

Advances in the approach to the patient with food allergy



Amy M. Scurlock, MD, and Stacie M. Jones, MD Little Rock, Ark

Advances in food allergy diagnosis, management, prevention, and therapeutic interventions have been significant over the past 2 decades. Evidence-based national and international guidelines have streamlined food allergy diagnosis and management, whereas paradigm-shifting work in primary prevention of peanut allergy has resulted in significant modifications in the approach to early food introduction in infants and toddlers. Innovative investigation of food allergy epidemiology, systems biology, effect, and management has provided important insights. Although active therapeutic approaches to food allergy remain experimental, progress toward licensed therapies has been substantial. Mechanistic understanding of the immunologic processes underlying food allergy and immunotherapy will inform the future design of therapeutic approaches targeting the food-induced allergic response. Global strategies to mitigate the substantial medical, economic, and psychosocial burden of food allergy in affected subjects and families will require engagement of stakeholders across multiple sectors in research, health care, public health, government, educational institutions, and industry. However, the relationship between the well-informed allergy care provider and the patient and family remains fundamental for optimizing the care of the patient with food allergy. (*J Allergy Clin Immunol* 2018;141:2002-14.)

Key words: Food allergy, diagnosis, management, prevalence, specific IgE, prevention, IgE-mediated food allergy, oral food challenge, early intervention, primary prevention, evidence-based guidelines, oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy

Abbreviations used

AE:	Adverse event
BAT:	Basophil activation test
CM:	Cow's milk
CoFAR:	Consortium of Food Allergy Research
ED:	Eliciting dose
EHR:	Electronic health record
EoE:	Eosinophilic esophagitis
EPIT:	Epicutaneous immunotherapy
EW:	Egg white
Foxp3:	Forkhead box protein 3
NASEM:	National Academies of Sciences, Engineering, and Medicine
OFC:	Oral food challenge
OIT:	Oral immunotherapy
QoL:	Quality of life
sIgE:	Specific IgE
SLIT:	Sublingual immunotherapy
SPT:	Skin prick test
SU:	Sustained unresponsiveness
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

From the Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital.

Disclosure of potential conflict of interest: A. M. Scurlock has consultant arrangements with Aimmune Therapeutics; is employed by the University of Arkansas for Medical Science; has received grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases and FARE; and has received travel support from Aimmune Therapeutics. S. M. Jones is on the research advisory board for FARE; has consultant arrangements with Aimmune Therapeutics; has received grants from Aimmune Therapeutics, DBV Technologies, Astellas, FARE, the National Peanut Board, the National Institutes of Health/National Institute of Allergy and Infectious Diseases Immune Tolerance Network, and the National Institutes of Health/National Institute of Allergy and Infectious Diseases Consortium of Food Allergy Research; and has done CSR review/preparation for DBV Technologies on behalf of EMMES Corporation.

Received for publication October 13, 2017; revised November 27, 2017; accepted for publication December 7, 2017.

Available online March 8, 2018.

Corresponding author: Stacie M. Jones, MD, University of Arkansas for Medical Sciences, Department of Pediatrics, 13 Children's Way, Slot 512-13, Little Rock, AR 72202. E-mail: jonesstaciem@uams.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/\$36.00

© 2018 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaci.2017.12.1008>

Food allergy is a significant health concern that has adverse medical, psychosocial, and economic effects on affected subjects and families.^{1,2} Advances in diagnostic and therapeutic approaches, including implementation and revision of evidence-based guidelines,^{1,3,4} along with enhanced insights into early intervention and prevention have shifted paradigms and improved the care of patients with food allergy.⁵ Furthermore, progress toward active therapeutic options to mitigate the life-altering effects of food allergy has been substantial, ushering in a new era in food allergy, with licensed active therapeutic interventions on the horizon.⁶ Collectively, these advances have shifted existing paradigms in the approach to the patient with food allergy. However, the therapeutic relationship between the allergist and the patient with food allergy and family remains of central importance. An informed and up-to-date allergy provider is critical in establishing the correct diagnosis and developing an integrated management plan that empowers patients with food allergy to safely engage in educational and extracurricular activities, as well as promoting broader inclusion and awareness within the community (Fig 1).

The following article integrates findings from recently published advances in food allergy epidemiology, diagnosis, management, prevention, and therapy with established evidence-based guidelines

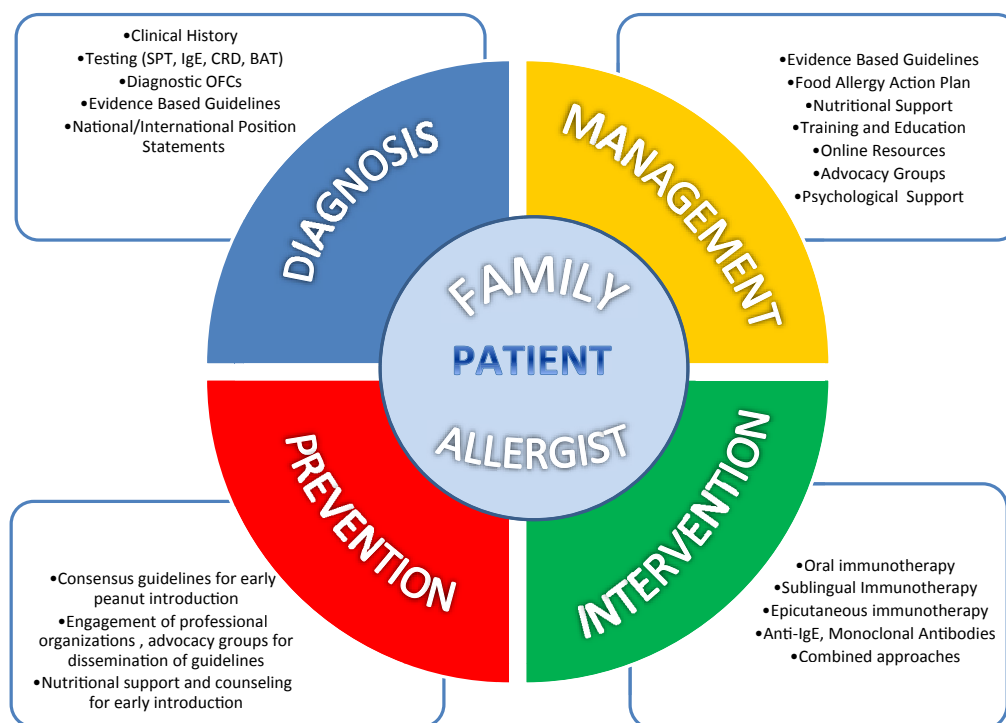


FIG 1. An integrated model for patient and family-centered care of the patient with food allergy. CRD, Component resolved diagnostics; SPT, skin prick test.

to provide a state-of-the-art approach to optimizing outcomes for patients with IgE-mediated food allergy.

EPIDEMIOLOGY OF FOOD ALLERGY

Although it appears to be increasing, the true prevalence of food allergy is difficult to assess. Indeed, the recently published National Academies of Sciences, Engineering, and Medicine (NASEM) report titled “Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management and public policy” (hereafter referred to as the NASEM report) highlighted this conundrum, noting that the self-reported prevalence of food allergy in adults approaches 15%, whereas in studies using more stringently defined criteria, the estimated prevalence is 4% of children and 1% of adults.^{1,2,7,8}

The prevalence of challenge-confirmed food allergy in Australian preschoolers participating in the HealthNuts population-based cohort study was 3.8% at age 4 years (1.9% for peanut allergy 1.2% for egg allergy), whereas the overall food allergy prevalence rate in this same cohort at age 1 year was previously reported to be 11%, which was the highest reported international prevalence of challenge confirmed food allergy in this age group.⁹ This same group of investigators surveyed Australian parents and students aged 10 to 14 years and then performed detailed clinical evaluation in adolescents suspected to have current food allergy. The prevalence of clinically defined food allergy based on history, sensitization, and oral food challenge (OFC) was 4.5% (95% CI, 3.9% to 5.1%) in this defined cohort compared with a self-reported prevalence of 5.5% (95% CI, 4.9% to 6.2%) in the subset who completed surveys but did not have parental responses or clinical evaluation, with peanuts and tree nuts the most commonly identified allergens in both groups.¹⁰

In the EuroPrevall birth cohort study, investigators followed 823 infants until age 2 years; suspected food reactions were evaluated further based on specific IgE (sIgE) levels and skin prick test (SPT) responses, and food hypersensitivity was defined as a positive double-blind, placebo-controlled food challenge with symptoms up to 48 hours after the challenge.¹¹ Investigators observed a 2.6% cumulative incidence of IgE-mediated food allergy by age 2 years, with 2.1% reacting to hen’s egg. The cumulative incidence of IgE- and non-IgE-mediated allergy was 5%, with almost half of infants with challenge-confirmed reactions having negative food sIgE values, suggesting different food allergy phenotypes.

