

# Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment

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

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

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

#### Activity Objectives

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

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

#### Disclosure of Significant Relationships with Relevant Commercial

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

This review focuses on advances and updates in the epidemiology, pathogenesis, diagnosis, and treatment of food allergy over the past 3 years since our last comprehensive review. On the basis of numerous studies, food allergy likely affects nearly 5% of adults and 8% of children, with growing evidence of an increase in prevalence. Potentially rectifiable risk factors include vitamin D insufficiency, unhealthful dietary fat, obesity, increased hygiene, and the timing of exposure to foods, but genetics and other lifestyle issues play a role as well. Interesting clinical insights into pathogenesis include discoveries regarding gene-environment interactions and an increasing understanding of the role of nonoral sensitizing exposures causing food allergy, such as delayed allergic reactions to carbohydrate moieties in mammalian meats caused by sensitization from homologous substances transferred during

tick bites. Component-resolved diagnosis is being rapidly incorporated into clinical use, and sophisticated diagnostic tests that indicate severity and prognosis are on the horizon. Current management relies heavily on avoidance and emergency preparedness, and recent studies, guidelines, and resources provide insight into improving the safety and well-being of patients and their families. Incorporation of extensively heated (heat-denatured) forms of milk and egg into the diets of children who tolerate these foods, rather than strict avoidance, represents a significant shift in clinical approach. Recommendations about the prevention of food allergy and atopic disease through diet have changed radically, with rescinding of many recommendations about extensive and prolonged allergen avoidance. Numerous therapies have reached clinical trials, with some showing promise to dramatically alter treatment. Ongoing studies will elucidate improved prevention, diagnosis, and treatment. (*J Allergy Clin Immunol* 2014;133:291-307.)

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

Discuss this article on the JACI Journal Club blog: [www.jaci-online.blogspot.com](http://www.jaci-online.blogspot.com).

This article is an update to our comprehensive review of the diagnosis and management of food allergy published in 2010.<sup>1</sup>

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**Abbreviations used**

AD:	Atopic dermatitis
APT:	Atopy patch test
CMA:	Cow's milk allergy
COFAR:	Consortium of Food Allergy Research
CRD:	Component-resolved diagnostics
EHCF:	Extensively hydrolyzed casein formula
EoE:	Eosinophilic esophagitis
FLG:	Filaggrin
$\alpha$ -Gal:	Galactose- $\alpha$ -1,3-galactose
LR:	Likelihood ratio
NHANES:	National Health and Nutrition Examination Survey
OFC:	Oral food challenge
OR:	Odds ratio
sIgE:	Allergen-specific serum IgE
PPV:	Positive predictive value
SPT:	Skin prick test

Since that publication, an expert panel sponsored by the National Institute of Allergy and Infectious Diseases defined *food allergy* as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” and *food intolerance* as nonimmune reactions that include metabolic, toxic, pharmacologic, and undefined mechanisms.<sup>2</sup> We encourage readers seeking an overview to refer to practice parameters, guidelines, and international consensus papers that emphasize key points in the diagnosis and management of food allergy<sup>3-5</sup> and related disorders.<sup>6,7</sup> Companion articles in this issue of the *Journal* focus on oral, sublingual, and epicutaneous immunotherapy<sup>8</sup> and insights obtained from murine models of food allergy,<sup>9</sup> and therefore we will not review these topics in detail. We highlight recent clinical observations and advances that inform prevention, diagnosis, and management now and, hopefully, in the near future.

