

Rocky Mountain Spotted Fever: A Physician's Challenge

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Author Disclosure

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Objectives After completing this article, readers should be able to:

1. Discuss the petechial rash and history of tick bite in relation to the diagnosis of Rocky Mountain spotted fever (RMSF).
2. Discuss the epidemiology of RMSF.
3. Know when, if ever, to withhold therapy for RMSF if clinically suspicious of the diagnosis.
4. Know the drug of choice for patients who have RMSF.

Introduction

RMSF is a tick-vectored disease that has been recognized in North America for more than a century. It remains a diagnostic challenge because of its varied clinical presentation and the overlap of signs and symptoms with other tick-borne diseases (eg, the *Ehrlichia* infections, human monocytic ehrlichiosis [HME]). Also known as tick fever, symptomatic presentations of RMSF are characterized by an acute febrile illness, headache, and rash. The causative agent is *Rickettsia rickettsii*, a gram-negative obligate intracellular bacterium. Because a delay in empiric antimicrobial therapy for RMSF can be fatal, clinicians need to be familiar with the presentation and management of this illness to avoid a poor outcome (Table 1).

Epidemiology

RMSF was recognized initially in the northern Rocky Mountain and Pacific states. Today, RMSF has been reported in almost every state in the continental United States. From 1994 to 2003, the median number of cases reported to the Centers for Disease Control and Prevention (CDC) was 585/y (range, 365 to 1,104/y). Most cases were reported from the south Atlantic region (Delaware, Maryland, Washington DC, Virginia, West Virginia, North Carolina, South Carolina, Georgia, and Florida), the Pacific region (Washington, Oregon, and California) and the west south-central region (Arkansas, Louisiana, Oklahoma, and Texas) of the United States. From 1994 to 2003, 54% of the reported cases were from five states (North Carolina, Tennessee, Oklahoma, South Carolina, and Arkansas); only approximately 2% of cases were reported from the Mountain states (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming). Infection with *R. rickettsii* also has been documented in Argentina, Brazil, Colombia, Costa Rica, Mexico, and Panama.

The common tick vectors that are known to transmit RMSF are *Dermacentor andersoni* (wood tick), *Dermacentor variabilis* (dog tick), and *Amblyomma americanum* (Lone Star tick). These tick vectors can be found in both urban and rural settings and can be brought into the home by household pets (eg, dogs, cats), making humans incidental hosts. Ninety percent of the cases are reported during the months of April through October, but cases of RMSF have been reported in every month of the year. Clinicians should not be dissuaded from considering the diagnosis of RMSF based solely on the geographic location of the patient or the month of year.

Two thirds of RMSF cases occur in children younger than age 15 years (peak age, 5 to 9 y), and 15% of reported deaths are in children younger than 10 years of age. Males are infected more commonly than are females (1.7 to 2.2:1), and Caucasians are affected more

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Table 1. How to Avoid a Poor Outcome in the Diagnosis and Treatment of Rocky Mountain Spotted Fever

- DON'T wait for a petechial rash to develop to suspect the diagnosis.
- DON'T exclude the diagnosis because there is no history of tick bite.
- DON'T exclude the diagnosis solely for geographic or seasonal reasons.
- DON'T withhold therapy if you are clinically suspicious.
- DON'T be afraid to use doxycycline at any age.

commonly than are African-Americans (1.5/1 million versus 0.8/1 million). These demographic data, however, are based on symptomatic cases of RMSF and might be dramatically different with better understanding of subclinical disease.

Serologic surveillance studies suggest that infections due to *R rickettsii* are much more common than indicated by the current reporting of symptomatic cases. A recent study of children living in the southeast and south-central regions of the United States indicated that as many as 12% had serologic test results that were consistent with past infection due to RMSF. These data suggest that infections with *R rickettsii* may be more common than has been recognized previously and that this organism is responsible for a significant amount of subclinical disease compared with symptomatic disease.

Pathogenesis

Ticks become infected with *R rickettsii* either transovarially or by feeding on infected mammals. Once infected, the ticks are not killed by the infection, thus allowing them to serve as both a reservoir and a vector of *R rickettsii*. The organisms usually are transmitted to humans through the saliva of a tick while it is feeding, although infections may occur following exposure to crushed tick tissues, fluids, or feces. Usually 12 to 24 hours of attachment and feeding is required for transmission of *R rickettsii* to a susceptible individual. The risk of exposure to a tick carrying *R rickettsii* is low. Even in areas where most human cases are reported, approximately 1% to 3% of the tick population carries *R rickettsii*.

