Clinical Commentary Review

Food Allergy from Infancy Through Adulthood

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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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Learning objectives:

1. To understand the natural course and etiology of food allergy from infancy through adulthood.
2. To identify food-allergic disorders that present differently according to age groups.
3. To provide food allergy management as appropriate for different age groups.

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Abbreviations used
AD- Atopic dermatitis
ED- Emergency department
EoE- Eosinophilic esophagitis
FPIAP- Food protein–induced allergic proctocolitis
FPIES- Food protein–induced enterocolitis
OAS- Oral allergy syndrome
OFC- Oral food challenge
OIT- Oral immunotherapy
PFAS- Pollen-food allergy syndrome
SLIT- Sublingual immunotherapy

Food allergies are the result of immune responses that cause adverse reactions to foods. Immune responses to foods may produce a spectrum of symptoms and disorders, including acute allergic reactions and anaphylaxis, food protein–induced allergic proctocolitis, food protein–induced enterocolitis syndrome, food-dependent, exercise-induced anaphylaxis, and oral allergy syndrome (pollen-food allergy syndrome). Food-allergic responses also contribute to chronic inflammatory disorders such as eosinophilic esophagitis and atopic dermatitis. Although food allergy affects people from infancy through adulthood, there are allergic features that differ according to age (ie, presentation, triggers, and natural course) and have important implications for diagnosis, prognosis, and management. New food allergies can develop at any age, and we propose similarities in the etiology of *de novo* food allergy whether in infancy or adulthood. The approach to managing food allergy changes dramatically over the life course, and physicians and patients must respond accordingly to optimize care. Food allergy therapies are emerging, and the efficacy and safety of these interventions could differ by age group of those treated. In this review, we highlight interesting observations on the etiology and characteristics of food allergy presenting at different ages and discuss clinical management as it relates to life stage. **© 2020 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2020;8:1854-64)**

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Food allergy is defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food."[1] The immune pathology distinguishes food allergy from other adverse reactions that can occur from foods, for example, intolerance, poisoning, and pharmacologic effects.[1] One may surmise that the characteristics of food allergy differ substantially from infancy through adulthood. Reviews and guidelines have emphasized that food allergies are more common in children than adults, that specific foods such as milk or egg are more common triggers for children and typically resolve, and that specific food-allergic disorders are typical in specific age groups (eg, protein-induced enterocolitis syndrome in infants and young children).[1-4] Emerging observations that we review here have questioned some of these tenets and provide interesting insights into the evolving epidemiology and pathophysiology of food allergy with implications for diagnosis, prevention, and treatment. In addition, it is clear that managing food allergies differs substantially for individuals at different ages and life stages, for which responsibilities and daily risks evolve through infancy, childhood, adolescence, young adulthood, for pregnant mothers, adults facing occupational exposure, and other situations that affect adults through their lifetime. Although data are sparse for many aspects of these topics, we review practical implications with guidance toward managing food allergy through the life course.

EPIDEMIOLOGY: AGE-RELATED INSIGHTS

There are many challenges in estimating food allergy prevalence.[1,4,5] Self-reported food allergy typically overestimates prevalence compared with estimates based on a diagnosis determined by allergy testing, particularly when oral food challenges (OFCs) are used, which remains the gold standard for food allergy diagnosis. The types of food-allergic reactions included in estimates of food allergy prevalence can also affect the estimates; for example, estimates differ whether mild allergic reactions from pollen-food allergy syndrome (PFAS) are included. In a 2015-2016 US household survey with 38,408 responses for children, Gupta et al[6] reported symptoms clearly consistent with acute, IgE-mediated reactions—excluding probable PFAS—which was used to define convincing cases of food allergy. This study also evaluated whether each reported allergy was physician diagnosed, as well as the specific testing (eg, confirmatory skin prick tests, serum food-specific IgE, or OFCs). The authors reported that the overall prevalence of convincing IgE-mediated food allergy was 7.6% (95% confidence interval [CI]: 7.1%-8.1%) after excluding the 4% whose parent-reported food allergy did not meet inclusion criteria. Two-thirds of the children with convincing food allergies had a physician diagnosis. The most common food allergens were peanut (2.2%), milk (1.9%), shellfish (1.3%), and tree nuts (1.2%). The rate of food allergy was 2.8% in infants under age 1 year, which peaked to 10% at age 2 years, and was 7.1% in adolescents aged 14 to 17 years. Cow's milk was the most common food allergen in early life, present among approximately 50% of convincingly food-allergic <1-year-olds, 40% of food-allergic 1- to 2-year-olds, and 30% of food-allergic 3- to 5-year-olds. Among children aged 6 to 10 years, peanut surpassed cow's milk allergy in prevalence, present among 1 in 3 food-allergic children, compared with 1 in 4 who were convincingly milk allergic. By early adolescence, tree nut and shellfish allergies also exceeded cow's milk allergy in prevalence, each present in approximately 1 in 5 food-allergic children.

