Critical Issues in Food Allergy: A National Academies Consensus Report

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The National Academies of Sciences, Engineering, and Medicine convened an expert, ad hoc committee to examine critical issues related to food allergy. The authors of the resulting report, “Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy,” evaluated the scientific evidence on the prevalence, diagnosis, prevention, and management of food allergy and made recommendations to bring about a safe environment for those affected. The committee recommended approaches to monitor prevalence, explore risk factors, improve diagnosis, and provide evidence-based health care. Regarding diagnostics, emphasis was placed on utilizing allergy tests judiciously in the context of the medical history because positive test results are not, in isolation, diagnostic. Evidence-based prevention strategies were advised (for example, a strategy to prevent peanut allergy through early dietary introduction). The report encourages improved education of stakeholders for recognizing and managing as well as preventing allergic reactions, including an emphasis on using intramuscular epinephrine promptly to treat anaphylaxis. The report recommends improved food allergen labeling and evaluation of the need for epinephrine autoinjectors with a dosage appropriate for infants. The committee recommended policies and guidelines to prevent and treat food allergic reactions in a various settings and suggested research priorities to address key questions about diagnostics, mechanisms, risk determinants, and management. Identifying safe and effective therapies is the ultimate goal. This article summarizes the key findings from the report and emphasizes recommendations for actions that are applicable to pediatricians and to the American Academy of Pediatrics.

Food allergy has become an increasingly recognized global health concern. Defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food,1 the disease impacts health and quality of life for sufferers and their caregivers.2 A new report entitled “Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy” (referred to hereafter as “the report”) was recently released by The National Academies of Sciences, Engineering and Medicine (NAS) (available at www.nationalacademies.org/FoodAllergies).3 Here we describe the Report, focusing on key findings and recommendations applicable to pediatricians and the American Academy of Pediatrics (AAP).

The National Academy of Sciences was established in 1863 by an Act of Congress signed by President Abraham Lincoln as a nongovernmental...
institution to advise the nation and, in concert with the National Academy of Engineering and the National Academy of Medicine (formerly the Institute of Medicine), now functions as the NAS to provide independent, objective advice to the nation. For the study on food allergy, support was received by 3 federal and 8 nonfederal sponsors* and was the product of a study by a committee of 15 international experts with diverse expertise who were vetted for conflicts of interest and who considered a vast array of issues in the field. The evidence base included selective literature reviews and evaluation of published guidelines and practice parameters, and it favored meta-analyses and systematic reviews as applicable to a variety of topics. Recognizing that the etiology and management of food allergy involves not only the patient, an ecological-developmental model of food allergy was considered to address numerous interacting facets including the environment, family, home, child care, the health care system, industry, cultural practices, and government policy and regulation.

The report underscores the central role of the immune response in defining food allergy, thus distinguishing it from other adverse responses to food. Food allergy results from immunoglobulin E (IgE)-mediated and/or non-IgE-mediated mechanisms, the former being more common (potentially resulting in anaphylaxis), and is the focus of the report. Often, alternative causes of adverse reactions to foods may be misinterpreted as a food allergy. Lactose intolerance is one example; the inability to digest the sugar lactose results in bloating and diarrhea, but is not an allergy. Adverse reactions to foods may be caused by metabolic, pharmacologic, or toxic factors that must be distinguished from allergy. In the United States, it is common for parents to avoid a food on the basis of the perception of food allergy when in fact most of the time diagnostic testing will reveal that there is none and the food could be added back to the diet.1,4,5 Here we review and comment on highlights of the report that are pertinent to pediatricians, pediatric care of food allergies, and the AAP as a professional organization named as a potential actor to accomplish some of the committee’s recommendations.

