 3 foods: peanut (3.0%; 95% CI, 2.4% to 3.8%), raw egg allergy (8.9%; 95% CI, 7.8% to 10.0%), and sesame allergy (0.8%; 95% CI, 0.5% to 1.1%).[23] In follow-up at age 4 years,[31] the overall allergy rate was 3.8%, with a peanut allergy prevalence of 1.9% (95% CI, 1.6% to 2.3%), egg allergy prevalence of 1.2% (95% CI, 0.9% to 1.6%), and sesame allergy prevalence of 0.4% (95% CI, 0.3% to 0.6%).

An interesting survey[32] by the World Allergy Organization that included 89 member countries and used experts in each noted wide variations in available prevalence data but observed that rates for those less than 5 years of age were lowest in Thailand and Iceland and highest in Canada, Finland, and Australia, although methodologies varied widely.

There is a strong impression that there has been an increase in prevalence. A survey study of government schools in Australia (>550,000 students) looking at those at risk of anaphylaxis noted a 41% increase from 2009 to 2014 (0.98% to 1.38%).[33] The US Centers for Disease Control and Prevention, using data from one question in the US National Health Interview Survey, reported that the prevalence of food allergies increased among children from 3.4% in 1997 to 1999 to 5.1% in 2009 to 2011.[34] A US survey relying on parental report of child peanut allergy but using identical methodology over time showed a rate of 0.4% in 1997 increasing to 1.4% in 2008.[35] An unrelated and unselected birth cohort study in eastern Massachusetts estimated a peanut allergy rate of 2% around 2010 by using stringent criteria (peanut IgE, ≥14 kU_A/L and prescribed epinephrine autoinjector), further suggesting at least a very high rate if not confirming an apparent increase in prevalence.[36] UK studies have also suggested an increase in peanut allergy,[37,38] and a cross-sectional study of infants in a single clinic in China from 1999-2009 suggested an increase in food allergy prevalence from 3.5% to 7.7% ($P = .17$).[39]

Keet et al[40] attempted an analysis of temporal trends in self-reported pediatric food allergy and, through analysis of 20 studies, concluded that there was an increase of 1.2 percentage points per decade. Study heterogeneity precluded prevalence estimation.

McGowen et al[41] investigated the prevalence of sensitization to food allergens using serum food-specific IgE (sIgE) antibody levels in 6- to 19-year-olds collected during the National Health and Nutrition Examination Survey in 1988-1994 and 2005-2006 to compare sensitization rates over a decade. They included 7896 participants and measured results for milk, egg, peanut, and shrimp, considering a level of 0.35 kU_A/L or greater as sensitized. There were no significant changes in the prevalence of sensitization to milk, egg, or peanut, and sensitization to shrimp decreased markedly. Overall, sensitization was 11.2% in 1988 to 1994 compared with 6.1% in 2005 to 2006. Although sensitization does not equate with clinical allergy, this finding raises questions that can be answered by investigating the factors that translate sensitization to clinical allergy, such as timing of oral exposure.

Another controversial issue is prevalence regarding differences by race, ethnicity, and other factors. Greenhawt et al[42] undertook a systematic review to address potential racial and ethnic disparities and evaluated 20 studies, identifying 12 in which black persons, primarily children, had increased food sensitization or food allergy, but issues of heterogeneity and study limitations precluded identification of a definitive disparity. Keet et al[40] noted that the rate of increase in self-reported pediatric food allergy was greater in non-Hispanic black subjects (2.1% per decade) compared with non-Hispanic white subjects (1% per decade). McGowan et al[43] evaluated a high-risk inner-city cohort of 516 children, 74% black and 18% Hispanic, noting a very high rate of food allergy (9.9%).

Individual studies suggest additional nuances. For example, Mahdavinia et al[44] analyzed data on 817 children in 2 urban tertiary care allergy clinics, noting that African American children had higher odds than white children of having allergy to wheat, soy, corn, fish, and shellfish; similar rates of peanut, milk, and egg allergy; and lower rates of tree nut allergy, but importantly, they also had higher rates of anaphylaxis and emergency department visits. Fox et al[45] noted in a UK allergy clinic from 1990-2004 an increase in the proportion of nonwhite patients with peanut allergy (but not egg allergy) from 26.8% to 50.3%, but the proportion of black subjects attending the clinic had not changed. Taylor-Black et al[46] investigated food allergy in New York City schools and did not identify a difference in food allergy rates between black and white children.

In sum, it is apparent that different findings in prevalence and allergy characteristics by race/ethnicity can be influenced by a variety of factors. Disparities, which need to be better characterized and understood, might reflect differing awareness of food allergy and/or access to health care, racial/ethnic or socioeconomic influences on childhood feeding practices, or true differences in prevalence.[47]

Risk factors

Like all chronic disease, expression of food allergy is influenced by genetics, environment, and genome-environment interactions, including epigenetic effects. Numerous risk factors have been identified or proposed to contribute to food allergy or sensitization, including[17,18,48,49] immutable risks, such as sex (male sex in children), race/ethnicity (increased among Asian and black children compared with white children), and genetics (familial associations, HLA, and specific genes), and potentially risk factors that can be addressed to reduce/prevent food allergy, such as atopic disease manifestations (comorbid atopic dermatitis [AD]), increased hygiene, the influence of the microbiome,[50,51] vitamin D insufficiency, dietary fat (reduced consumption of omega-3-polyunsaturated fatty acids), reduced consumption of antioxidants, increased use of antacids (reducing digestion of allergens), obesity (being an inflammatory state), and the timing and route of exposure to foods (increased risk for delaying oral ingestion of allergens with environmental exposure in the absence of oral exposure leading to sensitization and allergy).

A number of recent studies elucidated the above risk factors. Hong et al[52] performed a genome-wide association study in children of European ancestry with well-defined food allergies and their parents, finding peanut allergy–specific loci in the HLA-DR and HLA-DQ gene regions. The same group performed an epigenome-wide association study of cow's milk allergy evaluating 106 cases and 76 control subjects, measuring DNA methylation at 485,512 genomic loci and finding altered DNA methylation in genes involving the T_H1-T_H2 pathways (*IL1RL1*, *IL5RA*, *STAT4*, *IL4*, *CCL18*) and several novel candidate genes, including ones regulated by IL-4 and IL-13.[53] Sibling risk is often a clinical concern.

Gupta et al[54] evaluated the risk of food sensitization and allergy for siblings of a proband with food allergy. They evaluated 1120 children with food allergy with at least 1 sibling and found that 66.6% of the siblings were food sensitized but only 13.6% were clinically reactive.

Childhood vaccination has been a concern regarding risk, with a theory being that a switch to acellular pertussis might have resulted in a skew toward allergic immune responses.[55] However, Venter et al[55] evaluated a cohort of 819 children receiving one or the other type of vaccine around the same time almost randomly based on availability and found no differences in atopy.

