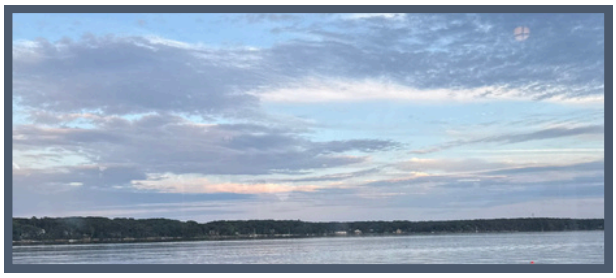
MAINE CHAPTER
American College of Emergency Physicians

Quarterly Newsletter | Summer 2026



Dear Maine ACEP Members,

Summer in Maine is delivering the usual: warm weather, visitors from “away,” tick-borne illnesses, and busy emergency departments. I hope this finds you with some much-deserved time away from the department, enjoying the best season this state has to offer.

Thanks to everyone who made the trek to Cabbage Island in June. We set an attendance record, with plenty of new faces and EM residents rounding out the group. A few updates as we look at the rest of 2026:

Leadership Summit

September 14, 2026

Harraseeket Inn, Freeport

We’re building on last year’s momentum with a strong line-up of speakers on all things leadership in emergency medicine. Last year brought record attendance, with real growth among people who don’t hold an official title. Let’s keep that going.

> ***New This Year***:
> A round-table in which you represent your institution and give the group an honest update on what’s happening in your ED — a struggle or a win; either is worth hearing.

Interested in participating? Email Sarah Nelson at snelson@mainephysicians.org.

Scientific Assembly & Reception

October 6, 2026

Chicago, Illinois

Our annual MEACEP/MMC-P reception takes place on October 6th during ACEP26. **We are capped at 25 guests**, so if you’re planning to attend, please let us know as soon as possible.

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MDPB Representative

Apply by **July 31, 2026**

Contact Sarah Nelson or Sheldon Stevenson

The Maine EMS Medical Direction and Practice Board has a vacancy for a MEACEP representative. This is a real opportunity to put emergency medicine at the table on statewide EMS policy, especially for protocol development and operational procedures. We can forward two candidates. Send your interest to Sarah or to me by July 31st.

Clinical Pearl: Alpha-Gal Syndrome

We've all become experts in Lyme and the other common tick-borne illnesses. This one may be next.

Alpha-gal syndrome is an IgE-mediated allergy to galactose-α-1,3-galactose, a sugar found in mammalian tissue. Sensitization comes from a tick bite — in the U.S., primarily the Lone Star tick. The reaction comes later, from eating mammalian meat: beef, pork, lamb, and their derivatives.

What makes this an EM conundrum? The delay. Symptoms usually occur two to six hours after the meal, which doesn't track with most anaphylaxis stories.

Take a look at the attached article if this is all news to you.

Enjoy the rest of the summer. Hope to see you in Chicago!

Sheldon

Sheldon H. Stevenson, DO, FACEP
President, Maine Chapter ACEP

Cabbage Island 2026

Clinical Presentation and Outcomes of Alpha-Gal Syndrome

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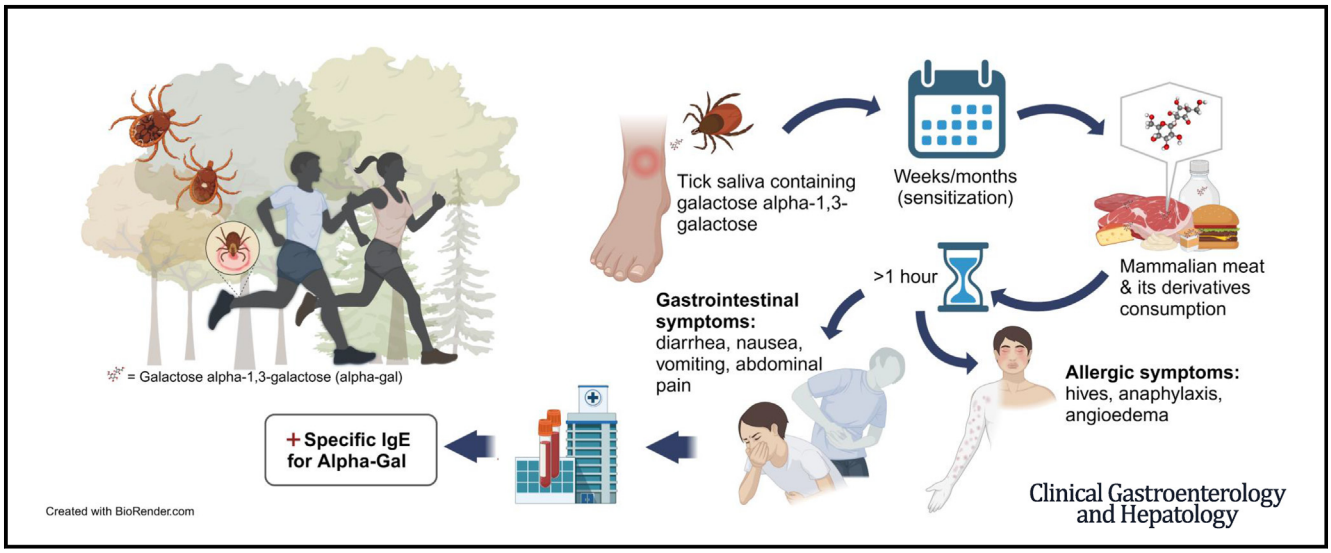

BACKGROUND AND AIMS: **Alpha-gal syndrome (AGS) is an IgE-mediated allergic reaction to galactose-α-1,3-galactose, primarily linked with Lone Star tick bites in the United States. It presents with symptoms ranging from urticaria and gastrointestinal (GI) manifestations to delayed anaphylaxis following red meat consumption. We aimed to study AGS patients' clinical manifestations, diagnosis, and outcomes.**

METHODS: **A retrospective chart review of patients who underwent serological testing for suspected AGS between 2014 and 2023 at Mayo Clinic was performed. Patients with positive serology were age and sex matched with those who tested negative. Clinical characteristics of seropositive cohort with and without GI symptoms were compared, and outcomes assessed.**

RESULTS: **Of 1260 patients who underwent testing, 124 tested positive for AGS. They were matched with 380 seronegative control subjects. AGS patients reported a higher frequency of tick bites (odds ratio [OR], 26.0; 95% confidence interval [CI], 9.8–68.3), reported a higher prevalence of urticaria (56% vs 37%; $P = .0008$), and were less likely to have asthma (OR, 0.4; 95% CI, 0.3–0.7). They had a lower prevalence of heartburn (6% vs 12%; $P = .03$) and bloating (6% vs 13%; $P = .03$). A total of 47% had GI symptoms, and a higher proportion were female than those without GI symptoms (69% vs 35%; $P = .002$). During a mean follow-up of 27 months, 22 of 40 patients reported symptom resolution after avoiding red meat, and 7 were able to transition to regular diet.**

*Authors share co-first authorship.

