

## FOCUS ON

# Alpha-gal Syndrome (AGS)



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## Introduction

This document explores the emergence, epidemiology and clinical presentation of alpha-gal syndrome (AGS) and the association between AGS and lone star ticks (*Amblyomma americanum*). AGS is a delayed allergic reaction to alpha-gal that typically develops two to six hours following consumption of red meat (e.g., beef, lamb, pork), meat-containing products (e.g., pharmaceuticals, gelatin), or dairy products.

Public Health Ontario (PHO) developed this Focus On to raise awareness of AGS among Ontario public health partners and healthcare providers. This resource is both timely and essential, given the recent emergence of AGS in the US, the lack of AGS surveillance in Canada, and the potential for lone star ticks to establish in Ontario.

## Key Messages

- AGS surveillance is lacking in North America and incidence rates are largely unknown, making the monitoring of AGS emergence challenging. Based on indirect evidence, the bite of a lone star tick is the primary source of alpha-gal antigens in those with AGS and AGS is an emerging condition wherever lone star ticks are established.
- AGS manifests similar to other food allergies, but is characterized by a delay in onset of symptoms such as itching, swelling, anaphylaxis, and vomiting.
- The risk of locally acquired AGS among Ontarians is low, since the primary tick responsible (lone star tick) is not established in the province, but has occasionally been detected. Climate change (e.g., increasing temperature) will make previously unfavourable habitat in Ontario more suitable for lone star ticks to survive the province's winters, aiding in their incursion and establishment.
- There is no evidence for AGS in Ontario, partly because there is no surveillance mechanism for AGS in the province or elsewhere in Canada.

## Background

Galactose-alpha-1,3-galactose (alpha-gal) is a sugar molecule found in non-primate mammalian meat. AGS is a delayed allergic reaction characterized by an IgE-mediated hypersensitivity to alpha-gal following consumption of red meat (e.g., beef, lamb, pork) or meat-containing products (e.g., pharmaceuticals, gelatin).<sup>1-3</sup> The discovery of AGS, also known as red meat allergy or alpha-gal allergy, began in the 2000s, with Commins et al. describing a series of 24 cases of delayed anaphylaxis, angioedema and urticaria following consumption of red meat in Missouri and Virginia, US.<sup>4</sup> Patients with AGS develop hypersensitivity to alpha-gal following tick bites, where immunogenicity arises from exposure to the alpha-gal sugar (antigen) attached to tick salivary proteins (epitopes). AGS occurs worldwide, but most of the epidemiological evidence for AGS is from the US and, to a lesser extent, Europe.<sup>1</sup>

## Methods

We conducted a literature search on August 22, 2023, in MEDLINE using key words "lone star", "*Amblyomma americanum*", "alpha-gal" and "red meat allergy". The exposure of interest was lone star tick bites and the outcome of interest was AGS. English-language peer-reviewed and non-peer-reviewed records that described AGS and lone star ticks were included. Out-of-scope for this document was a review of the pathophysiology and treatment of AGS. We will concentrate on epidemiological information most relevant to Ontario, i.e., scientific evidence from North America.

## Results

### Emergence of AGS

AGS surveillance is lacking in North America and incidence rates are largely unknown, making the monitoring of AGS emergence challenging. Using alpha-gal-specific IgE testing data from a commercial laboratory in the US (2017–2022), Thompson et al. reported 90,018 suspected cases of AGS with positive IgE tests and no clinical information; cases increased from 13,371 in 2017 to 18,885 in 2021.<sup>5</sup> Using a similar methodology from 2010 through 2018 in the US, Binder et al. reported an increase in IgE-positive AGS cases, from 2009 in 2010 to 7,798 in 2018.<sup>6</sup> The authors note that testing was likely the result of high clinical suspicion on the part of health care providers, thus results were not representative of the broader population.

