



CME Review

Adult-onset food allergies

Manish Ramesh, MD, PhD^{*}; Jay A. Lieberman, MD[†]^{*} Montefiore Medical Center, Bronx, New York[†] The University of Tennessee Health Science Center, Memphis, Tennessee

ARTICLE INFO

Article history:

Received for publication April 18, 2017.

Received in revised form May 11, 2017.

Accepted for publication May 15, 2017.

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test.
- Read the article and reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned. At this time, physicians will have earned up to 1.0 *AMA PRA Category 1 Credit*[™]. Minimum passing score on the post-test is 70%.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize which food allergies are likely to present initially in adulthood
- Describe sensitization patterns that lead to positive food allergy testing in adults

Release Date: August 1, 2017

Expiration Date: July 31, 2019

Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

Accreditation

The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation

The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Planning Committee Members

Manish Ramesh, MD, PhD (Author)

Jay Adam Lieberman, MD (Author)

Jonathan A. Bernstein, MD (CME Subcommittee)

Guha Krishnaswamy, MD (CME Subcommittee)

John J. Oppenheimer, MD (CME Subcommittee, Associate Editor)

Mitchell H. Grayson, MD (CME Series Editor, Deputy Editor)

Gailen D. Marshall, Jr, MD, PhD (Editor-in-Chief)

Disclosure Policy

As required by the Accreditation Council for Continuing Medical Education (ACCME) and in accordance with the American College of Allergy, Asthma and Immunology (ACAAI) policy, all educational planners, presenters, instructors, moderators, authors, reviewers, and other individuals in a position to control or influence the content of an activity must disclose all relevant financial relationships with any

Reprints: Jay A. Lieberman, MD, The University of Tennessee Health Science Center, 51 North Dunlap, Ste 400, Memphis, TN 38105; E-mail: jlieber1@uthsc.edu.

Disclosures: Jay A. Lieberman, MD, serves on the editorial board for *Annals of Allergy, Asthma & Immunology*.

<http://dx.doi.org/10.1016/j.anai.2017.05.014>

1081-1206/© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

commercial interest that have occurred within the past 12 months. All identified conflicts of interest must be resolved and the educational content thoroughly vetted for fair balance, scientific objectivity, and appropriateness of patient care recommendations. It is required that disclosure be provided to the learners prior to the start of the activity. Individuals with no relevant financial relationships must also inform the learners that no relevant financial relationships exist. Learners must also be informed when off-label, experimental/investigational uses of drugs or devices are discussed in an educational activity or included in related materials. Disclosure in no way implies that the information presented is biased or of lesser quality. It is incumbent upon course participants to be aware of these factors in interpreting the program contents and evaluating recommendations. Moreover, expressed views do not necessarily reflect the opinions of ACAAI.

All identified conflicts of interest have been resolved.

Disclosure of Relevant Financial Relationships:

M. Ramesh and J. Lieberman have no relevant financial relationships to disclose. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted. J.A. Bernstein – PI, Consultant, Speaker for AstraZeneca, CSL Behring, Novartis/Genentech, and Shire, he received research grants and fees; Speaker for Baxalta, he received fees; Consultant for Imedics, he received fees; PI and Consultant for Boehringer Ingelheim and GlaxoSmithKline, he received research grants and fees. G. Krishnaswamy – Clinical Research for CSL Behring, he received a research grant; J. Oppenheimer – Consultant for DBV Technologies, GlaxoSmithKline, and Kaleo, he received other financial gains; Clinical research for AstraZeneca, Boehringer Ingelheim, and Novartis, he received research grants. M.H. Grayson – Clinical research for Polyphor, Ltd., he received a research grant. G.D. Marshall – Clinical Research for Stallergens and Sanofi, he received research grants.

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

Copyright Statement: Copyright © 2017 American College of Allergy, Asthma & Immunology. All rights reserved.

CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

Introduction

Although it is known that many food allergies that start in childhood will remain into adulthood (eg, peanut, tree nuts, and seafood), there is a paucity of data and literature on adult-onset food allergies. Although not as common as childhood-onset food allergy, clinicians caring for patients with allergy should be aware of these various presentations and syndromes. In this review, we examine food allergies in adults, with a focus on those syndromes that more commonly have an onset in adulthood. We discuss the prevalence of adult food allergy and sensitization, common clinical scenarios, and pathophysiology of these syndromes and examine individual allergens and syndromes.

Prevalence

Prevalence of food sensitization among adults is high. In the United States, it was reported to be 14.9% in 2010.¹ At the same time, physician-diagnosed food allergy was reported to be 6.5%.¹ In Europe, the rates of sensitization to any food range from 11% to 24% as estimated by the European Community Respiratory Health Survey.² Similarly high rates of prevalence of sensitization or positive serologic test results have been reported from India (EuroPrevall Inco study).³ Like sensitization rates, self-reported food allergy among adults varies widely but is quite common. In a meta-analysis, it was reported to be approximately 3% to 35% for any food.⁴ Directed questionnaire-based methods may improve accuracy.⁵ However, it is difficult to estimate true allergy from these questionnaires because only a fraction of those reporting allergy are sensitized to any food⁶ and only a subset of those sensitized have challenge substantiated food allergy.⁴ Thus, currently we do not know the true prevalence of food allergy (IgE mediated or other) in the adult population.

IgE-Mediated Food Allergies

Pathogenesis

Allergic sensitization to foods can occur in 2 different ways. Primary sensitization can occur, which leads to the most classic form of food allergy. This type of allergy commonly develops early in childhood and will not be covered in depth in this review. In other instances, primary sensitization can occur to a nonfood allergen, such as pollen, which, because of sequence homology or antigenic similarity, cross-reacts with the food. This scenario can

often manifest as loss of tolerance to previously tolerated food. Table 1 lists some examples of these.

Clinical Features

The dominant hypersensitivity reaction to food is IgE-mediated food allergy. There are 4 distinct presentations of IgE-mediated allergy (Table 2): typical anaphylactic-type food allergy; oral allergy syndrome, also referred to as pollen food syndrome (PFS) (mainly caused by plant-based foods); delayed anaphylaxis (principally mammalian meats in galactose- α -1,3-galactose [α -gal] allergy); and food-dependent exercise-induced anaphylaxis (most often caused by wheat). Although chronic urticaria, a common problem in adults, can present with similar symptoms (and can thus be confusing to patients), it is not caused by foods and should not warrant a workup for food triggers.

The diagnosis of food allergy is dependent on a history of typical symptoms, most importantly appropriate temporal association with the food, combined with evidence of sensitization on skin prick or serologic testing. Tests such as component testing and basophil activation test can improve diagnostic accuracy.^{7,8} As referenced above, only a fraction of those sensitized to foods are truly allergic.

Many adult patients presenting for evaluation for food allergy will present with more nonspecific symptoms, such as abdominal pain, bloating, constipation, and fatigue. These symptoms clearly are not associated with IgE-mediated food allergy and are rarely associated with other food hypersensitivity syndromes. Thus, typical skin prick testing or serum IgE testing is not likely to be of benefit in these cases. Tests such as specific IgG testing, lymphocyte stimulation, and cytotoxicity assays, which may be offered to patients through online vendors, have no proven role in the diagnosis of food allergies.⁹

In all cases though, physician supervised oral food challenges remain the gold standard for confirming allergy¹⁰ and should be used when the diagnosis is not clear from presentation and testing.

