



'Doc, will I ever eat steak again?': diagnosis and management of alpha-gal syndrome

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Purpose of review

Alpha-gal syndrome encompasses a constellation of symptoms associated with immune-mediated hypersensitivity responses to galactose-alpha-1,3-galactose (alpha-gal). The purpose of this review is to discuss our current understanding of the etiology, clinical symptoms, natural history, epidemiology, and management of alpha-gal syndrome.

Recent findings

Sensitization to alpha-gal is associated with bites from ectoparasites like the lone star tick *Amblyomma americanum*. Allergic reactions in alpha-gal syndrome are often delayed and inconsistent. The magnitude of the allergic response depends on co-factors like exercise and alcohol consumption and the amount of alpha-gal and fat present in the food. Assaying alpha-gal-specific IgE in the serum is the primary diagnostic test used to confirm the allergy. Long-term management of the condition involves avoidance of both mammalian food products and tick bites.

Summary

Alpha-gal syndrome disrupts the current paradigm for understanding food allergy. Exposure to an ectoparasite is critical for the development of specific IgE antibodies underlying sensitization, and allergic reactions depend on the activation of mast cells and basophils sensitized with IgE against a carbohydrate rather than a protein. Research in this field may lead to the development of improved diagnostic and therapeutic tools that can revolutionize the management of patients with alpha-gal syndrome.

Keywords

alpha-gal syndrome, glycolipid, mammalian meat, red meat allergy, tick

INTRODUCTION: WHAT IS ALPHA-GAL SYNDROME

Alpha-gal syndrome encompasses a constellation of symptoms associated with immune-mediated hypersensitivity responses to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal). Galactose-alpha-1,3-galactose moieties are present in several glycoproteins and glycolipids found in nonprimate mammals (cow, pig, goat, sheep, etc.). Alpha-gal syndrome includes both drug allergy, characterized by immediate hypersensitivity responses to injected pharmaceutical products containing alpha-gal, and food allergy, characterized by delayed reactions after ingestion of mammal-derived foods (meat, innards, organs, and dairy). Allergic reactions to alpha-gal were first described by Chung *et al.* [1]. Their report grew from observations that cancer patients living in the Southeastern United States experienced significantly more anaphylactic reactions than patients in New England, California, or Europe following intravenous

doses of cetuximab, a monoclonal antibody and cancer chemotherapeutic agent [2]. Chung *et al.* [1] found that IgE antibodies specific for galactose-alpha-1,3-galactose glycosylating the monoclonal antibody were critical for the development of these immediate hypersensitivity responses. Shortly afterward, Commins *et al.* [3] and Van Nunen *et al.* [4] published case series with scores of patients from the Southeastern United States and Australia,

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KEY POINTS

- Alpha-gal syndrome is an allergic condition with global reach.
- Alpha-gal syndrome refers to the symptoms associated with IgE-mediated hypersensitivity responses to the carbohydrate galactose-alpha-1,3-galactose.
- Alpha-gal syndrome manifests as both immediate hypersensitivity responses to intravenously administered pharmaceuticals containing alpha-gal and delayed hypersensitivity responses following the ingestion of mammalian food products, especially meat, innards, and organs.
- Sensitization to alpha-gal is linked to bites from ectoparasites, including the lone star tick *Amblyomma americanum*.
- Delayed allergic reactions following the ingestion of alpha-gal may reflect the hours required for alpha-gal glycolipid absorption, metabolism, and trafficking to sensitized allergic effector cells in the blood and tissues.

respectively, describing allergic symptoms including pruritus, urticaria, angioedema, and abdominal discomfort hours after eating mammalian meat. Commins *et al.* [3] identified the presence of circulating alpha-gal-specific IgE in these patients. Both groups also reported that history of tick bite was common to all these patients.

