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Management of Food Allergies and Food-Related Anaphylaxis

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IMPORTANCE An estimated 7.6% of children and 10.8% of adults have IgE-mediated food-protein allergies in the US. IgE-mediated food allergies may cause anaphylaxis and death. A delayed, IgE-mediated allergic response to the food-carbohydrate galactose-α-1,3-galactose (alpha-gal) in mammalian meat affects an estimated 96 000 to 450 000 individuals in the US and is currently a leading cause of food-related anaphylaxis in adults.

OBSERVATIONS In the US, 9 foods account for more than 90% of IgE-mediated food allergies—crustacean shellfish, dairy, peanut, tree nuts, fin fish, egg, wheat, soy, and sesame. Peanut is the leading food-related cause of fatal and near-fatal anaphylaxis in the US, followed by tree nuts and shellfish. The fatality rate from anaphylaxis due to food in the US is estimated to be 0.04 per million per year. Alpha-gal syndrome, which is associated with tick bites, is a rising cause of IgE-mediated food anaphylaxis. The seroprevalence of sensitization to alpha-gal ranges from 20% to 31% in the southeastern US. Self-injectable epinephrine is the first-line treatment for food-related anaphylaxis. The cornerstone of IgE-food allergy management is avoidance of the culprit food allergen. There are emerging immunotherapies to desensitize to one or more foods, with one current US Food and Drug Administration–approved oral immunotherapy product for treatment of peanut allergy.

CONCLUSIONS AND RELEVANCE IgE-mediated food allergies, including delayed IgE-mediated allergic responses to red meat in alpha-gal syndrome, are common in the US, and may cause anaphylaxis and rarely, death. IgE-mediated anaphylaxis to food requires prompt treatment with epinephrine injection. Both food-protein allergy and alpha-gal syndrome management require avoiding allergenic foods, whereas alpha-gal syndrome also requires avoiding tick bites.

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In the US, IgE-mediated food allergies affect an estimated 7.6% of children and 10.8% of adults.[1,2] (**Box**). Food-related, IgE-mediated allergic reactions can cause hives, red eyes, nasal congestion, oropharyngeal swelling, shortness of breath, even anaphylaxis within seconds of allergen exposure. Fatality due to food-related anaphylaxis is rare (0.04 deaths per million per year).[3] This clinical review summarizes the epidemiology, pathophysiology, clinical presentation, prevention, diagnosis, and management of IgE-mediated food allergy and food allergy–related anaphylaxis due to food-proteins and food-glycans, specifically galactose-α-1,3-galactose (alpha-gal) in alpha-gal syndrome. Alpha-gal syndrome is a tick-associated allergic condition that frequently presents as a delayed reaction after mammalian meat ingestion.[4,5]

Methods

We searched the PubMed database and the Cochrane Library for original English-language studies of the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of IgE-mediated food allergy and food allergy–related anaphylaxis published between January 1, 2000, and November 30, 2023. We identified additional articles from a review of the references of relevant articles. We prioritized randomized clinical trials; meta-analyses and systematic reviews; evidence-based guidelines; and large, population-based, high-quality observational studies. We identified 126 reports: 8 randomized clinical trials, 7 meta-analyses, 3 systematic reviews, 60 observational studies (longitudinal, cross-sectional, case series, case reports), 8 evidence-based guidelines, 8 expert-consensus guidelines, 1 piece of legislation, 17 narrative reviews (5 with expert recommendations), 6 preclinical basic science reports, and 8 basic science reviews.

Pathophysiology

The development of food allergy begins with the sensitization phase, in which susceptible individuals develop food-specific IgE antibodies after food-protein antigen contacts, gut, respiratory tract, or skin (**Figure 1**). It is unclear why some become food-allergen sensitized and develop clinical allergies while others do not; possible explanations for this have been explored elsewhere.[6-8]

The second phase of food allergy development occurs when sensitized individuals are reexposed to a food allergen. The allergen binds simultaneously to multiple food-specific IgE-IgE receptor complexes, cross-linking these complexes on basophils and mast cells

(the allergic effector phase).[9] This cross-linkage induces rapid release of inflammatory mediators (histamine and proteases, including tryptase[10]), allergic and inflammatory cytokines (IL-4, IL-6, and tumor necrosis factor[10,11]), platelet-activating factor,[12] leukotrienes, and prostaglandins.[13] These mediators lead to increased vascular permeability, mucosal and submucosal edema, and smooth muscle hyperreactivity, driving rapid development of urticaria, angioedema, wheezing, bronchoconstriction, nasal hyperreactivity, intestinal spasms, abdominal pain, and anaphylactic shock.[10,14]

In contrast to food-protein allergy, allergic reactions to mammalian products (red meat) in alpha-gal syndrome are associated with IgE to the carbohydrate, galactose-α-1,3-galactose (alpha-gal). Typically, humans generate alpha-gal–specific IgG, IgA, and IgM antibodies, but not alpha-gal IgE, following exposure to dietary mammalian meat and microbial alpha-gal in the gut.[15] In the US, development of alpha-gal–specific IgE is associated with exposure to alpha-gal in tick saliva from lone star tick (*Amblyomma americanum*) bites (**Figure 2**).[16-20] Other tick species associated with alpha-gal syndrome include *Ixodes holocyclus*, *Amblyomma sculptum*, *Ixodes ricinus*, and *Haemaphysalis longicornis*.[21]

In contrast to the rapid onset of symptoms in food-protein allergy, symptoms from alpha-gal syndrome frequently appear 2 or more hours after ingesting mammalian meat (Figure 2),[4,5,17] although isolated gastrointestinal symptoms may occur sooner than 2 hours in some patients.[22,23] The reasons for delayed allergic symptom onset in alpha-gal syndrome are not completely understood.[24-28]

Box. Common Questions About IgE-Mediated Food Allergy

What Are the Preferred Tests for the Evaluation of IgE-Mediated Food Allergies?