Typical IgE-Mediated Food Allergy

Typical anaphylactic-type food allergy appears to be the most common of the IgE-mediated food allergy presentations. It is usually characterized by immediate onset of symptoms within 1 to 2 hours, presenting with urticaria and/or angioedema,

Table 1
Food Allergy Syndromes with Primary Sensitization to Nonfood Allergens

Syndrome	Primary sensitization (Protein)	Secondary sensitization
Pollen food syndromes	PR10 proteins examples: Birch (Bet v 1) Oak (que a 1) Profilin examples: Birch (Bet v 2) Mugwort (Art v 4) Ragweed (Amb a 8) Lipid transfer proteins examples: Ragweed (Amb a 6) Mugwort (Art v 3)	Peach (Pru p 1) Apple (Mal d 1) Peanut (Ara h 8) Hazelnut (Cor a 1) Carrot (Dau c 1) Soy (Gly m 4) Celery (Api g 1) Kiwi (Act d 9) Pineapple (Ana c 1) Celery (Api g 4) Peanut (Ara h 5) Carrot (Dau c 4) Soy (Gly m 3) Apple (Mal d 4) Banana (Mus a 1) Peach (Pru p 4) Kiwi (Act d 10) Cashew (Ana o 3) Peanut (Ara h 9) Hazelnut (Cor a 8) Soybean (Gly m 1) Latex (Hev b 12) Walnut (Jug r 1) Apple (Mal d 3) Wheat (Tri a 14) Peach (Pru p 3)
		Shrimp (Pen a 1) Lobster (Hom a 1) Anisakis (Ani s 3)
Shellfish allergy	Tropomyosin examples: Dust mite (Der p 10) Cockroach (Bla g 7)	
Delayed anaphylaxis to mammalian meats	Tick salivary proteins (Galactose- α -1,3-galactose (α -gal) residues)	Mammalian meats
Pork-cat syndrome	Cat albumin (Fel d 3)	Pork (albumin)

bronchospasm, nausea, vomiting, occasionally diarrhea, and, in severe cases, hypotension and rarely death.

Fish and shellfish allergy

Seafood allergy is one of the more frequent causes of food allergy in adults. On the basis of a recent meta-analysis, in the United States the prevalence of self-reported shellfish allergy in adults ranged from 1.7% to 9.0%, and the prevalence of self-reported fish allergy ranged from 0.0% to 7.0%.¹¹ Prevalence of physician-diagnosed seafood allergy in adults is not known; however, it appears to be one of, if not the most common, adult food allergies. In a recent analysis of adult food allergies from a single center, seafood was clearly the most common trigger.¹²

Table 2
Clinical Presentation of Food Hypersensitivity Disorders

Hypersensitivity Disorders	Timing	Symptoms
IgE-mediated anaphylaxis	Minutes to hours	Urticaria and/or angioedema, oropharyngeal pruritus, abdominal pain, nausea, vomiting and or diarrhea (rare), bronchospasm, hypotension, loss of consciousness, impending sense of doom
Food-dependent, exercise-induced anaphylaxis	When food is consumed up to 30 min after exercise or up to 2 h before exercise	Similar to above
Oral allergy syndrome	Immediate	Oropharyngeal pruritus, ear pruritus, oropharyngeal angioedema, anaphylaxis (rare)
Delayed anaphylaxis to mammalian meats	Approximately 6 h after consumption of food	Urticaria, angioedema, abdominal cramping, vomiting, anaphylaxis
FPIES	2–4 h after consumption of food	Projectile vomiting, diarrhea, lethargy, hypotension
Eosinophilic esophagitis	Delayed (weeks to months)	Abdominal pain, nausea, vomiting, regurgitation, dysphagia, food impaction

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.

Although one may think that most of these cases likely represent childhood-onset allergy that persisted through adulthood, in fact many appear to have an onset in adulthood. In one telephone survey regarding seafood allergy in the United States, 60% of cases of shellfish allergy and 40% of cases of fish allergy had onset during adulthood.¹³ These numbers were mirrored in one analysis of physician-diagnosed food allergies in which 40% of all physician-diagnosed cases of adult-onset food allergy were reported to be caused by fish or shellfish.¹² Thus, it seems that both self-reported and physician-diagnosed cases of seafood allergy in adulthood may have their onset later in life. It is not known exactly why fish and shellfish appear to have a high relative frequency of adult-onset disease.

It is helpful to have some understanding of the allergen-binding patterns when caring for patients with seafood allergy because this can have a clinical effect on their presentation. For example, the major allergen in bony fish is parvalbumin (eg, Gal c 1 in cod fish). Parvalbumins have a 60% to 80% sequence homology, and thus-cross reactivity across fish is common. However, clinical heterogeneity has been observed, and some patients who react to most fish are able to tolerate extensively cooked tuna and salmon in canned form. Three possible explanations of this phenomenon include the 100-fold lower parvalbumin content in the muscle of fish such as tuna and salmon,¹⁴ degradation of proteins during the cooking process, and the involvement of minor allergens, such as fish enolases and aldolases. Some patients who react to tropical fish are sensitized to unique allergens other than parvalbumin.¹⁴

Reactions to fish can also be caused by nonfish allergens. Allergy to the fish nematode *Anisakis*, for example, can develop in some individuals and leads to a history of inconsistent fish allergic reactions.¹⁵ There is cross-reactivity between *Anisakis* and other invertebrate allergens. In addition, clinicians need always be aware of scombroid poisoning, or histamine fish poisoning, which is a non-IgE-mediated reaction that mimics a true allergic reaction because it is attributable to histamine. This is typically caused by mishandling of fish, and although the symptoms can be identical to a true allergic reaction, they will occur rarely and sporadically with fish ingestion compared with IgE-mediated reactions that will occur on every ingestion.

Tropomyosin (eg, Pen a 1 in shrimp) is the major allergen in adults with crustacean shell fish allergy. It widely cross-reacts with tropomyosins in other invertebrates, including dust mite and cockroach.¹⁶ Myosin light chain is another major allergen that has been identified in shell fish allergies. In children, the sarcoplasmic calcium-binding protein has been identified as the major allergen.¹⁷ It has been hypothesized that, like fruit and vegetable allergies, shellfish allergy in adolescents and adults may be secondary to sensitization to aero-allergens, such as dust mite and cockroach, which contain a cross-reacting tropomyosin (eg, Der p 10 in dust mite).

