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Climate Change: Ticks, Food Allergies – What's the Connection and why should I Care?

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Improving People's Lives
through innovations in personalized health care



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Why are allergists so concerned about ticks



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Disclosures

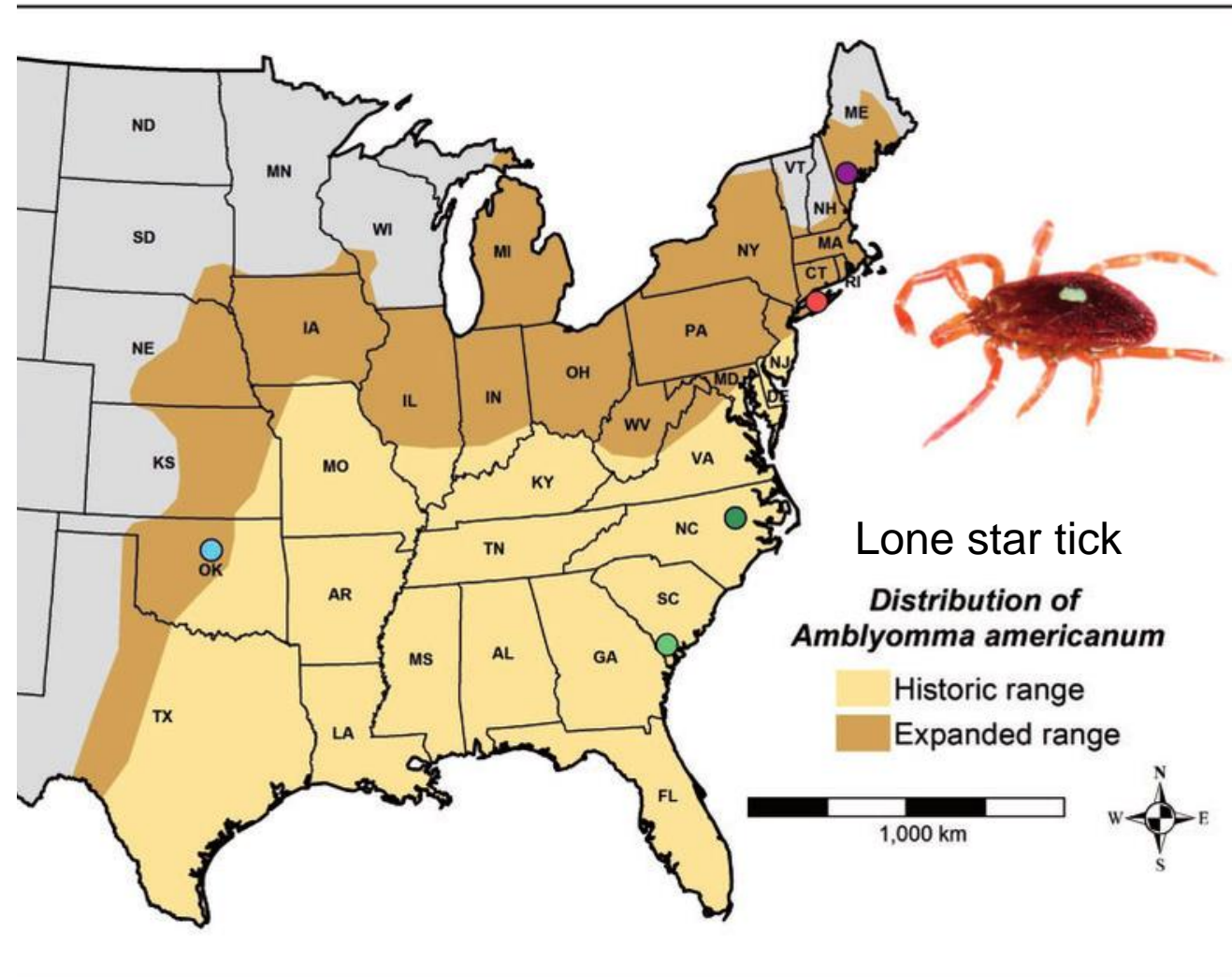
- Consultant: ALK
- Past-president, ACAAI; President Elect, WAO.
- I was a program Director in AI for over 16 years, and have a brother who was also a program director in AI.

