



## Rocky Mountain spotted fever

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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.<sup>1–3</sup> RMSF is among the most virulent infections identified in human beings,<sup>4</sup> and its diagnosis often presents a dilemma for clinicians.<sup>5–9</sup>

### 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”.<sup>10</sup> This description became the first report of RMSF to be published in the medical literature.<sup>11</sup>

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.<sup>12</sup> In 1906, *Dermacentor* spp ticks were categorically implicated in the transmission of the agent of RMSF, which was unnamed at that time.<sup>13,14</sup> 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.<sup>14–16</sup> Tragically, this talented rickettsiologist was affected by epidemic typhus and died in 1910, at the age of 39 years.<sup>17</sup>

Soon afterward, E R Le Count described the fundamental histopathology finding (ie, the vascular lesion) of RMSF.<sup>18</sup> In 1919, S Burt Wolbach published an extensive study on the agent of RMSF, confirming that ticks carried the bacterium.<sup>19</sup> 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 *Rickettsia* was proposed in 1922 by Brumpt.<sup>20</sup>

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

### The pathogen

*Rickettsia 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.<sup>24–26</sup> Most cell-surface antigens are recognised by antibodies present in sera of human beings and animals with active RMSF.<sup>26–28</sup> *Rickettsia 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 immunofluorescence assays.<sup>17</sup>

As with other rickettsiae, *Rickettsia rickettsii* retains basic fuchsin when stained using the Gimenez method,<sup>29</sup> 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).<sup>30,31</sup> *Rickettsia rickettsii* typically infects vascular endothelial cells.<sup>32–34</sup> Unlike other intracellular bacteria that may cause disease in human beings (eg, *Ehrlichia* spp), *Rickettsia rickettsii* is not surrounded by a host cell membrane and can be found in the nucleus or in the cytoplasm of the host cell.<sup>32,34</sup>

#### Panel 1: Classification of *Rickettsia rickettsii*

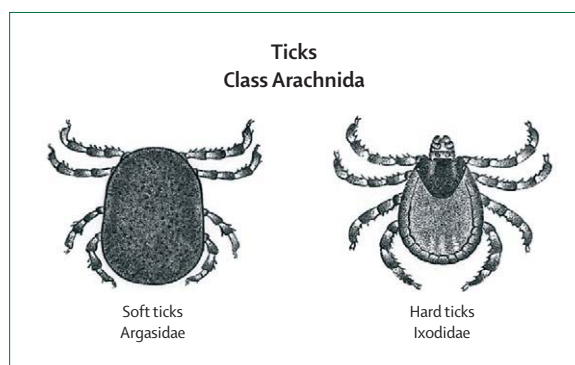
Kingdom: Bacteria  
Phylum: Proteobacteria  
Class: Alphaproteobacteria  
Order: Rickettsiales  
Family: Rickettsiaceae  
Genus: *Rickettsia*  
Species: *Rickettsia rickettsii*

Genomes of various *Rickettsia* spp have been sequenced previously.<sup>35–37</sup> Data from rickettsiae genomics are likely to improve the current understanding of the mechanism of rickettsial pathogenicity,<sup>38</sup> and may help the development of new diagnostic tools and vaccines.<sup>17</sup> 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.<sup>39</sup> 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.<sup>17,39–43</sup> Some of these animals may serve as secondary reservoirs or amplifying hosts.<sup>44</sup>

The American dog tick (*Dermacentor variabilis*; figure 2), is the primary vector of *R. rickettsii* in most of the USA. The



**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.

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,<sup>45</sup> has recently been implicated in the transmission of the pathogen in eastern Arizona.<sup>46</sup> Although the role of *Rh. sanguineus* as a vector of *R. rickettsii* has been determined in the laboratory,<sup>47</sup> it has a low affinity for human beings.<sup>31</sup> However, human parasitism by *Rh. sanguineus* may be more common than previously recognised,<sup>48</sup> and this tick may eventually act as a vector of *R. rickettsii* in other areas where the infection is endemic.<sup>17</sup> The Cayenne tick (*Amblyomma cajennense*), which is thought to be a common vector of *R. rickettsii* in Central and South America,<sup>9</sup> has a high affinity for human beings,<sup>31</sup> and has been found naturally infected with *R. rickettsii* in Panama and Brazil.<sup>49–51</sup> The tick *Amblyomma aureolatum*, commonly known in Brazil as *carrapato-amarelo-do-cao* (the yellow dog tick), has recently been implicated as a vector for *R. rickettsii* in Brazil.<sup>52</sup>

