Rocky Mountain Spotted Fever

A. Agent

Rickettsia rickettsii, the causative agent of Rocky Mountain spotted fever (RMSF) is an obligate intracellular bacterium and a member of the Spotted Fever group[1,2]. In addition to RMSF, human illness has also been associated with a multitude of other spotted fever group *Rickettsia* species. In Arizona, there have also been reports of infections caused by *Rickettsia parkeri.*[1,2]

B. Clinical Description

Rocky Mountain spotted fever (RMSF) is the most severe and commonly reported tick-borne rickettsial illness in the United States[1,2,3,4]. Since it was first detected in Arizona on tribal lands in 2003, over 500 cases have been identified in the state, with nearly 30 fatalities. The case fatality rate for Arizona (6%) is higher than the U.S. rate (<1%), and the disease disproportionately affects children under the age of 18 years[3,11]. There are several epidemiological and ecological features that make RMSF unique in Arizona. This includes differences in the vector, seasonality and populations affected compared to other areas of the U.S.[2,3,5,6,11,14,15]

RMSF usually presents with non-specific symptoms, but can be a serious illness with death occurring in the first 8 days if not diagnosed and treated appropriately.[1,2] Illness is characterized by acute onset of fever, and may be accompanied by headache, malaise, myalgia, nausea/vomiting, or neurologic signs.[1,2] The majority of people with RMSF develop some type of rash during illness; however, the rash may not appear until 4–7 days following illness onset, and should not be used as a criteria to rule out illness. Approximately 10% of RMSF cases do not develop a rash.[1,2] The hallmark RMSF rash usually appears within 2–5 days after symptom onset as small, flat, non-itchy, pink macules on the wrists, forearms, and ankles. This rash may then spread to the truck of the body.[1,2] About 35–60% of cases develop a petechial rash around day 5 or 6 of illness. This can progress to a purpuric type of rash (reddish-purple non-blanching spots), which often indicates severe disease.[1,2]

Clinical laboratory findings indicative of RMSF may include thrombocytopenia, anemia, leukopenia, and/or hepatic transaminase elevation.[1-4,9,13-15]

Severe illness and vascular damage can lead to prolonged hospitalization and long-term health problems.[1,2,4,9]

C. Reservoir

The most common tick vectors that transmit RMSF in the United States are the American dog tick (*Dermacentor variabilis*) and the Rocky Mountain wood tick (*Dermacentor andersoni*)[1,2,5]; however, emergence of the disease in Arizona in 2003 was associated with the brown dog tick (*Rhipicephalus sanguineus*), a relatively new vector for RMSF in the United States.[3,5,11] *R. sanguineus* is a one-host tick that prefers to live on dogs and in and around homes. This ecology is distinct from the *Dermacentor* tick vectors, and has created a unique epidemiology of RMSF in Arizona compared with the rest of the country.[3,5,11]

In northern Arizona, the Rocky Mountain wood tick also transmits RMSF.[1]
Rickettsia parkeri has been associated with Gulf Coast ticks (*Amblyomma maculatum*) in the Gulf Coast region of the United States, and most recently in Southern Arizona.[1,2]

D. Modes of Transmission

- RMSF is spread by the bite of an infected tick. In Arizona, the vector reservoir is the brown dog tick (*R. sanguineus*).[1,2,5] Transmission occurs from the bite of an infected tick. At least 4–6 hours of tick attachment are required before the bacteria can be transmitted and cause disease in people.[1,2]
- Contamination of cuts, scrapes, or wounds in the skin or mucous membranes with crushed tissues or feces of the tick may also lead to infection. Laboratory-acquired infection has resulted from accidental inoculation and aerosol contamination.[1,2] Transmission has occurred on rare occasions by blood transfusions.[1,2]
- RMSF is not directly transmitted from person-to-person.[1,2]

E. Incubation Period

Symptoms of RMSF usually occur 2–14 days after the bite of an infected tick.[1,2]

F. Period of Communicability

Ticks remain infected for life, and female ticks can pass the bacteria transovarially to offspring. Life span is commonly as long as 18 months.[1,5]

G. Susceptibility and Resistance

Susceptibility is universal. After infection, immunity is believed to be life-long. Antibodies can persist in the body for months to years after initial infection.[1,2]

H. Treatment

Doxycycline is the first line treatment for adults and children.[1-4,9,13-15] This should be prescribed whenever RMSF is suspected. Chloramphenicol is an alternative when there are contraindications to tetracyclines, such as life-threatening allergies.[2]

Disease Management

I. Clinical Case Definition[1,2]

Fever as reported by the patient or a healthcare provider, AND one or more of the following:

- rash
- eschar
- headache
- myalgia
- anemia
- thrombocytopenia, or
- any hepatic transaminase elevation.

