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

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

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

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

EPIDEMIOLOGY AND NATURAL HISTORY

Prevalence

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

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Disclosure of potential conflict of interest: S. H. Sicherer is employed by Icahn School of Medicine at Mount Sinai; has received grants from Food Allergy Research and Education, the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID), and HAL Allergy; has received royalties from UpToDate and Johns Hopkins University Press; and is an Associate Editor for the American Academy of Allergy, Asthma & Immunology. H. A. Sampson has received grants from the NIAID (AI-44236; CoFAR; ITN); has consultant arrangements with Allertein Therapeutics, Hycor, and UCB; is employed by DBV Technologies as Chief Scientific Officer (0.6 FTE); has received royalties from UpToDate; and has received stock options from DBV Technologies.

Received for publication October 17, 2017; revised October 31, 2017; accepted for publication November 3, 2017.

Available online November 21, 2017.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2017.11.003

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

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

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

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

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

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

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

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

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

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

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

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