Nebraska Department of Health and Human Services

HEALTH ALERT NETWORK

Advisory

TO: Primary care providers, ERs, labs, infectious disease, infection control, and public health

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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 phagocytophilium,* and a Lyme-like illness called Southern Tick Associated Rash illness.

The two most important tick species believed to be associated with disease in Nebraska are *Dermacentor variabilis* (overlapping with the less common *Dermacentor andersoni* [Rocky Mountain wood tick] in northwest Nebraska) and *Amblyomma americanum* ("Texas Lone Star tick"). *Ixodes scapularis* (formerly *Ixodes dammini*) is the only known vector of *Borrelia burgdorferi* and *Anaplasma phagocytophilium*, 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 risk overlooking this diagnosis. RMSF NEEDS TO 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.** In 2015 Nebraska experienced one fatal case of RMSF. The patient made two Emergency Room visits without a correct diagnosis, prior to a third ER visit where the patient was admitted, and subsequently died.

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. Treatment requires tetracycline-class of antibiotics or chloramphenicol. Use of beta lactam antibiotics or flouroquinolones are contraindicated. **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*. Treatment with a tetracycline-class antibiotic 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. **Last year there were 24 cases reported in Nebraska, the highest number in 25 years. No deaths were reported.**

Illness from *F. tularensis* ranges from mild to life-threatening. 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 and sometimes the only symptoms are lymph node swelling, fatigue, or muscle and joint pains. Diagnosis can be made by isolation of *F. tularensis* in a clinical specimen or by a four-fold rise or greater change between acute and convalescent serum antibody titers to *F. tularensis* antigen. Although tularemia can be life-threatening, most infections are successfully treated with antibiotics. While streptomycin is the drug of choice, gentamicin is an acceptable alternative, but some series have reported a lower primary success rate. Tetracyclines may be a suitable alternative to aminoglycosides for patients who are less severely ill. Ciprofloxacin and other fluoroquinolones are not FDA-approved for treatment of tularemia but have shown good efficacy in vitro, in animals, and in humans.

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.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 natively. 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 is reported as positive. While some of these persons reported a tick-borne 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*).

Serologic testing for Lyme disease requires a two-step process consisting of an ELISA which if positive should be 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. This testing algorithm optimizes 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. 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. While the etiology of this condition is unknown, a 21-day course of a tetracycline-class antibiotic is recommended.

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 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) 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).

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

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