Once the rickettsial organisms enter the body, they multiply within the endothelial cells lining the small blood vessels and are disseminated via the bloodstream. Focal areas of endothelial proliferation and perivascular mononuclear cell infiltration lead to thrombosis and leakage of red blood cells into the surrounding tissues. These changes are reflected most obviously in the skin

(rash) and the central nervous system (headache, mental confusion).

Clinical Aspects Symptoms/Signs

Even among experienced clinicians, RMSF can be difficult to diagnose in its early stages. A history of tick bite is elicited in only 50% to 60% of patients, especially in rural areas where children often remove ticks without telling their parents. Fol-

lowing an incubation period after the tick bite of approximately 7 days (range, 2 to 14 d), clinical symptoms begin. The incubation period varies, based on the size of the rickettsial inoculum. A large inoculum has a shorter incubation period. In the early stages of the disease (eg, first 2 to 3 d), the clinical signs and symptoms of infection are nonspecific and often mimic a viral syndrome. Fever, nausea, vomiting, severe headache, anorexia, and malaise are reported commonly in the early stages of illness. Other nonspecific signs or symptoms include myalgia (especially bilateral calf pain), photophobia, and abdominal pain. Later signs include rash, joint pain, and diarrhea

The classic triad of RMSF symptoms is fever, rash, and headache, but this combination is not always present when the patient initially presents for care. Rash is the most characteristic physical finding of RMSF and appears between the second and fifth day of illness (Figure). Blanching, erythematous macules appear initially around the ankles and feet and later the wrists and hands; palms and soles also become involved. The rash spreads to the trunk and head within hours. The characteristic petechial



Figure. A characteristic petechial rash on the lower extremity of a patient who has RMSF.

rash of RMSF usually is not seen until the sixth day or later after the onset of symptoms, and it occurs in only 35% to 60% of patients. As many as 10% to 15% of patients never develop a rash, and the rash may be not be recognized in patients whose skin is darkly pigmented. In severe cases, gangrene, scarring, and loss of digits or limbs can occur, as with patients who have disseminated meningococcal disease.

The central nervous system also may be affected. Patients complain of headache and show signs of altered mental status or meningismus. When the severity of the disease progresses, coma, seizures, cranial nerve palsies (eg, sixth nerve), central deafness, and cortical blindness have been reported.

Less commonly, conjunctivitis, periorbital edema, peripheral edema, arrhythmias, congestive heart failure, myocarditis, shock, hepatosplenomegaly, and jaundice have been reported. Pneumonitis or pulmonary edema may reflect pulmonary involvement. Critically ill patients show evidence of disseminated intravascular coagulation or acute respiratory distress syndrome.

Clinicians should understand that HME is indistinguishable clinically from RMSF. Although children are more likely than adults to have a rash with HME (66% versus 33%), the remainder of the clinical signs and symptoms are identical to those of RMSF.

Laboratory Tests

The classic laboratory abnormalities reported in patients who have RMSF are hyponatremia (≤ 130 mEq/L [130 mmol/L]) and thrombocytopenia ($\leq 150 \times 10^3$ /mL [150×10^9 /L]). Hyponatremia (20% of patients) is postulated to be due to increased vascular permeability and loss of sodium through the kidneys. Thrombocytopenia (33% of patients) is believed to be due to the adherence of platelets to the surface of *Rickettsia*-infected endothelial cells. Total leukocyte counts usually are normal, but may be elevated or depressed, with a neutrophil predominance. Anemia, an increase in liver function abnormalities, and an elevated blood urea nitrogen value also may be present in up to 25% of patients. Patients who have central nervous system disease may have normal cerebrospinal fluid (CSF) findings, but approximately one third have a mononuclear pleocytosis (11 to 300 cells/mcL). An elevated CSF protein concentration (41 to 200 mg/dL [41 to 200 g/L]) has been described in approximately 20% of patients, and most have normal CSF glucose levels.

Children who have HME also may present with hyponatremia (65%) and thrombocytopenia ($\geq 80\%$). Such patients are more likely to demonstrate leukopenia with

lymphopenia ($\geq 70\%$) and mildly elevated serum aminotransferase levels ($\geq 80\%$), but these data have been gathered from far fewer children than the data gathered from children who have RMSF. CSF abnormalities similar to those in RMSF also have been reported in patients who have HME.

Diagnosis

The classic triad of fever, headache, and rash should make the clinician consider RMSF or HME, but these symptoms are not specific for the diagnosis (Table 2). Disseminated meningococcal disease and measles (during times of outbreaks) are the easiest to confuse with RMSF or HME. Unfortunately, no widely available laboratory assays can provide rapid confirmation of early RMSF.

