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Tick-Induced Cutaneous and Allergic Manifestations: Differential Diagnosis Between Lyme Borreliosis and Alpha-Gal Syndrome

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ABSTRACT

Background. Ticks serve as common vectors for both the infectious Lyme Borreliosis and the allergic Alpha-Gal Syndrome creating significant diagnostic challenges when patients present with non-specific skin reactions. Distinguishing between these entities is vital to prevent the misdiagnosis and to ensure correct treatment, ranging from antibiotics for LB to strict dietary avoidance for AGS.

Aim. The primary objective of this review is to provide a comprehensive comparative analysis of the cutaneous and allergic manifestations induced by tick bites, specifically focusing on the differentiation between Lyme Borreliosis and Alpha-Gal Syndrome.

Materials and methods. A comprehensive literature search was performed across multiple scientific databases, including PubMed, Web of Science, Scopus, and Google Scholar, for peer-reviewed articles and clinical studies. The search focused on publications in English and Polish to ensure a broad geographical and clinical perspective on tick-borne pathologies.

Results. Lyme Borreliosis primarily presents as erythema migrans, whereas Alpha-Gal Syndrome manifests as a unique, delayed allergic reaction (urticaria or anaphylaxis) occurring 3–6 hours after mammalian meat consumption. A key clinical differentiator is the quality of the tick bite.

Conclusions. Tick bites represent a common origin for both infectious Lyme Borreliosis and the unique, IgE-mediated Alpha-Gal Syndrome, necessitating a precise differential diagnosis. Distinguishing between these entities is vital, as the hallmark delayed urticaria of Alpha-Gal Syndrome is frequently misdiagnosed as chronic idiopathic urticaria or misunderstood as a primary symptom of a bacterial infection. Enhanced clinical awareness and the implementation of molecular component diagnostics are essential for ensuring the correct therapeutic path, ranging from targeted antibiotic therapy to strict dietary exclusion.

Key words: Lyme borreliosis, Lyme disease, alpha-gal syndrome, AGS, red meat allergy, tick-mediated allergy disease, utricaria, alpha-gal, erythema migrans,

1. Introduction

Ticks are globally recognized as primary vectors for a variety of pathogens and the initiators of unique allergic sensitizations [1][2]. Lyme Borreliosis (LB), a multi-system bacterial infection caused by spirochetes of the *Borrelia burgdorferi sensu lato* complex, remains the most prevalent tick-borne disease in the Northern Hemisphere [3]. While its pathognomonic and most characteristic cutaneous manifestation is erythema migrans (EM), disseminated stages of the disease can rarely present with atypical skin reactions, such as urticaria. In recent decades, the spectrum of tick-associated health issues has expanded to include Alpha-Gal Syndrome (AGS), which represents a novel paradigm in the field of allergology [4][5]. AGS is an IgE-mediated Type I hypersensitivity directed against the oligosaccharide galactose-α-1,3-galactose (alpha-gal), a carbohydrate found in most non-primate mammals but absent in humans [6]. Unlike traditional protein-based food allergies, reactions in AGS are characteristically delayed by 3 to 6 hours following the ingestion of red meat or offal [7]. This delay is attributed to the specific metabolic processing required for glycolipids containing the alpha-gal epitope to enter the bloodstream [8]. A significant clinical challenge lies in the differential diagnosis between these two entities, particularly when a patient presents with urticaria following a tick bite. While urticaria is a dominant clinical feature in Alpha-Gal Syndrome—occurring in over 90% of patients—it is considered a rare and atypical manifestation in the course of early disseminated Lyme disease [9]. Furthermore, the quality of the bite itself serves as a vital diagnostic indicator: patients with AGS frequently report persistently and intensely itchy tick bite sites lasting for two weeks or longer, whereas bites from ticks primarily associated with *Borrelia* transmission typically do not induce such prolonged pruritus [10]. Understanding the distinct underlying mechanisms—infectious for Lyme Borreliosis and immunological for Alpha-Gal Syndrome—is essential to prevent misdiagnoses, such as chronic idiopathic urticaria. The implementation of modern diagnostic tools, specifically molecular Component-Resolved Diagnostics (CRD) such as the FABER test (which identifies the Bos d CA marker), allows for the precise differentiation of these conditions. Accurate identification ensures the commencement of appropriate management, ranging from targeted antibiotic therapy for LB to strict dietary exclusion and anaphylaxis prevention for AGS [11].

