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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Alpha-Gal Syndrome for the GI Clinician: Commentary

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DESCRIPTION: **Alpha-gal syndrome is an emerging allergy first described in the early 2000s. The allergy can cause anaphylaxis, gastrointestinal (GI) symptoms, and skin changes one to several hours after ingestion of mammalian products. A GI phenotype that is increasingly recognized manifests with nonspecific symptoms like abdominal pain, diarrhea, nausea or vomiting without predominant skin, respiratory or circulatory symptoms. Though the syndrome has been reported on all continents except Antarctica, in the United States most reports are within the range of the Lone Star tick, extending from New York and Iowa to Texas and Florida. The purpose of this AGA Clinical Practice Update (CPU) Commentary is to increase awareness among gastroenterologists about the presentation and management of alpha-gal syndrome.**

METHODS: **This CPU commentary was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the CPUC and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. This expert commentary incorporates important as well as recently published studies in this field, and it reflects the experiences of the authors. Formal ratings regarding the quality of evidence or strength of the presented considerations were not included since systematic reviews were not performed.**

keywords: alpha-gal syndrome; food allergy; abdominal pain; diarrhea.

Introduction

Alpha-gal syndrome causes an IgE-mediated reaction hours after eating beef, pork, other mammalian meat, or mammalian-derived products.[1] Although the allergy was first described in patients with anaphylaxis and urticaria, gastrointestinal (GI) alpha-gal is a phenotype that increasingly is recognized and manifests with GI symptoms such as abdominal pain, diarrhea, nausea, and vomiting without predominant skin, respiratory, or circulatory symptoms.[2–9] It is important for gastroenterologists to be aware of this condition and to be capable of diagnosing and treating it in a timely manner. Research on GI alpha-gal is nascent, and we discuss relevant current knowledge.

The allergy in alpha-gal syndrome is to galactose alpha-1,3-galactose, an oligosaccharide on the cells of all nonprimate mammals. Surprisingly, sensitization to alpha-gal, that is, the process by which human beings develop IgE antibodies to the sugar, is understood to occur after the bite of a tick[10] or parasitic infection.[11] In the United States, the Lone Star tick, an ectoparasite whose principal host is deer, is strongly implicated.[12] The proposed pathophysiology is described in Figure 1. When the sensitized human eats mammalian meat or mammalian-derived products, the antigen alpha-gal is absorbed by the GI tract bound to fat in a glycolipid, and incorporated into chylomicrons, which enter the circulation in roughly 2 hours.[13] When the antigen alpha-gal then binds to IgE antibodies present on mast cells that richly populate the GI tract, these mast cells degranulate and release their abundant supplies of histamine and other mediators. These mediators in turn can act on sensory nerve endings to cause pain on intestinal smooth muscles to cause contractions, and on mucous glands to secrete mucous.[14]

Two observational studies by GI clinicians have described patients with GI alpha-gal syndrome.[4–7] Among 16 alpha-gal IgE+ GI clinic patients in North Carolina[4] and 359 in Virginia,[5] roughly three-quarters reported symptom improvement on an alpha-

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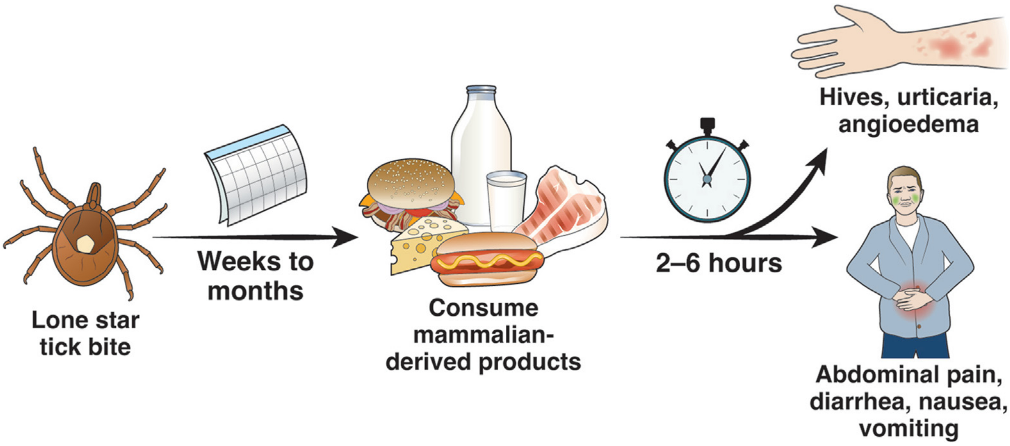