Table 3
Infrequently Reported Food Allergic Reactions

Food or Incidental Allergen	Reference
Amaranth flour	19
Annatto	20
Beer	21,22
Bell pepper	23
Buckwheat	24–26
Cabbage	27
Carmines	28
Cauliflower	29
Celery	30
Chicken	31
Citrus fruits	32
Cucumber	33
Cumin	34
Garlic	35
Goji berries	36
Grape	37
Honey	38,39
Jackfruit	40
Jellyfish	41
Limpet	42,43
Lupine	44
Lychee	45
Mango	46,47
Millet seeds	48
Mushroom	49
Oats	50,51
Paw-paw	52
Pine nut	53
Quinoa	54
Royal jelly	55
Salmon caviar	56
Sunflower seeds	57
Tomato	58
Wild boar meat	59
Anisakis	60
Mold	61
Dust mite	62

Thus far, no clinical trials aimed at treating shellfish allergy have been published. However, T-cell epitope–based immunotherapy in a mouse model has shown promise.¹⁸

Other foods

Many other foods have been associated with adult-onset, typical IgE-mediated food allergy. Largely presented as case reports, these are highlighted in Table 3. One recent report from a single institution suggested that other than seafood, tree nuts were the most common culprit of adult-onset food allergies,

accounting for approximately 25% of the cases. However, other than tree nuts and seafood, no single food was a prominent cause.¹²

Fruit and Vegetable Allergies and PFS

New-onset fruit and vegetable allergies in adults are most often due to PFS also known as pollen food allergy syndrome or oral allergy syndrome, which refers to food allergies caused by cross-reactivity between aeroallergens and food. Primary sensitization is believed to occur to pollen proteins, such as birch pollen, whose major allergen, Bet v 1, cross-reacts with similar proteins from a variety of fruits and vegetables. Recognition of specific cross-reactivity patterns has resulted in a number of named syndromes, such as mugwort-celery-spice syndrome (mugwort pollen cross-reacting with celery and spices, such as mustard).⁶³ This type of allergy manifests as immediate-onset oropharyngeal symptoms on ingestion of raw fruit. The thermolability of these proteins often abrogates symptoms when ingesting cooked fruits. Similarly, susceptibility to denaturation in the stomach likely protects against systemic symptoms.⁶⁴ There is, however, a variant of PFS seen in the Mediterranean region of Europe that is attributable to lipid transfer protein (LTP) that can present with anaphylaxis, discussed later.

The self-reported prevalence of PFS, assessed using a validated questionnaire in the general population, was approximately 2%. The same study reported an overall self-reported prevalence of allergy as 5.8%. It is the most prevalent new-onset food allergy in adults.⁶⁵ Although anaphylaxis is uncommon, PFS is associated with significant impairment of health-related quality of life.⁶⁶ At the molecular level, thermolabile allergens, such as PR10 proteins and profilins, are the most common culprit allergens. PR10 proteins are the major allergens from fruits of species belonging to the Rosaceae family (peach [Pru p 1], apple [Mal d 1], cherry [Pru av 1], apricot [Pru ar 1], and pear [Pyr c 1]) and Apiaceae species (carrot [Dau c 1], celery [Api g 1]). In contrast, anaphylactic reactions caused by Rosaceae fruits are typically caused by LTP antigens (eg, Pru p 3 in peach and Mal d 3 in apple).⁶⁷ Allergy to LTP appears to be almost exclusive to the Mediterranean region of southern Europe. Areas outside this region, including northern Europe, do not report a similar prevalence of LTP allergy. The basis for this geographic restriction is not well understood.⁶⁷

Diagnosis of PFS relies on typical clinical presentation. Skin prick testing with manufactured extracts can be inaccurate.⁶⁸ At least one study has reported the value of fresh food prick testing.⁶⁸ Food challenges can be safely performed and are the gold standard. However, concealing the food for double-blind, placebo-controlled

Table 4
Selected Studies Examining Immunotherapy as a Treatment for Pollen Food Syndrome

Study	Food	Treatment modality		No. of study participants		Outcome for PFS
		Allergen	Route	Treatment	Control	
Asero et al, ⁷² 1998	Apple	Birch	SCIT	49	26	84% patients undergoing SCIT and 0% of controls had resolution of PFS
Bucher et al, ⁷³ 2004	Apple & Hazelnut	Birch	SCIT	27	12	87% of patients and 8% of controls had significant increase in amount of apple tolerated but the increase was small.
Hansen et al, ⁷⁴ 2004	Apple	Birch	SCIT	10	10	No significant difference
			SLIT	4		
Kinaciyan et al, ⁷⁵ 2007	Apple	Birch	SLIT	9	13	No change
Mauro et al, ⁷⁶ 2011	Apple	Birch	SCIT	8		2 of 8 SCIT-treated patients and 1 of 7 SLIT-treated patients (14.2%) developed complete tolerance to apple. 3 of 8 SCIT-treated and 2 of 7 SLIT-treated patients increase in provocative dose
			SLIT	7		
Kopac et al, ⁷¹ 2012	Apple	Apple	OIT	27	13	17 of 27 patients and 0 of 13 controls were able to tolerate a whole apple.

Abbreviations: OIT, oral immunotherapy; PFS, pollen food syndrome; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

food challenges may not be practical because of potential degradation of the proteins during preparation.

In view of its association with pollen allergies, intuitively, immunotherapy directed against pollen should be effective in treating PFS. Indeed, case reports and case series have supported this view for various combinations of pollens and fruits.^{69–71} However, in controlled trials, pollen-specific aeroallergen immunotherapy has had underwhelming outcomes in treating PFS (Table 4). A single oral immunotherapy trial using the food (apple) showed promising results.⁷⁷

α -gal Allergy

α -gal is a carbohydrate moiety found in all nonprimate mammals. It has been known for some time that humans produce abundant antibody to α -gal, with approximately 1% of all human immunoglobulin recognizing this carbohydrate epitope and antibodies to this epitope leading to xenograft rejection in some cases.⁷⁸ More recently, however, IgE that recognizes α -gal has been found to lead to acute reactions to the monoclonal antibody cetuximab and to be associated with delayed reactions to mammalian meats (beef, pork, lamb).^{79,80} The food allergic reaction to α -gal is a delayed reaction (hours after ingestion) compared with other IgE-mediated food allergies. It has now been described throughout the globe and is typically found more often in adults, although it is well described in children.^{81,82} Because of the delayed nature of the reactions, they often present at night time. In fact, most seek care after 6 PM with approximately 1 in 5 seeking emergency care after midnight.⁸¹ This late night presentation can be a clue to aid in the diagnosis of this condition.

Current lines of evidence suggest that the sensitization occurs after being bit by a tick. In fact, the earliest reported associations of tick bite and red meat anaphylaxis were described outside the α -gal research story.⁸³ In the United States, various lines of evidence now suggest that bites from *Amblyomma americanum* (Lone Star tick) lead to sensitization of α -gal, with other ticks being responsible in other parts of the world.^{81,84} This line of evidence would explain why α -gal is largely considered an adult-onset food allergy. In a population study in Denmark and Spain, IgE to α -gal was detectable (≥ 0.1 kUA/L) in 5.5% of Danish adults and 8.1% in Spanish adults, and this was strongly associated with a history of tick bites.⁸⁵ More recently, a group in Germany found a high prevalence (35%) of detectable IgE to α -gal (>0.10 kUA/L) in forest workers, once again with association with a tick bite history. For forest service employees and hunters, the odds ratio for α -gal specific IgE positivity was 2.48 compared with the residential population, and in that cohort, mammalian meat-induced delayed anaphylaxis was found in 8.6% of the participants with α -gal specific IgE levels greater than 0.35 kUA/L.⁸⁶

Thus, clinicians who care for adults, especially in areas where ticks are common, should be well versed in this clinical entity, and it should be part of the differential diagnosis for any person who presents with idiopathic anaphylaxis, especially if symptoms occur in the middle of the night. Diagnosis can be made with the correct clinical history and positive test results. Although the results of skin prick testing with extracts of beef, pork, or lamb can be positive, they are often small, and intradermal tests have been used.⁸⁶ Serum testing is often helpful, with some suggestion that IgE to α -gal can decrease over time if the patient avoids tick bites, and the reactions will also improve.⁸⁷ Challenges are typically performed only in research settings. Avoidance of all mammalian meats is recommended if the diagnosis is confirmed, and patients should be supplied an epinephrine autoinjector.

