Nebraska Department of Health and Human Services

Health Alert Network

UPDATE

May 5, 2025

Tickborne Diseases in Nebraska

Spotted Fever Rickettsia (SFR)/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. Nebraska has reported an average of 6.6 cases with SFR annually over the last five years (2020–2024). SFR, particularly **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 has experienced fatal cases of RMSF.

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. rickettsia* might remain elevated for many months after the disease has resolved.
- In certain people, high titers of antibodies against *R. rickettsia* 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 provide 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 and might also be used to amplify DNA from a skin biopsy of a rash lesion, or in post-mortem tissue specimens.
- *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 based on a negative result.

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 the use of doxycycline. Doxycycline 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 an average of 13 cases annually over the last 5 years (2020–2024) with outbreaks of disease having been reported in 2015 and 2024 (2024 DHHS Increase in Tularemia HAN).

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. Forms of this disease include:

- **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 infected 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 dust 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. Depending on the form of illness, appropriate specimens include swabs or scrapings of skin lesions, lymph node aspirates or biopsies, pharyngeal swabs, sputum specimens, or gastric aspirates. 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 four 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 exposure

and 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* (less commonly *Ehrlichia ewingii*), an intracellular bacteria 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. Although rare, severe outcomes including death are possible. Nebraska has reported an average of 11.2 cases annually over the last five years (2019-2023) with it being the most reported tickborne disease in the state in 2022 and 2023. With the expansion of the Lone star tick (*Amblyomma americanum*) in Nebraska, this disease is likely underdiagnosed. **Providers suspecting a SFR or RMSF diagnosis should also consider ehrlichiosis as a potential diagnosis**.

Laboratory Diagnosis:

PCR

- PCR amplification is typically performed on whole blood specimens but might also be used to amplify DNA in solid tissue and bone marrow 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 based on a negative result.

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 offered by reference laboratories 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 ehrlichiosis 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 provide 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.

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 between *Ehrlichia* species or between *Ehrlichia* and *Anaplasma*

Recommended therapy is with doxycycline. Immediate empiric therapy is recommended and should not be delayed while awaiting diagnostic results.

Anaplasmosis

Anaplasmosis is caused by *Anaplasma phagocytophilum*, an intracellular bacteria 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 transmitted by the *Ixodes scapularis* tick. Established populations (meeting CDC criteria) of this tick have been identified in Douglas, Sarpy, and Saunders counties in 2019 and Thurston County in 2021. **This fact increases suspicion that anaplasmosis, caused by *Anaplasma phagocytophilum*, might be acquired in eastern Nebraska. However, even with these established populations, Nebraska is presently considered a low prevalence state for anaplasmosis. At this time, local human health risk is unknown, but clearly of increased concern.** Nebraska has reported an average of <1 case annually over the last five years (2020-2024).

Laboratory diagnosis:

PCR

- PCR is typically performed on DNA extracted from whole blood specimens but might also be used to amplify DNA in solid tissue, bone marrow, and autopsy tissue 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 on the basis of a negative result.

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 anaplasmosis infection exists. For these reasons, IgM antibody titers alone should not be used for laboratory diagnosis.

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 provide 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.
- Culture and IHC assays can also be applied to autopsy tissue specimens.

Recommended therapy is with doxycycline. Immediate empiric therapy is recommended and should not be delayed while awaiting diagnostic results.

Lyme Disease

Lyme disease is caused by the bacteria *Borrelia burgdorferi*. This bacteria is transmitted via the bite of *Ixodes scapularis* ("Blacklegged or deer tick"). Early-stage symptoms may include fever, chills, headache, fatigue, muscle and joint pain, swollen lymph nodes, and erythema migrans (EM) rash and typically begins within 3 – 30 days after a tick bite. The EM rash occurs in 70 – 80% of infections and will sometimes clear as it enlarges resulting in the "bull's-eye" appearance. However, most EM rashes due to Lyme disease do not appear as the classic bull's-eye rash. Late-stage symptoms of Lyme disease typically begin weeks to months after the initial infection and can include severe headache, neck stiffness, facial palsy, arthritis (particularly of large joints), heart palpitations or irregular heartbeat, and inflammation of the brain and spinal cord. Nebraska has reported an average of 6.8 cases annually over the last five years (2020-2024). In 2019, established populations of this tick were identified in Douglas, Sarpy, and Saunders counties. In 2021, as part of an epidemiological investigation into a cluster of Lyme disease cases, an established population was detected for the first time in Thurston County. The ticks collected from Thurston County were tested and positive for *Borrelia burgdorferi*, the bacteria that causes Lyme disease. This was the first time the *B. burgdorferi* has ever been detected in ticks collected in Nebraska. **The local identification of both the vector and pathogen of Lyme disease, in association with documented Lyme disease cases, demonstrates that *B. burgdorferi* can be acquired in eastern Nebraska. However, Nebraska will likely remain a low prevalence state for Lyme disease. Providers suspecting Lyme disease must be vigilant and obtain thorough patient histories including: any travel 30 days prior to symptom onset, reported tick attachments/bites, reported exposure to tick habitat (e.g., tall grass or wooded areas), etc. Additionally, providers should take great care to order the correct serologic tests in the correct order**.