Alpha-gal syndrome challenges the current paradigm for food allergy. Whereas in conventional food allergies, individuals develop allergic symptoms typically within minutes of eating the food, in alpha-gal syndrome, allergic symptoms frequently begin greater than 2 h after ingesting mammalian products [5[•],6[•],7^{••}]. Moreover, the IgE antibodies driving allergic responses in alpha-gal syndrome form against the carbohydrate alpha-gal, rather than a protein antigen [7^{••}]. Typically, sensitization, or the development of IgE antibodies to food proteins, occur after a primary exposure to that food via an epithelial barrier like the oral mucosa, gastrointestinal epithelium, or the skin [8]. With alpha-gal syndrome, sensitization is associated with exposure to ectoparasites; in the United States, the culprit ectoparasite is the lone star tick (*Amblyomma americanum*) [9,10^{••}].

CLINICAL PRESENTATION

In alpha-gal syndrome, allergic reactions are frequently delayed and may not occur with each ingestion. The variability in the magnitude of the allergic

response depends on co-factors including exercise and alcohol, which can also impact speed and severity of conventional allergic responses to food proteins [7^{••},11]. The dose and form of alpha-gal consumed also seems to influence the magnitude and speed of the allergic response. Allergic symptoms may appear rapidly in alpha-gal allergic individuals who consume organ meats like pork kidney, which contains high concentrations of alpha-gal [12,13]. By contrast, consuming fatty mammalian products delays allergic reactions [14[•]]. This may be related to differences in how alpha-gal allergic and nonallergic patients metabolize proteins and lipids [15]. Prior to the first episode of allergic symptoms, patients with alpha-gal syndrome often report a large local reaction to a tick or arthropod bite, with this bite frequently serving as the herald of the development of alpha-gal syndrome [7^{••}].

Alpha-gal syndrome in children highlights different clinical phenotypes

Although alpha-gal syndrome was first described in adult patients who had safely consumed meat for years, the condition has also been reported in children [5[•],6[•],16,17[•],18]. Kennedy *et al.* published the first case series of 51 children (ages 4–17 years) reporting delayed urticaria, angioedema, and/or anaphylaxis after eating mammalian meat. They detected alpha-gal-specific IgE in nearly 90% of these children [16]. Using electronic health records of pediatric patients in southwest Missouri, another study found that the average age of diagnosis among pediatric patients was 9.95 years with most presenting with urticaria and angioedema (99%) followed by anaphylaxis (29%) and gastrointestinal symptoms (17%) [17[•]].

Studies involving children in the United States, Spain, and South Africa have led to increasing recognition of different clinical phenotypes for alpha-gal syndrome [5[•],16,17[•],18]. Multiple groups have reported that cutaneous symptoms characterized by urticaria, angioedema, and pruritus are the presenting symptoms for 80–90% of individuals with alpha-gal syndrome [5[•],6[•]], followed by anaphylaxis (60%) [6[•]]. A gastrointestinal-predominant form of alpha-gal syndrome has also emerged, affecting approximately 20% of patients; patients describe severe, persistent abdominal cramping and diarrhea [5[•],17[•]]. Moreover, gastrointestinal reflux can be an early symptom, occurring within minutes to 1 h after ingestion of mammalian products [7^{••}].

Alpha-gal syndrome may be the underlying cause for many cases of idiopathic anaphylaxis. A 2018 study from the University of Tennessee reported that alpha-gal syndrome accounted for

33% of anaphylaxis cases with known cause [19]. Moreover, the ability to diagnose alpha-gal syndrome led to a noticeable drop in the number of idiopathic anaphylaxis cases reported in this center, from 59% in 2006 to 35% in 2018 [19]. A study from the National Institutes of Health, found 9% of subjects diagnosed with idiopathic anaphylaxis had circulating, detectable alpha-gal-specific IgE (≥ 0.35 kU/l), reported a tick bite history, and resided within the Southeastern and Mid-Atlantic United States where lone star ticks also live [20].