Differences in food allergy phenotype related to racial and ethnic differences were also observed in a retrospective cohort study of 817 children with food allergy (age, 0-17 years; 35% African American, 12% Hispanic, 53% non-Hispanic white) at 2 urban tertiary care centers.¹² When compared with non-Hispanic white children, African American and Hispanic children had significantly greater odds of comorbid asthma, eczema, or both; allergy to less well-recognized food allergens, such as wheat, soy, corn, fish, and shellfish; and increased rates of food-induced anaphylaxis and emergency department use, factors that place them at greater risk of adverse food allergy outcomes. Enhanced understanding of different food allergy phenotypes is an important step toward subsequent identification of potential disease endotypes (defined as phenotypic subclasses associated with specific mechanisms underlying the disease) and development of precision medicine strategies, as highlighted in the PRACTALL consensus document summarizing the current progress toward precision medicine approaches in asthma, drug allergy, food allergy, and anaphylaxis.¹³

In addition to enhanced understanding of overall food allergy prevalence rates, important work examining the rates of severe reactions has been published. The European Anaphylaxis Registry characterized severe allergic reactions in children and adolescents during the period between July 2007 and March 2015, identifying 1970 reports of anaphylaxis in subjects less than 18 years of age, 66% of which were triggered by foods.¹⁴ Age-specific differences in triggering foods were observed, with cow's milk (CM) and hen's egg the most common triggers in children younger than 2 years, hazelnut and cashew the most common in school-aged children, and peanut common in all age groups. Intensive care unit admissions and fatal reactions occurred in 26 (1.3%) patients and hospital-based emergency management by using intramuscular epinephrine increased from 12% to 25% from 2011-2014.

The multicenter prevalence of anaphylaxis during open OFCs in non-research-based clinical settings provided important safety insights into the largest national survey of outcomes in nonacademic centers in the United States.¹⁵ Analysis of 6377 clinic-based OFCs (peanut and egg being most common allergens) indicated a pooled anaphylaxis estimate of 2% (95% CI 1-3%), a rate of allergic reactions of 14% (range 13-33%), and more frequent reactions in male patients.

Using retrospective chart review from the electronic health record (EHR), investigators evaluated 35,328 children in a subspecialty care network to characterize patients with eosinophilic esophagitis (EoE) and IgE-mediated food allergy.¹⁶ The prevalence of EoE in pediatric patients with IgE-mediated food allergy was greater than in the general population (4.7% vs 0.04%), and IgE-mediated allergy to egg, milk, or shellfish was associated significantly with a diagnosis of EoE.

The utility of EHRs as a tool for clinical and epidemiologic research was further highlighted by Acker et al.¹⁷ Using the EHR allergy module, these investigators examined the prevalence of food allergies, food intolerances, and severe reactions over the period from 2000-2013 and correlated their results with sIgE data, where available. Among 2.7 million patients, 97,482 (3.6%) reported 1 or more food allergies or intolerances, with 103,659 adverse food reactions identified. The most commonly identified food triggers were milk, peanut, shellfish, and fruit. Refinement and standardization of clinical evaluation tools to better define and differentiate the spectrum of IgE-mediated vs non-IgE-mediated food allergy will be critical for accurate future analysis and definition of clinical phenotypes and endotypes.

ETIOLOGY (SYSTEMS BIOLOGY/GENETICS/MICROBIOME)

Although epidemiologic data suggest an increase in food allergy prevalence, factors contributing to the apparent increase have been speculative to date. Accumulating evidence supports potential gene-environment interactions and early-life gastrointestinal microbiota along with the enduring hygiene hypothesis as proposed explanations for the increase in allergic disease. In a cross-sectional family-based study that included 1359 children, 832 (61.2%) with food allergy and 406 (30%) with asthma, investigators examined the association of hygiene factors (eg, number of siblings, antibiotic use, infection history, pet exposure, child care exposure, and maternal-child factors) with childhood food allergy.¹⁸ Increased prevalence of food allergy was associated with skin infection or eczema, whereas a larger number of

siblings was associated with decreased prevalence of both food allergy and asthma.

The contribution of genetic variants in the development of food allergy was another important area of study over the past year. Australian investigators identified associations between a variant in serine peptidase inhibitor Kazal type 5 (SPINK5) and challenge-proved IgE-mediated food allergy in 12-month-old infants, further supporting a role for defects in skin barrier function in the development of food allergy.¹⁹ In this same cohort genetic variation in the *IL13* gene was also associated with challenge-proved food allergy.²⁰ A genome-wide association study comparing 73 infants with challenge-proved IgE-mediated peanut allergy and 148 nonallergic infants (age approximately 1 year) reproduced findings demonstrating genetic determinants for challenge-confirmed peanut allergy in alleles at the *HLA-DRB1* locus.²¹ The first epigenome-wide association study of CM allergy in US children identified significant differentially methylated regions in specific gene loci, including genes involved in T_H1-T_H2 regulation and cellular signaling.²² Although further study is needed, identification of genetic and epigenetic alterations associated with food allergy is important to advance our understanding of the gene-environment interactions that underlie the development of food allergy.

The role of the gastrointestinal microbiome in both the development and resolution of food allergy, as well as recognition of the potential therapeutic strategies to manipulate the microbiome, are areas of significant interest and ongoing investigation.^{23,24} Recognition of the potential role of the microbiota in modulating asthma, atopic dermatitis, and food allergy culminated in publication of the 2017 PRACTALL consensus report from the American Academy of Allergy, Asthma & Immunology and European Academy of Allergy and Clinical Immunology, which summarizes the current understanding, existing knowledge gaps, and future strategies to harness the potentially beneficial immunomodulatory effects of the microbiome to intervene in the progression of allergic disease.²⁵ The association between the early-life gut microbiota and resolution of CM allergy was examined in the Consortium of Food Allergy Research (CoFAR) observational cohort, which included 226 children with milk allergy; in the 128 (56.6%) children whose milk allergy was outgrown, enrichment of the gut microbiome with Clostridia and Firmicutes at age 3 to 6 months was associated with resolution of milk allergy by age 8 years.²⁶ The potentially causal role of the microbiome in development of food allergy was examined in a prospective microbiome-wide association study in early childhood, highlighting differences in microbial genera in children with food allergy and those with food sensitization.²⁷

A novel hypothesis for the increased incidence of food allergy in developed countries was proposed by investigators in the United States and Australia, indicating a potential role for high levels of dietary advanced glycation end-products derived from cooked meats, oils, and cheese in the presence of high sugar concentrations.²⁸ These dietary advanced glycation end-products subsequently mimic alarmins, endogenous molecules secreted from cells undergoing nonprogrammed cell death that signal tissue and cell damage, and promote proallergic innate immune responses. This "false-alarm" hypothesis is another possible explanation theorized to account for the increase in food allergy in westernized societies, although further study is needed.

PREVENTION/EARLY INTERVENTION

One of the most significant paradigm shifts in the management of food allergy is the transition from recommending delayed introduction of allergenic foods, such as peanut, into the diets of infants and toddlers, to the current consensus recommendations for early peanut introduction to prevent peanut allergy.⁴ This shift was inspired by the seminal randomized, controlled Learning Early About Peanut study and associated long-term follow-up studies, which hypothesized that regular consumption of peanut-containing products starting in infancy would promote a protective immune response and dietary tolerance to peanut.^{5,29} More than 600 children (age, 4-11 months) at high risk for peanut allergy were randomized to either avoid or consume peanut at least 3 times weekly until age 5 years. The rate of peanut allergy by age 5 years was only 3% among children eating peanuts compared with 17% in those who avoided peanuts. Overall, sustained consumption of peanut beginning in the first 11 months of life was highly effective in preventing the development of peanut allergy.

Based on these results, new dietary guidelines recommend the introduction of peanuts in the first 4 to 6 months of life based on classifying infants into 3 risk categories.⁴ For the highest-risk infants, who are defined as those with severe eczema, egg allergy, or both, allergy testing should be performed, and then, if appropriate, peanut should be introduced as early as 4 to 6 months of age. Infants with mild-to-moderate eczema require no testing and should undergo peanut introduction around 6 months of age to decrease their risk of having peanut allergy. In low-risk infants without eczema or food allergy, guidelines recommend *ad libitum* dietary peanut introduction together with other complementary foods.

The same investigators conducted a randomized trial of early introduction (the Enquiring About Tolerance study) of 6 allergenic foods (CM, cooked egg, peanut, sesame, whitefish, and wheat) versus a standard feeding pattern in 1303 exclusively breast-fed infants beginning at 3 months of age.³⁰ In the intention-to-treat analysis, no differences were noted, but the per-protocol analysis revealed significant reductions in allergy to peanut and egg at the time of analysis between ages 1 and 3 years. Consumption of greater amounts of the food protein (2 g/wk) was associated with lower prevalence of peanut and egg allergy. The report also highlighted the difficulty in achieving early introduction of all foods that might have negatively affected the results.

In a 2017 editorial, Drs Turner and Campbell highlighted practical considerations for implementation of peanut allergy primary prevention at a population level.³¹ While recognizing the compelling evidence for early peanut introduction in high-risk infants, the authors expressed concern that the complex risk stratification, resource-intensive screening process, and narrow 4- to 6-month window for introduction can hinder broad implementation, uptake, and ultimate success of the recommendations and recommended that perhaps at a population level the advice should be simplified. Furthermore, they highlighted a possible unintended consequence of the new guidelines, “screening creep,” in which infants who are not in a high-risk category undergo screening because of parental anxiety or overdiagnosis of eczema, leading to delays in introduction while navigating the screening and challenge process.