Both skin prick testing (percutaneous scratch testing) and serum food allergen–specific IgE testing in patients with clinical histories consistent with allergic hypersensitivity responses to the suspected food may be used to support a diagnosis of IgE-mediated food allergy.

What Is the Most Effective Treatment for Symptoms Triggered By Food Allergies?

Intramuscular injection of epinephrine should be administered for signs and symptoms suggestive of anaphylaxis such as hypotension, tachycardia, tongue or throat swelling, generalized hives, wheeze, hoarseness, stridor, dizziness, syncope, palpitations, nausea, vomiting, and diarrhea.

For mild allergic symptoms triggered by food allergies, an oral antihistamine such as cetirizine or diphenhydramine can decrease symptoms. Mild symptoms include itching, mild gastrointestinal upset, or small areas of isolated hives and swelling.

How Is Alpha-Gal Syndrome Different From the Top 9 Food-Protein Allergies in the US?

In contrast to food-protein allergy, allergic reactions to mammalian products (red meat) in alpha-gal syndrome are associated with IgE to the carbohydrate galactose-α-1,3-galactose (alpha-gal). Symptoms from alpha-gal syndrome frequently appear at least 2 hours after ingesting mammalian meat, although isolated gastrointestinal symptoms may occur sooner than 2 hours in some patients. Individuals with alpha-gal syndrome develop alpha-gal–specific IgE following tick bites.

Epidemiology, Common Food Allergens, and Natural History

According to a 2015-2016 population-based survey in the US, 10.8% of adults and 7.6% of children have self-reported IgE-mediated food allergy.[1,2] The most recent seroprevalence estimates for food-specific IgE antibodies in children were as high as 9% for peanut allergy (2005-2006 National Health and Nutrition Examination Survey data).[29] Not all patients with food allergen–specific IgE antibodies have symptoms; thus, seroprevalence estimates are often higher than food allergy prevalence estimates from self-report or clinical confirmation.

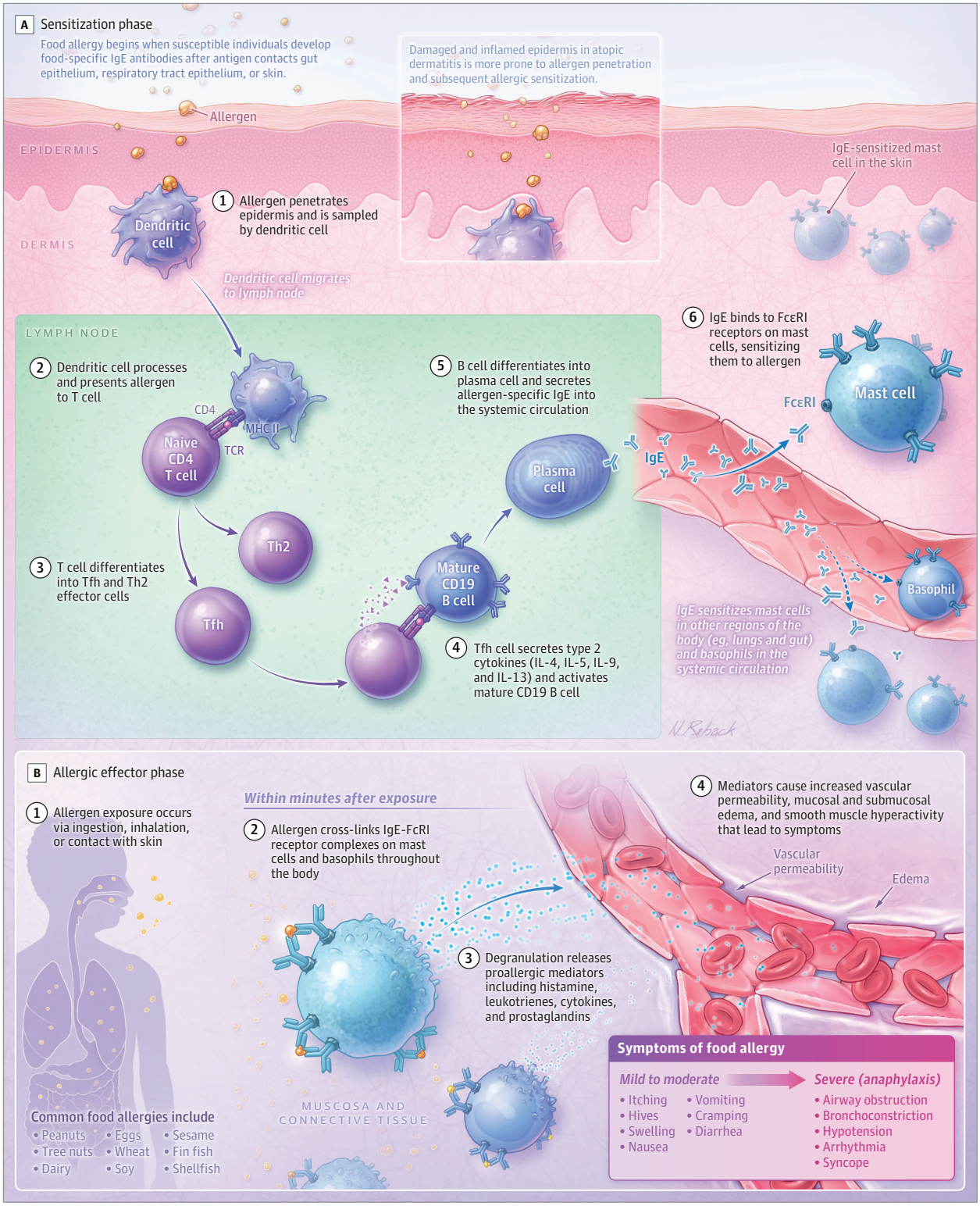
Genetic susceptibility, microbiome alterations, skin exposure to detergents, and pollutant exposures can contribute to the risk of IgE-mediated food sensitization and allergy.[8] Infantile eczema is the strongest risk factor for food allergies.[30,31] In eczema, an impaired, inflamed skin barrier promotes allergic sensitization when exposed to ambient food proteins (Figure 1).[31] In a population-based cohort where oral food challenges were the reference standard (5276 1-year-old infants in Australia), 20% of children with at least 3 family members who had an atopic condition (allergic rhinitis, asthma, eczema, or any food allergy) had IgE-mediated food allergy, compared with only 5.6% of those with fewer affected family members.[32] Compared with children who were exposed to potentially allergenic food in infancy, children with later exposure were more likely to develop food allergies.[6,33-48]

