Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment

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This review focuses on advances and updates in the epidemiology, pathogenesis, diagnosis, and treatment of food allergy over the past 3 years since our last comprehensive review. On the basis of numerous studies, food allergy likely affects nearly 5% of adults and 8% of children, with growing evidence of an increase in prevalence. Potentially rectifiable risk factors include vitamin D insufficiency, unhealthful dietary fat, obesity, increased hygiene, and the timing of exposure to foods, but genetics and other lifestyle issues play a role as well. Interesting clinical insights into pathogenesis include discoveries regarding gene-environment interactions and an increasing understanding of the role of nonoral sensitizing exposures causing food allergy, such as delayed allergic reactions to heat-denatured forms of milk and egg into the diets of children who tolerate these foods, rather than strict avoidance, represents a significant shift in clinical approach. Recommendations about the prevention of food allergy and atopic disease through diet have changed radically, with rescaling of many recommendations about extensive and tick bites. Component-resolved diagnosis is being rapidly incorporated into clinical use, and sophisticated diagnostic tests that indicate severity and prognosis are on the horizon. Current management relies heavily on avoidance and emergency preparedness, and recent studies, guidelines, and resources provide insight into improving the safety and well-being of patients and their families. Incorporation of extensively heated (heat-denatured) forms of milk and egg into the diets of children who tolerate these foods, rather than strict avoidance, represents a significant shift in clinical approach.

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

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This article is an update to our comprehensive review of the diagnosis and management of food allergy published in 2010.

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Received for publication November 4, 2013; revised November 25, 2013; accepted for publication November 25, 2013.

Available online December 31, 2013.

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http://dx.doi.org/10.1016/j.jaci.2013.11.020

List of Design Committee Members: Scott H. Sicherer, MD, and Hugh A. Sampson, MD

Activity Objectives
1. To describe the current epidemiology of food allergy.
2. To learn pearls and pitfalls regarding the diagnosis of food allergy.
3. To understand the management of food allergy, including attention to quality-of-life issues.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: S. H. Sicherer is on the American Board of Allergy and Immunology; has received consultancy fees from Novartis and Food Allergy Research & Education; has received research support from the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy Research & Education; and receives royalties from UpToDate. H. A. Sampson has received research support from the NIAID/National Institutes of Health and Food Allergy Research & Education; has received travel support as Chair of the PhARF Award review committee; has received consultancy fees from Allerent Therapeutics and Regeneron; and has received lecture fees from Thermo Fisher Scientific, UCB, and Pfizer.

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Abbreviations used
AD: Atopic dermatitis
APT: Atopy patch test
CMA: Cow’s milk allergy
COFAR: Consortium of Food Allergy Research
CRD: Component-resolved diagnostics
EHCF: Extensively hydrolyzed casein formula
EoE: Eosinophilic esophagitis
FLG: Filaggrin
α-Gal: Galactose-α-1,3-galactose
LR: Likelihood ratio
NHANES: National Health and Nutrition Examination Survey
OFC: Oral food challenge
OR: Odds ratio
sIgE: Allergen-specific serum IgE
PPV: Positive predictive value
SPT: Skin prick test

Since that publication, an expert panel sponsored by the National Institute of Allergy and Infectious Diseases 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 non-immune reactions that include metabolic, toxic, pharmacologic, and undefined mechanisms. We encourage readers seeking an overview to refer to practice parameters, guidelines, and international consensus papers that emphasize key points in the diagnosis and management of food allergy and related disorders. Companion articles in this issue of the *Journal* focus on oral, sublingual, and epicutaneous immunotherapy and insights obtained from murine models of food allergy, and therefore we will not review these topics in detail. We highlight recent clinical observations and advances that inform prevention, diagnosis, and management now and, hopefully, in the near future.

**EPIDEMIOLOGY AND NATURAL HISTORY**

**Prevalence**

Accurate determinations of food allergy prevalence are elusive because factors such as allergy definitions, study populations, methodologies, geographic variation, ages, dietary exposures, and other factors influence the estimates. A comprehensive review of the literature concluded that “food allergy affects more than 1% to 2% but less than 10% of the population” and that it remains unclear whether the prevalence is increasing. A number of recent studies provide spectacularly high estimates of food allergy. Gupta et al 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 approximately 3% experience severe reactions. Soller et al surveyed 9667 subjects from 10 Canadian provinces for self-reported food allergy and found an overall rate of 8%. When they excluded adults reporting unlikely allergies and adjusted for nonresponders, the final estimates were 6.7% in the overall population, with 7.1% of children and 6.6% of adults reporting food allergy. Cow’s milk (2.2%), peanut (1.8%), and tree nuts (1.7%) were the most common allergens in children, and shellfish (1.9%), fruits (1.6%), and vegetables (1.3%) were the most common allergens in adults. Taking a different perspective using food allergen-specific serum IgE (sIgE) results obtained in the National Health and Nutrition Examination Survey (NHANES) in the United States (2005-2006), Liu et al estimated clinical allergy to cow’s milk, egg, and peanut at 1.8% each in children age 1 to 5 years. The 2 most recent NHANES performed from 2007-2010 with 20,686 US participants included queries on self-reported food allergies. Overall, 8.96% reported food allergy, with 6.5% among children. Self-report or reliance on serology is notoriously inaccurate, but few studies include oral food challenges (OFCs) on a population level. Osborne et al evaluated a population-based cohort of 2848 (73% participation rate) 1-year-old infants in Melbourne, Australia, in a study that included OFCs and estimated prevalence as follows: peanut, 3.0%; raw egg, 8.9%; and sesame, 0.8%. A United Kingdom study on early childhood peanut allergy, which included OFCs, estimated a peanut allergy prevalence of 2% at age 8 years. A population-based study on the prevalence of cow’s milk protein–induced enterocolitis syndrome revealed a cumulative incidence of 0.34% (44/13019) in Israel. Taken together, these studies substantiate food allergy rates nearing 5% in adults and approaching 8% in children, with a number of estimates nearing 2% for peanut allergy. Whether perceived or confirmed allergy, the economic, emotional, and safety burden is substantial.

Data generally support an increase in prevalence. A 2013 data brief from the US Centers for Disease Control and Prevention relying on data from a single question in the US National Health Interview Survey concluded that among children age 0 to 17 years, the prevalence of food allergies increased from 3.4% in 1997-1999 to 5.1% in 2009-2011. Estimates based on a single query are suspect, but a number of pediatric studies also support an increased prevalence. A US survey repeated on 3 occasions presented the opportunity to compare results from 1997 to 2008 in surrogate-reported peanut allergy in children. The rate increased significantly from 0.4% to 1.4%. Limitations of the studies included decreasing participation rates and self-assessment of allergy. However, as indicated above, similar or higher rates of peanut allergy were determined in a number of studies using various methodologies, including OFCs, around the same period. Additional recent publications focusing on peanut allergy indicated increases with a doubling (United Kingdom) or tripling (United States) in diagnoses. A cross-sectional study of infants from a single clinic in China over a 10-year period used OFCs for diagnosis and estimated an increase in food allergy from 3.5% to 7.7% (P = .17). Although there are methodological limitations, the impression of an international increase in allergy and food allergy remains strong.

**Risk factors**

A plethora of risk factors are proposed to influence food allergy or sensitization, including sex (male sex in children), race/ethnicity (increased among Asian and black children compared with white children), genetics (familial associations, HLA, and specific genes), atopy (comorbid atopic dermatitis [AD]), 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), increased hygiene, and the timing and route of exposure to foods (increased risk for delaying allergens with possible environmental
sensitization. Some of these factors might provide opportunities for prevention or treatment.