While not a nationally notifiable disease in the US, the Council of State and Territorial Epidemiologists (CTSE) have developed a surveillance case definition for AGS and a case reporting form.<sup>7</sup> States can adopt the case definition and report cases nationally on a voluntary basis. Additional means of AGS surveillance suggested by the CSTE and the Centers for Disease Control and Prevention include monitoring of:

1. commercial laboratory data,
2. emergency room visits, hospital admission and discharge records, and
3. physician billing and reporting data.

## Distribution of AGS and Lone Star Ticks

Based on indirect evidence, the lone star tick is the primary source of alpha-gal antigens in those with AGS. The distribution of AGS cases in the US overlaps that of the lone star tick and the pathogens it spreads (i.e., *Ehrlichia chaffeensis* and *Ehrlichia ewingii*), with most cases of ehrlichiosis in the Midwest Region (Arkansas, Missouri, Kentucky) and Mid-Atlantic Division of the Northeast Region (Virginia; Long Island, New York).<sup>5</sup> Compared to the West Region in US, the highest risk of AGS was in the South Region (risk ratio [RR]: 5.4, 95% confidence interval [CI]: 4.1–6.9), followed by the Northeast Region (RR: 4.8, 95% CI: 3.7–6.2).<sup>6</sup> Further evidence implicating the lone star tick as the source of alpha-gal in AGS includes a laboratory-based study in which Crispell et al. noted that lone star ticks and blacklegged ticks (*Ixodes scapularis*) maintained alpha-gal in saliva and salivary glands after feeding on sheep (1–11 days).<sup>8</sup> There is no evidence that blacklegged ticks are the primary source of alpha-gal in AGS cases. Documented cases of AGS following the bite of a lone star tick are uncommon, limiting a definitive origin for AGS.<sup>1</sup> To understand tick-AGS associations, testing of field-collected ticks for alpha-gal-specific antigens is needed.

The lone star tick occurs throughout the eastern US and south into Mexico and feeds on small to medium mammals (e.g., dogs, raccoons) and large mammals (white-tailed deer), birds (wild turkey) and humans.<sup>9,10</sup> The lone star tick is found in low numbers (50–85 submitted annually during passive surveillance) in Ontario, especially when compared to the thousands of blacklegged ticks and American dog ticks (*Dermacentor variabilis*) submitted every year. Research has not demonstrated established lone star tick populations in the province, nor has it been detected during active surveillance.<sup>11</sup> *Amblyomma americanum* are usually removed from hosts with known travel to parts of the US. Occasionally, these ticks are removed from hosts in Ontario who did not travel, and we assume these specimens were introduced into Canada on migratory birds or other host animals. In addition, there is a possibility that ephemeral populations emerge in Ontario, only to die-out during the winter. The lone star tick prefers similar habitats as the blacklegged tick, such as deciduous forests with dense undergrowth. Climate and land use changes, along with increased host densities (e.g., white-tailed deer, wild turkey), are aiding a northward range expansion of the lone star tick into coastal Maine and southern portions of Michigan, New York, Ohio, Pennsylvania and Wisconsin.<sup>12-17</sup>

## Clinical Presentation

AGS manifests similar to other food allergies, but is characterized by a delay in onset of symptoms. AGS typically develops two to six hours following consumption of red meat or meat products; however, this delay may vary among cases and is not pathognomonic.<sup>2</sup> In a systematic review of 3,105 AGS cases from observational studies, the mean time from consumption of red meat to start of allergy symptoms was from two to six hours (<0.5 to 24 hours).<sup>1</sup> In case reports of 232 patients with AGS, the most common food items that elicited an allergic reaction were beef (33%), pork (29%), lamb (19%) and gelatin-

containing products (19%). The time from tick exposure to AGS symptoms ranged from one week to several years (n=26). In a random sample of 100 AGS patients, the most commonly reported foods eliciting allergic reactions were unspecified red meats (56%), beef (47%), pork (32%) and dairy (32%).<sup>18</sup> The median time from tick exposure to AGS symptoms was two months (interquartile range [IQR]: 1–4; n=15). There is evidence that certain mammalian organ meats and innards (kidneys, heart, liver) speed up the onset of AGS symptoms.<sup>7,19,20</sup>

