

**A Physician's
Reference Manual**

**ALPHA-GAL SYNDROME
IN MASSACHUSETTS**

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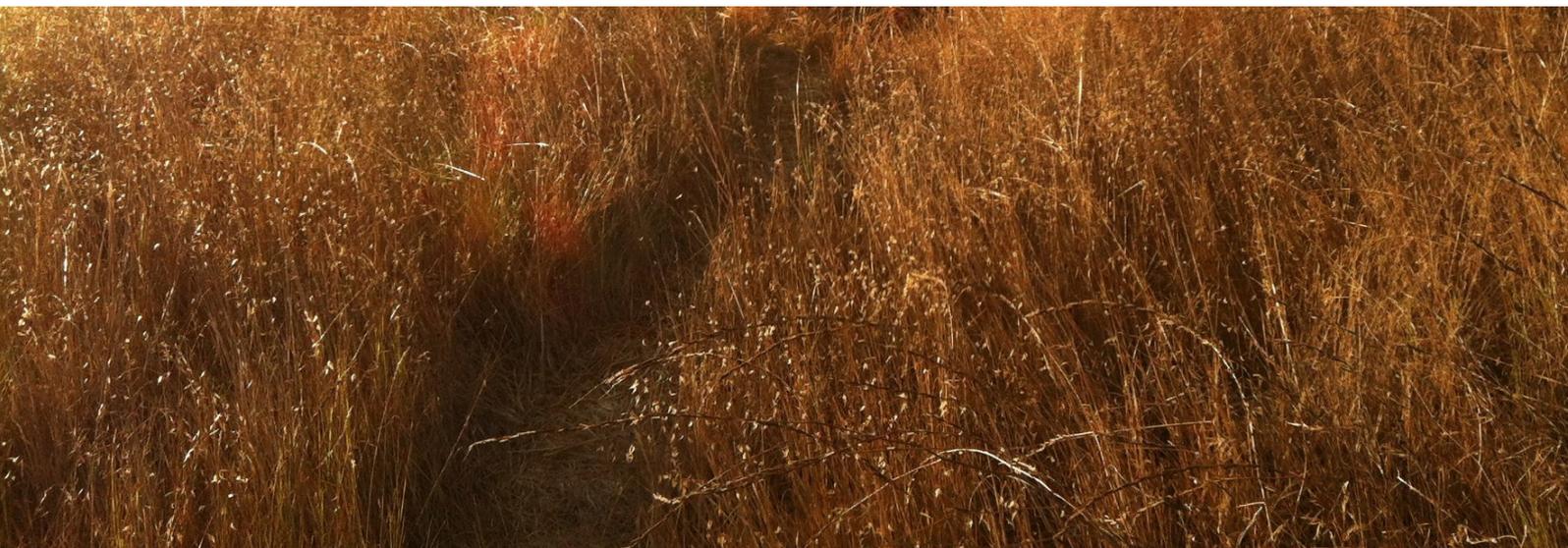


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Alpha-Gal Syndrome

Alpha-gal syndrome (AGS) is a novel tick-borne illness that is rapidly emerging throughout the world. Since its formal recognition within the medical community in 2009, the condition has become a prominent concern among experts in the field of public health. In the United States, AGS is most common in southeastern states. However, the presence of AGS is quickly moving up the east coast and into New England. There is little existing literature on AGS, and rates of diagnosis are relatively low due to a lack of awareness among physicians.

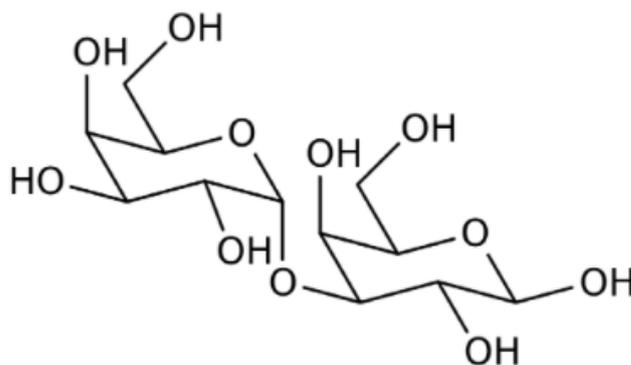
This handbook provides a comprehensive framework for understanding and identifying AGS. It is designed to educate health care professionals and spread awareness about the condition throughout Massachusetts.