Abbreviations used in this paper: AGS, alpha-gal syndrome; alpha-gal, galactose-alpha-1,3-galactose; CI, confidence interval; GI, gastrointestinal; sIgE, specific IgE.

Most current article

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CONCLUSIONS: **A diagnosis of AGS should be strongly considered in patients with a history of tick bites and clinical presentation of allergic or GI manifestations. Dietary intervention is effective in most but not all patients.**

Keywords: Hypersensitivity; Urticaria; Gastrointestinal; Mammalian Meat; Tick Bite.

Alpha-gal syndrome (AGS) is an IgE-mediated allergic reaction to galactose-alpha-1,3-galactose (alpha-gal) and its derivatives, an oligosaccharide found in beef, pork, and other nonprimate mammalian meats. The primary cause of alpha-gal sensitization in the United States is believed to be Lone Star tick (*Amblyomma americanum*) bite, making the condition highly prevalent in areas endemic to Lone Star ticks, the Southeast, the Midwest, Mid-Atlantic, and the East Central Census Bureau regions in the United States.[1] However, the increasing prevalence of AGS beyond these areas in the United States suggest the potential involvement of other tick species or vectors (eg, chiggers).[2] Globally, other tick species linked to AGS include *Ixodes ricinus*, *Ixodes holocyclus*, and *Haemaphysalis longicornis*.[3] This allergy was initially recognized after reports of serious hypersensitivity reactions to cetuximab (an epidermal growth factor inhibitor used for colorectal, and metastatic head and neck cancer), a drug glycosylated with alpha-galactose,[4] and most often presents with hives, gastrointestinal (GI) symptoms such as nausea, vomiting, abdominal pain, and diarrhea,[5] and in some cases delayed-onset anaphylaxis.

Alpha-gal can be found in nonprimate mammalian meats (pork, beef, rabbit, lamb, horse, venison, etc.) and products made from mammals (gelatin, cow's milk, and milk products). However, not all patients with AGS have reactions to every ingredient containing alpha-gal. For example, only a small percentage of clinically significant AGS patients have reactions with dairy products. Alpha-gal–containing IgE-binding proteins do not appear to significantly denature on cooking; however, experts have suggested that cooking may reduce reaction severity, possibly by lowering the fat content.[6]

The onset of symptoms typically occurs 3–6 hours after eating, making the diagnosis challenging.[3,7] While the exact cause of this delayed onset remains unclear, it is hypothesized that it is due to the gradual absorption of alpha-gal glycolipids and glycoproteins in the GI tract.[3,7,8] This hypothesis gains support from the observation that reactions to cetuximab infusions,[4,9] as well as responses to skin tests using cetuximab and meat extracts, that do not need to be absorbed through the GI tract, occur rapidly.[10] Considering the postprandial symptoms, many patients with GI symptoms get misdiagnosed with irritable bowel syndrome or other GI conditions. In fact, in a recent study, approximately half of the AGS patients met the criteria for diarrhea-predominant irritable bowel syndrome.[7]

The most utilized test for diagnosis of AGS is alpha-gal IgE serology.[11] While it has been reported to have a sensitivity of 100% and a specificity of 92% with the alpha-gal IgE threshold of 0.35 IU/mL,[12] it is crucial to interpret these results in conjunction with patients' clinical symptoms and serological titers, as a study found that only 9% of patients with positive titers (>0.35 IU/mL) reported clinical symptoms.[13] Recent studies have demonstrated the utility of using an alpha-gal IgE threshold of 0.1 IU/mL as an alternative for diagnosis; however, it may have a weaker correlation with clinically significant AGS.[14] Reports on associations between serum IgE titers and symptom severity have shown conflicting results.[15,16] Furthermore, the outcomes of AGS patients have not been well studied. Here, we aim to assess the prevalence of AGS among those tested due to clinical suspicion and explore clinical symptoms (GI and non-GI), management and outcomes (clinical and serological) of AGS patients at our tertiary referral center.

Materials and Methods

Study Design

This retrospective cohort study was performed at the Mayo Clinic in Rochester, Minnesota. The protocol was reviewed by the Mayo Clinic Institutional Review Board (23-008105) and determined to be exempt. All authors had access to the study data and reviewed and approved the final manuscript.

Study Participants

Using a digital data exploration and retrieval tool (Mayo Data Explorer) housed at Mayo Clinic, we assembled a cohort of individuals who underwent serological testing for suspected AGS between February 2014 and September 2023 at the Mayo Clinic in Rochester, Minnesota. Individuals with positive AGS serology (seropositive) were age and sex matched with randomly selected AGS-negative control subjects (1:3) tested during the same time period. A comprehensive retrospective medical record review was conducted to extract clinical correlates, including patient demographics, symptoms, laboratory values, treatment, and outcomes.

The seropositive AGS cohort was further categorized into 2 subsets based on the presence or absence of GI symptoms. Outcomes were assessed in a subset of patients with at least 1 follow-up visit to determine changes in symptoms and serological markers.

Statistical Methods

Descriptive statistics (number and percentage for categorical variables, mean ± SD or median [range] for continuous variables) were used to summarize data.

The Mann-Whitney test was used to compare differences in continuous variables and the chi-square test for categorical variables. A Pearson correlation test was also performed to determine the correlation between alpha-gal specific IgE (sIgE) and sIgE for various types of meats. A paired *t*-test was performed to compare alpha-gal IgE titers at the initial and latest follow-up visits. For all analyses, if the levels of alpha-gal IgE titers were more than 100 IU/mL, the reference value used was 100 IU/mL, and if the alpha-gal IgE titers and meat sIgE titers were <0.1 IU/mL, the reference value used was 0.1 IU/mL. All statistical analyses were done using GraphPad Prism v. 10.0.0 (GraphPad Software). A P value <.05 was considered statistically significant.

