21-ID-07

Committee: Infectious Disease

Title: Standardized Case Definition for Alpha-Gal Syndrome

☐Check this box if this position statement is an update to an existing standardized surveillance case definition and include the most recent position statement number here: ___N/A_____.

Synopsis:
This position statement creates a standardized case definition for surveillance of alpha-gal (galactose-alpha-1,3-galactose) syndrome, also known as red meat allergy or alpha-gal allergy. [1–3]

I. Statement of the Problem

Alpha-gal Syndrome (AGS) is a hypersensitivity reaction to galactose-α-1,3-galactose (alpha-gal), found in non-primate mammalian meat and certain derivative products.[4,5] Unlike typical food allergies, symptoms are often delayed by two hours or more after exposure and can arise suddenly following years of safe meat consumption.[6–8] Evidence suggests that the bite of some tick species induces immunoglobulin E (IgE) antibodies to alpha-gal, sensitizing patients to subsequent alpha-gal exposures.[1,9–12] Symptoms typically include abdominal cramping, urticaria, and anaphylaxis.[8] Diagnosis relies on a history of symptoms following exposure to mammalian products, and an elevated serum IgE specific to alpha-gal.[6] AGS has been reported worldwide[13]; in the United States, it is most closely associated with lone star tick (*Amblyomma americanum*) bites.[10] Research has suggested that other tick species, including *Ixodes* spp., may also be associated with AGS development.[14,15] Reports of AGS in the scientific literature have been increasing over the last decade, but the true burden of cases is unknown. Additionally, much of the country may be at risk given the expanding geographic range of lone star and other ticks.[16] Responding to the increased diagnosis of cases and public interest, multiple states have expressed a desire to quantify the burden of AGS. The standardization of case definition and reporting criteria is necessary in order to characterize disease burden, compare interstate disease incidence, and monitor trends in patient demographics, morbidity, mortality, and geographic distribution of risk. This will inform public health recommendations and guidance. Preventing tick bites is the main strategy for AGS intervention[1–3]; disease surveillance could, therefore, inform activities to strengthen occupational health protocols of suspected risk groups and public health messaging regarding tick bite prevention behaviors, with the goal of reducing tick borne disease risk.[11,23]

II. Background and Justification

AGS is an IgE-mediated hypersensitivity reaction specific to alpha-gal, an oligosaccharide found on the cells of non-primate mammals and their product derivatives. Clinical presentation is broad with no one symptom or cluster of symptoms consistently predominating in patients with AGS. Skin reactions, like urticaria, and anaphylaxis are common; patients may also present with gastrointestinal or respiratory symptoms. Time to symptom onset may depend on the mode of exposure, with delayed onset (usually 2-6 hours, with longer intervals reported) after consumption of red meat or mammalian-derived products, including gelatin and dairy products.[6,14,17] Hypersensitivity reactions in patients exposed to alpha-gal-containing products (e.g., gelatin-containing vaccines, heparin, antivenoms) have been reported to occur within two hours after intravenous, subcutaneous, or intramuscular administration, as well as in patients receiving xenotransplants.[4,18] Patients can experience life-threatening anaphylaxis following all modes of exposure. Available diagnostics include allergy skin tests demonstrating sensitization to beef, pork, or lamb antigens and alpha-gal-specific IgE (sIgE) tests that are widely available through commercial laboratories, with a value of ≥0.1k IU/ml or ≥0.1 kU/L generally considered positive.[19] Management of AGS includes use of antihistamines, epinephrine, and the elimination of mammalian meat and other alpha-gal-containing products from the diet. Avoidance diets and prevention of additional tick bites allow many patients to slowly reintroduce meat into their diets.[7]

