

TICK- & LOUSE-BORNE RELAPSING FEVER, EHRLICHIOSIS, COLORADO TICK FEVER

✓ DISEASE AND EPIDEMIOLOGY

Clinical Description:

Relapsing Fever:

Often referred to as Tick-borne Relapsing Fever (TBRF) or Louse-borne Relapsing Fever (LBRF). Relapsing Fever is a disease characterized by relapsing (i.e. recurring) episodes of fever, often accompanied by other symptoms. Initial symptoms include fever, generalized body aches, myalgias, arthralgias, headache, chills and sweats. Other/later symptoms include nausea, vomiting, anorexia, dry cough, photophobia, rash, neck pain, eye pain, confusion and dizziness. Given appropriate antibiotics, most patients feel better within a few days. Patients with TBRF, however, often report prolonged symptoms and time to recovery. Often this is due to delayed diagnosis and treatment. Long-term sequelae of TBRF include cardiac and renal disturbances, peripheral nerve involvement, ophthalmia, and abortion. With treatment the mortality is very low. The mortality without treatment is not known but it has been estimated at 5-10%.

Ehrlichiosis:

The human granulocytic ehrlichiosis (HGE), and human monocytic ehrlichiosis (HME) agents infect different white blood cells, but the signs, symptoms, and clinical courses of the two diseases are similar. Both cause sudden illness, with fever being the predominant sign. The clinical illness is similar to the early phase of Rocky Mountain spotted fever (RMSF), although patients more often have low white blood cell counts and less often develop rash. In addition to fever, patients may have headache, malaise, chills, muscle and joint aches, nausea, vomiting, and loss of appetite. Patients with HGE rarely have a rash, while about 40% with HME have a rash. Many people with HGE or HME may be asymptomatic or may have a very mild, self-limited illness. Treatment for both infections is antibiotics. Response to treatment is usually apparent within 24–48 hours. Severe complications are associated with delayed treatment, older age, or with the case being immunocompromised or having diabetes. These complications may affect the lungs, bone marrow, brain, meninges (linings of the brain and spinal cord), kidneys, and blood. Fatal infections have been reported. Coinfections with other tickborne agents, such as the agents of Lyme disease and babesiosis, may complicate the clinical picture.

Colorado Tick Fever:

Colorado Tick Fever (CTF) is an acute nonspecific febrile illness with infrequent rash. After initial onset, a brief remission is usual, followed by a second bout of fever lasting 2-3 days. Neutropenia and thrombocytopenia almost always occur on

the 4th to 5th day of fever. Characteristically, CTF is a moderately severe disease, with occasional encephalitis, myocarditis or tendency to bleed.

Causative Agent:

Relapsing Fever:

The relapsing fever *Borrelia spp* are gram negative helical bacteria normally 0.2 to 0.5 microns in width and 5 to 20 microns in length. They are visible with light microscopy and have the cork-screw shape typical of all spirochetes. They have a unique process of DNA rearrangement in their linear DNA. Each time the DNA is read a different antigenic marker, also known as a variable major protein, is created, which allows the organism to evade the immune system and therefore cause recurrent patterns of fever and other symptoms.

- **Tick-borne relapsing fever:** This is caused by *B. hermsii*, *B. parkerii*, and *B. turicatae*.
- **Louse-borne relapsing fever:** This is caused by *Borrelia recurrentis*.

Note: Borrelia bergdorferii causes Lyme disease and is not associated with relapsing fever.

Ehrlichiosis:

Human granulocytic ehrlichiosis (HGE), or human granulocytotropic anaplasmosis, is a bacterial infection caused by *Anaplasma phagocytophilum* (formerly *Ehrlichia phagocytophila*). Human monocytic ehrlichiosis (HME) is caused by the bacterium *Ehrlichia chaffeensis*. The etiologic agents are rickettsiae and intracellular pathogens.

Colorado Tick Fever:

Colorado tick fever is a viral infection transmitted by the bite of the wood tick *Dermacentor andersoni*. The disease occurs almost exclusively in the western United States and Canada. The causative agent, an RNA virus formerly classified as an Orbivirus of the family Reoviridae, is limited to *D andersoni*. The newer International Committee on Taxonomy of Viruses has reclassified the agent of Colorado tick fever as a Coltivirus (still in the family of Reoviridae). A closely related Coltivirus has been implicated in human disease in Europe. Attempts to isolate this agent from other species of ticks have failed, although closely related viruses have been isolated from *Ixodes* ticks in Europe.