What You Need to Know

Background

The aims of our study were to describe the clinical presentation and outcomes of alpha-gal syndrome (AGS).

Findings

Nearly 10% of patients tested were seropositive for AGS, and almost half experienced gastrointestinal symptoms. Seropositive patients were more likely to have urticaria and less likely to have heartburn, bloating, and asthma. Fifty-five percent achieved complete symptom resolution with dietary restrictions.

Implications for patient care

AGS diagnosis should be considered in an individual with allergic and/or gastrointestinal symptoms, particularly in endemic areas. Dietary intervention is effective in many patients but not all.

Results

Characteristics of AGS Patients

Of 1260 patients tested for alpha-gal serologies between 2014 and 2023, 124 (9.84%) were positive. Among these, 120 had alpha-gal IgE levels exceeding 0.35 IU/mL, the threshold used at Mayo Clinic for AGS diagnosis. Four patients with levels between 0.1 and 0.35 IU/mL were diagnosed based on clinical symptoms and high titers to specific red meat antigens, such as pork IgE, mutton IgE, and beef IgE.

Non-GI symptoms in AGS patients included urticaria (56.4%), angioedema (37.9%), anaphylaxis (36.3%), and chest pressure (7.3%). GI symptoms (45.2%) were also common in AGS patients, including diarrhea (32.3%), nausea (31.4%), vomiting (22.6%), abdominal pain (21.8%), cramps (17.7%), bloating (6.4%), heartburn (5.6%), and constipation (4.8%). In addition to red meats, 14 (11.3%) patients reported symptoms after milk consumption (Table 1).

Eleven percent showed symptoms within an hour of red meat ingestion, 20% showed symptoms between 1 and 4 hours, and 29% had late-onset symptoms (>4 hours). Around 6% experienced variable symptom onset, and no specific onset time was noted for 33% of patients. Fifty-nine (48%) patients required emergency care, and 16 (13%) were hospitalized at least once for AGS episodes. Two patients experienced cardiac arrest, requiring advanced cardiac life support, with 1 case triggered by a cetuximab infusion. Among those with comorbidities, 2 of 5 patients with rheumatoid arthritis reported worsening of joint symptoms post-AGS diagnosis.

Comparison of AGS Patients With Seronegative Individuals

Compared with seronegative patients, AGS patients demonstrated a higher prevalence of urticaria (56.4% vs 36.8%; $P = .0008$). Interestingly, this group also demonstrated a diminished propensity for heartburn (5.6% vs 12.4%; $P = .036$) and bloating (6.4% vs 13.4%; $P = .036$) relative to those with seronegative control subjects. A history of tick bite was reported more likely (odds ratio, 26.0; 95% confidence interval, 9.8–68.3) in the seropositive patients. Conversely, a lower prevalence of asthma history was noted in this group, compared with seronegative patients (odds ratio, 0.45; 95% confidence interval, 0.3–0.7) (Table 1).

Association With Serological Titers

Nineteen (15.8%) patients had levels of 0.35–0.7 IU/mL, 41 (34.2%) had 0.7–3.5 IU/mL, 32 (26.7%) had 3.5–17.5 IU/mL, and 28 (23.3%) exceeded 17.5 IU/mL. Higher serological titers correlated with an affirmative history of tick bites (P-trend = .005) and increased incidence of urticaria (P-trend = .001). Symptom onset varied with different alpha-gal IgE levels. In patients with levels of 0.35–0.7 IU/mL, symptoms appeared within an hour in 15.8%, within 1–4 hours in 10.5%, and after 4 hours in 5.3%; 31.6% had variable onset and 36.8% lacked data. Symptom onset and clinical features with specific titer levels are presented in Table 2.

Specific IgE levels for various mammalian types of meat were assessed, with 80.8% of patients reacting to beef, 59.2% to mutton, 61.5% to pork, and 42.5% to milk. Pearson correlation revealed significant correlations between overall alpha-gal IgE and sIgEs to beef, pork, mutton and milk (correlation coefficients: 0.87, 0.74, 0.6, and 0.58, respectively; $P < .0001$). (Figure 1).

Comparison of AGS Patients With and Without GI Symptoms

Fifty-eight (46.8%) AGS patients exhibited at least 1 GI symptom during an acute episode, while 66 (53.2%) patients reported no GI complaints. The proportion of

Table 1. Demographic and Clinical Characteristics of AGS Patients and Seronegative Control Subjects

Characteristic	Seropositive AGS Patients (n = 124)	Seronegative Control Subjects (n = 380)	*P* Value
Age at AGS testing, y	60 (11–82)	53 (25–89)	.10
Female	63 (50.8)	229 (60.3)	.06
Race/ethnicity			
White	116 (93.55)	349 (91.84)	.87
Asian	4 (3.23)	12 (3.16)	
American Indian/Alaskan Native	1 (0.81)	10 (2.63)	
African American	0 (0)	8 (2.11)	
Unknown	3 (2.4)	1 (0.26)	
Symptoms			
Urticaria	70 (56.45)	140 (36.84)	.01
Angioedema	47 (37.90)	168 (44.21)	.25
Anaphylaxis	45 (36.29)	103 (27.11)	.05
Chest pressure	9 (7.26)	32 (8.42)	.68
GI symptoms	56 (45.16)	178 (46.84)	.74
Nausea	39 (31.45)	98 (25.79)	.22
Vomiting	28 (22.58)	73 (19.21)	.42
Heartburn	7 (5.65)	47 (12.37)	.04
Bloating	8 (6.45)	51 (13.42)	.04
Abdominal cramp	22 (17.74)	69 (18.16)	.92
Abdominal pain	27 (21.77)	114 (30)	.08
Constipation	6 (4.84)	39 (10.26)	.07
Diarrhea	40 (32.26)	104 (27.37)	.30
Only GI symptoms	14 (11.29)	76 (20)	.03
Time to symptoms			
<1 h	14 (11.29)	46 (12.11)	<.01
1–4 h	25 (20.16)	28 (7.37)	
>4 h	36 (29.03)	28 (7.37)	
Variable	8 (6.45)	8 (2.10)	
Not specified	41 (33.06)	270 (71.05)	
History of asthma	36 (35.64), n = 101	132 (55), n = 240	<.01
History of tick bite	88 (95.6), n = 92	82 (45.81), n = 179	<.01
Total IgE, IU/mL	200.5 (116.8–344.2), n = 29	109 (3.6–10820), n = 92	.51
Alpha-gal sIgE titers			
sIgE >0.35 IU/mL	120 (96.77)		
sIgE, IU/mL	4.38 (3.25–5.91)		
sIgE, 0.35–0.7 IU/mL	19 (15.83)		
sIgE, 0.7–3.5 IU/mL	41 (34.17)		
sIgE, 3.5–17.5 IU/mL	32 (26.67)		
sIgE >17.5 IU/mL	28 (23.33)		
Beef sIgE >0.35 IU/mL (n = 78)	63 (80.77)		
Beef sIgE (n = 63), IU/mL	2.77 (1.94–3.96)		
Mutton/lamb sIgE >0.35 IU/mL (n = 76)	45 (59.21)		
Mutton/lamb sIgE (n = 45), IU/mL	1.78 (1.32–2.42)		
Pork sIgE >0.35 IU/mL (n = 78)	48 (61.54)		
Pork sIgE (n = 48), IU/mL	2.51 (1.80–3.49)		
Milk sIgE >0.35 IU/mL (n = 40)	17 (42.5)		
Milk sIgE (n = 17), IU/mL	2.51 (1.40–4.5)		