Assessment of commercial laboratory data from 2010-2018 documented that the majority of positive alpha-gal sIgE antibody tests were submitted from the southeast region of the United States, and the number of tests performed increased 81-fold during this period.[20] Early case studies identified a geographic distribution overlapping with that of the lone star tick (LST).[10] Studies have also demonstrated the presence of the alpha-gal moiety in LST saliva, and an increase in alpha-gal sIgE following a LST bite.[10,15] Together, these findings suggest that the bite of a LST can sensitize patients to alpha-gal and lead to AGS. Blacklegged tick saliva has also been shown to contain the alpha-gal moiety, and bites from these ticks might similarly sensitize patients, expanding the distribution of people at risk.[15] At this time, sensitization to alpha-gal has only been associated with tick bites.[10,21] Once sensitized, patients may have reactions following exposure to sources of alpha-gal via dietary or parenteral routes. Estimates from 2013 suggest that at least 5,000 cases of AGS had been diagnosed in the United States at that time.[22] One commercial laboratory tested 105,674 people between 2010 and 2018, and 32% were positive for alpha-gal sIgE.[20] Accurate, up-to-date estimates of burden, disease trends and geographic distribution are hampered by the absence of a standardized case definition and reporting.

This position statement establishes a standardized, surveillance AGS case definition for states that wish to include AGS in their list of reportable conditions or, depending on capacity and resources, conduct pilot studies or targeted surveillance for this emerging syndrome. Though this case definition is not intended for clinical use, public health officials could utilize it to help inform clinicians about the estimated burden and trends of AGS in their regions.

III. Statement of the desired action(s) to be taken

CSTE recommends the following actions:

1. Implement a standardized surveillance case definition for AGS.
    A. Utilize standard sources (e.g., reporting*) for AGS case ascertainment. Surveillance for AGS should use the recommended sources of data to the extent of coverage presented in Section V.

    B. Utilize standardized criteria for AGS case ascertainment presented in Section VI and Table VI in Technical Supplement.

    C. Utilize standardized criteria for AGS case classification presented in Section VII and Table VII in Technical Supplement.

    Note: this action does NOT add AGS to the *Nationally Notifiable Condition List*. If requested by CDC, jurisdictions (e.g., states and territories) conducting surveillance according to these methods may voluntarily submit case information to CDC.

*Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance TO local, state, or territorial public health.

IV. Goals of Surveillance

The goal of surveillance is to characterize the spatiotemporal distribution and burden of AGS. A standardized definition allows for comparability of data across jurisdictions. This is not a recommendation to require national notification.

V. Methods for Surveillance: Surveillance for alpha-gal syndrome should use the recommended sources of data and the extent of coverage listed in Table V.

The most common data source for case ascertainment will be laboratory reporting, followed by clinician reporting. Laboratories should generate reports of positive alpha-gal sIgE tests. Clinical information will be obtained from clinician reporting or review of medical records. Hospital discharge data may be used as supplementary method for case finding.

An alpha-gal sIgE test along with compatible clinical symptoms are required for confirmed cases. These data will be collected via laboratory and clinician reporting. Allergy skin testing results consistent with alpha-gal

allergy and compatible clinical symptoms are necessary for a probable case classification; therefore, clinician reporting of these results will be required. A positive alpha-gal sIgE test without corresponding clinical information is sufficient for a suspect case classification, and these data will be collected via laboratory reporting.

Table V. Recommended sources of data and extent of coverage for ascertainment of cases of alpha-gal syndrome.

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	X	
Laboratory reporting	X	
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers), specify: Hospitals	X	
Death certificates	X	
Hospital discharge or outpatient records	X	
Data from electronic medical records	X	
Telephone survey		
School-based survey		
Other, specify: N/A		

VI. Criteria for case ascertainment

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

In public health jurisdictions where AGS is a reportable condition, laboratories, clinicians, and outpatient clinics should report based on the following criteria:

A1. Clinical Criteria for Reporting
Not applicable.

A2. Laboratory Criteria for Reporting

Any of the following criteria warrant reporting to public health authorities:

- Serum or plasma immunoglobulin E specific to alpha-gal (sIgE) ≥ 0.1 IU/mL or ≥ 0.1 kU/L.
- An allergy skin test result that is interpreted by the ordering provider as consistent with alpha-gal allergy based on sensitivity to one or more mammalian meats (e.g., pork, beef, lamb) or other mammalian-derived products.