The NAS report considered the evidence behind a number of environmental factors and theories that have been proposed to influence risk on food allergy outcomes.[17] The "dual allergen exposure hypothesis" attributed to Gideon Lack was considered by this group to have limited but consistent evidence that an impaired skin barrier plays a role in sensitization as a first step toward food allergy. The theory suggests that low-dose cutaneous exposure is sensitizing and facilitated by an impaired skin barrier and inflammation, whereas oral exposure could be potentially tolerizing but might come too late to avert allergy. Support for the hypothesis includes the efficacy of peanut early feeding in infants with eczema[56] and the increased risk of food allergy in those with mutations in filaggrin, a protein responsible in part for maintaining the skin barrier.[57]

A demonstration of the relationship of skin exposure to food allergy risks was noted in a study of a cohort of atopic infants performed in collaboration with the Consortium for Food Allergy Research (CoFAR): the risk of likely peanut allergy increased in association with the amount of peanut detected in the infants' house dust, but the relationship was augmented for infants with severe AD.[58] Additional theories regarding risk that were reviewed in the NAS report are shown in Table I.

Natural course

The natural course of childhood food allergy has been reviewed recently.[59] Some food allergies have a high rate of resolution in childhood, such as milk (>50% by age 5-10 years), egg (approximately 50% by ages 2-9 years), wheat (50% by age 7 years), and soy (45% by age 6 years), with continued resolution into adolescence.[59] Other food allergies typically persist or have low rates of childhood resolution: peanut allergy (approximately 20% by age 4 years), tree nut allergy (approximately 10%), and allergy to seeds, fish, and shellfish are also considered persistent, but studies are lacking to define the course.[59]

A number of recent studies provide more insight into the natural course and prognosis, including identification of early prognostic markers. For example, in following 213 infants with egg allergy from CoFAR, allergy resolved in 49.3% by a median age of 72 months; lower baseline egg sIgE levels and having experienced an initial reaction with isolated urticaria/angioedema rather than having AD or other symptoms were most strongly associated with resolution.[60]

TABLE I. Hypotheses and observations regarding environmental risk factors for food allergy summarized from a report by the NAS

Theory	Key features	Assessment (risk and prevention)
Microbial exposure hypothesis (hygiene hypothesis, old friends hypothesis)	Decreased microbial exposure hinders immunoregulatory responses.	(1) Changes in microbiota and food sensitization: evidence limited (2) Supplementation with prebiotics/probiotics: limited evidence, does not support decrease in food allergy (3) Route of delivery: limited evidence that cesarean section delivery is a risk for food allergy (4) Antibiotic exposure as a risk: limited evidence (5) Pet/animal exposure as protective: limited evidence
Allergen avoidance hypothesis	This hypothesis is predicated on the concept that early-life avoidance would prevent sensitization/allergy.	(1) Maternal avoidance diets during pregnancy/lactation: limited evidence to support or discourage eliminating allergens from the maternal diet of high-risk infants (2) Hypoallergenic formula: evidence that extensive or partially hydrolyzed infant formula prevents food allergies is limited; high- quality trials are needed before recommendations to use for prevention
Dual allergen exposure hypothesis	Sensitizing skin exposure overrides tolerizing oral exposure.	(1) Strong evidence that early introduction of peanut is protective in those at high risk (2) Limited evidence regarding effect of delayed allergen introduction as a risk
Nutritional immunomodulation hypothesis	Dietary factors with immunomodulatory potential might affect risks.	(1) Limited evidence that low vitamin D levels at critical periods increases risk (2) Current evidence does not support a link between increased maternal omega-3 intake and protection from food allergy (3) Lack of evidence regarding causal relationship of folate (4) Lack of evidence regarding other nutrients (antioxidants)
Other hypotheses (eg, obesity, processed foods, food additives, and genetically modified foods)	Obesity might represent an inflammatory state, additives might have a toxic immune effect, modified foods might present new allergens, and so on.	Speculation abounds; lack of data for firm conclusions

In the Australian HealthNuts study, a distinction in natural course was noted according to baked egg tolerance and ingestion.[61] Overall, egg allergy resolved in 47% of infants by age 2 years, but those with baked egg tolerance had a resolution rate of 56% compared with 13% for those without, with a better chance for resolution if baked egg products were ingested frequently, suggesting tolerance induction. The same group followed infants with challenge-proved peanut allergy, noting resolution in 22% by age 4 years; persistent allergy was highly likely (>95%) for those infants with skin prick test (SPT) responses of 13 mm or greater and a peanut sIgE level of 5 kU_A/L or greater. In a cohort of 202 children given a diagnosis of peanut allergy at about age 1 year and followed into adolescence, cumulative resolution rates by the ages of 4, 8, and 12 years were 10%, 22%, and 27%, respectively, suggesting that most resolution occurs early.[62]

In a EuroPrevall study of birth cohorts across Europe, challenge-proved cow's milk allergy was noted in 0.54%; allergy resolved by 1 year after diagnosis in all patients without detectable milk sIgE levels and in 57% of those with milk sIgE levels.[30] In the CoFAR study resolution of milk allergy, which occurred in 56.6% by age 8 years, was associated with gut microbiome composition, with favorable outcomes for those with enrichment of Clostridia and Firmicutes.[63]

Little is published about the natural course of food allergies in adults. Kamdar et al[64] identified 171 cases of adult-onset food allergy from a data warehouse using a diagnostic codes search and chart review. The age of onset peaked in the early 30s, 49% reported anaphylaxis, and shellfish (54 cases), tree nut (43 cases), fish (15 cases), soy (13 cases), and peanut (9 cases) were the most common new allergies in these adults. The above studies are just some examples of new insights into and observations on natural course. Prognostics are becoming an increasingly important area of investigation because application of early treatments that can carry risks might be targeted to those with lower chances of attaining natural tolerance. Some of these areas of investigation are discussed below.

PATHOGENESIS/MECHANISMS

Molecular and cellular mechanisms of food allergy and tolerance have been reviewed recently[65-67] and in a companion article.[20] Major advances at the basic, translational, and clinical research levels have provided new insights into immunologic

mechanisms leading to food allergies and suggest novel therapeutic and preventive strategies. The common mechanism leading to various food allergies is the breakdown of immunologic and clinical tolerance to an ingested food, which results in IgE-mediated reactions or non–IgE-mediated disorders, such as eosinophilic esophagitis, food protein–induced enterocolitis syndrome (FPIES), or food protein–induced proctocolitis. Sensitization to food allergens can occur through the gastrointestinal tract, the skin, and, less commonly, the respiratory tract, presumably in conjunction with impaired and/or inflamed barrier function.[58,68] Induction and maintenance of tolerance to food antigens requires active generation of food antigen–specific regulatory T (Treg) cells, which are likely influenced by the resident microbiome.[69,70]

The default response to food antigens is typically one of immune tolerance, which is mediated by presentation of antigen by $CD103^+$ dendritic cells (DCs) in the gastrointestinal tract and $CD11b^+$ dermal DCs and Langerhans cells in the skin.[67] These antigen-presenting cells traverse to the mesenteric and regional lymph nodes, respectively, where they induce Treg cells. In patients with food allergy, induction of Treg cells is believed to be compromised and replaced by generation of unique antigen-specific T_H2 cells that drive IgE class-switching and expansion of allergic effector cells.[71] There has been considerable effort to identify the factors responsible for this deviated immune response. In murine models oral feeding of antigen plus adjuvant stimulates gut epithelial cells to express IL-33, which induces OX40 ligand expression on $CD103^+$ intestinal DCs that promote a T_H2 response.[72] Similarly, applying antigen to damaged mouse or human skin, such as that induced by tape-stripping, induces keratinocytes to express IL-33, IL-25, and thymic stromal lymphopoietin and activates OX40 ligand on $CD11b^+$ dermal DCs to promote T_H2 skewing.[67]