Values are median (range), n (%), or geometric mean (95% confidence interval).
AGS, alpha-gal syndrome; GI, gastrointestinal; sIgE, specific IgE.

females was significantly higher in the group of patients who experienced GI symptoms compared with those without GI symptoms (69% vs 35%; $P = .002$); however, the 2 groups had similar demographic characteristics, such as age, non-GI symptoms, and serological titers.

Among those with GI symptoms, 11% of the patients experienced exclusively GI manifestations. The remainder exhibited a blend of 1 or several GI symptoms alongside other allergic reactions. The most frequent non-GI symptoms in AGS patients with GI manifestation

Table 2. Demographic and Clinical Characteristics of AGS Symptoms in Patients With Different Alpha-Gal sIgE Titers

Characteristic	0.35–0.7 IU/mL (n = 19)	0.7–3.5 IU/mL (n = 41)	3.5–17.5 IU/mL (n = 32)	≥17.5 IU/mL (n = 28)	*P* Value
Age at AGS testing, y	58 (17–77)	57 (15–82)	62 (11–82)	64.5 (24–79)	.05
Female	9 (47.37)	24 (58.54)	16 (50)	11 (39.29)	.34
Race/ethnicity					
White	18 (94.74)	37 (90.24)	30 (93.75)	27 (96.43)	.32
Asian	0 (0)	1 (2.44)	2 (6.25)	1 (35.71)	
American Indian/Alaskan Native	0 (0)	1 (2.44)	0 (0)	0 (0)	
African American	0 (0)	0 (0)	0 (0)	0 (0)	
Unknown	1 (5.56)	2 (4.88)	0 (0)	0 (0)	
Symptoms					
Urticaria	6 (31.58)	21 (51.22)	19 (59.38)	22 (78.57)	<.01
Angioedema	7 (36.84)	13 (51.2)	16 (50)	10 (35.71)	.71
Anaphylaxis	5 (26.32)	17 (41.46)	12 (37.5)	11 (39.29)	.56
Chest pressure	0 (0)	4 (9.76)	3 (9.38)	1 (3.57)	.89
GI symptoms	8 (42.11)	19 (46.34)	14 (43.75)	14 (50)	.67
Nausea	6 (31.58)	13 (31.71)	12 (37.5)	8 (28.57)	.93
Vomiting	3 (15.79)	10 (24.39)	7 (21.88)	8 (28.57)	.41
Heartburn	1 (5.26)	3 (7.32)	2 (6.25)	1 (3.57)	.69
Bloating	1 (5.26)	1 (2.38)	2 (6.25)	2 (6.25)	.51
Abdominal cramp	3 (15.79)	4 (9.76)	9 (28.13)	6 (21.43)	.21
Abdominal pain	4 (21.05)	9 (21.95)	7 (21.88)	4 (14.29)	.53
Constipation	1 (5.26)	1 (2.44)	2 (6.25)	1 (3.57)	.96
Diarrhea	2 (10.53)	13 (31.71)	12 (37.5)	10 (35.71)	.09
Only GI symptoms	3 (15.79)	6 (14.63)	2 (6.25)	2 (7.14)	.19
Time to symptoms					
<1 h	3 (15.79)	7 (17.07)	1 (3.13)	3 (10.71)	<.01
1–4 h	2 (10.53)	9 (21.95)	5 (15.63)	9 (32.14)	
>4 h	1 (5.26)	10 (24.39)	15 (46.88)	10 (35.71)	
Variably	6 (31.58)	1 (2.44)	0 (0)	0 (0)	
Not specified	7 (36.84)	14 (34.14)	11 (34.38)	6 (21.43)	
History of asthma	7 (41.18)	9 (27.27)	12 (50)	6 (26.09)	.75
History of tick bite	10 (76.92)	32 (100)	23 (100)	22 (100)	<.01
Total IgE, IU/mL	119 (11.3–1960)	139 (36.10–2349)	336 (59.80–1084)	116 (115–1548)	.96

Values are median (range), n (%), or geometric mean (95% confidence interval).
AGS, alpha-gal syndrome; alpha-gal, galactose-alpha-1,3-galactose; GI, gastrointestinal; sIgE, specific IgE.

were urticaria (63.8%), followed by angioedema (41.4%), anaphylaxis (36.2%), and chest pressure (10.3%) (Table 3).

Outcomes of AGS Patients

At least 1 follow-up encounter data was available on 40 of 124 AGS patients. All patients were advised to maintain a red meat–free diet and avoid further tick exposure. The follow-up period for these patients ranged from 0.5 to 105 months, with a mean of 27 months. 22/40 patients reported complete resolution of symptoms after dietary restrictions, while 14 patients noted a decrease in severity and frequency of symptoms, and 4 patients reported no change in their symptoms. Additionally, of the 22 patients who reported complete resolution of symptoms after dietary restrictions, 7 successfully reintroduced a regular diet without subsequent AGS episodes over an average period of 20 months (range 3–40 months) (Figure 2).

