



Nebraska Department of Health and Human Services
HEALTH ALERT NETWORK
Advisory



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

FROM Thomas J. Safranek, M.D. Jeff Hamik
State Epidemiologist Vector-borne Disease Epidemiologist
402-471-2937 PHONE 402-471-1374 PHONE
402-471-3601 FAX 402-471-3601 FAX

RE: TICK-BORNE DISEASES IN NEBRASKA

DATE: March 19, 2019

The arrival of spring marks the beginning of another tick season. In the interest of public health and prevention, our office seeks to inform Nebraska health care providers about the known tick-borne diseases in our state.

Spotted fever rickettsia (SFR) including Rocky Mountain spotted fever (RMSF)

SFR is a group of related bacteria that can cause spotted fevers including RMSF. Several of these SFR have similar signs and symptoms, including fever, headache, and rash, but are often less severe than RMSF. SFR are the most commonly reported tick-borne disease in Nebraska. Our office has reported a median of 26 cases (range 13-48) with SFR over the last 5 years (2014-2018), an increase from 9 median cases (range 6-18) reported during 2009-2013. SFR, especially **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 is not always present when the patient first presents to a physician. **RMSF is frequently overlooked or misdiagnosed, with numerous reports of serious and sometimes fatal consequences.** Nebraska experienced a fatal case of confirmed RMSF in 2015 where the diagnosis was missed and treatment was delayed until the disease was well advanced.

Laboratory diagnosis:

Serology

- The standard serologic test for diagnosis of RMSF is the indirect immunofluorescence antibody (IFA) assay for immunoglobulin G (IgG) using *R. rickettsii* antigen.
- IgG IFA assays should be performed on paired acute and convalescent serum samples collected 2–4 weeks apart to demonstrate evidence of a 4-fold seroconversion.
- Antibody titers are frequently negative in the first week of illness. RMSF cannot be confirmed using single acute antibody results.
- Immunoglobulin M (IgM) IFA assays are available through some reference laboratories, however results might be less specific than IgG IFA assays for diagnosing a recent infection.

- *R. rickettsii* is closely related to other pathogenic SFR species, including *R. akari*, *R. parkeri*, and *Rickettsia 364D*. Closely related species of SFR share similar antigens such that antibodies directed to one of these antigens can cross-react with other heterologous spotted fever group antigens.
- Most commercial labs are unable to differentiate one spotted fever infection from another using these serologic methods.

Persistent Antibodies

- Antibodies to *R. rickettsii* might remain elevated for many months after the disease has resolved.
- In certain people, high titers of antibodies against *R. rickettsii* have been observed up to four years after the acute illness.
- Ten percent or more of healthy people in some areas might have elevated antibody titers due to past exposure to *R. rickettsii* or other SFR.
- Comparison of paired, and appropriately timed, serologic assays provides the best evidence of recent infection.
- Single or inappropriately timed serologic tests, in relation to clinical illness, can lead to misinterpretation of results.

PCR

- Polymerase chain reaction (PCR) amplification is performed on DNA extracted from whole blood.
- *R. rickettsii* infect the endothelial cells that line blood vessels and may not circulate in large numbers in the blood until the disease has progressed to a severe phase of infection.
- Although a positive PCR result is helpful, a negative result does not rule out the diagnosis, and treatment should not be withheld due to a negative result.
- PCR might also be used to amplify DNA from a skin biopsy of a rash lesion, or in post-mortem tissue specimens.

IHC and Culture

- Culture and immunohistochemistry (IHC) assays can also be performed on skin biopsies of a rash lesion, or post-mortem tissue specimens.
- Culture isolation and IHC assays of *R. rickettsii* are only available at specialized laboratories; routine hospital blood cultures cannot detect the organism.

Treatment requires tetracycline-class of antibiotics or chloramphenicol. Tetracycline-class treatment is recommended for persons of all ages, including children. Beta lactam antibiotics and fluoroquinolones are contraindicated. Immediate empiric therapy is recommended and should not be delayed while awaiting diagnostic results.