Another pathway by which IL-33 promotes food allergy is through expansion and activation of group 2 innate lymphoid cells, which respond by producing large amounts of IL-4, which suppresses generation of Treg cells in the skin, lung, and small intestine.[73,74] In addition, IL-33 contributes to acute reactions to food by acting directly on mast cells and enhancing IgE-mediated activation.[68]

IL-9 also has emerged as a key cytokine associated with allergic responses to foods in human subjects and mouse models.[67] IL-9 is a growth factor for mast cells and has been shown in mouse models to play an essential role in the pathogenesis of food allergy. A novel population of mucosal mast cells was identified recently in the duodenum of patients with food allergy that produces high levels of IL-9 and IL-13 compared with those in healthy subjects in addition to tryptase, chymase, and carboxypeptidase.[75] Activation of mast cells through IgE leads to suppression of Treg cell generation and amplification of the T_H2 response. In patients with food allergy, a subset of allergen-specific Treg cells can also be reprogrammed to coexpress IL-4 and IL-13, a subset not found in healthy control subjects or those outgrowing food allergies.[76]

Despite ongoing investigation, there continues to be little basic understanding of the immunopathogenic mechanisms underlying non–IgE-mediated food allergies. Although IgE does not appear to play role in eosinophilic esophagitis, it is primarily a form of T_H2-driven food allergy with increased levels of IL-5, IL-13, and IL-9 increased numbers of eosinophils, mucosal mast cells, and $CD4^+$ T cells in esophageal tissue.[77] Similarly, in patients with FPIES, eosinophils and T_H2 cells are present in the intestinal mucosa, but recent studies suggest there might be a major role of the innate immune system in the pathogenesis of this disorder.[78] With increasing focus on non–IgE-mediated food allergies and continuing advances in technologies, new insights into the immunopathology of these disorders should be at hand.

DIAGNOSIS

Arguably the most important single "test" for diagnosing a food allergy is the clinical history. To hone a diagnosis, the history must be reviewed in context of knowledge about the clinical manifestations and epidemiology of food allergy and with an understanding of disorders with similar clinical manifestations that might be misconstrued as food allergies. For example, consider a 3-year-old presenting with a complaint of generalized urticaria that started 15 minutes after peanut ingestion. If we learn that this child routinely tolerated peanut in large amounts, is not atopic, and had symptoms of a viral infection and that the urticaria persisted for 7 days, we would conclude that the symptoms were not related to peanut but rather to a viral infection. If the history instead disclosed that the child had moderate AD and had resolved egg allergy before rejection of offered peanut, that this was the first ingestion, and that the urticaria was treated with antihistamines and did not recur, we would already be highly convinced of a peanut allergy. These conclusions are based on understanding prior probabilities based on epidemiologic risks and details of the history; in the former case testing is unnecessary, and in the latter case testing would likely be confirmatory. Additional diagnostic information is obtained by appropriately selecting and interpreting tests, such as SPTs, sIgE measurements, and OFCs, which in turn must be interpreted within the context of the epidemiology, pathophysiology, and clinical history associated with the clinical scenario under consideration. Our prior review[1] highlighted the clinical disorders and diagnostic approaches described in a 2010 NIAID-sponsored expert panel report,[3] and the following discussion builds on this, incorporating recent reviews, practice parameters, systematic reviews, and guidelines.[5,7,10,12,79]

Clinical disorders

Having a good understanding of the clinical disorders and symptoms comprising food allergies is important for determining a proper diagnosis. Both the NIAID Expert Panel[3] and the European Academy of Allergy and Clinical Immunology food allergy guidelines[5] classify immune-mediated adverse food reactions (eg, food allergies) according to presumed primary pathophysiology, although with some differences. Allergies are defined differently from other adverse reactions to foods because allergies involve an immune response. Therefore intolerance (eg, lactose intolerance) or toxic (food poisoning) or pharmacologic (eg, caffeine) adverse reactions are not food allergies. Regarding food allergy, in general, there are IgE-mediated, non–IgE-mediated (cell-mediated), or mixed (IgE and cell-mediated) pathophysiologies, although the NIAID guidelines suggested a separate category from non–IgE-mediated pathophysiologies termed "cell mediated" for allergic contact dermatitis to foods and including celiac disease as non-IgE mediated. Distinctions in pathophysiology are important clinically because they help define what testing might be appropriate to confirm, exclude, or monitor disease. Table E1 in this article's Online Repository at

www.jacionline.org emphasizes the key features of various food allergies, immunopathophysiology, natural course, and diagnostic considerations.

Several food-induced allergic disorders or manifestations of food allergy have peculiar features of note that are helpful to know to aid in the diagnostic process. Delayed allergic reactions from mammalian meats are attributable to IgE to carbohydrate galactose-alpha-1,3-galactose (alpha-gal), with sensitization triggered from tick bites.[80] Eliciting (augmentation) factors might alter the threshold of reactivity, leading to reactions to otherwise tolerated foods, and these factors include ingestion of nonsteroidal anti-inflammatory drugs or alcohol, exercise, menstruation, and illness.[81,82] FPIES, a non–IgE-mediated food allergy characterized by delayed profuse vomiting, is often misdiagnosed initially and usually resolves, and a subset of infants can have eventual IgE sensitization and typical allergic reactions to the trigger food, typically milk.[10,83]

Eosinophilic esophagitis can present with dysphagia, leading a patient to suspect the food causing the response, such as beef if steak was eaten. However, a small number of foods account for most of the food-related inflammation in patients with eosinophilic esophagitis, and the more likely causal triggers not identifiable by simple tests are milk, wheat, egg, and soy.[84] A rare form of food allergy, fixed food eruption, manifests as recurrent rash or urticaria in a specific location after ingestion of a food, and usually sIgE levels cannot be detected.[85]

Determining whether symptoms are attributable to a food allergy and which food or foods are causal is challenging, and consideration must also be given to reactions/symptoms that masquerade as food allergies. Scombroid fish poisoning, during which spoiled dark meat fish contains histamine-like toxins (or other adverse reactions to ingested dietary histamine),[86] or neurologic responses, such as auriculotemporal syndrome, when foods that trigger increased salivation also result in a reflex facial vasodilation of the lower cheek or gustatory rhinitis when spicy foods result in rhinorrhea, all can mimic food allergies.[1] It is also notable that chronic asthma and rhinitis are not typically attributable to food-induced allergic reactions. Food are often excluded from the diet in children with AD because of suspicion of contributing to the rash; foods can be a trigger, but many additional triggers exist, including irritants, infection, and environmental allergens.[3,7] In patients with AD, foods are eliminated often without clear indications, which can have nutritional, social, and possibly immunologic consequences (acute allergic reactions to previously ingested foods),[87,88] underscoring the need for careful diagnostic approaches.

Diagnostic approaches

We have proposed a schematic diagnostic algorithm that considers the history, epidemiology, pathophysiology, and test results leading to a diagnosis, including identification of the trigger food or foods, as shown in Fig 1,[1,89] and similar schematics have been proposed by others.[5,90] Expert panels, practice parameters, systematic reviews, and guidelines have identified a number of recommended diagnostic modalities.[3,5,7,17,79] These tests include medical history, physical examination, elimination diets, SPTs, sIgE tests, and OFCs. Among tests not recommended or not recommended for routine use are intradermal tests, total serum IgE measurements, atopy patch tests, and a number of nonstandardized and unproved tests are specifically not recommended, including applied kinesiology, allergen-specific IgG_4 measurement, electrodermal testing, and several others.