A similar clinical syndrome to α -gal allergy is the pork-cat syndrome. This uncommon syndrome describes an IgE-mediated reaction that occurs immediately after ingesting pork in patients who are sensitized to cat albumin (Fel d 2) and thought to be caused

by cross-reactivity of porcine and cat albumins.⁸⁸ Because the primary sensitization occurs to cat albumin, reactions are typically first described in adolescence or adulthood. In fact, in the lone US series of patients to date, more than half presented after the fourth decade of life. In addition, the natural history of this disease is not known. The symptoms abate with avoidance of pork; however, it may be that patients can eat pork again if sensitization to cat albumin wanes. Although α -gal allergy is a delayed reaction, pork-cat syndrome is typically more immediate in nature.

Food-Dependent, Exercise-Induced Anaphylaxis and Wheat Allergy

Wheat is responsible for a number of different manifestations. One key presentation of wheat allergy is food-dependent, exercise-induced anaphylaxis. In patients reporting this condition, anaphylaxis only ensues when food intake is closely associated with exercise. In most cases, exercise must occur in the half an hour preceding or in the 2 hours after ingestion of the culprit food. A key feature of this allergy is that the reaction may resolve if the patient stops exercising and rests.⁸⁹ Besides exercise, other predisposing factors include nonsteroidal anti-inflammatory drugs, such as aspirin, alcohol, and infections.^{90–92} Contrast this with conventional exercise-independent food allergy in which reactions ensue regardless of exercise. These 2 forms of wheat allergy are distinguished at the molecular level by sensitization to different wheat components. ω -5 gliadin (Tri a 19) is the principal component associated with food-dependent, exercise-induced anaphylaxis, although in some ω -5 gliadin sensitized individuals experience food-induced, exercise-independent anaphylaxis.⁶⁶ The globulin and glutenins are major wheat allergens (eg, Tri a 20, Tri a 26) and are involved in wheat anaphylaxis independent of exercise. Although wheat is the most common cause of food-dependent, exercise-induced anaphylaxis, other foods, such as shellfish and celery, have been associated with this condition.⁹² Other causes of wheat-related disorders include occupational respiratory disease (eg, bakers' asthma), the wheat-dependent autoimmune disease, gluten enteropathy, or celiac disease.⁹³ In China, wheat-induced anaphylaxis is the leading cause of anaphylaxis in adults and is responsible for 42% of reactions.⁹⁴ Although food-dependent, exercise-induced anaphylaxis in the context of wheat consumption was not explicitly documented, 39% of all causes of anaphylaxis were associated with exercise.⁹⁴

Wheat occupational asthma follows sensitization by LTPs (Tri a 14),⁹⁵ α -amylase inhibitors, and α -amylase/trypsin inhibitors, such as Tri a 15 (monomeric α -amylase inhibitor) and peroxidase.⁹⁶ Sensitization to wheat and barley LTPs is also involved in beer allergic reactions in beers brewed from wheat and barley.

Non-IgE-Mediated Food Allergies

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is an antigen-mediated inflammatory disease defined clinically by gastrointestinal symptoms and pathologically by an eosinophilic infiltrate localized to the esophagus that occurs in the pediatric and adult populations.⁹⁷ Cases have been documented in patients younger than 1 year to almost 100 years of age. It may be more common in adults, with one population study finding that the most common time of diagnosis was in the fourth decade of life, not in younger adults and children.⁹⁸ Prevalence estimates in adult populations have ranged from approximately 23 to 400 per 100,000 persons.⁹⁹

It is unclear whether EoE in adults represents new-onset disease or a chronic inflammatory disease that started earlier in life and ultimately led to diagnosis in adulthood. In one Swiss database study on adults with EoE, the median delay in diagnosis from the onset of symptoms was 6 years.¹⁰⁰ This delay in diagnosis increases

the likelihood of the development of strictures and stenosis, with estimates suggesting a doubling of the likelihood of development of strictures or a fibrostenotic phenotype with each decade that the EoE is left untreated.^{100,101} This concept of adults with EoE having a chronic, long-term inflammatory condition is also evidenced by the fact that adults with EoE present more often with food impaction than do children with EoE.⁹⁷

Treatment of EoE in adults is similar to that in children. Adults respond to dietary therapy (ie, elimination diets), suggesting that the pathophysiology of the disease remains the same in adults and children.^{102–104} Unfortunately, long-term adherence of diet appears to be difficult to maintain in adults.^{104,105}

Swallowed, topical corticosteroids (eg, budesonide and fluticasone) are also a treatment option in adults, and various preparations have been used.^{106–108} Like elimination diets, corticosteroids appear to be as equally efficacious in adults and children.¹⁰⁹

Anecdotally, dilation seems to be a more common treatment strategy used in adults with EoE vs children. Dilation can be an overall safe and effective procedure; however, most patients will require repeat dilation, many within 1 year of the procedure, especially if not concomitantly treated with other therapy.^{110,111} Although the natural history of untreated EoE does appear to lead to fibrosis, strictures, and, in some studies, Barrett esophagus, there is no evidence that it leads to dysplasia or malignant tumors.^{99,111} Thus, goals of therapy should be to alleviate the symptoms of the adult patient first and foremost, with an understanding that symptoms will likely continue and persist if dilation is used alone.

Food Protein–Induced Enterocolitis Syndrome

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated syndrome of rapid-onset gastrointestinal symptoms developing after the ingestion of the culprit food. FPIES is principally known as a disorder of infancy and young children. Although resolution in childhood is the norm, occasional persistence into adulthood has been reported. Adult-onset FPIES has been limited to case reports and case series.^{112–114} Unlike children in whom milk, soy, and rice are the most common causative foods,¹¹⁵ in adults, seafood (crustacean and molluscan shellfish) and fish were by far the most common causes.^{113,114} In adults, a 3:1 female predominance has been observed.¹¹³ As in children, abdominal pain, vomiting and diarrhea are the most common symptoms. Symptoms may be more rapid in onset compared with children and develop 1 to 2 hours after ingestion of food.¹¹¹ Chronic FPIES has been reported in infants and presents with recurrent diarrhea and failure to thrive; however, this condition has not been reported in adults. Perhaps the ability of adults to recognize symptoms and the diversity of their diet protects them from this manifestation.