Recent studies provide additional insights regarding risk factors. For example, a study evaluating 3136 children and adolescents in the 2005-2006 NHANES found that vitamin D levels of less than 15 ng/mL compared with levels of greater than 30 ng/mL were associated with an increased risk (P < .005) of peanut sensitization (odds ratio [OR], 2.39; 95% CI, 1.29-4.45). An Australian study using a well-characterized cohort undergoing OFCs showed a latitude gradient for IgE-mediated egg and peanut allergy, with higher rates in regions farther from the equator with less ambient UV radiation. Additional studies supporting the vitamin D hypothesis include the following: season of birth is a risk factor, pediatric food-induced anaphylaxis is more common in northern areas of the United States, vitamin D sufficiency is protective against food allergy, and maternal intake of vitamin D during pregnancy is associated with decreased risk of food sensitization. Not all studies support the theory; for example, Weisse et al reported 378 mother-infant pairs studied in a German cohort in which increased maternal vitamin D levels were associated with the children receiving a diagnosis of food allergy (OR, 3.66; 95% CI, 1.36-9.87). Controlled trials will be needed to determine whether interventions can affect outcomes.

In the past several years, attention has shifted from assumptions that early infant allergen exposure was a risk factor for food allergy to the opposite notion that prolonged allergen avoidance might be a risk factor because oral tolerance induction would be bypassed while alternative sensitizing routes of exposure, particularly through the skin (especially nonintact inflamed epidermis in patients with AD), was ongoing. Epidemiologic studies have mostly continued to support this hypothesis, which is discussed further below in the context of approaches to allergy prevention.

A number of risk factors are immutable but might provide insights into the cause. Boys appear to be at higher risk than girls and perhaps women more than men, suggesting genetic or endocrinologic influences. One study showed a higher risk for increased affluence, suggesting lifestyle influence. Racial and ethnic differences in food allergies are being increasingly explored. In telephone surveys shellfish allergy was reported at a significantly higher rate among black/African American than white subjects (3.1% vs 1.8%). Non-Hispanic black subjects also had increased risks of having serologic results, indicating likely food allergy in the NHANES study (OR, 3.1). An interesting example is the very high rate of shellfish sensitization among inner-city atopic children, which might relate to exposure to cross-reactive proteins in cockroach, the clinical ramifications of which remain mostly unexplored.

Exposure to microbes might also influence food allergy risk. For example, Kusumoki et al evaluated 11,454 Japanese children by means of a survey and found food allergy decreased with increasing birth order, possibly reflecting exposure to more infection from siblings. The NHANES database was used to evaluate rates of food sensitization against urinary levels of endocrine-disrupting compounds, and only the compound triclosan, which has an antimicrobial effect, was associated with an increased risk for food sensitization (among male subjects). However, in a systematic review of studies looking at microbial exposure influence on food allergy, including cesarean section, having siblings, attending childcare, and treatment with probiotics, there was a lack of clear evidence to support microbial protection and too much study heterogeneity for a meta-analysis. Although a murine model recently provided impressive evidence of the influence of the microbiota on food allergy, more human studies are needed.

Studies focusing on food allergy outcomes also identify combinations of factors that conspire to define risk. Koplin et al evaluated 453 Australian infants with egg allergy confirmed by using OFCs from a population-based sample of 5276 infants and identified a number of risk factors: parental or sibling allergy history and parents born in East Asia rather than Australia, as well as protective factors, such as older siblings and having a dog in the home. Du Toit et al, in preparing a cohort of 4- to 10-month-olds for evaluation of the effect of early introduction of peanut on peanut allergy, noted that egg allergy and severe eczema were the strongest predictors of peanut sensitization.

Comorbidities might identify patients at risk for increased food allergy morbidity. For example, several studies have indicated that having food allergy might be a risk for problematic asthma and having asthma might be a risk for severe/fatal food allergy. Overall, the risk factors discussed add insights about outcomes and provide avenues for prevention, such as probiotics, and possibly future treatments, such as nutritional interventions.

Natural course

The course of resolution of food allergy has been well characterized and recently reviewed. In general, childhood food allergies to milk, egg, wheat, and soy typically resolve during childhood, whereas allergies to peanut, tree nuts, fish, and shellfish are persistent. Prognosis also varies by disorder; for example, food allergy–related eosinophilic esophagitis (EOE) appears to have a relatively poor chance of resolution. There is evidence that resolution rates have slowed for allergies that have been commonly “outgrown,” such as those to milk, egg, wheat, and soy. For example, Savage et al reported in a referral practice that soy allergy resolved in 25% by age 4 years, 45% by age 6 years, and only 69% by age 10 years.

Early prediction of future tolerance would be useful in planning whether to apply immunotherapeutic interventions and to provide personalized insights on prognosis. Higher early sIgE levels appear to carry a poorer prognosis than lower values, and decreases in these test results over time might signal resolution. The possibility of providing long-term prognostic information based on early markers is evolving. Elizur et al reported on 54 children with IgE-mediated cow’s milk allergy (CMA) who were identified in a population-based study and followed for as long as 5 years. Thirty-one (57.4%) infants resolved their allergy, and risk factors for persistence included a reaction to less than 10 mL of milk on OFC (or on first exposure, P = .01), a larger skin
prick test (SPT) weal size \((P = .014)\), and age of 30 days or less at the time of the first reaction \((P = .05)\). Early markers of resolution of CMA were also evaluated in the Consortium of Food Allergy Research (COFAR) observational study in which 154 (52.6%) subjects experienced CMA resolution at a median age of 63 months. \(^{38}\) Baseline (age, 3-15 months) characteristics that were most predictive of resolution included milk sIgE levels, SPT-induced weal sizes, and AD severity \((P < .001)\). A calculator to estimate resolution probabilities using these frequently obtained variables was devised for use in the clinical setting when evaluating children 3 to 15 months of age (available at www.cofargroup.org), although more validation is needed. Advanced tests evaluating the specific proteins to which IgE binds in a food, the epitopes within the protein that are recognized, and the affinity of binding might carry additional prognostic indicators. \(^{59-61}\) Additional studies, perhaps combining clinical and additional laboratory investigations, might provide more insight into prognostication.

**PATHOGENESIS**

There is a complex interplay of environmental influence and genetics that underlie the immunopathogenesis of food allergy and the manifestations of various food-induced allergic disorders. In this issue of the *Journal*, Oyoshi et al\(^7\) describe insights on etiology determined from murine models. Prior reviews address the role of antigen-presenting cells, T cells, humoral immune responses, homing receptors, signaling pathways, dietary factors, underlying inflammatory states, microbiota, effector cell function, and other aspects of the immune response to dietary antigens. \(^{62-67}\) Here we consider several observations from clinical studies that have recently revised our understanding of the cause of food allergy.

Elucidating gene-environment interactions is crucial for understanding pathogenesis. For example, in a prospective study of 970 children, breast-feeding was associated with an increased risk of food sensitization, but the effect was dependent on functional genetic variants in the IL-12 receptor \(\beta 1\), Toll-like receptor 9, and thymic stromal lymphopoietin genes. \(^{68}\) In another study taking a deeper look at the vitamin D hypothesis, Liu et al\(^69\) evaluated a Boston birth cohort \((n = 649)\) and did not find an association of cord blood vitamin D levels with sensitization to food allergens in early childhood. However, when examined with candidate gene single nucleotide polymorphisms, a significant interaction indicating a risk for sensitization was identified for an \(IL4\) gene polymorphism and 3 other genes.

The microbiome is emerging as an important “internal” environmental exposure, \(^70\) and treatment with prebiotics and probiotics is an avenue of therapy in response to this influence. The immune consequences are slowly being elucidated. Forsberg et al\(^71\) reported on children undergoing probiotic supplementation in a controlled trial and found that this supplementation was associated with decreased allergen-induced production of IL-5 and IL-10 and higher levels of ovalbumin-induced CXCL10 at birth and CCL17 at 24 months, suggesting a greater capacity for immune regulation.

The key immune factors responsible for allergy outcomes are under intense investigation. In the COFAR cohort described above, \(^7\) mononuclear cell allergen stimulation screening was performed with PCR analysis to 7 key markers of immune regulation and \(T_{H1}/T_{H2}\) bias. Only allergen-induced \(IL4\) expression was associated with clinical allergy to milk and sensitization to milk and peanut. This was noted in the absence of increased \(GATA3\) mRNA expression, identifying a potential marker but also raising a question about the IL-4 not being of T-cell origin.