## EPIDEMIOLOGY AND NATURAL HISTORY

### Prevalence

Accurate determinations of food allergy prevalence are elusive because factors such as allergy definitions, study populations, methodologies, geographic variation, ages, dietary exposures, and other factors influence the estimates.<sup>10</sup> A comprehensive review of the literature concluded that “food allergy affects more than 1% to 2% but less than 10% of the population” and that it remains unclear whether the prevalence is increasing.<sup>11</sup> A number of recent studies provide spectacularly high estimates of food allergy. Gupta et al<sup>12</sup> used an electronic US household survey ( $n = 38,480$ ) in 2009-2010 and estimated that 8% of children have food allergy, 2.4% have multiple food allergies, and approximately 3% experience severe reactions. Solter et al<sup>13</sup> surveyed 9667 subjects from 10 Canadian provinces for self-reported food allergy and found an overall rate of 8%. When they excluded adults reporting unlikely allergies and adjusted for nonresponders, the final estimates were 6.7% in the overall population, with 7.1% of children and 6.6% of adults reporting food allergy. Cow's milk (2.2%), peanut (1.8%), and tree nuts (1.7%) were the most common allergens in children, and shellfish (1.9%), fruits (1.6%), and vegetables (1.3%) were the most common allergens in adults. Taking a different perspective using food allergen-specific serum IgE (sIgE) results

obtained in the National Health and Nutrition Examination Survey (NHANES) in the United States (2005-2006), Liu et al<sup>14</sup> estimated clinical allergy to cow's milk, egg, and peanut at 1.8% each in children age 1 to 5 years. The 2 most recent NHANES performed from 2007-2010 with 20,686 US participants included queries on self-reported food allergies. Overall, 8.96% reported food allergy, with 6.53% among children.<sup>15</sup> Self-report or reliance on serology is notoriously inaccurate,<sup>15,16</sup> but few studies include oral food challenges (OFCs) on a population level. Osborne et al<sup>17</sup> evaluated a population-based cohort of 2848 (73% participation rate) 1-year-old infants in Melbourne, Australia, in a study that included OFCs and estimated prevalence as follows: peanut, 3.0%; raw egg, 8.9%; and sesame, 0.8%. A United Kingdom study on early childhood peanut allergy, which included OFCs, estimated a peanut allergy prevalence of 2% at age 8 years.<sup>18</sup> A population-based study on the prevalence of cow's milk protein-induced enterocolitis syndrome revealed a cumulative incidence of 0.34% (44/13019) in Israel.<sup>19</sup> Taken together, these studies substantiate food allergy rates nearing 5% in adults and approaching 8% in children, with a number of estimates nearing 2% for peanut allergy. Whether perceived or confirmed allergy, the economic,<sup>20,21</sup> emotional,<sup>22</sup> and safety burden is substantial.

Data generally support an increase in prevalence. A 2013 data brief from the US Centers for Disease Control and Prevention relying on data from a single question in the US National Health Interview Survey concluded that among children age 0 to 17 years, the prevalence of food allergies increased from 3.4% in 1997-1999 to 5.1% in 2009-2011.<sup>23</sup> Estimates based on a single query are suspect, but a number of pediatric studies also support an increased prevalence. A US survey<sup>24</sup> repeated on 3 occasions presented the opportunity to compare results from 1997 to 2008 in surrogate-reported peanut allergy in children. The rate increased significantly from 0.4% to 1.4%. Limitations of the studies included decreasing participation rates and self-assessment of allergy. However, as indicated above, similar or higher rates of peanut allergy were determined in a number of studies using various methodologies, including OFCs, around the same period. Additional recent publications focusing on peanut allergy indicated increases with a doubling (United Kingdom)<sup>25</sup> or tripling (United States)<sup>26</sup> in diagnoses. A cross-sectional study of infants from a single clinic in China over a 10-year period used OFCs for diagnosis and estimated an increase in food allergy from 3.5% to 7.7% ( $P = .17$ ).<sup>27</sup> Although there are methodological limitations, the impression of an international increase in allergy and food allergy remains strong.<sup>3,10</sup>

### Risk factors

A plethora of risk factors are proposed to influence food allergy or sensitization, including sex (male sex in children), race/ethnicity (increased among Asian and black children compared with white children), genetics (familial associations, HLA, and specific genes), atopy (comorbid atopic dermatitis [AD]), vitamin D insufficiency, dietary fat (reduced consumption of omega-3-polyunsaturated fatty acids), reduced consumption of antioxidants, increased use of antacids (reducing digestion of allergens), obesity (being an inflammatory state),<sup>28</sup> increased hygiene, and the timing and route of exposure to foods (increased risk for delaying allergens with possible environmental

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