Objectives

- Understand how climate change can effect allergic conditions
- Raise awareness of delayed hypersensitivity to mammalian meat products and other hypersensitivity reactions due to Alpha-Gal syndrome (AGS)
- Review clinical manifestations of AGS

Ticks are with us

Tick Presence by Species



Tick borne diseases

- Most tick borne diseases are infectious in nature
- One tick borne condition is likely to bring a patient to the attention of an allergist.
 - We should all know about it
 - Alpha-gal reaction

Dr. Glenn Needham, Entomologist

Seen in action at Allergy Immunology Weed and Wasp Walks at Ohio State University. Glenn also had a bed bug lab





Sweeping
For ticks



Botany graduate student

PhD Botanist

PhD Entomologist



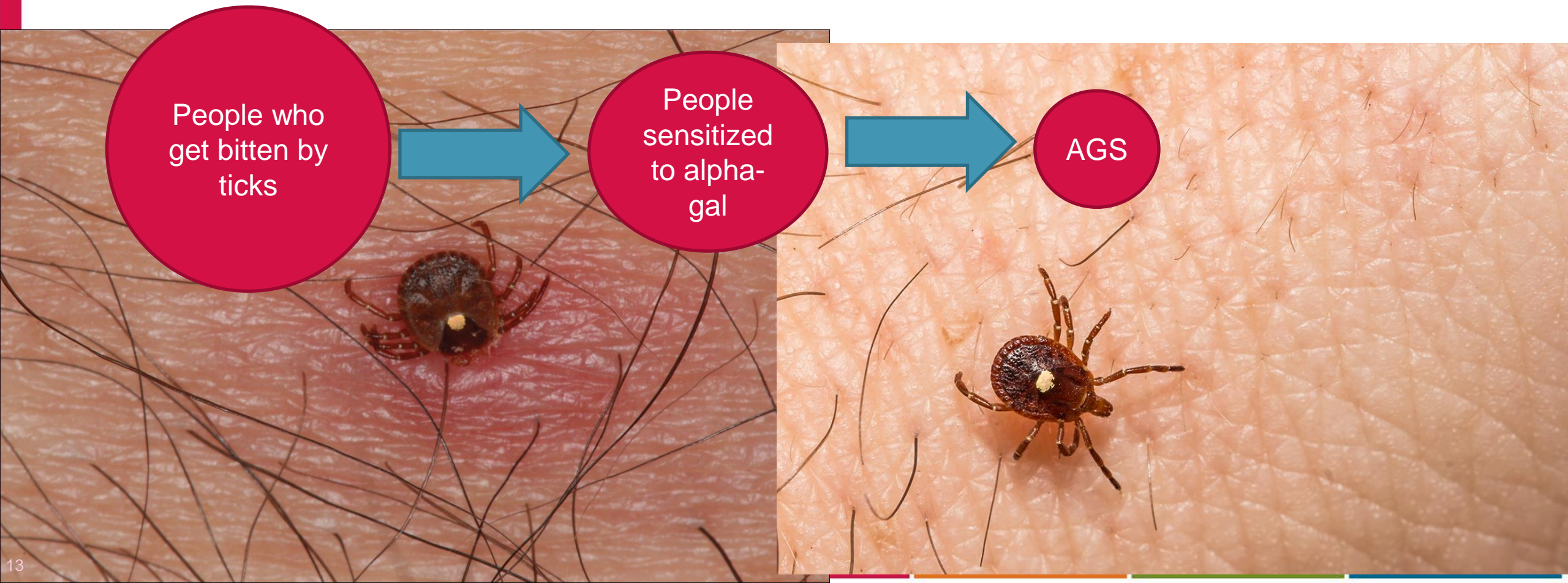
Case study

- JO is 45 year old male who presents to your office frustrated and angry
- No history of prior allergies to environmental exposures, food or drugs.
- Has had anaphylaxis twice: it MIGHT be related to eating, but he there is no single food that seems to be causing his reactions, and the reactions didn't occur while eating
- Now he is afraid to eat... pretty much anything
- What do we ask him?
- What do we tell him?
- What tests do we order?


Is this Alpha-gal syndrome?

- Delayed allergic reaction to galactose-alpha-1,3-galactose that occurs after consumption of mammalian meat.
- Current data suggests that exposure occurs through tick bites that may lead to Alpha-gal sensitization, which leads to Alpha-gal syndrome in some patients.