Other primary prevention studies published this year focused predominantly on affecting the development of egg allergy. The Prevention of Egg Allergy with Tiny Amount Intake (PETIT) Study, which was conducted in Japan, is a randomized, placebo-

controlled trial conducted in 218 infants 4 to 5 months of age with eczema.³² Participants received aggressive treatment for eczema and were randomized to either placebo or egg powder; those in the egg group consumed 50 mg of heated egg powder daily from 6 to 9 months of age and 250 mg/d thereafter until age 12 months. Open food challenges were performed at age 12 months to assess for egg allergy. The trial was terminated early because of significant results at the interim analysis of the first 100 infants that showed 9% of those in the egg group compared with 38% of infants in the placebo group demonstrating egg allergy ($P = .0012$).

There were 2 other randomized, placebo-controlled trials of hen's egg consumption in 4- to 6-month-old infants, neither of which found evidence that hen's egg consumption at age 4 to 6 months prevented egg allergy. In fact, both studies highlighted that some 4- to 6-month-olds already had egg allergy or had reactions with consumption.^{33,34}

In a meta-analysis regarding food allergy prevention published in 2016, studies supported early introduction of both peanut and heated egg protein to prevent food allergy to specific allergens.³⁵

In another prevention approach, investigators performed a randomized, parallel, single-blind, controlled trial of twice-daily application of a new ceramide dominant emollient (EpiCeram; PuraCap Pharmaceuticals, Piscataway Township, NJ) as lipid barrier replacement in the PEBBLES pilot study.³⁶ Infants who were treated with EpiCeram during the first 6 months of life exhibited a trend toward reduced atopic dermatitis and food sensitization at 12 months. However, whether the use of emollients prevents atopic dermatitis beyond the treatment period or whether this intervention reduced long-term allergic sensitization requires further study.

Evidence-based guidelines

The 2010 “Guidelines for the diagnosis and management of food allergy in the United States” provided evidence-based recommendations that have guided the approach to food allergy over the past 7 years.¹ After publication of findings from the Learning Early About Peanut study and related follow-up studies in the United Kingdom,^{5,29} updated dietary recommendations for peanut allergy prevention were published as an addendum to the original guidelines.⁴ European guidelines were also published in 2014 addressing recommendations for primary prevention.³ The NASEM convened an *ad hoc* expert committee to examine critical issues in food allergy, generating a landmark report.² Six major action steps involving multiple stakeholders were proposed, including (1) improved collection of prevalence data to better estimate the global burden, coupled with exploration of risk factors; (2) improved diagnostics and evidence-based care; (3) evidence-based prevention strategies; (4) enhanced education and training for recognition, management, and prevention of acute allergic reactions; (5) development of policies and practices to prevent and treat severe allergic reactions; and (6) addressing key questions related to diagnostics, mechanisms, risk determinants, and management, with a goal of identifying safe and effective therapies (Table I).

Diagnostic approach to food allergy

The 2010 National Institute of Allergy and Infectious Diseases guidelines define food allergy as an “adverse health effect arising

TABLE I. Current concepts and future directions in the diagnosis, prevention, and management of food allergy

Food allergy issue	Accepted concepts	Future directions
Prevalence	Population prevalence is not fully known but generally accepted.	Understanding food allergy prevalence, especially in diverse populations, is important.
Role of genetics, epigenetics, microbiome	Importance is implied by current studies.	Further work is needed to better define the role of genetics, environment, and the microbiome in development, prevention and treatment of food allergy.
Prevention	Early dietary introduction of peanut and egg is associated with reductions in allergy.	Implementation of early implementation guidelines for peanut is needed in addition to further information on other major food allergens. Other strategies for prevention are needed.
OFC in diagnosis and management	OFC remains the gold standard for diagnosis and long-term management.	Improved standardization across age groups and clinical settings is needed.
Epinephrine as first-line treatment for anaphylaxis	Epinephrine is widely accepted as first-line therapy but not widely implemented.	Strategies are needed to fully implement epinephrine as first-line therapy and to develop newer treatment forms for use.
Emerging therapy for food allergy	Current strategies under investigation show promise for active therapeutic intervention.	Novel approaches to treatment are needed to most significantly affect all ages and single-allergen and multiallergen disease and provide both safe and effective treatment.
Biomarkers/mechanistic predictors of disease and treatment response	Limited biomarkers are available that accurately predict diagnosis and track disease.	Further work is needed to more fully define biomarkers and mechanistic factors associated with food allergy, anaphylaxis, and disease prognosis and severity.
Education for patients, care providers, schools, and so on	Education is critical for appropriate diagnosis, ongoing management, and prevention of anaphylaxis.	New and more comprehensive educational strategies are needed for patients, care providers, schools, and other stakeholders to fully manage disease and increase awareness.

from a specific immune response that occurs reproducibly on exposure to a given food” and provided an evidence-based framework for diagnosis of food allergy.¹ A multistep approach to diagnosis of food allergy integrating data from the clinical history and physical examination with specific laboratory studies and/or diagnostic food challenges enhances diagnostic accuracy. Quantification of allergen sIgE and measurements of SPT wheal diameters are established diagnostic parameters. However, advanced laboratory approaches, including measurement of sIgE to allergen components and use of the basophil activation test (BAT) are increasingly available testing modalities.³⁷ Indeed, the BAT has superior specificity and comparable sensitivity to food sIgE measurements and SPTs for the diagnosis of food allergy.³⁸ The BAT also has use in monitoring resolution of food allergy and clinical response to immunotherapy and potentially reducing the number of OFCs required to make an accurate diagnosis of food allergy.³⁸

OFCs

OFCs are considered the gold standard for confirming a diagnosis of food allergy or, conversely, evaluating food allergy resolution.¹ Because serum food sIgE levels and SPT responses are insufficient predictors of OFC outcomes, investigators applied a Standardized Clinical Assessment and Management Plan to evaluate and adjust sIgE and SPT thresholds to best select patients for OFC.³⁹ During a 3-year period, 2368 OFCs were performed in 1580 patients in either an outpatient clinic setting (n = 1386

OFCs: 13% reaction rate, 6 requiring epinephrine) or higher-level infusion center (n = 945 OFCs: 23% reaction rate, 22 requiring epinephrine). Continual refinement of IgE and SPT thresholds for OFCs using control chart methods allowed for identification of high- and low-risk OFC categories that allowed for triage to the most appropriate clinical setting.

In the Australian HealthNuts study investigators characterized reaction profiles during OFCs to assess potential predictors of reaction severity.⁴⁰ A total of 2047 peanut, egg, or sesame challenges were performed in 916 children at age 1 year and 357 at age 4 years. Urticaria was the most common symptom during positive OFCs at both age 1 year (88.7%) and age 4 years (71.2%); angioedema was observed more frequently at age 4 years (40.1%) than at age 1 year (12.9%). Anaphylaxis complicated 2.1% of positive challenges at age 1 year and 2.8% at age 4 years and was more commonly associated with peanut than egg. Food sIgE levels of greater than 15 kU/L were associated with moderate-to-severe reactions for peanut, egg, and sesame at age 1 year but only for peanut by age 4 years.

In a retrospective study investigators reported the outcomes of 84 baked milk OFCs performed in a food allergy referral clinic, observing that 72% were baked milk tolerant and 12% of all subjects challenged (42% of reactors) had mild anaphylaxis that responded to in-office medications and did not require prolonged monitoring beyond the 2-hour prespecified observation period.⁴¹ Milk sIgE levels were greater in reactive patients, whereas SPT wheal size was similar in baked milk-tolerant and baked milk-reactive subjects.

Interestingly, when assessing the overall rate of food introduction after a negative OFC result in pediatric patients at this same referral center, investigators found that 20% of children did not incorporate the food into their diet regularly, citing fear of a reaction, disliking the food, or the food not being a routine part of the family's diet.⁴² Peanuts and tree nuts were the most common allergens (60%) that were not incorporated regularly into the diet despite a negative OFC result. The effect of allergic reactions on SPT wheal size and milk, egg, and peanut sIgE concentrations was investigated in 377 children before and after OFC or accidental exposure; the authors concluded that allergic reactions during OFC or accidental exposure were not associated with increased sensitization.⁴³

After publication of the addendum guidelines for early peanut introduction, it is anticipated that allergists will see an increased demand for OFCs in infants, a unique population that requires special considerations. The recently published American Academy of Allergy, Asthma & Immunology Workgroup Report provides a comprehensive review of the protocols and procedures necessary to conduct a safe OFC in infants.⁴⁴ Specifically addressed are OFC standard procedures and stopping criteria in addition to postchallenge monitoring and instructions and critically important safety guidelines specific to OFCs in infants.

Significant interest has evolved in identifying threshold eliciting doses (EDs) in patients with food allergy. In the Peanut Allergy Threshold Study investigators at 3 centers performed single-dose 1.5-mg (predicted ED₀₅) peanut challenges that resulted in objective symptoms in fewer than the predicted 5% of patients with peanut allergy.⁴⁵ This approach was safe and well tolerated, with improvement in food allergy–related quality of life (QoL) from baseline to 1 month after challenge, regardless of the outcome. Although this approach identified a highly dose-sensitive population not identifiable based on peanut SPT or sIgE levels, this approach is not validated for individual risk assessment of patients with peanut allergy. EDs for adults with walnut allergy were evaluated by using low-dose, double-blind, placebo-controlled food challenge, and cumulative EDs were calculated as follows: ED5 (3.1–4.1 mg), ED10 (10.6–14.6 mg), and ED50 (590–625 mg).⁴⁶ Defining minimal reaction thresholds for food allergens has the potential to inform and improve policies regulating food manufacturing, preparation, and labeling.