Figure 1. Sensitization and mechanism of injury in alpha-gal allergy.

gal–avoidance diet, and several patients reported reproduction of GI symptoms on self-challenge with mammalian meat.[4] In addition, isolated GI reactions have been observed in alpha-gal–allergic patients at oral food challenge. Among 91 oral food challenge–proven alpha-gal allergic patients in 2 studies,[6,7] the most common GI symptoms were abdominal pain (71% of all patients) and vomiting (22%). A significant minority (40.7%) of these patients developed GI symptoms alone.[15]

How Can Alpha-Gal Syndrome Present Clinically?

Most individuals with alpha-gal antibodies in the population are asymptomatic and tolerate mammalian meat ingestion,[16,17] but the consequences of continued mammalian meat intake among these sensitized individuals are unclear. Recent studies have suggested that this may affect the heart by driving mast cell activation in coronary arteries, leading to coronary artery disease.[18,19] The primary focus of this Clinical Practice Update Commentary are patients with alpha-gal syndrome who experience GI symptoms such as abdominal pain, vomiting, and diarrhea without skin findings, or anaphylaxis. In most cases, these patients present to primary care practices, emergency rooms, or GI practices, and the relevance of a reaction to food derived from mammals often is not recognized without the specific blood test for IgE to alpha-gal. These patients may otherwise be diagnosed with irritable bowel syndrome or other functional GI illnesses. Although a few prior studies have linked non-IgE allergies to irritable bowel syndrome,[20,21] the recognition of alpha-gal syndrome as an IgE-mediated entity that causes GI illness represents a departure from current paradigms.

Initial understanding of the significance of alpha-gal IgE started with the investigation of immediate and often severe reactions to infusion of the monoclonal antibody cetuximab in 2007. Severe infusion reactions were occurring in 1 of every 5 patients in North Carolina and Tennessee, although clinical trials before the drug's approval to treat metastatic colorectal cancer reported few reactions.[22,23] Studies first established that patients had IgE antibodies specific for cetuximab, and that those antibodies were specific for the alpha-gal oligosaccharide that heavily glycosylated the fragment antigen binding portion of the molecule. It also became clear that most of those subjects were asymptomatic upon eating mammalian meat.

A separate group of patients who presented with delayed allergic reactions (hives or anaphylaxis) to mammalian meat and who were found to have specific IgE to alpha-gal were identified.[3] These patients generally develop hives 3 to 5 hours after eating mammalian meat and many of them have a decrease in blood pressure consistent with anaphylaxis. A significant proportion of these cases also have abdominal symptoms, particularly pain. Almost all of those patients' symptoms resolve or improve with careful avoidance of mammalian meat and mammalian-derived products.

When Should Gastroenterological Clinicians Consider Alpha-Gal Syndrome in the Differential Diagnosis?

Clinicians should consider alpha-gal syndrome in the differential diagnosis of patients with unexplained GI symptoms of abdominal pain, diarrhea, nausea, and vomiting, particularly those who live or have lived in an alpha-gal–prevalent area (Figure 2). Such patients should undergo serum testing for alpha-gal IgE antibodies. Clinicians should consider not testing those with red flag symptoms such as anemia, GI bleeding, or weight loss because the allergy does not cause these symptoms. Skin symptoms such as urticaria and angioedema may or may not be present.

The US geographic area of alpha-gal syndrome mirrors the range of the tick *Amblyomma americanum*. This includes the Southeast, mid-Atlantic, the Midwest, and the East Central Census Bureau regions. The Lone Star tick is the only tick that bites human beings in the larval