In the US, 9 foods account for more than 90% of symptomatic IgE-mediated food-protein allergies. The prevalence in adults and children, respectively, for crustacean shellfish is 2.9% and 1.3%; for dairy, 1.9% and 1.9%; for peanut, 1.8% and 2.2%; for tree nuts, 1.2% and 1.2%; for fin fish, 0.9% and 0.6%; for egg, 0.8% and 0.9%; for wheat, 0.8% and 0.5%; for soy, 0.6% and 0.5%; and for sesame, 0.2% and 0.2%.[1,2] Infants (<1 year) have higher rates of symptomatic egg allergy (8.9%),[49] and rates of symptomatic cow's milk protein allergy are approximately 2% to 3% in children 3 years or younger.[50,51] Retrospective observational studies of 807 patients with cow's milk protein allergy reported resolution in 19% by age 4 years and 79% by 16 years.[50] Prospective studies suggest egg allergy resolves in 89% by age 6 years.[52] Peanut and tree nut allergies are more durable than egg and milk allergies. Depending on the study population, peanut allergy resolved in 14.8% to 29% by ages 6 through 10 years,[52,53] and tree nut allergy resolved in 9% by a median age of 10 years (range, 5.8-15.7 years).[54]

The leading food-related causes of fatal and near-fatal anaphylaxis are due to allergies to peanut, tree nuts, crustacean shellfish, and cow's milk; however, there is regional variability.[55,56] For example, peanut is the leading cause of anaphylaxis in the US, whereas cow's milk is the most common cause of food-related fatal anaphylaxis in the UK.[57] For children in the US, peanut and tree nut allergic reactions accounted for the highest annual rates of emergency department visits for food allergy in 2014 (peanut, 5.85 visits per 100 000 individuals; tree nuts, 4.62 visits per 100 000 individuals).[58]

Pollen-food allergy (oral allergy) syndrome occurs in individuals—sensitized to aerosolized environmental plant pollens via the respiratory tract—who ingest plant-based foods that cross-link