A mean decrease of 17 IU/mL was observed in alpha-gal IgE from the initial to the latest follow-up visit when analyzed with a paired *t* test ($P = .0009$) (Figure 3). Out of 37 patients, 28 (76%) had a decrease in levels of alpha-gal IgE on follow-up, while 9 had an increase in alpha-gal IgE titers. Only 4 patients became seronegative along with complete resolution of symptoms after dietary restrictions. Their alpha-gal IgE levels at diagnosis were 0.79, 0.8, 1.22, and 4.94 IU/mL with transition to normal serology in 39, 14, 34, and 40 months, respectively. Of these 4 patients, 3 were able to transition to a regular diet.

Discussion

AGS manifests as an acute hypersensitivity reaction to red meat products following sensitization to the alpha-

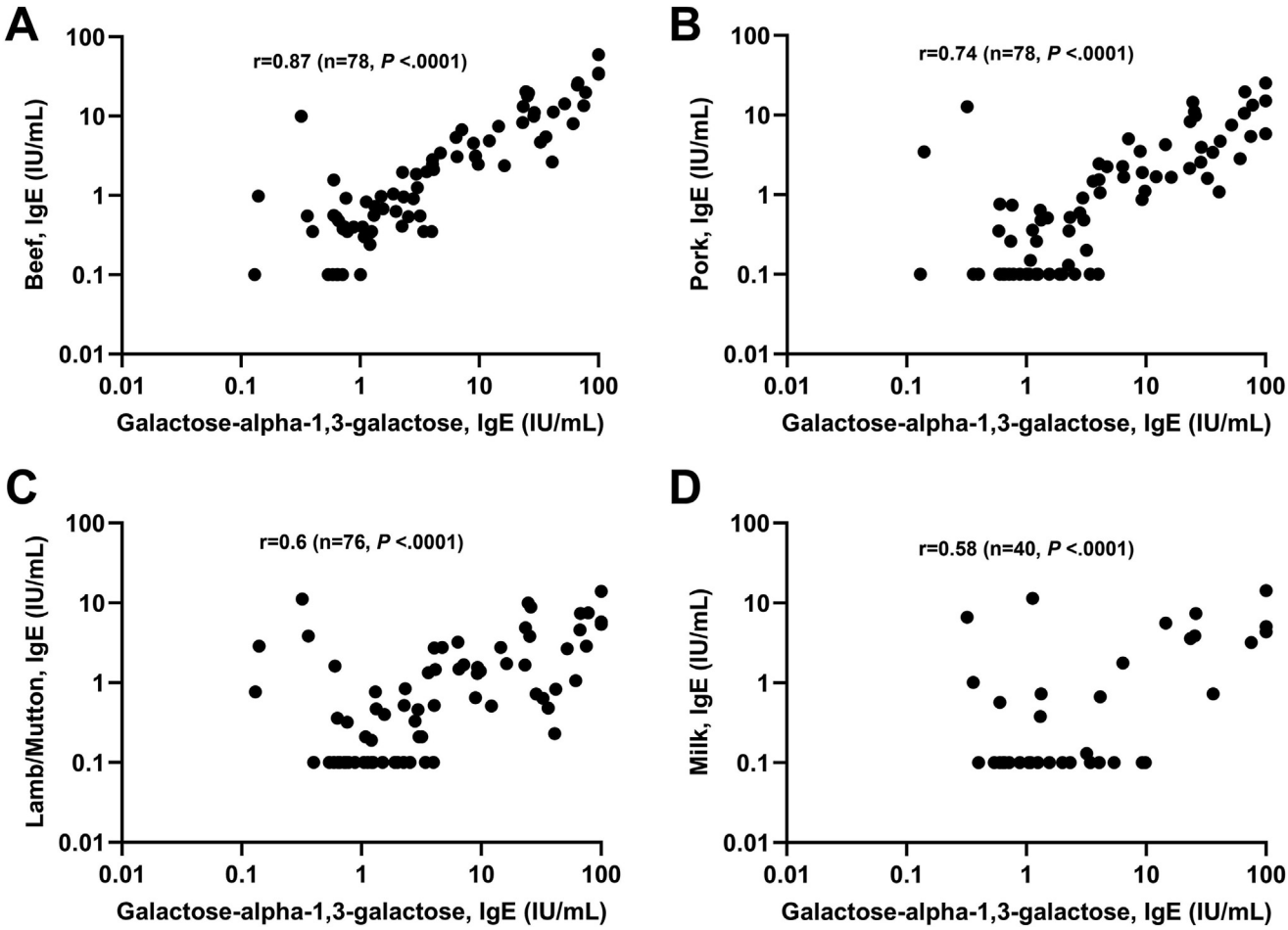

Figure 1. Scatter plot graphs showing the correlation between alpha-gal IgE titers and various meat sIgE titers: (*A*) beef IgE, (*B*) pork IgE, (*C*) lamb IgE, and (*D*) milk IgE. Significant correlations were observed for beef IgE, pork IgE, lamb IgE, and milk IgE with alpha-gal IgE in Pearson correlation analysis (*P* value $<$.0001 for all).

gal antigen through a tick bite. Its heterogeneous clinical presentation makes diagnosis challenging. In this study, nearly half of the AGS patients experienced at least 1 GI symptom, such as diarrhea, nausea, vomiting, abdominal pain, abdominal cramps, bloating, heartburn, and constipation, in descending order of frequency. Adding to the complexity of diagnosing AGS, about 11% of AGS patients presented solely with GI symptoms.

A significant differentiator to aid in diagnosis was a confirmed history of tick bites, which was 26 times more prevalent in the seropositive group. This underscores the importance of inquiring about tick bite history in patients with ambiguous allergic or GI symptoms especially in regions with a high prevalence of AGS, such as the Southern, Midwestern, and Mid-Atlantic U.S. regions.[1] Additional differentiating factors were the higher frequency of urticaria and a reduced tendency to develop heartburn and bloating in the seropositive group, and the higher prevalence of asthma in the seronegative cohort. However, it is essential to note that most patients in the seronegative cohorts were tested for alpha-gal due to allergic reactions, potentially skewing the comparison. The prevalence of asthma in the seropositive group was 35.6%, significantly higher than the 8% prevalence in the general population of the United States.[17]

A positive correlation emerged between alpha-gal–specific antibody titer and prevalence of urticaria. This may be due to the increased propensity of mast cells and basophils to release histamines and other inflammatory mediators to higher alpha-gal–specific antibodies. This enhanced release may provoke a more pronounced allergic reaction, such as urticaria, in those with elevated antibody titers.[18,19] However, in our study, we found no statistical correlation between increasing sIgE levels with the occurrence of anaphylaxis, angioedema, or other symptoms besides urticaria.