Differential Diagnosis:

Relapsing Fever:

The following infectious disease should be considered in someone with recurrent episodes of a febrile illness: Colorado tick fever, Yellow fever, dengue fever, malaria, brucellosis, infectious mononucleosis, African hemorrhagic fevers, leptospirosis, chronic meningococemia, rat bite fever, ascending (intermittent) cholangitis, lymphocytic choriomeningitis, infection with echovirus 9, and infections with Bartonella species.

Ehrlichiosis:

Rocky Mountain spotted fever, Lyme disease, babesiosis, sepsis, toxic shock syndrome, gastroenteritis, meningoenzephalitis, tularemia, CTF, leptospirosis, hepatitis, typhoid fever and blood malignancies.

Colorado Tick Fever:

Encephalitis, myocarditis, some strains of CTF can cause hepatitis.

Laboratory identification:

Relapsing Fever:

The definitive diagnosis of relapsing fever is based on the observation of *Borrelia* spirochetes in smears of peripheral blood, bone marrow, or cerebrospinal fluid in a symptomatic person. The organisms are best detected in blood obtained while a person is febrile. With subsequent febrile episodes, the number of circulating spirochetes decreases, making it harder to detect spirochetes on a peripheral blood smear. Even during the initial episode spirochetes will only be seen 70% of the time.

Serology testing is not widely available and results can be difficult to interpret due to cross reactivity with *Borrelia bergdorferii*. Incidental laboratory findings include normal to increased white blood cell count with a left shift towards immature cells, a mildly increased serum bilirubin level, mild to moderate thrombocytopenia (low platelet count), elevated ESR and slightly prolonged coagulation tests, PT and APTT.

Ehrlichiosis:

Ehrlichiosis is typically identified serologically, and requires evidence of an increase in titer between acute and convalescent sera, as antibodies are slow to appear. Immunohistology is specific, but not sensitive. PCR is sensitive but not widely available.

Colorado Tick Fever:

Laboratory confirmation for CTF is made by isolation of virus from blood or by demonstration of antigen in erythrocytes by indirect immunofluorescence. Antibody is detectable as early as 10 days after onset of illness. Diagnostic methods for confirming other tick-borne viral fevers vary only slightly, except that serum is used for virus isolation instead of erythrocytes.

Treatment:

Relapsing Fever:

Five to ten days of doxycycline is the treatment of choice for TBRF, and erythromycin and ceftriaxone are also effective. In contrast, LBRF can be treated with a single dose of erythromycin. The CDC has not developed specific treatment guidelines for TBRF.

Ehrlichiosis:

Doxycycline is the drug of choice for adults and children. Rifampin has been used for HGE in pregnant and pediatric patients. Quinolones have activity but clinical efficacy data is limited.

Colorado Tick Fever:

There is no specific treatment for CTF. Symptomatic relief includes treatment of fever and pain with acetaminophen and analgesics. Salicylates should not be used because of thrombocytopenia and the rare occurrence of bleeding disorders following CTF virus infection.

Case fatality:

Relapsing Fever:

The mortality without treatment is not known but it has been estimated at 5-10%.

Ehrlichiosis:

Severe complications are associated with delayed treatment, older age, or with the case being immunocompromised or having diabetes. These complications may affect the lungs, bone marrow, brain, meninges (linings of the brain and spinal cord), kidneys, and blood. Fatal infections have been reported.

Colorado Tick Fever:

Although prompt recovery is the expected outcome, rare fatalities are reported. Complications seem to occur more frequently in children than in adults, most often in patients whose conditions are diagnosed late.

Reservoir:

Relapsing Fever:

The tick *Ornithodoros* usually feed on small animals such as squirrels, mice, chipmunks, or rabbits. The ticks live in rodent nests which can be found under flooring and between walls. If these rodents are scarce, the ticks will take a meal from other warm-blooded animals including humans.

