



Review Article

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Rocky Mountain Spotted Fever: A Review
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Abstract

Rocky Mountain spotted fever is a severe infection caused by *Rickettsia rickettsii* transmitted to man by various species of ticks in the United States since the 1920's. The 60-70% of patients with the disease reports a history of tick bite or exposure to tick-infested areas. There are two major vectors of *R. rickettsii* in the United States, the American dog tick and the Rocky Mountain wood tick. The symptoms of RMSF is characterized by a sudden onset of moderate to high fever, severe headache, fatigue, deep muscle pain, chills and rash. Early diagnosis of RMSF is critical, since untreated infection may cause irreversible damage to the central nervous and cardiovascular systems. Diagnostic confirmation relied on serologic testing, by culture preparation, immuno histochemical methods and by PCR and sequencing methods. Treatment involves careful removal of the tick from the skin and antibiotics to get rid of the infection. Doxycycline or tetracycline is the drugs of choice for both confirmed and suspected cases. Chloramphenicol is also the drug of choice for children less than eight years of age. This review concerns with the detail information of Rocky Mountain spotted fever. All cases of Rocky Mountain spotted fever must be reported to the Centers for Disease Control (CDC).

Keywords: Rocky Mountain spotted fever, Tick, *Rickettsia rickettsii*, CDC.

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1. Introduction

Rocky Mountain spotted fever is a most lethal¹ and fulminant² severe infection caused by *Rickettsia rickettsii* transmitted to man by various species of ticks. High-incidence areas exist in the southeast and south central United States. Only 60-70% of patients with the disease report a history of tick bite or exposure to tick-infested areas.³ Some synonyms for Rocky Mountain spotted fever in other countries include "tick typhus," "Tobia fever" (Colombia), "São Paulo fever" or "febre maculosa" (Brazil), and "fiebre manchada" (Mexico). It is distinct from the viral tick-borne infection, Colorado tick fever. The name Rocky Mountain spotted fever is somewhat of a misnomer. 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.⁴

Rocky Mountain spotted fever has become increasingly common in certain areas of Arizona over the last several years. Between 2003 and 2012 over 250 cases and 19 fatalities occurred. RMSF can be rapidly fatal if not treated within the first 5 days of symptoms. Before tetracycline antibiotics were available, case fatality rates ranged from 20–80%.⁵ Rocky Mountain spotted fever remains a serious and potentially life-threatening infectious disease today. In the pre-antibiotic era, 20-25% of previously healthy, infected persons died of the illness. Today, even with antimicrobial agents that are highly effective, 3-5% of persons die mainly because of late or mis-diagnosed infection and delayed or ineffective antimicrobial treatment. Before the discovery of tetracycline and chloramphenicol in the late 1940s, as many as 30% of individuals infected with *R. rickettsii* died.

In humans, *Rickettsia rickettsii* 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. The disease is caused by *Rickettsia rickettsii*, and the bacteria are spread to humans by ixodid (hard) ticks. The onset of disease follows an infective bite by a week (range 2-14 days), beginning with fever, severe headache, and muscle pain, followed by development of rash. The disease can be difficult to diagnose in the early stages, and without prompt and appropriate treatment, it can be fatal.⁴

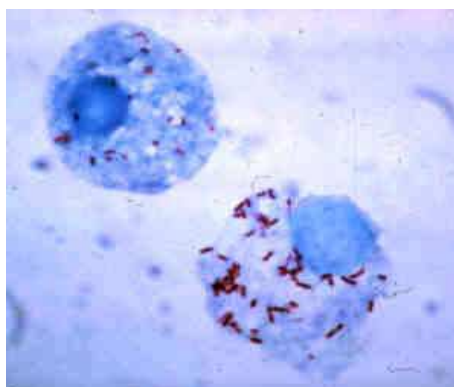


Figure 1. The causative agent of Rocky Mountain spotted fever: Gimenez stain of tick hemolymph cells infected with *R. rickettsii*.

The reasons are that up to 40% of patients are unaware of a tick bite, which is painless and may go unnoticed or be forgotten, and that the rash does not usually appear until 3-5 days after onset of illness.