Although most adult patients had a single food trigger, a few had reactions to 2 or 3 foods. Unlike IgE-mediated allergies, cross-reactivity within closely related groups of foods, such as mollusks or crustaceans, is not widespread.¹¹³ The authors note that patients frequently attributed their symptoms to food poisoning, suggesting that this condition may be underreported.¹¹³ Although resolution is the norm in children, there is little information regarding this in adults.

Transfer of Food Allergies Attributable to Organ Transplant

The transfer of food allergy because of organ transplant is a minor but well-described cause of new-onset food allergies in adults.^{116–118} There is a spectrum of food allergy transfer, ranging from passive sensitization without clinical allergy,¹¹⁹ transient allergy,^{120,121} or seemingly persistent allergy.^{116–118} These conditions have been reported in solid organ transplants without concomitant bone marrow transplant. Transfer of sensitized mast cells and lymphoid tissue has been implicated.¹¹⁹ It has been hypothesized

that organs with larger amount of lymphoid tissue, such as bowel or liver, are more likely to transfer sensitization compared with organs such as kidney, which have relatively little lymphoid tissue. The effect of immunosuppressives, such as tacrolimus, in modulating this response has not been studied formally in a prospective trial, although it may affect the transfer of allergy.¹¹⁶ This phenomenon has also been reported with cord blood transplants.¹²²

Uncommon Presentations

Anaphylactic reaction caused by ingestion of aeroallergens incidentally present in food has been described. Perhaps the most well described is the so-called pancake syndrome, which describes systemic symptoms after ingestion of pancake mix contaminated with dust mites. This phenomenon has been described in multiple countries and can present in adulthood.¹²³ Conversely, food allergens may lead to respiratory disease when inhaled, best described as occupational asthma, which is caused by various foods: wheat⁹⁶ and barley flours,¹²⁴ shellfish,^{125,126} spices,¹²⁷ and even the fish parasite *Anisakis simplex*.¹²⁸

Contact dermatitis caused by foods has also been described. Sensitization likely occurs through the skin, and consumption of foods that contain large amounts of allergen leads to skin symptoms without direct topical contact at the site, a presentation known as systemic contact dermatitis.¹²⁹ The most common items contained in food that cause such a presentation are nickel and Balsam of Peru.¹³⁰ Reliable estimates of systemic contact dermatitis are lacking because of a lack of well-controlled clinical studies and estimates vary widely. In many cases, dietary avoidance is recommended. This is, however, hard to adhere to because of the wide distribution of allergens. For example, nickel is found in legumes, rice, oats, canned foods, foods cooked in stainless steel vessels, and a wide variety of fruits and vegetables.¹²⁹ Balsam of Peru is also widely distributed in fruits, such as citrus and tomatoes, and spices and aromatics, such as cinnamon, vanilla, cloves, and anise.¹³⁰ Other causative foods include chamomile tea, which contains sesquiterpene lactones, aspartame, and cobalt-containing foods.

Food eruptions analogous to fixed-drug eruptions have been described rarely.¹³¹ It is an urticarial or bullous recurrent rash that occurs at the same locations when the patient consumes the allergen. Anaphylaxis has not been reported. The precise allergen(s) involved are not known. The foods that have been implicated include peanut, cashew, fish, kiwi, asparagus, and lentils.^{131–134} Reported reactions to tonic water are presumably to the quinine in it.¹³⁵

Discussion

Adult food allergy is not uncommon, and adult perceived food allergy seems to be even more common. Although some of these clinical scenarios may represent persistence of childhood food allergy into adulthood, many may actually have their onset in adulthood. Thus, any clinician caring for adults with allergies should be aware of these clinical scenarios. An understanding of the pathophysiology can aid the practitioner in deciding on appropriate treatment plans and whether the allergy is life-threatening. In adult-onset IgE-mediated disease, it is most important for practitioners to be aware of timing, specific allergens, and possible cofactors to accurately diagnosis the condition, risk stratify the patient, and recommend appropriate avoidance measures if needed.

Although food-related symptoms are commonplace, diagnosis of true food hypersensitivity diseases requires sound clinical knowledge and a high index of suspicion. EOE has insidious symptoms and a long lag time for diagnosis. Food protein–induced enterocolitis masquerades as other diseases and is easily dismissed. Exercise-induced anaphylaxis can be confusing because symptoms

are not consistent or reproducible and require cofactors to be present. Similarly, the symptoms of α -gal allergy are acute in presentation but temporally removed from food exposure. For these and other described conditions, it is important to be able to inform patients about whether the allergy is life-threatening and whether the food may be consumed in certain circumstances or must be avoided in all cases.

Definitive treatment for most of these conditions is lacking, and avoidance is the norm. Encouraging results have emerged for the treatment of major allergens, such as peanut, egg, and milk, especially in the pediatric population. However, the treatment of exercise-induced anaphylaxis, shellfish allergy, or even PFS is going to need substantial research.

