



Nebraska Department of Health and Human Services
HEALTH ALERT NETWORK
Advisory



TO: Primary care providers, Infectious Disease, Clinical Laboratories, Infection Control, and Local Health Departments

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RE: Tick Borne Diseases in Nebraska

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Every year, as humans move to the great outdoors during the spring and summer seasons, public health authorities note an increase in reported tick-borne disease. This article addresses the three tick-borne diseases known to be present in Nebraska. In addition, we discuss other possible tick-borne diseases, whose presence in Nebraska is unproven and which require cooperation between patients, doctors and public health officials to define their epidemiology.

The three well-characterized tick-borne illnesses endemic to Nebraska are Rocky Mountain spotted fever, ehrlichiosis, and tularemia. Unproven tick borne diseases which require further study to determine their presence and extent in Nebraska are Lyme disease, caused by *Borrelia burgdorferi* and transmitted by *Ixodes scapularis* ticks, anaplasmosis (formerly called human granulocytic ehrlichiosis) caused by *Anaplasma phagocytophilum*, and a Lyme-like illness called Southern Tick Associated Rash illness.

The two most important tick species believed to be associated with these diseases in Nebraska are *Dermacentor variabilis* (overlapping with the less common *Dermacentor andersoni* [Rocky Mountain wood tick] in northwest Nebraska) and *Amblyomma americanum*. *Ixodes scapularis* (formerly *Ixodes dammini*) is the only known vector of *Borrelia burgdorferi* and *Anaplasma phagocytophilum*, the causative agents of Lyme disease and anaplasmosis, respectively. This tick is not established in Nebraska: its absence makes indigenous acquisition of Lyme disease and anaplasmosis highly suspect.

Rocky Mountain spotted fever (RMSF)

RMSF has long been endemic in Nebraska, with fewer than ten cases reported every year. Because RMSF occurs infrequently in Nebraska, health care providers might overlook this diagnosis. RMSF should be a diagnostic consideration in any person with a fever and a history of exposure to environments where ticks might be present. The skin rash which gives this illness its name is not always present when the patient first presents to a physician. **This disease is frequently overlooked or misdiagnosed, with numerous reports of serious and sometimes fatal consequences.** Laboratory diagnosis is made by detecting a rise in antibody titer to *Rickettsia rickettsii* between acute and convalescent sera. The organism can also be detected

using PCR, fluorescent antibody methods on tissue biopsy, or isolation in cell culture. **The disease responds to tetracycline-class of antibiotics and chloramphenicol.** Immediate empiric therapy is recommended and should not be delayed while awaiting diagnostic results.

Ehrlichiosis

Ehrlichiosis is caused by *Ehrlichia chaffeensis*, an intracellular bacterium that grows within cytoplasmic phagosomes of white blood cells, and can cause leukopenia. The symptoms of this disease vary and may include severe malaise, fever and headache. A maculo-papular rash may occur in some patients, but dermatologic signs are not common features of the disease. The absence of a rash should not be used to rule out infection. Untreated, the illness may progress with hypotension, coagulopathy, hemorrhage of internal organs and renal failure.

Presumptive diagnosis can be made by identifying the classic inclusion or morulae in the cytoplasm of monocytes or macrophages. While a review of the peripheral blood smear can suggest the diagnosis, confirmation requires a four-fold rise in IgG antibody titer between acute and convalescent sera or by molecular detection of *Ehrlichia* DNA in clinical specimens. Recently *Ehrlichia ewingii*, transmitted by the lone star tick, has emerged as an important etiology of human ehrlichiosis. *E. ewingii* does not cross react with *E. chaffeensis*. Doxycycline is the first line treatment for adults and children of all ages and should be initiated immediately whenever ehrlichiosis is suspected. Treatment should be initiated based upon clinical suspicion while awaiting results from confirmatory laboratory testing.