SENSITIZATION TO ALPHA-GAL AND CARDIOVASCULAR DISEASE

Alpha-gal specific IgE has also been linked to two cases of premature bioprosthetic heart valve degeneration in patients who developed alpha-gal syndrome years after their aortic valve replacements [21]. Clinical symptoms, including chest pain and dyspnea, in conjunction with prosthetic valvular insufficiency and degeneration, developed 1–2 years after diagnosis with alpha-gal syndrome, requiring replacement with mechanical prosthetic valves [21]. By contrast, another case series showed that porcine or bovine valve replacement in patients with preexisting alpha-gal syndrome was associated with perioperative and postoperative anaphylaxis attributed to the rapid release of residual alpha-gal antigen in bioprosthetic valves, but longer term tolerance of their valve replacements [22]. Immediate allergic reactions were managed with epinephrine and adjunctive therapies like H1 and H2 blockers and corticosteroids. At 6–12 months of follow-up, they were tolerating their bioprosthetic valves, possibly because of a significant reduction in alpha-gal antigen release from the valve over time [22]. Longitudinal observational studies are clearly needed to determine definitively if alpha-gal-specific IgE is associated with untimely bioprosthetic valve degeneration.

Circulating alpha-gal-specific IgE has also been associated with an increased atherosclerotic burden and unstable plaques in the setting of coronary artery disease, although the association is not causal. This has led some to hypothesize that in alpha-gal sensitized subjects, allergic effector cells activated by alpha-gal promote the production of inflammatory chemicals that contribute to vessel wall damage [23,24]. Further investigation into the potential relationship between alpha-gal sensitization and atherosclerotic disease would enhance our understanding of alpha-gal avoidance and its impact on the natural history and management of atherosclerotic disease.

EPIDEMIOLOGY

There are currently no estimates of the global prevalence of alpha-gal syndrome. Yet, cases of alpha-gal syndrome, both self-reported and physician-diagnosed have been described across the world, including North, Central and South America, Europe, Southern and Western Africa, East and South Asia, Australia and New Zealand [10²²,25]. A global heat map of Google searches for the term ‘Alpha-gal allergy’ over a 15-year period from 2004 to 2019 showed the highest search volumes in Sweden, the United States, Canada, Australia and South Africa [26]. There is significant variation in the prevalence of sensitization to alpha-gal, depending on the region of the world and the patient population studied. Importantly, sensitization to alpha-gal does not always reflect the presence of symptomatic disease. For example, 35% of a rural population of German forest service employees and hunters were sensitized to alpha-gal but only 8.6% of those with detectable circulating alpha-gal-specific IgE at least 0.35 kU/l were symptomatic [27]. An Italian study found that rural populations had sensitization frequencies 20 times higher than urban populations [28], likely because of increased tick exposure and the strong association of alpha-gal-specific IgE with tick bite history.

The prevalence of alpha-gal syndrome in the United States remains unknown. Estimated rates of sensitization in the Southeastern United States range from 15 to 25% based on small studies of 40–250 patients [2,29,30]. In our institution, the University of North Carolina – Chapel Hill, at least 2500 cases have been identified since 2014 [7²²]. Over 34 000 cases of alpha-gal syndrome have been identified nationwide using 105 000 unique patient samples tested for circulating alpha-gal-specific IgE by Viracor (P. Armstrong, S.P. Commins, personal communication). The high rate (32%) identified among Viracor samples likely reflects the fact that, unlike patient samples in the studies from Europe and the Southeastern US, Viracor’s patient samples are enriched for samples from symptomatic individuals with high pretest probabilities for having alpha-gal syndrome.

There continues to be a critical need for large studies to determine the prevalence of both alpha-gal sensitization and alpha-gal syndrome itself. Some have used regional and temporal patterns of web-based search activity for alpha-gal allergy as a surrogate for monitoring disease emergence. Using online search traffic on Google, looking at searches for ‘Alpha-gal allergy’ and ‘lone star tick’, from 2004 to 2019, Iglesia *et al.* [26] found that these terms were topics of interest in 47 out of 50 states with the

top 5 states (Arkansas, Kentucky, Tennessee, Virginia and North Carolina) located in the Southeastern United States. They also found that the search volume for alpha-gal allergy queries increased over time with search query peaks coinciding with popular news media coverage of the condition [26].

Similarly, publically available maps show that the geographic distribution of the lone star tick is expanding (https://www.cdc.gov/ticks/geographic_distribution.html). When juxtaposed with maps from crowd-sourced, web-based applications like Zee Maps, which allows individuals to share their locations, it becomes evident that the geographic distribution of the lone star tick mirrors the geographic distribution of self-reported alpha-gal syndrome cases (<https://www.zeemaps.com/map?group=555038#>).

