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Clinical characteristics of Rocky Mountain spotted fever in the United States: A literature review

Riley Jay[1] & Paige A. Armstrong[2]

[1]*Augusta University/University of Georgia Medical Partnership, Athens, GA, USA;* [2]*Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA*

ABSTRACT

Background and objectives: Rocky Mountain spotted fever (RMSF) is a rapidly progressive and potentially fatal tickborne disease caused by *Rickettsia rickettsii*. Despite current recommendations and information on the severity of RMSF, studies show that delayed recognition and treatment continues to occur.

Methods: A literature search was performed on cases published in English between 1990–2017. The frequencies for demographic, clinical, and treatment variables was calculated.

Results: A total of 340 cases from 34 articles were included. Data on rash were available for 322 patients, and 261 (80%) noted rash. Mortality was 4% (2) in those who received doxycycline within the first five days of illness, and 35% (18) when treatment was delayed beyond Day five. Twenty-four (16%) reported chronic sequelae, including speech impairment (7, 5%) and ataxia (5, 3%).

Interpretation and conclusion: These data highlight the importance of early treatment, and add to our understanding of long-term sequelae. Early recognition by providers will facilitate appropriate treatment and reduction in morbidity and mortality.

Key words Rocky Mountain spotted fever, spotted fever group rickettsiosis, *Rickettsia rickettsii,* tickborne disease, vector borne disease

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a rapidly progressive and potentially lethal tickborne disease caused by the obligate intracellular bacterium *Rickettsia rickettsii*. Most often, RMSF is spread by the American dog tick (*Dermacentor variabilis)* in the eastern United States, but may also be transmitted by the Rocky Mountain wood tick (*Dermacentor andersoni*) in the Rocky Mountain states[1]. Additionally, the brown dog tick (*Rhipicephalus sanguineus*) has become a prominent vector in parts of southwestern US. Current national surveillance reports on Spotted Fever group rickettsioses (SFGR), of which RMSF is the most fatal, has noted an increase from 8.5 cases per million people in 2008 to 13.3 cases per million people in 2016. The majority of cases of SFGR are reported from five states: Oklahoma, Arkansas, Missouri, Tennessee, and North Carolina[2, 3]. Diagnostic limitations and availability make differentiating cases of non-RMSF SFGR from RMSF difficult, though we know that the presentation and severity are very different. Combined mortality from SFGR is less than 0.5%, whereas recent clusters of RMSF in Arizona have reported mortality rates as high as 7.3% [2, 4].

Early clinical consideration is critical in RMSF because treatment within the first five days of illness significantly reduces the severity of disease and probability of death[2, 5]. RMSF initially presents with nonspecific symptoms such as fever, headache, rash, myalgia, and nausea, which can be mistaken for other illnesses[2, 6]. Laboratory findings are often within normal limits early in the disease course and confirmatory diagnostic results can take weeks to become available[5]. The decision to treat is based on clinical suspicion, and failure to treat appropriately within the first five days of illness is linked to higher mortality rates[6–8]. Doxycycline is the first-line treatment of choice for RMSF for all age groups recommended by both the American Academy of Pediatrics and the Centers for Disease Control and Prevention[5–6, 9–10].

Despite current recommendations and available information on the severity of RMSF, studies show that providers delay anti-rickettsial treatment outside the recommended five-day window and are reticent to prescribe doxycycline to pediatric patients[6, 8]. Current literature has shown that tooth staining and enamel hypoplasia are not associated with short courses of doxycycline, even in children under eight years of age[5, 11]. A questionnaire conducted in Tennessee in 2009 showed that 76% of providers recognized the importance of initiating treatment within the first five days, and yet only 39% reported that

they would prescribe doxycycline to children under eight years of age in whom they suspected RMSF[6]. A subsequent DocStyles survey in 2013 revealed that only 35% of primary care physicians, internists, pediatricians and nurse practitioners selected doxycycline as the appropriate treatment for RMSF in children under eight years[8]. Misconceptions about diagnosis and treatment of RMSF are particularly concerning when considering the importance of early diagnosis and appropriate treatment with doxycycline. To better inform providers about the clinical presentation of RMSF cases occurring in the United States, enhance awareness, and promote early diagnosis, we summarized clinical characteristics of published cases of RMSF from 1990–2017.