The importance of considering the route of sensitization on food allergy has been recently highlighted, \(^73\) such as sensitization through nonoral routes. It has long been appreciated that respiratory sensitization can result in food allergy, as demonstrated by pollen-food–related allergies, as well as some more esoteric examples, including cat-pork–related allergy (pork meat allergy attributed to initial environmental sensitization to cat serum albumin), \(^74\) and wheat allergy induced by using wheat protein–based soap. \(^75\) Here again environment and genetics conspire. Skin exposure to environmental food allergens might be a sensitizing route, particularly when there is epithelial barrier dysfunction, such as in those with AD. \(^76\) This theory was supported by a study showing that filaggrin \((FLG)\) loss-of-function mutations are associated with peanut allergy, and interestingly, the association remained significant \((P = .0008)\) after controlling for coexistent AD. \(^77\) \(FLG\) loss-of-function mutations were determined in a subset \((n = 700)\) from a large cohort that was extensively tested for sensitization and clinical food allergy. \(^77\) After adjusting for eczema, \(FLG\) mutations were associated with food sensitization (OR, 3.0; 95% CI, 1.0-8.7; \(P = .043\)). However, after adjustment for risk of clinical food allergy among those sensitized, there was no further influence of \(FLG\) mutations, suggesting this mutation is not playing a role in progression of sensitization to clinical allergy.

A very interesting and novel form of food allergy that is manifested clinically by delayed allergic responses and anaphylaxis hours after ingestion of mammalian meat has been linked to sensitization to carbohydrate galactose-\(\alpha1,3\)-galactose \((\alpha\)-Gal\). \(^78\) The route of sensitization appears to be from tick bites based on clinical circumstances and detection of \(\alpha\)-Gal in the gut of the tick *Ixodes ricinus*. \(^79,81\) The \(\alpha\)-Gal epitope is a major blood group substance of nonprimate mammals, and there is likely a predilection for sensitization among those with B-negative blood groups. \(^82\) The reason for the delayed reactions remains to be elucidated. Thus \(\alpha\)-Gal allergy is unique for the allergen being a carbohydrate, the exposure being through the intracutaneous route, and the time course of the reaction being delayed. Elucidating these factors further will likely provide more insights on the pathophysiology of other food allergies as well.

The manner of food preparation and processing and the nonprotein components of foods also likely play a role in pathogenesis. This might go beyond the notion that heating destroys some relevant food allergens, such as birch homologous proteins in fruits or tertiary protein structures in milk or egg, or creates more potent allergens, such as through the Maillard reaction of nonenzymatic browning in which heating results in a chemical reaction between reducing sugars and proteins to form advanced glycation end-products in roasted peanut. \(^83\) For example, invariant natural killer T cells can be activated by sphingolipids presented through CD1d molecules to produce \(T_{H2}\) cytokines, raising the possibility that these components in foods might direct an allergic response to foods. In a series of experiments comparing PBMC responses from children with CMA, egg allergy with tolerance of milk, and healthy control subjects, Jyonouchi et al\(^84\) showed that milk sphingomyelin can induce invariant natural killer T-cell activation and \(T_{H2}\) cytokine...
production and that the response is more exuberant in children with CMA. Ichmann et al90 observed that heating ovalbumin with glucose enhanced activation of ovalbumin-specific CD4+ T cells and increased IL-4 levels. Myeloid dendritic cell uptake of the processed ovalbumin was enhanced, and specific dendritic cell receptors were identified that mediated this process. Masila-

mani et al86 showed that dietary isoflavones suppressed allergic sensitization to peanut; these are abundant in soy and not peanut, perhaps explaining why one legume is more allergenic than another. These observations and others86 set the stage for additional work to identify characteristics of foods that promote allergic responses and might elucidate immune intervention strategies.

**DIAGNOSIS**

The overarching approach to diagnosis requires a careful history linked to an understanding of the clinical manifestations, an understanding of the epidemiology and immune cause, and incorporation and interpretation of appropriate tests.1,2 A detailed familiarity with the gamut of food-induced allergic disorders and their pathophysiology is necessary to achieve a successful diagnosis.

**Clinical disorders**

The National Institute of Allergy and Infectious Diseases’ Expert Panel identified 4 categories of immune-mediated adverse food reactions (eg, food allergies), namely IgE-mediated, non–IgE-mediated, mixed, or cell-mediated reactions, and placed celiac disease among non–IgE-mediated disorders and allergic contact dermatitis among cell-mediated disorders.7 Considering that various target organs can be affected by food allergies (eg, the skin, gut, respiratory tract, and cardiovascular system) and the numerous immune pathologies, a wide spectrum of disease falls under the umbrella of food allergies. Table E1 in this article’s Online Repository at www.jacionline.org shows clinical disorders, their key features, immunopathophysiology, natural course, and diagnostic considerations.1,2,7,8,78-80 There are a number of disorders that are not food allergies but might appear similar. For example, toxic reactions, such as scombroid fish poisoning, in which spoiled dark meat fish contains histamine-like toxins; neurologic responses, such as auriculotemporal syndrome, in which foods that trigger increased salivation also result in a reflex facial vasodilatation of the lower cheek; or gustatory rhinitis, in which spicy foods result in rhinorrhea, all mimic food allergies. It is important to recognize that chronic asthma and chronic rhinitis are not likely solely related to food-induced allergic reactions. Similarly, although food can trigger AD in a subset of patients, many additional triggers exist, including irritants, infection, and environmental allergens.

Recent studies have further elucidated the important role of foods in patients with EoE. Henderson et al90 evaluated their dietetic approach using 98 children with EoE and found remission for 96% among 49 patients treated with an elemental diet, 81% for 26 patients on a 6-food elimination diet (2 variations were used, with avoidance of milk, egg, wheat, soy, peanuts, tree nuts, fish, and shellfish for all, and 15 avoided additional foods that resulted in positive test results), and 65% for 23 patients whose diets were determined by SPTs, atopy patch tests (APTs), or both. Similarly, Kagalwalla et al91 used a 6-food elimination diet with 36 children, finding that one food was a trigger for 72% and that milk (74%), wheat (26%) and egg (16%) were the 3 most common causes.

Spergel et al92 performed a review of 941 patients, of whom 319 had definitive food-responsive disease diagnosed based on biopsy results. An empiric 6-food elimination diet or removal of foods eliciting positive test results had a success rate of 53%, although test-directed diets resulted in an average of only 3 foods removed. Milk, egg, wheat, and soy were the most common culprits. Removal of foods identified on skin testing with empiric elimination of milk led to resolution in 77% of patients, milk alone had a 30% response, and milk, egg, wheat, soy, and meats had a 77% response rate. Lucendo et al93 used a food elimination diet for 67 adults, avoiding milk, egg, cereals, fish/shellfish, peanut/legumes, and soy with a 73% response rate. Reintroducing foods revealed that 36% of the responding patients had 1 trigger and 31% had 3 or more triggers. Overall, although there is some debate about the utility of diagnostic tests, a diagnosis of EoE should raise suspicion about food triggers, with a motivation to attempt dietary treatment.

**Diagnostic approaches**

The general approach to diagnosis of food allergy has been reviewed previously.1 Modalities that were recommended in the 2010 Expert Panel Guidelines include medical history and physical examination, elimination diets, SPTs, sIgE measurements, and OFCs.6 Among tests not recommended or not recommended for routine use were intradermal tests, total serum IgE measurements, APTs, and the use of APTs, sIgE measurements, and SPTs in combination, and a number of nonstandardized and unproved tests were specifically not recommended, including measurement of basophil histamine release, applied kinesiology, allergen-specific IgG4 measurement, electrodermal testing, and several others.

