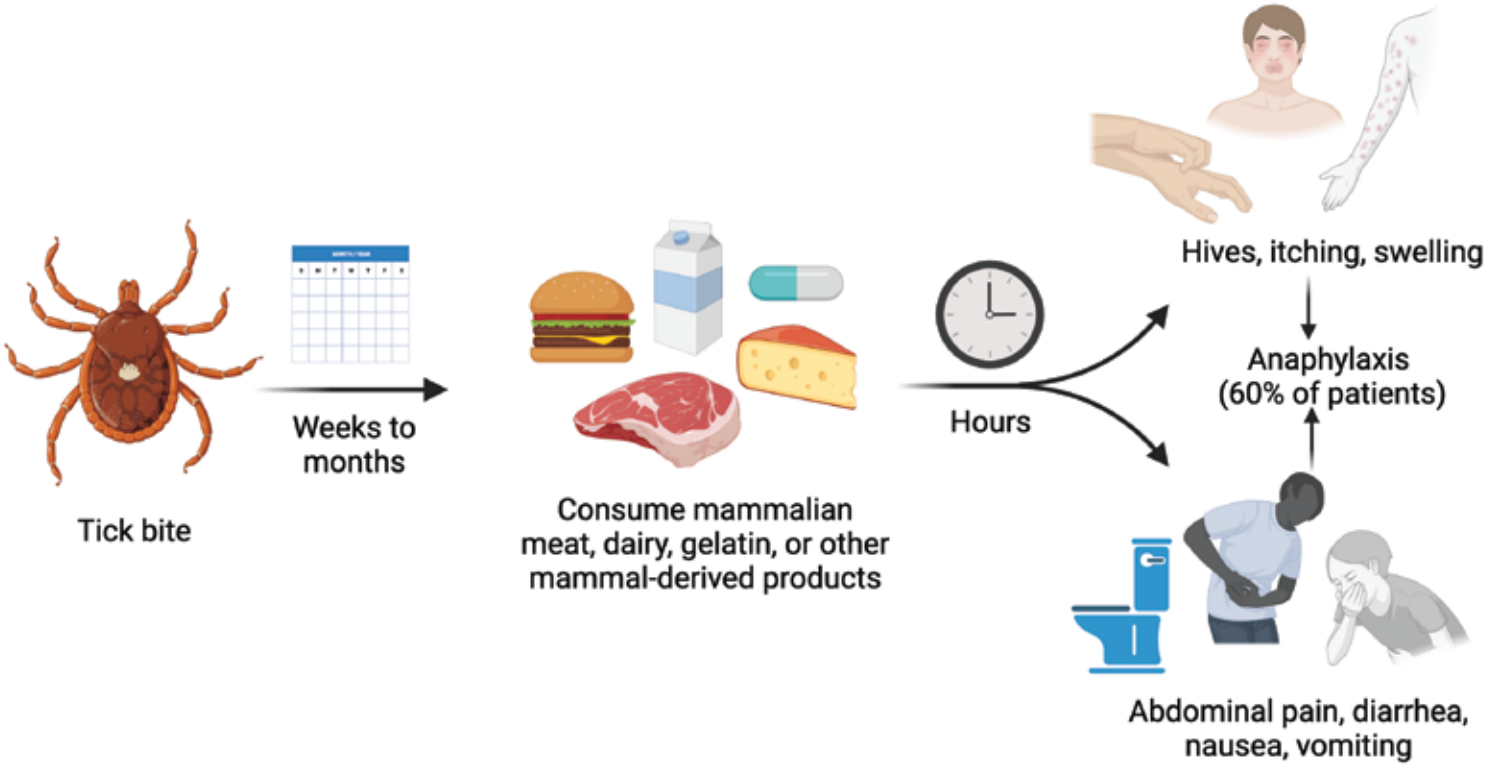
ALPHA-GAL SYNDROME:
A Growing Public Health Crisis



Adapted in part from McGill SK, Hashash JG, Platts-Mills TA. AGA Clinical Practice Update on Alpha-Gal Syndrome for the GI Clinician: Commentary. *Clin Gastroenterol Hepatol.*

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ALPHA-GAL SYNDROME

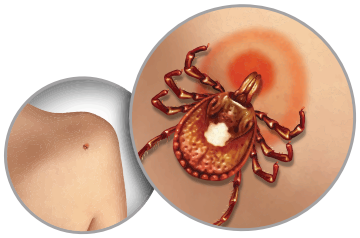
Alpha-gal syndrome (AGS) is an emerging tick bite-associated allergy to alpha-gal (galactose-α-1,3-galactose), a sugar molecule found in most mammals and products derived from them. These products include foods, drugs, medical devices, personal care products, and others. Up to 450,000 Americans are estimated to be affected by AGS, making it the 10th most common food allergy in the U.S.

