Rocky Mountain spotted fever

Filipe Dantas-Torres

Lancet Infect Dis 2007; 7: 724–32

Department of Immunology, Centre of Research Aggeu Magalhães, Oswaldo Cruz Foundation, Recife, Pernambuco, Brazil
(F Dantas-Torres MSc)

Correspondence to:
Dr Filipe Dantas-Torres, Departamento de Imunologia, Centro de Pesquisas Aggeu Magalhães, Fundação Oswaldo Cruz, CP 7472, Recife 50670-420, Pernambuco, Brazil.
Tel +55 81 21012562; fax +55 81 34532449;
fdt@cpqam.fiocruz.br

Rocky Mountain spotted fever (RMSF) is a life-threatening disease caused by *Rickettsia rickettsii*, an obligately intracellular bacterium that is spread to human beings by ticks. More than a century after its first clinical description, this disease is still among the most virulent human infections identified, being potentially fatal even in previously healthy young people. The diagnosis of RMSF is based on the patient's history and a physical examination, and often presents a dilemma for clinicians because of the non-specific presentation of the disease in its early course. Early empirical treatment is essential to prevent severe complications or a fatal outcome, and treatment should be initiated even in unconfirmed cases. Because there is no vaccine available against RMSF, avoidance of tick-infested areas is still the best way to prevent the infection.

Introduction

Rocky Mountain spotted fever (RMSF) is a life-threatening disease caused by *Rickettsia rickettsii*, an obligately intracellular bacterium that is spread to human beings by infected ticks. The disease is the most common tickborne rickettsial disease in the USA and is potentially fatal even in previously healthy young people.[1–3] RMSF is among the most virulent infections identified in human beings,[4] and its diagnosis often presents a dilemma for clinicians.[5–9]

The so-called spotted fever of Idaho: early history

The history of RMSF began in the late 19th century, when Edward E Maxey provided the first clinical description of the so-called spotted fever of Idaho: "a febrile disease, characterized clinically by a continuous moderately high fever, and a profuse or purpuric eruption in the skin, appearing first on ankles, wrists, and forehead, but rapidly spreading to all parts of body".[10] This description became the first report of RMSF to be published in the medical literature.[11]

In 1904, Louis B Wilson and William M Chowning studied records of 126 cases of RMSF and concluded that wood ticks (genus *Dermacentor*) were responsible for transmitting the infection.[12] In 1906, *Dermacentor* spp ticks were categorically implicated in the transmission of the agent of RMSF, which was unnamed at that time.[13,14] From 1906 to 1910, Howard T Ricketts isolated the pathogen and showed that it circulated among ticks and mammals in the wild. He also showed that infected ticks could transmit the disease transovarially to their offspring.[14–16] Tragically, this talented rickettsiologist was affected by epidemic typhus and died in 1910, at the age of 39 years.[17]

Soon afterward, E R Le Count described the fundamental histopathology finding (ie, the vascular lesion) of RMSF.[18] In 1919, S Burt Wolbach published an extensive study on the agent of RMSF, confirming that ticks carried the bacterium.[19] He also noted the intracellular nature of the pathogen, which principally infected endothelial cells. Wolbach named the agent of RMSF as *Dermacentroxenus rickettsii* in honour of Howard T Ricketts. The use of the generic term *Dermacentroxenus* derived from the generic name of the tick vector, *Dermacentor andersoni*. However, the genus *Dermacentroxenus* was not universally accepted, and then rapidly unified with the genus *Rickettsia*, previously used for *Rickettsia prowazekii*, the causative agent of epidemic typhus. On this basis, the name *R rickettsii* was proposed in 1922 by Brumpt.[20]

Before the discovery of tetracycline and chloramphenicol in the late 1940s, there was no specific treatment for RMSF.[21] Only modest success was achieved in treating RMSF with para-aminobenzoic acid and with rabbit hyperimmune serum.[22,23] At that time, up to 87% of those affected did not survive.[12]

The pathogen

R rickettsii (panel 1) is a fastidious, small (0·2–0·5 µm by 0·3–2·0 µm), pleomorphic Gram-negative coccobacillus. The cell-wall composition and lipopolysaccharide of the pathogen resemble that seen in other Gram-negative bacteria.[24–26] Most cell-surface antigens are recognised by antibodies present in sera of human beings and animals with active RMSF.[26–28] *R rickettsii* possesses two major immunodominant surface proteins of 190 kDa and 135 kDa: outer membrane protein A (OmpA) and outer membrane protein B (OmpB), respectively. OmpB is the most abundant surface protein of rickettsiae. OmpA and OmpB contain species-specific epitopes that provide the basis for rickettsial serotyping by use of comparative indirect microimmunofluorescence assays.[17]

As with other rickettsiae, *R rickettsii* retains basic fuchsin when stained using the Gimenez method,[29] and its cultivation in the laboratory requires the use of living host cells (animal models, embryonated eggs) or cell cultures (Vero, L929, human embryonic lung, MRC5 cells).[30,31] *R rickettsii* typically infects vascular endothelial cells.[32–34] Unlike other intracellular bacteria that may cause disease in human beings (eg, *Ehrlichia* spp), *R rickettsii* is not surrounded by a host cell membrane and can be found in the nucleus or in the cytoplasm of the host cell.[32,34]

Panel 1:* Classification of *R rickettsii

Kingdom: Bacteria
Phylum: Proteobacteria
Class: Alphaproteobacteria
Order: Rickettsiales
Family: Rickettsiaceae
Genus: Rickettsia
Species: *Rickettsia rickettsii*

Genomes of various *Rickettsia* spp have been sequenced previously.[35–37] Data from rickettsiae genomics are likely to improve the current understanding of the mechanism of rickettsial pathogenicity,[38] and may help the development of new diagnostic tools and vaccines.[17] The unpublished complete genome sequence of *R rickettsii* (size 1257710 bp) has recently been deposited in GenBank (accession number AADJ01000001). The complete genomes of five *Rickettsia* spp (*R bellii*, *R conorii*, *R felis*, *R prowazekii*, and *R typhi*) and the unfinished genomes of another six (*R africae*, *R akari*, *R canadensis*, *R massiliae*, *R sibirica*, and *R slovaca*) are also available in the GenBank database.

Natural reservoir hosts and mode of transmission

Natural reservoirs of *R rickettsii* include hard ticks (family Ixodidae; figure 1) of various genera and species.[39] The pathogen is maintained in nature, across several tick generations, through transovarial passage (from an infected female tick to her progeny) and transstadial passage (between developmental life stages). Although *R rickettsii* can also be found in domestic (eg, dogs) and wild mammals, the role of these animals as reservoirs of infection is not well understood.[17,39–43] Some of these animals may serve as secondary reservoirs or amplifying hosts.[44]

The American dog tick (*Dermacentor variabilis*; figure 2), is the primary vector of *R rickettsii* in most of the USA. The Rocky Mountain wood tick (*D andersoni*) is a major vector in the Rocky Mountain region and Canada. The brown dog tick (*Rhipicephalus sanguineus*; figure 3), thought to be the primary vector of *R rickettsii* in Mexico,[45] has recently been implicated in the transmission of the pathogen in eastern Arizona.[46] Although the role of *Rh sanguineus* as a vector of *R rickettsii* has been determined in the laboratory,[47] it has a low affinity for human beings.[31] However, human parasitism by *Rh sanguineus* may be more common than previously recognised,[48] and this tick may eventually act as a vector of *R rickettsii* in other areas where the infection is endemic.[17] The Cayenne tick (*Amblyomma cajennense*), which is thought to be a common vector of *R rickettsii* in Central and South America,[9] has a high affinity for human beings,[31] and has been found naturally infected with *R rickettsii* in Panama and Brazil.[49–51] The tick *Amblyomma aureolatum*, commonly known in Brazil as *carrapato-amarelo-do-cão* (the yellow dog tick), has recently been implicated as a vector for *R rickettsii* in Brazil.[52]