Other tick species are suspected to be involved in the transmission of *R. rickettsii*.<sup>53–55</sup> 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*)<sup>56–61</sup> 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.<sup>11,62,63</sup> 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),<sup>64</sup> or through blood transfusion.<sup>65</sup> 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,<sup>66</sup> western and central Mexico,<sup>67,68</sup> Panama,<sup>69</sup> Costa Rica,<sup>70</sup> northwestern Argentina,<sup>71</sup> Brazil (states of São Paulo, Minas Gerais, Rio de Janeiro, Espírito Santo, Bahia, and Santa Catarina),<sup>51</sup> and Colombia.<sup>72</sup> In the USA, RMSF occurs in all contiguous 48 states, except for Vermont and Maine;<sup>73,74</sup> 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.

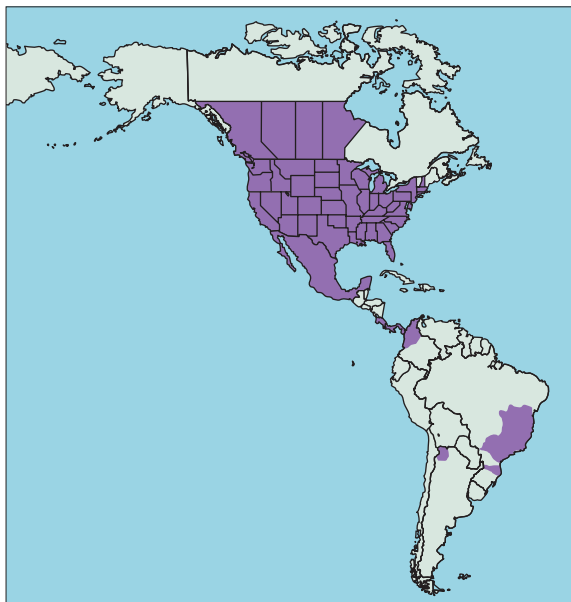


Figure 4: Approximate geographical distribution of RMSF in the American continent  
Shaded areas show regions where RMSF is endemic.

and in the South Atlantic region, particularly Maryland, Virginia, and North and South Carolina.<sup>9,73,74</sup>

Between 1873 and 1920, 431 cases of RMSF were described in the USA.<sup>75</sup> Between 1997 and 2002, the average annual incidence of the disease was 2.2 cases per million people.<sup>9</sup> Historically, approximately 250–1200 cases of RMSF have been reported annually in the USA, although it is likely that many more cases go unreported.<sup>76,77</sup> Cyclic fluctuations of the incidence of RMSF have been observed through the decades.<sup>78</sup> Of note, the number of RMSF cases reported in the USA in 2004, 2005, and 2006 were 1713,<sup>79</sup> 1936,<sup>80</sup> and 2092,<sup>81</sup> 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),<sup>74,78</sup> and among adults aged 40–64 years.<sup>80</sup> The incidence is also high among men and white people.<sup>82,83</sup>

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.<sup>84</sup> In the past, the disease would kill up to 87% of those infected.<sup>12</sup> Today, a fatal outcome has been reported in up to 20% of untreated cases and 5% of treated cases.<sup>9</sup> Geographical variations in case fatality of RMSF are known to occur in the USA.<sup>75</sup> Different isolates of *R. rickettsii* show different levels of pathogenicity in endothelial cell culture;<sup>85</sup> 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%.<sup>86</sup>

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.<sup>74,83,87</sup> Fulminant RMSF in African-American men with glucose-6-phosphate dehydrogenase deficiency has been reported.<sup>88</sup> In the USA, most cases of RMSF (90–93%) occur between April and September when the tick vectors are most active.<sup>17,83</sup> RMSF cases are usually found in rural areas,<sup>4,17,89</sup> although autochthonous cases have also been reported in urban settings,<sup>78</sup> such as New York.<sup>90</sup> Residence in wooded areas or in areas with high grass and exposure to dogs increases the risk of *R. rickettsii* infection.<sup>91–94</sup> 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.<sup>91</sup>