Tularemia

Tularemia is caused by *Francisella tularensis*. This agent is found in nature in rabbits, muskrats, prairie dogs and other rodents. Human infection occurs 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. Nebraska has reported a median of 7 cases (range: 6-24) over the last 5 years (2014-2018).

Disease signs and symptoms vary depending on how the bacteria enter the body. Illness ranges from mild to life-threatening. All forms are accompanied by fever, which can be as high as 104°F. Main forms of this disease are:

- **Ulceroglandular** This is the most common form of tularemia and usually occurs following a tick or deer fly bite or after handling of an infected animal. A skin ulcer appears at the site where the bacteria entered the body. The ulcer is accompanied by swelling of regional lymph glands, usually in the armpit or groin.
- **Glandular** Similar to ulceroglandular tularemia but without an ulcer. Also generally acquired through the bite of an infected tick or deer fly or from handling sick or dead animals.
- **Oculoglandular** This form occurs when the bacteria enter through the eye. This can occur when a person is butchering an infected animal and touches his or her eyes. Symptoms include irritation and inflammation of the eye and swelling of lymph glands in front of the ear.
- **Oropharyngeal** This form results from eating or drinking contaminated food or water. Patients with oropharyngeal tularemia may have sore throat, mouth ulcers, tonsillitis, and swelling of lymph glands in the neck.
- **Pneumonic** This is the most serious form of tularemia. Symptoms include cough, chest pain, and difficulty breathing. This form results from breathing dusts or aerosols containing the organism. It can also occur when other forms of tularemia (e.g. ulceroglandular) are left untreated and the bacteria spread through the bloodstream to the lungs.
- **Typhoidal** This form is characterized by any combination of the general symptoms (without the localizing symptoms of other syndromes).

Laboratory diagnosis:

- Growth of *F. tularensis* in culture is the definitive means of confirming the diagnosis of tularemia. Appropriate specimens include swabs or scrapings of skin lesions, lymph node aspirates or biopsies, pharyngeal swabs, sputum specimens, or gastric aspirates, depending on the form of illness. Paradoxically, blood cultures are often negative.
- A presumptive diagnosis of tularemia may be made through testing of specimens using IFA, IHC staining, or PCR.
- The diagnosis of tularemia can also be established serologically by demonstrating a 4-fold change in specific antibody titers between acute and convalescent sera. Convalescent sera are best drawn at least 4 weeks after illness onset; hence this method may be useful for confirming the diagnosis but not for clinical management.

In patients that present with symptoms and/or history highly suggestive of tularemia, clinicians should consider culture which will facilitate typing if an isolate is recovered. For surveillance purposes, typing of isolates is highly advantageous. If tularemia is suspected, laboratory staff should be alerted to ensure safety precautions are in place to prevent infection in the lab workers.

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. Tetracyclines may be a suitable alternative to aminoglycosides for patients who are less severely ill.

Ehrlichiosis

Ehrlichiosis is caused most commonly by *Ehrlichia chaffeensis*, an intracellular bacterium that grows within cytoplasmic phagosomes of white blood cells, and can cause leukopenia. This bacteria is transmitted via the tick bite of *Amblyomma americanum* ("Lone star tick"). Symptoms may include severe malaise, fever and headache. If left untreated, the illness may progress with hypotension, coagulopathy, hemorrhage of internal organs and renal failure. Nebraska has reported a 5 year median of 3 cases (range: 2-7). However with the expansion of the Lone star

tick (*Amblyomma americanum*) in Nebraska, this disease is most likely underdiagnosed. ***Providers suspecting a SFR or RMSF diagnosis should consider ehrlichiosis as a differential diagnosis.***

Laboratory diagnosis:

Serology

- The reference standard serologic test for diagnosis of ehrlichiosis is the IFA assay for IgG.
- IgG IFA assays should be performed on paired acute and convalescent serum samples collected 2–4 weeks apart to demonstrate evidence of a 4-fold seroconversion.
- Antibody titers are frequently negative in the first week of illness. Ehrlichiosis cannot be confirmed using single acute antibody results.
- IgM IFA assays may also be offered by reference laboratories, however, are not necessarily indicators of acute infection and might be less specific than IgG antibodies.
- Antibodies, particularly IgM antibodies, might remain elevated in patients for whom no other supportive evidence of a recent rickettsiosis infection exists. For these reasons, IgM antibody titers alone should not be used for laboratory diagnosis.