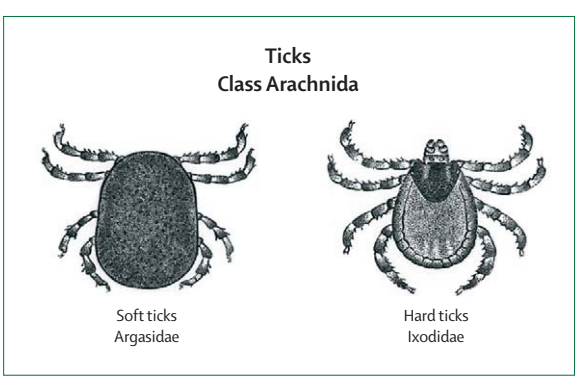

Figure 1: **Morphological differences between soft ticks and hard ticks**
Adapted from image in the CDC Public Health Image Library.

Figure 2: **Dorsal view of a female *Dermacentor variabilis***
Photo courtesy of the CDC Public Health Image Library/CDC Division of Vector-Borne Infectious Diseases/Gary O Maupin.

Other tick species are suspected to be involved in the transmission of *R rickettsii*.[53–55] However, some of these tick species seldom bite human beings. Most of the reports on natural infection of ticks with rickettsial agents are based on techniques that are not able to distinguish the *Rickettsia* species involved. These techniques, particularly the haemolymph test, were (and are still) widely used because of their low cost and simplicity. When assessing the role of a given tick species as a vector of *R rickettsii*, the presence of confounding organisms (eg, *R felis*, *R bellii*, *R amblyommii*, *R parkeri*, *R prowazekii*, and *R massiliae*)[56–61] should not be ignored. Thus, the use of techniques (eg, PCR amplification and sequencing) that could accurately identify the *Rickettsia* spp involved is highly desirable.

R rickettsii is transmitted by the bite of an infected tick, which acts as both reservoir and vector of the pathogen. When the tick is attached to and feeding on a human being, a reactivation phenomenon takes place and *R rickettsii* transforms from a dormant, avirulent state to a highly pathogenic one. This process requires a minimum period of attachment that often ranges from 4 h to 6 h, although it may be as long as 24 h.[11,62,63] There is also a possibility of acquiring *R rickettsii* infection by contact with tick tissues or fluids, by inhalation of contaminated aerosol (reported only in laboratories),[64] or through blood transfusion.[65] Particular care needs to be taken when removing ticks to avoid contact with tick tissues or fluids.

Epidemiology

The geographical distribution of RMSF is restricted to countries of the western hemisphere (figure 4). The disease has been found in the USA, western Canada,[66] western and central Mexico,[67,68] Panama,[69] Costa Rica,[70] northwestern Argentina,[71] Brazil (states of São Paulo, Minas Gerais, Rio de Janeiro, Espírito Santo, Bahia, and Santa Catarina),[51] and Colombia.[72] In the USA, RMSF occurs in all contiguous 48 states, except for Vermont and Maine;[73,74] half of the cases are found in Oklahoma, Tennessee, and Arkansas,

For more information on **the GenBank database** see http://www.ncbi.nlm.nih.gov/Genbank/GenbankOverview.html

Figure 3: **Dorsal view of a male *Rhipicephalus sanguineus***
Photo courtesy of the CDC Public Health Image Library/James Gathany/William Nicholson.

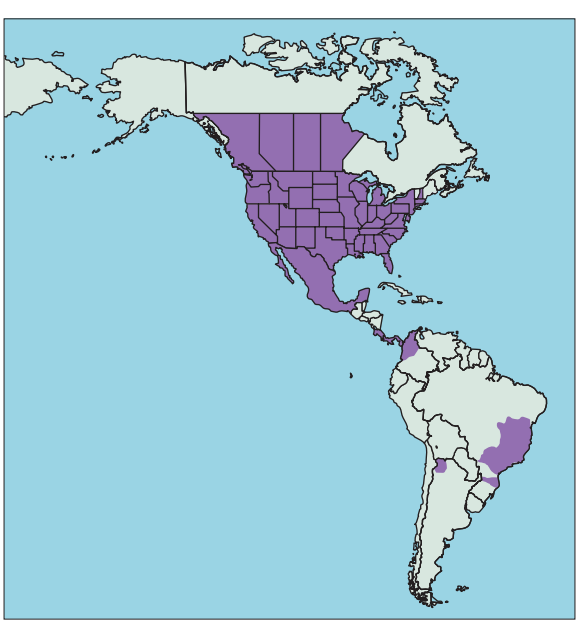

Figure 4: **Approximate geographical distribution of RMSF in the American continent**
Shaded areas show regions where RMSF is endemic.

and in the South Atlantic region, particularly Maryland, Virginia, and North and South Carolina.[9,73,74]

Between 1873 and 1920, 431 cases of RMSF were described in the USA.[75] Between 1997 and 2002, the average annual incidence of the disease was 2·2 cases per million people.[9] Historically, approximately 250–1200 cases of RMSF have been reported annually in the USA, although it is likely that many more cases go unreported.[76,77] Cyclic fluctuations of the incidence of RMSF have been observed through the decades.[78] Of note, the number of RMSF cases reported in the USA in 2004, 2005, and 2006 were 1713,[79] 1936,[80] and 2092,[81] respectively (each of these numbers represents the highest number of cases ever previously reported). The highest incidence has been observed in children aged less than 10 years (peak age-group, 5–9 years),[74,78] and among adults aged 40–64 years.[80] The incidence is also high among men and white people.[82,83]

Between 1983 and 1998, five to 39 deaths caused by RMSF were reported annually in the USA, and it has been estimated that some 400 additional deaths were not reported during the same period.[84] In the past, the disease would kill up to 87% of those infected.[12] Today, a fatal outcome has been reported in up to 20% of untreated cases and 5% of treated cases.[9] Geographical variations in case fatality of RMSF are known to occur in the USA.[75] Different isolates of *R rickettsii* show different levels of pathogenicity in endothelial cell culture;[85] this might explain, in part, the variation in disease severity across distinct geographical regions. In other countries, the case fatality of RMSF can be even higher, as has been reported in Brazil (figure 5), where the average case fatality during 1995–2004 was 29·1%.[86]

Fatal outcome is associated with older patients (over 60 years), with a greater than 5-day interval between disease onset and treatment, with a lack of tetracycline treatment, or with chloramphenicol-only treatment.[74,83,87] Fulminant RMSF in African-American men with glucose-6-phosphate dehydrogenase deficiency has been reported.[88] In the USA, most cases of RMSF (90–93%) occur between April and September when the tick vectors are most active.[17,83] RMSF cases are usually found in rural areas,[4,17,89] although autochthonous cases have also been reported in urban settings,[78] such as New York.[90] Residence in wooded areas or in areas with high grass and exposure to dogs increases the risk of *R rickettsii* infection.[91–94] The disease is sporadic and is clustered in limited geographical regions. By contrast with what occurs in certain endemic areas (eg, Brazil), most cases of RMSF in the USA occur as widely spread single patients and the disease is seldom reported in clusters; only 4·4% of the cases are familial clusters.[91]

Clinical manifestations

Patients with RMSF display a diverse range of systemic, cutaneous, cardiac, pulmonary, gastrointestinal, renal, neurological, ocular, and skeletal muscle manifestations.[30] Most patients have moderate or severe illness,[30,32] and a

substantial proportion of them need to be admitted to hospital.[83,93] The mean incubation period of RMSF is 7 days (range 2–14 days).[17,30,32,34,74] Initial clinical signs and symptoms are similar to those observed in other tickborne rickettsial diseases, making the clinical diagnosis difficult in this early phase when treatment would be most effective.

