Infectious Disease Epidemiology Section
Office of Public Health, Louisiana Dept of Health & Hospitals
800-256-2748 (24 hr. number)
www.infectiousdisease.dhh.louisiana.gov

ROCKY MOUNTAIN SPOTTED FEVER

Revised 11/24/2015

Rocky Mountain Spotted Fever (RMSF) is caused by *Rickettsia rickettsii*, a species of bacteria that is spread to humans by ixodid (hard) ticks. Beginning in the 1930s, it became clear that this disease occurred in many areas of the United States other than the Rocky Mountain region. It is now recognized that this disease is broadly distributed throughout the continental United States, as well as southern Canada, Central America, Mexico and parts of South America. Between 1981 and 1996, this disease was reported from every U.S. state except Hawaii, Vermont, Maine and Alaska.

The genus *Rickettsia* is included in the bacterial tribe Rickettsieae, family Rickettsiaceae and order Rickettsiales. This genus includes many other species of bacteria associated with human disease, including those in the spotted fever group and in the typhus group. There are 18 species currently recognized in the spotted fever group.

In humans, rickettsiae live and multiply primarily within cells that line small- to medium-sized blood vessels. Spotted fever group rickettsiae can grow in the nucleus or in the cytoplasm of the host cell. Once inside the host, the rickettsiae multiply, resulting in damage and death of these cells. This causes blood to leak through tiny holes in vessel walls into adjacent tissues. This process causes the rash that is traditionally associated with Rocky Mountain spotted fever and causes damage to organs and tissues.

Spotted Fever Group Rickettsiae Causing Human Disease Around The World

Organism	Disease	Geographic Location
Rickettsia rickettsii	Rocky Mountain spotted fever	North, Central and South America
Rickettsia conorii	Mediterranean spotted fever, boutonneuse fever, Israeli spotted fever, Astrakhan fever	Europe, Asia, Africa, Israel Portugal, Sicily, Russia
Rickettsia akari	Rickettsialpox	Worldwide
Rickettsia sibirica including *R. mongolotimonae*	Siberian tick typhus, North Asian tick typhus	Siberia, People's Republic of China, Mongolia, France
Rickettsia australis	Queensland tick typhus	Australia
Rickettsia honei	Flinders Island spotted fever	Australia
Rickettsia africae	African tick-bite fever	Africa, West Indies
Rickettsia japonica	Japanese or Oriental spotted fever	Japan
Rickettsia felis"	no common name	United States, Mexico
Rickettsia slovaca	no common name	Europe

Epidemiology

Rocky Mountain spotted fever (RMSF) is the most severe and most frequently reported rickettsial illness in the United States.

Over 90% of patients with RMSF are infected during April through September. This period is the season for increased numbers of adult and nymphal Dermacentor ticks. A history of tick bite or exposure to tick-infested habitats is reported in approximately 60% of all cases of RMSF.

Two-thirds of the RMSF cases occur in children under the age of 15 years, with the peak age being five to nine years old. Individuals with frequent exposure to dogs and who reside near wooded areas or areas with high grass may also be at increased risk of infection.

The incubation period is about five to ten days after a tick bite.

Clinical Description

Rocky Mountain spotted fever can be very difficult to diagnose in its early stages, even among experienced physicians who are familiar with the disease.

Patients infected with *R. rickettsii* generally visit a physician in the first week of their illness. The early clinical presentation RMSF is nonspecific and may resemble a variety of other infectious and non-infectious diseases.

Initial symptoms may include fever, nausea, vomiting, severe headache, muscle pain and lack of appetite. Later signs and symptoms include rash, abdominal pain, joint pain and diarrhea

The classic triad of findings for this disease are fever, rash and history of tick bite. However, this combination is often not identified when the patient initially presents for care.