Alpha-Gal

Galactose- α -1,3-galactose (alpha-gal or α -gal) is an oligosaccharide sugar found in most mammals. It is extremely active in nonprimate mammals, prosimians, and New World monkeys. The epitope is entirely inactive in Old World primates, including humans. Humans have evolved to produce high counts of a natural antibody to combat α -gal, referred to as anti-Gal. Anti-Gal makes up 1% of circulating immunoglobulins and easily binds to α -gal epitopes.

Certain tick bites induce high levels of anti-IgE antibodies against α -gal that is present on tick salivary glycoproteins and tissues of deer. Once a tick attaches onto a mammalian host (i.e., deer), feeds on its blood, and transfers to a second host, a human, they introduce α -gal to the body. This may result in the activation of a novel IgE antibody response to combat the seemingly parasitic epitope and cause a range of allergic reactions.



SOURCES OF ALPHA-GAL

- Mammalian meats
- Internal organs of mammals
- Mammalian gut sausage casings
- Mammalian fat
- Bones and bone marrow
- Testicles
- Mammalian collagen
- Meat broth, bouillon, and stock
- Gravy
- Mammalian blood
- Meat extracts
- All mammalian body parts, organs, tissues, cells, and fluids
- Natural flavors or flavorings
- Mammalian byproducts
- Cross-contamination
- Medications, vaccines, medical devices, and other medical products
- Personal care and household products containing mammal-derived ingredients
 - Many cleaning products
 - Cosmetic products
- Carrageenan
- Flounder eggs
- Rennet
- Dairy products
- Gelatin and foods containing gelatin

The Lone Star Tick

The lone star tick, *A. americanum*, is suspected to be the primary transmitter of AGS in the United States. Researchers suggest that other tick species or vectors may also play a role in α -Gal sensitization due to the existence of case clusters in areas outside of *A. americanum*'s usual habitat. A few other tick species are implicated in causing AGS throughout the world, including *Ixodes ricinus*, *Ixodes holocyclus*, and *Haemaphysalis longicornis*. For the purpose of providing evidence-based information for Massachusetts providers, this handbook will primarily focus on the lone star tick.

The effects of climate change may rapidly expand the geographic distribution of tick vectors, including *A. americanum*, in the near future. Additionally, warmer temperatures may accelerate the tick's life cycle, which heightens their prevalence and frequency of seasonal questing ventures.

HABITAT

Lone star ticks are found throughout the eastern, southeastern and south-central states. They generally live in grassy or second growth woodland habitats that have populations of white-tailed deer. They are attracted to the body heat and carbon dioxide produced by humans. Lone star ticks actively travel to their host, unlike most ticks that wait to transfer to potential hosts only when one brushes directly against them.

REACTION TO BITE

Once a human is bitten by *A. americanum*, they will normally develop an itchy spot or bump. Responses to salivary components of lone star ticks may cause itching and redness around the bite that may last for two weeks or more.

The lone star tick does not transmit Lyme disease.

History of AGS

~2000 : 2 or more groups report meat allergy cases after tick bite



2004 : New cancer drug cetuximab comes on the market. As more people become exposed to the drug, more hypersensitive reactions occur. In NC and Tennessee, 25 out of 88 patients become hypersensitive immediately. These reactions range from breakouts in hives to ER visits resulting in death (1 case Bentonville, Alabama).



2006 - 2008 : Dr. Thomas Platts-Mills of UVA's allergy center hears of deadly allergic reaction in Alabama. He and his team test allergy sensitive cancer patients for antibodies that could produce hypersensitivity. They are able to discover the cause of reactions; high levels of IgE antibodies in patients are due to the presence of the carb alpha gal.