Using a similar approach, Gupta et al[7] concomitantly surveyed 40,443 adults (aged 18 years and older) and found convincing food allergies in 10.8% (95% CI: 10.4%-11.1%), with an additional 8.2% reporting reaction symptomatology deemed inconsistent with an IgE-mediated reaction. Among all adults, the most common allergies were shellfish (2.9%), milk (1.9%), peanut (1.8%), tree nuts (1.2%), and fin fish (0.9%). Table I provides rates of convincing food allergies for selected foods and selected ages from these 2 studies,[6,7] and also indicates the rate of new-onset food allergy among the adults with the specific allergy. Remarkably, approximately half of US food-allergic adults report developing at least one of their food allergies during adulthood, with shellfish allergy responsible for the largest number of such cases. Although the national survey did not report allergic reactions to alcoholic beverages, these occur and are, by default, observed in teenagers and adults.[8]

It is generally thought that some childhood food allergies, such as those to milk and egg, are more likely to resolve than others, such as peanut, tree nuts, fish, and shellfish allergies,

TABLE I. Rates (percent) of convincing food allergy in US surveys 2015-2016[6,7]

Food	All children	All adults	<1 y	2 y	6-10 y	14-17 y	18-29 y	40-49 y	≥60 y	Percent of adults with adult-onset allergy
Any	7.6	10.8	2.8	10.0	8.0	7.1	11.3	10.0	8.8	48
Peanut	2.2	1.8	0.6	2.4	2.6	2.1	2.5	1.8	0.8	17.5
Tree nut	1.2	1.2	0.2	1.1	1.4	0.9	1.6	1.1	0.6	34.6
Milk	1.9	1.9	1.5	4.3	1.9	1.1	2.4	2.0	1.9	22.7
Shellfish	1.3	2.9	0.2	1.1	1.5	1.5	2.8	2.5	2.6	48.2
Fin fish	0.6	0.9	0.1	0.6	0.6	0.6	1.1	0.8	0.6	39.9
Egg	0.9	0.8	0.4	1.4	0.9	0.5	1.1	0.7	0.5	29.0
Wheat	0.5	0.8	0.4	1.0	0.5	0.4	1.0	0.8	0.6	52.6
Soy	0.5	0.6	0.4	0.9	0.5	0.2	0.7	0.6	0.4	45.4
Sesame	0.2	0.2	0.1	0.2	0.3	0.1	0.3	0.2	0.1	25.7

which frequently persist into adulthood.[9] The 2015-2016 US surveys[6,7] (Table I) also provide interesting data suggesting that higher-than-anticipated numbers of adults have food allergies to "childhood" allergens, with, in some cases, surprisingly high rates of new-onset allergy to typical "childhood" allergens (eg, milk 22.7%, egg 29%, wheat 52.6%, and soy 45.4%). It is also notable that in childhood, males predominate, and in adulthood, females predominate (Figure 1).[6,7] In a chart review of 171 Chicago-area patients with clinically confirmed food allergies, 15% were adult-onset.[10] These studies excluded PFAS, which may be the most common type of adult food allergy.[11] Rates are quite different across the globe. In a study of 8 European countries using symptoms and evidence of IgE sensitization to define probable food allergy in general population surveys of adults, the lowest rate of allergy was in Athens (0.3%) and the highest in Zurich (5.6%).[12] The European surveys included adults with PFAS. A study of Israeli young adults (aged 17-18 years) that included OFCs confirmed a prevalence of 0.67%, with tree nuts (0.28%), milk (0.16%), and peanut (0.14%) as most common.[13]

These epidemiological findings, especially the high rates in westernized countries, if confirmed by replication/validation studies, reflect an even greater urgency for clinicians to identify primary and secondary prevention approaches, in addition to treatment approaches, and address this new, concerning trend toward greater pediatric allergy persistence, and higher rates of adult-onset (age 18 years and older) allergies.

DOES ETIOLOGY DIFFER BY AGE?

Food allergy is the result of numerous genetic and environmental factors, resulting in a lack or loss of tolerance to certain foods.[14-18] Immune alteration and/or digestion/absorption of the foods may influence allergy occurrence, which matches the notion that infants and children are at greater risk than adults for developing food allergies. Mounting evidence for the "dual allergen exposure hypothesis" of Lack[19-22] suggests that non-ingestion exposures via the skin, especially on inflamed skin, with a lack of oral exposure, can result in allergic sensitization. This has led to the encouragement of early ingestion of peanut for infants as a prevention strategy, particularly for infants with atopic dermatitis (AD).[23,24] In a study of twins, Kivisto et al[25] found a significantly higher concordance rate for peanut allergy among monozygotic twins than among dizygotic twins (0.64 vs 0.07), strengthening the evidence of heritability of peanut allergy, and found that AD was a significant risk factor for food allergy, independent of genetic factors, highlighting the potential importance of AD control and prevention among children to reduce the risk of food allergy.