History:

First recognized in 1896 in the Snake River Valley of Idaho, this disease was originally called "black measles" due to its characteristic rash appearance. Howard T. Ricketts was first in identifying the infectious organism of the cause of the disease. He and his colleagues also identified hard ticks as the vectors. A bit of a misnomer, Rocky Mountain spotted fever is now known to be spread throughout the continental U.S., as well as Canada, Central America, Mexico, and parts of South America. It has thus been reported in every U.S. state except Hawaii, Vermont, Maine, and Alaska.⁶

In the late 1800's, Edward E. Maxey provided the first clinical description of what was initially named, "spotted fever of Idaho" based on the unique clinical presentation of a continuously moderate to high fever with a characteristic red, spotted (petechial) rash that has a centripetal or inward pattern of spread beginning at the extremities, moving toward the trunk⁷ and does not usually appear until at least 6 days after the onset of symptoms. Maxey's description became the first report of RMSF to be published in medical literature.⁸ In response to this health problem, the U.S. Public Health Service sent University of Chicago pathologist Dr. Howard T. Ricketts to the Bitterroot Valley of Montana, one of the disease hotspots. In 1906 Dr. Ricketts showed that the disease was transmitted by the bite of the Rocky Mountain wood tick. This species is supported in nature by a complex cycle involving ticks and mammals. Human beings are considered to be accidental hosts, and they are not involved in the natural transmission cycle of this pathogen. The work of Dr. Ricketts laid the foundation for what later became the Rocky Mountain Laboratories (RML) in Hamilton, Montana. Today, dozens of scientists continue to study tickborne and other diseases at RML, which is part of NIAID. Though U.S. healthcare providers typically report about 250 to 1,200 cases of RMSF each year to the Centers for Disease Control and Prevention, a record 2,563 cases were

reported in 2008.⁶ Dr. Ricketts died of typhus (another rickettsial disease) in Mexico in 1910, shortly after completing his remarkable studies on Rocky Mountain spotted fever. Prior to 1922, Doctors McCray and McClintic both died while doing research on Rocky Mountain spotted fever. Also did an aide of Noguchi's at the Rockefeller Institute. McCalla and Brerton also did early research into Rocky Mountain spotted fever.

Research began in 1922 in western Montana in the Bitterroot Valley around Hamilton, Montana, after the Governor's daughter and his son-in-law died of the fever. Past Assistant Surgeon R.R. Spencer of the Hygienic Laboratory of the U.S. Public Health Service was ordered to the region, and he led a research team at an abandoned schoolhouse through about 1924. Spencer's crucial day was on May 19, 1924, when he put a large dose of mashed wood ticks from lot 2351B and some weak carbolic acid into his arm by injection. This vaccine worked.⁹ Spencer was assisted by R. R. Parker, Bill Gettinger, Henry Cowan, Henry Greenup, Elmer Greenup, Gene Hughes, Salsbury, and Kerlee, et al. Gettinger, Cowan and Kerlee all died of Rocky Mountain Spotted Fever during the research efforts. Much of the early research was conducted at Rocky Mountain Laboratories (part of the National Institute of Allergy and Infectious Diseases), which is the source of the name of the condition.⁶

Tick-Borne Rickettsiae

There are two major vectors of *R. rickettsii* in the United States, the American dog tick and the Rocky Mountain wood tick. The American dog tick (*Dermacentor variabilis*) is widely distributed east of the Rocky Mountains and also occurs in limited areas along the Pacific Coast. Dogs and medium-sized mammals are the preferred hosts of adult *D. variabilis*, although it feeds on other large mammals, including humans. Two species found in nations south of the U.S., the brown dog tick (*Rhipicephalus sanguineus*) and the *Amblyomma cajennense* tick, also may transmit the disease. The illness usually develops between five and 10 days after the victim is bitten.



Figure 2. American Dog Tick



Figure 3. Approximate distribution of the American dog tick. (CDC)

The Rocky Mountain wood tick (*Dermacentor andersoni*) is found in the Rocky Mountain states and in southwestern Canada. Adult ticks feed primarily on large mammals.