➔ Patients in southeastern states are experiencing the most severe allergic reactions, which leads to further study of why these specific places are most affected. Platts-Mills' team analyzes a CDC map of Rocky Mountain spotted fever prevalence that precisely overlaps the hot spots of the cetuximab reactions. Researchers begin to hypothesize that there is a link between alpha-gal and tick-borne illness.



2008 - 2010 : As the specificity of the IgE antibodies to alpha gal that caused reactions to cetuximab became clearer, the number of reports describing delayed reactions to red meat is also increasing. Previous research performed in Australia suggests that there was a relationship between red meat allergy and tick bites, but it is yet to be discovered in the United States. Patients begin arriving at Platts-Mill's clinic with symptoms similar to those of the cancer patients. Their blood tests also show high levels of IgE antibodies to alpha-gal. Many of the clinic patients state that they believe their reactions start after eating meat, and they also note that they had recently been bitten by a tick.



2009 - Present : Cases are steadily increasing in the United States and the condition is generally unexplored in the research community.

Burden

- The prevalence of AGS continues to rise throughout the United States. The lone star tick population is rapidly expanding and reaching new territories.
- In 2019, over 34,000 cases had been identified in the country. This number is up from 12 diagnoses in 2009.
- The highest burden of AGS occurs in rural and suburban neighborhoods throughout the southeastern states.
- Between 15-35% of the population may be sensitized to α -Gal in high-exposure communities.

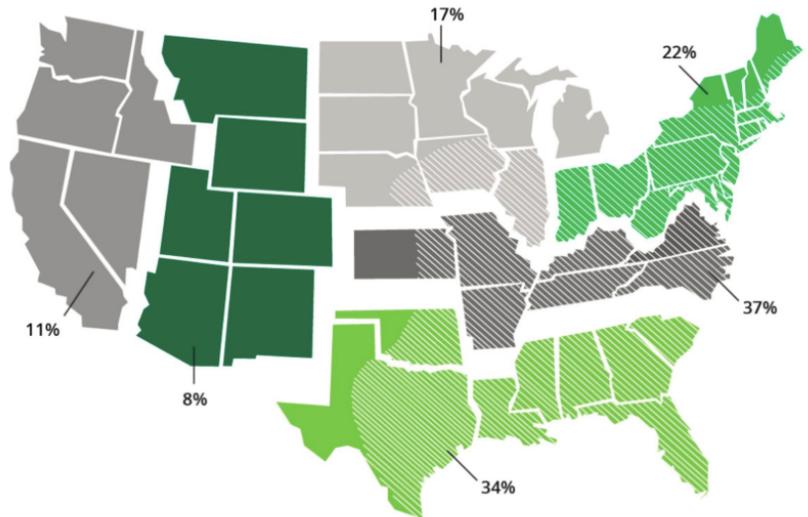


Figure 1. Surveillance for IgE against alpha-gal Percent positive rates are presented for IgE against alpha-gal within each of six regions in the United States, 2012-2013 (7300 samples). The shaded white lines on the map illustrate the known habitat of the Lone Star tick. (DATA AND MAP FROM OLAFSON, 2015)

ANAPHYLAXIS

AGS is the primary source of adult-onset allergy and anaphylaxis among southeast and eastern states.

A vast majority of AGS patients who have clinical AGS with anaphylactic reactions are undiagnosed or misdiagnosed.

