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The expanding spectrum of disease caused by the Lone Star Tick, *Amblyomma americanum*

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SUMMARY

Ticks are remarkable vectors of a diverse and growing list of infectious agents of importance to both medical and veterinary disciplines. The tick *Amblyomma americanum* is one of the most frequently identified ticks in the United States with an expanding spectrum of human disease given its vast geographic range. The recently described Bourbon and Heartland viruses are likely transmitted by the Lone Star tick and are just two of the several novel tick-borne pathogens discovered in recent decades. The review will focus on these two viruses that can cause illness with similar characteristics to other diseases transmitted by the Lone Star tick. Healthcare professionals should consider these viruses in patients presenting with an ailment suggestive of a tick-born rickettsial disease that fails to improve with treatment with doxycycline. Additionally, some individuals may develop life-threatening allergic reactions triggered by the bite of the Lone Star tick.

Keywords: tickborne, *Amblyoma americanum*, Lone Star tick.

INTRODUCTION

In the United States, the incidence of tick-borne diseases is increasing as these ticks expands their geographic range [1-3]. The number of reported cases of bacterial and protozoan diseases transmitted by ticks in the United Sates increased from over 22,000 cases in 2004 to over 48,000 cases in 2016 [2]. The Lone Star tick, *Amblyomma americanum*, has geographically expanded to the upper midwestern and northeastern regions of the United States and eastern Canada [3] (Figure 1). Imperfect surveillance and reporting systems in addition to the limitations of the currently available diagnostics underappreciate their true public health footprint [4].

Amblyomma americanum is the most common *Amblyomma* spp. in the United States. The female is aggressive, widely distributed, and has a characteristic white macula on the posterior region of the dorsal shield, hence the name Lone Star Tick [5] (Figure 2). *Amblyomma americanum* is a vector of *Ehrlichia chaffeensis*, *E. ewingii*, *Franciscella tularensis*, and the Southern Tick Associated Rash Illness (STARI). There is also mounting evidence of its competence as a vector of *Rickettsia rickettsii* [5-10]. In addition, *Amblyomma americanum* is likely the only vector of two newly identified viruses in the United States. Furthermore, the bite of *A. americanum* can trigger the alpha-gal (galactose-α-1,3-galactose) syndrome (AGS). In this review, we provide an update on these emergent viral and allergic conditions related to *A. americanum*.

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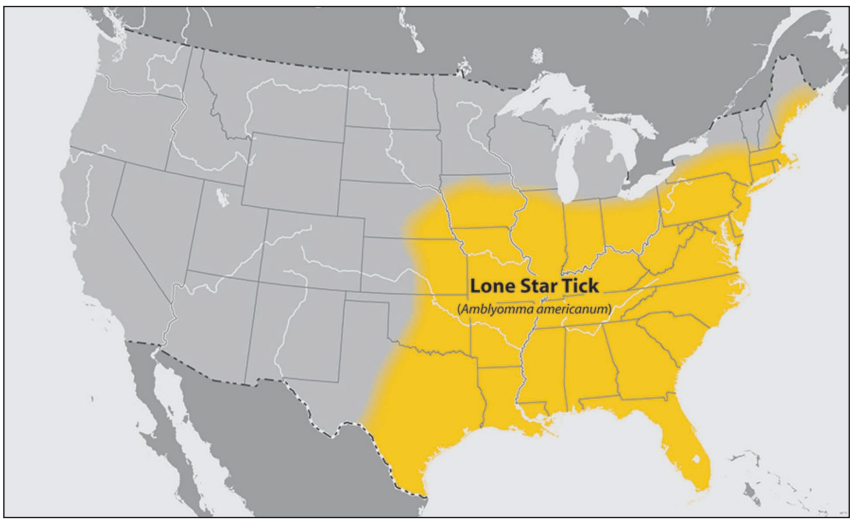

Figure 1 - Geographical distribution of *Amblyomma americanum* in the United States. (From Centers for Disease Control and Prevention [CDC], Atlanta, GA., with permission)