Blood type also appears to influence the risk of developing alpha-gal syndrome. Rispens *et al.* [31] and Apostolovic *et al.* [32] found that alpha-gal-specific IgE antibodies were significantly less abundant in individuals with blood groups B or AB. Hamsten *et al.* [33] showed that 80% of healthy blood donors and Lyme disease patients sensitized to alpha-gal were B-negative. A meta-analysis that pooled data from four different cohorts from different countries, Japan, Spain, Sweden and the United States, found that the observed frequency of blood types B and AB among those with red (mammalian) meat allergy was five times lower than expected [34[■]]. By contrast, Fischer *et al.* [27] were not able to associate any relationship between susceptibility to the development of alpha-gal-specific IgE antibodies in their patient cohort and blood type B. This discrepancy may result from different techniques used to determine blood types, or may be a finding unique to the patient cohort studied. All the studies demonstrate that even if the association is lower, the risk of developing sensitization or allergy to alpha-gal remains, even in those with blood type B.

The working hypothesis to explain the effect of blood type on alpha-gal sensitization and allergy proposes that individuals with blood type B make low quantities of alpha-gal IgE with possibly low binding affinity for alpha-gal. Alpha-gal is closer in structure to blood type B than to A and O; individuals with blood type B may be less likely to create an antibody against a foreign carbohydrate (alpha-gal) very similar in structure to a self-carbohydrate (group B antigen) [35].

PATHOPHYSIOLOGY

The process driving sensitization to alpha-gal and the delayed allergic reaction following oral consumption of alpha-gal is not well understood.

Sensitization has been linked to bites from ectoparasites, that is, adult and nymphal stage seed ticks [10[■],36,37]. Mouse models have also been used to show that live tick infestation [38] or injection of tick components, including whole body tick extract [39]; tick salivary gland extract (TSGE) and tick saliva [40] can generate alpha-gal-specific IgE responses in galactosyltransferase-deficient (AGKO) mice that lack the ability to make alpha-gal. Moreover, the kinetics of rising alpha-gal-specific IgE levels in AGKO mice after TSGE injection mirror the kinetics of alpha-gal-specific IgE rise after exposure to ticks like *A. americanum* [40].

How a tick bite promotes the generation of alpha-gal-specific IgE; however, remains unclear. Humans make high titers of IgG, IgM, and IgA antibodies against alpha-gal, likely driven by chronic antigen stimulation by glycans from the commensal microbiota [41,42]. Several tick species, including species linked to alpha-gal syndrome, contain alpha-gal epitopes in the gastrointestinal tract [33] and in the saliva and salivary glands [43,44[■]]. One possibility is that culprit tick species introduce alpha-gal antigen into the host through the skin while simultaneously injecting adjuvant compounds that skew the immune response to alpha-gal to a type 2 (allergic) response that promotes alpha-gal-specific antibody class switching from IgG to IgE [39]. Other contributing factors could include type 2 allergic immune deviation in the setting of trauma to the skin barrier or alteration of the host skin microbiome. Such insults may drive epithelial cell production of cytokines like TSLP, IL-33 and IL-25, known to promote allergic responses through their influence on dendritic cells, basophils and innate lymphocytes [8].

The B-cell population that produces alpha-gal-specific IgE has not been fully characterized, and may include plasmablasts and short-lived plasma cells, perhaps explaining why alpha-gal IgE levels wane over time. Mouse models suggest that alpha-gal-specific B-cell function may depend in part on the presence of functional CD4⁺ T cells [39]. However, innate T-lymphocyte populations like gamma delta T cells or invariant natural killer T cells that recognize glycolipids could also be involved in the sensitization phase in alpha-gal allergy, and a possible role for these cell populations in alpha-gal allergy is under active investigation [45].