2. Research materials and methods.

The methodology for this review involved a systematic and comprehensive search of established scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search focused on peer-reviewed literature, clinical case reports, and diagnostic algorithms. The literature search was conducted using a combination of keywords and Boolean operators to identify relevant studies. Primary search terms included "Lyme Borreliosis," "Lyme Disease," "Alpha-Gal Syndrome," "tick-mediated allergic disease," "urticaria," "erythema migrans," and "differential diagnosis", “AGS”, “alpha-gal”. A total of 15 core scientific sources were synthesized for this review, including materials published in English and Polish to ensure a broad geographical and clinical perspective. Data extraction prioritized information regarding epidemiological trends, biological mechanisms, clinical timelines, and the efficacy of current diagnostic tools. The synthesized findings were organized to provide a comparative framework for distinguishing between the infectious spread of Lyme Borreliosis and the unique carbohydrate-based allergy of Alpha-Gal Syndrome.

3. Cutaneous Manifestations of Lyme Borreliosis

Lyme Borreliosis (LB), a multi-system infectious disease caused by spirochetes of the *Borrelia burgdorferi sensu lato* complex, is primarily recognized through its dermatological presentations, which evolve across different stages of the infection. These manifestations are classically divided into stages: early localized, early disseminated, and late stage.

3.1 Classic and Proven Manifestations

- Erythema Migrans (EM): The pathognomonic hallmark of early LB, EM occurs in approximately 70% to 90% of patients. It appears as an enlarging erythematous patch, typically reaching at least 5 cm in diameter, and may present with central clearing or more atypical features like vesicles, purpura, or induration [12].
- Borrelial Lymphocytoma (LABC): A less common early sign characterized by a painless, reddish-blue nodule or plaque, most frequently located on the earlobe, nipple, or scrotum.
- Acrodermatitis Chronica Atrophicans (ACA): A late-stage chronic progressive condition common in Europe. It begins with bluish-red discoloration and edema,

eventually leading to severe skin atrophy, giving the skin a "cigarette-paper" appearance.

3.2. Manifestations of Early Disseminated Stage

As the infection spreads hematogenously, patients may develop multiple annular erythemas (MAE). These secondary lesions are usually smaller and less migratory than the primary EM rash and indicate that the spirochetes have disseminated through the bloodstream [13].

3.3. Atypical Signs: Urticaria and Reactive Lesions

While EM is the standard marker, LB can present with atypical skin signs that mimic other conditions. Notably, urticaria (hives) is recognized as a reactive cutaneous manifestation of LB.

- Incidence: Clinical data suggest that diffuse urticaria is a rare manifestation of early disseminated Lyme disease, occurring in approximately 1% of patients [14].
- Clinical Presentations: Case reports have identified instances where chronic urticaria was the primary or sole clinical feature of disseminated Lyme disease, which only resolved after appropriate antibiotic therapy.
- Other Reactive Signs: LB has also been associated with conditions such as erythema nodosum, granuloma annulare, and even localized alopecia at the site of an EM lesion.

3.4. Biological Mechanism of Allergic-like Reactions

The presence of urticarial rashes in a bacterial infection like LB is explained by the direct interaction between the pathogen and the host’s immune system. Research indicates that Borrelia burgdorferi spirochetes can directly induce mast cell activation. This activation triggers the release of pro-inflammatory cytokines and histamine, providing a mechanistic basis for the appearance of allergic-like skin reactions during the course of the infection.

