

Ticks and the Mammalian Meat Allergy

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Warmer temperatures and longer days signal the start to spring and summer chores on most cattle ranches. While the time spent outdoors is refreshing after the winter months, it brings with it an increased risk for not only heat exhaustion and dehydration but also for exposure to disease-transmitting insects and ticks. Within the past three years, the novel Heartland and Bourbon viruses were discovered, both of which are transmitted via tick bites and resulted in human illnesses in Missouri, Tennessee and Kansas.^[4, 2] Tick-borne diseases of humans and livestock are well documented, as are immediate allergic skin reactions that can occur upon being bitten. But what if a tick bite could also cause a food allergy to red meat? It may sound like something straight out of the Twilight Zone, but tick bites and specific sugar modifications on red meat are actually the major players in the intriguing, highly publicized mammalian meat allergy.^[3, 4] Patients experiencing this allergy report intense itching, swelling, and/or develop hives at 3 – 6 hours after eating red meat, i.e. beef, lamb, pork, venison. The delayed reactions, a hallmark of this allergic response, can be severe enough in cases to warrant emergency room visits or hospitalization, and they can occur in individuals who have previously consumed red meat without problems (adult-onset). This food allergy disorder affects children and adults alike, and it has been reported worldwide. Further, a significant proportion of those affected report a history of tick bites.

Mammalian meat allergy is a delayed allergic reaction to red meat that results from a heightened immune response to a sugar modification, alpha-gal^a, present on tissues and meat from non-primate mammals, e.g. cattle, swine, sheep, deer, rabbits, but not poultry and fish. Drs. Scott Commins, Thomas Platts-Mills, and a collaborative team of clinical researchers at the University of Virginia Health System's Allergy Division, revealed that the delayed red meat allergy was mediated by circulating immunoglobulin E (IgE) antibodies that recognize and bind to alpha-gal, a signal to the immune system to mount an aggressive response to the 'foreign' substance. This finding resulted from separate studies with cancer patients that exhibited a rapid, allergic reaction upon a first infusion with the chemotherapy agent, cetuximab. Cetuximab contains an alpha-gal region that elicited an allergic reaction (IgE response) in these cancer patients, signifying that they had IgE to alpha-gal even before receiving cetuximab. Patients describing a delayed red meat allergy were then screened and found to also be positive for IgE to alpha-gal. The common thread between these patients was their geography - the southeastern United States. There is a higher prevalence of IgE to alpha-gal in this region compared with four other regions across the US^[5] (**Figure 1**), indicating that eating food containing alpha-gal (mammalian meat or their by-products) does not itself prime the immune system to produce IgE to the carbohydrate. Rather, Drs. Commins and Platts-Mills proposed that the Lone Star tick, *Amblyomma americanum* (**Figure 2**), had an important role in mammalian meat allergy in the US. This connection was based on the overlap between the distribution of the tick and the patients with IgE to alpha-gal and on studies documenting an observable increase in the level of IgE to alpha-gal after patients experienced a tick bite from the Lone Star tick. The American dog tick, *Dermacentor variabilis*, is also prevalent in this region, but its bites do not appear to induce elevated production of IgE to alpha-gal, further supporting the importance of the Lone Star tick. Tick bites from the Australian paralysis tick, *Ixodes holocyclus*, and the castor

^agalactose-alpha-1-, 3-galactose



bean tick, *Ixodes ricinus*, are also associated with a delayed red meat allergy in Australia and Europe, respectively, and there are now cases reported in Asia, Africa and Central America although the responsible tick species in these continents is still unclear. Tick saliva comprises a cocktail of biomolecules that are secreted into its host upon tick attachment, and these molecules enable the tick to evade the host's immune system and promote blood-feeding^[6]. Some tick species are known to regurgitate gut contents into the host while feeding, and regurgitation can also occur upon being improperly detached from its host. However, it remains unknown what exactly the tick is transmitting to its human host (via either its salivary secretions or its gut contents) that would stimulate production of IgE antibodies that specifically recognize alpha-gal.