MATERIAL AND METHODS

Search strategy

We performed a literature search of case reports, case series, and retrospective chart reviews published in English from 1990 to 2017 using Scopus, Pubmed, and Ovid/MEDLINE current through December 31 2018. Search terms included "Rocky Mountain Spotted Fever", "*R. rickettsii*", "United States", and "Spotted fever group rickettsiosis". We filtered for availability in English language and involvement of human subjects.

Inclusion and exclusion criteria

Patients were included if specifically identified as a case of Rocky Mountain spotted fever. We used the current Council of State and Territorial Epidemiologists (CSTE) case definition for SFGR, under which RMSF is currently reported, as the model for inclusion. We required both clinically compatible illness and an indication that diagnostic testing had been performed and was consistent with a SFGR. We included all cases where *R. rickettsii* DNA was identified by PCR or IHC. We also included cases diagnosed by Indirect Immunofluorescence Antibody Assay (IFA) to *R. rickettsii* antigen when the clinical picture was more suggestive of RMSF than another SFGR or rickettsial disease. Though a case must have fever to satisfy the current SFGR case definition, we included patients without fever if the illness was otherwise compatible and there was supportive laboratory evidence[2, 5, 12].

Exclusion criteria

We excluded cases with diagnoses other than RMSF, including other spotted fever group rickettsioses, such as *Rickettsia parkeri, Rickettsia conorii*, or *Rickettsia africae*. Other exclusion criteria included: no report of laboratory evidence, lack of clinical data, publication dates earlier than 1990, and lack of availability in English. Papers addressing cases that occurred outside of the United States were also excluded as these were considered outside the scope of the current study.

Data gathering

We calculated frequencies for demographic, clinical, and treatment variables. When patient-level data were not available, we presented findings in aggregate. All variables were not available for all cases; unknown and missing data were treated equally. Since tick exposure was not presented uniformly, we further defined it as direct or indirect; however, these were not mutually exclusive categories. Direct tick exposure was defined as a known tick bite, or visualization on the body. Indirect exposure was defined as engaging in activities in endemic areas that might bring the patient into close contact with ticks. When available, we also noted geographic information associated with cases. We further defined states as "endemic" or "highly endemic". Endemic states were those in which an incidence of $\geq$20 cases of spotted fever rickettsiosis (SFR) per one million people were reported in any county, based on national surveillance data from 2010–2013[5]. This included Oklahoma, Arkansas, Missouri, Tennessee, North Carolina, South Carolina, Virginia, Alabama, Delaware, Maryland, New Jersey, Pennsylvania, Illinois, Arizona, Idaho, Nevada, Montana, Iowa, North Dakota, South Dakota, Kentucky, Indiana, Ohio, Texas, Utah, Wyoming, Mississippi, Georgia, and Nebraska. Highly endemic states are the five states from which over 60% of SFR cases are reported through the National Notifiable Diseases Surveillance System (NNDSS); *viz* Arkansas, Oklahoma, Tennessee, Missouri, and North Carolina.[3, 5]

Ethical statement

Ethics review was not required as our study utilized already published data.

RESULTS

Article selection

Our initial literature search yielded 837 abstracts. Application of inclusion and exclusion criteria resulted in 44 articles eligible for full text review. The most common reasons articles were excluded initially were: lack of clinical data, case occurring or acquired outside of the United States, and lack of laboratory evidence. Thirty-four articles satisfied all criteria and were included in the analysis; four were retrospective chart reviews and 30 were case reports or case series (Fig. 1).