MANAGEMENT

The present standard of care for the management of IgE-mediated food allergy includes strict dietary avoidance of culprit food allergens with an anaphylaxis management plan that includes ready access to injectable epinephrine to treat reactions associated with accidental ingestion/exposure, a plan to seek emergency medical care if epinephrine is used, and ongoing follow-up and education.¹ Despite its recognized benefit as first-line treatment in preventing fatal anaphylaxis, epinephrine continues to be vastly underprescribed and underused by health care providers and patients. In a retrospective survey of epinephrine autoinjector prescribing patterns in an urban pediatric population (*n* = 9148), 70% of prescriptions originated in a primary care office with 90% of diagnoses related to food allergy.⁴⁷ However, only approximately 60% of patients were referred for allergy evaluation, and up to 6.6% of patients were prescribed an inadequate dose. Epinephrine underuse was also observed in a survey of children attending summer camps; among 3055 campers

attending 179 camps in Michigan, 2.5% (*n* = 424) had food allergy (22% multi-food allergic) but only 39.7% brought an epinephrine autoinjector to camp.⁴⁸

Ongoing nutritional support and comprehensive education for patients, families/care providers, schools, and other community stakeholders are essential components of food allergy management.¹ Adolescents and young adults are a particularly high-risk group for fatal and near-fatal anaphylaxis because of risk-taking behavior. Warren et al⁴⁹ identified factors associated with teens and young adults being ranked in lower- versus higher-risk categories, including presence of peanut allergy, supportive female friends, overprotective mothers, teachers awareness of the food allergy, history of being bullied, and an established 504 education plan at school. Those in the low-risk category also reported positive outcomes from their food allergy, including greater sense of responsibility, empathy, and better diet.

Ross et al⁵⁰ assessed Internet patterns using an anonymous survey in 530 patients with food allergy from the Mount Sinai Jaffe Food Allergy Institute e-mail list to determine the type of information they are seeking and their use of that information. Online resources and social media were used by 91% of respondents, with 85% reporting that they followed the advice received on these platforms. These findings emphasize the need to provide high-quality, evidence-based, user-friendly resources that are easily accessible for patients and families.

Several studies have been conducted with the overall aim of improving education for patients and caregivers and also for the development of validated assessment tools for knowledge, training, and needs assessment for the management of food allergy. Shemesh et al⁵¹ conducted a randomized controlled study of supervised injection of medication-free epinephrine autoinjectors in 60 adolescent/parent pairs. Self-injection was associated with immediate increase in comfort levels for administration and improvements in QoL and reductions in anxiety in more than 50% of participants at the 1-month, postintervention follow-up.

In a dual-center study investigators developed a tool, the Food Allergy Management Perceptions Questionnaire, for adolescents and young adults (*n* = 19; age, 13–21 years) to measure barriers and facilitators for food allergy management.⁵² They found that those who adhered to dietary avoidance and epinephrine access had high facilitator scores, whereas those with poor adherence had higher barrier scores. Other centers have partnered to develop a food allergy assessment and training curriculum for child care center workers; a significant lack of food allergy knowledge was observed in the 73 childcare providers during initial surveys with improved food allergy knowledge observed after curriculum implementation.⁵³

Ongoing work continues to expand our knowledge of epinephrine administration and training of school workers in the school environment. Tsuang et al⁵⁴ performed an anonymous survey of Colorado school nurses and nonnursing staff members. Up to 19% of those surveyed reported epinephrine administration at least once during each school year between 2013 and 2015 by nonnurse staff members, with higher percentages reported in schools with the highest student/school nurse ration. Additionally, nonnursing staff reported only minimal training, very low confidence in their ability to recognize and treat anaphylaxis, and an average of 72% correct answers on knowledge-based questions.

In another retrospective survey conducted among Massachusetts public school nurses, investigators sought to determine the effect of peanut-restrictive school policies on anaphylaxis and epinephrine administration.⁵⁵ When rates of epinephrine administration for allergic reaction were compared between schools with and without peanut-free school policies, no differences in epinephrine administration were found. However, schools with peanut-free tables compared with those without had lower rates of epinephrine administration (incidence rate per 10,000 students = 0.2 and 0.6, respectively; $P = .009$). These findings highlight the need for further school-based studies to address practical management of food allergy and anaphylaxis in schools. The US Centers for Disease Control and Prevention Voluntary Guidelines for Managing Food Allergy in Schools, published in 2013 (www.cdc.gov/HealthyYouth/foodallergies) is an excellent resource for schools, parents, and other stakeholders in defining best practice for school-based management of food allergies.

Lastly, the Section on Allergy and Immunology of the American Academy of Pediatrics published 2 educational articles targeting pediatricians: one on epinephrine as first-aid management for anaphylaxis and the other focused on guidance for completing a written allergy and anaphylaxis emergency plan.^{56,57} Addressing the psychological, behavioral, and educational components of food allergy management directly affects patients and families and establishes an evidence-based foundation for development of further innovative approaches.

THERAPEUTIC APPROACHES TO IgE-MEDIATED FOOD ALLERGY

A growing body of literature is available evaluating emerging and novel therapies for IgE-mediated food allergy. To date, clinical trials have focused predominantly on studies using oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) alone or in combination with monoclonal IgE; however, other immunomodulatory approaches are also under investigation. Despite ongoing advances in the field, the current therapeutic approaches remain experimental because none of these approaches have FDA or other regulatory approval for use in patients.⁶

A recent meta-analysis and systematic review of food allergen immunotherapy summarized evidence that treatment in children raises the threshold of reactivity to a variety of foods, whereas receiving therapy and after discontinuation of therapy was associated with a modest increase in the risk of serious systemic adverse reactions and a substantial increase in minor local adverse reactions.⁵⁸

OIT

OIT has been studied most extensively in the form of single-allergen therapy, primarily milk, egg, and peanut, whereas the capacity of multiallergen OIT to induce desensitization is an area of ongoing investigation.⁶ OIT results in successful desensitization (reduced reactivity while receiving therapy) in a majority of treated subjects, but sustained unresponsiveness (SU), which was defined as reduced clinical reactivity after a period of cessation of therapy, has been achieved in only a subset.

In a long-term egg OIT trial in children and adolescents, CoFAR investigators reported progressive benefit of continued therapy, with 50% of participants achieving SU by year 4

compared with only 28% by year 2.⁵⁹ Furthermore, 100% of those achieving SU were able to consume both baked and concentrated egg products *ad libitum* during a 4-year follow-up period.

In a provocative report of home-based peanut immunotherapy, Garvey et al⁶⁰ clinically treated (without institutional review board protocol) 16 children (age, 6-13 years) with a low-dose tolerant/high-dose mild reaction profile by using a strategy that included weekly home build-up doses of 1 to 4 peanuts consumed 3 to 7 d/wk through 6 months of therapy, followed by an open OFC. Of the 10 patients with evaluable OFC data, 63% were desensitized at the 6-month OFC, and 50% achieved SU (after a 6-week period of OIT cessation) to a dose of 8 peanuts (roughly equivalent to 2400 mg of peanut); no safety events were reported. In all OIT trials to date, dosing is hampered by side effects, with gastrointestinal side effects occurring most commonly in approximately 20% of those receiving active therapy and associated with an increased risk for induction or activation of EoE in up to 2% of study participants. In addition, participants treated with OIT are at higher risk for allergic reactions associated with dosing.

New studies incorporating omalizumab pretreatment for 12 to 16 weeks before milk or peanut OIT have demonstrated enhanced safety with reduced side effect profiles, shortened time to maintenance therapy, and higher tolerated OIT dose but no significant change in clinical efficacy outcomes.^{61,62} When milk OIT and omalizumab were combined, investigators found that a baseline basophil activity threshold of less than 40% was associated with lower clinical symptoms during OIT, and those with higher basophil reactivity at baseline had less symptoms when omalizumab was combined with milk OIT.⁶³ Furthermore, a combination of lower baseline basophil reactivity and lower sIgE ratios were associated with attainment of SU after treatment, indicating that early biomarkers can predict OIT outcomes. EoE has been associated with peanut OIT despite treatment with omalizumab.⁶⁴

Virkud et al⁶⁵ provided additional insight into risk factors predicting side effects associated with peanut OIT by evaluating adverse events (AEs) in 104 participants in 3 peanut OIT trials. The authors reported that 80% of participants experienced AEs, with 42% having systemic symptoms and 49% having gastrointestinal symptoms; 20% dropped out during the study, half because of gastrointestinal symptoms. Asthma and allergic rhinitis predicted systemic symptoms, and higher SPT wheal size was predictive of gastrointestinal AEs.

Perhaps the most intriguing OIT trial in the last year attempted to harness the potential immunologic plasticity of younger children to enhance the therapeutic efficacy of peanut OIT. Vickery et al⁶⁶ reported the safety, efficacy, and feasibility of early peanut OIT in 37 children (age, 9-36 months) randomized to either low-dose (300 mg/d) or high-dose (3000 mg/d) maintenance therapy. The primary end point, SU 4 weeks after OIT cessation, was achieved in 29 (78%) of 37 in the intent-to-treat analysis (300-mg arm, 17/20 [85%]; 3000-mg arm, 12/17 [71%]) and in 29 (91%) of 32 in the per-protocol analysis over a median of 29 months. Additionally, peanut OIT-treated children were 19 times more likely to successfully integrate peanut into their diets when compared with matched control subjects with peanut allergy receiving standard care. Although further study is needed, this foundational study supports both the value of early OIT to maximize response to therapy, as well as the efficacy of lower maintenance doses to achieve similar therapeutic response.

