

Rocky Mountain spotted fever

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Rocky Mountain spotted fever (RMSF), a classic metazoonosis that involves both vertebrate and non-vertebrate reservoir hosts, is a seasonal disease of dogs and humans in the Americas. The clinical illness was first described among Native Americans, soldiers, and settlers in the Bitterroot River and Snake River valleys of Montana and Idaho during the late 1890s, but remained unrecognized in dogs until the late 1970s. The causative organism, *Rickettsia rickettsii*, was first described by Howard T. Ricketts in 1909 and is maintained in nature by ixodid (hard-bodied) ticks via transmission to-and-from various rodent reservoirs. As primary reservoir hosts, the ticks vector *R rickettsii* to larger mammals; however, dogs and humans are the only ones that display clinically recognizable illnesses. *Rickettsia rickettsii* are not naturally transmitted dog-to-dog, dog-to-human, or human-to-human. Public health surveillance, since the 1930s, has revealed RMSF to be the most frequently reported and most severe human rickettsial illness in the United States and, probably, in the Western Hemisphere. Reducing exposure to ticks, prompt removal of ticks, and early diagnosis with appropriate antibiotic treatment are the most important factors in reducing morbidity and mortality from RMSF.

The Causative Organism

Rickettsia rickettsii are small ($0.2 \times 0.5 \mu\text{m}$ to $0.3 \times 2.0 \mu\text{m}$) coccobacillary, gram-negative, obligate intracellular parasites in the family *Rickettsiaceae*. Like most other spotted fever group (SFG) rickettsiae, *R rickettsii* are conveyed to vertebrate hosts by tick vectors.^{1,2} Once they infect dogs or humans, *R rickettsii* multiply within vascular endothelium and vascular smooth muscle, inducing vasculitis and thrombosis in many organs, notably those with an abundant endarterial circulation (eg, brain, dermis, gastrointestinal organs, heart, lungs, kidneys, and skeletal muscles).^{2,4} These organisms are generally susceptible to doxycycline, tetracycline, and chloramphenicol. Special stains (ie, Giemsa, Gimenez, or immunohistochemical) are required to demonstrate *R rickettsii* in histologic sections.^{1,2,4} Although other

SFG rickettsiae are transmitted by arthropods and cause various illnesses worldwide, *R rickettsii* is the only one known to be pathogenic for both animals and humans in the Western Hemisphere.

Cycle of the Organism in Nature and the Vectors

Rickettsia rickettsii are maintained in nature by transstadial passage within, and transovarial (vertical) transmission between, generations of ixodid ticks. These ticks also vector *R rickettsii* to and from various rodent reservoirs and other small mammals. Naive larval and nymphal ticks become infected while feeding on small rodents (eg, mice, voles, squirrels, or chipmunks) with acute rickettsemia.^{2,5} To enable transovarial transmission, female ticks need to ingest numerous rickettsiae or be infected transstadially. Male ticks can transfer *R rickettsii* to females during the mating process via spermatozoa or other body fluids, thus contributing to the maintenance of the organism from one generation to another. Ticks can remain infective for life (possibly 2 to 5 years), especially if there are long periods between blood meals.^{2,3,6}

Ticks transmit *R rickettsii* to a vertebrate principally during their feeding behavior. However, human infection has occurred much less often following transdermal or inhalation exposure to tick fluids (hemolymph), tick feces, or crushed tick tissues. In the natural history of *R rickettsii* transmission, human and domestic dog infections are considered incidental events (Fig 1). Even in areas where RMSF is most endemic, only 1 to 5% of ticks (in a particular eco-