Ehrlichiosis:

The vector of HGE is the deer tick, *Ixodes scapularis*, which is the same tick associated with Lyme disease and babesiosis. Deer ticks may be co-infected with and capable of transmitting more than one disease agent at the same time. Deer, elk, and wild rodents are likely reservoirs for HGE. The primary vector of HME is the lone star tick, *Amblyoma americanum*. This tick is named for the prominent white spot or “star” on the back of the adult female. The lone star tick is predominantly found in the southeastern U.S. Lone star ticks infected with *E. chaffeensis* have been found in Connecticut and Rhode Island. White-tailed deer are a major host of lone star ticks and appear to represent a natural reservoir for *E. chaffeensis*. Another important reservoir appears to be dogs.

Colorado Tick Fever:

Reservoirs for CTF include small mammals such as ground squirrels, porcupines, chipmunks and *Peromyscus* spp.; also ticks principally *D. andersoni*.

Transmission:

Relapsing Fever:

Borrelia is transmitted to humans through the bite of infected soft ticks of the genus *Ornithodoros*. Soft ticks (family Argasidae) differ in many ways from the so-called hard ticks (family Ixodidae), including the more familiar dog tick and deer tick.



Ornithodoros hermsi

In contrast to hard ticks, soft ticks take brief blood meals lasting less than a half hour, usually at night. Between meals the ticks live in the nesting materials in their host burrows. Individual ticks will take many such blood meals during each stage of their life cycles, including the development of eggs by adult females. The bites of soft ticks are usually painless and the persons who are bitten while asleep are usually unaware that they were bitten.

The individual *Borrelia* species that cause TBRF are usually associated with specific tick vectors. For instance, *B. hermsii* is transmitted to humans by *O. hermsi* ticks, while *B. parkerii* is transmitted by *O. parkeri* and *B. turicatae* is transmitted by *O. turicata*. Each tick has a preferred environment and preferred set of hosts. *O. hermsi* tends to be found at higher altitudes (1500 – 8000 feet) where it is associated primarily with ground or tree squirrels and chipmunks. *O. parkeri* occurs at lower altitudes, where they inhabit caves and the burrows of ground squirrels and prairie dogs, as well as those of burrowing owls. *O. turicata* occurs in caves and ground squirrel or prairie dog burrows in the plains regions of the Southwest, feeding off these animals and occasionally burrowing owls or other burrow- or cave-dwelling animals.

IN PREGNANCY: TBRF contacted during pregnancy can cause spontaneous abortion, premature birth, and neonatal death. The maternal-fetal transmission of *Borrelia* is believed to occur either transplacentally or while traversing the birth canal. In one study, perinatal infection with TBRF was shown to lead to lower birth weights, younger gestational age, and higher perinatal mortality. In general, pregnant women have higher spirochete loads and more severe symptoms than non-pregnant women. Higher spirochete loads have not, however, been found to correlate with fetal outcome.

Ehrlichiosis:

Anaplasma phagocytophilum, the agent responsible for HGE, is transmitted through the bite of an infected deer tick. *E. chaffeensis*, the agent responsible for HME, is transmitted through the bite of an infected lone star tick. Limited data suggest that the longer an infected tick remains attached, the higher the likelihood of successful transmission of *A. phagocytophilum* or *E. chaffeensis*. Since tick bites are often painless and may occur on parts of the body that are difficult to observe, cases of HGE and HME may have no known history of tick bite.

Colorado Tick Fever:

CTF is transmitted through the bite of an infected tick. Immature ticks (*D. andersoni*) acquire CTF virus by feeding on viremic animals; they pass the virus transstadially and transmit virus to humans when feeding as adult ticks. Can be passed through blood donation.

Susceptibility:

Relapsing Fever:

Susceptibility is general. Duration and degree of immunity after clinical attack is unknown. Repeated infections may occur.

Ehrlichiosis:

Susceptibility is believed to be general; older or immunocompromised individuals are likely to suffer a more serious illness. No data are available on protective immunity in humans due to infections caused by these organisms. Reinfection is rare, but has been reported.

Colorado Tick Fever:

Susceptibility is apparently universal. Second attacks are rare.

Incubation period:

Relapsing Fever:

Incubation period is usually 7 days. It is usually another 7 days after the resolution of the initial illness that a relapse will be experienced. Relapses can occur up to 10 times in untreated persons.