During the first 3 days of illness, the classic clinical triad of fever, headache, and rash is observed in only 3% of patients with RMSF.[92] Initially, the disease is characterised by sudden onset of fever (usually greater than 38·9°C), significant malaise, and severe headache (patients often describe the headache as the worst they have ever had), usually accompanied by myalgia, anorexia, nausea, vomiting, abdominal pain, and photophobia.[5,9,83,92,95–97] During this phase, RMSF may be misdiagnosed as a viral illness.[98]

During the 2 weeks after a tick bite, the classic clinical triad is seen in 60–70% of patients.[11,99,100] A rash appears typically 2–5 days after onset of fever.[17,32,34] First, the rash appears as small (1–5 mm diameter), blanching erythematous macules initially on the wrists (figure 6) and ankles, with subsequent centrifugal progression to the palms and soles. Then the rash spreads centripetally from the wrists and ankles to the arms (figure 7), leg, and trunk.[12,98] By the end of the first week, the eruption becomes maculopapular with central petechiae.[92,101] The continuous skin and tissue damage caused by *R rickettsii* may result in skin necrosis and gangrene, requiring amputation in severe cases.[11,102] However, 9–12% of patients do not break out in a rash.[5,6,92,103,104] Lack of rash occurs most commonly in cases that are fatal, in older patients, and in African Americans.[32,91] Other cutaneous manifestations include mucosal ulcers, postinflammatory hyperpigmentation, and jaundice.[30,105] Unlike other tickborne rickettsial diseases, the presence of inoculation eschar is rare in RMSF.[106]

Myocarditis is uncommon in patients with RMSF.[92,107] Pulmonary manifestations such as cough and pneumonia have been reported.[92,108] Although hepatomegaly is noted at necropsy in almost all fatal cases, this finding is noticed in the physical examination of only 12–25% of patients.[92] Acute renal failure is often observed in severe cases.[92,109] Various neurological manifestations have been reported.[3,30,110] Some 40% of patients may develop lethargy, photophobia, meningismus, amnesia, bizarre behaviour suggestive of psychiatric illness, or transient deafness.[92,94,111] Ocular manifestations include conjunctivitis (30% of patients), optic disc oedema, arterial occlusion, retinal vein engorgement, retinal haemorrhage, and retinal sheathing.[92,96,112,113] Cases of skeletal muscle involvement with high concentrations of creatine kinase have also been reported.[114,115]

Diagnosis: a dilemma for clinicians

The diagnosis of RMSF is based on physical examination of the patient and epidemiological data. However, clinical diagnosis is difficult because initial signs and symptoms are often non-specific and may lead clinicians to make the wrong diagnosis.[5,106,116–123]

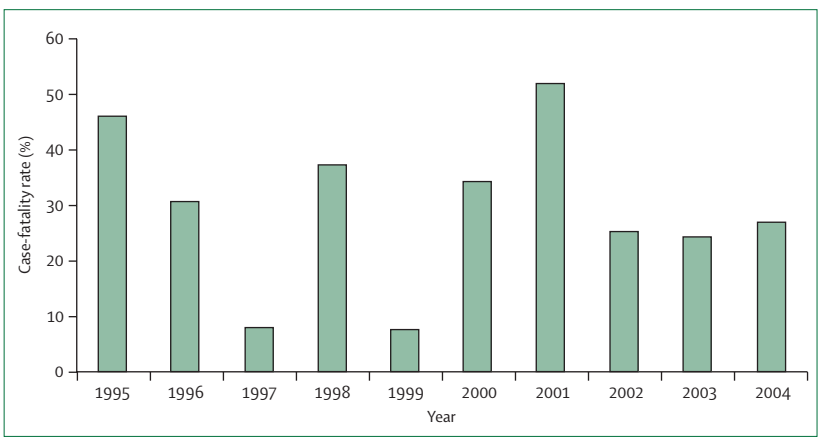

Figure 5: **Case fatality of RMSF in Brazil (as reported by the Brazilian Ministry of Health)[86]**

Antibodies to *R rickettsii* are not detectable until 7–10 days after disease onset;[124] thus, serological tests are of limited diagnostic value.[17,30] A negative result does not exclude the possibility of infection and a positive result does not necessarily confirm presence of the infection.[17] The Weil-Felix test, the oldest serological assay in use, lacks sensitivity and specificity and is falling into disuse.[11,17,125] The indirect fluorescent antibody test, currently the gold standard of

Figure 6: **Typical rash on the right hand and wrist of a child with RMSF**
Photo courtesy of the CDC Public Health Image Library.

Figure 7: **Typical rash on the right arm of a child with RMSF**
Photo courtesy of the CDC Public Health Image Library.

serological testing for rickettsioses,[9,104,124] is highly sensitive, but cannot distinguish between infection with *R rickettsii* and other spotted-fever-group rickettsiae.[17] A four-fold increase of titres in paired samples, or a convalescent titre greater than 1/64, is thought to be diagnostic.[34,124] ELISA has also been used,[9] and is reputed to be highly sensitive and reproducible.[33]

Immunohistochemical staining of rickettsiae antigens in formalin-fixed, paraffin-embedded biopsied tissues may be useful during the acute stage of RMSF, particularly in patients with a rash.[9,126,127] The immunohistochemical staining of skin biopsy specimens has been reported to be 100% specific and 70% sensitive. Although this method has been used to diagnose non-fatal cases of RMSF, it seems to be more useful for detecting rickettsiae in necropsy tissues such as liver, spleen, lung, heart, kidney, and brain.[9,126–130] Immunostaining for spotted-fever-group rickettsiae is offered by the US Centers for Disease Control and Prevention (CDC) and certain US university-based hospitals and commercial laboratories.[9]

The use of PCR for the diagnosis of RMSF is limited because of its inferior sensitivity in detecting *R rickettsii* DNA in blood specimens.[9,11,131–133] The number of rickettsiae circulating in the blood is typically low, particularly in the absence of advanced disease or fulminant infection.[45] This technique seems to be more useful for the detection of *R rickettsii* in a skin biopsy or necropsy tissue specimen.[55] In acute RMSF, laboratory confirmation is improved when the PCR is used in association with immunohistochemical staining.[9] New PCR-based methods (eg, quantitative PCR assay)[134] have been developed for the detection and quantification of *R rickettsii*, and other closely related spotted-fever-group rickettsiae, in different types of samples. These techniques can offer advantages in terms of speed, sensitivity, and reproducibility when compared with conventional PCR.

Because *R rickettsii* is classified as a biosafety level-3 agent, laboratorial cultivation has not been routinely used for diagnostic purposes.[9,11] Laboratory findings such as anaemia, thrombocytopenia, raised aminotransferase concentrations, increased bilirubin, increased creatine kinase, and hyponatraemia have been reported in RMSF.[92,94,135] The diagnostic use of these findings is limited because they are unspecific.