Figure 4. Rocky Mountain Wood Tick



Figure 5. Approximate distribution of the Rocky Mountain wood tick (CDC)

Other tick species have been shown to be naturally infected with *R. rickettsii*, but these species are likely to play only a minor role in the ecology of *R. rickettsii*. Dogs and people become infected with *Rickettsia rickettsii* when feeding ticks inoculate rickettsial organisms. Cats may be seropositive but are not known to develop clinically apparent disease. Transmission is generally thought to occur 5 to 20 hours after tick attachment. This tick is the most commonly identified species responsible for transmitting *R. rickettsii* to humans. Rocky Mountain wood ticks (*Dermacentor andersoni*) are found in the Rocky Mountain states and in southwestern Canada. There are only 800 cases of Rocky Mountain Spotted Fever reported in the United States per year, and in only about 20 percent can the tick be found.^{10,11}

2. Statistics and Epidemiology

Epidemiology

Rocky Mountain spotted fever (RMSF) has been a reportable disease in the United States since the 1920's. CDC compiles the number of cases reported by state health departments. The incidence of RMSF (the number of RMSF cases for every million persons) has increased during the last decade, from less than 2 cases per million persons in 2000 to over 6 cases per million in 2010. During the same time period, the proportion of RMSF cases resulting in death (case fatality) has declined to a low of less than 0.5%.

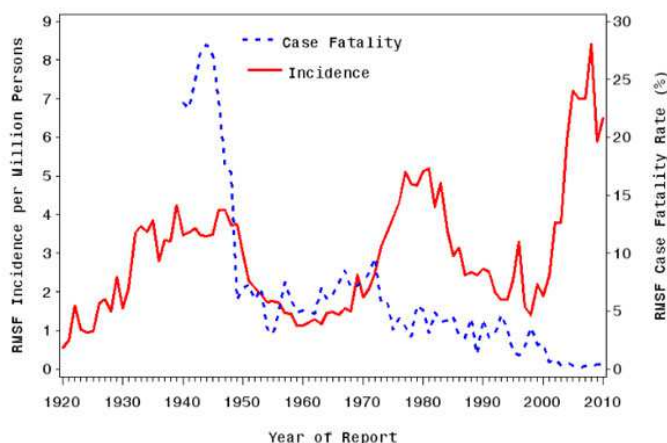


Figure 6. Reported incidence and case fatality of RMSF in the U.S., 1920–2010

Cases of RMSF have been recorded from the 1920s through present day. Trends in RMSF incidence can be observed as ebbs and flows of several years at a time. Periods of increased incidence can be seen between 1930 and 1950 and 1968 through 1990. More recently there has been a more dramatic increase in incidence of RMSF increasing from 1.9 cases per million persons in 2000 to an all-time high of 8.4 cases per million persons in 2008. Case fatality rate was first reported in 1940. Fatality rates vary from year-to-year, but have had an overall decreasing trend from 28% case fatality in 1944 to <1% case fatality beginning in 2001.¹² Number of U.S. annual RMSF cases reported to CDC 1993-2010 is shown in Figure 7. The graph displays the number of human cases of RMSF cases reported to CDC annually from 1993 through 2010. The numbers of cases of RMSF reported to CDC have generally increased annually from 345 cases in 1993, to 2553 cases reported in 2008. Cases decreased significantly in 2009 to 1791 cases and increased slightly in 2010.