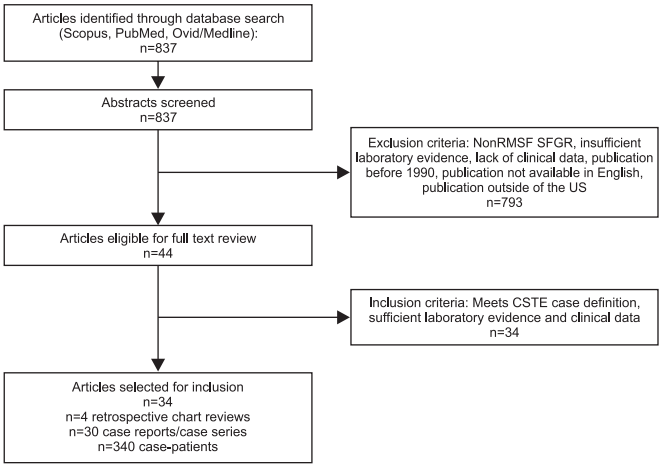

Fig. 1: Search strategy and criteria used to select articles for review of Rocky Mountain spotted fever (RMSF) cases in the United States 1990–2017.

Demographic Information

A total of 340 patients were included. A combined median could not be calculated as individual-level data were available for only 135 patients. Median age for 135 patients was 5.8 years (range: 13 months–86 years), and the median age for 205 patients was 11 years (range: 7 months–78 years). Overall, 235 (69%) were ≤18 years of age, and 105 (31%) were >18 years. Of the 336 patients for whom data on sex were available, 175 (52%) were male and 164 (48%) were female (Table 1).

Geographic distribution and exposure

State-level geographic data were available for 246 patients; the majority with state-level data were from Arizona (205, 83%). Ninety-three were described as having occurred in southeastern United States. Three hundred and thirty-five (99%) cases of illness were found to have occurred in the endemic states. Seventeen (5%) were reported in highly endemic states (Table 1).

Tick exposure data were available for 261 patients; 134 (51%) reported direct tick exposure, and 121 (46%) reported indirect tick exposure. There were five clusters (defined as >1 case). Each cluster was characterized by subsequent patients becoming symptomatic shortly after the sentinel event. All clusters included patients that were members of the same household. In one cluster, two dogs died from RMSF 14 and 22 days before their owner succumbed to her illness.

Clinical characteristics

Data on fever were available for 336 cases; 291 (86%) experienced fever at some point in their clinical course. One hundred fifty-four (57%) of 270 cases reported headache. Rash was reported in 261 (80%) of 322 cases with available data. Details on appearance of rash were available for 255 patients; 136 (63%) had maculopapular rash, and 106 (49%) reported petechial appearance. Location was available for 132, and 76 (58%) noted involvement of palms and soles. Thirty-eight (11%) patients reported meningismus, and 27 (8%) experienced seizures (Table 2).

Table 1. Demographic and geographic characteristics of Rocky Mountain spotted fever (RMSF) patients in the United States 1990–2017

Characteristic	N=340	%	Missing Values
Median age, years (range)			
	5.8	(13 months–86 years)	205
	11	(7 months–78 years)	135
Age			0
≤18	235	69	
>18	105	31	
Sex			4
Male	175	52	
Female	164	48	
Outcome			0
Mortality	32	9	
Geographic distribution			1
SFGR Endemic states	335	99	
SFGR Highly endemic sates	17	5	
Tick Exposure			79
Direct exposure	134	51	
Indirect exposure	121	46	

*SFGR (Spotted Fever group rickettsiosis) is the category within which RMSF is currently reported in US national surveillance.