The rash

- first appears two to five days after the onset of fever and is often not present or may be very subtle when the patient is initially seen by a physician. Younger patients usually develop the rash earlier than older patients. Most often it begins as small, flat, pink, non-itchy spots (macules) on the wrists, forearms and ankles. These spots turn pale when pressure is applied and eventually become raised on the skin.
- The characteristic red, spotted (petechial) rash of RMSF is usually not seen until the sixth day or later after onset of symptoms; this type of rash occurs in only 35% to 60% of patients with RMSF. The rash involves the palms or soles in as many as 50% to 80% of patients; however, this distribution may not occur until later in the course of the disease. As many as 10% to 15% of patients may never develop a rash.
- The clinical syndrome, especially early RMSF, may be confused with atypical measles, with meningococcemia and with enteroviral infection.

Abnormal laboratory findings seen in patients with RMSF may include thrombocytopenia, hyponatremia, or elevated liver enzyme levels.

Rocky Mountain spotted fever can be a very severe illness and patients often require hospitalization. Because *R. rickettsii* infects the cells lining blood vessels throughout the body, severe manifestations of this disease may involve the respiratory system, central nervous system, gastrointestinal system, or renal system. Host factors associated with severe or fatal RMSF include advanced age, male sex, African-American race, chronic alcohol abuse and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Deficiency of G6PD is a sex-linked genetic condition affecting approximately 12% of the U.S. African-American male population; deficiency of this enzyme is associated with a high proportion of severe cases of RMSF. This is a rare clinical course that is often fatal within five days of onset of illness.

Long-term health problems following acute RMSF infection include partial paralysis of the lower extremities, gangrene requiring amputation of fingers, toes, arms or legs, hearing loss, loss of bowel or bladder control, movement disorders and language disorders. These complications are most frequent in persons recovering from severe, life-threatening disease, often following lengthy hospitalizations.

Approximately 20% of the cases and 15% of reported deaths were in persons aged less than 10 years. Because of RMSF's rapid course, half the RMSF deaths in this age group occurred within 9 days of illness onset, leaving no more than several days to establish the diagnosis and initiate specific antibiotic therapy. Before the discovery of effective antirickettsial drugs, 13% of children with RMSF died. Despite the availability of treatment and advances in supportive medical care, the case-fatality ratio is 2% to 3% for patients aged less than ten years with RMSF.

In its early stages, RMSF may resemble other infectious and noninfectious conditions and can be difficult to diagnose even for physicians familiar with the disease. Because only 3% to 18% of patients present with rash, fever and a history of tick exposure on their first visit, physicians should consider RMSF in infants and children even when one feature is lacking. The absence of tick exposure should not dissuade the clinician from suspecting RMSF. Laboratory abnormalities such as thrombocytopenia and hyponatremia should also raise the possibility of RMSF.

Laboratory Tests

Serologic assays are the most widely available and frequently used methods for confirming cases of Rocky Mountain spotted fever.

The indirect immunofluorescence assay (IFA) is generally considered the reference standard in RMSF serology and is the test currently used by the Centers for Disease Control and Prevention (CDC). IFA can be used to detect either IgG or IgM antibodies. Blood samples taken early (acute) and late (convalescent) in the disease are the preferred specimens for evaluation.

- Most patients demonstrate increased IgM titers by the end of the first week of illness.
- Diagnostic levels of IgG antibody generally do not appear until seven to ten days after the onset of illness.

It is important to consider the amount of time it takes for antibodies to appear when ordering laboratory tests, especially because most patients visit their physician relatively early in the course of the illness, before diagnostic antibody levels may be present. The value of testing two sequential serum or plasma samples together to show a rising antibody level is considerably more important in confirming acute infection with rickettsial agents because antibody titers may persist in some patients for years after the original exposure.

Another approach to RMSF diagnostics is immunostaining. This method is used by taking a skin biopsy of the rash from an infected patient prior to therapy or within the first 48 hours after antibiotic therapy has been started. Because rickettsiae are focally distributed in lesions of RMSF, this test may not always detect the agent. Even in laboratories with expertise in performing this test, the sensitivity is only about 70% on biopsied tissues.

This assay may also be used to test tissues obtained at autopsy and has been used to confirm RMSF in otherwise unexplained deaths.