Since the time of the expert panel guidelines, a number of studies have refined the way currently available testing can be used, including the next generation of sIgE tests, those evaluating “components” or specific proteins within foods, often termed component-resolved diagnostics (CRD). However, the basic approach to diagnosis remains essentially unchanged and is summarized in Fig 1. The medical history is used to estimate the chance (prior probability) of allergy and culprit food(s), and appropriately selected and interpreted minimally invasive tests are used to arrive at a posttest probability of allergy.94 Short of a conclusion that there is a high probability or extremely low probability of allergy, an OFC might be required for a final diagnosis. Allergists appear to avoid performing OFCs, apparently because of risk, cost, time, and other factors.95 However, it is crucial to include OFCs in the diagnostic armamentarium. Recent studies underscore why. Concerning efficacy, in a study of 125 children primarily with AD who were avoiding foods for a variety of reasons, 89% of 364 OFC results were negative, allowing significant dietary expansion.96 Regarding safety, an office-based study of 701 OFCs had 19% positive challenge results, with only 2% of the challenges requiring treatment with epinephrine.97 Additionally, performing OFCs can improve quality of life, particularly when results are favorable.98 It is important to ensure a full portion of the tested food is successfully ingested to reduce the risk that an uneventful OFC is followed by allergic reactions on a subsequent ingestion, which theoretically could be due to gradual escalating portions
that result in temporary desensitization. A manual for office-based OFCs was devised, and a consensus report toward standardizing double-blind, placebo-controlled OFCs was published. In 2013, 2 new Current Procedural Terminology codes replaced a single prior code for OFCs, likely improving reimbursement, and hopefully resulting in increased use of the procedure.

Clearly, physicians and patients would prefer to have better diagnostic tests to avoid OFCs. Standard SPTs and sIgE tests go a long way in assisting in diagnosis. Lessons learned from a number of studies are compiled in Table I, showing pearls and pitfalls. Unfortunately, there remain relatively few studies correlating food allergy outcomes against skin test size or sIgE concentration, and it is clear that such calculations are influenced by referral base, decisions to undergo testing by patient/family and physician, geography, test characteristics, interpretation of OFC outcomes, age of patients, underlying disease, and other factors.

For example, in a unique population-based Australian cohort of infants who underwent testing and OFCs, 95% predictive values for allergic reactions were determined as follows: egg (SPT wheal, ≥4 mm; sIgE level, ≥1.7 kU/L), peanut (SPT wheal, ≥8 mm; sIgE level, ≥34 kU/L), sesame (SPT wheal, ≥8 mm), and these results vary from those of studies with other cohorts. Additional recent observations of clinical note are that fresh fruits can be frozen and then reused for “fresh” skin testing and that a sesame oil “contact test” might be helpful to identify patients who are reactive to sesame proteins that are oil based (oleosins) and might otherwise have negative test results with standard reagents. Although evaluating sIgE in the context of total IgE is not recommended based on one study, another recent study noted correlations in total to specific IgE levels for children tested to egg, milk, soy, and peanut, and another noted that consideration of total IgE levels was helpful in predicting allergy in combination with other parameters. More studies are needed to elucidate whether evaluating ratios of levels of sIgE to total IgE is informative over sIgE levels alone. For non–IgE-mediated allergy, the utility of the APT for EoE remains controversial, but studies now suggest the approach does not elucidate reactivity in food protein–induced enterocolitis.

The increasing availability of CRD is further refining the diagnosis of IgE-mediated allergy. The reasons that evaluating IgE binding to specific proteins within a food might provide additional diagnostic information includes the following possibilities: (1) recognition of specific proteins that behave as potent allergens (ie, ones that are stable to digestion) might be relevant compared with recognition of proteins that are heat labile or homologous to pollens; (2) binding to multiple proteins within an allergen might carry diagnostic significance; and (3) differentiation of degrees of binding to component proteins might disclose relevant reactivity. However, the methods suffer from some of the same limitations that the standard tests carry. For example, the degree of binding is relevant, specific test platforms might differ, and there could be differences by geography, age, and target organ reactivity. More studies are needed.

FIG 1. General approach to diagnosis of adverse reactions to foods. See text and Tables 1 and E1 for details.
<table>
<thead>
<tr>
<th>Pearl/observation</th>
<th>Additional details</th>
<th>Clinical application</th>
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| A positive skin test or serum food-specific IgE test result indicates sensitization but not necessarily clinical allergy. | Screening with indiscriminate panels of tests is poorly informative. Screening tests with 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). | 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).  
  
  - History should focus on amounts triggering a reaction and ancillary factors.  
  - History should explore the types of foods tolerated or not tolerated.  
  - Care should be taken 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.  
  - Care must be taken in evaluating test results over time when different manufacturers are used.  
  - Concentration of IgE binding to components also relates to outcomes, but similar to standard tests, correlations have not been established and vary by, for example, center and patient selection.  
  - Caution: severe reactions can occur despite lack of noted binding to measured allergen (see text). |
| Dose, manner of preparation, and ancillary (eliciting) factors might alter reaction outcomes. | Alcohol, NSAIDs, and exercise are among eliciting factors that might facilitate a reaction.  
  - Heating might alter allergenicity (eg, bakery products with egg/milk might be tolerated when whole forms are not and cooked foods might be tolerated when raw fruits are not).  
  - A low dose might be tolerated while larger amounts are not. |  
  - History should focus on amounts triggering a reaction and ancillary factors.  
  - 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:  
  - Allergy to:  
    - Peanut  
    - A tree nut  
    - A fish  
    - Shellfish  
    - Grain  
    - Milk  
  - Related food:  
    - Most legumes  
    - Other tree nut  
    - Other fish  
    - Another shellfish  
    - Another grain  
    - Goat/sheep milk  
    - Mare milk  
    - Beef  
  - Approximate clinical reaction rate:  
    - Peanut:  
      - Higher for: walnut-pecan, almond-hazel, cashew-pistachio  
    - A tree nut:  
      - Higher  
    - A fish:  
      - 50%  
    - Shellfish:  
      - 75%  
    - Grain:  
      - 20%  
    - Milk:  
      - 5%  
    - Beef:  
      - 10%  
 |  
  - Care should be taken 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.  
  - Care must be taken in evaluating test results over time when different manufacturers are used.  
  - Concentration of IgE binding to components also relates to outcomes, but similar to standard tests, correlations have not been established and vary by, for example, center and patient selection.  
  - Caution: severe reactions can occur despite lack of noted binding to measured allergen (see text). |
| Tests for serum food-specific IgE might not provide comparable results among manufacturers. | In the United States, there are 3 major test manufacturers.  
  - Food  
    - Peanut  
    - Hazelnut  
    - Soy  
  - Labile:  
    - Ara h 8  
    - Cor a 1, Cor a 2  
    - Gly m 3, Gly m 4  
  - Stable:  
    - Ara h 1, Ara h 2, Ara h 3, Ara h 6  
    - Cor a 9, Cor a 11, Cor a 14  
    - Gly m 5, Gly m 6  |
| Component testing might differentiate clinical reactivity (IgE binding to "potent" stable allergens) from less clinically relevant sensitization (binding to labile proteins). |  
  - Food  
    - Peanut  
    - Hazelnut  
    - Soy  
  - Labile:  
    - Ara h 8  
    - Cor a 1, Cor a 2  
    - Gly m 3, Gly m 4  
  - Stable:  
    - Ara h 1, Ara h 2, Ara h 3, Ara h 6  
    - Cor a 9, Cor a 11, Cor a 14  
    - Gly m 5, Gly m 6  |
| Serum/skin test results might be negative despite clinical reactivity. |  
  - This could be due to reagent lacking relevant protein.  
  - This could be because the 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.  
  - Test results 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. |
| Increasingly high serum food-specific IgE levels or increasingly larger skin test wheal size indicate higher chances of clinical allergy. |  
  - Correlation of tests with outcomes vary by center, age, and disease (equivalent results are generally more predictive of allergy in a younger patient).  
  - Results are not highly correlated with severity. |  
  - Test results 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. |
to correlate test results with clinical outcomes in various patient populations, but proof of concept has been attained for many foods, including egg, milk, wheat, soy, fruits, shrimp, hazelnut, peanut, and others.

Studies on peanut provide helpful illustrations of the utility and limitations of CRD. With regard to geographic differences, a good example is illustrated by Vereda et al, who evaluated component testing in children with peanut allergy from 3 regions, showing that Spanish patients were primarily sensitized to lipid transfer protein (Ara h 9), Swedish patients to birch-related protein (Ara h 8), and US patients to seed storage proteins (Ara h 1-3). These results also correlated with severity of outcomes, with the least severe being related to birch sensitization and the most severe associated with reactivity to seed storage proteins.