Table 2. Clinical course, laboratory data, and treatment of Rocky Mountain spotted fever (RMSF) patients in the United States 1990–2017

Characteristic	N=340	%	Missing Values
Clinical Presentation			
Fever	291	86	4
Rash	261	80	13
Petechiae	106	49	125
Macular, popular, or maculopapular	136	63	125
Involvement of soles and palms	76	58	208
Headache	154	57	70
Severe clinical course			0
Hospitalized	196	58	
ICU admission	70	21	
Intubation	50	15	

Characteristic	N=340	%	Missing Values
Meningismus	38	11	
Seizures	27	8	
Coagulopathy	22	6	
Laboratory Diagnostic			274
PCR	22	33	
IHC	9	14	
IFA (Serology)*	35	53	
IgM	8	23	
IgG	14	40	
Paired	17	49	
Treatment			
Initial antimicrobial			299
Doxycycline	16	49	
Ceftriaxone	9	22	
Vancomycin	4	10	
Cephalexin	3	7	
Other tetracycline	1	2	
Antirickettsial treatment type			117
Doxycycline	193	89	
Chloramphenicol	17	8	
Other tetracycline	10	5	
No antirickettsial treatment	3	1	
Time to treatment (median, range, days)			
First antimicrobial	3	1-8	308
Doxycycline	5.6	1-49	145
Any antirickettsial	5.6	1-49	107
Any antirickettsial (mean)	6.5		
Between first antimicrobial and doxycycline	2	0-15	301
Onset of symptoms to doxycycline			222
On or before Day 5	52	44	
After Day 5	66	56	
Time to doxycycline by patient age (median, range, days)			329
18 years	7	1-21	
> 18 years	5	2-13	
Time to doxycycline by year (median, range, days)			311
Cases before 2013	8	2-21	
Cases after 2013	6.5	2-9	
Time to doxycycline in atypical presentations	10.4	2-49	
Doxycycline in fatal cases (n=32)			
On or before Day 5	2	4	288
After Day 5	18	35	289

*The categories are not mutually exclusive and some of those captured in the IgG category are also represented in pair (four-fold increase between acute and convalescent sample). Not all specified as paired had detailed information on IgG versus IgM.

Outcomes

Outcome data were available for all cases; among hospitalized patients (196, 58%), mortality was 9% (32). Seventy (21%) patients were admitted to the intensive care unit, fifty (15%) were intubated, and twenty-two (6%) had coagulopathy.

Laboratory tests

Individual-level results on laboratory data were available for 66 cases. Twenty-two (33%) were positive by PCR, nine (14%) were confirmed by immunohistochemistry staining of biopsy samples (skin biopsies and autopsy specimens). Thirty-five (53%) had serologic evidence of exposure to SFGR and titer values ≥1:64 on IFA against *R. rickettsii* antigen; of those, eight (23%) were by immunoglobulin M (IgM) and 14 (40%) were by elevated IgG. Seventeen (49%) reported on paired serology with a four-fold rise in titers, this was not mutually exclusive of those reporting IgG results (Table 2).

Treatment

Time from illness onset to initiation of doxycycline was available for 118 patients; of those, 52 (44%) received doxycycline within the first five days of symptoms. The median time from symptom onset to initiation of doxycycline was 5.6 days (range: 1–49). Individual-level treatment and mortality data were available for 103 cases. Mortality was 4% (2) in the 52 who received doxycycline within the first five days of illness, and 35% (18) in the 51 patients whose treatment was delayed beyond Day five. Sixteen (39%) of 41 for whom detailed data on initial antimicrobials were available received doxycycline as the first antibiotic administered. Other commonly prescribed antibiotics were ceftriaxone (10, 24%), vancomycin (4, 10%), cephalexin (3, 7%), and other tetracycline (1, 2%). The median time until administration of first antimicrobial was three days (range: 1–8). The median time between receiving first antimicrobial and doxycycline was two days (range: 0–15) for the 39 cases who received an antimicrobial other than doxycycline prior to the appropriate treatment. In cases occurring prior to 2013, the median time to doxycycline was eight days (range: 2–21), and after 2013 it decreased to 6.5 days (range: 2–9) (Table 2).