### Clinical manifestations

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

substantial proportion of them need to be admitted to hospital.<sup>83,93</sup> The mean incubation period of RMSF is 7 days (range 2–14 days).<sup>17,30,32,34,74</sup> 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.<sup>92</sup> 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.<sup>5,9,83,92,95–97</sup> During this phase, RMSF may be misdiagnosed as a viral illness.<sup>98</sup>

During the 2 weeks after a tick bite, the classic clinical triad is seen in 60–70% of patients.<sup>11,99,100</sup> A rash appears typically 2–5 days after onset of fever.<sup>17,32,34</sup> 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.<sup>12,98</sup> By the end of the first week, the eruption becomes maculopapular with central petechiae.<sup>92,101</sup> The continuous skin and tissue damage caused by *R. rickettsii* may result in skin necrosis and gangrene, requiring amputation in severe cases.<sup>11,102</sup> However, 9–12% of patients do not break out in a rash.<sup>5,6,92,103,104</sup> Lack of rash occurs most commonly in cases that are fatal, in older patients, and in African Americans.<sup>32,91</sup> Other cutaneous manifestations include mucosal ulcers, postinflammatory hyperpigmentation, and jaundice.<sup>30,105</sup> Unlike other tickborne rickettsial diseases, the presence of inoculation eschar is rare in RMSF.<sup>106</sup>

Myocarditis is uncommon in patients with RMSF.<sup>92,107</sup> Pulmonary manifestations such as cough and pneumonia have been reported.<sup>92,108</sup> 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.<sup>92</sup> Acute renal failure is often observed in severe cases.<sup>92,109</sup> Various neurological manifestations have been reported.<sup>3,30,110</sup> Some 40% of patients may develop lethargy, photophobia, meningismus, amnesia, bizarre behaviour suggestive of psychiatric illness, or transient deafness.<sup>92,94,111</sup> Ocular manifestations include conjunctivitis (30% of patients), optic disc oedema, arterial occlusion, retinal vein engorgement, retinal haemorrhage, and retinal sheathing.<sup>92,96,112,113</sup> Cases of skeletal muscle involvement with high concentrations of creatine kinase have also been reported.<sup>114,115</sup>

### 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

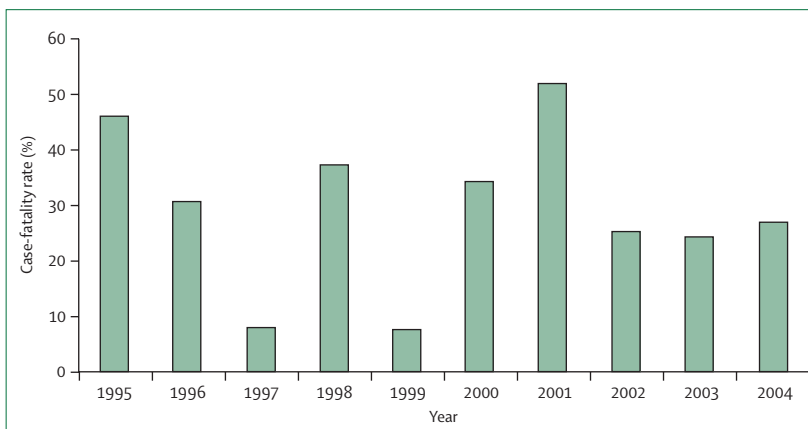


Figure 5: Case fatality of RMSF in Brazil (as reported by the Brazilian Ministry of Health)<sup>86</sup>

are often non-specific and may lead clinicians to make the wrong diagnosis.<sup>5,106,116–123</sup>