4. Clinical Spectrum of Alpha-Gal Syndrome

The clinical presentation of alpha-gal syndrome (AGS) is remarkably heterogeneous, ranging from mild localized skin irritations to life-threatening systemic collapse [15]. The most pathognomonic feature of this syndrome, which distinguishes it from conventional IgE-mediated food allergies, is the characteristically delayed onset of symptoms, typically manifesting 2 to 6 hours after the ingestion of mammalian products [16]. This delay is attributed

to the complex metabolic processing and transport of alpha-gal glycolipids and glycoproteins into the bloodstream [17].

4.1 Cutaneous and Mucosal Manifestations

Dermatological symptoms are the most frequent initial presentation of AGS. These typically include:

- Urticaria (hives) and generalized pruritus: intense itching, often starting on the palms or soles, frequently precedes the appearance of erythematous wheals and plaques.
- Angioedema: significant swelling often affects the lips, tongue, soft palate, and periorbital tissues. Oropharyngeal involvement can lead to a sensation of throat tightness and difficulty swallowing, raising concerns for airway compromise.
- Flushing and erythema**:** generalized redness of the skin is commonly reported during acute episodes [18].

4.2 Gastrointestinal Involvement

Gastrointestinal (GI) symptoms are a distinctive and often severe feature of AGS, occurring in approximately 73% to 83% of patients [19]. Symptoms include severe abdominal cramping, nausea, vomiting, and diarrhoea. Notably, a subset of patients exhibits a "GI-predominant phenotype," experiencing isolated abdominal distress without concurrent skin or respiratory involvement. These cases are frequently misdiagnosed as irritable bowel syndrome or other primary GI disorders before the link to mammalian meat is identified [20].

4.3 Anaphylaxis and Systemic Crisis

Anaphylaxis represents the most dangerous clinical expression of AGS, affecting an estimated 47% to 60% of patients [21]. Unlike typical food allergies, AGS-related anaphylaxis often occurs during the night, hours after a late dinner.

- Cardiovascular impact: severe reactions may lead to profound hypotension, dizziness, syncope, and cardiovascular collapse.
- Respiratory distress: symptoms include dyspnoea, wheezing, and laryngeal oedema.
- Biphasic reactions: some patients experience a recurrence of symptoms several hours after initial resolution, necessitating prolonged medical observation.

4.4 Impact of Triggers and Cofactors

The severity and timing of the clinical response can be influenced by the specific trigger and the presence of cofactors:

- Organ meats vs. muscle meat: ingestion of mammalian innards, particularly pork kidney, which contains high concentrations of alpha-gal, can trigger more rapid (within 2 hours) and reliably severe anaphylactic reactions compared to skeletal muscle meat [22][23].
- Cofactors: The threshold for a reaction is significantly lowered by cofactors such as alcohol consumption, physical exercise, NSAIDs (like aspirin), and acute infections. These factors may increase allergen absorption or cellular activation, potentially turning a previously tolerated dose into a life-threatening event [24][25].

4.5 Atypical and Chronic Manifestations

Emerging evidence suggests AGS may have chronic implications beyond acute allergic episodes:

- Coronary Artery Disease: alpha-gal sensitization has been associated with an increased atheroma burden and plaque instability, suggesting it may be a modifiable risk factor for atherosclerosis [26].
- Bioprosthetic Valve Failure: patients with anti-alpha-gal IgE may experience premature degeneration of bioprosthetic heart valves (bovine or porcine) due to chronic immune-mediated inflammation against the residual alpha-gal epitopes on the valve tissue [27].
- Chronic Urticaria: some patients present with persistent hives without an obvious temporal link to meat consumption, which resolve only after strict avoidance of mammalian products [28].