Figure 1. Sensitization and Effector Phases in Food-Protein Allergy

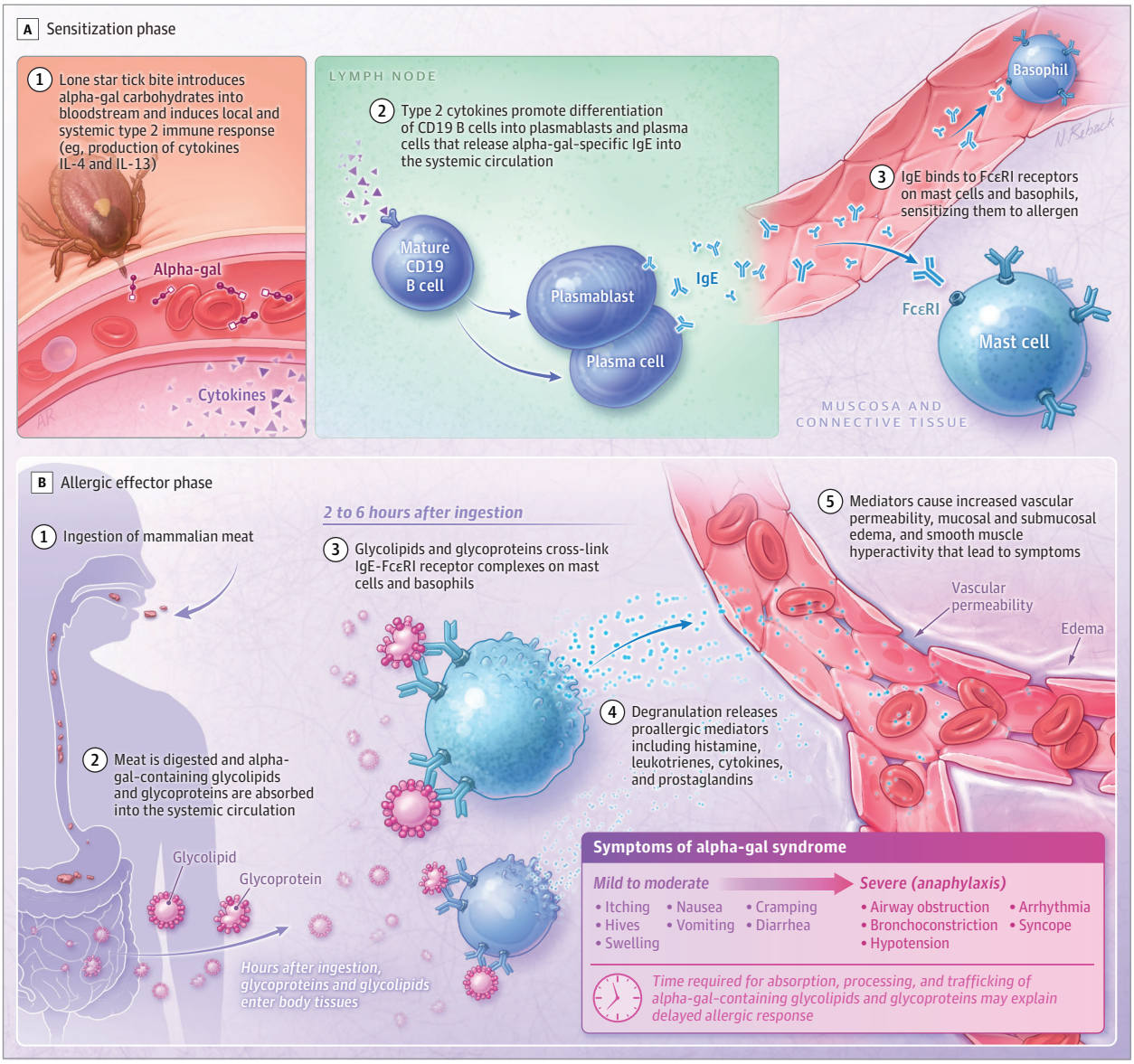


MHC II indicates major histocompatibility complex class II; Tfh, T-follicular helper; Th2, T-helper 2.

the pollen-specific IgE. Adverse reactions are typically limited to immediate local oropharyngeal pruritus and angioedema, although anaphylaxis has been reported in 1.7% of patients with the syndrome.[59]

The prevalence and distribution is unknown in the US, but 20% to 43% of children and adults with allergic rhinitis in Asia and Europe reported pollen-food allergy symptoms.[60]

Figure 2. Sensitization and Effector Phases in Alpha-Gal Syndrome



Other cells thought to be involved but not depicted include skin-resident dendritic cells, migrating dendritic cells, T-helper 2 cells, T-follicular helper cells, and invariant natural killer cells. Alpha-gal indicates galactose-α-1,3-galactose.

In the southeastern US, alpha-gal syndrome prevalence correlates with regional endemicity of the lone star tick, with this food allergy emerging as a leading cause of anaphylaxis in adults.[61] Among individuals referred to the National Institutes of Health for a study of idiopathic anaphylaxis, 9% had detectable levels of alpha-gal–specific IgE antibodies (≥0.35 kU/L), described a tick bite history, and lived in endemic regions of the lone star tick (Missouri, Virginia, Tennessee, Alabama, and New Jersey).[62] Surveillance maps published by the Centers for Disease Control and Prevention (CDC) show the lone star tick's expanding reach across the southern and eastern US.[63] A CDC review of 233 521 individuals undergoing serological testing for alpha-gal syndrome suggests that suspected cases occurred primarily in the southern, midwestern, and mid-Atlantic US Census Bureau regions.[64] Seroprevalence estimates of alpha-gal sensitization in the southeastern US range from 20% to 31%.[65-67] A study evaluating 122 068 sera samples from more than 100 000 patients in the US with suspected mammalian meat allergy reported an alpha-gal sensitization rate of 32.4%. Individuals 70 years or older were most likely to test positive, and those between 0 and 9 years, the least likely. From 2011 to 2018, there was a 6-fold increase in alpha-gal–specific IgE antibody tests,[68] suggesting that alpha-gal sensitization rates in the US may be increasing and/or testing is increasing. One CDC report estimates that between 96 000 and 450 000 individuals in the US may have developed alpha-gal syndrome since 2010.[64]

Clinical Presentation and Diagnosis

Anaphylaxis

The World Allergy Organization 2020 guidelines includes 2 criteria for diagnosing anaphylaxis.[69] First, an acute onset of an illness within minutes to hours that occurs at the same time as skin or mucosal tissue involvement or both, which could include generalized hives; pruritus or flushing; or swollen lips, tongue, or uvula, and at least 1 of the following: (1) respiratory signs or symptoms, including dyspnea, wheeze-bronchospasm, stridor, hypoxemia; (2) reduced blood pressure or end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence); and (3) gastrointestinal symptoms that include frequent vomiting and abdominal pain with severe cramping. Second, an acute and rapid onset—within minutes to hours—of hypotension or bronchospasm or laryngeal involvement after a patient is exposed to a known or highly probable allergen. Symptoms may not include skin involvement.