Persistent Antibodies

- Antibodies against *Ehrlichia* species might remain elevated for many months after disease has resolved.
- Comparison of paired, and appropriately timed, serologic assays provides the best evidence of recent infection.
- Single or inappropriately timed serologic tests, in relation to clinical illness, can lead to misinterpretation of results.

Cross Reactivity

- Closely related organisms, including those in the *Ehrlichia* and *Anaplasma* genera, share similar antigens such that antibodies directed to one of these antigens can cross-react.
- Most commercial labs are unable to differentiate between *Ehrlichia* species.
- In areas endemic for Ehrlichiosis and Anaplasmosis, IFA using antigen from both *Ehrlichia* and *Anaplasma* species should be run side-by-side.

PCR

- PCR amplification is performed on whole blood specimens.
- This method is most sensitive in the first week of illness and decreases in sensitivity following the administration of appropriate antibiotics (within 48 hours).
- Although a positive PCR result is helpful, a negative result does not rule out the diagnosis, and treatment should not be withheld due to a negative result.
- PCR might also be used to amplify DNA in solid tissue and bone marrow specimens.

IHC and Culture

- Culture isolation and IHC assays of *Ehrlichia* species are only available at specialized laboratories; routine hospital blood cultures cannot detect the organism.
- PCR, culture, and IHC assays can also be applied to post-mortem specimens.
- If a bone marrow biopsy is performed as part of the investigation of cytopenias, immunostaining of the bone marrow biopsy specimen can diagnose ehrlichiosis.

Blood-smear Microscopy

- During the first week of illness, a microscopic examination of a peripheral blood smear might reveal morulae (microcolonies of *Ehrlichiae*) in the cytoplasm of white blood cells and is highly suggestive of a diagnosis.
 - *E. chaffeensis* most commonly infects monocytes.
 - *E. ewingii* more commonly infects granulocytes.
- Blood smear examination is relatively insensitive and should not be relied upon solely to diagnose ehrlichiosis.
- The observance of morulae in a particular cell type cannot conclusively differentiate among *Ehrlichia* species or between *Ehrlichia* and *Anaplasma*

Recommended therapy is with a tetracycline-class antibiotic. Immediate empiric therapy is recommended and should not be delayed while awaiting diagnostic results.

Anaplasmosis

Anaplasmosis is caused by *Anaplasma phagocytophilum*, an intracellular bacterium that targets neutrophils, altering their function, and forms morulae within vacuoles. Symptoms are similar to ehrlichiosis and include malaise, fever, and headache. If left untreated, anaplasmosis can be fatal, even in previously healthy people. Severe clinical presentations may include difficulty breathing, hemorrhage, renal failure or neurological deficits. Like Lyme disease, anaplasmosis is highly regional and transmitted by the *Ixodes scapularis* tick. This **makes any diagnosis of Nebraska-acquired anaplasmosis highly suspect**. Nebraska has reported from zero to two cases annually, none for 2018. As with Lyme disease reports, these patients reported exposure/acquisition in regions of the country known to be endemic for *Ixodes scapularis* ticks.

Laboratory diagnosis:

Serology

- The reference standard serologic test for diagnosis of ehrlichiosis is the IFA assay for IgG using *A. phagocytophilum* antigen.
- IgG IFA assays should be performed on paired acute and convalescent serum samples collected 2–4 weeks apart to demonstrate evidence of a 4-fold seroconversion.
- Antibody titers are frequently negative in the first week of illness. Anaplasmosis cannot be confirmed using single acute antibody results.
- IgM IFA assays may also be offered by reference laboratories, however, are not necessarily indicators of acute infection and might be less specific than IgG antibodies.
- Antibodies, particularly IgM antibodies, might remain elevated in patients for whom no other supportive evidence of a recent rickettsiosis infection exists. For these reasons, IgM antibody titers alone should not be used for laboratory diagnosis.