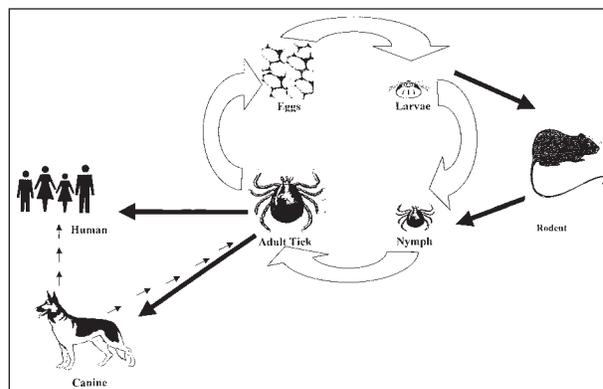


Figure 1—Pathways of natural transmission for *Rickettsia rickettsii*. Large open arrows are between stages of tick hosts, solid-line arrows are between tick vectors and vertebrates, and dashed-line arrows are unlikely or very rare routes of natural transmission via tick bites.^{2,3,5-7,10}

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niche) harbor *R. rickettsii*.^{2,7,8} It usually requires several (6 to 20) hours of tick attachment and feeding before the rickettsiae are transferred to a vertebrate, depending on the developmental stage and species of tick.^{2,5,7} Consequently, the risk of exposure to *R. rickettsii* following an individual tick bite is considered to be low.

In southeastern and mid-Atlantic regions of the United States, the most common vector of *R. rickettsii* is *Dermacentor variabilis* (American dog tick); in the northwestern United States and southwestern Canada, the common vector is *D. andersoni* (Rocky Mountain wood tick). *Dermacentor variabilis* is a 3-host tick found in southern Oregon, California, and from the Great Plains to the Atlantic coast of the United States, and in southeastern Canada. The 3-host *D. andersoni* is found from the Cascade and Sierra Nevada mountains through the Rocky Mountains, to western Nebraska and South Dakota, and into southwestern Canada. In Latin America, *Amblyomma cajennense* (Cayenne tick) is reported to be the primary vector of *R. rickettsii*.^{2,3,6}

Dermacentor variabilis larvae and nymphs feed on various small mammals, particularly rodents, after which they drop off and develop to the next stage. Unfed larvae may live up to 15 months; unfed nymphs, up to 20 months. Adults of this tick prefer medium-sized mammals (eg, raccoon, skunk, and canid species, especially the domestic dog), but will readily feed on humans. Unfed adults can live up to 30 months. Following a blood meal, adults drop off, lay from 4,000 to 6,500 eggs, and die. Unfed larvae of *D. andersoni* can live up to 4 months; unfed nymphs, up to 10 months. Adults of this tick prefer large mammals (eg, deer, bison, sheep, or cattle), including humans. Unfed adults may live up to 14 months or longer. Following a blood meal, they drop off, lay approximately 4,000 eggs, and then die.^{5,6}

In the United States, 3 other tick species have been suggested to vector *R. rickettsii*. *Amblyomma americanum* (Lone Star tick), a 3-host tick, is found from central Texas to the Gulf of Mexico and Atlantic coasts, as far north as Iowa, and New Jersey. *Rhipicephalus sanguineus* (brown dog tick), found from southern Canada into tropical South America, is a 1-host tick; all 3 developmental stages prefer to feed and develop on the same dog or other canid. This tick is most often found in and around the homes of dog owners (seldom found near woodlots or uninhabited buildings), and some evidence suggests it may be becoming more anthrophilic.^{2,3,6} *Haemaphysalis leporispalustris* (rabbit tick), found throughout the Western Hemisphere, has yielded rickettsiae that are antigenically similar to *R. rickettsii*; however, these are not known to cause clinical illness in humans or laboratory mammals, including dogs and rodents.²

Epidemiology of RMSF in Dogs

Rocky Mountain spotted fever tends to be more common in young (≤ 3 years old) dogs, and $> 80\%$ of clinical cases occur in dogs that are frequently outdoors. Incubation ranges from 2 to 14 days, following infection via tick transmission. In the United States, most dogs with RMSF are presented to veterinarians during March through October.² German Shepherd

Dogs have been reported to experience a higher incidence of illness, and English Springer Spaniels with suspected phosphofructokinase deficiency are reported to have a more severe and fulminant form of the disease.²