> *"If testing trends continue, and the geographic range of the lone star tick continues to expand, the number of AGS cases in the United States is predicted to increase during the coming years, presenting a critical need for synergistic public health activities including 1) community education targeting tick bite prevention to reduce the risk for acquiring AGS, 2) HCP education to improve timely diagnosis and management, and 3) improved surveillance to aid public health decision-making.[1]"*

MORE THAN RED MEAT
Examples of products that contain alpha-gal:
- **Mammalian meats and organs (beef, pork, lamb, etc.)**
- **Milk and dairy products**
- **Gelatin/collagen**
- **Hundreds of mammalian byproducts**
- **Carrageenan**
- **Thousands of drugs and medical devices**
- **Many personal care and household products**

A TICK-BORNE CONDITION

Alpha-gal syndrome develops after tick bites. In the United States, most cases are associated with lone star ticks.



AN UNUSUAL ALLERGY

Alpha-gal syndrome has many atypical features which make diagnosis and management difficult.

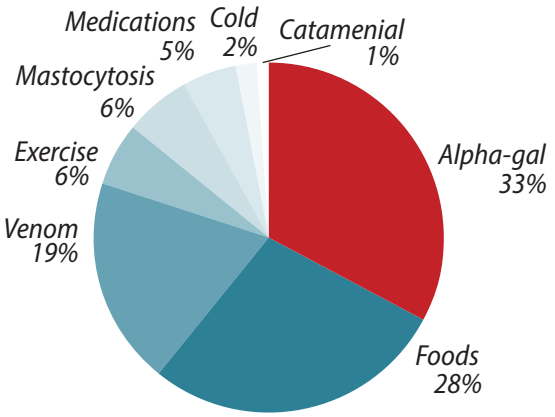
ATYPICAL FEATURES

- **Carbohydrate allergy**
- **In fats as well as proteins**
- **Delayed reactions, often late at night.**
- **Inconsistent reactions**
- **Can present like IBS or arthritis, without classic, allergic symptoms**
- **Develops weeks or months after a tick bite, not immediately**
- **Reactions wax and wane based on tick bite exposure**

A LEADING CAUSE OF ANAPHYLAXIS

Up to 75% of people with AGS have life-threatening anaphylactic reactions, an even higher percentage than peanut allergy. In high-prevalence areas, alpha-gal reactions can be the number one cause of anaphylaxis in adults, causing more adult anaphylaxis than all other food allergies combined. A number of fatalities have occurred.

> *"...this report demonstrates that AGS is both a severe allergy, with nearly 75% of patients meeting criteria for anaphylaxis, and also distinct from other food allergies in its symptom profile.[2]"*



Source: Pattanaik D, Lieberman P, Lieberman J, Pongdee T, Keene AT. The changing face of anaphylaxis in adults and adolescents. Ann Allergy Asthma Immunol. 2018;121(5):594-597.

Figure 1. Etiologies of anaphylaxis based on proposed "definitive cause." Alpha-gal, galactose-a-1,3-galactose

AN EMERGING EPIDEMIC

Environmental changes and growing white-tailed deer populations are driving increases in lone star tick populations and the expansion of their geographic range. While lone star ticks were once confined to the Southeast, they are now found as far west as Colorado and Wyoming and as far north as Maine. Consequently, AGS cases are surging. However, in the absence of national surveillance, the true extent of AGS is unknown.

> *"AGS is a growing clinical and public health concern for persons in the United States, yet in the absence of a national surveillance system, the prevalence of this condition is largely unknown.[3]"*