J. Laboratory Criteria for Diagnosis[17]

- Serology is the best diagnostic option and is widely used for detecting antibodies against RMSF. However, paired samples (acute and convalescent) are **essential** for confirmation because antibody responses are rarely detectable in acute samples.[1,2,3]
    - Always recommend doxycycline as soon as RMSF is suspected!
- Polymerase chain reaction (PCR) or immunohistochemical (IHC) testing methods are appropriate only for cases of severe illness, or from post-mortem specimens before doxycycline has been given.[1,2]
    - Biopsies of the rash are appropriate when present; however, the rash may not be present until late in disease progression and should always be coupled with serology (negative PCR does not rule out disease).[1,2]

K. Laboratory Testing

LABORATORY EVIDENCE	CRITERIA
Confirmatory	• Detection of spotted fever group *Rickettsiae* (SFGR) nucleic acid in a clinical specimen via amplification of a Rickettsia genus- or species-specific target by polymerase chain reaction (PCR) assay; OR • Serological evidence of a fourfold increase in IgG-specific antibody titer reactive with SFGR antigen by immunofluorescence assay (IFA) between paired serum specimens (one taken in the first two weeks after illness onset and a second taken two to ten weeks after acute specimen collection)*; OR • Demonstration of SFGR antigen in a biopsy or autopsy specimen by immunohistochemical methods (IHC); OR • Isolation of SFGR from a clinical specimen in cell culture and molecular confirmation (e.g., PCR or sequence).
Presumptive	• Serologic evidence of elevated IgG antibody at a titer ≥1:128 reactive with SFGR antigen by IFA in a sample taken within 60 days of illness onset.**
Supportive	• Serologic evidence of elevated IgG antibody at a titer <1:128 reactive with SFGR antigen by IFA in a sample taken within 60 days of illness onset.

*A four-fold rise in titer should not be excluded (as confirmatory laboratory criteria) if the acute and convalescent specimens are collected within two weeks of one another.

**This includes paired serum specimens without evidence of fourfold rise in titer, but with at least one single titer ≥1:128 in IgG-specific antibody titers reactive with SFGR antigen by IFA. The 60-day cut-off is especially important for probable cases with a single IgG titer to better capture real acute infection.

Note: Current commercially available ELISA tests are not quantitative, and as such cannot be used to evaluate changes in antibody titer; therefore, these cannot be used for serologic 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 (making it harder to identify how recent the infection was). 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.

L. Case Classification[3,17]

CASE CLASSIFICATION	CRITERIA See here the ADHS RMSF Case Classification Algorithm and ADHS Case Definition Manual
Clinical criteria	Fever as reported by the patient or a healthcare provider, AND one or more of the following: • rash • eschar • headache • myalgia • anemia • thrombocytopenia, or • any hepatic transaminase elevation
Confirmed	• A clinically compatible case that is laboratory confirmed.
Probable	• A clinically compatible case that has presumptive laboratory evidence.
Suspect	• A case with confirmatory or presumptive laboratory evidence of infection with no clinical information available; OR • A clinically compatible case (meets clinical case definition above) that has supportive laboratory evidence.

Criteria to Distinguish a New Case from an Existing Case

A person previously reported as a probable or confirmed case-patient may be counted as a new case-patient when there is an episode of new clinically compatible illness with confirmatory laboratory evidence. For the purposes of entering new laboratory information for an existing case, the timeframe of 6 months can be used as a rule of thumb for creating a new case, until evidence is obtained to determine whether there is a new episode of clinically compatible illness.

M. Assessing Laboratory Results[1,3,17]

Paired serology is the most common diagnostic test for RMSF to look for increasing levels of RMSF-specific IgG antibodies. This suggests a recent infection. Early in any tick-borne rickettsial disease, most of the acute tests will be negative. This is because it takes typically 7–10 days after symptom onset for the body to make enough antibodies to reach detectable levels.