Antibody titer (IFA can be done by the state lab).

Collect one red-topped tube of blood within seven (7) to ten (10) days after the onset of illness and a second specimen 14-21 days later.

Submit blood as spun down sera or as refrigerated whole blood.

It is imperative that the lab slip indicates the onset date of the signs and symptoms and the date of blood collection. Without this information, the lab cannot accurately interpret the results. Also, contact the laboratory prior to submitting the blood, so that special reagents will be on hand to begin the analysis without unnecessary delay.

The State Laboratory will report the results as follows:

1. Presence of IgG antibody
   a. Negative for spotted fever group specific IgG
   b. Equivocal probable negative sample-another sample requested
   c. Equivocal probable positive sample-another sample requested
   d. Positive for spotted fever group specific IgG

The IgM antibodies are the first to appear in response to an infection and usually are measurable within Seven to ten days after antigen (virus or bacteria) enters the body. These IgM antibodies normally persist for four to six weeks after onset of infection and the level falls rapidly as the IgG antibody synthesis begins; therefore, detection of IgM is indicative of a current infection. IgG antibodies may be measurable at low levels for many years and in some cases for a lifetime.

Treatment

Appropriate antibiotic treatment should be initiated immediately when there is a suspicion of RMSF on the basis of clinical and epidemiologic findings. Treatment should not be delayed until laboratory confirmation is obtained.

Most broad-spectrum antibiotics, including penicillins, cephalosporins and sulfa-containing antimicrobials, are ineffective treatments for RMSF.

Preventive therapy in non-ill patients who have had recent tick bites is not recommended and may, in fact, only delay the onset of disease.

Doxycycline (100 mg bid for adults or 4 mg/kg/day in two divided doses for children under 45 kg [100 lbs]) is the drug of choice for patients with RMSF. Therapy is continued for at least three days after fever subsides and until there is unequivocal evidence of clinical improvement, generally for a minimum total course of five to ten days.

Doxycycline in children: Misperceptions about the use of doxycycline for children prevent children from getting lifesaving treatment. Physicians often avoid prescribing doxycycline to young children because of a warning that tooth staining may occur when used in children younger than eight years old. Doxycycline is the most effective antibiotic for the treatment of suspected rickettsial infections, including RMSF. Delay in treatment of rickettsial diseases may lead to severe illness or death. Children are five times more likely than adults to die from RMSF. In a new study, experts at the CDC and Indian Health Service (IHS) found that short courses of the antibiotic doxycycline can be used in children without causing tooth staining or weakening of tooth enamel.

Delayed diagnosis and late initiation of specific antirickettsial therapy (e.g., on or after day five of the illness) is associated with substantially greater risk for a fatal outcome. Treatment never should be delayed pending a laboratory diagnosis.

Surveillance

RMSF is a condition reportable within five business days of diagnosis.

Case Definition

Clinical Presentation

Rocky Mountain Spotted Fever (RMSF) is an illness caused by *Rickettsia rickettsii*, a bacterial pathogen transmitted to humans through contact with ticks. The Dermacentor species of ticks are most commonly associated with infection, including *Dermacentor variabilis* (the American dog tick), *Dermacentor ander-*

soni (the Rocky Mountain wood tick), and more recently *Rhiphicephalus sanguineus* (the brown dog tick). Disease onset averages one week following a tick bite. Age-specific illness is highest for children and older adults. Illness is characterized by acute onset of fever, and may be accompanied by headache, malaise, myalgia, nausea/vomiting, or neurologic signs; a macular or maculopapular rash appears four to seven days following onset in many (~80%) patients, often present on the palms and soles. RMSF may be fatal in as many as 20% of untreated cases and severe, fulminant disease can occur.

Acute illness is best detected by polymerase chain reaction (PCR) and immunohistochemical methods (IHC) in skin biopsy specimens, and occasionally by PCR in appropriate whole blood specimens taken during the first week of illness, prior to antibiotic treatment. Serology can also be employed for detection, however an antibody response may not be detectable in initial samples, and paired acute and convalescent samples are essential for confirmation.