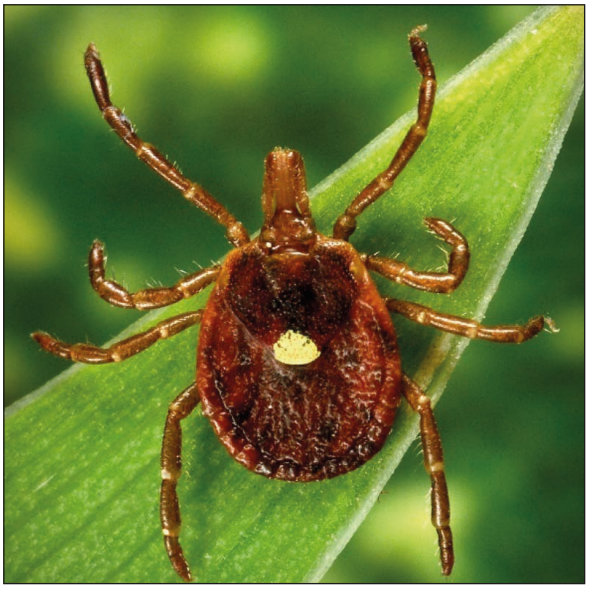

Figure 2 - *Amblyomma americanum*, the Lone Star tick. Note the characteristic "lone star" mark located on the dorsum of the female at the tip of the scutum. (From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Public Health Image Library, image 8683. Photo credit: James Gathany)

BOURBON VIRUS

Bourbon virus (BRBV) was first isolated in 2014 from the blood sample of a male resident of Bourbon County, Kansas [11]. The virus is a member of the genus *Thogotovirus* of the family *Orthomyxoviridae* and is the first *Thogotovirus* to be associated with human illness in the Western Hemisphere [11, 12].

The life cycle is poorly understood and is an area of active research. The virus has been isolated from the hard tick *Amblyomma americanum* in northwestern Missouri and eastern Kansas and experimental studies have confirmed the Lone Star tick as a competent vector [13-15]. Transmission of the virus by the tick is further supported by its phylogenetic relationship to Dhori and Bakten viruses within the genus *Thogotovirus* which have been identified in hard tick species [11]. In addition, in the report of the sentinel case an engorged tick was found attached to the shoulder of the patient. Human cases have also been reported from Payne County, Oklahoma and St. Louis, Missouri, states where this tick species is prevalent [11, 13, 16].

There is scant BRBV infection prevalence data in *A. americanum* ticks, animals, and humans. The first epidemiologic study was performed in Missouri in 2013. A total of 39,096 ticks collected from six sites in northwestern Missouri were retrospectively tested for BRBV. The BRBV infection rates (IR) per 1,000 adult ticks and nymphs for all sites and for the entire 2013 season were 0.32 and 0.07, respectively [13]. The second epidemiologic study was performed in Bourbon County and adjacent southern Linn County, Kansas, in 2015 [14]. In this study, the BRBV IR per 1,000 adult ticks for all sites was 0.25 [14].

Lastly, the same group of investigators, and based on the results of the 2015 study, tried to further

identify virus infected ticks to better delineate the vectors and life stages involved in virus transmission to humans. A total of 14,193 ticks representing four species were collected at four sites including the sites were Heartland virus (HRTV) and BRBV were detected in 2015. All pools tested negative for BRBV [17]. The authors concluded that BRBV seems to be less frequently isolated from field-collected *A. americanum* ticks than HRTV. The authors further speculate that BRBV might not be as efficiently transmitted, both vertically and horizontally [17].

Antibodies to BRBV have also been detected in non-human vertebrates. In a study performed in northwest Missouri, investigators evaluated banked serum and plasma of wild and domestic animals for evidence of BRBV antibodies using a plaque-reduction neutralization assay (PRNT) [18]. Antibodies to BRBV were detected in dogs, horses, white-tail deer, raccoons, and rabbits with the deer having the highest seropositivity rate of 86% [18]. In another study performed in North Carolina, 18 out of 32 white-tailed deer had reactive antibodies to BRBV by PRNT translating to a seroprevalence of 56% [19].