The predictive value of CRD is best studied for peanut allergy. When binding is only identified to the birch protein homolog Ara h 8, prognosis is excellent. In evaluation of 144 Swedish children only sensitized to Ara h 8, all but 1 could tolerate peanut ingestion, as reported from natural ingestion or during OFCs to roasted peanut. Binding to Ara h 6, which is not often measured, might be attributed to missing the diagnosis. Interpretation becomes trickier when there is binding to the stable proteins in peanut (Ara h 1-3). Studies on peanut provide helpful illustrations of the utility and limitations of CRD. With regard to geographic differences, a good example is illustrated by Vereda et al, who evaluated component testing in children with peanut allergy from 3 regions, showing that Spanish patients were primarily sensitized to lipid transfer protein (Ara h 9), Swedish patients to birch-related protein (Ara h 8), and US patients to seed storage proteins (Ara h 1-3). These results also correlated with severity of outcomes, with the least severe being related to birch sensitization and the most severe associated with reactivity to seed storage proteins.

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As indicated above, CRD for additional foods are emerging. With regard to milk and egg, clinical reactivity to whole or baked forms has garnered diagnostic interest, pitting standard tests against component testing. Considering egg, studies have suggested that IgE binding to ovomucoid is superior to standard tests, but there are contradictory results. Caubet et al related outcomes of baked egg OFCs to levels of specific IgE and IgG4 to ovomucoid and ovalbumin, establishing whether IgE/IgG4 ratios were additionally informative. The rationale for this approach is that IgG4 levels increase during successful immunotherapy. Indeed, baked egg–reactive children had higher ratios, and inclusion of IgG4 levels in logistic regression models was more informative than sIgE levels alone. However, standard sIgE tests provide helpful information that should not be ignored. Lieberman et al reported the results of 100 OFCs to baked egg in children, with a 66% rate of tolerance. Measurement of serum IgE levels to egg white and SPTs was performed. The skin test wheal size was not informative for predicting outcomes, but an egg white sIgE level of 2.5 kUA/L had a negative predictive value of 0.89, and a level of 10 kUA/L had a PPV of 0.60. The median level for those who reacted was 5.85 kUA/L compared with 2.81 kUA/L in those who were tolerant.

Ultimately, stepped approaches to testing might be the most effective. Dang et al compared 5 strategies for diagnosing peanut allergy by evaluating test parameters in 200 Australian children with a median age of 14 months, with the test population derived from a population-based study. They considered using high/low diagnostic values of peanut IgE of greater than 15 or less than 0.35 kUA/L, SPT wheal sizes of greater than 8 or less than 3 mm, or Ara h 2 levels of greater than 1.0 or less than 0.01 kUA/L based on prior studies. Using peanut IgE alone would have resulted in 95 OFCs, SPT alone would have resulted in 50 OFCs, and Ara h 2 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 SPTs followed by Ara h 2 would have reduced the need to only 21 OFCs. In a further sophistication of using available data, Dunn Galvin et al showed that by using a predictive model based on 6 parameters, SPT, serum food-specific IgE, total IgE, symptom history, sex, and age, they could calculate the likelihood of reactions (97% accuracy) or tolerance (94% accuracy) to peanut, milk, and egg better than with individual parameters. This approach was validated in another setting.

### TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Pearl/observation</th>
<th>Food</th>
<th>Mean age, 5 y; 50% react</th>
<th>Mean age, 5 y; ~95% react</th>
<th>Age &lt;2 y; ~95% react</th>
</tr>
</thead>
<tbody>
<tr>
<td>At specific high levels of IgE or large skin tests, clinical reactivity is highly likely; however, studies are limited, and variations in “diagnostic cutoff” values are reported.</td>
<td>Egg</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Milk</td>
<td>2</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Peanut</td>
<td>2/5</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

*Values are kUA/L, the dual notation for peanut indicates with/without a clinical history.

Revised from Sicherer and Sampson.

**NSAIDs**: Nonsteroidal anti-inflammatory drugs.
Further refinement of diagnosis in the future, with the goal of improved prognostics and less reliance on OFCs, will likely be based on cellular and humoral testing and more sophisticated algorithms to interpret test results. Beyond CRD, one can measure binding to specific epitopes within proteins, evaluating binding patterns, degree, and affinity. Considering shrimp as an example, diagnostic efficiency was higher when binding to individual epitopes rather than when specific proteins were used, and more intense and diverse epitope recognition defined those with clinical allergy rather than clinically irrelevant sensitization.\textsuperscript{146} Another example with CMA\textsuperscript{61} compared the progression of epitope binding of milk proteins in children with resolved or persistent

<table>
<thead>
<tr>
<th>TABLE II. Management considerations (selected examples)</th>
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</thead>
<tbody>
<tr>
<td>Area</td>
</tr>
<tr>
<td>Avoidance</td>
</tr>
<tr>
<td>Restaurants</td>
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<tr>
<td>Travel</td>
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<tr>
<td>School</td>
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<td>By age</td>
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<tr>
<td>Vigilance</td>
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<td>Experimentation</td>
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<tr>
<td>Caregivers</td>
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<tr>
<td>Anxiety, emotional</td>
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<tr>
<td>Nutrition</td>
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<tr>
<td>Ingestion vs noningestion</td>
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<tr>
<td>Resources (examples)</td>
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<tr>
<td>Emergency management</td>
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<tr>
<td>Prevention (primary)</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
allergy. Binding patterns were stable over time for those with persistent allergy, but among those with early recovery, IgG4 epitope binding increased while IgE binding to corresponding epitopes decreased. Different epitope-binding patterns were also noted to differentiate clinical phenotypes of CMA: a wider diversity of IgE epitope binding was noted for those with persistent CMA and more severe reactions and was more likely to occur in children who could not tolerate extensively heated forms of milk (eg, in muffins) compared with those who could tolerate such foods. In competitive peptide microarray assays, children with persistent CMA were fully differentiated from those with resolved allergy or tolerance of extensively heated forms by having high compared with low affinity binding, respectively. Increasingly sophisticated approaches are being evaluated. Lin et al. used microarray immunoasays to map epitopes on the major peanut proteins and then used a bioinformatics approach to identify patterns that were most informative. This approach performed significantly better than standard methods.

In addition to testing humoral responses, diagnosis with T-cell proliferative responses, metabolomics, and basophil activation are under study.

**MANAGEMENT/TREATMENT**

**Avoidance and emergency management**

The current approach to management substantially relies on allergen avoidance and preparation to promptly treat allergic reactions. These tenets of treatment require significant patient education. Aspects of care that have been recently reviewed in this Journal include the following: circumstances warranting prescription of self-injectable epinephrine, the importance of education about prehospital treatment of reactions, education about avoidance (eg, cross-contact, traveling, restaurants, school issues, and label reading), legislation regarding labeling, food manufacturing, and increasing access to epinephrine, the availability of advocacy organizations, and numerous resources for education developed by a number of constituencies.

A number of important management lessons were revealed by a multicenter observational study of 512 infants with likely milk or egg allergy (COFAR). Over a median follow-up of 36 months, despite receiving care in food allergy centers, the annualized reaction rate was 0.81 per year for all foods (367/512 subjects reporting 1171 reactions), with 56% reporting more than 1 reaction. Most reactions were attributed to lack of vigilance (eg, label checking errors and unintentional ingestion), with additional errors including cross-contact in meal preparation and food not provided by the parent. Approximately 11% of reactions were attributed to nonaccidental exposure, indicating in some cases that families might have tried a food to explore whether it would be tolerated outside of medical supervision. Of the 11.4% of reactions that were severe, only 29% of them were treated with epinephrine because the caregiver did not recognize the severity, the epinephrine was unavailable, or the caregiver was afraid to administer it. Educational opportunities to improve safety are evident.