Differential diagnosis of RMSF includes an extensive list of tickborne and non-tickborne diseases (panel 2).

Panel 2: Diseases and conditions to consider in the differential diagnosis of RMSF[11,17,33,34]

- Typhus
- Ehrlichiosis
- Other rickettsial diseases
- Immune complex vasculitis
- Meningococcaemia
- Thrombotic thrombocytopenia purpura
- Enterovirus infection
- Typhoid fever
- Leptospirosis
- Dengue
- Infectious mononucleosis
- Bacterial sepsis
- Gastroenteritis or acute abdomen
- Bronchitis or pneumonia

Treatment

Because fatal cases of RMSF are often associated with delayed diagnosis, the decision to treat should never be delayed by laboratory confirmation.[9,17,30,34] Any patient with a fever and rash should be considered for hospital admission and antimicrobial therapy.[136]

Tetracyclines and chloramphenicol are the only drugs proven to be effective for the treatment of RMSF.[11] Because of its effectiveness, broad margin of safety, and convenient dosing schedule, doxycycline is currently considered the drug of choice for nearly all patients, including young children.[7,9,88,137–140] The current recommended regimens of treatment with doxycycline are 100 mg per dose given twice daily for adults, and 2·2 mg/kg bodyweight per dose given twice daily for children weighing less than 45 kg.[9] These recommended doses may be given orally or intravenously and treatment should be maintained for 5–7 days.[11] Doxycycline therapy should be continued until the patient is afebrile for at least 2 or 3 days.[9] Intravenous therapy is often indicated for hospital inpatients,[9] particularly for those with vomiting, unstable vital signs, and neurological symptoms.[104]

The use of tetracyclines in the treatment of tickborne rickettsial diseases in children was controversial in the past because the risk of permanent tooth discolouration.[140] Today, there is a consensus that doxycycline is the drug of choice for treating presumptive or confirmed RMSF in children of any age.[9] A prospective study reported that children treated with doxycycline for RMSF did not show substantial discolouration of permanent teeth compared with those who had never received the drug.[141]

Chloramphenicol remains the recommended therapy for RMSF in pregnant women, despite the risk of grey baby syndrome.[9,32,142–144] The indicated dose of chloramphenicol is 50–75 mg/kg per day, divided into four doses, given for 7 days, or until 2 days after the fever has subsided.[142,143] In life-threatening situations, the use of tetracyclines might be warranted during pregnancy.[9]

A study of the knowledge of physicians about the diagnosis and management of RMSF in Mississippi has shown that only 21% of family physicians and 25% of emergency medicine physicians correctly identified doxycycline for treating children with RMSF.[145] Moreover, 23% of physicians reported that waiting for the development of a rash before the treatment decision is an appropriate strategy.[145] This suggests that continuing education is essential to prevent deaths caused by delay of doxycycline therapy.

Panel 3: General recommendations for prevention of RMSF[11,17,33,34]

- Avoid tick habitats, such as highly wooded areas, grassy edge of forests, stream banks, trails, and grassy fields
- Adopt personal protective measures to limit the possibility of tick exposure
- Frequently examine yourself to check for any attached ticks
- Remove attached ticks properly to reduce the risk of *R rickettsii* transmission

Panel 4: Recommendations for proper tick removal[11,17,34,153-155]

- Wear protective gloves
- Grasp the tick carefully with fine forceps, as close to the point of attachment as possible, and pull straight outward with gentle traction to remove the tick
- Do not jerk, twist, squeeze, or burn the tick
- Folk remedies (eg, petroleum jelly) should never be used
- Disinfect the bite wound after tick removal

Prevention

The development of vaccines against rickettsial diseases remains a low priority, as a result of the development of effective and safe antibiotics, and mainly because of the decreased perceived threat posed by these diseases. Although some rickettsial pathogens (*R rickettsii* and *R prowazekii*) are considered by the CDC to be select agents, there are no vaccines for any rickettsial disease currently approved by the US Food and Drug Administration.[146] Thus, it is essential to emphasise that avoidance of tick-infested habitats (eg, heavily wooded areas) is still the best way to prevent RMSF (panel 3).[34,143,147]

Sometimes, it is not possible to avoid tick habitats, especially for people who live, work, or enjoy recreational activities in these environments.[148] In these cases, individual protective measures must be adopted. People in contact with tick-infested habitats are advised to wear light-coloured, long-sleeved clothing and footwear, tuck trousers into socks, and bind the exposed edges. The use of permethrin on clothes as an acaricide may also be useful. Removal and decontamination of clothes immediately after leaving tick-infested areas is also suggested.[9,34,147–149] Because the transmission of *R rickettsii* requires a minimum period of attachment,[11,62,63] early tick removal is crucial to diminish the possibility of infection. Frequent physical examination to find and remove attached ticks is recommended.[9,78,144,150–152] This is particularly important when undergoing activities in tick-infested areas, particularly during tick season (eg, April to September in the USA), when risk of tick exposure increases substantially. The basic recommendations for proper tick removal are shown in panel 4.

Search strategy and selection criteria

Data for this Review were identified by searching PubMed. Search terms (alone or in combination) were "Rocky Mountain spotted fever", "*Rickettsia rickettsii*", "*Dermacentor* ticks", and "tick-borne rickettsioses". English, Portuguese, and Spanish languages papers were reviewed, without date restriction. Selected articles were also searched for relevant references. Papers already known to the author were also included, as well as several review articles, since they provided comprehensive overviews that are beyond the scope of the present article.

Punch, shave, or even complete excisional biopsies have been used in some cases when the tick removal is extremely difficult or when mouthparts cannot be removed with fine forceps.[156] However, experience in successfully removing ticks with ease makes the use of such invasive procedures unnecessary. Moreover, the clinical significance of leaving tick mouthparts embedded in the skin has not been assessed fully,[148] and the risk-to-benefit ratio of the use of invasive procedures to remove ticks or their mouthparts is unknown.

Chemoprophylaxis should be helpful in certain situations and consists of the use of the tick repellent DEET (N,N-diethyl-meta-toluamide) on the exposed skin.[34] Prophylactic antibiotic administration after a tick bite is not indicated to prevent RMSF.[11] Experimental animal models of *R rickettsii* infection have shown that the illness was not prevented, but only delayed.[78]

Conclusions

Over a century has elapsed since the first clinical description of RMSF. Despite this, the disease remains among the most severe vector-borne diseases recognised to date, and many aspects of its natural history are still unknown. The diagnosis of RMSF remains a dilemma for clinicians because the diagnostic value of current tools is very limited, particularly during the early course of the illness. Better serological methods to detect specific antibodies to *R rickettsii* in the early phase of infection are needed. A better understanding of the mechanisms involved in the interaction between *R rickettsii* and the host immune system would help the development of an effective vaccine against RMSF; however, many question whether it is really a priority to develop a vaccine for such sporadic (but persistent) and treatable disease. Given that RMSF is one of the oldest and most virulent vector-borne diseases known, which is still killing many of its victims, the answer should be "yes".

Conflicts of interest

FDT is supported by a PhD scholarship from the Coordination for the Improvement of Higher Education Personnel (CAPES) and declares he has no conflicts of interest.

Acknowledgments

I thank Frederico Abath, Mércia Arruda, and Sinval P Brandão-Filho for their opinion on a draft of this manuscript; the reviewers for their valuable

comments and suggestions; and Sidney Pratt for English revision. I am also indebted to the CDC and to the providers of the images used to illustrate this Review. This Review is dedicated to the memory of Frederico Abath, who passed away on March 1, 2007, in recognition of his excellent academic and research contributions, and for his inspiring passion for knowledge.