Ehrlichiosis:

The period between exposure to infection and the first symptoms of HME or HGE ranges from 7–14 days.

Colorado Tick Fever:

Incubation period for CTF is usually 4-5 days.

Period of communicability:

Relapsing Fever:

Not directly transmitted from person to person, except in rare cases such as the maternal-fetal transmission of *Borrelia* that is believed to occur either transplacentally or while traversing the birth canal.

Ehrlichiosis:

HGE and HME are not communicable from person to person.

Colorado Tick Fever:

Not directly transmitted from person to person except by transfusion. Patient should not donate blood for 4 months following infection.

Epidemiology:

Relapsing Fever:

TBRF is endemic in the western US, southern British Columbia, plateau regions of Mexico, Central and South America, the Mediterranean, Central Asia, and much of Africa. The first endemic focus of TBRF in the US was identified in 1915 in Colorado though the first case was actually in 1905 in New York in a traveler to Texas. Since then, TBRF has been reported in 14 states: Arizona, California, Colorado, Idaho, Kansas, Montana, Nevada, New Mexico, Ohio, Oklahoma, Oregon, Texas, Utah, Washington, and Wyoming. Most recent cases and outbreaks have occurred in rustic cabin or vacation home settings at higher elevations (> 8,000 feet) in coniferous forests in the western US.

TBRF normally occurs in summer months when people are traveling to mountainous areas on vacation. TBRF can, however, occur in winter, particularly when people go into rodent infested cabins and start fires, warming the cabin and producing carbon dioxide and warmth that attract the ticks that transmit TBRF. There hasn't been a reported case of Relapsing Fever in Utah since 1992. Before that, Utah had a 5-year average of 1 case per 5 years.

Ehrlichiosis:

In the U.S., HGE is most often reported in the northeastern and upper-midwestern states. HME is most often reported in the southeastern and southcentral states, reflecting the range of its tick vector. In Utah, Ehrlichiosis was just recently added to our list of reportable diseases in 2000. There have been no cases since that time.

Colorado Tick Fever:

Several hundred cases are reported to the Centers for Disease Control and Prevention annually. These cases are contracted in the states of California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, South Dakota, Utah, Washington, and Wyoming, as well as the Canadian provinces of British Columbia and Alberta. In this endemic area, the disease is limited to elevations above 4000 ft. The number of reported cases likely represents a small fraction of actual cases, since reporting is not mandatory. Furthermore, in endemic areas, the

disease is sufficiently common that it might not be conscientiously reported. Many cases of this nonspecific illness likely remain undiagnosed or unproven. A seasonal peak exists from April through August. Currently, Utah averages 1-2 cases of CTF a year, but saw 10-30 cases per year in the 1990's.

✓ PUBLIC HEALTH CONTROL MEASURES

Public health responsibility:

- Investigate all suspect cases of disease and fill out and submit appropriate disease investigation forms.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention.
- Identify clusters or outbreaks of this disease.
- Identify sources of exposure and stop further transmission.

Prevention:

Managing Special Situations: Response to a Tick Bite

The longer a tick remains attached to someone, the higher the likelihood of disease transmission. Individuals should promptly remove any attached tick using fine-point tweezers. The tick should not be squeezed or twisted, but grasped close to the skin and pulled straight out using steady pressure. Whenever an attached tick is removed from the body, one should monitor one's health for the appearance of rash, fever, or flu-like symptoms, and should immediately seek the advice of a health care provider should any symptoms occur, especially if the tick was attached for more than 24 hours. It may be helpful to save the tick after removal for two reasons: 1) if the person who was bitten goes on to develop signs or symptoms such as fever, flu-like symptoms, or a rash, it may be helpful for the physician to know the type of tick; and 2) depending on the circumstances of the bite (i.e., when a person was bitten, the type of tick, how long it was attached), a physician may choose to treat the person who was bitten. The tick may be kept either securely sealed in a small plastic bag or attached, with clear tape, to a piece of paper. For individuals who do not wish to keep the tick, it can be either drowned in alcohol or flushed down the toilet.

Preventive Measures

Environmental Measures

Prevention of diseases spread by ticks, involves making the yard less attractive to ticks.