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**PREVALENCE**

A previous US review concluded that food allergy affects >1% to 2% and <10% of the population.6 A US study published in Pediatrics that was based on parental report of allergy concluded that up to 8% of children have food allergy.7 Several studies, including data presented by the Centers for Disease Control and Prevention (CDC), suggest an increase in prevalence in the United States.8,9 However, the report points out that prevalence estimates vary among studies depending on numerous factors, including the definition of allergy; the foods being considered; whether diagnosis is by self-report, testing, or a combination of factors; selection of participants; age of participants; geographical regions; and many other factors. Ideal studies include medically supervised feeding to confirm allergy or tolerance (an oral food challenge [OFC]). Studies of self-reported allergy typically overestimate prevalence.10 Few studies include gold standard, medically supervised feeding tests, with no US studies including them since the 1980s.5 Although many foods have been noted to cause allergic reactions, it is clear that cow’s milk, hen’s egg, peanuts, tree nuts, and seafood are responsible for most of the serious allergic reactions.1,11 Despite an exhaustive literature search, the authors of the report could not present definitive prevalence data for the United States. The committee recommended approaches for performing studies to obtain more accurate prevalence estimates, including using modalities such as the National Health and Nutrition Examination Survey with incorporation of additional testing of subsamples with OFCs.

**DIAGNOSIS AND PROGNOSIS**

The committee recommended that “physicians use evidence-based, standardized procedures as the basis for food allergy diagnosis and avoid nonstandardized and unproven procedures....When food allergy is suspected, the patient should be evaluated by a physician who has the training and experience to select and interpret appropriate diagnostic tests.” The AAP’s Clinical Report on allergy testing emphasizes these fundamentals12 and, like the National Academies report, suggests consideration of referral to or consultation with a physician specialist (for example, an allergist-immunologist).

The basis of these comments stems in part from the observation that self-reported allergy typically overestimates true allergy, and no simple tests provide a diagnosis.
In one meta-analysis, the rate of self-reported food allergy among children was 12%, compared with 3% when confirmatory testing was performed.\textsuperscript{10} A serious misconception about food allergy diagnostics relates to equating a “positive test result” by a serum food-specific IgE (sIgE) blood test or skin prick test (SPT) to having an allergy to the tested food. These tests detect IgE antibodies to the food but are not typically intrinsically diagnostic. For example, in 111 OFCs performed in 44 children avoiding foods because of positive test results, 93% were tolerant of the avoided food.\textsuperscript{13} It is clear that these tests are misunderstood by physicians. For example, in a survey of 407 primary care physicians, 38% indicated incorrectly that these sIgE blood tests or SPTs were sufficient for diagnosis.\textsuperscript{14} Although overdiagnosis is a concern and may be driven by overtesting and misinterpretation of results, under- or misdiagnosis must also be addressed. Assuming incorrectly that an allergen has been identified without confirmatory testing could lead to reexposure to the true culprit, resulting in serious reactions if the unidentified trigger is consumed again. The report summarized information from previously published guidelines and systematic reviews to highlight appropriate tests and their use and to discuss tests that are not recommended.\textsuperscript{1,15,16}

A previous guideline\textsuperscript{1} suggests that the medical history is key in diagnosis, and food allergy should be considered when allergic symptoms occur proximate (within minutes to hours) to ingestion of a specific food, especially when symptoms occur on more than 1 occasion. For example, suspicion would be high if a child developed urticaria within minutes after the ingestion of a peanut, especially if an acute reaction such as this occurred with more than 1 exposure. However, suspicion might be low if the child routinely ingested peanuts and the urticaria persisted for days, suggesting a viral rash. Food allergy diagnostic testing may also be warranted for infants and children with moderate to severe atopic dermatitis because there is a higher rate of food allergy in this population, and the food allergy may be contributing to the rash. Disorders with subacute or chronic symptoms that are indicative of a food-related origin, such as food protein–induced enterocolitis syndrome (severe vomiting, lethargy, and sometimes hypotension and acidosis starting 2 hours after ingestion) and allergic colitis (mucous-containing, bloody stools) also warrant investigation for food-allergic triggers, but these disorders occur without IgE antibodies.\textsuperscript{1} Food allergy should also be considered in children with eosinophilic esophagitis. Importantly, food allergy is not a typical trigger of chronic asthma or chronic rhinitis in childhood.