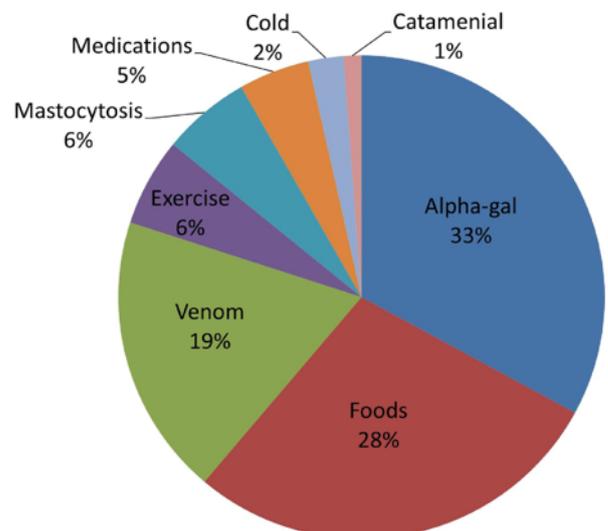


Figure 2. Etiologies of anaphylaxis Data is based on a sample of 85 clinic patients who experienced anaphylaxis with a definitive cause of reaction. This study was performed at a private Tennessee allergy and immunology clinic from 2006-2016. (DATA AND GRAPH FROM PATTANAIAK, 2018)

Tick Identification

Lone Star Tick

Amblyomma americanum

Diseases

Ehrlichiosis, Tularemia, Alpha-gal Syndrome

What bites

Nymph and adult females

When

April through September in New England, year-round in southern U.S.

Coloring

Adult females: brown body, white spot on hood

Nymph: Light brown body, no white spot

Size

Nymph: Poppy seed

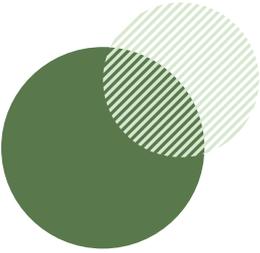
Unfed Adults: Sesame seed



Adult Female Lone Star Tick (CDC PHOTO)



(CDC PHOTO)



Prevention

MA providers should be aware of effective practices known to prevent AGS. Relaying this information to patients who spend time outdoors could reduce an individual's risk of contracting AGS.

Gear Up: Individuals should cover their skin when going outdoors. Wear shoes, long pants tucked into socks, a long-sleeved shirt, a hat, and gloves in grassy or wooded areas. Light-colored, protective clothing makes tick identification easier. Make sure to stick to marked trails and avoid walking through low shrubbery and tall grass.

Insect repellent: Apply insect repellent containing DEET, picaridin, IR3535, Oil of Lemon Eucalyptus (OLE), para-menthane-diol (PMD), or 2-undecanone to exposed skin. . Recommend purchasing products with 0.5% permethrin to apply to clothing and gear, or buy pre-treated products. Parents should apply repellent to their children and make sure to avoid their hands, eyes and mouths. Products containing OLE or PMD should not be used on children under 3 years old. Remind patients that chemical repellents may be toxic when misused, so follow directions carefully. Suggest using the EPA Insect Repellent Search Tool to choose the right product and meet the patient's needs.

➔ www.epa.gov/insect-repellents/find-repellent-right-you

Pets: Keep pets on a leash when walking in grassy or wooded environments. Make sure to check them for ticks after being outdoors. Pet-safe tick repellent is commercially available.

Tick-Proof Yards: Suggest the regular removal of brush and leaves from yards. Keep woodpiles in sunny areas.

After Being Outdoors: Make sure patients perform full body checks on themselves, children, and pets after coming indoors, especially after entering wooded or grassy areas. Pay special attention to the back of the knees, inside the bellybutton, in and around the ears and hair, between the legs, under the arms, and around the waist. Showering and using a washcloth immediately may help to remove unattached ticks.

Proper Removal: It is crucial to remove ticks as soon as possible. Patients should use tweezers to gently grasp the tick close to its head or mouth. Be sure to pull cautiously and steadily - do NOT squeeze or crush the tick. After removal, dispose of the tick and apply antiseptic to the bite.