The differential diagnosis of anaphylaxis includes acute bronchospasm, syncope, and anxiety and/or panic attacks.[70]

When evaluating patients with suspected IgE-mediated food allergy, the exposure history (eg, foods, drugs, stinging insects) and possible cofactors should be identified. Cofactors are elements that lower the threshold to develop food-induced allergic symptoms and include concurrent illness, fever, exercise, alcohol consumption, menstruation, and aspirin and other nonsteroidal anti-inflammatory drugs. In food-dependent exercise-induced anaphylaxis, for example, affected patients may have anaphylaxis if they exercise within 4 to 6 hours of culprit food ingestion (commonly wheat).[60]

The results of a serum tryptase test obtained 90 minutes to 4 hours after a suspected food-induced anaphylaxis event that show an increase by at least 1.2 times the patient's baseline value plus 2 ng/mL is highly suggestive of mast cell degranulation and can assist allergy specialists in confirming the diagnosis. The baseline tryptase value can be obtained at a follow-up visit when the patient has recovered and is well. In one study,[71] in which serum tryptase levels were measured before and during an oral food challenge to induce anaphylaxis, serum tryptase levels increased above baseline in 100 of 160 cases and increased above the upper limit of normal (11.4 ng/mL) in 4 out of 160 cases.

IgE-Mediated Reactions, Recognition, and Identification

Hallmarks of IgE-mediated, food-protein allergy include generalized hives; pruritus; flushing; swelling of the lips, tongue, or uvula; paroxysmal sneezing; crampy abdominal pain; and vomiting that occur with repeated exposure to the causative food allergen.[51] Early-symptom onset (minutes to 2 hours) following food exposure is a key feature, with the exception of alpha-gal syndrome for which delayed symptom onset of more than 2 hours is common. There is no uniform minimum dose across all food allergens that induces allergic symptoms. Some individuals may react to trace amounts of food allergens, whereas others may tolerate higher amounts of food allergen before experiencing symptoms.[72-74] Symptom duration varies in susceptible individuals, depending on the severity of initial allergic symptoms, whether and when symptoms were treated, and medication used for treatment.[75]

Confirming the Diagnosis

IgE-mediated food allergy is confirmed by (1) a comprehensive clinical history compatible with an IgE-mediated reaction and (2) serological or skin prick testing demonstrating the presence of food allergen–specific IgE (ie, food-specific allergic sensitization) and/or observation of IgE-mediated signs and symptoms that are reproduced upon specific food exposure.[76] Establishing the pretest probability of an IgE-mediated food reaction via a detailed clinical history guides the selection of diagnostic tests, including skin prick testing, specific IgE serological tests, and oral food challenges, all of which are typically performed by allergy specialists.[76]

The reference standard for the diagnosis of IgE-mediated food allergy is the oral food challenge.[77,78] Observed symptoms compatible with IgE-mediated food allergy that manifest within 2 hours after food ingestion confirm the diagnosis. The absence of such findings following a serving of the suspected allergen, particularly in children, makes IgE-mediated food-protein allergy unlikely. In contrast, meat challenges for alpha-gal syndrome may not consistently induce allergic symptoms because allergic responses may depend on cofactors such as exercise after eating meat; in addition, symptoms may not occur for 6 hours or more after ingestion.[79] In practice, oral food challenges require significant time and clinical resources and inherently incur the risk of inducing allergic reactions. Thus, a convincing clinical history along with positive skin prick testing and/or food allergen–specific IgE in serum confirming allergic sensitization make the probability of IgE-mediated food allergy high enough to obviate the need for diagnostic food challenges.[76]

Allergic sensitization to suspected foods can be assessed by measuring food-specific serum IgE levels or performing skin prick testing. These tests are typically requested by allergists as part of a comprehensive assessment for suspected food allergy. In skin prick testing, allergenic extracts, saline, and histamine are placed percutaneously and the resulting wheals are compared.[80] Although allergic sensitization in an individual who has never ingested the allergen is insufficient to confirm the diagnosis of food allergy, the likelihood of a positive oral food challenge increases as serum-specific IgE levels or skin prick testing wheal size increase.[81,82] Given imprecise, variable predictive values, both skin prick testing and allergen-specific IgE, whether for single foods or in multifood panels, have limited utility as screening tools for food-protein allergies when interpreted without a history of allergic symptoms to a specific suspected food.[83] Allergy specialists typically engage in shared decision-making during discussions of screening for food allergies[84] with patients and families. In general, comorbid allergic conditions such as allergic rhinitis, allergic asthma, and atopic dermatitis are not sole indications to test for food-specific allergic sensitization.[85,86]

The presence of serum alpha-gal–specific IgE supports a diagnosis of alpha-gal syndrome for patients with allergic symptoms after mammalian meat ingestion. An alpha-gal IgE concentration of 0.1 kU/L or more is suggestive of the diagnosis, whereas an alpha-gal–specific IgE concentration lower than 0.1 kU/L is considered a negative result.[21,22,66,87-91] In populations with high alpha-gal sensitization rates, alpha-gal IgE levels of at least 2 kU/L or more than 2% of the total IgE concentration increases the likelihood of a positive mammalian meat challenge to greater than 50%,[21,22,87]

Table. Prevention and Treatment Strategies for Food-Protein Allergy and Anaphylaxis

Strategy	Goal	Patient education and support needs
Infant allergenic food consumption	Prevent the development of specific food allergies	• Education on timing, amount, and frequency of specific allergenic foods (eg, peanut, egg) • Awareness of infant-safe forms of allergenic foods (eg, thinned peanut butter, mashed boiled egg) • Identification of food allergy risk factors (eg, eczema) • Shared decision-making regarding screening for sensitization • Awareness of index allergic reactions
Dietary avoidance of culprit foods	Prevent and reduce severity of allergic reactions	• Reading and understanding of nutrition labels • Awareness of cross-contact and cross-contamination • Appropriate vigilance against potentially hidden ingredients • Developing food allergy-specific self-advocacy and communication skills (eg, for schools, restaurants, social event hosts, airlines) • Access to safe foods
Oral immunotherapy (food allergy desensitization)	Prevent and reduce severity of allergic reactions	• Individualized shared decision-making to choose oral immunotherapy • Understanding the potential benefits, potential risks, and behavioral advisories while undergoing oral immunotherapy
Emergency medications, including intramuscular epinephrine	Treat severe allergic reactions (anaphylaxis); reduce severity of allergic symptoms	• Understanding of individualized emergency action plan • Education about when to use epinephrine and role for adjunctive medications (eg, antihistamines, inhalers) to treat symptoms of severe allergic reactions and anaphylaxis

whereas values of at least 5.5 kU/L confer a 95% or more positive predictive value.[22]