Additional work in peanut OIT has focused on analyzing the specific allergen profiles of peanut foods, diagnostic reagents, and therapeutic allergen-based products.^{67,68} Results indicate the presence of all major peanut allergens in the preparations but significant variability of allergen and peanut component content of the tested products, thus highlighting the need for well-characterized and standardized products, particularly for therapeutics.

Using a highly characterized and purified peanut OIT product (AR101; Aimmune Therapeutics, Brisbane, Calif), investigators recently reported initial results of their first randomized, placebo-controlled, multicenter trial.⁶⁹ In this phase 2 study from 8 centers, 55 subjects (age, 4-26 years) were enrolled based on screening criteria and positive OFC results to 143 mg of cumulative peanut protein or less and then randomized to treatment with peanut OIT (AR101) to 300 mg or placebo OIT. The primary end point, the proportion of subjects in each arm able to tolerate 443 mg of cumulative peanut protein or greater at exit blinded OFC, was measured after 20 to 34 weeks of OIT dosing based on OIT protocol dosing (median, 22 weeks). In the intention-to-treat analysis, 79% of AR101 subjects tolerated 443 mg or greater and 62% tolerated 1043 mg of peanut protein compared with 19% and 0% of placebo-treated subjects, respectively ($P < .0001$). The AR101 subjects had less severe symptoms at exit OFC compared with those receiving placebo. There were more treatment-emergent AEs in the AR101 group compared with the placebo group, with a rate of 35.9 events per year of exposure in the AR101 group compared with 12.1 events per year in the placebo group (predominantly mild in both groups). Gastrointestinal symptoms were the most common AEs reported in 66% of the AR101 group and 27% of the placebo group, respectively, resulting in withdrawal of 21% of AR101-treated subjects. These results indicate induction of desensitization after AR101 treatment.⁶⁹ Peanut OIT with AR101 is currently in phase 3 clinical trials to assess this highly characterized peanut OIT product for efficacy and safety for the induction of clinical desensitization in peanut allergic children, with results anticipated in the next 1 to 2 years.

SLIT

SLIT for IgE-mediated food allergy has focused predominantly on treatment for patients allergic to milk, peanuts, tree nuts (eg, hazelnut), and fresh fruits (eg, peach and kiwi). These studies have shown clinical efficacy with moderate allergen-specific desensitization and a low side effect profile limited predominantly to oral mucosal symptoms. As with other forms of SLIT, interpretation of outcomes in food allergy studies has been limited by reduced participant adherence to therapy over time.⁷⁰

To better predict response to peanut SLIT from a cohort of 33 children previously treated for 1 year and assessed by using OFCs, Burk et al⁷¹ evaluated the ability of peanut components to predict treatment outcome. The authors reported an association of lower baseline peanut (Ara h 2 and Ara h 3) sIgE with successful desensitization. In a recent Austrian study of SLIT using recombinant allergen to treat birch pollen-related apple allergy, investigators compared SLIT with the major birch pollen allergen (Bet v 1) to SLIT with the major apple allergy allergen (Mal d 1).⁷² Among 60 adults (age, 18-65 years) treated during 4 months of therapy, both extracts resulted in minor oral mucosal symptoms, but only SLIT with recombinant Mal d 1 reduced symptoms

significantly and enhanced IgG₄/IgE ratios. The benefits of SLIT for food allergy and pollen-food allergy syndrome include a moderate treatment response and low AE rates, but additional studies in various age groups among participants with enhanced adherence and with new formulations, potentially using adjuvants to enhance response rates, are necessary to realize full utility in clinical care.

EPIT

EPIT has been investigated for the treatment of peanut and milk allergy and involves daily application of an allergen patch to the back or upper arm.

A significant number of preclinical studies in murine models of food allergy have reported the clinical and immunologic effect of treatment; however, only 2 clinical trials have been published using EPIT for the treatment of peanut allergy. The first was a phase 1 safety trial of the Viaskin Peanut patch (DBV Technologies, Bagnex, France), which showed high adherence rates and low side effect profiles.⁷³ More recently, a multicenter, randomized controlled trial was published by CoFAR investigators evaluating the safety and efficacy of the Viaskin Peanut patch in children and young adults aged 4 to 25 years.⁷⁴ After 52 weeks of treatment, peanut EPIT was associated with modest desensitization and immunologic changes when the 100- and 250- μ g doses were compared with placebo EPIT ($P = .003$), with the greatest response noted in younger children aged 4 to 11 years compared with those older than 11 years ($P = .003$). Peanut EPIT was well tolerated; adherence to therapy approached 97%, with the majority reporting only mild skin irritation at the patch site and no systemic allergic reactions to date.

Most recently, results of the largest phase 2 trial of peanut EPIT using the Viaskin Peanut patch were published.⁷⁵ In this study 221 subjects (age, 6-55 years) were enrolled from 22 centers based on enrollment criteria, including a positive blinded OFC result with an ED of 300 mg or less of cumulative peanut protein. Subjects were then randomized to one of 3 doses of Viaskin Peanut (50, 100, or 250 μ g/d) versus placebo Viaskin for 12 months of therapy, followed by 2 years of open label treatment. The primary end point, the percentage of treatment responders (defined as and ED ≥ 10 times increase from baseline OFC and/or reaching ≥ 1000 mg of peanut protein) in each treatment group, was measured at 12 months through follow-up blinded OFCs. In the intention-to-treat analysis the primary end point was reached in the 250- μ g patch group compared with the placebo group (50% vs 25%, $P = .01$) but not in other groups. Interaction by age group was significant only for the 250- μ g Viaskin Peanut patch ($P = .04$), with significance reached in the 6- to 11-year-old age group ($P = .008$) compared to placebo and no differences noted in the adolescent/adult age group. The mean cumulative reactive dose at month 12 was greater for the 250- μ g Viaskin Peanut patch (1117.8 mg) compared with placebo (469.3 mg). Treatment-emergent AEs were noted in each Viaskin Peanut group (range, 98.2% to 100%) and placebo group (92.9%), with predominantly mild reactions at the patch site; overall adherence was 97.6% after 12 months. At 12 months, 171 subjects were all continued on 250- μ g Viaskin Peanut open-label dosing, followed by OFCs at 12 and 24 months, with response rates of 59.7% and 64.5% noted, respectively. Findings indicate safety of Viaskin Peanut dosing and some level of desensitization noted in younger subjects.⁷⁵ Ongoing phase 2 and phase 3 studies are in progress for both

peanut and milk allergy, with results forthcoming in the next 1 to 2 years.

Other forms of therapy for food allergy

Novel investigation of innovative strategies to target food allergy is critical for development of new therapies, refinement of existing approaches, and continued progress toward active interventions for food allergy. Recently, investigators conducted a pilot study of dietary supplementation with isoflavones without significant changes in clinical outcomes but with reduction in basophil reactivity *in vitro*, yet this type of novel investigation is an example of innovative investigation that helps to propel the field forward.⁷⁶ Likewise, investigative teams continue to use pre-clinical mouse models to explore novel immunotherapeutic approaches. Srivastava et al⁷⁷ from the Jaffe Food Allergy Institute at Mount Sinai investigated the efficacy and safety of peanut OIT by using CpG-coated polyananoparticles containing peanut extract to treat mice with peanut allergy. Mice treated with CpG-peanut by means of gavage were significantly protected from anaphylaxis when compared with untreated control mice with lower symptoms scores and plasma histamine levels after challenge; sustained reductions in peanut sIgE and IgG₁, T_H2 cytokine, and increased specific IgG₂ and IFN- γ levels were observed.

This same group of investigators combined a Chinese herbal therapy product (B-FAHF-2) with peanut OIT to treat mice with peanut allergy.⁷⁸ Findings indicated a significant improvement in clinical and immunologic outcomes in mice treated with both products compared with those treated with peanut OIT alone.

Pagovich et al⁷⁹ evaluated a different approach using anti-humanized IgE gene therapy to treat peanut allergy in a novel pre-clinical study. First, investigators developed a new humanized murine model of peanut allergy that mimics human anaphylaxis to peanuts by transferring mononuclear cells from donors with peanut allergy to NOD-Scid mice followed by sensitization with peanut extract. Investigators then tested an adeno-associated vector coding for a full-length, high-affinity, anti-hIgE antibody derived from the Fab fragment of omalizumab (AAVrh.10anti-hIgE) for its ability to modulate the allergic response to peanut. A single administration of AAVrh.10anti-hIgE either before sensitization or after induction of peanut allergy blocked anaphylaxis scores and death from anaphylaxis, minimized peanut-induced histamine release, and reduced total, peanut-specific, and free IgE levels. These results were noted to a lesser degree in omalizumab-treated control mice not treated with AAVrh.10anti-hIgE, with results sustainable only in those mice receiving gene therapy.