References

1 Harrell GT. Rocky Mountain spotted fever. *Medicine (Baltimore)* 1949; **28:** 333–70.

2 Walker DH, Fishbein DB. Epidemiology of rickettsial diseases. *Eur J Epidemiol* 1991; **7:** 237–45.

3 Zavala-Castro JE, Zavala-Velazquez JE, Walker DH, et al. Fatal human infection with *Rickettsia rickettsii*, Yucatan, Mexico. *Emerg Infect Dis* 2006; **12:** 672–74.

4 Dumler JS, Walker DH. Rocky Mountain spotted fever—changing ecology and persisting virulence. *N Engl J Med* 2005; **353:** 551–53.

5 Kaplowitz LG, Fischer JJ, Sparling PF. Rocky Mountain spotted fever: a clinical dilemma. *Curr Clin Top Infect Dis* 1981; **2:** 89–108.

6 Westerman EL. Rocky Mountain spotless fever. A dilemma for the clinician. *Arch Intern Med* 1982; **142:** 1106–07.

7 Masters EJ, Olson GS, Weiner SJ, Paddock CD. Rocky Mountain spotted fever: a clinician's dilemma. *Arch Intern Med* 2003; **163:** 769–74.

8 Razzaq S, Schutze GE. Rocky Mountain spotted fever: a physician's challenge. *Pediatr Rev* 2005; **26:** 125–30.

9 Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep* 2006; **55:** 1–27.

10 Maxey EE. Some observations on the so-called spotted fever of Idaho. *Med Sentinel* 1899; **7:** 433–38.

11 Thorner AR, Walker DH, Petri WA Jr. Rocky Mountain spotted fever. *Clin Infect Dis* 1998; **27:** 1353–59.

12 Wilson LB, Chowning WM. Studies in *Pyroplasmosis hominis* ("spotted fever" or "tick fever" of the Rocky Mountains). *J Infect Dis* 1904; **1:** 31–57.

13 King WW. Experimental transmission of Rocky Mountain spotted fever by means of the tick. Preliminary note. *Public Health Rep* 1906; **21:** 863–64.

14 Ricketts HT. The study of "Rocky Mountain spotted fever" (tick fever?) by means of animal inoculations. A preliminary communication. *JAMA* 1906; **47:** 33–36.

15 Ricketts HT, Gomez L. Studies on immunity in Rocky Mountain spotted fever: first communication. *J Infect Dis* 1908; **5:** 221–44.

16 Ricketts HT. Some aspects of Rocky Mountain spotted fever as shown by recent investigations. *Med Rec* 1909; **76:** 843–55.

17 Parola P, Paddock CD, Raoult D. Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. *Clin Microbiol Rev* 2005; **18:** 719–56.

18 Le Count ER. A contribution to the pathological anatomy of Rocky Mountain spotted fever. *J Infect Dis* 1911; **8:** 421–26.

19 Wolbach SB. Studies on Rocky Mountain spotted fever. *J Med Res* 1919; **41:** 2–197.

20 Bengtson IA. Classification of the Rickettsiae of Rocky Mountain spotted fever and of endemic (Murine) typhus. *J Bacteriol* 1947; **53:** 325–27.

21 Philip CB. Rocky Mountain spotted fever. *Bull Med Libr Assoc* 1940; **29:** 86–92.

22 Harrell GT, Venning W, Wolff WA. The treatment of Rocky Mountain spotted fever with particular reference to intravenous fluids: a new approach to basic supportive therapy. *JAMA* 1944; **126:** 929–34.

23 Topping NH. Rocky Mountain spotted fever: further experience in the therapeutic use of immune rabbit serum. *Public Health Rep* 1947; **58:** 757–75.

24 Obijeski JR, Palmer EL, Tzianabos T. Proteins of purified rickettsiae. *Microbios* 1974; **11:** 61–76.

25 Pedersen CE Jr, Walters VD. Comparative electrophoresis of spotted fever group rickettsial proteins. *Life Sci* 1978; **22:** 583–87.

26 Anacker RL, List RH, Mann RE, Hayes SF, Thomas LA. Characterization of monoclonal antibodies protecting mice against *Rickettsia rickettsii*. *J Infect Dis* 1985; **151:** 1052–60.

27 Feng HM, Kirkman C, Walker DH. Radioimmunoprecipitation of [^{35}S]methionine-radiolabeled proteins of *Rickettsia conorii* and *Rickettsia rickettsii*. *J Infect Dis* 1986; **154:** 717–21.

28 Williams JC, Walker DH, Peacock MG, Stewart ST. Humoral immune response to Rocky Mountain spotted fever in experimentally infected guinea pigs: immunoprecipitation of lactoperoxidase ^{125}I-labeled proteins and detection of soluble antigens of *Rickettsia rickettsii*. *Infect Immun* 1986; **52:** 120–27.

29 Raoult D, Roux V. Rickettsioses as paradigms of new or emerging infectious diseases. *Clin Microbiol Rev* 1997; **10:** 694–719.

30 Silber JL. Rocky Mountain spotted fever. *Clin Dermatol* 1996; **14:** 245–58.

31 Parola P, Raoult D. Ticks and tickborne bacterial diseases in humans: an emerging infectious threat. *Clin Infect Dis* 2001; **32:** 897–928.

32 Harrell GT, Aikawa JK. Pathogenesis of circulatory failure in Rocky Mountain spotted fever. *Arch Intern Med* 1949; **83:** 331–47.

33 Walker DH. Rocky Mountain spotted fever: a disease in need of microbiological concern. *Clin Microbiol Rev* 1989; **2:** 227–40.

34 Lacz NL, Schwartz RA, Kapila R. Rocky Mountain spotted fever. *J Eur Acad Dermatol Venereol* 2006; **20:** 411–17.

35 Andersson SG, Zomorodipour A, Andersson JO, et al. The genome sequence of *Rickettsia prowazekii* and the origin of mitochondria. *Nature* 1998; **396:** 133–40.

36 Ogata H, Audic S, Renesto-Audiffren P, et al. Mechanisms of evolution in *Rickettsia conorii* and *R prowazekii*. *Science* 2001; **293:** 2093–98.

37 McLeod MP, Qin X, Karpathy SE, et al. Complete genome sequence of *Rickettsia typhi* and comparison with sequences of other rickettsiae. *J Bacteriol* 2004; **186:** 5842–55.

38 Renesto P, Ogata H, Audic S, Claverie JM, Raoult D. Some lessons from *Rickettsia* genomics. *FEMS Microbiol Rev* 2005; **29:** 99–117.

39 Azad AF, Beard CB. Rickettsial pathogens and their arthropod vectors. *Emerg Infect Dis* 1998; **4:** 179–86.

40 Mariotte CO, Bustamante ME, Varela G. Discovery of the *Rhipicephalus sanguineus* Latreille naturally infected with Rocky Mountain spotted fever in Sonora (Mexico) 1944. *Rev Inst Salubr Enferm Trop* 1944; **5:** 297–300 (in Spanish).

41 Magnarelli LA, Anderson JF, Burgdorfer W, Philip RN, Chappell WA. Spotted fever group rickettsiae in immature and adult ticks (Acari: Ixodidae) from a focus of Rocky Mountain spotted fever in Connecticut. *Can J Microbiol* 1985; **31:** 1131–35.

42 Bischof R, Rogers DG. Serologic survey of select infectious diseases in coyotes and raccoons in Nebraska. *J Wildl Dis* 2005; **41:** 787–91.