A3. Epidemiologic Linkage Criteria for Reporting
Not applicable.

A4. Vital Records Criteria for Reporting
Report any person whose death certificate lists AGS as a cause of death or a significant condition contributing to death.

A5. Other Criteria for Reporting
Report any person whose healthcare or medical record contains a diagnosis, active problem, or finding of AGS.

B. Disease-specific data elements to be included in the initial report

None.

VII. Case Definition for Case Classification

A. Narrative: Description of criteria to determine how a case should be classified.

A1. Clinical Criteria

- Acute onset of any one or more of the following allergic and/or gastrointestinal symptoms that occur 2–10 hours after ingestion of pork, beef, lamb, any other mammalian meat, or any mammalian-derived product (e.g. gelatin), OR within two hours after intramuscular, intravenous, or subcutaneous administration of alpha-gal-containing vaccination or medication (see Appendix 1):
    - Abdominal pain
    - Nausea
    - Diarrhea
    - Vomiting
    - Heartburn/indigestion
    - Hives
    - Itching
    - Anaphylaxis as diagnosed by a provider
    - Swelling of one or more of the following: lips, tongue, throat, face, eyelids, or other associated structures
    - Shortness of breath
    - Cough
    - Wheezing
    - Acute episode of hypotension*

AND

- the absence of a clear alternative diagnosis.

** Normal values for systolic blood pressure vary by age. Hypotension is classified by systolic blood pressure <90 mmHg for ages 11+ years; < [70 mmHg + 2 x age] for ages 1 -10 years; <70 mmHg for ages less than 1 year.*

A2. Laboratory Criteria

Confirmatory laboratory evidence:

- Serum or plasma immunoglobulin E specific to alpha-gal (sIgE) ≥ 0.1 IU/mL or ≥ 0.1 kU/L.

Presumptive laboratory evidence:

- An allergy skin test result that is interpreted by the ordering provider as consistent with alpha-gal allergy based on sensitivity to one or more mammalian meats (e.g., pork, beef, lamb) or other mammalian-derived products.

Supportive laboratory evidence:
N/A

Note: The categorical labels used here to stratify laboratory evidence are intended to support the standardization of case classifications for public health surveillance. The categorical labels should not be used to interpret the utility or validity of any laboratory test methodology.

A3. Epidemiologic Linkage

Not applicable.

A4. Case Classifications

Confirmed:

- Meets clinical criteria AND confirmatory laboratory evidence.

Probable:

- Meets clinical criteria AND presumptive laboratory evidence.

Suspect:

- Meets confirmatory laboratory evidence with no clinical information available.

B. Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance

A case should only be counted if not previously reported to public health authorities.

VIII. Period of Surveillance

Surveillance is expected to be on-going.

IX. Data sharing/release and print criteria

CSTE recommends the following case statuses* be included in the 'case' count released outside of the public health agency:

☒Confirmed
☒Probable
☐Suspect
☐Unknown

* Which case statuses are included in the case counts constitute the "print criteria."

Jurisdictions (e.g., States and Territories) conducting surveillance under this case definition can voluntarily submit de-identified case information to CDC, if requested and in a mutually agreed upon format.

Production of national data summaries and national data re-release for non-NNCs:

- Prior to release of national data summaries CDC should follow the CDC/ATSDR Policy on Releasing & Sharing Data, issued on April 16, 2003 and referenced in 11-SI-01 and custodians of such data should consult the CDC-CSTE Intergovernmental Data Release Guidelines Working Group report (www.cste2.org/webpdfs/drgwgreport.pdf) which contains data release guidelines and procedures for CDC programs re-releasing state, local, or territorial-provided data.
- CDC programs have a responsibility, in collaboration with states, localities, and territories, to ensure that CDC program-specific data re-release procedures meet the needs of those responsible for protecting data in the states and territories.