Physicians and allergists are becoming more aware of the tick-induced delayed allergy to red meat, and a laboratory diagnostic test is available to screen patients for the presence of IgE to alpha-gal. According to Dr. Commins, "As part of this work, we've also begun to find that the IgE response to the sugar seems to go down or wane over time....it can be boosted again by additional tick bites, but it's certainly something that does not appear to be a forever diagnosis."^[7] Tick bite prevention, then, is an essential component to reducing prevalence of the allergy. The CDC^[8] recommends measures be taken before and after spending time in areas known to be tick-infested, e.g. brushland, wooded areas, etc. These include the application of repellents containing 20 – 30% DEET to exposed skin and clothing as instructed on the product label, the treatment of clothing and gear (boots, hats) with products containing 0.5% permethrin, and conducting a full-body tick check after working in tick-infested areas in order to locate and properly remove attached ticks of various life stages (**Figure 2**). For more information regarding tick identification and tick bite prevention and removal, please visit the excellent resources available at the CDC (<https://www.cdc.gov/ticks/>) and TickEncounter (<https://tickencounter.org/>) websites.

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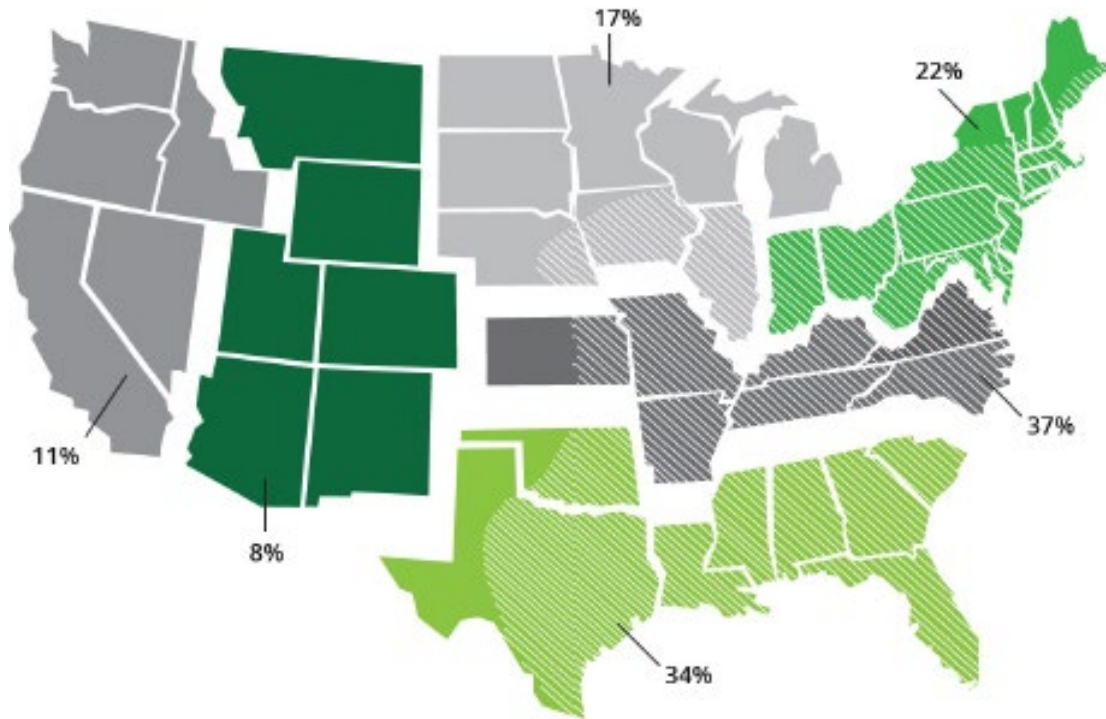


Figure 1. Surveillance for IgE to alpha-gal. Percent positive rates are presented for IgE to alpha-gal within each of six regions in the United States, 2012-2013 (7300 samples). Diagonal white lines on the map represent the known geographic distribution of the Lone Star tick (Data and map, Viracor-IBT Laboratories; Tick distribution, CDC).



Figure 2. (A) Lone Star tick life stages. The iridescent, solitary white spot on its dorsal surface is a marking that distinguishes adult, female Lone Star ticks from other tick species. Representative images of larval, nymphal and adult male Lone Star ticks are also presented. Photo, URI TickEncounter Resource Center, with permission. (B) Size comparison of Lone Star tick life stages. A nymph, unfed adult female and unfed adult male tick are shown relative to a quarter (from left to right). Photo, SCS, Ltd., tickinfo.com, with permission. (C) Unfed, partially fed and engorged female Lone Star ticks are shown. Note that the solitary white spot remains visible. Photo, SCS, Ltd., tickinfo.com, with permission.

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