Clinical RMSF in Dogs

An early and usually consistent finding is fever (39.2°C [102.6°F] to 40.5°C [104.9°F]), occurring 4 or 5 days following a tick bite. If present, petechiae and ecchymoses tend to be in oral, ocular, and genital mucous membranes, and there may be focal retinal hemorrhages. Edema of extremities is often noticed in dogs and may involve the lips, pinna of ears, penile sheath, and scrotum.² In late-stage disease or during recovery, necrosis (acryl gangrene) of the extremities can develop in dogs. One of the authors (RDW) noted this on the planum nasale of a military working dog that had recovered from RMSF in central Alabama in the early 1980s. Other findings in dogs may include evidence of abdominal pain, anorexia, or both; altered mental status (signs of depression, stupor); myalgia, polyarthritis, or both; vestibular deficits (circling, head tilt, or nystagmus); and dyspnea or cough.² Such signs indicate more disseminated lesions, substantial organ edema, and a worse prognosis.

The most likely abnormal clinical laboratory findings are hypoalbuminemia, moderate leukocytosis (minimal left shift), and thrombocytopenia. Platelet counts usually range from 25,000 to 250,000/ μL .² If hypoalbuminemia develops, it probably results from widespread damage to the vascular endothelium and subsequent intercellular leakage. In dogs that are examined primarily because of cough or dyspnea, thoracic radiography typically reveals diffuse interstitial densities (pneumonitis).² Criteria for laboratory confirmation are described later.

Treatment of RMSF in Dogs

The antibiotics of choice for treating RMSF in dogs are tetracycline (25 to 30 mg/kg [11.3 to 13.6 mg/lb]), doxycycline (10 to 20 mg/kg [4.5 to 9.1 mg/lb]), or chloramphenicol (15 to 30 mg/kg [6.8 to 13.6 mg/lb]). Of course, adequate supportive care must be provided if the dog has evidence of dehydration, kidney failure, shock, or a hemorrhagic diathesis.² In dogs, mortality from RMSF is directly related to incorrect treatment, delayed diagnosis, or both. Appropriate antibiotics promptly reduce the severity of illness only if they are given before tissue necrosis (thrombotic lesions) or coagulation disorders develop.² Naturally acquired immunity most likely plays a role in limiting or protecting against clinical illness. Healthy dogs from endemic areas often possess anti-SFG antibodies, possibly a result of prior *R. rickettsii* infection or exposure to nonpathogenic SFG rickettsiae.²

Epidemiology of RMSF in Humans

In the United States, a seasonal pattern of RMSF in humans parallels what is seen in dogs. Although many clinical cases were likely not reported, the Centers for Disease Control and Prevention (CDC) has received 200 to 1,120 human case reports annually during the past 50 years.⁹⁻¹¹ Cases have been reported from all con-

tiguous states except Vermont and Maine. To encourage consistency among state reports, the CDC has advised using a standard clinical definition for human cases: an acute febrile illness, usually accompanied by myalgia, headache, and petechial rash (visible on palms, soles, or both in two-thirds of those who have the rash).¹² Criteria for laboratory confirmation are described in a later section.

Oklahoma, North Carolina, South Carolina, Tennessee, and Arkansas reported the highest incidences (per million) of RMSF in humans from 1981 through 1992. Wyoming replaced South Carolina from 1993 through 1996.⁹ North Carolina and Oklahoma reported 35% of total US cases from 1993 through 1996. Rocky Mountain states reported < 3% (Fig 2).¹¹ Nearly 95% of humans with RMSF are infected during April through September, the same period that gives rise to the greatest number of nymphal and adult *Dermacentor* ticks.^{6,9,11} The gender, ethnicity, and age profile of most reported human cases is male, Caucasian, child (5 to 9 years old).^{3,9,11} Approximately 66% of human cases of RMSF are in those < 15 years old.