Aside from physical reactions, having food allergy can affect quality of life, and the psychological welfare of children with food allergies is important to address. Shemesh et al. noted that 45% of children with food allergies reported being bullied, most often without parents being aware. The bullied children had lower quality of life and increased anxiety compared with those not being bullied, but parental awareness of the bullying was associated with a significantly less affected quality of life. The educational advice responsive to these study findings, as well as selected key management issues from other publications, are incorporated in Table II. School food allergy management guidelines from the US Centers for Disease Control and Prevention are now available (www.cdc.gov/HealthyYouth), and educational materials developed and validated through COFAR are available at www.cofargroup.org. When completing written emergency anaphylaxis treatment plans that include an antihistamine, the physician should consider a recent study indicating the equivalent effectiveness of cetirizine and diphenhydramine, with more potential of the former to avoid sedation, and address the increasing options for autoinjectors that are currently available.

Avoidance and emergency management is how to manage advisory (“may contain”) food labeling, which is voluntary in most countries. Ford et al. evaluated a sample of 401 foods for the presence of milk, egg, or peanut when those foods had advisory labels (eg, “may contain”) or did not have such warnings. Overall, 5.3% of the products with advisory labels had detectable protein, whereas 1.9% of the products with no warnings were contaminated. The latter were primarily accounted for by small companies, and these results were not observed for peanut. Crotty and Taylor focused on products with advisory labeling for milk and found high rates of contamination (42%) primarily accounted for by chocolates. Although the level of allergen is low in many cases, there are clearly risks present for sensitive patients. To potentially improve this conundrum, more data are needed on thresholds of reactivity, which are emerging, and also guidance from regulatory agencies, consumers, manufacturers, and other stakeholders so that labeling can be regulated without overestimating or underestimating risk. Currently, it is potentially safer to advise patients to avoid such labeled products, but avoidance carries an effect on quality of life, and individualizing advice might be rational for selected patients who are deemed less sensitive. A good example of allowing some trace exposure (very small risk) against a stronger benefit is the influenza vaccine. The residual amount of egg protein in the influenza vaccine appears to be low risk, immunization is generally recommended, and egg-free vaccines are becoming more available.

**Prevention**

Several guidelines contain updated dietary prevention recommendations that rescinded those promulgated more than a decade ago, particularly expunging prolonged allergen avoidance as a means to prevent atopic disease or food allergies. Updated summaries are included in Table II.

Regarding pregnancy diets, allergen avoidance is not recommended, although studies remain conflicting. In a Danish birth cohort (n = 61,980), children of mothers with frequent intake of peanut during pregnancy compared with those without were less likely (OR, 0.66; 95% CI, 0.44-0.98) to have children with asthma at 18 months of age, with a similar finding for tree nut consumption. In contrast, a study from COFAR noted that maternal ingestion of peanut during pregnancy had a positive dose-response association with risk of the infant having increased peanut IgE antibody levels (however, clinical peanut allergy rates have not yet been determined). Although exclusive breast-feeding is recommended for at least 4 months, data about allergy...
prevention from this approach are also mixed. Among 51,119 randomly selected 8- to 12-year-old schoolchildren in 21 countries, there was a small increase in the risk of reported eczema in association with ever having breast-fed (adjusted OR, 1.11; 95% CI, 1.0-1.2), and there was no significant association between reported “eczema ever” and breast-feeding for greater than 6 months (adjusted OR, 1.09; 95% CI, 0.9-1.3). For substitutions of formula, soy is not considered to have a prevention effect, but for infants at risk of atopic disease, a hydrolyzed formula with a possibly better advantage of extensively hydrolyzed casein formula (EHCF) might offer protection against eczema over whole milk-based formulas. However, recent studies on this topic also remain conflicting, including a single-blind, randomized controlled trial of a partially hydrolyzed whey-based formula and a soy or conventional milk-based formula at weaning in high-risk infants, which did not show differences in outcomes for eczema, food reactions, or sensitization.\(^{174}\) In contrast, a 10-year follow-up of a randomized trial of 4 formulas as breast milk substitutes in infants at risk of atopy continued to show a reduced cumulative relative risk of AD for specific hydrolyzed infant formulas compared with whole cow’s milk infant formula, with a relative risk of 0.72 (95% CI, 0.58-0.88) for the extensive hydrolysate of casein. The protection was noted only for AD and not sensitization to foods. In another study of 679 infants who were consistently fed the same formula for the first 6 months of life, comparing 345 with hydrolyzed formula with 334 with cow’s milk formula, the percentage sensitized to milk protein was significantly lower in the group receiving the hydrolyzed formula (12.7% vs 23.4%, \(P = 0.048\)).\(^{176}\) Considering these and past studies,\(^{2,171,172}\) formula selection might provide some atopy preventive advantage with regard to atopy or food allergy prevention.\(^{175}\) For example, Koplin et al\(^ {39}\) used a cross-sectional study of 2589 infants and noted that delayed introduction of egg was associated with increased risk of egg allergy compared with introduction at 4 to 6 months, delaying beyond 12 months carried an adjusted OR of 3.4 (95% CI, 1.8-6.5). In a Finnish birth cohort study of 3781 consecutively born children,\(^ {177,178}\) introduction of egg at 11 months or less was inversely associated with asthma, allergic rhinitis, and atopic sensitization, whereas introduction of fish at 9 months or less was inversely associated with allergic rhinitis and atopic sensitization. Less food diversity already at 3 months of age was associated with a later increase in atopic sensitization. A birth cohort study in Detroit, Michigan, found that feeding of complementary foods before 4 months was associated with a reduced risk of food sensitization to peanut and possibly egg by age 2 or 3 years in a subset of the cohort having a parental history of asthma or allergy.\(^ {179}\) If there is a period of opportunity in which ingestion is tolerizing, it might vary by food, environmental factors, and genetics. Katz et al\(^ {40}\) evaluated a cohort of greater than 13,000 infants and calculated an OR of 19.3 (95% CI, 6.0-62.1) for development of IgE-mediated CMA among infants exposed after 15 days of age. Yet another study looking at food allergy outcomes\(^ {180}\) found no difference in the presolids infant diet, but those without food allergies were more likely to ingest a “healthy” diet of fruits, vegetables, and home-prepared foods. Although many studies attempt to control for reverse causation, there might be a subtle effect in which parents of at-risk infants delay allergen exposure, influencing the conclusions of these studies toward potentially erroneous conclusions of an ill effect from delaying introduction. In a controlled trial randomizing early exposure to egg in 86 infants at risk for egg allergy, a lower but not significant proportion of infants in the egg group compared with control subjects were given a diagnosis of egg allergy at 12 months of age (33% vs 51%, \(P = .11\)), possibly suggesting that earlier exposure might not increase egg allergy. Taken together, the studies indicate that in an otherwise healthy infant, there is no rationale to delay introduction of solids and no rationale to defer allergenic foods, although it seems that some cautions are warranted, such as using less allergenic foods as initial weaning foods, proceeding gradually, and pursuing more evaluations, particularly if the infant shows signs of atopy or food-induced allergic reactions. A comprehensive approach was recently outlined.\(^ {163}\)

An active approach to prevention has focused on prebiotics, probiotics, symbiotics, and bacterial lysates, essentially combating the allergy-eliciting nature of a hygienic environment by providing and nurturing nonpathogenic, health-promoting bacteria.\(^ {181}\) There is some promise, with studies suggesting certain strains, especially when administered both prenatally and postnatally, might at least reduce eczema.\(^ {182}\) However, studies remain conflicting and inconclusive. For example, Jensen et al\(^ {183}\) presented 5-year follow-up on a randomized postnatal study of 6 months of treatment with Lactobacillus acidophilus, showing no protective effect for any physician-diagnosed allergic disease, but earlier findings of increased risk for sensitization in treated children were no longer cumulatively significant. A Cochrane database review on prebiotics for prevention of allergy in infants, evaluating 4 studies with 1428 infants, concluded that there is some evidence for eczema prevention but also concluded that further research is needed before routine use.\(^ {184}\) A 2012 World Allergy Organization review concluded that probiotics do not have an established role in the prevention or treatment of allergy.\(^ {185}\) Clearly, study results can be affected by strain selection and other factors. With an increasing number of studies that are sensitive to the selection of subjects, timing of treatment, and strain selection, more definitive conclusions are likely to emerge.