In our study, the prevalence of GI symptoms among AGS patients was observed, with a notable finding that females were twice as likely to report GI symptoms compared with males. Notably, 11% of AGS patients in our study exhibited exclusively GI symptoms, significantly less than 20% of AGS patients in a South African cohort.[20,21] In a prior study, heartburn and bloating were experienced by 2 and 1 out of 16 AGS patients, respectively, and were less frequently encountered than other GI symptoms, which aligns with our findings.[7] These

Table 3. Comparison Between Seropositive AGS Patients With and Without GI Symptoms

Characteristic	Seropositive AGS Patients With GI Symptoms (n = 58)	Seropositive AGS Patients Without GI Symptoms (n = 66)	*P* Value
Age at AGS testing	58 (15–82)	61 (11–82)	.16
Female	40 (68.97)	23 (34.85)	<.01
Race/ethnicity			
White	56 (96.55)	60 (90.91)	.2
Asian	1 (1.72)	2 (3.03)	
American Indian/Alaskan Native	1 (1.72)	1 (1.52)	
Unknown	0 (0)	3 (4.55)	
Symptoms			
Urticaria	37 (63.79)	33 (50)	.12
Angioedema	24 (41.38)	23 (34.85)	.45
Anaphylaxis	21 (36.21)	24 (36.36)	.99
Chest pressure	6 (10.34)	3 (4.55)	.21
Time to symptoms			
<1 h	8 (13.79)	6 (9.09)	.27
1–4 h	14 (24.14)	11 (16.67)	
>4 h	19 (32.76)	17 (25.76)	
Variably	2 (3.45)	6 (9.09)	
Not specified	15 (25.86)	26 (39.39)	
History of asthma	16 (34.04), n = 47	20 (37.03), n = 54	.75
History of tick bite	44 (100), n = 44	44 (91.67), n = 48	.05
Total IgE, IU/mL	163.7 (67.59–396.4), n = 15	249.3 (122.9–505.6), n = 14	.88
Alpha-gal sIgE titers			
sIgE >0.35 IU/mL	55 (96.49), n = 57	65 (98.48), n = 66	.51
sIgE, IU/mL	4.854 (3.063–7.69), n = 55	3.678 (2.47–5.48), n = 65	.23
sIgE 0.35–0.7 IU/mL	8 (14.55), n = 55	11 (16.92), n = 65	.95
sIgE 0.7–3.5 IU/mL	19 (34.55), n = 55	22 (33.85), n = 65	
sIgE 3.5–17.5 IU/mL	14 (25.45), n = 55	18 (27.69), n = 65	
sIgE >17.5 IU/mL	14 (25.45), n = 55	14 (21.54), n = 65	
Beef sIgE >0.35 IU/mL	28 (80), n = 35	35 (81.40), n = 43	.88
Beef sIgE (n = 63), IU/mL	2.88 (1.65–5.05)	2.68 (1.65–4.37)	.65
Mutton/lamb sIgE >0.35 IU/mL	20 (58.82), n = 34	25 (59.52), n = 42	.96
Mutton/lamb sIgE (n = 45), IU/mL	1.65 (1.06–2.56)	1.9 (1.21–2.98)	.51
Pork sIgE >0.35 IU/mL	22 (61.11), n = 36	26 (61.90), n = 42	.94
Pork sIgE (n = 48), IU/mL	2.50 (1.57–3.96)	2.52 (1.53–4.16)	.64
Milk sIgE >0.35 IU/mL	5 (33.33), n = 15	12 (48), n = 25	.95
Milk sIgE (n = 17), IU/mL	2.64 (0.52–13.48)	2.46 (1.20–5.01)	.67

Values are median (range), n (%), or geometric mean (95% confidence interval).
AGS, alpha-gal syndrome; GI, gastrointestinal; sIgE, specific IgE.

findings emphasize the need for further research to better understand the presentation of GI manifestations in AGS.

Symptom onset in AGS typically occurs more than 4 hours after allergen exposure, with studies emphasizing a tight association with delayed reactions within the 3- to 6-hour range.[3,22] Yet, the mechanisms behind these delayed reactions, particularly the incidence of GI symptoms, remain unclear. The prevailing hypothesis suggests that alpha-gal glycolipids are likely to be incorporated into chylomicrons which are subsequently metabolized into low-density lipoprotein or smaller fat droplets. Thus, they undergo processing and transport into the lymph via the lacteal vein, reaching the bloodstream few hours after a meal, before becoming exposed to the surface of chylomicrons. These alpha-gal molecules facilitate crosslinking of IgE antibodies directed against alpha-gal.[18] However, alpha-gal glycoproteins and glycolipids were found to induce allergic effector in standard basophil testing in within 30–60 minutes.[23] Interestingly, significant disparities have been identified in the metabolic pathways of lipids and fatty acids between individuals with and without AGS.[24] Therefore, the delayed allergic responses observed in alpha-gal allergies could be attributed to the time needed for the absorption and metabolism of lipids. It is worth noting that symptoms can also appear within 1–4 hours after allergen exposure, and we also observed variable symptom onset among patients. A European AGS patient study found no significant difference in alpha-gal IgE levels based on