It has also been reported that children with AD and positive IgE antibodies to specific foods have a fairly significant risk of developing acute food-allergic reactions when foods are removed from their diet to treat the AD.[26,27] For example, 1 in 5 patients with food-triggered AD and no previous history of IgE-mediated food hypersensitivity reactions developed new immediate reactions to a variety of newly avoided foods (eg, cow's milk, peanut, fish, wheat, and others), with nearly one-third of such patients experiencing anaphylaxis.[27] This circumstance, as well as other examples of food allergies in children after removal of an ostensibly tolerated food,[28-30] suggests that atopic individuals may be in a state of natural desensitization that can be lost with allergen avoidance. Clearly, the airway is also a powerful sensitizing route of exposure because PFAS occurs despite ingestion of fruits with the proteins that are homologous to the pollen.[31]

Do these notions of alteration in gut permeability, skin and lung exposure as a sensitizing route, and loss of desensitization apply to adult-onset food allergy? The evidence suggests the answer is "yes." The reports that acid suppressors may be a risk factor for adult food allergy,[32,33] and also reports of food-dependent, exercise-induced anaphylaxis occurring to otherwise tolerated foods (another example of alteration in gut permeability)[34] suggest that adults may be prone to gut-level disturbances that may affect food-allergy outcomes. Many of the foods accounting for adult-onset food allergies, such as shellfish or tree nuts, are not eaten regularly, and loss of a desensitized state may be an explanation, given periods of no oral exposure. There are also examples of new-onset acute allergic reactions to milk in atopic adults who avoided milk.[35] Occupational/airborne and skin exposure may sensitize adults—not just young children—with AD. For example, cases of adult-onset milk[36] and lupin[37] allergy have been attributed to occupational skin and respiratory exposure, and adult soy allergy may be triggered by pollen exposure.[38] The skin as a sensitizing route for adult food allergy is also demonstrated by alpha-gal syndrome from tick bites[39,40] as well as cases of milk/cheese,[41,42] wheat,[43,44] and soy[45] allergies in adults who use cosmetics and skin-care products containing these ingredients. Although more studies are needed, it is possible that the etiology of risks for developing food allergies do not change significantly over the life course, although the absolute risks may be different and likely decrease with age.

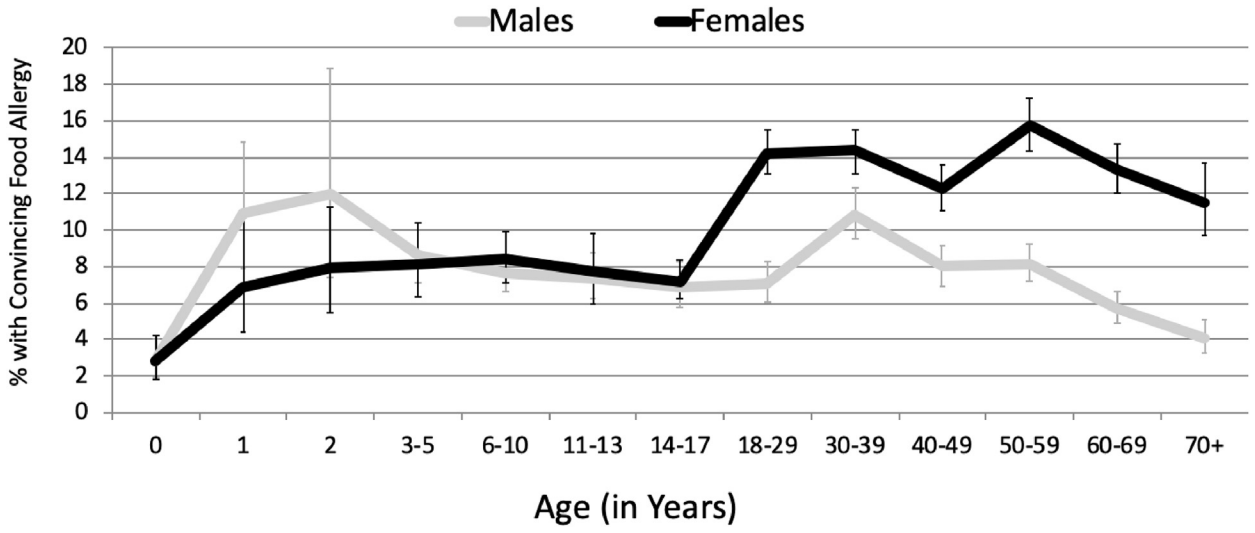

FIGURE 1. Age- and sex-specific prevalence estimates of convincing IgE-mediated food allergy.

MANIFESTATIONS AND DISORDERS: FOCUS ON AGE

In the following sections, we discuss the age-relevant features of food-allergic disorders, and in Table II, we summarize the key age-related features and natural course of the disorders.