Symptoms

COMMON SYMPTOMS

SKIN

- Pruritus
 - ➔ Itching of the palms and soles of feet are common initial symptoms of a reaction
- Urticaria
- Erythema

GASTROINTESTINAL

- Abdominal pain and cramping
- Nausea
- Vomiting
- Diarrhea
- Heartburn

ANAPHYLAXIS

- Anaphylaxis is a life-threatening condition involving a range of symptoms
- See FARE guide to anaphylaxis for information about symptoms
 - ➔ www.foodallergy.org/our-initiatives/education-programs-training/fare-training/recognizing-responding-anaphylaxis

CARDIOVASCULAR

- Hypotension
- Light-headedness / dizziness
- Weak and rapid pulse
- Pre-syncope
- Syncope
- Shock
- Refer to FARE guide for additional cardiovascular symptoms

RESPIRATORY

- Shortness of breath
- Wheezing
- Chest tightness
- Cough
- Hoarseness
- Dyspnea
- Refer to FARE guide for additional respiratory symptoms

ANGIOEDEMA

- Particularly palms and soles of feet

LESS COMMON SYMPTOMS

- Arthritis/joint pain
- Chronic pruritus
- Symptoms consistent with Mast Cell Syndrome
- Uterine cramping
- Fibromyalgia (anecdotal)
- Migraine (anecdotal)

RARE SYMPTOMS

- Exfoliative erythroderma
- Temporary loss of vision
- Other rashes, including urticarial vasculitis, serpiginous urticarial rash, purpuric rash, psoriasiform rash, nummular eczema, and subcutaneous nodules
- Oral lichen planus and other mouth sores (anecdotal)
- <1% patients report itching or swelling of the mouth or tongue

Symptoms (Cont.)

AGS is characterized by both inter-individual and intra-individual variability. Not all individuals who contract AGS are symptomatic. Patients who are symptomatic may experience a range of different reactions from one occasion to the next, regardless of the amount of mammalian product consumed.

The titer of α -gal specific IgE is not strongly associated with the severity of symptoms.

RISK FACTORS

- Spend time outdoors
- Have received multiple Lone Star tick bites
- Have a mast cell abnormality such as indolent systemic mastocytosis

CO-FACTORS

→ Exogenous and endogenous conditions that lower a patient's reactivity threshold

- Exercise
- Alcohol Consumption
- The use of certain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDS)
- Illness
- Menstrual cycle
- Stress
- Lack of sleep

REACTION PERIOD

DELAYED ONSET REACTIONS

Allergic reactions to α -gal usually occur between 3-8 hours after consuming a mammalian product. It is hypothesized that the lengthy process of metabolizing the glycolipid form of α -gal may contribute to this delayed response.

- **Late-night anaphylaxis common**

RAPID ONSET REACTIONS

- Reactions to drugs, vaccines, and other medical products
 - Infusions of drugs (i.e., cetuximab)
 - Infusions or injections of medical products containing gelatin
- Reactions to airborne alpha-gal, such as meat fumes - occur immediately
- Reactions to topical exposures (i.e., lotions and bandage adhesives)
- Reactions to dairy products and carrageenan

Diagnosis

DIAGNOSTIC CONSIDERATIONS

A clinical diagnosis of AGS should be considered if a patient:

- Has onset of symptoms in adult life after consuming mammalian products without issues for an extended period of time
- Experiences one or a combination of recognized symptoms
- Reactions occur immediately after or, more commonly, 3-8 hours after consuming mammalian products
- Has positive specific IgE for α -Gal
- Clinical response to avoidance of mammalian products

DIAGNOSTIC QUESTIONS

Understanding an individual's symptoms and history is critical for accurately diagnosing AGS. These are guiding questions to ask a patient:

- When did you begin noticing symptoms?
- What type of mammalian product did you consume and how much did you eat before symptoms appeared?
- After consuming the mammalian product, how long did it take for symptoms to appear?
- Are you currently spending time or have you in the past spent time outdoors in wooded or grassy areas?
- Do you have a history of tick bites?
 - How many times?
 - What did these ticks look like?
- Did you take any over-the-counter allergy medications to manage symptoms, such as antihistamines?
 - Did they help?
- How severe are your symptoms?
- What, if anything, seems to improve your symptoms?
- What, if anything, appears to worsen your symptoms?