The clinical manifestations of BRBV in humans are limited to two published reports [11, 16]. The first patient was a previously healthy man over the age of 50 years that presented with non-specific complaints following a tick bite. Initial symptoms included nausea, vomiting, diarrhea, anorexia, myalgias, arthralgias, headache and fever. The patient later developed decreased level of consciousness resulting in admission to a local hospital. Exam at admission was remarkable for a papular rash on his trunk. Laboratory findings showed leukopenia with lymphopenia, thrombocytopenia, mild hyponatremia and elevated levels of aspartate aminotransferase and alanine aminotransferase. The patient deteriorated despite treatment with doxycycline and required invasive mechanical ventilation and vasopressor support. The patient passed away 11 days after becoming ill. During the patient's hospitalization a thorough evaluation for an infectious agent was unfruitful. The novel infectious agent was subsequently identified as a novel Orthomyxovirus of the genus *Thogotovirus* by partial-genomic high throughput sequencing and microscopy. No autopsy was performed [11].

The second case involved a 53-year-old female with history of follicular lymphoma. She had a similar flu-like illness and laboratory abnormalities as described in the case above, and approximately 1 week after several tick bites. The patient followed a similar course as the first patient, with deterioration during her hospital stay despite treatment with doxycycline and other broad-spectrum antibiotics. She also developed oral ulcers and a progressive rash with marked involvement of her palms and soles. In addition to developing respiratory failure, she also developed features suggestive of hemophagocytic lymphohistiocytosis for which she was treated with etoposide; again, without improvement. The patient died on hospital day 23 [16].

There are no routine diagnostic tests available for BRBV. Healthcare providers should contact their state health departments to coordinate testing at the Centers for Disease Control and Prevention (CDC). There is no specific treatment for BRBV other than supportive measures. Further studies to confirm the promising role of antivirals such as favipiravir seen in murine models are needed [16].

HEARTLAND VIRUS

Heartland virus was first isolated in 2009 from two men living in northwestern Missouri. The virus was identified by next-generation sequencing and based on phylogenetic analysis as a novel member of the *Phlebovirus* genus of the *Bunyaviridae* family [20]. The virus is closely related to severe fever with thrombocytopenia syndrome virus (SFTSV), a virus first identified in China in 2009 [20, 21].

Following the isolation of the virus from the sentinel human case, the virus was detected in both nymphs and adult ticks from the property of patients with HRTV [22, 23]. Further evidence to support the role of *Amblyomma americanum* as the vector for HRTV is its ability to transmit the virus both horizontally and transstadially [24]. Wild animals from 13 central and eastern states have been identified as harboring HRTV antibodies. The vast majority of these states are in the known geographic distribution of the Lone Star tick [25]. Nevertheless, HRTV seropositive white-tail deer have been identified in northern New England, a region where established *A. americanum* populations are unknown [26].

Heartland virus infected humans have been described from Oklahoma, Kansas, Missouri, Arkansas, Kentucky, Tennessee, Indiana, Illinois, Georgia, and South Carolina [27-30]. In the largest cohort of patients with HRTV, the phenotype of the disease was similar to that of other tick-borne disease such as ehrlichiosis, anaplasmosis, BRBV and Colorado tick fever [30]. Most were older males that became ill between the months of April and September [27, 30]. The typical presentation is that of fever, headache, myalgias, fatigue, and nausea within a 2-week window of tick attachment or finding a tick crawling on the body. A diffuse rash is usually not seen, and some patients develop neurocognitive dysfunction characterized by gait abnormalities, dizziness and confusion. Leukopenia with lymphopenia, thrombocytopenia, hyponatremia, and elevated aminotransferases are common laboratory abnormalities. Severe and fatal complications such as hemophagocytic lymphohistiocytosis, septic shock, and multiorgan failure have also been reported [20, 29-31]. The few autopsy reports have described the identification of HRTV antigens in lymph nodes, spleen, liver, kidneys, small and large intestines, gallbladder, pancreas, lung, heart, testes and brain [32, 33].

As with BRBV, HRTV diagnostics are not readily available and testing of suspected cases should be done in coordination with state health departments. It is important to note that in acute HRTV infection, the duration of viremia is of approximately 1-2 weeks. Furthermore, the detection of both viral RNA by RT-PCR after 21 days and IgM antibodies approximately 2 weeks after symptom onset have important implications related to modes of transmission and diagnostics [30].