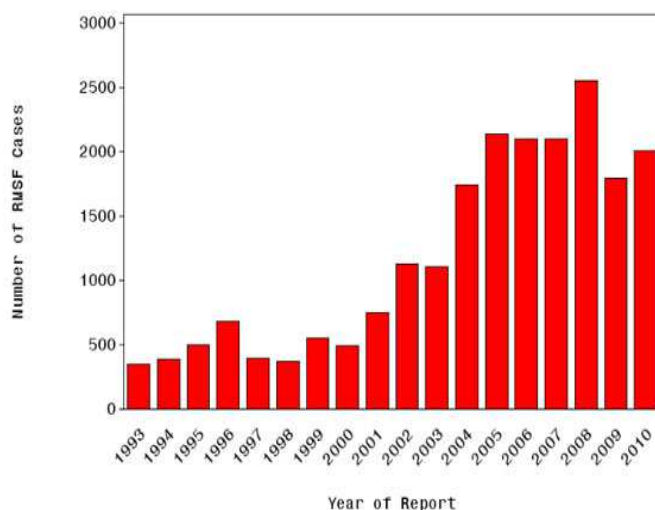


Figure 7. Number of U.S. RMSF cases reported to CDC, 1993–2010

Geography

The disease is more common in the eastern, southern and western states. RMSF cases have been reported throughout most of the contiguous United States, yet confirmed cases reported in five states (North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri) account for over 60% of RMSF cases. The primary tick that transmits *R. rickettsii* in these states is the American dog tick (*Dermacentor variabilis* *Dermacentor andersoni*). In eastern Arizona, RMSF cases have recently been identified in an area where the disease had not been previously seen. Between 2003 and 2010, roughly 140 cases had been reported, and approximately 10% of the people diagnosed with the disease in this part of the state have died. The tick responsible for transmission of *R. rickettsii* in Arizona is the brown dog tick (*Rhipicephalus sanguineus*), which is found on dogs and around people's homes. Almost all of the cases occurred within communities with a large number of free-roaming dogs.^{10,13}

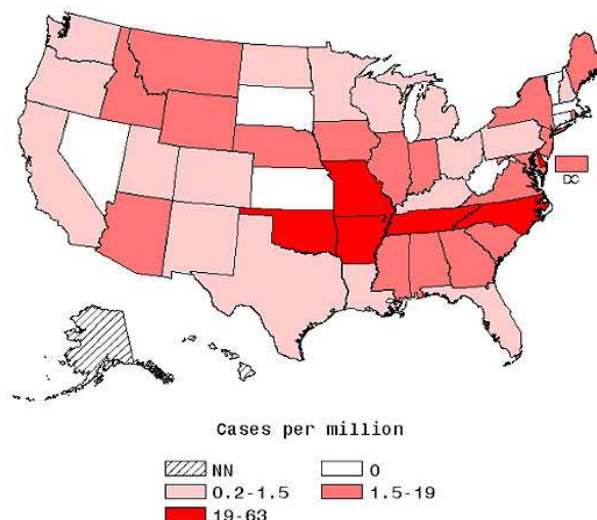


Figure 8: Annual reported incidence (per million populations) for RMSF in the United States for 2010. (NN= Not notifiable)

This figure shows the annual reported incidence of RMSF cases by state in 2010 per million persons. RMSF was not notifiable in Alaska and Hawaii in 2010. The incidence rate was zero for Connecticut, Kansas, Massachusetts, Nevada, South Dakota, Vermont and West Virginia. Incidence ranged between 0.2 to 1.5 cases per million persons for California, Colorado, Florida, Kentucky, Louisiana, Michigan, Minnesota, New Hampshire, New Mexico, North Dakota, Ohio, Oregon, Pennsylvania, Texas, Utah, Washington and Wisconsin. Annual incidence ranged from 1.5 to 19 cases per million persons in Alabama, Arizona, the District of Columbia, Georgia, Idaho, Illinois, Indiana, Iowa, Maine, Maryland, Mississippi, Montana, Nebraska, New Jersey, New York, Rhode Island, South Carolina, Virginia and Wyoming. The highest incidence rates, ranging from 19 to 63 cases per million persons were found in Arkansas, Delaware, Missouri, North Carolina, Oklahoma, and Tennessee.¹¹

Seasonality

Cases of RMSF can occur during any month of the year, yet the majority of reported cases have an illness onset during the summer months and a peak in cases typically occurs in the months of June and July.¹³ Seasonality may vary by region of the country due to variations in temperatures and climates throughout the U.S. and the primary tick vectors involved. In Arizona, where transmission is associated with the brown dog tick, peak months of illness onset are April through October.