**Future therapies**

Companion articles in this issue of the *Journal*\(^ {8,9}\) describe advances in oral, sublingual, and epicutaneous immunotherapies for foods, as well as a number of approaches under evaluation in murine models.\(^ {186,187}\) It will be interesting to see whether additional routes, such as intralymphatic immunotherapy, become viable for food immunotherapy.\(^ {188}\) Allergen-specific immunotherapeutic approaches include not only oral, sublingual, or epicutaneous immunotherapy with whole allergen but also immunotherapy with modified proteins that were designed to be hypoallergenic to reduce the risk of reactions. Unfortunately, in a pilot safety study of heat-killed, Escherichia coli—expressing modified Ara h 1, 2, and 3 as rectal immunotherapy, there were frequent allergic reactions, necessitating a redesign of the study dosing or product.\(^ {189}\) Additional antigen-specific approaches are under preclinical investigation, but combination approaches, such as using allergen oral immunotherapy while also treating with anti-IgE antibodies, has been studied in human subjects, with some promise of increased safety.\(^ {190,191}\) Although not initially considered an
immunotherapeutic approach, a major recent advance in management is the observation that a majority of children with egg or CMA can tolerate extensively heated forms of these allergens, such as in bakery goods, and that ingesting these products might speed recovery. In a long-term follow up of children who were able to add baked milk products (eg, muffins) to their diet, tolerance of regular milk was 16 times more likely compared with a group treated with standard-of-care avoidance. A trial of omalizumab for peanut allergy was stopped early for a safety concern related to the food challenge approach but showed some trend toward efficacy in children with egg allergy was stopped early for a safety concern related to the food challenge approach but showed some trend toward efficacy in children with egg allergy. Similarly, Leonard et al performed a follow-up study in children with egg allergy who were successfully challenged with baked egg products and ate them routinely. These children were 14.6 times more likely than comparison control subjects (P < .0001) to have tolerance to unheated egg. However, these were not randomized trials, and not all studies suggest an immunotherapeutic response. A study is underway in COFAR evaluating baked egg versus egg oral immunotherapy.

Therapies that are not allergen specific are especially attractive because many patients have multiple food allergies. These approaches include various mAbs, traditional Chinese medicine, probiotics, and others. A trial of omalizumab for peanut allergy was stopped early for a safety concern related to the food challenge approach but showed some trend toward efficacy in increasing the threshold of reactivity. An herbal formula to treat food allergy was evaluated in a safety trial for 6 months with no significant side effects and a trend toward decreasing eosinophil and basophil numbers, and in vitro tests showed a decrease in basophil activation. Individual studies are looking at probiotics for treatment. For example, in one study otherwise healthy infants with CMA were given EHCFS (n = 55), EHCF with Lactobacillus rhamnosus GG (n = 71), hydrolyzed rice formula (n = 46), soy formula (n = 55), or amino acid–based formula (n = 33), and OFCs were performed after 12 months to assess acquisition of tolerance. The rate of tolerance after 12 months was significantly higher (P < .05) in the groups receiving EHCF (43.6%) or EHCF plus Lactobacillus rhamnosus GG (78.9%) compared with the other groups: hydrolyzed rice formula (32.6%), soy formula (23.6%), and amino acid–based formula (18.2%). More studies are needed to evaluate the safety and efficacy of all of these approaches, as well as combination approaches, by using allergen-specific and nonspecific modalities or combining approaches serially (sublingual immunotherapy leading to oral immunotherapy) or concomitantly. Table E2 in this article’s Online Repository at www.jacionline.org lists examples of therapies under preclinical and clinical studies.

SUMMARY
In the 3 years since our last review, remarkable advances have occurred in understanding and managing food allergies. Unfortunately, the intense efforts to improve diagnosis, treatment, and prevention are partly the result of an unexplained significant increase in prevalence. Although conflicting studies and disappointing results in some clinical treatment trials are frustrating, remarkable advances in diagnosis and treatment are already apparent, and new insights on cause and pathogenesis are resulting in renewed efforts with novel approaches toward prevention, diagnosis, and treatment. With deeper insights into genetics and the microbiome, incorporation of bioinformatics, and numerous approaches to treatment in preclinical and clinical studies, we are poised to witness a revolution in our approach to food allergy over the next several years.

What do we know?
- The prevalence of food allergy is high, up to 10% of the population, and likely increased in the past decades.
- Numerous genetic and environmental risk factors have been identified.
- Insights on route of sensitization, allergen characterization, and immune response provide insights for diagnosis and treatment.
- There is a wide spectrum of disease caused by food allergy related to different immune mechanisms and the target organs affected. Diagnosis depends on combining a knowledge of pathophysiology and epidemiology with the patient’s history and test results. It is clearly possible to have sensitization without clinical reactivity and vice versa.
- The use of CRD is entering 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.
- Numerous clinical trials are underway for more definitive therapies.

What is still unknown?
- The cause for an increase in food allergy
- 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.

Key concepts and therapeutic implications
- Identification of food-specific IgE by means of testing indicates sensitization but is not, in isolation, diagnostic.
- Knowledge of the epidemiology, natural course, pathophysiology, and clinical manifestations of food allergies and other adverse reactions to foods is required to approach diagnosis and management. The medical history is key, noninvasive tests are supportive and possibly diagnostic, and the OFC is the most definitive test.
- Management requires attention to education about avoidance and prompt appropriate treatment of anaphylaxis.
- Various approaches to treatment are under investigation, and patients should be alerted to clinical trials.

