


| | | |
|---|---|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 1 of 9 |

Rocky Mountain Spotted Fever Table of Contents

[Rocky Mountain Spotted Fever](#)

[Rocky Mountain Spotted Fever Questions and Answers \(CDC Website\)](#)

[Disease Case Report \(CD-1\)](#) [PDF format](#) [Word format](#)


[Tick-Borne Rickettsial Disease Case Report \(MO 580-2602 – 5/08\)](#)

[Missouri Outbreak Surveillance Report \(CD-51\)](#)

[CDC Specimen Submission Form \(CDC 50.34\) \(CDC website\)](#)

[Rocky Mountain Spotted Fever Public Outreach and Education Materials](#)

[Rocky Mountain Spotted Fever Physician Education Materials](#)

| | | |
|---|--|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 2 of 9 |

Rocky Mountain Spotted Fever

Overview ^(1,2,3)

Rocky Mountain spotted fever (RMSF) is a zoonotic disease caused by a genus of bacteria called *Rickettsia*. This tick-borne illness typically begins with a sudden onset of influenza-like symptoms, which may include fever, chills, severe headache, muscle pain, and fatigue. Some patients report nausea, vomiting, and a lack of appetite. The classic spotted rash is usually not apparent until the fifth or sixth day and may be an indicator of potentially serious illness.

RMSF is the most frequently reported rickettsial illness in both Missouri and the United States. Because early symptoms resemble other infectious and non-infectious diseases, RMSF can be difficult to diagnose. Without prompt treatment, it can be fatal. Treatment decisions should be based on epidemiologic and clinical clues, and never be delayed while waiting for laboratory results. Doxycycline is the accepted treatment of presumptive RMSF in adults and children. In spite of its name, the highest incidences of RMSF in the United States are reported in the mid-southern states of Oklahoma, North Carolina, South Carolina, Arkansas, and Missouri.

Ticks are the transmitter of *Rickettsia rickettsii*, the agent that causes the disease, primarily by their bite. Less commonly, infections may occur following exposure to fluids from crushed ticks or tick feces. The principle vector of RMSF in Missouri is the American dog tick. The risk of exposure to a tick carrying *R. rickettsii* is low. In general, about 1%-3% of tick populations are infected with *R. rickettsii*, even in areas where the majority of human cases are reported.

Prevention

- Avoid tick habitats during the peak time of year (generally April through September).
- Tick repellents with 20 to 50% DEET offer the best protection. The American Academy of Pediatrics has recommended that repellents containing up to 30% DEET can be used on children over 2 months of age.
- Wear clothes that will help shield you from ticks.
- Check frequently for ticks and remove them promptly.

For a more complete description of Rocky Mountain spotted fever, refer to:

- *Control of Communicable Diseases Manual* (CCDM), American Public Health Association, 2004
- American Academy of Pediatrics. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. 2006.
- U.S. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report, Recommendations and Reports #4, Diagnosis and Management of Tick-borne Rickettsial Diseases, 2006.



Case Definition ⁽⁴⁾

Clinical presentation

Rocky Mountain spotted fever (RMSF) is an illness caused by *Rickettsia rickettsii*, a bacterial pathogen transmitted to humans through contact with ticks. *Dermacentor* species of ticks are most commonly associated with infection, including *Dermacentor variabilis* (the American dog tick), *Dermacentor andersoni* (the Rocky Mountain wood tick), and more recently *Rhipicephalus 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 4-7 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 1st week of illness, before 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.

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.**

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 2-4 weeks later), **or**

| | | |
|---|---|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 4 of 9 |

- 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/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.

Notes:

Current commercially available ELISA tests are not quantitative and 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 $\geq 1:64$), preferring simultaneous testing of paired specimens, and does not use IgM results for routine diagnostic testing.

Detailed definitions for 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).

Information Needed for Investigation

Verify the diagnosis.

- Determine what laboratory tests were conducted and the results.
 - Patients might lack diagnostic IgG and IgM antibody titers in the first 7 days of illness. A positive IgG titer or index value can indicate a past infection or early response to current infection. IgM tests are not always specific and the

| | | |
|---|---|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 5 of 9 |

IgM response may be persistent. For these reasons, IgM titers or index values without IgG response should be interpreted with caution.

- Determine whether complete blood cell count and comprehensive metabolic panel laboratory findings exist, indicating anemia, thrombocytopenia, or any hepatic transaminase elevation.
- Verify with the care provider the presence of a clinically compatible illness, i.e., acute onset of fever, which may be accompanied by headache, malaise, myalgia, nausea/vomiting, or neurologic signs. In addition, a characteristic macular or maculopapular rash is reported in most patients; rash fails to develop in up to 20% of cases.⁽³⁾
- Lack of a confirmed recent tick bite does not exclude the diagnosis.