Tularemia

Tularemia is a disease of animals and humans caused by the gram negative bacterium *Francisella tularensis*. Rabbits, hares, and rodents are especially susceptible and often die in large numbers during outbreaks. Humans can become infected through several routes, including tick or deer fly bites, skin contact with infected animals, bites from infected cats, ingestion of contaminated water, or inhalation of contaminated dusts or aerosols.

Illness from *F. tularensis* ranges from mild to life-threatening. Disease is accompanied by fever, which can be as high as 104°F. Disease following a tick bite or deerfly bite is usually ulceroglandular and is the most common form of tularemia. A skin ulcer appears at the site where the organism entered the body, and is typically accompanied by swelling of regional lymph glands, usually in the armpit or groin. Tularemia can present without an ulcer, the so-called "glandular form." Diagnosis can be made by isolation of *F. tularensis* in a clinical specimen or by a four-fold rise or greater change in serum antibody titer to *F. tularensis* antigen. Although tularemia can be life-threatening, most infections are successfully treated with antibiotics. Streptomycin is the drug of choice based on experience, efficacy and FDA approval. Gentamicin is considered an acceptable alternative, but some series have reported a lower primary success rate. Treatment with aminoglycosides should be continued for 10 days.

Lyme Disease

Lyme disease, caused by a spirochete called *Borrelia burgdorferi*, is now the most prevalent tick-borne disease in the United States. This organism is transmitted by the tick *Ixodes scapularis* which is not established in Nebraska. This fact makes any diagnosis of Nebraska-acquired Lyme disease caused by *B. burgdorferi* highly suspect. Lyme disease is highly regional in the United States (<http://www.cdc.gov/lyme/stats/maps/map2012.html>). As a result of a long-established rule for assigning reportable diseases to the patient's state of residence, some confusion regarding the distribution of Lyme disease exists: persons who have

had out-of-state exposure to ticks in highly endemic areas are reported by states where classic Lyme disease is not thought to occur. The situation in Nebraska is a classic example: in 2009 we reported four such cases to the national reportable disease system at the CDC. All had out-of-state exposure.

Further confusion exists regarding the endemic acquisition of Lyme disease in Nebraska because of technical issues with the diagnostic tests. Two laboratory diagnostic approaches are used to confirm the diagnosis of Lyme disease: serologic tests looking for antibody to *B. burgdorferi*, and tissue culture or other molecular detection methods. There has never been a tissue culture or other molecular/antigenic confirmation of *B. burgdorferi* in a person suspected of indigenous acquisition of Lyme disease in Nebraska. However, every year Nebraska's state and local public health agencies receive reports of Nebraskans whose serologic test for Lyme disease was reported as positive. While some of these persons reported a tick-prone exposure in regions of the country where classic Lyme disease is clearly established and likely represent true cases of Lyme disease, many of these persons have never left Nebraska. The positive Lyme disease serology in this latter group of patients is likely explained by a lack of specificity of the laboratory tests. These are likely false-positive tests. They may reflect underlying medical conditions such as rheumatoid arthritis, or prior exposure to other spirochetal organisms similar to *B. burgdorferi* that lead to a cross reaction with the Lyme serologic test (e.g., *Leptospira* species, treponemal species, or *Borrelia* species other than *B. burgdorferi*).

Current recommendations for serologic testing for Lyme disease are to always perform a two test process consisting of an ELISA followed by a Western blot. The tests may be performed using the same blood sample. The Western blot should include both an IgG and IgM assay. Positive serologic evidence requires both the ELISA and Western blot to be positive. The assays have greatly improved sensitivity and specificity in untreated patients tested two to three weeks following exposure. IgM positivity is transient, and if present greater than four weeks following exposure is likely to be a false-positive. The extent to which current serologic tests may cross-react with *Borrelia* species other than *B. burgdorferi* is not established.