Exposure to tick-infested habitats or a history of tick bite(s) is reported for nearly 60% of all human cases.^{3,13,14} People who live near wooded lots or have frequent exposure to dogs may also be at some increased risk of *R. rickettsii* infection, compared with urban or nondog-owning populations. Approximately 10% of humans with RMSF report only a known exposure to dogs or a dog's ticks. Common exposure to the same population of ticks (in surrounding environment) is the likely source of these human infections.^{2,3} Although RMSF is primarily a rural and suburban disease, microecologic niches have also been found in large metropolitan areas.¹⁵

Clinical RMSF in Humans

The incubation period in humans generally varies from 3 to 12 (median, 7) days after an infective tick bite. Early signs and symptoms are nonspecific and usually consist of fever (37.8°C [100.0°F] to 39.0°C [102.2°F]),

headache, fatigue, muscle pain, nausea or vomiting, and loss of appetite.^{3,10,14} If a rash develops, it appears 2 to 5 days after the fever begins. The rash begins as small, flat, blanching macules on the wrists, arms, and ankles. The typical red rash (viz, "spotted" fever) is not seen until 6 or more days following the nonspecific symptoms. This rash will involve the palms, soles, or both in 50 to 80% of patients and eventually becomes petechial.^{3,7,10} A rash may never develop in 10 to 15% of patients.

Six or more days after initial clinical onset, especially without definitive treatment, more severe signs and symptoms develop, which include crampy abdominal pains, joint pain, diarrhea, and a more severe headache. At this point, the rash is generally maculopapular with central petechiae. The eruptions usually spread centripetally with relative sparing of the face.^{7,10} One of the authors (RDW) investigated a point-source outbreak of RMSF that occurred in Arkansas among 44 young, otherwise healthy, military security police personnel. Other than fever, the 4 most common signs and symptoms reported from the 10 serologically confirmed cases were extreme fatigue (100%), severe headache (82%), skin rash (73%), and myalgia, arthralgia, or both (55%).¹⁶

Most patients have normal total WBC counts, with normal differentials; however, thrombocytopenia is a common finding, even in early or mild cases of disease. In the early phase of the disease, serum biochemical analyses usually reveal hyponatremia and high hepatic enzyme activities. Later, anemia and high sedimentation rates are frequently detected; high BUN and creatinine concentrations indicate renal failure.^{3,10,17} Results of other routine laboratory tests are often nonspecific. In the acute stage of illness, a diagnosis of RMSF should be made largely on the basis of patient history, examination findings, and epidemiologic reasoning.

Because *R. rickettsii* induce substantial multi-system vasculitis, septic shock can develop and lead to acute respiratory distress. Dark feces may indicate gastrointestinal hemorrhage. Central nervous system vasculitis will often present as aseptic meningitis and may lead to thrombotic stroke. Occlusion of other small arteries may lead to renal failure and gangrene of the fingers or toes.^{4,17} Other than delayed treatment or misdiagnosis, there are specific risk factors for more severe disease or fatal outcome. These include male gender, history of alcohol abuse, advanced age, glucose-6-phosphate dehydrogenase deficiency, and non-Caucasian ethnicity. Unless it appears on the palms or soles, the typical rash of RMSF can be difficult to recognize on dark-skinned individuals.^{3,10,13}

Treatment of RMSF in Humans

Doxycycline is the antibiotic of choice: 4 mg/kg (1.8 mg/lb) for children, divided in 2 doses (every 12 hours) orally or IV, to a maximum of 200 mg/day; for adults, 100 mg orally or IV every 12 hours.^{3,10} If the patient is treated within 4 to 5 days of disease onset, the fever usually subsides within 24 to 48 hours, and improvement is rapid. Doxycycline should be continued for at least 3 days after the fever subsides and until there is unequivocal evidence of disease resolu-

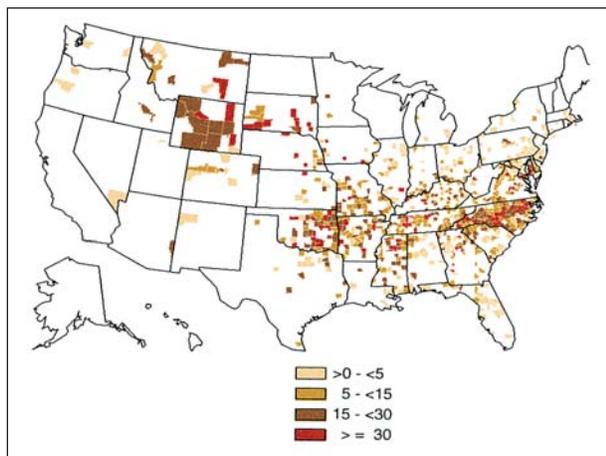


Figure 2—Average annual human incidence per million population of Rocky Mountain spotted fever by county in the United States, 1993 through 1996, based on cases reported to the National Electronic Telecommunications System for Surveillance. Reprinted with permission from the American Journal of Tropical Medicine and Hygiene.¹¹