References

- Verrill L, Bruns R, Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. *Allergy Asthma Proc.* 2015;36:458–467.
- Burney P, Summers C, Chinn S, Hooper R, van Ree R, Lidholm J. Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis. *Allergy.* 2010;65:1182–1188.
- Mahesh PA, Wong GW, Ogorodova L, et al. Prevalence of food sensitization and probable food allergy among adults in India: the EuroPrevall INCO study. *Allergy.* 2016;71:1010–1019.
- Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol.* 2007;120:638–646.
- Silva LA, Silva AF, Ribeiro AC, Silva AO, Vieira FA, Segundo GR. Adult food allergy prevalence: reducing questionnaire bias. *Int Arch Allergy Immunol.* 2016;171:261–264.
- Woods RK, Thien F, Raven J, Walters EH, Abramson M. Prevalence of food allergies in young adults and their relationship to asthma, nasal allergies, and eczema. *Ann Allergy Asthma Immunol.* 2002;88:183–189.
- Song Y, Wang J, Leung N, et al. Correlations between basophil activation, allergen-specific IgE with outcome and severity of oral food challenges. *Ann Allergy Asthma Immunol.* 2015;114:319–326.
- Van Erp FC, Klemans RJ, Meijer Y, van der Ent CK, Knulst AC. Using component-resolved diagnostics in the management of peanut-allergic patients. *Curr Treat Options Allergy.* 2016;3:169–180.
- Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol.* 2014;134:1016–1025.e43.
- Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol.* 2012;130:1260–1274.
- Moonesinghe H, Mackenzie H, Venter C, et al. Prevalence of fish and shellfish allergy: a systematic review. *Ann Allergy Asthma Immunol.* 2016;117:264–272.
- Kamdar TA, Peterson S, Lau CH, Saltoun CA, Gupta RS, Bryce PJ. Prevalence and characteristics of adult-onset food allergy. *J Allergy Clin Immunol Pract.* 2015;3:114–115.e1.
- Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol.* 2004;114:159–165.
- Kuehn A, Swoboda I, Arumugam K, Hilger C, Hentges F. Fish allergens at a glance: variable allergenicity of parvalbumins, the major fish allergens. *Front Immunol.* 2014;5:179.
- Nieuwenhuizen N, Lopata A. Allergic reactions to Anisakis found in fish. *Curr Allergy Asthma Rep.* 2014;14:1–6.
- Reese G, Ayuso R, Lehrer SB. Tropomyosin: an invertebrate pan-allergen. *Int Arch Allergy Immunol.* 1999;119:247–258.
- Pascal M, Grishina G, Yang AC, et al. Molecular diagnosis of shrimp allergy: efficiency of several allergens to predict clinical reactivity. *J Allergy Clin Immunol Pract.* 2015;3:521–529.
- Wai CYY, Leung NY, Leung PS, Chu KH. T cell epitope immunotherapy ameliorates allergic responses in a murine model of shrimp allergy. *Clin Exp Allergy.* 2016;46:491–503.
- Kasera R, Niphadkar PV, Saran A, Mathur C, Singh AB. First case report of anaphylaxis caused by Rajgira seed flour (*Amaranthus paniculatus*) from India: a clinico-immunologic evaluation. *Asian Pacific J Allergy Immunol.* 2013;31:79–83.
- Nish WA, Whisman BA, Goetz DW, Ramirez DA. Anaphylaxis to annatto dye: a case report. *Ann Allergy.* 1991;66:129–131.
- Figueredo E, Quirce S, del Amo A, et al. Beer-induced anaphylaxis: identification of allergens. *Allergy.* 1999;54:630–634.
- Herzinger T, Kick G, Ludolph-Hauser D, Przybilla B. Anaphylaxis to wheat beer. *Ann Allergy Asthma Immunol.* 2004;92:673–675.
- Callero A, Perez E, Ledesma A, et al. A case report of bell pepper anaphylaxis: could 1, 3-beta-glucanase be the culprit allergen? *Ann Allergy Asthma Immunol.* 2012;109:474–475.
- Davidson AE, Passero MA, Settignano GA. Buckwheat-induced anaphylaxis: a case report. *Ann Allergy.* 1992;69:439–440.
- Wang TC, Shyur SD, Wen DC, Kao YH, Huang LH. Buckwheat anaphylaxis: an unusual allergen in Taiwan. *Asian Pacific J Allergy Immunol.* 2006;24:167–170.
- Rui T, Hongyu Z, Ruiqi W. Seven Chinese patients with buckwheat allergy. *Am J Med Sci.* 2010;339:22–24.
- Blaiss MS, McCants ML, Lehrer SB. Anaphylaxis to cabbage: detection of allergens. *Ann Allergy.* 1987;58:248–250.
- Wuthrich B, Kagi MK, Stucker W. Anaphylactic reactions to ingested carmine (E120). *Allergy.* 1997;52:1133–1137.
- Hernandez E, Quirce S, Villalba M, Cuesta J, Sastre J. Anaphylaxis caused by cauliflower. *J Investig Allergol Clin Immunol.* 2005;15:158–159.
- Palgan K, Gotz-Zbikowska M, Tykwinska M, Napiorkowska K, Bartuzi Z. Celery—cause of severe anaphylactic shock. *Postepy Hig Med Dosw (Online).* 2012;66:132–134.
- Zacharisen MC. Severe allergy to chicken meat. *WMJ.* 2006;105:50–52.
- Ebo DG, Ahrazem O, Lopez-Torres J, Briedts CH, Salcedo G, Stevens WJ. Anaphylaxis from mandarin (*Citrus reticulata*): identification of potential responsible allergens. *Int Arch Allergy Immunol.* 2007;144:39–43.
- Vlaicu PC, Rusu LC, Ledesma A, et al. Cucumber anaphylaxis in a latex-sensitized patient. *J Investig Allergol Clin Immunol.* 2011;21:236–239.
- Boxer M, Roberts M, Grammer L. Cumin anaphylaxis: a case report. *J Allergy Clin Immunol.* 1997;99:722–723.
- Ma S, Yin J. Anaphylaxis induced by ingestion of raw garlic. *Foodborne Pathog Dis.* 2012;9:773–775.
- Zauli D, Mirarchi MG. Anaphylaxis induced by Goji berries. *Ann Allergy Asthma Immunol.* 2015;114:535–536.
- Caiaffa MF, Tursi A, Macchia L. Grape anaphylaxis. *J Investig Allergol Clin Immunol.* 2003;13:211–212.
- Karakaya G, Fuat Kalyoncu A. Honey allergy in adult allergy practice. *Allergol Immunopathol (Madr).* 1999;27:271–272.
- Fuiano N, Incorvaia C, Riario-Sforza GG, Casino G. Anaphylaxis to honey in pollinosis to mugwort: a case report. *Eur Ann Allergy Clin Immunol.* 2006;38:364–365.
- Wongrakpanich S, Klaewsongkram J, Chantaphakul H, Ruxrungtham K. Jackfruit anaphylaxis in a latex allergic patient. *Asian Pacific J Allergy Immunol.* 2015;33:65–68.
- Imamura K, Tsuruta D, Tsuchisaka A, et al. Anaphylaxis caused by ingestion of jellyfish. *Eur J Dermatol.* 2013;23:392–395.
- Morikawa A, Kato M, Tokuyama K, Kuroume T, Minoshima M, Iwata S. Anaphylaxis to grand keyhole limpet (abalone-like shellfish) and abalone. *Ann Allergy.* 1990;65:415–417.
- Carrillo T, de Castro FR, Cuevas M, Caminero J, Cabrera P. Allergy to limpet. *Allergy.* 1991;46:515–519.
- Matheu V, de Barrio M, Sierra Z, Gracia-Bara MT, Tornero P, Baeza ML. Lupine-induced anaphylaxis. *Ann Allergy Asthma Immunol.* 1999;83:406–408.
- Raap U, Schaefer T, Kapp A, Wedi B. Exotic food allergy: anaphylactic reaction to lychee. *J Investig Allergol Clin Immunol.* 2007;17:199–201.
- Dang RW, Bell DB II. Anaphylactic reaction to the ingestion of mango: case report. *Hawaii Med J.* 1967;27:149–150.
- Hegde VL, Venkatesh YP. Anaphylaxis following ingestion of mango fruit. *J Investig Allergol Clin Immunol.* 2007;17:341–344.
- Parker JL, Yunginger JW, Swedlund HA. Anaphylaxis after ingestion of millet seeds. *J Allergy Clin Immunol.* 1981;67:78–80.
- Toda T, Yamaguchi M, Nakase Y, et al. A case of anaphylactic reaction following matsutake mushroom ingestion: demonstration of histamine release reaction of basophils. *Allergol Int.* 2010;59:417–419.
- Prados-Castano M, Pinero-Saavedra M, Leguizamón-Milla S, Pastor C, Cuesta P, Bartolomé B. Anaphylaxis due to oat ingestion. *J Investig Allergol Clin Immunol.* 2016;26:68–69.
- Otake Y, Inomata N, Sano S, Takahashi S, Aihara M. A case of an anaphylactic reaction due to oats in granola. *Allergol Int.* 2015;64:386–387.
- Ezeoke AC. Hypersensitivity to paw-paw (*Cerica papaya*): report of a case. *Afr J Med Med Sci.* 1985;14:121–124.
- Meysman M, Schelfaut D, Vincken W. A not so healthy muesli: a case report. *Acta Clin Belg.* 2009;64:366–368.
- Astier C, Moneret-Vautrin DA, Puillandre E, Bihain BE. First case report of anaphylaxis to quinoa, a novel food in France. *Allergy.* 2009;64:819–820.
- Takahama H, Shimazu T. Food-induced anaphylaxis caused by ingestion of royal jelly. *J Dermatol.* 2006;33:424–426.
- Flais MJ, Kim SS, Harris KE, Greenberger PA. Salmon caviar-induced anaphylactic shock. *Allergy Asthma Proc.* 2004;25:233–236.
- Axelsson IG, Ihre E, Zetterstrom O. Anaphylactic reactions to sunflower seed. *Allergy.* 1994;49:517–520.
- Zacharisen MC, Elms NP, Kurup VP. Severe tomato allergy (*Lycopersicon esculentum*). *Allergy Asthma Proc.* 2002;23:149–152.
- Drouet M, Sabbah A, Le Sellin J, Bonneau JC, Gay G, Dubois-Gosnet C. Fatal anaphylaxis after eating wild boar meat in a patient with pork-cat syndrome [in French]. *Allerg Immunol (Paris).* 2001;33:163–165.
- Hoshino C, Narita M. Anisakis simplex-induced anaphylaxis. *J Infect Chemother.* 2011;17:544–546.
- Bennett AT, Collins KA. An unusual case of anaphylaxis: mold in pancake mix. *Am J Forensic Med Pathol.* 2001;22:292–295.
- Tay SY, Tham E, Yeo CT, et al. Anaphylaxis following the ingestion of flour contaminated by house dust mites: a report of two cases from Singapore. *Asian Pacific J Allergy Immunol.* 2008;26:165–170.