PCR

- PCR is performed on DNA extracted from whole blood specimens.
- This method is most sensitive in the first week of illness, and decreases in sensitivity following the administration of appropriate antibiotics (within 24–48 hours).
- Although a positive PCR result is helpful, a negative result does not rule out the diagnosis, and treatment should not be withheld due to a negative result.
- PCR might also be used to amplify DNA in solid tissue and bone marrow specimens.

Persistent Antibodies

- Antibodies to *A. phagocytophilum* might remain elevated for many months after the disease has resolved.

- In certain people, high titers of antibodies against *A. phagocytophilum* have been observed up to four years after the acute illness.
- Between 5–10% of healthy people in some areas might have elevated antibody titers due to past exposure to *A. phagocytophilum* or similar organisms.
- Comparison of paired, and appropriately timed, serologic assays provides the best evidence of recent infection.
- Single or inappropriately timed serologic tests, in relation to clinical illness, can lead to misinterpretation of results.

Blood-smear Microscopy

- During the first week of illness a microscopic examination of a peripheral blood smear might reveal morulae (microcolonies of anaplasmae) in the cytoplasm of granulocytes and is highly suggestive of a diagnosis.
- However, blood smear examination is relatively insensitive and should not be relied upon solely to diagnose anaplasmosis.
- The observance of morulae in a particular cell type cannot conclusively differentiate between *Anaplasma* and *Ehrlichia* species.

IHC and Culture

- IHC assays of *A. phagocytophilum* are only available at specialized laboratories; routine hospital blood cultures cannot detect the organism.
- PCR, culture, and IHC assays can also be applied to autopsy tissue specimens.

Recommended therapy is with a tetracycline-class antibiotic. Immediate empiric therapy is recommended and should not be delayed while awaiting diagnostic results.

Lyme Disease

This will be addressed in a separate HAN in several weeks.

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 are infectious or allergic/toxin mediated remains speculative. Studies have shown that **the rash is not caused by *Borrelia burgdorferi***, the causative agent of Lyme disease. Though once thought to be caused by another species of *Borrelia*, research has not supported this idea. While experts including CDC are uncertain as to the necessity for antibiotic treatment for this condition, since its etiology is unknown, a 21-day course of a tetracycline-class antibiotic is often prescribed (<https://www.cdc.gov/stari/symptoms/index.html>).

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	Ehrlichiosis (formerly human monocytic ehrlichiosis)	<i>Ehrlichia chaffeensis</i>
		Southern Tick Associated Rash illness	Unknown etiology
		Tularemia	<i>Francisella tularensis</i>
<i>Ixodes scapularis</i> (deer tick or blacklegged tick)	Not established in Nebraska	Lyme disease	<i>Borrelia burgdorferi</i>
		Anaplasmosis (formerly human granulocytic ehrlichiosis)	<i>Anaplasma phagocytophilum</i>

Acknowledgement: We are indebted to Dr. Roberto Cortinas Assistant Professor, Entomology/Veterinary and Biomedical Sciences, University of Nebraska, Lincoln, for providing editorial and content assistance.

For more information please visit:

CDC RMSF Page: <https://www.cdc.gov/rmsf/>

CDC Tularemia Page: <https://www.cdc.gov/tularemia/>

CDC Ehrlichiosis Page: <https://www.cdc.gov/ehrlichiosis/>

CDC Anaplasmosis Page: <https://www.cdc.gov/anaplasmosis/index.html>

CDC STARI Page: <https://www.cdc.gov/stari/>

CDC Tickborne Diseases of the US: A Reference Manual for Health Care Providers, Fourth Edition (2017): <https://www.cdc.gov/lyme/resources/TickborneDiseases.pdf>