4.6 Immunological Foundations of Alpha-Gal Syndrome Development

Alpha-Gal Syndrome (AGS) represents a unique paradigm in clinical immunology as the first identified IgE-mediated food allergy to a carbohydrate epitope rather than a protein. The sensitization process is initiated when a tick bite introduces alpha-gal antigens into the dermis while simultaneously delivering immunomodulatory molecules that polarize the local immune environment toward a pro-allergic Th2 response [29]. This specific microenvironment facilitates the reactivation of pre-existing memory B cells—originally primed by alpha-gal-

expressing gut microbiota—and triggers class-switch recombination from natural IgG or IgM production to pathogenic, alpha-gal-specific IgE [30].

Furthermore, susceptibility to this syndrome is significantly modulated by the host's ABO blood group [31]. Individuals with blood group B or AB exhibit a 75–80% reduced risk of developing AGS because the B-antigen is structurally similar to the alpha-gal epitope. This structural resemblance is thought to induce immunological cross-tolerance, eliminating or reducing the B-cell clones that would otherwise generate a robust IgE response to the carbohydrate.

5. Tick Bite Characteristics as a Diagnostic Indicator

The clinical history and physical characteristics of the tick bite itself serve as essential diagnostic clues for differentiating between Alpha-Gal Syndrome (AGS) and Lyme Borreliosis (LB). While both conditions are initiated by a tick vector, the local skin reaction at the site of attachment follows distinct patterns that can guide clinicians toward a correct diagnosis [32].

5.1 Pruritus and Localized Reactions

The most prominent feature of tick bites that lead to AGS is intense and persistent pruritus (itching). Patients who develop AGS frequently report large local reactions at the bite site, where the itching can last for two weeks or longer. This is in sharp contrast to the tick bites that transmit *Borrelia burgdorferi* (the causative agent of Lyme disease), which are typically painless and not associated with itching, often causing them to go entirely unnoticed by the patient [33].

5.2 Morphological Evolution of the Lesion

In early Lyme disease, the diagnostic hallmark is Erythema migrans (EM), an expanding annular rash that typically appears 4 to 30 days after the bite. This lesion is generally asymptomatic (not itchy or painful). Conversely, the primary reaction to a tick bite in AGS is often a persistent, itchy papule or an edematous-urticarial odder. This reaction is a direct result of hypersensitivity to components in the tick's saliva, including alpha-gal epitopes, which may be upregulated as the tick feeds [34].

5.3 The Recall Phenomenon

A unique diagnostic indicator for AGS is the "recall phenomenon," where a patient experiences a recurrence of itching or redness at the site of an old tick bite specifically after the ingestion of mammalian meat. This suggests that effector cells like mast cells or basophils remain localized

at the original bite site and are reactivated by alpha-gal antigens circulating in the bloodstream [35]. Lyme borreliosis does not exhibit any such dietary-linked cutaneous reactivation.

5.4 Vector Exposure and Attachment Patterns

The risk of AGS sensitization is significantly increased by multiple simultaneous tick attachments, such as encountering larval "seed ticks" in late summer. While *Ixodes ricinus* is a common vector for both diseases in Europe, the requirements for transmission differ: *Borrelia* transmission generally requires the tick to be attached for 24 to 48 hours, whereas alpha-gal sensitization can occur more rapidly because the carbohydrate is present directly in the tick's saliva and gastrointestinal tract [36].

In summary, a history of prolonged, severely itchy tick bites is a significant clinical red flag for the eventual development of Alpha-Gal Syndrome, while an asymptomatic bite followed by an expanding, painless rash is pathognomonic for early Lyme Borreliosis.

6. Comparative Diagnostics: Serology vs. Molecular Methods

Accurate differentiation between Lyme Borreliosis (LB) and Alpha-Gal Syndrome (AGS) requires a multi-faceted diagnostic approach. While both are initiated by tick bites, their laboratory profiles differ significantly, transitioning from traditional serological windows to advanced molecular and functional assays.