Dermatological and gastrointestinal symptoms dominate AGS. In a systematic review of 232 cases, the most commonly reported symptoms were dermatological (75%; e.g., urticaria, angioedema, pruritus), followed by anaphylaxis (52%), gastrointestinal symptoms (30%; e.g., abdominal pain, diarrhea, vomiting) and respiratory symptoms (17%; e.g., wheezing, chest tightness, cough).<sup>5</sup> Approximately 9% of cases visited an emergency department, but no deaths were reported. In a study of 91 patients with AGS, approximately 73% of patients developed gastrointestinal symptoms such as abdominal pain and vomiting.<sup>21</sup> Binder et al. reported that in a random sample of 100 AGS cases, 41% required emergency care (75% had anaphylaxis), with 87% reporting mucocutaneous symptoms and 66% gastrointestinal symptoms.<sup>18</sup>

## Patient Demographics

The number of persons receiving positive test results for AGS increased with age and male sex. Young et al. reported that the mean age of AGS cases was 51.3 years (standard deviation [SD]: 16.7, range 5–85, n=229) and most were male (68%, n=226); in 77 cases with information on ethnicity, all were white.<sup>1</sup> In the largest study to date in the US, Thompson et al. reported the mean age of suspected AGS cases was 48.2 years (SD: 19.9; n=90,018) and cases distributed equally by sex (female: 50.3%).<sup>5</sup> Compared to negative alpha-gal-specific IgE test individuals (n=205,382), the risk of AGS increased with age (highest in those >70 years; RR: 3.2; 95% CI: 3.0–3.4; compared to 0–9 years) and was higher in males (RR: 2.3, 95% CI: 2.2–2.3). From 2010 through 2018 in the US, Binder et al. reported a mean age of AGS cases was 46.9 years (SD: 19.8); risk increased with age (highest in those >70 years: RR: 2.2, 95% CI: 2.1–2.3) and in males (RR: 1.7, 95% CI: 1.6–1.7).<sup>6</sup> In a random sample of AGS cases (2010–2019), Binder et al. reported that the median age of cases was 53 years (IQR: 42–60), 66% were female and 95% were white.<sup>18</sup> A diverse, population-wide assessment of AGS is needed, as there is likely inequity in access to testing.

## Environmental Risk Factors

The factors contributing to increased risk of AGS are largely unknown; however, we can assume a correlation between the risk of AGS and exposure to lone star ticks. In a case-control study conducted in North Carolina, US, Kersh et al. reported that patients with AGS were more likely to report finding a tick on themselves (odds ratio [OR]: 11.2, 95% CI: 4.97–25.15) and spend >17 hours a week in wooded areas (OR: 5.6, 95% CI: 2.56–12.19).<sup>22</sup> In a systematic review of 236 cases, non-B blood type was the most commonly reported risk factor (38%), followed by outdoor activities (12%); however, these results were not compared to control populations.<sup>1</sup> Not all patients with elevated alpha-gal-specific IgE will develop AGS; the leading hypotheses for differential sensitivities to alpha-gal include host factors such as blood type, atopy, microbiome, diet and medications.<sup>2</sup>

## Summary

AGS is an emerging tick-borne allergic reaction in the US; however, there is no evidence for AGS in Ontario, partly because there is no surveillance mechanism for AGS in the province or elsewhere in Canada. It is unclear whether the increased numbers of AGS cases in the US are from increased awareness, increased exposure to lone star ticks or both.<sup>5</sup> Further hindering AGS surveillance, health care provider and public awareness surrounding AGS is lacking. In a survey of 1,500 health care providers in the US, 42% of respondents had never heard of AGS and an additional 35% reported that they would not be able to effectively diagnose or manage the condition.<sup>23</sup>

## Conclusion

The risk of locally acquired AGS among Ontarians is low, since the primary tick responsible (lone star tick) is not established in the province. However, as climate and land use changes make areas of Ontario more suitable for lone star tick incursion and establishment, the risk of AGS increases.

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