Every tick bite does not lead to AGS



Alpha-gal syndrome: An emerging cause of food and drug allergy

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Abstract

Alpha-gal syndrome (AGS) describes a wide spectrum of hypersensitivity reactions mediated by specific IgE to the α -gal epitope (galactose- α -1,3-galactose) ubiquitously expressed on glycolipids/glycoproteins of most mammals. This fascinating new entity has completely changed the paradigms of allergy as allergic response is directed against an oligosaccharide and the reactions can be both immediate and delayed. They appear to be stimulated only by tick bites which induce production of α -gal specific IgE antibodies that lead to (at times fatal) hypersensitivity response. AGS is completely different to previously described anaphylaxis to tick saliva. It provides unique insight into the interplay between different arms of the immune system and

Rutkowski K, et al.
Clinical &
Experimental
Allergy. (2020)
50:894-903.

Alpha Gal? Is this just another name for food allergy?

- “Atypical” allergy
- The alpha-gal epitope is ubiquitously expressed on glycoproteins and glycolipids of all mammals except apes, old world monkeys and humans.
- This epitope can be expressed on ticks and other parasites and microorganisms
- Humans can develop an antibody response to Alpha Gal.
- We can produce IgG, IgE or both to exposure to Alpha Gal presented through tick bites

We become suspicious...

- Earlier this century
 - Australia: 25 patients reported who had new-onset meat allergy associated with tick bites
 - Could this be due to cross reacting antibodies to tick saliva that then reacted to meat protein?
 - About the same time in the US there was a marked uptick in cases on anaphylaxis to cetuximab, a chimeric mouse-human monoclonal antibody against epidermal growth factor used for colorectal and squamous head and neck cancer
 - High incidence in the Carolinas, Tennessee, Missouri, Arkansas and northern Georgia, but not in other parts of the US.
- Ticks appeared to be the common denominator

Alpha Gal gets studied

- 2009: specific IgE to alpha gal was identified as the cause of delayed-onset red meat allergy after eating beef, lamb or pork.
 - Patients had both anaphylaxis and/or urticaria
- Different from known tick-induced anaphylaxis mediated by specific IgE to tick salivary proteins.
- At first, this was thought to be due to a tick feeding on a mammal prior to biting a human
- Studies revealed that UNFED ticks could cause this.
 - The reaction is to a substance found on the tick itself.
- Repeated tick bites seems to increase the possibility of Alpha Gal sensitization.

So ticks can cause an alpha gal sensitization

- Odd reaction: this antibody is not to a protein, but to a carbohydrate moiety.
- This IgE reaction is not induced (that is not begun) by exposure to red meat. Current evidence is that ticks are its main inducer
 - Some evidence in rural Zimbabwe that parasites may cause this is children with no clear history of tick bite.
- International studies are consistent: this has been shown in the US, in South America, Australia, Europe, Asia and Africa
- Blood types O and A are susceptible.
 - There is structural similarity between Alpha-gal and blood group B antigen

Alpha-Gal Sensitization and Blood Groups

- Blood groups O and A are susceptible
- Blood group B is similar in structure to Alpha-gal
- Blood groups B and AB have some degree of protection