The effector phase of the allergic response to alpha-gal, especially the delay in the development of allergic symptoms following oral ingestion of alpha-gal are also under active study. During experimental mammalian meat challenges, Commins *et al.* [46] found that basophils from alpha-gal allergic subjects are activated 4 h after alpha-gal

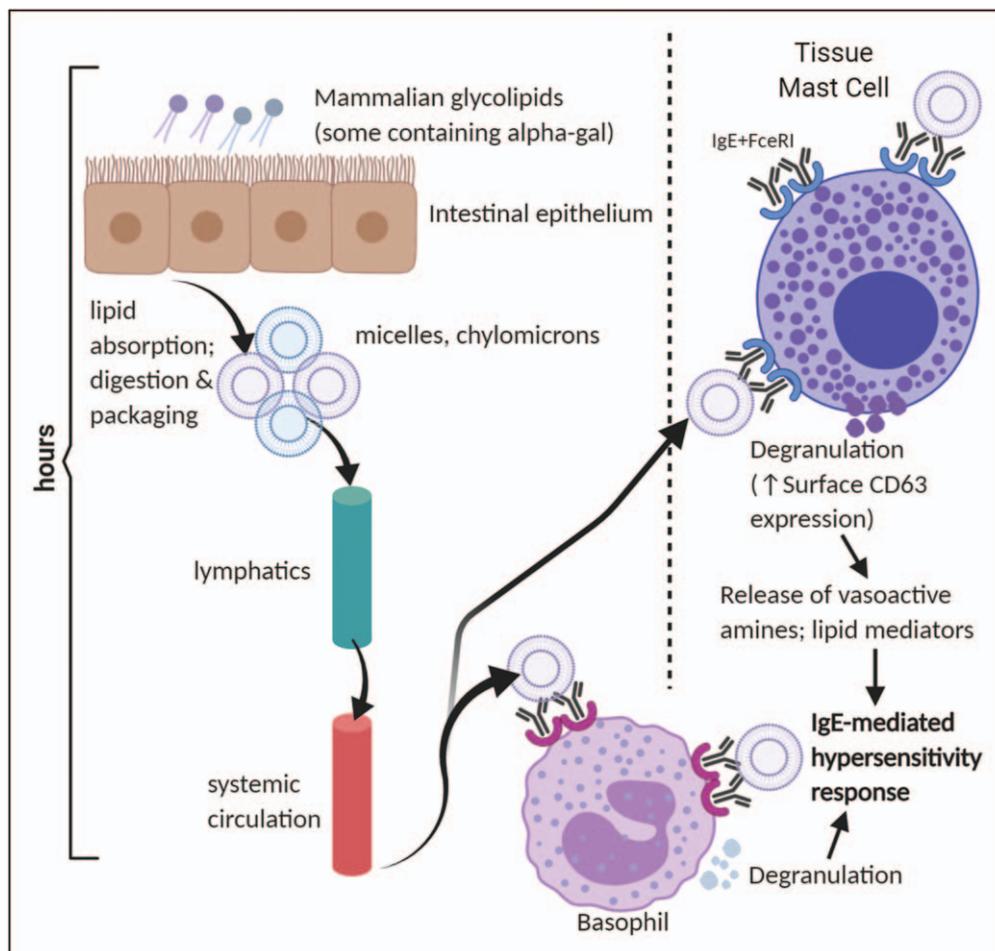


FIGURE 1. Mammalian glycolipids containing alpha-gal are absorbed, entering the hepatic (not shown) and systemic circulation. Alpha-gal glycolipids, packaged in micelles or chylomicrons or incorporated into lipid bilayers, crosslink alpha-gal-specific IgE-FcεRI complexes on basophils and mast cells. The hours required for absorption, processing and delivery of alpha-gal glycolipids to allergic effector cells may explain the delay in symptoms in alpha-gal syndrome.

ingestion. The delay in basophil activation does not seem to be attributable to the alpha-gal antigen itself as alpha-gal glycoproteins and glycolipids can induce allergic effector cell activation in standard basophil activation tests within 30–60 min [13,14,47]. Interestingly, significant differences in lipid and fatty acid metabolism pathways between individuals with and without alpha-gal syndrome have been reported [15]. Thus, delayed allergic reactions in alpha-gal allergy may reflect the hours required for lipid absorption and metabolism (Fig. 1).