6.1 Serological Diagnostics: Standards and Nuances

- Alpha-Gal Syndrome: The gold standard for diagnosing AGS is the quantification of serum-specific IgE (sIgE) antibodies directed against the carbohydrate epitope galactose-α-1,3-galactose [37]. While a threshold of >0.10 kUA/L is technically positive, clinical reactivity is much more likely when sIgE levels are ≥2 kUA/L or account for more than 2% of the patient’s total IgE [38]. A major complication is asymptomatic sensitization, where up to 35% of individuals in endemic regions may possess alpha-gal sIgE without experiencing clinical symptoms after eating meat.

- Lyme Borreliosis: Standard serology follows a two-tier protocol, typically starting with an ELISA followed by an immunoblot confirmation. In the early phase—particularly when LB presents atypically as acute urticaria—initial serologic screening may be negative, requiring repeat testing four weeks later to capture the seroconversion window.

6.2 Molecular and Component-Resolved Diagnostics (CRD)

- Component Precision in AGS: Component-resolved diagnostics (CRD) have refined the diagnostic process. Testing for IgE targeting specific proteins like bovine thyroglobulin (bTG) has shown 100% sensitivity and over 90% specificity for AGS [39]. Modern molecular panels, such as the FABER test, allow for the simultaneous screening of 244 allergen components. This includes the alpha-gal marker Bos d CA, enabling clinicians to distinguish AGS from classical protein-mediated meat allergies or pork-cat syndrome (driven by Fel d 2).
- PCR in Lyme Borreliosis: PCR is an essential molecular tool for LB, primarily used to detect *Borrelia burgdorferi* DNA directly in skin biopsies. This is especially useful in cases of atypical cutaneous manifestations where serology is unreliable or inconclusive.

6.3 Functional Assays and In Vivo Testing

- Basophil Activation Test (BAT): The BAT is an advanced functional assay that measures the expression of activation markers (such as CD63) on basophils following *in vitro* exposure to alpha-gal [40]. It serves as a vital tool to differentiate true clinical AGS from simple serological sensitization, providing a biological confirmation of the patient's reactive status.
- Unreliability of Skin Prick Tests (SPT): Traditional SPT using commercial meat extracts is notably unreliable for AGS, frequently producing false-negative or ambiguous results [41]. This is due to the lack of standardized concentrations of the alpha-gal carbohydrate in these protein-focused solutions. In contrast, "prick-to-prick" testing with fresh tissues like pork kidney is more sensitive but increases the risk of triggering systemic reactions.

6.4 Summary

While serology is the primary diagnostic tier for both conditions, molecular methods (CRD and PCR) and functional assays (BAT) are necessary for high-precision differentiation. These tools are critical for managing the diagnostic challenges of early-stage Lyme infection and the high prevalence of asymptomatic alpha-gal sensitization.

7. Management and Prevention

The clinical management of Lyme Borreliosis (LB) and Alpha-Gal Syndrome (AGS) is governed by fundamentally different medical paradigms: while LB necessitates etiological treatment (antibiotic therapy) aimed at eradicating the *Borrelia burgdorferi* spirochete, AGS management focuses on exposure prevention (allergen avoidance) and the symptomatic control of hypersensitivity reactions.

7.1 Comparative Summary of Management Strategies

Feature	Alpha-Gal Syndrome	Lyme Borreliosis
Primary Goal	Avoidance of triggers and control of allergic reactivity [42].	Eradication of *Borrelia burgdorferi* spirochetes.
Main Treatment	Elimination Diet: Strict exclusion of mammalian meat and offal, particularly pork kidney.	Antibiotic Therapy: Standard regimens include doxycycline, amoxicillin, or cefuroxime.
Acute Management	Epinephrine as first-line treatment for anaphylaxis; antihistamines and corticosteroids for milder reactions.	Not applicable for primary infection (management focuses on organ-specific complications in late stages).
Adjuvant Therapy	Mast cell stabilizers (e.g., oral cromolyn) for GI-predominant phenotypes; omalizumab for refractory cases.	Symptomatic treatment for joint pain or neurological manifestations.
Medical Products	Vigilance regarding gelatin-containing drugs, monoclonal antibodies (cetuximab), and bioprosthetic valves [43].	No specific ingredient restrictions (outside of standard drug allergies).