- Keep grass cut short.
- Remove leaf litter and brush from around the yard.
- Prune low lying bushes to let in more sunlight.
- Keep woodpiles and bird feeders off the ground and away from the home.
- Keep the plants around stone walls cut short.
- Use a three-foot wide woodchip, mulch, or gravel barrier where the lawn meets the woods, and remind children not to cross that barrier.
- Ask a landscaper or local nursery about plants to use in the yard that do not attract deer.

- Use deer fencing (for yards 15 acres or more).

If an individual chooses to use a pesticide to reduce the number of ticks on his/her property, he/she should be advised to hire a licensed applicator who is experienced with tick control. A local landscaper or arborist may be a licensed applicator. In general, good tick control can be achieved with no more than two pesticide applications in any year. Advise individuals to ask, when selecting an applicator, if they will provide:

- A written pest control plan that includes information on the pesticide to be used.
- Information about non-chemical pest control alternatives.
- Signs to be posted around the property after the application.

Personal Preventive Measures/Education

There is no human vaccine for Ehrlichiosis, Relapsing Fever or CTF. If someone lives, works, or spends leisure time in an area likely to have ticks, they should be advised of the following:

- The single most important thing one can do to prevent a tickborne disease is to check oneself for ticks once a day. Favorite places ticks like to go on the body include areas between the toes, back of the knees, groin, armpits, neck, along the hairline, and behind the ears. Remember to check children and pets too. Promptly remove any attached tick using fine-point tweezers. The tick should not be squeezed or twisted but grasped close to the skin and pulled straight out using steady pressure.
- Stick to main pathways and the centers of trails when hiking.
- Wear long-sleeved, light-colored shirts, and long pants tucked into socks.
- Talk to a veterinarian about the best ways to protect pets and livestock from ticks.

Use repellents containing DEET (N,N-diethyl-m-toluamide), and choose a product that will provide sufficient protection for the amount of time spent outdoors. Product labels often indicate the length of time that someone can expect protection from a product. DEET is considered safe when used according to the manufacturer's directions. The efficacy of DEET levels off at a concentration of 30%, which is the highest concentration recommended for children and adults. DEET products should not be used on children <2 months of age. The following precautions should be observed when using DEET products:

- Avoid using DEET products that combine the repellent with a sunscreen. Sunscreens may need to be reapplied too often, resulting in an over application of DEET.
- Apply DEET on exposed skin, using only as much as needed.
- Do not use DEET on the hands of young children, and avoid applying repellent to areas around the eyes and mouth.
- Do not use DEET over cuts, wounds, or irritated skin.
- Wash treated skin with soap and water after returning indoors, and wash treated clothing.
- Avoid spraying DEET products in enclosed areas.

Permethrin-containing products will kill mosquitoes and ticks on contact. Permethrin products are not designed to be applied to the skin. Clothing should be treated and allowed to dry in a well-ventilated area prior to wearing. Because permethrin binds very tightly to fabrics, once the fabric is dry, very little of the permethrin gets onto the skin.

Chemoprophylaxis:

None.

Vaccine:

None.

Isolation and quarantine requirements:

Relapsing Fever: None

Ehrlichiosis: None

Colorado Tick Fever: Standard body substance precautions. No blood or blood product donation for 4 months.

CASE INVESTIGATION

Reporting:

Report all suspect and confirmed cases of Ehrlichiosis, Relapsing Fever, and Colorado Tick Fever.

Case definition:

Relapsing Fever (Utah 2015):

Clinical description

An acute febrile illness with four major symptoms: headache, fever (greater than or equal to 99 degrees), shaking chills and myalgia. Symptoms may relapse after afebrile periods of 2-4 days. Total duration of the illness averages from 13-16 days with louse-borne illness and longer with tick-borne.

Laboratory criteria for diagnosis

- Demonstration of visible spirochetes in a peripheral blood smear, OR
- Demonstration of spirochetemia in inoculated swiss mice, OR
- Serological evidence of non-treponemal spirochetes in persons not visiting endemic Lyme disease area.