REFERENCES


REFERENCES


### TABLE E1. Food-induced allergic disorders (also see text)

<table>
<thead>
<tr>
<th>Immunopathology</th>
<th>Disorder</th>
<th>Key features</th>
<th>Additional immunopathology</th>
<th>Typical age</th>
<th>Most common causal foods</th>
<th>Natural course</th>
<th>Diagnostic considerations (in addition to history, possible food challenges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE antibody dependent (acute onset)</td>
<td>Urticaria/angioedema</td>
<td>Triggered by ingestion or direct skin contact (contact urticaria); food commonly causes acute (20%) but rarely chronic (2%) urticaria</td>
<td></td>
<td>Children &gt; adults</td>
<td>Primarily “major allergens”: egg, milk, wheat, soy, peanut, tree nuts, fish, shellfish</td>
<td>Depending on food</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td></td>
<td>Oral allergy syndrome (pollen associated, food allergy syndrome)</td>
<td>Pruritus, mild edema confined to oral cavity; uncommonly progresses beyond mouth (~7%) or anaphylaxis (1% to 2%); might increase after pollen season</td>
<td>Sensitization to pollen proteins through respiratory route results in IgE that binds certain homologous, typically labile, food proteins (in certain fruits/vegetables, such as apple Mal d 1 and birch bet v 1)</td>
<td>Onset after pollen allergy established (adult &gt; young child)</td>
<td>Raw fruit/vegetables; cooked forms tolerated; examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)</td>
<td>Might be long-lived and vary with seasons</td>
<td>SPT and/or sIgE measurement, Fresh (raw) prick-prick testing</td>
</tr>
<tr>
<td></td>
<td>Rhinitis, asthma</td>
<td>Symptoms might accompany a food-induced allergic reaction but rarely an isolated or chronic symptom; might also be triggered by inhalation of aerosolized food protein</td>
<td></td>
<td>Infant/child &gt; adult, except for occupational disease (eg, Baker’s asthma)</td>
<td>Generally: major allergens; Occupational: wheat, egg, seafood, for example</td>
<td>Depending on food</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td></td>
<td>Immediate gastrointestinal hypersensitivity</td>
<td>Immediate isolated vomiting (more often, gastrointestinal symptoms are associated with anaphylaxis)</td>
<td></td>
<td>Major food allergens</td>
<td>Depends on food</td>
<td>SPT and/or sIgE measurement</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Immunopathology</th>
<th>Disorder</th>
<th>Key features</th>
<th>Additional immunopathology</th>
<th>Typical age</th>
<th>Most common causal foods</th>
<th>Natural course</th>
<th>Diagnostic considerations (in addition to history, possible food challenges)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td>Rapidly progressive, multiple organ system reaction can include cardiovascular collapse</td>
<td>Massive release of mediators, such as histamine, although mast cell tryptase not always increased; key role of platelet-activating factor</td>
<td>Any</td>
<td>Any but more commonly peanut, tree nuts, shellfish, fish, milk, and egg</td>
<td>Depending on food</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td></td>
<td>Delayed food-induced anaphylaxis to mammalian meats</td>
<td>Several-hour delay after ingestion</td>
<td>Related to antibodies to carbohydrate moiety α-Gal (see text)</td>
<td>Related to tick bites</td>
<td>Beef, pork, lamb</td>
<td>Uncertain</td>
<td>Serum test for IgE to α-Gal</td>
</tr>
<tr>
<td></td>
<td>Food-associated, exercise-induced anaphylaxis</td>
<td>Food triggers anaphylaxis only if ingestion followed temporally by exercise</td>
<td>Exercise presumed to alter gut absorption and/or allergen digestion</td>
<td>Onset more commonly is later childhood/ adulthood</td>
<td>Wheat, shellfish, celery most described</td>
<td>Presumed persistent</td>
<td>SPT and/or sIgE measurement</td>
</tr>
<tr>
<td></td>
<td>Mixed IgE antibody-associated/cell-mediated (delayed-onset/chronic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Component testing Exercise test (might be poorly reproducible)</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Associated with food in ~35% of children with moderate-to-severe rash</td>
<td>Might relate to homing of food-responsive T cells to the skin</td>
<td>Infants &gt; child &gt; adult</td>
<td>Major allergens, particularly egg, milk</td>
<td>Typically resolves</td>
<td>SPT and/or sIgE measurement APT not generally recommended</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic gastroenteropathies</td>
<td>Symptoms vary on site(s)/degree of eosinophilic inflammation: Esophageal: dysphagia, pain Generalized: ascites, weight loss, edema, obstruction</td>
<td>Mediators that home and activate eosinophils play a role, such as eotaxin, IL-5</td>
<td>Any</td>
<td>Multiple</td>
<td>Likely persistent</td>
<td>Empiric diets Endoscopy SPT and/or sIgE measurement APT not generally recommended</td>
</tr>
<tr>
<td></td>
<td>Non–IgE-mediated (delayed-onset/chronic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food protein induced enterocolitis syndrome</td>
<td>Primarily affects infants&lt;br&gt;Chronic exposure: emesis, diarrhea, poor growth, lethargy&lt;br&gt;Re-exposure after restriction: emesis, diarrhea, hypotension (15%) 2 hours after ingestion</td>
<td>Increased TNF-α response, decreased response to TGF-β</td>
<td>Infancy</td>
<td>Cow’s milk, soy, rice, oat&lt;br&gt;Multiple other solids have been identified</td>
<td>Usually resolves&lt;br&gt;SPT and/or sIgE measurements are typically negative but can become positive&lt;br&gt;APTs not helpful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food protein induced allergic proctocolitis</td>
<td>Mucus-laden bloody stools in infants</td>
<td>Eosinophilic inflammation</td>
<td>Infancy</td>
<td>Milk (through breastfeeding)</td>
<td>Usually resolves</td>
<td>Empiric diets</td>
<td></td>
</tr>
<tr>
<td>Heiner syndrome</td>
<td>Rare disorder; pulmonary infiltrates, upper respiratory tract symptoms, failure to thrive, iron deficiency anemia</td>
<td>Infancy</td>
<td>Milk</td>
<td>Undefined</td>
<td>No evidence of IgE; might have precipitating milk-specific IgG antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Autoimmune disorder leading to enteropathy and malabsorption; occurs in persons with a genetic disposition and is triggered by gliadin, a gluten protein found in wheat and related grains</td>
<td>Might include anemia, poor growth, gastrointestinal symptoms, bone abnormalities, IgA deficiency, dermatitis herpetiformis, malignancy risk</td>
<td>Might be asymptomatic or present at any age</td>
<td>Gluten (ie, wheat, rye, barley)</td>
<td>Lifelong</td>
<td>Serologies (while ingesting wheat including IgA against tissue transglutaminase, gliadin), HLA typing (for DQ2/DQ8), and biopsies</td>
<td></td>
</tr>
<tr>
<td>Cell mediated</td>
<td>Allergic contact dermatitis</td>
<td>A form of eczema to chemical hapten that are additives or naturally occurring in foods</td>
<td>Similar to other forms of contact dermatitis, subtype includes systemic contact dermatitis (rare) and possibly “fixed food eruptions”</td>
<td>Adult</td>
<td>Metals</td>
<td>APT</td>
<td></td>
</tr>
</tbody>
</table>

Revised from Sicherer and Sampson.¹²
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Immune rationale</th>
<th>Benefits</th>
<th>Observations to date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard subcutaneous immunotherapy (native allergens)</td>
<td>Antigen presentation in nonmucosal sites results in Th1 skewing</td>
<td>Proved for venom and respiratory allergy, possible benefit (pollen) for oral allergy syndrome</td>
<td>Primarily avoided for risk of anaphylaxis (eg, peanut)</td>
</tr>
<tr>
<td>Sublingual/oral immunotherapy</td>
<td>Antigen presentation to mucosal site provides desensitization and might induce tolerance</td>
<td>Natural foods, reduced risk of systemic anaphylaxis compared with injections</td>
<td>Mounting evidence for desensitization and relative safety; unclear effect on tolerance</td>
</tr>
<tr>
<td>Epicutaneous immunotherapy</td>
<td>Antigen presentation through skin</td>
<td>Low risk, natural food</td>
<td>Pilot studies show promise for safety and efficacy, trials underway</td>
</tr>
<tr>
<td>Modified protein vaccine</td>
<td>Reduced IgE activation by mutation of IgE-binding epitopes</td>
<td>A safer form of immunotherapy compared with injection of native protein</td>
<td>Murine models show promise, human study of peanut showed reactions</td>
</tr>
<tr>
<td>Peptide vaccine (overlapping peptides)</td>
<td>Peptides are less likely to cross-link IgE, avoiding mast cell activation</td>
<td>No requirement for IgE epitope mapping/mutation</td>
<td>Limited</td>
</tr>
<tr>
<td>Conjugation of immune stimulatory sequences to allergen and additional adjuvant methods</td>
<td>Enhance Th2 response by activating innate immune receptors (using specific sequences or whole bacteria)</td>
<td>Increased efficacy, possibly improved safety</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>Plasmid DNA-encoded vaccines</td>
<td>Endogenous production of allergen might result in tolerance</td>
<td>Possible 1-dose treatment</td>
<td>Murine models reveal strain-specific response</td>
</tr>
<tr>
<td>Anti-IgE antibodies</td>
<td>Targeted toward Fc portion of antibody, can inactivate IgE with reduced risk for activating mast cells</td>
<td>Not food-specific</td>
<td>Preliminary studies showed improved threshold overall but did not show uniform protection</td>
</tr>
<tr>
<td>Anti-IgE plus oral immunotherapy</td>
<td>Might reduce side effects of oral immunotherapy, speed desensitization, improve tolerance</td>
<td>Food specific but might not require long periods of anti-IgE</td>
<td>Pilot studies show promise, clinical trials underway</td>
</tr>
<tr>
<td>Traditional Chinese medicine</td>
<td>Mechanism appears to include altered T-cell responses with increased IFN-γ and IL-10</td>
<td>Not food specific</td>
<td>Murine models show efficacy; human safety studies completed; clinical trials underway</td>
</tr>
<tr>
<td>Cytokine/anticytokine/antireceptor/antimediator</td>
<td>To interrupt inflammatory signals</td>
<td>Might allow directed interruption of inflammatory processes without need for food restriction</td>
<td>Primarily preclinical</td>
</tr>
<tr>
<td>Fusion proteins</td>
<td>To inhibit degranulation, enhance effectiveness of immunotherapy</td>
<td>Targeted reduction of effector responses, possible directed immunotherapy</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Probiotics, <em>Trichuris suis ova</em></td>
<td>Alter immune response</td>
<td>Not food specific</td>
<td>Mixed results in trials thus far or too preliminary</td>
</tr>
</tbody>
</table>

Revised from Sicherer and Sampson.²³