Acute allergic reactions and anaphylaxis

IgE-mediated acute allergic reactions can vary from mild to severe. Pollen-related food allergy, discussed later, involves sensitization to primarily fruits and vegetables and tends to be mild, whereas anaphylaxis is more often triggered by foods such as peanut, tree nuts, fish, and shellfish and tends to be severe—sometimes fatal. Fatalities from allergic reactions are rare overall, but appear to be slightly more common among children,[46,47] possibly reflecting certain risk factors in adolescents and young adults such as delaying epinephrine injections.[48] Infants less than 1 year of age seem to have milder symptoms compared with older children with the main symptoms being hives, rash, or vomiting and less commonly respiratory or cardiovascular.[49] The recent report of 2 child deaths from OFC underscores the importance of maintaining up-to-date national and international registries on food-associated fatalities.[50] Gupta et al estimated the proportion of food-allergic adults[7] and children[6] in the United States who have experienced at least 1 severe reaction—characterized by reports of specific symptoms across multiple organ systems (eg, hives, swelling, difficulty swallowing, throat tightening, vomiting, wheezing, dizziness, etc.). A history of at least 1 "severe" reaction over the lifetime was estimated to be present in 42.3% (95% CI: 39.1%-45.4%) of US food-allergic children and 51.1% (95% CI: 49.3%-52.9%) of US food-allergic adults. Among children and adults, those foods with the highest rates of severe reactions were identical (child rate/adult rate): peanut (59.2%/67.8%), tree nut (56.1%/61.3%), shrimp (51.1%/56.6%), and fish (49.0%/56.5%). All of the major food allergens (milk, egg, wheat, soy, peanut, tree nuts, fish, shellfish, sesame) had severe reaction rates over 27%. In these studies, interestingly, the rates of severe reactions to milk were 25.3% in children versus 39.3% in adults, and for egg, severe reactions were 28.1% in children versus 39.4% in adults. In these adults, allergies represented mostly childhood-onset allergies, suggesting persistence of the more severe phenotypes. Also, when asked about health care utilization, 1 in 5 children reported a visit to the emergency department (ED) for a food-allergic reaction in the past year compared with 1 in 10 adults. Overall, there appear to be some differences in severity and anaphylaxis rates across the age spectrum, but the triggers of severe reactions are substantially similar.

Food protein–induced allergic proctocolitis (FPIAP)

FPIAP presents in infants who are generally healthy but have visible specks or streaks of blood mixed with mucous in the stool.[1] Food-specific IgE is typically undetectable in infants with FPIAP. The diagnosis is clinical and includes noting improvement in symptoms with dietary exclusion and a lack of systemic symptoms, vomiting, diarrhea, and poor growth. Biopsies of the rectal or colonic mucosa are not typically undertaken for diagnosis, but when obtained, there is eosinophilic infiltration.[51] FPIAP is considered a disease of infancy that resolves in the first year of life.[1,51,52] However, eosinophilic colitis (as a specific diagnosis) and colonic eosinophilia (from a variety of triggers or part of systemic illness) are well described in adults.[53] Eosinophilic colitis is grouped among eosinophilic gastrointestinal disorders, with varied symptoms and etiologies; however, some patients present with blood in the stool and association with atopy and food allergy. A Canadian report described 7 adults with FPIAP, including a 70-year-old and a 57-year-old having bloody diarrhea and food "sensitivities" to cow's milk and other foods. The symptoms were self-limiting. Whether there is any specific relationship between FPIAP of infancy to the food-related subtypes of eosinophilic colitis in adults remains unexplored and there are no long-term outcome studies in infants with FPIAP.

Food protein–induced enterocolitis (FPIES)

FPIES is a non–IgE-mediated food allergy that typically presents in infancy, with repetitive protracted vomiting that begins approximately 1 to 4 hours after ingestion of the trigger food ("acute" FPIES reaction).[54] Vomiting may be accompanied by lethargy; pallor and diarrhea may follow. Severe reactions can progress to hypothermia, methemoglobinemia, acidemia, and

TABLE II. Characteristics of food-allergic disorders emphasizing life course

Disorder	Age-related features	Natural course
IgE-mediated food allergies/anaphylaxis	Foods triggering the most severe reactions are similar across the life course (peanut, tree nuts, shrimp, fish)	More severe egg/milk allergies in adults are those carried over from childhood
	Severity is similar across the life course with 42%-53% having severe reactions	Egg, milk, wheat, soy allergies more likely to resolve than peanut, tree nuts, fish, shellfish allergies
Food protein–induced allergic proctocolitis (FPIAP)	Characteristically a disease of infancy	Resolution during infancy
	Some overlap features with adult eosinophilic colitis	
Food protein–induced enterocolitis (FPIES)	Typical onset in infancy from milk, soy, oat, rice with males > females	Typically resolves in infancy/early childhood
	Geographic variation in triggers	
	Adult onset described in various cases/case series more often shellfish, fish and females > males	
Eosinophilic esophagitis (EoE)	Infant and young children presenting symptoms characterized by reflux, poor growth	Persistent
	Older child/adult presenting with heartburn, dysphagia, chest pain, impaction	
	Increasing fibrosis noted on biopsy by age, reflecting years of ongoing inflammation	
Atopic dermatitis (AD)	Roughly one-third of children with moderate-severe AD experience food allergy (food allergy as a cause of chronic rash is less common)	Course associated with food allergy natural course
	Limited data on contribution of food allergy to adult AD	
Pollen-food allergy syndrome	Not described in infancy	Likely persistent with variations in severity
	Common allergic disease in children and adults, possibly increase in prevalence with age	

hypotension, all mimicking sepsis. A "chronic" form of FPIES may occur when the offending food is ingested regularly. The triggers are classically milk, soy, oat, and rice, but these triggers vary internationally, with fish being a more common trigger in Italy and Spain.[54,55] This typically infant-onset disorder usually resolves; however, the number of affected children appears to be growing. For example, a recent US population-based cross-sectional prevalence survey estimated that 0.51% (95% CI: 0.42-0.62) of the pediatric population aged <18 years had physician-diagnosed FPIES at some point in their lifetime. Although it is important to note that these "physician-diagnosed" cases were parent reported and not clinically confirmed by the study epidemiologists, these rates are consistent with cumulative FPIES incidence rates during infancy of 0.34 to 0.70 reported by single-center birth cohorts in Israel and Spain.[56] These pediatric estimates can be contrasted with the 0.22% (95% CI: 0.17-0.28) of adults in the aforementioned US population-based survey reporting that they themselves had received a physician diagnosis of FPIES at some point in their lifetime.[57]