43 Bozeman FM, Shiral A, Humphries JW, Fuller HS. Ecology of Rocky Mountain spotted fever. II. Natural infection of wild mammals and birds in Virginia and Maryland. *Am J Trop Med Hyg* 1967; **16:** 48–59.

44 Burgdorfer W, Newhouse VF, Pickens EG, Lackman DB. Ecology of Rocky Mountain spotted fever in western Montana. I. Isolation of *Rickettsia rickettsii* from wild mammals. *Am J Hyg* 1962; **76:** 293–301.

45 Bustamante ME, Varela G IV. Studies on spotted fever in Mexico: the role of *Rhipicephalus sanguineus* in the transmission of spotted fever in the Mexican republic. *Rev Inst Salubr Enferm Trop* 1947; **8:** 139–41 (in Spanish).

46 Demma LJ, Traeger MS, Nicholson WL, et al. Rocky Mountain spotted fever from an unexpected tick vector in Arizona. *N Engl J Med* 2005; **353:** 587–94.

47 Parker RR, Philip CB, Jellison WL. Rocky Mountain spotted fever. Potentialities of tick transmission in relation to geographical occurrence in the United States. *Am J Trop Med Hyg* 1933; **8:** 341–79.

48 Dantas-Torres F, Figueredo LA, Brandao-Filho SP. *Rhipicephalus sanguineus* (Acari: Ixodidae), the brown dog tick, parasitizing humans in Brazil. *Rev Soc Bras Med Trop* 2006; **39:** 64–67.

49 Rodaniche EC. Natural infection of the tick, *Amblyomma cajennense* with *Rickettsia rickettsii* in Panama. *Am J Trop Med Hyg* 1953; **2:** 696–99.

50 Dias E, Martins AV. Spotted fever in Brazil. A summary. *Am J Trop Med Hyg* 1939; **19:** 103–08.

51 Guedes E, Leite RC, Prata MC, Pacheco RC, Walker DH, Labruna MB. Detection of *Rickettsia rickettsii* in the tick *Amblyomma cajennense* in a new Brazilian spotted fever endemic area in the state of Minas Gerais. *Mem Inst Oswaldo Cruz* 2005; **100:** 841–45.

52 Pinter A, Labruna MB. Isolation of *Rickettsia rickettsii* and *Rickettsia bellii* in cell culture from the tick *Amblyomma aureolatum* in Brazil. *Ann N Y Acad Sci* 2006; **1078:** 523–29.

53 Davis GE. Experimental transmission of the spotted fevers of the United States, Colombia, and Brazil by the argasid tick *Ornithodoros parkeri*. *Public Health Rep* 1943; **58:** 1201–08.

54 Parker RR, Bell JF, Chalgren WS, Thrailkill FB, McKee MT. The recovery of strains of Rocky Mountain spotted fever and tularemia from ticks of the eastern United States. *J Infect Dis* 1952; **91:** 231–37.

55 McDade JE, Newhouse VF. Natural history of *Rickettsia rickettsii*. *Annu Rev Microbiol* 1986; **40:** 287–309.

56 Labruna MB, Whitworth T, Horta MC, et al. *Rickettsia* species infecting *Amblyomma cooperi* ticks from an area in the state of São Paulo, Brazil, where Brazilian spotted fever is endemic. *J Clin Microbiol* 2004; **42:** 90–98.

57 Labruna MB, McBride JW, Bouyer DH, Camargo LM, Camargo EP, Walker DH. Molecular evidence for a spotted fever group *Rickettsia* species in the tick *Amblyomma longirostre* in Brazil. *J Med Entomol* 2004; **41:** 533–37.

58 Labruna MB, Whitworth T, Bouyer DH, et al. *Rickettsia bellii* and *Rickettsia amblyommii* in *Amblyomma* ticks from the State of Rondonia, Western Amazon, Brazil. *J Med Entomol* 2004; **41:** 1073–81.

59 Medina-Sanchez A, Bouyer DH, Alcantara-Rodriguez V, et al. Detection of a typhus group *Rickettsia* in *Amblyomma* ticks in the state of Nuevo Leon, Mexico. *Ann N Y Acad Sci* 2005; **1063:** 327–32.

60 Cardoso LD, Freitas RN, Mafra CL, et al. Characterization of *Rickettsia spp* circulating in a silent peri-urban focus for Brazilian spotted fever in Caratinga, Minas Gerais, Brazil. *Cad Saude Publica* 2006; **22:** 495–501 (in Portuguese).

61 Eremeeva ME, Bosserman EA, Demma LJ, Zambrano ML, Blau DM, Dasch GA. Isolation and identification of *Rickettsia massiliae* from *Rhipicephalus sanguineus* ticks collected in Arizona. *Appl Environ Microbiol* 2006; **72:** 5569–77.

62 Moore JJ. Time relationships of the wood-tick in the transmission of Rocky Mountain spotted fever. *J Infect Dis* 1911; **8:** 339–47.

63 Spencer RR, Parker RR. Rocky Mountain spotted fever: infectivity of fasting and recently fed ticks. *Public Health Rep* 1923; **38:** 333–39.

64 Johnson JE, Kadull PJ. Rocky Mountain spotted fever acquired in a laboratory. *N Engl J Med* 1967; **277:** 842–47.

65 Wells GM, Woodward TE, Fiset P, Hornick RB. Rocky Mountain spotted fever caused by blood transfusion. *JAMA* 1978; **239:** 2763–65.

66 McKiel JA. The rodent and avian-borne diseases in Canada. *Can J Public Health* 1950; **51:** 220–25.

67 Bustamente ME, Varela G. A new rickettsiosis in Mexico. The existence of American spotted fever in the states of Sinoloa and Sonora. *Rev Inst Salubr Enferm Trop* 1943; **4:** 189–210 (in Spanish).

68 Bustamente ME, Varela G. Distribution of rickettsioses in Mexico. *Rev Inst Salubr Enferm Trop* 1947; **8:** 3–14 (in Spanish).

69 Rodaniche EC, Rodaniche A. Spotted fever in Panama: isolation of the etiologic agent from a fatal case. *Am J Trop Med* 1950; **30:** 511–17.

70 Fuentes LG. First case of Rocky Mountain spotted fever in Costa Rica, Central America. *Rev Latinoam Microbiol* 1979; **21:** 167–72 (in Spanish).

71 Ripoll CM, Remondegui CE, Ordonez G, et al. Evidence of rickettsial spotted fever and ehrlichial infections in a subtropical territory of Jujuy, Argentina. *Am J Trop Med Hyg* 1999; **61:** 350–54.

72 Patino L, Afanador A, Paul JH. A spotted fever in Tobia, Colombia. Preliminary report. *Am J Trop Med* 1937; **17:** 639–53.

73 Centers for Disease Control. Rocky Mountain spotted fever—United States, 1990. *MMWR Morb Mortal Wkly Rep* 1991; **40:** 451–53, 459.

74 Treadwell TA, Holman RC, Clarke MJ, Krebs JW, Paddock CD, Childs JE. Rocky Mountain spotted fever in the United States, 1993–1996. *Am J Trop Med Hyg* 2000; **63:** 21–26.

75 Childs JE, Paddock CD. Passive surveillance as an instrument to identify risk factors for fatal Rocky Mountain spotted fever: is there more to learn? *Am J Trop Med Hyg* 2002; **66:** 450–57.