Primary Prevention of Food Allergy

Randomized trials and meta-analyses have demonstrated that timely and consistent feeding of allergenic foods such as peanuts and eggs during infancy and into early childhood (**Table**) is an effective primary prevention strategy against the development of food allergy, especially in infants with eczema.[33,34,37-39,92-94] Dietary introduction of peanuts in infancy reduces the risk of peanut allergy (relative risk reduction, 71%; 95% CI, 26%-89%; 18 cases of peanut allergy prevented per 1000 individuals in a population with 2.5% peanut allergy prevalence). Dietary introduction of hen's egg in infancy reduces the risk of egg allergy (relative risk reduction, 44%; 95% CI, 13%-64%).[39,95] In population modeling that used data from trials and cohort studies, the greatest reductions in peanut allergy are achieved when peanut ingestion occurs at an early age, providing insight into an early "critical window of opportunity" at 4 to 6 months of age to reduce the risk of peanut allergy.[7]

Treatment of Patients With Food Allergies

Emergency Care Plans and Medication

All patients with IgE-mediated food allergy should have an emergency care plan that details medications to use for mild and severe allergic reactions (Table). Injectable epinephrine is the first-line treatment of severe allergic reactions and/or anaphylaxis.[75,96] Self-injectable epinephrine devices can be used to deliver doses in rapid succession (eg, 5 minutes apart), which may be required to slow symptom progression and reduce symptom severity. A 2021 meta-analysis of 86 studies, comprising datasets from 20 prospective and 68 retrospective observational studies (36 557 anaphylaxis events), showed that although 1 in 10 anaphylactic events were associated with the need for more than 1 epinephrine dose, only 2.2% (95% CI, 1.1%-4.1%) of reactions were associated with failure to respond to 2 doses of epinephrine.[97] Arrhythmia and acute coronary syndrome after intramuscular epinephrine are rare with only 7 case reports described in the literature.[98] Antihistamines, corticosteroids, and mast cell stabilizers such as cromolyn are commonly prescribed in the acute setting because they may mitigate certain symptoms of allergic reactions (eg, pruritus, urticaria, abdominal discomfort), and patients and clinicians express more comfort and familiarity with these medications than with epinephrine.[75] However, unlike epinephrine, these medications do not interrupt acute mast cell degranulation and do not stop anaphylaxis. Thus, administering these medications should not interfere with early epinephrine administration to treat anaphylaxis.[75]

Corticosteroids are also commonly given in practice to reduce the risk of biphasic anaphylaxis. However, there are no studies to support a consensus on the appropriate dosing or duration of steroid treatment for anaphylaxis. In a systematic review of 26 observational studies addressing whether to use corticosteroids to prevent biphasic anaphylaxis, the effect sizes across the studies ranged from 67 fewer to 4 more episodes of biphasic anaphylaxis per 1000 with corticosteroid use. Study authors also noted that confounding factors in these studies likely affected the results. Thus, published studies provide "very low certainty evidence" suggesting that no benefit from corticosteroids in reducing the risk of biphasic anaphylaxis exists (OR, 0.8; 95% CI, 0.74-1.02).[75]

Avoidance and Related Behaviors for IgE-Mediated Food Allergies

The cornerstone of managing IgE-mediated food allergy is avoidance of the culprit food allergen (Table).[29] Individuals and families managing food allergies require essential knowledge and skills to limit encounters with both known and hidden sources of culprit food allergens. These skills include food label literacy to identify major allergens in packaged foods; proactive communication skills to discuss food allergies with families, schools, restaurant workers, and food vendors;

cognizance of cross-contact and cross-contamination in places where foods may be prepared and served; and an ability to recognize dishes and meals across cultural cuisines that traditionally contain specific food allergens.[99-103] Federal statute mandates that the "top 9" food allergens are disclosed on all food packaging labels. Because precautionary allergen labeling (ie, language such as "may contain," "processed in a facility with") is not federally mandated and does not have the same regulatory standards, avoidance of products with such labels should be based on shared decision-making between families and their allergists that incorporates food allergic reaction severity, personal risk tolerance, and quality of life.[104,105] The vigilance needed to avoid food allergens is often associated with a significant impairment in the quality of life for both patients and caregiver.[106] Patient and clinician resources beyond the generalist and specialist clinic include professional advocacy organizations, counselors and psychologists, and registered dieticians for nutritional support, both in correcting nutritional deficiencies and in providing coaching for practical alternatives for eliminated foods.