Tab. 1. Comparative Summary of Management Strategies

7.2 Prevention and the Role of the Vector

The common denominator for both conditions is tick bite prevention, which includes the use of repellents (e.g., permethrin or DEET), wearing light-colored protective clothing, and the prompt removal of attached ticks.

In Alpha-Gal Syndrome, avoiding re-exposure to tick bites carries a critical therapeutic dimension: evidence demonstrates that anti-alpha-gal IgE titers naturally decline over months or years if the patient is not subjected to new bites [44]. Successful avoidance can eventually lead to seronegative status and the potential restoration of mammalian meat tolerance. In contrast, secondary prevention in Lyme Borreliosis serves only to prevent new, independent infections rather than influencing the trajectory of an existing one.

In summary, while Lyme Borreliosis typically requires a short-term, intensive pharmacological intervention, Alpha-Gal Syndrome necessitates a permanent lifestyle modification and constant vigilance regarding hidden allergen sources in food, vaccines, and pharmaceutical products.

8. Discussion

The emergence of alpha-gal syndrome (AGS) has fundamentally challenged traditional paradigms in clinical allergy and infectious disease, necessitating a robust differential diagnosis against established tick-borne illnesses like Lyme borreliosis (LB). While both conditions share a common tick vector, they represent two distinct medical pathways: one an infectious process requiring etiological eradication and the other a novel IgE-mediated food allergy requiring lifelong allergen avoidance.

A primary diagnostic challenge is the characteristically delayed onset of symptoms in AGS, which typically manifest 2 to 6 hours after mammalian product ingestion. This delay contrasts sharply with the immediate reactions seen in protein-mediated food allergies and the gradual, often subtle progression of early Lyme symptoms. Furthermore, the heterogeneity of AGS, particularly the gastrointestinal-predominant phenotype without cutaneous involvement, often leads to misdiagnosis as irritable bowel syndrome or other primary GI disorders. In contrast, the pathognomonic erythema migrans of early Lyme disease is often painless and may go unnoticed, whereas tick bites associated with AGS are frequently described as intensely itchy and persistent.

Research highlights that the tick vector is not merely a carrier of pathogens but a primary sensitizer. Tick saliva contains immunomodulatory molecules which disrupt the skin's barrier and polarize the local environment toward a pro-allergic Th2 response. This specific

microenvironment is essential for the class-switch recombination of B cells to produce alpha-gal-specific IgE. An important clinical pearl identified in our analysis is the "recall phenomenon," where old tick bite sites undergo reactivation and itching specifically following mammalian meat ingestion, a feature entirely absent in Lyme borreliosis.

The management of these two conditions reflects their divergent etiologies. Lyme borreliosis typically resolves with a short course of antibiotics, whereas AGS mandates a permanent lifestyle modification regarding diet and medical products. However, a unique therapeutic aspect of AGS is that anti-alpha-gal IgE titers naturally decline over months or years if the patient successfully avoids subsequent tick bites. This highlights that tick bite prevention is not only a prophylactic measure against infection but a crucial therapeutic intervention to potentially achieve clinical remission in AGS.

9. Conclusion

In summary, clinicians must maintain a high index of suspicion for Alpha-Gal Syndrome in patients presenting with delayed anaphylaxis or unexplained GI distress, especially in tick-endemic areas. Distinguishing it from Lyme borreliosis requires careful attention to the character of the tick bite, the timing of systemic reactions, and the use of molecular diagnostic tools. Future research should focus on the exact role of tick-derived molecules in driving sensitization to help develop targeted preventive strategies.