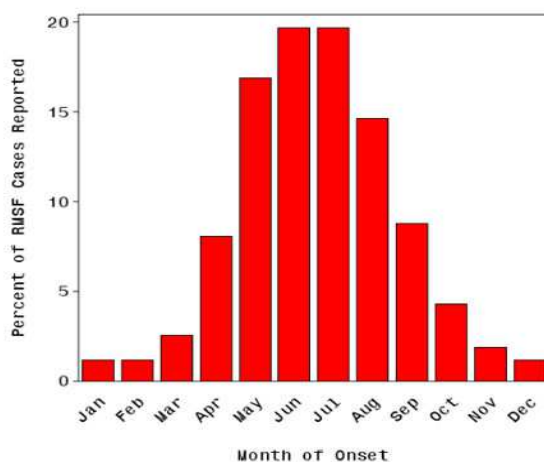


Figure 9. Proportion of RMSF cases reported to CDC by month of onset 1993 through 2010

Over 90% of patients with Rocky Mountain spotted fever are infected during April through September. This period is the season for increased numbers of adult and nymphal Dermacentor ticks.

Persons at Risk:

The frequency of reported cases of Rocky Mountain spotted fever is highest among males, American Indians, and people at least 40 years old. Individuals with frequent exposure to dogs and who reside near wooded areas or areas with high grass may be at increased risk of infection. Children under 10 years old, American Indians, people with a compromised immune system, and people with delayed treatment are at an increased risk of fatal outcome from RMSF.¹¹

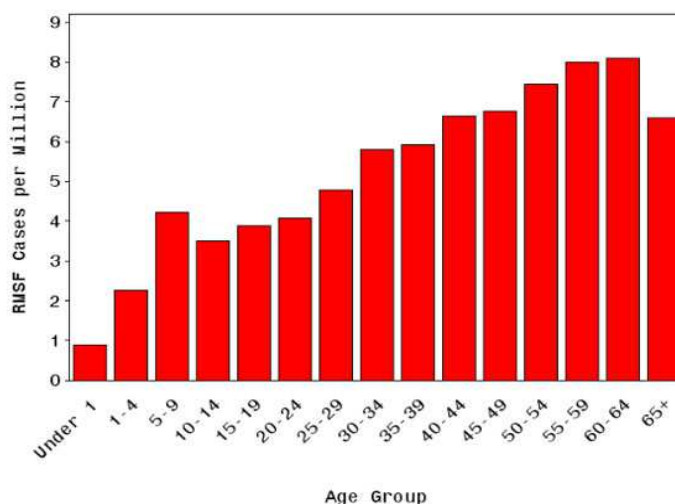


Figure 10. Average annual incidence of Rocky Mountain spotted fever by age group, 2000 through 2010

3. Symptoms and Diagnosis

RMSF is characterized by a sudden onset of moderate to high fever (which can last for two or three weeks), severe headache, fatigue, deep muscle pain, chills and rash. The rash begins on the legs or arms may include the soles of the feet or palms of the hands and may spread rapidly to the trunk or rest of the body. Not every case of RMSF will have the rash. The first symptoms of Rocky Mountain spotted fever typically begin an average of 7 days after the bite of a an infected tick—but may occur anywhere from 2-14 days afterwards⁸. A tick bite is usually painless and less than half of people who develop RMSF recall being bitten by a tick.¹⁴ Initial infection with RMSF is frequently followed several days later by a skin rash, (often referred to a maculopapular rash which progresses into a papular or petechial rash). A classic case of RMSF involves a rash that first appears 2-5 days after the onset of fever as small, flat, pink, non-itchy spots (macules) on the ankles, wrists or forearms and spreads to include the trunk and may include the palms and soles. The classic spotted or petechial rash is often not apparent until the fifth or sixth day of illness. Often the rash may vary from this description and is difficult to discern in darker skinned individuals. A rash may not develop or be atypical in approximately 10-20% of cases of RMSF. People who fail to develop a rash, or develop an atypical rash, are at increased risk of being misdiagnosed. The rash on the palms and soles of the feet is not characteristic for infection with RMSF and can occur in other illnesses or reactions caused by drug hypersensitivities.

The rash commonly occurs earlier in children than in adults and may be observed in up to 90% of children with RMSF infection¹⁵.

Symptoms are nonspecific.