Antibodies to *R. rickettsii* are not detectable until 7–10 days after disease onset;<sup>124</sup> thus, serological tests are of limited diagnostic value.<sup>17,30</sup> A negative result does not exclude the possibility of infection and a positive result does not necessarily confirm presence of the infection.<sup>17</sup> The Weil-Felix test, the oldest serological assay in use, lacks sensitivity and specificity and is falling into disuse.<sup>11,17,125</sup> 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,<sup>9,104,124</sup> is highly sensitive, but cannot distinguish between infection with *R. rickettsii* and other spotted-fever-group rickettsiae.<sup>17</sup> A four-fold increase of titres in paired samples, or a convalescent titre greater than 1/64, is thought to be diagnostic.<sup>34,124</sup> ELISA has also been used,<sup>9</sup> and is reputed to be highly sensitive and reproducible.<sup>33</sup>

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.<sup>9,126,127</sup> 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.<sup>9,126–130</sup> 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.<sup>9</sup>

The use of PCR for the diagnosis of RMSF is limited because of its inferior sensitivity in detecting *R. rickettsii* DNA in blood specimens.<sup>9,11,131–133</sup> The number of rickettsiae circulating in the blood is typically low, particularly in the absence of advanced disease or fulminant infection.<sup>45</sup> This technique seems to be more useful for the detection of *R. rickettsii* in a skin biopsy or necropsy tissue specimen.<sup>55</sup> In acute RMSF, laboratory confirmation is improved when the PCR is used in association with immunohistochemical staining.<sup>9</sup> New PCR-based methods (eg, quantitative PCR assay)<sup>134</sup> 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.<sup>9,11</sup> Laboratory findings such as anaemia, thrombocytopenia, raised aminotransferase concentrations, increased bilirubin, increased creatine kinase, and hyponatraemia have been reported in RMSF.<sup>92,94,135</sup> 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).

### Treatment

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

Tetracyclines and chloramphenicol are the only drugs proven to be effective for the treatment of RMSF.<sup>11</sup> Because of its effectiveness, broad margin of safety, and convenient dosing schedule, doxycycline is currently considered the

#### Panel 2: Diseases and conditions to consider in the differential diagnosis of RMSF<sup>11,17,33,34</sup>

- 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

drug of choice for nearly all patients, including young children.<sup>7,9,88,137–140</sup> 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.<sup>9</sup> These recommended doses may be given orally or intravenously and treatment should be maintained for 5–7 days.<sup>11</sup> Doxycycline therapy should be continued until the patient is afebrile for at least 2 or 3 days.<sup>9</sup> Intravenous therapy is often indicated for hospital inpatients,<sup>9</sup> particularly for those with vomiting, unstable vital signs, and neurological symptoms.<sup>104</sup>

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.<sup>140</sup> Today, there is a consensus that doxycycline is the drug of choice for treating presumptive or confirmed RMSF in children of any age.<sup>9</sup> 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.<sup>141</sup>

Chloramphenicol remains the recommended therapy for RMSF in pregnant women, despite the risk of grey baby syndrome.<sup>9,32,142–144</sup> 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.<sup>142,143</sup> In life-threatening situations, the use of tetracyclines might be warranted during pregnancy.<sup>9</sup>

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.<sup>145</sup> Moreover, 23% of physicians reported that waiting for the development of a rash before the treatment decision is an appropriate strategy.<sup>145</sup> This suggests that continuing education is essential to prevent deaths caused by delay of doxycycline therapy.

### Panel 3: General recommendations for prevention of RMSF<sup>11,17,33,34</sup>

- 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 *Rickettsia* transmission

### Panel 4: Recommendations for proper tick removal<sup>11,17,34,153-155</sup>

- 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.<sup>146</sup> 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).<sup>34,143,147</sup>

Sometimes, it is not possible to avoid tick habitats, especially for people who live, work, or enjoy recreational activities in these environments.<sup>148</sup> 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.<sup>9,34,147-149</sup> Because the transmission of *R. rickettsii* requires a minimum period of attachment,<sup>11,62,63</sup> early tick removal is crucial to diminish the possibility of infection. Frequent physical examination to find and remove attached ticks is recommended.<sup>9,78,144,150-152</sup> 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.<sup>156</sup> 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,<sup>148</sup> 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.<sup>34</sup> Prophylactic antibiotic administration after a tick bite is not indicated to prevent RMSF.<sup>11</sup> Experimental animal models of *R. rickettsii* infection have shown that the illness was not prevented, but only delayed.<sup>78</sup>

## 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.

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