Molecular or component-resolved diagnostics (CRD) tests have been considered promising, and studies continue to emerge regarding their utility. The general premise is that IgE binding to specific proteins in a food might provide more specific diagnostic information than tests that report IgE binding to extracts comprised of mixtures of proteins. For example, Ara h 2 is a major peanut protein, a 2S albumin associated with clinical reactions, whereas in contrast, Ara h 8 is a birch pollen Bet v 1 homolog and is labile and not likely to be attributable to significant clinical reactions. Although a positive peanut sIgE result might suggest potential allergy, finding CRD to peanut with undetectable levels to Ara h 1, 2, 3, and 9 (stable proteins) and an isolated positive result to Ara h 8 would usually suggest general tolerance.[91] Still, the level of component sIgE can also provide diagnostic information and not simply the presence of a positive test result; for example, increasing concentrations of sIgE to Ara h 2 are associated with an increasing risk of reaction to peanut.[92] Many CRD tests have become commercially available and are in widespread use. The basophil activation test, an *in vitro* assessment of basophil activation, is also considered promising,[5] although there are challenges to using this outside of a research setting.[93]

There is a dizzying array of disparate results when studying the correlation of SPT and sIgE test results with clinical outcomes. The ideal of a "yes/no" result is generally lacking, sensitivity is typically better than specificity, and, in general, increasing SPT response size or sIgE level correlates with increasing likelihood of an allergy.[3,5,7,17,79] However, there are remarkable exceptions in which subjects with exceptionally strong test results (ie, Ara h 2 level >100 kU_A/L) tolerate the food[92,94] or those with undetectable results react (emphasizing the importance of addressing the history when choosing and interpreting diagnostic tests).[95] The greatest source of misdiagnosis in food allergy might well be the lack of appreciation that a positive test result (sensitization) does not equate with allergy and that indiscriminate "panel testing" can result in a disaster of misdiagnosis.[17,18] In a national sampling of pediatricians and family practice physicians, fewer than 30% of the participants felt comfortable interpreting laboratory tests to diagnose food allergy.[96]

It should also be appreciated that diagnosis is not generally based on a single test. A stepped approach is usually used, in which history can lead to test selection, and the result of that test (ie, SPT and/or sIgE measurement) can be used to determine whether an OFC is warranted. As an example, Dang et al[97] compared strategies for diagnosing peanut allergy in children at a median age of 14 months in the HealthNuts study population. Using peanut IgE alone (cutoff of >15 kU_A/L or <0.35 kU_A/L) would have resulted in the need for 95 OFCs, SPT alone (using cutoff of >8 or <3 mm) would have resulted in the need for 50 OFCs, and Ara h 2 (>1.0 or <0.1 kU_A/L) measurement would have resulted in the need for 44 OFCs. However, a stepped approach of testing peanut IgE followed by Ara h 2 would have reduced the need for OFCs to 32 and an SPT followed by Ara h 2 reduced the need to only 21 OFCs.

Nuances regarding the predictive value of tests must also be appreciated. Although sensitivity and specificity have been calculated for SPTs and sIgE tests for a number of foods,[79] it is clear that individual studies are affected by variables that seem to influence test result–clinical outcome relationships. The application of study results to an individual patient or practice should

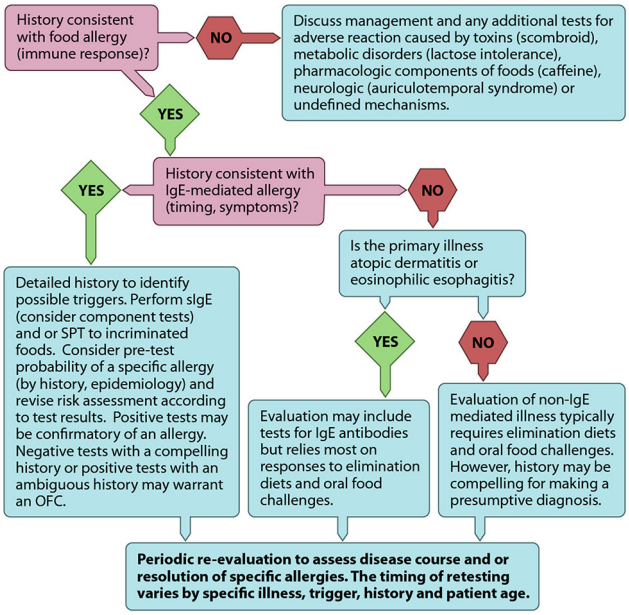

FIG 1. Diagnostic approach.

consider these nuances. Age appears to influence outcomes; for example, a given sIgE level (eg, 5 kU_A/L) might be more predictive of allergy in an infant compared with an older child.[98,99] Geography might influence results because of the effect of sensitization to cross-reacting pollens.[100] Atopic disposition, race, methods, definition of allergy, and other factors also influence the outcomes of specific studies.[79,101]

Regarding methods, skin test device selection matters. Tversky et al[102] evaluated 10 commercial skin test devices, noting that mean wheal diameter differed from 3.0 to 6.8 mm by using 1 mg/mL histamine ($P < .001$). Whether results are evaluated as the widest diameter or the mean of the widest diameter and its perpendicular would also provide different results. The results reported by using different automated sIgE systems are also not entirely comparable.[103]

Cross-reactivity among foods and pollens might result in observing positive test results to related foods that might not have clinical implications, further confusing test interpretation.[104] Considering legumes, for example, there are multiple types of lentils that have homologous proteins with each other and with other beans, and yet individual patients can react to distinct types, despite a high degree of identity at the protein level and having multiple positive test results.[105] Sensitization to pollens, such as birch, can result in positive test results to multiple foods, such as peanut, almond, hazelnut, and numerous fruits and vegetables, and allergy to cockroach or dust mite can result in positive test results to crustacean shellfish.[106]

Dissecting the relevance of these influences has resulted in an explosion of research on CRD,[92,106-117] as recently reviewed by Santos and Brough.[101] There remains some equipoise with limited data regarding whether sIgE, increased epitope binding diversity, CRD, or basophil activation test results can predict the severity of the reaction.[93,113,118-123] The expectation that *in vitro* testing can determine severity on an individual basis might be faulty given that variables, such as dose, presence and activity of asthma, and individual sensitivity, can vary. Various pearls and pitfalls of diagnostic testing are shown in Table II.