Reports of FPIES in adults are increasing, and some nuances are apparent compared with the disorder in infants/children. What may be the first case report of adult FPIES was published in 2012 and described a 53-year-old man whose trigger, verified by OFC, was scallops.[58] Subsequent chart reviews of 31 adults from Australia[59] and 20 adults from Canada[60] showed a range of FPIES triggers (mostly shellfish, fish, milk, egg, wheat), adult-onset, with the trigger being previously tolerated, and symptoms similar in timing and pattern to infant FPIES. These adult-case series revealed some distinctions compared with infants and children because those affected have different trigger foods and were predominantly females (infant FPIES predominantly affects males). Interestingly, these sex differences mirror findings in IgE-mediated food allergy, which disproportionately impacts male infants and female adults.[6,7,57] Whether the pathophysiology of the adult onset form is distinct from the infantile/early child form remains to be determined, and the natural course of FPIES in adults is also unexplored.

Eosinophilic esophagitis (EoE)

EoE is a chronic inflammatory disorder characterized by eosinophilic inflammation of the esophagus resulting in esophageal dysfunction.[61] An esophageal biopsy is undertaken when there is a suggestive history of such esophageal dysfunction (dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain, and malnutrition). The diagnosis requires the presence of esophageal eosinophilia (≥15 eosinophils per high-powered microscope field). Food is an important EoE trigger and management can include dietary elimination of allergens, often undertaken empirically. Medical management involves the off-label use of corticosteroids, such as swallowing puffs from an asthma inhaler, and the use of proton-pump inhibitors.

Children and adults may have different EoE presenting characteristics.[62,63] Infants and young children may experience reflux symptoms, vomiting, pain, and poor growth; older children, adolescents, and adults describe not only heartburn but also dysphagia with solid/chunky foods, chest pain, and experience food impaction.[62,64-66] Endoscopy and biopsy findings may

differ with age, based on increasing fibrosis and stenosis with time.[66,67] In a retrospective review of 426 patients with biopsies fulfilling EoE criteria at the University of Michigan, fewer adults than children were diagnosed with EoE, referred to an allergist, started on swallowed corticosteroids, or had repeated evaluations. Treatments described previously can be effective across age groups, including dietary elimination for adults.[68] However, adults are more likely to experience stenosis and require esophageal dilatation. EoE appears to be persistent.[62,67] Ridolo et al[69] compared risk factors associated with EoE that was refractory to treatment in adults and children. In children, risks for refractory disease were female gender and high visual analog scale scores at follow-up; for adults, risks were longer periods of follow-up, diagnostic delay, use of antibiotics during infancy, and food allergies. Estimates from a 2016 population-based survey[70] found that 0.16% (95% CI: 0.12-0.22) of the US pediatric population and 0.18% (95% CI: 0.14-0.23) of US adults reported lifetime physician-diagnosed EoE—corresponding to roughly 550,000 patients. Notably, this cross-sectional survey also found that the highest rates of lifetime physician-diagnosed EoE were reported by male respondents aged 30 to 39 (0.35% [95% CI: 0.20-0.61]). Overall, EoE appears to have different presenting features and findings over the life course, but much of this may be related to the length of time patients experience chronic inflammation.

Atopic dermatitis (AD)

Experts conclude that about one-third of children with moderate-to-severe AD also have food allergy.[71] However, there is more controversy about the degree to which food allergy contributes to chronic AD and whether or to what degree eliminating foods from the diet improves AD in infants versus children versus adults.[1,71,72] Studies of diets that eliminate specific targeted foods or common food allergens in children suggest that at least a subset of them may improve AD, and this approach can be supported for diets excluding specific foods in select patients, depending on their age.[73] If using this approach, clinicians must carefully evaluate patients to prove a relationship between the specific food and AD to avoid unnecessary avoidance diets.[72] Although AD in infants and young children can resolve, there is a well-recognized increased risk of sequential progression from AD to other atopic diseases, including food allergy, allergic rhinitis, allergic asthma, and allergic rhinoconjunctivitis, a process referred to as the atopic march.[74] In addition, there are concerns that elimination diets to treat AD in infants and children may lead to nutritional deficits, reduced quality of life, and possible anaphylactic reactions to previously tolerated foods.[27,72] Although recent reviews describe clinical evidence from over 24 studies pointing to a causal role of food allergy in at least some infants and children with AD,[72,73] there is little information about adults. A randomized, 3-week, double-blind trial of 33 hospitalized adult patients with severe AD used an antigen-free formula or placebo diet and found no significant difference between diet groups of 25 evaluable patients.[75] However, in another trial, 37 adults with AD and birch pollen sensitization were fed a diet eliminating birch-related foods followed by double-blind, placebo-controlled OFC, and 17 adults (46%) reacted with increased AD.[76] The possible role of food allergy in adult AD is clearly understudied. There are also no studies evaluating the role of food allergies triggering AD over the life course, and overall, especially in adults, this remains an underinvestigated area.