Note: Blood samples obtained before antibiotic treatment can be cultured using BSK medium or by inoculating immature mice. The spirochete will usually be evident within 24 hours if the blood was drawn during a febrile episode. Acute serum should be taken within 7 days of symptom onset and convalescent serum should be taken at least 21 days after symptoms start. Early antibiotic treatment may blunt the antibody response and the antibody levels may wane quickly during the months after exposure.

Epidemiological Criteria

Exposure is defined as having been (≤ 30 days before onset of symptoms) in wooded, brushy, grassy areas, exposure to soft ticks in rustic cabins, caves or firewood (e.g., potential tick habitats)

Case classification

Confirmed:

A case that is laboratory confirmed, with either a consistent history of exposure or epidemiologically linked to a confirmed case.

Probable:

A compatible history of exposure and at least three of the major symptoms

Classification Tables	Confirmed	Probable
<i>Clinical Evidence</i>		
Fever ≥ 99		O ₁
Headache		O ₁
Chills		O ₁
Myalgia		O ₁
<i>Laboratory Findings</i>		
Demonstration of visible spirochetes in a peripheral blood smear	O	
Demonstration of spirochetemia in inoculated swiss mice	O	
Serological evidence of non-treponemal spirochetes in persons not visiting endemic Lyme disease area	O	
<i>Epidemiological Criteria</i>		
Exposure is defined as having been (≤ 30 days before onset of symptoms) in wooded, brushy, grassy areas, exposure to soft ticks in rustic cabins, caves or firewood (e.g., potential tick habitats)	O	N
Epidemiologically linked to a confirmed case	O	

Notes:

O = At least one of these “O” criteria in each category (e.g., clinical presentation and laboratory findings)—in conjunction with all other “N” criteria in the same column—is required to classify a case.

O₁ = At least three criteria is required

Ehrlichiosis (2010):

Clinical presentation

A tick-borne illness characterized by acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases. Nausea, vomiting, or rash may be present in some cases.

Clinical evidence

Any reported fever and one or more of the following: headache, myalgia, anemia, leukopenia, thrombocytopenia, or any hepatic transaminase elevation.

Epidemiologic evidence

A history of having been in a tick habitat in the 14 days before illness onset; history of a tick bite is not required. List occupation if relevant to exposure. Travel in the past 14 days; location of travel.

Laboratory evidence

For the purposes of surveillance,

1. ***Ehrlichia chaffeensis* infection** (formerly included in the category Human Monocytic Ehrlichiosis [HME]):

Laboratory confirmed:

- Serological evidence of a fourfold change in immunoglobulin G (IgG)-specific antibody titer to *E. chaffeensis* antigen by indirect immunofluorescence assay (IFA) between paired serum samples (one taken in first week of illness and a second 2-4 weeks later), **or**
- Detection of *E. chaffeensis* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, **or**
- Demonstration of ehrlichial antigen in a biopsy or autopsy sample by immunohistochemical methods, **or**
- Isolation of *E. chaffeensis* from a clinical specimen in cell culture.

Laboratory supportive:

- Serological evidence of elevated IgG or IgM antibody reactive with *E. chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of $\geq 1:64$ and does not use IgM test results independently as diagnostic support criteria.), **or**
- Identification of morulae in the cytoplasm of monocytes or macrophages by microscopic examination.

2. ***Ehrlichia ewingii* infection** (formerly included in the category Ehrlichiosis [unspecified, or other agent]):

Laboratory confirmed:

- Because the organism has never been cultured, antigens are not available. Thus, *Ehrlichia ewingii* infections may only be diagnosed by molecular detection methods: *E. ewingii* DNA detected in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay.

3. *Anaplasma phagocytophilum* infection (formerly included in the category Human Granulocytic Ehrlichiosis [HGE]):

Laboratory confirmed:

- Serological evidence of a fourfold change in IgG-specific antibody titer to *A. phagocytophilum* antigen by indirect immunofluorescence assay (IFA) in paired serum samples (one taken in first week of illness and a second 2-4 weeks later), **or**
- Detection of *A. phagocytophilum* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, **or**
- Demonstration of anaplasma antigen in a biopsy/autopsy sample by immunohistochemical methods, **or**
- Isolation of *A. phagocytophilum* from a clinical specimen in cell culture.