ALPHA-GAL SYNDROME

In the first decade of this century, reports of a higher incidence of hypersensitivity reactions to cetuximab in patients from Tennessee and North Carolina (22%) compared to other regions of the country (3%) ignited research into the mechanisms responsible for this geographic association [34, 35]. In a seminal study, pre-treatment IgE specific antibodies to the oligosaccharide, galactose-α-1,3-galactose (alpha-gal), were found in patients that experienced hypersensitivity reactions to cetuximab. The allergic reaction occurred as the oligosaccharide is present in the Fab portion of the cetuximab heavy chain. This specific oligosaccharide is not found in humans or other primates [36, 37]. Some individuals with IgE specific antibodies to alpha-gal also experienced a higher rate of allergic reactions after consumption of meat of mammalian origin. In contrast to the immediate allergic reaction seen after administration of cetuximab, sensitized individuals experienced a delayed-onset allergic reaction of several hours after consumption of animal food products [36, 38].

The link between tick bites and the alpha gal syndrome in the United States was entertained after reports of such association in Australia [39] and the geographic overlap between reported cases of allergy to mammalian meat, cetuximab, and that of the tick *A. americanum* [37, 40]. The sensitization to galactose-α-1,3-galactose in humans is produced by the bite of a tick that has fed on non-primate mammals containing the oligosaccharide. It is also possible that the alpha gal could be transmitted trans-stadially or be present in the tick's saliva [41].

The alpha gal syndrome is seen in individuals with IgE specific to alpha gal who develop an allergic reaction to red meat and other animal-derived products such as milk, cheese, gelatin, certain biologics, and gelatin-containing vaccines [38, 42]. A study that characterized the phenotype of the syndrome in 248 individuals showed no difference in the nature or timing of symptomatology between adults and children. Most patients present with gastrointestinal complaints (e.g. abdominal cramping, nausea, vomiting), urticaria, angioedema, and anaphylaxis 3-6 hours after consumption of mammal-derived meat products. Symptomatology can also ensue acutely (i.e. within 2 hours), especially in women and be limited to the gastrointestinal tract. There is no association with the alpha-gal syndrome and atopy and there is a non-absolute negative association with blood group B [42]. The delayed onset of symptoms is thought to be related to the slower digestion and absorption of alpha-gal bound to lipids, and not to proteins [43].

The syndrome causes significant morbidity and is a concerning public health problem due to its increasing incidence and prevalence in the United States [44]. A retrospective study identified over 30,000 individuals with positive alpha-gal specific

IgE antibodies and showed a 6-fold increase in seropositivity rates between 2011 and 2018. The locations of the identified individuals mirrored the geographic distribution of the Lone Star tick [44]. The diagnosis of the alpha-gal syndrome is challenging and based on clinical presentation, identification of alpha-gal IgE specific antibodies, and response to red meat avoidance [45, 46]. Antihistamines and elimination of consumption of mammalian animal products including dairy is the mainstay of treatment. Most can reintroduce mammalian animal products into their life with time.

DISCUSSION

In the current world order, the emergence and re-emergence of infectious diseases, some with pandemic potential, are occurring with more frequency and at a greater scale and duration [47]. Tick-borne diseases are not the exception; known tick vectors are expanding their geographic range and new tick associated pathogens continue to be discovered [48]. Warmer temperature due to climate change affect the tick's life cycle and behavior by for example increasing the egg rate development, accelerating the tick's developmental cycle, promoting host questing, and lengthening their active season [1, 3, 49, 50]. *Amblyomma americanum* has historically been established in southern, southeastern, and midwestern states but is rapidly expanding into new areas of the northwest and north including Canada. Genetic differences between the species isolated in states like New York from species located in the traditional range could facilitate pathogen transmission [3, 51, 52].

The proportion of asymptomatic infection due to both viruses is currently unknown. Adults represent the preponderance of published cases with older individuals with comorbidities, not characterized further in the reports, being at highest risk for severe disease and poor outcome. The hospitalization rate and case-fatality ratio have not been established. The largest cohort of patients with HRTV infection reported a 13% case-fatality ratio although there is likely case ascertainment bias due to physicians requesting testing for the virus in more severe cases [30]. Besides age greater than 60 years and comorbidities no further defined, no other risk factors have been consistently associated with disease severity and prognosis. The severe fever with thrombocytopenia virus, a *Phlebovirus* closely related to HRTV, has a case-fatality ratio of approximately 17%. Risk factors for poor outcome include older age, decreased level of consciousness and an elevated lactate dehydrogenase (>1,200 U/L) and creatine kinase levels (>800 U/L). Higher levels of serum cytokines such as interleukin 6 (IL-6), IL-10, and interferon -gamma (IFN-γ) and IL-10 were also observed in fatal cases [53].