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References:

1. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. The J Allergy Clin Immunol. 2015;135(3):589-596; quiz 597.
2. Molaei G, Little EAH, Williams SC, Stafford KC. Bracing for the worst – range expansion of the lone star tick in the northeastern United States. New Engl J Med. 2019;381(23):2189-2192.
3. G. Trevisan, P. Cattonar, C. Nobile, V. Perkan, G. Stinc.o Dermatological manifestations of lyme borreliosis. Acta dermatovenerologia A.P.A. Vol 5, 96, No 3-4, 101-107
4. Patel C, Iweala OI. 'Doc, will I ever eat steak again?': diagnosis and management of alpha-gal syndrome. Curr Opin Pediatr. 2020;32(6):816–824. doi:10.1097/MOP.0000000000000955
5. Román-CarrascoP,HemmerW,Cabezas-CruzA,etal.Theα-Galsyndromeandpotential mechanisms. Frontiers in Allergy. 2021;2:783279.
6. Commins SP, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS, 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 May;127(5):1286-93.

7. Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM. Diagnosis and management of patients with the α-Gal syndrome. J Allergy Clin Immunol Pract. 2020;8(1):15-23.e11.
8. Román-CarrascoP,HemmerW,Cabezas-CruzA,etal.Theα-Galsyndromeandpotential mechanisms. Frontiers in Allergy. 2021;2:783279.
9. Weala OI, Choudhary SK, Addison CT, Commins SP. T and B lymphocyte transcriptional states differentiate between sensitized and unsensitized individuals in alpha-gal syndrome. Int J Mol Sci. 2021;22(6):3185.
10. Fischer J, Hebsaker J, Caponetto P, Platts-Mills TA, Biedermann T. Galactose-alpha-1,3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis. J Allergy Clin Immunol. 2014;134(3):755-9.
11. Tripathi A, Commins SP, Heymann PW, Platts-Mills TA. Delayed anaphylaxis to redmeat masquerading as idiopathic anaphylaxis. J Allergy Clin Immunol Pract. 2014May-Jun;2(3):259-65.
12. Berger BW. Dermatologic manifestations of Lyme disease. Rev Infect Dis 1989, 11 (Suppl 6): S1475-81.
13. Trevisan G, Cinco M. Lyme Borreliosis in Childhood. Eur J Pediat Dermatol 1992; 2: 81-112
14. Mary Michael, tamara Gmitter. A Case of Disseminated Lyme Disease Presenting as Chronic Urticaria. Cureus. 2019 Seo 9;11(9):e5600. doi: 10.7759/cureus.5600
15. Patel C, Iweala OI. 'Doc, will I ever eat steak again?': diagnosis and management of alpha-gal syndrome. Curr Opin Pediatr. 2020;32(6):816–824. doi:10.1097/MOP.0000000000000955
16. Mabelane T, Basera W, Botha M, Thomas HF, Ramjith J, Levin ME. 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(8):841–849.
17. Berg EA, Platts-Mills TA, Commins SP. Drug allergens and food - the cetuximab and galactose-alpha-1,3-galactose story. Ann Allergy Asthma Immunol. 2014 Feb;112(2):97-101.
18. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. The J Allergy Clin Immunol. 2015;135(3):589-596; quiz 597.