Laboratory supportive:

- Serological evidence of elevated IgG or IgM antibody reactive with *A. phagocytophilum* antigen by IFA, enzyme-linked immunosorbent Assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of $\geq 1:64$ and does not use IgM test results independently as diagnostic support criteria.), **or**
- Identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination.

4. Human ehrlichiosis/anaplasmosis – undetermined:

- See below.

Exposure

Exposure is defined as having been in potential tick habitats within the past 14 days before onset of symptoms. A history of a tick bite is not required.

Case Classification

Confirmed: A clinically compatible case (meets clinical evidence criteria) that is laboratory confirmed.

Probable: A clinically compatible case (meets clinical evidence criteria) that has supportive laboratory results. For ehrlichiosis/anaplasmosis – an undetermined case can only be classified as probable. This occurs when a case has compatible clinical criteria with laboratory evidence to support ehrlichia/anaplasma infection, but not with sufficient clarity to definitively place it in one of the categories previously described. This may

include the identification of morulae in white cells by microscopic examination in the absence of other supportive laboratory results.

Suspect: A case with laboratory evidence of past or present infection but no clinical information available (e.g. a laboratory report).

Comment

There are at least three species of bacteria, all intracellular, responsible for ehrlichiosis/anaplasmosis in the United States: *Ehrlichia chaffeensis*, found primarily in monocytes, and *Anaplasma phagocytophilum* and *Ehrlichia ewingii*, found primarily in granulocytes. The clinical signs of disease that result from infection with these agents are similar, and the range distributions of the agents overlap, so testing for one or more species may be indicated. Serologic cross-reactions may occur among tests for these etiologic agents.

Four sub-categories of confirmed or probable ehrlichiosis/anaplasmosis should be reported: 1) human ehrlichiosis caused by *Ehrlichia chaffeensis*, 2) human ehrlichiosis caused by *E. ewingii*, 3) human anaplasmosis caused by *Anaplasma phagocytophilum*, or 4) human ehrlichiosis/anaplasmosis - undetermined. Cases reported in the fourth sub-category can only be reported as “probable” because the cases are only weakly supported by ambiguous laboratory test results.

Problem cases for which sera demonstrate elevated antibody IFA responses to more than a single infectious agent are usually resolvable by comparing the levels of the antibody responses, the greater antibody response generally being that directed at the actual agent involved. Tests of additional sera and further evaluation via the use of PCR, IHC, and isolation via cell culture may be needed for further clarification. Cases involving persons infected with more than a single etiologic agent, while possible, are extremely rare and every effort should be undertaken to resolve cases that appear as such (equivalent IFA antibody titers) via other explanations.

Current commercially available ELISA tests are not quantitative, cannot be used to evaluate changes in antibody titer, and hence are not useful for serological confirmation. Furthermore, IgM tests are not always specific and the IgM response may be persistent. Therefore, IgM tests are not strongly supported for use in serodiagnosis of acute disease.

Case Definition	Confirmed	Probable	Suspected
<i>Clinical Presentation</i>			
Fever	N	N	
Headache	O	O	
Myalgias	O	O	
Anemia	O	O	
Leukopenia	O	O	
Thrombocytopenia	O	O	

Elevated Hepatic Transaminases	O	O	
Nausea	C	C	
Vomiting	C	C	
Rash	C	C	
<i>Laboratory findings</i>			
A fourfold change in <i>Ehrlichia chaffeensis</i> specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples	O1		O1
Detection of <i>Ehrlichia chaffeensis</i> - specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O1		O1
Demonstration of <i>Ehrlichia chaffeensis</i> antigen in a biopsy or autopsy sample by immunohistochemical methods	O1		O1
Isolation of <i>Ehrlichia chaffeensis</i> from a clinical specimen in cell culture	O1		O1
Elevated IgG antibody to Ehrlichia chaffeensis antigen by IFA, enzyme- linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O1	O1
Elevated IgM antibody to <i>Ehrlichia chaffeensis</i> antigen by IFA, enzyme- linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O1	O1
Detection of <i>Ehrlichia ewingii</i> -specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	N2		O2
A fourfold change in <i>Anaplasma phagocytophilum</i> -specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples	O3		O3
Detection of <i>Anaplasma phagocytophilum</i> - specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O3		O3