DIAGNOSIS

The standard of care to confirm a diagnosis of alpha-gal syndrome is to use serologic testing for alpha-gal-specific IgE. The sensitivity of skin prick testing for alpha-gal using commercially available mammalian meat extracts is too low to confirm alpha-gal

syndrome, with skin prick tests often negative or borderline-positive [3]. Intradermal testing with commercially available food extracts is more reliably positive [9], but is outside the standard of care because of concerns of inducing anaphylaxis during testing. Some centers perform prick-to-prick testing with cooked meats, or skin prick and/or intradermal testing with cetuximab or gelatin. These produce large, consistent wheals (≥ 5 mm) in alpha-gal allergic subjects [48,49,50].

Regarding serologic testing, the source of alpha-gal differs depending on the testing center. The University of Virginia, which published the first cases of alpha-gal syndrome in the United States, uses the alpha-gal-rich cetuximab, estimated to have 2040 μg alpha-gal content per gram cetuximab [51], as an alpha-gal glycoprotein source. Commercially available testing conducted by Viracor in the United States and Thermofisher/Phadia in Europe relies on beef thyroglobulin (5.6 μg alpha-gal/gram protein,

[51]) as the source of alpha-gal. Surprisingly, despite the 350-fold difference in alpha-gal content between cetuximab and beef thyroglobulin, there is a strong correlation between alpha-gal-specific IgE levels detected using each source [52].

With a convincing clinical history, alpha-gal IgE levels at least 0.1 kU/l confirm the diagnosis of alpha-gal syndrome [7^{***}]. With a murky clinical history, some have argued that an alpha-gal IgE at least 2 kU/l or at least 2% of the total IgE should be used to confirm the diagnosis of alpha-gal syndrome [50^{***}]. Some test sites include alpha-gal-specific IgE testing within an 'alpha-gal panel', which also includes beef, mutton/lamb, pork, and cow's milk-specific IgE testing as patients allergic to alpha-gal frequently have specific IgE that binds to multiple mammal-derived allergens [3], presumably binding to alpha-gal glycans rather than peptide epitopes. This testing, in conjunction with testing for IgE to cat and dog aeroallergens, serves as a crude surrogate to confirm alpha-gal syndrome if alpha-gal-specific IgE testing is not readily available. However, the alpha-gal-specific IgE and total IgE levels are the most useful serologic tests for confirming the diagnosis of alpha-gal syndrome.

We also check basal serum tryptase levels, as a surrogate for mast cell burden, particularly in those who present with anaphylaxis. Just as anaphylaxis to stinging insect venom can unmask an underlying systemic mastocytosis [53], individuals with alpha-gal syndrome have also been subsequently diagnosed with indolent systemic mastocytosis (ISM). One study showed that individuals with concurrent alpha-gal syndrome and systemic mastocytosis had more severe clinical reactions after alpha-gal ingestion; elevated serum tryptase levels that were four-fold higher; and alpha-gal-specific IgE levels that were three-fold lower than alpha-gal allergic subjects without ISM [20].

MANAGEMENT

As with all food or drug allergies, acute management of alpha-gal-induced anaphylaxis requires recognition and immediate treatment with an epinephrine autoinjector. We counsel our patients that they should treat any sign of respiratory or cardiovascular distress following known or suspected exposure to alpha-gal or physical signs involving two or more organ systems with epinephrine and activate emergency medical services [54]. When patients present to the emergency department or urgent care setting, it is also helpful to obtain total serum tryptase levels, especially if patients present within 4 h of the event. If the tryptase obtained acutely is elevated compared with basal tryptase levels, this confirms anaphylaxis.

Results can take several days to return; however, and are not always elevated in the setting of food-induced anaphylaxis [55]. If both acutely obtained and basal tryptase levels are above normal, this suggests an elevated mast cell burden and possible mastocytosis [20].