76 Spach DH, Liles WC, Campbell GL, Quick RE, Anderson DE, Fritsche TR. Tick-borne diseases in the United States. *N Engl J Med* 1993; **329:** 936–47.

77 Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1996. *MMWR Morb Mortal Wkly Rep* 1997; **45:** 1–87.

78 Walker DH. Tick-transmitted infectious diseases in the United States. *Annu Rev Public Health* 1998; **19:** 237–69.

79 Jajosky RA, Hall PA, Adams DA, et al. Summary of notifiable diseases—United States, 2004. *MMWR Morb Mortal Wkly Rep* 2006; **53:** 1–79.

80 McNabb SJ, Jajosky RA, Hall-Baker PA, et al. Summary of notifiable diseases—United States, 2005. *MMWR Morb Mortal Wkly Rep* 2007; **54:** 1–92.

81 Centers for Disease Control and Prevention. Table II. (Part 6) Provisional cases of selected notifiable diseases, United States, week ending December 30, 2006. http://wonder.cdc.gov/mmwr/mmwr_reps.asp?mmwr_table=2F&mmwr_year=2006&mmwr_week=52 (accessed Sept 4, 2007).

82 McDade JE. Evidence supporting the hypothesis that rickettsial virulence factors determine the severity of spotted fever and typhus group infections. *Ann NY Acad Sci* 1991; **590:** 20–26.

83 Dalton MJ, Clarke MJ, Holman RC, et al. National surveillance for Rocky Mountain spotted fever, 1981–1992: epidemiologic summary and evaluation of risk factors for fatal outcome. *Am J Trop Med Hyg* 1995; **52:** 405–13.

84 Paddock CD, Holman RC, Krebs JW, Childs JE. Assessing the magnitude of fatal Rocky Mountain spotted fever in the United States: comparison of two national data sources. *Am J Trop Med Hyg* 2002; **67:** 349–54.

85 Eremeeva ME, Dasch GA, Silverman DJ. Quantitative analyses of variations in the injury of endothelial cells elicited by 11 isolates of *Rickettsia rickettsii*. *Clin Diagn Lab Immunol* 2001; **8:** 788–96.

86 Ministério da Saúde, Secretaria de Vigilância em Saúde. Outbreak of Brazilian spotted fever in the municipality of Petrópolis—RJ (2005). http://portal.saude.gov.br/portal/arquivos/pdf/nota_maculosa_corrigida.pdf (accessed Sept 5, 2007).

87 Holman RC, Paddock CD, Curns AT, Krebs JW, McQuiston JH, Childs JE. Analysis of risk factors for fatal Rocky Mountain spotted fever: evidence for superiority of tetracyclines for therapy. *J Infect Dis* 2001; **184:** 1437–44.

88 Walker DH, Hawkins HK, Hudson P. Fulminant Rocky Mountain spotted fever. Its pathologic characteristics associated with glucose-6-phosphate dehydrogenase deficiency. *Arch Pathol Lab Med* 1983; **107:** 121–25.

89 Centers for Disease Control and Prevention. Fatal cases of Rocky Mountain spotted fever in family clusters—three states, 2003. *MMWR Morb Mortal Wkly Rep* 2004; **53:** 407–10.

90 Salgo MP, Telzak EE, Currie B, et al. A focus of Rocky Mountain spotted fever within New York City. *N Engl J Med* 1988; **318:** 1345–48.

91 Hattwick MA, O'Brien RJ, Hanson BF. Rocky Mountain spotted fever: epidemiology of an increasing problem. *Ann Intern Med* 1976; **84:** 732–39.

92 Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. *J Infect Dis* 1984; **150:** 480–88.

93 Wilfert CM, MacCormack JN, Kleeman D, et al. Epidemiology of Rocky Mountain spotted fever as determined by active surveillance. *J Infect Dis* 1984; **150:** 469–79.

94 Kirk JL, Fine IX, Sexton DJ, Muchmore HG. Rocky Mountain spotted fever: a clinical review based on 48 confirmed cases, 1943–1986. *Medicine (Baltimore)* 1990; **69:** 35–45.

95 Vianna NJ, Hinman AR. Rocky Mountain spotted fever on Long Island. Epidemiologic and clinical aspects. *Am J Med* 1971; **51:** 725–30.

96 Linnemann CC Jr, Janson PJ. The clinical presentations of Rocky Mountain spotted fever. Comments on recognition and management based on a study of 63 patients. *Clin Pediatr (Phila)* 1978; **17:** 673–79.

97 Elston DM. Rickettsial skin disease: uncommon presentations. *Clin Dermatol* 2005; **23:** 541–44.

98 Ramos-e-Silva M, Pereira AL. Life-threatening eruptions due to infectious agents. *Clin Dermatol* 2005; **23:** 148–56.

99 Kaufmann JM, Zaenglein AL, Kaul A, Chang MW. Fever and rash in a 3-year-old girl: Rocky Mountain spotted fever. *Cutis* 2002; **70:** 165–68.

100 Hayden AM, Marshall GS. Rocky Mountain spotted fever at Koair Children's Hospital, 1990–2002. *J Ky Med Assoc* 2004; **102:** 209–14.

101 Myers SA, Sexton DJ. Dermatologic manifestations of arthropod-borne diseases. *Infect Dis Clin North Am* 1994; **8:** 689–712.

102 Kirkland KB, Marcom PK, Sexton DJ, Dumler JS, Walker DH. Rocky Mountain spotted fever complicated by gangrene: report of six cases and review. *Clin Infect Dis* 1993; **16:** 629–34.

103 Green WR, Walker DH, Cain BG. Fatal viscerotropic Rocky Mountain spotted fever: report of a case diagnosed by immunofluorescence. *Am J Med* 1978; **64:** 523–28.

104 Sexton DJ, Kaye KS. Rocky Mountain spotted fever. *Med Clin North Am* 2002; **86:** 351–60.

105 Hughes C. Rocky Mountain "spotless" fever with an erythema migrans-like skin lesion. *Clin Infect Dis* 1995; **21:** 1328–29.

106 Walker DH, Gay RM, Valdes-Dapena M. The occurrence of eschars in Rocky Mountain spotted fever. *J Am Acad Dermatol* 1981; **4:** 571–76.

107 Walker DH, Paletta CE, Cain BG. Pathogenesis of myocarditis in Rocky Mountain spotted fever. *Arch Pathol Lab Med* 1980; **104:** 171–74.

108 Donohue JF. Lower respiratory tract involvement in Rocky Mountain spotted fever. *Arch Intern Med* 1980; **140:** 223–27.

109 Walker DH, Mattern WD. Acute renal failure in Rocky Mountain spotted fever. *Arch Intern Med* 1979; **139:** 443–48.

110 Bleck TP. Central nervous system involvement in rickettsial diseases. *Neurol Clin* 1999; **17:** 801–12.

111 Massey EW, Thames T, Coffey CE, Gallis HA. Neurologic complications of Rocky Mountain spotted fever. *South Med J* 1985; **78:** 1288–90.

112 Weber DJ, Walker DH. Rocky Mountain spotted fever. *Infect Dis Clin North Am* 1991; **5:** 19–35.

113 Vaphiades MS. Rocky Mountain spotted fever as a cause of macular star figure. *J Neuroophthalmol* 2003; **23:** 276–78.

114 Sexton DJ, Gallis HA, McRae JR, Cate TR. Possible needle-associated Rocky Mountain spotted fever [letter]. *N Engl J Med* 1975; **292:** 645.