Serologic tests are the most available and frequently used methods for confirming cases of RMSF. The immunofluorescence assay generally is considered the reference standard and is used by the CDC and most state public health laboratories (Table 3). However, other methods, such as latex agglutination, complement fixation, microagglutination, or indirect hemagglutination antibody tests, also can be used. Acute and convalescent titers (≥ 3 wk apart) usually are required to demonstrate a positive test because immunoglobulin G antibodies generally do not form until 7 to 10 days after the onset of illness. Other tests, such as polymerase chain reaction, immunostaining of skin biopsies, or culture techniques for *R. rickettsii*, can be used, but they are not widely available. Febrile agglutinins, which include rickettsial serology using the Weil-Felix, no longer should be performed due to its poor sensitivity and specificity. RMSF also must be differentiated from HME through the use of specific serologic testing.

Table 2. Common Diseases That Mimic Rocky Mountain Spotted Fever

- Human monocytic ehrlichiosis
- Meningococcemia
- Enterovirus infection
- Staphylococcal sepsis
- Toxic shock syndrome
- Adenovirus infection
- Drug hypersensitivity
- Immune thrombocytopenic purpura
- Henoch-Schönlein purpura
- Infectious mononucleosis
- Kawasaki disease

Table 3. Case Definition From the Centers for Disease Control and Prevention for Rocky Mountain Spotted Fever

Laboratory Criteria for Diagnosis

- Fourfold or greater rise in antibody titer to *R rickettsii* in acute- and convalescent-phase specimens ideally taken ≥ 3 weeks apart, or
- Positive polymerase chain reaction assay to *R rickettsii*, or
- Demonstration of positive immunofluorescence of skin lesion (biopsy) or organ tissue (autopsy), or
- Isolation of *R rickettsii* from a clinical specimen

Case Classification

Probable: A clinically compatible case with a single indirect immunofluorescence assay serologic titer ≥ 64 or ≥ 16 with single complement fixation titer or other supportive serology (eg, ≥ 128 by latex agglutination, microagglutination, or indirect hemagglutination test)

Confirmed: A clinically compatible case that is confirmed by laboratory findings

Management

Appropriate antimicrobial therapy should be started immediately when the diagnosis of RMSF is suspected. Treatment should not be delayed until laboratory confirmation is obtained. The decision to treat should be based on a detailed history and the clinical presentation.

The drug of choice for treating RMSF is doxycycline regardless of the patient's age. Historically, tetracyclines and chloramphenicol were the only two antimicrobial agents that had clinically proven efficacy against *R rickettsii*. Tetracyclines were reserved for children 9 years of age and older due to the adverse effects of the drugs (eg, tooth staining). Recent data have demonstrated, however, that children treated with doxycycline for RMSF had better outcomes than those treated with chloramphenicol.

In addition, it appears that problems with teeth staining are dose-related (eg, requires five to six courses before teeth staining occurs), and doxycycline is effective against HME, while chloramphenicol may not be. It also is worth noting that oral preparations of chloramphenicol no longer are available in the United States, and intravenous preparations are difficult to locate. In addition, there are no life-threatening adverse effects with doxycycline (eg, aplastic anemia) or a requirement to monitor serum levels.

Doxycycline (100 mg twice daily for adults; 4 mg/kg per day orally or intravenously for patients up to 45 kg) is administered in two divided doses and is continued for 3 days after defervescence and demonstration of clinical improvement. The usual duration of therapy is 7 to

10 days, but severe cases may require longer therapy. In addition to doxycycline, the initial antimicrobial management might include an agent that is active against *Neisseria meningitidis* (eg, cefotaxime, ceftriaxone), especially for patients who have life-threatening disease. These agents can be used in conjunction with doxycycline until the clinician is comfortable that the patient does not have meningococcal disease.

Other classes of antimicrobial agents, such as the macrolides (eg, clarithromycin), the quinolones (eg, levofloxacin), the ketolides (eg, telithromycin), and the streptogramins (eg, pristinamycin), have been demonstrated to be effective

in vitro or with animal models against *R rickettsii*, but no human clinical studies are available to support their routine use.

Prognosis

RMSF carries a mortality rate of 2% to 4%. The risk of death increases when therapy is delayed for more than 5 days. Long-term morbidity is uncommon if therapy is begun early. Immunity against reinfection by *R rickettsii* after natural infection is believed to be complete.

Prevention

Avoiding tick exposure is the most effective means of prevention. Regular inspections of pets also can reduce the incidence of tick exposure. When exposure is unavoidable, wearing protective clothing and using tick repellents can be useful. Skin repellents containing N-N-diethyl-M-toluamide (DEET) have shown to be the most effective in repelling ticks. Systemic reactions to DEET can occur when concentrations greater than 35% are used or in patients who repetitively use repellents that have lesser concentrations. It may be prudent to avoid the use of DEET-containing compounds in children younger than 1 year of age. If DEET-containing agents are used, they should be used sparingly on the exposed skin and avoided on the face and hands. Repellents containing permethrin, which can be sprayed on clothes, act on the nervous system of ticks, killing them on contact. The use of DEET-containing compounds on the skin and permethrin on the clothing is the most

effective combination against ticks. Citronella-based compounds appear to have little benefit against ticks.