Currently, as with all food and drug allergies, long-term management of alpha-gal allergic patients centers on avoidance of alpha-gal-containing foods and drugs. We suggest three different tiers of alpha-gal avoidance (Fig. 2). 'Tier 1' avoidance involves elimination of dietary beef, pork, lamb, venison and other mammalian meats and innards as well as intravenous medications with high alpha-gal content including cetuximab, gelatin-based colloid agents, and – after weighing risks and benefits – antivenom therapies. We also remind our patients to watch for 'hidden sources' of alpha-gal including beef broth in soups, animal fat drippings in gravy, pork encasings for chicken or turkey sausages, or fatback or bacon in vegetable dishes and salads. Unless the patient reports an adverse reaction following the ingestion of dairy products, we encourage patients to incorporate moderate amounts of dairy in their diets. In our clinical experience, hard cheeses like cheddar or parmesan, skim (0%), low-fat (1–2%) or whole (4%) milk are typically well tolerated. Heavy cream (18–36% milkfat), soft cheeses like brie or mozzarella and full-fat ice cream are more likely to induce adverse responses. Symptoms resolve in ~80% of alpha-gal allergic patients with Tier 1 avoidance.

'Tier 2' avoidance includes tier 1 avoidance combined with the elimination of dietary dairy products; avoiding heart valve replacements with bovine or porcine products; and avoiding (if possible), gelatin-containing vaccines [e.g. Zostavax; measles, mumps, and rubella (MMR)]. Symptoms resolve in 95% of alpha-gal allergic patients with tier 2 avoidance. 'Tier 3' avoidance involves not only tiers 1 and 2 avoidance but also elimination of gelatin-containing foods (some puddings or yogurt), gelcaps, heparin and pancreatic enzyme replacement that might contain trace amounts of alpha-gal [7^{***}, 50^{***}].

Importantly, the vast majority of patients with alpha-gal syndrome tolerate most orally delivered pharmaceutical products, even those with trace amounts of alpha-gal. If a medication that may contain alpha-gal is critical for the good health of an alpha-gal allergic patient and there are no suitable alternatives, we recommend referral to an allergist for an oral challenge with this medication [56], even in patients with confirmed alpha-gal syndrome and positive skin testing to the drug [57]. For those patients who remain symptomatic, even after