- [63] Egger M, Mutschlechner S, Wopfner N, Gadermaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. *Allergy*. 2006;61:461–476.
- [64] Rodriguez-Perez R, Crespo JF, Rodriguez J, Salcedo G. Profilin is a relevant melon allergen susceptible to pepsin digestion in patients with oral allergy syndrome. *J Allergy Clin Immunol*. 2003;111:634–639.
- [65] Skypala LJ, Bull S, Deegan K, et al. The prevalence of PFS and prevalence and characteristics of reported food allergy; a survey of UK adults aged 18–75 incorporating a validated PFS diagnostic questionnaire. *Clin Exp Allergy*. 2013;43:928–940.
- [66] Beyer S, Franke A, Simon JC, Treudler R. Measurement of health-related quality of life in adult patients with birch pollen-associated food allergy. *J Dtsch Dermatol Ges*. 2016;14:397–404.
- [67] Asero R, Pravettoni V. Anaphylaxis to plant-foods and pollen allergens in patients with lipid transfer protein syndrome. *Curr Opin Allergy Clin Immunol*. 2013;13:379–385.
- [68] Anhoej C, Backer V, Nolte H. Diagnostic evaluation of grass- and birch-allergic patients with oral allergy syndrome. *Allergy*. 2001;56:548–552.
- [69] Kelso JM, Jones RT, Tellez R, Yunginger JW. Oral allergy syndrome successfully treated with pollen immunotherapy. *Ann Allergy Asthma Immunol*. 1995;74:391–396.
- [70] Asero R, Fennel, cucumber, and melon allergy successfully treated with pollen-specific injection immunotherapy. *Ann Allergy Asthma Immunol*. 2000;84:460–462.
- [71] Asero R. How long does the effect of birch pollen injection SIT on apple allergy last? *Allergy*. 2003;58:435–438.
- [72] Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy*. 1998;28:1368–1373.
- [73] Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy*. 2004;59:1272–1276.
- [74] Hansen KS, Khinchi MS, Skov PS, Bindsvlev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. *Mol Nutr Food Res*. 2004;48:441–448.
- [75] Kinaciyan T, Jahn-Schmid B, Radakovics A, et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol*. 2007;119:937–943.
- [76] Mauro M, Russello M, Incorvaia C, et al. Birch-apple syndrome treated with birch pollen immunotherapy. *Int Arch Allergy Immunol*. 2011;156:416–422.
- [77] Kopac P, Rudin M, Gentinetta T, et al. Continuous apple consumption induces oral tolerance in birch-pollen-associated apple allergy. *Allergy*. 2012;67:280–285.
- [78] Galili U. Anti-Gal: an abundant human natural antibody of multiple pathogenesis and clinical benefits. *Immunology*. 2013;140:1–11.
- [79] Chung CH, Mirakhor B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med*. 2008;358:1109–1117.
- [80] Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose. *J Allergy Clin Immunol*. 2009;123:426–433.
- [81] Platts-Mills TA, Schuyler AJ, Hoyt AE, Commins SP. Delayed anaphylaxis involving IgE to galactose- α -1,3-galactose. *Curr Allergy Asthma Rep*. 2015;15:12.
- [82] Kennedy JL, Stallings AP, Platts-Mills TA, et al. Galactose- α -1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. *Pediatrics*. 2013;131:e1545–e1552.
- [83] Van Nunen SA, O'Connor KS, Clarke LR, Boyle RX, Fernando SL. An association between tick bite reactions and red meat allergy in humans. *Med J Aust*. 2009;190:510–511.
- [84] Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose- α -1,3-galactose. *J Allergy Clin Immunol*. 2011;127:1286–1293.
- [85] Gonzalez-Quintela A, Dam Laursen AS, Vidal C, Skaaby T, Gude F, Linneberg A. IgE antibodies to α -gal in the general adult population: relationship with tick bites, atopy, and cat ownership. *Clin Exp Allergy*. 2014;44:1061–1068.
- [86] Fischer J, Lupberger E, Hebsaker J, et al. Prevalence of type I sensitization to α -gal in forest service employees and hunters [published online March 8, 2017]. *Allergy*. <http://dx.doi.org/10.1111/all.13156>.
- [87] Platts-Mills TA, Schuyler AJ, Erwin EA, Commins SP, Woodfolk JA. IgE in the diagnosis and treatment of allergic disease. *J Allergy Clin Immunol*. 2016;137:1662–1670.
- [88] Posthumus J, James HR, Lane CJ, Matos LA, Platts-Mills TA, Commins SP. Initial description of pork-cat syndrome in the United States. *J Allergy Clin Immunol*. 2013;131:923–925.
- [89] Feldweg AM. Food-dependent, exercise-induced anaphylaxis: diagnosis and management in the outpatient setting. *J Allergy Clin Immunol Pract*. 2017;5:283–288.
- [90] Aihara M, Miyazawa M, Osuna H, et al. Food-dependent exercise-induced anaphylaxis: influence of concurrent aspirin administration on skin testing and provocation. *Br J Dermatol*. 2002;146:466–472.
- [91] Dohi M, Suko M, Sugiyama H, et al. Food-dependent, exercise-induced anaphylaxis: a study on 11 Japanese cases. *J Allergy Clin Immunol*. 1991;87:34–40.
- [92] Shadick NA, Liang MH, Partridge AJ, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. *J Allergy Clin Immunol*. 1999;104:123–127.
- [93] Quirce S, Boyano-Martinez T, Diaz-Perales A. Clinical presentation, allergens, and management of wheat allergy. *Exp Rev Clin Immunol*. 2016;12:563–572.
- [94] Jiang N, Yin J, Wen L, Li H. Characteristics of anaphylaxis in 907 Chinese patients referred to a tertiary allergy center: a retrospective study of 1,952 episodes. *Allergy Asthma Immunol Res*. 2016;8:353–361.
- [95] Palacin A, Quirce S, Armentia A, et al. Wheat lipid transfer protein is a major allergen associated with baker's asthma. *J Allergy Clin Immunol*. 2007;120:1132–1138.
- [96] SÁÑchez-Monge R, García-Casado G, López-Otín C, Armentia A, Salcedo G. Wheat flour peroxidase is a prominent allergen associated with baker's asthma. *Clin Exp Allergy*. 1997;27:1130–1137.
- [97] Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128:3–20.
- [98] Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology*. 2008;134:1316–1321.
- [99] Dellon ES. Epidemiology of eosinophilic esophagitis. *Gastroenterol Clin North Am*. 2014;43:201–218.
- [100] Schoepfer AM, Saffoneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology*. 2013;145:1230–1236.e1–2.
- [101] Dellon ES, Kim HP, Sperry SL, Rybníček DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc*. 2014;79:577–585.e4.
- [102] Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology*. 2012;142:1451–1459.
- [103] Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sánchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. *J Allergy Clin Immunol*. 2014;134:1093–1099.
- [104] Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol*. 2013;131:797–804.
- [105] Philpott H, Nandurkar S, Royce SC, Thien F, Gibson PR. A prospective open clinical trial of a proton pump inhibitor, elimination diet and/or budesonide for eosinophilic oesophagitis. *Aliment Pharmacol Ther*. 2016;43:985–993.
- [106] Murali AR, Gupta A, Attar BM, Ravi V, Koduru P. Topical steroids in eosinophilic esophagitis: Systematic review and meta-analysis of placebo-controlled randomized clinical trials. *J Gastroenterol Hepatol*. 2016;31:1111–1119.
- [107] Dellon ES, Katzka DA, Collins MH, et al. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. *Gastroenterology*. 2017;152:776–786.
- [108] Miehleke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. *Gut*. 2016;65:390–399.
- [109] Albert D, Heifert TA, Min SB, et al. Comparisons of fluticasone to budesonide in the treatment of eosinophilic esophagitis. *Dig Dis Sci*. 2016;61:1996–2001.
- [110] Runge TM, Eluri S, Cotton CC, et al. Outcomes of esophageal dilation in eosinophilic esophagitis: safety, efficacy, and persistence of the fibrostenotic phenotype. *Am J Gastroenterol*. 2016;111:206–213.
- [111] Lipka S, Keshishian J, Boyce HW, Estores D, Richter JE. The natural history of steroid-naïve eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. *Gastrointest Endosc*. 2014;80:592–598.
- [112] Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. *J Allergy Clin Immunol*. 2012;130:1199–1200.
- [113] Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. *J Allergy Clin Immunol Pract*. 2014;2:355–357.
- [114] Gleich GJ, Sebastian K, Firszt R, Wagner LA. Shrimp allergy: gastrointestinal symptoms commonly occur in the absence of IgE sensitization. *J Allergy Clin Immunol Pract*. 2016;4:316–318.
- [115] Nowak-Węgrzyn A, Jarocka-Cyrt E, Moschione Castro A. Food protein-induced enterocolitis syndrome. *J Invest Allergol Clin Immunol*. 2017;27:1–18.
- [116] Khalid I, Zoratti E, Stagner L, Betensley AD, Nemeh H, Allenspach L. Transfer of peanut allergy from the donor to a lung transplant recipient. *J Heart Lung Transplant*. 2008;27:1162–1164.
- [117] Legendre C, Caillat-Zucman S, Samuel D, et al. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med*. 1997;337:822–824.
- [118] Phan TG, Strasser SI, Koorey D, et al. Passive transfer of nut allergy after liver transplantation. *Arch Intern Med*. 2003;163:237–239.
- [119] Berry A, Campen J, Shihab F, Firszt R. Transfer of peanut IgE sensitisation after combined pancreas-kidney transplant. *Clin Exp Allergy*. 2014;44:1020–1022.
- [120] Bhinder S, Heffer MJ, Lee JK, Chaparro C, Carlo SM. Development of transient peanut allergy following lung transplantation: a case report. *Can Respir J*. 2011;18:154–156.