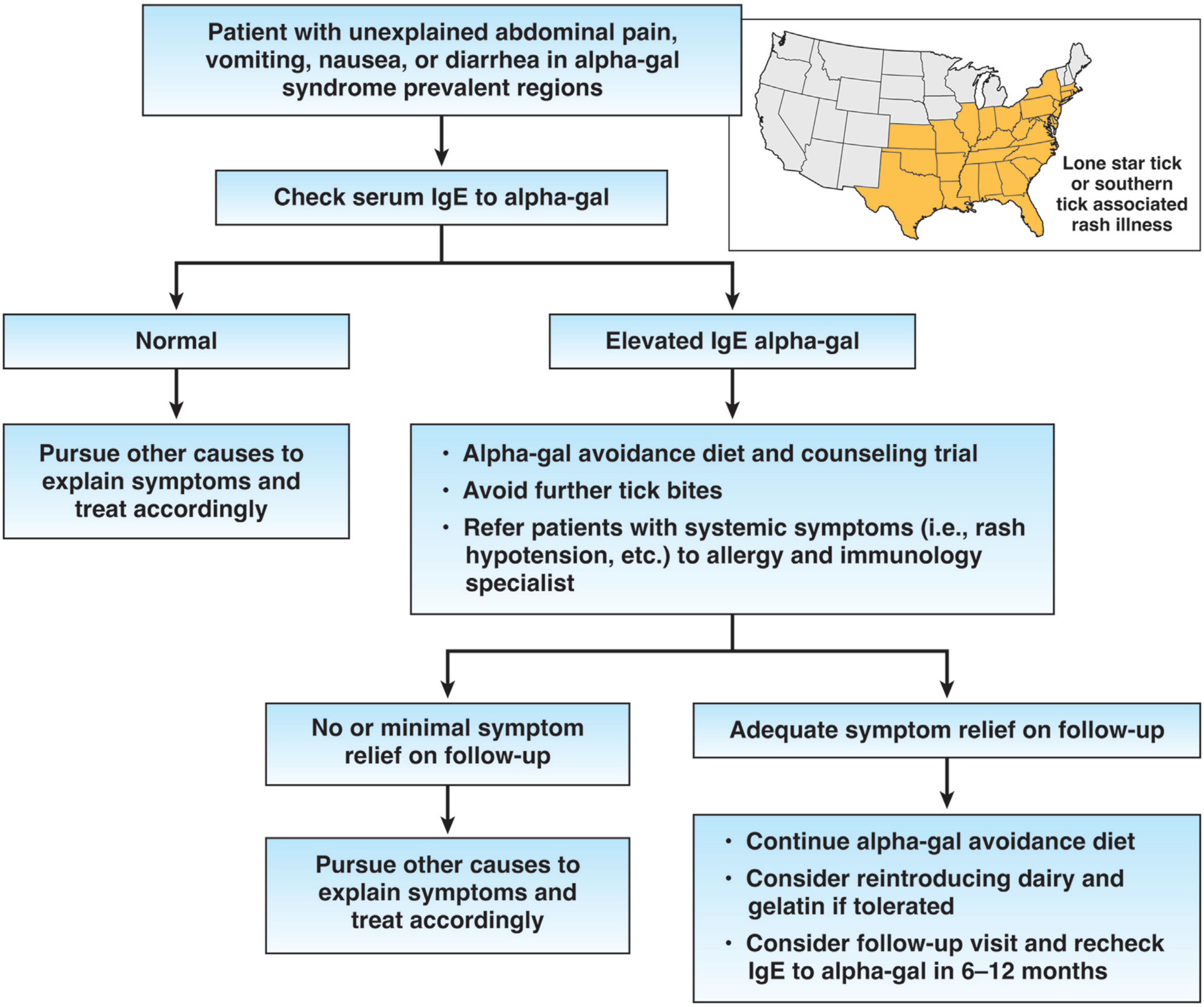

Figure 2. Suggested diagnostic and management algorithm. CDC, Centers for Disease Control and Prevention.

phase, which may be why it is the principal cause of sensitization in the United States. Internationally, alpha-gal syndrome has been reported in Australia, South Africa, Western Europe, and Japan.

The following clinical characteristics may make a diagnosis of alpha-gal syndrome more likely. A history of awakening at night from sleep with GI distress may suggest alpha-gal given the typical hours in delay from alpha-gal ingestion to reaction,[9] and patients who have a history of tick bites or enjoy outdoor pursuits are at higher risk for the allergy.

How Is Alpha-Gal Syndrome Diagnosed?