Establish the extent of illness. Investigation should consider family members, coworkers, pets, and other contacts that have or have recently had a febrile illness and shared environmental exposures with the patient.⁽⁵⁾ Transmission has occurred on rare occasions by blood transfusion.⁽²⁾ There have been cases reported in people who removed infected ticks from other people or animals, in doing so, crushed the ticks, and exposed themselves to infectious fluids from the tick.⁽⁶⁾

Notification and Control Measures

RMSF is not transmitted person to person, so contact follow up is not required.


Prevention and Control Measures *(For detailed information see)*

- American Academy of Pediatrics. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. 2006, “Prevention of Tick-borne Infections”
- U.S. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report, Recommendations and Reports #4, Diagnosis and Management of Tick-borne Rickettsial Diseases*, 2006, “Prevention”

Laboratory Procedures for Tick-Borne Rickettsial Diseases

Laboratory confirmation of infection is vital to understanding the epidemiology and public health impact of tick-borne rickettsial diseases (e.g., Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis). The Missouri State Public Health Laboratory (SPHL) cannot overemphasize the importance of obtaining paired, appropriately timed specimens for serological analysis. Traditional diagnosis and confirmation of rickettsial diseases is fundamentally retrospective in nature, and based upon serology. A single serologic test does not provide the diagnostic strength of the standard testing strategy (paired acute and convalescent specimens).

At no time should the empiric treatment of the patient with doxycycline be delayed for laboratory testing results.

| | | |
|---|---|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 6 of 9 |

RECOMMENDATIONS

- The SPHL will submit whole blood in EDTA and biopsies for PCR testing and paired serum specimens for serological analysis to the U.S. Centers for Disease Control and Prevention (CDC) for testing. The SPHL does not test for rickettsial diseases. Negative results on any of the tests do not rule out rickettsial diseases.
- No fees are assessed for specimens referred to CDC through the SPHL.
- The most efficient diagnostic testing strategy for acutely ill patients is to obtain:
 - An EDTA whole blood specimen
 - A skin punch biopsy (for rash-associated illnesses)
 - Paired acute and convalescent serum specimens
- Many commercial reference laboratories offer several diagnostic methods, including PCR and serology.
 - 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 always specific and the IgM response may be persistent. Therefore, IgM tests are not strongly supported for use in serodiagnosis of acute disease.


CONFIRMATORY DIAGNOSTIC TESTS

FOR MOLECULAR (PCR) TESTING

- Whole blood in EDTA is very useful for ehrlichiosis and anaplasmosis diagnosis.
- Whole blood is not the best possible specimen for RMSF. This is due to the low numbers of organisms circulating in the blood during acute illness.
- Skin punch biopsies, taken at the site of the rash and before antibiotic therapy, are extremely valuable. These biopsies contain larger numbers of organisms due to their localization within the endothelial cells of blood vessels and capillaries.
- **PCR may not be useful if the patient has been on antibiotics for > 24 hours.**

FOR SEROLOGIC TESTING

- The first sample in a red top tube should be taken within the first week after onset of illness. The second sample should be taken 2-4 weeks later. Beyond this interval, diagnostic success cannot be assured. Testing a second sample, several months later will not provide helpful information.
- The acute-phase serum should be retained and submitted at the same time with a follow-up convalescent serum specimen obtained 2-4 weeks later. In some cases, a third late convalescent serum specimen, taken 2 weeks later, may be necessary to show rising levels.
- Acute blood can be collected, centrifuged, and the serum removed and frozen until the convalescent blood is collected. Alternatively, the SPHL will hold

| | | |
|---|---|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 7 of 9 |

the blood and send a reminder letter for the convalescent specimen. Single acute-phase specimens will not be submitted to CDC for analysis.

- **CSF is not the optimal specimen for serologic testing.**

IMMUNOHISTOCHEMICAL (IHC) STAINING

- Skin punch biopsies, taken at the site of the rash and before antibiotic therapy, are extremely valuable. These biopsies contain larger numbers of organisms due to their localization within the endothelial cells of blood vessels and capillaries.
- IHC may be performed on autopsy specimens.

CELL CULTURE

- Culture is not readily available due to the biosafety risks, the Select Agent issues, and technical difficulty. As a result, culture is rarely used for diagnosis, and other methods (e.g., serology, PCR, or immunostaining) are used to confirm infection.

CDC SPECIMEN SUBMISSION FORM

To submit laboratory specimens, complete a CDC specimen submission form (CDC 50.34) which can be downloaded from:

http://www.cdc.gov/ncidod/dvbid/misc/CDC50_34.pdf, or call the Missouri State Public Health Laboratory at (573) 751-0633.


NOTE: Testing will not be initiated without the inclusion of:

- a. Type of specimen (e.g. serum, csf, skin punch biopsy)
- b. Suspected etiology
- c. Date of onset of symptoms
- d. Brief clinical description
- e. Date of specimen collection
- f. Pertinent travel history
- g. Antibiotic treatment received and date

For information on shipping, specimen types and amount, or for additional information on rickettsial detection can be obtained from the Virology Unit at the SPHL (573) 751-0633.