115 Krober MS. Skeletal muscle involvement in Rocky Mountain spotted fever. *South Med J* 1978; **71:** 1575–76.

116 Hattwick MA, Retailliau H, O'Brien RJ, Slutzker M, Fontaine RE, Hanson B. Fatal Rocky Mountain spotted fever. *JAMA* 1978; **240:** 1499–503.

117 Middleton DB. Rocky Mountain spotted fever: gastrointestinal and laboratory manifestations. *South Med J* 1978; **71:** 629–32.

118 Davis AE, Bradford WD. Abdominal pain resembling acute appendicitis in Rocky Mountain spotted fever. *JAMA* 1982; **247:** 2811–12.

119 Jiminez J, Byrne WJ, Seibert JJ, Euler AR. Gastrointestinal symptoms in Rocky Mountain spotted fever. Histopathologic finding of ulcerative enteritis with vascular. *Clin Pediatr (Phila)* 1982; **21:** 581–84.

120 Walker DH, Lesesne HR, Varma VA, Thacker WC. Rocky Mountain spotted fever mimicking acute cholecystitis. *Arch Intern Med* 1985; **145:** 2194–96.

121 Walker DH. Gastroenterology of Rocky Mountain spotted fever. *Pract Gastroenterol* 1986; **10:** 25–39.

122 Walker DH, Henderson FW, Hutchins GM. Rocky Mountain spotted fever: mimicry of appendicitis or acute surgical abdomen? *Am J Dis Child* 1986; **140:** 742–44.

123 Horney LF, Walker DH. Meningoencephalitis as a major manifestation of Rocky Mountain spotted fever. *South Med J* 1988; **81:** 915–18.

124 Kaplan JE, Schonberger LB. The sensitivity of various serologic tests in the diagnosis of Rocky Mountain spotted fever. *Am J Trop Med Hyg* 1986; **35:** 840–44.

125 Singh-Behl D, La Rosa SP, Tomecki KJ. Tick-borne infections. *Dermatol Clin* 2003; **21:** 237–44.

126 Procop GW, Burchette JL Jr, Howell DN, Sexton DJ. Immunoperoxidase and immunofluorescent staining of *Rickettsia rickettsii* in skin biopsies. A comparative study. *Arch Pathol Lab Med* 1997; **121:** 894–99.

127 Kostman JR. Laboratory diagnosis of rickettsial diseases. *Clin Dermatol* 1996; **14:** 301–06.

128 Walker DH, Cain BG, Olmstead M. Laboratory diagnosis of Rocky Mountain spotted fever by immunofluorescent demonstration of *Rickettsia* in cutaneous lesions. *Am J Clin Pathol* 1978; **69:** 619–23.

129 Dumler JS, Gage WR, Pettis GL, Azad AF, Kuhadja FP. Rapid immunoperoxidase demonstration of *Rickettsia rickettsii* in fixed cutaneous specimens from patients with Rocky Mountain spotted fever. *Am J Clin Pathol* 1990; **93:** 410–14.

130 Paddock CD, Greer PW, Ferebee TL, et al. Hidden mortality attributable to Rocky Mountain spotted fever: immunohistochemical detection of fatal, serologically unconfirmed disease. *J Infect Dis* 1999; **179:** 1469–76.

131 Tzianabos T, Anderson BE, McDade JE. Detection of *Rickettsia rickettsii* DNA in clinical specimens by using polymerase chain reaction technology. *J Clin Microbiol* 1989; **27:** 2866–68.

132 Dumler JS, Walker DH. Diagnostic tests for Rocky Mountain spotted fever and other rickettsial diseases. *Dermatol Clin* 1994; **12:** 25–36.

133 Sexton DJ, Kanj SS, Wilson K, et al. The use of a polymerase chain reaction as a diagnostic test for Rocky Mountain spotted fever. *Am J Trop Med Hyg* 1994; **50:** 59–63.

134 Eremeeva ME, Dasch GA, Silverman DJ. Evaluation of a PCR assay for quantitation of *Rickettsia rickettsii* and closely related spotted fever group rickettsiae. *J Clin Microbiol* 2003; **41:** 5466–72.

135 Bratton RL, Corey R. Tick-borne disease. *Am Fam Physician* 2005; **71:** 2323–30.

136 McKinnon HD Jr, Howard T. Evaluating the febrile patient with a rash. *Am Fam Physician* 2000; **62:** 804–16.

137 Cale DF, McCarthy MW. Treatment of Rocky Mountain spotted fever in children. *Ann Pharmacother* 1997; **31:** 492–94.

138 Purvis JJ, Edwards MS. Doxycycline use for rickettsial disease in pediatric patients. *Pediatr Infect Dis J* 2000; **19:** 871–74.

139 Donovan BJ, Weber DJ, Rublein JC, Raasch RH. Treatment of tick-borne diseases. *Ann Pharmacother* 2002; **36:** 1590–97.

140 Grossman ER, Walchek A, Freedman H. Tetracyclines and permanent teeth: the relation between dose and tooth color. *Pediatrics* 1971; **47:** 567–70.

141 Lochary ME, Lockhart PB, Williams WT Jr. Doxycycline and staining of permanent teeth. *Pediatr Infect Dis J* 1998; **17:** 429–31.

142 Herbert WN, Seeds JW, Koontz WL, Cefalo RC. Rocky Mountain spotted fever in pregnancy: differential diagnosis and treatment. *South Med J* 1982; **75:** 1063–66.

143 Markley KC, Levine AB, Chan Y. Rocky Mountain spotted fever in pregnancy. *Obstet Gynecol* 1998; **91:** 860.

144 Stallings SP. Rocky Mountain spotted fever and pregnancy: a case report and review of the literature. *Obstet Gynecol Surv* 2001; **56:** 37–42.

145 O'Reilly M, Paddock C, Elchos B, Goddard J, Childs J, Currie M. Physician knowledge of the diagnosis and management of Rocky Mountain spotted fever: Mississippi, 2002. *Ann N Y Acad Sci* 2003; **990:** 295–301.

146 Richards AL. Rickettsial vaccines: the old and the new. *Expert Rev Vaccines* 2004; **3:** 541–55.

147 Wilson ME. Prevention of tick-borne diseases. *Med Clin North Am* 2002; **86:** 219–38.

148 McGinley-Smith DE, Tsao SS. Dermatoses from ticks. *J Am Acad Dermatol* 2003; **49:** 363–92.

149 Cupp EW. Biology of ticks. *Vet Clin North Am Small Anim Pract* 1991; **21:** 1–26.

150 Krinsky WL. Dermatoses associated with the bites of mites and ticks (Arthropoda: Acari). *Int J Dermatol* 1983; **22:** 75–91.

151 Kaplan LI. Other spotted fevers. *Clin Dermatol* 1996; **14:** 259–67.

152 Abrahamian FM. Consequences of delayed diagnosis of Rocky Mountain spotted fever in children—West Virginia, Michigan, Tennessee, and Oklahoma, May–July 2000. *Ann Emerg Med* 2001; **37:** 537–40.

153 Needham GR Evaluation of five popular methods for tick removal. *Pediatrics* 1985; **75:** 997–1002.

154 Gammons M, Salam G. Tick removal. *Am Fam Physician* 2002; **66:** 643–45.

155 Lanschuetzer CM, Wieser M, Laimer M, Emberger M, Hintner H. Improving the removal of intact ticks. *Australas J Dermatol* 2003; **44:** 301.

156 Patterson JW, Fitzwater JE, Connell J. Localized tick bite reaction. *Cutis* 1979; **24:** 168–69, 172.