Testing

TESTING METHODS

Prick tests using beef or pork extracts are unreliable for diagnosing AGS

BLOOD TEST

- IgE specific test for α -Gal
- Diagnosis is probable if the antibodies are greater than or equal to 1 IU/mL or more than 1% of the total IgE.
- Recommended diagnostic method

SKIN TESTS

- Intradermal skin tests to beef, pork, and milk
- Less common diagnostic method

TEST CODES

ALPHA-GAL IgE BLOOD TEST

- Quest Alpha-gal IgE Test Code: 95241
- Labcorp Alpha-gal IgE Test Code: 806562

ALPHA-GAL PANNEL

Experts do *not* recommend the routine use of this test for AGS diagnosis. In rare cases, the additional tests can be helpful for ruling out other diagnoses.

- Quest Alpha-gal Panel Test Code: 91380
- Labcorp Alpha-gal Panel Test Code: 807003

INCORRECT TESTING CODES

These codes are for diagnosing Fabry disease

- Alpha-galactosidase
- Alpha-galactosidase A deficiency

Testing for AGS is not advised for patients who have recently received a tick bite and are asymptomatic.

A patient's IgE level does not determine their sensitivity to α -Gal.

Management

There is currently no treatment for AGS. Remission may be possible using these management recommendations established by experts.

AVOID TICK BITES

- After an AGS diagnosis, additional tick bites can maintain or lead to increases in the patient's titer of IgE to α -Gal.
- Patients who avoid tick bites will eventually experience a decrease in the severity of reactions to α -Gal and evading may result in regaining tolerance to mammalian products.
- Taking preventative measures is critical for avoiding future tick bites.

AVOID MAMMALIAN PRODUCTS

- Mammalian products, especially red meat, should be completely avoided for new AGS diagnoses.
- Patients should be educated on the potential dangers linked to consuming these products, including possible sensitization to dairy or certain immunizations.

SYMPTOM MANAGEMENT

AGS symptoms should be managed and treated as an allergy.

- Antihistamines, steroids or other management regimens may be recommended
- Most patients should be prescribed an epinephrine autoinjector upon diagnosis
- Alternative approaches may lessen symptoms
 - Auricular acupuncture and kinesiology

Medications to Avoid

KNOWN TO TRIGGER ALLERGIC REACTION

- Cetuximab
- Intravenous colloids
- Certain vaccinations
- Animal derived prosthetic heart valves
- Anti-venom
- Heart patches
- Collagen scaffolding
- All gelatin and mammalian derived medical products
- Heparin

THYROID HORMONE FORMULATIONS AND POTENTIAL INGREDIENTS THAT MAY CONTAIN ANIMAL BYPRODUCTS

Thyroid hormone formulations	Company name	Potential source of animal byproduct
Synthroid™	AbbVie	Magnesium stearate, lactose monohydrate
Levothyroxine (authorized generic)	Bryant Ranch Prepack	Magnesium stearate
Levoxyl™	Pfizer	Magnesium stearate
Levothroid™	Physicians Total Care	Magnesium stearate
Euthyrox™	Provell Pharmaceuticals	Magnesium stearate, gelatin
Tirosint™	IBSA Pharma	Gelatin
Liothyronine sodium (authorized generic)	Greenstone	Gelatin
Cytomel™	Pfizer	Gelatin
Triostat™*	Par Pharmaceutical	Animal thyroid extract
Thyrolar™	Allergan	Magnesium stearate and gelatin
Armour thyroid™	Allergan	Animal thyroid extract
Nature-Throid™	RLC Labs	Animal thyroid extract, magnesium stearate, lactose monohydrate

*Strictly parenteral option

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Additional Resources



FOR MORE INFORMATION ON ALPHA-GAL SYNDROME:

Centers for Disease Control and Prevention

www.cdc.gov/ticks/alpha-gal/

Alpha-gal Information (AGI)

www.alphagalinformation.org

TO REPORT A CASE OF ALPHA-GAL SYNDROME:

Massachusetts Department of Public Health

Office of Integrated Surveillance and Informatics Services

617-983-6801

OTHER RESOURCES:

Continuing Medical Education for Clinicians

www.emergency.cdc.gov/coca/

The Clinician Outreach and Communication Activity (COCA) course taught by the CDC aims to educate providers on proper identification and management of tick-borne diseases, including AGS.