Ideally, the first (acute) sample should be taken early (within the first week of symptoms) to provide a recent baseline antibody level and the second (convalescent) sample should be taken 2–4 weeks later after the body has a full antibody response.
Antibody levels may remain high for months following illness.

N. Outbreak Definition:
An outbreak in endemic areas is defined as a significant increase in cases above the level normally seen in the area during the time period in question. In non-endemic areas, an outbreak is one or more case(s) of confirmed RMSF with no history of travel to endemic areas.

O. Time Frame
RMSF is a nationally notifiable condition and should be reported within 5 working days to the local health jurisdiction.

P. Forms
Local county and tribal public health is responsible for conducting an investigation on any reported cases. Use the rickettsial disease MEDSIS DSO. A CDC Rickettsial Disease investigation form is available for use but not required.

Q. Investigation Steps:

1. <u>Confirm the Diagnosis</u> with an appropriate medical provider/laboratory.
Before contacting the patient or family, determine what information is available from medical records and healthcare providers.

I. Obtain information that supports clinical findings in the case definition, and information on the onset date, order of the symptoms, etc., including:
   a. Hospitalizations
   b. Life threatening complications
   c. Clinical symptoms of fever, rash, eschar, headache, myalgia, anemia, thrombocytopenia, leukopenia, elevated hepatic transaminases or others
   d. Underlying immunosuppressive condition.

II. Outcome status: survived or date of death.

III. Area of residence and tribal affiliation (if any).

IV. Obtain information on any laboratory tests performed and results or date results are expected.
   a. If laboratory tests have not been run to test for RMSF IgG, coordinate testing of an acute specimen with ADHS. IgM results are not reliable and should not be considered.
   b. Arrange to have a convalescent sample drawn at the hospital, public health clinic or primary care providers 2–6 weeks after symptom onset.

V. Obtain date when doxycycline treatment was initiated.
   a. If doxycycline has not been initiated, arrange for doxycycline to be administered with the provider.

2. <u>Conduct Case Investigation</u> —

Epidemiological investigation report should be submitted in MEDSIS by filling out the full DSO and Travel Table. Interview case to determine source, risk factors and transmission settings.

Interview the case or proxy to determine source and risk factors; focus on the 2 week incubation period prior to illness onset. Consider:

I. Recent travel to endemic areas or history of possible exposure to ticks. List geographic location(s) and date(s).
II. Ownership or contact with a dog.
III. Exposure to animals or pets with ticks.
IV. Other people who might have been exposed.
    a. If case is resident in an area with free roaming dogs, assume other household members are at risk.
V. Outdoor activities.
VI. Occupational risks (e.g., forestry worker, landscape worker, etc.). History of tick bites, include geographic location of bite and date.
VII. Time spent in any area with free roaming dogs.

3. <u>Conduct Contact Investigation</u> — Locate additional cases and/or contacts

Contacts are those with possible exposure to the source of infection. Contacts are not persons in close proximity to a case; the disease is not transmitted person-to person. Consideration should be given to any higher than normal incidence in reports of spotted fever symptoms in individuals that were in the same geographic location as the case's suspected exposure. For suspected outbreaks, refer to the Managing Special Situations section. Follow up with symptomatic contacts as suspect cases.

4. <u>Isolation, Work and Child Care Restrictions</u> — None

5. <u>Case Management</u>

Ensure all suspect cases receive doxycycline as soon as possible. Do not wait for laboratory results to begin treatment! Delaying treatment can result in death.

6. <u>Contact Management, Including Susceptible Contacts</u>

Instruct the contacts of the case who had similar exposures (i.e., contact with ticks, contact with free roaming dogs, travel to endemic areas, etc.) to monitor themselves for symptoms. Preventive treatment is not warranted. Treatment is necessary only if symptoms develop. Those who exhibit any signs or symptoms compatible with tick-borne illness should be referred to their medical provider for evaluation.

7. <u>Environmental Measures</u>

In cooperation with ADHS, a local health agency or another local agency responsible for vector control within a jurisdiction shall conduct an assessment of the environment

surrounding each spotted fever rickettsiosis case or suspect case and implement vector control measures as necessary.