Laboratory Diagnosis:

Serology

- The serologic tests for diagnosis of Lyme disease include:
    - Standard two-tier test (STTT)
        - The first tier is a serum antibody test and may be an enzyme immunoassay (EIA) or IFA for IgM and/or IgG.
        - If the EIA/IFA is positive or equivocal, this is reflexed to a Western immunoblot. If this is positive, the STTT is considered positive.
    - Modified two-tier test (MTTT)
        - Approved MTTTs will run two EIA tests concurrently or sequentially.

        - The first tier EIA tests for IgM/IgG and if positive or equivocal, second tier individual EIA is run to distinguish between IgM and IgG antibodies.
- Positive second tier IgM Western blot (STTT) and second tier IgM EIA (MTTT) results should be disregarded if the patient has been ill for more than 30 days.
- Association of Public Health Laboratories Suggested Reporting, Language and Interpretation For Lyme Disease Serological Test Results (https://www.aphl.org/aboutAPHL/publications/Documents/ID-2024-Lyme-Disease-Serologic-Testing-Reporting.pdf)

PCR

- PCR testing is not generally recommended because of low sensitivity. This is due to low levels of the bacteria circulating in the blood.
- It may be useful in certain situations, such as testing synovial fluid to help differentiate Lyme arthritis from other types of arthritis.

Cross Reactivity

- False positive cross-reactions may occur in patients with other conditions including relapsing fever, syphilis, rheumatoid arthritis, and Epstein-Barr virus infection.

Recommended therapy is with proper antibiotic treatment regimens from the Infectious Disease Society of America, American Academy of Neurology, and American College of Rheumatology (https://www.cdc.gov/lyme/hcp/clinical-care/index.html)

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 in such patients 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 hypothesis. 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.

Heartland and Bourbon Virus

Heartland and Bourbon viruses are both RNA viruses. Heartland virus was first discovered in 2009 in Missouri and is believed to be transmitted by *Amblyomma americanum* ("Lone star tick"). Initial symptoms are similar to ehrlichiosis which include fever, fatigue, anorexia, nausea, and diarrhea. Bourbon virus was discovered in Bourbon County, Kansas in 2014. Like Heartland virus, Bourbon virus is also believed to be transmitted by *Amblyomma americanum.* Symptoms reported by patients include fever, fatigue, anorexia, nausea, vomiting, and maculopapular rash. Leukopenia, thrombocytopenia, and mild to moderate elevation of liver transaminases have also been seen in patients diagnosed with Heartland or Bourbon viruses. To date, no cases of Heartland or Bourbon virus have been identified in Nebraska residents. Infection with Heartland or Bourbon virus should be considered in patients being treated for suspected tick-borne disease who do not respond to treatment (e.g., doxycycline). Presently, no routine testing is available commercially for Heartland or Bourbon viruses. However, protocols are in place to allow people to be tested for evidence of infection through the CDC. **Providers must contact their local health department to determine if suspected patients meet CDC criteria for testing.**

CDC specimen submission criteria for Heartland and Bourbon virus testing

Testing for Heartland or Bourbon virus should be considered for patients with an acute febrile illness within the past three months AND at least one epidemiologic criterion AND at least one clinical criterion:

- Epidemiologic criteria
    - Known tick bite, finding tick on body, or potential exposure to ticks through outdoor activities in the three weeks prior to illness onset during spring through fall (April–October); OR

- Resides in or recently traveled to an area with previous evidence of Heartland or Bourbon virus. These areas can be found here: https://www.cdc.gov/heartland-virus/data-maps/index.html.

- Clinical criteria
  - Leukopenia (white blood cells <4,500 cells/µL) or thrombocytopenia (platelets <150,000 cells/mL) not explained by another known condition; OR
  - Suspected tickborne disease (e.g., RMSF, ehrlichiosis) with no clinical response to appropriate treatment (e.g., doxycycline).

Samples collected >3 months after symptom onset will not be tested at this time based on limitations of current understanding of antibody kinetics.

As of July 2018, the following tests for Heartland and Bourbon virus are available at CDC:

Test	Heartland Virus	Bourbon Virus
RT-PCR	Yes	Yes
IgM MIA	Yes	Not available
IgG MIA	Yes	Not available
PRNT	Yes	Yes

Alpha-gal Syndrome (Red meat allergy)
An alpha-gal syndrome specific health alert network (HAN) will be sent out in the near future.

For More Information, Please Visit

Nebraska DHHS Tickborne Disease Information for Health Professionals

Nebraska DHHS Tick Surveillance Maps

Association of Public Health Laboratories Suggested Reporting, Language and Interpretation For Lyme Disease Serological Test Results

CDC RMSF Healthcare Providers

CDC Tularemia Healthcare Providers

CDC Ehrlichiosis Healthcare Providers

CDC Anaplasmosis Healthcare Providers

CDC Lyme Disease Healthcare Providers

CDC Heartland Virus

CDC Bourbon Virus

CDC STARI

Tickborne Diseases of the US: A Reference Manual for Health Care Providers, Sixth Edition (2022)

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