MECHANISMS OF FOOD ALLERGY AND IMMUNOTHERAPY

As highlighted in the NASEM report, enhanced understanding of the immunologic mechanisms underlying food allergy is important for the strategic design of therapeutic approaches targeting food allergy.² Tordesillas et al⁸⁰ summarized the existing evidence for multiple immunologic mechanisms underlying the food-induced allergic response, including innate, adaptive, and effector cell responses.

An expanding role for the pro-T_H2 cytokines thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 in the genesis of food

allergy was identified over the past year.⁸¹ In a BALB/c mouse model of experimental egg allergy induced by means of oral gavage with a combination of medium-chain triglycerides plus egg white (EW), injection of mAb to either IL-25, IL-33 receptor, or TSLP robustly inhibited development of food allergy in this model, whereas suppression of established food allergy required treatment with a combination of all 3 pro-T_H2 cytokines for optimal suppression because no single mAb to TSLP, IL-33, or IL-25 could reverse established food allergy.

Another group of investigators highlighted the importance of the TSLP–basophil–IL-4 axis in epicutaneous sensitization to food antigens and downstream development of IgE-mediated food allergy mediated through IL-4.⁸² Examination of Notch-2–mediated signaling in the differentiation and recruitment of mast cells to the intestinal mucosa indicated pharmacologic inhibition of Notch signaling–suppressed mucosal mast cell hyperplasia and reduced symptoms of diarrhea and systemic anaphylaxis in challenged mice.⁸³

Burton et al⁸⁴ examined the role of allergen-specific IgG in both the prevention of IgE-mediated food allergy and treatment of established disease in IL4raF709 allergy-prone mice. Co-administration of specific IgG during initial food antigen exposure prevented sensitization through effects on IgE and T_H2 responses, resulting in reduced anaphylactic responses during challenge, whereas coadministration of IgG-specific antibody during oral desensitization promoted tolerogenic responses mediated by expansion of forkhead box protein 3 (Foxp3)–positive regulatory T (Treg) cells and suppression of established T_H2 and IgE responses.

This same group also reported breakthrough work in development of a humanized mouse model that exhibited robust human T- and B-cell engraftment, with significant numbers of human mast cells identified in mouse tissues, providing an important tool for advancing knowledge of immune mechanisms in patients with food allergy.⁸⁵ Investigation of the mechanisms underlying life-long and persistent peanut allergy across the 18- to 20-month mouse lifespan provided insight into B-cell memory responses, suggesting that clinically relevant IgE responses were conferred by allergen-specific long-lived memory B cells that replenish the IgE⁺ plasma cell compartment.⁸⁶

In a model of EPIT, C3H/HeJ mice were sensitized to ovalbumin either orally or epicutaneously and treated with OVA–Viaskin patches or OIT, and antigen-specific Treg cell induction was assessed.⁸⁷ Treatment with EPIT promoted a gastrointestinal tract–homing latency-associated peptide (LAP)⁺Foxp3⁺ Treg cell population mediated through TGF- β –dependent Treg cell inhibition of mast cells.

Use of dendritic cell immunotherapy to reverse established ovalbumin or peanut allergies was evaluated in a mouse model.⁸⁸ Investigators generated mature retinoic acid–skewed tolerogenic dendritic cells and evaluated their effectiveness in reversing established peanut or ovalbumin allergy in mouse models. Reduction of allergic symptoms was observed in half-maximally sensitized mice, with immunomodulation of T_H2, IgE, IgG₁, and mast cell responses and promotion of Foxp3⁺ Treg cells to promote immunomodulatory effects.

Expansion of our understanding of novel immune mechanisms underlying the beneficial responses to food allergen immunotherapy in human subjects provided important insights into therapeutic mechanisms. Transcriptional profiling of EW protein–stimulated PBMCs obtained from children with egg

allergy defined as being either baked egg reactive or baked egg tolerant or control subjects not allergic to egg but with food allergy were examined.⁸⁹ Both the baked egg-reactive and baked egg-tolerant groups had similar increased expression of genes associated with proallergic inflammatory pathways, including IL-5, IL-9, and TNF- α . Component-resolved analysis of IgA, IgE, and IgG₄ responses during egg OIT identified predictors associated with SU, including EW-specific IgG₄, IgA, and IgA₂, with lower pretreatment EW sIgE and ovomucoid sIgE associated with SU.⁹⁰

In a retrospective analysis of natural tolerance acquisition to CM, IgE and IgG₄ binding to sequential epitopes of 5 major CM proteins were measured by using a peptide microarray-based immunoassay in sera from 35 children with milk allergy (22 were CM tolerant at a median age of 51 months).⁹¹ Children who acquired natural tolerance to CM had IgE and IgG₄ antibodies that more often recognized the same epitopes, and when evaluated from baseline until the time of tolerance development, both IgE and IgG₄ binding intensity decreased significantly.

Important studies investigating T-cell phenotype and function expanded our understanding of T-cell subsets involved in allergic responses and effective immunotherapy in human subjects, advancing progress toward development of biomarkers that might predict therapeutic outcomes. Using allergen-specific T-cell sorting and single-cell gene expression, investigators monitored the transcriptional pathway of CD4⁺ T cells in patients with peanut allergy, discovering that effective immunotherapy shifts allergen-specific CD4⁺ T cells to an “anergic” T_H2 phenotype that was not observed before peanut OIT or in healthy control subjects.⁹²

Wambre et al⁹³ defined a distinct human memory T_H2 subpopulation specific to atopic subjects, the T_H2A subset, which was defined phenotypically as terminally differentiated CD4⁺ T cells (CD27[−]CD45RB[−]) coexpressing chemoattractant-receptor homologous molecule expressed on T_H2 cells, CD49d, and CD161. T_H2A cells are functionally distinct from conventional T_H2 cells, and responses to allergen are initiated through distinct signaling pathways; elimination of this pathogenic T_H2A subset was associated with beneficial clinical outcomes induced during effective immunotherapy. Using PBMCs from patients with peanut allergy and healthy control subjects, investigators were able to induce regulatory type 1 T (Tr1) cells expressing CD49b and lymphocyte-activation gene 3 at comparable frequencies; however, the regulatory type 1 T cells induced from patients with peanut allergy maintained T_H2 cytokine production when restimulated with peanut protein, supporting functional immunoregulatory impairment that was independent of OIT.⁹⁴

EFFECTS OF FOOD ALLERGY

The pervasive effect of food allergy on subjects and families has been highlighted in important investigations over the past year. Cross-cultural validation and application of the Food Allergy Quality of Life Questionnaire–Parent Form in the United States and 9 other European countries, as well as validation of a Spanish-language version of this assessment tool, provides an important tool for assessment and evaluation.^{95,96} Identification of sex differences in patients with perceived food allergy affect and severity indicated that female subjects reported increased effect of food allergy on health-related QoL related specifically to meal preparation, family social activities, stress/free time, and

limitations on the affected child’s social life.^{97,98} However, investigators postulated that differences in the level of involvement in care might explain the different perceptions because fathers who more frequently attended medical appointments appreciated a greater effect on meal preparation than less-involved fathers.^{97,98} Lower peanut threshold dose to elicit reaction, but not reaction severity, was identified as having a negative effect on food allergy-related QoL. Parents of young children with food allergy reported significant mealtime behavioral concerns comparable with those in parents of children with type 1 diabetes and feeding disorders; these concerns correlated positively with parental perception of food allergy-related risk, parenting stress, and QoL.⁹⁹ Patients with food allergy were more likely to exhibit attachment avoidance and discomfort, with close relationships in a cross-sectional European study, highlighting the need to carefully balance safety and psychological well-being.¹⁰⁰ The effect of OIT on QoL was examined, and investigators observed that patients with impaired QoL at baseline improved significantly despite the burdensome demands of therapy, whereas some patients with acceptable QoL at baseline had deterioration because of the demands associated with OIT.¹⁰¹

FUTURE DIRECTIONS

A paradigm-shifting investigation into primary prevention strategies and active therapies for established food allergy, as well as publication of evidence-based guidelines for diagnosis and management, has advanced the approach to patients with food allergy. The food allergy field is entering an exciting new era with potential for lasting effect on disease burden. Indeed, in the pivotal NASEM report the authors identified 2 overarching long-term goals to “(1) develop safe and effective therapies and (2) prevent onset of food allergies.” This roadmap to food allergy safety provides a compelling and unified vision and delineates an important mission that, with collective action, can continue to advance and improve the lives of those affected by food allergy. However, despite great progress, significant gaps in knowledge must be addressed to refine existing approaches and inform the development of “next-generation” approaches to food allergy management. Current immunotherapeutic strategies, such as OIT, EPIT, and SLIT, are not without associated risk, and further investigation is critical to address existing knowledge gaps, including optimal dose, duration, maintenance regimen, long-term outcomes, predictors of response, cost-effectiveness, and psychosocial effect that will maximize efficacy, minimize risk, and develop individualized approaches for future clinical application. Improved understanding of the complexities of mucosal immune regulation and systems biology underlying food allergy, as well as enhanced understanding of predictors of food allergy severity, natural history, and response to therapy will further inform the refinement of existing approaches and development of personalized therapeutic strategies to positively affect patients and families affected by food allergy.

REFERENCES

1. Boyce JA, Assa’ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(suppl):S1-58.
2. Stallings VA, Oria MP. Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy. Washington (DC): National Academies Press; 2016.

3. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;69:590-601.
4. Togias A, Cooper SF, Acebal ML, Assa'ad A, Baker JR Jr, Beck LA, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol* 2017;139:29-44.
5. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
6. Wood RA. Food allergen immunotherapy: current status and prospects for the future. *J Allergy Clin Immunol* 2016;137:973-82.
7. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124:1549-55.
8. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9-17.
9. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017;140:145-53.
10. Sasaki M, Koplin JJ, Dharmage SC, Field MJ, Sawyer SM, McWilliam V, et al. Prevalence of clinic-defined food allergy in early adolescence: the SchoolNuts study. *J Allergy Clin Immunol* 2018;141:391-8.e4.
11. Grimshaw KE, Bryant T, Oliver EM, Martin J, Maskell J, Kemp T, et al. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. *Clin Transl Allergy* 2015;6:1.
12. Mahdavinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial Differences in food allergy phenotype and health care utilization among US children. *J Allergy Clin Immunol Pract* 2017;5:352-7.
13. Muraro A, Lemanske RF Jr, Castells M, Torres MJ, Khan D, Simon HU, et al. Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 2017;72:1006-21.
14. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, Kohli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European Anaphylaxis Registry. *J Allergy Clin Immunol* 2016;137:1128-37.
15. Akuete K, Guffey D, Israelsen RB, Broyles JM, Higgins LJ, Green TD, et al. Multicenter prevalence of anaphylaxis in clinic-based oral food challenges. *Ann Allergy Asthma Immunol* 2017;119:339-48.
16. Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with IgE-mediated food allergy. *J Allergy Clin Immunol Pract* 2017;5:369-75.
17. Acker WW, Plasek JM, Blumenthal KG, Lai KH, Topaz M, Seger DL, et al. Prevalence of food allergies and intolerances documented in electronic health records. *J Allergy Clin Immunol* 2017;140:1587-91.e1.
18. Gupta RS, Singh AM, Walkner M, Caruso D, Bryce PJ, Wang X, et al. Hygiene factors associated with childhood food allergy and asthma. *Allergy Asthma Proc* 2016;37:140-6.
19. Ashley SE, Tan HT, Vuillermin P, Dharmage SC, Tang MLK, Koplin J, et al. The skin barrier function gene SPINK5 is associated with challenge-proven IgE-mediated food allergy in infants. *Allergy* 2017;72:1356-64.
20. Ashley SE, Tan HT, Peters R, Allen KJ, Vuillermin P, Dharmage SC, et al. Genetic variation at the Th2 immune gene IL13 is associated with IgE-mediated paediatric food allergy. *Clin Exp Allergy* 2017;47:1032-7.
21. Martino DJ, Ashley S, Koplin J, Ellis J, Saffery R, Dharmage SC, et al. Genome-wide association study of peanut allergy reproduces association with amino acid polymorphisms in HLA-DRB1. *Clin Exp Allergy* 2017;47:217-23.
22. Hong X, Ladd-Acosta C, Hao K, Sherwood B, Ji H, Keet CA, et al. Epigenome-wide association study links site-specific DNA methylation changes with cow's milk allergy. *J Allergy Clin Immunol* 2016;138:908-11.
23. Blazquez AB, Berin MC. Microbiome and food allergy. *Transl Res* 2017;179:199-203.
24. Plunkett CH, Nagler CR. The influence of the microbiome on allergic sensitization to food. *J Immunol* 2017;198:581-9.
25. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DY, Muraro A, et al. The microbiome in allergic disease: current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 2017;139:1099-110.
26. Bunyavanich S, Shen N, Grishin A, Wood R, Burks W, Dawson P, et al. Early-life gut microbiome composition and milk allergy resolution. *J Allergy Clin Immunol* 2016;138:1122-30.
27. Savage JH, Lee-Sarwar KA, Sordillo J, Bunyavanich S, Zhou Y, O'Connor G, et al. A prospective microbiome-wide association study of food sensitization and food allergy in early childhood. *Allergy* 2018;73:145-52.
28. Smith PK, Masilamani M, Li XM, Sampson HA. The false alarm hypothesis: food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. *J Allergy Clin Immunol* 2017;139:429-37.
29. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016;374:1435-43.
30. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374:1733-43.
31. Turner PJ, Campbell DE. Implementing primary prevention for peanut allergy at a population level. *JAMA* 2017;317:1111-2.
32. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:276-86.
33. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksunger O, Kalb B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol* 2017;139:1591-9.
34. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. *J Allergy Clin Immunol* 2017;139:1600-7.
35. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *JAMA* 2016;316:1181-92.
36. Lowe AJ, Su JC, Allen KJ, Abramson MJ, Cranswick N, Robertson CF, et al. A randomised trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitisation: the PEBBLES Pilot Study. *Br J Dermatol* 2018;178:e19-21.
37. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. *J Allergy Clin Immunol Pract* 2017;5:237-48.
38. Santos AF, Shreffler WG. Road map for the clinical application of the basophil activation test in food allergy. *Clin Exp Allergy* 2017;47:1115-24.
39. Simberloff T, Parambi R, Bartnikas LM, Broyles AD, Hamel V, Timmons KG, et al. Implementation of a standardized clinical assessment and management plan (SCAMP) for food challenges. *J Allergy Clin Immunol Pract* 2017;5:335-44.
40. Chan JC, Peters RL, Koplin JJ, Dharmage SC, Gurrin LC, Wake M, et al. Food challenge and community-reported reaction profiles in food-allergic children aged 1 and 4 years: a population-based study. *J Allergy Clin Immunol Pract* 2017;5:398-409.
41. Agyemang A, Feuille E, Tang J, Steinwandtner I, Sampson H, Nowak-Wegrzyn A. Outcomes of 84 consecutive open food challenges to extensively heated (baked) milk in the allergy office. *J Allergy Clin Immunol Pract* 2018;6:653-5.e2.
42. Gau J, Wang J. Rate of food introduction after a negative oral food challenge in the pediatric population. *J Allergy Clin Immunol Pract* 2017;5:475-6.
43. Sicherer SH, Wood RA, Vickery BP, Perry TT, Jones SM, Leung DY, et al. Impact of allergic reactions on food-specific IgE concentrations and skin test results. *J Allergy Clin Immunol Pract* 2016;4:239-45.
44. Bird JA, Groetch M, Allen KJ, Bock SA, Leonard S, Nowak-Wegrzyn AH, et al. Conducting an oral food challenge to peanut in an infant. *J Allergy Clin Immunol Pract* 2017;5:301-11.
45. Hourihane JO, Allen KJ, Shreffler WG, Dunnigalvin G, Nordlee JA, Zurzolo GA, et al. Peanut Allergen Threshold Study (PATS): novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J Allergy Clin Immunol* 2017;139:1583-90.
46. Blankestijn MA, Remington BC, Houben GF, Baumert JL, Knulst AC, Blom WM, et al. Threshold dose distribution in walnut allergy. *J Allergy Clin Immunol Pract* 2017;5:376-80.
47. Sann J, Bunyavanich S, Wang J. Epinephrine autoinjector prescribing patterns in an urban pediatric population. *J Allergy Clin Immunol Pract* 2016;4:989-90.
48. Schellpfeffer NR, Leo HL, Ambrose M, Hashikawa AN. Food allergy trends and epinephrine autoinjector presence in summer camps. *J Allergy Clin Immunol Pract* 2017;5:358-62.
49. Warren CM, Dyer AA, Otto AK, Smith BM, Kauke K, Dinakar C, et al. Food allergy-related risk-taking and management behaviors among adolescents and young adults. *J Allergy Clin Immunol Pract* 2017;5:381-90.
50. Ross J, Fishman J, Wang J. Internet and food allergy: what patients are seeking and what they do with the information. *J Allergy Clin Immunol Pract* 2017;5:494-5.