Community-based integrated tick management strategies may reduce the incidence of tick-borne infections. Limiting exposure to ticks is presently the most effective prevention method. Tick management approaches include the following:

- Community-wide application of an acaricide (i.e., chemicals that kill ticks and mites) and control of tick habitats (e.g., tall grass, leaf litter, and brush, as well as non-traditional tick-breeding sites such as objects with fabric that ticks might try to breed in such as rugs, couches, or clothing around the outside of a home).
- Use of a topical or systemic tick-control treatment such as permethrin, fipronil, seasonal dips, or the use of impregnated collars containing amitraz or propoxur to prevent tick attachment to dogs.
- In areas with free roaming dogs, effective animal control programs and tick collaring/tick treatment of owned and stray dogs is critical to the reduction of *Rhipicephalus sanguineus* populations.

8. <u>Education and Prevention:</u>

As opportunities allow, the following general messages should be distributed:

- In tick-infested areas, the highest risk for bites occurs from March–July, but due to the warmth of the Arizona climate, ticks can be found year-round and tick prevention measures must also continue year-round[3,5,11].
- The use of protective clothing, including light-colored garments, long pants tucked into socks, long-sleeved shirts, hats, as well as tick repellents (particularly those containing DEET), may reduce risk.
- Outdoor activities in tick-infested areas present many opportunities for exposure.
- Keep yards clear of excessive leaves, brush, tall grasses, and non-traditional tick-breeding sites such as objects with fabric that ticks might try to breed in such as rugs, couches, or clothing around the outside of a home.
- Keep pets free of ticks.
- Remove attached ticks intact, do not leave embedded head parts. Use gentle, direct traction with tweezers or hemostat. Other methods, such as application of a hot match or petroleum products to the tick, are not effective. Do not crush ticks.
    - **Tick Removal Procedure:**
        - Do not handle the tick with bare hands because infectious agents may enter through mucous membranes or breaks in the skin. This precaution is particularly directed to individuals who remove ticks from domestic animals with unprotected fingers. Children, the elderly and immunocompromised persons may be at greater risk of infection and should avoid this procedure.
        - Use fine-tipped tweezers or shield fingers with a tissue, paper towel, or rubber gloves.
        - 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.
    - Do not squeeze, crush, or puncture the body of the tick because its fluids (e.g., saliva, hemolymph and gut contents) may contain infectious organisms.
    - After removing the tick, thoroughly disinfect the bite site and wash hands with soap and water.
    - Dispose of the tick by flushing down the toilet. Do not throw in garbage as the tick can escape and lay eggs in the home.
- Since it is easy to miss ticks on a pet's body if they are small or due to a large amount of fur, **it is important to follow up manual tick removal with the use of a topical or oral tick treatment** to ensure all ticks will be controlled. If a pet has a tick burden that makes tick removal not practical, the use of topical or oral tick treatments as the main treatment is warranted.

9. <u>Notifications:</u>

- All confirmed and suspect cases of RMSF should be reported within five working days to the local health jurisdiction.
- Report all confirmed, probable and suspect cases to ADHS Office of Infectious Disease Services Vector-borne and Zoonotic Disease program, within five working days of initial report.

R. Outbreak Guidelines:

There are no formal outbreak definitions; however, the investigator may consider the possibility of an outbreak if an RMSF case with no history of travel to an endemic area is detected in a non-endemic area, particularly if the case resides in an area with a large population of free roaming dogs. Under these circumstances:

1. Notify the local health jurisdiction and request that they alert providers and hospitals to implement the RMSF algorithm (Appendix I).
2. Request that the hospital submit serum specimens to the Arizona State Public Health Laboratory (ASPHL. If the patient is critically ill, request whole blood and (if possible) rash punch biopsy specimens for PCR testing at CDC.
3. ADHS will notify CDC Rickettsial Zoonoses Branch and request PCR testing of whole blood and IHC of punch biopsy.
4. Advise the local health jurisdiction to conduct a home and community assessment. The case's home should be treated for ticks, and all dogs in the home should be on tick-prevention products.
5. Educate household members about the symptoms of RMSF and request that they immediately seek care if they experience fever.
6. The local health jurisdiction can consider conducting chart reviews or a canine serosurvey to determine the RMSF risk in the community.

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