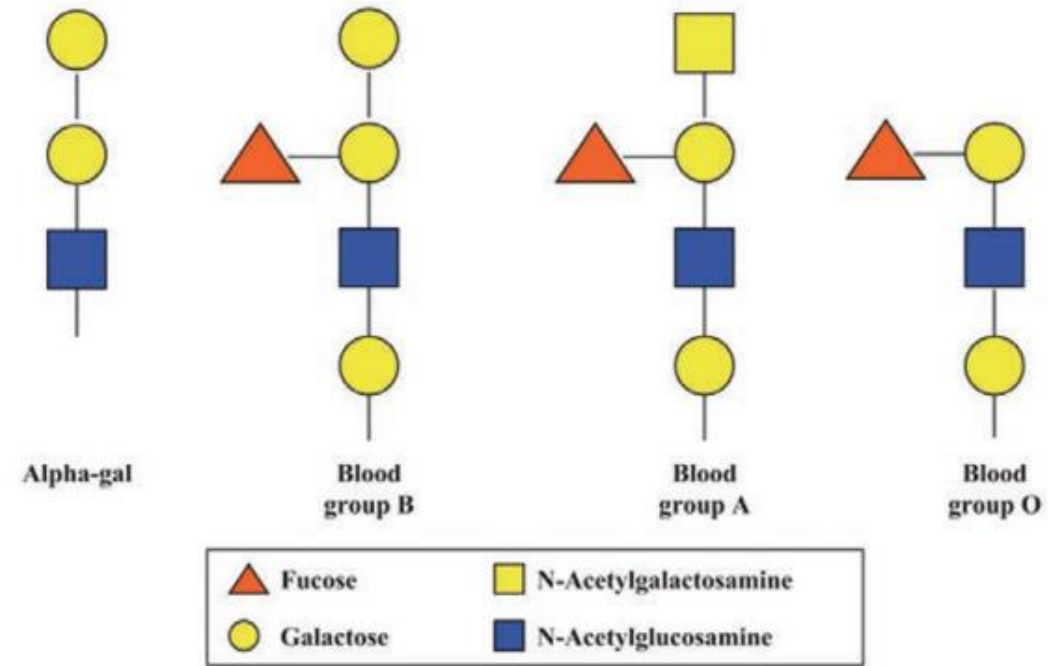


Figure 1. Glycan structures of alpha-gal and human blood groups. Used with permission from Platts-Mills et al.³ and Bircher et al.⁹

Presentation of the patient with alpha-gal syndrome

- Symptoms to non-primate mammalian meat
 - Delayed onset of symptoms by 3-6 hours is the cardinal feature of alpha-gal related meat allergy.
 - Symptoms can range from GI symptoms to urticaria and anaphylaxis
 - Study of 261 patients aged 5-82 with self reported mammalian meat allergy in Virginia (endemic for lone star tick)
 - Specific IgE to alpha gal was found in 245 patients: (94%)
- Important to differentiate this from classical immediate meat allergy triggered by specific IgE to meat proteins.

Sensitization to Alpha gal does not mean disease

- As is often seen in allergy, having an allergic antibody does not mean a patient will have symptoms
 - The majority of alpha-gal sensitized individuals do NOT report symptoms of AGS
 - Among 300 foresters sensitized to Alpha gal, 90% had no allergic symptoms*
- **The majority of patients sensitized to Alpha gal do not have symptoms.**

Venturini M, Lobera T, Sebastián A, Portillo A, Oteo JA. IgE to α -gal in foresters and forest workers from La Rioja, North of Spain. J Investig Allergol Clin Immunol. 2018;28:106-112.

TABLE 2 Risk factors for alpha-gal syndrome
(AGS)^{4,6,31,32,35,36,39,58,64-66}

AGS: risk factors

Employment (foresters, hunters) and outdoor activities

Ecological conditions supporting tick development/spread and repeated bites

Non-B blood groups

Co-factors that impact development/severity of AGS: NSAID, exertion

Older age: in Danish and Korean but not German, Spanish and Italian studies

Sex: male in Danish cohort only

No clear correlation with atopy

What other problems can alpha gal sensitization cause?

- Reactions to cetuximab
 - Chimeric mouse-human IgG1 monoclonal antibody
 - Geographical variation in rate of hypersensitivity reactions range from less than 5% to up to 30%
 - Highest in the south-eastern US
 - Fatal reactions to the first exposure have been reported.
- Increased reactions to gelatin
- Hypersensitivity in 8-20% of patients receiving antivenoms
- Chronic urticaria (very rare)

Back to JO

- First: get a good and specific history
 - What blood group is he?
 - What does he do for a living?
 - What outdoor activities does he engage in?
 - Is there any history of tick bite?
 - Does the patient live in an area where Lone star ticks are known to live? If not, has the patient recently visited such an area?
 - Why does he think it might be related to foods?
 - What foods can be identified as potential culprits?
 - How long after eating do symptoms occur?

How do we make diagnosis of Alpha-gal syndrome?