Clinical Evidence

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

Laboratory Evidence

For the purposes of surveillance,

Laboratory confirmed:

> Serological evidence of a fourfold change in immunoglobulin G (IgG)-specific antibody titer reactive with *Rickettsia rickettsii* antigen by indirect immunofluorescence assay (IFA) between paired serum specimens (one taken in the first week of illness and a second two to four weeks later), **or**
> Detection of *R. rickettsii* DNA in a clinical specimen via amplification of a specific target by PCR assay, **or**
> Demonstration of spotted fever group antigen in a biopsy or autopsy specimen by IHC, **or**
> Isolation of *R. rickettsii* from a clinical specimen in cell culture.

Laboratory supportive:

> Has serologic evidence of elevated IgG or IgM antibody reactive with *R. rickettsii* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or latex agglutination.

Note: 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. IgM tests are not strongly supported for use in serodiagnosis of acute disease, as the response may not be specific for the agent (resulting in false positives), and the IgM response may be persistent. Complement fixation (CF) tests and other older test methods are neither readily available nor commonly used. CDC uses in-house IFA IgG testing (cutoff of ≥1:64), preferring simultaneous testing of paired specimens and does not use IgM results for routine diagnostic testing.

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.

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

Investigation

The purpose of investigation is to identify cases, to confirm the diagnosis, to identify high risk areas of the State and to provide information to the communities involved.

- Upon receipt of a report of a case of RMSF, contact the physician and/or hospital to confirm the dianosis.
- If the diagnosis is based on symptoms and a rise in the nonspecific Weil-Felix reaction (Proteus OX-19 or OX-2 agglutination), encourage the physician to obtain paired sera to be tested by serologic tests that yield more accurate diagnostic information (indirect fluorescent antibody the preferred method, complement fixation, latex agglutination, indirect hemagglutination, or microagglutination).
- Check the patient's history for exposure to ticks (i.e., own dogs, travel history, camping, etc).
- Counsel regarding the careful removal of all ticks from patients. (Be sure head of tick is not left beneath the skin).

Prevention

Limiting exposure to ticks is the most effective way to reduce the likelihood of RMSF infection. In persons exposed to tick-infested habitats, prompt careful inspection and removal of crawling or attached ticks is an important method of preventing disease. It may take several hours of attachment before organisms are transmitted from the tick to the host. Currently, no licensed vaccine is available for RMSF.

It is unreasonable to assume that a person can completely eliminate activities that may result in tick exposure. Therefore, prevention measures should be aimed at personal protection:

- Wear light-colored clothing to allow you to see ticks that are crawling on your clothing.
- Tuck your pants legs into your socks so that ticks cannot crawl up the inside of your pants legs.
- Apply repellants to discourage tick attachment. Repellents containing permethrin can be sprayed on boots and clothing and will last for several days. Repellents containing DEET (n, n-diethyl-m-toluamide) can be applied to the skin, but will last only a few hours before reapplication is necessary. Use DEET with caution on children. Application of large amounts of DEET on children has been associated with adverse reactions.
- Conduct a body check upon return from potentially tick-infested areas by searching your entire body for ticks. Use a hand-held or full-length mirror to view all parts of your body. Remove any tick you find on your body. Parents should check their children for ticks, especially in the hair, when returning from potentially tick-infested areas. Additionally, ticks may be carried into the household on clothing and pets. Both should be examined carefully.

To remove attached ticks, use the following procedure:

1. Use fine-tipped tweezers or shield your fingers with a tissue, paper towel, or rubber gloves. When possible, persons should avoid removing ticks with bare hands.
2. Grasp the tick as close to the skin surface as possible and pull upward with steady, even pressure. Do not twist or jerk the tick; this may cause the mouthparts to break off and remain in the skin. (If this happens, remove mouthparts with tweezers.

Hospital precaution and isolation: Standard precautions.