Atypical presentations

Fifty-two (15%) of 337 cases had documented atypical manifestations. Forty-six (14%) cases were afebrile. Two (0.6%) cases experienced myocarditis; one presented with chest pain after being treated for RMSF with a full course of doxycycline, while the other developed myocarditis on the second day of symptoms. Another two (0.6%)

Table 3. Atypical manifestations and chronic sequelae following Rocky Mountain spotted fever (RMSF) in the United States 1990–2017

Characteristic	N=340	%	Missing Values
Atypical manifestations	52	15	3
Afebrile	46	14	
Myocarditis	2	1	
Altered vision	2	1	
Acute arthritis	2	1	
Chronic sequelae	24	16	193
Neurologic	16	11	
Speech impairment	7	5	
Dysphagia	6	4	
Ataxia	5	3	
Memory loss	2	1	
Attention deficit	1	1	
Cortical blindness	1	1	
Necrosis	3	2	
Amputation	2	1	
Visual	2	1	
Persistent rash	1	1	

cases experienced reduced visual acuity; one suffered bilateral vision loss, while the other experienced decreased vision in one eye. Two (0.6%) cases experienced arthritis; one was mono-articular affecting the knee, while the other was polyarticular and affected both hands. The mean time until treatment with anti-rickettsial medications in these cases was 10.4 days (range: 2–49) (Table 3).

Chronic sequelae

Condition at discharge was described for 147 cases; of those 24 (16%) had documented sequelae. Sixteen (11%) reported neurologic complications, including seven (5%) impaired speech, six (4%) dysphagia, five (3%) ataxia, two (1%) memory loss, one (0.7%) decreased attention span, and one (0.7%) cortical blindness. Three (2%) cases experienced necrosis of the skin or digits; two required amputation, and one experienced gangrene and necrosis of the skin requiring surgical debridement and grafting. The two patients who presented with visual impairment continued to have deficits at discharge; however, both ultimately improved with treatment. One patient was initially diagnosed with retinitis and had 20/40 in the right eye and could only count fingers (severe impairment) in the left at the time of diagnosis. After treatment with doxycycline, vision improved to 20/100[13]. A second patient experienced diminished visual acuity in the right eye, which improved from 20/200 to 20/20 with doxycycline and corticosteroids[14]. The other reports of neurologic sequelae range from 10 days to four years in duration (Table 3).

DISCUSSION

RMSF is a fatal and rapidly progressive disease that requires early recognition and treatment to avoid mortality. Since most diagnostic results are not available within the first five days of illness, the ideal treatment period and diagnosis remains primarily clinical. Recognition of behaviors that increase exposure to ticks and key clinical patterns is critical for healthcare providers. The constellation of fever, rash, and tick bite is commonly taught to identify RMSF[15–16]; however, our review showed that these are not consistently present nor reliable as the only means of diagnosis. Instead, healthcare providers should look for these indicators, but also recognize that failure to report tick exposure, fever, or rash does not preclude RMSF. History of tick bite can assist in risk stratification, but is not always present in confirmed cases of RMSF[5]. Furthermore, we noted that 14% of patients did not report fever during their illness. Fever has long been considered necessary for diagnosis of RMSF, and continues to be a requirement in the CSTE surveillance definition. However, lack of fever should not preclude the clinical diagnosis of RMSF and we encourage providers to consider RMSF in afebrile patients that may otherwise fit the diagnosis, especially in endemic areas.

Clustered cases of RMSF can prove useful in helping providers diagnose subsequent cases. This is especially true when animals are sentinel cases. Dogs develop clinical signs and symptoms similar to those in humans, and can serve as an important warning sign that *R. rickettsii* is circulating in ticks in the nearby environment. Unfortunately, in our review, the cluster involving canine and human patients resulted in the death of all involved. Despite two dogs dying from confirmed RMSF, when the patient herself became ill, her disease was not immediately recognized and she did not receive appropriate treatment[17]. This further emphasizes the need for awareness and the role of counseling for both veterinary and human healthcare providers.