Desensitization via Immunotherapy

For food-protein allergies, allergen desensitization via immunotherapy is a therapeutic option (Table).[107] Immunotherapy can increase the minimum amount of food allergen consumed that elicits a clinical allergic reaction.[108] In oral immunotherapy, an individual consumes small, successively increasing doses of a food allergen and then is maintained on a daily target dose indefinitely for ongoing exposure.[109] Currently, pharmaceutical grade peanut (*Arachis hypogaea)* allergen powder (PTAH, Palforzia, Aimummune Therapeutics) is the only food allergy immunotherapy approved by the US Food and Drug Administration (FDA) and is used for peanut allergy.[110,111] In the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADES)[108] randomized trial, 250 of 372 participants being actively treated tolerated exposure to at least 600 mg of peanut protein (equivalent to approximately 2 peanut kernels) at the end of the trial compared with only 5 of 124 patients who received placebo. Subsequently, this peanut allergen powder became the first FDA-approved immunotherapy product for food allergy. Oral immunotherapy for multiple food allergens, including peanut, using readily available but nonstandardized dietary sources is an emerging clinical allergy practice initiated in the allergist's office and continued at home. Allergic reaction associated with oral immunotherapy is the inherent risk of desensitization therapy. The risk of such reactions can increase after exercise, sleep deprivation, illness, and fever and with use of medications such as nonsteroidal anti-inflammatory drugs, but may decrease with use of biologics currently approved to treat atopic dermatitis and allergic asthma.[108] Given the need to balance the benefit of protecting against accidental exposures with the risks of allergic reactions to the therapy itself, choosing to pursue oral immunotherapy remains an important decision to be shared between the treating specialist and family.[84]

Management of Alpha-Gal Syndrome

Allergic Reactions and Anaphylaxis

The management of acute allergic reactions and anaphylaxis in alpha-gal syndrome mirrors the approach used to manage allergic reactions in food-protein allergy, including prompt treatment of severe allergic reactions with epinephrine and use of antihistamines and corticosteroids as adjunctive treatments.[96] For individuals with alpha-gal sensitization and mild, chronic symptoms that involve solely the gastrointestinal tract (gastroesophageal reflux or loose stools), or skin (pruritus and hives), H_1 and H_2 antihistamines and oral mast cell stabilizers (cromolyn sodium) may be used.[89] Individuals with alpha-gal syndrome and a history of anaphylaxis with elevated serum tryptase concentration both during an acute reaction and at baseline should prompt suspicion for an underlying mast cell disorder, such as indolent systemic mastocytosis. Patients with both alpha-gal syndrome and indolent systemic mastocytosis experienced more severe allergic reactions than those with alpha-gal syndrome alone even though alpha-gal–specific IgE levels were 3-fold lower in patients with concurrent alpha-gal syndrome and indolent systemic mastocytosis.[62]

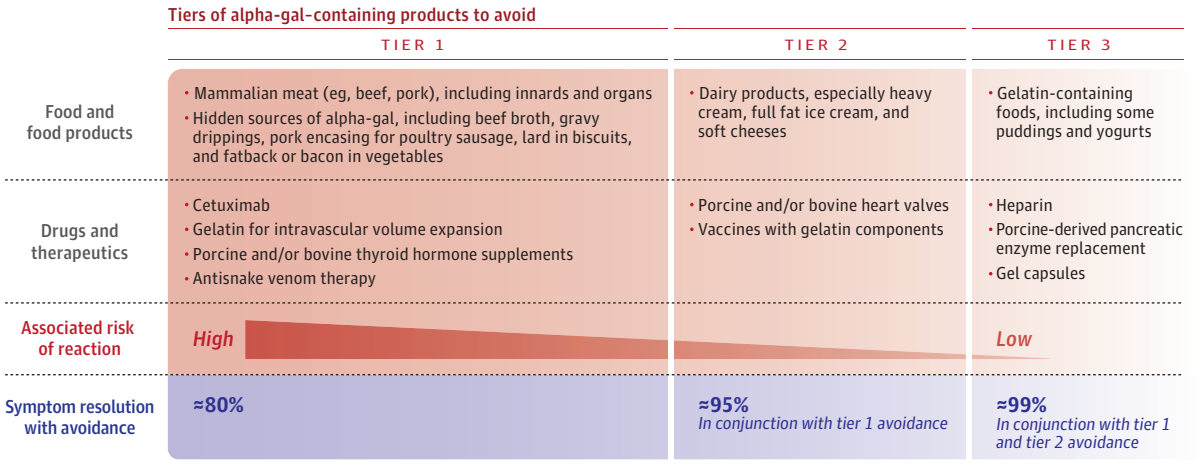
Avoidance and Related Behaviors

Bites from ticks associated with alpha-gal syndrome have been shown to increase alpha-gal–specific IgE levels and the likelihood of a reaction following alpha-gal consumption.[16,19,21,89,112,113] Therefore, patients with alpha-gal syndrome should be counseled to avoid repeat tick bites. Patients who are outdoors in areas where ticks live should wear clothing that covers exposed skin, walk in the center of trails, and avoid grassy, brushy, and wooded areas if possible. The application of Environmental Protection Agency–registered insect repellant, and insecticide (permethrin) to clothing and gear is also recommended. Once indoors, patients should shower within 2 hours of being outdoors and check skin and clothing for ticks. If ticks are found on the body, they should be removed with fine-tipped tweezers.[63]