Medical history can help to identify the likelihood of a food allergy diagnosis (pretest probability) and can suggest whether the pathophysiology is IgE- or non-IgE–mediated, which is pertinent for test selection and helps to identify potential triggers. Importantly, details of the history may disclose alternative reasons for symptoms other than a food allergy. Additional diagnostic modalities include diagnostic elimination diets, SPT, sIgE blood test, and OFC. Neither SPT nor sIgE blood test results alone are considered sufficient for diagnosis. However, in the presence of a strong suggestive history of food allergy, these can confirm the diagnosis without further need for an OFC.\textsuperscript{1,12} Increasingly large skin test wheal sizes or sIgE levels correlate with higher risks of allergy, but sensitivity and specificity are often inadequate to confirm a diagnosis.\textsuperscript{16} Tests that measure sIgE to specific proteins in foods, a modality called “component testing,” may improve specificity of tests. For example, Ara h 2 is a protein in peanuts associated with clinical reactions.\textsuperscript{15,17} The OFC, particularly when performed in a double-blind manner with a placebo, is considered a gold standard.\textsuperscript{18} Unmasked OFCs are typically performed for clinical purposes, and double-blind procedures are used more often for research. The report concluded that a number of diagnostic modalities were not recommended for routine use, including food allergy patch testing (atopy patch test), measurement of total IgE, and the basophil activation test. Other tests were not recommended and were considered “unproven and non-standardized” for diagnosing food allergy. These tests include allergen-specific IgA, IgG, or IgG;\textsuperscript{19} provocation neutralization; immune complexes; human leukocyte antigen screening; lymphocyte stimulation; facial thermography; gastric juice analysis; endoscopic allergen provocation; hair analysis; applied kinesiology; cytotoxic assays; electrodermal testing; mediator release assays; bioresonance; and iridology.

Although some studies suggest laboratory results might help to provide insights on severity and prognosis,\textsuperscript{19–23} there are no simple reliable means currently to identify these aspects of food allergy. The report emphasizes that on the basis of test limitations, particularly that sensitization alone is not diagnostic, physicians should not order “panels” of food tests without a rationale.

**RISK AND PREVENTION**

Food allergy is undoubtedly caused by a combination of genetic and environmental factors.\textsuperscript{24} The report presents a number of risk factors and prevention strategies that have been evaluated in published studies.

Regarding solid food introduction, the authors of the report concluded that
there is strong evidence regarding the early introduction of peanuts as being protective against peanut allergy in infants at high risk, defined by early-onset eczema or coexistent egg allergy. This is generally in line with recent consensus publications and guidelines25,26 that have been endorsed by the AAP and whose authors have promoted the introduction of peanut protein in infant-safe forms for high-risk infants as early as 4 to 6 months of age after appropriate testing.

Regarding foods other than peanuts, the report indicates that more studies are needed to assess whether early introduction affects food allergy. However, the report concludes that “limited evidence...suggests that delaying the introduction of egg, cow milk and wheat to decrease risk of those food allergies has no benefits” and discusses a potential benefit of introducing these foods in the first year of life when the infant is developmentally ready (at ~6 months but not before 4 months of age).

The committee also concluded that there is limited evidence to support or discourage eliminating allergenic foods from the diet of pregnant or lactating women and that evidence for a protective effect of breastfeeding is also limited.

There were no changes in recommending breastfeeding as the preferred feeding for all infants. However, the authors of the report gave recommendations and drew conclusions that differ from findings and recommendations on allergy prevention that were published in a 2008 AAP Clinical Report.27 The authors of the AAP Clinical Report suggested that specific types of infant formulas may be useful for allergy prevention in high-risk infants if the infants could not exclusively be breastfed. In contrast, the NAS committee concluded that studies on the effects of partially or extensively hydrolyzed infant formulas for preventing food allergies are inconsistent or have methodologic flaws and that evidence is therefore limited. They concluded that high-quality randomized clinical studies would be needed before these formulas could be recommended for food allergy prevention.

As a global recommendation, the committee advised that public health authorities and clinical practice guidelines include consistent, clear, and evidence-based advice for families and health care providers about the potential benefits of introducing allergenic foods in the first year of life to infants when the infant is developmentally ready (at ~6 months of age but not before 4 months of age, particularly for those at high risk of allergy). As noted above, the AAP has been involved in updating such guidelines28 and is in the process of creating an updated Clinical Report on prevention of atopic disease.