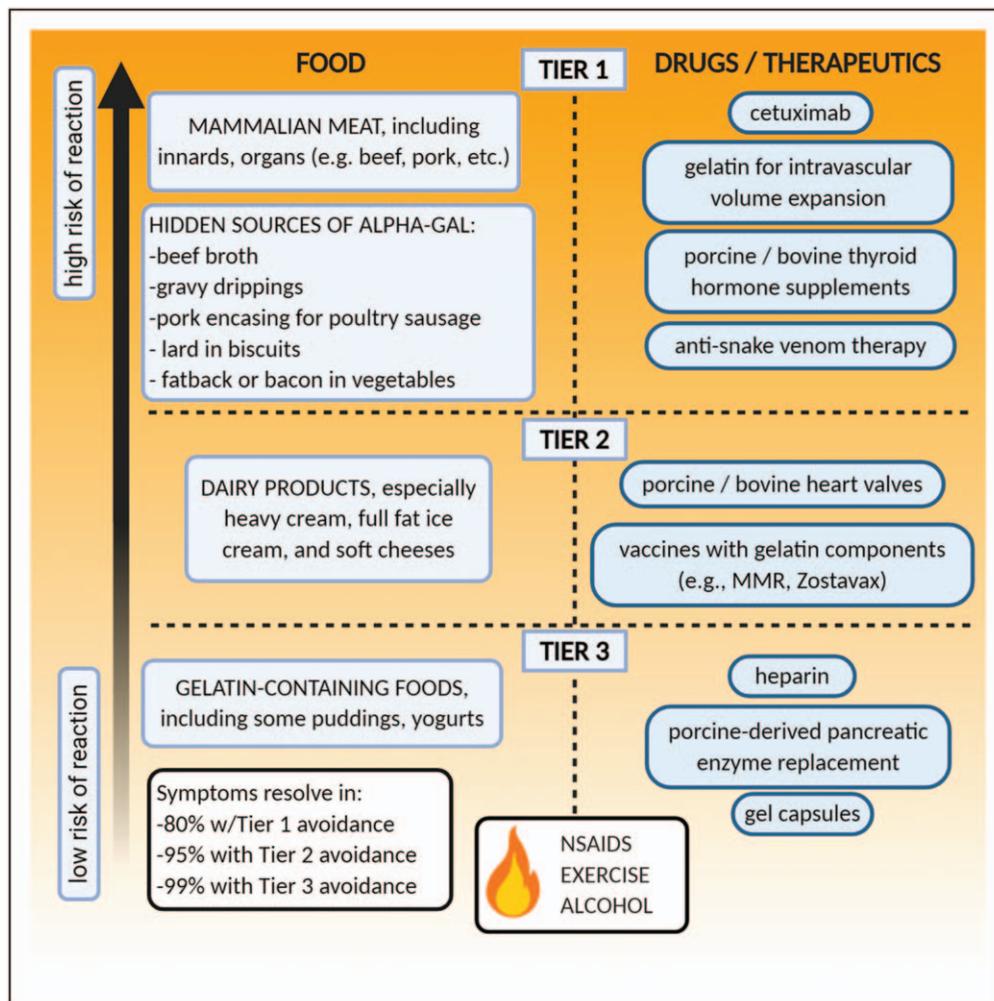


FIGURE 2. Long-term management of alpha-gal syndrome involves avoidance of alpha-gal containing foods and medications, including hidden sources of alpha-gal, and counseling on the accelerant effects of co-factors like exercise and alcohol on allergic responses to alpha-gal.

removing all known sources of alpha-gal from the diet and medication regimen, we recommend as needed use of H1 antihistamines to block allergic mediators produced by mast cells and basophils, and cromolyn to stabilize mast cells, especially in the gut.

Finally, we counsel patients to avoid bites from both adult and nymphal stage ticks (sometimes referred to as seed ticks or ‘chiggers’ in the South-eastern United States [58]) as these bites have been associated with acute increases in both total and alpha-gal-specific IgE levels [58].

NATURAL HISTORY AND REINTRODUCING MAMMALIAN MEAT

‘Will I ever be able to eat steak again, Doc?’

No studies currently address whether individuals can “outgrow” alpha-gal allergy and reintroduce

dietary mammalian meat. Kim *et al.* [59] have shown that alpha-gal allergic individuals who avoid tick bites experience a decline in alpha-gal-specific IgE levels. Therefore, we check alpha-gal-specific IgE and total IgE levels in our alpha-gal allergic patients at least once yearly. No tools currently exist to predict the likelihood or rate of decline for alpha-gal-specific IgE levels. In our patients practicing tier 1 avoidance, if after at least 12 months of monitoring, alpha-gal-specific IgE levels have dropped to less than 0.35 kU/l or 2% or less of the total IgE, with no adverse reactions to accidental mammalian meat ingestion or known dairy ingestion, we discuss reintroducing mammalian products back into the diet. For most patients, the risk of anaphylaxis outweighs any benefit of reintroducing mammal meat. We counsel those who elect to add back mammalian meat to their diet on when and how to use their epinephrine autoinjectors and seek emergency help. The process is done slowly and cautiously, starting

with very small portions of low-fat, lean meats in the presence of a friend or family member.

At our center, between 1 and 10% of alpha-gal allergic patients each year have reintroduced mammalian meat successfully into their diets. Patients whose symptoms are controlled with tier 1 avoidance (i.e. they tolerate dairy), who avoid tick bites and have significant drops in alpha-gal-specific IgE are more likely to successfully re-incorporate mammalian food products into their diet if desired [7[■]].

Re-introduction of mammalian meat into an alpha-gal-allergic person's diet was also described in a case report about the successful desensitization of a child with alpha-gal syndrome to beef, an integral part of his family's diet that he could not avoid [60]. Similar to oral immunotherapy for food-protein allergy, this subject must eat a serving of beef daily or risk re-developing adverse symptoms to mammalian meat [60].

CONCLUSION

With its delayed symptom onset driven by IgE antibodies to a glycan rather than a protein, alpha-gal syndrome challenges conventional conceptions of food allergy. Research on this allergic condition continues to expand. Probing how bites from certain tick species drive sensitization to alpha-gal, and exploring host characteristics that predispose to developing alpha-gal syndrome, be they immune, genetic, metabolic, and beyond, will inform future diagnostic and therapeutic interventions critical for the management of individuals with this condition.

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Conflicts of interest

C.P. reports no relevant disclosures. O.I.I. is a consultant for Matzellen Bio and Blueprint Medicines.

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