Southern Tick-Associated Rash Illness (STARI)

A red, expanding "bull's-eye" rash similar to those seen in patients with Lyme disease has also been observed in people bitten by *Amblyomma americanum*, often referred to as the lone-star tick. The condition has been named Southern Tick-Associated Rash illness and occasionally patients may also experience fever, malaise and headache. Whether the lesions and illness described in patients following an *Amblyomma americanum* tick bite is infectious or allergic/toxin mediated remains speculative. Studies have shown that the rash is not caused by *Borrelia burgdorferi*; though once thought to be caused by another species of *Borrelia*, research has not supported this idea. The etiology remains to be determined and best treatment practices are not understood.

The lone star tick is common in eastern and south central Nebraska. While this disease may be endemic to Nebraska, its occurrence is speculative and unproven. We have never identified organisms that might explain human STARI disease from tick or human samples collected in Nebraska. Researchers are currently attempting to better characterize this disease, and its causative agent, and to develop diagnostic tests.

Heartland Virus Disease: A New Tick Borne Virus

Scientists at CDC have recently identified a novel phlebovirus that has been named Heartland virus. It was first isolated from two Missouri farmers hospitalized with fever, and a severe drop

in their white blood cells and platelets in 2009. Six additional confirmed cases with similar clinical and laboratory findings were identified during 2012-2013; five from Missouri, and the other from Tennessee. Four of the cases required hospitalization, and one with comorbidities died. Tick bites within 14 days prior to onset of the disease were reported in 5 of the 6 cases. Further discussion of these cases has recently been published (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6312a4.htm?s_cid=mm6312a4_w).

Studies to date have shown that Heartland Virus is carried by *Amblyomma americanum*. The ticks likely become infected by feeding on viremic hosts during the larval stage, and transmission to humans occurs during the spring and early summer when nymphs are abundant and actively host-seeking. While the virus has not been isolated from Nebraska ticks, clinicians should consider testing in patients with a compatible clinical and epidemiologic history who have tested negative for ehrlichiosis and anaplasmosis or have not responded to empiric therapy. Clinicians suspecting this diagnosis should contact their local or state health department to arrange for diagnostic testing. There is no vaccine or specific treatment available for the disease.

Work in Progress: We Need Your Help

Nebraska's state and local health departments need the assistance of patients and doctors to accurately define the spectrum of tick-borne disease in Nebraska. People who want ticks identified should contact the UNL Vet Science Department (402-472-2952). Physicians who suspect non-endemic tick-borne disease (e.g., Lyme disease, anaplasmosis, or STARI-related disease) should contact a public health official (your local health department, or Tom Safranek, M.D., State Epidemiologist or Dr. Bryan Buss 402-471-2937) for assistance in a diagnostic work-up. Lesions consistent with erythema migrans found in Lyme disease should undergo punch biopsy of the leading edge of the skin lesion with tissue sent for culture and diagnostic testing at CDC, together with serologic testing. PCR can be done on CSF, synovial fluid, or skin punch biopsy. Details for specimen collection and transport can be obtained by contacting the Nebraska Public Health Laboratory (Toll-Free: 1-866-290-1406; Call Pager: 402-888-2086).

Further Reference: CDC has an excellent website which has detailed information regarding tick-borne disease in the United States:

<http://www.cdc.gov/ticks/diseases/>

Tick	Distribution	Associated Illness	Infectious Agent
<i>Dermacentor variabilis</i> (American dog tick or wood tick)	Statewide	Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>
		Tularemia	<i>Francisella tularensis</i>
<i>Dermacentor andersoni</i>	NW Nebraska	Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>
		Tularemia	<i>Francisella tularensis</i>
<i>Amblyomma americanum</i> (Lone star tick)	Southern and central Nebraska	Human monocytic ehrlichiosis	<i>Ehrlichia chaffeensis</i>
		Southern Tick Associated Rash illness	<i>Unknown etiology</i>
		Tularemia	<i>Francisella tularensis</i>
		Heartland Virus Disease	Heartland virus
<i>Ixodes scapularis</i> (deer tick or blacklegged tick)	Not established in Nebraska	Lyme disease	<i>Borrelia burgdorferi</i>
		Human granulocytic ehrlichiosis	<i>Anaplasma phagocytophilum</i>

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