- High degree of clinical suspicion
- Detailed history
- Knowledge of geographical distribution of relevant ticks
- Skin testing
 - Commercial meat protein extracts yield small positive reactions
 - Fresh meat prick-prick testing may be more useful
 - Cetuximab and beef/pork gelatin SPT can be used.
- Specific IgE alpha gal assays are available, but not perfect

JO asks some questions

- Why don't I have a reaction every time I eat meat?
 - Great question
 - While this does not occur with every ingestion of meat, there is no way to tell when someone will have a reaction.
- Can I eat well done meat? Won't this destroy the antigen
 - No; There are more than one involved antigen, and many are heat stable
- Are all meats a problem?
 - No fish, seafood and chicken are non mammalian meat sources
- Is there a relationship between pet ownership and alpha-gal
 - This has not been shown in studies to date.
- Will I ever eat meat again?
 - Natural history of AGS is largely unknown



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis



Tick exposures and alpha-gal syndrome: A systematic review of the evidence



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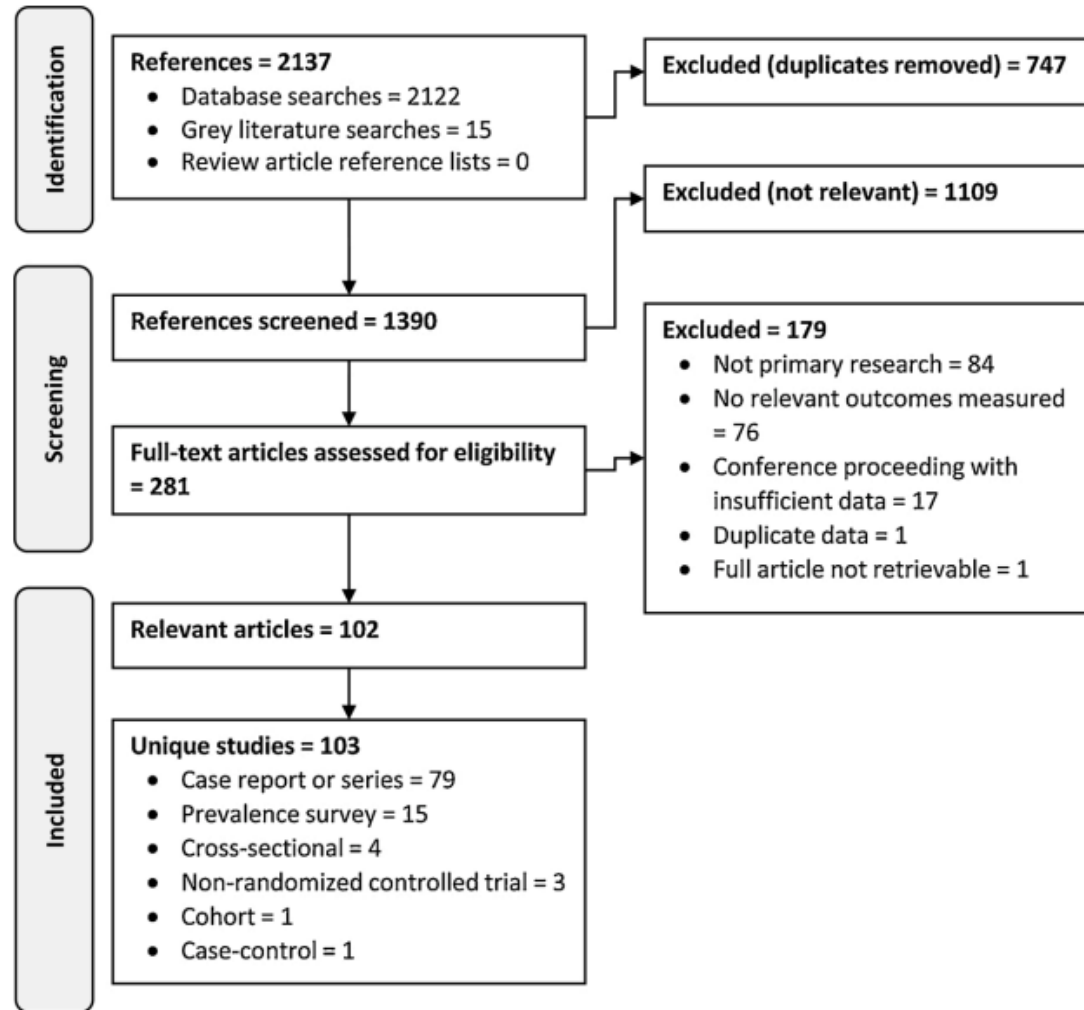
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ABSTRACT

Alpha-gal syndrome (AGS) refers to a delayed allergic reaction to galactose- α -1,3-galactose (α -Gal) that occurs following the consumption of mammalian meat or exposure to other animal-based foods and products. Increasing evidence suggests that bites from certain tick species can lead to AGS through sensitization of a person's α -Gal

We need more studies



- 1390 references screened
- 103 relevant
- 79 case reports or case studies
- Publication dates from 2009-2020
- 40.8% from US
- 40.8% Europe

Fig. 1. Systematic review flow diagram.