Initial symptoms:¹⁶ fever, nausea, vomiting, severe headache, muscle pain, lack of appetite

Later symptoms: rash, abdominal pain, joint pain, diarrhea

Rocky Mountain spotted fever can be a very serious and fatal illness requiring hospitalization. Since *R. rickettsii* infect the cells lining blood vessels throughout the body, severe cases of this disease can affect the respiratory system, central nervous system, gastrointestinal system, or renal system. Long term health problems following acute infection can include partial paralysis of lower extremities, gangrene requiring amputation of fingers, toes, or arms or legs, hearing loss, loss of bowel or bladder control, movement disorders, and language disorders.⁴

Diagnosis:

Diagnosis of RMSF is based on symptoms, a thorough medical history and history of a tick bite or exposure to tick-infested habitat or previous travel to known regions where RMSF occurs. The unique appearance and characteristics of the rash are also important.

Laboratory Detection:

R. rickettsii infects the endothelial cells which line the blood vessels and usually are not found in large numbers circulating in the blood therefore direct detection methods to detect *R. rickettsii* are not typically reliable methods unless the patient has progressed to a severe stage of infection⁸. The specific methods for the diagnosis of rickettsioses have been recently reviewed.¹⁷

Serology:

Serological tests are the most frequently used and widely available methods for diagnosis. The Weil-Felix test, the oldest assay, is based on the detection of antibodies to various *Proteus* antigens that cross-react with rickettsiae. Although it lacks specificity and sensitivity, it continues to be used in many developing countries and in countries with higher level of technical development¹⁸. The indirect immunofluorescence assay (IFA) is generally considered the reference standard in Rocky Mountain spotted fever serology and is the test currently used by CDC and most state public health laboratories.

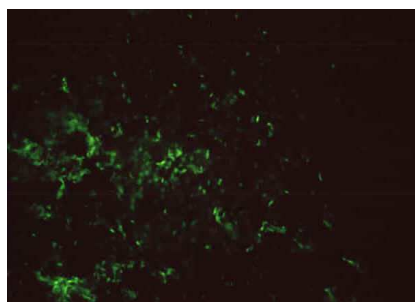


Figure 11. IFA reaction of a positive human serum on *Rickettsia rickettsii* grown in chicken yolk sacs, 400X.

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 7-10 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.⁴

Histochemical and Immunohistochemical Methods

Rickettsiae can be detected occasionally in tissue specimens by various histochemical stains, including Giemsa or Gimenez stains¹⁷. 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 Rocky Mountain spotted fever, 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 Rocky Mountain spotted fever in otherwise unexplained deaths. Immunostaining for spotted fever group rickettsiae is offered by the CDC, a few state health departments, and some university-based hospitals and commercial laboratories in the United States.⁴

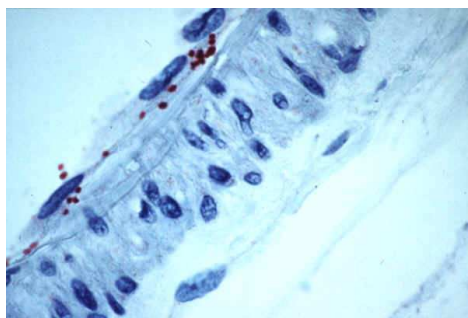


Figure 12. Red structures indicate immunohistological staining of *Rickettsia rickettsii* in endothelial cells of a blood vessel from a patient with fatal RMSF (CDC)

Culture

Although rickettsial isolation in culture remains the most definitive diagnostic method, this technique is typically performed only in reference laboratories with a P3 safety level and requires staff capable of maintaining living host cells (animal mouse models or embryonated eggs) or cell cultures (Vero, L929, HEL, XTC-2, or MRC5 cells). The centrifugation shellvial technique using HEL fibroblasts is an effective application of this method¹⁹. Isolation of rickettsiae can be performed routinely in this type of laboratory by using buffy coat preparations of heparinized or EDTA-anticoagulated whole blood, skin biopsy specimens, or arthropods. Although this technique is versatile, approximately one-third of rickettsial isolates may be lost when passaged to new cells.