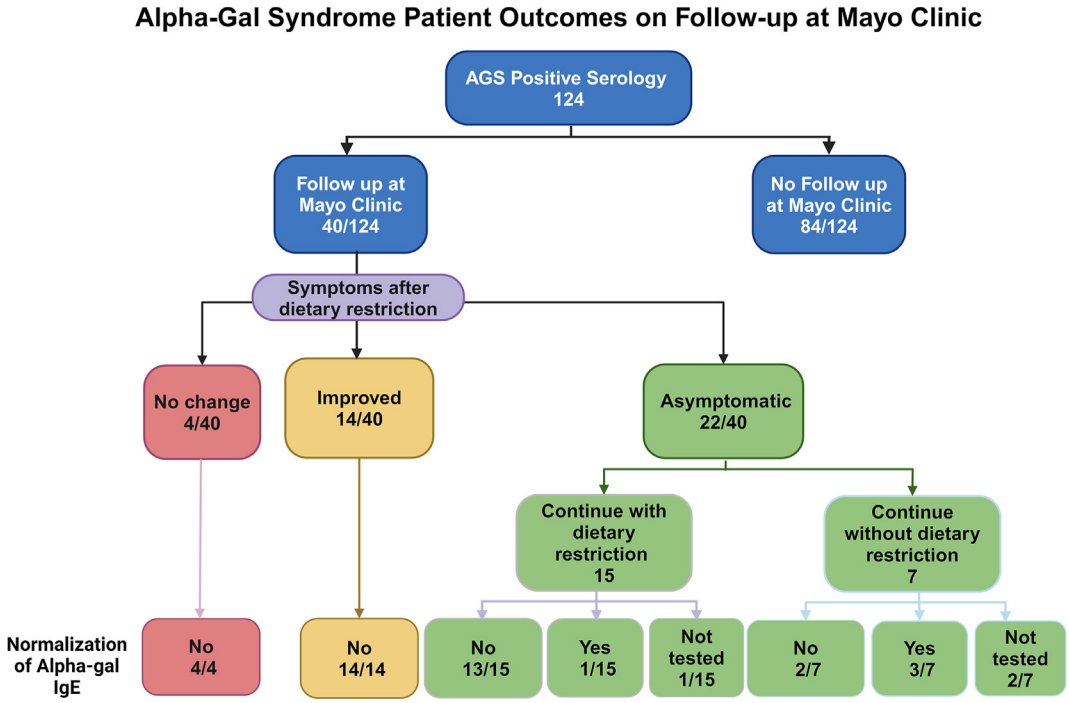

Figure 2. AGS patient outcomes on follow-up at Mayo Clinic.

symptom onset times.[15] In contrast, our study identified significant differences in symptom onset related to serological titers. Lower titer patients (sIgE = 0.35–0.7 IU/mL) tended to experience variable or early onset (<1 hour), while higher titer patients (sIgE = 0.7–3.5 IU/mL, 3.5–17.5 IU/mL, and >17.5 IU/mL) had later onset (>1 hour). Additionally, in the European cohort, positive sIgE levels for beef, pork, and milk were found in 98.4%, 96.1%, and 91.4% of patients, respectively.[15] In contrast, in our study, the positivity rates among patients for beef, pork, and milk were 80.8%, 61.5%, and 42.5%, respectively. These differences raise questions regarding potential variations in AGS between the United States and Europe. Furthermore, correlation analysis within our cohort revealed that among meat sIgE, beef IgE exhibits the strongest correlation with alpha-gal IgE. Considering our correlation analysis along with the high seropositivity in our cohort and the European study, sIgE targeting beef protein might be the most reliable meat sIgE to predict AGS.

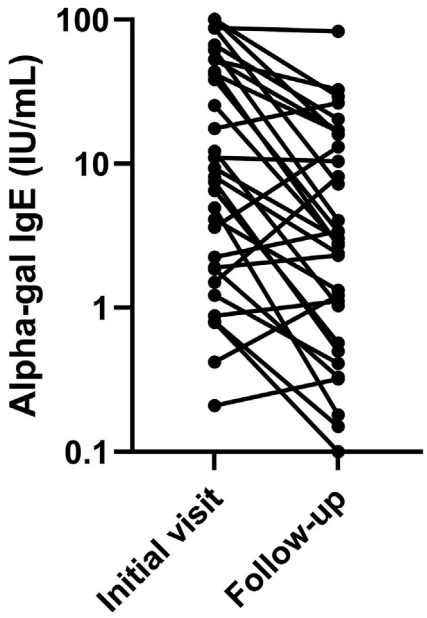

Figure 3. Changes in serum alpha-gal IgE levels during follow-up after adopting a meat-free diet and avoiding ticks. Among the 37 patients, 28 experienced a reduction in alpha-gal IgE levels, while 9 showed an increase during follow-up. Mean decrease of 17 IU/mL (paired *t* test; $P = .0009$).

Patients diagnosed with AGS are typically advised to adopt a red meat–free diet and take precautions to avoid further tick exposure. Previous studies have shown that tick avoidance can reduce the levels of alpha-gal IgE.[25] In our study, we observed 76% of patients showed a decrease in alpha-gal IgE titers on follow-up when instructed to avoid further tick exposure and adhere to a red meat–free diet. However, the impact of red meat avoidance on this decline is not well established, as there are no studies demonstrating eating red meat can influence alpha-gal IgE in AGS patients. It is also noteworthy that milk and dairy products, though less common, can also induce allergic reactions in AGS patients.[26] In our study, around 10% of AGS patients reported experiencing new-onset acute episodes after consuming milk, highlighting the importance of considering dairy avoidance in some cases.

A study reported that symptoms can resolve in 80%–99% of patients with AGS upon avoidance of alpha-gal–containing products, depending on the degree of

avoidance.[27] Another study showed that of 15 AGS patients who followed a red meat–free diet, 9 reported complete resolution of symptoms, 4 reported partial resolution of symptoms, and 1 reported no change in symptoms.[28] Similar results were observed in our cohort of 40 patients who adhered to a red meat–free diet and underwent follow-up. Approximately 55% reported complete resolution of symptoms, while 35% reported partial improvement. However, these figures may underestimate the effectiveness of avoiding red meat derivatives, as everyday foods may contain cryptic alpha-gal antigens, potentially leading to inadvertent allergic exposure. Careful scrutinization of all ingredients in home-cooked meals or when dining out may lead to a higher rate of complete symptom resolution.

The natural progression of alpha-gal has not been well established yet. In a large AGS registry, nearly 12% of patients had negative titers and successfully reintroduced mammalian meat into their diet on follow-up for at least 5 years.[22] In our study, with a mean follow-up duration of 27 months, 18% (n = 7 of 40) had successfully reintroduced red meat into their diet. Remarkably, only 3 of these 7 patients had normal serology on follow-up, demonstrating that clinical resolution may not necessarily coincide with the normalization of serological markers. Overall, 11% (n = 4 of 37) AGS patients had normalization of serology on follow-up, and all of them had achieved complete symptomatic resolution by adhering to dietary restrictions. This suggests that symptomatic patients, even with dietary restrictions, are likely to have abnormal serology. There is a need for a large-scale prospective study to understand the outcomes of this complex disorder.