Diagnostics for RMSF vary in their utility and interpretation. Immuno Fluorescence Assay (IFA) comparing IgG titers between acute and convalescent samples is considered the gold standard. However, IgG antibodies can take 7–10 days after illness onset to be detectable and can remain elevated for months to years past the time of acute infection or may develop slowly and be missed. Reports have shown that as much as 11% of the US population has titers greater >64 while being asymptomatic[5]. The use of IgM IFA has declined due to inadequate specificity[5]. Testing tissue samples with PCR is less common but sensitive. The sensitivity is diminished by prior administration

of doxycycline[5]. Immunohistochemistry is an effective diagnostic tool, but less readily available[5]. Cultures are seldom used due to the fact that *R. rickettsii* is an obligate intracellular organism and difficult to culture[5].

Doxycycline is the recommended treatment in patients of all ages, and it considerably reduces morbidity and mortality when administered within the first five days of symptoms[5–10]. Failure to consider RMSF in the differential diagnosis can lead to delay in appropriate treatment. In our review, less than half of the patients received doxycycline or other antirickettsial therapies within the recommended five-day timeframe. The median time to initial antimicrobial was three days (range: 1–8), whereas median time to doxycycline was 5.6 days (range: 1–49), suggesting that patients received antimicrobials before the definitive antirickettsial therapy. Furthermore, the median time until doxycycline therapy in patients ≤18 years was 7 days (range: 1–21), while the median time was 5 days (range: 2–13) for patients over 18 years, suggesting there is a discrepancy between time to treat young children and older patients. The literature further demonstrated the afforded mortality benefit for those who received doxycycline prior to Day five versus after (4%, 35%). The data also suggest that the time till initiation of doxycycline may be improving, as the median time to administration was 8 days (range: 2–21) in cases prior to 2013 and 6.5 days (range: 2–9) in cases after 2013. Continued education of healthcare providers about the importance of early doxycycline initiation is key to reducing mortality from RMSF.

Atypical manifestations of RMSF are not well characterized in literature, but remain important for clinician awareness. Patients that present with either primarily generalized neurologic complaints, myocarditis, visual disturbances, or generalized weakness could represent cases of RMSF. Healthcare providers, especially in endemic areas, should consider RMSF in the differential of patients with these manifestations. Further documentation and characterization of atypical manifestations are still needed to deepen our clinical knowledge, prevent adverse outcomes, and enhance clinical diagnosis of RMSF.

Chronic sequelae following RMSF are also not fully understood, and yet were reported in 16% of patients upon discharge. The most common sequelae included neurologic deficits and necrosis of the skin or extremities. Lack of information about long-term consequences of RMSF contributes to uncertainty faced by providers and patients after acute illness. Better understanding could provide evidence-based counseling for patients and the ability to coordinate appropriate follow-up care.

Our review was limited by several factors; being a literature review it relied on cases being reported as RMSF. The most widely available and utilized laboratory diagnostic is IFA, but this exhibits cross-reactivity with other SFGR. While 31 (22 PCR, and 9 IHC) cases were confirmed as RMSF, the remainder were included on the basis of clinical presentation and laboratory evidence of SFGR, without certainty that this was specific to *R. rickettsii*. It is possible that some of these cases, reported as RMSF, may actually represent SFGR. However, the cumulative CFR of 9% seen in this review, suggests that the majority of cases represent RMSF. The overall sample size (n=340) is small, and not all patients had data available for each variable. Published cases are also more likely to be unusual or severe, which could lead to overrepresentation of these severe or atypical presentations in our data.

CONCLUSION

Education of healthcare providers on RMSF is key to early identification, clinical diagnosis, and early and appropriate treatment. Providers, especially those in endemic areas, should be aware of the various presentations of RMSF. Additionally, further understanding and dissemination of findings about atypical presentations and chronic sequelae can improve management of these patients and reduce morbidity and mortality among RMSF cases in the United States.

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Correspondence to: Riley Jay, MD, MPH, Augusta University/University of Georgia Medical Partnership, 200 Henry Clay Avenue, New Orleans, LA 70118, United States.
E-mail: rileyejay@gmail.com

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