Alpha gal syndrome

- Patients present clinically with delayed allergic reactions to mammalian meat
 - Sometimes to other products that contain alpha-gal
 - Dairy products
 - Gelatin-containing colloids
 - Pharmaceuticals
- Delayed: typically within several hours
- Symptoms are varied: GI symptoms, urticaria, pruritis, angioedema to severe anaphylaxis.

Systematic review results

- This was not a meta-analysis due to the variability of studies reviewed
- Mechanism not fully understood:
 - Probably alpha gal antigen in tick saliva
 - There are case clusters in areas where lone star tick is not endemic
- Climate change is enlarging the range of Lone star ticks
 - May also lead to more abundance and more tick bites
- Most studies were case reports or series, which tend to report on the more serious cases.
- One west US Coast woman had never been in an area where lone star ticks are known – other species may be able to transmit

More systemic review results

- Time to onset of symptoms ranged from 10 minutes to four hours
- Organ meats such as kidney led to more rapid onset of symptoms, and more severe symptoms
 - May be due to higher levels of alpha gal on these products
- Delay in symptoms after ingestion of meat or dairy may be related to the length of time necessary to digest and absorb alpha-gal containing glycolipids, but this is an area that requires more research.
- The diagnostic utility of specific IgE to alpha gal is as yet unknown; however, there is evidence that IgE levels may decrease if the patient does not have additional tick exposure.

Symptoms reported

- Anaphylaxis 51.7%
- Skin reactions 74.6%
- Urticaria 71.2%
- GI symptoms 30.0%
- Angioedema 25.0%
- Pruritis 14.4%
- Dyspnea 11.0%

CME

What Does a Red Meat Allergy Have to Do With Anesthesia? Perioperative Management of Alpha-Gal Syndrome

W. Jonathan Dunkman, MD,* Wendy Rycek, PharmD,† and Michael W. Manning, MD, PhD*

Over the past decade, there has been a growing awareness of a new allergic syndrome known as alpha-gal allergy or alpha-gal syndrome, commonly recognized as a red meat allergy. We performed a review of the literature to identify articles that provide both background on this syndrome in general and any reports of reactions to medications or medical devices related to alpha-gal syndrome. Alpha-gal syndrome results from IgE to the oligosaccharide galactose- α -1,3-galactose, expressed in the meat and tissues of noncatarrhine mammals. It is triggered by the bite of the lone star tick and has been implicated in immediate-onset hypersensitivity to the monoclonal antibody cetuximab and delayed-onset hypersensitivity reactions after the consumption of red meat. There is growing recognition of allergic reactions in these patients to other drugs and medical devices that contain alpha-gal. Many of these reactions result from inactive substances that are part of the manufacturing or preparation process such as gelatin or stearic acid. This allergy may be documented in a variety of ways or informally reported by the patient, requiring vigilance on the part of the anesthesiologist to detect this syndrome, given its serious implications. This allergy presents a number of unique challenges to the anesthesiologist, including proper identification of a patient with alpha-gal syndrome and selection of anesthetic and adjunctive medications that will not trigger this allergy. (Anesth Analg 2019;129:1242–8)

The Anesthesiologist's view

- Alpha gal syndrome (AGS) should be listed in the chart
- Systems with and EHR that does not currently have this as a drop down list choice should do so.
- Many drugs have Alpha gal and the patient could react to these drugs.
- Remember it was due to a reaction with a medication (cetuximab) that allowed us to understand that alpha gal was an issue.