Expert opinion also recommends a tiered avoidance approach for specific foods and drugs (**Figure 3**). Avoiding the wide variety and sometimes surprising sources of alpha-gal requires careful planning by patients and clinicians. All symptomatic patients with alpha-gal syndrome should avoid mammalian meat, innards, and organs.[21,87,89] They should also be counseled on other sources of dietary alpha-gal such as mammal-derived gelatin, lard in biscuits, pork encasings used for poultry-based sausages, gravy drippings, beef broth, and fatback or bacon in vegetable dishes. Avoidance of gelatin-containing foods, including powdered gelatin desserts, and some puddings and yogurts, is recommended.[87,88] Most patients can continue to consume small to moderate amounts of dairy (skim or low-fat milk, hard cheeses). Symptoms resolve in approximately 80% of individuals who follow this food avoidance strategy.[88] The estimated 20% of patients whose allergic symptoms persist despite following these guidelines should be counseled to also avoid dairy products, especially whole milk, ice cream, heavy cream, and soft cheeses. To date, there are no data on potential adverse or positive effects of consuming dairy products as tolerated in patients with alpha-gal syndrome, although dairy tolerance has been associated with syndrome resolution.[89] Dietary alpha-gal does not always trigger allergic reactions, but certain cofactors such as exercise, alcohol ingestion, and/or nonsteroidal anti-inflammatory medication use may increase the likelihood of allergic symptoms.[87,88]

Clinicians should be aware that individuals with alpha-gal syndrome should avoid injections of alpha-gal–containing medications such as cetuximab and intravenous gelatin (sometimes used for

Figure 3. Tiered Avoidance Approach of Alpha-Gal–Containing Foods and Drugs



Alpha-gal indicates galactose-α-1,3-galactose.

volume resuscitation outside the US). In general, patients with alpha-gal syndrome should also avoid oral medications and supplements of porcine and bovine origin such as commercially available non-FDA approved thyroid hormone supplements (Armour thyroid) and medications encased in mammal-derived gelatin capsules. However, there are case reports of patients with alpha-gal syndrome who have tolerated porcine-derived pancreatic enzyme replacement therapy.[114,115] In addition, there are case reports describing both anaphylaxis[116,117] and tolerance[118] to vaccines with gelatin excipients. Thus, the general recommendation is to avoid alpha-gal–containing medications whenever possible, favoring preparations that come in tablet form rather than gelatin capsules. However, these case reports suggest that if an alpha-gal–containing medication or vaccine is absolutely required for treatment with no viable alternatives, these therapeutics may be able to be administered to patients under the supervision of allergy and immunology specialists.

Sensitization to alpha-gal may complicate surgical procedures, particularly bovine or porcine heart valve replacements and anticoagulation with high doses of porcine heparin.[119-121] Via immunoblotting, sera from patients with alpha-gal syndrome were shown to bind mammalian-derived implants, including cardiac patches, vascular grafts, and heart valves similarly to a monoclonal anti–alpha-gal IgM antibody.[119] Although the relationship between alpha-gal–specific IgE levels and strength of binding to these implants was not established in this study, this observation suggests that such implants may pose a long-term nidus for chronic inflammation in patients with alpha-gal syndrome.[119] However, studies have not compared longevity of bioprosthetic heart valves and other mammalian-derived grafts in patients with and without alpha-gal syndrome.

Heparin produced from porcine mucosa and bovine lungs contains detectable alpha-gal.[121] Single-center retrospective studies suggest that allergic reactions to heparin among patients with alpha-gal syndrome are more likely following intravenous (IV) unfractionated heparin than subcutaneous low-molecular-weight heparin. Four of 17 patients (24%) sensitized to alpha-gal and undergoing cardiac surgery had a documented allergic reaction after receiving IV unfractionated heparin[122] compared with 1 of 39 (2.6%) administered subcutaneous unfractionated heparin[123] and 0 of 22 (0%) sensitized patients receiving low-molecular-weight heparin.[124] Thus, if high-dose IV unfractionated heparin cannot be avoided among patients with alpha-gal syndrome, expert opinion suggests pretreatment with steroids and antihistamines prior to administration.[122] Although no data suggest that pretreatment will lower the risk of IgE-mediated hypersensitivity to heparin, the favorable side effect profiles of pretreatment medications and potential benefits of reducing risk or severity of IV heparin–induced allergic reactions have led some to adopt this practice.[122]

Among patients with alpha-gal syndrome, serum alpha-gal–specific IgE levels are typically monitored every 6 to 18 months. Alph-gal–specific IgE levels wane over time, so alpha-gal syndrome may resolve spontaneously, especially if additional tick bites are avoided.[113] Oral mammalian meat challenge can be considered when alpha-gal specific IgE is either less than 2 kU/L or less than 2% of total IgE levels,[89] although thresholds may vary depending on the population.[22] Strategies for reincorporating mammal meat back into the diet if alpha-gal syndrome has resolved depend on patient and clinician comfort and include a supervised, in-office, oral food challenge with a serving of mammalian meat followed by several hours of observation or gradual reintroduction in the home setting with access to intramuscular epinephrine. Oral immunotherapy with cow's milk or beef to treat alpha-gal syndrome remains investigational.[21,124,125] Creation of an FDA-approved pig genetically engineered not to have alpha-galactosyl transferase enzymes may provide future avenues for hypoallergenic mammalian meat preparations and may allow use of mammalian products in therapeutics for patients with alpha-gal syndrome.[126]

Limitations

This review has several limitations. First, the quality of the evidence presented was not systematically evaluated with formal quality grade levels. Second, given the breadth of the field, all relevant references may not have been included. Third, emerging IgE-mediated food glycan-allergies, aside from alpha-gal syndrome, were not discussed.

Conclusion

IgE-mediated food allergies, including delayed IgE-mediated allergic responses to red meat in alpha-gal syndrome, are common in the US, and may cause anaphylaxis and rarely, death. IgE-mediated anaphylaxis to food requires prompt treatment with epinephrine injection. Both food-protein allergy and alpha-gal syndrome management require avoiding allergenic foods, whereas alpha-gal syndrome also requires avoiding tick bites.

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