Reporting Requirements


Rocky Mountain Spotted Fever is a Category II disease and shall be reported to the local health authority or to the Missouri Department of Health and Senior Services (DHSS) within three days of first knowledge or suspicion by telephone, facsimile or other rapid communication.

| | | |
|---|--|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 8 of 9 |

1. For all cases, complete a “[Disease Case Report](#)” (CD-1).
2. For all cases, complete a “[Tick-Borne Rickettsial Disease Case Report](#)” (MO 580-2602, 5-08).
 - Obtain the pertinent symptoms, treatment, and health history from the patient’s health care provider or other affiliated health care professional.
 - Exposure and travel history can be obtained from the patient or the patient’s health care provider, social worker, or family.
3. Entry of the completed CD-1 into MOHSIS negates the need for the paper CD-1 to be forwarded to the District Health Office.
4. Send the completed secondary investigation form to the [District Health Office](#).
5. All outbreaks or “suspected” outbreaks must be reported as soon as possible (by phone, fax, or e-mail) to the District Communicable Disease Coordinator. This can be accomplished by completing the [Missouri Outbreak Surveillance Report](#) (CD-51)
6. Within 90 days of the conclusion of an outbreak, submit the final outbreak report to the [District Communicable Disease Coordinator](#).

References

1. Control of Communicable Diseases Manual. “Rocky Mountain Spotted Fever (North American tick typhus, New World spotted fever, Tickborne typhus fever, São Paulo fever).” Heymann, David L., ed. 18th ed. Washington, D.C.: American Public Health Association, 2004: 459-461.
2. American Academy of Pediatrics. “Rocky Mountain Spotted Fever.” In: Pickering, LK., ed. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL. American Academy of Pediatrics; 2006: 570-572.
3. Centers for Disease Control and Prevention. *Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis – United States*. MMWR 2006: 55 (Recommendation and Report 4): 1-27. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm> (4/08)
4. Centers for Disease Control and Prevention. *Nationally Notifiable Infectious Diseases United States*, Epidemiology Program Office, Division of Public Health Surveillance and Informatics, <http://www.cdc.gov/epo/dphsi/phs/infdis.htm> (4/08)
5. Centers for Disease Control and Prevention. “Fatal Cases of Rocky Mountain Spotted Fever in Family Clusters – Three States, 2003.” MMWR 2004: 53: 407-410. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5319a1.htm> (4/08)
6. Mandell, Douglas and *Bennett’s Principles and Practice of Infectious Diseases*. “*Rickettsia rickettsii* and Other Spotted Fever Group Rickettsiae (Rocky Mountain Spotted Fever and Other Spotted Fevers).” G. Mandell, J. Bennett, R. Dolin, eds. 6th ed. Vol.2, 2005: 2288-2295, 3312-3315.

| | | |
|---|---|--------------|
|  | Division of Community and Public Health | |
| | Section: 4.0 Diseases and Conditions | Revised 4/08 |
| | Subsection: Rocky Mountain Spotted Fever | Page 9 of 9 |

Other Sources of Information

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2. Archives of Internal Medicine. Rocky Mountain Spotted Fever: A Clinician's Dilemma. Masters, E.J., et. al., 2003;163:769-774.
3. *The Merck Veterinary Manual*. Rocky Mountain Spotted Fever (*Rickettsia rickettsii* infection, Tick fever). In Kahn, Cynthia M, ed., 9th ed. Whitehouse Station, NJ: Merck & Co., Inc; 2005: 45, 641 –642, 1020, 2554. <http://www.merckvetmanual.com/mvm/index.jsp> – search “Rocky Mountain spotted fever,” “Dermacentor,” or “Amblyomma.” (4/08)

Web Resources and Information

1. Free tick-borne disease prevention posters and bookmarks from the Missouri Department of Health and Senior Services (DHSS website). <http://www.dhss.mo.gov/TicksCarryDisease/Publications.html> (4/08)
2. Downloadable tick-check promotion radio public service announcements (DHSS website – spots require .mp3 player such as Windows Media Player or Real Player) <http://www.dhss.mo.gov/TicksCarryDisease/Prevention.html> (4/08)
3. University of Missouri Outreach and Extension Home and Garden Guide “Ticks,” (University of Missouri Extension website) <http://muextension.missouri.edu/explore/agguides/pests/g07382.htm> (4/08)
4. MedlinePlus Medical Encyclopedia for Rocky Mountain Spotted Fever (MedlinePlus website – National Library of Medicine) <http://www.nlm.nih.gov/medlineplus/ency/article/000654.htm> (4/08)
5. Centers for Disease Control and Prevention, *Rocky Mountain Spotted Fever Home Page*, <http://www.cdc.gov/ncidod/dvrd/rmsf/index.htm> (4/08)

Rocky Mountain Spotted Fever Physician Education Materials

Diagnosis and Management of Tick-borne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis – United States. MMWR 2006: 55 (Recommendation and Report 4): 1-27. (CDC website) <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm> (4/08)