Estimated cases of AGS, 2009-2022

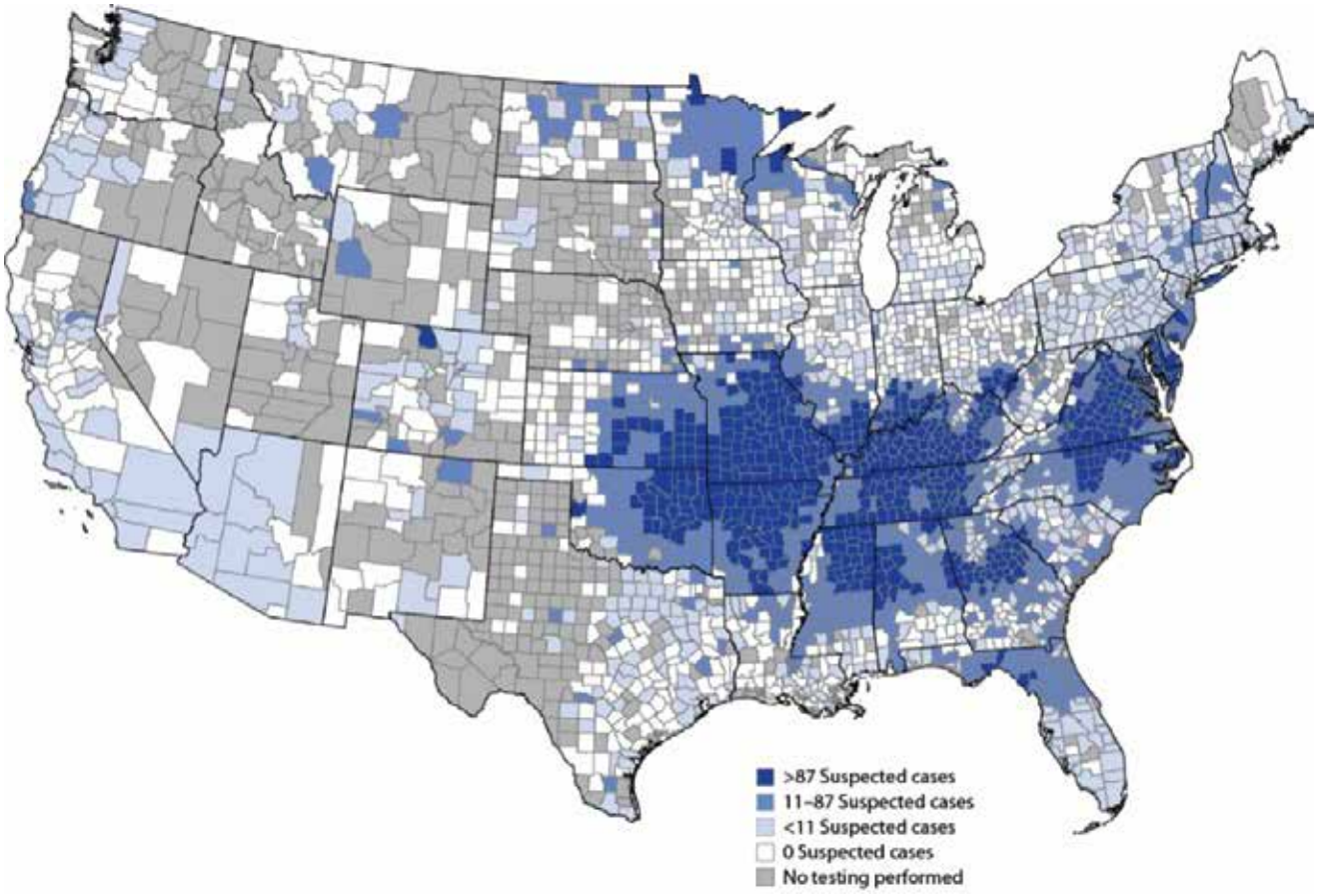
WHO IS AT RISK?

People whose occupations and hobbies expose them to ticks are at high risk of developing AGS. Those at highest risk include military personnel, park rangers, farmers and ranchers, agricultural laborers, hunters, gardeners, and hikers. Children who participate in scouts, 4-H, and other outdoor activities are also at elevated risk.




Alpha-gal syndrome is most common in the southern, midwestern, and mid-Atlantic United States, where up to 3% of the population can be affected. However, AGS impacts people in all 50 states. A study of military recruits found that 8% of recruits from Hawaii and 17% of Alaskan recruits tested positive for alpha-gal IgE, showing that AGS is more widespread in the U.S. than previously believed.

Rural areas are most impacted. People living in rural areas are up to 20 times more likely to develop AGS.



AN URGENT NEED FOR HEALTHCARE PROVIDER EDUCATION

Up to 78% of healthcare providers (HCPs) have little to no knowledge of AGS. As a result, AGS is significantly underdiagnosed and misdiagnosed. On average, it takes more than 7 years for a patient with AGS to be diagnosed. During this long time interval, people affected by AGS often experience debilitating symptoms. On average, more than half require emergency department-based treatment, 7% require multiple hospitalizations, and many are subjected to unnecessary, invasive procedures and surgeries, at a high cost to our healthcare system and to the affected individuals.

> *"Increased HCP education and awareness of AGS are needed to hasten and improve the accuracy of AGS diagnoses, patient care, and the understanding of the epidemiology of this emerging condition.* [4] *"*

UNIQUE CHALLENGES

Alpha-gal syndrome is a uniquely challenging allergy due to the severity of alpha-gal reactions and the ubiquitous presence of mammal-derived byproducts in foods, drugs, and other products.