Full body examinations should be performed when returning from tick-infested areas, and any tick found should be removed as soon as possible. Before tick removal, the area with the tick should be disinfected. The tick should be grasped with forceps as close to the skin as possible. With steady, even pressure, the tick should be pulled straight out. After removal, the skin should be disinfected a second time. Other popular methods of removal, such as the use of petroleum jelly or fingernail polish, inhibit the ability of the tick to move. The use of isopropyl alcohol might disinfect the bite site, but it has no effect on the tick. Burning the tick with hot objects not only endangers the individual's skin but allows the tick to burst and aerosolize infected body fluids. Such irritating practices not only fail to detach the tick, but may induce the tick to salivate, defecate, or regurgitate infected fluids into the individual. The use of prophylactic antimicrobial agents is not indicated after a tick bite

because even in endemic areas of RMSF, the number of infected ticks in the area is low, and the use of such agents has been demonstrated to be ineffective in preventing disease.

Suggested Reading

- Abramson JS, Givner LB. Rocky Mountain spotted fever. *Pediatr Infect Dis J*. 1999;18:539–540
- Buckingham SC. Rocky Mountain spotted fever: a review for the pediatrician. *Pediatr Ann*. 2002;31:163–168
- Centers for Disease Control and Prevention. Rocky Mountain spotted fever. Available at: <http://www.cdc.gov/ncidod/dvrd/rmsf/index.htm>
- Donovan BJ, Weber DJ, Rublein JC, Raasch RH. Treatment of tick-borne diseases. *Ann Pharmacother*. 2002;36:1590–1597
- Marshall GS, Stout GG, Jacobs RF, et al. Antibodies reactive to *Rickettsia rickettsii* among children living in the southeast and south central regions of the United States. *Arch Pediatr Adolesc Med*. 2003;157:443–448
- Masters EJ, Olson GS, Weiner SJ, Paddock CD. Rocky Mountain spotted fever: a clinician's dilemma. *Arch Intern Med*. 2003;163:769–774

PIR Quiz

Quiz also available online at www.pedsinreview.org.

5. Patients who are diagnosed with RMSF often have a triad of signs and symptoms that includes fever, rash, and headaches. The typical rash seen with RMSF:
 - A. Initially appears petechial.
 - B. Is always present on day 1 of the illness.
 - C. Is intensely pruritic.
 - D. Presents initially as blanching erythematous macules.
 - E. Spreads from the trunk to the extremities.

6. A 2-year-old boy recently returned from a camping trip with his parents in North Carolina. During the past 24 hours, the child has had increased lethargy and a temperature to 104°F (40°C). On physical examination, he has a blanching rash on his arms and legs, with a few areas of petechiae. A complete blood count reveals a total white blood cell count of $5 \times 10^3/\text{mCL}$ ($5 \times 10^9/\text{L}$), with a differential count of 60% segmented neutrophils, 12% bands, and 38% lymphocytes, a platelet count of $50 \times 10^3/\text{mCL}$ ($50 \times 10^9/\text{L}$), and a hematocrit of 35% (0.35). Although there is no history of a tick bite, you suspect that this child has RMSF. Your *best* course of action with this patient is admission to the hospital and:
 - A. Close observation and a repeat complete blood count in 6 hours.
 - B. Immediate treatment with doxycycline.
 - C. Immunofluorescence assay serologic test for RMSF, followed by treatment if the result is positive.
 - D. Initiation of treatment with chloramphenicol.
 - E. Initiation of treatment with doxycycline and ceftriaxone.

7. It often is extremely difficult for the clinician to differentiate RMSF from other serious diseases in children. Some of these diseases can mimic the same signs and symptoms that often are associated with this serious rickettsial infection. Of the following, which disease is nearly indistinguishable from RMSF?
 - A. Human monocytic ehrlichiosis.
 - B. Kawasaki disease.
 - C. Meningococemia.
 - D. Rubeola.
 - E. Toxic shock syndrome.

8. *Rickettsia rickettsii*, the organism responsible for the disease RMSF, has some unique epidemiologic features. Of the following, the feature that is *most* likely to be seen with this disease is:
 - A. A higher incidence in African-Americans.
 - B. Case distribution limited to the mountainous regions of the western United States.
 - C. Lack of seasonal occurrence.
 - D. More often diagnosed in males.
 - E. Transmission by a single tick species.