19. Platts-Mills TAE, Li RC, Keshavarz B, et al. Diagnosis and management of patients with the α-Gal syndrome. Journal of Allergy and Clinical Immunology in Practice. 2020;8(1):15-23.
20. Richards NE, Richards RD Jr. Alpha-gal allergy as a cause of intestinal symptoms in a gastroenterology community practice. South Med J. 2021;114(3):169–173.
21. 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.
22. Morisset M, Richard C, Astier C, et al. Anaphylaxis to pork kidney is related to IgE antibodies specific for galactose-alpha-1,3-galactose. Allergy. 2012;67(5):699–704.
23. Fischer J, Hebsaker J, Caponetto P, Platts-Mills TA, Biedermann T. Galactose-alpha-1,3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis. J Allergy Clin Immunol. 2014;134(3):755–759
24. Fischer J, Hebsaker J, Caponetto P, Platts-Mills TA, Biedermann T. Galactose-alpha-1, 3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis. J Allergy Clin Immunol. 2014;134(3):755-9.
25. Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM. Diagnosis and management of patients with the α-Gal syndrome. J Allergy Clin Immunol Pract. 2020;8(1):15-23.e11.
26. Wilson JM, Nguyen AT, Schuyler AJ, et al. IgE to the mammalian oligosaccharide galactose-alpha-1,3-galactose is associated with increased atheroma volume and plaques with unstable characteristics-brief report. Arterioscler Thromb Vasc Biol. 2018;38(7):1665–1669.
27. Kuravi KV, Sorrells LT, Nellis JR, et al. Allergic response to medical products in patients with alpha-gal syndrome. J Thorac Cardiovasc Surg. 2021. doi:10.1016/j.jtcvs.2021.03.100
28. KeshavarzB,SmithAR,WilsonJM,Platts-MillsTAE.A-Galsyndromeunmaskedinchronic spontaneous urticaria cohorts. Annals of Allergy, Asthma & Immunology. 2019;123(5):454-461.
29. Iweala OI, Burks AW. Food allergy: our evolving understanding of its pathogenesis, prevention, and treatment. Curr Allergy Asthma Rep. 2016;16(5):37
30. Brestoff JR, Tesfazghi MT, Zaydman MA, et al. The B antigen protects against the development of red meat allergy. J Allergy Clin Immunol Pract. 2018;6(5):1790–1791.

31. Bircher AJ, Hofmeier KS, Link S, Heijnen I. Food allergy to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal): four case reports and a review. Eur J Dermatol. 2017;27(1):3–9
32. Commins SP, James HR, Stevens W, Pochan SL, Land MH, King C, 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 Jul;134(1):108-15.
33. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. The J Allergy Clin Immunol. 2015;135(3):589-596; quiz 597.
34. Carson AS, Gardner A, Iweala OI. Where's the beef? Understanding allergic responses to red meat in alpha-gal syndrome. J Immunol. 2022;208 (2):267–277.
35. Commins SP, James HR, Stevens W, Pochan SL, Land MH, King C, 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 Jul;134(1):108-15.
36. Park Y, Kim D, Boorgula GD, et al. Alpha-gal and cross-reactive carbohydrate determinants in the N-glycans of salivary glands in the lone star tick, Amblyomma americanum. Vaccines. 2020;8(1):18.
37. im DW, Lee JS, Park KH, et al. Accurate assessment of alpha-gal syndrome using cetuximab and bovine thyroglobulin-specific IgE. Mol NutrFood Res. 2017;61(10):1601046.
38. Li J, Fulton RB, O'Connell R, Jang HS, Fernando SL. Specific-IgE to galactose-alpha-1,3-galactose (alpha-gal) has limited utility in diagnosing meat allergy in a tick-endemic population. Ann Allergy Asthma Immunol. 2018;121(4):509–511.
39. Commins SP, Platts-Mills TAE. Specific IgE to α-Gal-containing proteins: Diagnostic considerations. Journal of Allergy and Clinical Immunology. 2018;142(4):1189-1195
40. Iweala OI, Choudhary SK, Addison CT, et al. Glycolipid-mediated basophil activation in alpha-gal allergy. J Allergy Clin Immunol. 2020;146 (2):450–452.
41. Kollmann D, Nagl B, Ebner C, et al. The quantity and quality of alpha-gal-specific antibodies differ in individuals with and without delayed red meat allergy. Allergy. 2017;72(2):266–273.
42. Tripathi A, Commins SP, Heymann PW, Platts-Mills TA. Delayed anaphylaxis to red meat masquerading as idiopathic anaphylaxis. J Allergy Clin Immunol Pract. 2014 May-Jun;2(3):259-65.

43. Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM. Diagnosis and management of patients with the α-Gal syndrome. J Allergy Clin Immunol Pract. 2020;8(1):15-23.e11.
44. Commins SP, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS, 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 May;127(5):1286-93.