Alpha-gal syndrome is a clinical diagnosis with supporting laboratory findings. A diagnosis of alpha-gal syndrome may be made in patients with consistent symptoms and an increased alpha-gal IgE titer whose symptoms resolve or improve after adherence to an alpha-gal–avoidance diet. A positive IgE antibody to alpha-gal alone is not enough to establish the diagnosis of alpha-gal syndrome, particularly in patients with isolated GI distress, because those symptoms are common and sensitized individuals can be asymptomatic to meat ingestion. Clinicians should direct patients with increased IgE antibodies to alpha-gal and GI distress to adopt an alpha-gal–avoidance diet that eliminates mammalian meat (beef, pork, venison) and related products such as lard, dairy, and ice cream for at least a month. During this time, patients may want to avoid eating at restaurants, which can easily cross-contaminate food, and processed food, which may contain alpha-gal in additives. Patients then should be re-evaluated after the trial to determine whether symptoms have improved or persisted. It should be noted that allergies typically are diagnosed formally via oral food challenge, but the hours-long delay time to reaction and the inconsistent reactions to exposures that characterize alpha-gal syndrome make this impractical for routine care. During oral food challenges, allergists monitor patients who consume the allergen in a clinical setting and document and manage symptoms that develop.

Management of Patients Diagnosed With Alpha-Gal Syndrome

The cornerstone of managing alpha-gal syndrome is eliminating alpha-gal from the diet. Patients should be counseled to not eat pork, beef, venison, and other mammalian meat—in essence, any animal with hair, as well as products made from these mammals, such as lard, butter, milk, and others should be avoided. Dairy does contain smaller amounts of alpha-gal, particularly ice cream, cream, and cream cheese, which have a high fat content. Fish, seafood, turkey, chicken, and other fowl are acceptable for patients with alpha-gal. Gelatin is derived from the collagen in pig or cow bones. As such, foods that contain gelatin, such as marshmallows, gummy bears, gelatin candies, and desserts also may be problematic. In addition, processed foods can have small amounts of other animal-derived products, and restaurants may cross-contaminate foods with alpha-gal, which may be a problem for patients with high levels of sensitivity. Some patients have reported reactions from inhaling aerosolized alpha-gal (ie, from frying bacon or beef products).

Gastroenterologists should work with their local dieticians and increase awareness about alpha-gal syndrome before referring patients to them.

In the case of accidental exposure to alpha-gal, patients should inform someone they can rely on, take 1 or 2 diphenhydramine 25 milligram tablets, and make sure that they have access to self-injectable epinephrine, in case they have worsening symptoms, especially if there is concern for respiratory compromise.

Some acupuncture clinics advertise cures for alpha-gal, but there are no prospective controlled studies that document acupuncture as an effective treatment.

What Other Counsel Is Important Regarding Tick Bites and Medical Products?

Alpha-gal–allergic individuals should take measures to avoid further tick bites because additional tick bites may worsen the allergy.[1] Performing tick checks and showering soon after activities in woody areas, creating a barrier at the ankles by pulling up tight mesh socks over the pant cuffs on hikes, and treating clothes and boots with permethrin help reduce tick bites. Some medications and medical products contain alpha-gal, which potentially can cause reactions in sensitized or allergic individuals. Cetuximab has alpha-gal, and the early patients who had severe anaphylaxis to this infusion did not have an identified allergy to mammalian products before their reaction.[22] Pancreatic enzymes are derived from pigs and may cause problems in allergic individuals.

Regarding medical devices, serum alpha-gal IgE from allergic individuals showed strong affinity to bioprosthetic (bovine or porcine) cardiac valves, patches, and veins in vitro, but there are no long-term studies that show that this causes early device failure. There have been at least 2 reports of anaphylaxis after a bioprosthetic valve placement in alpha-gal–allergic patients.[24] Revivicor (Blacksburg, VA) develops alpha-gal–-free medical devices. They recently provided the alpha-gal–knockout pig kidneys transplanted into brain-dead human beings, who did not experience hyperacute rejection, a first for xenotransplantation.[25] Their alpha-gal–-free pork, approved by the Food and Drug Administration for human consumption, is not yet widely available.

How Should Gastrointestinal Clinicians Follow-Up Patients Diagnosed With Alpha-Gal Syndrome?

Alpha-gal syndrome is a dynamic condition. Symptoms may fluctuate over time. Patients who avoid tick bites and whose sensitization fades may be able to tolerate eating meat in the future, whereas additional tick bites can heighten sensitization and worsen reactions. If patients are able to avoid tick bites, it may be reasonable to repeat alpha-gal IgE levels 6 to 12 months after diagnosis. As the IgE level decreases or becomes negative, patients may be able to tolerate resuming first dairy, and then mammalian meat products, initially with small portions. Patients with significant systemic symptoms (itching, hives) should work with their allergist before self-challenge because of their risk for anaphylaxis. Patients who do self-challenge should take only modest doses (quarter serving of meat) of mammalian-related foods, have availability of antihistamines and autoinjectable epinephrine, and someone else present to be aware of any progressing symptoms.