In addition, SFTV can be transmitted from human to human through transfusion of infected blood or contact with bloody secretions [54]. Although there are no reports of transmission of HRTV by this route, the prolonged duration of viremia and its relatedness to SFTV raises the possibility of potential human-to-human transmission. Furthermore, SFTV is transmitted by the Asian Longhorn tick, *Haemaphysalis longicornis*, which until recently was not present in the Western Hemisphere. The tick was first found in sheep in New Jersey in 2017 and has now been reported in several other states [55, 56]. The tick is aggressive, feeding for up to 19 days from animals, and is able to reproduce through parthenogenesis resulting in massive host infestations. The tick has been found to be infected with *Anaplasma*, *Ehrlichia*, *Rickettsia*, and *Borrelia* species in other endemic regions outside the United States [56-58]. Experimental studies have shown that *H. longicornis* is a competent vector for *R. rickettsii* and unlikely to transmit *Anaplasma phagocytophilum* and *B. burgdorferi* [59-61]. Further studies are needed to define the vector's competence and capacity for other tick-borne diseases, such as HRTV and BRBV, present in the continental United States.

Polymicrobial tick infections can increase the risk of disease severity and complicate the interpretation of available diagnostics [62]. For example, *A. americanum* is often infected by *Rickettsia amblyommatis*, a spotted-fever group rickettsia (SFGR) of undetermined pathogenicity. *R. amblyommatis* elicits an immune response that can cause reactivity with the antigens used commercially to diagnose other SFGR such as Rocky Mountain Spotted Fever (RMSF). Moreover, other non-rickettsial pathogens such as BRBV and HRTV could be misdiagnosed with an infection caused by a SFGR if the individual has preexistent antibodies to *R. amblyommatis* [63, 64]. The diagnosis of both HRTV and BRBV is restricted to a few research laboratories and CDC. There is an urgent need

to refine the existent diagnostics for tick-borne diseases and to develop accurate, affordable, and more readily available test for tick-borne emergent agents.

There is no specific treatment for HRTV and BRBV and management consists of supportive care. The mechanisms by which both viruses induce severe illness remains undefined. Murine models suggest that BRBV is exquisitely sensitive to the host's interferon (IFN) system and that the few persons with severe BRBV described in the literature might have had an inborn or acquired defect in their innate antiviral immune system [65].

As previously mentioned, SFTV is closely related to HRTV and available data suggests shared risk factors for poor outcome. In-vitro studies have shown that HRTV infection antagonizes both type I and III IFN system similar to SFTV [66]. Furthermore, SFTV leads to changes in CD4-T cell subsets such as skewing of the Th1/Th2 and Th17/Treg ratios, the later leading to increased IL-6 levels and associated with poor outcome. Blockage of IL-6 signal with tocilizumab could restore the Th17/Treg ratio [67]. In addition, a robust elevation of several cytokines such as IL-1RA, IL-6, IL-10 in SFTV is associated with poor prognosis. Identification of existent and new therapeutics targeting the virus-induced "cytokine storm" and their potential applicability and role in management should be examined further [68, 69].

It is also important to remember that HRTV and BRBV are clinically undistinguishable from treatable rickettsial diseases such as ehrlichiosis and RMSF and doxycycline should be therefore empirically prescribed when considering a tick-borne disease, including children younger than 8 years of age [70].

Finally, the AGS is a relatively new entity of increasing importance given its rising incidence and associated morbidity. However, the interactions between ticks and vertebrate hosts, such as human, is not always harmful. AGS could represent the trade-off to development of immunity against organisms that produce the carbohydrate α-gal such as *Plasmodium* spp., *Trypanosoma cruzi*, and *Leishmania* spp. [71].

In summary, *Amblyomma americanum* is a prolific arachnid capable of rapidly adapting to new geographic locations. It is a competent vector of a growing list of important pathogens, and its bite is a potential allergen able to induce life-threatening allergic reactions to meat and other mammalian derived products. The health, economic, societal, and environmental impact of these three new conditions associated with the Lone Star tick and that of *H. longicornis* needs to be further characterized. Public health interventions aimed at prevention and control of tick-borne disease should be based on a better understanding on the effect climate change is having in the evolution of the pathogen, host, and pathogen-host interactions.

Conflicts of interest
None.

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