Pollen-food allergy syndrome (PFAS)/oral allergy syndrome (OAS)

PFAS/OAS occurs in individuals with pollen allergy or those sensitized to pollens.[1] Affected individuals typically report oral or throat pruritus when ingesting raw fruits or vegetables that have proteins homologous to the pollen proteins. The trigger food proteins are easily denatured by heat or digestion, hence the typically mild and localized symptoms. Systemic reactions may occur either because allergy to the food is due to stable proteins, a primary food allergy not related to cross-reacting labile proteins, or augmentation factors (large amounts of food, exercise, etc.) that increase reaction severity. The etiology is related to pollen sensitization, and therefore the syndrome is not expected to present in infancy or early childhood before pollen exposure. Although PFAS prevalence varies by region according to pollen exposure, prevalence rates overlap between children and adults.[77] A review of the literature as of 2018 reported PFAS prevalence from 4.7% to more than 20% among children and 13% to 58% among adults.[31] Clearly, this is a common allergy that affects a broad age range. In a study of 1360 children in Italy with pollen-related allergic rhinitis, 23.9% reported PFAS/OAS, and a longer duration of allergic rhinitis symptoms was related to developing PFAS/OAS.[78] This finding may be a sign that individuals living in areas with more pollen seasons have a higher rate of PFAS, and reflects the higher range of prevalence in adults. Although the descriptions of PFAS/OAS are similar across the life course and the disorder may be persistent, studies have not reported long-term outcomes over the lifespan.

NATURAL COURSE

Various studies suggest that IgE-mediated allergies to milk, egg, wheat, and soy typically resolve in childhood, whereas allergies to peanut, tree nuts, fish, and shellfish are generally persistent.[9,79,80] There are limited data on the natural course of allergies during adulthood. In a study of infants followed into childhood with persistent (n = 28) versus transient (n = 30) egg allergy, a decline in specific IgE (rather than increase in egg IgG4 alone) was associated with natural tolerance.[81] In another study, a small group of adults (n = 13) with wheat allergy were followed over 5 years, and 9 (69.2%) became wheat tolerant, suggesting that resolution is possible, but the study was limited by size and possibly patient selection.[82] As shown in Table I, adults allergic to most of the common food allergens had carried that allergy since childhood, indicating that the majority of adult food allergies begin in childhood and are persistent. However, recent US survey data suggest that adult-onset food allergy may be more common than previously acknowledged—affecting up to half of food-allergic adults.[7] Non−IgE-mediated allergies of infancy and childhood—FPIAP and FPIES—usually resolve.[1,54] EoE[83] and PFAS appear to be persistent, but their natural history across the lifespan is not well studied via prospective, longitudinal approaches.

MANAGEMENT ACROSS THE LIFE COURSE

Managing food allergies involves avoiding the allergen and preparing to recognize and treat an allergic reaction or anaphylaxis. The responsibility for managing food allergy changes dramatically over the life course. Table III summarizes the challenges to managing food allergies from infancy through adulthood. From birth until adolescence, supervising adults play

TABLE III. Challenges to food allergy management change across the lifespan

Age group	Responsibility (primary stakeholders)	Primary challenges
Infant	Parent/guardian, day care	Difficulty in recognizing allergic reactions due to lack of verbalization of subjective symptoms
Toddler	Parent/guardian, day care	Preventing the child from grabbing or accepting foods Significant hand-to-mouth play
Grade school children	Patient, parent/guardian, school	Balancing independence with the child's limited ability to self-manage
High school adolescents	Patient, parent/guardian, school	Risk-taking behaviors More time without supervision causing more reliance on self-management
College/young adults	Patient	Full dependence on self-management skills Risk-taking behaviors
Adults	Patient	Balancing self-management with independence, work obligations, travel, responsibilities to others

a critical role in ensuring safety. Infants are entirely dependent on their parents or guardians, or those in day care, but supervising infants may be easier than supervising toddlers who are able to independently grab food and require additional observation, possibly from paid caregivers and school personnel to whom responsibilities are delegated.[84-86] Grade-school children require sharing of responsibilities between the child and adults. Depending on developmental abilities, children can gradually be given responsibilities that are often undertaken with continued supervision from adults, such as informing adults of their allergies and any allergic symptoms, not sharing foods, reading ingredient labels, informing restaurants of their allergy, and carrying their medications.

Transition of responsibilities from adults to the allergic child is a process. In separate studies, Simons et al asked pediatric allergists[87] and parents[88] about the timing of transferring responsibilities. Allergists indicated that transferring responsibilities to recognize anaphylaxis and appropriately use epinephrine should not occur earlier than ages 9 to 11 years, but by 12 to 14 years, adolescents should be able to recognize anaphylaxis symptoms, carry an autoinjector, and self-inject.[87] Interestingly, parents expected that this shift toward child self-management would occur at earlier ages: by 6 years for describing anaphylaxis and by 6 to 11 years for using an epinephrine autoinjector.[88] It is important to note that these surveys stated that a supervising adult would ultimately be responsible for recognizing and treating anaphylaxis.