We acknowledge that this study has limitations largely related to its design. A retrospective review of records relies on appropriate physician documentation, and there may have been missing data with regard to the patient's clinical history and laboratory results. Long-term longitudinal follow-up is lacking in several patients, given their transition back to the primary care setting following an evaluation at our tertiary center.

In conclusion, AGS can have a diverse and often severe presentation, ranging from GI disturbances to allergic reactions like urticaria and anaphylaxis, and with some patients notably presenting exclusively with GI symptoms. Additionally, female AGS patients may have a higher likelihood of developing GI symptoms. While dietary intervention proves effective for most patients, it may not work for everyone. Future studies with larger, prospectively enrolling registries are necessary to further elucidate the complexities of AGS and refine diagnostic and therapeutic approaches.

References

1. Thompson JM, Carpenter A, Kersh GJ, et al. Geographic distribution of suspected alpha-gal syndrome cases — United States, January 2017–December 2022. MMWR Morb Mortal Wkly Rep 2023;72:815–820.
2. Ailsworth SM, Susi A, Workman LJ, et al. Alpha-gal IgE prevalence patterns in the United States: an investigation of 3,000 military recruits. J Allergy Clin Immunol Pract 2024;12:175–184.e5.
3. Young I, Prematunge C, Pussegoda K, et al. Tick exposures and alpha-gal syndrome: a systematic review of the evidence. Ticks Tick Borne Dis 2021;12:101674.
4. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 2008;358:1109–1117.
5. McGill SK, Hashash JG, Platts-Mills TA. AGA clinical practice update on alpha-gal syndrome for the GI clinician: commentary. Clin Gastroenterol Hepatol 2023;21:891–896.
6. Apostolovic D, Tran TA, Hamsten C, et al. Immunoproteomics of processed beef proteins reveal novel galactose-alpha-1,3-galactose-containing allergens. Allergy 2014;69:1308–1315.
7. Croglio MP, Commins SP, McGill SK. Isolated gastrointestinal alpha-gal meat allergy is a cause for gastrointestinal distress without anaphylaxis. Gastroenterology 2021;160:2178–2180.e1.
8. Tripathi A, Commins SP, Heymann PW, et al. Delayed anaphylaxis to red meat masquerading as idiopathic anaphylaxis. J Allergy Clin Immunol Pract 2014;2:259–265.
9. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. J Clin Oncol 2007;25:3644–3648.
10. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. J Allergy Clin Immunol 2015;135:589–596; quiz 597.
11. Vaz-Rodrigues R, Mazuecos L, de la Fuente J. Current and future strategies for the diagnosis and treatment of the alpha-gal syndrome (AGS). J Asthma Allergy 2022;15:957–970.
12. Brestoff JR, Zaydman MA, Scott MG, et al. Diagnosis of red meat allergy with antigen-specific IgE tests in serum. J Allergy Clin Immunol 2017;140:608–610.e5.
13. Fischer J, Lupberger E, Hebsaker J, et al. Prevalence of type I sensitization to alpha-gal in forest service employees and hunters. Allergy 2017;72:1540–1547.
14. German-Sanchez A, Alonso-Llamazares A, Garcia-Gonzalez F, et al. Diagnostic validity of specific IgE levels to alpha-gal in alpha-gal syndrome: a cross-sectional analysis. Allergy Asthma Clin Immunol 2023;19:102.
15. Kiewiet MBG, Apostolovic D, Starkhammar M, et al. Clinical and serological characterization of the alpha-gal syndrome-importance of atopy for symptom severity in a European cohort. J Allergy Clin Immunol Pract 2020;8:2027–2034.e2.
16. Commins SP, James HR, Stevens W, et al. Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. J Allergy Clin Immunol 2014;134:108–115.
17. Pate CA, Zahran HS, Qin X, et al. Asthma surveillance - United States, 2006–2018. MMWR Surveill Summ 2021;70:1–32.
18. Roman-Carrasco P, Hemmer W, Cabezas-Cruz A, et al. The alpha-gal syndrome and potential mechanisms. Front Allergy 2021;2:783279.
19. Sharma SR, Karim S. Tick saliva and the alpha-gal syndrome: finding a needle in a haystack. Front Cell Infect Microbiol 2021;11:680264.
20. Macdougall JD, Thomas KO, Iweala OI. The meat of the matter: understanding and managing alpha-gal syndrome. Immunotargets Ther 2022;11:37–54.

21. Mabelane T, Basera W, Botha M, et al. Predictive values of alpha-gal IgE levels and alpha-gal IgE: total IgE ratio and oral food challenge-proven meat allergy in a population with a high prevalence of reported red meat allergy. Pediatr Allergy Immunol 2018;29:841–849.
22. Commins SP. Diagnosis and management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol 2020;16:667–677.
23. Iweala OI, Choudhary SK, Addison CT, et al. Glycolipid-mediated basophil activation in alpha-gal allergy. J Allergy Clin Immunol 2020;146:450–452.
24. Steinke JW, Pochan SL, James HR, et al. Altered metabolic profile in patients with IgE to galactose-alpha-1,3-galactose following in vivo food challenge. J Allergy Clin Immunol 2016; 138:1465–1467.e8.
25. Commins SP, James HR, Kelly LA, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. J Allergy Clin Immunol 2011;127:1286–1293.e6.
26. Perusko M, Apostolovic D, Kiewiet MBG, et al. Bovine gammaglobulin, lactoferrin, and lactoperoxidase are relevant bovine milk allergens in patients with alpha-Gal syndrome. Allergy 2021;76:3766–3775.
27. Patel C, Iweala OI. 'Doc, will I ever eat steak again?': diagnosis and management of alpha-gal syndrome. Curr Opin Pediatr 2020;32:816–824.
28. Pollack K, Zlotoff BJ, Borish LC, et al. Alpha-gal syndrome vs chronic urticaria. JAMA Dermatol 2019;155:115–116.

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Ashley Keehn (Project administration: Supporting; Resources: Supporting; Supervision: Equal; Writing – review & editing: Supporting)
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