Molecular Tools

PCR and sequencing methods are now used as sensitive and rapid tools to detect and identify rickettsiae in blood and skin biopsy specimens throughout the world where these facilities are available. Primers amplifying sequences of several genes, including *ompA*, *ompB*, *gltA*, and gene D, have been used. Ticks may also be used as epidemiological tools to detect the presence of a pathogen in a specific area, providing insights to and discoveries of rickettsiae of unknown pathogenicity.²⁰

4. Treatment

Rocky Mountain spotted fever remains a serious and potentially life-threatening infectious disease today. Despite the availability of effective treatment and advances in medical care, approximately 3- 5% of individuals who become ill with Rocky Mountain spotted fever die from the infection. However, effective antibiotic therapy has dramatically reduced the number of deaths caused by Rocky Mountain spotted fever. Treatment involves careful removal of the tick from the skin and antibiotics to get rid of the infection. After the introduction of antibiotics such as tetracyclines, doxycycline (200 mg per day) and chloramphenicol, it remains the treatment of choice for RMSF²¹. Although tetracyclines are contraindicated for general use in children less than 9 years of age, Doxycycline remains the treatment of choice for all patients, including young children, with RMSF.²

Table 1. Antibiotic treatments for RMSF^{22,23}

Rickettsiosis	Patient	Selected antibiotic regimens
Rocky Mountain spotted fever	Adults	Doxycycline, 100 mg every 12 h for 5 to 10 days
	Children	Doxycycline, 2.2 mg/kg every 12 h for children weighing <99 lb (45 kg) or adult dosage if >100 lb, for 5 to 10 days Chloramphenicol, 12.5 to 25 mg/kg every 6 h for 5 to 10 days
	Pregnant women	Doxycycline, 100 mg every 12 h for 5 to 10 days

Appropriate antibiotic treatment should be started immediately when there is a suspicion of Rocky Mountain spotted fever on the basis of clinical and epidemiological findings. Treatment should not be delayed until laboratory

confirmation is obtained. In fact, failure to respond to tetracycline argues against a diagnosis of Rocky Mountain spotted fever. Severely ill patients may require longer periods before their fever resolves, especially if they have experienced damage to multiple organ systems. Preventive therapy in healthy patients who have had recent tick bites is not recommended and may, in fact, only delay the onset of disease.²⁴

Complications

Rocky Mountain spotted fever (RMSF) can be a very severe illness that requires treatment in a hospital. The bacteria infect cells that line blood vessels throughout the body. This infection can cause problems in the respiratory system, central nervous system, gastrointestinal system, kidneys, lung failure and shock.²⁵

Some people infected with RMSF develop long-term health problems including;

- a. Partial paralysis of the legs
- b. Gangrene requiring amputation of fingers, toes, arms, or legs
- c. Hearing loss
- d. Loss of bowel or bladder control
- e. Difficulty moving
- f. Language disorders.

These problems are most frequent in those recovering from severe, life-threatening disease, often following a long stay in the hospital.^{6,26}

Prevention

RMSF can be prevented by avoiding tick-infested areas, like woods and tall grasses, brush, shrubs, and low tree branches, and by taking precautions when spending time outdoors. Limiting exposure to ticks is the most effective way to reduce the likelihood of Rocky Mountain spotted fever 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 Rocky Mountain spotted fever. 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.

CDC recommends the following prevention measures:

- a. Wear light-colored clothing.
- b. Tuck your pants legs into your socks so ticks can't get up inside your pants legs.
- c. Spray insecticide containing permethrin on boots and clothing. The effects will last several days.
- d. Apply insect repellent containing DEET (diethyltoluamide) to your skin. Because DEET lasts only a few hours, you may need to reapply it.
- e. Look for ticks on your body, including in your hair, when you return from hiking or walking.
- f. Check children and pets for ticks.⁶

5. Conclusion

In summary, Rocky Mountain spotted fever tends to be most common to specific geographic locales, disease. The frequency of reported cases of Rocky Mountain spotted fever is highest among males, American Indians, and people at least 40 years old. High-incidence areas exist in the southeast and south central United States. Since the spring and summer months coincide with peak infestation of the ticks responsible for the disease, clinical awareness with clinical preparedness can be instrumental in early recognition of this RMSF disease. This review article includes history of Rocky Mountain spotted fever disease, geographical distribution, statistics, their symptoms, diagnosis and treatment. All cases of Rocky Mountain spotted fever must be reported to the Centers for Disease Control. The best ways to decrease the morbidity and mortality of the disease are to increase awareness of its signs and symptoms and to prevent exposure to ticks.

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