OFCs are generally offered when the odds of tolerating the food, based on history and other tests, are reasonable for the circumstances (eg, age, dietary preference, and nutritional issues). Reviews are available regarding the details for performing OFCs,[12,124-126] with the gold standard being the double-blind, placebo-controlled OFC. Although highly reliable, about 3% experience reactions during placebo testing, and about 3% can have reactions to the food later, despite tolerance during the procedure. Many families who are offered an OFC might decline for reasons such as fear about the procedure or lack of appreciation of the benefits, issues that can be addressed in counseling.[127] The procedure is generally safe, although it must be conducted with appropriate precautions by experienced personnel because severe reactions and even fatality are possible.[12,15,124,125] Surprisingly, families might not incorporate the food despite tolerance during an OFC, and counseling to do so should be included in the discussions about the procedure.[128] It might also be helpful for families to know that quality of life often improves, even when the procedure results in an allergic reaction,[129] and that a reaction is not likely to cause an increase in sensitization.[130]

It would be preferable to have an improved surrogate test to avoid performing OFCs because they are time-consuming and resource intensive and carry risk. Although the tests described above can be used judiciously to reduce the need for OFCs, studies on alternative diagnostic methods are underway. Evaluation of IgE binding to areas (epitopes) on allergens, including affinity of binding, is a modality that shows promise to improve diagnostic accuracy.[131-133] Additional markers being evaluated include cytokines, Treg cells, and T-cell number and function; B-cell activity; and DNA methylation signatures.[134-138] Bioinformatics approaches with machine learning technology that take into consideration multiple variables should allow improved diagnostics[139] and could include data from numerous biologic markers and "omics,"[140] such as genomic, transcriptomic, proteomic, metabolomics, microbiome, and various laboratory tests, allowing for assessment of billions of variables.

MANAGEMENT

With the absence of a cure, effective management of food allergy requires avoidance of ingestion and prompt treatment in the event of an allergic reaction. Achieving successful avoidance and proper reactionary treatment can be complex and involves a variety of stakeholders beyond a patient and his or her family, including schools, the workplace, the food industry, government agencies, public health authorities, and others.[17] Management concerns were reviewed recently,[141] and here we highlight some illustrative examples of the scope of issues that affect those managing food allergies. Table III provides a broad range of examples of management issues.

Regarding allergen avoidance, a high level of education is needed to maintain safety. A systematic review confirmed concerns about labeling vagaries or errors, restaurant meals, eating at home and outside the home, and risky behaviors leading to unexpected reactions.[142]

For example, manufactured food product ingredient labels can have unregulated precautionary labeling, such as "may contain," that causes confusion. A US and Canadian survey with 6684 participants managing food allergies showed that consumers erroneously think such labels are regulated, and they self-interpret the risk they perceive in reading these label terms, with 11%

TABLE II. Pearls and pitfalls regarding diagnosis of food allergy

Pearl/observation	Additional details			Clinical application
A positive skin test or serum food sIgE test result indicates sensitization but not necessarily clinical allergy.	Screening with indiscriminate panels of tests is poorly informative. Screening tests using common allergens that have not been ingested and tolerated but pose increased risk can be considered (eg, tree nuts for a child who reacted to peanut but has not ingested nuts).			The history and epidemiologic considerations should guide test selection: Tolerated foods generally need not be tested. Differential diagnosis should include alternative allergen triggers (environmental aeroallergens) and nonallergic diseases (eg, intolerance).
Dose, manner of preparation, and ancillary (eliciting) factors can alter reaction outcomes.	Alcohol, NSAIDs, and exercise are among eliciting factors that can facilitate a reaction. Heating can alter allergenicity (eg, bakery products with egg/milk can be tolerated when whole forms are not and cooked fruits can be tolerated when raw foods are not). A low dose can be tolerated when larger amounts cannot.			The history should focus on amounts triggering a reaction and ancillary factors. The history should explore the types of foods tolerated or not tolerated.
IgE binding to homologous proteins among food groups and between foods and pollens might have variable clinical relevance.	Rates of clinical cross-reactivity:			Care in not "overtesting" For some categories, food avoidance of entire group might be prudent, especially to avoid cross-contact in preparation, but individualization might be possible.
	Allergy to:	Related food	Approximate clinical reaction rate	
	Peanut	Most legumes	5%	
	A tree nut	Other tree nut	35% Higher for: walnut-pecan, almond-hazel, cashew-pistachio	
	A fish	Other fish	50%	
	Shellfish	Another shellfish	75%	
	Grain	Another grain	20%	
	Milk	Goat/sheep milk	>90%	
		Mare milk	5%	
		Beef	10%	
Tests for serum food sIgE might not provide comparable results among manufacturers.	In the United States there are 3 major test manufacturers.			Care must be taken in evaluating test results over time when different manufacturers are used.
Component testing can differentiate clinical reactivity (IgE binding to "potent" stable allergens) from less clinically relevant sensitization (binding to labile proteins).	Food	Stable protein(s)		The concentration of IgE binding to components also relates to outcomes, but similar to standard tests, the correlations have not been established and vary by, for example, center and patient selection. Caution as severe reactions can occur despite lack of noted binding to measured allergen (see text). Tolerance can occur despite positive test results to stable protein.
	Peanut	Ara h 1, Ara h 2, Ara h 3, Ara h 6, and Ara h 9 (especially southern Europe)		
	Hazelnut	Cor a 9, Cor a 11, Cor a 14		
	Walnut	Jug r 1, Jug r 3		
	Cashew	Ana o 3		
	Brazil	Ber e 1		
	Egg	Ovomucoid		
	Milk	Casein		
	Soy	Gly m 5, Gly m 6, Gly m 8		
	Wheat	Tri a 19		

(Continued)

TABLE II. *(Continued)*

Pearl/observation	Additional details					Clinical application
Serum/skin test results might be negative, despite clinical reactivity.	This might be due to reagent lacking relevant protein. This might be because reaction is not IgE mediated.					Do not discount a convincing history because of a negative test result. Consider testing with fresh food (prick-prick test); these can be stored frozen. Be cognizant of non–IgE-mediated allergic reactions.
Increasingly high serum food sIgE levels or increasingly larger skin test wheal size indicates higher chances of clinical allergy.	Correlation of tests with outcomes vary by center, age, and disease (equivalent results generally more predictive of allergy in a younger patient). Results are not highly correlated with severity.					Tests should not be viewed solely as positive/negative. Results can be followed over time to monitor allergy persistence/resolution. Specific correlative values might not be applicable over all patient groups.
Sensitivity is generally higher than specificity.		SPT Sn	SPT Sp	sIgE Sn	sIgE Sp	
	Milk	88%	68%	87%	48%	
	Egg	92%	58%	93%	49%	
	Wheat	73%	73%	83%	43%	
	Soy	55%	68%	83%	38%	
	Peanut	95%	61%	96%	59%	
At specific high levels of IgE or large skin test results, clinical reactivity is highly likely; however, studies are limited, and variations in "diagnostic cutoff" values are reported.	Food	Mean age, 5 y; 50% react	Mean age, 5 y; ~95% react	Age <2 y; ~95% react		OFCs can be deferred, particularly if there is a clinical history. When evaluating individual studies, predictive values might not apply to populations with different demographic and referral patterns.
	Egg	2	7	2		
	Milk	2	15	5		
	Peanut	2/5	14			
	Units are kilounits of allergen per liter; the dual notation for peanut represents with/without a reaction history.					

Revised from Sicherer and Sampson.[1]
NSAID, Nonsteroidal anti-inflammatory drug; *Sn*, sensitivity; *Sp*, specificity.

purchasing "may contain" and 40% purchasing "in a facility that also processes," despite no difference in actual risk.[143]

Regarding schools, legislation regarding food allergy, encouraging education, and allowing for stock epinephrine can have a positive effect.[144,145] Allergen avoidance can be controversial when "food bans" are considered.[146] In a 5-year study of Massachusetts public schools, no policy regarding peanut restrictions was associated with absence of reactions, and epinephrine administration rates were not different when comparing schools with various forms of restriction.[147] However, schools with peanut-free tables, compared with those without, had lower rates of reactions: 2 versus 6 per 100,000 students ($P = .009$).