When Should Gastrointestinal Clinicians Refer to Allergists?

GI clinicians should consider referring alpha-gal patients to an allergist when the patient reports skin or systemic changes such as swelling of the face or throat, voice changes, difficulty breathing, hives, or fainting with reactions. These patients are at risk for anaphylaxis and need formal counseling on the use of an epinephrine autoinjector.

We are not aware of any allergists who have established a desensitization protocol for alpha-gal syndrome. Desensitization is when patients are given increasing amounts of the allergen with the goal of promoting immune tolerance and allergy resolution.

If a Patient Eats Red Meat and Tolerates It, Can They Still Be Alpha-Gal Allergic?

Importantly, a sensitized individual who is able to eat mammalian meat at one time point and have no reaction afterward still may have the allergy because alpha-gal allergic reactions often do not happen after every exposure. Fatter cuts of meat as well as co-factors such as nonsteroidal anti-inflammatory drugs, exercise, and alcohol can increase the risk as well as the severity of reactions for unclear reasons.[26]

Are There Consequences for Asymptomatic People With Alpha-Gal Sensitization?

Some research has suggested that alpha-gal sensitization (alpha-gal IgE+ antibodies) may be largely asymptomatic, while other research has indicated that sensitization can have adverse cardiovascular effects.

Regarding asymptomatic sensitization, in a German study that evaluated alpha-gal IgE antibodies, symptoms, and mammalian meat intake in a group of hunters and forest workers, seroprevalence was high at 35% (n = 105 of 300), and only 5 sensitized participants had alpha-gal syndrome, with the rest endorsing tolerance to eating mammalian meat and organs. Similarly, in a study that performed alpha-gal IgE titers on biobanked serum from 403 screening colonoscopy patients in North Carolina, serum positivity was common at 31% and was not associated with decreased mammalian meat intake or higher rates of abdominal pain or diarrhea.[17]

However, sensitized individuals who continue to eat mammalian meat may increase their risk of coronary artery disease. In 2018, a significant association between alpha-gal antibodies and the presence and severity of arteriosclerotic plaques in the left main coronary artery were found among 118 patients who underwent intravascular coronary artery ultrasound.[19] Most recently, in an Australian study, alpha-gal sensitization was associated with coronary artery disease burden—both noncalcified plaque and obstructive coronary artery disease—among 1056 patients referred for computed tomography coronary angiography.[18]

What Should Be the Goals of Future Research on Gastrointestinal Alpha-Gal Syndrome?

Prospective studies that focus on patients with GI alpha-gal syndrome do not exist currently. Blinded oral food challenges with alpha-gal–free or wild-type pork should help us better understand the symptom course and immune response after alpha-gal ingestion in sensitized patients with GI symptoms. Future prospective studies can better inform us on GI alpha-gal syndrome's clinical characteristics, how quickly patients can expect symptom response after adopting an alpha-gal–avoidance diet, and characteristics that predict symptom improvement on the diet. Large database studies could shed light on the possible health consequences of asymptomatic sensitization.

Take-Home Messages

Gastroenterology clinicians should be aware of the diagnosis and management of alpha-gal syndrome because a subset of alpha-gal allergic patients show GI symptoms such as abdominal pain, diarrhea, nausea, or vomiting without skin changes or anaphylaxis. The diagnosis of alpha-gal syndrome can be made among patients with GI distress and increased serum alpha-gal IgE antibodies whose symptoms are relieved adequately on an alpha-gal–avoidance diet that eliminates pork, beef, and mammalian-derived products. Patients with suspected alpha-gal allergy should be counseled on an alpha-gal–avoidance diet because that is the primary management. Counseling also should include measures to avoid tick bites because further bites can drive alpha-gal IgE titers higher and worsen the allergy. Patients who also have reactions such as facial swelling, urticaria, and respiratory difficulty should be referred to allergists. GI alpha-gal syndrome recently was described, and prospective studies are needed to better understand this condition.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://10.1016/j.cgh.2022.12.035.

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