The greatest transitions for transferring responsibilities for self-management occur in adolescents and young adults during high school and college. In a study of 190 children and 59 adolescents and their parents, children and parents generally reported congruent expectations for who was primarily responsible for identifying allergic reactions, following dietary restrictions, and explaining their allergy to others.[89] However, parental and adolescent perceptions of who is responsible for self-management differed dramatically, with adolescents much more likely to report that they are fully responsible for their allergy management compared with their parents—who were more likely to view responsibilities as shared or fully parental. Increasing independence means potentially taking increasing risks, with a Canadian study finding that peanut-allergic teenagers and youth living with a single parent had elevated risk of accidental allergen exposure.[90] These longitudinal findings are consistent with cross-sectional surveys in Australian and US adolescents with food allergy reporting high rates of not carrying their epinephrine, not informing others of their allergy, and ingesting foods that are potentially risky.[91,92] In another survey of adolescents and young adults,[93] less risky behavior was associated with individuals having peanut allergy, those with supportive female friends, overprotective mothers, teachers aware of the food allergy, and individuals with a history of being bullied and having an educational 504 (disability) plan. A different study[94] comparing determinants of epinephrine carriage behaviors among US children and adolescents reported that the perceived frequency of epinephrine carriage by family and friends was a significant predictor of actual epinephrine carriage among adolescents aged 13 to 17 years, but not younger children. Similarly, food allergy–related quality of life was much more influenced by perceived family and social support among food-allergic adolescents compared with their younger counterparts, suggesting that efforts to improve peer support for anaphylaxis management might be particularly beneficial for food-allergic adolescents. Finally, a European study of children aged 8 to 12 years found that, even when food-allergic children and their parents agree on the perceived severity of the child's allergy, parents may systematically underestimate the adverse psychosocial impact of the child's food allergy, relative to the child's own perceived impairment.[95] Therefore, providers should be attentive to potential differences in perceived disease burden within parent-child dyads and consider how they might mediate and address such differential concerns to maximize food allergy–related quality of life. Food allergy management of college-aged individuals appears particularly poor.[96] Dyer et al[97] suggested that colleges can help by increasing awareness of food allergy signs and symptoms, establishing roles and responsibilities for adults and stakeholders, and notifying stakeholders on campus about those students with allergies.

Managing food allergy into adulthood has not been extensively studied, but clearly requires addressing food allergies for employees in the workplace, during pregnancy, and during travel, and often, responsibilities fall to a person who may be responsible for many others. Data from recent US population-based surveys[6,7] indicate that patient-reporting of having a current epinephrine prescription declines with age (Figure 2). Although approximately 2 in 3 children/adolescents with physician-confirmed food allergy reported a current epinephrine autoinjector prescription, this dropped to 1 in 3 among patients aged 50+. By age 60, fewer than

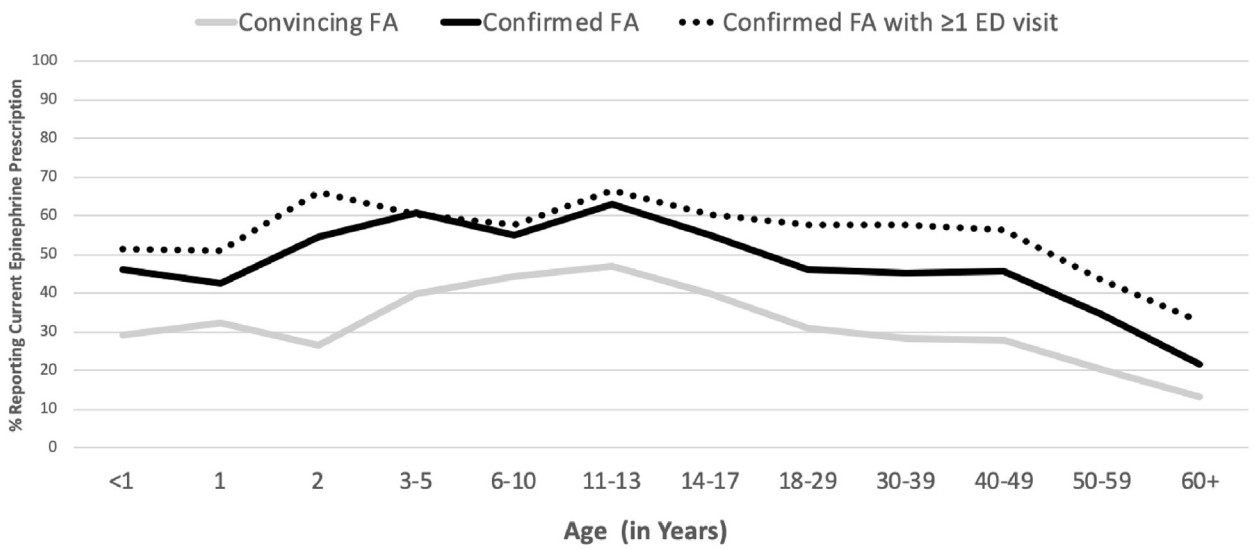

FIGURE 2. Age-specific report of current epinephrine autoinjector prescription. *ED*, Emergency department; *FA*, food allergy.