tion, generally 5 to 10 days of treatment.^{3,10} People with severe or complicated disease may require longer courses of treatment. In people with mild or early stages of disease (ie, without significant comorbidity), failure to respond to adequate doses of doxycycline argues against a diagnosis of RMSF. Chloramphenicol is an alternate antibiotic for treating RMSF in humans, especially if renal failure, pregnancy, or allergy to doxycycline is documented. However, this drug is associated with a range of adverse effects and requires careful monitoring of plasma (therapeutic) concentrations.^{3,10}

Similar signs and symptoms often result from ehrlichiosis and borreliosis (Lyme disease), and both are tickborne zoonoses that occur in some locations that overlap RMSF-endemic areas. Therefore, doxycycline should be initially prescribed if either is suspected. In the Arkansas RMSF outbreak mentioned, the initial clinical diagnosis was Lyme disease, but none of the people who met the case definition, or the controls, seroconverted to *Borrelia burgdorferi*. One person who met the case definition, but did not have a rash, seroconverted (IgM) to *Ehrlichia chaffeensis* but not to SFG rickettsial antigens.¹⁶

Only Maryland appears on both lists of the top 10 states for incidence of human RMSF or Lyme disease (1992–1998).^{9,11,18} However, Lyme disease has received more publicity during the past 25 years, likely resulting in overdiagnosis and inappropriate prophylaxis with doxycycline for those with a history of tick bite.^{3,10} Several studies estimate that 38 to 60% of Lyme diagnoses in the northeastern United States may be incorrect.^{19,20} Fortunately, as yet, this has not resulted in any clinical evidence that the agents of RMSF or the other 2 diseases are developing resistance to the appropriate antibiotics.

Criteria for Confirmation of RMSF Diagnoses in Dogs and Humans

Comparing acute and convalescent titers is the most practical means of confirming a clinical diagnosis. Investigators and clinicians consider the **indirect immunofluorescence assay (IFA)**, which can detect either IgM or IgG antibodies, to be the serologic standard for a diagnosis of RMSF.²¹ A 4-fold or greater increase in IgM titers to SFG antigens, from acute to convalescent (≥ 3 weeks apart) sera, is considered diagnostic for recent infection.¹² Serum samples should be assayed in parallel after collection of the convalescent sample. Most infected individuals develop increasing IgM titers by the seventh day of infection; however, peaks may be delayed in those who promptly receive a correct antibiotic.^{10,16} A clinically probable, epidemiologically compatible case with a single IFA titer of ≥ 64 for IgM antibodies may be considered diagnostic.^{10,12} A single IgG titer is more problematic because SFG IgG may remain high several years after an infection.^{10,21} Other current serologic procedures are considered less sensitive, less specific, or both.^{2,3,10}

A positive polymerase chain reaction for *Rickettsia* antigen, positive immunofluorescence from a skin lesion biopsy or autopsy specimen, or the isolation of *Rickettsia* from a clinical specimen are also considered

diagnostic.¹² However, these may not be as practical, timely, or widely available.^{7,10,21} Because there is no widely available rapid laboratory assay to provide early confirmation of RMSF, specific antibiotic treatment decisions should be made on the basis of epidemiologic and clinical clues rather than awaiting laboratory confirmation. An acutely ill 9-year-old human who is presented for care in late May through late August, has not responded to treatment for a viral syndrome, and has a history of camping in a RMSF-endemic area 10 days prior to disease onset should prompt the inclusion of RMSF in the differential diagnosis.^{3,10,17}