51. Shemesh E, D'Urso C, Knight C, Rubes M, Picerno KM, Posillico AM, et al. Food-allergic adolescents at risk for anaphylaxis: a randomized controlled study of supervised injection to improve comfort with epinephrine self-injection. *J Allergy Clin Immunol Pract* 2017;5:391-7.
52. Herbert LJ, Lin A, Matsui E, Wood RA, Sharma H. Development of a tool to measure youths' food allergy management facilitators and barriers. *J Pediatr Psychol* 2016;41:363-72.
53. Lanser BJ, Covar R, Bird JA. Food allergy needs assessment, training curriculum, and knowledge assessment for child care. *Ann Allergy Asthma Immunol* 2016; 116:533-7.
54. Tsuang A, Demain H, Patrick K, Pistiner M, Wang J. Epinephrine use and training in schools for food-induced anaphylaxis among non-nursing staff. *J Allergy Clin Immunol Pract* 2017;5:1418-20.
55. Bartnikas LM, Huffaker MF, Sheehan WJ, Kanchongkittiphon W, Petty CR, Leibowitz R, et al. Impact of school peanut-free policies on epinephrine administration. *J Allergy Clin Immunol* 2017;140:465-73.
56. Sicherer SH, Simons FER. Section on Allergy and Immunology. Epinephrine for first-aid management of anaphylaxis. *Pediatrics* 2017 [Epub ahead of print].
57. Wang J, Sicherer SH. Section on Allergy and Immunology. Guidance on completing a written allergy and anaphylaxis emergency plan. *Pediatrics* 2017; 139 [Epub ahead of print].
58. Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72:1133-47.
59. Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016;137: 1117-27.
60. Garvey AA, O'Sullivan D, Hourihane JO. Home-based induction of sustained unresponsiveness in children with mild reactions to high doses of peanut. *J Allergy Clin Immunol Pract* 2017;5:1757-9.
61. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2017;139:873-81.
62. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol* 2016;137:1103-10.
63. Frischmeyer-Guerrero PA, Masilamani M, Gu W, Brittain E, Wood R, Kim J, et al. Mechanistic correlates of clinical responses to omalizumab in the setting of oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2017;140: 1043-53.
64. Burk CM, Dellon ES, Steele PH, Virkud YV, Kulis M, Burks AW, et al. Eosinophilic esophagitis during peanut oral immunotherapy with omalizumab. *J Allergy Clin Immunol Pract* 2017;5:498-501.
65. Virkud YV, Burks AW, Steele PH, Edwards LJ, Berglund JP, Jones SM, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol* 2017; 139:882-8.
66. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017;139:173-81.
67. Berglund JP, Szczepanski N, Penumarti A, Beavers A, Kesselring J, Orgel K, et al. Preparation and analysis of peanut flour used in oral immunotherapy clinical trials. *J Allergy Clin Immunol Pract* 2017;5:1098-104.
68. Filep S, Block DS, Smith BRE, King EM, Commins S, Kulis M, et al. Specific allergen profiles of peanut foods and diagnostic or therapeutic allergenic products. *J Allergy Clin Immunol* 2018;141:626-31.e7.
69. Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. *J Allergy Clin Immunol Pract* 2018;6:476-85.e3.
70. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. *J Allergy Clin Immunol* 2015;135:1240-8.
71. Burk CM, Kulis M, Leung N, Kim EH, Burks AW, Vickery BP. Utility of component analyses in subjects undergoing sublingual immunotherapy for peanut allergy. *Clin Exp Allergy* 2016;46:347-53.
72. Kinaciyan T, Nagl B, Faustmann S, Frommlet F, Kopp S, Wolkersdorfer M, et al. Efficacy and safety of 4 months of sublingual immunotherapy with recombinant Mal d 1 and Bet v 1 in patients with birch pollen-related apple allergy. *J Allergy Clin Immunol* 2018;141:1002-8.
73. Jones SM, Agbotounou WK, Fleischer DM, Burks W, Pesek RD, Harris MW, et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: a phase 1 study using viaskin patch. *J Allergy Clin Immunol* 2016;137: 1258-61.e10.
74. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol* 2017;139:1242-52.
75. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. *JAMA* 2017;318:1798-809.
76. Masilamani M, Chang LM, Kamalakannan M, Schussler E, Rassbach W, Sampson HA. Dietary isoflavone supplementation for food allergy: a pilot study. *J Allergy Clin Immunol Pract* 2017;5:1760-2.
77. Srivastava KD, Siefert A, Fahmy TM, Caplan MJ, Li XM, Sampson HA. Investigation of peanut oral immunotherapy with CpG/peanut nanoparticles in a murine model of peanut allergy. *J Allergy Clin Immunol* 2016;138:536-43.
78. Srivastava KD, Song Y, Yang N, Liu C, Goldberg IE, Nowak-Wegrzyn A, et al. B-FAHF-2 plus oral immunotherapy (OIT) is safer and more effective than OIT alone in a murine model of concurrent peanut/tree nut allergy. *Clin Exp Allergy* 2017;47:1038-49.
79. Pagovich OE, Wang B, Chiuchio MJ, Kaminsky SM, Sondhi D, Jose CL, et al. Anti-IgE gene therapy of peanut-induced anaphylaxis in a humanized murine model of peanut allergy. *J Allergy Clin Immunol* 2016;138:1652-62.
80. Tordesillas L, Berin MC, Sampson HA. Immunology of food allergy. *Immunity* 2017;47:32-50.
81. Khodoun MV, Tomar S, Tocker JE, Wang YH, Finkelman FD. Prevention of food allergy development and suppression of established food allergy by neutralization of thymic stromal lymphopoietin, IL-25, and IL-33. *J Allergy Clin Immunol* 2018;141:171-9.e1.
82. Hussain M, Borcard L, Walsh KP, Pena Rodriguez M, Mueller C, Kim BS, et al. Basophil-derived IL-4 promotes epicutaneous antigen sensitization concomitant with the development of food allergy. *J Allergy Clin Immunol* 2018;141: 223-34.e5.
83. Honjo A, Nakano N, Yamazaki S, Hara M, Uchida K, Kitauro J, et al. Pharmacologic inhibition of Notch signaling suppresses food antigen-induced mucosal mast cell hyperplasia. *J Allergy Clin Immunol* 2017;139:987-96.
84. Burton OT, Tamayo JM, Stranks AJ, Koleoglou KJ, Oettgen HC. Allergen-specific IgG antibody signaling through FcγRIIb promotes food tolerance. *J Allergy Clin Immunol* 2018;141:189-201.e3.
85. Burton OT, Stranks AJ, Tamayo JM, Koleoglou KJ, Schwartz LB, Oettgen HC. A humanized mouse model of anaphylactic peanut allergy. *J Allergy Clin Immunol* 2017;139:314-22.
86. Jimenez-Saiz R, Chu DK, Mandur TS, Walker TD, Gordon ME, Chaudhary R, et al. Lifelong memory responses perpetuate humoral TH2 immunity and anaphylaxis in food allergy. *J Allergy Clin Immunol* 2017;140:1604-15.e5.
87. Tordesillas L, Mondoulet L, Blazquez AB, Benhamou PH, Sampson HA, Berin MC. Epicutaneous immunotherapy induces gastrointestinal LAP+ regulatory T cells and prevents food-induced anaphylaxis. *J Allergy Clin Immunol* 2017; 139:189-201.
88. Dawicki W, Li C, Town J, Zhang X, Gordon JR. Therapeutic reversal of food allergen sensitivity by mature retinoic acid-differentiated dendritic cell induction of LAG3+CD49b-Foxp3- regulatory T cells. *J Allergy Clin Immunol* 2017;139: 1608-20.
89. Kosoy R, Agashe C, Grishin A, Leung DY, Wood RA, Sicherer SH, et al. Transcriptional profiling of egg allergy and relationship to disease phenotype. *PLoS One* 2016;11:e0163831.
90. Wright BL, Kulis M, Orgel KA, Burks AW, Dawson P, Henning AK, et al. Component-resolved analysis of IgA, IgE, and IgG4 during egg OIT identifies markers associated with sustained unresponsiveness. *Allergy* 2016;71:1552-60.
91. Caubet JC, Lin J, Ahrens B, Gimenez G, Bardina L, Niggemann B, et al. Natural tolerance development in cow's milk allergic children: IgE and IgG4 epitope binding. *Allergy* 2017;72:1677-85.
92. Ryan JF, Hovde R, Glanville J, Lyu SC, Ji X, Gupta S, et al. Successful immunotherapy induces previously unidentified allergen-specific CD4+ T-cell subsets. *Proc Natl Acad Sci U S A* 2016;113:E1286-95.
93. Wambre E, Bajzik V, DeLong JH, O'Brien K, Nguyen QA, Speake C, et al. A phenotypically and functionally distinct human TH2 cell subpopulation is associated with allergic disorders. *Sci Transl Med* 2017;9.
94. Pellerin L, Jenks JA, Chinthrajah S, Dominguez T, Block W, Zhou X, et al. Peanut-specific type 1 regulatory T cells induced in vitro from allergic subjects are functionally impaired. *J Allergy Clin Immunol* 2018;141:202-13.e8.
95. DunnGalvin A, Koman E, Raver E, Frome H, Adams M, Keena A, et al. An examination of the food allergy quality of life questionnaire performance in a country-wide American sample of children: cross-cultural differences in age and impact in the United States and Europe. *J Allergy Clin Immunol Pract* 2017;5:363-8.

96. Manso L, Pineda R, Huertas B, Fernandez-Rivas M, Dieguez MC, Cerecedo I, et al. Validation of the Spanish version of the food allergy quality of life questionnaire-parent form (S-FAQLQ-PF). *J Investig Allergol Clin Immunol* 2017;27:363-9.
97. Hoehn JL, Dahlquist LM, Hahn AL, Bollinger ME. Parents of children with food allergy: gender differences in perceived impact and perceived food allergy severity. *J Pediatr Psychol* 2017;42:186-97.
98. Stensgaard A, Bindslev-Jensen C, Nielsen D, Munch M, DunnGalvin A. Quality of life in childhood, adolescence and adult food allergy: patient and parent perspectives. *Clin Exp Allergy* 2017;47:530-9.
99. Herbert LJ, Mehta P, Sharma H. Mealtime behavior among parents and their young children with food allergy. *Ann Allergy Asthma Immunol* 2017;118:345-50.
100. Polloni L, Schiff S, Ferruzza E, Lazzarotto F, Bonaguro R, Toniolo A, et al. Food allergy and attitudes to close interpersonal relationships: an exploratory study on attachment. *Pediatr Allergy Immunol* 2017;28:458-63.
101. Rigbi NE, Goldberg MR, Levy MB, Nachshon L, Golobov K, Elizur A. Changes in patient quality of life during oral immunotherapy for food allergy. *Allergy* 2017;72:1883-90.