A study of 278 US restaurants revealed that fewer than half of the staff reported any food allergy training,[148] and staff often have deficits in their knowledge,[149] emphasizing the need for patrons to explain issues, such as hidden ingredients and cross-contact.

Education and consideration about food allergies extends to all caregivers and circumstances. For example, a survey of 153 nannies disclosed 37% cared for children with food allergies, but they had discomfort in recognizing a food allergy emergency (36%) and treating with epinephrine (46%) and had misconceptions, such as safety in eating a small amount (6%).[150]

Patients and families might seek advice from the Internet. In a survey of a food allergy referral population, 91% of 371 responding noted use of online resources or social media, with 82% searching for management advice.[151] Interestingly, 25% reported a mismatch between advice from the Internet and their medical professional, and 21% followed the online advice. A number of "apps" exist for food allergy education and management, but caution is advised because a review of 77 of them suggested most were a poor source of information, had limited databases and poor function, or both.[152]

With regard to dietary management, strict avoidance is usually advised. However, approximately 70% of children with milk and egg allergy can tolerate these foods when extensively heated in bakery goods.[153] Patients strictly avoiding milk or egg must be carefully evaluated, such as by using supervised OFCs, to determine whether they can tolerate the baked forms because severe allergic reactions are possible. Ingestion of the baked forms, for those who are able, might result in faster resolution of the allergy,[154,155] although the evidence is not firm.[156]

Allergen avoidance diets can result in nutritional deficiencies. For example, in a study of 245 children with a mean age of 4 years avoiding 1 to 7 foods, those less than 2 years of age had lower weight-for-length percentiles and those age 2 years and older had lower body mass index profiles compared with healthy control subjects.[157] Differences were especially pronounced for those avoiding milk (as noted in other studies[158,159]) or multiple foods. A systematic review of 6 studies emphasized risks for malnutrition and reduced height and noted that children with food allergies who did not receive nutritional counseling were more likely to have inadequate calcium and vitamin D.[160] Nutritional counseling and growth monitoring are recommended for children with food allergy.[3]

Prompt treatment of severe allergic reactions with epinephrine is a cornerstone of therapy,[4-16] but numerous barriers exist. Teenagers and young adults are considered at high risk for fatal reactions based on risk-taking behavior and lack of prompt treatment. A survey of college students reporting food allergy[161] disclosed only 266 of 748 with food allergy carried epinephrine, and only half of these young adults had it available at all times. Numerous studies suggest that epinephrine is underused during anaphylaxis.[8] Some of the reluctance can be related to fears of needles and side effects of the medication.[162] Shemesh et al[163] performed an intervention in which adolescents practiced self-injection with an empty needle/syringe to address needle phobia and found significant improvement in comfort with self-treatment.

Recent studies speak to the safety and efficacy of self-injectable epinephrine and can be counseling points in encouraging liberal treatment. Fleming et al[164] evaluated 384 emergency department evaluations for food-induced anaphylaxis and found that those receiving prehospital epinephrine compared with those treated on arrival were less likely to be hospitalized (17% vs 43%, $P < .001$). Campbell et al[165] evaluated outcomes of 362 doses of epinephrine given to 301 emergency department patients (67.7% by autoinjector, 27.9% by intramuscular or subcutaneous injection, and 8.3% by intravenous administration) and found 4 patients had overdoses, all through intravenous treatment, and 8 patients had cardiovascular side effects, 10% among the 30 intravenous doses and 1.3% among the 316 intramuscular doses ($P = .006$), emphasizing safety of autoinjection/intramuscular injection. In addition to counseling about efficacy and safety, health care providers should provide and review a written plan for management.[8]

A study of 188 teenagers with food allergy noted only 16% had full adherence to food allergy self-care behaviors.[166] Adherence was more likely if the teens were in a support group (odds ratio [OR], 2.54) or had an anaphylaxis management plan (OR, 3.22). Increasing costs of epinephrine autoinjectors also represent a barrier.[167] Alternatives for convenient and safe administration, such as prefilling a syringe,[168] are few, and generally have limitations[9]; recommendations to develop cheaper alternatives, investigate shelf-life labeling, and develop infant dose forms have been proposed.[17,18]

The financial costs[169] and emotional effect of living with food allergy cannot be underestimated. Numerous studies detail the negative effect of food allergy on health- related quality of life.[170] Some of the themes identified include feeling different because of the diet, worrying about foods, the presence of physical and emotional distress, increased responsibility, effect on social activities (social restrictions, school, travel, and restaurants), and greater caution.[171] Anxiety and stress have also been noted.[172]

Children with food allergies experience a higher rate of bullying than others. In a longitudinal study of 124 families, in which 32.5% reported food-related bullying at baseline, resolution of bullying was associated with parental report of the incidents to schools and resulted in improved quality of life.[173] Parents might be unaware of bullying, and therefore discussion in the clinical setting can be helpful to address the concerns.[174] Given the effect of food allergy on quality of life, anxiety, bullying, and stress, mental health support should be considered.[175]

PREVENTION

Many of the food allergy risk factors and hypotheses to explain the apparent increase in the prevalence of this disease, as described above (dual allergen exposure hypothesis,[176] vitamin D hypothesis, dietary fat hypothesis, and hygiene hypothesis), lend themselves to interventions that could reduce the risk of food allergy (ie, primary prevention). A number of recent reviews,[48,177] including one in this issue of the *Journal*,[22] describe opportunities for prevention. Selected approaches and supporting data are reviewed here briefly. Table I provides conclusions from the NAS regarding the potential translation of possible causal risk factors into prevention strategies.

The prevention approach backed by the most convincing data is in regard to early peanut introduction in high-risk infants. In the Learning Early About Peanut (LEAP) trial, infants aged 4 to 11 months at high risk (severe eczema and or egg allergy) for peanut allergy but with peanut SPT wheals of 4 mm or less were randomized to consume or avoid peanut to age 5 years.[56] Those who were sensitized to peanut and randomized to consumption had a 10.6% rate of peanut allergy compared with 35.3% in the avoidance group ($P = .004$; relative risk [RR] reduction, 70%). Among infants not sensitized, 13.7% in the avoidance group and 1.9% in the ingestion group had peanut allergy ($P < .001$; relative reduction, 86.1%). Additional studies having the consumption group avoid peanut for 1 year[178] and evaluating nutritional outcomes[179] suggest that the protection was durable and did not result in reduced breast-feeding or nutritional concerns.