Regarding risk factors, the committee identified limited but consistent evidence that skin barrier defects (for example, eczema or filaggrin gene mutations) play a role in sensitization. Although individuals with 1 type of atopy (eg, eczema) may be at risk for another manifestation (eg, food allergy), a new theory suggests that skin barrier defects and inflammation may provide a sensitizing route of exposure to proteins in the environment. Unfortunately, firm conclusions could most often not be reached on a number of issues because of limited data. The committee considered, but could not identify because of limited evidence, a link between food allergy and nutritional factors such as vitamin D, maternal omega-3 fatty acid intake, folate supplementation, and other nutrients. The committee could not identify randomized clinical trials or other convincing evidence to address other potential hypotheses for an increase in food allergy. Only a few studies have been published on the relationship between changes in the microbiota and food allergen sensitization, so evidence supporting the relationship is limited. Trials on probiotics and prebiotics also have methodologic limitations, and the committee concluded that there is not yet evidence to support a decreased risk of food allergy from using these interventions. Also with regard to microbial exposure and the “hygiene hypothesis,” firm conclusions could not be reached regarding a relationship between food allergy and cesarean delivery, use of antibiotics, or exposure to pets or animals. Although there is indirect evidence that genetics contributes to the development of food allergies, with those with a family history at moderately increased risk, there are no conclusive findings regarding specific loci. Similarly, epigenetic mechanisms are likely involved because the apparent rise in food allergy has occurred in a short period of time and therefore is presumed to be secondary to environmental causes. These hypotheses are underpinned by a recent finding that Asian infants born in Asia who migrate to Australia in the first 5 years of life are protected from nut allergy, whereas Australian-born Asian infants are at a 2 to 3 times higher risk of nut allergy than white infants born in Australia when evaluated for allergy at age 5 years.28

**EMERGENCY MANAGEMENT**

The authors of the report reviewed the management of food allergic reactions and anaphylaxis and focuses on prompt use of epinephrine to treat anaphylaxis. Researchers suggest that epinephrine is safe but often underutilized29–31 and that there is poor recognition about both how and when to use epinephrine autoinjectors. The authors of the report identified teenagers as a high-risk group because they may take risks that result in ingestion of an allergen and may postpone proper treatment. In addition, those with
food allergy and comorbid asthma are considered at high risk because they may be prone to more severe reactions. Epinephrine autoinjectors are currently only available in doses of 0.15 and 0.30 mg, which are not ideal for infants. The committee recommended that the Food and Drug Administration (FDA) evaluate the need for an epinephrine autoinjector with a dosage appropriate for use in infants and, if indicated, that industry should develop an autoinjector with 0.075 mg of epinephrine specifically designed for use in infants. The authors of an AAP Clinical Report discuss the dosing of epinephrine autoinjectors for first aid management of anaphylaxis in the community and also raise concerns regarding the best dosing for infants.32,33

**DAILY MANAGEMENT**

Pediatricians should counsel families on allergen avoidance for a variety of settings, including home, school, and travel. At home, care is needed during food preparation to avoid cross-contact of allergen with safe foods. Information about obtaining safely packaged foods and managing food allergy outside the home is reviewed below. Two additional areas of emphasis especially pertinent to pediatric patients are (1) the need for careful nutritional monitoring and intervention for children avoiding foods because of allergy34; and (2) attention to psychosocial aspects of managing food allergy, including an increased risk of bullying.35,36 The committee recommended that the CDC work with other public health authorities to initiate a public health campaign for the general public, those with food allergy, and relevant stakeholders to increase awareness and empathy as well as to dispel misconceptions about food allergy and its management. This global approach could reduce bullying and risk-taking behavior by raising awareness. The committee made a number of additional recommendations applicable to pediatricians and to the AAP as outlined in Table 1.

**Packaged Foods, Travel, Restaurants**

Patients and families living with food allergies often depend on others to obtain safe foods. Obtaining safely packaged food is one consideration. The current status of labeling is often confusing for allergic consumers. In the United States, labeling laws require plain English terminology to identify “major allergens” as ingredients, including cow’s milk, hen’s egg, wheat, soy, peanuts, tree nuts, fish, and crustacean shellfish. For categorical foods, specific types must be listed (for example, codfish instead of “fish” or walnut instead of “nuts”). However, the foods considered “nuts” include ones that are not necessarily true nuts. The committee identified, for example, that lychee is erroneously considered a nut by the FDA (when botanically it is actually a fruit). Other allergens, such as sesame, are not included in US labeling laws and yet different countries include different foods in their labeling laws, including sesame and others. Advisory labeling, also called precautionary labeling (eg, “may contain” or “in a facility with”), is voluntary and not regulated. There has been a proliferation of advisory labeling, leading to consumer concerns about the veracity of the warnings. The committee provided a number of recommendations directed toward the FDA to improve labeling and create a system in which advisory labeling is meaningful. For example, evaluation of a risk-based labeling system like the Voluntary Incidental Trace Allergen Labelling program, which is used in Australia, could be considered.