X. Revision History

Not applicable.

XI. References

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Technical Supplement

Table VI. Table of criteria to determine whether a case should be reported to public health authorities.

Criterion	Alpha-gal Syndrome
Clinical Criteria for Reporting	
N/A	
Laboratory Criteria for Reporting	
Serum or plasma immunoglobulin E specific to alpha-gal (sIgE) ≥ 0.1 IU/mL or ≥ 0.1 kU/L	S
Allergy skin test result consistent with allergy to alpha-gal[†]	S
Epidemiological Linkage Criteria for Reporting	
N/A	
Vital records criteria for reporting	
A person whose death certificate lists Alpha-gal syndrome as a cause of death or a significant condition contributing to death.	S
Other criteria for reporting	
A person whose healthcare/medical record contains a diagnosis, active problem, or finding of Alpha-gal Syndrome.	S

Notes:
S = This criterion alone is SUFFICIENT to report a case.
[†] An allergy skin test result that is interpreted by the ordering provider as consistent with allergy to alpha-gal based on sensitivity to one or more mammalian meats (e.g., pork, beef, lamb) or other mammalian-derived products.

Table VII. Classification Table: Criteria for defining a case of alpha-gal syndrome.

Criterion	Suspect	Probable		Confirmed	
Clinical Evidence					
Acute onset of symptoms occurs 2–10 hours after ingestion of pork, beef, lamb, or other mammalian meat or mammalian-derived product		N		N	
Acute onset of symptoms occurs within 2 hours of intramuscular, intravenous, or subcutaneous administration of alpha-gal containing vaccine or medication			N		N
Abdominal pain		O	O	O	O
Nausea		O	O	O	O
Diarrhea		O	O	O	O
Vomiting		O	O	O	O
Heartburn/indigestion		O	O	O	O
Hives		O	O	O	O
Itching		O	O	O	O
Anaphylaxis as diagnosed by a provider		O	O	O	O
Swelling of one or more of the following: lips, tongue, throat, face, eyelids, or other associated structures		O	O	O	O
Shortness of breath		O	O	O	O
Cough		O	O	O	O
Wheezing		O	O	O	O
Acute episode of hypotension[‡]		O	O	O	O
Absence of a clear alternative diagnosis		N	N	N	N
No clinical information available	N				
Laboratory Evidence					
Serum or plasma immunoglobulin E specific to alpha-gal (sIgE) ≥ 0.1 IU/mL or ≥ 0.1 kU/L	N			N	N
Allergy skin test result consistent with allergy to alpha-gal[†]		N	N		
Epidemiologic Linkage Evidence					
N/A					
Criteria to distinguish a new case:					
Case not previously reported to public health authorities	N	N	N	N	N

Notes:

N = All "N" criteria in the same column are NECESSARY to classify a case. A number following an "N" indicates that this criterion is only required for a specific disease/condition subtype (see below). If the absence of a criterion (i.e., criterion NOT present) is required for the case to meet the classification criteria, list the absence of criterion as a necessary component.

O = At least one of these "O" (ONE OR MORE) criteria in **each category** (categories=clinical evidence, laboratory evidence, and epidemiologic evidence) **in the same column**—in conjunction with all "N" criteria in the same column—is required to classify a case.

[‡] *Normal values for systolic blood pressure vary by age. Hypotension is classified by systolic blood pressure <90 mmHg for ages 11+ years; < [70 mmHg + 2 x age] for ages 1 -10 years; <70 mmHg for ages less than 1 year.*

[†] *An allergy skin test result that is interpreted by the ordering provider as consistent with allergy to alpha-gal based on sensitivity to one or more mammalian meats (e.g., pork, beef, lamb) or other mammalian-derived products.*

Appendix 1. List of common medication stabilizers (which is often the alpha-gal containing component of a vaccine or medication) and other helpful resources.

Note: This appendix is currently in development as of July 2021 and will be updated as soon as possible.