The results of this study, with supporting evidence of possible protection in nonselected infants,[180] provided the basis for an NIAID-sponsored expert panel to suggest essentially applying the LEAP study results to high-risk infants and encouraging introduction of peanut early also for those at moderate risk.[11] These new guidelines (Table IV) go farther than prior ones that essentially suggest that allergenic foods be introduced without any particular delay compared with nonallergenic foods.[3,181,182] For high-risk infants, introducing peanut "as early as 4 to 6 months" can broach exclusive breast-feeding, which is generally recommended to around 6 months, but the rationale to feed peanut earlier (in infant-safe forms and after proof that the infant can manage solids) was to reduce the chance of infants having increasing sensitization with time and also timing the instructions with pediatric visits for immunization.[11,183] US Food and Drug

TABLE III. Management considerations (selected examples)

Area	Topics	Examples of educational advice, pearls, and resources
Avoidance	Manufactured products	Label reading for each purchase, understanding labeling laws (which differ by country), avoidance of products with advisory warnings
	Restaurants	Discuss allergy with staff, use written "chef cards," educate about severity and cross-contact, suggest methods to avoid inclusion of allergens (eg, aluminum foil on grill)
	Cross-reactivity and cross-contact	Address concerns about diet, such as safety of ingesting related foods, when there is allergy to a member of a group (eg, avoiding all tree nuts or allowing ingestion of tolerated ones if there is an allergy to one type); educate on avoidance of cross-contact of allergens
	Travel	Prepare ahead for extra medications, safe meals, nearby medical assistance, consider rooms with kitchenette, carry written materials
	School	Written emergency plans in place, avoidance strategies (eg, craft projects), provisions for mealtimes, field trips, substitute teachers, bus travel, delegation of care
	Home	Avoid cross-contact in meal preparation, organize cupboards, emergency medications on hand
	By age	Tight supervision for toddlers; young school age taught not to take food or share; older school age transition to read labels, speak to restaurant staff, and discuss allergy and symptoms and therapy; teens carry and know when and how to self-treat and education of peers
	Vigilance	Education on always having medications ready, plans in place, ensuring safe food, medical identification jewelry
	Experimentation	Specify that if there is doubt of a true allergy, ingestion should be discussed in the context of medically supervised food challenge and not home trials
	Caregivers	Educate all caregivers on avoidance and emergency management
	Anxiety, emotional	Acknowledge anxiety, potential bullying, need for balance of caution, and maintenance of a normal lifestyle, refer for mental health support
	Nutrition	Nutritional counseling and growth monitoring for children
	Ingestion vs noningestion	Emphasize differences in risk from ingestion exposure (higher risk) vs skin contact (low risk unless transfer to mouth) vs inhalation (depends on food and density of exposure) with regard to potential symptom severity and treatment taking into consideration age, specific allergies, and circumstances of exposure
	Resources (examples)	Web sites: foodallergy.org, cofargroup.org, aaaai.org, acaai.org, aafa.org, allergyready.com, www.cdc.gov/HealthyYouth
Emergency management	Carrying medications	Emphasize having medications at all times, even if no planned food ingestion; make provisions to increase ease of carrying or access (packs, holsters, and larger purses)
	Using medications	Review specifics on when (symptoms) and how to use medications and alerting emergency teams (call 911, not necessarily linked to administration of epinephrine) and educate about safety of epinephrine and need for early administration, not to rely on antihistamines or inhaled bronchodilators
	Preparedness	Plans tailored to age, ability to self-treat, allergy, locations, wearing medical identification jewelry
	By age	Transition responsibility of anaphylaxis management gradually through preteen to teen years, carry and know when and how to self-treat
	Emergency Plans	Establish written emergency plans, as well as a team approach to manage a reaction
	Dosing	Generally transition from 0.15 mg administered through an autoinjector to 0.3 mg at around 55 lbs; for infants, weigh options of autoinjector versus ampule/syringe
	Resources (examples)	Web sites: foodallergy.org, cofargroup.org, aaaai.org, acaai.org Commercial autoinjector Web sites: medicalert.org
Other	High-risk age group, adolescents and young adults	Counsel on adherence to allergen avoidance and carrying/using emergency medications. Caution about alcohol (altered judgment and eliciting factor for more severe reactions); discuss interpersonal relationships, intimate behaviors (intimate kissing as a source of food allergen exposure)
	Encourage education about and participation in research studies	Web sites: clinicaltrials.gov, foodallergy.org

Revised from Sicherer and Sampson.[1]

Administration (FDA) health claims regarding peanut prevention were subsequently added to peanut products based on the guidelines. For high-risk infants, the guidelines suggest evaluation for sensitization and possible OFCs and then dosing regimens that mimic the LEAP study. The effect of the recommendations on resource use, uptake of the recommendations, and outcomes remains to be evaluated.[184,185]

The potential for allergy prevention through early introduction of other foods remains less certain based on or because of limited studies. The Enquiring About Tolerance trial attempted to have early introduction of 6 allergenic foods starting around 4 months of age.[180] An intention-to-treat analysis from this study did not show a prevention effect, but a per-protocol analysis suggested effectiveness for peanut and egg. Five additional studies evaluated early

TABLE IV. Guidelines for introduction of peanut for peanut allergy prevention

Infant criteria	Recommendations	Earliest age of peanut introduction	Rationale/comments
Guideline no. 1: Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE or SPT and, if necessary, an OFC Based on test results, introduce peanut-containing foods	4-6 mo	Potential advantage to identify infants early (pediatric vaccination visits) and begin peanut before increased sensitization Firm evidence of prevention effect is a rationale for early interruption of exclusive breast-feeding
Guideline no. 2: Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 mo	Extrapolation of effect to moderate risk from results of a randomized trial on high risk Potential to reduce overall disease burden from a larger group at risk Insufficient proof to broach exclusive breast-feeding
Guideline no. 3: No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices	Similar rationale to guideline no. 2 above, not introducing before 6 mo but less emphasis on very early introduction for this lowest-risk group

egg introduction but evaluated different approaches (raw or cooked egg, different dosing strategies, and different risk groups and entry criteria).[186-190] Two of the studies[187,189] showed a statistically significant reduction in egg allergy (intention-to-treat and per-protocol, respectively), whereas another trial favored control subjects.[188] A systematic review[191] concluded that there was "moderate certainty" of evidence for reduced egg allergy with introduction at 4 to 6 months (RR, 0.56; 95% CI, 0.36-0.87), but the conclusion was heavily based on results of the Natsume study,[189] which showed greater sensitization in the placebo group, produced low stepped cooked egg dosing, and measured outcomes against the egg product used in prevention treatment, which might have enhanced the results or reflected treatment rather than prevention.

Although there is currently no recommendation to purposefully feed egg early, there remain recommendations not to avoid including egg in the early infant diet.[181,182] The above referenced egg studies[186,188] noted high rates of reaction on raw egg introduction, raising questions of safety and the possibility that high-risk infants might already be allergic by 4 to 6 months. Data on milk are limited but also suggest delayed introduction can be associated with increased risk.[192]

Additional potential prevention strategies have less scientific support at this time but warrant further study (Table I). Ensuring vitamin D sufficiency could be a simple intervention. The Australian HealthNuts study found that infants with vitamin D deficiency had increased risk of peanut (adjusted OR, 11.51; 95% CI, 2.01-65.79) and egg (adjusted OR, 3.79; 95% CI, 1.19-12.08) allergy,[193] but there are many conflicting studies,[177] and a clinical trial is underway.[194] Improving the skin barrier early through moisturizing can reduce the risk of eczema[195,196] and theoretically food allergy, but more studies are needed.

The potential for probiotics as a prevention strategy remains open. Berni Canani et al[197] reported a randomized trial of a hypoallergenic infant formula with or without addition of *Lactobacillus rhamnosus* in infants with cow's milk allergy (n = 220; median age, 5 months) and noted a risk reduction in the infants receiving probiotics for having additional atopic disease (eczema, asthma, rhinoconjunctivitis, and other food allergies), with a the number of children needed to treat to prevent the occurrence of at least 1 additional allergic manifestation over a 36-month period estimated at 4 (95% CI, 3-10). The potential preventative influences of components and diversity of the diet, including dietary fat and antioxidant properties, as reviewed above, remain active areas of investigation.[17] The potential for specific infant formulas to provide allergy protection is now questioned and not founded.[17,198] There remains insufficient data to know whether breast-feeding delays or prevents food allergy, although a signal for prevention has not been identified.[17,181,199,200] The strongest current evidence for prevention is regarding early introduction of peanut for infants at high risk.