Regarding restaurants and food service as well as foods prepared in groceries, the committee recommended a number of training approaches and regulatory actions to improve safety and the flow of information...
for consumers. In the meantime, it is important for pediatricians to advise patients to inform restaurants and food service establishments of their allergy and to discuss details of the food’s safety with staff. With regard to airline travel, where concerns include the safety of food provided and exposure to food proteins in the closed environment, recommendations are directed toward food safety and also anaphylaxis recognition and management. The recommendations include ensuring emergency epinephrine capabilities are in place for children. The AAP has been committed to these issues, and recently resolutions were submitted at the Annual Leadership Forum regarding availability of epinephrine for children on airplanes.

**Schools and Early Child Care and Education Settings**

The committee recommended that various stakeholders, including advocates such as the AAP, participate in a task force to address emergency management and prevention strategies for venues such as schools and early care and education settings. The authors of the report review some of the approaches, including state and federal policies, which are important for managing food allergy in early care and education settings and schools. The AAP has been committed to these issues as well. The AAP produced a Clinical Report on food allergy management in schools and had representation on the CDC Voluntary Guidelines for Food Allergy in Schools that was referred to in the report and was recommended for implementation. The CDC guidelines report is available at: http://www.cdc.gov/healthyschools/foodallergies/pdf/13_243135_a_food_allergy_web_508.pdf.

**RESEARCH NEEDS**

The committee identified numerous areas in need of additional research. Some of the priority areas include the prevalence and cost of food allergies; diagnosis and prognosis; risk determinants and prevention; management in health care settings, food establishments, schools and traveling; and curative therapies. Some of the areas that may be of interest to general pediatric research include the best modalities to educate families and physicians about management, examining barriers to proper testing, identifying educational approaches and tools to improve physician and patient education, utilizing birth cohorts and other opportunities for prevalence estimates, determining the effectiveness of evidence-based guidelines and educational programs on food allergy management, improving the understanding of nutritional needs, establishing the best means to identify and manage psychosocial concerns, monitoring the number of food allergic reactions that occur in settings such as schools, and defining best practices regarding management.

**SIX MAJOR ACTIONS REQUIRED TO ACHIEVE FOOD ALLERGY SAFETY**

The committee conceptualized a roadmap to safety involving 6 major actions that require input from various stakeholders, including pediatricians and professional organizations such as the AAP, to achieve short- and long-term goals. The first action would involve collecting better information about prevalence (which is crucial for identifying the scope of the problem), prioritizing food allergy in context of other health diseases, and exploring risk factors. The second action involves improving the quality of diagnosis and providing evidence-based health care. The third action concerns evidence-based prevention strategies. As noted previously, data are lacking on a variety of potential interventional strategies, but exciting new approaches, particularly regarding prevention of peanut allergy, are being promulgated. The fourth action is to improve education and training of all stakeholders for recognizing and managing as well as preventing allergic reactions. This work includes updating, creating, and implementing various guidelines and educational programs. The fifth action is to develop policies and related practices to help prevent and treat severe reactions. The sixth and most critical action regards research priorities to address key questions about diagnostics, mechanisms, risk determinants, and management. Identifying safe and effective therapies is the ultimate goal.

**CONCLUSIONS**

Food allergy appears to be increasing in prevalence and particularly affects children. The National Academies report identifies a large number of immediately obtainable practice goals to improve safety for children with food allergies. The committee also identified numerous research goals. Although the recommendations of the report are directed toward numerous stakeholders (including consumers, patients, allergy researchers, health care providers, school leaders, manufacturers, government agencies, and others), pediatricians and the AAP can take a prominent seat at the table to ensure that the report’s smorgasbord of findings and recommendations are digested and implemented to reduce risks and improve safety for children with food allergies.

**ABBREVIATIONS**

AAP: American Academy of Pediatrics
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
IgE: immunoglobulin E
NAS: National Academies of Sciences, Engineering, and Medicine
OFC: oral food challenge
slgE: serum food-specific IgE
SPT: skin prick test
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