Dunkman WJ et al. Anesthetic Clinical Pharmacology. (2019) 129(5): 1242-1248

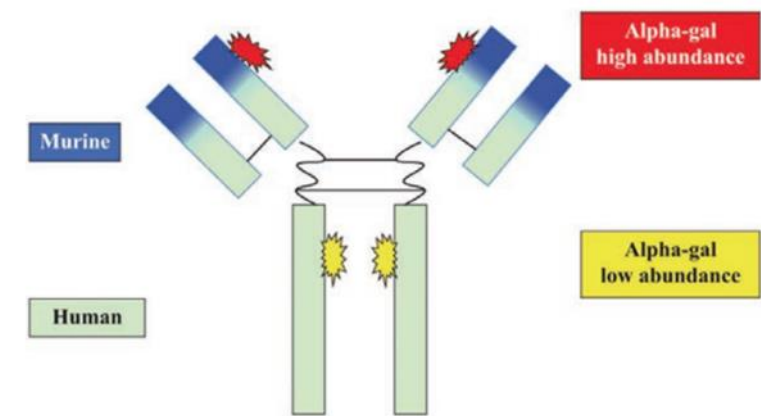


Figure 2. Structure of cetuximab highlighting alpha-gal location in red. Used with permission from Platts-Mills et al³ and Bircher et al.⁹

Alpha Gal

- May be hidden in medications
- Inactive ingredients may be changed without notice

Table 1. Common Inactive Ingredients That May Contain Alpha-Gal and Examples of Medications in Which They Are Found

Inactive Ingredient Which May Be Animal Derived	Examples of Medications That Contain Inactive Ingredient
Stearic acid	Oxycodone tablets (Hospira, Mallinckrodt)
Lactic acid	Hydromorphone injection (Hospira), haloperidol injection
Magnesium stearate	Acetaminophen tablets, Oxycontin
Glycerin	Ibuprofen suspension, methadone solution, acetaminophen liquid
Gelatin	Alvimopan, aprepitant celecoxib, pregabalin, gabapentin capsules, lidocaine patch, Surgifoam powder

Common Perioperative Medications and Alpha-gal Content			
Drug Name	Manufacturer	Ok to use?	Notes
Albumin 5% & 25%	Grifols	Yes	Contains no animal or mammalian by-products per manufacturer
Acetaminophen 325mg tablet	McNeill Mckesson	No	Contains magnesium stearate and gelatin
Clevidipine 0.5mg/mL injection	Fresenius Kabi	Yes	Glycerin is plant-derived per manufacturer
Dexmedetomidine 4mcg/mL	Hospira	Yes	
Fentanyl Injection	Hospira Akorn	Yes	
Haloperidol 5mg/mL injection	Fresenius Kabi	No	Lactic acid may be animal derived.
Hydromorphone injection	Hospira	No	Lactic acid may be animal derived. Manufacturer contacted and was unable to confirm or deny if animal derived
Insulin, human regular	Lilly	Yes	Per manufacturer: glycerin is plant derived
Pregabalin	Pfizer	No	Gelatin of animal origin; lot-specific ingredient sourcing
Propofol 10mg/mL injection	Fresenius Kabi	Yes	Per manufacturer: glycerol is plant-based
Surgifoam powder	Ethicon	No	Contains gelatin – bovine derived
<p>Pharmacy maintains an active list of commonly used perioperative medications and alpha-gal content, updated as formulations change or more information becomes available. Alpha-gal content varies with manufacturer and lot of medication so an accurate list will vary from institution to institution. This abridged table provides an example of how our pharmacy tracks and presents this information but should not be taken as a universal reference for alpha-gal content.</p>			
<p>*Disclaimer: Information is subject to change based on the lot of medication. Please contact Pharmacy for review of medications prior to ordering.</p> <p>**Disclaimer: There may be cases where risk versus benefit needs to be assessed in deciding whether to use alpha-gal medications. Please consult pharmacy to determine if there are potential alternatives that should be considered as part of this assessment.</p>			

Figure 5. Abridged example of table tracking alpha-gal content in common perioperative medications.

Conclusions:

- Tick bites may lead to Alpha-gal syndrome (AGS)
- Many people seem to be sensitized to Alpha-gal without having symptoms. These patients do not have AGS
 - Don't diagnose a patient with Alpha-gal Syndrome only because of tick bite or presence of Alpha-gal IgE.
- We must have a strong clinical suspicion regarding these patients, particularly among patients who live in or visit areas known to have lone star ticks.
 - May lead to delayed reactions to mammalian meat and anaphylaxis to cetuximab.
- Alpha-gal Syndrome should be listed on the chart when recognized



Questions?