FUTURE THERAPIES

Treatment of food allergy is reviewed in a companion article in this issue of the *Journal*.[19] It is acknowledged that allergen avoidance is an effective form of management, but avoidance is not tantamount to a true treatment. Allergen immunotherapy aims typically to provide desensitization, a temporary increase in threshold to provide a measure of safety that is dependent on continued treatment exposure. Ideally, a curative therapy would allow any amount of ingestion with no effect from augmentation factors, such as illness or exercise (true full tolerance). Studies often evaluate whether a threshold of reactivity is lost over a period off therapy, looking for at least a temporary remission or "sustained unresponsiveness." Currently, the most intense areas of immunotherapy investigation regard the OIT, EPIT, and SLIT routes, as detailed in the companion review.[19] A recent systematic review and meta-analysis[201] considered 31 studies of allergen immunotherapy, mostly in children, and summarized that there was a substantial benefit of desensitization (RR, 0.16; 95% CI, 0.10-0.26) and a suggestion of sustained unresponsiveness (RR, 0.29; 95% CI, 0.08-1.13). The analysis also showed that the risk of experiencing systemic adverse reactions was modestly greater in those treated, and there was a substantial increase in local adverse reactions. The balance of benefit and risk underscore the clinical equipoise for these treatments.

Studies of OIT, SLIT, and EPIT generally reveal a relative robustness of OIT over SLIT and EPIT, with a higher risk of side

TABLE V. Selected therapeutic strategies with clinical trials

Therapy	Benefits	Limitations	Additional comments
OIT	Robust, possible sustained unresponsiveness	Time-consuming, side effects	Peanut in phase 3
SLIT	Minor side effects, brief exposure	Less robust than OIT	
EPIT	Minor side effects	Less robust than OIT, more effective in younger age group	Peanut in phase 3, milk in phase 2
Subcutaneous immunotherapy with chemically modified, aluminum hydroxide–adsorbed peanut proteins	Convenience	Injection	Safety and efficacy largely unknown, phase 1
Intradermal/intramuscular immunotherapy with lysosome-associated membrane protein DNA vaccine	Convenience, presumed safety	Unexplored	Safety and efficacy largely unknown, phase 1
Omalizumab	Multiple foods	Cost, IgE levels/weight limitations	More studies to characterize efficacy
Dupilumab	Multiple foods (?)		Potential largely unknown; might need OIT in combination
Traditional Chinese medicine	Safe	No effect in phase 2, poor adherence	Trial with OIT underway
Omalizumab plus OIT	Fewer reactions, faster updosing	Cost, convenience, OIT side effects	Trials underway
OIT and probiotics and other adjuvants	Potential to increase efficacy, persistence of effect	As per OIT	Trials underway

effects (allergic reactions and eosinophilic esophagitis).[202-213] Studies of SLIT and EPIT show better safety profiles with less robust responses than OIT, although there are impressive increases in reactive thresholds considering the very low exposure doses (eg, 2 mg for SLIT and 250 μg for EPIT).[206,211,213,214] Because OIT uses "food" for treatment, there is some controversy regarding whether non–FDA-approved use of food as therapy is appropriate.[215] However, phase 3 studies of peanut OIT and EPIT are nearing completion, and studies with omalizumab (anti-IgE antibodies) to reduce side effects of OIT seem to allow for more rapid dosing,[208,216] might facilitate OIT with multiple foods,[207] and overall result in fewer side effects but might not ultimately change the efficacy profile[208] and carry increased costs. Omalizumab as monotherapy to alter thresholds of reactivity has also shown promise, with about an 80-fold increase in threshold in one study,[217] although more studies are needed to characterize benefits.

Additional allergen immunotherapy approaches under phase 1 study include a modified, alum-absorbed peanut vaccine for subcutaneous immunotherapy administration (NCT02991885) and a plasmid DNA vaccine platform in which peanut allergen DNA is combined with sequences for lysosome-associated membrane proteins (NCT02851277). The construct is taken up by antigen-presenting cells, peanut–lysosome-associated membrane protein is produced, and allergen presentation activates $CD4^+$ T_H cells, as well as $CD8^+$ cytotoxic T cells. Additional potential allergen-specific strategies include peptide immunotherapy, adjuvant-assisted immunotherapy, and others.[218,219] Additional strategies that might not be allergen specific, in addition to omalizumab, as already mentioned above, include traditional Chinese medicine,[220,221] dupilumab, and other biologics.[222]

The field of therapeutics is advancing rapidly, providing great hope for better therapies, as summarized in Table V. The potential for combination therapies (OIT plus immune modulation, such as with traditional Chinese medicine or probiotics[223]) or follow-on therapies (EPIT then OIT) is also evident.

SUMMARY

In the 4 years since our last review, remarkable advances have occurred in understanding, diagnosing, preventing, and treating food allergies. Insights into epidemiology have provided the basis for investigations of risk, management, and prevention that are already being translated into clinical use. Documentation of the significant disease burden has resulted in a surge of research. CRD has already improved the diagnostic armamentarium, and there are more sophisticated tests under development to hopefully improve the ability to predict prognosis and severity and reduce the need for OFCs. Many practical clinical studies provide an evidence base for improved daily management of patients, allowing the informed clinician to address avoidance and emergency management strategies effectively and to consider nuances, such as quality of life, anxiety, and bullying. With numerous studies ongoing and planned with OIT, EPIT, SLIT, modified subcutaneous immunotherapy, DNA-based vaccines, and various biologics and other approaches, we are clearly at the precipice of entering a promising new landscape in which we will be truly treating and not just managing food allergies. With deeper insights into genetics, epigenetics, environmental influences, and the microbiome and incorporation of bioinformatics and with numerous approaches to prevention and treatment under study, we are poised to witness a revolution in our approach to food allergy, with a precision medicine approach[224] emerging over the next several years.

What do we know?

- **The prevalence of food allergy is high, up to 10% of the population, and has likely increased in the past decades.**
- **Numerous genetic and environmental risk factors have been identified.**
- **Insights into route of sensitization, allergen characterization, and immune response provide insights for diagnosis and treatment.**
- **Diagnosis depends on combining a knowledge of pathophysiology and epidemiology with patient history and test results. It is clearly possible to have sensitization without clinical reactivity and *vice versa*.**
- **CRD has entered clinical practice.**
- **Management currently requires attention to allergen avoidance and emergency treatment, and numerous resources are available to patients and physicians to promote education and counseling to improve safety and quality of life.**
- **Early introduction of peanut to high-risk infants can reduce the risk of peanut allergy.**
- **Numerous clinical trials are underway, and FDA-approved therapies are likely to reach clinics soon.**

What is still unknown?

- **A full understanding of the cause for an increase in food allergy**
- **Further translation of environmental and genetic risk factors into improved prevention**
- **The best diagnostic approaches**
- **How to maximize safety and quality of life during management**
- **The best novel therapeutic options**
- **A "personalized medicine" approach to diagnosis and treatment of food allergy is likely required but remains elusive.**

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