1 in 3 patients with physician-confirmed food allergy and a history of food allergy—related ED visits reported a current epinephrine autoinjector prescription. Although these data are limited by the fact that epinephrine carriage practices were not assessed, they nonetheless suggest that greater investigation of food allergy management practices among older adults are warranted, given the relative dearth of data in these populations. The allergist who counsels patients with food allergies over the lifespan should consider how disease management challenges may vary at different developmental phases and discuss approaches as appropriate. Practical management includes counseling on avoidance (label reading, cross-contact, restaurant, and food service, etc.), approaches to grade school and college, bullying and emotional aspects of living with food allergy, travel, and recognizing allergic reactions, and emergency management.[1] These topics are reviewed in greater detail elsewhere.[1,84,85,93,98-100]

TREATMENT

There are many emerging therapies for food allergy, and their safety and efficacy are a consideration when considering the age group to which they are applied. Studies already suggest that epicutaneous immunotherapy with a commercial product may be ineffective in older children.[101,102] Oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) may also be more effective, or have longer lasting effects, or induce prolonged remission in very young children compared with patients in other age groups.[103-105] In children and young adults (mean age, 8.7 years) enrolled in a double-blinded trial, low- and high-dose vital wheat gluten OIT induced desensitization in approximately half of the patients after 1 year of treatment. Two years of low-dose wheat gluten OIT desensitized 30%, and 13% had sustained unresponsiveness.[106] In another long-term randomized, blinded trial of 120 adults and children (aged 7-55 years) with peanut allergy over 156 weeks, Chinthrajah et al[107] found that peanut OIT could desensitize individuals with peanut allergy to 4000 mg peanut protein, but discontinuing or even reducing to 300 mg daily, could increase the likelihood of regaining clinical reactivity to peanut. No differences in clinical responses in adult versus children were seen. Changing how providers inform patients about non—life-threatening symptoms is one promising avenue for improving treatment. Howe et al[108] surveyed 50 families with allergy-challenged adolescents and found that compared with those families that informed that symptoms are side effects, those that informed that symptoms can signal desensitization were less anxious, less likely to contact staff about symptoms, experienced fewer non—life-threatening symptoms as doses increased, and less likely to skip/reduce doses.

Furthermore, in a randomized trial with omalizumab to test continued versus discontinued dosing in multifood-allergic children and young adults (5-22 years), Andorf et al[109] found that sustained sensitization after omalizumab-facilitated multi-OIT was best achieved by maintaining OIT dosing of either 300 mg or 1 g of each food allergen instead of discontinuing multi-OIT: similar efficacy and safety was shown in all ages. OIT and SLIT have both shown promise in treating peanut and milk allergy, across different ages. In all ages with common food allergies, a combination of SLIT and OIT may induce a significant increase in challenge thresholds with fewer adverse events.[110]

Current immunotherapy studies in infants, children, and adults are encouraging, and the lengthy treatment period and relatively high rates of adverse reactions are being addressed through the use of adjunctive therapy, such as anti-IgE antibodies, Chinese herbal therapy, and probiotics.[111-114] With our increased understanding of the molecular mechanisms involved in food allergies and other atopic and immune diseases, we have made much progress in identifying and developing other biologics. Besides anti-IL4Rα and anti-IL-33, which is currently being evaluated for food allergies,[115] other biologics that alter immune response have been developed and are in varying stages of preclinical and clinical development or have been approved for specific diseases. In both children and adults, there are common mechanisms underlying atopic diseases and asthma and an understanding of the mechanisms underlying one disease can assist with our understanding and treatments of other immune diseases. Biomarkers for diagnosis and prognosis may soon assist us with identifying those patients at different ages best positioned to benefit from immunotherapy.[111] Our analysis of a large standard

food challenge dataset in adults found that readily obtainable biomarker values and patient demographics may help predict OFC outcomes.[116] Recent advances in high-throughput technologies such as mass cytometry and next-gen sequencing along with concomitant advances in data analytics have enabled us to monitor single cells, increasing the research focus on upstream cellular factors involved in the efficacy of immunotherapy for food allergies, particularly the role of T cells. As our appreciation of different T-cell subsets (memory and naïve that differ in infants, children, and adults) and their plasticity increases, the initial simplistic view that restoring Th1/Th2 balance by decreasing Th2 or increasing Th1 responses can ameliorate food allergy is being enhanced by a more complex model involving other T-cell subsets, particularly Treg.[117]

Future studies must aim to further unravel the mechanisms related to the initiation or resolution of food allergy over the life course and apply this knowledge to identify better methods of prevention and treatment, which likely need to be adjusted from infancy through adulthood.

SUMMARY

There are many manifestations of food allergy, and for some disorders, the presentation and course are unique to the patient's age. It is remarkable that some aspects of food allergy such as common triggers of severe reactions (peanut, tree nuts, shellfish) or mild reactions (fruits and vegetables related to pollen sensitization) are similar over the lifespan, and the etiology of new-onset food allergy may also be similar over the lifespan. Clearly, management strategies must change with age to address different potential obstacles. As new therapeutics emerge, it will be important to consider their potential impact at different ages.

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