> *"Due to the ubiquitous inclusion of mammal-derived materials in foods, medications, personal products and stabilizing compounds, full avoidance is difficult to achieve.*
>
> *As with management for any food allergy, AGS management is based on allergen avoidance. For patients with AGS, however, this tenet of self-protection is made difficult by the lack of adequate labeling for mammalian-derived sources in foods, medications, and vaccines.*[5] *"*

There are hundreds of mammalian byproducts with obscure names. No comprehensive list of these ingredients exists. In the absence of laws requiring that mammalian byproducts be disclosed on labels, it is virtually impossible to determine which products contain them.

EXAMPLES OF MAMMALIAN BYPRODUCTS

Acetylmethionyl Methylsilanol Elastinate
Allantoin
C12-15 Pareth-9 Hydrogenated Tallowate
Calfactant
Chymotrypsin
Copper Acetyl Tyrosinate Methylsilanol
Dihydrogenated Tallow Benzylmonium Chloride
Elastin
Erythropoietin
Glucagon
Glyceryl tristearate
Laneth
Oleic acid
Pepsin
Quaternium-18
Rennet
Sodium chondroitin sulfate
Stearic acid
Thyrotropin Alfa

A DRUG ALLERGY

Unlike other food allergens, alpha-gal is also a major drug allergen and a top cause of surgery- and drug-related anaphylaxis. Some alpha-gal-containing drugs and medical products are even more dangerous for people with AGS than mammalian meat. Numerous life-threatening reactions and a number of fatalities due to alpha-gal reactions to medical products have been documented.

> *"Mammalian-derived by-products are common in medications and devices, both as active and inactive ingredients. This poses a potential safety risk during receipt of healthcare services.*
>
> *Inactive ingredients such as magnesium stearate, glycerin and gelatin may be made from animal, plant or synthetic sources. Sources for inactive ingredients may vary by the manufacturer lot number (identifier assigned to a batch of medications during the manufacturing process) since companies are not obligated to report the source to any agency. If there is no known safe alternative, the manufacturer should be contacted and asked if the source (animal vs synthetic) is known. Unfortunately, many companies do not have this information easily available and may not be able to supply this information for several days.[7]"*

More than 230,000 drugs in the DailyMed database (over 64%) contain active or inactive ingredients that are either mammal-derived or potentially mammal-derived. Numerous other medical products, including many used during surgery, also contain alpha-gal.

> *"Because patients with AGS can display symptoms after exposure to not just meat, but also medications and inactive ingredients derived from animals, there is a potential risk for unintentional intraoperative exposure.*
>
> *Every medication used in an AGS patient in the entire perioperative period must be screened in order to limit exposure to mammalian products.[6]"*

Examples of drugs and medical devices that can contain mammal-derived ingredients

- **Many prescription and OTC drugs**
- **Gelcaps/drugs in gelatin capsules**
- **Monoclonal antibodies, like cetuximab and infliximab**
- **Thyroid medication**
- **Pancreatic enzyme replacements**
- **Some vaccines, like MMR**
- **Anti-venom**
- **Heparin**
- **Surgical mesh**
- **Bioprosthetic heart valves**
- **Suppositories and vaginal capsules**
- **Topical products**
- **Extracellular matrix**
- **Heart patches**
- **Surgical mesh**
- **Hemostatic agents/sponges**
- **Plasma volume expanders**
- **Suture**
- **Lubricants**
- **Viscosurgical devices**
- **Thrombin glues**

BEYOND ALLERGY

Alpha-gal allergy is only one dimension of a complex immune response that may have other health implications. In high-prevalence areas, 20% or more of the population can be sensitized to alpha-gal. Not all of these people have obvious, allergic reactions to alpha-gal, but research suggests that they may be at increased risk of cardiovascular disease. Other conditions that have been tentatively linked to the alpha-gal immune response include some autoimmune diseases, Alzheimer's disease, and arthritis. AGS is also associated with the onset of mast cell syndromes.

> *"We are beginning to recognize that alpha-gal food allergy is the tip of the iceberg for this immune response.[8]"*

> *"Alpha-gal sensitization is independently associated with noncalcified plaque burden and obstructive CAD and occurs at higher frequency in patients with STEMI than those with stable or no CAD. These findings may have implications for individuals exposed to ticks, as well as public health policy.[9]"*

RESEARCH POTENTIAL

Alpha-gal syndrome is a paradigm-shifting allergic syndrome. Although it was only first described in 2009, AGS has already radically revised our understanding of both the pathogenesis of allergy and its implications. As the only allergy for which a definitive cause (tick bites) has been established, AGS offers a unique lens through which to study the cellular and molecular mechanisms that drive allergy. Research on the natural history of AGS is needed both to elucidate its novel features and to broaden our understanding of allergic response in general.

> *"Although there are many ways that a-Gal could be considered to "break the rules," investigation into this unusual allergen is likely to reveal novel insights into the causes and consequences of all allergic diseases.[10]"*

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For more references: www.alphagalaction.org

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