- [121] Dewachter P, Vezinet C, Nicaise-Roland P, et al. Passive transient transfer of peanut allergy by liver transplantation. *Am J Transplant*. 2011;11:1531–1534.
- [122] Vaughan LA, Vu M, Sengsayadeth S, et al. New allergies after cord blood transplantation. *Cytotherapy*. 2013;15:1259–1265.
- [123] Takahashi K, Taniguchi M, Fukutomi Y, et al. Oral mite anaphylaxis caused by mite-contaminated okonomiyaki/pancake-mix in Japan: 8 case reports and a review of 28 reported cases. *Allergol Int*. 2014;63:51–56.
- [124] Vidal C, Gonzalez-Quintela A. Food-induced and occupational asthma due to barley flour. *Ann Allergy Asthma Immunol*. 1995;75:121–124.
- [125] Goetz DW, Whisman BA. Occupational asthma in a seafood restaurant worker: cross-reactivity of shrimp and scallops. *Ann Allergy*. 2000;85:461–466.
- [126] Uriarte SA, Fernandez-Nieto M, Arochena L, Sastre J. Occupational asthma in seafood manufacturing and food allergy to seafood. *J Investig Allergol Clin Immunol*. 2015;25:59–60.
- [127] Sastre J, Olmo M, Novalvos A, Ibanez D, Lahoz C. Occupational asthma due to different spices. *Allergy*. 1996;51:117–120.
- [128] Armentia A, Lombardero M, Callejo A, et al. Occupational asthma by Anisakis simplex. *J Allergy Clin Immunol*. 1998;102:831–834.
- [129] Veien NK. Systemic contact dermatitis. *Int J Dermatol*. 2011;50:1445–1456.
- [130] Fabbro SK, Zirwas MJ. Systemic contact dermatitis to foods: nickel, BOP, and more. *Curr Allergy Asthma Rep*. 2014;14:463.
- [131] Parker AL, Pinson ML, Wohltmann WE, Gomez R. Fixed food eruption caused by peanut and cashew: a case report and review of the literature. *J Allergy Clin Immunol Pract*. 2015;3:119–122.
- [132] Sohn KH, Kim BK, Kim JY, et al. Fixed food eruption caused by *Actinidia arguta* (hardy kiwi): a case report and literature review. *Allergy Asthma Immunol Res*. 2017;9:182–184.
- [133] Yanguas I, Oleaga JM, González-Güemes M, Goday JJ, Soloeta R. Fixed food eruption caused by lentils. *J Am Acad Dermatol*. 1998;38:640–641.
- [134] Volz T, Berner D, Weigert C, Rocken M, Biedermann T. Fixed food eruption caused by asparagus. *J Allergy Clin Immunol*. 2005;116:1390–1392.
- [135] Muso Y, Kentarou O, Itami S, Yoshikawa K. Fixed eruption due to quinine: report of two cases. *J Dermatol*. 2007;34:385–386.