Demonstration of <i>Anaplasma phagocytophilum</i> antigen in a biopsy or autopsy sample by immunohistochemical methods	O3		O3
Isolation of <i>Anaplasma phagocytophilum</i> from a clinical specimen in cell culture	O3		O3
Elevated IgG antibody to <i>Anaplasma phagocytophilum</i> antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O3	O3
Elevated IgM antibody <i>Anaplasma phagocytophilum</i> antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O3	O3
Identification of morulae in monocytes, granulocytes, or macrophages	C1,C2,C3	C1,C2,C3,N4	O4
<i>Epidemiological risk factors</i>			
History of having been in potential tick habitat in the 14 days prior to the onset of illness	C	C	
History of a tick bite	C	C	

Notes:

N = This criterion in conjunction with all other “N” and any “O” criteria in the same column is required to classify a case. A number following an “N” indicates that this criterion is only required for a specific clinical presentation

O = At least one of these “O” criteria in each category in the same column (e.g., clinical presentation and laboratory findings)—in conjunction with all other “N” criteria in the same column—is required to classify a case. A number following an “O” indicates that this criterion is only required for a specific clinical presentation.

C = This finding corroborates (i.e., supports) the diagnosis of—or is associated with—Ehrlichiosis, but is not included in the case definition and is not required for classification. A number following a “C” indicates that this criterion is compatible with a specific clinical presentation.

1 = Ehrlichia chaffeensis infection

2 = Ehrlichia ewingii infection

3 = Anaplasma phagocytophilum infection

4 = Human ehrlichiosis/anaplasmosis – undetermined

Colorado Tick Fever (Utah 2015):

Clinical description

An acute viral disease characterized by fever greater than or equal to 99 degrees, and one or more of the following: chills, lethargy, headache and myalgias with infrequent macular or maculopapular rash. After initial onset, a remission is usual, followed by a second bout of fever lasting 2-3 days.

Laboratory criteria for diagnosis

Confirmatory:

- Isolation of Colorado tick fever virus from blood or CSF, or
- Fourfold or greater change in serum antibody

Probable:

- Demonstration of single serological test result suggestive of recent infection with no history of previous infection, by use of hemagglutination, IFA or ELISA.

Epidemiological Criteria:

Within ≤30 days before onset of symptoms, history of tick exposure or having been in wooded, brushy, grassy areas

Case classification

Confirmed: A case that is laboratory confirmed with symptoms and history as above.

Probable: A compatible exposure history, plus clinical symptoms with supportive laboratory results.

Criterion	Case Status	
	Confirmed	Probable
<i>Clinical Presentation</i>		
Fever	N	N
Chills	O	O
Lethargy	O	O
Headache	O	O
Myalgia	O	O
Infrequent macular or maculopapular rash	C	C
Remission of symptoms	C	C
<i>Laboratory Findings</i>		
Isolation of Colorado tick fever virus from blood or CSF	O	

Fourfold or greater change in serum antibody	O	
Demonstration of single serological test result suggestive of recent infection with no history of previous infection, by use of hemagglutination, IFA or ELISA		N
<i>Epidemiological Criteria</i>		
History of tick exposure (≤ 30 days before onset of symptoms)		O
Having been (≤ 30 days before onset of symptoms) in wooded, brushy, grassy areas		O

Notes:

N = This criterion in conjunction with all other “N” and any “O” criteria in the same column is required to classify a case.

O = At least one of these “O” criteria in each category in the same column (e.g., clinical presentation and laboratory findings)—in conjunction with all other “N” criteria in the same column—is required to classify a case.

C = This finding corroborates (i.e., supports) the diagnosis of—or is associated with—Colorado tick fever

Case Investigation Process:

- Fill out morbidity form.
- Verify case status.
- Fill out disease investigation form.
- Determine whether patient had travel/exposure history consistent with acquisition of disease in Utah or elsewhere.
- If patient acquired disease in Utah, identify the source of transmission and eliminate it.

Outbreaks:

More than one case of Relapsing Fever, Ehrlichiosis or Colorado Tick Fever in a one month period would constitute an outbreak.

Identification of case contacts:

None.

Case contact management:

None.

✓ REFERENCES

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