Preventing RMSF

Preventing or limiting exposure to ticks, applying repellants to skin and outer clothing, and rapid and safe removal of attached ticks are effective ways to reduce the risk of RMSF in humans.^{3,10,14} For dog owners, the best methods of keeping ticks off the pets may be topical or systemic tick-control treatments such as permethrin, fipronil,²² or seasonal dips, along with limiting access to tick-infested areas. Alternatively, these efforts could include the use of impregnated collars (eg, containing amitraz)²³ or regular applications of an acaricidal treatment to kennels. Obviously, the best approach will depend on the geographic region where the dog resides, the habit of the dog (most time spent indoors vs outdoors), and what the dog does (house pet vs field-trial or hunting). In addition, any ticks attached to dogs should be promptly and carefully removed.² There are no antirickettsial vaccines available for use in either dogs or humans.

For humans, the following personal protective measures ensure the most effective risk reduction when tick-infested areas cannot be avoided.^{3,10,14,24:}

- Apply tick repellants to exposed skin. The most effective is DEET (N, n-diethyl-m-toluamide); 20 to 35% active ingredient for adults, and 6 to 10% for children ≤ 12 years old. If skin becomes wet from perspiration or water, reapply DEET to dry skin. Now known as N, n-diethyl-3-methyl-benzamide, concentrations of $\geq 35\%$ DEET may be appropriate for those adults who work for many hours in tick-infested areas (brush and tall grass; woodlots, powerline rights-of-way, etc).²⁵
- Spray permethrin-containing products on outer clothing and footwear.
- Wear long-sleeved shirts and long pants. Tuck pant legs into socks.
- Wear light-colored clothing to facilitate seeing ticks that crawl on the surface.
- Conduct body checks immediately after returning from outdoor activities in tick-infested areas; use mirrors to view all body areas. Remove all ticks found.
- Check children returning from infested areas, especially behind the ears, back of the neck, around the waist, and in and along the hairline.
- Remove attached ticks by using fine-tipped tweezers. Alternatively, shield fingers with tissue paper, a foil-covered gum wrapper, or plastic sandwich bag and grasp the tick as close to the skin as possible, pulling upward with steady, even pressure. Do not

twist the tick or cause tick's mouthparts to remain in the skin. Do not burn, puncture, squeeze, or crush the tick's body because its fluids may be infectious. Wash the affected area with soap and water, and disinfect the bite site and your hands. Ordinary household brands of 70% isopropyl (rubbing) alcohol or 2% tincture of iodine are adequate skin-surface disinfectants.

Remember that SFG rickettsiae are obligate intracellular parasites and will not survive long once outside of a host's body.

Public Health Considerations

Rocky Mountain spotted fever is important from the public health perspective.^{2,10} Based on current knowledge and available antibiotics, RMSF is preventable and, failing that, theoretically, a nonfatal illness. Why, then, is it currently the most frequently reported and most severe human rickettsial disease in the United States? Possibly because biologic and medical knowledge is not communicated with the public or shared between the professions.^{2,3,10} Veterinarians and physicians need to increase their diagnostic suspicion between the months of April and September. As a zoonosis, RMSF in dogs can serve as a sentinel event in the community.²

Veterinarians need to inform and encourage more pet owners about measures to prevent RMSF and share more information about local zoonoses with physicians in the community.² Likewise, physicians need to be more suspicious of RMSF in patients with spring or summer flu-like illness, especially in children, without evidence of coryza, sore throat, or cough.^{4,17} Doxycycline is proven safe and effective in treating RMSF, and courses of therapy for ≤ 14 days have not resulted in staining of children's teeth.^{7,10} Members of both professions should report all RMSF cases to local or state public health authorities.

Everyone needs to be aware that RMSF continues to be endemic in densely populated areas of many states, least commonly in the Rocky Mountains, and the typical rash is not often part of the clinical presentation.^{10,13-15} Community health education efforts need to stress that age-specific incidence is high in children, there are effective preventive measures, and treatment needs to begin as early as possible. Otherwise there can be serious sequelae, with the untreated case fatality rate ranging from 15 to 30%.^{4,10,11,17,24} If we all do as much health education as possible, RMSF should be much less of a threat in our communities.

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